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Review

Marine Mannitol: Extraction, Structures, Properties, and Applications

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Abstract: Mannitol is the most abundant polyol in nature and has wide commercial applications due to its properties in the food, chemical, medical, and pharmaceutical industries. Mannitol was traditionally produced from kelp, but this process was eliminated due to high water and energy consumption and gradually replaced by methods with less energy consumption and environmentally friendly practices. Studies show that brown seaweed contains large amounts of mannitol. Therefore, this paper intends to describe the structure of this sugar alcohol present in brown algae, its commercial production, and its biosynthetic pathway in algae, as well as its medical and nutritional applications.

Keywords: mannitol; marine bioactive compound; seaweed

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1. Introduction

Sugar alcohols, also known as polyhydric alcohols or polyols, are mostly natural substances and are considered natural alternatives to processed sugars [1]. They are derived from carbohydrates by reducing the aldehyde or ketone group to a hydroxyl group through chemical or biochemical processes. Therefore, they are different from other polyols produced in the petrochemical industry, such as ethylene glycol, propylene glycol, and pentaerythritol. The approved family of sugar alcohols used in food products internationally includes hydrogenated mono- (erythritol, xylitol, sorbitol, mannitol), di- (lactitol, isomalt, maltitol), or polysaccharides (maltitol and sorbitol extracts) [1,2]. Mannitol, a six-carbon non-cyclic polyol/sugar alcohol, is naturally found in a variety of organisms, except for Archaea and mammals, where it has a different physiological role. In some photosynthetic organisms, mannitol is a prominent main photosynthetic product employed as a carbon storage and translocator compound, as well as an essential osmolyte/compatible solute and antioxidant [3].

Mannitol has numerous applications in the food, pharmaceutical, medical, and chemical industries [4]. Currently, the majority of commercial manufacturing is accomplished through the chemical hydrogenation of a glucose and fructose mixture, resulting in the synthesis of mannitol and sorbitol, which are then separated using selective crystallization [4,5]. However, due to issues associated with chemical manufacture and an increasing demand for natural products, the production of mannitol from natural sources, particularly marine sources, has received significant attention in recent years [4]. Brown algae (Phaeophyceae) are marine photosynthetic organisms that can produce mannitol. They are classified as multicellular eukaryotes, and their genomic content has been altered by horizontal gene transfers and serial plastid endosymbiosis [6,7].

Research over the past 80 years has predominantly focused on kelps such as *Laminaria* [8–10], *Macrocystis*, and *Nereocystis* [11] when studying storage compounds in brown algae. Only a limited number of studies have explored *Sargassum* [12,13] and other brown algae species [14,15]. These investigations revealed that mannitol, along with other storage

compounds like laminaran, tends to be lowest during the initial growth period and increases as the algae mature [16]. Notably, mannitol constitutes approximately 20 to 30% of the dry weight in brown algae, making it a valuable compound with diverse applications in the food, chemical, medical, and pharmaceutical industries [17–19].

Algae, with their rapid growth rate and capacity to produce abundant mannitol, offer an economically efficient option for industrial mannitol production. Additionally, extracting mannitol from algae is more cost-effective than extracting it from terrestrial plants due to reduced resource requirements and specific environmental conditions. Consequently, this research aims to comprehensively explore algae-derived mannitol.

1.1. Primary Sources of Mannitol

Mannitol, as the most abundant sugar alcohol in nature, was initially extracted and described from the manna tree (*Fraxinus ornus*) and was commercially produced for a long time by heating the bark of the manna tree or its exudates [20]. Due to its role in carbon and energy supply and osmoprotection, mannitol is found in many vegetables and fruits, including pumpkin, celery, carrot, onion, and pineapple, albeit in small amounts [21]. Mannitol is also found in significant quantities in the secretions of trees and shrubs (such as plane trees, approximately 80–90%) and in olive trees [22,23]. Studies in this field have shown that plants under water-limited conditions accumulate nearly twice as much mannitol as those under good irrigation conditions, indicating the role of mannitol in osmotic regulation and protection against water stress [21].

Other sources of mannitol extraction include fungi, yeasts, bacteria, and lichens. Filamentous fungi such as strains of *Aspergillus* and *Penicillium*, single-cell microscopic fungi (yeasts), and some osmophilic fungi such as *Torulopsis* and *Candida* are capable of producing mannitol [24]. Two homofermentative and heterofermentative lactic acid bacteria (LAB) strains, namely *Lactobacillus homohiochi* and *Lactobacillus heterohiochi*, have been identified as the main strains for mannitol production [4]. Several inexpensive carbon sources, such as carob syrup [25] and molasses from sugar cane [26], have been used to support LAB metabolism for mannitol production, but the fructose-to-total sugar ratio in these sources is less than 50%, requiring supplementation with expensive fructose [27]. In some plants' glands and roots, such as Jerusalem artichoke, dandelion, and rose, a natural carbon source called inulin exists, which has a high content of fructose for mannitol production and can be used as a raw material for the production of biofuels and bioproducts [28–30]. In a study, inulin was used as a fructose source for mannitol production by the bacterium Lactobacillus intermedius, resulting in a yield of 222 g of mannitol per liter [31].

1.2. Marine Algae as a Source of Mannitol

Marine algae, due to their specific chemical composition and the possibility of large-scale cultivation, are potential raw materials for the production of chemicals and renewable fuels. Some brown algae species, especially kelps, have been studied as a source of alginate, ethanol, and butanol [32–35]. Moreover, marine algae, particularly brown algae, produce 10 to 20% mannitol as the main product of photosynthesis, with seasonal variations in mannitol content. In summer and autumn, it can exceed 20% [36]. Some species that have been investigated as substrates for bioconversion to ethanol include brown algae such as *Laminaria* [24,37], *Sacchoriza* and *Alaria* [38], *Turbinaria* [39], *Sargassum* [40–42], green algae *Ulva* [43], red algae *Macrocystis* [44], and *Kappaphycus* [45,46]. The most important brown algae species with commercial significance due to their high mannitol content are *Laminaria digitata* and *Alaria nodosum*. Horn et al. [24] also reported that mannitol constitutes approximately 20–30% of the dry weight of *Sargassum* spp. brown algae [32,47], and the absence of lignin in the cell walls of these macroalgae makes the extraction of fermentable substrates easier [48].

1.3. Chemical Properties of Mannitol

Non-cyclic alcohols and polyhydric alcohols, known as alditols due to the presence of an additional hydroxyl group, are derived from the loss of the carbonyl group from aldoses or ketoses and have broad commercial applications [49,50]. In this group, D-mannitol was the first naturally occurring crystalline alditol to be discovered. D-mannitol is a natural hexahedral sugar alcohol (six carbons) with an open chain structure, a chemical formula of $C_6H_{14}O_6$ (Figure 1A), a molecular weight of 182.17 g per mole, a melting point of 165–170 degrees Celsius (it crystallizes in small white needles), a boiling point of 290–295 degrees Celsius, and a specific gravity of 1.49 (at 25 degrees Celsius). It is an isomer of sorbitol (Figure 1B), which is industrially produced by hydrogenating fructose or pure glucose extract, resulting in white crystalline powder or granular forms. Its high negative heat of solution (−121 kilojoules per kilogram) gives mannitol a cool, sweet taste. Its sweetness is approximately half that of sucrose, with a caloric value of 1.99 kilocalories per gram. It has low solubility in water, equivalent to 18% (*w*/*v*) at 25 degrees Celsius. In alkaline solutions, it acts as a strong metal ion chelator and does not oxidize when exposed to air [51].

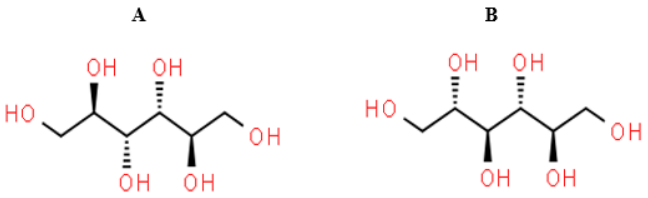

Figure 1. Chemical structures of D-Mannitol (**A**) and D-Sorbitol (**B**) [51].

2. Mannitol Synthesis Methods

2.1. Chemical Synthesis of Mannitol

Currently, commercial production of mannitol is achieved through chemical methods, specifically catalytic hydrogenation of a fructose/glucose mixture at high pressure (70–140 atmospheres) and elevated temperatures (120–160 degrees Celsius) [52–54]. In this process, Raney-Nickel acts as a catalyst, resulting in a production yield of 50% mannitol and 50% sorbitol [55,56]. In this case, the lower solubility of mannitol compared to sorbitol can be utilized for partial crystallization of the mixture and purification of mannitol. However, subsequent time-consuming and energy-intensive purification steps cannot be avoided.

The difficulties associated with separating mannitol from other components prompted researchers to develop alternative extraction methods. In the 1950s, the precipitation of mannitol from marine algae using water, alcohol, pyridine, and aqueous calcium chloride was proposed by Black et al. [57]. In the 1970s, in the United States, a method involving mixing a mass containing mannitol with an aliphatic carbonyl compound (resulting in a triester compound) and subsequent hydrolysis of the resulting compound using dilute acid was suggested by Chapman [58]. Bambase et al. [59] employed the solvent extraction method introduced by Black et al. [57] for extracting mannitol from the brown algae *Sargassum*. In this method, for every 9.40 g of dried powdered marine algae, 132 milliliters of methanol was added, homogenized, and boiled for 15 min. The resulting mixture was filtered while still warm. The filtrate was then stored in a freezer for 3–5 days to allow for crystallization. After storage at 4 °C, the crystallized mannitol precipitates were recovered through filtration and drying. Chades et al. [60] used HCl for mannitol extraction from *A. nodosum* and dH_2O for *L. digitata*. Zhang et al. [61] extracted mannitol from four different brown algae species (*Carpophyllum flexuosum*, *Carpophyllum plumosum*, *Ecklonia radiate*, and *Undaria pinnatifida*) by first extracting pigments using ethanol to remove them, followed by drying the remaining algae powder in an oven at 60 degrees Celsius. Subsequently, mannitol was extracted using Milli-Q water (Elix® MILLIPORE, Merck; Boston, MA, USA) at a 1:15 ratio of biomass to water, mechanically homogenized at room temperature, filtered, washed with absolute ethanol, and precipitated with acetone. According to the

study, simultaneous extraction of aromatic polyphenols and alginate along with mannitol extraction may result in partial impurities compared to pure commercial mannitol samples when extracting mannitol from natural sources such as algae [61].

2.2. Enzymatic Method for Mannitol Production

In the presence of mannitol dehydrogenase (MDH) as the key enzyme, the direct conversion of fructose to mannitol is catalyzed [51]. The requirement of cofactors (NADH or NADPH) for MDH leads to increased production costs and serves as the primary limiting factor in the utilization of this method. Wichmann et al. [62] proposed a two-enzyme system in which the enzymes mannitol dehydrogenase and glucose dehydrogenase and a common cofactor NADH2 are capable of simultaneously converting a mixture of glucose/fructose into gluconic acid and mannitol. Continuous cofactor regeneration through reductive reactions by the formate dehydrogenase enzyme occurs in this cycle. CO_2 serves as the sole byproduct of this cycle, which not only poses no issues regarding enzyme inactivation or inhibition but can be easily separated. However, in practice, several challenging issues exist, such as retaining the cofactor in reactors with specialized membranes, strong inhibition of the mannitol dehydrogenase product, and its high Km value for residual fructose [55].

2.3. Stages of Biorefinery for Mannitol Extraction

Investigations have indicated that the production efficiency of D-mannitol using chemical methods is low, and considering the major drawbacks in terms of technological, economic, and especially environmental aspects, the development of suitable alternative methods with high and optimized performance that can meet the increasing demand for this substance appears to be essential [63]. In the early 1930s, mannitol production was first proposed through fermentation. Fermentation, derived from the Latin word “fevere”, is an ancient and important technology in food processing. Recently, due to its potential application in converting a wide range of substrates, such as low-cost agricultural and industrial by-products, into valuable products like microbial biomass and primary and secondary microbial metabolites, fermentation has gained attention.

Certain fungi and yeasts can store mannitol intracellularly (several Penicillium strains), while others can excrete it extracellularly (osmophilic yeasts). This group of organisms has been considered suitable candidates for mannitol production [4]. In the literature, mannitol produced through fermentation is described as the result of the complete conversion of fructose to mannitol by homofermentative and heterofermentative lactic acid bacteria (LAB) [64]. Heterofermentative lactic acid bacteria (LAB) are efficient mannitol producers due to their capability to convert fructose into mannitol through a one-step intracellular reaction catalyzed by NAD(P)H-dependent mannitol-2-dehydrogenase (MDH) [65]. The key enzymes involved in these fermentation pathways are mannitol 1-phosphate dehydrogenase for homofermentative bacteria and mannitol dehydrogenase for heterofermentative lactic acid bacteria [21,31,51]. The absence of hardly removable by-products, average production conditions, and the lack of need for highly purified substrates are among the advantages of this method [66], making it an excellent alternative for commercial mannitol production [55].

2.3.1. Mannitol Production by Heterofermentative LAB

Several heterofermentative lactic acid bacteria (LAB) from the genera *Lactobacillus*, *Leuconostoc*, and *Oenococcus* can utilize the intracellular enzyme MDH to transform fructose into mannitol [4,64]. Researchers have conducted numerous studies over the last two decades to explore mannitol production by heterofermentative lactic acid bacteria. These investigations have focused on utilizing fructose, sucrose, or combinations of glucose and fructose as substrates. Yun and Kim [67] isolated two heterofermentative *lactobacillus* strains (Y-107 and *Leuconostoc* sp. Y-002) during kimchi fermentation. These strains produced mannitol when cultivated on fructose, sucrose, or an equimolar glucose/fructose mixture. Mannitol biosynthesis relies on fructose, as previously mentioned. It is suggested that the

fructose component of the disaccharide plays a key role in mannitol formation, particularly in the context of mannitol production from sucrose [68]. To our knowledge, no published research exists on utilizing LAB for extracting mannitol or producing it from marine algae. However, other bacterial genera contribute to mannitol production from marine algae, as demonstrated by Chades et al. [60].

2.3.2. Production of Mannitol from Agro-Industrial Waste or Inexpensive Substrate

To make mannitol production via fermentation economically viable for large-scale implementation, two cost-reduction alternatives exist. The first approach involves utilizing more affordable sugar sources, particularly those rich in fructose. Fructose is crucial for mannitol production in lactic acid bacteria (LAB) and constitutes nearly 50% of the overall production cost [52]. Mannitol production can be achieved using various methods, including microbial fermentation, enzymatic synthesis, and natural extraction. Among these, biotechnological production using agro-industrial residues or low-cost substrates has gained attention due to its advantages over chemical synthesis and plant extraction. Another cost-reduction approach involves substituting expensive nitrogen sources (such as yeast extract, peptone, or beef extract) with more economical organic or inorganic alternatives. For instance, Ortiz et al. [65] modified the MRS medium by replacing costly nitrogen sources with sugarcane molasses, enabling mannitol production by *Lactobacillus reuteri* CRL 1101 in batch fermentation. The resulting mannitol volumetric productivity was 1.60 g L^{-1} h^{-1}, with a yield of 0.87 mol mannitol per mol of fructose consumed. In a recent study, Ortiz et al. [69] designed a simplified culture medium using yeast extract and beef extract as nitrogen sources, along with sugarcane molasses as the carbon source. They conducted batch fermentations under constant pH conditions. Remarkably, the highest mannitol volumetric productivity (1.73 g L^{-1} h^{-1}) and yield (1.05 mol mannitol per mol of fructose consumed) were attained at a pH of 5.0. In a study by Saha [70], the nitrogen and carbon sources in the simplified MRS medium were replaced with low-cost alternatives. Bacto-yeast extract and bacto-peptone were substituted with corn steep liquor (CSL) and soy peptone D. CSL serves as a nitrogen source rich in essential vitamins and minerals. Additionally, sugar cane molasses and fructose syrup replaced pure glucose and fructose. A batch culture using this low-cost medium achieved a mannitol volumetric productivity of 4.76 g L^{-1} h^{-1}, comparable to the value reported by Saha and Nakamura [71] for the simplified MRS medium (4.86 g L^{-1} h^{-1}). Thus, the low-cost medium effectively supported mannitol production. In a subsequent study, Saha [72] investigated the impact of various salt nutrients on mannitol production by *Lactobacillus intermedius* NRRL B-3693. Using fructose syrup as the carbon source and the same nitrogen sources as the low-cost culture medium, they found that only $MnSO_4$ was essential for mannitol production from fructose. The highest mannitol concentration (200 g L^{-1}) and volumetric productivity (2.98 g L^{-1} h^{-1}) were achieved with 0.033 g L^{-1} of $MnSO_4$ and 50 g L^{-1} of CSL. Despite lower volumetric productivity compared to the previous study [70], mannitol production remained significant.

3. Physiological Functions

Mannitol can protect cells under stress conditions, including osmotic stress. This polyol acts as an osmotic regulator, a transfer compound, and a coenzyme regulator [73], providing cell protection through various mechanisms such as maintaining turgor pressure [73,74], stabilizing the structure of lipids and membrane proteins [75], and preventing oxidative damage. However, the precise mechanism of cell protection by polyols like mannitol has not been fully elucidated. Mannitol is a potent antioxidant that can inhibit air pollutants and hydroxyl radicals, which can cause DNA and tissue damage [76]. Additionally, the addition of mannitol to foods and the use of lactic acid bacteria can lead to the production of functional and nutritionally enhanced foods [21]. This substance can also contribute to dental health and assist diabetic patients. Overall, mannitol is utilized as a valuable food additive and sweetener [66].

Bioactive compounds such as mannitol, sugar alcohol, and triterpenes such as maslinic acid and oleanolic acid possess food-preserving properties (increased food shelf life by reducing sugar crystallization) and low-calorie sweetening capabilities [77]. Furthermore, mannitol is used as a medication for the treatment of acute stroke [78], as a potent osmotic diuretic for toxicity treatment and preventive measures against diseases (such as anti-inflammatory, antihyperlipidemic, antitumor, and antimicrobial activities) [79–83], and as a protective and therapeutic agent in cases of neural or renal insufficiency [78,84]. Mannitol can be extracted using aqueous alcohol solutions along with phenolic compounds [22]. It is also utilized in scientific research, particularly in microbiology [85].

The safety of mannitol has been assessed and approved by health authorities worldwide, including the World Health Organization, the European Union, and countries such as Australia, Canada, Iran, and Japan. The United States Food and Drug Administration (FDA) also recognizes mannitol as safe.

4. Other Applications

Today, the high heat value property of mannitol (3025 kJ/mol), which is higher than glucose (2805 kJ/mol) as mentioned in previous sources, is utilized in the synthesis of biofuels, particularly bioethanol [32,47]. The complex of boric acid with mannitol is used in the production of solid-state electrolyte capacitors. In chemistry, it is used for the production of resins and surfactants. Mannitol is used in analytical chemistry for the determination of boron (B). Furthermore, it has extensive applications in scientific research, particularly in microbiology [66].

5. Conclusions

Today, mannitol has found widespread applications as a beneficial food ingredient in the food, chemical, medical, and pharmaceutical industries due to its unique and important properties. In comparison to chemical synthesis and extraction from plants, the biotechnological strategy for mannitol production offers significant advantages. Additionally, factors such as abundant resources, the ability to grow in water, and the presence of unique metabolites in algae (especially marine species) have made them suitable candidates for extracting bioactive compounds. Despite the promising studies on mannitol extraction as a bioactive and beneficial compound from marine sources, especially brown algae, research on microbial production of mannitol from these sources is still in the early stages. Therefore, there is a need for a comprehensive understanding of economically and sustainably cultivating and harvesting algae, as well as exploring different perspectives for commercial mannitol production from algae and marine sources. Technical and economic evaluations are necessary to determine the profitability of mannitol production from algae. The use of genetic techniques should be employed to improve microalgae strains for simultaneous biomass and mannitol production in terms of technical and economic feasibility. Despite this, the multi-dimensional use of primary raw algae in addition to mannitol extraction (such as the production of pigments, aromatic phenols, alginate, etc.) can be more economical from an economic standpoint.

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