Immune modulating effects of β-glucan

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Purpose of review

To examine the recent scientific literature on the immune modulating effects of β-glucans and subsequent benefits on infection and cancer.

Recent findings

β-Glucans have been investigated for their ability to protect against infection and cancer and more recently for their therapeutic potential when combined with cancer therapy. Their immune modulating effects are attributed to the ability to bind to pattern recognition receptors including complement receptor 3, scavenger receptors, lactosylceramide, and dectin-1 that results in activation of different aspects of the immune response depending on the cell types and species involved although there is some controversy about the relative importance of each of these receptors. Most of the available evidence comes from preclinical data and human studies are just now beginning to appear in the literature, therefore firm conclusions on its clinical importance cannot yet be made. Perhaps the most promising evidence to date in human trials has come from recent studies on a benefit of β-glucan on quality of life and survival when given in combination with cancer treatment. We identify the need for future studies that compare purified forms of β-glucans from different sources to further the understanding of the mechanisms of action and aid in the development of clinical studies.

Summary

β-Glucans appear to be effective at enhancing immune function and reducing susceptibility to infection and cancer. A better understanding of the mechanisms of β-glucan recognition and subsequent immune activation is necessary for the design of effective treatment approaches in future clinical trials.

Keywords

cancer, immune function, infection, nutrition

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Introduction

The popularity of nonsynthesized, naturally occurring supplements to maintain health and prevent disease has increased dramatically in recent years due in part to the fact that they are more easily accessed, generally less expensive, and are thought to have fewer side-effects than manufactured drugs. Utilization of supplements for these purposes has occurred for millennia but not until recently have these substances been subjected to systematic experimental validation. One important supplement that has been studied for its biological effects in mammals is β-glucan. β-Glucans are naturally occurring carbohydrates that are major structural components of the cell walls of fungi, yeast, some bacteria and cereals such as oats and barley. β-Glucans are most well known for their ability to simulate the immune system and boost resistance to various viral, bacterial, protozoan, and fungal diseases as well as promote antitumor activity. This novel immunomodulating substance is thought to mediate its stimulatory effects through activation of various immune system components including macrophages, neutrophils, natural killer (NK) cells, and lymphocytes. This review will briefly examine the recent available literature on the immune modulating effects of β-glucan and its subsequent benefits on susceptibility to infection and cancer. It is not intended to be a comprehensive review because of space limitations and is weighted more heavily on the recent advances that have been made.

β-Glucan structure

Structurally, all β-glucans are glucose polymers linked together by a $1 \rightarrow 3$ linear β-glycosidic chain core that differ from each other by their length and branching configuration (Table 1). The branches derived from the glycosidic chain core are either $1 \rightarrow 4$ or $1 \rightarrow 6$ glycosidic chains that appear to be dependent on the source. For example, β-glucans of yeast have $1 \rightarrow 6$ side branches with additional $1 \rightarrow 3$ regions, β-glucans derived from fungi have short $1 \rightarrow 6$ linked branches whereas those of oats and barley are primarily linear with large regions of

Table 1 Common β-glucans and their sources and structures

Name	Source	Structure
GRN (grifolan)	*Grifola frondosa* (fungus/mushroom)	1,3 1,6 branched
LNT (lentinan)	*Lentinus* (fungus/mushroom)	1,3 1,6 branched
P-SG (polysaccharide)	*G. Lucidum* (Fungus/mushroom)	1,3 1,6 branched
SPG (sonifilan)	*Schizophyllum commune* (fungus)	1,3 1,6 branched
SSG (*Sclerotinia sclerotiorum* glucan)	*S. Sclerotiorum* (fungus)	1,3 1,6 highly branched
PGG (betafectin)	*Saccharomyces cerevisiae* (yeast)	1,3 1,6 highly branched
S. cerevisiae	*S. cerevisiae* (yeast)	1,3 and small numbers of 1,6 branches and 1,6 linked
Zymozan	*S. cerevisiae* (yeast)	Nonuniform branches and backbone units
Barley, oat, wheat, rye, rice	(Cereal)	1,3 1,4 mixed linkage, unbranched

$1 \rightarrow 4$ linkages separating shorter $1 \rightarrow 3$ structures. The biological activity of β-glucans are dependent on their conformational complexity including length of polysaccharide chain, extent of branching and length of branches; a higher degree of structural complexity is thought to be associated with more potent immunmodulatory activity. Unfortunately, however, often in the literature, the activity of one β-glucan is inappropriately generalized to all β-glucans; future research on the comparison of purified β-glucans from different sources is warranted.

β-Glucan receptors

The ability of our immune system to recognize and respond to β-glucan is dependent on pattern recognition receptors (PRRs) that have been identified on various immune cells including monocytes, macrophages, neutrophils, and NK cells. To date, there have been four different β-glucan PRRs described including complement receptor 3 (CR3) [1], scavenger receptors [2], lactosylceramide [3], and most recently dectin-1 [4].

CR3, present on a wide range of immune cells including monocytes, macrophages, neutrophils, NK cells, and some B and T cells has the ability to recognize β-glucans through a lectin domain [1,5]. The biological effects of this interaction have been most extensively studied in neutrophils; recognition of β-glucan by CR3 has been shown to mediate neutrophil chemotaxis, adhesion, and transendothelial migration [6,7] as well as complement-mediated priming of leukocytes for CR3-dependent cytotoxicity of iC3b-coated target cells [8]. Recently, van Bruggen *et al.* described CR3 as the major receptor for β-glucan particles on human neutrophils; phagocytosis of yeast particles was completely dependent on CR3 [9•]. Scavenger receptors involved in initiating an immune response are expressed by myeloid cells [10]. Although their ability to recognize β-glucans has been well established there is currently very little evidence on biological consequences that can result from this interaction. Lactosylceramide has been shown to recognize β-glucans leading to activation of several immune responses, for example, an increased production of macrophage inflammatory protein (MIP)-2 and tumor necrosis factor (TNF-α) through activation of nuclear factor-κB (NF-kB) [11,12] has been reported. Binding of β-glucans by lactosylceramide has also been shown to stimulate migration of neutrophil chemotaxis [13]. Dectin-1, a member of a superfamily of C-type lectin receptors, has recently emerged as the primary receptor for β-glucans [4,14]. This receptor is expressed primarily by cells of myeloid origin, including macrophages, dentritic cells, and neutrophils [15]. Recently, dectin-1 was also detected on B and T lymphocytes but its function on these cells has yet to be determined [15]. Binding of β-glucan to dectin-1 has been shown to result in a variety of macrophage and neutrophil responses, including phagocytosis, oxidative burst, neutrophil degranulation, and the production of cytokines and chemokines that recruit and activate other immune responses [5]. Further support for a central role of dectin-1 β-glucan receptor on the immune function comes from dectin-1 knockout studies in mice [16]. Recently, Werner *et al.* [16] examined the immune response to *Asperigillus fumigates* in dectin-1 knockout mice; dectin-1 (−/−) showed an impaired interleukin (IL)-1α, IL-1β, TNF-α, MIP-1α, MIP-1β, and chemokine ligand (CXCL)-1 production that resulted in insufficient lung neutrophil recruitment and uncontrolled *A. fumigates* lung growth [16].

Although it is clear that each of these receptors can recognize and respond to β-glucan it is possible that other receptors still remain to be identified. Further, there is still some debate about the relative importance of each of these receptors in initiating a response to β-glucan. It is likely that these receptors activate different aspects of the immune response depending on the cell types and species involved. A better understanding of the mechanisms of β-glucan recognition and subsequent immune activation, especially in human immune cells, is necessary to the design of effective treatment approaches in clinical studies.

Immune modulation by β-glucan

β-Glucans are most well known for their ability to simulate the immune system and boost resistance to various viral, bacterial, protozoan, and fungal diseases as well as promote antitumor activity. In contrast to

immune therapies, β-glucans can be administered orally, are generally less expensive, are thought to have fewer side-effects, and appear to act by stimulating the whole immune system. In general, the evidence in this area is limited by a lack of clinical trials, but is strongly supported by data in animal models.

β-Glucans are potent activators of the innate immune system, including macrophages, neutrophils, and NK cells, however most of this evidence comes from preclinical data. For example, a recent study reported that β-glucan derived from the mushroom *Astraeus hygrometricus* increased production of nitric oxide and IL-1 from macrophages and also exhibited an increased phagocytic potential and enhanced NK cell activation [17]. Similarly, β-glucan purified from zymosan has been shown to increase production of IL-10, reactive oxygen species and TNF in a dose-dependent manner [18]. We have shown in mice that β-glucan from oats can offset the detrimental effects of stressful exercise on intrinsic antiviral resistance of macrophages to herpes simplex virus (HSV)-1 but has no effect on NK cell activity [19,20]. We also recently reported that oat β-glucan can increase neutrophil number and oxidative burst activity in mice [21].

To date, the benefits of β-glucan on the adaptive immune response is much less clearly defined than that of the innate immune response. Nonetheless there have been numerous studies that have reported a beneficial effect on T and B cell responses [17,22–24]. For example, Inoue *et al.* reported that β-glucan from maitake mushroom potentiated the activation of helper T cells resulting in increased cellular immunity and also induced the production of interferon (IFN)-γ, IL-12, and IL-18 by spleen cells and lymph node cells [23]. A recent study reported that β-glucan derived from *Paenibacillus polymyxa* JB115 increased the percentage of blood cytotoxic T cells in rats but there was no change in circulating B lymphocytes [24]. Studies that examine a combination treatment effect of β-glucan and immune therapies are also now beginning to appear in the literature. For example, a synergistic effect on adaptive immune responses has been reported following combination treatment with IFN-γ or Bacillus Calmette-Guérin (BCG) [25,26].

Although the animal data clearly provide support for an immunomodulatory effect of β-glucan, the few human studies that are available are less clear. For example, β-glucan from the mushroom *Sparassis crispa* enhanced cytokine synthesis of leukocytes [27] but there was no effect of oat β-glucan on plasma cytokines and leukocyte mRNA expression of cytokines in humans following exercise stress [28]. There was also no effect of oat β-glucan on NK cell activity, neutrophil respiratory burst or phytohemagglutinin-stimulated lymphocytes following oat β-glucan treatment [28]. More clinical data are clearly needed before firm conclusions on the efficacy of β-glucan as an immune modulator are made.

β-Glucan and infection

As a result of their ability to enhance immune function β-glucans have been shown to elicit a wide range of anti-infective activity including enhanced host resistance to various bacterial, viral, protozoan, and fungal diseases [29]. The majority of evidence comes from animal data with relatively few human studies available.

Various β-glucans have been shown to elicit a broad range of anti-infective activity in animal models. In fact, some β-glucans have been shown to be effective against almost all known pathogens. We have shown that β-glucan derived from oats can decrease susceptibility to HSV-1 respiratory infection in mice following stressful exercise [19,20], the effects of which were at least in part attributed to macrophages [30]. Similarly, an enhanced resistance to *Mycobacteriaum tuberculosis* was reported in mice following treatment with lentinin from shiitake mushroom that contains β-glucan [31], as well as a protective effect against *Streptococcus pneumoniae* infection [32].

Although the ability of β-glucan to enhance host resistance in rodents has not been questioned, there are very few studies to support this effect in humans. A recent study reported that oat β-glucan had potent activity against a primary isolate of HIV-1 in peripheral blood mononuclear cells [33]. There is also some evidence that β-glucan from lentinin given in combination with the drug didanosine can increase CD4 numbers in HIV-positive patients [34]. A follow-up study by the same group reported a trend for an increase in CD4 cells and neutrophil activity in the same population following intravenous administration of lentinan (1 or 5 mg of lentinan twice a week for 12 weeks) [35]. It has also been reported that glucan from *Saccharomyces cerevisiae* administered intravenously to high-risk surgical patients resulted in decreased infection incidence and need for antibiotics [36]. In addition β-glucan from this source decreased overall mortality and septic morbidity compared to a placebo treatment in trauma patients [37].

Although the beneficial effect of β-glucan in animal models has not been questioned, there is a lack of evidence among human trials to support an effect of β-glucan on the incidence of infection. Well designed clinical studies are clearly needed to corroborate the animal data before the efficacy of β-glucan on infection can be determined.

β-Glucan and cancer

Although most of the evidence for a beneficial effect of bioactive food components in cancer is based on

preclinical evidence their use among cancer patients is common. β-Glucans have been widely examined in animal models for their direct immunomodulatory and cytotoxic effects in cancer models and more recently their therapeutic potential when administered in combination with cancer therapy.

Preclinical data show good evidence for a beneficial effect of β-glucan in cancer [38–40]; however, there is some debate about whether these effects are due to direct cytotoxic effects or immunomodulatory mechanisms [41,42]. For example, Yoon *et al.* reported that β-glucan purified from mutated *S. cerevisiae* inhibited lung metastasis of colon 26-M3.1 carcinoma that was associated with splenocyte proliferation, tumoricidal activity of peritoneal macrophages, and NK cell cytotoxicity but there was no effect of this treatment on direct cytotoxicty of colon 26-M3.1 cells *in vitro* [43]. Several investigations have reported a direct cytotoxic effect of *Ganoderma lucidum* from Lingzho mushroom that contains β-glucan; however these effects are thought to be attributed to other active components such as ganoderic acid and triterpenes that have been shown to have direct anticancer effects independent of β-glucan [44,45]. It is most likely that β-glucans themselves exert their anticancer effects through immunodulatory mechanisms and many of the implicated direct cytotoxic effects are due to nonpurified β-glucans that contain other active components with direct anticancer effects [44,45].

As with the benefits of β-glucan on infection, there are very few human studies that have examined the ability of β-glucan to alter tumor progression and most human data that are available have examined the immune response following β-glucan treatment without measuring a direct effect on tumorigenesis. Demir *et al.* [46] examined the short-term effects of oral administration of β-glucan derived from *S. cerevisiae* on immune activation in patients with advanced breast cancer. It was reported that β-glucan can stimulate proliferation and activation of peripheral blood monocytes, but there was no attempt to measure changes in grade of the tumor. A recent study reported that β-glucan from lentinan was safe and effective for use in advanced pancreatic cancer patients [47]. Similarly, it was reported that lentinin can improve quality of life in advanced colorectal cancer [48•] and survival in hepatocellular patients [49•]. Although several clinical trials have shown possible treatment benefits of β-glucans the data are still preliminary and controversial.

Perhaps the most promising evidence to date in human trials has come from recent studies on the use of β-glucan in combination with cancer treatment [48•,50]. For example, it was reported that lentinin was safe and effective for suppressing the adverse events of chemotherapy as well as improving quality of life in patients with advanced colorectal [48•] and gastric [51•] cancers. In a randomized controlled trial Schizophyllan (SPG), a β-glucan from *Schizophyllan commune*, administered in combination with chemotherapy improved the long-term survival rate of patients with ovarian cancer [52]. Similarly, β-glucan from *Grifola frondosa* combined with chemotherapy decreased the size of lung, liver, and breast tumors in over 60% of patients compared to chemotherapy alone [53]. A trial on 78 patients with hepatocellular carcinoma was conducted to examine the combination treatment of lentinan, multielectrode radiofrequency ablation (RFA), and transcatheter arterial chemoembolization (TACE) compared with RFA only, TACE only, and RFA with TACE. The combination treatment had significantly higher levels of TNFα, lower tumor recurrence rates, and a greater mean survival compared to the other treatment groups [54]. A recent study also reported that β-glucan enhances the efficacy of benacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), in terms of tumor progression and long-term survival in a xenograft model of human lung adenocarcinoma [55•].

Long-term intervention trials are clearly needed to substantiate the claims from preclinical studies for a beneficial effect of β-glucan on the tumor response. Further, a clear understanding of the mechanisms of action of β-glucan is crucial to the evaluation of its potential role as an antitumor agent and adjuvant to cancer therapy.

Conclusion

β-Glucan is emerging as a possible safe and effective nutritional strategy to prevent susceptibility to infection and cancer. Its anti-infective and anticancer properties have been attributed to its ability to bind to PRRs on various immune cells resulting in a cascade of immune defenses that can boost resistance to infection and promote antitumor activity. Although its biological effects, at least in preclinical studies, have not been questioned there are limitations to the current available research including, lack of studies that compare β-glucans from different sources, use of extracts rather than purified β-glucans, lack of dose–response studies, and a lack of a complete understanding of the mechanisms of action. Further, the preponderance of evidence comes from preclinical studies and the results from a small number of available clinical studies are inconsistent and inconclusive, which is not uncommon in the early stages of any investigation of a nutritional supplement in humans. At minimum, the current findings provide a compelling argument for further research, especially well designed clinical trials, to determine the specific role of β-glucan as an immune modulator with a clear understanding of the mechanisms of action.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 745–746).

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