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β-Glucans and Probiotics

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Abstract: In the recent decades, several health-promoting features have been ascribed to β-glucans. Biological properties such as anti-cancer, anti-inflammatory and immune-modulating activity have been claimed for these polysaccharides. Moreover, when β-glucans were used in association with probiotic bacteria, prebiotic effects have been demonstrated, due to their ability to enhance growth, metabolism and/or beneficial activities of probiotics. This review shall present an overview of those studies, which have documented the diverse health-benefits of β-glucans and their association with probiotics.

Keywords: β-Glucans, Probiotic, Prebiotic, Synbiotic, Immune-Modulation

Introduction

Chemistry and Occurrence of β-Glucans

β-Glucans are long chain complex carbohydrates which can be found in cereals, seaweeds, mushrooms, yeast and in some bacteria. From a chemical point of view, β-glucans are glucose polymers consisting of linear D-glucose core chains which can contain up to 250,000 glucose residues linked by β-glycosidic bonds. Such core can be branched by further side chains of sugar, whose characteristic branching depends on the source (Vannucci *et al.*, 2013). For example, the chemical structure of β-glucans isolated from bacteria is a simple linear β(1,3)-D-glycopyranosyl polymer with none, or sometimes limited, β(1,3)- and β(1,2)-D-glycopyranosyl branch chains (Lam and Cheung, 2013). Members of the *Agrobacterium* genera, produce linear β-glucans, commonly known as Curdlan, which can contain up to 12,000 glucose units and is biosynthesized during the post-stationary growth phase (Futatsuyama *et al*., 1999; Kim *et al.*, 2003). However, also cyclic β(1,3)- and β(1,6)- D-glycopyranosyl linked glucans have been isolated from bacteria, e.g., from several plant-symbiotic bacterial species including *Bradyrhizobium japonicum* and *Rhizobium loti*, in which the cyclic structure seems to play a role in their symbiotic association with plant, helping the nodulation forming (Gay-Fraret *et al*., 2012). The cyclic structure of these compounds is given by two β(1,3)-linked trisaccharides interrelated through two β(1,6)-linked trisaccharides presenting none or a single side branch linked to free C6 (Komaniecka and Choma, 2003). Furthermore, *Streptococcus pneumoniae* synthesizes branched β-glucans with a β(1,3)-glucose backbone structure and β(1,2)-linked side-branches, which are found to be implicated in bacterial virulence (McIntosh *et al.*, 2005).

Microbial β-glucans can be part of microbial cell wall (structural polysaccharides), intracellularly accumulated (storage polysaccharides used as carbon source), or exocellularly excreted to form protection layers around the cell wall (capsular polysaccharides) or loose slime biofilms of exopolysaccharide (EPS) (Karunaratne, 2012; Lee *et al.*, 2016).

In general, either linear, cyclic or branched, β-glucans play a significant role in the bacterial tolerance to several stresses and, consequentially, in adaptation to the environment (Caggianiello *et al.*, 2016; Stack *et al.*, 2010). The intrinsic ability to produce β-glucans characterizes also several bacterial strains claimed for their probiotic features (Fanning *et al.*, 2012). The production of β-glucans is considered an intriguing trait for probiotics as they improve their capability to tolerate the gastrointestinal transit, to modulate the immune response of the host and to contrast the pathogenic bacteria in the human gut (Remus *et al.*, 2012; Stack *et al*., 2010).

β-Glucans are also localized in the cell wall of yeast and fungi, where they confere rigidity and backing (Robledo-Briones and Ruiz-Herrera, 2013). In these organisms, the strength of β-glucan backbone is ensured by β(1,3)-D-glycopyranosyl residues with high (yeast) or low (fungi) degree of polymerization (Synytsya and Novák, 2013; Petravić-Tominac *et al*., 2010). The structure of side branches is highly variable; β(1,3)- or β(1,6)-D-glycopyranosyl linkages can be found both in fungi and yeast (Chen and Seviour, 2007). Moreover, β-glucans occur in some plants, being usually contained in the endosperm cell walls and in the subaleurone layer of several cereals, such as oat, barley, sorghum, triticale, wheat and rice. β-Glucans from such species generally exhibit a linear chemical structure with β(1,3)- and β(1,4)-D-glycopyranosyl residues, with β(1,2)- or (1,6)-glucopyranosyl branches units (Barsanti *et al*., 2011).

β-Glucans and their Physiological Activities

β-Glucans from bacteria, fungal, yeast and vegetal sources, share the anomeric configurations of the β-glycosidic bonds, which connect the sugar residues. β-Linkages-containing sugars are non-digestible to humans, who lack the enzymes able to split such type of glycosidic bond (Barsanti *et al.*, 2011). Despite their unsuitability for nutritional purposes, β-glucans own notable physiological effects which attract much attention and, at the same time, create skepticism. In fact, their physiological activities are connected to numerous factors which are not yet completely clarified. The biological effects of β-glucans seem to depend on some of their structural features, including their degree of polymerization, type of core and branch linkages, tridimensional conformation and solubility (Synytsya and Novák, 2013). Furthermore, some chemical modifications, such as sulfonylation, carboxymethylation, phosphorylation and acetylation, can determine an intensification of beneficial properties (Tranquilan-Aranilla *et al.*, 2012; Jindal *et al.*, 2013). Each of these aforementioned factors could influence a particular biological activity, including anticoagulant, antithrombotic, antioxidant, cholesterol reducing, anti-inflammatory, anti-cancer activities (Kagimura *et al.*, 2015).

There are many evidences highlighting the ability of β-glucans to bind to macrophages and interact with specific receptors, thus provoking cascade of signals that influence the expression of genes involved in the regulation of apoptosis, cell proliferation and invasion (Novak and Vetvicka, 2009). Fungal β-glucans (principally from basidiomycetes) have long been used in traditional Chinese and Japanese medicines to treat and prevent human disease conditions (Chang, 2002; Kidd, 2000). In Japan, Lentinan, a glucan extracted from *Lentinula edodes* and Polysaccharide K from *Coriolus versicolor*, are approved for use as immunoadjuvants for cancer therapy (Chihara *et al*., 1987), principally against gastric and colorectal (Nakano *et al*., 1999), prostate (Tari *et al*., 1994; Hazama *et al*., 2009) and breast (Kan *et al*., 1992) cancer. How glucans contrast carcinoma is not yet elucidated, although it can be supposed that they could bind the COOH-terminal region of a subunit of Complement Receptor 3 (CR3) (Xia *et al*., 1999) and, plausibly, activate neutrophils or natural killer cells for cytotoxicity via complement activation by anti-tumor antibodies (Yan *et al*., 1999). Several studies hypothesized that the interaction between β-glucans and NK cells could inhibit the invasion of cancer cells (Volman *et al.*, 2008). Some studies indicated that the solubility of these compounds is very important for anti-tumor activity, as more water soluble molecules are more active against cancer cells (Tao *et al*., 2006; Bohn and BeMiller, 1995). Studies on animal models indicated that several fungal β-glucans may also be helpful during chemotherapy and radiation treatments (Harada *et al.*, 2002; Gu *et al.*, 2005).

The efficacy of fungal glucans has been investigated also in the treatment of Alzheimer's disease, AIDS (Acquired Immunodeficiency Syndrome), multiple sclerosis and cardiovascular diseases (Kagimura *et al.*, 2015). β-Glucans are even able to enhance the host defense against protozoa, bacteria, yeast and virus infections, such as those determined by *Leishmania major*, *Candida albicans*, *Toxoplasma gondii*, *Staphylococcus aureus*, *Escherichia coli* and Swine Influenza Virus (SIV) (Wiater *et al.*, 2012; Vetvicka and Novak, 2011; Jung *et al*., 2004). β-Glucans from yeast have been ascribed the ability to absorb mycotoxins (such as zearalenon, aflatoxin B1, ochratoxin A and patulin), supposedly due to hydrogen bonds and van der Waals forces (Jouany *et al*., 2005; Shetty and Jespersen, 2006; Jung *et al.*, 2004). The Minimum Inhibitory Concentration (MIC) value of β-glucans was investigated against several Gram-positive and Gram-negative bacteria, such as *Bacillus megaterium*, *Enterococcus phoeniculicola*, *Klebsiella peneumoniae* (Zhu *et al.*, 2016). Fungal β-glucans extracted from *Agaricus brasiliensis* were shown to inhibit *in vitro* the replication of bovine herpes virus 1 (BoHV-1), probably by disturbing the viral penetration into host cells (Minari *et al.*, 2011). Studies on animal models indicate that both cereal and fungal β-glucans can reduce blood cholesterol levels and exert a hypoglycemic effect (Dong *et al.*, 2011; Sikora *et al.*, 2013; Miranda-Nantes *et al.*, 2011; Fukushima *et al.*, 2001). The cholesterol lowering properties of oat β-glucans have been confirmed also by clinical studies and such fibers are currently used as ingredients of marketed functional food (Othman *et al*., 2011). The

hypoglycemic effect is ascribable to glucan viscosity, which could determine a slower glucose absorption thought the gastrointestinal tract. In addition, the viscosity of β-glucans has been indicated to contribute to limit the insulin secretions (Wood, 2004; Brennan and Cleary, 2005) and to reduce the risk of coronary heart disease (FDA, 1997; Bell *et al.*, 2001). These and other features render β-glucans particularly suitable for the formulation of functional food products and or supplements with health promoting effect such as the prevention of cardiovascular diseases, the facilitation of bowel motility and prevention of obstipation (Dongowski *et al.*, 2002; Tsukada *et al*., 2003; Zhu *et al.*, 2015).

Additionally, β-glucans display antioxidant properties that can be useful in anti-aging formulations for cosmetic preparations (Deng *et al.*, 2012). Moreover, in *in vivo* studies, β-glucans were able also to stimulate both the collagen biosynthesis, through the activation of macrophages in healing wounds (Pillai *et al.*, 2005), and the repairing of damaged tissues by enhancing the activity of macrophages, granulocytes and monocytes (Lee *et al.*, 2003).

β-Glucans and their Immune-Modulating Properties

β-Glucans can be classified as Biological Response Modifiers (BRM) as they own the ability to influence physiological processes (Leung *et al*., 2006). BRM comprise various molecules including the large family of cytokines (the "messenger proteins" of the immune system) and, on the other hand, the immune-modulators, which can be either immunopotentiators or immunosuppressors (Novak and Vetvicka, 2008). β-Glucans from fungi, yeast, bacteria and cereals have been proved to be immunopotentiating functional molecules against pathogens and cancer (Brown and Gordon, 2003; Volman *et al.*, 2008; Goodridge *et al.*, 2009; Murphy *et al.*, 2010). In vertebrates, fungal β-glucans have been demonstrated to activate leukocytes, thus increasing phagocytosis and the production of pro-inflammatory cytokines and chemokines (Smiderle *et al*., 2013). Additionally, the growth of several cancer cell lines were found to be inhibited by treatment with glucans *in vitro* (Chan *et al*., 2009), e.g., from prostate (Fullerton *et al*., 2000) and breast cancer (Vetvicka and Yvin, 2004). The anti-cancer ability of β-glucans is probably related to the enhancement of phagocytosis and proliferation of monocytes, granulocytes and macrophages, which have different glucan-binding receptors (e.g., TLR-2, Dectin-1 and CR3). Furthermore, chemokinesis, chemotaxis, degranulation, migration of macrophages are induced and intracellular processes, such as respiratory burst after phagocytosis of invading cells, activity of hydrolytic and metabolic enzymes, signaling processes leading to activation of other phagocytes, secretion of cytokines, are also demonstrated to be enhanced by β-glucans in several *in vitro* studies (Vetvicka and Vetvickova, 2012).

The conformational structure of β-glucans is apparently responsible for their immune-modulating and anti-cancer activity (Ross *et al.*, 1999). More specifically, a backbone of β(1,3)-linkages associated to β(1,6) branches seems to be the most effective coupling structure for immune stimulation, as it was found to enhance higher expression of pro-inflammatory cytokines in *in vivo*, *in vitro* and *ex vivo* trials (Chanput *et al.*, 2012; Vannucci *et al.*, 2013). Additionally, the degree of solubility (i.e., soluble, gel-forming, or particle-forming), which depends in turn on the degree of polymerization, type of linkages, extent of branching and chemical derivation, is crucial in immune-modulation, as soluble glucans have been showed to strongly induce inflammatory cytokine production (Soltanian *et al.*, 2009).

Anti-inflammatory activities of β-glucans from fungi were emphasized by other studies that proved their ability to significantly reduce NO production and secretion of TNF-α and IL-6 in LPS-stimulated macrophages (Jo *et al*., 2010). β-Glucans, from both fungi and yeast, were demonstrated to hinder the secretion of TNF-α, IL-1α, IL-1 and NO, decreasing the relative gene expression possibly via suppression of MAP kinases JNK1/2 and ERK1/2 (Xu *et al.*, 2012a, 2012b). Alkali-treated β-glucans, showing single helical 3D conformation, enhanced, *in vivo,* IL-1α, IL-6, TNF-α and NO synthesis, contrarily to β-glucans with triple helical structure, thus highlighting the relevance of function-structure relationship in such compounds (Ohno *et al.*, 1996). Moreover, β-glucans with a lower molecular weight were found to have higher activity *in vivo*, while higher molecular weight polymers were more active *in vitro* (Zhang *et al*., 2005).

Yeast β-glucans were able to reduce Prostaglandin E2 (PGE2) production, a prostanoid lipid mediator, during Th17 cell expansion (Gagliardi *et al.*, 2010). Other authors found that baker's yeast β-glucans contrast oxidative stress in human blood platelets, which play a key role in inflammation process caused by LPS (Saluk *et al.*, 2013). Some *in vivo* approaches have substantiated the anti-inflammatory potential of fungal β-glucans. Polysaccharide components of yeast cell wall (principally β-glucans) have been shown to alleviate intestinal inflammation in DSS-induced mice models (Jawhara *et al.*, 2012). In humans, the anti-inflammatory effectiveness of β-glucans was investigated in different *in vivo* trials, which indicated a reduction of cytokine levels in whole blood from healthy volunteers, (Johnson *et al*., 2009), as well as in plasma and faeces from patients with chronic inflammatory bowel disease

(Førland *et al*., 2011), after oral intake of β-glucans, principally from fungi.

β-Glucans and Probiotics

Probiotics, i.e., the beneficial microorganisms that positively influence the human health (FAO/WHO, 2002), include numerous strains of bacteria, mainly belonging to *Bifidobacterium* and *Lactobacillus* genera and yeast (Arena *et al.*, 2014a). The beneficial actions for which they are claimed include the fortification of the intestinal mucosal barrier, the competition against pathogenic microflora, the ability to synthetize vitamins and short-chain fatty acids, the balancing action on the gut microbiota and the capability to stimulate host immune response by modulating the Gut Associated Lymphoid Tissue (GALT) (Scholz-Ahrens, 2016; van Baarlen *et al.*, 2013). Besides probiotics, also prebiotic compounds are gaining increasing attention and popularity in nutritional science and among consumers. To be qualified as a prebiotic, a food ingredient should be non-digestible by humans but serve as fermentable substrate for specific, endogenous microorganisms of the gut micro flora. In this way, prebiotics can selectively stimulate the growth and/or activity of beneficial microorganisms, thus improving their health benefits to the host (Gibson *et al*., 2004). Hence, embracing the probiotics and prebiotics concepts, the term "synbiotic" denotes those products containing both probiotics and prebiotics, resulting in potential overall enhancement of the beneficial effects on health (Schrezenmeir and de Vrese, 2001; Paineau *et al.*, 2014).

Most of the prebiotics currently used in the food industry comprise non-digestible oligosaccharides, such as inulin, Fructo-Oligosaccharides (FOS) and Galacto-Oligosaccharides (GOS). However, accumulating evidences indicate also β-glucans as potential source of prebiotics. β-Glucans could be comprised in prebiotic compounds because they meet the characteristics required to have this status. In fact, β-glucans are non-digestible through human gastrointestinal tract and numerous studies have shown their ability to selectively intensify probiotic action, including potentiation of immune-modulation, inhibition of cancer, reduction of cholesterol and decrease of cardiovascular disease (Arena *et al*., 2015; Patel *et al.*, 2010; Patel and Goyal, 2012; Arena *et al*., 2016). In addition, β-glucans have been shown to be a carbon source for some probiotic microorganisms, influencing their growth rate and lactic acid production in the intestinal environment (Snart *et al*., 2006; Zhao and Cheung, 2011). Obviously, the ability to catabolize prebiotics, including β-glucans, is species- and strain-dependent, as only some microorganisms have the necessary enzymatic pathways (Hughes *et al.*, 2008; Su *et al.*, 2007). Although little is known about how bacteria catabolize long chain, non-digestible fibers, numerous studies have showed that the fermentation of glucans could occur outside or inside the cell (Sarbini and Rastall, 2011). Moreover, in the complex environment of the gut microbiota, the fermentation of β-glucans is likey to occur by pathways involving metabolic cooperation mechanisms (Crittenden *et al*., 2002). Several gut commensals possess specific genes encoding for cell-associated glycosidases, which are assigned to hydrolyze monosaccharides from the non-reducing ends of oligo- and polysaccharides in the extracellular environment. Such enzymes work in association to ATP-Binding Cassette (ABC) transporters, permeases, proton symporters and Phosphoenolpyruvate-Phosphotransferase (PEP- PTS) systems, which transport the hydrolyzed sugar into the cell (Katayama *et al*., 2005; Perrin *et al*., 2001). Other microorganisms are able to internalize long chain prebiotics into the cytoplasm via specific transport systems and then, catabolize them thought hydrolases, phosphorylases, epimerases, mutases and/or kinases (Bottacini *et al*., 2014; Pokusaeva *et al*., 2014). In the probiotic *Bifidobacterium longum* subsp. *infantis*, different metabolic pathways are activated, depending on which type of β-glucans occurs inthe growth medium. For instance, ABC transporter systems and PTS proteins, followed by intracellular glucanase, constitute the central pathways triggered with by β-glucans from barley and seaweed (Zhao and Cheung, 2013; Goh and Klaenhammer, 2015).

Interestingly, since the survival of probiotics is conditioned by the ability to pass through the gastrointestinal tract, particular attention has been focused on microorganisms able to produce exopolysaccharides, due to the ability of these compounds to increase the tolerance to acid and enzymatic stress (Stack *et al.*, 2010; Caggianiello *et al*., 2016). Accordingly, food matrices containing barley β-glucans were also able to ameliorate the persistence of *Lactobacillus* strains to *in vitro* gastrointestinal transit (Arena *et al.*, 2014a). Additionally, symbiotic mixtures of oat β-glucans and *Bifidobacterium longum*, *Lactobacillus plantarum*, or *Lactobacillus paracasei* have been shown to prolong the viability of these microorganisms within food matrices, such as yogurt and fermented skimmed milk (Rosburg *et al*., 2010; Kiliç and Akpinar, 2013; Lazaridou *et al*., 2014). Beside the prebiotic purpose, the addition of prebiotic compounds to food matrix could ameliorate functional, technological and organoleptic properties of food (Singh *et al*., 2012), albeit it remains necessary to individuate the most perform-ant synbiotic formulation (Vasiljevic *et al*., 2007; Zhao and Cheung, 2011; Hughes *et al*., 2008; Angelov *et al*., 2006; Kalpa and Preetha, 2016). Oat β-lucans were found to promote the viability of lactobacilli used for yogurt production and to have positive effects in terms of lactic acid content and pH reduction (Kilic and Kankaya, 2016). β-Glucans from microbial origin have

been investigated for their prebiotic features and were proved to advantage *Bifidobacterium* spp., to decrease cholesterol levels in humans (Mårtensson *et al*., 2005) and to improve rheology and texture of fermented foods (Mårtensson *et al*., 2002). Moreover, a 2-substituted-(1,3)-β-D-glucan of bacterial origin was shown to ameliorate *in vitro* the adhesion of *Lactobacillus* strains to the human intestinal epithelium, thus suggesting that it could contribute to improve colonization and persistence of probiotics into the host, with related beneficial effects (Russo *et al.*, 2012). Food matrices containing barley β-glucans were reported to improve growth and probiotic features of different *Lactobacillus* strains during both unstressed conditions and after exposure to *in vitro* simulation of the digestive tract. In addition, β-glucans-containing food was shown to positively influence the adhesion of probiotics to human enterocytes *in vitro* (Arena *et al.*, 2014b). Several researches have tried to determine the optimal ratio between prebiotics and probiotics in synbiotic formulations for hypocholesterolaemic and anti-hypertensive effects (Miremadi *et al.*, 2016). Moreover, synbiotic functional foods have been found to beneficially change the profile of intestinal bacterial metabolites, including the enhancement of ketones, carbon disulfide methyl acetate and short chainfatty acids (Vitali *et al.*, 2010).

A few studies have considered the impact of dietary β-glucans on the immunomodulatory properties of human probiotics. Chanput *et al*., (2012) demonstrated that β-glucans from different sources could modulate *in vitro* the expression of various human inflammation-related genes, while earlier experiments on dendritic cells pointed to an anti-inflammatory potential of cereal β-glucans, suggesting they could contribute to immune homeostasis in the highly exposed intestinal environment (Wismar *et al*., 2011). Recently, we have investigated *in vitro* whether oat and barley β-glucans could influence the probiotic features of diverse lactobacilli strains as well as some aspect of their interaction with the host (Arena *et al.*, 2016). Although no significant effect was found on bacterial survival to simulated digestive tract nor on microbial adhesion properties, interestingly, combinations of microorganisms and β-glucans could synergistically modulate the expression of several immune-related genes, resulting in an overall enhanced anti-inflammatory effect of probiotics. The impact that β-glucans could have on immunomodulatory (as well as other) activities of probiotic bacteria highlights the therapeutic potential of dietary-based approaches for the treatment of gut immune dysfunctions. Therefore, studying the effects and the immune-modulating activity of combinations of β-glucans and probiotics on human host would deserve deeper researches.

In the aquaculture field, the scientific literature offers several contributions that deal with the effects of mixtures of β-glucans and probiotics on model organism. In one example, combination of yeast and vegetable β-glucans with probiotic *Pseudomonas synxantha* and *Pseudomonas aeruginosa* were able to beneficially influence the growth, survival and immune response of prawns (*Penaeus latisulcatus*) (Van Hai and Fotedar, 2009). Likewise, the combination of β-glucans isolated from algae and *Shewanella putrefaciens* strain, a probiotic isolated from gilthead seabream skin, was shown to modulate the immune response and stimulate growth of the gilthead seabream, i.e., up-regulating the transcriptional levels of IL-1β and INFγ genes and down regulating IgM gene expression (Rodríguez *et al.*, 2007). Such studies underlie the possibility to substantially improve breeding conditions and health status of farmed fishes (and so of consumers) by adequate dietary intervention.

Concluding Remarks

Synbiotic functional foods are obtaining large attention as they hold promising applications for health-promoting purpose. As documented by both *in vitro* and *in vivo* trials, β-glucans own several beneficial properties, including immuno-modulation, cancer and metastasis inhibition, anti-inflammatory activity, cholesterol reduction, digestion and constipation problem improvement and, interestingly, potentiation of probiotic effects, i.e., prebiotic activity. The prebiotic aptitude of β-glucans relies on their ability to positively influence growth rate and health-promotion effects of probiotic microorganisms. β-Glucans from different sources, e.g., microbial, fungal, yeast and cereal, have been isolated, purified and characterized in the last years, focusing on their commercial applicability alone and in combination with microorganisms. Such studies indicate that β-glucans have major characteristics to become profitable prebiotic ingredients of synbiotic food. Nonetheless, numerous aspects of their biological activity still need to be elucidated, as the complexity of the microbiota-host relationships is not easily outlined and predictable.

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Author’s Contributions

Mattia Pia Arena and Giuseppe Spano: Contribute in drafting the article and reviewing it critically for significant intellectual content.

Daniela Fiocco: Give final approval of the version to be submitted and any revised version.

Ethics

Authors declares no ethical issues.

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