



Permeable gut syndrome, gluten, and autoimmune disease: an integrative review

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Abstract

Introduction: Leaky Bowel Syndrome or intestinal permeability is a gastrointestinal condition that affects many people. A leaky gut is a trigger for many changes like food allergies and intolerances, autoimmune diseases, colitis, Crohn's and celiac disease, inflammatory diseases, depression, insulin resistance and even cancer have been linked. **Objective:** To analyze basic information for a better understanding of this topic, from the functioning of the gastrointestinal tract, as the diseases that are associated with it, how the immune system responds to these injuries, the quality, and importance of proteins, and the consequence of this disorder to the body human. **Methods:** Conducted an integrative literature review. The Pubmed, Google Scholar, and Scielo databases were consulted. **Results:** The intestine is naturally permeable to many small molecules, so it can absorb vital nutrients. Regulating intestinal permeability is one of the most basic functions of the cells that make up the intestinal wall. But one factor calls our attention, what is the role of gluten in the development of this disease and the worsening of symptoms? Insensitive people, gluten can cause cells to release zonulin, a protein that can break the tight junctions of intestinal tissue. Other factors—such as infections, toxins, stress, and age—can also cause these joints to come apart. Once strong joints break, you have a leaky gut. Gluten, therefore, is the number one cause of

this process. A person with a leaky intestine tends to be highly allergic and intolerant to foods and substances, and may or may not manifest intestinal discomfort such as gas and bloating. **Conclusion:** Based on the literature that supports this theme, it is considered that gluten is a possible villain in the intestinal tract and is related to many autoimmune diseases. Furthermore, as an interventional measure, it is necessary to reduce some carbohydrate-rich foods and the maintenance of the body's balance with specific diets and physical activities.

Keywords: Intestinal permeability. Autoimmune diseases. Gluten sensitivity. Leaky gut.

Introduction

The inside of the intestine is lined with a single layer of cells that make up the mucosal barrier (the barrier between the inside of the intestine and the rest of the body). This barrier is effective at absorbing nutrients but prevents most large molecules and germs from passing from within the intestine into the bloodstream and potentially causing widespread symptoms [1].

However, in some circumstances, this barrier can become less effective and "permeable", although this in itself is not generally considered sufficient to cause serious problems [2]. When this happens, we call this phenomenon leaky gut or "intestinal permeability", meaning it is a condi-

tion in which the lining of the small intestine is damaged, causing undigested food particles, toxic waste, and bacteria to "leak" through the intestines. and flood the bloodstream [3].

Foreign substances entering the blood can cause an autoimmune response in the body, including inflammatory and allergic reactions such as migraines, irritable bowel, eczema, chronic fatigue, food allergies, rheumatoid arthritis, and more. According to Galland (2005) [4], leaky bowel can also be caused by medications, including antibiotics, steroids, or over-the-counter pain relievers such as aspirin and acetaminophen, which can irritate the intestinal lining

and damage the protective mucus layers. This irritation can initiate or continue the cycle of inflammation that leads to intestinal permeability [3].

From this premise, the following symptoms can be signs of leaky bowel: chronic diarrhea, constipation, gas or bloating, nutritional deficiencies, poor immune system, headaches, brain fog, memory loss, excessive fatigue, rashes, and problems such as acne, eczema or rosacea, sugar or carbohydrate cravings, arthritis or joint pain, depression, anxiety, autoimmune diseases such as rheumatoid arthritis, lupus, celiac disease or Crohn's disease [5].

By contrast, exponents of "leakable bowel syndrome" - largely alternative and complementary medicine practitioners - believe that the intestinal lining can become irritated and leaky as a result of a much wider range of factors, including yeast overgrowth or bacteria in the gut, a poor diet and overuse of antibiotics, which we call intestinal dysbiosis [6].

In many cases, the leaky gut is caused by the diet adopted by each individual. Certain foods present in daily food, such as gluten, soy, and dairy products, can be treated by the body as invaders that need to be fought. Eating these foods triggers the production of antibodies as an immune response that includes diarrhea, headaches, fatigue, and joint pain. Gluten is therefore one of the biggest villains contributing to the leaky gut [7,8].

In this sense, given the attention that the expression "leaky bowel and/or leaky bowel" has been receiving lately on medical blogs and social media, it has become a topic with a great focus on basic sciences. However, there is growing interest in developing drugs that can be used in patients to combat the effects of this problem. Therefore, given the growing number of cases of gluten intolerance, the present study aimed to relate intestinal permeability and consequent food allergies, emphasizing gluten hypersensitivity as a risk factor [9,10]. Thus, the present study addressed analyzes of information

that indicate the complex characteristics of a leaky bowel, which require health professionals to have the necessary knowledge to identify its manifestation, resulting in a more efficient diagnosis.

Methods

The method used in this integrative literature review study was based on the research and analysis of published and available materials on the subject, considering articles in Portuguese and English, including books, reports and specialized websites, highlighting the knowledge of Brazilian and foreign physicians thus aiming to seek and integrate the various theoretical approaches in other areas of knowledge, providing a convergence of knowledge. The Pubmed, Google Scholar and Scielo databases were consulted, as well as scientific journals indexed by the descriptors *Intestinal permeability*, *autoimmune diseases*, *gluten sensitivity*, *leaky intestine*.

Permeable Intestine – Concept and Risk Factors

The gastrointestinal tract (GIT) contains a continuous epithelium that presents several characteristics concerning the substances present in the intestinal lumen, generating their transport function as well as the barrier function [11]. The term intestinal permeability refers to this barrier function, capable of allowing or not allowing the passage of molecules through non-mediated diffusion mechanisms, by differences in concentration or pressure gradients, without the assistance of a passive or active biochemical carrier system.

In other words, inside our bellies, we have an extensive intestinal lining covering over 4,000 square feet of surface area. When it works properly, it forms a tight barrier that controls what gets absorbed into the bloodstream. An unhealthy intestinal lining can have large spaces, allowing partially digested food and toxins to penetrate the tissues below it. This can lead to inflammation and changes in the intestinal flora (normal bacteria) that can lead to problems in the digestive tract and beyond. Research is growing on this subject, with studies showing that changes in intestinal bacteria and inflammation may play a role in the development of several common chronic diseases [7].

It is possible to say that all people have some degree of loose bowel, as this barrier is not completely impenetrable. However, some individuals may have a genetic predisposition and may be more sensitive to changes in the digestive system that may have different prognoses, such as diet and stress routine, in addition to heavy alcohol use, they also seem to disturb this balance.

The standard American diet, which is low in fiber and high in sugar and saturated fats, is an example of triggering this process [12].

For Bjarnason et al. (1995) [8] the expression intestinal permeability is related to the barrier function performed by the epithelium and is translated by its property of allowing the passage of molecules through the non-mediated diffusion mechanism, regardless of the gradient of concentration or pressure, and without the assistance of a passive or active biochemical carrier system.

For Vilela (2005) [9] the permeation to macromolecules increases in processes that lead to an inflammatory reaction in the intestinal mucosa, favored by loosening in the intercellular junctions, while the permeation of monosaccharides portrays the intestinal absorptive area, although there is no consensus to elucidate the pathways of permeation.

But after all, what is a leaky gut or "Leaky gut syndrome"? It is not a ready-made diagnosis taught in medical school. Instead, "loose bowel means that the diagnosis has yet to be made". In a very simple vocabulary, it can be termed that the leaky intestine happens when tight junctions in the intestine, which control what passes through the lining of the small intestine, do not work properly. This could let the substances leak into the bloodstream [13].

Intestinal permeability results from an alteration in the intestinal mucosa, with the main characteristic being the increase in the space between the lining cells, with a resulting mucosal irritation or inflammation. Thus, foreign materials such as fungi, bacteria, and proteins penetrate more easily into the bloodstream [11]. However, there is an efficient multifaceted intestinal barrier system with physical, biochemical, and immunological components that prevent the entry of most pathogens. These components coordinate with each other to prevent uncontrolled translocation of luminal content into the body.

Rosenfeldt et al. (2004) [11] report that the breakdown of the integrity of the intestinal barrier and increased permeation of macromolecules have been associated with etiopathogenic mechanisms common to various diseases of an inflammatory character of the digestive tract, as well as autoimmune diseases. For the mucosa to perform its function properly, its integrity must be preserved and the use of probiotic bacteria has been associated with this maintenance of the integrity of the intestinal epithelium.

But the biggest issue is the association of a leaky bowel with autoimmune diseases (lupus, type 1 diabetes,

multiple sclerosis), chronic fatigue syndrome, fibromyalgia, arthritis, allergies, asthma, acne, obesity, and even mental illness [12]. However, we still do not have clinical studies in humans that demonstrate such cause and effect [12,13]. The intestine is the largest organ of the immune system, it is the gateway to health. This is where nearly 80% of the immune system lives and where up to 95% of serotonin (the main neurotransmitter responsible for mood) is produced. If the intestine is healthy, the chances of good health and quality of life are increased.

The Leaky Gut and The Autoimmune Connection

When the intestine is "leaking", meaning there is a leaky gut syndrome, particles after particles can escape into the bloodstream, the immune system reacts by sending wave after wave of inflammation to attack the invaders. This high-alert state causes the immune system to become overwhelmed and shoot less accurately, sometimes causing your tissues to get caught in the crosshairs. Eventually, this will develop into autoimmunity if the bowel is not repaired [14].

According to Fasano (2012) [15], the immune system begins to produce antibodies against substances that have escaped into the bloodstream and many of these invaders are gluten and dairy products that look very similar to the body's cells, making the system immune confuses and accidentally attacks the tissues. This process of mistaken identity is called molecular mimicry, and it's another way the leaky gut can trigger autoimmune diseases. In this sense, leaky bowel is a necessary precondition for the development of autoimmune disease [16].

In this context, Sampson (2004) [17] states that adverse reactions to food are represented by an abnormal reaction to the ingestion of food or food additives, which can be classified as toxic and non-toxic. Toxic substances are more dependent on the ingested substance or the pharmacological properties of certain substances present in food. Non-toxic are those that are dependent on individual susceptibility and can be classified as non-immune mediated (food intolerance) or immune-mediated (food hypersensitivity or food allergy).

Sometimes clinical manifestations resulting from intolerance are confused, such as lactose intolerance secondary to primary or secondary lactase deficiency, with food allergy - which is a term used to describe adverse reactions to foods, dependent on immunological mechanisms, mediated IgE or not, according to the Supplement to the Brazilian Consensus on Food Allergy (2008) [18].

The term intolerance, in turn, can be defined as any mechanism that cannot be identified as a "true" allergic rea-

tion, including immunological reactions, which are difficult to relate to food, but whose moderate pathology can trigger a series of uncharacteristic symptoms, such as for overweight, digestive disorders, diarrhea, irritable bowel, skin manifestations, headaches, psychological disorders, respiratory disorders, arthritis, joint inflammation and other manifestations [3].

Nunes et al. (2012) [19] report that food intolerance is distinguished by an adverse, reproducible reaction that occurs after exposure to a certain food, but which, unlike food allergy, does not cover the immune system. Poor nutrition can increase bacterial growth in the gut and intestinal permeability. When this occurs, bacteria, viruses, toxins, and partially digested foods, all of which are antigenic, can cross the intestinal barrier and enter the bloodstream.

Autoimmune disease is a syndrome determined by tissue damage or functional change triggered by an autoimmune response. Therefore, autoimmune diseases are a group of characteristic diseases that come from the fact that the immune system starts to produce antibodies against components of the organism itself. For several reasons and not always elucidated, the body begins to confuse its proteins with invading agents, starting to attack them. Thus, autoimmune disease is a disease determined by the immune system, which starts to function inappropriately [2].

In this sense, Leonard et al. (2013) [20] report that autoimmune diseases (AIDs) correspond to a set of manifestations associated with changes in the immune system (B and T lymphocytes), in which there is a breakdown of the mechanism of distinction between external antigens and self-antigens. The development of autoimmunity is sufficiently expressive to result in tissue damage, which can be limited to a specific organ disease or proceed to systemic disease. As an example, we have that in type 1 diabetes there is inadequate production of antibodies against the insulin-producing cells of the pancreas, destroying them and leading to the appearance of diabetes.

According to Kivity and Ehrenfeld (2010) [21] over the past few years, there has been an increase in the prevalence of autoimmune diseases, especially in Western countries, affecting about 5% of the population, especially women.

Gluten and Its Characteristics

The first action in nutrition to prevent or treat the leaky gut is to remove gluten from daily foods. Gluten is a set of wheat proteins composed of gliadin and gluten. It constitutes 80% of wheat protein and is responsible for

providing elasticity to bread dough.

In reality, gluten is a source of health problems. According to Biesiekierski et al. (2018) [22], gluten intake is correlated with intestinal permeability and the ease of autoantibody production by the immune system. In addition, gluten weakens the villi of the intestine and hinders the absorption of nutrients increasing the risk of developing chronic diseases, gastrointestinal problems, and contributing to irritable bowel syndrome, which can be prevented by eliminating gluten from the diet. Gluten negatively affects the health of a large part of the human population that is hypersensitive to a greater or lesser extent and more negatively to celiac patients. The negative effect of gluten on health is so important that antibodies against gluten are even detected in patients with multiple sclerosis, and multiple sclerosis is one of the autoimmune diseases. Almeida and Sá (2017) [23] report that gluten is included in the group of glycoproteins of prolamines. Insoluble in water, gluten is responsible for the texture of pasta, cakes, and bread. It is also found in certain cereals, such as wheat, barley, oats, and rye, and can cause tissue damage in sensitive individuals, leading to disease.

There is currently an increasing number of gluten-related diseases, some of which are well known as celiac disease or gluten-sensitive enteropathy, which affects 1 in 133 people in the US, with the highest prevalence in relatives of celiac people. Starting from lactation to adulthood, but in 20% of cases occur in adults over 60 years. Gluten is a protein found in cereals: wheat (*Triticumaestivum*), rye (*Secalecerale*), barley (*Hordeum Vulgare*), and oats (*Avena sativa*); and is obtained after the removal of starch by washing the flour of these cereals. Each cereal has its respective protein fraction of gluten, toxic to patients with celiac diseases, called prolamins, which represent 50% of the total amount of this protein, namely: gliadin in wheat, secalin in the rye, hordein in barley, and avenin in oats [24].

The total amount of protein in the wheat grain varies between 8 and 21%. Of these, approximately 15% correspond to globulins and albumins that do not form gluten and 85% correspond to gliadin and glutenin, which combined have the property of forming together with water and mechanical energy a viscoelastic and water-insoluble three-dimensional network: gluten. The more gluten in the flour, the harder the dough [19].

To human food, rye, barley, oats, and wheat have wide application, especially wheat, which is due exactly to the fact that these cereals have gluten in their composition, which guarantees the property of water absorption, elasticity, and retention of gas, thus allowing to stretch and extend through the action of mixing, beating and kneading the preparation, promoting its use in various foods [18]

Flours obtained by grinding cereal grains contain gluten-forming proteins and are used not only as a basic ingredient in preparations but can also be added during processing, processing, and/or in food preparation [23].

Consumption of Cereals Containing Gluten and Its Application in Human Food

Rye was introduced to Brazil by German and Polish immigrants two centuries ago. Until today, its cultivation is carried out largely by European descendants and its main use is in the production of bread. Barley comes from the Middle East and is produced in Brazil mainly in the South and Southeast regions; and the main use of barley is malting for use in the production of beer and spirits, but it is also used in the composition of flours or flakes for baking, in the formulation of diet products and coffee substitutes [23].

Oats have been used in the production of children's foods, breakfast cereals (hot or cold), granola, cereal bars, baked or baked products (bread, cookies, cakes, among others), an additional component to thicken soups, sauces and to increase the volume of meat products [14]. However, its use in the gluten-free diet is still controversial, as it has a low content of prolamines, but still present and also due to the risk of contamination with other gluten-containing cereals in the industry [11].

Among the cereals that contain gluten, the one with the greatest production and consumption in the world is wheat [17]. According to the Ministry of Agriculture (2012) [19], wheat is the second most-produced cereal in the world, after rice, with a significant weight in the global agricultural economy. In Brazil, wheat is cultivated in the South, Southeast, and Midwest regions, receiving systematic reinforcement from government agencies, since weather conditions are unfavorable to the crop, as one of the actions developed to increase wheat production and reduce dependence country on the cereal. Ministry estimates predict an increase in wheat consumption of 1.31% per year and it is believed that imports may be reduced due to investments in self-sufficiency in the internal production of the cereal. In 2009, the incentive policy launched by the ministry provided an increase of 50% compared to the previous year's harvest.

According to data from CONAB (National Supply Company), Brazil had 2,359 hectares of wheat, 357 thousand oats, 143 thousand barley, and 4 thousand rye planted area, which produced 4,885 thousand tons of wheat respectively, 517 thousand tons of oats, 399 thousand tons of barley and 7 thousand tons of rye [18]. This large production of gluten-containing cereals stimulates its application in the food industry, making

treatment difficult for patients with CD.

Wheat flour is used in the production of pasta, confectionery, and bakery products where it is widely used, as gliadin and glutenin proteins can absorb up to 200% of their initial weight in contact with water and gluten acquires an elastic structure, with great adhesiveness and gas retention capacity, allowing it to be stretched and extended by mixing, beating and kneading [20].

It is also used in thickening preparations and wheat is often used in the production of "instant coffee, powdered chocolate, ice cream, chewing gum, canned/dehydrated soups, and porridge, sausages, meat, mayonnaise, tomato sauces, mustards, yogurts, baby food". Gliadin and glutenin are the basis for using wheat flour in the preparation of bakery and pasta products. This is due to the functionality of these proteins, which determine important characteristics in food acceptance, significantly influencing their sensory quality. These properties result from their ability to develop sensory, hydration, structural characteristics, among others [22].

Gliadins are single-chain, sticky, gummy proteins responsible for the consistency and viscosity of the dough, but they have little resistance to extension. Glutenins, on the other hand, have branched chains, elastic but not cohesive, and are responsible for the extensibility of the dough, important for its ability to influence the quality of bakery products and the quality of the doughs [22].

Due to its wide application in human nutrition, the lack of knowledge about CD, and the growing need to use food services outside the home, it becomes difficult for celiac patients to maintain adherence to a gluten-free diet [23]. To understand new research on gluten sensitivity, it is first important to understand the two other gluten-induced diseases: celiac disease and wheat allergy. Both diseases involve the immune system.

How to Improve Intestine Health

The Mediterranean diet and frugal food are the most advisable to reduce bacterial overgrowth and bowel permeability. Therefore, food (food intolerance and allergies), bacteria, viruses, chemicals, excess bacterial growth in the intestine, intestinal permeability, and contaminants play a role in the etiology of autoimmune diseases [25]. A gluten-free diet GFD may improve symptoms in a subgroup of patients with Irritable bowel syndrome. The possible interaction between Irritable bowel syndrome and gluten-related disorders represents a scientific and clinically challenging question. More studies are needed to confirm these data and better clarify the pathophysiological mechanisms involved

Conclusion

As exposed in this research, food has its importance in all body systems. However, regardless of whether it is a restrictive diet or not, it is important to have a multidisciplinary follow-up to help in the best way to maintain good eating habits, as the prevalence of chronic and autoimmune diseases has increased significantly. Studies have shown that these diseases are related to food. Over the last decade, both the number of patients and the number of publications on leaky bowel syndrome have increased significantly. Considering the high rate of perception of gluten sensitivity and the possible placebo effect of any dietary intervention, it was observed that there is a clear relationship between gluten intake and the onset of symptoms that trigger the leaky bowel syndrome and consequently affect the individual's immune system. Although there is no availability of validated biomarker(s) in the diagnosis of the syndrome, the criteria that lead to the diagnosis of this condition described in this article can help to optimize the clinical treatment, and to prevent the progress of triggering other diseases. Therefore, gluten is a villain for the intestine and that is why it is important to restrict your diet.

References

- 1 Canakis A, Haroon M, Weber HC. Irritable bowel syndrome and gut microbiota. *Curr Opin Endocrinol Diabetes Obes.* 2020 Feb;27(1):28-35. doi: 10.1097/MED.0000000000000523. PMID: 31789724.
- 2 Khoshbin K, Camilleri M. Effects of dietary components on intestinal permeability in health and disease. *Am J Physiol Gastrointest Liver Physiol.* 2020 Nov 1;319(5):G589-G608. doi: 10.1152/ajpgi.00245.2020. Epub 2020 Sep 9. PMID: 32902315; PMCID: PMC8087346.
- 3 Kinashi Y, Hase K. Partners in Leaky Gut Syndrome: Intestinal Dysbiosis and Autoimmunity. *Front Immunol.* 2021 Apr 22;12:673708. doi: 10.3389/fimmu.2021.673708. PMID: 33968085; PMCID: PMC8100306.
- 4 Galand PE. et al. Pathways for methanogenesis and diversity of methanogenic Archaea in three boreal peatland ecosystems. *Applied and Environmental Microbiology*, v. 71, n. 4, p. 2195, 2005.
- 5 Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA.* 2015 Mar 3;313(9):949-58. doi: 10.1001/jama.2015.0954. PMID: 25734736.
- 6 Obrenovich MEM. Leaky Gut, Leaky Brain? *Microorganisms.* 2018 Oct 18;6(4):107. doi: 10.3390/microorganisms6040107. PMID: 30340384; PMCID: PMC6313445.
- 7 Lin R, L Zhou, Zhang J, Wang B. Permeabilidade intestinal anormal e microbiota em pacientes com hepatite auto-imune. *Int J Clin Exp Pathol* (2015) 8 (5): 5153-60.
- 8 Bjarnason, I.; Macpherson, A.; Hollander, D. Intestinal Permeability: An Overview. *Gastroenterol.* v. 108, p. 1566- 1581, 1995.
- 9 Vilela, E. G. A influência do *Saccharomyces boulardii* na permeabilidade intestinal de pacientes com doença de Crohn em fase de remissão. 2005. 131p. Tese (Doutorado em Medicina), Universidade Federal de Minas Gerais, Belo Horizonte, 2005
- 10 Khaleghi S, JM Ju, Lamba A, Murray JA. A utilidade potencial da regulação da junção apertada na doença celíaca: foco no acetato de larazotide. *Therap Adv Gastroenterol* (2016).
- 11 Rosenfeldt, V.; Benefeldt, E.; Valerius, N.H. et al. Effect of pro-biotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. *J Pediatr* 2004; 145(5): 612-6.
- 12 Gerbe F, Legraverend C, Jay P. As células do tufo do epitélio intestinal: especificação e função. *Cell Mol Life Sci* (2012).
- 13 Hooper LV, Littman DR, Macpherson AJ. Interações entre a microbiota e o sistema imunológico. *Ciência* (2012).
- 14 T de Pelaseyed, Bergstrom JH, Gustafsson JK, Ermund A, GM Birchenough, Schutte A, et al. O muco e as mucinas das células caliciformes e enterócitos fornecem a primeira linha de defesa do trato gastrointestinal e interagem com o sistema imunológico. *Immunol Rev* (2014).
- 15 Fasano A, Shea-Donohue T. Mecanismos da doença: o papel da função da barreira intestinal na patogênese das doenças autoimunes gastrointestinais. *Nat Clin Pract Gastroenterol Hepatol* (2005).
- 16 Fasano A. Zonulin, regulação de junções apertadas e doenças auto-imunes. *Ann NY Acad Sci* (2012).
- 17 Sampson, H. A. Update on food allergy. *J Allergy Clin Immunol.* 2004; 113(5): 805 – 19; quiz 20.
- 18 Consenso Brasileiro sobre Alergia Alimentar: Documento conjunto elaborado pela Sociedade Brasileira de Pediatria e Associação Brasileira de Alergia e Imunopatologia, *Rev. Bras. Alerg. Imunopatol.* v. 31, n. 2, p. 64- 89, 2008.
- 19 Nunes, M., et al. (2012). *Alergia Alimentar. Direção Geral da Educação e Ministério da Saúde*, pp. 22.

- Leonard; Wartofsky and Kenneth D. Burman Alterations in Thyroid Function in Patients with Systemic Illness: The "Euthyroid Sick Syndrome" Endocrine Rewiews July 01, 2013.
- 20 Kivity S, Ehrenfeld M. (2010) Can we explain the higher prevalence of autoimmune disease in women? Expert Review Clin Immunol 6 (5): 691-694.
- 21 Biesiekierski, J. R.; Newnham, E.D.; Irving, P.M. et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. **Am J Gastroenterol.** v. 106, n.3, p. 508-14, 2018.
- 22 Almeida, S. G.; SÁ, W. A. C. Amaranto (amaranthus ssp) e quinoa (chenopodium quinoa) alimentos alternativos para doentes celíacos. Ensaios e Ciência: Ciências Biológicas, Agrárias e da Saúde, v. 13, n. 1, p. 77-92, 2009.
- 23 Anand BS, Piris J, Truelove SC. The role of various cereals in celiac disease. Q J Med; 2005.
- 24 Wolters VM, Alizadeh BZ, Weijerman ME, Zhernakova A, van Hoogstraten IM, Mearin ML, Wapenaar MC, Wijmenga C, Schreurs MW. Intestinal barrier gene variants may not explain the increased levels of antigliadin antibodies, suggesting other mechanisms than altered permeability. Hum Immunol. 2010 Apr;71(4):392-6. doi: 10.1016/j.humimm.2010.01.016. Epub 2010 Feb 4. PMID: 20096742.
- 25 Usai-Satta P, Bassotti G, Bellini M, Oppia F, Lai M, Cabras F. Irritable Bowel Syndrome and Gluten-Related Disorders. Nutrients. 2020 Apr 17;12(4):1117. doi: 10.3390/nu12041117. PMID: 32316404; PMCID: PMC7231142.

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