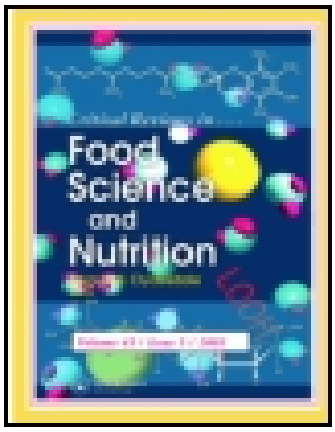

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Structural Characterization, Technological Functionality and Physiological Aspects of Fungal β-D-Glucans: A Review

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Structural Characterization, Technological Functionality and Physiological Aspects of Fungal β-D-Glucans: A Review

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β-D-Glucans are a (1→3)-linked glucose polymer with (1→6)-linked side chains and a major component of fungal cell walls. They exhibit structural integrity to the fungal cell wall. Additionally, β-glucans are widely used as food adjuvant in food and pharmaceutical industries because of their physico-chemical properties. Several studies focus on different isolation process of (1→3) (1→6)-β-glucan which could be affect the physico-chemical and functional properties of β-glucan such as chemical composition, solubility, viscosity, hydration properties and oil

binding capacity. Immunological activity is one of the most important properties of β-glucans. Thus, they are effectives in inhibiting cancer cell growth and metastasis and preventing bacterial infection. In humans, β-glucans reduce blood cholesterol, improve glucose absorption by body cells and so help wound healing. This review described the prebiotic potentiality of fungal β-D-glucans with the objective to detail the methodologies applied for their extraction, their structure and their techno-functional properties and finally their biological effects.

Keywords ϐ-D-Glucans, fungal cell wall, isolation process, structure, techno-functional properties, prebiotic potentiality

INTRODUCTION

ɓ-Glucans are structurally complex, insoluble glucose homopolymers, found in the cell wall of fungi, algae and bacteria (Iorio et al., 2008). Their main molecular structure is relatively homogeneous, although the type of bonding, molecular mass and molecular configuration may be variable and dependant of the microbial source (Bohn and BeMiller, 1995).

The fungal and yeast glucans have a common structure that consists of a ɓ-D-(1→3)-linked glucopyranosyl backbone possessing ɓ-D-(1→6)-linked side chains of varying distribution and length (Hromádková et al., 2003). In general, between 65% and 90% of the cell wall glucan is found to be ɓ-(1→3)-glucan, but other glucans have been found in various fungal cell walls (Bowman and Free, 2006). The ɓ-(1→3)-glucan serves as the basic structural component to which other cell wall constituents are covalently attached (Bowman and Free, 2006).

Biologically, ɓ-glucans are well recognized as potent immunological stimulators in humans and animals. These ɓ-glucans are effective in treating many diseases like diabetes, hypercholesterolaemia, a range of microbial infections and cancer (Chen and Seviour, 2007; Iorio et al., 2008; Jaehrig et al., 2008; Klis et al., 2001). Thus, the bakerôs yeast cell wall (Zymosan) was the first defined pharmaceutical yeast product with immunostimulatory activity (Hromádková et al., 2003). Its active component was ɓ-D-glucan which was reported to contain phagocytic and candidacidal activities (Hromádková et al., 2003). Moreover, recent studies found that ɓ-D-(1→3)-glucan from *Saccharomyces cerevisiae* cell walls exhibits antioxidative activity in terms of free radical scavenging (Jaehrig et al., 2008). Keeping in view of its health benefits, a range of functional foods containing ɓ-D-glucan are now being commercially

distributed in the market (Burkus and Temelli, 2000). Thus, the ß-glucan of spent brewerôs yeast had high apparent viscosity, water holding, oil binding and emulsion stabilizing capacities (Thammakiti et al., 2004).

In view of the beneficial properties of ß-D-glucan for human health, many processes for the isolation and purification of this polysaccharide have been grown. Most of them use hot alkali, acids or combination of both which contribute to a more or less strong degradation of the glucose chains, low yields and limited purity (Magnani et al., 2009). Therefore, other process involving hot water and enzyme treatment has been developed (Freimund et al., 2003; Jaehrig et al., 2008, Magnani et al., 2009). This review summarise recent research on the isolation process, structure and technological functionality of fungal ß-glucans justifying their interest for human health.

ISOLATION PROCESS OF FUNGAL ß-D-GLUCANS

Fractionation of fungal cell walls aims to quantify those constituents, to isolate fractions of interest and to remove undesirable compounds. For example, during the purification process of ß-D-(1→3), (1→6)-glucan from cell wall of bakerôs yeast *Saccharomyces cerevisiae*, other cell components such as proteins, lipids, nucleic acids, minerals and mannans are eliminated to a large extent (Hunter et al., 2002).

Processing may affect the ß-glucan properties including the molecular, structural and functional properties, which, in turn, affect the sensory, physiological and health benefits of ß-glucan. As extraction and purification processes remarkably influence the glucan purity and yield, several publishes have been reported on the subject (Table 1). Due to the biological activities of yeasts

and fungi ɓ-glucans, many extraction methods have been recently published in order to get a prebiotic ingredient that could be easily incorporated in foodstuffs (Laroche and Michaud, 2007).

Previous research have been developed an acid-alkaline method to extract ɓ-glucans from the cell wall of *Saccharomyces cerevisiae* (Hunter et al., 2002). However, Müller et al. (1997) reported that using these methods had some disadvantages. Thus, the most quantity of ɓ-glucans were degraded and distributed in all levels in the supernatant. Subsequently, this led to lower ɓ-glucans yields with respect to the initial content in the cell walls and considerably influenced on its biological function. From fungi, the problems relative to glucan extraction are in relation with the cell wall complexity and with the undesirable presence of pigments in the extracts (Laroche and Michaud, 2007).

Extraction and fractionation from these sources generally involve hot water resulting weakening or destructing hydrogen bonding in cell walls of fungi, followed sometimes by extraction under a strong alkaline condition as decribed with *Basidiomycetes aphyllophorales* mushrooms (Laroche and Michaud, 2007).

More recent publications have focused on the new extraction methods, in order to increase ɓ-glucan purity and to decrease production cost. These methods associate original extraction and purification procedures combined or not with enzymatic treatment. Among them, the use of enzyme treatment after hot water extraction or high pressure homogenization exhibit a good extraction of ɓ-glucan compared to traditional strategies (Freimund et al., 2003; Liu et al., 2008). Jaehrig et al. (2008) also reported extraction with hot water and enzyme treatments (Savinase and Lipolase) for obtaining ɓ-glucan from *Saccharomyces cerevisiae*. In the case of fungi like

Pleurotus cornucopiae, enzymatic hydrolysis is sometimes used in order to obtain a water soluble ɓ-glucan fraction easily recovered (Nagase et al., 2005).

STRUCTURAL FEATURES

The fungal cell wall is rigid giving the organism its shape and exhibiting physical protection from the environment. Although its potential as an anti-fungal drug target, the biosynthesis and structure of the cell wall has only been widely investigated in a few species of fungi, such as *Aspergillus* (Fontaine et al., 2000), *Candida* (Klis et al., 2001) and *Saccharomyces* (Klis et al., 2002). Many fungal species produce ɓ-D-(1→3), (1→6)-glucans (Sutherland, 2001). These polymers contains a tertiary triple helix structure, and a main chain of ɓ-D-(1→3) linked glucose residues branched with (1→6)-ɓ-D-glucosyl units (Figure 1) (Laroche and Michaud, 2007; Schmid et al., 2001). The synthesis of ɓ-D-(1→3)-glucan is necessary for the cell wall formation and the normal development of fungi.

Original works focuses on the synthesis and composition of glucan from *Saccharomyces cerevisiae* and *Candida albicans*. These works showed that yeast cell walls possess branched ɓ-(1→ 3) and ɓ-(1→6)-glucans (Cabib et al., 1988). Recent studies demonstrated that the cell walls of several filamentous fungi like Neurospora crassa and Aspergillus fumigatus do not have ɓ-(1→6)-glucan (Borkovich et al., 2004; Fontaine et al., 2000).

Schmid et al. (2001) reported that wide variations can be observed in the extent of the side-chain substitutions. Thus, much fungi including schizophyllan from *Schizophyllum commune* and scleroglucan from *Sclerotium glucanicum* both contain a ɓ-(1→3)-linked backbone, with on average one ɓ-(1→6)-glucose substitution every three backbone residues. The initial molecular

weight can vary between 1.3×10^6 and 6×10^6 (Saito et al., 1979). So, epiglucan from *Epicoccum nigrum* contain a backbone of ɓ-(1→3)-linked glucose residues, but now with two ɓ-(1→6) substitutions on average every three residues. However, lentinan from *Lentinus edodes* has ɓ-(1→3)-linked backbone, with two ɓ-(1→6)-side chains every five residues (Schmid et al., 2001), while the ɓ-(1→3)-linked backbone of pestalotan from *Pestalotia sp. 815* has three ɓ-(1→6)-side chains every five residues (Misaki et al., 1984). The degree of branching and the molecular weight of ɓ-glucan range between 0.2-0.33 and 100-200 KDa, respectively, and a triple-helix structure are strong effective biologically (Zekovic et al., 2005).

TECHNOLOGICAL FUNCTIONALITY

Solubility

The solubility is related to the structure of polysaccharides; they can be set regularly (insoluble) or irregularly (soluble) on the backbone or as side chains. The presence of a substitution group like COOH increases solubility (Elleuch et al., 2011).

The solubility of ɓ-glucans depends also on their degree of polymerization. Thus, ɓ-glucan is totally insoluble in water if degree of polymerization is superior to 100. According to its solubility properties, ɓ-glucan can be divided: firstly in (1) alkali insoluble, acetic acid insoluble (1→3)-ɓ-glucan; secondly in (2) alkali soluble (1→3)-ɓ-glucan; and thirdly in (3) highly branched (1→6)-ɓ-glucan (Zekovic et al., 2005). In the previous litteraure, soluble ɓ-glucans appear to be more immunostimulators than insoluble ones (Xiao et al., 2004). Recently, Mantovani et al. (2008) reported also that the insolubility property for most ɓ-glucans limits their application in human being.

Moreover, the solubility is affected by the oxidation treatment. Thus, Byun et al. (2008) studied the influence of gamma irradiation on the solubility of ɓ-glucan from black yeast (*Aureobasidium sp.*). They demonstrated that the water solubility of ɓ-glucan has increased following to an increase in the absorbed dose of gamma irradiation.

Hydration Properties and Oil Binding Capacity

Hydration properties of polysaccharides are evaluated by measuring water absorption, water holding capacity and swelling power. Water absorption is the kinetic of water uptake determined by a Baumann apparatus. This property gives detailed information about the polysaccharide, particularly its substrate pore volume. Water holding capacity is defined as the amount of water that is retained by 1 g of dry samples under specified conditions of temperature, time soaked and centrifugation. Swelling can be evaluated by the bed volume technique, determined by swelling the polysaccharides in water overnight, in a volumetric cylinder (Elleuch et al., 2011).

Possible ɓ-glucan application in food industry as a supplement for various purposes is already mentioned in literature. Water holding and oil binding capacities are beneficial properties for the use of these preparations in food like sausages and hamburgers. Water holding capacity of each preparation is essential for juiciness of a final product (Thammakiti et al., 2004). According to recent research, Petravić-Tominac et al. (2011) studied the water holding, swelling and oil binding capacities of ɓ-glucan isolated from spent brewerôs yeast. Other authors reported also that bakerôs yeast ɓ-glucan contains an interesting water holding properties (Thammakiti et al., 2004). Actually, polysaccharides insoluble in water can absorb and retain water, which contributes to their swelling (Hromádková et al., 2003).

Viscosity

Viscosity, resistance to flow, is defined as the ratio of shear stress to shear rate. Most polysaccharides solutions provide non-Newtonian flow and an increased shear rate can increase or decrease viscosity (Elleuch et al., 2011). It is important to study the rheological properties of ß-glucan isolated from different sources since its potential applications as food ingredient may affect the quality of final products. However, there has been a little works about the rheological properties of fungal ß-glucan such as yeasts and mushrooms. Thammakiti et al. (2004) found that the ß-glucan obtained from brewerôs yeast had higher apparent viscosity compared to ß-glucan from bakerôs yeast. They also reported that the viscosity of yeast ß-glucan suspensions decreases by heating and increases by cooling. Hence, yeast ß-glucan can be dispersed easily in cold and hot systems (Thammakiti et al., 2004). PetraviĆ-Tominac et al. (2011) examined the rheological properties using 1 and 2% suspensions of ß-glucan isolated from brewerôs yeast by different procedures. Other recent study focuses on the influence of gamma irradiation on the viscosity of ß-glucan purified from black yeast *Aureobasidium sp*. This study showed that Gamma irradiation produced significant changes in the viscosity of a 10 % (w/v) of ß-glucan solution. A significant decrease of viscosity was observed as the absorbed dose increases (Byun et al., 2008).

Antioxidant Properties

Antioxidants are natural substances which are able to protect living organisms from the attack of reactive radical species, and to reduce the risk of many diseases (Babincová and Sourivong, 2001). Although numerous researchers applied and studied natural antioxidants such as ascorbic acid (vitamin C) and Ŭ-tocopherol (vitamin E), recently growing attention has been paid to the antioxidants of polysaccharide origin (Xie et al., 2001). Among the representatives of this class

of antioxidants are (1→3)-ɓ-D-linked glucose polymers that occur as a primary component in the cell wall of fungi and bacteria (Bohn and BeMiller, 1995). Recent studies found that (1→3)-ɓ-D- glucan from the yeast *Saccharomyces cerevisiae* cell walls exhibits antioxidative activity in terms of free radical scavenging (Jaehrig et al., 2008). Besides, the antioxidant capacities of ɓ-glucan isolated from *Aspergillus* species are investigated. Thus, it has demonstrated that an increase in ɓ-glucan concentration increases the antioxidant activity at a maximum of 78.31% at 100 µg/ml of concentration. This value is higher than that of ascorbic acid which resulted in a maximum of 51.80% radical scavenging activity at the same concentration (Paulraj and Saravanan, 2012).

PRACTICAL APPLICATIONS IN THE FOOD INDUSTRY

The potential incorporation of ɓ-glucans as hydrocolloids in the food industry is based principally on their rheological properties, i.e. their gelling capacity and ability to increase the viscosity of aqueous solutions. Thus, ɓ-glucans was used as thickening agents to modify the texture and the appearance of food formulations. Besides, they may be used as stabilizers in the manufacture of low fat products such as salad dressings, cookies, ice creams, yoghurts and cheese (Laroche and Michaud, 2007; Lazaridou and Biliaderis, 2007). Recently, yeast ɓ-glucans have also been examined as a fat replacer in mayonnaise and other food products (Worrasinchai et al., 2006).

BIOLOGICAL ASPECTS

Immuno-Regulatory Effect

Recently, in vitro and in vivo studies in animals and humans show that ß-glucans derived from fungi and yeasts have immunomodulting properties. The most often investigated are their effects on leukocyte activity (Petravić-Tominac et al., 2010).

The immune-regulatory activities of ß-glucan depend mainly on its ability to stimulate or inhibit macrophage release of cytokines involved in immune system or to modulate macrophage phagocytosis (Bohn and BeMiller, 1995; Gardiner, 2000; Vetvicka et al., 2002). For example, in vivo study in animals showed that orally administrated ß-glucan activates white blood cells like macrophages, granulocytes and monocytes (Vetvicka et al., 2002). Yeast ß-glucan has shown especially high immune-modulatory activity affecting the immune response of the host (Petravić-Tominac et al., 2010). Thus, ß-glucans from yeast *Candida albicans* activate macrophages and induce interleukin (IL-6) and tumor necrosis factor (TNF) in vitro. It has demonstrated that ß-glucan from both yeasts and mushrooms have similar ability in the induction of macrophages and chemotactic factor (Mantovani et al., 2008).

Anti-Carcinogen Effect

Fungal ß-glucans may exert numerous effects on cancer cells and reduce preventatively the overall risks of cancer. Thus, their mechanisms seem to be complex and the regulation by ß-glucans of the signalling pathways of tumour production involves many key elements (Chen and Seviour, 2007).

Several animal experiments have revealed the remarkable effects of some fungal ß-glucans on a range of tumours (Chen and Seviour, 2007). Many human clinical tests have also demonstrated possible treatment benefits. In fact, lentinan, schizophyllan and PSK are approved in Japan for clinical use in human cancer treatment (Mizuno et al., 1999). In literature, it has been reported 48

publications about clinical trials using PSK which has been successful in postoperative treatment of resectable cancer in humans, increasing survival rates (Chen and Seviour, 2007). Lentinan has also been used in similar clinical trials and been shown to prolong survival times of humans with gastric cancer from 199 to 297 days of the medium survival period (Nakano et al., 1999). Furthemore, ɓ-(1→6)-glucan derived from *Agaricus blazei* basidiocarps induced apoptosis or programmed cell death in human ovarian cancer HRA cells (Kobayashi et al., 2005).

Anti-Infectious Effect

The major current problem in surveillance infectious diseases is antibiotic resistance. For this reason, some fungal ɓ-glucans are effective against pathogenic microbes, by acting through many different immune-regulatory mechanisms (Chen and Seviour, 2007). Several works and clinical tests have showed that soluble ɓ-glucans ameliorate resistance to bacterial infection (Petraví-Tominac et al., 2010). Vetvicka et al. (2002) showed that orally administration of insoluble yeast ɓ-glucan (2-20 mg/kg) gave a maximal antrax-protective effect in mice, without using antibiotics.

ɓ-(1→3) (1→6)-glucan enhances resistance to many diseases increasing leucocytes anti-infective activity in human blood, without increasing the inflammatory cytokine production. Zymosan from *Saccharomyces cerevisiae* appears to have antimicrobial activity in mice, against *Staphylococcus aureus* resistant to antibiotics. ɓ-glucan administration helps to eliminate the bacteria and enhances the number of monocytes and neutrophils. Studies in vitro on rats showed the synergism of ɓ-glucan and antibiotics (Petraví-Tominac et al., 2010). Additionally, ɓ-glucan from *Saccharomyces cerevisiae* is also effective against viral infections. Thus, it increased the immune response in human administered the human immunodeficiency virus (HIV) vaccine by

activating Th cell-mediated immunity by activation of the complement system and interferon gamma (Chen and Seviour, 2007). The even ɓ-glucan also reduced viral nucleic acid levels in cells of pigs infected with influenza virus, and contributed to increases in their interferon gamma and nitric oxide levels (Jung et al., 2004).

Lowering of Cholesterol

Yeast ɓ-glucans seem to be effective in reducing blood cholesterol concentrations, although the mechanism by which this occurs is still unclear (Chen and Seviour, 2007; Petravić-Tominac et al., 2010). Several human studies showed that ɓ-glucans are safe, powerful and inexpensive way to reduce blood cholesterol and high lipid level, and in turn out, to prevent high blood pressure and arteriosclerosis (Petravić-Tominac et al., 2010). Besides, the studies of the hypocholesterolemic effect of ɓ-glucans in vivo showed that cationic ɓ-glucans have a stronger effect in lowering cholesterol compared to the native form. However, sulphated ɓ-glucans are less effective in reducing cholesterol levels due to reduced viscosity (Mantovani et al., 2008). ɓ-glucans have been shown to decrease LDL cholesterol and increase HDL to alleviate possibly dyslipidemia and reduce cardiovascular risks (Kapur et al., 2008).

Blood Pressure

Some fungal ɓ-glucans may control blood pressure. Tam et al. (1986) found that the decrease of blood pressure in rats is induced by an intravenous infusion of an aqueous extract of *Pleurotus sajor-caju* mycelium. However, in genitically deficient rats with spontaneous hypertension, a diet containing 5% maitake from *Grifola frondosa* had the same effect (Kabir et al., 1987). Additionally, *Pleurotus cornucopiae* from Tamogi-take mushroom which decreased blood

pressure in rats with spontaneous hypertension was shown to be D-mannitol (Hagiwara et al., 2005).

The possible use of ɓ-glucans in reducing hypertension is not yet clear, and as with several of the biological effects discussed here, now appears the time to orient our efforts to evaluating more carefully purified, and structurally characterized individual fungal ɓ-glucans (Chen and Seviour, 2007).

Diabetes

Many fungal ɓ-glucans may also reduce blood glucose concentrations after eating, possibly by delaying stomach emptying so that glucose is absorbed more gradually (Chen and Seviour, 2007). Kiho et al. (1995) showed that orally ingestion of *Tremella mesenterica* and *Tremella auantia* both reduced blood glucose concentrations in induced diabetic rats. Kiho et al. (2000) reported also that *Phellinus baummi* provided hypoglycaemic effects in stretotozotocin-induced diabetic rats. In genetically diabetic mice fed 20 % whole mushroom maitake powder prevented an increase in blood glucose levels by increasing insulin sensitivity (Mayell, 2001). However, no purified fungal ɓ-glucans whose chemical structure has been completely characterized has yet been examined against diabetes (Chen and Seviour, 2007).

Wound Healing

It is known that macrophage activities stimulated by yeast ɓ-glucans from *Saccharomyces cerevisiae* play important role in wound healing and reduce scar tissue levels after surgey or trauma, as demonstrated by both animal and human studies (Mayell, 2001). Based on the experimental wounds, the rate of repair was faster for the ɓ-glucan than for the polysaccharides carrageenan, levan, inulin, dextran and starch. In humans, a topical application of ɓ- (1→3)-

glucan and an antibiotic appears to be effective for wound healing and hence improves epithelialization (PetraviĆ-Tominac et al., 2010). Some recent researchers investigated the applications of ß-glucans in healing of burns and topical damages. Their topical application reveals a greater number of macrophages and stimulates the formation of granulomas (Wei et al., 2002). Furthermore, ß-glucans stimulates also procollagen mRNA and collagen biosynthesis, together with increased NF-1 in human dermal fibroblasts (Wei et al., 2002).

PREBIOTIC APPLICATIONS

The concept of prebiotics is based on the premise that there are microorganisms in the intestinal tract which have a beneficial health effect on the host. Among these effects, there are lactose digestion enhancement, cholesterol reduction, antimicrobial effects and immune system stimulation (Laroche and Michaud, 2007). Several publications have concentrated on the prebiotic applications of ß-glucan which can improve the growth of lactic acid bacteria from genus *Lactobacillus* and *Bifidobacterium*, microorganisms living in intestinal tract that have healthy effect in human (Gardiner, 2000). Thus, yoghurt is milk which has been transformed to a solid by the fermentative action of microorganisms like *Lactobacillus delbrueckii ssp. bulgaricus* and *Streptococcus salivarus ssp. thermophilus*. Latters don't have the ability to colonize the intestinal tract in large amount since they are not resistant to the gastric acidity and bile salts. Hence, the use of prebiotic foods in the diet may enhance the population of beneficial bacteria (Laroche and Michaud, 2007).

CONCLUSIONS

Fungual ɓ-glucans having functional properties as well as biological activities are used as supplement in food and drugs industries for various purposes. In this review, the physico-chemical structure and technological functionality of fungal ɓ-glucans are reported. In fact, they are affected by different isolation process of ɓ-glucan. Furthermore, ɓ-glucans are classified as biological response modifiers and immunostimulator properties. Thus, fungal ɓ-glucans are involved in treating diseases like cancer, a range of microbial infection, hypocholesterolaemia, diabetes and wound healing. Studies of fungal ɓ-glucans mainly yeast ɓ-glucans seem to be important substances in the promotion of human health, but further clinical trials are still necessary.

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Table 1 Effect of different extraction processes on ɓ-D-glucan purity and yield

Glucan (G)	Purity	Yield	Extraction processes	References
G1	92[a]	10.4	Alkaline extraction	Xiaozhong et al. (2000)
G2	55	8.4	Alkaline-acid extraction	Saowanee et al. (2004)
G3	59	8.4	Homogenization-alkaline-acid	Saowanee et al. (2004)
G4	nd	3.7	Sodium hypochlorite-dimethyl sulfoxide	Ohno et al. (2001)
G5	nd	22.9[b]	Autolysis-sodium hypochlorite oxidation	Yajun et al. (2003)
G6	85-83	26-25[b]	Mild enzymatic isolation	Freimund et al. (2003); Jaehrig et al. (2008)
G7	93	11.2	Autolysis-homogeneization-protease treatment	Liu et al. (2008)
G8[c]	79	nd	Alkaline-acid extraction	

All data represented weight ratios. « nd » meant not determined.

[a] Determination following to phenol-sulfuric acid method.

[b] Compared to dry weight of yeast cell wall.

[c] Referring to commercially available D-glucans from Zhuhai, China.

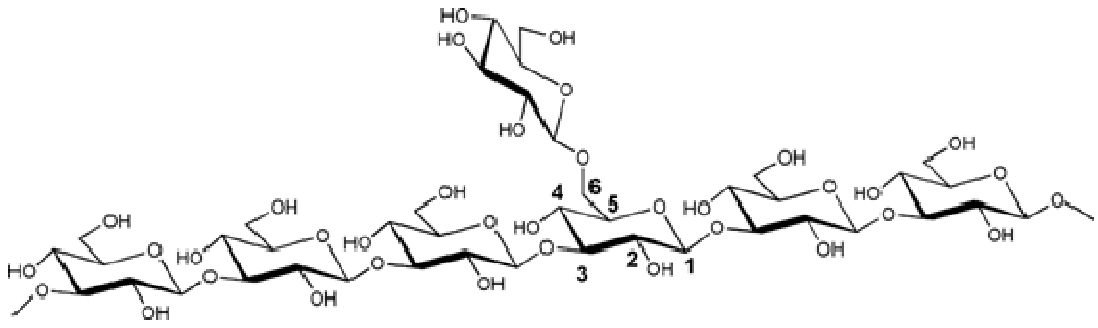

Figure 1 Chemical structure of (1Ÿ 3)-ɓ-D-glucan with (1Ÿ 6)-linked branches of glucopyranosyl units (Freimund et al., 2003)