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Review

Biological activities of derivatized D-glucans: A review

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ABSTRACT

D-Glucans have triggered increasing interest in commercial applications in the chemical and pharmaceutical sectors because of their technological properties and biological activities.

The glucans are foremost among the polysaccharide groups produced by microorganisms with demonstrated activity in stimulating the immune system, and have potential in treating human disease conditions. Chemical alterations in the structure of D-glucans through derivatization (sulfonylation, carboxymethylation, phosphorylation, acetylation) contributes to their increased solubility that, in turn, can alter their biological activities such as antioxidation and anticoagulation. This review surveys and cites the latest advances on the biological and technological potential of D-glucans following chemical modifications through sulfonylation, carboxymethylation, phosphorylation or acetylation, and discusses the findings of their activities. Several studies suggest that chemically modified D-glucans have potentiated biological activity as anticoagulants, antitumors, antioxidants, and antivirals. This review shows that in-depth future studies on chemically modified glucans with amplified biological effects will be relevant in the biotechnological field because of their potential to prevent and treat numerous human disease conditions and their clinical complications.

Contents

1. Introduction

D-Glucans have triggered much interest in chemical and pharmaceutical applications and in various research groups worldwide. Research has revealed that glucans, called Biological Response Modifiers (BRM), can act on the immune system [1]. Such biomacromolecules display anticoagulant, antithrombotic, antioxidant, and anti-inflammatory activities, and have also been described as being effective in reducing blood cholesterol levels and the risk of cardiovascular problems, and in treating various illnesses such as cancer, diabetes and microbial infections [2–4]. These carbohydrate biopolymers are made up of glucose units joined by α- or β-linked glucosidic units with different number of units, degree

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Table 1
Selected examples of D-glucans from different sources grouped according to type, structure and biological properties.

Source	Type	Structure	Biological properties	Reference
Plants and algae	α-glucan from the roots of *Ipomoea batatas*	(1→6)-α-D-glucan	Immunomodulatory activity	Zhao et al. [15]
	oat β-glucan	(1→3)(1→4)-β-D-glucan	Activation of intestinal leukocytes	Volman et al. [16]
	α-glucan from *Lonicera japonica* Thunb.	(1→4)-α-D-glucan	Attenuation of neurotoxicity	Wang et al. [17]
	β-glucan from *Isochrysis galbana*	(1→3;1→6)-β-D-glucan	Anti-tumor activity	Sadovskaya et al. [18]
Microbial	β-glucan from *Lasiodiplodia theobromae* MMPI (*exocellular*)	(1→6)-β-D-glucan (*Lasiodiplodan*)	Anti-proliferative effect on breast cancer MCF-7 cells	Cunha et al. [6]
	β-glucan from *Botryosphaeria rhodina* (*exocellular*)	(1→3;1→6)-β-D-glucan (*Botryosphaeran*)	Hypoglycemic and hypocholesterolemic properties	Miranda-Nantes et al. [19]
	β-glucan from *B. rhodina* (*exocellular*)	(1→3;1→6)-β-D-glucan (*Botryosphaeran*)	Immunomodulatory properties	Weng et al. [20]
	α-glucan from *Lactobacillus plantarum* (*exocellular*)	(1→3;1→6)-α-D-glucan	Prebiotic properties	Das et al. [21]
	β-glucan from *Agaricus bisporus* and *A. brasiliensis* (*exocellular*)	(1→6)-β-D-glucan	Immunostimulatory activity	Smiderle et al. [22]
	β-glucan from *Pleurotus sajor-caju* (*cell wall*)	(1→3)-β-D-glucan	Anti-inflammatory activity	Silveira et al. [23]
	β-glucan from Jinqian mushroom (*cell wall*)	(1→3;1→6)-β-D-glucan	Antioxidant activities	Liu et al. [24]
	β-glucan from *Rhodotorula mucilaginosa* (*cell wall*)	(1→3)-β-D-glucan	Antinociceptive effect	Valasques et al. [25]

and frequency of branching, type of connections, and chain lengths. Biopolymers extracted from plants and cereals (cellulose, starch, β-glucans, hemicellulose, gum arabic and pectins), seaweeds (alginate, carrageenan, and agar), and crustaceans (chitin) dominate the current commercial market, while microbial polysaccharides (xanthan gum, dextran, gellan, pullulan and bacterial alginate) represent only a small fraction of the biopolymers market [5].

Different physicochemical parameters such as solubility, molecular structure, molecular weight, and branching can influence the biological activity of the D-glucan group of polysaccharides [4]. This diversity results in a wide range of applications for these polysaccharides in the food, biomedical, pharmaceutical and cosmetic commercial sectors [6–8]. In the biological area, polysaccharides can be used in tissue engineering, skin replacement for burn's victims, enzyme immobilization, biosensors, and as vehicles for controlled release of drugs.

Sulfonated polysaccharides have important biological applications as anti-inflammatory, anticoagulant, and antithrombotic agents and are similar in structure to heparin in being sulfonated [9]. Carboxymethylated polysaccharides have demonstrated antioxidant properties, lipid peroxidation inhibition activity, and bile acid-binding capacity in a dose-dependent manner [10,11]. Similarly, phosphorylated derivatives show demonstrated anti-inflammatory, anti-viral, and anti-proliferative activity [12]. Acetylated derivatives of polysaccharides show potentiated antioxidant capacity and inhibitory effects in carotene-linoleic acid systems as compared with the unmodified polysaccharides [13].

The present study reviews the biological and technological potential of D-glucans after chemical modifications through sulfonylation, carboxymethylation, phosphorylation and acetylation as reported in the literature.

2. D-Glucans

Glucans are carbohydrate biomacromolecules made up of D-glucopyranoside units linked by glucosidic bonds through either α or β anomeric configurations. Despite the simplicity of their monosaccharide composition, great diversity can be found in the number and anomeric configuration of D-glucopyranoside units, the position and sequence of glucosidic bonds along the polymer backbone chain, the degree of branching as well as the frequency of branched points along the chain, and the chain conformation [3,14].

These biopolymers are produced by bacteria, yeasts, fungi, algae and plants (in particular, cereals such as oats and barley), and differ in structure and/or solubility in water and alkali (Table 1). They may, however, show similar or almost identical responses in macroorganisms and animal models [26,27]. Different sources of glucans grouped according to type, structure and biological application are presented in Table 1.

Glucans are divided into 2 groups depending upon their anomeric configurations; *i.e.*, α- and β-D-glucans. L-Glucans have not been studied for their bioactivities, and will not be discussed here. α- and β-Glucans differ in the stereochemical aspect, α-glucosidic bonds are formed in an axial position, while β-glucosidic bonds take up an equatorial position of the chair conformation of carbohydrates. Common examples of microbial α-glucans include pullulan [28] and dextran [29], while β-glucans can include those found in the cell wall of fungi and yeasts, or produced exocellularly (xanthan, scleroglucan), or are found in cereals.

α-Glucans are homo-polysaccharides constructed of glucose monomers linked by α-glucosidic bonds. In this group are: dextran (1→6)-α-glucan with a low degree of branching with (1→2)-, (1→3)-, and (1→4)- α-linked glucose residues) [29], glycogen-like α-glucans (highly branched polysaccharide of (1→4)-linked α-glucans with branches attached by (1→6)-α-glucosidic linkages) [30], pullulan (repeat units of maltotriose linked through (1→6)-α-glucosidic bonds to other maltotriose units along the polymer chain) [28], and starch (branched polymer of glucose units linked by (1→4)- and (1→6)- α-glucosidic bonds) [31]. Starch is a plant polysaccharide of the (1→4)(1→6)-α-glucan type, and is highly branched like glycogen.

Microbial β-glucans can typically consist of repeat units of glucose linked by various glucosidic bonds (mainly (1→3)-, (1→3;1→6)- and (1→6)-) that can be branched along the glucan backbone chain with regular (bacterial) or irregular (fungal, algal) repeat sequences of either single or multiple glucose residues also of different linkages; (1→3)-, (1→6)-. They differ from cereal β-glucans that consists of chains of (1→4)-linked D-glucose residues juxtapositioned with D-glucose units linked by (1→3)-bonds along the backbone chain, but share similar biological properties.

The β-glucans too constitute homopolysaccharides of complex structures that may be soluble or sparingly soluble in aqueous solution, or insoluble (*e.g.*, bacterial curdlan). Microorganisms produce β-glucans of three distinct types that are localized: intracellularly (storage), exocellularly (capsular, slime or biofilm) and in the cell