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GRAIN FREE DIET RESEARCH

Is Grain-Free the New Gluten-Free for Autoimmune Disease?

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Abstract

1) Estimates suggest that 1 in 6 Americans has an autoimmune disease.
2) Grains, including non-glutenous grains play a role in the etiology of autoimmune disease.
3) Studies investigating the mucosal recovery and mortality in adults with Celiac Disease that mucosal recovery was absent, despite treatment with a gluten-free diet.
4. A pseudograin and grain-free diet is superior to a gluten-free diet for management of autoimmune disease.

KEYWORDS
Grains, pseudograins, prolamins, glutelins, leaky gut, molecular mimicry, gluten.

1 | INTRODUCTION

The American Autoimmune Related Diseases Association (AARDA) estimates that there are around 50 million people in the United States with an autoimmune disease [1], and its prevalence may be increasing. To put that another way, that is 1 in 6 individuals in the United States. And although autoimmune diseases and their etiologies are becoming better understood, there are still some misgivings about the benefits of a gluten-free diet that warrant further investigation.

Many health practitioners believe that avoiding gluten— a protein in wheat, barley, rye, and oats— is only necessary for individuals diagnosed with Celiac's Disease. However, evidence suggests that it may be important for anyone with an autoimmune condition to remove gluten from their diet, along with other non-glutenous grains because of the role that cereal grains play in the development of autoimmune diseases [2].

2 | GRAINS AND PSEUDOGRAINS

Grains and pseudograins are botanically related, technically seeds, which have different compounds and features that impact human health differently. Grains are the individual fruit (caryopsis) that is typical of the family Gramineae (Poaceae), which include several different types of commonly known grains. These include rice, wheat, barley, rye, oats corn, sorghum, millet, and teff.

Like grains, pseudograins may be used much in the same way as true cereals or grasses. Unlike grains, pseudograins are not from grass, but instead from a flowering broadleaf pseudo-cereal. Pseudograins come from the family Polygonaceae, Amaranthaceae, Chenopodiaceae and include Buckwheat, Amaranth, and Quinoa. [3] [Appendix]

Reproductively speaking, all plants evolved in specific ways to disperse their seeds so that their progeny may grow into a plant. Some plants evolved to enlist the help of animals that will eat, fertilize, and disperse their seeds. Other plants evolved so that their seeds may be carried through the wind or clinging to the fur of a passing animal, and were not necessarily intended for consumption by humans.

The seeds of the grasses and broadleaf pseudocereal plants evolved biochemical defense mechanisms to deter their consumption, as opposed to encouraging it.

Some of the known defense mechanisms of grains and seeds can be particularly dangerous for humans. Some contain toxic compounds, some inhibit the absorption of nutrients, while others are known to contain other autoimmunigenic compounds and chemical triggers for autoimmune-mediated disease.

3 | BIOCHEMICAL DEFENSES OF GRAINS AND PSEUDOGRAINS

Although many dietary guidelines worldwide suggest consuming a portion of whole grains daily as a healthful part of a human diet, grains and pseudograins do contain various biochemical components which can cause immunogenic dysfunction and disease in susceptible individuals. And, while sprouting, soaking, and cooking grains and pseudograins does mitigate many of the undesirable traits of consuming grains in the raw seed state, these processes do not always render grains and pseudograins benign for human health.

Most dietary interventions for autoimmune conditions like Celiac Disease have focused on the exclusion of the protein matrix known as gluten. [Appendix] However, emerging evidence suggests that other non-glutenous cereal grains may contribute to the manifestation of inflammation and autoimmunity by way of fostering intestinal permeability and may initiate pro-inflammatory responses and other disease states, as well. [4]

DEFENSE PROTEINS

The proteins of grains and pseudograins are classified into water-soluble and salt-soluble albumin and globulins, alcohol-soluble prolamins, and insoluble glutelins. [5, 6] Albumins and globulins are considered "metabolic proteins" while prolamins and glutelins are biologically considered to be the "storage proteins" or "defense proteins" of the plants. [7]

PROLAMINS

Prolamins are plant storage proteins that are necessary for seed growth that are found in both grains and pseudograins. Prolamins make up roughly 50% of the protein content in some mature cereal grains, and contain a high amount of proline and glutamine. [8]

Alcohol-soluble prolamins are resistant to degradation by gastric and intestinal proteases, and have been detected undigested, and translocated into other organs of the body as soon as 30 minutes after ingestion. [9] This lack of degradation and subsequent translocation is known to cause inflammation, insulin resistance, and influence fat metabolism [10] as well as induce autoimmunity in susceptible individuals. [11] [12].

GLUTELINS

Glutelin is another type of seed protein similar to prolamins, that are found in grains and pseudograins. Both prolamins and glutelins are made of highly repetitive sequences of glutamine and proline. The greatest difference between the prolamin and glutelin is the size of the amino acid glutamine and proline sequences, and their solubility.

While the prolamin gliadin (a component of gluten) is the most well known and well-studied biologically active autoimmunigenic peptide involved in the manifestation of Celiac Disease, in vivo and in vitro tests reveal the *under-appreciated potential* for autoimmunigenic activity of glutelin storage proteins. [13]

Research suggests that not only do the well-studied prolamin fractions of grains have autoimmunigenic and pro-inflammatory properties, glutelin fractions of grains and pseudograins may also contain harmful sequences for other autoimmune conditions as well. [14, 15, 16, 17]

These molecular sequences are involved in the molecular mimicry, the pathogenic mechanism of autoimmune disease. [18]. [19]

4 | MOLECULAR MIMICRY

The immune system has a number of 'recognition' or 'identification' mechanisms which allow the body to distinguish between its own proteins and foreign proteins. This identification system allows for foreign bodies such as bacteria and viruses to be discovered, identified, and subsequently destroyed.

This system enables the body to initiate an immune response to intrusions by viruses, bacteria, etc. When an antigen, or "foreign invader" is presented, immunoglobulins make antibodies to combat them.

Gluten is one of the most well-known antigenic stimuli, comprised of gliadin and glutenin. During the digestion process, gluten is broken down into strings of amino acids, called peptides. However, because the gluten matrix is poorly degraded by heat or digestion, some will remain an intact, 33-mer polypeptide during digestion [20]. If this intact polypeptide enters into the systemic circulation due to gut permeability, an autoimmune response may occur if the peptide sequence mimics the three-dimensional structure of an individual's tissues.

In this event, the immune system "confuses" non-self proteins with self-proteins— a case of 'mistaken identity' better known as molecular mimicry— the pathogenic mechanism of *autoimmune diseases.* [19]

In other words, chronic autoimmune diseases are the byproduct of the immune system recognizing self-antigens as foreign, whereby immunological self-tolerance is broken, leading to the immunopathological destruction of specific tissues and organs [21].

Anti-gliadin antibodies have been widely accepted as the hallmark for Celiac Disease. [22] However, research has shown elevated levels of these same anti-gliadin antibodies occur in *several* autoimmune conditions, not just Celiac's Disease. These include Lupus [22], Autoimmune Diabetes [23], Multiple Sclerosis [24], Rheumatoid Arthritis [25], Psoriatic Arthritis [26], Crohn's Disease [22], Graves Disease [22], Pemphigus vulgaris [22], and Autism [27] (while not classified as an autoimmune condition, there is autoimmune activity involved.)

Although the etiology of autoimmune disease is not fully elucidated, the causes are likely based on a combination of hereditary and environmental factors. Evidence suggests that for many autoimmune conditions there is an environmental trigger such as a viral or bacterial infection [28], dietary proteins such as prolamins and glutelins may also serve as an antigenic stimulus in the etiology of autoimmunity as a cross-reactive immune response to tissue antigen(s) [29].

5 | CASE FOR A GRAIN-FREE DIET

In light of this information, at the very least it makes sense that those affected by an autoimmune disease should adopt a gluten-free diet. However, a recent study found that "mucosal recovery was absent" in the gut in a substantial portion of adults with Celiac Disease even after treatment with a gluten-free diet. [30] The study also indicated that immunoreactivity was still present, meaning, a gluten-free diet *wasn't enough to improve their disease state.*

"LEAKY GUT"

There are a few potential reasons for this. While a large body of research supports the theory that molecular mimicry is the culprit in autoimmune disease, it's also hypothesized that impaired intestinal barrier function, commonly known as "gut permeability" [**Image 1**] is also required for the development of autoimmunity. [31, 32, 33, 34]

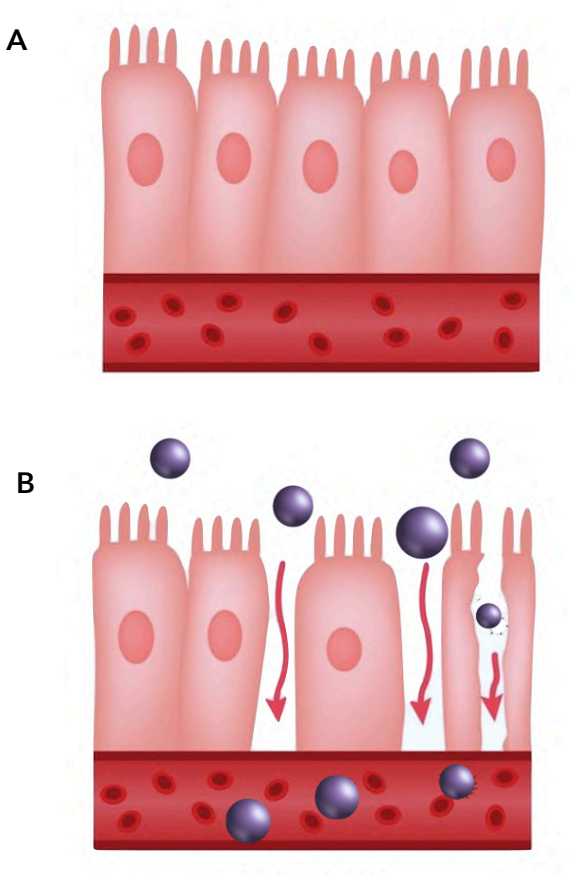

IMAGE 1: A: Normal Tight Junction. B: "Leaky Gut" showing compromised transcellular integrity, with zonulin entering circulation.

Not only do prolamins and glutelins from various non-glutenous grains and pseudograins contain prolamins and glutelins that serve as an antigenic stimulus **[Table 1, 2, 3]**, they are also associated with the development of leaky gut [35, 36] and the release of zonulin [37, 38] a toxin that promotes intestinal damage and compromises tight junction integrity.

Grain	Prolamin	Prolamin (%)
Wheat	Gliadin	40
Rye	Secalin	50
Barley	Hordein	52
Oats	Avenin	16
Corn	Zein	55
Rice	Orzenin	5
Teff	Eragrostin	40
Sorghum	Kafirin	52
Millet	Panicin	40

Table 1: Prolamin and content of various grains.

Grain	Glutelin	Glutelin (%)
Wheat	Glutenin	46
Rye	Secalinin	30
Barley	Hordeninin	23
Oats	Avenalin	23
Corn	Zeanin	39
Rice	G029	80
Teff	Eragrostosin	45
Sorghum	G047	23
Millet	G047	45

Table 2: Glutelins, and content in various grains.

Pseudograin	Prolamin (%)	Glutelin (%)
Wheat	Glutenin	46
Buckwheat	2-10.5%	25-59%
Quinoa	6-20%	18-31%

Table 3: Pseudograins, and their respective prolamin and glutelin contents.

IMMUNOREACTIVITY IN GLUTEN FREE GRAINS

For example, the prolamin zein in corn was found to illicit immunoreactivity in individuals with Celiac's Disease. [39]

The prolamin orzenin found in rice is now being reevaluated as a hypoallergenic food because it is recognized as a common and severe cause of food protein-induced enterocolitis syndrome [40]. Enterocolitis is commonly induced by an auto-immune targeting of glial cells. [41]

Millet and Sorghum, which are common as the starch in many gluten-free products are Panicoid grains which are resistant to digestion [42], act like zeins [43], and have been implicated in the process of inducing molecular mimicry [44].

6 | DISCUSSION

While the majority of the population does not have an autoimmune disease, research indicates that non-Celiac, healthy individuals who consume gluten still experience mucosal changes and damage to enterocytes (gut cells), leading to intestinal permeability. [45]

And while the scope of this particular article focuses on the safety of grains for individuals with an autoimmune condition, emerging evidence does indicate that increased intestinal permeability is involved in several disorders associated with low-grade inflammation. This includes obesity [46], obesity-associated insulin resistance [47], type 2 diabetes [48], and cancer. [49]

In short, just because a grain or pseudograin is gluten-free does not inherently mean that it safe for individuals with autoimmune conditions, yet non-glutenous grains and pseudograins are nevertheless routinely offered as viable alternatives by the booming gluten-free industry.

In light of this information, we believe that a massive shift in gluten-free messaging towards a grain-free focus is warranted.

Luckily, according to industry analytics company SPINS' "State of the Natural Industry Report 2019," this drastic change in attitudes towards grains is already underway. The SPINS data suggests that paleo-positioned products grew up to $536.7 million, growing at 45.3 percent, while Grain-free products are up to $271.5 million, growing at 76 percent—with even faster growth in the mainstream food retail space. Further, the grain-free snacks saw a whopping 258.3% to 29.7 million, indicating the power and mainstream opportunity of the grain-free trend. [47]

Our expectation is that the demand for grain-free foods will continue to grow as emerging evidence supports a grain-free diet over the now antiquated gluten-free-only focused messaging.

Grain-Free is the new Gluten-Free, indeed.

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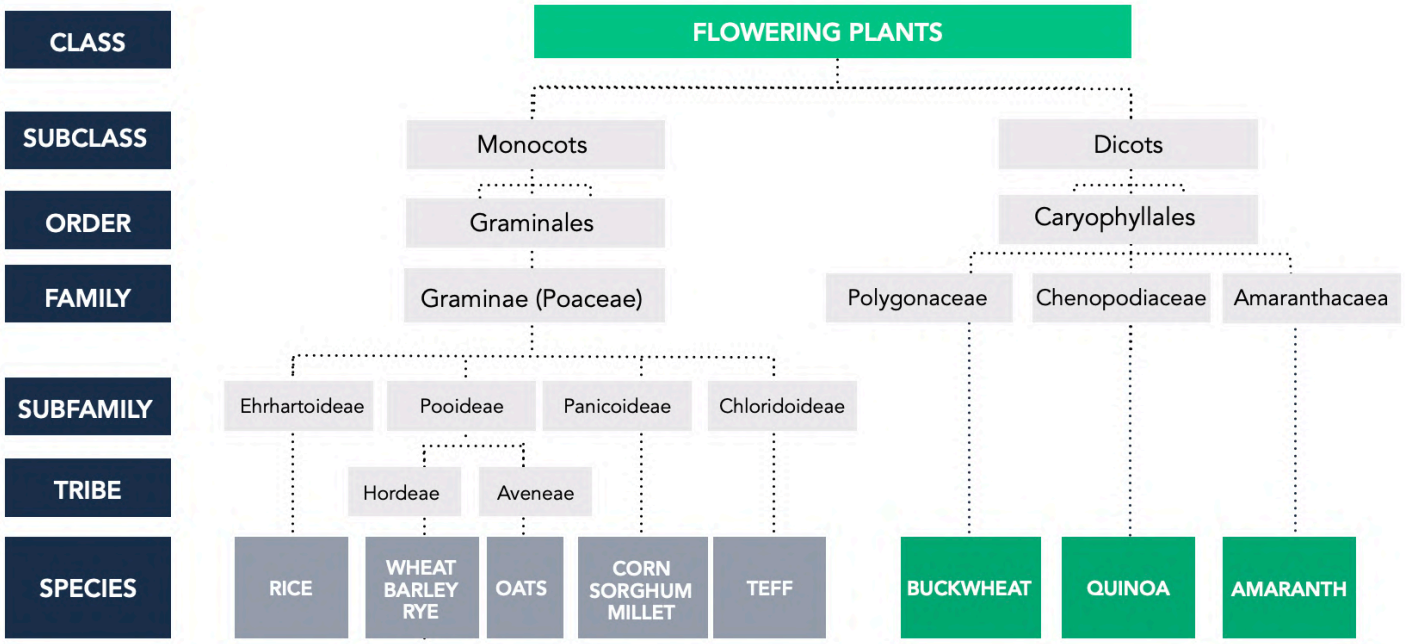
8 | APPENDIX

PSEUDO-GRAINS

Pseudo-grains come from the family Polygonaceae, Amaranthaceae, Chenopodiaceae and include Buckwheat, Amaranth, and Quinoa.

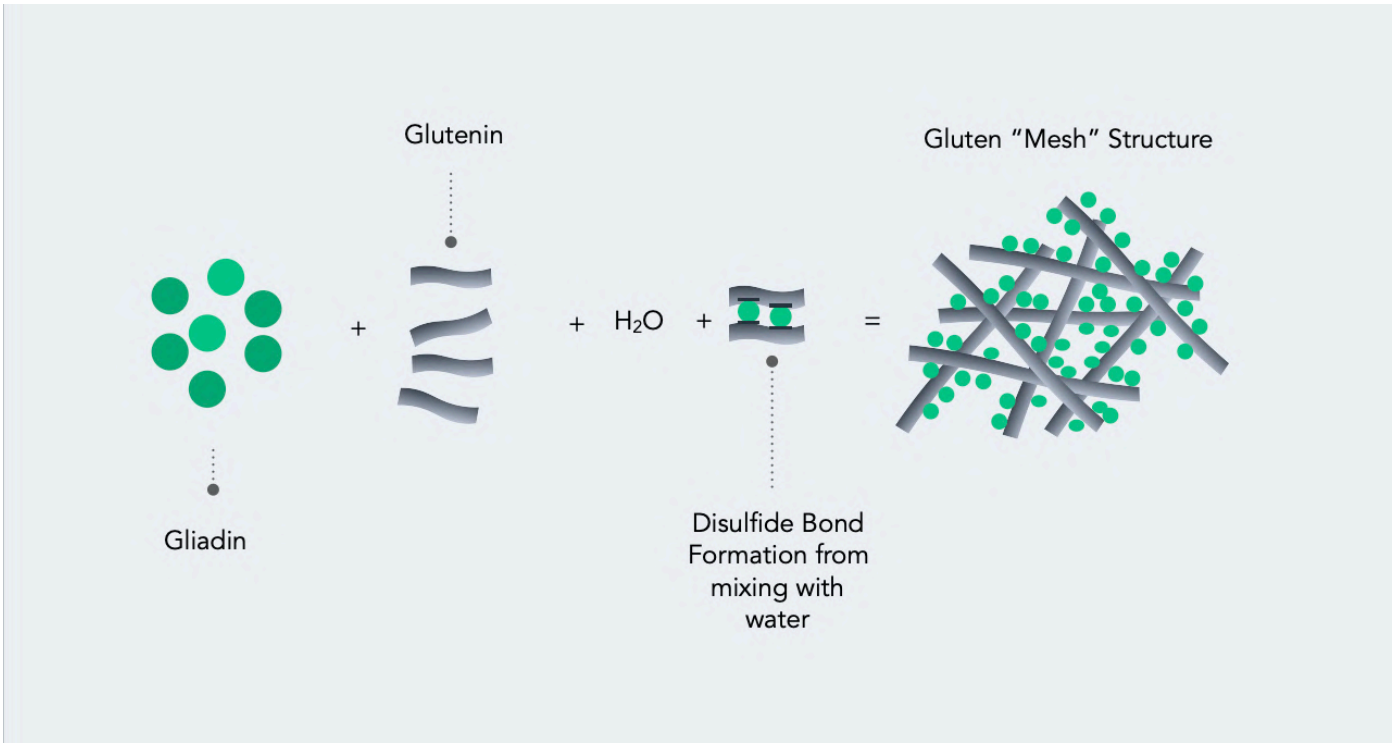


GLUTEN

The majority of wheat's protein content comes from the endosperm. Albumin and globulin represent roughly 15-20% of the total protein content of the endosperm, and gliadin and glutenin make up the remaining 80-85%. In wheat, gliadin (a prolamin) represents 30-40% of the total protein, and the glutenin (a glutelin) represents 40-50%.

The gliadin and glutenin protein amounts are in similar amounts. gluten is not a single protein. It is a long, molecular structure or "mesh" formed by two seed storage proteins, gliadin, and glutenin that are connected by disulfide bridges, created by way of mechanical stress in an aqueous environment. In other words, when gliadin and glutenin combine with water, a three-dimensional gluten "mesh" structure is formed. In the gluten mesh, gliadin gives the dough plasticity and elasticity, while glutenin provides strength and structure.

Due to the formation of these intermolecular bonds, the "mesh" traps starch granules and carbon dioxide that is produced during the leavening process, causing the dough to 'rise. It is the "gluten-mesh-trap" that givens the final product a doughy, airy, and highly desired texture. These are the properties that make gluten products so appealing in the food industry.



Pendergrass, K. (2019) **Is Grain-Free the New Gluten-Free for Autoimmune Disease? Grain Free Research.** The Paleo Foundation.