

The effects of β -glucans on intestinal health

Julia Atanasov, Wiebke Schlörmann, Ulrike Trautvetter, Michael Gleib

Abstract

The rising incidence of intestinal diseases combined with the high level of suffering and loss of quality of life leads to a growing interest in prevention strategies that are easy to implement. Such strategies include the deliberate consumption of more fiber-rich foods, and especially those with a high β -glucan content. Whereas there has been much discussion about the potential of β -glucans to lower cholesterol and blood glucose levels to date, the present article focuses on summarizing papers investigating how β -glucans affect the intestinal environment, the intestinal barrier, the intestinal immune system, and intestinal inflammation.

Keywords: β -glucan, barley, oats, fiber, intestinal barrier, inflammatory bowel disease, short-chain fatty acids, microbiome, intestinal immune system

Introduction

Interest in intestinal diseases and their prevention is continually growing due to their increasing prevalence and the resulting health problems they cause. In Europe, ulcerative colitis (UC) now affects 1 in 198 people and Crohn's disease (CD) affects 1 in 311 people, so inflammatory bowel disease (IBD) is no longer a rare occurrence [1]. At the same time, the number of people for whom the consumption of gluten triggers the multi-faceted clinical picture of celiac disease is also increasing globally, although morbidity across the entire population is currently around 1% [2]. Furthermore, it is estimated that 8.1% of the adult population in Western countries suffer from irritable bowel syndrome (IBS), a chronic functional impairment of the gut that causes abdominal pain along with diarrhea and/or constipation [3]. The intestines are also particularly susceptible to cancer [4].

In addition, gut health and the development of intestinal diseases are strongly influenced by environmental factors such as nutrition, lifestyle or infections [1]. These diseases can affect the intestinal environment, the intestinal immune system and the integrity of the intestinal barrier. They have the potential to cause increased intestinal permeability (leaky gut), together with loss of intestinal homeostasis and increased displacement of unfavorable substances into the interior of the body [5, 6]. A dysfunctional, leaky intestinal barrier has also been reported in association with IBD, IBS, celiac disease and early-onset bowel cancer [6, 7]. Certain metabolic diseases (such as type 2 diabetes mellitus) and autoimmune diseases (such as type 1 diabetes or multiple sclerosis), as well as overweight, depression and food allergies also appear to be associated with altered intestinal permeability [5, 7].

However, certain food components can have a positive modulating effect on parameters of intestinal health, either directly or indirectly (through the formation of bioactive metabolites), thus reducing the risk of disease. It appears that such a modulation can be achieved

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through the consumption of β -glucans in particular. The potential of the β -glucans in barley and oats to reduce both cholesterol and postprandial glucose concentrations (Umschau Ernährung 10/2017, [8]) has been proven in a large number of studies and confirmed by the European Food Safety Authority (EFSA) with health claims [9–11]. In addition, there is increasing scientific evidence that β -glucans have positive effects on intestinal health.

In light of this, this article presents a summary of results from cell, animal and human studies on the potential influence of β -glucans on the intestinal environment, the intestinal barrier, the intestinal immune system and intestinal inflammation. ♦ Figure 1 provides an overview of the various health-related effects of β -glucans discussed below.

β -glucans—a heterogeneous group of substances

The β -glucans are a group of polysaccharides that are composed of linked D-glucose monomers linked by β -glycosidic bonds. They occur in the cell walls of plants, fungi and bacteria as components that provide structural support [12–14]. In the Western diet, cereals such as barley (3–11% β -glucans) and oats (3–7% β -glucans) are the most relevant β -glucan sources in terms of the quantity provided [15].

The primary structure, molecular weight, degree of branching, polymer charge and solubility of β -glucans influence their biological activity and these attributes may differ depending on the source and isolation method [12, 13]. The β -glucans found in cereals are mostly linear, unbranched molecules consisting of glucose units linked by $\beta(1\rightarrow3)$ and $\beta(1\rightarrow4)$ glycosidic bonds,

with the proportion of linkages varying depending on the cereal species [16, 17]. Due to the polymer's β -glycosidic bonds, after consumption, β -glucans enter the human colon almost undigested. Once there, they can be fermented by the microorganisms in the caecum and colon [18–20].

There are also some other foods that are relevant sources of β -glucans. It is well established that glucans are present in various edible mushroom species, for instance the shiitake (*Lentinus edodes*), which is the most commonly consumed mushroom in Japan, and oyster mushrooms (*Pleurotus* spp.), [21, 22]. The β -glucan content of these mushroom species is 0.2–0.5% of dry matter [23]. Other edible fungi and yeasts whose β -glucans are currently in the focus of research include *Schizophyllum commune*, *Coriolus versicolus*, *Saccharomyces cerevisiae* and *Agaricus blazei* [12, 21]. In contrast to cereals, a polymer of $\beta(1\rightarrow3)$ -linked glucose with a variable number of $\beta(1\rightarrow6)$ branches has been identified as the most common form of β -glucan in fungi [24]. Due to their proven high levels of bioactivity, some isolated fungal polysaccharides are already being sold as commercial products. In addition, there is currently a debate about fungal β -glucans as potentially promising components for use in nutraceuticals and functional food [21, 25].

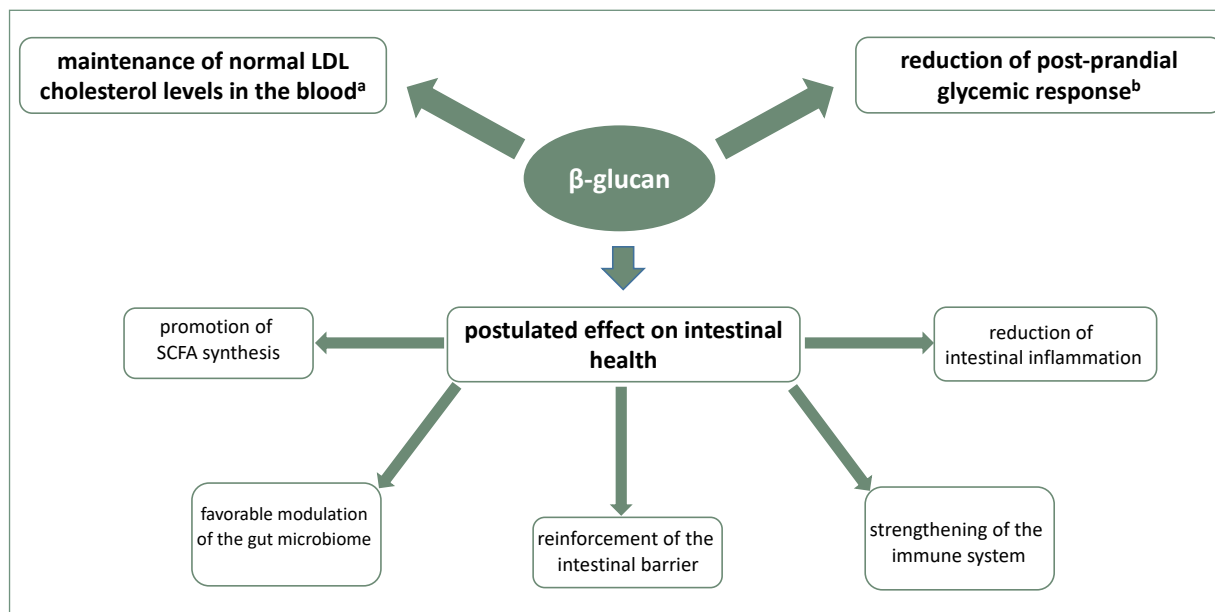


Fig. 1: Summary of the already accepted^{a, b} or postulated effects of the consumption of β -glucans

LDL = low-density lipoprotein; SCFA = short-chain fatty acids

^a Health claim, EFSA 2011 – Consumption of beta-glucan from barley, oats or bran (3 g per day) contributes to the maintenance of normal blood cholesterol levels

^b Health claim, EFSA 2011 – Consumption of beta-glucan from barley and oats (4 g per 30 g of available carbohydrates per meal) contributes to the reduction of post-prandial glycemic responses

Initial animal studies also suggest that $\beta(1\rightarrow3)$ -glucans from algae and bacteria have a potential health benefit [26, 27].

The effects of β -glucans on the intestinal environment

Formation of short-chain fatty acids

Fermentation of β -glucans by microbes in the lower part of the small intestine and in the colon results in the production of short-chain fatty acids (SCFAs) [28–30]. SCFAs have been described as having various positive effects on gastrointestinal and systemic health [31, 32]. For instance, SCFAs cause a reduction in the pH of the gut, which helps to inhibit the growth of pathogenic microorganisms [33]. One SCFA that is particularly relevant to health and colon function is butyric acid (and its salt, butyrate). Butyrate is the main energy source of the epithelial cells of the colon and it is thought to have a high anti-carcinogenic potential [34–36]. Study results also suggest that butyrate may have an anti-inflammatory effect in intestinal cells and that it may help strengthen intestinal barrier function [35].

When β -glucans from oats or barley were fermented under *in vitro* conditions, mainly acetate was formed, but some propionate and butyrate was also formed [28, 30, 37]. In line with this, an increase in intestinal SCFA concentrations was observed in animal models following interventions with β -glucans from oats, barley or bacteria [26, 38, 39]. For example, after a two-week diet with 3% barley β -glucans, rats had twice the concentration of propionate and about five times the amount of butyrate in the cecum compared to the baseline values [38]. The results of a human intervention study in 26 healthy subjects [40] and a controlled crossover study in 30 volunteers with mild hypercholesterolemia [29] indicate that in humans too, consuming food containing barley β -glucan can lead to a significant increase in SCFA levels in stool samples.

Modulation of the intestinal microbiome

Many scientific studies have shown that β -glucans from cereals, algae and yeasts influence the growth of intestinal microorganisms [37, 41–45], which can in turn affect the health of the human host [46–49]. This means that commensal bacteria in the gut are not only involved in the development of tissues and the immune system, but rather they also perform important metabolic functions, such as breaking down indigestible carbohydrates and synthesizing vitamins. Furthermore, they can inhibit the colonization of the digestive tract by pathogens and can increase the barrier function of the intestines. The interactions between bacteria and host that may exist vary depending on the composition of the microbiome [50]. Microbiome composition varies widely between individuals and is influenced by various factors, including drugs and nutrition [46, 50]. Changes in bacterial diversity and a disturbed balance between bacterial species in the gut (dysbiosis) have been observed in diseases such as Crohn's disease [51], type 2 diabetes [52], infections, obesity and autoimmune diseases [53] and it is possible that such changes contribute to the development of these conditions [54].

However, dietary fiber can have positive health effects in the gastrointestinal tract through selective modulation of the microbiome, for instance by increasing the number or activity of species of the genera *Lactobacillus* and *Bifidobacterium* [55, 56]. For example, results from *in vitro* [57–60] and animal [39, 61–64] studies indicate that β -glucans from oats and barley promote colonization of the intestines by *Lactobacillus* and *Bifidobacterium* species. However, this prebiotic effect of barley β -glucan has only been observed in some, but not all of the human studies available to date. For example, consumption of 3 g of barley β -glucan daily for two months in 26 healthy subjects led to a significant increase in fecal lactobacilli [40], and in a study in 52 healthy subjects who were supplemented with only 0.75 g of barley β -glucan per day, a bifidogenic effect was observed after 30 days [65]. By contrast, 14 volunteers with metabolic syndrome who took 6 g of barley β -glucan per day for 4 weeks and 11 patients who had undergone polypectomy and took 3 g of barley β -glucan per day for 3 months did not exhibit any effects in terms of numbers of intestinal bifidobacteria or lactobacilli compared to controls [66, 67]. There is currently a discussion around whether these varying effects could be attributable to differences in the molecular weight of the β -glucans used [58, 61].

The effects of β -glucans on the intestinal barrier

The functionality of the intestinal barrier depends on the integrity of its individual components such as the microbiome, the intestinal mucosa, the intestinal epithelium, the *Lamina propria* and the intestinal immune system [7]. Thanks to the close joining of epithelial cells through cell-cell junctions, the intestinal epithelium forms an important physical barrier. Importantly, tight junction protein complexes between the cells restrict paracellular flow. The intestines' highly viscous mucus, which consists of cross-linked mucins, antimicrobial factors (e.g. antimicrobial proteins, secretory immunoglobulin A [sIgA] and lysozyme) and trefoil peptides acts as an additional physical and chemical barrier layer that protects the intestinal epithelium against direct contact with microorganisms [47]. A change in the composition of tight junction proteins and mucus

components due to β -glucan could therefore also affect intestinal permeability.

Various studies on animals have shown that there is a positive association between the consumption of β -glucan-containing cereal products or cereal fibers and intestinal barrier function. Rats on a completely parenteral or elemental diet with oral administration of 2 g oat fiber exhibited significantly reduced displacement of enteric bacteria into mesenteric lymph nodes [68]. In addition, adding barley malt (0.5–1.2 g β -glucan per 100 g dry matter) to animal feed successfully prevented the increase in amino acid concentration in the portal serum that would be expected as a consequence of a high-fat diet. This effect was associated with an altered expression of the tight junction proteins occludin and *Zonula occludens 1* (ZO-1) and was evaluated as an expression of reduced permeability in the small intestine and distal colon [69]. In mice (high-fat diet [70]) and pigs (diet with normal fat content [71]), enrichment of feed with β -glucan from barley and oats (10% and 5%, respectively) also resulted in altered intestinal gene expression of tight junction proteins, which was considered conducive to intestinal barrier function. Studies in pigs also suggest that β -glucan from oats may increase mucosal protective function. For example, increasing the β -glucan content of animal feed (to 1.5% and 7.0%) resulted in reduced mucus permeability [72] and increased activity of goblet cells (a cell type that produces mucin) [73]. However, there are also some indications that β -glucans could impair intestinal barrier function. For instance, feeding 3 mg of oat β -glucan to mice resulted in lower lysozyme expression in the small intestine and impaired intestinal epithelial integrity compared to control animals [74]. In addition, following high β -glucan consumption (73.7 g/kg feed), weaned young pigs exhibited increased intestinal permeability (mannitol flux) in the ileum and increased adhesion of *E. coli* to isolated enterocytes compared to the controls (6.4 g/kg feed) [75].

The results of the studies conducted in humans to date also vary widely. In a randomized human intervention study in 20 healthy subjects, consumption of a standardized breakfast with barley seed bread (6.6 g soluble non-starch polysaccharides per day) for three days led to a postprandial increase in plasma concentration of glucagon-like peptide 2 (GLP-2) [76]. This peptide is considered a marker of intestinal barrier function and it is assumed

to be relevant to epithelial cell proliferation and intestinal growth. However, in a second interventional study in 21 students who consumed barley seed bread (5.0 g soluble non-starch polysaccharides per day) for four days, the increase in GLP-2 could not be confirmed. In this case, a positive effect was only observed when probiotics were also taken [77].

The effects of β -glucans on the intestinal immune system

β -glucans are generally considered potent stimulators of the immune system, with the ability to influence the activity of immune cells [12, 13, 78]. The immunomodulatory properties of β -glucans include activation of macrophages, T helper cells, neutrophils and natural killer cells, promotion of T-cell differentiation and activation of an alternative complement pathway, which together can affect humoral immunity as well as cellular immunity [12, 78]. Animal studies have demonstrated several times that this immunostimulatory effect also leads to higher resistance to various pathogens (e.g. *Staphylococcus aureus*, *Salmonella enteritidis*) *in vivo* and a better survival rate in infected animals [79–82]. The majority of these studies investigated the immunological potential of $\beta(1\rightarrow3)$ -glucans from fungi and yeasts. However, the *in vitro* [28, 83] and *in vivo* studies [75, 79] that are available suggest that β -glucans from cereals also have an immunomodulatory effect. Furthermore, observations from cell and animal models of the intestine suggest that β -glucans from cereals and from fungi, yeasts, algae and bacteria also strengthen intestinal immune function [42, 84–87]. For example, human small intestine and colonic cell lines incubated with fecal water from ileostomy patients who were on a diet enriched with oat β -glucan (5 g/day) were found to have better immune defenses than those incubated with placebo fecal water [85]. These increased immune defenses were characterized by significantly increased chemokine production and expression of adhesion molecules. In a mouse model, oral administration of β -glucans also resulted in stimulation of the intestinal immune system, which manifested as activation of Peyer's patch immune cells (fungal β -glucan [84]) or a mild inflammatory state in enterocytes (β -glucan from oat [88]).

In mechanistic terms, the immunomodulatory effect of $\beta(1\rightarrow3)$ -glucans can likely be explained by the binding of polysaccharides to certain receptors (immune receptor membrane complement receptor 3 [CR3] and Dectin-1) on the surface of immune cells (e.g. natural killer cells and macrophages) [78]. Dectin-1 binding can trigger glucan uptake and signaling pathways for phagocytosis as well as the production of cytokines and reactive oxygen species [89]. Expression of Dectin-1 has also been demonstrated in isolated human intestinal epithelial cells and in different epithelial cell lines of the colon (HT-29 and SW480). In this case, binding of β -glucans led to chemokine induction [86, 90].

The effects of β -glucans on intestinal inflammation

The immunomodulatory effects of consumption of dietary fibers such as β -glucans can contribute to the prevention and treatment of acute and chronic inflammations of the intestine [78]. Currently, corticosteroids, aminosaliculates and immunomodulators are used as standard therapy for IBD, but the use of anti-TNF- α antibodies (e.g. Infliximab) has proven to be the most promising treatment strategy. These options involve both side effects and high costs. The use of dietary fibers therefore appears to be a useful supplementary approach and/or alternative, because fiber is thought to have the potential to prevent IBD [91–93]. In a randomized, placebo-controlled study, for example, the treatment of 50 IBD patients (UC or CD) with a mushroom extract containing β -glucan (AndoSan™) led to an insignificant but clear increase in quality of life and a slight improvement in proinflammatory markers. This was thought to be the expression of a weak systemic anti-inflammatory effect [94, 95]. Furthermore, additional administration of a mixture of β -glucan, inositol and digestive enzymes in IBD patients was associated with a reduction in gastrointestinal symptoms compared to conventional therapy (treatment with 5-aminosalicylic acid) [96].

Administration of isolated β -glucans caused a reduction of proinflammatory markers in the colons of piglets [42, 97, 98]. In addition, studies in various animal models of intestinal inflammation have demonstrated an intestinal protective effect following oral and intragastric administration of β -glucan before or after chemical induction of colitis. For example, β -glucans from yeasts, fungi, bacteria and oats reduced the expression of proinflammatory markers in the colon, improved the clinical symptoms of colitis and protected the gut from lesions, epithelial changes and leukocyte infiltration [14, 99–103]. The strength of the effect appears to depend on the structural properties of the polysaccharides [99].

Conclusion

β -glucans have a variety of effects that are relevant to health. The potential of this group of substances to reduce both cholesterol and postprandial glucose concentrations has been proven in a large number of studies and has been confirmed by the EFSA with health claims in the context of authorizations. However, the current data is less clear-cut in terms of effects on intestinal health markers. Nevertheless, there is increasing scientific evidence that β -glucans have positive effects on intestinal parameters. For example, studies show that regular consumption of foods that contain β -glucan is associated with increased formation of health-promoting short-chain fatty acids, with a favorable effect on the intestinal microbiome, with activation of the intestinal immune system and with a strengthened intestinal barrier, as well as with a reduction of inflammatory processes in the intestine. Therefore, consumption of at least 3 g of β -glucans per day appears to be advisable for intestinal health.

Conflict of Interest

The authors declare no conflict of interest.

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