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Review

Dextran of Diverse Molecular-Configurations Used as a Blood-Plasma Substitute, Drug-Delivery Vehicle and Food Additive Biosynthesized by *Leuconostoc, Lactobacillus* and *Weissella*

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Abstract: Dextran, a microbial metabolite of diverse molecular configurations, can be biosynthesized employing selected strains of characterized species of bacteria. Dextran molecules are secreted as an extracellular polysaccharide in the culture medium of the bacterial fermentation system. This microbially produced polymer of glucose possesses multi-faceted characteristics such as its solubility in different solvents and formation of dextran solutions of needed viscosity. Several preparations can be formulated for the desired thermal and rheological properties. Due to such multifunctional characteristics, dextran with different structural specifications is a desired polysaccharide for clinical, pharmaceutical, and food industry commercial applications. Dextran and its derivative products with various molecular weights, in a range of high and low, have established their uses in drug delivery and in analytical devices using columns packed with polysaccharide gel. Therefore, being a neutral raw material, the resourcefulness of dextran preparations of different molecular weights and linkages in their polymer configuration is important. For this purpose, several studies have been performed to produce this commercially important polysaccharide under optimized bacterial cultivation processes. This article aims to overview recently published research reports on some significant applications of dextran in the pharmaceutical and food industries. Studies conducted under optimized conditions in fermentation processes for the biosynthesis of dextran of diverse molecular configurations, which are responsible for its multifunctional properties, have been summarized. Concise information has been presented in three separate tables for each group of specific bacterial species employed to obtain this extracellular microbial polysaccharide.

Keywords: polysaccharide; dextran; clinical; drug delivery; dextranase; food; pharmaceutical; sucrose; *Leuconostoc*; *Lactobacillus*; bacteria

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1. Introduction

Dextran has been regarded as one of the very significant exo-polysaccharides (EPS) with several established applications in various industrial interests. EPS are important metabolites generally synthesized by some bacteria in bioprocesses. Although not all EPS are useful, beneficial polysaccharides are produced by certain bacteria characterized as probiotics in nature. Therefore, the selection of appropriate strain/s to perform a fermentation process is of utmost importance to synthesize extracellular polysaccharide products suitable for commercial application/s. EPS are widely studied, and their valuable effects correlate with the sustainability of gut health and wellness by alleviating certain ailments [1]. Food products containing EPS produced by probiotic bacteria are reported as dietary therapeutic representatives to re-establish the weakened gut microbiota, which is necessary to ease inflammation in the gastrointestinal tract, IBD, or IBS, and can avert

the initiation of colon cancer [2]. EPS produced in fermented milk beverages have been studied in detail for their properties of improving shelf-life and boosting nutrition with functional properties in dairy products [3,4]. Furthermore, exopolysaccharides produced as the secondary metabolites of bacteria, employed in food fermentation, have many potential and well-established functions in products that are classified as nutraceuticals. These products have been studied for their therapeutic activity, improving gut health in certain consumers who experience allergy and discomfort responses to some foods or their ingredients and additives used in products [5]. Valuable polysaccharides are produced by probiotic cultures in the GI tract through the support of dietary fibers, ingested as diet ingredients that are prebiotic in nature, and available in functional beverages and foods [6,7].

Polymeric carbohydrate structures are high molecular weight polysaccharides that are formed of monosaccharide units linked by glycosidic bonds. Dextran is one of those polysaccharides of commercial importance. A bacterial strain of *Leuconostoc mesenteroides* has been studied for its potential to produce its extracellular metabolite, a glucose polymer, which is biodegradable in nature. This EPS, characterized as dextran, has been reported as a value-added product useful in a range of industrial applications [8].

The aim of this article is to review a few important applications of dextran, a significant material used in different sectors such as blood transfusion, clinical, pharmaceutical, and food. Hence, the requirement of dextran preparations of diverse molecular weights and structural configurations has become essential for their specialized utility in each industry. For that purpose, the studies conducted for the biosynthesis of a diverse range of dextran products, employing specific microbial species as efficient and productive biocatalysts, have been presented in this article.

2. Description of Dextran Polysaccharide

Dextran polymer is a homo-polysaccharide of α-d-glucopyranosyl units through α-(1,6) links with α-(1,2), α-(1,3) or α-(1,4) branches. Shingle determined structural peculiarities of dextran molecules by Fourier-transform IR spectroscopy [9]. Particularly due to variable branching in its molecular configuration, delivery systems based on dextran have been widely studied for a diverse range of applications in food, nutraceuticals, pharmaceuticals, and medicine. Deng et al. investigated a green preparation process of doxorubicin–BSA–dextran nanoparticles, their characterization, and antitumor effects [10]. On a commercial scale, the most widely employed bacterial strain as the producer of dextran is standard strain NRRL B-512F of *Leuconostoc mesenteroides*, which is capable of synthesizing a polysaccharide, particularly with its linear structure. The molecular configuration of EPS synthesized by *L. mesenteroides* has been characterized as consisting of α-(1,6) linkage in glucose polymer up to the level of 95%, and the remaining polymer chain of 5% includes the α-(1,3) and α-(1,4) branches. The varied application of this type of molecular structure EPS is due to its possession of adequate rheological properties, which are required for several applications in industries. Dextran has been widely studied for its structure and characteristics [8–11]; hence, its structure is not graphically presented in this article.

Clinical Derivatives from Dextran

Dextran has been considered a multifunctional biopolymer starting material for designing varied molecular configurations that are suitable for wide-ranging applications. Its molecular weight range with substantial availability of active hydroxyl groups in the polymer chain are favorable characteristics for dextran's modifications. Since dextran is a neutral material, it has been illustrated as a promising macromolecular vehicle and carrier for drug chemicals [12]. Hence, numerous glycol-conjugates have been prepared as derivatives of dextran in suitable reactions selected for the required product, such as a relevant process of oxidation, esterification, or etherification [13].

Li et al. reported the effect of the reaction of esterification on structural, physicochemical, and flocculation characteristics of dextran, which could be useful in different

applications. Researchers suggested that esters of dextran can be prepared by adding an alkaline amino acid, lysine, onto the dextran polymer chain [14]. Dextran-ester demonstrated remarkable flocculation characteristics at low pH, caused by its extended polymer chain with amino groups, which can interact with substances having points with negative charges. In a different study conducted by Liebert et al., a long-chain fatty ester of dextran was prepared through in situ activation of carboxylic acid using iminium chloride [15]. Meltable dextran esters with significant melting behavior and biocompatibility are good functional coating materials. The dextran esters have the ability to form durable layers of films on several materials, for instance, glass and nitrided titanium implants, to facilitate the prevention of persistent inflammatory stimulus. This ester as a dextran derivative extends applications of a useful polysaccharide in the biomedical sciences. Dextran has also been applied in the spray-drying method of preparing powders that are used for the encapsulation of drugs and additives used in the pharmaceutical and food industries [11].

Dextran is a bacterial polysaccharide that has exceptional biodegradability, biocompatibility, and non-toxicity characteristics. Dextran molecules meet critical requirements of nanomaterials for their applications in pharmaceutics. Therefore, distinct derivatives of dextran have been developed through its modification because of the presence of a substantial number of reactive hydroxyl groups in its chain [12,13]. Unique delivery systems based on dextran, for example, micelles, magnetic nanoparticles, mini emulsions, hydrogels, and spray-dried powders, have been the subject of research and development. Their physicochemical properties, release mechanisms, and therapeutic effects performed in in vivo animal experiments have been studied in detail to establish their extensive applications in medicine and formulations of pharmaceutical compounds. Jin et al. have testified that the use of amphipathic prodrug micelles of dextran-doxorubicin is suitable for the treatment of solid tumors [16]. Table 1 presents some of the useful dextran derivatives.

Table 1. Dextran derivatives and their application and functions *.

Derivatives of Dextran	Product Known as	Applications	Functions
Dextran magnetite: Hydrophilic colloidal solution of superparamagnetic iron oxide coated with various dextran derivative	DM Magnetic iron oxide-dextran complex	Magnetic particle imaging for diagnostic imaging; Tracer for sentinel lymph node biopsy, safer than radioisotope tracer; Reagent; A contrast medium used for magnetic resonance imaging	Various functionalities obtained by changing the structure of the coating material around the magnetic core of iron oxide
Iron dextran complex	DFe	Iron supplement for animals	Prevention and treatment of anemia in piglets
Cationic dextran: Raw material for cosmetics added for a superior conditioning effect for hair and skin. A desired conditioning effect is achieved by choosing its molecular weight.	CDCL (MW 10K); CDC (MW 40K); CDCH (MW 500K)	Cosmetic ingredient for hair care and skin care products	Conditioning, moisturizing and protective effect, wave retention
Dextran sulfate sodium: Sodium salt of sulfate ester that is prepared by sulfation of partial decomposition products of dextran	DSS	Drug substance; Additive; Medical device; to induce colitis in mice and rats	Treatment of hyperlipidemia; Cosmetic ingredient; Laboratory reagent for biochemistry; The raw material of medical devices
Sodium carboxymethyl dextran	CMD	Cosmetic ingredients for hair care and skin care products	Conditioning, moisturizing, and thickening effect, smooth feeling

Table 1. *Cont.*

Derivatives of Dextran	Product Known as	Applications	Functions
Dextran ester: Acyl groups substitution with different carbon numbers from acetate to laurate	Dextran valerate, Dextran hexanoate	Transparent coating for various materials, including polyvinyl alcohol (PVA) films, wood, glass, and aluminum	Hot-melt-type adhesives
Diethyl-aminoethyl-dextran: Polycationic derivative of dextran	DEAE	Nanocarrier of chemotherapeutic drugs	In pharmaceutical functions
Fluorescent dextran derivatives	Derivatives labeled with FITC, TRITC, ATTO-dyes	Mainly used for studies of permeability and microcirculation in cells and tissues	For studies of drug delivery, as molecular size markers.
Dextran methacrylate: 1. Propionyl dextran mixture ester 2. Isobutyryl dextran mixture ester	1. PDME 2. IDME	Contact lenses	
Doxorubicin–BSA–dextran	Nanoparticles carrier for pharmaceutical chemicals	Drug delivery	Antitumor effects
Amphipathic dextran-doxorubicin Prodrug micelles		Carrier for drug delivery to the site	Therapy for solid tumors
Phenyl-dextran		Used in the preparation of gels and coatings	Hydrophobic material
Meltable dextran esters		Significant melting behavior and biocompatibility	Good functional coating material
Dextran spray-dried powders		Required for the encapsulation of drugs and food additives	Used in the pharmaceutical and food industry

* Source of information References [11–16]; https://www.labonline.com.au/content/consumables/product/tdb-labs-dextran-and-dextran-derivatives-483479682 (accessed on 14 September 2023).

3. Functions of Dextran and Its Derivatives

Several industries use dextran molecules in different processes or in several products due to the accessibility of a diverse range of dextran products with various molecular weights and configurations. The following sections have summarized a few notable functions of dextran and its derivatives.

3.1. Dextran Preparations Used as a Blood Plasma Substitute

Dextrans are used as blood volume expanders, as they have an inhibitory effect on coagulation factors and thrombocyte aggregation. Clinical grade dextrans of 40, 60, and 70 kDa molecular weights in 6 or 10% aqueous solutions are available for use as substitutes for blood plasma. These function by restoring blood plasma lost through severe bleeding. Dextran can replace blood proteins like albumin to present colloid osmotic pressure so that the fluid is pulled into the plasma from the interstitial space. Dextran-40 can improve the flow of blood by lowering its viscosity and also inhibiting the accumulation of erythrocytes. An early report available on the use of dextran for the prevention of postoperative thromboembolic complications is available [17]. Klotz and Kroemer reported on the clinical pharmaco-kinetic importance and issues in the use of plasma expanders. An intravenous solution of dextran-60 is generally used as the expander of blood volume, and the parenteral nutrition provides an osmotically neutral fluid after it is digested into glucose and water [18]. Clinical forms, dextran-40 and dextran-70, are related to anaphylactoid reactions, which are initiated by dextran-reactive immunoglobulin G antibodies. A low-MW dextran-1 of 1K Da molecular weight is a fraction of a dextran polysaccharide. If it is used for infusion immediately before the clinical dextrans, it can reduce the incidence of severe anaphylactoid reactions. Hence, to moderate the probability of anaphylactoid

reactions, a regular administration of dextran-1 was suggested before a clinical dextran of higher MW was used for the infusion [19].

Dextran molecules have high water-binding capacity; for example, 1.0 g of dextran-40 holds up to 30 mL volume of water, while 1.0 g of dextran-70 is able to take up to 20–25 mL of water. The unique property of dextran is that after dissolving it in normal saline to form a solution of 6%, w/v, it demonstrates colloidal osmotic pressure and viscosity, which are identical to human blood. The isotonic versions of dextran solutions are prepared at 6.0 and 10%. Dextran has been applied as a plasma volume expander. Two products of molecular weights of 40 and 70 kDa, dextran-40 and 70, are used in cases of shock or impending shock after hemorrhage, burns, and trauma [20].

In an investigation, dextran-40 was used to accomplish an in vitro evaluation of haemodilution affecting the coagulation profile. The analytical assays were performed using thrombo-elastometry and multiple electrode aggregometry [21]. Although the application of albumin in patients with septic shock is helpful, the two factors that affect its use are the high cost of clinical-grade albumin and its regulated availability. Therefore, the use of a suitable alternative to albumin was investigated, where dextran-70 was tested during resuscitation for its impact on organ failure or mortality in patients (n = 778) suffering from severe septicemia or septic shock, in addition to the use of albumin and crystalloids. The evidence collected through investigation did not detect any harmful impact of dextran-70 on organ failures or mortality in patients diagnosed with critical sepsis [22].

Alternatives to albumin, used for the expansion of plasma, consist of crystalloids in the form of 0.9% sodium chloride solution as the normal saline, whereas the plasma protein fraction is used as alternate protein colloids. Dextran, a non-protein colloid, worked as an albumin alternative. These alternatives, whether the crystalloids or non-protein colloids have not proved superior to albumin; however, these materials are reasonably cost-effective choices. Dextrans are added in 0.9% sodium chloride isotonic medium to form a component of colloid solutions. A report on albumin and related products has informed that a hypertonic mixture Rescueflow can be used for its prehospital use during bleeding for the management of hypotension [23]. An article on fluid resuscitation and early management reported that colloid replacement was frequently needed in young pediatric burn patients who suffered injuries from major burns. It could be effective because the concentration of serum protein decreases rapidly during burn shock. In such cases, it is reported that dextran colloid is normally applied during resuscitation cases, where children had main injuries from burns [24].

Dextrans are also used in hematology. The following section presents information on applications of dextran products in the pharmaceutical industry, where various dextran derivatives, dextran conjugates, nanoemulsions, and micelles have been studied for their use as nanocarriers for nanomedicine drug delivery.

3.2. Dextran a Vehicle and Carrier for Drug Delivery

Dextran and its modified derivatives have attracted immense interest from researchers in the design of delivery procedures for pharmaceuticals of clinical relevance. Several delivery systems based on dextran have evolved with desired configurations for intended capabilities. The fabrication strategies included self-assembled micelles and nanoparticles, nanoemulsions, magnetic nanoparticles, microparticles, and hydrogels for diverse applications [25]. In contrast to chemically synthesized molecules, natural materials, such as polysaccharides, have many advantages, including biodegradability, biocompatibility, and non-toxicity. These materials can be used for the protected encapsulation of different bioactive entities [26], which is crucial for the safer delivery of functional pharmaceutical components [27]. In recent years, the development of effective and safer delivery practices constructed from dextran has been explored with considerable benefits [28]. Delivery systems based on dextran EPS with purposely designed compositions, such as nanoparticles, nano-complexes, nano emulsions, nano-crystals and micelles, have been produced [27,29,30].

Dextran, as a biopolymer, offers certain benefits if it is used to build nanomaterials as a clinical vehicle for the delivery of important pharmaceuticals due to its exceptional solubility and non-immunogenicity. Dextran has characteristics of its solubility in a choice of solvents from H_2O, dimethyl sulfoxide, ethylene glycol, or glycerol. This property is attached to the presence of α-1, 6 glycosidic bond, which supports the expansion in the mobility of the polymer chain. Some drugs have poor aqueous solubility; hence, their dissolution in the gastrointestinal fluids is a slow process that affects the bioavailability of drug molecules [9,31]. Dextran with high aqueous solubility is used in the fabrication of nanocarriers of drug molecules. It can facilitate the transportation of drugs and their effective bioavailability by permeation through the gastrointestinal membrane. The use of dextran in pharmaceutical delivery is preferred as it is a physiologically harmless biopolymer of saccharides and can, therefore, be metabolized by digestive enzymes. However, if synthetic polymers are used as vehicles, they might accrue in the system, causing side effects with their toxic degradation products [31].

The study was conducted to test subcutaneous implantation and tissue response evaluation; the results proposed in vivo biocompatibility of delivery systems based on dextran-polymer, as the dextran did not create a harmful or immunological effect on the body [32,33]. Unlike other polysaccharides such as starch, dextran cannot be hydrolyzed by common amylase enzymes, for instance, amylase in saliva. This stability makes dextran a safer nanomaterial for its use in oral delivery systems. Its satisfactory colloidal stability towards the enzymatic degradation supports the reliability of the delivery vehicle through a prolonged retention duration in the system for increased bioavailability of the drug molecules. The dextran chain can only be depolymerized by the enzyme dextranase if available in the gastrointestinal tract and other organs [9]. Consequently, dextran-based drug delivery arrangements can be used to safeguard pharmaceutical compounds during their passage by increasing their absorption by the epithelium. The neutral charge of dextran facilitates the efficiency of drug delivery.

Lai et al. investigated nanoparticles with the capability of mucus-penetrating for drug and gene delivery to mucosal tissues. The intestinal mucus layer generated by the goblet cells is negatively charged and is capable of trapping nanocarriers with a hydrophobic nature in their surface properties [34]. However, if the vehicle was negatively charged, it would be difficult for it to traverse the mucus layer caused by the negative-negative repulsion. Reports have recommended that delivery vehicles with neutral surfaces of a hydrophilic nature, as in dextran molecules, are perfect for mucus permeation of drug molecules [35]. Shan et al. investigated the issue of overcoming the diffusion barrier in mucus and the absorption barrier in epithelium by using self-assembled nanoparticles for the safer oral administration of insulin. Therefore, the above-mentioned properties make dextran an appropriate nanomaterial used to deliver micro concentrations of pharmaceutical compounds [36].

Kadota et al. studied the development of porous particles in a dry powder inhaler for enhanced delivery of rifampicin in the deep lung [37]. In this device, the acetalated dextran was applied as a sugar excipient. A suspension was prepared by mixing an ethanolic solution of rifampicin with an aqueous dextran solution, and then the powder was prepared by a spray-drying process of rifampicin suspension. Dextran-based nanoparticles have been explored as a vehicle for delivering therapeutic chemicals in the treatment of a few diseases. Although chemotherapy has been broadly used for the treatment of cancers, most drugs used as anticancer chemicals have insignificant water solubility and serious toxicity. The dextran nanocarriers have been suggested to enhance the bioavailability of pharmaceuticals. Carriers also lengthen the time for drugs' blood circulation and passively improve the accumulation of drugs in tumors by their higher permeation and retention [38,39]. Many forms of nanoparticulate systems based on dextran for anticancer drug delivery have been investigated in the last few years [40–43].

The current therapy for diabetes mellitus using insulin presents inconvenience and reduced conformity for patients' independence for physical intake; hence, nanocarriers

based on biopolymers have been developed for oral delivery of insulin [44,45]. The dextran-based biodegradable and biocompatible nanoparticles have been formulated to solve this issue. Alibolandi et al. performed in vitro and in vivo evaluation of dextran-b-poly (lactide-co-glycolide) polymersome for oral administration of insulin [46]. A new dextran-based glucose/pH-responsive insulin delivery method was fabricated, and the insulin release in response to varying pH levels and glucose concentrations was further investigated in vitro by Jamwal et al. [47]. In this design, an enzyme glucose oxidase was immobilized on acryloyl cross-linked dialdehyde dextran nanoparticles in a Schiff-base reaction.

Nanocarrier using dextran is one of the favorable agents for traumatic spinal cord injury treatment. In a study by Qi et al., methylprednisolone (MP) was integrated into ibuprofen-modified dextran nanoparticles for the delivery process; otherwise, it could cause serious side effects at high dosages [48]. The MP-loaded nanoparticles showed comparable therapeutic efficacy compared to free molecules of MP in in vivo experiments conducted on acute spinal cord injury model rats. Liu et al. formulated acetalated dextran nanoparticles for the delivery of paclitaxel in the treatment of spinal cord injury [49].

An effective delivery approach with a profile of sustained release was developed to eliminate the biofilm matrix and destroy contained pathogenic microbes causing skin infections. The biocide hydrogel for antibiofilm treatment was prepared with dextran methacrylate copolymer as a delivery vehicle for the destruction of bacterial growth in biofilms [50]. Hoque and Haldar have reported that these dextran hydrogels could release the biocide chemical for a prolonged time period of 5 days. The retention of biocide chemicals helped in completely clearing the infection caused by *Escherichia coli*, *Staphylococcus aureus*, and methicillin-resistant *S. aureus*. Some dextran-based hydrogels presented advantages over other cationic hydrogels based on chitosan, with a higher strength to eradicate biofilm [51]. In comparison to hydrogels based on peptides, dextran-hydrogels proved cost-effective for their simpler making process [52]. Dextran-hydrogels have been reported to have higher compatibility with mammalian cells than metal-based nanoparticles [53]. Therefore, in view of these characteristics, dextran could be efficiently used to design safe and functional antibiofilm agents.

3.3. Applications of Dextrans in Products of Food Industry

The main rationale for the application of dextran in food products is the property of dextran, being a fine white powder that dissolves readily in water at any temperature to prepare clear and viscous solutions. Moreover, dextran solutions are colorless, odorless, tasteless, and chemically inert, and therefore, these can be compatible with a variety of ingredients used in food items. Dextran has been suggested as a preservative coating for common perishable food products such as shrimp, meat, fruits, and cheese. Dextran can be produced by lactic acid bacteria, which are considered food-quality organisms that have been given the status of generally recognized as safe (GRAS) [5–7].

Few LABs synthesize extracellular polysaccharide, which is a material of commercial interest for its physical-chemical properties. Considering this fact, the EPS-forming Lactic acid bacteria have been used in food fermentations. The presence of dextran released by bacteria contributes to improving the rheological characteristics of dairy products, for instance, viscosity, texture, and mouthfeel [54]. EPS are categorized as heteropolysaccharides, which are composed of several types of sugar units, including glucose, galactose, fructose, and rhamnose, whereas homopolysaccharides type contain only one type of monosaccharide unit, glucose or fructose [55]. Homopolysaccharides studied in species of *Lactobacillus*, *Leuconostoc*, and *Streptococcus* are typically types of glucan or fructan, which are synthesized by extracellular enzyme glycan-sucrase consuming sucrose as the source of glycosyl (fructose or glucose) [56].

Semyonov et al. prepared dextran nanoparticles in the process of enzyme synthesis to study their application in delivery for nutraceuticals [57]. Food colloids binary and ternary complexes composed of up to three substances were studied for creating nanoparticles, which could be suitable for the fortification of bioactive composites in food products [28].

Conjugates of whey protein and dextran were used as stabilizers for the physicochemical strength and for the bio-accessibility of β-carotene nano emulsions [29].

The application of dextran in several food products is due to the characteristics of its flexibility in solubilization. The rheological properties in a product can be modified by using dextran of diverse molecular weights and types of branching in the polymer chain; hence, a dextran preparation matching the requirement can be selected accordingly [11]. Most applications of dextran as a polysaccharide have been investigated for food industry products. This polymer has been used in baking and confectionery for its exceptional moisturizing, stabilizing, and preserving properties [58]. Dextrans have also been explored for the improvement in flavor, texture, and consistency of several consumer-friendly products like ice creams, jellies, sauces, sweets, flour, breads, etc. [59].

Dextran polysaccharides act as stabilizers of culinary characteristics like texture, aroma, and flavor in finished food products. Other than that, it has been added to products prepared with the main ingredients of cheese, meat, and vegetables in order to slow down the oxidation of products [60,61]. Furthermore, dextran has been recommended as a suitable material for preparing biodegradable, edible coatings and films [62]. Dextran has been incorporated with another polymer, chitosan, in the fabrication of biodegradable material suitable as film for the packaging of mushrooms [63]. Dextran molecules of low molecular weights have been suggested as potential prebiotics for the sustainability of human gut microbiota [64,65].

4. Biosynthesis of Dextran in Optimized Microbial Processes

This section presents information on the synthesis of dextran polymer of diverse specifications in fermentation systems to obtain products produced as metabolites from selected bioagents, i.e., the strains of a few bacterial species.

4.1. Bioagents Used in the Production Process

Normally, the synthesis of polysaccharides by plants and production from agricultural products are relatively inexpensive. However, the cultivation of such resources requires favorable climates during a particular season in a year. Furthermore, plant-sourced materials have a vast inconsistency in their availability, purity, and properties. In contrast, the yield and properties of polysaccharides originating from microbial sources can be controlled by optimized parameters set for microbial fermentations. At the same time, microbial synthesis can be performed using economical substrates like by-products and residual materials produced in the agricultural and food industries [66,67]. Although the dextran is a neutral glucan with complex α-1, 6 glycosidic linkages between glucose units with branches with α-1, 2, α-1, 3, and α-1, 4 connections [60], nevertheless, the degree and nature of branching at 2, 3, or 4 positions can be manipulated by the selection of an appropriate dextran-producing strain in the synthesis process of dextran.

Dextran is mainly released extracellularly by fermenting lactic acid bacteria utilizing sucrose as a substrate in synthesis. Enzyme dextransucrase acts as a catalyst in the transfer of D-glucopyranosyl residues from sucrose to form dextran [60]. LAB are non-spore-forming, fermentative, facultatively anaerobic bacteria; products prepared using LAB are considered safe for human consumption. Several LAB strains approved as Generally Recognized As Safe (GRAS) have been given Qualified Presumption of Safety (QPS) status [68], which are widely employed in food production [69]. Characterized as effective probiotics, LAB have been used for the restoration of imbalanced gut microbiota affected in antibiotic-therapy-induced gut dysbiosis [70]. The clinical potential of LAB strains, which are used in fermentation for probiotic food and beverages and in the formulation of synbiotic supplements, has been recognized as a psychobiotic for cognitive treatment through gut-brain signaling [68], and for the biosynthesis of compounds for medical applications [71].

Due to their health-improving effects in nutrition and functional food and nutraceuticals, certain species of LAB have also been exploited as suitable bioagents for dextran production. Dextran biosynthesis by various strains differs in their glucosidic linkages, degree

and type of branching, molecular weight, and physical and chemical characteristics [61]. Dextransucrase can utilize the high binding energy of the glycosidic bond in sucrose to generate the α-1, 6 linkages of the polymer backbone without using adenosine triphosphate or cofactors. In the presence of dextransucrase, other natural or synthetic polymers such as lactulosucrose, α-D-glucopyranosyl fluoride, and p-nitrophenyl-α-D-glucopyranoside can also act as donor substrates to produce dextran [72]. The bulk production of dextran is required to meet its extensive needs in medical and food applications.

4.2. Dextran Synthesized by Specific Strains of Leuconostoc Species

The genus *Leuconostoc* belongs to a group of lactic acid bacteria usually isolated from fermented vegetables, which includes species involved in the production of exopolysaccharides with commercial potential. High molecular weight dextran produced by *Leuconostoc mesenteroides* AA1 have been characterized for their potential applications [61]. Dextrans produced by wild and mutant strains of *L. mesenteroides* were studied for their structural configuration and characterization [73]. Dextran production was studied using LAB strains isolated from the aguamiel of *Agave salmiana*; the product was structurally characterized to analyze the rheological properties of dextran [74].

Recently, in a study performed by Castro-Rodríguez et al. to produce and characterize dextran of different configurations, employing four strains of *L. mesenteroides*, which were isolated from *Agave salmiana*. The extracellular polysaccharides were produced in a 24 h process with sucrose substrate at optimized fermentation conditions set at pH 6 and incubated without mixing or shaking at 30 °C. The product with 20 g/L yield was precipitated as a gummy material by the addition of ethanol, and in its characterization, it was found to be a long-chain glucose polymer known as dextran. Dextrans produced by these strains have a polymer chain of α (1 → 6) linkages with branching of α (1 → 3). The rheological behavior of dextran solutions exhibited typical shear thinning and weak gel properties [74].

Commercial dextran is biosynthesized by the non-pathogenic organism *L. mesenteroides* strain NRRL B-512. For industrial production, a method is based on the batch-wise culture of fermentation medium containing sucrose as the main carbon source and supplemented with yeast extract, casein, peptone, malt extract, tryptone, and the salts of calcium and phosphate. During fermentation, the pH drops from 7 to 5 due to the generation of lactic acid; therefore, non-ionic compounds are usually added to maintain the stability of the bacteria and its enzymes [75]. Table 2 presents some fermentation studies performed for the production of dextran using selected strains of *Leuconostoc* species.

Table 2. Dextrans of diverse MW and configuration synthesized by specific isolate strains of *Leuconostoc* species.

Dextran Product Specification	Substrate/s Used in Biosynthesis	Strains Used to Conduct Fermentative-Production	Reference
358 MDa with α-(1→6) α-(1→3)	2%, *w*/*v* solution of sucrose	*Leuconostoc carnosum* strain CUPV411 an isolate from apple pomace	[76]
46 MDa 56% of α-(1→6) 44% of α-(1→3)	10%, *w*/*v* solution of sucrose	*L. citreum* strain SK24.002 an isolate from Fermented pickle	[77]
n.a.	15%, *w*/*v* solution of sucrose	*Leuconostoc* sp. strain LS1 an isolate from fermented cabbage	[78]
n.a.	15%, *w*/*v* solution of sucrose	*Leuconostoc* sp. strain LI1, an isolate from fermented rice batter	[78]
93% of α-(1→6) 07% of α-(1→3)	10%, *w*/*v* solution of sucrose	*L. mesenteroides* strain SD1, an isolate from green maguey—*Agave salmiana*	[74]
95% of α-(1→6) 05% of α-(1→3)	10%, *w*/*v* solution of sucrose	*L. mesenteroides* strain SD23, an isolate of *Agave salmiana*	[74]

Table 2. *Cont.*

Dextran Product Specification	Substrate/s Used in Biosynthesis	Strains Used to Conduct Fermentative-Production	Reference
94% of α-(1→6) 06% of α-(1→3)	10%, *w*/*v* solution of sucrose	*L. mesenteroides* strain SF2 an isolate from *Agave salmiana*	[74]
74% of α-(1→6) 26% of α-(1→3)	10%, *w*/*v* solution of sucrose	*L. mesenteroides* strain SF3 an isolate from *Agave salmiana*	[74]
970 KDa with α-(1→6) α-(1→3)	22%, *w*/*v* solution of sucrose	*L. mesenteroides* strain UICT/L18 an isolate from fermented rice batter	[79]
52% of α-(1→6) 48% of α-(1→3)	Solution of 10% sucrose with 5% maltose	*L. mesenteroides strain* NRRL B-1149	[80]
10–40 MDa	10%, *w*/*v* solution of sucrose	*L. mesenteroides* strain AA1 an isolate from fermented cabbage	[61]
960 MDa	Solution of 15%, *w*/*v* sucrose with pineapple juice	*L. mesenteroides* strain ATCC 10830	[81]
635 KDa 94% of α-(1→6) 06% of α-(1→3)	Solution of 15%, *w*/*v* sucrose with tomato juice	*L. mesenteroides* strain BD1710	[82]
25–40 MDa with α-(1→6) α-(1→3)	10%, *w*/*v* solution of sucrose	*L. mesenteroides* strain KIBGEIB22M20	[73]
15–20 MDa with α-(1→6) α-(1→3) ß-(2→6)	10%, *w*/*v* solution of sucrose	*L. mesenteroides* strain KIBGE-IB22	[73]
93% of α-(1→6) 07% of α-(1→3)	Solution of 5%, *w*/*v* sucrose with whey	*L. mesenteroides* strain BA08 an isolate from fermented rice batter	[83]
230 MDa 390 MDa 440 MDa 210 MDa	2%, *w*/*v* solution of sucrose	*L. mesenteroides* strains CM9, an isolate from camel milk, CM30, an isolate from camel milk, RTF10, an isolate from meat, SM34, an isolate from sheep milk	[84]
n.d.	Solutions of 2–10% whey with molasses; 6% cheese-whey	*L. mesenteroides* strain NRRL B512	[85]
<40 kDa	3%, *w*/*v* solution of sucrose	*L. mesenteroides* strain NRRL B512	[86]
<10 kDa	5% milk permeate	*L. mesenteroides* strain NRRL B512	[86]

4.3. Dextran Synthesized by Specific Strains of Lactobacillus Species

Strains of *Lactobacillus* sp. are grown in a fermentation medium of sucrose and used as the main carbon source to synthesize exopolysaccharide as an added-value microbial product. The sugar is metabolized by bacterial cells directly through the phosphotransferase system to produce dextran [87]. Bacteria secrete an enzyme dextransucrase extracellularly for the hydrolysis of sucrose in its monomers, fructose, and glucose. Glucose molecules are used to form an intermediate with glycosyl-enzyme for their subsequent polymerization into polysaccharide molecules of dextran, while fructose could be utilized for cell growth [88]. Table 3 presents some fermentation studies performed for the production of dextran using selected strains of *Lactobacillus* species.

4.4. Dextran Synthesized by Specific Strains of a Few Weissella Species

Weissella genus was earlier considered to be a member of the Leuconostocaceae family, but later it was placed in Lactobacillaceae. *Weissella confusa* was formerly known as *Lactobacillus confusus* as it resembles in numerous properties with other *Lactobacillus* bacteria. Hence, it has often been mistaken for bacteria of the *Leuconostoc* and *Pediococcus*. It is a non-motile coccus Gram-positive, catalase-negative, facultative anaerobic with an efficient fermentative metabolism. Although there are about 22 known species of *Weissella*, *W. confusa* has been generally employed in fermentation for its utilities (Table 4). The studies for dextran synthesis mainly employed two species of *Weissella*, namely *confusa and ciberia*; some relevant references have been summarized in Table 4.

Table 3. Dextrans of diverse MW and configuration synthesized by specific isolate strains of *Lactobacillus* species.

Dextran Product Specification	Substrate/s Used in Biosynthesis	Strains Used to Conduct Fermentative-Production	Reference
87% of α-(1→6) 13% of α-(1→3)	5%, *w*/*v* solution of sucrose	*Lactobacillus plantarum* Strain DM5 An isolate from fermented beverage	[89]
55% of α-(1→6) 45% of α-(1→3)	15%, *w*/*v* solution of sucrose	*L. satsumensis* Strain NRRL B-59839 isolated from Kefir grains	[90]
n.a.	15%, *w*/*v* solution of sucrose	*L. acidophilus* Strains LV3, LV4, LV5 isolate from vaginal swabs	[91]
170 MDa	2%, *w*/*v* solution of sucrose	*L. sakei* Strain MN1 isolated from meat products	[92]
n.a.	15%, *w*/*v* solution of sucrose	*L. fermentum* Strain LS2 isolated from the stool sample	[91]
n.a.	15%, *w*/*v* solution of sucrose	*L. plantarum* Strain LS3 isolated from the stool sample	[91]
123 MDa with α-(1→6) α-(1→3)	2%, *w*/*v* solution of sucrose	*L. mali* Strain CUPV271 an isolate from the ropy slime of ham	[76]
n.a.	15%, *w*/*v* solution of sucrose	*L. gasseri* Strains LV1, LV2, isolated from vaginal swabs, strain LS1 isolated from stool samples	[91]
High molecular weight dextran	5.0%, *w*/*v* sucrose	*L. sakei* strain TMW 1.411, isolated from sauerkraut	[87]
High molecular weight dextran with increasing viscosity	15%, *w*/*v* solution of sucrose	*L. acidophilus* strain ST76480.01 an isolate from fermented vegetables	[88]

Table 4. Dextrans of diverse MW and configuration synthesized by specific isolate strains of *Weissella* species.

Dextran Product Specification	Substrate/s Used in Biosynthesis	Strains Used to Conduct Fermentative-Production	Reference
180 kDa 96% of α-(1→6) 04% of α-(1→3)	4%, *w*/*v* solution of sucrose	*Weissella* sp. Strain TN610 isolated from pear	[93]
120–870 kDa 96% of α-(1→6) 04% of α-(1→3)	8%, *w*/*v* solution of sucrose	*W. confusa* Strain PP29 isolated from yogurt	[94]
120–250 kDa 96% of α-(1→6) 04% of α-(1→3)	Solution of 8%, *w*/*v* sucrose with milk	*W. confusa* Strain PP29 isolated from yogurt	[94]
10 MDa 97% of α-(1→6) 03% of α-(1→3)	5%, *w*/*v* solution of sucrose	*W. confusa* Strain QS813, a sourdough inoculum	[95]
10 MDa 97% of α-(1→6) 03% of α-(1→3)	10%, *w*/*v* solution of sucrose	*W. confusa* Strain R003 isolated from sugarcane juice	[96]
>20 MDa 97% of α-(1→6) 03% of α-(1→3)	10%, *w*/*v* solution of sucrose	*W. confusa* Strains A3/2-1, A4/2-1, F3/2-2, E5/2-1, G3/2-2 isolated from fermented cassava	[97]
1158 kDa α-(1→6) α-(1→3)	10%, *w*/*v* solution of sucrose	*W. confusa* Strain K1-Lb5 isolated from kimchi (fermented food product)	[98]
>20 MDa 97% of α-(1→6) 03% of α-(1→3)	10%, *w*/*v* solution of sucrose	*W. confusa* three strains 8CS-2, 11GU-1, 11GT-2, isolates of fermented milk	[97]
12 MDa α-(1→6)	20%, *w*/*v* solution of sucrose	*W. ciberia* Strain 27 isolated from kimchi (fermented food product)	[99]

Table 4. *Cont.*

Dextran Product Specification	Substrate/s Used in Biosynthesis	Strains Used to Conduct Fermentative-Production	Reference
800 kDa	10%, *w*/*v* solution of sucrose	*W. ciberia* Strain JAG8 isolated from apple skin	[100]
177 kDa 93% α-(1→6) 07% α-(1→3)	2%, *w*/*v* solution of sucrose	*W. ciberia* Strain JAG8 isolated from apple skin	[101]
390 KDa 96% α-(1→6) 04% α-(1→3)	5%, *w*/*v* solution of sucrose	*W. ciberia* Strain YB-1 isolated from fermented cabbage	[102]
97% α-(1→6) 03% α-(1→3)	2%, *w*/*v* solution of sucrose	*W. ciberia* Strain RBA-12 isolated from *Citrus maxima*	[103]
5–40 MDa	0.5 M solution of sucrose	*W. ciberia* Strain 10 M	[104]
>20 MDa 95% α-(1→6) 05% α-(1→3)	20%, *w*/*v* solution of sucrose	*W. ciberia* Strain 11GM-2 isolated from fermented milk	[97]
α-(1→6)	10%, *w*/*v* solution of sucrose	*W. ciberia* Strain MG1	[105]
>2 MDa 97% α-(1→6) 03% α-(1→3)	15%, *w*/*v* solution of sucrose	*W. ciberia* Strain CMGDEX3 isolated from fermented cabbage	[106]

5. Conclusions

This article has presented in the first few Sections 2 and 3 a review of the clinical and commercial importance of dextran polymer and its derivatives. In consideration of the multifunctional and important uses of dextran in several sectors, its supply in the form of a base raw material with specific molecular weights and configurations for the preparation of its structural derivatives is an important matter. Since the supply of polysaccharides from vegetative sources is not realistic for obtaining materials of desired specifications with structural uniformity throughout the year, frequent studies were aimed at the biosynthesis of dextran in a controlled optimized process of bacterial culture cultivation for its sufficient availability. Microbial fermentative processes employing purposely modified efficient microbial strains have been reported to be cost-effective and can be manipulated for the biosynthesis of products of commercial importance using cheaper raw materials; similarly, dextran can be synthesized from sucrose [107–110]. Selected bacterial strains under customized fermentation conditions can be cultivated to synthesize a good yield of dextran in the microbial production process. Moreover, it is easy to harvest dextran from the culture medium as an extracellular bacterial polysaccharide produced in the fermentation process.

6. Future Perspectives and Challenges

Different new probiotic and non-probiotic strains and appropriate culture conditions can be further explored to produce a variety of dextran polymers of varied molecular specifications suitable for specific applications. Such possibilities, having the availability of a diverse range of dextran molecules from lower to higher molecular weight and with different branching in the polymer chain, will increase their wider applications in several industries. Future perspectives for the requirement of dextran and its derivatives are numerous and will further expand in the pharmaceutical and food industries. Dextran will always be used as an ideal inert polysaccharide necessary for analytical procedures in research and development for clinical and various industrial products.

Although low molecular weight fractions of dextran polymer can be prepared by acid hydrolysis of high MW-dextran polysaccharide, low MW dextran fractions obtained by the action of acid in the chemical synthesis process would require a few steps of purification. That would increase the total cost of its production process. Therefore, a cost-effective method would be preferred, and for that, bio-synthesis employing specific strains of bacteria (Tables 2–4) metabolizing a common easily available carbon source like sucrose offers an economical process for obtaining different MW-dextran products. The challenges could be in optimizing bioprocesses from bench-scale to production-scale, when newer

strains are used. The bioreactors of different configurations for continuous cultivation of bacterial cultures could take considerable effort, depending on the type of bacterial species, to optimize the yield of dextran in a cost-effective production process. However, based on the information presented in the above tables, appropriate bacterial strains can be selected for a dextran product of the desired molecular specification, and subsequently, the production process can be upgraded for the rate and economic yield.

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