

Effects of β -glucan on some environmental toxins: An overview

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Background. Beta-glucans are naturally occurring polysaccharides and constituents of the cell wall of certain pathogenic bacteria and fungi. They have proven healing and immunostimulating properties, linked to enhanced macrophage and natural killer cell function which likely involves specific interaction with several cell surface receptors, such as lactosylceramide, selected scavenger receptors, and dectin-1 (betaGR). In particular, glucan reduces the immunosuppressive effects of a number of agents including chemo therapy and radiation. More recent studies suggest a positive function for glucan in the immunosuppression caused by toxic agents in the environment.

Aim. An overview of the effects of glucan on the mycotoxin, aflatoxin and other environmental toxins (mercury-thimerosal, depleted uranium).

Conclusion. Glucan is effective as a natural immunomodulator and could be used as an inexpensive solution to reducing the adverse effects of some environmental toxins.

Key words: beta-glucan, aflatoxin, mercury, depleted uranium, detoxification, immunity

Received: August 30, 2013; Accepted with revision: November 22, 2013; Available online: December 11, 2013
<http://dx.doi.org/10.5507/bp.2013.090>

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INTRODUCTION

Environmental toxins have significant adverse effects on the health of both animals and man. Such toxins increase host susceptibility to infections, compromise the immune system and increase the risk of autoimmune disease. These issues have led to large epidemiological studies that attempt to establish sets of immunologically relevant end points¹.

Glucans are a major constituent of the cell wall of certain saprophytic and pathogenic fungi. For many years, they have been shown to reduce the immunosuppressive effects of a number of factors, including chemo and radiation treatment^{2,5}. Following discovery of the effects of glucan on bone marrow protection and activation of bone marrow progenitor cells, studies have suggested new functions for glucan. These are based on the well-known fact that glucan strongly stimulates all facets of the immune system, from nonspecific response to both branches of the specific immune system⁶. From this, emerged the hypothesis that glucan might offset or at least reduce immunosuppression caused by toxic agents.

GLUCAN AND MYCOTOXINS

Contamination of the environment from the air to the soil, represents a serious danger not only to commercially farmed animals but also to humans. Some of the most deadly and persistent contaminants of animal feed are aflatoxins. These are naturally occurring mycotoxins that are produced by many species of *Aspergillus*, predominantly *Aspergillus flavus* and *Aspergillus parasiticus*.

High-level aflatoxin exposure causes acute hepatic necrosis that may later result in cirrhosis or carcinoma of the liver. Acute hepatic failure manifests as hemorrhage, edema, alteration in digestion and changes to the absorption and metabolism of nutrients^{7,8}. No animal species is immune to the acute toxic effects of aflatoxins and although humans are more resistant, the current data support the danger of hepatocellular cancer in man⁹.

The levels of aflatoxins in agriculture are controlled by a variety of strategies including use of fungicides and pesticides but these treatments have a significant negative impact on the environment and often incur similar health problems to aflatoxins themselves.

The first studies showed that (1-3)- β -D-glucan, particularly with the (1-6)- β -D-glucan side chains, can regulate the presence of aflatoxins. Subsequent research revealed that under physiological conditions, mostly temperature, glucan can absorb up to 50% of zearalenone molecules¹⁰, most probably via hydrogen bonding between the hydroxyl, lactone, and ketone groups of the zearalenone molecule with the glucan single helix and van der Waals interactions between the phenyl and the β -D-glucopyranose moieties.

Further studies focused on interactions between glucan and aflatoxin B1. These showed that glucan was involved in binding to aflatoxin B1. Using molecular methods, it was revealed that hydroxyl, lactone and ketone groups participated in formation of hydrogen bonds and van der Waals interactions between glucan and aflatoxin B1 (ref.¹¹). The first investigations of glucan as a decontaminant used insoluble glucans isolated from *Saccharomyces cerevisiae*¹². A later publication showed that glucan was chemically modified to form crosslinked

carboxymethyl glucan. The resulting glucan had greatly improved adsorption of the mycotoxin T-2 and zearalene¹³.

However, to further establish the exact mechanisms of the adsorption of these mycotoxins on glucans, more research will be needed, in particular using a large number of glucan derivatives. The exact molecular structure of tetraalkylammonium-modified carboxymethylglucan remains to be determined too.

Another interesting study used the known fact that manno-oligosaccharides can attenuate aflatoxicosis¹⁴ and that glucans protect DNA against oxidative stress-related damage¹⁵. In testing the mechanisms involved in the aflatoxin-inhibiting effects of *Lentinula edodes* cultures, the authors demonstrated that these cultures act as an external stimulus affecting the anti-oxidant status in the fungal cells, which subsequently inhibits aflatoxin. Glucan present in cultures activates the transcription factors related to the anti-oxidant response¹⁶. Based on this study, glucan acts not „only“ by absorption of mycotoxins but directly reduces aflatoxin production.

When we understand that mushrooms such as *L. edodes* can grow directly on waste materials such as olive mill wastewaters¹⁷, it is clear how significant this finding might be. After all, *Lentinula* isolated from this mushroom has been used for treating gastric cancer for more than 30 years¹⁸. In addition, *L. edodes*-based glucans have extremely low cellular toxicity. For this reason they can be used directly in animal feed, simultaneously strengthening the immune system of animals and detoxifying their feed¹⁹.

GLUCAN AND OTHER TOXINS-MERCURY, PERFLUOROCTANIC ACID, DEPLETED URANIUM

Glucan has been found to protect bone marrow against the toxic effects of both chemotherapy and irradiation^{20,21}, most probably via direct stimulation of bone marrow progenitor cells. It is not surprising that glucan is attracting interest as a supplement for reducing the side-effects of cancer treatments. Additional effects of glucan were found using a model of 2.45 GHz electromagnetic radiation and oxidative injury of the skin. This experiment showed that the prophylactic use of glucan reversed the radiation-caused changes in MDA levels and SOD activities. The authors hypothesized that glucan can offer protection against oxidative injury induced by electromagnetic radiation, most likely through its known anti-oxidant abilities^{22,23}.

Our laboratory focused on the ability of yeast-derived insoluble glucan #300 to decrease the immunosuppressive actions of various immunotoxins including mercury and perfluorooctanic acid. The presence of mercury salts in the environment represents a serious problem, resulting in accumulation of mercury in fish²⁴ and despite the fact that organic ethylmercury present in limited amounts in vaccines was apparently officially cleared from causing autism²⁵, it can still have strong immunosuppressive properties²⁶ including lowering of cellular and humoral reactions such as phagocytosis, IL-6 and IL-12 secretion

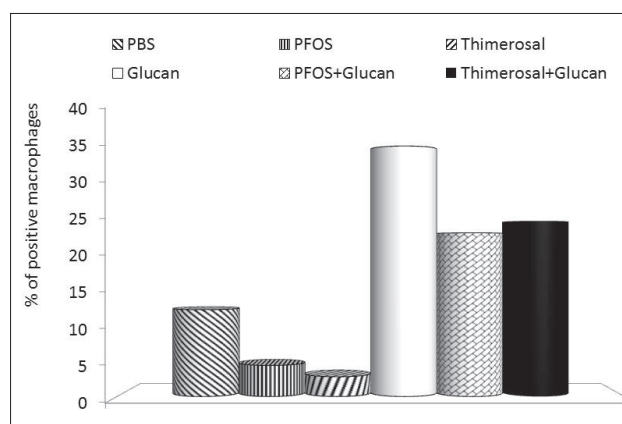


Fig. 1. Effects of orally-administered glucan on reduction of phagocytosis of peritoneal macrophages by thimerosal or perfluorooctane sulphuric acid.

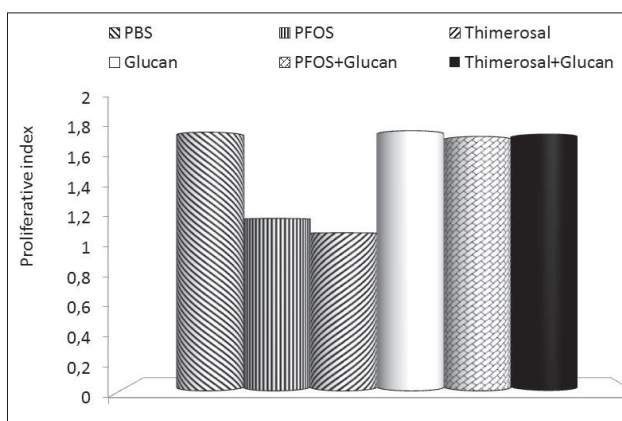


Fig. 2. Effects of orally-administered glucan on reduction of proliferation of spleen-derived T lymphocytes by thimerosal or perfluorooctane sulphuric acid.

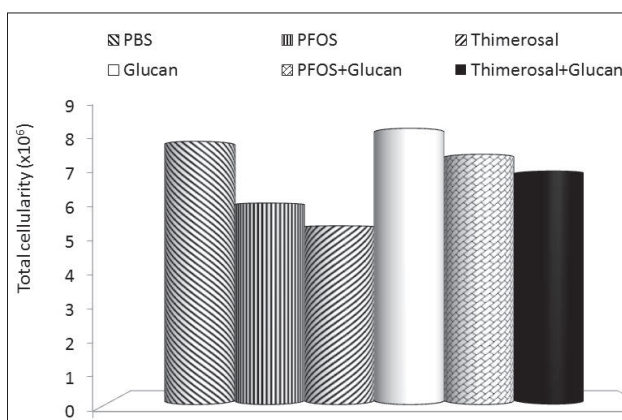


Fig. 3. Effects of orally-administered glucan on reduction of cellularity in spleen by thimerosal or perfluorooctane sulphuric acid.

and NK cell activity. Similarly, perfluorooctanesulfonates were found to decrease humoral immunity²⁷, IL-6 and IL-10 secretion²⁸ and natural killer cell activity²⁹.

Our studies showed that two-week oral administration of glucan greatly ameliorated the immunosuppressive action of mercury, including IL-6 and IL-12 production,

Table 1. Antitoxic activity of glucan *in vitro* and *in vivo*.

Type of glucan	Source	Effects on	Reference
Insoluble	<i>Saccharomyces cerevisiae</i>	Adsorption, animal protection	10
Insoluble	<i>Saccharomyces cerevisiae</i>	Myxotoxin complexation	11
Alkali-soluble	<i>Saccharomyces cerevisiae</i>	Myxotoxin complexation	11
Insoluble	<i>Saccharomyces cerevisiae</i>	Adsorption of aflatoxin	12
Soluble	<i>Saccharomyces cerevisiae</i>	Adsorption of zearalenone and T-2 toxin	13
Insoluble	<i>Saccharomyces cerevisiae</i>	Oxidative DNA damage	15
Soluble	<i>Lentinula edodes</i>	Antioxidant enzymes stimulation	16
Insoluble	<i>Saccharomyces cerevisiae</i>	Antioxidant enzymes	22
Insoluble	<i>Saccharomyces cerevisiae</i>	IL-6, IL-12, phagocytosis, antibodies	30
Insoluble	<i>Saccharomyces cerevisiae</i>	Proliferation, NK cell activity	31
Insoluble	<i>Saccharomyces cerevisiae</i>	Cellularity, proliferation, antibodies	32
Insoluble	<i>Saccharomyces cerevisiae</i>	Amikain-caused ototoxicity	33
Insoluble	<i>Saccharomyces cerevisiae</i>	ROS formation, GSH oxidation	35

antibody secretion, NK cell activity and phagocytosis of peripheral blood cells³⁰. Subsequent evaluations revealed that 7 day exposure to mercury caused a significant drop in cellularity in spleen, which was fully restored by glucan supplementation (Fig. 1). Similarly, the suppressed proliferation of T lymphocytes was returned to normal by feeding with glucan (Fig. 2). The older data on phagocytosis were confirmed using peritoneal macrophages. The stimulation of phagocytic activity caused by glucan was strong enough not only to return the inhibited activity to normal values but to a level that was significantly higher than the phagocytosis found in PBS-treated animals (Fig. 3).

The situation in perfluorooctanesulfonate-induced immunotoxicity closely resembled the toxicity of mercury. In all three tested immune reaction (proliferation of lymphocytes, phagocytic activity, and spleen cellularity), short-term exposure to perfluorooctanesulfonate caused significant reduction, whereas 2 weeks of food supplementation with glucan either returned the reaction to normal values or elevated it to near the level of glucan alone (Fig. 1-3). Previously, we showed that some of the suppression caused by perfluorooctanesulfonates can be decreased or even reversed by a glucan-resveratrol-vitamin C combination^{31,32}, but glucan alone clearly possesses similar effects.

There are additional reports describing the protective effects of glucan against toxicity. One is a report evaluating the effect of glucan on hearing loss caused by amikacin. Amikacin treatment showed significant ototoxicity by causing serious deterioration of hearing at most tested frequencies. Oral administration of glucan together with amikacin limited the hearing loss³³. In addition, glucan also showed some hearing improvement when used alone. The exact mechanisms are not known but the authors speculate that inhibition of free radical formation might be involved.

Glucan was also tested in the case of depleted uranium toxicity. The toxic effects of this compound manifests mostly via mitochondrial dysfunction, with the most relevant toxic mechanisms believed to be oxidative stress and reactive oxygen species³⁴. A detailed study showed that glucan attenuated the formation of depleted uranium-induced mitochondrial reactive oxygen species, lipid peroxidation and glutathione oxidation. In addition, further mitochondrial dysfunction including outer membrane damage and release of cytochrome c was prevented³⁵.

The mechanisms by which glucan supplementation blocks or at least lowers immunosuppression are currently unclear. One option is simple stimulation of immune reactions which supplements the lowering of immunity caused by exposure to toxins. A second option might be upregulation³⁶ or down-regulation³⁷ of some important genes, such as ERCC5, CASP9, CYPIA1, CDC42, OKC, BCl-2 or NF- κ B. Clearly, more research is needed before glucan can be fully established in the treatment immunotoxic disorders. The relevant activity of glucan *in vitro* and *in vivo* is summarized in Table 1.

CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The author stated that there are no conflicts of interest regarding the publication of this article.

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