Health benefits of oat: current evidence and molecular mechanisms

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ABSTRACT

Oat has historically been considered as a valuable crop due to its nutritional attributes. In recent years, oat has attracted growing attention as a healthy food due to its content of various bioactive compounds that can positively impact human health, such as β-glucan, avenanthramides, tocols, sterols, phytic acid and avenacosides. These compounds are involved in the reduction of the risk of cardiovascular diseases (CVD), type 2 diabetes mellitus (T2DM), gastrointestinal disorders and cancer. This short review summarize the current knowledge about the beneficial effects of oat consumption, with emphasis on oats bioactive compounds responsible of the health-promoting attributes of this cereal and their underlying molecular mechanisms.

Keywords: oat, health, bioactive compounds, molecular mechanisms

Introduction

Oat has been recognized as a valuable foodstuff since ancient times, due to its nutritional attributes. This cereal provides important amounts of carbohydrates, mainly in the form of starch, dietary soluble fiber, lipids, good-balanced proteins and several B vitamins. Recently, oat has received increased attention due to its health-related benefits. Consumption of oat products has been associated to reduction of serum cholesterol, and the risk of cardiovascular diseases (CVD), as well as with prevention of cancer, diabetes and gastrointestinal disorders [1]. Based on clinical studies, the U. S Food and Drug Administration and European Food and Safety Agency have approved health claims for oat-derived foods regarding the ability of oat β-glucan (OBG) to reduce the serum cholesterol and the risk of CVD [2,3]. However, the beneficial effects of oat consumption have been attributed not only to the presence of OBG but also to other bioactive compounds [1].

Oat can be included among gluten-free ingredients when it is produced, prepared, and/or processed in a way to avoid contamination with gluten-containing cereals [4]. However, the careful selection of oat cultivar is crucial prior to its consumption by celiac people, since the immunoreactivity associated with toxic prolamins depends on oat genotype [5]. The inclusion of oat in gluten-free diets may improve the nutritional status of celiac people and can offer a wider choice in their diets.

Despite the tremendous increase in oat popularity and consumption, its production has declined steadily over the last years, especially in Europe, due to the dominance of other cereals such as wheat and barley [6]. Nowadays the food industry is investing a great deal of effort in increasing the usage of oat as ingredient for formulating novel food products. The development of new oat products may increase the range of functional foods in the market and could contribute to the prevention of chronic diseases.

This short review summarizes the current knowledge about the beneficial effects of oat consumption, with emphasis on oat bioactive compounds responsible of the health-promoting attributes of this cereal and their underlying molecular mechanisms. The information provided in this review is based on very recent literature sources.

Bioactive compounds in oats.

The health beneficial properties of oat can be attributed to different bioactive compounds:

OBG is the main component of the soluble fiber in oats, consisting of a linear branched chain of D-glucose molecules bonded by mixed β-(1-3) and β-(1-4) linkages, with an approximate distribution of 30% to 70%, respectively [7]. This polysaccharide is located in oat aleurone and subaleurone endosperm cell walls, and its content varies from 1.8 to 7% [8,9]. The concentration and degree of polymerization of OBG depends not only on the cultivar, but also on the growing, processing and storage conditions of oats [10]. There is strong evidence showing that OBG is partially responsible for the reduction of blood glucose and serum cholesterol attributed to the consumption of this cereal [11]. The beneficial effects of OBG are related to its physico-chemical and rheological characteristics such as molecular weight, conformation, water solubility and viscosity [10, 12].

The health benefits of oat have also been associated to the presence of several antioxidant compounds, such as tocols, namely tocopherols and tocotrienols, phenolic compounds and sterols. **Tocols** (16-94 mg/kg) are composed of a polar chromanol ring linked to an isoprenoid-derived hydrocarbon chain. They act as strong free radical scavengers, showing also the ability to inhibit the proliferation of certain cancer cells [13]. Phenolic acids are the most abundant **phenolic compounds** in oat, especially

ferulic acid (250 mg/kg), that is present mainly bound to cell wall components by ester or ether linkages, but also exists as free forms [14]. Avenanthramides are hydroxycinnamoyl anthranilate alkaloids found exclusively in oats. Twenty-five avenanthramides have been identified. The AVA-A (2p), AVA-B (2f) and AVA-C (2c) are the most abundant in oats [15, 16]. Avenanthramides have documented antioxidant, anti-inflammatory and anti-proliferative activities [17,18]. Oat also contains other antioxidant phytochemicals such as **sterols** (447 mg/kg), being the most abundant β-sitosterol, Δ-5 and Δ-7 avenasterols [19] and **phytic acid** (5.6-8.7 mg/g) that exhibits antioxidant activity due to its ability to chelate metal ions, making it catalytically inactive and resulting in the inhibition of metal-mediated free radicals production. However, this chelation-activity reduces bioavailability of essential minerals [20].

Oat is the only saponin-containing cereal, comprising unique steroidal glycosides named **avenacosides A and B** (65.5 and 377.5 mg/kg, respectively) that have shown anticancer activity through diverse and complex mechanisms, including inhibition of tumour cell growth by cell cycle arrest and stimulation of apoptosis, among others [21].

Beneficial effects of oat on risk factors of CVD

Observational and controlled studies provide strong evidence for the beneficial effects of oat consumption in the reduction of CVD risk [22,23]. Results from literature reviews and meta-analysis demonstrate that long-term oat consumption reduces fasting total and LDL-cholesterol and to some extent triglycerides, particularly in hypercholesterolaemic, type-II diabetic and healthy subjects [23–25]. The described cholesterol reduction percentage varies between 3% and 10% that represents a 6-18% decrease in coronary heart disease risk. Increased oat consumption have also shown to

reduce other lipid/lipoprotein markers associated with CVD risk , such as non-HDL cholesterol and apolipoprotein B (apoB) [26].

Based on the current scientific evidence it is clear that beneficial effects of oat in blood lipid profile are largely attributed to OBG [26]. The fecal excretion of bile acids caused by OBG intake reduces the amount of hepatic bile acids and activates cholesterol biosynthesis through upregulation of cholesterol 7-α hydroxylase (CYP7A1) which ultimately lowers circulating LDL cholesterol levels [26]. Animal studies pointed out that oat proteins and lipids are also contributing to cholesterol-lowering effects of oat [27,28]. Oat proteins are able to decrease circulating total and LDL-cholesterol through similar mechanisms as described for OBG [28].

The beneficial effects of increased oat consumption in blood lipid profiles have also been associated to changes in microbiota composition [29]. In particular, C57BL/6J mice fed wholegrain oat have greater relative abundance of *Prevotellaceae*, *Lactobacillaceae*, and *Alcaligenaceae* and lower *Clostridiaceae* and *Lachnospiraceae* families as well as reduced total and non-HDL cholesterol levels.

Hypertension is a major risk factor for stroke and myocardial infarction [30]. Results from randomized controlled trials (RCT) found an association between higher consumption of OBG and reduction of systolic and diastolic arterial blood pressure in pre-hypertensive and hypertensive overweight subjects [31]. Nevertheless, as most of these studies were based on hypocaloric interventions with the aim of weight loss, changes in weight cannot be ruled out as contributing to the findings.

Moreover, several studies have demonstrated that increased oat consumption reduces systemic inflammatory markers of CVD risk although adequately powdered RCT with larger sample size are necessary to strengthen the evidence [23].

Beneficial effects of oat on type II diabetes and related risk factors

Oat products have been shown to elicit low-postprandial glycemic and insulinemic responses in either healthy or overweight subjects [32,33]. Many individual studies have also confirmed that subjects suffering T2DM may benefit from increased oat consumption [33]. However, contradictory results related to the efficacy of interventions with OBG alone in diabetic patients have been obtained [34]. Results from two meta-analysis comprising high quality RCT have concluded that mid-term daily OBG intake favored the glycemic control as lowers fasting plasma glucose and glycosylated hemoglobin (HbA_{1c}) levels in diabetic participants; however, these dietary interventions did not affect insulin sensitivity [35].

Much of the beneficial effects of oat products on glycemic response are attributed to OBG. In fact, European Commission has authorized health claims related to OBG and reduction of postprandial glycaemia. In order to obtain the claimed effect, 4 g of OBG for each 30 g of available carbohydrates should be consumed per meal. Further studies have demonstrated that lower doses of high molecular weight OBG may be sufficient to reduce postprandial glycaemia when consumed as a preload [36]. This finding is in line with a systematic review showing the efficacy of OBG is more strongly related to its content than to the ratio of OBG/available carbohydrates [32].

The mechanisms of action of OBG to attenuate glycemic response are related to its high viscosity that causes a delayed gastric emptying, reduces carbohydrates enzymatic digestion and retards glucose diffusion and absorption [32,37]. OBG has the ability to inhibit glucose transport by downregulation of glucose transporters in small intestinal epithelial cells [38]. At present, magnetic resonance imaging technique has provided new evidence indicating that reduced postprandial glycaemia of oatmeal is linked to a

synergistic effect of delayed gastric emptying and reduced frequency of gastric antral contraction waves [39].

Interesting findings from a meta-analysis of RCT have shown that oat intake resulted in a greater decrease in glycated HbA_{1c}, fasting glucose and insulin response than extracted OBG [33]. These findings suggest that besides OBG other factors might be affecting to the bioactivity of oat products. In agreement with this state, Xu and others [40] found that oat starch molecular features might also be contributing to low post-prandial glycemic response. Moreover, it has been reported that the interaction of OBG and food starch has the potential to influence starch digestibility [41]. OBG can decrease starch digestibility by changing the microstructure of food products or by limiting water availability due to soluble OBG hydration which ultimately reduces starch gelatinization. Thus, the inhibition of starch digestibility is correlated with OBG efficacy in reducing glycemic response.

Beneficial effects of oats on bowel disease

Bowel disease include a wide range of pathologies affecting small intestine, colon and rectum such as irritable bowel syndrome (IBS), colorectal cancer and various types of inflammatory disorders (Crohn´s disease and ulcerative colitis). Lately, a systematic literature review concluded that long-term dietary intake of oat or oat bran could present some benefits for patients with IBS and ulcerative colitis and a plausible but non convincing protective effect on adenoma and cancer [42]. Despite of these promising results, further appropriately powered well-designed RCT are required to assess the efficacy of increased oat consumption.

The protective role of oat against functional disorders affecting the gastrointestinal tract has been recently established. Anti-inflammatory effects of OBG are associated with its

ability to reduce the number of lymphocytes T and B and granulocytes, promote leukocyte infiltration in intestinal mucosa, lower the production of pro-inflammatory enzymes and cytokines and stimulate the release of anti-inflammatory cytokines [43,44]. The anti-inflammatory properties of OBG seem to be related with its molecular weight, but the available data are contradictory.

Beneficial effects of oat on body weight

Results from an observational study including children aged 2-18 participating in the National Health and Nutrition Examination Survey 2001-2010 have shown that consumption of cooked oatmeal was associated with reduced risk for central adiposity and obesity [45]. These findings agree with RCTs concluding that short and long-term wholegrain oat intake had significant effects on reducing weight in overweight T2DM [24] and healthy participants [46]. The weight reduction effect was primarily attributed to oat fibre that reduces energy intake and increases satiety. This statement was recently supported by RCT focused on the short-term effects of consumption of oat-based breakfast cereals on appetite, satiety and energy intake [47]. These studies demonstrated that consumption of oatmeal suppresses appetite, increases satiety and reduces subsequent energy intake especially in overweight subjects [47].

The majority of the evidence suggests that OBG is the main responsible for the positive effect of oat consumption on perceptions of satiety [48]. Plausible mechanisms for OBG inhibition of food intake and weight gain is through its viscous properties that delay gastric emptying and reduce or delay digestion/absorption of macronutrients [48]. The increased interaction of gastric content with the intestinal cells that secrete satiety hormones may stimulate the release of peptides involved in appetite regulation. Additionally, OBG may activate the gut hypothalamic axis, thereby, increasing satiety.

Further evidence provided additional mechanisms for the preventive effect of oat fiber and OBG on weight gain and obesity-related liver lipotoxicity [49,50]. Decreased fat accumulation in hepatocytes and adipose tissue in rodents fed a high fat diet were attributed to the increased protein expression of peroxisome proliferator-activated receptors α and γ as well as the decreased protein expression of sterol regulatory element binding protein-1 in liver and epididymal adipose tissue.

Dysbiosis of the gut microbiota has also found to play a key role in the development of obesity [51]. Recent research advances in metagenomics sequence have allowed the study of the complete profile of oat product-induced alterations in gut microbiota. Results from these studies have revealed that oat products individually modify gut microbiota composition and increase short chain fatty acids (SCFA) concentration, therefore, attenuating the high-fat diet induced obesity and related metabolic disorders in rats [52].

Beneficial effects of oat in cancer prevention

I*n vitro* and preclinical studies pointed out to the positive effects of oat biologically active compounds as anticarcinogenic agents. The ability of OBG as tumor growth inhibitor has been well established, even though its efficacy on tumor suppression depends on the type of tumor, the dose and timing of administration, the animal genetic background and tumor load [53]. The chemopreventive effects of OBG have been proven in 1,2-dimethylhydrazine-induced colon carcinoma in mice. One of the mechanisms involved in colon cancer prevention byOBG is the modulation of colon microbiota which reduces the conversion of primary bile acids to secondary bile acids that are known to be tumorigenic. Moreover, OBG promotes the synthesis of SCFA, which are well-known anticarcinogenic compounds by colonic anaerobic bacteria and

facilitates tumor cell apoptosis [54]. The induction of tumor cell apoptosis by low-molecular weight OBG has been also observed in human dermal cancer cells via activation of caspase-dependent apoptotic pathway [55].

Recently, inhibitory effects of avenacosides (steroidal saponins) against the growth of human colon cells HCT-116 and HT-29 have been reported [21]. The effects of these compounds as growth suppressors of colon cancer cells appears to be weak, but this study might open new perspectives for studying oat steroidal saponins as chemopreventive agents in different types of cancer.

Antioxidant and immunomodulatory properties of oat

Oxidative stress is involved in a wide spectrum of pathologies. Antioxidants play a key role in preventing damage induced by oxidative stress through free radical neutralization. A plethora of studies have demonstrated that oat AVAs possess strong antioxidant activity [56]. An *in vitro* study has shown that the antioxidant effects of AVA are mediated by the induction of heme oxygenase-I (HO-I) expression through the activation of translocation of nuclear factor-E2-related factor 2 (Nrf2) in human kidney cells [17]. OBG also exerts an important antioxidant activity, due to its ability to diminish lipid peroxidation or to increase antioxidant defenses (glutathione reductase, glutathione peroxidase and superoxide dismutase activities) and antioxidant status, as it has been recently reported in LPS-induced enteritis experimental models [44,57].

Several studies have provided valuable insights into the immunomodulatory properties of OBG. This activity is partially mediated by the activation of Dectin-1 receptors that trigger the production of cytokines resulting in the induction of adaptive immune responses, as it has been demonstrated in mice and human dendritic cells [58,59]. Moreover, OBG modulates the expression of various immune-related genes in LPS-

stimulated THP-1 macrophages, leading to an overall enhanced anti-inflammatory effect [60]. Structure, solubility and molecular characteristics of OBG are key features influencing the immune-stimulating activity of this compound [58,59].

Conclusions

Oat offers many opportunities for future functional food development. There is accumulating evidence demonstrating that oat consumption reduces the risk of CVD and T2DM due to its LDL-cholesterol and glucose lowering effects, respectively. So far, much of these beneficial effects have been attributed to OBG. Despite promising advances in clinical research there is still insufficient evidence to draw conclusions on beneficial effects of oat intake in blood pressure, weight gain, bowel inflammatory diseases and cancer. In these cases, adequately powered RCT with larger sample size are still required to strength the evidence. So far, there are a number of bioactivities that have been identified for oat constituents; however, further research efforts should be focused in the understanding of whether other bioactive constituents could be contributing to the health benefit of oats and the elucidation of their mechanisms of action.

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