Türkiye Klinikleri

Beta Glucans & Immune System

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Micronized Beta Glucan

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Türkiye Klinikleri

Beta Glucans and Immune System
Review

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Beta Glucans and Immune System

Abstract

Beta- (β-) glucans are biologically active substances that exert potent modulator effects on both innate and adaptive immune systems. They exert their effects especially via receptors associated with immunity, such as dectin-1 and CR3, and may trigger a wide range of immune responses. Owing to their immunomodulatory effects, they have been shown to benefit several clinical conditions, from infectious diseases to oncology. β-Glucans have a wide anti-infective activity, including various bacterial, viral, protozoal, and fungal illnesses. In several studies, β-glucans have provided significant clinical benefits in respiratory tract infections, including the flu and common cold, both in children and adults. Studies in patients with allergic rhinitis have revealed that β-glucan might be more advantageous compared to standard therapy. Moreover, it was determined that β-glucan provides significant clinical benefits in patients with aphthous stomatitis and certain oncological conditions. However, β-glucans differ by structure, particle size, receptor-binding affinity, and, thus, biological functions. Particle size is important for the efficacy of β-glucans, and small particles are absorbed better by macrophages. Studies have shown that β-glucan with a size less than 10 micron supports the immune system better. Therefore, it can be said that micronized β-glucan may provide better efficacy.

Keywords: β-glucan, immunity, immunomodulation, pharmacodynamic, pharmacokinetic, particle size, β-glucan receptors, infection, oncology, stomatitis, allergic rhinitis

Introduction

β-Glucans are part of a group of biologically active natural molecules and have attracted increasing attention not only as an important dietary supplement but also as an immunomodulator and a potential medication.[1]

β-Glucans differ by structure, particle size, receptor-binding affinity, and thus, biological functions.[2] This article discusses β-glucans (β-1,3-glucans) and their roles in various immune reactions.

Structure of β-glucans

Structurally, all β-glucans are glucose polymers bound to each other through 1–3 linear beta-glycosidic core chains differing by lengths and branching configurations. Branches emerging from the glycosidic core chain are 1–4 or 1–6 glycosidic chains, based on their source. The biological activity of β-glucans depends on the structural complexity, including the length of the polysaccharide chain, degree of branching, and length of the branches. Increased structural complexity is believed to be associated with more potent immunomodulator activity.[3] β-Glucans derived from yeast *Saccharomyces cerevisiae* have 1–6 side branches and are highly branched.[4] However, the association between their structure and function is not clear.

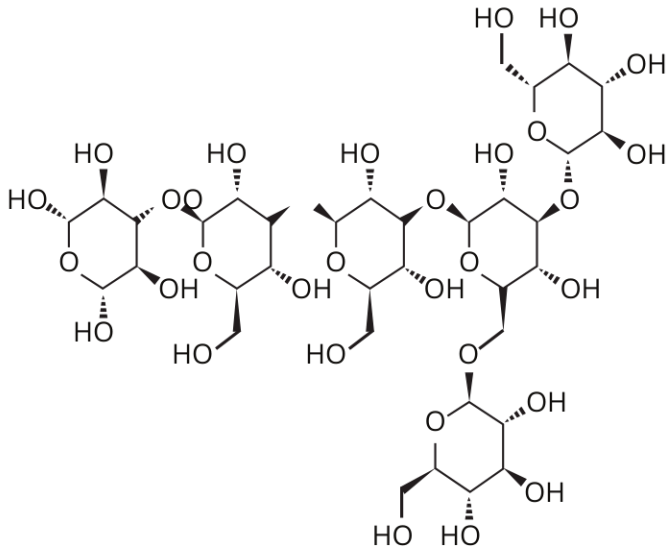

Figure 1. Molecular structure of β-glucan

Pharmacodynamics and Pharmacokinetics

β-Glucans are indigestible carbohydrates and are fermented at various degrees by the gut flora. Therefore, their immunomodulatory properties are believed to be partly dependent on the gut flora. However, β-glucans can directly bind to specific receptors of the immune cells, which indicates that the immunomodulatory effect is independent of the organization of the gut flora. Variations in molecule size, branching frequency, and solution structure have been shown to affect elimination half-life, the volume of distribution, and clearance.[3] The mechanism of the transport of β-glucans through the gastrointestinal system is yet to be clearly understood. At one point, it was even thought that oral glucan could not have biological activity due to the lack of enzymes necessary to degrade the glucan molecule within the human gastrointestinal tract. However, subsequent studies have revealed that the main route of entry of glucan is by direct binding to macrophages localized in the Peyer's patches, which are in close contact with the gut lumen. The higher efficacy of micronized β-glucans with their smaller sizes might be related to this direct binding process.[5] The effects of β-glucans on the immune system are determined by their structural and physical properties. Particle size is important for the efficacy of β-glucans, and small particles are absorbed more by macrophages than large particles.[2]

The fact that oral β-glucans are observed at lower levels in systemic circulation neither completely represents the pharmacodynamics of β-glucans nor rules out their *in vivo* effects. β-Glucans transported into the gastrointestinal system are taken up by macrophages via the dectin-1 receptor and then transported to the spleen, lymph nodes, and the bone marrow. In the bone marrow, macrophages are degraded to smaller β-1,3-glucan fragments. Later, these fragments are taken into marginal granulocytes through the complement receptor-3 (CR3). These granulocytes containing CR3-bound β-glucan have been demonstrated to kill inactivated complement 3b (İc3b)-opsonized tumor cells after being accumulated in a complement-activation site such as monoclonal antibody-coated tumor cells.[3]

To summarize, mostly based on animal data, β-glucans enter the proximal small intestine after oral administration and bind to macrophages. Later, β-glucan is degraded and transported into the endothelial-reticular system via the bone marrow. Later, small β-glucan fragments are released by macrophages and bind to circulating granulocytes, monocytes, and dendritic cells. The immune

reaction occurs through this mechanism. Apart from the formation of the immune response, it is also important that it is sustainable and is sustained by indirect mechanisms in its target, i.e., the bone marrow.[3]

β-Glucan Receptors

The ability of our immune system to recognize and respond to β-glucan depends on the pattern recognition receptors (PRR) defined in various immune cells, including monocytes, macrophages, neutrophils, and natural killer (NK) cells. The most important PRRs of β-glucan are CR3 and dectin-1.[4]

CR3, found in several types of immune cells, including monocytes, macrophages, neutrophils, NK cells, and some B and T cells, can recognize β-glucans via a lectin domain. The biological effects of this interaction are most comprehensively observed in neutrophils, wherein the recognition of β-glucan by CR3 has been demonstrated to mediate neutrophil chemotaxis, adhesion, trans-endothelial migration, and complement-mediated priming of the leukocytes for the CR3-dependent cytotoxicity of the iC3b-coated target cells. Recently, CR3 has been described to be the main receptor for β-glucan particles in human neutrophils.[4]

Dectin-1, a member of the C-type lectin receptor family, has started to stand out as a primary receptor for β-glucans. This receptor is mainly expressed in cells of myeloid origin, including macrophages, dendritic cells, and neutrophils. Recently, dectin-1 has also been detected in B and T lymphocytes, although its function on these cells is yet to be determined. The binding of β-glucan to dectin-1 has been shown to result in various macrophage and neutrophil reactions, including phagocytosis, oxidative burst, neutrophil degranulation, and other immune reactions.[4]

β-Glucan and Immunomodulation

Existing data suggest that β-glucans are potent immunomodulators that exert effects on both innate and adaptive immunity. Generally, findings in this field are strongly supported by the evidence obtained in both animal models and human trials.[3]

β-Glucans are potent activators of the innate immune system, including macrophages, neutrophils, and NK cells. It has recently been reported that β-glucan increases the production of nitric oxide and IL-1 from macrophages, provides an increased phagocytic potential, and increases the activation of NK cells. Similarly, β-glucan has been observed to increase the production of IL-10, ROS, and TNF in a dose-dependent matter. In mice, it has been demonstrated that β-glucan may balance the antiviral resistance of macrophages to herpes simplex virus type-1 (HSV-1). Moreover, it has been recently reported that β-glucan may increase the neutrophil count and oxidative burst activity in mice.[4]

The adaptive immune system functions through the combined effect of antigen-presenting cells and T cells. Specifically, antigen presentation of class I major histocompatibility complex (MHC-I) to CD8+ cytotoxic T cells is limited by the peptides produced by the proteasomes of the intracellular pathogens. On the other hand, the MHC-II endocytic pathway presents the proteolytic peptides only from extracellular pathogens to CD4+ T-helper cells. Polysaccharides such as β-glucans may activate the CD4+ T cells via the MHC-II endocytic pathway. β-Glucans are degraded into low-molecular-weight carbohydrates by a nitric oxide-mediated mechanism. These carbohydrates are later bound to MHC-II in the antigen-presenting cells, such as dendritic cells, to be presented

to the T-helper (Th) cells. The response of Th-1 is believed to occur through this mechanism, although the results on this are contradictory. Recent publications have suggested that β-glucans may induce the T cells to regulatory T cells (T-reg). More research on the effects of β-glucans on T-cell activation is necessary.[3]

β-Glucans differ by structure, physical properties, receptor-binding affinity, and thus, biological functions.[2] It is well known that the immunological activity of β-glucans is related to the particle size, and the immunological activity improves as the particle size decreases.[6] Particle size is believed to be possibly the main factor affecting the endocytic uptake of β-glucan particles.[7] Macrophages absorb the smaller particles (<10 μm) better.[2,7] It has been reported that preparations containing smaller β-glucan particles possibly have more positive immunostimulatory effects.[6] Various studies have shown the benefits of micronized β-glucan on the immune system.

Trained Innate Immunity (TRIM)

It is known that the innate, natural part of the immune system is less developed and does not have a memory function, unlike adaptive immunity. However, innate immunity in organisms, even without adaptive immunity, would exhibit a long-lasting developed functional structure following adequate preparation. During the last few years, this phenomenon has been described as "Trained Innate Immunity (TRIM)". Several types of immune cells play a role in both pathways. For example, certain T lymphocyte subsets function not only in the adaptive pathway but also as non-specific cell populations producing cytokines. Similarly, macrophages activated by the secretion of specific T cells are an important group of effector cells in the adaptive pathway.[8]

Monocytes and macrophages are the main trainable cells of innate immunity. Both BCG (via NOD2 signaling) and β-glucan (via dectin-1) have been demonstrated to induce epigenetic reprogramming, especially stable changes in the trimethylation of histones in H3K4. These epigenetic changes lead to cellular activation, increased cytokine production, and changes in the metabolic status of the cell by switching from oxidative phosphorylation to aerobic glycolysis.[8]

First, TRIM observations are obtained from BCG vaccination. In BCG-vaccinated subjects, it has been observed that the responses given to other unrelated stimuli also increase substantially. The most striking results obtained in this matter are the observations of Garly et al. (2003) on BCG vaccination in young West African children. They reported that BCG had a dramatic effect on survival during childhood, and this effect was not just explained by the specific effect of BCG, which is the prevention of death by mycobacterial infection.[8] A similar observation is the relatively lesser COVID-19-associated death rates in countries such as Turkey, which implemented a routine BCG vaccination program.[9] The association of TRIM and coronavirus is not only limited to this. The milder course of coronavirus infection in the pediatric patient group is also attributed to TRIM that is acquired because of childhood vaccinations.[10]

In vitro models have demonstrated that the training induced by *C. albicans* or β-glucan occurs via the receptor dectin-1 and non-canonical Raf-1-dependent pathway. Thus, epigenetic changes induce a function reprogramming in monocytes, which is especially associated with the stable changes in histone trimethylation in H3K4. These findings were further described in a later study in which changes in the genome diameter were observed in epigenetic markings such as H3K4 me1, H3K4 me, and H3K27Ac. Analyses of the pathway have led to the identification of the cAMP-PKA-dependent signaling as an important mechanism of the activation of TRIM.[11]

To provide the necessary energy for proper functioning, metabolic processes of the immune

system cells are regulated sensitively. Resting monocytes and macrophages obtain their energy via oxidative phosphorylation and when they are exposed to inflammatory stimulants, they switch to aerobic glycolysis (Warburg effect).[12] Recent studies have demonstrated that the pathway comprising dectin-1, Akt, mTOR, and HIF-1 is critical for the switch to the Warburg effect during β-glucan training. Histone modification of the mononuclear phagocytes trained by β-glucan provide a strong upregulation in glycolysis genes, and a biochemical shift from oxidative phosphorylation to aerobic glycolysis occurs, which is associated with an increase in glucose consumption, lactate production, and NAD/NADH ratio, as well as a decrease in the basal respiratory rate.[13]

To summarize, β-glucans exert their effects, especially via receptors associated with immunity, such as dectin-1 and CR3, and may trigger a wide range of immune responses. The immune cells targeted by β-glucans include macrophages, neutrophils, monocytes, NK cells, and dendritic cells. Immunomodulatory functions induced by β-glucans include both innate and adaptive immune responses.[4] β-glucans also increase the opsonic and non-opsonic phagocytosis.[3] Moreover, the effect of β-glucans on TRIM also supports their extensive effects on immunity pathways.[8]

β-Glucan and Infection

As a result of their immune development abilities, β-glucans exert an extensive anti-infective activity against various bacterial, viral, protozoal, and fungal illnesses.[4] Certain β-glucans are effective against almost all pathogens. The protective effects of glucan administration have been demonstrated in experimental models of infection created using *Leishmania donovani major, Candida albicans, Toxoplasma gondii, Streptococcus suis, Plasmodium berghei, Staphylococcus aureus, Escherichia coli, Mesocestoides corti, Trypanosoma cruzi, Eimeria vermiformis, and Bacillus anthracis*.[14] The activity of β-glucans in respiratory tract infections has been reported in several human trials.[15]

In a study by Dharsono et al., a total of 299 healthy individuals that had been reported to have at least three upper respiratory tract infections (URTI) during the previous year were randomized to receive placebo or yeast β-glucan daily for 16 weeks. Seventy subjects that received a placebo and 71 subjects that received β-glucan had at least one clinically confirmed URTI. In the β-glucan group, the severity of physical symptoms at all time points up to seven days were observed to be substantially lower.[16] In another placebo-controlled, double-blind, randomized, multicenter clinical trial by Auinger et al., 162 healthy participants with recurrent infections received placebo or β-glucan for 16 weeks. The authors evaluated the severity of 10 pre-specified symptoms during the infection period in a diary, from which a symptom score was calculated. In that study, β-glucan supplementation decreased the number of symptomatic common cold infections by 25% compared to placebo ($p = 0.041$). The mean symptom score was observed to be 15% lower in the β-glucan group ($p = 0.125$). β-Glucan significantly decreased the sleeping difficulties caused by common cold compared to placebo ($p = 0.028$).[17] In another placebo-controlled, double-blind, randomized, multicenter clinical trial, Jesenak et al. assessed the efficacy of β-glucan in a pediatric age group. A total of 175 children with more than five respiratory tract infections during the previous year were randomized to receive β-glucan plus vitamin C or only vitamin C for 12 months. No respiratory tract infection was observed in 36% of the children in the β-glucan group, compared to only 21% in the control group ($p<0.05$). Moreover, β-glucan supplementation significantly decreased the incidence of flu or flu-like illnesses and the frequency of lower respiratory tract infections, and significantly modulated the humoral and cellular immunity.[18] Fuller et al. assessed the efficacy of β-glucan in 100 elderly participants aged between 50 and 70 years, who were randomized in a double-blind manner to receive β-glucan or placebo for 90 days during the winter season. At the

end of that study, 17 medically confirmed URTIs were observed in the β-glucan group and 28 in the placebo group. There was a strong tendency toward a decrease in the number of days with symptoms in the β-glucan group ($p = 0.067$). In the β-glucan group, an increase in the interferon-γ (IFN-γ) concentration was observed on day-45 compared to the baseline ($p = 0.016$), and smaller decreases were observed in the monokines induced by IFN-γ concentration on days 45 and 90 ($p = 0.032$ and $p = 0.046$, respectively).[19] In a 12-week, randomized, double-blind, placebo-controlled trial, Feldman et al. assessed the efficacy of high-dose (500 mg/day) of non-micronized β-glucan in 40 healthy adults during the flu and common cold season. In that study, no significant difference was detected between the β-glucan and placebo groups in terms of incidences of symptomatic respiratory tract infections.[20] While it is not possible to compare these trials, the benefits observed in the studies with a high dose of non-micronized β-glucan appear to be relatively more limited, thus confirming the importance of the particle size.

The efficacy of micronized β-glucan was also demonstrated in Turkish trials. In a study conducted in Kırıkkale with micronized 1.3/1.6 β-glucan (Imuneks® 10 mg) derived from baker's yeast by Arık and Yiğit, 32 children of 1–8 years, who had presented with recurrent respiratory tract infections between September 2003 and April 2004, were assessed. A significant decrease in the incidence of respiratory tract infections was observed in 81% of the study participants (26/32) ($p<0.01$).[21] In another study conducted at the Erciyes University by İnal et al., 70 healthy subjects were treated with 10 mg of β-glucan twice a day for six weeks. While the overall incidence of the common cold was high, especially in Kayseri during the period between February 2017 and April 2017, 98.57% of the participants did not experience any symptoms of the common cold after the use of the medication.[22]

β-Glucan and Allergic Rhinitis

Allergic rhinitis (AR) is an illness that is characterized by IgE-mediated allergic inflammation of the nasal mucosa. Th2 cells play an important role in the development of IgE-mediated illnesses such as allergic rhinitis, and Th2 cytokines (IL-4, IL-5, and IL-13) are produced in large amounts locally at the allergic inflammation site. Th1 cytokines (IL-12 and IFN-γ) are known to facilitate the treatment of these illnesses by inhibiting the Th2 immune response. In a randomized, double-blind, placebo-controlled trial, Kırmaz et al. investigated whether β-glucan converted the Th2-mediated immune response to Th1-mediated response in a total of 24 allergic rhinitis patients sensitive to olive pollen. Half of the patients received a placebo for 12 weeks, and the other half received 10 mg of β-glucan daily. The study was conducted outside of the pollen season. The nasal provocation test (NPT) using the relevant allergen was performed at the beginning and end of the study, and after a positive NPT, nasal lavage was performed, and levels of IL-4, IL-5, IFN-γ, and IL-12 were measured. Eosinophil percentage in the peripheral blood was also determined. In the β-glucan group, IL-4 and IL-5 levels were significantly decreased in NPT ($p = 0.027$ and $p = 0.04$), whereas IL-12 levels were significantly increased ($p = 0.008$). Furthermore, eosinophil percentage was significantly decreased in the β-glucan group ($p = 0.01$) and remained unchanged in the placebo group. This study indicated that β-glucan added to standard therapy might be beneficial in allergic rhinitis patients.[23]

β-Glucan and Aphthous Stomatitis

Micronized β-glucan has been shown to have beneficial effects on recurrent aphthous stomatitis. In an open-label trial, Koray et al. evaluated the effects of β-glucan alone or combined with a

T-lymphocyte mitogen, phytohemagglutinin (PHA), on the lymphocyte responses in the treatment of recurrent aphthous stomatitis (TAS). The trial included 37 patients with TAS and 42 healthy controls without TAS. Twenty-seven out of 37 patients with TAS received 10 mg β-glucan (Imuneks®) twice a day, while ten patients received a placebo twice a day. Lymphocyte proliferation without PHA was observed to be significantly lower in patients with TAS than the control group without TAS (mean 24.89 vs. 53.31; $p<0.001$). The lymphocyte response to PHA was observed to be significantly higher in the TAS patients receiving β-glucan, compared to TAS patients receiving placebo ($p<0.05$). Moreover, the ulcer severity score was significantly lower in TAS patients receiving β-glucan compared to patients receiving placebo ($p<0.05$). In that study, it was concluded that the immunostimulatory effects of β-glucan could benefit TAS patients.[24]

β-Glucan and Oncology Patients

B-Glucans can stimulate the innate immunity via the activation of monocytes or macrophages. Human studies have demonstrated that β-glucan has an immunomodulatory effect in cancer patients and may enhance the effect of biological therapies. In a 2-week short-term prospective clinical trial, Demir et al. evaluated the *in vivo* effects of short-term oral β-glucan administration on peripheral blood monocytes and their activation markers in patients with advanced-stage breast cancer. The study included 23 female patients with advanced-stage breast cancer. A control group consisting of 16 healthy women was also formed to compare the baseline blood samples. The patients received 10 mg of β-glucan twice a day. In patients with breast cancer, the mean monocyte count increased from 326 ±124/mm^3 at baseline to 496 ±194/mm^3 on day-15 ($p = 0.015$). Moreover, the percentage of monocytes was observed to increase from 7.4% to 12% after 14 days of β-glucan treatment ($p = 0.003$). The expression of CD95 (Apo1/Fas) on CD14+ monocytes increased from 48.17% at baseline to 69.23% on day-15 ($p = 0.002$). Similarly, the expression of CD45RA on CD14+ monocytes was observed to significantly increase from 49.9% at baseline to 61.52% on day-15 ($p = 0.001$).[25]

Patients undergoing chemotherapy and radiotherapy become predisposed to infection, as their immune system is weak. β-glucan activates white blood cells such as macrophages, monocyte, and neutrophils, which are responsible for defense against infection. β-Glucan stimulates hematopoietic regeneration, provides protection against opportunistic infections and increases the regeneration of damaged tissues in the body. Papila et al. evaluated the effects of 10 or 20 mg β-glucan given daily depending on the body weight to 40 patients receiving therapy for head-neck cancer on chemotherapy-induced mucositis and leukopenia. Patients receiving three cycles of chemotherapy were equally divided into two equal groups, of which one group received oral β-glucan. When the leukocyte count was compared to pre-chemotherapy values (4305 ±1139), it was observed to be significantly lower after chemotherapy (2750 ±631.20; $p<0.001$). This decrease was more limited in the β-glucan group (6185 ±1549.96 and 5820 ±1859.99; $p = 0.05$). Moreover, secondary oral mucositis observed in patients receiving chemotherapy and radiotherapy was observed less in patients receiving β-glucan. The study investigators stated that β-glucan supplemented with chemotherapy strengthened the immune system and improved the quality of life.[26]

Conclusion

β-Glucans are potent immunomodulators that exert effects on both innate and adaptive immunity. With their immunoregulatory effects, they provide a wide range of benefits for patients suffering from infectious diseases to cancer. However, the effects of all β-glucans are not the

same. Several *in vivo* and *in vitro* trials have demonstrated that β-glucan with a particle size of < 10 microns is medically superior in supporting the immune system. Therefore, it can be concluded that micronized β-glucan may provide superior efficacy.

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