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Review

# Health effects of wheat lectins: A review

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ABSTRACT

Lectins are carbohydrate-binding proteins present in most plants. They play a role in protecting plants against external pathogens, like fungi, and other organisms. Some common dietary staples, such as cereal grains and legumes, have relatively high concentrations of a variety of lectins. A part of the proteins present in wheat germ is characterized as wheat germ agglutinin (WGA), in this respect. Authors of popular nutritional plans propose adverse health effects of this wheat lectin. With the use of different arguments, the consumption of foods high in lectins is discouraged. In this context, we discuss the effects of lectins from wheat on human health. Up-to-date research findings on mechanisms that wheat lectins have effects on health factors, such as obesity, autoimmune disease, and celiac disease, are critically reviewed. We conclude that there are many unsubstantiated assumptions made. Current data about health effects of dietary lectins, as consumed in cooked, baked, or extruded foods do not support negative health effects in humans. In contrast, consumption of WGA containing foods, such as cereals and whole grain products, has been shown to be associated with significantly reduced risks of type 2 diabetes, cardiovascular disease, some types of cancer, as well as a more favourable long-term weight management. Research is recommended to define actual active lectin contents in wheat-based foods after heat preparation for human consumption.



## 1. Introduction

Lectins are members of a superfamily of proteins that express the capacity to bind to specific carbohydrates reversibly without altering their covalent structure. Common dietary staples, such as cereal grains, legumes, and fruits have relatively high concentrations of a variety of lectins. Especially black beans, soybeans, kidney beans, and (whole) grains are known for significant quantities of different lectins (Chrispeels and Raikhel, 1991; Matucci et al., 2004).

In nature, lectins play a role in biological recognition phenomena involving cells and proteins and hereby protect plants against external pathogens such as fungi and other organisms. The ability to bind to and agglutinate red blood cells is well known and used for blood typing - hence the lectins are commonly called haemagglutinins (Liu et al., 2010). In the laboratory, lectins are used to obtain insights in essential biological processes including cell proliferation, cell arrest, apoptosis, neoplasm cell metastasis, leukocyte homing, and trafficking, and especially microbial infection. Also, lectins are widely used reagents for the study of glycoconjugates in solution and on cells, and for cell characterization and separation (Sharon, 2008). Next to this, lectins are also used as tools for novel techniques such as in a microarray for a high-throughout analysis of glycans and glycoproteins (Hu et al., 2012), and in new data-storing techniques, where carbohydrates are used as hardware for information coding (Gabius et al., 2011).

On a chemical level, a plethora of different types of lectins have been described in the literature (e.g.: Damme et al., 1998; Loris, 2002; Ramos et al., 2012; Schwefel et al., 2010; Sharon, 2008) and through well-described techniques (Kaji et al., 2003), novel lectins are continuously characterized and described in protein databases (Punta et al., 2012). In the nutrition literature, a specific lectin, Wheat Germ Agglutinin (WGA), has been described extensively and suggestions have been made about the possibility that this specific lectin *may* induce adverse health effects by binding to the epithelium in the gut, damaging the cells, resulting in a leaky gut epithelium, as well as a reduced nutrient-uptake (Biesiekierski et al., 2010; Cordain et al., 2000; de Punder and Pruimboom, 2013; Hamid and Masood, 2009; Jönsson et al., 2005; Lindeberg, 2012; Power, 1991). It is also stated that the lectin-induced

*Abbreviations:* IBS, irritable bowel syndrome; PHA, phytohemagglutinin; SCFA, short-chain fatty acid; WGA, wheat germ agglutinin.

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blockade of glucose- and insulin-receptors is contributing to celiac disease, and the growth of harmful bacteria (Cordain et al., 2000; Power, 1991).

Despite these growing concerns over WGA-rich foods, there have been no *in vivo* randomized controlled trials in humans assessing the health effects of WGA, in normal dietary concentrations as present in heat prepared foods, to the best of our knowledge. Even without such data, the consumption of foods high in WGA was discouraged (Hamid and Masood, 2009; Jönsson et al., 2005), while others found that through (heat) processing, such as extrusion, cooking, or baking, lectins denature and lose their binding activity (Srivastava and Vasishtha, 2013).

Given the positive health effects of whole-wheat foods (Jonnalagadda et al., 2011), we hypothesize that the possible adverse health effects of WGA are no reason to discourage the consumption of whole wheat-based foods. After providing a background on wheat lectins in the human diet, this hypothesis is tested by critically reviewing primary scientific evidence for the possible mechanisms.

## 2. Wheat lectins in the human diet

In 1980, Nachbar and Oppenheim (1980) analysed multiple unprocessed fruits, vegetables, cereals, and spices, and identified numerous dietary lectins. The authors classified the lectins according to the monosaccharide for which they exhibit the highest affinity. The five main groups were: mannose, galactose/N-acetylgalactosamine, N-acetylglucosamine, fucose, and sialic acid. Biochemically, WGA is a relatively small protein with a molecular weight of about 17,000 g/mol and has two highly specific binding sites for N-acetylglucosamine (Nagata and Burger, 1974).

More recently, albeit still more than a decade ago, plant lectin concentrations were described in more detail. In a 1998 study (Peumans and Van Damme, 1998), food plants with high lectin levels in edible parts were discussed. Herein, it was stated that cereals have up to a 0.5 g/kg lectin concentration, primarily present in the germ. Interestingly, the research concluded that, similar to wheat, lectins were found in the aforementioned concentration in rye, barley, and rice. The source of these data, including the detection method, is however not described.

Although the exact concentrations of WGA in raw plants remain unclear, more imminent is the subsequent uptake of WGA from wheat containing products. In this respect, recent research showed that lectins from raw plant foods are not efficiently degraded by digestive enzymes (Miyake et al., 2007) due to their globular tertiary structure, thus ensuring a high uptake. By not being degraded, WGA will remain in its active form which, in high concentrations, has been linked to adverse health effects (Vaz et al., 2012). For comparison, we describe data from a study by Wang et al. (1998) on lectins from peanuts. Herein, half of the ingested dietary lectin from peanuts was detectable in an active (*i.e.*: able to agglutinate) form in the faeces and, immunohistochemically, in rectal mucosal biopsies. The researchers found that after consuming 200 g of peanuts, up to 5 μg/mL intact dietary lectin was detected in the blood. The question remains as to what this means for wheat lectins, since these data appear to be very limited.

Interestingly, in a recent thesis (Kuzma, 2009), it was described that WGA was not detected in venous plasma samples following consumption of 50 g of wheat germ. To put this in context of a normal diet, wheat germ is only 3% of the total whole-grain kernel weight. Thus, 50 g wheat germ would represent an actual consumption of 1666 g wheat or >80 slices of bread.

As introduced, it is suspected that there is a significant influence of food processing on wheat lectin concentration and biological activity. For instance, the concentration is greatly dependent on the used flour in breads and pastas, where most only contain refined flour with traces of germ, even those enriched in bran fractions. Whole wheat flours, which are thought to be high in WGA are often reconstituted from different milling streams which impacts on WGA concentrations. Data supporting these assumptions, however, are again scarce. In the only available and controlled study (Matucci et al., 2004), it was shown that heat treatment greatly affects the biological activity of the dietary lectin WGA in Italian pastas. In a kitchen setting, it was shown that cooking pasta results in the inactivation of WGA. Moreover, another analysis followed by western blotting and ELISA assays with heat-treated WGA demonstrated that WGA activity was progressively reduced with increasing temperatures. At temperature values used around technological processing of pasta (65 °C), the reduction of WGA activity shows an apparent inflection point (after heat treatment of 10 min). Consequently, broad differences in WGA content are expected in uncooked pastas due to their minimal variation in the thermal treatment to which these wheat-derived products are subjected. In their study (Matucci et al., 2004), using a method to measure WGA-activity well validated earlier by Vincenzi et al. (2002), the authors concluded that WGA activity was undetectable in some uncooked wholemeal pasta, and that that was an indication that these products were subjected to more intense thermal treatments. Importantly, the authors concluded that traditional cooking practices of consumers will eliminate all WGA activity in pastas, if not already inactivated by technological processing (Matucci et al., 2004).

## 3. Effects of wheat lectins on health

Although data from human intervention studies, using heat-treated foods are lacking, there is evidence that native purified lectins affect health status. Several up-to-date *in vitro* research studies were described in the literature (Ovelgönne et al., 2000; Vincenzi et al., 2002; Yu et al., 1993). Furthermore, studies describing the effects of high doses of purified plant lectins on animal health were listed in scientific databases (Banwell et al., 1985, 1988; Jönsson et al., 2006; Pusztai, 1993; Pusztai et al., 1993, 1995). In such animal studies (Banwell et al., 1985; Banwell et al., 1988), rats were exposed to high concentrations of the phytohemagglutinin lectin (PHA) from uncooked red kidney beans (Phaseolus vulgaris) which led to bacterial (mainly *Escherichia coli*., *Streptococcus* sp., and *Lactobacillus*) and protozoa colonization in the intestine of the rat. This bacterial overgrowth and the resultant amplified gut cell proliferation, however, is described by some as undesirable (Wong and Wright, 1999), while others interpret it as favourable (Jordinson et al., 1999; Yu et al., 1993).

Moreover, multiple review articles, containing conclusions that lectins have adverse health effects based on the scarcely available and mostly animal and *in vitro data*, were found (Cordain et al., 2000; Freed, 1999; Jönsson et al., 2006; Jönsson et al., 2005; Liu et al., 2010; Miyake et al., 2007; Power, 1991). Other studies (Hamid and Masood, 2009; Miyake et al., 2007; Pusztai et al., 1993; Vasconcelos and Oliveira, 2004) implied that also WGA containing foods impair nutrient absorption. In the discussion below, we evaluate these conclusions by looking carefully at the primary research data.

### 3.1. Gut health

In a 1991 article, it was described that WGA binds to N-glycolylneuraminic acid (Neu5Ac), a sialic acid found in humans (Shaw et al., 1991). A very recent review article (de Punder and Pruimboom, 2013) discussed that, therefore, lectins can adhere to cell surfaces like the epithelial layer of the gut. Accordingly, WGA

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binding to Neu5Ac of human cells (and pathogens expressing Neu5Ac) allows for cell entry and could disturb immune tolerance by evoking a pro-inflammatory immune response.

In a review article by Cordain et al. (2000), potential evidence is provided for an interaction of dietary lectins with enterocytes and lymphocytes. This interaction *may* facilitate the translocation of both dietary and gut-derived pathogenic antigens to peripheral tissues, which in turn causes persistent peripheral antigenic responses. The authors propose that especially patients with rheumatoid arthritis should avoid lectin containing foods to avoid unwanted antigenic stimulation. Through a process called molecular mimicry, where lectins are mistaken as pathogens by antibodies or T-lymphocytes, which is more common in patients with rheumatoid arthritis, lectins *can* cause immunological responses in the gut in these patients (2000).

Additionally, Freed (1991, 1999) suggested that dietary lectins can stimulate class II HLA antigens on cells that do not normally display them such as pancreatic islet and thyroid cells. This triggered auto-immune hypothesis is supported by an animal study in genetically susceptible mice (Banwell et al., 1988). In this study, the fine protective layer of sialic acid was absent so that lectins could bind easily to the cell wall. Similarly, in a study in rats (Ovelgönne et al., 2000), it was observed that PHA (from unprocessed red kidney beans) and fractionated unprocessed WGA have an effect on proteins in intestinal cells which reduce the resistance of the intestinal wall. The question of what this means for the human situation remains unanswered.

In this respect, one study investigated a specific relation between lectins and gut health in humans. According to the gluten-lectin theory put forward by Fälth-Magnusson and Magnusson (1995), there is a direct relationship between lectin-intake and celiac disease. In their study, in which one of two groups received a gluten-free diet, the levels of IgA, IgG and IgM antibodies in response to WGA, were compared in both children with celiac disease and children without it. The researchers found that the levels of IgA and IgG in response to WGA were significantly higher in children with celiac disease with a gluten-containing diet compared to the children who had a gluten free diet and children without celiac disease. The scientists argue that these findings support the concept that WGA may act as a biologically important component of wheat in genetically predisposed celiac disease patients.

In addition to this apparent causal relationship, studies document that celiac disease incidence increased substantially over the last decades (Rewers, 2004), correlating with an increase in gluten and wheat lectin intake (and other changes in lifestyle and diet) (Rubio–Tapia et al., 2009). These studies resulted in much speculation regarding the effects that gluten or wheat lectins may have on causing disease in the general population. Although there is a correlation between the incidence of celiac patients and the production of grain in a geographical region (Catassi and Fasano, 2008; Fasano and Catassi, 2001), it should be stated that celiac disease results primarily from having a specific genetic condition. Wheat sensitivity, an etiologically heterogeneous syndrome including celiac disease, is easier to diagnose as result of a higher consumption of cereals (Green and Jabri, 2003), which *may* explain the aforementioned correlation.

Jonnalagadda et al. (2011) summarized the evidence concerning the positive effects of consuming whole grains, as recently presented at the American Society for Nutrition (2010) as follows: “whole grains provide the gastrointestinal tract with more than fibre, thus contributing to their role in maintaining gastrointestinal function and protection against disease. The various components present in whole grains may act synergistically to help improve bowel function and provide protection against gastrointestinal cancers, inflammation, and other disease states while strengthening barrier function and providing immune support. Increasing intake of whole grain products, by replacing grain products from isolated white flour, is generally recommended for improving gastrointestinal health” (Björck et al., 2011; Fardet, 2010; Hauner et al., 2012; Jonnalagadda et al., 2011).

### 3.2. Immunity

An effect of WGA on neutrophil granulocytes, the most abundant type of white blood cells in humans, has been described (Karlsson, 1999). In the research from human tissue, obtained exudate cells responded to *in vitro* WGA stimulation by both releasing reactive oxygen species into the extracellular milieu and producing oxygen metabolites intracellularly. The oxidative response to WGA increased with increasing levels of granule mobilization. The study shows that the binding of WGA to glycoconjugates on isolated human neutrophils results in an activation of the superoxide anion and hydrogen peroxide-generating NADPH-oxidase, similar to an earlier study (Magnusson et al., 1988). The resulting low-grade inflammations are expected to have a direct contribution to the pathogenesis of insulin resistance (Calder et al., 2011).

In addition, it is suggested that dietary lectins, including WGA, pose a potential threat to consumers due to their capacity to induce histamine release from basophils, as per shown *in vitro* (Haas et al., 1999). In a more recent research (Sodhi and Kesherwani, 2007), this finding was again found as treatment of macrophages with various doses of wheat germ agglutinin (WGA) for different time intervals resulted in enhanced expression of TNF-$\alpha$, IL-1$\beta$, IL-12 and IFN-$\gamma$. The maximum expressions were observed at 24 h with 100 ng/ml of WGA. It should be noted that these *in vitro* research are in no way comparable to the *in vivo* human situation, where WGA is never consumed at such rates.

These and other findings led various researchers to the conclusion that WGA intake has an effect on inflammatory markers and therefore play a role in immunological response (de Punder and Pruimboom, 2013; Pellegrina et al., 2009; Tchernychev and Wilchek, 1996). Interestingly, a 1986 study (Sollid et al., 1986) showed that significantly higher antibody levels to WGA were measured in patients with celiac disease compared to patients with other intestinal disorders or even healthy controls. These WGA antibodies did not cross-react with gluten antigens and were hypothesized to play an important role in the pathogenesis of celiac disease. However, the role of WGA in immunological response in celiac disease patients, as well as in the aetiology of the disease, have been re-evaluated extensively and proven to be non-significant (Abdulkarim et al., 2002; Davidson and Bridges, 1988; Schuppan et al., 2009).

### 3.3. Obesity

In one research article (Jönsson et al., 2005), it is hypothesized that an increase in dietary lectin uptake affects weight gain by means of leptin resistance. Leptin is a key hormone in regulating energy intake and energy expenditure. Leptin resistance, by means of malfunctioning leptin receptors, reduces satiation signals from the brain. A reduced feeling of satiation mediates overeating, resulting in obesity (Enriori et al., 2012; Spreadbury, 2012).

According to Jönssen et al. (2005), WGA is suspected to interact with leptin and/or the leptin receptor. Since lectins can bind to sugar structures of a membrane receptor, they *can* block the effect of the physiological ligand. This *could* theoretically lead to (partial) leptin resistance. However, no clinical data supporting this hypothesis have ever been presented. On the contrary, if such a link

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existed, this would also be seen in epidemiological studies and that is not the case. Koh-Banerjee et al. (2004) found that regular consumption of whole grains was negatively correlated with weight gain. These authors described 14 cross sectional studies, most of which were performed in the U.S., in which a larger whole grain intake was correlated with a lower BMI. In addition, they presented three studies in which a significantly lower waist circumference was noted. Similarly, Jonnalagadda et al. (2011), recently concluded that "the current evidence among a predominantly Caucasian population suggests that consuming 3 or more servings (90 g of more) of whole grains per day is associated with lower BMI, lower abdominal adiposity, and trends toward lower weight gain over time". In another review publication that summarized the outcomes of the Health Grain Europe EU consortium, academics concluded that in well controlled animal studies, a negative correlation was observed between the absorption of propionate, butyrate and total short-chain fatty acids (SCFA), resulting from whole grain fiber fermentation in the colon and the apparent insulin production. In addition, studies in humans have also linked enhanced SCFA production, and butyrate in particular (Brouns et al., 2002), to improved insulin sensitivity and glucose homeostasis (Björck et al., 2011). In other work (Gaskins et al., 2010; Jenkins et al., 2007; Masters, Liese et al., 2010; Qi et al., 2006; Raninen et al., 2011), it was concluded that the consumption of grain fibres is significantly related to improved blood glucose control, improved cholesterol levels, reduced blood pressure and lower serum concentrations of high sensitivity C-reactive protein (inflammation marker), all observations that are in favour of improving factors that pay a role in obesity related co-morbidities.

### 3.4. Toxicity

In multiple articles on the antinutritional properties of lectins (Gupta, 1987; Kumar et al., 2013; Vasconcelos and Oliveira, 2004), the (oral) toxicity of lectins was reviewed. It was reported that very high concentrations of particular raw lectins, such as isolated from uncooked red kidney beans (Freed, 1999), can cause toxic reactions when exposed as such to humans, characterized by general, nausea, bloating, vomiting and diarrhoea. Since these symptoms are extremely rare with normal intake of food prepared for human consumption, Paracelsus toxicological principle holds; the dose makes the poison. Evidence that WGA exerts toxic effects, after exposure to heat during food preparation, is lacking.

### 3.5. Cancer

Surprisingly, plant lectins attracted increasing attention from cancer biologists due to their *possible* anti-tumour properties. Lectins *could* bind to cancer cells which has beneficial effects for cancer patients (Abdullaev and Gonzalez de Mejia, 1997). A large-scale study in colorectal cancer patients and a control group showed some beneficial effects of consuming plant lectins in terms of relative risk. The pathways, however, remain unclear (Evans et al., 2002).

In a recent review, advances in elucidating the role of lectins in complex anti-cancer mechanisms implicated in apoptosis and autophagy were presented (Liu, Bian et al., 2010). In the review, significant advancements of the anti-tumour mechanisms of plant lectins *in vitro* are discussed. As a conclusion, the authors call for additional research, including clinical trials into the mechanisms of actions at the molecular level. This could help cancer scientists and clinicians to further their knowledge of the effects, nutritional benefits, and toxic consequences of plant lectins.

## 4. Conclusions

Hitherto, the consumption of most whole grain foods prepared for human consumption (cooked, baked, extruded) has been associated with numerous health benefits. It is therefore recognized and advised to consume breakfast cereals and a variety of whole-grain foods. Although this advice is contradicted by some health professionals based on their lectin contents, it can be concluded from the current available scientific evidence that there are no data to generalize this negative opinion to consumption of whole grain products.

On the contrary, regular consumption of whole grain products recently was shown to be associated with a significant reduction of risks for type 2 diabetes, heart disease, syndrome X related events, weight gain and some types of cancer, in several meta-analysis studies (Björck, Östman et al., 2011; Fardet, 2010; Hauner et al., 2012; Jonnalagadda et al., 2011). These findings are supported by the outcome of a recent cohort, where it was observed that individuals who consumed recommended amounts of (whole)-wheat had the least amount of visceral fat accumulation (Molenaar et al., 2009). The health benefits of whole-wheat have been attributed largely to the fibre (β-glucan and arabinoxylan) and phytochemicals (phenolics, sterols, tocols and vitamins) that are concentrated in the aleurone layer of the bran (Brouns et al., 2012), as well as present in the wheat germ fraction.

In this respect, Jonnalagadda et al. (2011) summarized that, based on the existing evidence, there are four consensus authoritative statements from national organizations, namely the U.S. FDA, the U.K. Joint Health Claims Initiative and the Sweden and Danish Dietary Recommendations that link consumption of whole grains with improved heart health. Dietary guidelines around the world emphasize the importance of grain foods, particularly whole grains in the diet. For example, U.K. products composed of whole grains can claim, "People with a healthy heart tend to eat more whole grains foods as part of a healthy lifestyle." In Sweden, products with at least 50% whole grains can state, "A healthy lifestyle and a balanced diet rich in whole grain products reduce the risk of heart disease. Product X is rich in whole grains".

The current scientific evidence is strong and consistent to suggest that whole grains have beneficial effects in individuals with no genetic pre-disposition for celiac disease, despite the dietary lectin content. Wheat lectins are not gluten proteins and should not be confused with these. Despite numerous speculative assumptions that wheat germ lectins cause intestinal damage and disease, there is at present neither evidence that this is the case nor reason to recommend the healthy population to abstain from whole grain food products. Further research is recommended to define actual active lectin contents in wheat-based foods after heat preparation for human consumption.

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