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A critical review on the impacts of β-glucans on gut microbiota and human health

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Abstract

The β-glucans are the glucose polymers present in the cells walls of yeast, fungi and cereals. β-Glucans are the major compositions of various nutritional diets such as oats, barley, seaweeds and mushrooms. Various biological activities of β-glucans have been reported such as anticancer, antidiabetic, anti-inflammatory and immune-modulating effects. The importance of β-glucans in food processing industries such as bread preparation, yogurt and pasta have been well elucidated. In recent findings on food science research gut microbiota plays a significant role and vastly studied for its intermediate role in regulating health. Several reports have suggested that β-glucans should have a significant impact on the gut microbiota changes and in turn on human health. The review was aimed to accumulate the evidence on types of β-glucans, their functional properties and the mechanism by how the β-glucans regulate the gut microbiota and human health. The various *in vitro*, *in vivo* and clinical studies, have been summarized, in particular, the changes happening upon the β-glucans supplementation on the gut microbiota. Overall, this review updates the recent studies on β-glucans and gut microbiota and also inputs the demanding questions to be addressed in β-glucans–microbiota research in the future.

Keywords: β-Glucans; Microbiota; Antidiabetic; Anticancer; SCFA; Immunomodulation

Contents

Abbreviations: CVD, cardiovascular disease; CSBG, *Candida* spp. β-glucan; cAMP, cyclic AMP; LNT, lentinan; LDL, low-density lipoprotein; OBG, oat β-glucan; SCFAs, short-chain fatty acids; SSG, *Sclerotinia sclerotiorum* glucan.

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1. Introduction

β-Glucan is a soluble fiber obtained from various plant sources such as oats, seaweed, cereals, mushrooms, yeast and barley [1]. β-Glucans also can be found in various bacteria and fungi such as *Cryptococcus neoformans, Pneumocystis carinii, Aspergillus fumigatus, Candida albicans, Histoplasma capsulatum* and *Saccharomyces cerevisiae*. β-Glucans are referred to as natural polysaccharides and consist of over 250,000 D-glucose linked with a β-glycosidic bond. The structures of β-glucan vary according to different sources; mushroom β-glucans have short β (1, 6)-linked branches from a β (1, 3) backbone. The β-glucans of oats and barley are linear β (1,4) linkages separating shorter chain of β (1,3) structures [2]. The bioactive and various functional activities of β-glucan-rich foods make it an important candidate for a healthy diet.

The microbial community (microbiota) of the higher animals includes bacteria, archaea, viruses, protozoa and fungi. The microbiota present in the gastrointestinal tract was found to be associated with various health-promoting activities [3]. The alterations in the microbial community have significant influence over the host's physiology and function. Prebiotics are the food ingredients provided to boost or promote the microbiota in the gastrointestinal tract; the predominant dietary sources of prebiotics are mushrooms, oats, barley, seaweed and other fiber-rich foods. As we saw earlier, β-glucans are a vital component of all these prebiotic sources [4]. Though the β-glucans research came to the limelight recently, the natural products containing β-glucans have been used for a thousand years for the benefits of human health [5,6]. β-Glucan is identified as a strong immune stimulant and an antagonist against benign and malignant tumors. β-Glucans also lower cholesterol and triglycerides, maintain blood glucose homeostasis and also account for several other health benefits. Apart from these specific health benefits, gut microbiota also offers several physiological support such as improving gut integrity [7], energy harvest [8] and protecting the host against the harmful pathogens [9]. Short-chain fatty acids (SCFAs), the polysaccharide metabolites obtained from the enzymic action of gut microbiota, play important roles in the gene expression, proliferation, chemotaxis, apoptosis and differentiation of cells [10].

It is well known that blood glucose homeostasis, lipids control and hypertension are the hallmarks in the management of diabetes. The dietary intake of β-glucans proved that it can reduce the burden of diabetes and its associated complications. Likewise, β-glucan-rich *Ganoderma lucidum* was used as an alternative therapy for treating cancer [11]. There may be two reasons how this work: either by direct cytotoxic effect or indirectly through the immunomodulatory action. Generally, the innate immune response is regulated by the dectin-1, which is a type II transmembrane protein receptor activated upon the β-1,3 and β-1,6 glucans interaction. Dectin-1 activates various signaling proteins in association in TLR 2 and 6 such as NF-κB (through Syk-mediated pathway), signaling adaptor protein CARD9 and nuclear factor of activated T cells. This further leads to the release of cytokines, which play an important role in the cancer treatment such as tumor necrosis factor-α, interleukin (IL)-12, IL-6 and IL-10. β-Glucans have proven to possess several properties (Table 1) such as anticancer [22], antidiabetic [23], anti-inflammatory [24] and immune modulation [25]. A review on skin health promotion effects of natural β-glucan derived from cereals and microorganism's states that β-glucans can improve the skin by virtue of its antioxidant, wound-healing, anti-ultraviolet light, antiwrinkle and moisturizing properties [26]. The physical properties such as water solubility, viscosity and gelation of β-glucans have made it a valuable material in the field of nutrition and food science research in recent days. An interesting review on mushroom β-glucans provides valuable information on their extraction, quantification, purification, structural characterization and biological activities [27].

Since β-glucans possess various health-promoting properties through gut microbiota regulation, the objective of the present review

Table 1
Types of β-glucans, sources, regulation of gut microbiota and health benefits

β-Glucans	Sources	Action on gut microbiota	Health benefits
Glomerellan	*Glomerella cingulata*	Glomerellan stimulates the immune system through microbiota.	Immune stimulant and anticancer property [12].
LNT (Lentinan)	Lentinus (*Lentinula edode*)	Upon LNT feeding, microbiota exhibit distinctly different space distribution. LNT reduced the diversity and evenness of gut microbiota	Synergistic action against breast cancer [13]. Effective against colorectal cancer [14].
PSG (polysaccharide ganoderma)	*G. lucidum* and *Ganoderma atrum*	Exact action on gut microbiota is not yet elucidated well.	Exerts antitumor activity by activating mitochondria-mediated apoptotic pathway and boosting the immune system [15].
Oats and barley beta glucans	Oats and barley	β-Glucans reduced the P-Cresyl Sulfate, LDL and total cholesterol levels through gut microbiota taxonomic composition modulation and changes in its metabolism.	Hypocholesterolemic activity [16].
SR (Scleroglucan)	*Sclerotium rolfsii* or *S. glucanicum*	Exact role in microbiota is not elucidated well	Effective against colorectal cancer [17].
PGG (betafectin)	*Saccharomyces cerevisiae*	The immunomodulation activity of PGG is through altering the microbiota population in gut	Immunomodulator property [18].
Zymocel	*Saccharomyces cerevisiae*	No alterations on microbiota have been seen.	Shows *in vivo* immunopharmacological activity in mice [19].
SPG (Sonifilan/schizophyllan)	*Schizophyllum commune*	The SCFAs produced from the action of microbiota on these prebiotics have the ability to prevent colon cancer.	Acts as a biological response modifier for mouse tumor systems [20]. Protects against colon cancer [17].
GRN (grifolan)	*Grifola frondosa* (maitake mushroom)	Butyrate is produced from this prebiotics *via* microbiota have many protective functions, such as differentiation, regulator of mucosal gene expression, and apoptosis	Grifolan from *Grifola frondosa* showed high antitumor activities [21].

is to elucidate how the soluble fiber β-glucan is used to treat various metabolic syndromes; this review also accumulates the valuable information on types of β-glucans, physiological functions and how the β-glucans regulate the gut microbiota first, followed by the in-depth analysis of various literature examining the health benefits of β-glucans and its application on particular field of research and industry; finally, the future perspectives of β-glucan and microbiota research are also made.

2. β-Glucans: an essential functional food and why it deserves special attention

Barley and oats are the principal sources of β-glucans; although barley is a rich source of β-glucans, oats and its products such as oatmeal, oat bran and oat flour gained much interest among researchers. Oats have some beneficial effects in reducing the serum cholesterol and preventing the occurrence of heart diseases [28]. The fields of food research gain a lot of interests as the functional foods are the safer method of treating various ailments. β-Glucans not only show powerful health benefits but also have several properties. In the preparation of sauces, soups, beverages and also other food products, β-glucans are used mainly based on its emulsification, thickening, stabilizing and gelation properties [29]. The addition of β-glucan into the preparation of bread and cakes improved their physical properties and increased the number of loafs of bread. The β-glucans also showed a low glycemic index in the pasta products, making it effective against metabolic diseases [30]. The inclusion of the β-glucan in bread increased the digestion of starch by delaying the glucose release, and by that, it prevented the hyperglycemic condition. The low-fat ice creams and yogurts made by the addition of β-glucans proved that it is not only used in cereal related foods and also in beverage industries which make its wide availability in different areas of food industries [31]. β-Glucan is well known for its cholesterol-lowering effects; the mechanism behind the cholesterol-lowering effects of oat β-glucans through gut microbiota is mainly due to the production of SCFA (propionate). The gut microbiota metabolizes the fibers and yields the SCFA to the host. The increase in the ratio of propionate to the acetic acid (main substrate for cholesterol biosynthesis) results in the decreased cholesterol biosynthesis [32]. With context to this, an interesting study has stated that the propionic acid and butyric acid have reduced the mRNA levels of 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-Co-A) (rate-limiting enzyme) of cholesterol synthesis in Caco-2/TC-7 enterocytes [33].

3. Types of β-glucans and its chemistry

Several β-glucans have been identified from different sources such as mushrooms, yeast, oats, barley and even some bacteria (Table 2). These β-glucans are identified with different physical functions and vary with each other. The following are the well-known β-glucans with their sources: glomerellan (*Glomerella cingulate*-1,3-1,6-linked glucan), LNT (lentinan) (Lentinus (*Lentinula edode*)-β-1,3 β-glucans with β-1,6 branching), SPG (sonifilan/schizophyllan) (*Schizophyllum commune*-β-1,3 β-glucans with β-1,6 branching), SSG (*Sclerotinia sclerotiorum* glucan-β-1,3-glucan) [*S. sclerotiorum* (ascomycotina)], glucan phosphate (GluP) (*Saccharomyces cerevisiae*-(1-3)-β-D glucan), zymocel (*Saccharomyces cerevisiae*), curdlan (*Alcaligenes faecalis*-β-1,3-glucan), krestin PSK (*Trametes versicolor*-β-1,4 main chain with β-1,3 and β-1,6 side chain), epiglucan [*Epicoccum nigrum*-(1 → 3;1 → 6)-β-glucan], GRN (grifolan) (*Grifola frondosa*-β-1,3-glucan), pneumocytis carinii (*Pneumocytis carinii*), scleroglucan [*Sclerotium rolfsii*-β(1-3) D-glucose backbone with one β(1-6) D-glucose side chain], CSBG (*Candida* spp. β-glucan) (*Candida albicans*-β-1,3- and β-1,6-glucans), betafectin [*Saccharomyces cerevisiae*-β-(1,6) branched β-(1,3) glucan], zymozan (*Saccharomyces cerevisiae* glucose units connected by β-1,3-glycosidic linkages), and pestolotan [*Pestalotia* sp. 815-β-(1,6) branched glucose residues for every five β-(1,3) residues]. The immune-modulating and anticancer activity of the β-glucans is based on the conformational structure [53]. For example, β-glucans with β(1,3)-linkages associated to β(1,6) branches possess strong immune action and also proved to have higher proinflammatory cytokine stimulation [54]. The type of linkage, branching and degree of solubility play an important role in the immune stimulation by β-glucans, and it has been proven that soluble glucans can induce inflammatory cytokine production strongly compared to least soluble ones [55].

Table 2
Sources of β-glucans with its molecular weight and linkages

β-Glucan	Source	Molecular weight (Da)	Structural linkages
β-Glucan oats	Oats	2.2×10^3–2.1×10^5	1,3 and 1,4 carbon linkages [34]
β-Glucan barley	Barley	2.5×10^5	1,3 and 1,4 β-d-glucan [35]
Pseudonigeran	*Aspergillus niger*	N/A	(1 → 3)-α-d-glucan [36]
Elsinan	*Elsinoe leucospila*	N/A	(1 → 4)-α-d-glucan [37]
Paramylon	*Euglena gracilis*	5×10^5	(1 → 3)-β-d-glucan [38]
Pullulan	*Aureobasidium pullulans*	N/A	(1 → 4)(1 → 6)-α-d-glucan [39]
N/A	Sea weed	6×10^3	β-1,3/1,6-glucan [40]
Pachyman	*Poria cocos*	2.6×10^4–26.9×10^4	(1 → 3)-β-d-glucan [41]
Curdlan	*Agrobacterium sp.,*	N/A	(1 → 3)-β-d-glucan [42]
Curdlan	*Alcaligenes faecalis*	5×10^5	(1 → 3)-β-d-glucan [43]
Pustulan	*Lasallia pustulata*	N/A	(1 → 6)-β-d-glucan [44]
Calocyban	*Calocybe indica*	N/A	(1 → 3)(1 → 4)-β-d-glucan [45]
Grifolan	*Grifola frondosa*	4.5×10^5	(1 → 3)(1 → 6)-β-d-glucan [46]
Curdlan	*Streptococcus mutans*	N/A	(1 → 3)-β-d-glucan [43]
Schizophyllan	*Schizophyllan commune*	4.5×105	(1 → 3)(1 → 6)-β-d-glucan [47]
Pleuran	*Pleurotus ostreatus*	N/A	(1 → 3)(1 → 6)-β-d-glucan [48]
Lentinan	*Lentinula edodes*	9.5×10^5–10.5×10^5	(1 → 3)(1 → 6)-β-d-glucan [49]
N/A	*Astraeus hygrometricus*	N/A	(1 → 6)(1 → 4)-α,β-glucan [50]
Scleroglucan	*Sclerotium sp.*	N/A	(1 → 3)(1 → 6)-β-d-glucan [51]
Piptoporan I	*Piptoporus betulinus*	2.5×105	(1 → 3)(1 → 6)-α,β-glucan [52]

4. Gut microbiota as a target of present and future research

In the past decade, the field of microbiota research has reached a new height and gained a lot of attention among food science researchers. The human body contains a microbial community that helps the host to protect against various external factors and offers a significant protection. The microbial community includes bacteria, viruses and protozoans. The adult gut microbiota majorly belongs to two phyla: Bacteroidetes and Firmicutes [56]. The bacterial flora presented in the gastrointestinal tract has already proven to heal the various pathological conditions experimentally and in various clinical trials. In the intestine, the epithelial cells are covered by the layer of mucous which serves as a lubricant for the intestine, and the mucous layer is secreted by the goblet cells; the main constituent of the mucous is a protein named mucin 2 [57]. This mucous layer also protects the intestine from the harmful bacterial invasion. The gut microbiota is enriched in genes encoding various metabolic enzymes such as glycoside hydrolases, carbohydrate esterases, amino acid decarboxylases, glycosyltransferases and polysaccharide lyases [58]. These enzymes are involved in the breakdown of various macronutrients including carbohydrates, lipids and proteins. Foods rich in

prebiotics such as mushrooms [59], barley and oats can regulate the gut microbiota.

5. Impact of β-glucans on gut microbiota (*in vitro, in vivo* and clinical trial)

The growth of *Lactobacilli* and *Bifidobacteria* is supported by the β-glucans both *in vivo* and *in vitro* [60–63]. A recent study has evaluated the *in vivo* effects of cereal β-glucans on gut microbiota. Three, 6 and 7 weeks after β-glucan administration, the experimental rats showed higher *Bifidobacterium* and *Lactobacillus* availability. The results also suggest that high doses are more effective than low doses and that β-glucans derived from oats are more effective in comparison to β-glucans from the barley [64]. In another study, different groups of rats were given different types of oats, and results of the study showed that the levels of SCFA were significantly increased in the oats-supplemented group compared to the control group, and oat β-glucans also increased the concentrations of *Bifidobacteria* [61].

A clinical trial was conducted in 52 healthy volunteers to examine the effects of low-dose barley β-glucans, which increased the count of *Bifidobacteria* significantly. Another clinical study has revealed that β-glucan-rich durum wheat flour and whole-grain barley pasta have increased the levels of *Roseburia hominis*, *Clostridiaceae* (*Clostridium orbiscindens* and *Clostridium* sp.) and *Ruminococcus* sp., and the levels of Firmicutes and Fusobacteria were lowered. The results also showed a marked increase in 2-methyl-propanoic, acetic, butyric and propionic acids [65]. The *in vitro* studies of different β-glucan sources revealed that it can enhance the growth of bacterial strains such as *Lactobacillus acidophilus*, *Lactobacillus casei* and *Bifidobacterium animalis lactis* [66]. In yogurt, β-glucans of barley and oats were found to increase the growth and viability of *B. animalis lactis* [67]. Another *in vitro* study found that the fermentation of oat and barley β-glucan inoculated in human fecal samples shows changes in the SCFA production and the bacterial mass (*Clostrium histolyticum* and *Bacteroides-Prevotella*) [68].

5.1. β-Glucan as an effective cardioprotector via gut microbiota

Cardiovascular disease (CVD) is a leading cause of death in developed countries and proven to increase drastically. Diverse factors can be a reason for the occurrence, but genetic and environmental factors play important roles in its initiation. Microbial dysbiosis plays an important role in the pathogenesis of various diseases. The microbiota helps in digestion and breakdown of macromolecules and regulates various pathways (such as TMAO and propionate pathway); by that, it controls the CVD and atherosclerosis. An interesting study found that gut microbiota has the potential to reduce the cardiovascular risks by modifying the drug, or it undergoes modification. In their study, they analyzed the plant sterol ester oat β-glucan (OBG), and compared with simvastatin, they have observed that OBG stimulates *Verrucomicrobia* population (*Akkermansia muciniphila*) expansion, and by that, it exerts prebiotic effects on the cecal microbiota, and also, OBG offered significant positive changes in the circulatory lipids, reduced the extent of plaques in the aortic walls and regulated the other changes associated with the high-fat/cholesterol-induced atherogenesis by regulating the gut microbiota, in particular *Verrucomicrobia* [69]. Another interesting study has found that β-glucans supplementation showed improved endothelial vascular reactivity in healthy individuals. They have carried out a pilot study with 26 healthy volunteers supplemented with Granoro "Cuore Mio" pasta abundant with barley β-glucans (3 g/100 g). The results of the study found that "Cuore Mio" pasta has significantly reduced the low-density lipoprotein (LDL) and total cholesterol. Also, they have observed a reduction in *p*-cresyl sulfate and flow-mediated dilation. The increase in the SCFA indicates the involvement of the gut microbiota with the β-glucans, but the elucidation of the role of gut microbiota is still not clear [70].

A study on the effects of β-glucans on the CVD showed that the supplementation of β-glucans reduced the LDL- and very low-density lipoprotein-cholesterol contents by 25%–31% and 0.2%–2.3% and also lowered the total cholesterol and the triglycerides [71]. The results also suggested that the levels of high-density lipoprotein were increased significantly; the research on the mechanism of involvement of intestinal bacteria is not reported yet. The overall findings suggest that the field of gut microbiota-mediated cardiovascular protection may be a promising area of research for testing various prebiotics such as β-glucans. Propionate has long been described as a hepatic gluconeogenic substrate [72]. However, a recent study has shown that propionate is converted into glucose by intestinal gluconeogenesis (IGN) (*i.e.*, in the intestine before it reaches the liver). Propionate and butyrate activate IGN *via* complementary mechanisms. Butyrate activates IGN gene expression through a cAMP-dependent mechanism, while propionate, itself a substrate of IGN, activates IGN gene expression *via* a gut–brain neural circuit involving the free fatty acid receptor FFAR3. The result of this study reveals that propionate promotes host physiology by initiating a gut–brain neural circuit [73]. The impact of β-glucan on the compositions of gut microbiota in mildly hypercholesterolemic individuals was evaluated. Individuals received for 5 weeks either a treatment breakfast containing 3 g high-molecular-weight (HMW), 3 g low-molecular-weight (LMW), 5 g LMW barley β-glucan, or wheat and rice. The study stated that, compared to the control group, supplementation of 3 g/d HMW β-glucan increased the population of Bacteroidetes and decreased Firmicutes abundance significantly ($P<.001$) at the phylum level. At the genus level, consumption of 3 g/d HMW β-glucan increased *Bacteroides* ($P<.003$), tended to increase *Prevotella* ($P<.1$) but decreased *Dorea* ($P<.1$), whereas a failed diet response of gut microbiota composition was observed in LMW (3 and 5 g) β-glucans. An overall result derives a conclusion that supplementation of HMW β-glucan regulates the gut microbiota favorably, and in that, it attenuates problems associated with CVD. Together, their study suggested that β-glucan induced shifts in gut microbiota in an MW-dependent manner [74].

5.2. β-Glucans as an immunomodulator

The immunomodulatory function of the β-glucans is generally referred to as microbiota independent because of its ability to bind to the immune cells directly. Since β-glucans are digested and fermented by various bacterial flora in the intestine, it is also speculated that the immune-modulatory action of β-glucans may be due to the microbial involvement. The gut microbiota can be a mediator of immune response; firstly, because of the prebiotic action of β-glucans, there occur changes in the biomass of microbiota in gut which bring the direct immune response, and in another way, the gut microbiota helps to digest the nondigestible oligosaccharide β-glucans into SCFAs with biological activity (Fig. 1) [75]. A strong anti-inflammatory effect was exerted by the butyrate (an important SCFA) by affecting the migration and adhesion of immune cells and the expression of cytokines, as well as by inhibiting the cellular processes like proliferation and apoptosis.

5.3. Emerging role of β-glucan as an anticancer food molecule

The higher degree of structural complexity of β-glucan is proven to associate with the anticancer effects. As per the studies achieved to date, no direct cytotoxic effects of β-glucans were found. In contrast, an interesting study has stated that *Ganoderma lucidum* polysaccharides, a

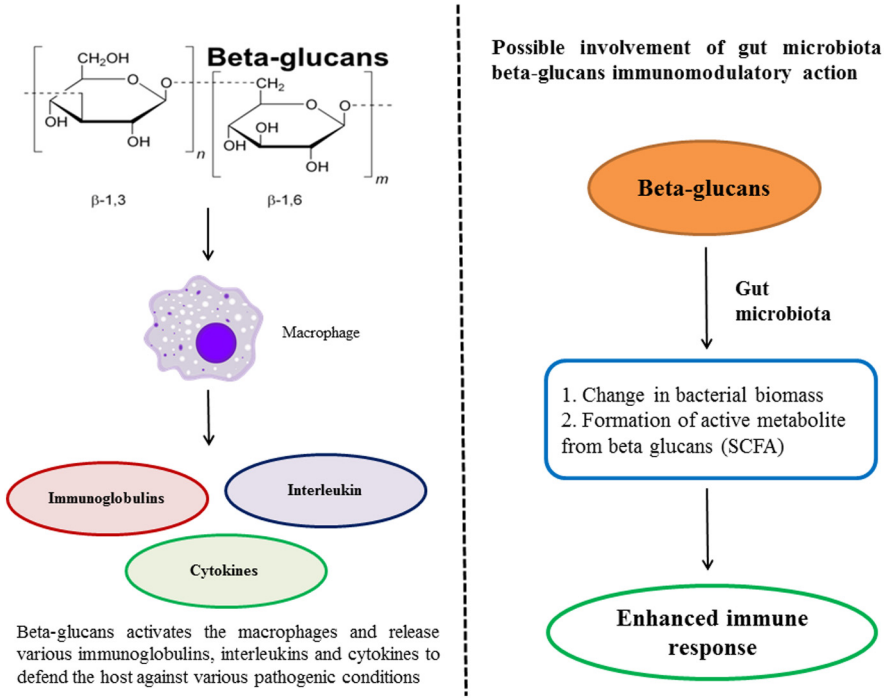

Fig. 1. Possible mechanism of action of β-glucans immunomodulatory activity *via* gut microbiota.

form of bioactive β-glucan, have stimulated the maturation of monocyte-derived dendritic cells. The effects of the β-glucans of GL are mainly due to its immunostimulatory ability which is involved in the suppression of cancer cells [76]. In an interesting study of 23 female patients with breast cancer treated with oral β-glucan, the results were compared with the 16 healthy females. The results of the study showed that β-glucan can stimulate the proliferation of circulatory monocytes in patients with breast cancer. β-Glucan did not have any direct effects on the cancer calls; the effects may be due to the interaction between the gut microbiota and β-glucan, which results in active metabolites which can increase the immune response and results in the apoptosis [77]. In another study, maitake D-fraction was found to reduce the effects of lung, liver and breast tumors, and the effects were efficient along with the chemotherapy [78]. The patients with lung cancer were treated with ganoderma polysaccharides for 12 weeks, which resulted in the altered cytokines levels [79]. Even though β-glucans are proven to inhibit the cancer growth, its direct role through the gut microbiota is not elucidated well.

5.4. Colon cancer prevention of β-glucans via gut microbiota

The colon cancer has more prevalence in the Western countries and accounts for severe mortality rate in the USA. Various strategies are involved in the treatment of colon cancer such as chemotherapy, radiation therapy and treatments involving natural products. An interesting study has found the effects of β-glucans on colon cancer prevention. In these studies, lentinan, grifolan, scleroglucan and schyzophyllan are the most studied β-glucans extracted from mushrooms on colon cancer. The results found that these β-glucans inhibited the colon cancer *via* the production of inflammatory cytokines, activation of leukocytes, and metastasis and by inhibiting tumor growth [17]. Based on the previous experimental animal studies, enteric bacteria may contribute to the development of colorectal cancer (CRC) by releasing genotoxic virulence factors and also by producing the cancer-associated metabolites [80–83]. The biological action of gut microbiota on the colon cancer may induce a chronic inflammatory state (*via* oxidative stress) by interfering with the cell cycle regulation by increasing the genotoxins; as we saw earlier that gut microbiome can metabolize various drugs, the toxic metabolites of drugs may directly affect the DNA [84,85]. The β-glucans are the polysaccharides that undergo fermentation in the cecum and colon by the microbiota [86,87], which also help in increasing the beneficial bacteria in the microflora. The SCFA production is the fermentation production of β-glucans by the intestinal and colonic bacteria; recent studies have found that SCFA (the fermented product of β-glucan) can inhibit the CRC initiation (Fig. 2). In a study conducted among healthy volunteers, 8 to 12 weeks of β-glucan consumption increased the butyrate concentration in feces [88]. In colon cancer, butyrate plays an important role; butyrate is known as an important SCFA that inhibits the colon cancer incidence, and this may be due to its ability to regenerate the epithelial cells of the intestine [15,89–92].

A recent study on the effects of β-glucans on breast cancer patients found that β-glucans had fewer effects on the white blood cells and had a significant effect on the IL-4, and the results also suggest that β-glucans can be useful as a complementary or adjuvant therapy and also as an immunomodulatory agent in the patients with breast cancer. β-Glucans also have an impact on liver cancer treatments. A study has shown that the combination of β-glucans and IFN-γ has entirely inhibited the growth of liver metastasis [17]. Based on the experimental results, researchers also carried out the clinical trials; one such trial was conducted by Okuyama et al. with β-glucans against metastasis. The 5-fluorouracil and mitomycin are generally used chemotherapy drugs to inhibit liver metastasis. In this study, lentinan (β-glucan) was used as an associate with these drugs, which provided better results than the drugs alone [93]. In a recent study, it was evident that lentinan has significant inhibitory effects on the pancreatic, gastric and colorectal cancer [94].

5.5. Diabetes control by β-glucan via gut microbiota

Diabetes mellitus is generally characterized by hyperglycemia with typical symptoms such as polydipsia, polyphagia, polyuria and weight loss

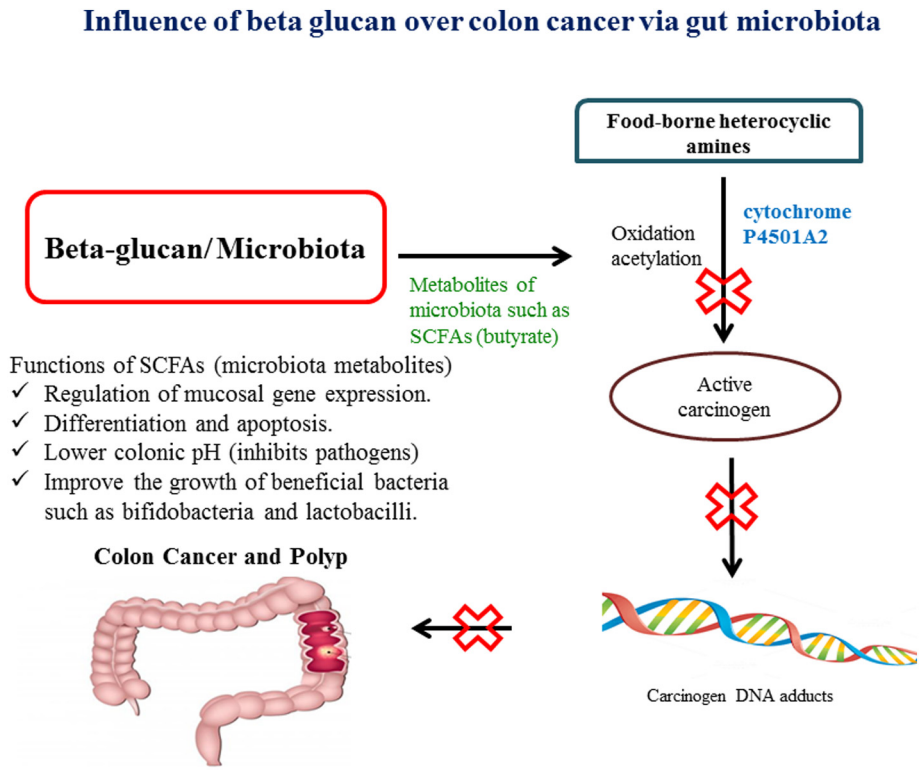

Fig. 2. Influence of β-glucans over colon cancer *via* gut microbiota.

[95]. In the recent decade, the interest of an association of microbiota with diabetes mellitus has gained much attention. Increasing research articles have demonstrated that gut microbiota of humans can regulate various physiological processes associated with diabetes (Fig. 3). A recent study has demonstrated that gut microbiota suppresses insulin-mediated fat accumulation *via* the SCFA receptor GPR43. The overall results suggest that, in adipocytes, the insulin signaling was suppressed by fatty-acid-mediated activation of GPR43, which prevents the accumulation of fats in

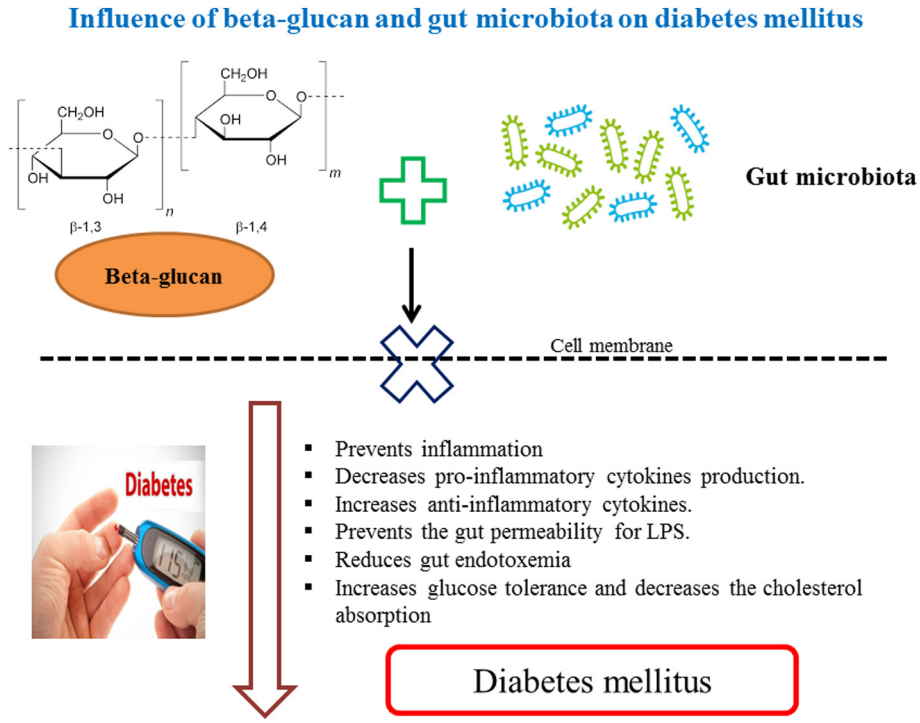

Fig. 3. Influence of β-glucans and gut microbiota on diabetes mellitus.

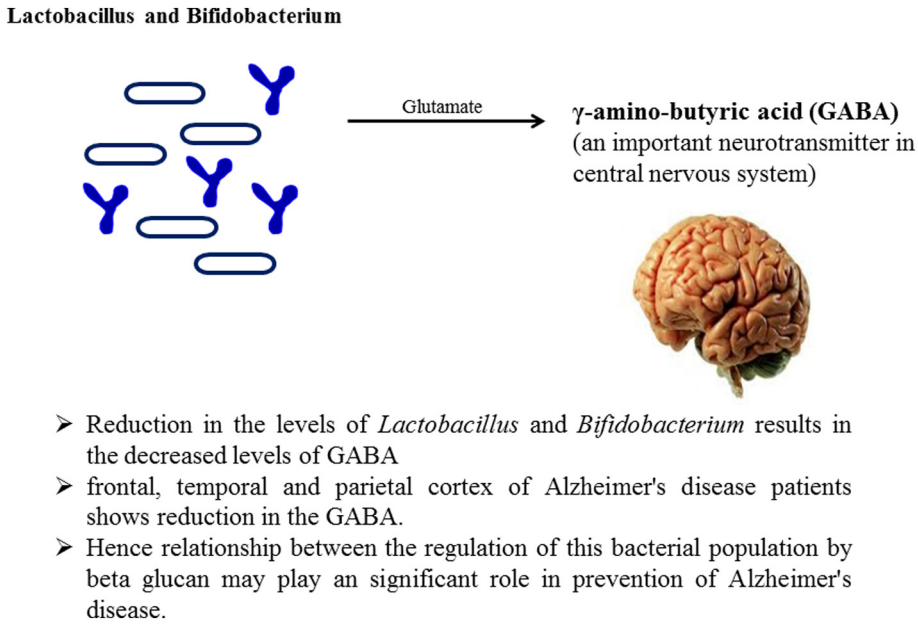

Fig. 4. Possible mechanism of β-glucans action over Alzheimer's disease *via* gut microbiota.

adipocytes and increases the lipid and glucose metabolism [96]. A recent dose-controlled trial has shown that the beverages rich in β-glucans had impact on glucose and insulin levels. The results from the study have found that 5 g of β-glucans from oats significantly lowered total cholesterol by 7.4%, glucose concentration postprandial at 30 min ($P = .005$) and insulin at 30 min ($P = .025$). The overall results suggest that intake of 5 g of β-glucans from oats can improve the insulin levels and maintain glucose homeostasis [97]. The changes in the microbial flora have been observed in the clinical studies on patients with insulin resistance; in particular, an elevation in *Firmicutes*/*Bacteroidetes* ratio was observed. *In vitro* study showed that oat supplementation can increase the population of *Bacteroides–Prevotella*; the propionate and butyrate production has been increased upon the digestion of oat glucans by microbiota. The clinical trial has shown that β-glucans-rich products can reduce the glucose and insulin responses more as compared to the low-dietary-fiber products [98]. An interesting study finds that dietary supplementation of 6% oat β-glucan concentrate to pigs significantly decreased the glucose levels, increased the levels of SCFAs and increased insulin; these changes are associated with gastric inhibitory peptide and GLP-1 [99]. In a recent study, diabetic mice were fed with oat β-glucan for 6 weeks, and it was suggested that β-glucans significantly decreased the fasting blood glucose and glycosylated serum protein. The hypoglycemic

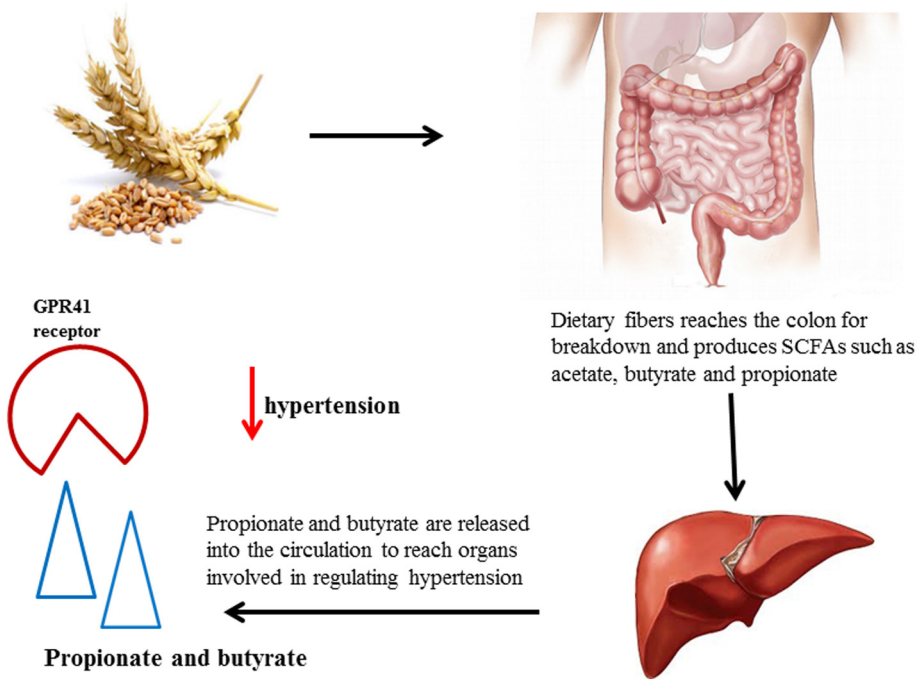

Fig. 5. Influence of dietary β-glucans over hypertension *via* gut microbiota.

effect of β-glucans was effective but not compared to that of standard drug metformin. The increased glycogen levels, decreased free fatty acids, and pancreas apoptosis inhibition are the other results of the oat β-glucan feeding [100]. In an interesting study, despite having the same genetic factors and diet, the C57Bl/6 mouse model has developed diabetic metabolic phenotype. This gut permeability and the change in the gut microbiota population may play an important role in the development of diabetic metabolic phenotype. Upon the treatment with dietary fibers, the changes were prevented [101]. The prolonged treatment with butyrate to rats has shown an increased lipolysis in adipocytes. Oat β-glucans have produced higher butyrate compared to other fibers, indicating that oat β-glucan should be a vital candidate in treating diabetes mellitus [102].

5.6. Other health benefits of β-glucans

Apart from the impact of β-glucans and microbiota on various major health problems such as cardiovascular disorder, diabetes mellitus and cancer, it also affects various conditions such as Alzheimer's disease (Fig. 4), hypertension (Fig. 5), obesity, type 1 diabetes mellitus, allergy, autism, fibromyalgia and pancreatitis for instance. The microbiota genes encoding for the enzymes involved in the breakdown of dietary polysaccharides were significantly increased in the microbiota associated with obesity in obese mice (*ob*/*ob*) [103]. Microbiota seems to have involvement in autism, but the underlying etiology is not clear yet. There are various reasons that strongly support its association, as follows: (1) after antimicrobial therapy, there is a disease onset; (2) changes in the gastrointestinal tract and related abnormalities on the onset of the disease; and (3) the symptoms of autism were reduced by antibiotic treatment and reoccurred once the treatment stopped [104]. The cross-border actions of gut microbiota cause systemic complications that can promote an entirely new collection of diseases which further target remote organs.

6. Conclusions and future perspectives

Changes in lifestyle factors such as a healthy, well-balanced nutrition rich in dietary fibers are proven to prevent various chronic diseases with no side effects. β-Glucans are naturally occurring polysaccharides proven to be beneficial in treating various diseases. In this review, we have summarized different types of β-glucans, their physical properties, the interaction between β-glucans and gut microbiota, and how their interaction can inhibit various pathological conditions. Though various studies have shown positive effects of β-glucan on microbiota, a complete study on the exact molecular mechanisms is still not elucidated. Hence, the future perspectives on microbiota research have vast openings to figure out, which may include (1) complete elucidation of metagenomic analysis of microbiota; (2) the molecular changes on microbiota upon the β-glucan exposing; (3) the changes happened on the drug metabolism by microbiota, and toxicity studies are warranted; and (4) comparison of the changes in microbial mass in the early and latent stages of the diseases. Upon achieving all the above clearly, this piece of research will open up new avenues, and hence, additional preclinical studies are needed to understand the mechanistic, genetic and other factors underlying the β-glucan–microbiota interaction, and its implication on health would be helpful in designing large-scale clinical trials in the future.

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Conflict of interest

None.

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