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Mini-review

β-Glucans in promoting health: Prevention against mutation and cancer

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Abstract

The polysaccharides β-glucans occur as a principal component of the cellular walls. Some microorganisms, such as yeast and mushrooms, and also cereals such as oats and barley, are of economic interest because they contain large amounts of β-glucans. These substances stimulate the immune system, modulating humoral and cellular immunity, and thereby have beneficial effect in fighting infections (bacterial, viral, fungal and parasitic). β-Glucans also exhibit hypocholesterolemic and anticoagulant properties. Recently, they have been demonstrated to be anti-cytotoxic, antimutagenic and anti-tumorogenic, making them promising candidate as pharmacological promoters of health.

Keywords: β-Glucans; Antimutagenesis; Biological activities; Chemoprevention; Anticarcinogenic

Contents

1. Introduction

Foods and natural products have been traditionally accepted as health remedies due to popular belief that they present minor adverse effects. Therefore, under-

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standing the mechanism by which foods and natural products exert possible beneficial effects is very important to human populations. Chemopreventive products that showed inhibition of genotoxic effects, anti-oxidant activity, inhibition of cell proliferation, induction of cell differentiation and interference with signal transduction pathways, may lead to protection against the carcinogenic process. A number of chemopreventive agents appear to work through multiple mechanisms and may be additive or synergistic in their effects. This paper reviews the general health-promoting activities of β-glucans.

2. Origin, structures, chemistry and biological effects

β-Glucans belong to a group of polysaccharides characterized by their location in the cell wall. Some microorganisms and cereals, such as barley and oats, are rich in β-glucans [1–5]. These polysaccharides are of great economic importance. In microorganisms, these compounds consist mainly of a linear central backbone of D-glucose linked in the β(1 → 3) position with glucose side branches (linkage β1 → 6) of various sizes (Fig. 1) which occur at different intervals along the central backbone [6]. The polysaccharide is localized in the intermediate layer of the cell wall, adjacent to the plasma membrane, with the function of maintaining the rigidity and shape of the cell [7]. Other β-glucans, derived from cereals, are polysaccharides of glucose residues with β(1 → 3) and β(1 → 4) linkages (Fig. 2)

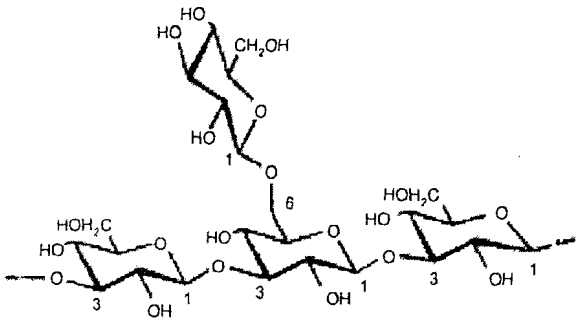

Fig. 1. Structure of (1 → 3)β-glucans with ramifications β(1 → 6).

[8]. In barley, the locus for the control of β-glucan production has been mapped on chromosome 2 [9]. This discovery can facilitate the characterization of the chemical and biological properties of this polysaccharide through biotechnology using insertion of specific genes for the production of a particular β-glucan in foods (food transgenic).

The macromolecular structure of β-glucans depends on both the source and method of isolation, varying mainly in the distribution and length of side chains, which provide for complex tertiary structures stabilized by inter-chain hydrogen bonds. Parameters such as primary structure, solubility, degree of branching (DB) and molecular weight (MW), as well as the charge of their polymers and structure in aqueous media, are involved in the biological activity that β-glucan exhibits [5]. β-Glucans with $0.2 \leq DB \geq 0.33$, $100 \leq MW \geq 200$ kDa, and a triple-helix structure are more effective biologically [5].

The solubility of β-glucans is associated with the degree of polymerization (DP). β-Glucans are completely insoluble in water when DP > 100. Solubility increases as DP decreases. β-Glucans can be classified according to their solubility properties: (a) alkali-insoluble, acetic acid insoluble (1 → 3)-β-glucan; (b) alkali-soluble (1 → 3)-β-glucan; and (c) highly branched (1 → 6)-β-glucan [5]. These properties impart a characteristic of insolubility for most β-glucans, limiting application and extrapolation of *in vitro* experimental data in human beings.

Among the natural β-glucans of clinical interest are lentinan, schizophyllan and krestin (PSK). Lentinan is a (1 → 3)-β-glucan obtained from the *Lentinula edodes* fruiting body, composed of five (1 → 3)-β-glucose linear residues and two (1 → 6)-β-glucopyranoside side branches, resulting in triple-helix structure. It has a molecular weight of 400–800 kDa. Schizophyllan is a (1 → 3)-β-glucan obtained from the microorganism *Schizophyllum commune*, which has a β-glucopyranosyl group linked (1 → 6) to every third or fourth residue of the main chain. It has a triple-helix structure and molecular weight of approximately 450 kDa. PSK is a β-glucan/protein compound consisting of 25–38%

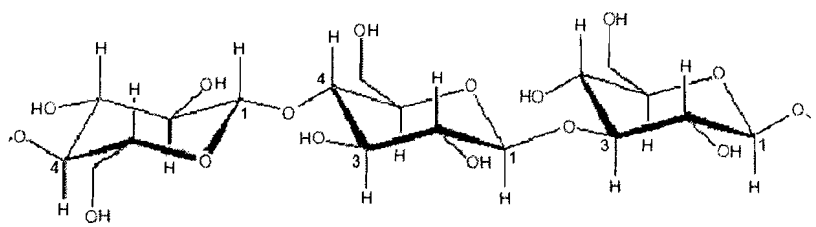

Fig. 2. Structure of (1 → 3)β-glucans with ramifications β(1 → 4).

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protein residues and (1 → 4)-β-glucan with (1 → 6)-β-glucopyranosidic lateral chains; it is prepared from *Coriolus versicolus* and has a molecular weight of 94 kDa [10].

Many investigators have been concerned with the characterization of other β-glucans. Among them are β-glucans of *Agaricus blazei* (*Agaricus brasiliensis*) and of oats, because the nutraceutical or chemopreventive properties of this mushroom are directly related to the presence of this polysaccharide. There have been efforts in the biochemical modification of β-glucans, to increase their commercial and scientific potential, mainly to improve solubility. Among these modifications, sulfation has received a great deal of attention due to the biological activities that sulfate groups promote, mainly because makes the molecule more soluble preventing granuloma formation [11].

Studies of alkali-soluble β-glucan from *Agaricus blazei* detected (1 → 6)-β-D-glucan, without (1 → 3)-β-linkages, and small but significant amount of (1 → 3)-β-D-glucan with antitumor properties [12,13]. However, (1 → 6)(1 → 3)-β-D-Glucan from aqueous extraction of the same species also has antitumor activity [14]. Recently, β-glucans from *Agaricus brasiliensis* (*A. blazei*) were isolated and characterized, where the maturation phase of the fruiting body was found to influence the nutraceutical potential of the products. The purification fractions showed large amounts of (1 → 6)-β-glucan and (1 → 3)-β-glucan which increased with fruiting body maturation. The fruiting body at the mature stage showed therapeutic benefits, which were attributed to side branching influencing in immunomodulatory and antitumor activities [15].

β-Glucan extracted from oats was submitted to reductive amination, producing cationic β-glucan, which demonstrated antimicrobial effect. That same molecule, when sulfated, showed a variety of other biological activities, for instance an anticoagulant effect [16]. The sulfation of β-glucan affects its molecular weight, its solubility in water and its viscosity, as well as binding capacity to bile acids [11].

β-Glucans of the microorganisms *Poria cocos* and *Pleurotus tuber-regium*, when sulfated, show an antitumor effect and antiviral activity [17,18]. The sulfation of (1 → 3)-β-glucans from *Alicaligenes faecalis* var. *myxogene* [19,20] and of (1 → 6)-β-glucans from the mushroom *Parmotrema mantiqueirense* [21] exhibit anti-thrombotic and anticoagulant effects. These activities can be explained by the increased solubility of sulfated β-glucan, due to a greater incorporation of ions, which result in pharmaceutical advantages [11].

3. Health-promoting activities

β-Glucans are believed to have various immunomodulatory properties. Studies *in vitro* and *in vivo* reveal that the immunostimulating activity of β-glucan depends on structure, molecular weight and number of branches [22,23]. β-Glucans act through stimulation of the immune system, exerting a beneficial effect against a variety of bacterial, viral, fungal and parasitic [16,24–27]. The immunostimulating effect of β-glucan is probably associated with the activation of cytotoxic macrophages and T-helper and natural killer (NK) cells and with the promotion of T lymphocyte differentiation and activation, for the alternative complement pathway [28]. β-Glucans have also been described as modulators of both humoral and cellular immunity [29–31]. β(1 → 3)-D-Glucans from fungi were shown to be capable of having beneficial effects in pre-inflammatory responses, indicating that β-glucan can be a modulator of the anti-inflammatory response as interleukin mediators [32].

Animal studies indicate that β-glucans, when used as a nutritional supplement, stimulate growth and improve nutrient retention and immune system function, the latter by stimulating CD8 and TCR1 cells [33].

It has been demonstrated that *Candida albicans* (yeast) β-glucans activate macrophages and induce interleukin (IL-6) and tumor necrosis factor (TNF) *in vitro*, promoting vascular permeability and stimulating the classic complement pathway [30]. β-Glucans from mushroom mycelium show larger molecular weights than β-glucans from yeasts. However, the two β-glucans demonstrate similar ability in the induction of macrophages and chemotactic factor [22].

When blood cells from hepatitis C patients were exposed to *Agaricus blazei* extract, a β-glucan-mediated immunomodulatory effect was observed in monocytes [34]. However, the immunomodulatory activity observed *in vitro* and in animal models [35,36] were not observed *in vivo* in humans, possibly due to the fact that β-glucans are not absorbed well by the intestine [34].

β-Glucan from oats has been demonstrated to have antimicrobial effects against *E. coli* and *B. subtilis*. In a comparison of cationic and native β-glucans, the latter was shown to inhibit the growth of these bacteria by approximately 35% while the cationic one was found to cause 80% inhibition in both microorganisms, indicating that β-glucan amination promotes antimicrobial effects. In this same study, cationic β-glucan was seen to be more effective against *E. coli* (Gram-negative) than *B. subtilis* (Gram-positive), which can be explained

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by the interaction of the polycations with the negative-charged bacterial surface, altering membrane permeability and thereby inhibiting growth [16].

Saccharomyces cerevisae β-glucan extract was shown have antimicrobial activity in mice, against *Staphylococcus aureus* resistant to antibiotics, because β-glucan administration helps in the elimination of bacteria and increases the number of monocytes and neutrophils, thereby resulting in antibiotic potential [37,38].

The combination of an antifungal agent and β-glucan in paracoccidiomycosis treatment was demonstrated to improve therapeutic response, where the patients that received only the antifungal agent had more frequent relapses than the group that received the β-glucan–antifungal combination [25].

The administration of β-glucan to mice infected with *Eimeria vermiformes* showed increased resistance to infection due to immunomodulation, which involved non-specific as well as specific response [26]. β-Glucans partially restored T and B cell response to the mitogen in mice infected by *Toxocara canis*, reducing the larval number found in the muscles of the animals that received β-glucans [27].

Survival increased in mice exposed to Venezuelan equine encephalomyelitis virus, when pre-treated with β-glucan. β-Glucan produced higher resistance in mice to virulent *Francisella tularensis* when pre-treatment was given intravenously in comparison with intranasal administration. In addition, the vaccine against Venezuelan equine encephalomyelitis virus combined with β-glucan was found to be more protective in mice and monkeys [24].

β-Glucans are not degraded by human enzymes, which provide them with nutritional fiber properties. The greatest interest in these fibers is due to their demonstrated protective hypocholesterolemic effect [5], reducing risk of chronic diseases. It is known that β-glucans reduce blood cholesterol levels. The ingestion of β-glucan increases intestinal viscosity and reduces cholesterol absorption, thereby promoting its excretion [36]. In a study of the hypocholesterolemic effect of β-glucan, it was observed that cationic β-glucan shows a greater effect compared to the native form, reducing cholesterol effects in vivo [16]. However, sulfated β-glucans are less effective in lowering cholesterol levels due to reduced viscosity [11].

Sulfated β-glucans show anticoagulant activity of less than 1% up to 135% [39], and have an anti-thrombotic effect, reducing hemorrhagic risks [40]. β-Glucans are therefore promising candidates as anticoagulant agents [11].

4. Chemoprotective effects

Recently, several works *in vitro* have demonstrated that β-glucans of different origin have effective protective activity against different mutagenic agents. The barley β-glucan was found to have a protective effect against damage induced by methyl methanesulfonate (MMS), in the CHO-K1 cell line (deficient in drug metabolism). The effects of the inducers MMS and 2-aminoanthracene (2AA) in the HTC cell line (proficient in drug metabolism) using different treatment protocols (pre-treatment, simultaneous, simultaneous with pre-incubation and post-treatment), indicated that the simultaneous protocol with pre-incubation provided the greatest reduction in DNA damage, suggesting that β-glucan may react with mutagenic agents impeding their interaction with DNA [41]. The protective effect against 2AA and MMS, in lower concentrations, was also seen in CHO-K1, in the presence of absence of a DNA polymerase inhibitor (Ara-C) [42].

In a study of the effect of β-glucan extracted from *S. cerevisae*, cell lines CHO-K1 and CHO-xrs5 (deficient in repair of DNA double-strand break) were protected against damage caused by MMS. However, reduction in damage in CHO-xrs5 was much less, indicating a possible effect in the repair of double-strand breaks [43]. The binding of β-glucan to different types of substances has been observed in experiments with ofloxacin and other mycotoxins [44,45]. Besides showing a protective effect against several chemical agents, β-glucans of different origin has been demonstrated to be potent anti-oxidants, prevent damage by H_2O_2 and other reactive oxygen species [44,46–48].

Some studies *in vivo* have also proven the efficacy of β-glucan in reducing the damage caused by various mutagenic agents. *S. cerevisae* β-glucan has a protective effect against genotoxicity and cytotoxicity when administered along with such drugs as cyclophosphamide, adriamycin and cisplatin. This protective effect could be attributed to the ability of β-glucan to trap free-radicals produced during the biotransformation of these drugs [8]. Studies have shown that fungal β-glucans can also act as chemopreventive agents [49,50], where these substances are capable of inhibiting isozymes of cytochrome P450 family (phase I enzymes), enzymes that are involved in the first activation stage of carcinogens such as benzo[*a*]pyrene. This decrease in their activation would aid in retarding mutagenic substances formation, suggesting a more efficient conjugation with phase II enzymes.

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The antitumor activity of polysaccharides is variable, and depends on chemical composition and physical properties. It has been demonstrated that lentinan and schizophyllan are antitumor polysaccharides with the same basic β-glucan structure, only differing in their glycoside side branches, which points to the importance of the β-glucan (1 → 3) structure with (1 → 6) branching for antitumor activity [10].

Studies of two β-glucans extracted from *S. cerevisae*, one soluble and the other particulate, demonstrated that both were capable of inhibiting the growth of mammary carcinoma and B16 melanoma cells, as well as increasing the survival of mice with subcutaneous tumor implants [6]. A synthetic β-glucan with a reduced number of lateral glucoses was found to have an antitumor effect in mice against sarcoma 180 cells. β-Glucans of both native structure and modified structure with glucose side chain reduction, have been shown to enhance the reticulo-endothelial system and macrophage activation; however, the non-branched β-glucan has been found to have greater antitumor activity [51]. Investigations *in vitro* and *in vivo* of β-glucan from *Lentinula edodes* have demonstrated that it has a strong antitumor activity against sarcoma 180. In triple-helix form, its growth-inhibitory effect *in vivo* is greater because of the loss flexibility of the chains, indicating that this structure plays an important part in the antitumor activity [52].

β-Glucan administration prior to methotrexate was found to abolish methotrexate-mediated depletion of GSH, lessening organ damage (ileum, liver and kidney) in mice, due to inhibition of leukocyte apoptosis. This suggests that β-glucan is an anti-oxidant and has immunomodulatory effects, which makes it of therapeutic value in tissue insult [53].

5. Future perspectives

β-Glucans have been shown to possess important biological properties regardless of origin (Table 1). This finding calls for future perspectives into wide production through biotechnology using microorganisms such as *S. cerevisae*, as well as the insertion of specific genes for the production control of a particular β-glucan in foods (food transgenic), depending on its eventual purpose as a pharmaceutical product or functional food, respectively.

The identification of foods that produce high levels of these polysaccharides and that can undergo modifications of the β-glucan gene control to improve their absorption and consequently efficacy, can be an approach in the production of functional foods with medicinal properties. Besides, the consumption of food with antimutagenic activity could contribute to a reduction in risk of cancer and of other degenerative

Table 1
Structure, origin and biological activities of β-glucans

Structure	Source	Effects	Reference
β (1 → 3) (1 → 6)	*Saccharomyces cerevisae*	Antiparasitic	[27]
		Antibacterial	[1,6,37,38]
		Antiviral	[24]
		Antifungal	[25]
		Antimutagenic/antigenotoxic	[8,43,44,46,47,53]
		Antitumoral	[6,51]
		Hematopoietic stimulator	[3]
		Mitogenic	[7]
	Candida albicans	Imunostimulating activity	[22]
	Poria cocus	Antitumoral	[18]
	Agaricus blazei	Cytokine induction	[34,35]
		Antimutagenic/antigenotoxic	[4]
		Inhibition of CYP450 isoenzymes	[49]
		Antitumor	[12–14]
	Lentinus edodes	Inhibition of CYP450 isoenzymes	[49,50]
		Antitumor	[10,52]
	Schizophyllum commune	Antitumor	[10]
	Coriolus versicolor	Antitumor	[10]
β (1 → 3) (1 → 4)	Oat	Antimicrobial	[16]
		Antiparasitic	[26]
		Hypocholesterolemic	[11,16,36,54]
		Anti-thrombotic	[11]
	Barley	Antimutagenic	[41,42,48]

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diseases. However, further studies are needed involving epidemiologic evaluation of the public's intake of cereals such as oats and barley which are β-glucan-rich foods, for the moment no epidemiological study concerning the incidence of cancer and consumption of β-glucan is available, the only epidemiological study involving β-glucan relates its consumption with the decrease of cholesterol levels [54].

Furthermore, a better future perspective would be the use of β-glucan in supporting the treatment of cancer patients submitted to chemotherapy, to improve immunologic status and reduce untoward effects on normal tissues, although attention must be paid once the reduction of isoenzymes of the CYP450 family could lead to low level of activation of the chemotherapeutic drug, leading to higher presence of the drug in the organism Also use of intravenous solution of β-glucan should be used carefully due to the possibility of granuloma formation and hepatosplenomegaly. β-Glucan may, in some cases, have use as an antitumor agent, but clinical trials in humans are still needed. Studies of β-glucans have shown these polysaccharides to be important and promising substances in the promotion of health in humans, and that further investigation is warranted. To date, in the present time studies with patients undergoing chemotherapy and receiving β-glucan are being performed in our lab, being this the first study of this type.

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