



Application of natural β -glucans as biocompatible functional nanomaterials

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ABSTRACT

Naturally-occurring β -glucans are mostly investigated for their antitumor activity and immunomodulatory property. They have been widely regarded as a natural source for functional foods and pharmaceuticals. However, the physico-chemically stable and biocompatible properties of β -glucans are rarely explored as a coating material for nanomaterials to overcome the problems of aggregation and cytotoxicity. This article reviews on the exploration of β -glucans, in particular those derived from mushrooms, as a natural coating material to modify the surface properties of bioactive substances as a relatively simple and cost-effective strategy to produce stable and biocompatible nanohybrids used for biopharmaceutical use. It is envisaged that such β -glucan-based coating method will provide new opportunities to design biocompatible functional nanomaterials for wider clinical applications.

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1. Introduction

1.1. Structural features of β -glucans

As natural nondigestible polysaccharides, β -glucans are widely distributed in cereal crops, bacteria, fungi and algae, where they form the cell wall or serve as energy source for metabolism [1]. Chemically, β -glucans are heterogeneous natural polymer of non-starch polysaccharides, composed of β -D-glucose connected by different types of linkages. In spite of the simple monosaccharide composition, β -glucans show considerable variability in structure. They vary greatly in molecular weight, degree of branching and linkage types, which are significant dependent on their source [2].

The simplest linear β -(1,3)-glucans (Fig. 1a) are found as structural cell wall polysaccharides or intracellular energy storage polysaccharides in bacteria and fungal sclerotia. Typically, curdlan is a linear β -(1,3)-glucan produced by gram-negative bacteria such

as *Agrobacterium* [3], which is used as food additives to stabilize the physical properties of products. Pachyman from the sclerotia of basidiomycete fungus *Poria cocos* are also linear β -(1,3)-glucan [4]. Unlike them, cellulose, the primary building blocks of cell walls of plants and algae, is linear β -(1,4)-D-glucan [2].

Another linear structure type is linear β -(1,3; 1,4)-glucan which are characteristically found in the cell wall of cereal grains, such as barley and oat (Fig. 1b) [5]. The order of β -(1,3)- and β -(1,4)-linkages in the chain is not completely random. In most cases, two or three β -(1,4)-linkages are separated by a single β -(1,3)-linkage, but longer blocks of up to 14 β -(1,4)-linked glucopyranose units may also present [6].

The branched β -(1,3; 1,6)-glucans are widespread in brown algae (known as laminarin) [7], baker's yeast [1], and mushrooms, such as *Lentinus edodes* (known as lentinan) [1] and *Schizophyllum commune* (known as schizophyllan) [8]. Lentinan and schizophyllan share the similar structure of a β -(1,3)-D-glucose backbone, with β -(1,6)-glucopyranoside branches residues at every third glucose unit (Fig. 1c). Also, complex branch structure, including cyclic β -(1,3; 1,6)-glucan (Fig. 1d), hyperbranched β -(1,3; 1,4; 1,6)-glucan are found in bacteria of *Rhizobiaceae* family and mushroom sclerotia of *Pleurotus tuber-regium*, respectively [9,10].

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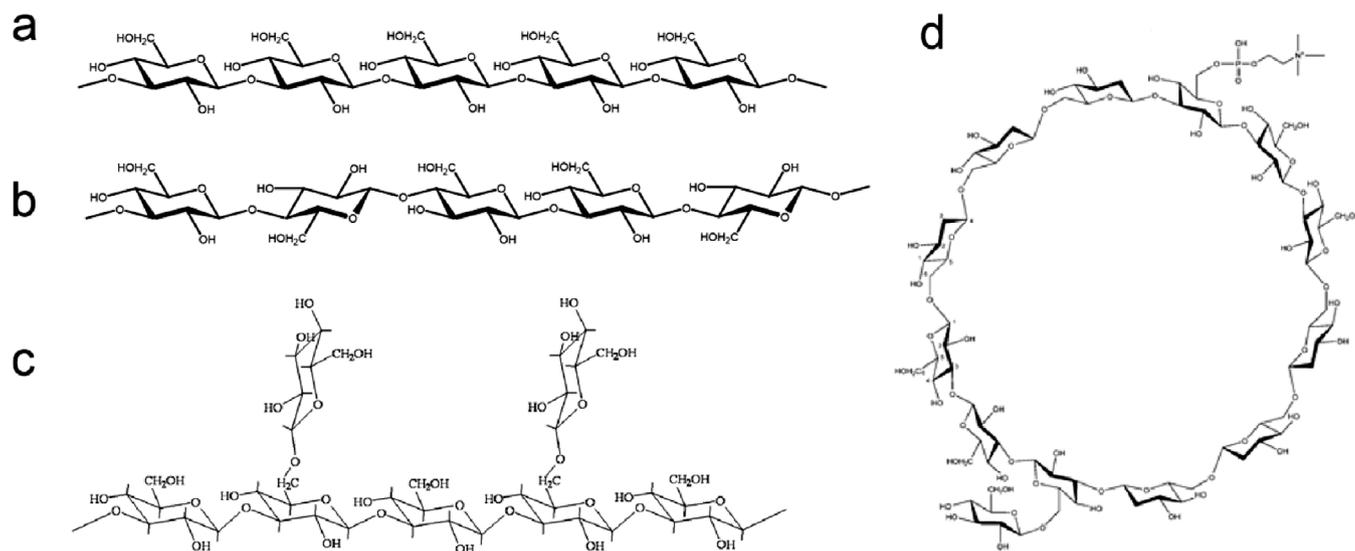


Fig. 1. (a) Linear β -(1,3)-glucan; (b) linear β -(1,3; 1,4)-glucan; (c) the structure of lentinan; (d) cyclic β -(1,3; 1,6)-glucans.

1.2. Beneficial effects of β -glucans

β -glucans have been known as functional foods since they are capable of boosting the both innate and adaptive immune systems, thus modulating the immunological responses against cancer, bacteria, viruses and inflammation [11]. Research studies have demonstrated that lentinan increased the NO production in bone marrow macrophages [12] and stimulated the secretion of tumor necrosis factor α (TNF- α) or interleukin-1 (IL-1) production from monocytes and macrophages [13,14]. Clinical studies also demonstrated that the combination of lentinan with conventional chemotherapy increased the life span in patients with advanced gastric cancer and reduced the side effects of chemotherapy [15]. β -glucans isolated from other mushrooms, such as *Agaricus* and *Schizophyllum commune* (schizophyllan) also exhibited immunostimulating property through stimulation of NK cells, dendritic cells to enhance excretion of cytokines [16–18]. Apart from the mushroom β -glucans, β -glucans from yeast also have a capacity to stimulate immune responses to suppress the chronic inflammation in diabetic mice [19].

Moreover, β -glucans from oat have been approved for reducing the risk of coronary heart disease by the United States Food and Drug Administration (FDA) [20]. In addition, consumption of cereal β -glucans are reported to reduce the level of plasma cholesterol and regulate blood glucose concentration as well as insulin responses [21,22]. Notably, mushroom β -glucans, such as lentinan also contribute to hypocholesterolemic effect in humans, by lowering the level of lipoproteins (both HDL and LDL) in blood [23,24]. Meanwhile, β -glucans are non-digestible and non-absorptive in small intestine due to the lack of digestive enzymes in human body to hydrolyze β -glucosidic bonds, therefore they may also act as dietary fibers with prebiotic properties to benefit the host by selectively regulating the growth and/or activity of gut microbiota [25]. It has been reported that laminarin, curdlan, β -glucans from barley and the mushroom sclerotia from *Pleurotus tuber-regium* all exhibited comparable bifidogenic effect as inulin in stimulating the growth of bifidobacteria [26].

2. Applications of β -glucans in nanotechnology

Schizophyllan with triple-helical structure (t-SPG) has been investigated to entrap single-wall carbon nanotubes (SWNTs)

forming “periodical” helical structure on the SWNTs surface. When dissolved in DMSO solution, t-SPG dissociated into single chains (s-SPG). After exchanging the DMSO for water, single chains retrieved the original triple-helix to entrap SWNTs or as a host to construct poly(diacetylene) nanofibers which are expected to exhibit an excellent conductivity [27] (Fig. 2).

Apart from applications based on the physiochemical properties of β -glucans, β -glucans also been used chemically in nanoparticle synthesis as reducing and stabilizing agents for drug delivery [29] and surface interactions with gold nanorods [30] having the application of photothermal cancer therapy [31,32]. The β -(1,3; 1,6)-*D*-glucan isolated from an edible mushroom *Pleurotus florida* was used to reduce chloroauric acid to prepare gold nanoparticles as well as stabilize them [28]. Leung and colleagues [33] synthesized silver nanoparticles using carboxymethyl curdlan (CM-curdlan) to reduce nitrate. Compared with conventional method, these silver nanoparticles were stable and comparable in size [33]. Zhang and colleagues developed water-dispersible selenium nanoparticles stabilized by natural hyperbranched β -glucan (Se-HBP) through the strong absorption between the hydroxyl groups and selenium surface (Fig. 3). Se-HBP showed improved water stability for at least 30 days attributed to the ligation with HBP [34]. These applications of renewable and environmental friendly β -glucans as reducing and stabilizing agents provide a green synthetic strategy to prepare metal nanoparticles.

β -glucan-based polysaccharides are also currently under investigation for delivery vehicles. Luan and colleagues [35] created a cellulose-based composite macrogel (CCNM) by using cellulose fiber (CFM) and TEMPO modified cellulose nanofiber (CNF) (Fig. 4). The authors found that CCNM are pH-responsive that could allow probiotics to colonize the interior of CCNM, thus improved the cell viability of probiotics in simulated gastric fluid and controlled the release of probiotics. The authors concluded that CCNM should be considered as an intestine delivery vehicle for bioactive agents [35]. In another study, the cores inside yeast β -glucan particles were developed as a delivery for small nanoparticles (<30 nm). As yeast β -glucan particles can be recognized by phagocytic cells in the immune system through receptor mediated pathway, these yeast β -glucan particles served as a macrophage targeted delivery system [36].

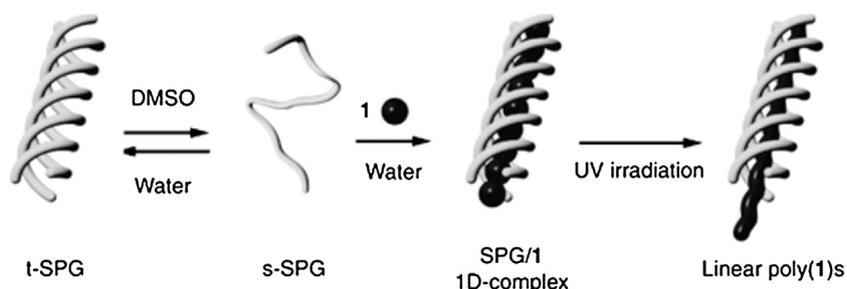


Fig. 2. Renaturation and denaturation processes of schizophyllan (SPG) and schematic illustration of using SPG as a host to construct poly(diacetylene) nanofibers [27].

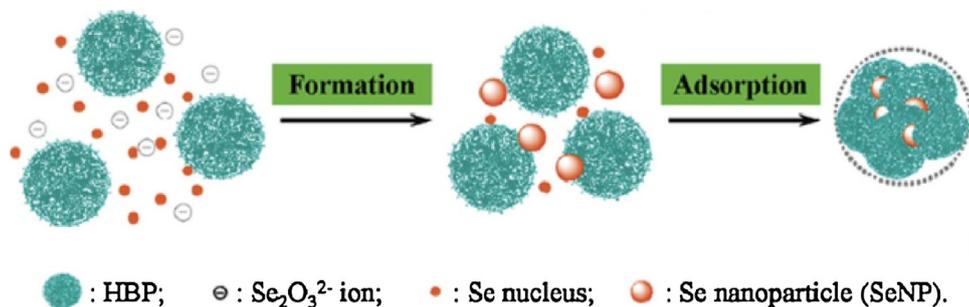


Fig. 3. Schematic illustration of the Se-HBP [34].

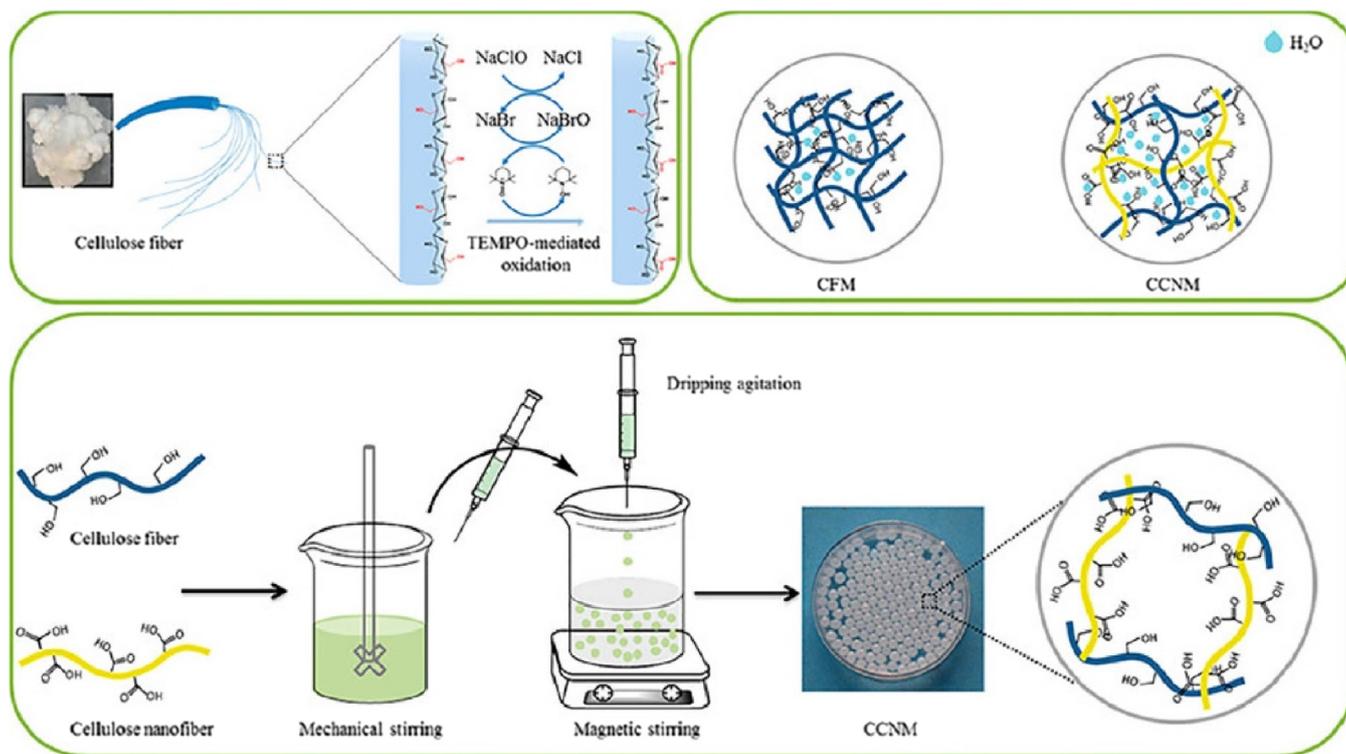


Fig. 4. Scheme of TEMPO-mediated oxidation of cellulose and preparation of CCNM [35].

In addition, Querejeta-Fernandez et al. [37] developed chiral plasmonic films using cellulose nanocrystals (CNCs) as a host to organize plasmonic gold nanorods (NRs) (Fig. 5). In this study, the synthesis of the chiral plasmonic films exerted synergetic influence on the structure and optical properties of CNCs while gold NRs were incorporated by the synthesis of the films [37].

3. β -Glucan from *Pleurotus tuber-regium* sclerotia as novel material to form nanohybrids

Pleurotus tuber-regium (Fig. 6a) is an edible mushroom of the *Pleurotaceae* family native to the tropical regions of the world, including Asia, Africa and Australasia [38]. It is not only consumed

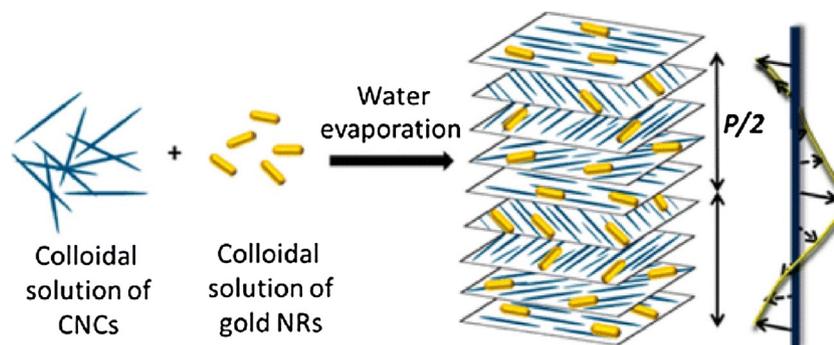


Fig. 5. Schematic of the preparation of the composite chiroptical plasmonic film by mixing aqueous suspensions of CNCs and gold NRs [37].

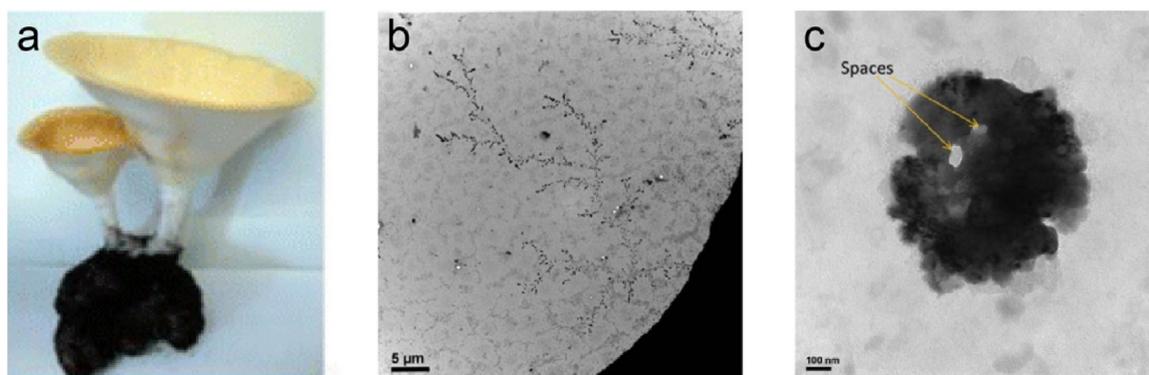


Fig. 6. (a) *Pleurotus tuber-regium*; (b) TEM image of highly branched alkali-soluble β -glucan from *P. tuber-regium* sclerotial and (c) TEM image of spherical particles of alkali-soluble β -glucan from *P. tuber-regium* sclerotial [44].

worldwide owing to their excellent sensory properties, but it also attracts much attention because of their medicinal properties that are used as a traditional cure for headache, asthma and colds [39]. *P. tuber-regium* is unique in the production of a sclerotium, which is a mass of mycelium used for food reserves under unfavorable conditions [40].

In fact, the sclerotia of *P. tuber-regium* are the rich source of bioactive β -glucans. These sclerotial β -glucans shows antitumor activity [41] immunostimulating activity [42] and antiviral activity after sulfation [41] especially when purified from the water extracts. In addition, *P. tuber-regium* sclerotia also produce alkali-soluble hyperbranched β -glucans with antitumor activity on tumor xenografted BALB/c mice, antiproliferative activity on HL-60 and HepG2 cell lines [43] and bifidogenic effect as potential prebiotics [26].

Interestingly, the β -glucan purified from the alkali-soluble polysaccharides is a highly branched spherical β -(1,3; 1,4; 1,6)-glucan with some spaces existed (Fig. 6b and c) [44], which might possess reservoir characteristics and provide protection for biopharmaceuticals in a core-shell structure. In addition, the large number of hydroxyl groups of the hyperbranched β -glucan offer reaction sites for possible chemical modification and functionalization. Therefore, as a hyperbranched polymer with core-shell structure features, β -glucan isolated from the sclerotia of *P. tuber-regium* (HBB Ptr) can be designed as a delivery carrier for guest-host encapsulation biopharmaceuticals or fabrication organic-inorganic hybrids.

Recent findings on the use HBB Ptr to form a nanohybrid with gold particle in photothermal cancer therapy have been reported [45,46]. The HBB Ptr coating remarkably enhanced the colloidal stability of the nanohybrid in various biological media and photothermal stability, both of which are essential characteristics as

photothermal agent for cancer therapy [45]. *In vitro* experiments showed that these nanohybrids were non-toxic to normal cells and caused effective cell ablation on MCF-7, SW480 and HT-29 under hyperthermia [45]. *In vivo* study further showed that solid tumors were effectively reduced by a single intravenous injection of these nanohybrids (25 mg/kg of body weight) [46]. Furthermore, no obvious harmful side effect of these nanohybrids was evident by histological analysis of major organs in treated mice, suggesting a promising application of AuNR-Glu in cancer PTT [46] and biomedicine [47,48].

4. Conclusion

β -glucans are natural biomaterials having the potential to form stable nanohybrids with excellent biopharmaceutical properties to be orally administrated for therapeutic cancer treatment. More research is required to investigate the biodistribution of these nanohybrids in the gastrointestinal tract. Moreover, the numerous hydroxyl groups in the β -glucans would allow the tandem surface modifications of the nanohybrids for other biomedical applications including targeted drug delivery.

Declaration of Competing Interest

The authors declare they have no competing interests.

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