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Mannan as a Promising Bioactive Material for Drug Nanocarrier Systems

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1. Introduction

Polysaccharides are natural, non-toxic and biodegradable polymers that cover the surface of most cells and play important roles in various biological mechanisms such as immune response, adhesion, infection and signal transduction. Investigations on the alternative treatments applied by different cultures throughout the history revealed the fact that the utilized plants and fungi were rich in bioactive polysaccharides with proven immunomodulatory activity and health promoting effects in the treatment of inflammatory diseases and cancer. Hence considerable research has been directed on elucidating the biological activity mechanism of these polysaccharides by structure-function analysis [1].

Hemicelluloses are structural polysaccharides which are the second most abundant heteropolymers present in nature accounting for one third of total components available in the plants (Figure 1) [2]. Mannans and xylans are the two most important hemicelluloses and hence a lot of research is mainly focused on their value-added applications and hydrolysis [3]. Mannan is a biodegradable and bioactive polysaccharide that has been a focus of interest by various sectors due to its valuable properties. The film forming capacity and biodegradability of mannans make them an interesting alternative to the petroleum-based materials. Mannan-based films and coatings were shown to exhibit low oxygen and grease permeability and, in some cases, relatively high tensile strength [4]. There are also interesting reports on the successful use of mannan as a bioactive material in health related applications.

Mannans are linear polymers of 1,4-linked mannose residues and contain less than 5% of galactose [5]. In nature, mannan is present in four different forms, each having a β -1,4-linked backbone containing mannose (linear mannan) or a combination of glucose and mannose residues (glucomannan) and occasional side chains of α -1,6-linked galactose residues (galac-

tomannan / galactoglucomannan). The mannose and glucose residues in the backbone are sometimes acetylated at C-2 or C-3 (3,5).

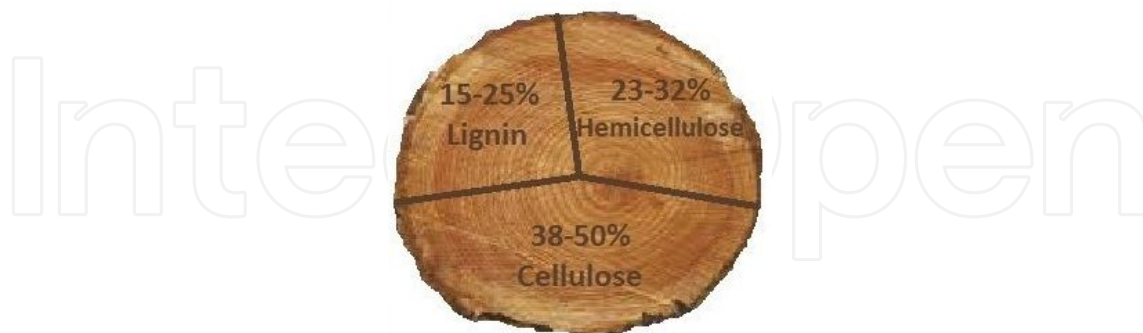


Figure 1. Polysaccharide composition of plants

In plants, mannans have a structural role by binding cellulose, but also they serve a storage function as a reserve carbohydrate in endosperm walls and vacuoles of seeds and vacuoles in vegetative tissues [5]. Recently, mannan has also been proposed as a signaling molecule in plant growth and development [6].

Mannan is a biodegradable and bioactive polysaccharide that has been a focus of interest by various sectors due to its valuable properties. The film forming capacity and biodegradability of mannans make them an interesting alternative to the petroleum-based materials. Mannan-based films and coatings were shown to exhibit low oxygen and grease permeability and, in some cases, relatively high tensile strength [4]. There are also interesting reports on the successful use of mannan as a bioactive material in health related applications. Mannan conjugated to vaccine preparations are already in the clinic [7,8]. Tang et al. [9] utilized a mannan-based system to target DNA vaccines to antigen presenting cells and demonstrated that it could induce far stronger immune responses in mice compared to naked DNA immunization. By further studies, they could explain the molecular basis of the observed immune enhancing attributes of mannan-based DNA vaccination [9]. Successful use of carboxylic mannan-coated iron oxide nanoparticles in targeting immune cells for *in vivo* lymph node-specific Magnetic Resonance Imaging was also reported recently [10]. Moreover, to target mannose receptor expressed on the surface of antigen-presenting cells, biocompatible self-assembled mannan nanogels were designed to provide a therapeutic or vaccine delivery platform [11,12]. In a recent review on oral drug delivery research in Europe, mannan based nanogels were considered as a new approach for the oral delivery of labile molecules [13].

In this chapter, after a brief description of mannan, its production by algae, fungi, bacteria and other eukaryotic microorganisms will be mentioned with special focus on microbial resources. Then, use of mannan as a bioactive material in nanocarrier systems for drug delivery applications will be covered in detail by giving examples from literature and industry. The final

section of the chapter will involve conclusions and future prospects on microbial mannan production and its potential uses in nanotechnology.

2. Structure of mannans

Mannan is one of the important member of the hemicellulose family and can be divided to four subfamilies: linear mannan, glucomannan, galactomannan, and galactoglucomannan [14]. Mannan is present in different forms, each having a β -1,4-linked backbone containing mannose (linear mannan) or a combination of glucose and mannose residues (glucomannan) and occasional side chains of α -1,6-linked galactose residues (galactomannan / galactoglucomannan) (Figure 2). In the backbone, mannose and glucose units can also be acetylated at C-2 or C-3 (3,5) .

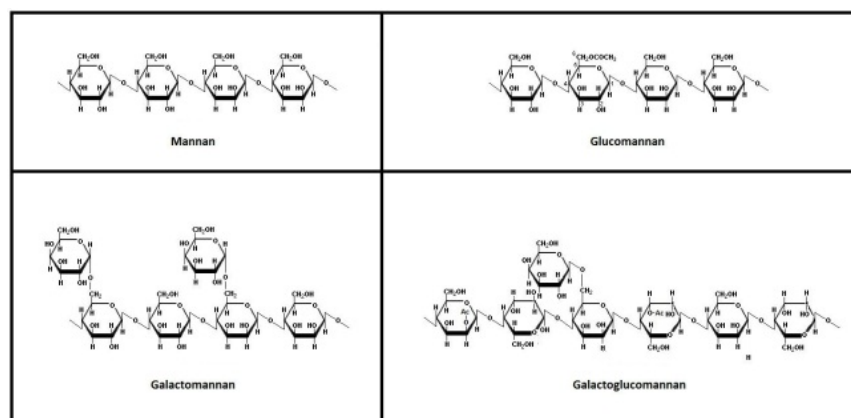


Figure 2. Four different forms of mannan

Glucomannan is mainly a straight-chain polymer, with a small amount of branching. The component sugars are β -(1,4)-linked D-mannose and D-glucose with a reported ratio of 1.6:1 [15], or 1.4:1 [16]. Softwoods and hardwoods consist of glucomannan with a glucose/mannose ratio of 1:3 and 1:1.5–2, respectively [17–20]. There is a significant similarity between conformation of glucomannan chains and those of cellulose. A two-fold screw axis was observed because of the extended chains. Due to axial position of the hydroxyl group at C-2 of mannose, the interaction between C-6 and O-2 atoms of contiguous residues is prevented, and the chains are loosened, weakening the packing and organization [17]. Different structures were reported for glucomannans isolated from different sources. For example, (1 \rightarrow 4)-linked structure, acetyl groups at C-2, C-3 positions and O-acetyl group at C-6 position were reported for glucomannan extracted from seeds of *Lupinus* [21]. Irregular distribution of acetyl groups was reported for pine glucomannan [22]. Studies on a nonionic glucomannan with a main chain of β -(1 \rightarrow 4)-linked mannopyranosyl units to which D-glucopyranosyl units are linked by α -(1 \rightarrow 6)

linkages, isolated from seeds of *Bryonia lacinosa* was also reported [23]. Galactomannans are polysaccharides consisting of 1,4-linked β -D-mannopyranose backbone with side chains of single 1,6-linked α -D-galactopyranose attached along the chain [24-26]. Galactose to mannose ratio show differences among different sources. More than 5% galactose residues can be considered as galactomannans [27]. They are mainly found in the seeds of the family of *Leguminosae* [28,29]. They are also present in the species of *Annonaceae*, *Convolvulaceae*, *Ebenaceae*, *Loganiaceae*, and *Palmae* [29]. Unusual backbone structure, containing (1 \rightarrow 3)-linked residues together with a small proportion of (1 \rightarrow 4)-linked β -D-mannopyranosyl residues with galactopyranosyl units attached at position 6, of galactomannan isolated from *Retama raetam* was reported in 2004 [30]. Presence of arabinosyl and glucosyl residues in the structure of galactomannans was observed in the studies of green and roasted coffee [31]. Several lichen species have been also reported as a source of galactomannan [32]. (1 \rightarrow 6)- α -D-mannopyranosyl backbone with a different substitution pattern at O-2 and O-4 was observed in galactomannans isolated from lichens. The four major galactomannans of commercial importance in food and non-food industries are guar gum (GG, *Cyamopsis tetragonoloba*, M/G ratio: 2:1), tara gum (TG, *Caesalpinia spinosa*, M/G ratio: 3:1), locust bean gum (LBG, *Ceratonia siliqua*, M/G ratio: 3.5:1) and Fenugreek (*Trigonella foenum-graecum* L., M/G ratio: 1:1) [33].

Galactoglucomannan consists of a backbone of randomly distributed (1 \rightarrow 4)-linked mannose and glucose units with (1 \rightarrow 6)-linked galactose units attached to mannose units. The hydroxyl groups in locations C2 and C3 in mannose are partially substituted by acetyl groups [34,18]. Molar ratio of mannose, glucose and galactose was reported as 3:1:1 in the study of Puls and Schuseil [35]. Some of the mannosyl units are partially substituted by O-acetyl groups, equally distributed between C-2 and C-3 on the average one group per three to four hexose units [18, 36]. 5.9%-8.8% acetyl content was also observed [18].

The acetylated galactoglucomannan is mainly found in hemicellulose of softwoods. They can be either galactose rich or galactose poor with 10-15% and 5-8% of the dry woods respectively [36-38]. Acetylation at C-2 and C-3 positions in the ratio of 2.2:1 was reported for galactoglucomannan backbone from native Norway spruce wood [36]. Formation of strong hydrogen bonds due to large content of D-galactose side-chains prevents the macromolecules from aligning themselves and hence galactoglucomannan is soluble in water [39].

3. Sources of mannans

Mannan is the predominant hemicellulosic polysaccharide in softwoods from gymnosperms, but is the minor hemicellulose in hardwood from angiosperms [35]. Unsubstituted beta-1,4-mannan, composed of a main chain of beta mannopyranose residues, is an important structural component of some marine algae [40] and terrestrial plants such as ivory nut [41] and coffee bean [42].

A variety of plants store energy in the form of mannans in their endosperm tissue, including members of the *Palmae*, *Liliaceae*, *Iridaceae*, and *Leguminosae* families [43,44]. Glucomannans also are used for energy storage in corms of plants within the genus *Amorphophallus*. In

addition to carbohydrate storage and structure, mannans serve a variety of other functions. In fern roots, mannans are deposited as constituents of cell wall appositions as a defense mechanism to limit microbial ingress [45]. Besides plants, algae are also a viable resource for mannan polysaccharides. In particular, the Dasycladalean alga *Acetabularia acetabulum*, also known as ‘mannan weed’, has long been known to contain mannan-rich walls [46]. Moreover, mannans are a common feature of fungal walls and a recent review points to the importance of cell surface mannans of pathogenic *Candida* species since they were found to participate in the adhesion to the epithelial cells, recognition by innate immune receptors and development of pathogenicity. Hence, clarification of the precise chemical structure of *Candida* mannan was reported as indispensable for understanding the mechanism of pathogenicity, and for development of new antifungal drugs and immunotherapeutic procedures [47]. Also, some yeast species stand out for their capability for excreting mannan to the fermentation medium. Yeast *Rhodotorula acheniorum* MC bioreactor cultures have been reported to produce 6.2 g/L mannan when grown for 96 hours in sucrose containing media [48]. Moreover, psychrophilic Antarctic yeast *Sporobolomyces salmonicolor* AL1 reached maximum glucomannan yield of 5.64 g/L in medium containing sucrose after a 5 days of fermentation [49]. Mannan synthesized by *R. acheniorum* MC, as well as the glucomannan, synthesized from strain *S. salmonicolor* AL₁ were both found to form stable emulsions making them suitable for various applications in pharmaceutical and cosmetic sectors [50]. On the other hand, studies also point to adverse toxic effects of fungal mannans when administered [51].

Although mannan production is established by numerous algal, fungi and other eukaryotic microorganisms, they are not normally products of bacteria [52]. There are only very few reported examples on extracellular mannan production by bacteria. Gram negative phytopathogenic bacterium *Pseudomonas syringae* pv. *ciccaronei* was reported to produce a highly branched phytotoxic mannopyranose polymer, which consisted of a backbone of α -(1,6)-linked mannopyranose units with 80% substituted at C-2 by mono-, di- and trisaccharide side chains [53]. Then, to understand the role of this mannan polymer in the activation of plant defence responses, various concentrations of the polymer was infiltrated in the abaxial side of tobacco leaves. Mannan polysaccharide was found to induce chlorotic and necrotic symptoms even at very low concentrations very effectively suggesting that it was identified by the plant cells as a signal of pathogen attack or environmental perturbation [54]. Two mannans at different chain lengths were reported to be produced by the marine bacterium *Edwardsiella tarda*, an opportunistic pathogen in human, and the polysaccharides were found to have good antioxidant and hydroxyl and DPPH radicals scavenging activities [55]. The lower molecular weight mannan was associated with higher antioxidant activity than the longer mannan and could be used as possible food supplement or ingredient in the pharmaceutical industry [55]. Recently, about 20-fold increase in mannan production has been reported in the pathogenic, constitutive biotin-producing *Pseudomonas putida* bacteria [56]. The rheological properties of the highly branched mannan isolated from *P. putida* T6 showed that its viscosity was over 30 times greater than that of the wild type *P. putida* ATCC 31014.

Table 1. illustrates mannan producer organisms.

Source	Organism	Mannan type	Reference
Plant	<i>Ebenaceae</i> family	Galactomannan	[29]
Plant	<i>Arabidopsis thaliana</i>	Mannan	[57]
Plant	seeds of the family of <i>Leguminosae</i>	Galactomannan	[28,29]
Plant	<i>Caesalpinia spinosa</i> Kuntze	Galactomannan	[33]
Plant	<i>Annonaceae</i> family	Galactomannan	[29]
Plant	<i>Amorphophallus konjac</i>	Glucomannan	[58]
Plant	<i>Ceratonia siliqua</i>	Galactomannan	[33]
Plant	<i>Convolvulaceae</i> family	Galactomannan	[29]
Plant	<i>Cyamopsis tetragonoloba</i>	Galactomannan	[33]
Plant	<i>Loganiaceae</i> family	Galactomannan	[29]
Plant	<i>Senna tora</i> seed	Galactomannan	[59]
Plant	<i>Trigonella foenum-graecum</i> L.	Galactomannan	[33]
Plant	<i>Palmae</i> family	Galactomannan	[29]
Plant	<i>Picea abies</i>	Galactoglucomannan	[60]
Plant	<i>Cercis siliquastrum</i>	Galactoglucomannan	[61]
Plant	<i>Nicotiana plumbaginifolia</i>	Galactoglucomannan	[62]
Yeast	<i>Hansenula holstii</i>	Phosphorylated mannan	[63]
Yeast	<i>Rhodotorula acheniorum</i>	Mannan	[48]
Yeast	<i>Sporobolomyces salmonicolor</i>	Glucomannan	[64]
Yeast	<i>Saccharomyces cerevisiae</i>	Mannan	[65]
Yeast	<i>Meyerozyma guilliermondii</i>	Mannan	[66]
Yeast	Brewers dried yeast	Mannan	[67]
Yeast	<i>Candida utilis</i>	Glucomannan	[68]
Algae	<i>Porphyra umbilicalis</i>	Mannan	[69]
Algae	<i>Acetabularia acetabulum</i>	Mannan	[46]
Algae	<i>Charophyceae</i>	Mannan	[70]
Fungus	<i>Dactylium dendroides</i>	Galactoglucomannan	[71]
Fungus	<i>Pseudocyphellaria clathrata</i>	Galactoglucomannan	[72]
Bacteria	<i>Pseudomonas mutabilis</i>	Mannan	[56]
Bacteria	<i>Pseudomonas syringae</i> pv. <i>ciccaronei</i>	Mannopyronose	[53]
Bacteria	<i>Edwardsiella tarda</i>	Mannan	[55]
Bacteria	<i>Pseudomonas aeruginosa</i>	Mannan	[73]
Bacteria	<i>Brevibacillus thermoruber</i>	Mannan	[74]

Table 1. Mannan producer organisms

4. Biosynthesis of mannans

Mannans are synthesized from activated nucleotide sugars such as GDP-mannose, GDP-glucose, and UDP-galactose [75]. Enzymes necessary for the nucleotide sugar conversion from sucrose to GDP-mannose and UDP-galactose have been reported in plants. However, the enzyme for the formation of GDP-glucose has not been identified [76]. Golgi-localized glycosyltransferases (GTs) utilize the activated nucleotide sugars and synthesize the polymer by facilitating the formation of the specific linkage between the monomers [77,78].

The cellulose synthase-like family A (CSLA) genes are considered the best candidates to encode enzymes that polymerize the backbones of β -linked noncellulosic polysaccharides [79,80]. Experimental evidence to support this hypothesis for the CslA family came first from Dhugga et al. [81]. In this research, the first β -mannan synthase (ManS), a member of the cellulose synthase-like family A (CSLA) from GT family 2, was identified in guar seeds (CtManS in *Cyamopsis tetragonoloba*, a AtCSLA9 ortholog) including the demonstration of its *in vitro* ManS activity [82]. One year later, three *Arabidopsis* CSLA genes were expressed in *Drosophila* Schneider 2 (S2) cells and demonstrated that the resulting CSLA proteins were capable of producing mannans when supplied with GDP-Man and glucomannans when provided with a mixture of GDP-Man and GDP-Glc [75]. CSLA genes appear to be present in all land plants, and ancestral genes with characteristics similar to CSLA sequences have been identified in a number of green algal genomes, in which they are thought to represent a homolog of the progenitor gene from which CSLA genes evolved [76]. In developing *Trigonella foenum-graecum* (Fenugreek) endosperm, a deep sequencing approach was used to identify genes involved in galactomannan biosynthesis [83]. This research reported a CSLA family protein involved in mannan backbone synthesis and a preference towards GDP-mannose as a donor substrate was observed from the activity assays with the heterologously expressed protein. Heterologously expressed CSLA proteins from a variety of species show mannan or glucomannan synthase activity *in vitro* [6,75,81,83]. Analysis of *Arabidopsis* CSLA mutants and over-expressing plants further confirmed that CSLA proteins function as glucomannan synthases *in vivo* [84]. Despite this progress in identifying and characterizing the enzymes responsible for galactoglucomannan biosynthesis, it is likely that other important enzymes are required, and many aspects of this process need to be better understood.

In tissues of *Arabidopsis*, that take role in tip-growth such as root hairs CSLD, (AtCSLD2, 3 and 5) proteins were found to mediate mannan biosynthesis [85-92]. In Fenugreek, it was found that additional genes were involved in mannan biosynthesis, such as a golgi-localized mannan synthesis-related (MSR) gene that was observed in the fenugreek endosperm [83,93]. TfMSR protein in Fenugreek and its homologs AtMSR1 and AtMSR2 in *Arabidopsis* were highly co-expressed with the ManS of the CSLA family. Glucomannan and ManS activity were significantly decreased in stems of AtMSR knock-out mutants [93]. While the biochemical activity of MSR proteins remains unknown, hypotheses include a role in primer synthesis to initiate mannan biosynthesis, the synthesis of oligosaccharides linked to CSLA or promoting folding, stability or activity of a mannan synthase complex [93].

Edwards et al. identified a mannan:galactosyltransferase (GalT) in *Trigonella foenum-graecum* [94], an enzyme that facilitates mannan *O*-acetylation. However, discovery of the involvement of a large plant-specific family of Trichome birefringence-like (TBL) proteins in *O*-acetylation of wall polymer as specific *O*-acetyltransferases suggested that this gene family encompassed a mannan *O*-acetyltransferase [95]. A highly expressed (among the 10 most abundant ESTs) homolog of AtTBL25 in the *Amorophophallus konjac* deep sequencing database [96] revealed that this protein or the closely related AtTBL26 could represent mannan *O*-acetyltransferase(s) in *Arabidopsis* [95].

5. Polysaccharide-based materials in drug delivery

Many properties of polysaccharides such as biocompatibility, solubility, potential for modification, and innate bioactivity provide great potential for their use in drug delivery systems (Figure 3).

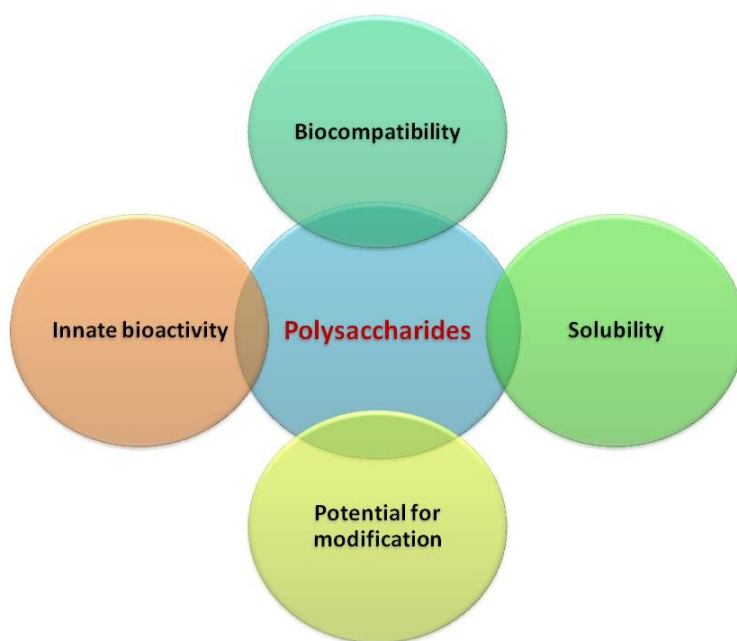


Figure 3. Properties of polysaccharides for potential use in drug delivery systems

Despite many synthetic polymers, polysaccharides have very low or no toxicity levels [97-100]. For example, dextrans are biopolymers composed of glucose with α -1,6 linkages, with possible branching from α -1,2, α -1,3, and α -1,4 linkages, that exhibit low toxicity and high biocompatibility, that makes them biocompatible hydrogels for controlled prolonged therapeutic release [101] and microspheres with no inflammatory response following subcutaneous injection into rats [102]. Since polysaccharides are naturally present in the body, most of them are degraded enzymatically. Through enzyme catalysis, polysaccharides can be broken down to their monomer or oligomer building blocks and recycled for use as storage,

structural support, or even cell signaling applications [103]. As a result, mechanism of release for therapeutics associated with polysaccharide-based carrier systems is provided by enzymatic degradation [104].

The functional groups of polysaccharides such as hydroxyl and amine groups yield high aqueous solubility. However, this solubility can often be adjusted via monomer modification. For example, *O*-acetylation of glucomannan can be used to modulate the formation of intermolecular hydrogen bonds with water, thereby altering aqueous solubility [105].

Due to the presence of various derivable groups on molecular chains, polysaccharides can be easily modified chemically and biochemically, resulting in many kinds of polysaccharide derivatives. These modifications can change the character of the polysaccharides. For instance, hydroxyl group oxidation enhances biodegradability, while sulfonation generates a heparin-like polysaccharide with increased blood compatibility [106]. Quaternization of the primary amines with various alkyl groups can be used to enhance solubility and alter bioactivity [107-109].

Many polysaccharides possess innate bioactivity, particularly mucoadhesive, antimicrobial, and anti-inflammatory properties. Positively charged polysaccharides are capable of binding to the negatively charged mucosal layers through charge interactions [110-112]. For neutral or negatively charged polysaccharides, hydrogen bonding provides an alternative mechanism for mucoadhesion [113]. Nanoparticle carriers made of bioadhesive polysaccharides could prolong the residence time and therefore increase the absorbance of loaded drugs [114]. Several polysaccharides are also antimicrobial in nature, such as chitosan [115]. Other polysaccharides are known to reduce inflammation. Anti-inflammatory activity is thought to be due to binding with immune-related acute phase and complement proteins [111,116] and polysaccharides are known to interact with a variety of proteins.

Nanocarriers are nanoparticle drug delivery systems that are used to deliver drugs or biomolecules. Nanocarriers are sub-micro particle structures smaller than 100 nm in at least one dimension and cover nanospheres, nanocapsules, nanomicelles, nanoliposomes, and nanodrugs, etc. Nanoparticle drug delivery systems have noticeable advantages. Due to the ultra-tiny volume of nanoparticle they can pass through the smallest capillary vessels and avoid rapid clearance by phagocytes, that lead to greatly prolonged duration in blood stream. Due to small dimensions, nanocarriers are able to cross the blood-brain-barrier (BBB) and operate on cellular level. They can easily penetrate cells and tissue gap to arrive at target organs such as spleen, spinal cord, liver, lung, and lymph. Because of the biodegradability, pH, ion and/or temperature sensibility of materials, they could show controlled release properties. They can improve the utility of drugs and reduce toxic side effects; etc. As drug delivery system, nanocarriers can entrap drugs or biomolecules into their interior structures and/or absorb drugs or biomolecules onto their exterior surfaces. Presently, nanoparticles have been widely used to deliver drugs, polypeptides, proteins, vaccines, nucleic acids, genes and so on.

In recent years, a large number of studies have been conducted on polysaccharides and their derivatives for their potential application as nanoparticle drug delivery systems [114,117-120] and among them, mannan is a very promising bioactive material for drug nanocarrier systems

since an amphiphilic form of mannan can spontaneously incorporate proteins and other agents, potentially providing a new nanostructure drug delivery system.

6. Medical potential of mannans as a drug nanocarrier systems

Glucomannans have a variety of applications, including food industry used as an emulsifier and thickener and medicine as a preventative of chronic disease and weight control agent [21]. Likewise, galactomannans also found many applications in food industrial as a thickener and food additive due to their rheological properties [121]. Moreover, galactomannans are widely used as versatile materials in industries such as textiles, paper, pharmaceuticals, cosmetics, petroleum, drilling and explosives [93,122].

Galactomannans have also significant potential in medical applications such as innate immune system stimulation. On the other hand, the mannooligosaccharides (MOS) derived from these polysaccharides have also prebiotic activity for selective growth of *Bifidobacterium* spp., and *Lactobacillus* spp. [123]. They have also been described to present anticoagulation and fibrinolytic activity [124] and the MOS may prevent adherence of toxic bacteria to the intestinal wall, mediated by lectins, thus presenting anti-infectious potential [123,125,126].

In the research of Apostolopoulos *et al.* oxidized mannan conjugated to MUC1 fusion protein (M-FP) was used as a target for tumour immunotherapy and M-FP appeared to confer the survival/disease-free interval advantage in patients with early stage breast cancer [8].

In another study, the factors important to gene delivery and DNA vaccination that could contribute to the improved immunogenicity of oxidized mannan poly-L-lysine (OMPLL)–DNA and reduced mannan poly-L-lysine (RMPLL)–DNA immunization were investigated [9]. It was shown that OMPLL and RMPLL were able to complex with DNA to form particles that were taken up by charge dependent binding and endocytic pathways. High possibility of delivery of DNA was observed since the particles formed were able to protect DNA from DNase I digestion. More significantly, direct effect of OMPLL and RMPLL was observed on the antigen presentation of dendritic cells (DCs).

In 2010, Guo *et al.* reported that marine bacterium *Edwardsiella tarda* produced two extracellular polysaccharides ETW1 and ETW2, mannans with different molecular mass, that exhibited strong antioxidant activities [55]. To investigate the antioxidant activities of the two polysaccharides, antioxidant properties based on hydroxyl, DPPH radical scavenging and lipid peroxidation inhibition assays were carried out. The scavenging abilities of ETW1 and ETW2 on DPPH radicals, hydroxyl radicals and lipid peroxidation inhibition were concentration-dependent.

In 2011, Ferreira *et al.* prepared nanogel made of mannan [11]. The properties of the resulting nanogel were characterized and cytocompatibility was tested by using two cell lines, namely, mouse embryo fibroblasts 3T3 and mouse macrophage-like J774. The results of study revealed that the mannose receptor binds ligands at the cell surface and these receptor-ligand complexes were internalized via the endocytic pathway. Internalization of the nanogel caused cytotoxicity

since the non-phagocytic cell line was not affected and internalization was confirmed with J774. The high nanogel toxicity observed with the macrophage cell line indicated that the cell line J774 was not suitable for studies with mannan-C16 nanogel and primary cultures of macrophages that do not exhibit cytotoxicity should be used instead.

In 2012, the mannan nanogel cytocompatibility was tested in mouse embryo fibroblast cell line 3T3 and mouse bone marrow-derived macrophages (BMDM). [12]. The essential focus of the study was to assess nanomaterial cytocompatibility and to analyze the internalization by macrophages. The results of this study indicated that the mannan nanogel was biocompatible to mouse embryo fibroblast 3T3 cells and mouse BMDM. Essentially, no cytotoxic effect was observed with mannan nanogel up to about 0.4 mg/mL in *in vitro* experiments. Cell survival rate only dropped significantly at higher tested concentration after 48 h of incubation. Comet assay, under tested conditions, revealed no DNA damage in mouse embryo fibroblast 3T3 cells but possible DNA damage in mouse BMDM. Upon internalization by mouse BMDM mannan nanogel was localized in vesicles, as judged by the non-even distribution over the cytoplasm, and concentration of the fluorescence in internalized structures. Exit of nanogel from the mouse BMDM was observed when cells were incubated in fresh medium. Confocal colocalization image analysis denoted that the entrance and exit of nanogel and FM 4-64 might occur by the same processes – endocytosis and exocytosis – in BMDM.

Sato et al. [127] examined the adhesion inhibitory effect of mannan coating on acrylic denture surfaces against *Candida albicans* and *Candida glabrata*. The outermost layer of the *Candida* cell wall is covered with hydrophilic polysaccharides, such as mannan or galactomannan [128]. These mannans on the fungal surface function as adhesins, which are involved not only in the adhesion to the host cell [129,130] but also in the adsorption to plastic plates. On the other hand, when the plastic surfaces of culture dishes were coated with mannan, the adherence of *C. albicans* to the dishes was significantly inhibited [131,132]. The results of this study indicated that mannan inhibited the adhesion of *Candida* in a concentration-dependent manner, but mannose was not able to inhibit *Candida* adhesion even at a high concentration. The application of 0.1 mg/mL of mannan coating overnight showed inhibitory effects on the adhesion of the hyphal form of *C. albicans*. In the case of *C. glabrata*, the inhibitory effect was also observed to occur in a concentration-dependent manner, and the 10 mg/mL of mannan led to significantly higher anti-adhesive effects. This indicated that mannan effectively prevented the adhesion of two major *Candida* species to the denture surface, indicating the possibility of applying such a coating for clinical dentistry.

Superparamagnetic iron oxide nanoparticles (SPIONs) have been used as a contrast agent in magnetic resonance imaging (MRI) or as a carrier platform in the applications of drug [133-135] and gene delivery [137,138]. It was previously reported that mannan-coated SPION (mannan-SPION) could be specifically targeted to macrophages by the interaction with mannose receptors on antigen-presenting cells (APCs) [139]. Vu-Quang et al., [10] investigated the physicochemical properties, the *in vitro* and *in vivo* uptakes of carboxylic mannan-coated SPION (CM-SPION) using MRI and assessment of systemic toxicity. Results of the study showed that CM-SPION achieve longer circulation than mannan-SPION without compromising specificity. The intracellular accumulation of CM-SPION in macrophages was higher than

those of either PVA-SPIONs or Dex-SPIONs. The intracellular localization of CM-SPIONs was pre-dominantly observed in the cytoplasm of APCs. In the light of these results, authors claimed that CM-SPION could be regarded as a safe and potential contrast agent in LN-targeted MR imaging.

The effective conjugation of iron oxide nanoparticles with various biomolecules has been used for novel therapeutic-and drug delivery purposes [139-142]. Ultrasmall superparamagnetic iron oxide (USPIO) targets biomarkers of atherosclerotic plaques and improvements of USPIO make possible to obtain better plaque images at lower doses. Mannose units of mannan polysaccharides are recognized by mannose receptors on immune macrophages and they lack of significant toxicity. As a result, in the study of Tsuchiya [143], MRI-and histologic analyses were performed to compare the uptake by the rabbit atherosclerotic wall of four types of SPIO particles, i.e. SPIO, mannan-coated SPIO (M-SPIO), ultrasmall SPIO (USPIO), and mannan-coated USPIO (M-USPIO). Results of study reveal that mannan-coated iron particles had a greater affinity for active atherosclerotic plaques than non mannan-coated iron particles. Intracellular iron uptake was also higher in cells treated with M-USPIO than USPIO.

Glucomannans have diverse applications in biomedical and pharmaceutical areas due to the advantages of the polysaccharide such as weight loss in obesity, decreased carbohydrate absorption in diabetes type 2, antitumor activity against sarcoma in cancer, decreased LDL levels in cholesterol, recognition of mannose receptors in targeting, antiseptic coating and sustained release profiles, increase of stability, improvement of the interaction between polymers, enhancement protein association of pharmaceutical forms of glucomannan. Glucomannan has been investigated as a pharmaceutical excipient in tablets, films, beads and hydrogels, due to its gelling, solubility and biodegradable properties [143-146].

Electrostatic interaction between the negative carboxylic groups of carboxymethylated-GM and the positive amino groups of chitosan was used for the preparation of nanoparticles made of carboxymethylated-GM and chitosan [147]. These nanoparticles were within size range of 50–1200 nm and exhibited a positive charge. Additionally, these nanoparticles elicited an ability to entrap and release bovine serum albumin (BSA) [147,148]. The objection of use of GM in these nanoparticles was to increase their stability and their controlled release properties. Sande et al. reported that the introduction of GM into the nanoparticles lead to a facilitated interaction with the intestinal epithelium both *in vitro* and *in vivo* [149, 150]. The results of studies revealed that GM–chitosan nanoparticles offer attractive features as carriers for transmucosal drug delivery applications.

In the report of Zhang et al., use of konjac glucomannan (KGM) in oral colon targeting drug delivery system (OCDDS) was reviewed [151]. Based on the previous studies of KGM, it could be considered as a significant natural polysaccharide in OCDDS. It was known that KGM gel systems were able to maintain integrity and control the release of theophylline and diltiazem for 8 hours [152]. KGM hydrolysate was reported to have prebiotic potential for beneficial gut microbiota [153,154]. KGM is a water soluble polysaccharide because of hydrogen bonding in its structure [155,156]. The stronger the hydrogen bonding between their molecules, the harder for it to dissolve in water. Water solubility can be either advantageous or disadvantageous according to its application. Due to the high water adsorption rate, deficiency of free water in

gastrointestinal tract occurs and leads to diarrhea when KGM was used in the applications such as pharmaceutical excipients or drugs. On the other hand, when prepared as styptic sponge, which used to stop bleeding, the higher the water adsorption rate of it, the better the hemostasis effect may be. Modifications of KGM lead to alteration in the water adsorption of it. Moreover, KGM have gel-forming and film-forming properties [157].

In the previous studies, it was reported that KGM can be specifically degraded by colon β -mannanase [158], an enzyme generated by human colon bacteria [159]. On the other hand, based on the toxicity tests Ancui et al. reported KGM as a stable and safety material for medicinal purposes [160].

Invention of a novel hydrogel systems designed for colon-targeting drug delivery was reported in 2004 [158]. This hydrogel was composed of KGM, copolymerized with acrylic acid, and crosslinked by the aromatic azo agent bis(methacryloylamino)-azobenzene. Chen, Liu and Zhuo, copolymerized KGM and acrylic acid (AA) with N, N-methylene-bis-(acrylamide) (MBAAm) to form a novel hydrogel system [161]. Studies on swelling behaviors and degradation showed that the gel is pH-sensitive and could be degraded by Cellulase E0240 containing β -mannanase. Further researches demonstrated that the IPN hydrogel composed of KGM and poly(acrylic acid) (PAA) and cross-linked by N, N-methylene-bis-(acrylamide) (MBAAm) was still pH-sensitive and a potential carrier for colon-targeting drug delivery. Xu et al., prepared oxidized konjac glucomannan (OKG) for OCDDS which was pH-sensitive and could be used without the destruction of drugs in gastric acid [162]. Furthermore, Korkiatithaweechai et al., prepared controlled release of diclofenac sodium (DFNa) film from CTS (chitosan)-OKG [163]. This study suggested that the proportion of OKG in the formulation may affect the release profile and the formulation may be used for further study as a long term intestine controlled release drug model (at least 3 days), including as colon targeting drug carrier.

Guar gum derived from the seeds of *Cyamopsis tetragonolobus* is a naturally occurring galactomannan polysaccharide that consists of 80% galactomannan, 12% water, 5% protein, 2% acid insoluble ash, 0.7% ash and 0.7% fat. Guar gum has been reported as an inexpensive and flexible carrier for oral extended release drug delivery [164]. Guar gum can be used for colon delivery since it can be degraded by specific enzymes in this region of the gastrointestinal tract. GG provides protection to the drug in the environment of the stomach and small intestine, and drug delivery to the colon where it is degraded by the enzymes excreted by specific microorganisms. Guar gum shows high potential as a carrier for oral controlled release matrix systems. Furthermore, excipients to GG can be used to modulate drug release from these matrix systems [165].

Locust bean gum also known as Carob bean gum consists mainly of a neutral galactomannan polymer made up of 1,4-linked D-mannopyranosyl units and every fourth or fifth chain unit is substituted on C6 with a D-galactopyranosyl unit. Locust bean gum is a neutral polymer and its viscosity and solubility are therefore little affected by pH changes within the range of 3-11 [166]. Locust bean gum was used to produce matrix tablets with and without the cross-linker, glutaraldehyde [101]. A commercially available tablet system (TIMERx®) developed

by Penwest Pharmaceuticals Company consisting of locust bean gum and xanthan gum showed both *in vitro* and *in vivo* controlled release potential [167].

Guar gum hydrates and swells in cold water [168]. This gelling cause to retardation of the drug release from the tablets [169,170]. Guar gum is being used to deliver drug to the colon due to its drug release retarding property and susceptibility to microbial degradation in the large intestine [171,172]. Guar gum based matrix tablets of dexamethasone and other antiinflammatory agents were prepared and used in colon targeting [173]. Whereas negligible drug release was observed in simulated gastric and intestinal fluids, significant increase in drug release was reported in simulated colonic fluid.

Colonic drug delivery system based on pectin (polygalacturonic acid) and galactomannan coating was reported by Lee et al. [174] and Pai et al. [175]. These two polysaccharides, pectin and galactomannan, were used as coating material of a conventional tablet or capsule. The coating of pectin/galactomannan mixture was shown to be strong, elastic and insoluble in simulated gastric and intestinal fluids such that it would protect drug from being released in the upper GI tract. Researches revealed that in the colon, bacterial degradability was preserved. Moreover, extended film resistance to hydration, subsequent solubilization, film degradation rate by enzymes and drug release rate were found to depend on the varying ratio of pectin to galactomannan. Higher galactomannan percentage caused to decreased bacterial degradation in the colon and prolonged duration of negligible drug release in the upper GI tract. Compared with the combination of pectin and ethyl cellulose [176] or amylose and ethyl cellulose [177], combination of pectin and galactomannan was advantageous due to faster *in vivo* degradation of both pectin and galactomannan by microflora in the colon.

Matrix tablet of indomethacin with guar gum was prepared and the suitability of guar gum as a carrier in colonic drug delivery was investigated in another study [178]. The results indicated the specificity of these matrices for enzymes triggered the drug release in the colon. In another *in vivo* study, matrix tablets containing around 77% guar gum were loaded with technetium-99m-DTPA as tracer and scintigraphs were taken at regular intervals in six healthy human male volunteers [179]. These tablets were found to remain intact releasing only small amount of tracer in the stomach and the small intestine. However, bulk of the tracer was released in the ascending colon thereby suggesting that the enzyme triggered degradation by colonic bacteria.

Rubinstein and Gliko-Kabir investigated a biodegradable property of guar gum cross-linked with borax [180]. The time required for degradation of these crosslinked guar gum and borax showed that release of drug would be in proximal colon. The same group analysed phosphated cross-linked guar gum hydrogels for their potential as colon drug carriers *in vitro* and *in vivo* in 2000 [181]. *In vitro* studies revealed that these hydrogels loaded with hydrocortisone were able to resist the release of 80% of the drug for 6 h in phosphate buffer. *In vivo* studies in rat showed that degradation of modified guar gum by enzymes was concentration dependent. Thus, the phosphated crosslinked guar gum could be considered suitable for colon drug delivery.

Alginate is a non-toxic polysaccharide that have properties such as pH sensitivity. This pH sensitivity is favorable for intestinal delivery of protein drugs. However, drug leaching during hydrogel preparation and rapid dissolution of alginate at higher pH are major limitations since when it enters the intestine, these limitations cause to very low entrapment efficiency and burst release of entrapped protein drug. To overcome these limitations, George and Abraham used another natural polysaccharide, guar gum which is included in the alginate matrix along with a cross linking agent to ensure maximum encapsulation efficiency and controlled drug release [182].

In the study of Coviello et al. [101], two galactomannans, guar gum and Locust bean gum, have been investigated for their possible use as matrices for modified drug delivery. They were crosslinked with glutaraldehyde (Ga) and then used for the preparation of tablets. This preparations increased the rate of release of small guest molecules due to the fact that the chemical reaction with Ga introduced meshes with a size larger than those present in the simply entangled systems.

In the study of Voepel et al. [183], hydrogels based on acetylated galactoglucomannan (AcGGM) were synthesized and examined for their properties in drug-release systems using two model substances of different molecular weight, size, and polarity (caffeine and vitasyn blue). AcGGM was synthetically modified to yield a polysaccharide with either neutral or ionic pendant groups. These precursors were formulated to produce either a neutral, covalent hydrogel or a physically cross linked hydrogel. Neutral and ionic hydrogels based on HEMA-Im- modified AcGGM (M-AcGGM) and maleic anhydride modified M-AcGGM (CM-AcGGM) were studied in view of their chemical, physical and drug release properties. In the case of the neutral hydrogels, half of the total drug release (50 wt % release) was reported to occur between 13 and 35 min and 50 to 90 min for caffeine and vitasyn blue, respectively. The majority of the caffeine (80 wt %) was released between 40 and 120 min, on the other hand, the majority of vitasyn blue was released between 125 and 250 min. When maleic anhydride was added to the M-AcGGM, ionic poly(CM-AcGGMco-HEMA) hydrogels could be achieved. Slower release of caffeine was found in these hydrogels, especially at acidic conditions because of the pH responsitivity obtained through the introduced carboxylic functionalities.

Roos et al. synthesized hydrogels from O-acetyl-galactoglucomannan (AcGGM) with encapsulated bovine serum albumin (BSA), to investigate the influence of substitutions and the feasibility of BSA-release mediated by the addition of β -mannanase to hydrolyze the hydrogel [184]. Hydrogels were prepared from AcGGM substituted with various amounts of 2-hydroxyethylmethacrylate groups and loaded with BSA. The degree of substitution of HEMA and the presence of β -mannanase *AnMan5A* were two parameters that influenced the release of BSA from the hydrogels in water. Increasing HEMA substitutions on the glucomannan backbone from 0.1 to 0.36 caused lesser spontaneous release of BSA. However, the addition of β -mannanase *AnMan5A* increased the BSA release due to enzymatic hydrolysis of AcGGM. The hydrogel with DS_{HEMA} (degree of sustitution) 0.36 released almost all remaining BSA from the hydrogel within 8 h after addition. The results of the study provided significant insights into further developments of AcGGM-based hydrogels for the application of drug delivery

Bioadhesive poly(D,L-lactide-co-glycolide) (PLGA) nanoparticles were reported as promising drug delivery systems [185], and surface modification of nanocarriers was provided by application of mannan-based PE-grafted ligands (MAN-PEs) [186]. Kong et al. investigated MAN-PE-modified bioadhesive PLGA nanoparticles as active targeting gene delivery system using plasmid enhanced green fluorescent protein (*pEGFP*) as the model gene [187]. In the reported study, in order to achieve active targeting to the liver, surface of PLGA nanoparticles was modified by the application of MAN-PEs. *In vitro* and *in vivo* behavior of mannan-modified DNA-loaded PLGA nanoparticles were compared with nonmodified DNA-loaded PLGA nanoparticles. Spherical shapes were observed for nonmodified DNA-NPs while the mannan-modified MAN-DNA-NPs had a dark coat on the white balls, that indicated the successful coating of mannan-PE. The mean particle size of NPs was around 100–200 nm, which was ideal for the nanoparticulate system. MAN-PEs-modified *pEGFP*-loaded bioadhesive PLGA-NPs could be targeted to the liver and successfully transfected the Kupffer cells (KCs).

In the study of Wu et al., mannan-PEG-PE (MN-PEG-PE) modified bioadhesive PLGA nanoparticles were obtained as a targeted gene delivery system [188]. Mannan was the target part that bind to the mannose receptor (MR) in the macrophage, and PEG-PE was the spacer linked into the surface of NPs. The results of this study confirmed that mannose-mediated targeting could successfully deliver genes into MR expressing cells. Improved transfection efficiency was observed in the case of mannose containing targeting ligands, such as in DNA loaded PLGA NPs. The results supported the active targeting ability of mannan containing PEG-PE modified bioadhesive PLGA nanoparticles, and the resulting vectors would be very useful in gene delivery both *in vitro* and *in vivo*.

In the study of Kaur, sustained and targeted release nanoparticles of didanosine were formulated using gelatin as polymer and mannan-coating to further enhance its macrophage uptake and its distribution in organs that act as major reservoirs of HIV [189]. Coating of nanoparticles with mannan further retarded the drug release ($42.5 \pm 1.7\%$ over 24 h) and increased the cellular uptake of nanoparticles (N-C3-M) as was evident by higher staining intensity and complete lysis within 2 h of incubation. The better cellular uptake of mannan-coated nanoparticles might be due to the presence of mannosyl receptor predominantly on the macrophage cell surface, which was used by the cells for endocytosis and phagocytosis [190,191]. The results showed higher accumulation of didanosine in brain when administered through mannan-coated nanoparticles. Didanosine is a hydrophilic drug and its ability to cross the blood brain barrier was very low; however, mannan-coated nanoparticles provided enhanced delivery of didanosine to brain. Hence, mannan-coated gelatin nanoparticles resulted in a significantly higher concentration of didanosine in spleen, lymph nodes and brain.

7. Future prospects

Overview of literature clearly shows the high potential of mannan-based biomaterials in health related applications. In these studies though, the monomer composition and structure of mannan polysaccharide plays the key role for a successful design. It is well known that the

composition of polysaccharides is highly influenced by the environmental conditions and strictly depends on the availability of the activated sugar monomers. Currently, main sources for mannan are plants, algae and fungi where production may take months and greatly depends on geographical or seasonal conditions. On the other hand, microbial sources could be a feasible alternative for the sustainable and economical production of mannan at industrial scale. Microbial fermentation would not only enable the use of low-cost resources for the economical production, but also provide control over the chemical structure, monomer composition and physicochemical and rheological properties of the final product. There are only few reports on microbial mannan production and from these, thermophiles stand out with their high production rates due to their high metabolic activity. Moreover, such simple systems enable the effective application of systems-based approaches to obtain tailor-made polymers.

Finally, mannan is a very promising bioactive material for drug nanocarrier systems since its amphiphilic structure can incorporate diverse biomolecules, potentially providing novel nanostructure drug delivery systems. Hence, development of high mannan producer cell factories would overcome the problems associated with the sustainable production of this important biomaterial.

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