World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i41.11825

World J Gastroenterol 2015 November 7; 21(41): 11825-11831
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

MINIREVIEWS

Role of oats in celiac disease

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Author contributions: Comino I and Moreno ML researched the topic; Comino I and Sousa C wrote the manuscript and reviewed the final manuscript.

Conflict-of-interest statement: No potential conflicts of interest.

Data sharing statement: No additional data are available.

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Received: June 27, 2015
Peer-review started: June 30, 2015
First decision: July 20, 2015
Revised: September 2, 2015
Accepted: September 15, 2015
Article in press: September 15, 2015
Published online: November 7, 2015

Abstract

A gluten-free diet is currently the only effective means of treating individuals with celiac disease. Such a diet enables celiac patients to control their symptoms and avoid various complications associated with this condition. However, while the quality of gluten-free foods has significantly improved during recent decades, maintenance of a gluten-free diet does not necessarily ensure adequate nutritional intake. Because oats are an important source of proteins, lipids, vitamins, minerals, and fibre, their inclusion in a gluten-free diet might improve the nutritional status of a celiac patient. Although oats are included in the list of gluten-free ingredients specified in European regulations, their safety when consumed by celiac patients remains debatable. Some studies claim that pure oats are safe for most celiac people, and contamination with other cereal sources is the main problem facing people with this disease. However, it is necessary to consider that oats include many varieties, containing various amino acid sequences and showing different immunoreactivities associated with toxic prolamins. As a result, several studies have shown that the immunogenicity of oats varies depending on the cultivar consumed. Thus, it is essential to thoroughly study the variety of oats used in a food ingredient before including it in a gluten-free diet.

Key words: Oats; Celiac disease; Gluten-free diet

Core tip: Symptoms of celiac disease are triggered by an abnormal reaction to gluten, and the only treatment for celiac disease is the patient's adherence to a strict gluten-free diet. While inclusion of oats in a gluten-free diet might improve its overall nutritional value, their use in such diets remains controversial. This review summarizes recent advances made in understanding the nutritional properties of oats and their role in celiac disease.

Comino I, Moreno ML, Sousa C. Role of oats in celiac disease. *World J Gastroenterol* 2015; 21(41): 11825-11831 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/

i41/11825.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i41.11825

INTRODUCTION

Celiac disease (CD) is a lifelong autoimmune disease characterized by an aberrant inflammatory response to dietary gluten in genetically susceptible individuals. CD is one of the most common chronic digestive disorders, and afflicts about 1% of the population in Western countries; moreover, recent studies suggest that its prevalence is increasing[1,2]. Certain individuals show a strong and complex genetic predisposition to this disease. Although 95% of celiac patients are *HLA-DQ2* or *-DQ8* positive, the presence of these alleles is not strongly predictive for the disease[3,4]. In recent years, the clinical spectrum of CD patients has been expanded to include asymptomatic individuals, as well as individuals with minimal symptoms (the most difficult to detect) and extra-intestinal symptoms[5-7]. However, regardless of its symptomatic presentation, virtually all cases of active CD occur after the susceptible individual has received dietary exposure to the environmental antigen, gluten. In patients with CD, the ingestion of gluten proteins contained in wheat, barley, and rye results in characteristic inflammation, villous atrophy, and crypt hyperplasia in the upper small intestine[5].

During the early 1980s, the spectrum of gluten-related disorders was relatively simple: CD and dermatitis herpetiformis (CD of the skin). While a gluten-free diet (GFD) is still recommended for all patients with CD, the area of CD research is changing rapidly, and wheat allergies, gluten ataxia, and nonceliac gluten sensitivity have recently been added as new gluten-related topics for study[8]. The only treatment for these disorders remains adherence to a GFD; however, many patients experience persistent CD-related symptoms despite their best efforts to avoid dietary gluten. A GFD is expensive and difficult to maintain because many products made from gluten-containing grains are Western dietary staples. Moreover, the contents of a GFD do not always ensure that an individual receives adequate nutrition[9,10]. In fact, medical problems related to inadequate nutrition have been described in CD patients following their long-term treatment with a strict GFD. Such observations might possibly be explained by the composition and nutritional quality of commercially available gluten-free products. While individuals on a GFD need to replace wheat, barley, rye, and their derivatives with foods derived from naturally gluten-free cereal grains (*e.g.*, rice, corn, buckwheat, sorghum, *etc.*), but the recommended amounts of fibre, iron and calcium can be more difficult to obtain on such a diet and good planning is required[11]. Oats contain both soluble and insoluble dietary fibre, B-complex vitamins, iron, and proteins[12,13], and have recently been considered for inclusion in a GFD. However, while oats might improve the nutritional value of a GFD, their safety for consumption by celiac patients has been the subject of controversy.

NUTRITIONAL AND PHARMACOLOGICAL PROPERTIES OF OATS

Composition

Oat grain is characterized by its good taste and dietetic properties, as well as an ability to stimulate metabolic changes in the bodies of humans and animals. Furthermore, oat grain is a rich source of proteins with favourable amino acid contents and high nutritional value, and as other beneficial ingredients including dietary fibre, antioxidants, vitamins, phenolic compounds, minerals, and essential unsaturated fatty acids[14-16]. When compared with other cereal grains, oat grain contains larger amounts of total protein and crude fat, and a small amount of crude fibre. The major nutritional components of oats are shown in Table 1.

Health benefits

Several studies have described oats as a functional food with the ability to lower blood cholesterol and sugar levels, reduce hypertension, help control childhood asthma, reduce body weight, and also provide immunomodulatory, antioxidant, and antiatherogenic effects[14,17-19] (Table 2). Oats also contain significant amounts of vitamins, minerals, fibre, and phytochemicals that regulate intestinal transit times and increase the production of butyrate and/or other faecal short chain fatty acids produced by gut microflora. As a result, the long-term dietary intake of oats or oat bran might benefit patients suffering from inflammatory bowel disease, ulcerative colitis, colorectal adenoma or cancer. However, further studies are required to accurately assess the benefits provided by increased oat consumption when treating bowel disorders[20].

Additionally, due to the well-established effect of oats on the risk for coronary heart disease, in 1997 the United States Food and Drug Administration (FDA) approved the heart-health benefit claim shown on the label of many foods containing soluble fibre derived from oats. Moreover, in 2010, a European Food Safety Authority (EFSA) panel concluded that current scientific evidence supports the following two-part statement: "Oat β-glucan has been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of coronary heart disease".

OATS AND CELIAC DISEASE

Oat avenins

As the prolamin components of oat seeds, the avenins are known to exist as both monomers and

Table 1 Main nutritional components of oats

	Components	Properties	Ref.
Proteins	Albumins, globulins, prolamins, and glutenins	Oats are distinct among cereals due to their higher protein concentration and distinct protein composition. The major storage proteins are globulins	[50, 51]
Carbohydrates	β-glucan, glucose, fructose, pentosans, saccharose, kestose, neokestose, bifurcose, neobifurcose, acid galactoarabinoxylan, *etc*	β-glucan is the most important component because it is a constituent of the dietary fibre obtained from oats. β-glucan has important functional and nutritional properties, and exhibits a high viscosity at relatively low concentrations	[52, 53]
Lipids	Oat lipids are highly unsaturated and contain several essential fatty acids	Oats, after corn, have the highest lipid content of any cereal. Oat lipids include very high levels of antioxidants	[54, 55]
Antioxidants	Vitamin E (tocols), phytic acid, phenolic compounds, avenanthramides, flavonoids, and sterols	Antioxidants may reduce serum cholesterol concentrations, and inhibit the growth of certain cancer cells	[55]

Table 2 Health benefits of oats

Effect	Findings	Ref.
Hypocholesterolemic	An effect derived from β-glucan content, and demonstrated in normal and hypercholesterolemic subjects. The statistical significance of this cholesterol reduction has been variable, and remains controversial	[15, 18]
Hypoglycaemic	Studies have suggested that oat consumption can significantly decrease insulin response, fasting blood glucose levels, and the incidence of postprandial hyperglycaemia. However, some studies have failed to identify a diet-related effect on glycaemic control or a person's insulinemic response to oat-enriched products	[56-58]
Prevention of cancer	Selenium, present in oats, is involved in DNA repair and associated with a reduced risk for cancer; especially colon cancer. Furthermore, it is found in foods with a high fibre content	[59-61]
Reduction of hypertension	Soluble fibre-rich whole oats may be effective when consumed as dietary therapy for the prevention and adjunct treatment of hypertension	[62]
Immunomodulatory	β-glucans act by stimulating the immune system and inhibiting the growth of various bacteria, viruses, fungi, and parasites	[63]
Antioxidant	Oats contain chemicals with potential antioxidant properties; *e.g.*, vitamin E (tocols), phytic acid, and phenolic compounds, *etc*	[55]
Antiatherogenic	*In vivo* studies of atherosclerosis showed that oat bran reduced plasma cholesterol levels. However, it was difficult to determine whether its antiatherogenic effect was a result of reduced plasma cholesterol alone, or if additional effects of other oat components contributed to the result	[64]
Obesity control	Studies revealed that oats effectively reduced obesity, as well as indexes of serum lipid levels and liver function. These effects were observed when using β-glucan with the proper molecular weight	[14, 52]

disulfide-linked aggregates[21]. Similar to other cereal prolamins, the avenin polypeptides in oats tend to be rich in proline and glutamine, and the protein regions enriched in these two amino acids are associated with elicitation of CD. However, when compared to prolamins in other cereal grains, oat prolamins show the following differences in their molecular size, percentage, and amino acid content: (1) prolamins account for 10%-20% of the total protein in oats, compared to 40%-50% of the total protein in wheat[22,23]; (2) among the accepted prolamins, those found in maize, sorghum, and rice generally have the lowest contents of proline and glutamine (25%-30%), while prolamines in the Triticeae tribe (wheat, barley, and rye) can have proline plus glutamine contents that exceed 70% of their total amino acids. In contrast, proline and glutamine generally comprise 35%-50% of amino acids found in the prolamins of oats[24]; (3) in contrast to the single longer repetitive domain found in Triticeae prolamins, oat avenins contain two shorter domains with high contents of proline and glutamine[24]; and (4) the disulfide pattern in oat prolamins is different from those reported in wheat γ-gliadins[25] and low molecular weight (LMW)-glutenins[26]. In particular, the tandem cysteines at positions 145-146 in oat prolamins form a disulfide bond. This is in contrast to wheat proteins, where the two tandem cysteines are bonded to more distant cysteines within the prolamin[24].

Despite these reported differences, the avenins have not been well studied. As a result, the complete avenin genes described in current genetic databases represent only a few genotypes, and the variability displayed by avenin genes in oats is not well represented[21].

Clinical studies

The inclusion of oats in gluten-free foods is controversial, as previous studies have shown contradictory results regarding their toxicity. Janatuinen *et al*[27] conducted the first controlled study on the toxic effects of oats in CD patients, and since that time several other similar investigations have been conducted. Some researchers have claimed that celiac patients can consume oats and show no signs of intestinal inflammation[12,28-31]. In a study conducted by Størsrud *et al*[32,33], a small number of adult celiac subjects consumed pure oats (93 g/d) for 2 years with no reported adverse effects. The same

researchers also conducted a study in which a group of celiac children ingested a median of 43 g (up to 81 g/d) of oats daily for 2 years[34] with no adverse effects. Moreover, a randomized double-blind study conducted with newly diagnosed CD children showed that consumption of an oat-containing GFD for 1 year did not interfere with their clinical, serological or small bowel mucosal recovery. However, despite those results, 26% of the children in the oat-containing GFD group withdrew from that study for unknown reasons[34,35].

While the previously mentioned studies appear to support the safety of oat consumption by celiac patients, the results of other studies suggest that regular consumption of certain types of oats may be impossible for such patients, due to their toxic effects. Those studies revealed that oats can trigger an immune reaction in celiac patients[28,36-38] that results in activation of mucosal T-cells, subsequent gut inflammation, and eventual villous atrophy[37]. In those patients, the immune response against avenins may have been triggered by a mechanism similar to that which triggers a response to gluten contained in wheat, rye, or barley. Lundin *et al*[36] studied 19 celiac patients who consumed 50 grams of oats/day for 12 wk, and found that one patient was oat sensitive. CD patients have circulating anti-avenin antibodies[39,40], and a recent study revealed that dietary oats can alter the mRNA immune status of intestinal mucosa cells; suggesting T-cell activation and the presence of leaky tight-junctions[41]. Such findings indicate the need to distinguish between groups of celiac patients based on their sensitivity to different cereal grains, and also to identify the source of immunogenicity in avenin peptides.

Gluten contamination of commercial oat products

The phrase "pure oats" is used to describe oats that after being analysed using current test methods, appear to be uncontaminated with gluten from other closely related cereal grains, such as wheat, barley, and rye. However, the differences in the oat products used and the testing and reporting of the purity of oats further limited a comprehensive safety assessment. When studying literature reports, the study design or protocol did not always clearly describe the specifications used for defining "pure and uncontaminated" oats. While the most recent reports usually indicate whether the oats used in a particular study were tested for purity, many studies fail to indicate the lower limit of detection for their testing techniques or the cut-off values used when reporting that oat samples were free of gluten from other cereal grains.

According to the Codex Standard for food for special dietary use by persons intolerant to gluten, CODEX STAN118-1979 (revised 2008, http://www.foedevarestyrelsen.dk/SiteCollectionDocuments/25_PDF_word_filer%20til%20download/07kontor/Maerkning/Codex%20standard%20for%20gluten.pdf), oats can be tolerated by most but not all people who are intolerant to gluten. Therefore, whether oats that are not contaminated with wheat, rye or barley and are contained in foods covered by this standard can be considered safe for consumption by celiac patients may eventually be determined at the national level. Moreover, according to Commission Regulation (EC) No 41/2009 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:016:0003:0005:EN:PDF), which addresses the composition and labelling of foodstuffs suitable for people intolerant to gluten, the risk that oats may become contaminated with wheat, rye or barley during grain harvesting, transport, storage or processing remains a major concern. Therefore, the risk that oat-containing products might be contaminated with exogenous gluten should be taken into consideration when creating their labels.

Some studies have utilized the R5 ELISA method to determine the level of contamination in wheat, barley, or rye in oat products[42-44]. Koerner *et al*[43] used this method to confirm that the commercial oat supply in Canada is heavily contaminated with gluten from other grains. For example, about 88% of the tested oat samples (n = 133) showed a gluten level > 20 mg/kg. However, the problem with using this method is that the R5 antibody can react with certain types of pure oat seed[45]; hence, a test result suggesting "suspected contamination" from exogenous toxic cereal grains may not be real, due the R5 antibody reacting with certain amino acid sequences in the native oat proteins.

Diversity in potential immunogenicity depends on oat cultivars

Differences in the type of oat grain, oat purity, study design, as well as the specifications for gluten-free products in different countries, are some reasons why the current studies have not clearly established whether or not oats can be safely consumed by all celiac patients. These apparent contradictions might be explained by the fact that the oat varieties used in the diverse studies were different in regards to their prolamin genes, protein amino acid sequences, and the immunoreactivities of their toxic prolamins[46,47].

Our research group conducted a study using nine different varieties of oats obtained from various Australian and Spanish commercial sources, and demonstrated that oat immunogenicity varies depending on the cultivar used[45]. The oat grains were carefully inspected, controlled to maintain purity, and shown to be free of contamination. An analysis of DNA amplification products confirmed that the oat samples were not contaminated with wheat, barley, rye, or any mixture of these grains. The toxicity of each oat variety was evaluated using a moAb G12 immunoassay. The antibody used in the assay was obtained from the

α-2 gliadin 33-mer peptide, which is one of the most toxic peptides for CD patients. The nine varieties of oats were classified into three groups (high reactivity, intermediate activity, and no reactivity) based on their moAb G12 reactivity. We found that reactivity with the anti-33-mer moAb shown by the different oat varieties was correlated with T-cell proliferation and interferon gamma production by blood T-cells isolated from CD patients. These results suggest that a moAb G12-based immunotechnique may be a pragmatic method for evaluating the potential immunotoxicity of commercial cereals and grains[45,48].

Subsequent studies confirmed a direct correlation between the immunogenicity of the different varieties of oats and the presence of specific peptides with higher/lower potential immunotoxicity. This finding may explain why certain varieties of oats produce toxic effects when consumed by celiac patients, while others produce no adverse effects[21,49]. Moreover, oat peptides obtained from toxic cultivars have showed to differentially stimulate bona fide circulating dendritic cells obtained from celiac patients.

While inclusion of oats in a GFD might be beneficial due to their nutritional and health benefits, the source of the oats used and the cultivar selected are important factors to be considered. These factors must also be taken into account when developing food safety regulations, labelling oat-containing products as gluten-free, and designing clinical trials to study the effect of oats in celiac patients.

CONCLUSION

In summary, oats possess a variety of pharmacological activities and may exert antioxidant, anti-inflammatory, antidiabetic, and anticholesterolaemic effects. These properties have led to their wider use in human food. Inclusion of oats in a gluten-free diet might be valuable due to their nutritional and health benefits, and several countries currently permit oats to be included as an ingredient in such diets. However, it is extremely important to remember that *in vitro* studies have shown that the immunogenicity of oats varies depending on the cultivar used. Future clinical studies should be directed to the development of clinical trials with varieties previously identified as safe by reliable *in vitro* methods, such as moAb G12-based immunotechniques.

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P- Reviewer: Brown IS, Rodrigo L **S- Editor**: Ma YJ **L- Editor**: A
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ISSN 1007-9327
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