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Review article

Beta-glucans and cancer: The influence of inflammation and gut peptide

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ABSTRACT

Dietary β-glucans are soluble fibers with potentially health-promoting effects. Gut peptides are important signals in the regulation of energy and glucose homeostasis. This article reviews the effects of different enriched β-glucan food consumption on immune responses, inflammation, gut hormone and cancer.

Gut hormones are influenced by enriched β-glucan food consumption and levels of such peptide as YY, ghrelin, glucagon-like peptide 1 and 2 in humans influence serum glucose concentration as well as innate and adaptive immunity. Cancer cell development is also regulated by obesity and glucose dishomeostasy that are influenced by β-glucan food consumption that in turn regulated gut hormones.

Contents

1. Introduction

β-glucans have gained much interest in the field of functional foods, since they are regarded as a potentially health-promoting food ingredients [1]. β-glucans are soluble fibers located in endosperm cell walls of cereals, baker's yeast, certain fungi, mushrooms and bacteria. They are polysaccharides of D-glucose monomers

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linked by a mixture of β-(1 → 3) and β-(1 → 4) glycosidic linkages or consist of a backbone of β-(1 → 3)- linked-D-glucopyranosyl units with β-(1 → 6)-linked side chains of variable distribution and size. The differences in the structure, size of the polysaccharide chain, branches, and molecular weight influence the activity of the β-glucans.

Oat and barley are rich sources of β-glucans, whereas other cereals like rye and wheat have a lower concentration [2]. Thanks to their physicochemical properties β-glucans are used in the food industry as thickening agents, stabilizers and fat replacers, besides they have a extensive range of biological effects and actions including antioxidant effects, free radical scavenging, immunostimulatory effects, differentiation induction in cancer cells, and antitumor effects via the activation of different immune responses in the host [3].

The anti-cancer effect of β-glucans can be related in one hand to their control of inflammation via immunostimulatory patterns [4] on the other hand it might be relate to the possible effect on gut hormones control [5,6].

Besides, The European Food Safety Authority gave a positive opinion about the ability of foods containing β-glucans from oats and barley to reduce post-prandial glucose which in turn can be associate to obesity, cardiovascular disease reduction and cancer [7–11].

The ability of β-glucans to lower postprandial glycemic response has been attributed to the viscosity of the solution in which the fiber is solubilized [12–14]. Soluble fibers increase the viscosity of the chyme, and hence lengthen the gastric emptying, intestinal transit times and nutrient absorption, which are reflected in lower postprandial glycaemic and insulinaemic responses [15,16]. The presence of fibers delay the interaction of the enzyme with its substrate reducing the digestion and absorption of part of the ingested carbohydrates [17]. The fibers also influence the gut microbiota composition that it is of primary importance for the ability to prevent inflammation. It can modulate host gene expression and metabolism playing a role in nutritional imbalance that lead to obesity, diabetes and cancer [18,19].

In addition to the positive mechanical and physical effects on the gastrointestinal function, soluble fibers seem also to influence the secretion of gut peptides that in turn can be relate to cancer [20–22].

Thus, it is likely to suppose that enriched β-glucan foods might act at different levels that sometimes come together. Therefore, the mechanism by which β-glucan has beneficial health effects, could be in part due to an effect on gut hormones, inflammation and immunology modulation.

Besides, stimulation of the endogenous hormones represents an appealing therapeutic strategy. Given the highly attractive of gut peptides, and particularly of peptide YY (PYY), ghrelin and glucagon-like peptide (GLP) 1 and 2 to anti-obesity and anti-diabetic therapy, it is of interest to review the effects of β-glucan containing foods on gut hormones. Obesity is a state of low-grade, chronic inflammation that promotes the development of insulin resistance, diabetes and cancer. Thus, the review focuses 1) on the effects β-glucan on cancer via the influence on inflammation and immunomodulation and 2) the influence of β-glucan foods on gut peptide levels in humans and possible role on cancer.

2. Cancer, β-glucans and inflammation

In response to tissue injury elicited by trauma or infection the inflammatory response sets in, as a complex network of molecular and cellular interactions directed to facilitate a return to physiological homeostasis and tissue repair. The main cellular players in inflammation are immune cells, which can be roughly divided into pro- and anti-inflammatory immune cells whose relative balance and functions tightly control the inflammation processes [23].

A low-grade systemic inflammation characterizes several biological mechanisms responsible inflammatory diseases, including cancer [23]. The importance of the immune system in preventing tumor formation, immunosurveillance, has been repeatedly shown in animal models and is supported by epidemiological evidence, such as increased frequency of certain cancer types in immunosuppressed individuals [24,25].

Macrophages play an important role in all phases of host defence either concerning innate either adaptive immunity by cytokines secretion (IL-1, IL-6, IL-8, IL-12, TNF-alfa) and inflammatory mediators like nitric oxide (NO) and hydrogen peroxide (H2O2) [26]. Javmen and collaborators [27] showed that Balb-c mice fedeed with S. Cerevisiae β-glucans 0.1 mg once a week increase serum interferon-gamma and macrophage phagocytic capacity.

Several studies suggests that β-glucans are potent immunomodulators influencing both innate and adaptive immunity [28]. In vivo peritoneum macrophages stimulated by beta-glucans increase NO production and elicit TNF-alfa production by complement receptor 3 (CR3, CD11b/CD18) [29], Detectin-1(beta GR) [30] and Toll like receptors 2 surface receptor [31]. Bose et al. [32] investigated the use of different receptors (dectin-1 and CR3) for oxidative burst in reaction to different physical forms of β-glucans that in human monocytes.

In vitro β-glucans, via dectectin-1receptor, elicit archidonic acid release and Cyclooxigenase expression [28]. The cytoplasmatic receptor, dectin-1, work in collaboration with Toll-like receptors 2 and 6 (TLR-2/6) [33] activating an entire signalling pathway downstream that brings to NF-κB (through Syk-mediate pathway), signalling adaptor protein CARD9, nuclear factor of activated T cells (NFAT) and eventually cytokines production as interleukin (IL)-12, IL-6, tumor necrosis factor (TNF)-α, and IL-10 [34–36].

Furthermore, it has been found that β-glucans can induce human peripheral blood mononuclear cells proliferation and monocyte derived dendritic cells maturation via cytokines production [37]. So, It seems that β-glucans might stimulate a wide immune responses including phagocytosis and proinflammatory effects that it may lead to the elimination of infectious agents as for example like *Staphylococcus aureus, Escherichia coli*, *Candida albicans*, *Pneumocystis carinii*, *Listeria monocytogenes*, *Leishmania donovani* and *Influenza* virus [38]. In animal models, several studies confirmed that systemic β-glucans treatment enhanced migration of neutrophils into a site of inflammation and improve antimicrobial function [39].

Additionally, β-glucans via CR3 (complement protein 3) working through focal adhesion kinase (FAK) is essential for ROS production and cytokine production in neutrophils and macrophages in order to enhanced microbial killing [40].

Mo and collaborators [41] evaluate the effect of (1 → 3) β-glucans on the tumor volume in S180-bearing mice after the intragastrically administration for 16 days. The tumor inihibition rate in mice treated with low, medium, and high doses of (1 → 3) β-glucans were significantly higher compared with that in the control group ($P < 0.01$) showing that β-glucans suppress tumor growth in dose dependent manner. Whereas the immunopotentiation ability was evaluated by spleen index, CD4\CD8 ratio and cytokines concentration showing no difference in CD4\CD8 ratio but increase, in dose dependent manner, of spleen index and IL-6, TNF-alfa and IL-2 cytokine levels. Furthermore, the authors showed an increased transcription levels of Bcl-2/Bax ratio in β-glucans dose dependent manner suggesting a role of β-glucans in apoptosis.

As immunostimulation, β-glucans treatments showed interesting features as in the work of Albeituni and Yan where β-Glucan bind to DCs and macrophage receptors triggering their antigen-