



e-ISSN: 2319-8753 | p-ISSN: 2347-6710

IJRSET

International Journal of Innovative Research in
SCIENCE | ENGINEERING | TECHNOLOGY



INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 13, Issue 6, June 2024

ISSN INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA

Impact Factor: 8.423

9940 572 462

6381 907 438

ijirset@gmail.com

www.ijirset.com

Comprehensive Insights into Gluten-Related Disorders: A Review

Jyothsna M. R¹, Tipale Mayuri², Jadhav Balaji³

M. Sc, Department of Food Technology, NIMS Institute of Allied Medical Science & Technology, NIMS University,
Jaipur, Rajasthan, India¹

Assistant Professor, NIMS Institute of Allied Medical Science & Technology, NIMS University, Jaipur,
Rajasthan, India^{2,3}

ABSTRACT: Gluten, a key protein in wheat, greatly influences the texture of baked goods. This review delves into gluten-related issues such as celiac disease (CD), non-celiac gluten sensitivity (NCGS), wheat allergy (WA), and dermatitis herpetiformis (DH). It highlights the roles of gluten's components, gliadin, and glutenin, in dough elasticity and the importance of understanding gluten's immunogenic properties and breakdown mechanisms for managing these disorders. The review discusses the challenges in diagnosing various gluten intolerances and the autoimmune complexities of CD. It emphasizes the critical role of a gluten-free diet in effectively managing CD and the need for a nuanced understanding of NCGS for better management. The interplay between gluten, intestinal barrier functions, and symptoms suggests potential relief through dietary interventions like a gluten-free diet and fermentable oligo-, di-, and monosaccharides and polyols (FODMAPs) for conditions like irritable bowel syndrome (IBS). While promising, interventions like the gluten-free casein-free (GFCF) diet for autism and the potential benefits of a gluten-free diet for schizophrenia require further investigation through larger trials. This review navigates the intricate landscape of gluten-related issues, highlighting its significance in culinary arts and healthcare. Ongoing efforts are essential for improved diagnosis, management, and treatment, enhancing the quality of life for affected individuals.

KEYWORDS: Celiac Disease, Gluten, Non-Celiac Gluten Sensitivity, Wheat Allergy

I. INTRODUCTION

Gluten, a complex protein found in wheat, is essential for the texture and structure of various baked goods, due to its components, gliadin, and glutenin, which contribute to dough elasticity. However, gluten poses challenges for individuals with gluten-related disorders like celiac disease, non-celiac gluten sensitivity, wheat allergy, and dermatitis herpetiformis. Diagnosing these conditions is difficult due to varied adverse reactions.

This review explores gluten's structure, focusing on gliadin and glutenin's roles in dough formation. It also examines gluten digestion and its impact on those with gluten-related disorders. Beyond baking, gluten's properties are significant in the food industry, influencing ingredient interaction and sensory attributes. Ongoing research aims to enhance our understanding of gluten's biochemical properties and its implications for culinary arts and food science.

1.1 What is gluten?

Wheat holds a prominent position as one of the primary food crops worldwide, cultivated, consumed, and traded extensively. The common wheat species, *Triticum aestivum* L., often serves as a reference for numerous other cultivated wheat varieties and genotypes. Within the wheat kernel, protein content ranges from 8% to 15%, with approximately 10% to 15% comprising albumin/globulin and 85% to 90% constituting gluten [1]. Gluten, an intricate mixture of many closely interconnected yet different proteins, mainly comprises of gliadin and glutenin. Protein content, as well as the makeup and arrangement of gluten proteins, vary between different types of wheat. Gliadin and glutenin, together known as prolamins, are seed proteins that do not dissolve in water but can be extracted in aqueous ethanol [1]. Based on essential factors like sulfur content and molecular weight, gluten proteins are sorted into subcategories. They are then classified into alpha, beta, gamma, and omega (α , β , γ , and ω) gliadins according to their primary compositions. The strong covalent and non-covalent bonds formed between individual gluten proteins, along with their structural interactions, greatly influence the unique characteristics of gluten [2].

1.2 Structure

Gluten, known for its complex nature, contains a variety of specific proteins, namely glutenin and gliadin, due to its high allelic polymorphism. Different types and quantities of these proteins are produced by each wheat variant, influenced by various growth conditions and processing techniques. The environmental factors during growth can affect the expression of proteins (and carbohydrates) in a particular genotype; for example, elevated fertilization and warmer temperatures during maturity can increase the presence of ω -5 gliadin. Moreover, certain α -gliadins situated in the sub-aleurone layer of the wheat grain can be partially extracted through roller milling [1].

When flour is mixed with water, gliadins and glutenins combine to create gluten strands, facilitated by the formation of disulfide bonds. This initial mixing stage begins the process of gluten development. During the subsequent kneading process, the mechanical energy applied helps align and cross-link these gluten molecules more tightly, further reinforcing the structure. As the dough is worked, the gluten strands lengthen and become more interconnected, thereby forming a robust network. This mesh-like network is stabilized by the continued formation of disulfide bonds, which contribute to the dough's elasticity and strength. Kneading also ensures that moisture and air bubbles are evenly distributed throughout the dough, enhancing its texture and structural integrity. Consequently, the more the dough is kneaded, the stronger and more elastic the gluten network becomes, which is crucial for trapping the gases released by yeast during fermentation, leading to better leavening and a lighter texture in the baked product [3].

1.3 Digestibility of Gluten

The resilience of gluten proteins, especially gliadin and glutenin, to digestion arises from their high proline and glutamine content, which fosters dense and compact structures challenging for digestive enzymes to degrade effectively. Consequently, gluten peptides may persist in the gastrointestinal tract, potentially provoking adverse immune reactions in susceptible individuals. Additionally, recent investigations explored gluten protein digestibility through both in vitro and in vivo models, offering insights into the mechanisms governing gluten breakdown and the factors influencing it, such as the presence of specific enzymes like tissue transglutaminase (tTG). This underscores the significance of comprehending gluten protein digestibility within the context of gluten-related disorders, including CD and NCGS. By elucidating the contributors to gluten's resilience to digestion, researchers can devise strategies to enhance gluten tolerance and alleviate the negative consequences of gluten consumption in affected individuals [4].

II. GLUTEN INTOLERANCE

Gluten intolerance encompasses various conditions triggered by gluten ingestion. The most recognized is celiac disease, an autoimmune disorder causing damage to the small intestine, leading to gastrointestinal discomfort and nutrient malabsorption. NCGS causes similar symptoms without the immune response and intestinal damage seen in CD. Other issues include wheat allergy, an immune reaction to wheat proteins, and dermatitis herpetiformis, a skin condition linked to CD. Understanding these conditions is crucial for proper diagnosis and management.

2.1 Potential Toxic Components

Gliadin contains peptide sequences, known as epitopes, resistant to digestion by gastric, pancreatic, and intestinal enzymes due to their high proline and glutamine content [5]. These proline-rich structures can trigger immune reactions in CD. Various sequences from α , γ , and ω gliadins, as well as glutenins, are CD activators. Hundreds of gluten peptides are predicted to elicit T-cell responses, with the dominant epitope from α gliadin showing cross-reactivity with peptides from gluten, secalin, and hordein [6].

Amylase-trypsin inhibitors (ATIs), making up 2%-4% of modern wheat protein, can activate a toll-like receptor-4 pathway, releasing pro-inflammatory cytokines in both celiac and non-celiac individuals [7]. Wheat germ agglutinin, a lectin in wheat kernels, shows epithelial-damaging and immune effects in vitro, potentially contributing to gluten-related symptoms [8].

2.2 Wheat Allergy

In individuals genetically predisposed, wheat consumption can trigger specific immune responses, broadly categorized into IgE-mediated and non-IgE-mediated reactions. IgE-mediated reactions activate T helper type 2 cells, leading to the production of wheat-specific IgE antibodies and immediate responses, potentially causing severe allergic reactions like anaphylaxis. Respiratory allergies such as baker's asthma can also occur. Non-IgE-mediated reactions involve chronic inflammation of the gastrointestinal tract, seen in conditions like eosinophilic esophagitis (EoE) and eosinophilic

gastritis (EG). EG requires treatment with oral steroids due to severe inflammation, while EoE can lead to complications like feeding intolerance and fibrosis [9].

2.3 Celiac Disease

As mentioned by the Celiac Society of India, in individuals with a healthy digestive system, nutrients are absorbed in the small intestine through villi. In CD, gluten ingestion triggers an immune response, damaging the villi and causing villous atrophy, which impairs nutrient absorption and leads to malabsorption syndrome. CD can cause weight loss, malnutrition, and other severe effects if untreated [10].

CD is an autoimmune disorder identified by tissue transglutaminase as the autoantigen. It is influenced by genetic factors, particularly HLA-DQ2 and HLA-DQ8 genes, which encode proteins that present gluten fragments to immune cells, triggering an immune response. Environmental factors like viral infections and gut microbiota changes also contribute to CD onset [11]. CD affects about 1% of the population, with a higher prevalence in females, and can manifest at any age with a variety of symptoms, leading to different clinical phenotypes.

According to the Celiac Society of India, CD is lifelong and requires gluten ingestion to manifest. Symptoms vary widely, and onset can occur from childhood to adulthood. It often goes undiagnosed, with 97% of cases unrecognized. Typical CD shows gastrointestinal symptoms, while atypical CD, more common in adults, includes symptoms like anaemia and osteoporosis. Silent CD lacks gastrointestinal symptoms but can lead to complications. Potential and latent CD show minimal mucosal changes or positive blood tests but normal mucosa. Dermatitis herpetiformis is a skin condition related to CD [10].

In "Wheat Less: A Guide to Gluten-Free Life," R. Fernando describes diagnostic tests for CD, including blood tests (tTg-IgA, EMA), small intestine biopsy, capsule endoscopy, and genetic testing for HLA-DQ2 and HLA-DQ8. Home testing options are available but may vary in reliability [12].

The primary treatment for CD is a lifelong gluten-free diet, avoiding wheat, barley, and rye, which usually resolves symptoms and restores villous architecture. However, maintaining this diet can be challenging due to financial costs, potential nutrient deficiencies, psychological stress, constipation, and increased cardiovascular disease risk [13].

2.4 Non-Celiac Gluten Sensitivity

Gluten Sensitivity (GS) was initially recognized in the 1980s [14] and has recently regained attention as a separate medical condition. This syndrome, marked by both intestinal and non-intestinal symptoms after consuming gluten-containing foods, impacts individuals without CD or a wheat allergy. Pioneering research by Sapone and colleagues in 2010 emphasized the clinical and diagnostic dimensions of GS, sparking a wave of research affirming GS as a significant aspect of gluten-related disorders [15].

The global growth of the gluten-free market, partly fueled by individuals citing medical reasons for adopting a gluten-free diet, has highlighted the importance of distinguishing genuine medical conditions from trends. This clarification is anticipated to be achieved through accurate scientific data, agreed-upon terminology, and comprehensive, multi-center prospective studies aimed at addressing unresolved questions regarding GS. In response, an expert panel convened in London in February 2011 to establish a consensus on the terminology and classification of gluten-related disorders. This meeting resulted in the development of a diagnostic framework and a set of definitions recently published. Subsequently, research on GS expanded, with new studies aiding in estimating its prevalence and refining its clinical characteristics, including potential overlaps with IBS and the first documented cases in children [16].

2.4.1 Non-Celiac Gluten Sensitivity and Irritable Bowel Syndrome

Irritable bowel syndrome is a functional gastrointestinal disorder diagnosed primarily through the Rome criteria, emphasizing pain as a key symptom [17]. In NCGS, patients often experience bloating, flatulence, and diarrhoea, complicating IBS diagnosis. The overlap raises the question: are these food intolerance cases mimicking IBS, or is it a food-induced IBS variant?

Research by Vazquez-Roque et al. (2013) indicates that individuals with diarrhoea-predominant IBS (IBS-D) experience worsened symptoms on a gluten-containing diet (GCD), particularly those with HLA-DQ2 or DQ8 genotypes. These patients showed increased bowel movements, elevated small bowel permeability, and decreased tight

junction protein expression [18]. These findings suggest gluten can impair intestinal barrier function in IBS-D patients, especially those genetically predisposed. However, GCD did not affect gastrointestinal transit times or tissue histology.

A gluten-free diet (GFD) may relieve IBS symptoms due to lower fibre content, which is easier to digest. Psychological factors could influence symptomatology, as similar quality of life measures was observed between CD and NCGS patients, indicating overlapping psychological issues [19]. A meta-analysis found 38% of treated CD patients experienced IBS-like symptoms, more common compared to controls (pooled OR of 5.60). Non-adherence to a GFD was linked to higher IBS-like symptoms (pooled OR of 2.69) [16].

Other wheat components, like amylase-trypsin inhibitors (ATIs) and fructans, may also contribute to IBS symptoms. Biesiekirski et al. (2013) found reducing FODMAP intake alleviated symptoms in IBS or self-reported NCGS patients, while reintroducing gluten or whey proteins worsened them, suggesting FODMAPs play a role in symptom onset [20]. This indicates some IBS cases may be solely triggered by FODMAPs, distinct from NCGS.

2.4.2 Autism and NCGS

Autism Spectrum Disorders (ASD) are behavioural conditions identified before age three, featuring repetitive behaviours, social difficulties, and language impairments. ASD also includes behaviours like hyperactivity, aggression, anxiety, and depression. While behavioural therapy and medication can provide some relief, there's growing interest in diet and nutrition, particularly the gluten-free casein-free (GFCF) diet [16].

Although no definitive link between ASD and CD exists, the GFCF diet is popular for ASD. It is theorized that certain ASD symptoms might be triggered by opioid peptides from the incomplete breakdown of gluten and casein proteins, possibly due to increased intestinal permeability ("leaky gut syndrome"). Studies have noted abnormal intestinal permeability in individuals with autism, with improvements on a GFCF diet [21].

However, evidence for the GFCF diet's effectiveness in improving autistic behaviours is inconclusive. Some studies report improvements, while others find limited proof. Large-scale, well-designed randomized controlled trials are needed to assess the potential benefits of dietary changes in ASD. The GFCF diet may benefit only a minority of children with ASD, requiring further research to identify specific phenotypes and biological factors linked to dietary response before considering dietary interventions for ASD management [16].

2.5 Gluten-Related Disorders and Schizophrenia

The association between schizophrenia and CD has been noted since the 1960s [22]. Early studies like Vlissides et al. (1986) showed symptom changes in schizophrenics on a gluten-free diet [23], but others, such as Potkin et al. (1981) found no clinical differences with gluten challenges [24]. Similarly, Storms et al. found no significant psychological test differences in schizophrenic patients on gluten-free vs. high-gluten diets [25]. Recent research from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) found a high prevalence of anti-tTG antibodies in schizophrenics, indicating an immune response to gluten. However, few met CD diagnostic criteria [26]. Most anti-tTG positive subjects were tTG-6 positive, suggesting neuro-inflammation rather than CD [27]. The mechanism for symptom improvement with a gluten-free diet (GFD) in schizophrenia remains unclear, despite a high prevalence of antibodies to gliadin [27].

A subgroup of schizophrenics may benefit from a GFD due to gluten sensitivity, potentially improving their quality of life more efficiently than neuroleptics [16]. Diagnosing non-celiac gluten sensitivity (NCGS) involves excluding CD and wheat allergy (WA) through serological/biopsy tests and observing symptom relief on a GFD. Confirmation requires a gluten challenge after at least three weeks of GFD [15]. Distinguishing NCGS from IBS responsive to a low FODMAP diet is challenging due to overlap. Regular reassessment, including dietary interviews every 6-12 months, is advised for proper management.

III. CONCLUSION

Gluten is crucial in baking for texture and flavour but poses challenges for those with gluten-related disorders. Research has advanced our understanding of gluten's impact on conditions like celiac disease, non-celiac gluten sensitivity, wheat allergy, and dermatitis herpetiformis. Effective management relies on accurate diagnosis through serological and genetic testing and a lifelong gluten-free diet. Non-celiac gluten sensitivity remains hard to diagnose

due to the lack of specific biomarkers, often requiring differentiation from celiac disease, wheat allergy, and irritable bowel syndrome .

Future research should aim to develop standardized diagnostic criteria and biomarkers for non-celiac gluten sensitivity, conduct large-scale trials to assess the efficacy of gluten-free diets in autism spectrum disorder and schizophrenia, and investigate the role of other wheat components in gluten-related symptoms. Long-term studies on the effects of gluten-free diets and interdisciplinary research could provide deeper insights and improve treatment strategies for gluten-related disorders. Regular reassessment and detailed dietary interviews remain crucial for effective management.

CONFLICT OF INTEREST: Hereby, the author hereby declares that there is no conflict of interest in the current study.

REFERENCES

- [1] Biesiekierski, J.R. 2017. What is gluten?. *Journal of Gastroenterology and Hepatology*, 32, 78–81.
- [2] Shewry, P.R., Lookhart, G.L., 2003. *Wheat Gluten Protein Analysis*. American Association of Cereal Chemists: St Paul, Minnesota.
- [3] Hosney, R. Carl. 2010. *Principles of Cereal Science and Technology*. AACC International Press, 3rd Edition.
- [4] Drabińska, N., et al. 2020. Gluten Protein Digestibility: An Overview of Recent Studies. *Nutrients*, 12(5), 1461.
- [5] Hausch, F., Shan, L., Santiago, N.A, Gray G.M, Khosla C. 2002. Intestinal digestive resistance of immunodominant gliadin peptides. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, 283, G996–G1003.
- [6] Arentz-Hansen, H., McAdam, S.N., Molberg, O., Fleckenstein B., Lundin, EA, K. 2002. Celiac lesion T cells recognize epitopes that cluster in regions of gliadins rich in proline residues. *Gastroenterology*, 123, 803–9.
- [7] Junker, Y., Zeissig, S., Kim, S.J., et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. 2012. *Journal of Experimental Medicine*, 209, 2395–2408.
- [8] De Punder, K., Pruimboom, L. 2013. The dietary intake of wheat and other cereal grains and their role in inflammation. *Nutrients*, 5, 771–87.
- [9] Cianferoni, A., 2016. Wheat allergy: diagnosis and management. *Journal of Asthma and Allergy*, 9, 13–25.
- [10] Celiac Society of India. celiacsocietyofindia.com
- [11] Caio, G., Volta, U., Sapone, A., Leffler, D.A., De Giorgio, R., Catassi, C., Fasano, A., 2019. Celiac disease: a comprehensive current review. *BMC medicine*, 17, 1-20.
- [12] Fernando, R., 2023. *Wheat less: A guide to a gluten-free life*. Rupa Publications.
- [13] Tarar, Z.I., Zafar, M.U., Farooq, U., Basar, O., Tahan, V., Daglilar, E. 2021. The Progression of Celiac Disease, Diagnostic Modalities, and Treatment Options. *Journal of Investigative Medicine High Impact Case Reports*, 9.
- [14] Cooper, B.T., Holmes, G.K., Ferguson, R., Thompson, R.A., Allan, R.N., Cooke, W.T. 1980. Gluten-sensitive diarrhea without evidence of celiac disease. *Gastroenterology*, 81, 192–194.
- [15] Sapone, A., Lammers, K.M., Mazzarella, G., Mikhailenko, I., Carteni, M., Casolaro, V., Fasano, A. 2010. Differential mucosal IL-17 expression in two gliadin-induced disorders: Gluten sensitivity and the autoimmune enteropathy celiac disease. *International Archives of Allergy and Immunology*, 152, 75–80.
- [16] Catassi, C., Bai, J., Bonaz, B., Bouma, G., Calabrò, A., Carroccio, A., & Fasano A. 2013. Non-Celiac Gluten Sensitivity: The New Frontier of Gluten Related Disorders. *Nutrients*, 5(10), 3839–3853.
- [17] Thompson, W.G., Longstreth, G.F., Drossman, D.A., et al. 1999. Functional bowel disorders and functional abdominal pain. *Gut*, 45(Suppl 2), II43–7.
- [18] Vazquez-Roque, M.I., Camilleri, M., Smirk, T., 2013. A controlled trial of gluten-free diet in patients with irritable bowel syndrome diarrhea: Effects on bowel frequency and intestinal function. *Gastroenterology*, 144, 903–911.
- [19] Rathi, P.M., Zanwar, V.G. 2016. Non-celiac Gluten Sensitivity (NCGS): A Review article. *Journal of The Association of Physicians of India*, 64.
- [20] Biesiekierski, J.R., Peters, S.L., Newnham, E.D., Rosella, O., Muir, J.G., Gibson, P.R. 2013. No effects of gluten in patients with self-reported non-celiac gluten sensitivity following dietary reduction of low-fermentable, poorly absorbed, short-chain carbohydrates. *Gastroenterology*, 145, 320–328.
- [21] Marcason, W. 2009. What is the current status of research concerning use of a gluten-free, casein-free diet for children diagnosed with autism? *Journal of the American Dietetic Association*, 109, 572.
- [22] Dohan, F.C. 1966. Cereals and schizophrenia data and hypothesis. *Acta Psychiatrica Scandinavica*, 42, 125–152.

- [23] Vlissides, D.M., Venulet, A., Jenner, F.A. 1986. A double-blind gluten-free/gluten-load controlled trial in a secure ward population. *British Journal of Psychiatry*, 148, 447–452.
- [24] Potkin, S.G., Weinberger, D., Kleinman, J., Nasrallah, H., Luchins, D., Bigelow, L., Linnoila, M., et al. 1981. Wheat gluten challenge in schizophrenic patients. *American Journal of Psychiatry*, 138, 1208–1211.
- [25] Storms, L.H., Clopton, J.M., Wright, C. 1982. Effects of gluten in schizophrenics. *Archives of General Psychiatry*, 39, 323–327.
- [26] Cascella, N.G., Kryszak, D., Bhatti, B., Gregory, P., Kelly, D.L., McEvoy, J.P., Fasano, A., Eaton, W.W. 2011. Prevalence of celiac disease and gluten sensitivity in the United States clinical antipsychotic trials of intervention effectiveness study population. *Schizophrenia Bulletin*, 37, 94–100.
- [27] Cascella, N.G., Santora, D., Gregory, P., Kelly, D.L., Fasano, A., Eaton, W.W. 2013. Increased prevalence of transglutaminase 6 antibodies in sera from schizophrenia patients. *Schizophrenia Bulletin*, 39, 867–871.



INTERNATIONAL
STANDARD
SERIAL
NUMBER
INDIA



INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

 9940 572 462  6381 907 438  ijirset@gmail.com



www.ijirset.com

Scan to save the contact details