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Review

Glucans as New Anticancer Agents

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Abstract. *For decades, glucans have been studied for their biological and immunological activities. The scientific community has mainly focused on immune reactions, but other areas, such as cholesterol levels and diabetic retinopathy, have shown the positive effects of glucan supplementation. However, the majority of studies focused on possible cancer suppression, where glucans showed clear and significant effects on numerous types of cancers, leading not only to clinical trials, but to approval as an official drug. The aim of this review is to describe the current knowledge of this field.*

The use of natural immunomodulators remains one of the primary interests of both the general public and health professionals. In this review we focus on the up-to-date knowledge on the use of glucans in medicine.

Throughout history, people have been aware that some mushrooms have healing properties. An ancient text found in India, written more than 5,000 years ago, focuses on the medicinal effects of mushrooms, and a Japanese legend described monkeys without serious diseases after feasting on the mushroom *Lentinula edodes*. Much later, Japanese interest in chemical components was based on this legend, resulting in development of lentinan. African shamans and Native Americans have used similar knowledge (1).

β-1,3-D-Glucans (hereafter referred to as glucans) are natural molecules able to significantly improve our health. They represent highly conserved structures often named pathogen-associated molecular patterns [for review, see Zipfel and Robatzek (2)]. There are many chemically heterogeneous polymers of beta glucose differing in glycosidic bond position. Some have a linear molecule with (1→3)-beta-D-glycosidic linkages, and some have a branched one, with side chains bound by (1→6)-beta-D-glycosidic linkages. All glucans may cause nearly identical immunological responses within multicellular organisms regardless of their origin, structure and water solubility. In addition, they elicit numerous other physiological effects and, therefore, are generally classified as immunomodulators within a large group of so-called biological response modifiers (3-6). Glucans as structural components of fungal, yeast, and seaweed cells are ranked among immuno-stimulants such as endotoxin of Gram-negative microorganisms, muramyldipeptide, zymosan, and polynucleotides.

A proper history of polysaccharides considered to be immunomodulators can be traced back almost 80 years when Shear and Turner described a polysaccharide isolated from *Serratia marcescens* that sometimes caused tumor necrosis (7). In Europe and Northern America, the investigation of polysaccharides in medicine started in the 1960s and 1970s. It was originally based on the immunomodulatory effects of zymosan, which was isolated by Pillemer and Ecker from baker's yeast, *Saccharomyces cerevisiae* (8). Zymosan is a mixture of various polysaccharides in which the glucan-rich fraction exerts the main biological activity (8). Various types of glucans have now been isolated which differ in molecular weight, branching, and biological activities. It is important to note that some of these glucans have shown no or very low biological activity (9).

Initially, most research studies on glucans focused on the effects on the murine immune system. However, subsequent research has clearly established that glucan has strong immunostimulatory effects in a wide variety of species, including earthworms, bees, shrimp, fish, chicken, rats, rabbits, guinea pigs, sheep, goats, pigs, cows, monkeys, and humans (10-12). It has been concluded that glucans represent unique immunostimulants that are active in every species; it is one of the few immunostimulants active across the evolutionary spectrum (13). Some surprising experiments

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have even demonstrated that glucan supports plant protection against disease (14, 15).

Glucans are considered strong activators of cellular immunity, with macrophages being their most important targets. Originally, glucans were established as playing a role in protection against infection. Since the original study published more than 35 years ago showing possible cancer suppression (16), the antitumor activity of glucans has been established. In fact, numerous animal and human studies have shown glucans to have remarkable activity against a wide variety of tumors (17-21), leading to use of glucan as an official drug (22). Studies focused on mechanism of action have revealed that glucans have strong synergy with naturally occurring anticancer antibodies (19, 23, 24).

Glucans have pleiotropic effects on individual branches of the defense reactions. The individual components of the immune system affected by glucans are summarized in Figure 1. Glucans are recognized by various receptors present on membranes of cells such as macrophages, monocytes, dendritic cells, and natural killer cells. The most important receptors are dectin-1 and complement receptor 3 (CR3; CD11b/CD18); additional receptors include toll-like receptor 2 (TOLL2), lactosylceramides, and the scavenger receptor family [for review, see Vetvicka (25)]. Upon binding, various biological processes occur, including direct receptor activation and cellular pathway activation (25).

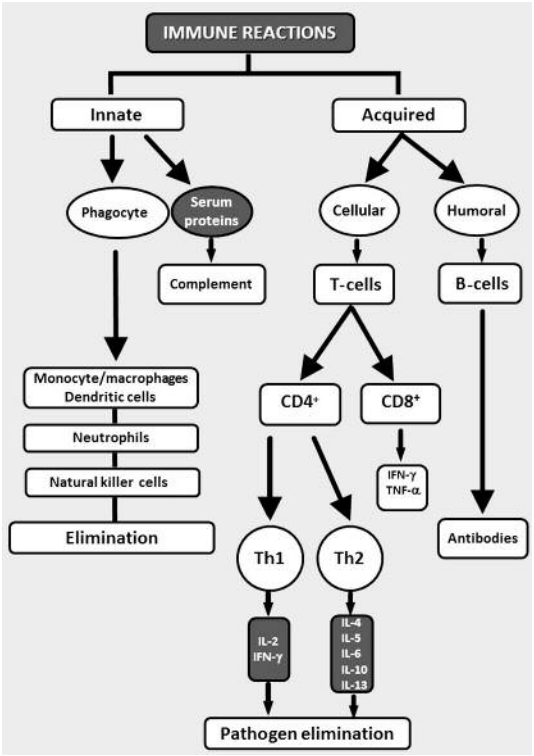

Figure 1. *Various aspects of cellular and humoral branches of immune reactions. Reactions known to be influenced by glucans are represented in white; reactions where glucans have no confirmed effects are shown in black. IFN-γ: Interferon gamma, TNF-α: tumor necrosis factor alpha, CD4+: CD4-positive lymphocytes, CD8+: CD8-positive lymphocytes, Th1: T-helper 1 cells, Th2: T-helper 2 cells, IL: interleukin.*

Glucans in Clinical Use

In addition to immune reactions, glucans also act as dietary fiber. In this role, they may positively influence numerous widespread noncommunicable diseases such as cardiovascular disease, cancer, and diabetes type 2 [for review see Brown, *et al*. (26)]. Glucans fulfill the modern definition of dietary fiber (27), which now includes all types of carbohydrates that resist enzymatic digestion in the small intestine and are not absorbed there (28, 29). Similarly to other types of dietary fiber, glucans can bind bile acids, thus lowering blood cholesterol (30). Glucans also possess the ability to affect phosphorylation of adenosine monophosphate-activated protein kinase, which regulates energy exchange (31).

Glucans and Cancer

Since the 1970s, several articles reported that glucan administration caused significant stimulation of phagocytic activity of the reticuloendothelial system with subsequent enhancement of host defense mechanisms (32, 33). Augmentation of proliferative activity and phagocytic function of granulocytes, monocytes, dendritic cells, and macrophages and stimulation of cytokine production (such as interleukin-1, -2, and -6) was confirmed (34, 35). Increased production of these cytokines subsequently stimulates immune effector cells, resulting in increased anti-infectious and mainly anticancer immunity (22, 36). Besides these direct effects, glucans scavenge free radicals, which are the main initiators of carcinogenesis (16, 37). Japanese scientists focused traditionally on mushroom-derived glucans and their effects on antitumor immunity (38, 39). Studies with immunomodulatory glucans from *L. edodes* resulted in approval of lentinan as an official drug in Japan. Many types of cancers have been shown to be sensitive to glucan therapy as demonstrated in both animal (40) and human models (41). Examples of the main types of glucans used in the form of dietary supplements for the support of treatment of various types of cancer are summarized in Table I.

Additional Effects

Several additional important effects of glucans were later demonstrated including hypoglycemic effects, reduction of cholesterol level (42), and improvements of ulcerative colitis. There is a large amount of data on the health and nutritional benefits of glucans, proposing their use as novel

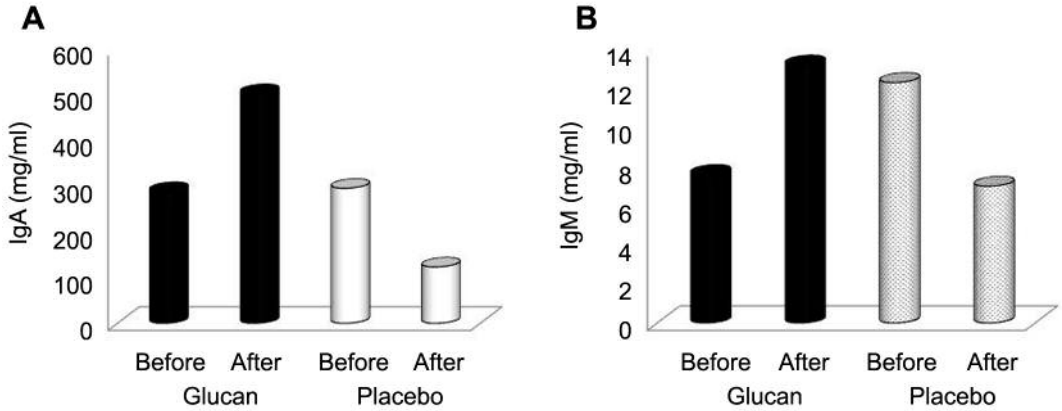

Figure 2. *Salivary IgA (A) and IgM (B) in children with chronic respiratory problems at the start and end of 30-day supplementation with glucan or placebo*.

Table I. *Glucans used in treatment of cancer.*

Cancer	Betaglucan/origin
Gastric	Schizophyllan/ *Schizophyllum commune*
	Lentinan/*Lentinula edodes*
Esophageal cancer	Lentinan/*Lentinula edodes*
Colorectal cancer	Lentinan/*Lentinula edodes*
	Agaricus sylvaticus
Hepatocellular cancer	Lentinan/*Lentinula edodes*
Pancreatic cancer	Lentinan/*Lentinula edodes*
Bone, brain, liver, breast, gastric, lung, leukemia	Maitake/*Grifola frondosa*
Cervix, endometrium, ovarian cancer	*Agaricus blazei*
Bladder cancer	Maitake/*Grifola frondosa*
Breast	Maitake/*Grifola frondosa*
	Agaricus sylvaticus
Cervical	Schizophyllan/ *Schizophyllum commune*
	Agaricus blazei
Ovarian	Schizophyllan/ *Schizophyllum commune*
Neck and head	Schizophyllan/ *Schizophyllum commune*

pharmaceuticals to support therapy of many communicable and non-communicable diseases [for review see (43)].

Glucans were also found to be active in the reduction of intestinal injury (44), in protection against liver injury (45), in regulation of hematopoiesis of patients with cancer (46), and in the improvement of benign hyperplasia of the prostate (9). Because glucans have been shown to stimulate the immune system directly, they can be useful in alleviating the symptoms of inflammatory conditions such as irritable bowel syndrome (47).

Glucans can also act as potent antioxidative agents, which lower oxidative stress, particularly in the endothelium. Oxidative stress causes the dysfunction of mitochondrial respiration chain, leading to damage to various tissues including endothelia. Endothelial dysfunction begins with imbalance of oxidant and antioxidants and results in atherosclerosis (48). Sargovo *et al*. demonstrated that application of glucans from the mushroom *Ganoderma lucidum*, which has been used for millennia in China (ling zhi) and Japan (reishi), significantly reduced pro-oxidative

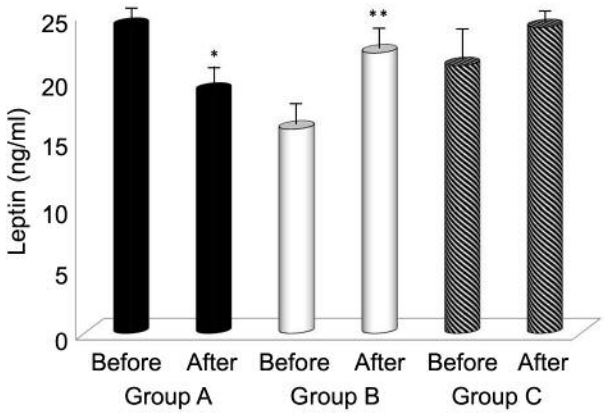

Figure 3. *Effect of glucan and vitamin D supplementation on leptin levels. Groups of 72 patients received supplementation with vitamin D and β-glucan (group A), vitamin D and placebo (group B), or vitamin D alone (group C) for 3 months. The serum level (ng/ml) of leptin was measured at the start and end of supplementation. In group A, the results were significant at p<0.05 level (*), at Group B the differences were significant at p<0.001 level (**). The differences in group C were not significant.*

status in both patients with high-risk and those with stable angina pectoris, and improved endothelial function (49).

Our own studies focused on the possible effects of glucan in children suffering from chronic respiratory disease. Using Transfer Point Glucan #300, we found that short-term (30-day) oral application of 100 mg/day of glucan resulted in significant improvements of calprotectin, albumin, and lysozyme levels. Direct measurements of salivary immunoglobulins found strong stimulation of IgA (Figure 2A) and IgM production (Figure 2B). In addition, we found levels of exhaled nitric oxide to be depressed and physical endurance significantly improved (10, 50), leading to the conclusion that this type of food supplementation represents a highly promising and inexpensive tool for treatment of chronic respiratory problems in children.

We also focused on the possible effects of glucan supplementation in patients with diabetic retinopathy, which is a common complication of both types of diabetes, affecting the eyes and often leading to blindness. We used a combination of glucan and vitamin D and found significant reduction of body weight, which correlated with reduced levels of leptin (Figure 3). We concluded that feeding with the glucan–vitamin D combination affects levels of leptin, apolipoproteins, and general nutrition in patients with diabetic retinopathy (51, 52). Additional findings showing significantly reduced orosomucoid levels at the end of a 3-month treatment indicate that continual supplementation with glucans is necessary for patients with diabetes and diabetic retinopathy. We understand that in a population with poor dietary habits, this might be difficult. The direct addition of glucan and fiber into some foodstuffs could represent a solution to this problem.

Conclusion

In short, glucans have clearly demonstrated an ability to significantly influence various biological reactions. The main focus of the scientific community has been on immune reactions, but other areas, such as cholesterol improvements and diabetic retinopathy, have shown the positive effects of glucan supplementation. Based on the studies mentioned in this review, we propose that oral application of high-quality glucan would constitute a novel approach to rationally enhance various aspects of immune reactions.

Conflicts of Interest

The Authors declare no conflicts of interests and have no affiliation with any product mentioned in this review.

Authors' Contributions

All Authors contributed equally to the preparation of this review.

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