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Review

Promising Effects of Beta-Glucans on Metabolism and on the Immune Responses: Review Article

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Abstract: A public health issue, Diabetes *mellitus,* affects millions of people around the globe. Ingestion of foods with a low glycemic index - fiber-rich meals-such as beta-glucans, is increasing as an important alternative for diabetes control. These compounds act reducing parameters such as blood glucose, cholesterol and triglycerides, by decreasing the absorption of glucose and lipids by enterocytes and eventually promote weight loss. Beta-glucans are also described as immunomodulatory agents by stimulating phagocytosis and the production of pro-inflammatory cytokines, increasing host resistance to viral, bacterial, fungal and parasitic infections; or production of anti-inflammatory cytokinesto return homeostasis after an immune response. Besides, some studies are also evidencing anti-tumoral activity. Beta-glucans main effect depends on their origin-yeast, plants or bacteria. Reports of collateral effects and/or toxicity associated with the use of beta-glucans are rare, which contribute to consider this compound for inclusion in a range of therapies. This review aims to evaluate the most different effects of beta-glucans in metabolic and immune systems, discussing its advantages and limitations.

Keywords: Prebiotics, Functional Food, Glucose, Immunity

Introduction

The interest in the study of natural compounds, such as prebiotics, has grown exponentially in recent years. This demand is because these products may have different functions in the human body. Thus, research involving the same active ingredient that promotes pleiotropic effects is of extreme interest. In this context, appears beta-glucans.

Beta-glucans have been widely used in research for medical purposes (King *et al*., 2005; Sener *et al*., 2006; Harnack *et al*., 2011; Vetvicka 2011; Samuelsen *et al*., 2014; Chen *et al*., 2013; Tosh, 2013; Silva *et al*., 2015). These are polysaccharides from the cell wall of a variety of plants, fungi, yeasts, algae and some bacteria. Beta-glucans belong to a class of compounds which are described as biological response modifiers. Apparently, they can modulate the immune system by stimulating phagocytosis and the production of pro-inflammatory cytokines (Vetvicka, 2011; Rubin-Bejerano *et al*., 2007). They stimulate the defense mechanisms of the host against disease instead of attacking the infectious agent, so these agents remain non-toxic to the cells of the host organism (Zeković *et al*., 2005).

In some cases beta-glucans can exert anti-inflammatory activity (Silveira *et al*., 2014; Ruthes *et al*., 2013; Smeekens *et al*., 2015). According to Li *et al.* (2015), the association of Acetoxychavicol Acetate (ACA) with isolated beta-glucans of *Aureobasidium pullulans* (a type of yeast) inhibited the activation of NF-kβ indicating an anti-inflammatory effect from this complex ACA/beta-glucan, *in vivo* and *in vitro*. In another study, rats with chronic enteritis induced by LPS were supplemented with beta-glucans from oat (low and high molecular weight fractions). The results showed that supplementation with both fractions significantly decreased leucocytes counting: Lymphocytes T and B, granulocytes and lymphocytes Tc (Suchecka *et al*., 2015).

The main functions of beta-glucans, related to stimulation of the immune system include increased host resistance to viral, bacterial, fungal and parasitic infections, as well as an anti-tumor adjuvant effect and prevention of the carcinogenicity (Bohn and BeMiller, 1995). Besides, they reduce plasma concentrations of glucose, cholesterol and triglycerides, despite a decrease intestinal absorption of glucose and lipids (De Paula *et al*., 2005; Lo *et al*., 2006; Vieira Lobato *et al*., 2015; Francelino Andrade *et al*., 2014). Furthermore, they are used as adjuvants in the development of various types of vaccines, by boosting the cellular immune response without the toxicity exhibited by other adjuvants (Petrovsky and Aguilar, 2004; Temizoz *et al*., 2016).

With this panorama, the present review aims to analyze the effects of beta-glucans in different functions (metabolic, immunomodulatory, etc.) discussing its advantages and limitations.

Beta-Glucans-General Characteristics

Wide varieties of compounds have been studied for their prebiotic attributes, so the beta-glucans are an important class of such food additives (Collins and Reid, 2016). Beta-glucans are one of the most abundant forms of structural cell wall polysaccharides of yeast (Rahar *et al*., 2011), plants (Volman *et al*., 2008) and some bacteria (Gacto *et al*., 2000; Chan *et al*., 2009). The chemical structure of beta-glucans has a central linear β (1- 3) ligation composed of glucose units linked to the main chain, which differ according to their length and branching (Xiao *et al*., 2004; Sonck *et al*., 2010). The ramifications of the glycosidic chain are highly variable and the two main groups of branch are the β (1 → 4) and β (1 → 6). These ramifications distinguishes beta-glucans source, e.g., beta-glucans of fungi have side β(1 → 6) branches while bacteria and plants have β (1 → 4). The position of the branch also generally defines the biological activity that fiber (Rahar *et al*., 2011; Chan *et al*., 2009). Various methods can be used to determine the composition or structure of beta-glucans. Among these, stand out the Liquid Chromatography/Mass Spectrometry (LC/MS), High Performance Liquid Chromatography (HPLC) and X-ray crystallography (Jelsma and Kreger, 1975; Rolin *et al*., 1992; Hanada *et al*., 1993).

Most beta-glucans are considered as non-digestible hydrates of carbon, so they are fermented in different degrees by the intestinal microbiota (Wang *et al*., 2008). Therefore, it is speculated that their immunomodulatory properties could be partially attributed to a microbial dependent effect. However, beta-glucans can bind directly to specific receptors of immune cells, suggesting a microbial independent immunomodulatory effect (Vos *et al*., 2007). The pharmacokinetics and pharmacodynamics of beta-glucans were studied in animal and human models (Wang *et al*., 2008, Chan *et al*., 2009). Regarding its toxicity, oral administration for four weeks of these fibers showed no toxic signs even in large quantities (Chen *et al*., 2013, Túrmina *et al*., 2012).

Diabetes *Mellitus* and Beta-Glucans

Diabetes Mellitus

Diabetes *mellitus* is a disease in which the metabolism homeostasis of carbohydrates, proteins and lipids is inadequately regulated. It can be caused by deficiency in the production of the pancreatic hormone insulin and/or insulin resistance, resulting in an increase in blood glucose level (Sunil *et al*., 2011). The most common signs and symptoms of diabetes *mellitus* are: Polyuria, polydipsia, glycosuria, polyphagia, visual changes, skin lesions, heart, mouth and kidney disorders (Seino *et al*., 2010). This disease is one of the main problems of public health and has been aggravated rapidly especially in developing nations. The World Health Organization estimated in 2014 that diabetes *mellitus* affects 422 million people worldwide. This number has increased substantially between 1980 and 2014, from 108 million people to the current 422 million, a value about four times higher (WHO, 2016).

Two main types of diabetes mellitus are recognized. Type 1 diabetes *mellitus*, is a deficiency in insulin production due to autoimmune destruction of pancreatic β cells. In general, in this type of the disease, the patients are young (before 30 years old) and non-obese when the symptoms first appear and its treatment generally requires the use of insulin. In type 2 diabetes *mellitus*, there is resistance to insulin action. In this case the disease has polygenic inheritance origin, not yet fully defined. The pathogenesis of Type 2 diabetes *mellitus* is complex and involves interaction between genetic and environmental factors, especially those from obesity due to physical inactivity and excessive food intake. Oral hypoglycemic agents and/or insulin therapy often become necessary (DeFronzo, 2004; Malandrino and Smith, 2011).

The great importance of diabetes *mellitus* as a public health problem is the fact that most of the chronic complications of the disease is highly disabling to carry out the daily and productive activities, compromising individual's quality of the life. In addition, the treatment of the disease is extremely costly for the public health system (Fazeli Farsani *et al*., 2013).

The development of new alternatives for diabetes treatment is significant, especially because of the worldwide prevalence of the disease. Besides, the fact that diabetes has a chronic nature, it predisposes patients to a variety of other long term complications, especially those associated with the circulatory system (micro and macroangiopathies), which have complex and costly treatments. The intake of foods with a low glycemic index, for example fibers and especially beta-glucans, become an important alternative for diabetes control (Schalkwijk and Stehouwer, 2005; Francelino Andrade *et al*., 2014).

Metabolic Activity of Beta-Glucans

The positive effects of beta-glucans on metabolism in diabetic rats are well known (Lo *et al*., 2006; Kim *et al*., 2005). The reduction of these parameters such as blood glucose and cholesterol, may be related to physicochemical interactions of these fibers with the digestive bolus. These polysaccharides form a gelatinous layer which acts as a barrier hindering the absorption of nutrients, thus leading to a lower concentration of glucose and lipids in blood (Tappy *et al*., 1996; Reyna *et al*., 2003; Liatis *et al*., 2009; Choi *et al*., 2010; Dong *et al*., 2011). This layer is due to the viscosity formed in the intestinal lumen, which acts as a sieve filtering small molecules, retarding the digestion and the absorption of certain nutrients. There is also the hypothesis that this gelatinous layer delays the interaction of the starch and its digestive enzyme, causing a reduction in the absorption of carbohydrates and, consequently, the reduction of glycemia. This particularity of the beta-glucan fibers derives from its molecular weight and solubility, of their predisposition to water retention, viscosity, emulsification, fermentability, resistance to degradation by intestinal bacteria and their propensity to absorb nutrients (Battilana *et al*., 2001; Schneeman, 1987).

Significant improvements in glycemia, triacylglycerols and total cholesterol levels were found in diabetic rats treated with beta-glucans, explaining their beneficial effect on glucose tolerance and lipid metabolism (Miranda-Nantes *et al*., 2011; Gao *et al*., 2012). According to Lo *et al*. (2006), both oat and fungi beta-glucans are able to reduce rodents glycemia. The aqueous extract of beta-glucans of *Agaricus blazei basidiocarpos* showed anti-hyperglycemic, anti-hypertriglyceridemic, anti-hypercholesterolemic and anti-atherosclerotic activity in diabetic rats (Kim *et al*., 2005). According to Francelino Andrade *et al*. (2014) who conducted a systematic review using human experiments and found that ingestion of doses around 6.0 g/person of beta-glucans per day, for at least four weeks were sufficient to provoke improvements in the blood glucose levels and also lipid parameters of individuals with diabetes *mellitus*. However, glucose levels do not reach normal levels using beta-glucan alone. Low doses of beta-glucan for at least 12 weeks were also reported to promote metabolic benefits.

Vieira Lobato *et al*. (2015) observed in diabetes-induced rats treated with leaven beta-glucans (*Saccharomyces cerevisiae)* significant reduction in plasma glucose concentration (30%), triacylglycerols (32%) and alanine aminotransferase (41%). Complementarily, beta-glucans also decreased blood levels of total cholesterol (13%), triglycerides (17%) and glucose (24%), in obese rats (induced by high fat diet) when compared to untreated obese animals (de Araújo *et al*., 2016). Reduction of total cholesterol and LDL fraction were also reported elsewhere (Tiwari and Cummins, 2011).

In addition, beta-glucans can be reduce the risk of cardiovascular and metabolic diseases through the mediation of the inflammatory process (Liu *et al*., 2002; Liu 2003). The hypotheses of these mechanisms have shown that beta-glucans may decrease the oxidation of glucose and lipids, promoting a healthy intestinal environment by preventing inflammation and by changing the adipocytokines in adipose tissue and also, enhancing the enterohepatic circulation of lipids and lipophilic compounds (King *et al*., 2005).

Beta-Glucans and Body Weight

Beta-glucans participate in physiological processes related to the metabolism of fats in the human's body. Thus, it was expected that the consumption of those fibers may also contribute to reductions in body weight (Rop *et al*., 2009). Observational studies showed that the ingestion of dietary fiber decreases the energy intake (Lissner *et al*., 1998) and that the obesity rate is lower if food intake contains an adequate amount of fiber (Kimm, 1995). Thus, an inverse correlation has been reported between the fiber intake and weight (Alfieri *et al*., 1995) and body mass index (Kim *et al*., 2006; Liu *et al*., 2002).

The effect of fiber on weight control is affected by the blood sugar level, which is related to hunger, insulin secretion, gastric emptying time and the intestinal hormones response (Slavin, 2005). However, because most clinical experiments do not distinguish between the different types of fiber, it is not totally clear if a specific fiber, such as beta-glucan, is effective in reducing body weight (Kim *et al*., 2006).

Three types of viscous fibers, pectin, alginate and cereal beta-glucan, were identified as potential satiety-enhancing ingredients, because they appear to be more effective for appetite control (reduce subjective appetite, energy intake and/or body weight) (Slavin, 2005; Benelam, 2009; Wanders *et al*., 2011), especially when included in beverages or liquid test meals, ensuring that they are consumed in a fully hydrated form for higher efficacy (Ho *et al*., 2015). Pectins and most glucans were the types of fibers which exhibited the largest proportion of appetite-reducing effects over a 4-h time interval (Wanders *et al*., 2011; Blundell *et al*., 2010).

Studies with diabetic patients reported that the supplementation of beta-glucan through oats did not have significant effect on body weight (Ripsin *et al*., 1992; Pick *et al*., 1996). In another study, no significant effect on weight was observed in 68 hyperlipidemic patients that received high fiber (beta-glucan) diet compared with a control group who received normal diet (Jenkins *et al*., 2002).

In a systematic review, the percentage of treatments comparing the effects of fiber consumption with controls that significantly reduced subjective appetite rating was 39%. The percentage that significantly reduced food or energy intake was 22%. The satiety-enhancing effects of beta-glucan, lupin kernel fiber, rye bran, whole grain rye, or a mixed high-fiber diet were supported in more than one publication (Clark and Slavin, 2013).

Unfortunately, some studies do not provide clear and precise information or conclusion regarding the effect on weight, but some of them have provided a good perspective about this parameter. More data on the effect of dietary or supplementary beta-glucan on weight need to be developed (Kim *et al*., 2006).

Immunomodulatory Activity of Beta-Glucans

Beta-glucans from fungal cell walls are linear polymers made up of glucose units β(1-3)-D-glucopyranosyl with β(1-6) branches of different sizes that have immunomodulatory activity (Xiao *et al*., 2004; Sonck *et al*., 2010). They have been shown to be able to modulate the immune nonspecific response (Samuelsen *et al*., 2014), stimulating phagocytosis and production of proinflammatory cytokines (Vetvicka, 2011; Rubin-Bejerano *et al*., 2007).

The protective involvement of beta-glucans have been reported as non-specific immunomodulation, by engaging different pathways of the immune system. These pathways include activation of macrophages, stimulation of the reticulum endothelial system and natural killer cell activation. By the other hand, the specific immunomodulation of beta-glucans can activate the classical and alternative complement pathways, stimulate T cells and increase an antibody production (Zeković *et al*., 2005; Czop, 1986).

The immunological potency of beta-glucans also can be associated with their ability to activate leukocytes (Sandvik *et al*., 2007). It is assigned and dependent on the molecular mass, conformation, solubility and also the degree and position of its ramifications. In general, it has been suggested that beta-glucans of high molecular weight (more prevalent in nature) can directly activate leukocytes, stimulating their phagocytic and antimicrobial functions and also their cytotoxic activity (Akramiene *et al*., 2007). Beta-glucans of intermediate molecular weight have biological activity *in vivo*, but its cellular effects are less evident, while beta-glucans of low molecular weight are generally considered inactive (Akramiene *et al*., 2007).

Macrophages are the main and best-characterized targets for the beta-glucans that activate these cells increasing their size and number, stimulating Tumor Necrosis Factor (TNF) secretion and increasing the phagocytosis of antigens. The stimulation of macrophages occurs via Toll-Like receptor 2 and with beta-glucan, recruits Toll-Like receptors 2 and send signals to the production of TNF-α by pathway of the Nuclear Factor- kβ (NF-kβ) (Zeković *et al*., 2005; Czop, 1986; Meira *et al*., 1996; Pivarcsi *et al*., 2003).

Beta-glucans solutions obtained from fungi, when administered orally, reduced alveolar bone loss in rats with gingival inflammation (Breivik *et al*., 2005). Besides, in another study with diabetic rats induced to a similar inflammatory challenge, daily doses of beta-glucans, was effective in reducing alveolar bone loss both diabetics and non-diabetics animals. The treatment reduced the expression of COX-2 and RANK-L and increased the OPG expression in animals with diabetes and periodontal disease. This result may indicate a modulatory action of beta-glucan directly on the immune system as well as its anti-inflammatory effects (Silva *et al*., 2015).

Beta-glucans have been extensively used as a preventive agent against infections. In several experimental models, these compounds have shown protection against infections by bacteria and protozoa, as well as an improvement in antimicrobial efficiency in infections caused by resistant bacteria (Rice *et al*., 2005). The protective effect of beta-glucans has been shown in experimental infections with *Leishmania major* and *L. donovani*, *Candida albicans*, *Toxoplasma gondii*, *Streptococcus suis*, *Plasmodium berghei*, *Staphylococcus aureus*, *Escherichia coli*, *Mesocestoidescorti*, *Trypanosomacruzi*, *Eimeria vermiformis* and *Bacillus anthracis* (Vetvicka, 2011).

Vaccine Adjuvants

Vaccination is the main preventive strategy of public health to populations worldwide, especially those more vulnerable to some infectious diseases and challenging pathogens (Di Pasquale *et al*., 2015). Some vaccines generate an adaptive immune response stimulating the immune system by using an antigen pathogen and/or activating the antigen present in cells. However, the use of recombinant, highly purified or synthetic antigenic determinants (epitopes) may have diminished immunostimulatory action when compared to vaccines containing living organisms. The approach used for decades to enhance the immunogenicity of the purified antigens resides in the use of adjuvants (Petrovsky and Aguilar, 2004; Di Pasquale *et al*., 2015).

New technologies have been employed both in vaccines development and selection of powerful adjuvants. The adequate combination of the antigen and adjuvant may contribute either to the initial innate immune response and efficacy of the downstream adaptive immune response (Cordeiro *et al*., 2015). Adjuvants may be bacteria derived, liposome, aluminum salts, emulsions, tensoactives and carbohydrate based. Polysaccharides like glucans, dextrans, lentinans, galactomannans and glucomannans have been described as adjuvants (Di Pasquale *et al*., 2015). The mechanism described for these carbohydrates action as adjuvants involves the free-cellular toxicity response enhancement promoted by gamma inulin. However, as a complex carbohydrate, some polysaccharides based adjuvants may be metabolized to fructose and glucose reducing its efficacy (Petrovsky and Aguilar, 2004).

As beta-glucans are present in some bacteria, yeast and seaweed cell walls (Goodridge *et al*., 2009), it led to the exploration of these polysaccharides as immunostimulatory agents of the Pattern Recognition Receptors (PRRs) (Soltanian *et al*., 2009). Used as adjuvant, beta-glucans can deliver the antigen into cells and induce an antigen-specific immune response (Temizoz *et al*., 2016).

Intervention of beta glucans in immunity is mainly due to their interaction with specific cell receptors. CR3 (complement receptor), present in myeloid cells such as macrophages, Dendritic Cells (DCs) and NK cells, was the first receptor described for the recognition of beta-glucans (Cordeiro *et al*., 2015).

The most studied beta-glucan receptor Dectin-1 is a type II transmembrane protein present in myeloid cells. The interaction of this receptor with beta-glucans adjuvants induce the production of Reactive Oxygen Species (ROS), internalization of pathogens (Goodridge *et al*., 2009; Lipinski *et al*., 2013; Mochizuki and Sakurai, 2011), pro-inflammatory cytokines production, via the spleen tyrosine kinase (Syk)/NFκB pathway (Temizoz *et al*., 2016). This interaction also allowed the use of beta-glucans for the enhancement of immune responses triggering also the internalization of pathogens via phagocytosis (Cordeiro *et al*., 2015).

Influenza A virus is a dangerous pathogen and its H5N1 subtype can be transmitted directly from domestic fowls to humans leading to respiratory diseases and even death. Vaccination is the preventive approach to avoid seasonal pandemia, however, the use of adjuvants is important for vaccine effectiveness. Wang *et al.* (2016) showed that *Saccharomyces cerevisiae* had effects on the *in vitro* splenic lymphocyte cells of mice, promoting significantly lymphocyte proliferation singly or synergistically with Con A and LPS and stimulated the cells to secrete IL-2 and INF-γ. The same study evaluated the adjuvant activity of *Saccharomyces cerevisiae* in BALB/c mice inoculated with inactivated H5N1vaccine *in vivo*, showing that *Saccharomyces cerevisiae* could significantly enhance lymphocyte proliferation, effectively increase the percentage of CD4+ T cells, decrease the percentage of CD8+ T cells and elevate the CD4+/CD8+ ratio; enhance the HI antibody title and promote the production of IL-2, INF-, IL-4 and IL-6 at medium level. These results indicated that sulfated glucan showed an excellent adjuvant effect on H5N1vaccine in a mice model.

Beta-glucans from *Saccharomyces cerevisiae*are important bioactive compounds for animal and human health, but its low solubility has led to some issues. Sulfate modification could improve its solubility and change its bioactivities. Sulfated yeast glucan could stimulate animal cells proliferation, promote cytokine secretion and enhance antibody titer of vaccine (Wang *et al*., 2016).

Dube *et al.* (2014) used chitosan-coated PLGA nanoparticles functionalized with 1,3-beta-glucan from *Euglena gracilis* for Dectin-1 targeting and reported an increased intracellular delivery of the encapsulated anti-tuberculosis drug, enhanced pro-inflammatory reaction with relevant production of reactive oxygen and nitrogen species (Cordeiro *et al*., 2015). It is important to notice that beta-glucan adjuvant properties are different between each other, depending on many configurations of molecular structures, size and branches responsible for the differences (Soltanian *et al*., 2009; Adams *et al*., 2008; Barsanti *et al*., 2011; Sletmoen and Stokke, 2008).

Overall, beta-glucans present interesting immunomodulating properties as adjuvants for vaccine development and further research should test the limits for its applications.

Antitumor Activity

Beta-glucans have been therapeutically used as antitumor agents. These compounds can exercise their functions both within tumor microenvironments and systemically. This can occur by activation or recruitment of immune effectors cells in tumors or increasing the adaptive immune responses stimulated by concomitant immunotherapy (Barton *et al*., 2016). Thus, beta-glucans act as potent immunostimulant, stimulating the innate and adaptive immune response, which contributes to their antitumor properties (Tian *et al*., 2013). In addition, these polysaccharides have been described as biological response modifiers with antitumor properties which lead to potent immune responses through its recognition by a variety of pattern recognition receptors on dendritic cells, macrophages and neutrophils. The activation of these cells triggers adaptive immune cell responses, such as CD4, CD8, T cells and B cells, resulting in inhibition of tumor growth and metastasis (Albeituni and Yan, 2013; Yoon *et al*., 2013).

Numerous studies have highlighted the importance of these assets as effective contributors in anticancer therapies. A study in mice with mammary tumors showed the effectiveness of oral use of beta-glucans as an adjuvant for monoclonal antibody antitumor in cancer immunotherapy, activating the Th1 response which promotes the activity of cytotoxic T lymphocyte, resulting in a more effective way to remove tumors (Baran *et al*., 2007).

According to Hong *et al.* (2003) multiple tumor models were induced in mice that were subjected to treatments with antitumor antibodies, beta-glucans and beta-glucan combined with antitumor monoclonal antibodies. The combined treatment led to a greater tumor regression in all models that included breast carcinoma and liver tumors, indicating that the therapeutic efficacy of the antitumor antibodies can be significantly enhanced by concurrent administration of beta-glucan. This action is due to the recruitment of granulocytes as tumor killer cells which are powered by recognition of the complement system via CR3 (Hong *et al*., 2003).

Other pre-clinical studies in mice revealed that beta-glucan can improve anti-tumor immune responses by activating the complement system and recruiting tumoricidal granulocytes in addition to the activation of the Dectin-1 signaling pathway. On the other hand, although some clinical trials, conducted in Japan and China, demonstrated the anti-tumor effect of beta-glucan in carcinoma and leukemia patients, clinical studies are still scarce (Temizoz *et al*., 2016).

A short-term clinical study was conducted in which female patients with breast cancer at an advanced stage receiving daily doses of beta-glucan orally for 15 days. The cancer patients were compared with healthy patients/control group. Despite a relatively low initial white blood cell count, the administration of beta-glucan stimulated the proliferation and activation of monocytes in patients with advanced breast cancer (Demir *et al*., 2007).

Generally, a variety of species of edible fungi containing beta-glucan have been widely used as assets with potential anticancer activity (Chan *et al*., 2009). Fractions of Maitake mushrooms decreased the size of lung, liver and breast cancer when combined with chemotherapy. On the other hand, these effects were less evident in patients with leukemia, stomach and brain cancer which were also treated with Maitake mushroom extracts (Kodama *et al*., 2002; 2003). The D-fraction Maitake combined with the agonist nine of the Toll-like receptor increased the expression of dendritic cell maturation markers and also, increased the interleukin-12 in dendritic cells, but did not increase the production of interleukin-10. These results provide the basis for a potent antitumor therapy using a combination of immunological agents for future immunotherapy clinical studies in the patients (Masuda *et al*., 2015).

Conclusion

Beta-glucans from yeast (β-1,3/1,6) have a higher immunomodulatory activity, while those from plants and bacteria (β-1,3/1,4) have characteristics that confer greater metabolic potential. The low incidence of collateral effects associated with the use of beta-glucans should be considered for its inclusion in a range of immune prevention and therapies.

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Author’s Contributions

The authors contributed equally to this work. All authors read and approved the final manuscript.

Ethics

Not applicable.

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