Biological Effects of Yeast β-Glucans

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Summary

β-Glucans are glucose polymers that naturally occur in yeasts, molds, algae, mushrooms, bacteria, oats and barley. Immunostimulation is one of the most important properties of β-glucans. They are classified as biological response modifiers and because of their biological activities they can be used in human and veterinary medicine and pharmacy. Additionally, β-glucans show interesting physicochemical properties and therefore could be applied in food and feed production as well as in cosmetic and chemical industries. Immunomodulation by β-glucan, both *in vitro* and *in vivo*, inhibits cancer cell growth and metastasis and prevents or reduces bacterial infection. In humans, dietary β-glucan lowers blood cholesterol, improves glucose utilization by body cells and also helps wound healing. β-Glucans work, in part, by stimulating the innate immune mechanism to fight a range of foreign challenges and could be used as an adjuvant, in combination with anti-infective or antineoplastic agents, radiotherapy, and a range of topical agents and nutrients. The structure of β-glucans depends on the source they are isolated from. Native β-glucan molecules can be linked and branched in several ways. Biological properties of different β-glucan molecules are dependent on their molecular structure. Some authors claim that the β-(1→3),(1→6)-glucan derived from yeast *Saccharomyces cerevisiae* produce the highest biological effects. Thus, in this review the β-glucans and their metabolic activity are discussed, with the special accent on those isolated from yeast. Other possible β-glucan applications, directed to cosmetic production, non-medical application in pharmaceutical and chemical industry, are also discussed.

Key words

β-glucan, biological activity, immunomodulation, yeast

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Introduction

β-Glucans are polysaccharides of glucose that can be produced by many prokaryotic and eukaryotic organisms. This group of compounds has several beneficial properties and because of that they have found a wide variety of uses in human and in veterinary medicine, pharmaceutical, cosmetic and chemical industries as well as food and feed production (Zeković et al., 2005; Laroche and Michaud, 2007). The properties of various β-glucans beneficial for food industry are discussed elsewhere (Zechner-Krpan et al., 2009).

β-Glucan activates the immune response through the immune cells, called macrophages, showing various therapeutic effects. In recent years β-glucan has been in a focus of intensive research, primarily because it is a safe and very potent biological response modifier (BRM) (Bohn and BeMiller, 1995; Gardiner, 2000). Use of β-glucans is beneficial in fight against bacteria, viruses, parasites and fungus (Bohn and BeMiller, 1995; DiLuzio, 1983).

Immunomodulation by β-glucan was confirmed both *in vitro* and *in vivo* in numerous animal and human studies involving a wide range of tumors, including breast, lung and gastrointestinal cancers. The immunomodulating and cancerostatic properties make β-glucan one of the substances with a great potential in the ongoing fight against cancer (DiLuzio, 1983; Laroche and Michaud, 2007; Novak and Vetvicka, 2008). At the same time, only a few drugs have similar advantages as β-glucan. In Japan, β-glucan is used as natural immunostimulant for cancer treatment since 1980. Numerous clinical trials (Mantovani et al., 2008) are currently under study in the USA and several European countries. β-Glucans are also effective against allogeneic, syngeneic, and even autochthonous tumors (Adachi et al., 1987; Chichara et al., 1987; Nanba and Kuroda, 1987).

Many patients worldwide are suffering from various diseases such as infections, cancer, hematological disorders, chemotherapy, surgery, radiation, etc. They have a compromised immune system which could be partially the result of malnutrition (Gardiner, 2000; Laroche and Michaud, 2007). In such cases, use of β-glucan would be beneficial.

β-Glucans have also antioxidant attributes and some of them have demonstrated wound healing activity (Wagner et al., 1988; Ohno et al., 1990; Ross et al., 2004; Salvador et al., 2008).

Both soluble and insoluble (particulate) β-glucans could find their medical applications. Oral administration of microparticulate preparations is suitable to consumers and the effectiveness of orally applied preparations was proven (Vetvicka et al., 2002).

β-Glucan, taken orally, passes through the stomach virtually unchanged, because it is acid-resistant. Furthermore, intestines lack enzymes that break it down to molecules that can be absorbed through the intestinal wall (Ber, 1997). There are cellular receptors and plasma binding proteins in human bodies that are specific for β-glucan (Ross et al., 1999). Glucan receptor activity has been identified on both immune and non-immune cells, including monocytes, macrophages, neutrophils and Langerhans cells, eosinophils, natural killer (NK) cells, endothelial cells, alveolar epithelial cells and fibroblasts (Brown and Gordon, 2003). It is known that (1→3)-β-glucano-heptasaccharide is the smallest fragment that could be bind on β-glucan receptors, such as dectin-1, CR3 complement receptor, glucan receptor on neutrophils *etc.* (DiLuzio, 1983).

Most β-glucans are insoluble resulting in limited application in humans. When injected, such microparticulate preparations cause granuloma formation, inflammation, pain, *etc.* (Vetvicka, 2001). Water-soluble β-glucan preparations, obtained by chemical derivatization (Williams et al., 1991), would have several advantages in intravenous application. The length of such obtained soluble glucan molecules could be further modified using enzymes or ultrasonic treatment (Machova et al., 1995; Šandula et al., 1999).

β-Glucan origin, structure and isolation

β-Glucan is a biopolymer of glucose that is widely distributed throughout the biosphere (Ruiz-Herrera, 1991). Various types of β-glucans are commonly found in baker's and brewer's yeast, but also in certain mushrooms, molds, algae and in the bran of oats and barely. β-Glucans derived from various sources have similar structure, but small structure differences influence their biological activity.

The innermost layer of the yeast cell wall is built of β-glucans, proteins, mannan and small amounts of chitin (Vetvicka, 2001). So, yeast, as a well known microorganism that is used in biotechnology since ancient times, is a good source of β-glucan. Structure and composition of the yeast cell wall depends on yeast species and strain as well as on culturing conditions (Stone and Clarke, 1992; Klis et al., 1997; Lipke and Ovalle, 1998; Nguyen et al., 1998; Osumi, 1998; Kath and Kulicke, 1999; Aguilar-Uscanga and Francois, 2003). The β-glucan component in the *Saccharomyces cerevisiae* cell wall, with the function of maintaining the rigidity and shape of the cell, is often named simply glucan or yeast glucan. That polysaccharide consists mainly of a linear central backbone of D-glucose linked in the β-(1→3) position with glucose side branches (β-(1→6)-linkage) of various sizes, which occurs at different intervals along the central backbone (Gardiner, 2000). Triple helical multimer provides structure and support to the yeast cell wall.

The native structure of β-glucans as well as their biological activities could be changed during isolation if harsh procedures are applied. Primary structure, solubility, degree of branching and molecular weight, as well as the charge of their polymers and structure in aqueous media, are responsible for biological activity of β-glucan. Solubility of β-glucan increases as degree of branching decreases, so classification of glucans can be made according to their solubility properties.

The available commercial products containing glucan from various sources have several activities due to mentioned differences in structure and conformation (DiLuzio, 1983; Mueller et al., 2000).

During the complex purification process of β-(1→3),(1→6)-glucan from cell wall fraction of baker's yeast *Saccharomyces cerevisiae,* other cell components like proteins, lipids, nucleic acids, minerals and mannans are removed to a large extent (Lee et al., 2001; Hunter et al., 2002). Some of these impurities may induce undesirable side effects (protein induced allergies are sometimes mentioned as a possibility, although it is very rare). It is more

important that impurities can interfere with the recognition of the β-(1→3),(1→6)-glucan active molecule, so the removal of those components is desirable. Depending on the isolation procedure native structure of β-glucan could be degraded, resulting in its changed biological activity.

Hunter et al. (2002) developed the method for the preparation of immunologically active, homogenous, non-aggregated β-glucan particles of appropriate dimensions for macrophage immunostimulation. Insoluble yeast cell wall material was subjected to alkaline and acidic treatment followed by sonication and spray-drying of β-glucan particles.

β-Glucans from various sources posses different characteristics and consequently many interesting properties, so immunopotentiation is only one of them (Zeković et al., 2005). Branched or linear (1→4)-glucans have limited activity and β-glucans with a 1,3-configuration with additional branching at the position C-6 of the 1→3 linked D-glucose residues have the highest immunostimulating activity (Vetvicka, 2001; Freimund et al., 2003).

Alternative biological sources for the preparation of β-glucan are barley, oats, mushrooms, algae and bacteria. Those glucans have different structures and consequently different biological activities. Commercial β-(1→3)-glucans, isolated from bacteria or algae, have no poly-branching (Kedzierska, 2007).

The mechanism of β-glucan biological activity is not yet fully elucidated. There are various opinions which molecular structure could reach the physiological effect (DiLuzio, 1983; Tokunaka et al., 2000). Several physicochemical factors (primary structure, conformation, charge of polymers, solubility, particle dimensions) are important for β-glucan biological activity (Tzianabos, 2000; Vetvicka, 2001, Hunter et al., 2002). Structure essential for biological activity of glucans has not yet been explained in details, but some authors consider that triple helix is the most active conformation (DiLuzio, 1983; Hromádková et al., 2003) while other authors claim that helical structure has no influence on activity at all (Kulicke et al., 1997; Ha et al., 2002).

Vetvicka and Vetvickova (2007) compared the basic immunological activities of a group of commercially available β-glucans, chosen among those heavily advertised, commonly available and easily obtained in the USA, Europe, Southeast Asia and Japan. Both soluble and insoluble glucans from various sources, including yeast, mushrooms and cereals were included in their study. The tested biological reactions (phagocytosis, surface markers on splenocytes, cytokine synthesis, and stimulation of antibody response) showed that some of the commercial glucans had surprisingly low activity and differed in biological effects. According to their results, it is imperative to find a β-glucan from a solid vendor that is able to back the claims with solid scientific data.

Although some β-glucans lost their biological activity during isolation due to harsh procedures applied they could still have other beneficial properties useful for non-medical application in other areas, as will be discussed later.

Enhancement of the Immune System

It is believed that the most important biological activity of β-glucan is its ability to stimulate the immune system, since many of its other effects are related to this activity (Bohn and BeMiller, 1995). Immune system is unbelievable complex in humans and is designed to protect us from attack by pathogenic microbes or harmful effects of environmental toxins and carcinogens (Vetvicka and Yvin, 2004; Brown and Gordon, 2005) that may cause harm or disease. The immune system is primary natural defense against any disease and even aging. But, glucans are not synthesized by human body so they have to be recognized by immune systems, inducing immune responses (Brown and Gordon, 2005).

In vitro and *in vivo* studies in animals and humans show that β-glucans derived from fungi and yeasts have immunomodulating properties. Most frequently evaluated are their effects on leukocyte activity. Immune response is influenced by both parenteral and enteral administration of β-glucan (Volman et al., 2008).

β-Glucan nutritionally promotes regeneration of immune system. Some of publications have stated that β-glucan is a fuel for immune system to enable a faster, better, smarter and extended response. For that purposes insoluble yeast β-glucans, with particles of 1-2 μ have to be used (Hunter et al., 2002; Jordan et al., 2002).

The immunoregulatory activities of β-glucan relate mainly to its ability to stimulate or inhibit macrophage release of cytokines involved in immune system control or to modulate macrophage phagocytosis (Bohn and BeMiller, 1995; Gardiner, 2000; Vetvicka et al., 2002; Vetvicka et al., 2007). *In vivo* study in animals has shown that orally administered β-glucan activates white blood cells, such as macrophages, granulocytes and monocytes, responsible for defense against infections, and supports the repair of damaged tissues in the body (Vetvicka et al., 2002; Rice et al., 2002). In this regard yeast β-glucan with (1→3) (1→6)-glycosidic linkage has demonstrated particularly strong immunomodulatory activity influencing the immune response of the host and is often described as biological response modifier (DiLuzio, 1983).

All cells involved in immune reactions originate from common precursors – stem cells originating from bone marrow (Kougias et al., 2001; Rice et al., 2002). So, β-glucan stimulates the production of precursor cells in bone marrow, resulting in a bloodstream flow of new immunocytes into the various lymphoid organs throughout the body. The increased amount of immunocytes in circulation means increased protection from potential invaders. It is important particularly in case of extreme stress (e.g. in case of cancer), when immune system is exhausted by treatments such as irradiation and chemotherapy (Kougias et al., 2001; Hong et al., 2003). β-Glucan did not show any genotoxic and/or clastogenic damage, so it may become an important adjuvant in chemotherapy while it has capacity to diminish adverse effects of drugs (Oliveira et al., 2006).

Medical applications

β-Glucan, derived from yeast, could have numerous applications in curing of patients by improving their immune system. Among the most attractive properties of β-glucans are activities against many types of cancer and infectious diseases. They can also prevent negative effects of radiation exposure, septic shock, allergic rhinitis, elevated blood cholesterol and fatty acids and help in wound healing, arthritis etc.

Cancer

Cancer cells have mechanisms to evade the body's defense and make them difficult to destroy. These cells have changed their normal characteristics and constantly attack the body in effort to either overcome the immune system that, after some time, becomes exhausted, or escape recognition and subsequent destruction by the natural defense mechanisms. Cancer overpowers the immune cells, including macrophages, white blood cells, dendritic cells and NK cells.

β-Glucan has influence on NK cells and macrophages, which are the first line of defense and protect the body against any type of invading cells – including cancer cells. NK cells represent a special subtype of "bloodthirsty" lymphocytes, with a function to specifically recognize and kill tumor cells. In healthy bodies, these defender cells successfully manage to fight the invading pathogens and tumor cells. But many factors, such as stress, allergies, pollutants and age, have negative effects on the strength of the natural defensive reactions (Ross et al., 1999). Under normal conditions, the immune system is able to overcome the invasion of cancer cells, but at extreme conditions, it is not strong enough. Unfavorable factors like physical and mental stress, UV-radiation and an unbalanced diet may impair the immune functions of the body. So, when the immune system is compromised, an immunomodulator, such as β-(1→3)(1→6)-glucan can compensate for such factors, and help the immune cells. β-Glucan binds to the surface of macrophages and NK cells, interacting with the surface molecules, and in that way it triggers activation processes. As a result of those processes activated killer cells circulate in the body, seeking and at the end destroying their preferred targets (Volman et al., 2008).

Since 1980 many studies have pointed out the positive effects of β-glucan in tumor therapy (Morikawa et al., 1985; Hong et al., 2003; Gelderman, 2004). In some studies it was demonstrated that branched β-glucans can enhance the effect of chemotherapy with cyclophosphamide (Thompson et al., 1987).

There is a growing amount of data supporting the ability of yeast β-glucans to benefit immune function and the body's efforts to protect itself from disease. Preclinical experiments have shown that a commercial soluble yeast β-glucan product, derived from the cell walls of baker's yeast *Saccharomyces cerevisiae,* in combination with certain monoclonal antibodies or cancer vaccines improves in long-term survival better than monoclonal antibodies alone (Vetvicka et al., 1996; Ross et al., 1999).

Another β-(1→6) branched β-(1→3)-glucan was purified from the cell walls of *Saccharomyces cerevisiae* (Hong et al., 2003). The antitumor activity is caused by a killing mechanism involving neutrophils that are primed with the mentioned β-glucan preparation and that are not normally involved in the fight against tumor. When neutrophils bind to tumor cells, the β-glucan preparation allows them to recognize cancer, as it was yeast pathogen and that system provides killing. As a matter of fact, β-glucan engages neutrophils in the fight against tumor cells, enhancing synergistically the effectiveness of monoclonal antibodies and vaccines through a different killing mechanism. The β-glucan improves the effects of all complement-activating monoclonal antibodies tested, including breast, liver and lung cancer. Complement-antibody complexes kill the tumor cells. The same authors (Hong et al., 2004) also demonstrated that this action is effective against some kind of cancers when used in combinations with specific monoclonal antibodies.

The receptor on the surface of innate immune cells is named Complement Receptor 3 (CR3 or CD11b/CD18). It is responsible for binding to fungi or yeast, allowing the immune cells to recognize them as "non-self" (Hanaue et al., 1989; Vetvicka et al., 2002; Ross et al., 2004; Li et al., 2006) and it has two binding sites. The first site of this receptor is responsible for binding of soluble blood protein C3 (or iC3b), which is attached to pathogens that specific antibodies have targeted. The second site binds to carbohydrate on yeast or fungal cells that allows an innate immune cells to recognize yeast or fungi as being "non-self" (Hong et al., 2003; 2004).The innate immune cell will destroy the yeast or fungi only in case when both of these receptor sites are simultaneously occupied. It was also discovered that fragment of the tested β-glucan specifically binds to the second CR3 receptor site on neutrophils. β-Glucans are bound by CR3 and, in concern with target-associated complement fragment iC3b, elicit phagocytosis and killing of yeast (Ross et al., 2004).

Weitberg (2008) reported a phase I/II trial of β-(1→3)(1→6)-D-glucan in the treatment of patients with advanced malignancies receiving chemotherapy. The results leaded to conclusion that β-glucan is well tolerated in cancer patients receiving chemotherapy, and may have a beneficial effect on hematopoiesis in these patients.

Salvador et al. (2008) showed in their recent study how significantly can β-glucan improve the therapeutic efficacy on cancer mediated by Bevacizumab, recombinant IgG1 humanized monoclonal antibody against vascular endothelial growth factor (VEGF). The cooperation of antibodies with β-glucan is more active that either irradiation or chemotherapy. Compared to traditional treatment of cancer, this type of treatment has no negative side effects.

Some researchers have proved that the oral form of β-glucans have similar protective effects against cancer as injected preparations (Hanaue et al., 1989; Vetvicka et al., 2002; Rice et al., 2005). It was also found, that orally taken β-glucan significantly increases proliferation and activation of monocytes in the peripheral blood of patient with advanced breast cancer (Demir et al., 2007). The recommended dosages differ, from 300-3000 mg daily, depending on characteristics and immunostimulatory potential of applied preparations. In treatment of cancer or another serious health conditions, Mason (2001) suggests an intake from 300-500 mg of yeast β-(1→3)(1→6)-glucan daily during one year and 100 mg daily afterwards.

In vivo growth inhibition of cancer cells in mice was obtained by insoluble orally administered yeast β-glucan used in concentration of 28.4 mg/kg for 21 consecutive days (Vetvicka et al., 2002), without using any other treatment.

An interesting study of orally applied particulate yeast β-glucan in treatment of various cancer types was described by Ueno (2000). Relapse was not observed in glucan-treated patients compared to 22% of relapse in untreated group. Even the treatment of patients in terminal phase of illness showed impressive results by mortality decreasing.

Prevention of infection

One of the most important biological activities of β-glucan is prevention of bacterial infection. It can elevate the general level of resistance to pathogens and reduce the risk of infections. Numerous studies and clinical trials have proved that soluble β-glucans improve resistance to bacterial infection (Kernodle et al., 1998; Dellinger et al., 1999).

Orally-administered insoluble yeast β-glucan (2-20 mg/kg) provided a maximal antrax-protective effect in mice, without using antibiotics (Vetvicka et al., 2002).

β-(1→3)(1→6)-glucan increases resistance to many diseases enhancing leukocyte antiinfective activity in human whole blood, without increasing the inflammatory cytokine production (Wakshull et al., 1999). *Saccharomyces cerevisiae* β-glucan extract was shown to have antimicrobial activity in mice, against *Staphylococcus aureus* resistant to antibiotics. β-Glucan administration helps in the elimination of bacteria and increases the number of monocytes and neutrophils. *In vitro* experiments on rats improved the full action of β-glucans and antibiotics against *Escherichia coli* and *Staphylococcus aureus* (Tzianabos and Cisneros, 1996). It is an example of synergism of β-glucan and antibiotics.

Special attention has been paid to post-surgical infection, which occurs in 25-27% of cases. For that reason, practical human clinical trials of β-glucan impact for reducing the incidence of infection were studied (Dellinger et al., 1999). The results of clinical trials demonstrated that β-glucan therapy reduce postoperative infections by 39%. Studying the addition of injectable form of β-glucan in humans, most researchers have concluded that yeast β-glucan promotes phagocytoses and subsequent killing of phatogenic bacteria (Tzianabos and Cisneros, 1996; Kernodle et al., 1998; Dellinger et al., 1999). The *in vivo* study on rats showed that systemic β-glucan treatment would result in enhanced migration of neutrophils into a site of inflammation and improve antimicrobial function (LeBlanc et al., 2006).

The similar trials have been done with the orally consumed β-glucan. The studies proved that oral consumption of β-glucan pills are as effective as the injections in improvement of natural immunity (Vetvicka et al., 2007).

Some researchers investigated the ability of yeast β-glucan to reduce septic infection using *in vivo* models. Onderdonk et al. (1992), in their early studies, found that mice provoked with *Escherichia coli* or *Staphylococcus aureus* bacteria were protected against septic infection if they were injected by PGG-glucan 4-6 hours before the incubation. On the other hand, Kernodle et al. (1998) showed that preventive amounts of yeast β-glucan prior to infection with *S. aureus* inhibited the sepsis in a guinea pig. Additional research work supports the theses that yeast β-glucan reduces septic shock by killing bacteria in blood (DiLuzio et al., 1979; Kulicke et al., 1997; Liang et al., 1998; Tzianabos et al., 1998; Chen and Seviour, 2007).

Lowering of cholesterol

Yeast β-glucan is Generally Recognized as Safe (GRAS) product, which can be used as food additive. Additionally, β-glucans from various sources have effective cholesterol and lipids lowering properties (Mason, 2001). Worldwide human studies have demonstrated that β-glucan is a safe, powerful and inexpensive way to lower blood cholesterol and high lipid level (Nicolosi et al., 1999; Bell et al., 2001; Keogh et al., 2003; Steriti, 2007). Lowering the blood lipids and total and LDL cholesterol is the best way to prevent high blood pressure and arteriosclerosis.

Natural preparations of β-glucans like oat milk, barley or yeast β-glucans preparations added to juicy drinks could be used instead of expensive drugs with dangerous side-effects (Naumann et al., 2006).

Wound healing

It is also known that macrophage activity plays a main role in wound healing, from surgery or trauma. There have been numerous clinical studies with soluble yeast β-glucan and the whole glucan particles. In both animal and human studies, therapy with β-glucan showed improvements like reduced mortality, lowered infection, and stronger tensile strength of scar tissue (Browder et al., 1990; Portera et al., 1997). Based on these results they have concluded that immunomodulators that enhance macrophage activity have positive effects on collagen biosynthesis in the healing wounds in experiments using animal and human models.

These properties are of special advantage in injured diabetic people, who have increased susceptibility to infection, frequent occurrence of ulcers and delayed wound healing which is in diabetic organism caused by neuropathy, vascular changes and impaired cellular response to injury. Berdal et al. (2007) demonstrated, in experiments with diabetic mice, that macrophages are crucial in improvement of wound healing. They concluded that the structurally well-defined macrophage stimulant (like curdlan, glucan isolated from bacterium *Alcaligenes faecalis*) has a significant wound healing effect. They also suggest that such immunomodulators can be applied for wound healing in diabetic patients.

A rapid repair of experimental wounds with topical application of a β-glucan from yeast was explained by Lloyd et al. (1998). Experimental data showed that the rate of repair was faster for the β-glucan than for the polysaccharides carrageenan, levan, inulin, dextran and starch and inorganic talcum powder. In humans, a topical combination of β-(1→3)-D-glucan and an antibiotic as an adjuvant for wound-healing applications seems to be working, which improves epithelialization. One of the topical glucan applications is treatment of decubitus wounds (Ber, 1997).

β-Glucan was recently applied in healing of burns and topical damages. Glucan treated wounds showed a higher number of macrophages in the early, inflammatory stage of repair. Its topical application also stimulates the formation of granulomas, collagen deponing and reepithelialization, and at the same time it increases the elasticity of treated wound (Wei et al., 2002; Pillai et al., 2005).

Dellate et al. (2001) described the application of temporary coverage for partial thickness burns, which combines β-glucan with collagen in a meshed reinforced wound dressing, named beta-glucan collagen matrix (BGC). β-Glucan stimulates macrophages, which are vital in inflammatory phase of healing, providing phagocytosis and secretion of chemokines that promote the formation of new tissue. BGC is temporary wound dressing intended for the management of partial-thickness burns, donor

sites, and other shallow wounds. It is applied to the wound immediately after cleansing and debridement, and BGC matrix may remain on the wound as a barrier or protective dressing until healing is complete. This method is applied in wound healing of adults and children. Advantages are in avoidance of daily dressing changes, fluid loss and infections, as well as in pain reduction, improved healing, and better scar appearance (Delatte et al., 2001).

Lee et al. (2003) described a possibility of β-glucan application as a component of so called bio-artificial skin, composed of gelatin and β-glucan. This treatment showed to be useful to promote wound healing.

Other therapeutic applications

Many other therapeutic applications of β-glucans have been published. One of those is their use as a radioprotective agent (Patchen et al., 1987; Ostroff and Ross, 2004). Indeed, preparations of soluble β-glucans are able to protect blood macrophages from free radical attack during and after the radiation allowing the cells to continue their function in the irradiated body. Hematopoietic activity was demonstrated with yeast β-glucan as granulocyte monocyte-colony stimulating factor (GM-CSF). Mice exposed to γ-radiation exhibited a significantly enhanced recovery of blood leukocyte, platelet and red blood cells if treated by soluble β-glucan (Patchen and MacVittie, 1987).

β-Glucans could also be used to prevent some digestion problems, like constipation and stomach troubles. β-Glucans as prebiotics can improve the growth of lactic acid bacteria from genus *Lactobacillus* and *Bifidobacterium*, microorganisms living in intestinal tract that have healthy effect in humans (Gardiner, 2000).

Allergic rhinitis, which is caused by allergic inflammation of the nasal mucosa, could be decreased by β-glucan treatments. Based on these results Kirmaz et al. (2005) suggested that β-glucan may have a role as an adjunct to treatment with allergic diseases. On the other hand, Kogan et al. (2005) demonstrated that yeast derived-glucan can reduce the oxidative tissue damage during progress of arthritic disease.

Non-medical applications

Cosmetics

Last few decades β-glucans were introduced in some non-clinical applications as aging prevention and moisture retention agents in cosmetics. β-Glucan can find its application in cosmetic production, in creams and lotions for sensitive and irritated skin (Wheatcroft et al., 2002). Preparations isolated from oat, containing β-glucan, are used for skin irritated by different causes. Their characteristics are fast skin hydration and soothing of redness and irritation (Pillai et al., 2005). Antiirritant effect of β-glucan was also shown in combination with otherwise severe, irritation-causing levels of lactic acid (Ber, 1997).

One of the solutions for maintaining skin in health is a supplementation with biologically active compounds. Cosmetic application of β-glucans is one of its potentially profitable uses. β-Glucans are very active for improving and preventing skin diseases or irritation, so they are usually used due to their moisture retention action, aging prevention and skin injury restoring properties. Moreover, they have radio-protective effects, antioxidant properties and free radicals scavenging capabilities (Takahashi et al., 1978; Patchen et al., 1987). Some authors describe β-glucan properties in promoting of hair regeneration and growth by activation of hair follicles (Donzis, 1993; Bohn and BeMiller, 1995).

In most skin formulas β-glucan is used for its moisture retention capability and providing proper applicability. They are also used as stabilizers in emulsified cosmetic or in formulations of gel products obtaining pleasant texture (Gardiner, 2000).

An interesting effect of topical application of β-glucans was observed in non-wounded skin with some signs of ageing. Revitalizing, such as reducing number, depth and length of wrinkles, as well as thickening and reducing roughness and dryness of the skin, was shown in a group of female volunteers. β-Glucan has also synergistic effect with other topical antiageing agents (Ber, 1997). The obtained effect is visible during some time, but is not permanent. It is supposed that continuous application of such products would result in improved skin appearance. Application of β-glucan could be an alternative to other, more invasive treatment of wrinkle reduction (Pillai et al., 2005).

Because it is capable of epidermal macrophage (Langerhans cells) activations and free-radical scavenging effect, β-glucan could be applied as a photoprotective agent in sunscreens. Its application resulted in the reduction of UV-induced erythema and preservation of the amount of Langerhans cells in the epidermis. Commercial sunscreens prevent burns, but they can not ensure the adequate prevention from several skin cancers, including melanoma. UV-rays cause the loss of Langerhans cells even when the skin is already tanned. In that way, its immunological function is diminished. A combination of a sunscreen and glucan is suggested, because glucan added to sunscreens helps in preservation of Langerhans cells (Ber, 1997). The possibility of β-glucan application in sunscreens was also mentioned by Wheatcroft et al. (2002).

Other applications

Even though glucans are interesting mainly because of their biological properties, what is described in literature, they could also find many other applications (Laroche and Michaud, 2007).

Its adhesive properties are used in production of adhesive layer for patch manufacture. Curdlan has been also used as antisegregating agent in concrete and mortar preparations. Sulphated-glucans are incorporated in new cigarette's filters (Laroche and Michaud, 2007).

Other possible application include use of glucan as a solid support material for chromatographic separations (Anonymous, 2010). β-(1→3)-Glucans, isolated from bacteria *Alcaligenes faecalis* and *Agrobacterium radiobacter*, and from fungi *Poria cocos* when activated with cyanogen halide gained ability of ligation to compounds that contain primary or secondary amino-groups. Such derivatives β-(1→3)-glucans could be used as insoluble support material for preparation of immobilized enzymes or ligands suitable for affinity chromatography (Takahashi et al., 1978).

Insoluble yeast β-glucan (IYG) has been explored as a support matrix for enzyme immobilization. Epoxy-activated IYG can be employed as a support for enzyme immobilization and was evaluated for immobilization of *Candida rugosa* lipase (CRL).

Immobilization of CRL on activated IYG support has improved pH, temperature as well as storage stability. The biocatalytic IYG support showed considerable operational stability and reusability in non-aqueous medium (Vaidya and Singhal, 2008).

In vitro β-glucan binds many yeast proteins as well as proteins from other sources (Teparić and Mrša, 1997). The exceptions are mainly focused on some yeast proteins, such as acid phosphatase and invertase. The authors applied a single-step purification of β-glucan from yeast and obtained partially purified yeast glucan preparation. It was used for one-step purification of acid phosphatase from the *Saccharomyces cerevisiae* cell extract, as well as for the purification of invertase from several commercially available preparations. In both cases pure enzymes were obtained by the adsorption of impurities to glucan. The biotechnological significance of the method is that the purified enzymes have broad laboratory and industrial application. This simple protein purification method also provides high yields, causes no significant protein denaturation and is inexpensive. It can most probably be used for other yeast extracellular proteins, as well as for proteins from other sources that have low binding potential for yeast glucan.

β-Glucan could be also applied in the pharmacy, in the production of sustained release tablets and not only as an active component as previously described (Jamas et al., 1991; Laroche and Michaud, 2007).

It is also shown that β-glucan is active in a broad spectrum of biological species that is important for its application (Vetvicka, 2001). Consequently, it could be applied in production of feed and veterinary drugs, used for pets and economically important animals. Application of β-glucan in animal farm feed lowered antibiotics consumption and reduced harmful residues in food (Hayen and Pollmann, 1995). By the use of β-glucan as feed additive during intensive growth of poultry, cattle, fish and crabs, infections were lowered, improving growth and lowering needs for antibiotics addition (Donzis, 1993).

Investigations of substances acting non-specifically on immunoreactions are becoming more and more significant from the point of view of veterinary medicine. Commercially important animals are grown in stressful conditions and it is important to stimulate their immunity by immunostimulants to lower mortality induced by stress. In animals, β-glucan was tested not only as specific stimulant but also as addition to currently used vaccines (Vetvicka, 2001).

β-Glucan was at first used to prevent infections in hatchery-raised fish (Keller, 2000). Nikl and Allbright (1993) explained the possibility of stimulating the immune system of a fish *Salmonidae* and enhancing the efficacy of vaccines for treating fish diseases.

The application of β-glucan in combination with vitamins improves the resistance of aquatic animals and especially of fish, shrimps and invertebrates, as well as warm and cold water decorative fish (Kürzinger, 2001).

Cook et al. (2003) investigated the effects of prolonged administration of a commercial β-glucan based immunostimulant preparation, EcoActiva™, in the form of a feed supplement, on non-specific immune parameters and the growth rate of snapper (*Pagrus auratus*). The preparation contained glucan and mannan and the average particle dimensions were less than 1 μm. Their results suggest that routine incorporation of similar β-glucan preparations in fish feed has beneficial effect.

Hayen and Pollmann (1995) investigated the orally administering the animal with glucan isolated from the yeast, as the component of feed for enhancing animal growth.

Preparations containing glucan and mannan, isolated from spent brewer's yeast, which was added into a feed in concentration of 0.1% w/w showed its efficiency as immunoactivators and diminished the mortality at fishes and crabs due to infection (0.1% w/w in the food). The same product when added in concentration of 1 g/kg into poultry feed resulted in high resistance to diseases (Lee et al., 2003).

One original application of curdlan-sulphate is its use as an elicitor agent in stimulating natural plant protection (Laroche and Michaud, 2007).

There are some examples of glucan use as an antiviral agent in plants, for example in protecting many species of tobacco plant against invasion by the tobacco mosaic virus and tomato black ring virus. Plants can be either injected or sprayed with the glucan polymer (Anonymous, 2010).

Conclusions

β-Glucans have several beneficial properties and many useful applications. Except their potential use in medicine, they have also found a wide variety of non-medical uses in the food and feed, pharmaceutical and chemical industries. Different β-glucan molecules, isolated from various natural sources, showed biological activity.

One of the good sources of β-glucan is yeast that is a well studied microorganism whose culturing conditions are very well known. From the biotechnological standpoint that would be an advantage because large amount of cheap yeast biomass could be easily grown and growth conditions could be adjusted to maximize β-glucan yield. Additionally, the yeast biomass is a byproduct in beer and wine production and could be also used as a raw material for β-glucan production. The important fact is also that yeast β-glucan has a GRAS status.

β-Glucans are classified as biologic response modifiers and immunopotentiation is one of the β-glucans most often investigated properties. Due to structure differences between glucans isolated from various sources and potential degradation changes resulting from isolation or derivation procedures, it is important to define the biological activity of each commercial glucan preparation. In humans, dietary β-glucan lowers blood cholesterol, improves glucose utilization by body cells and also helps wound healing. Studies of β-glucan have shown this polysaccharide to be important substance in the promotion of humans health, but further clinical trials and investigations are still needed.

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