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Review

Gluten Is a Nutritional Adjuvant That Fulfils ASIA Syndrome Criteria

Aaron Lerner [1,*,†], Carina BenZvi [1,†] and Aristo Vojdani [2,†]

[1] Chaim Sheba Medical Center, The Zabludowicz Research Center for Autoimmune Diseases, Tel Hashomer 5262000, Israel
[2] Immunosciences Lab., Inc., Los Angeles, CA 90035, USA
* Correspondence: aaronlerner1948@gmail.com; Tel.: +972-525-919484
† These authors contributed equally to this work.

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Abstract: The incidence of autoimmune diseases is on the rise, and multiple pathophysiological mechanisms may contribute to this trend. These include sequence similarity, cross reactive antibodies, molecular mimicry, dysbiosis, post-translational modification of processed nutrients, and luminal horizontal gene transfer. Recently, environmental adjuvants have been suggested to play an active role in auto-immunogenesis, collectively referred to as the ASIA syndrome (autoimmune/inflammatory syndrome induced by adjuvants). The present narrative review provides a comprehensive overview of gluten, a widely consumed food additive, known for its pro-inflammatory and immunogenic properties. Gluten is implicated in several autoimmune conditions and meets both the major and minor diagnostic criteria for ASIA syndrome as an adjuvant. It is hoped that this present review will stimulate furthermore research on gluten, aiming to mitigate its risky aspects for public health.

Keywords: ASIA syndrome; adjuvant; gluten; food additive; pro-inflammatory nutrients; autoimmune diseases

1. Introduction

Chronic Inflammatory conditions in tissues or organs represent a significant pathogenic response, closely linked to human health protection against hostile environment [1–4]. Genetics and environmental factors are significant drivers of autoimmunity and the list of them is constantly increasing. Processed nutrients have been implicated in playing a crucial role by transforming naïve molecules to immunogenic ones, thereby contributing to inflammation and autoimmunity [3–7]. The incidence of autoimmune diseases (ADs) is increasing, alongside multiple inflammatory conditions [8–11]. As a result, the surge in these conditions and the tight intricate interplay between food components and autoimmunity have made anti-inflammatory dietary therapy became a primary focus of scientific and clinical interest [2,12–15].

However, the understanding of immune-driven, food-induced inflammation and its role in disease progression remains incomplete. The contribution of nutritional factors to metabolic, inflammatory, autoimmune, cancerous, and even neurodegenerative diseases remains poorly explored. Notably, in contrast to the industrially processed foods, non-processed vegetarian and traditional natural foods are proposed as anti-inflammatory options [16–18]. Actually, we will delve into the role of gluten/gliadin as immune adjuvants, not only in classical gluten dependent conditions, but also in non-celiac systemic inflammatory and ADs. The recently defined entity, namely the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) encompasses various environmental adjuvants [19–23]. This manuscript introduces a novel perspective on the syndrome, highlighting the role of nutritional adjuvants, such as gluten, in activating the autoimmune cascade.

1.1. ASIA Syndrome

In 2011, Prof. Yehuda Shoenfeld highlighted several conditions related to environmental adjuvants, including the Gulf war syndrome, silicosis, the macrophagic myo-fasciitis syndrome and post-vaccination phenomena, which shared comparable symptoms and signs [19,24]. These observations laid groundwork for the ASIA syndrome, also known as Shoenfeld's syndrome [19–23]. The common thread among these conditions was the active role of multiple adjuvants in the pathogenesis of autoimmune and inflammatory diseases. Since its conceptualization in 2011 [19], the list of adjuvants-induced medical conditions has expanded to include Sjögren's syndrome, sarcoidosis, undifferentiated connective tissue disease, silicone implant incompatibility syndrome, immune-related adverse events, biomaterial injections and prostheses (mainly silicone, hyaluronic acid, acrylamides and methacrylate compounds), squalene, gluteal biopolymer remodeling injections, mesh Implants, and the list is continually growing [21,23,25–33]. Moreover, following the COVID-19 pandemic, the potential auto-immunogenic nature of the virus, side effects of anti-SARS-CoV-2 vaccines, and the characterization of the post—COVID syndrome have further broadened the spectrum of autoimmune and inflammatory syndromes [30,31,34–36].

Several pathophysiological pathways have been proposed to explain the multifactorial and multi-etiological nature of ASIA syndrome. These include genetic factors, molecular mimicry, innate immune dysregulation, immune hyperstimulation, sequence similarity, release of pro-inflammatory cytokines, T cell failure, imbalance between the Th1/Th2 immune response ratio with excessive Th1 response, enhanced Th17 cell activation, B cell overactivation, cross-reactive antibodies, and epigenetic modifications [21,28,36]. Due to the complexity and dynamic expansion of ASIA syndrome, along with the increasing number of publications and patient registries, the diagnostic criteria have been recently summarized [21,30,36]. These criteria include major and minor criteria, such as clinical manifestations, improvement upon removal of the inciting agent, typical biopsy findings of involved organs, specific HLA associations, development of an autoimmune disease, other clinical manifestations, and the appearance of autoantibodies or antibodies directed against the suspected adjuvant. In this context, we will discuss a novel aspect of ASIA syndrome by extending the list of adjuvants to include gluten, a major processed food additive.

1.2. Increased Consumption of Gluten in the Processed Food Industries

Gluten is a major ingredient in the processed food industry due to its versatility and economic benefits. It serves as a cheap stabilizer, food thickener, emulsifier, and its ability to extend shelf life makes it highly advantageous for manufacturers. Traditionally, gluten is prominent in baked goods, but it is also used in hundreds of processed foods and multiple non-dietary products. As the dough-forming protein, it comprises about 80% of wheat proteins. Gluten consumption surpasses that of all other crops combined, making it the world's most favored staple nutrient [4,37,38].

In the 20th century, global wheat output increased by approximately fivefold. Since then, there has been a dramatic tenfold increase in the rate of wheat yield improvement per year. Parallel to this surge in agricultural production, the processed food industry has also expanded. It is estimated that the net fold percentage increase in gluten usage as an industrial food additive over the last four to six decades is approximately 1.8 ± 0.4 per year. The global vital wheat gluten market was valued at $2 billion in 2019 and is projected to reach $2.74 billion by 2027, growing at a compound annual growth rate (CAGR) of 4% during the forecast period [39]. Another market analysis predicts that the global vital wheat gluten market will grow at a CAGR of 4.00% from 2021 to 2028, driven by the increasing recognition of wheat's health benefits, such as lowering blood sugar levels and alleviating stress and anxiety [40].

1.3. Gluten Peptides Are Highly Available in the Human Intestinal Lumen

As the major protein in wheat, gluten intake is increasing not only because wheat is the most abundant staple prolamin (with gliadins in wheat, hordein in rye, secalin in barley, and glutenin in wheat) but also due to its widespread use as a food additive in the processed food industry. In Western countries, gluten consumption is estimated to be around 10–20 g per person per day [41,42]. Even Africa goes celiac [43], and interestingly, in traditional rice consuming regions like Asia and the Pacific, wheat intake [44] is rising, and celiac disease incidence is surging worldwide [45]. The increased luminal content of gluten not only affects multiple intestinal ecological events but also enhances the systemic distribution of the molecule to more peripheral and remote organs and tissues [4,6,9,10,46,47]. Noteworthy, the relationship between gut-originated axes and remote organ diseases is well-documented. Autoimmune diseases affecting the brain, joints, bones, endocrine system, liver, kidneys, heart, lungs,

and skin are connected to deregulated events in the intestinal luminal compartment, forming the gut-systemic organs axes [46].

1.4. Gluten Peptides Are Systemically Distributed

Gluten is widely present in the environment and in the intestinal lumen, where it has close contact with the epithelial monolayer and local mucosal immune cells. Several clinical and scientific observations support the systemic spread of these peptides, with suggested mechanisms including:

a. Clinically, celiac disease can present acutely and manifest as a symptomatic and even life-threatening event at both the intestinal level and in remote extraintestinal peripheral organs [48,49]. These abrupt phenotypic, pathological, cellular, and laboratory events indicate the ability of gluten peptides to affect the entire human body [46,48–50].
b. Gluten can pass Transepithelially through the gut monolayer. Both transcellular and paracellular pathways were documented [51]. Three mechanisms for transporting gluten through the epithelial layer have been demonstrated: endocytosis [51,52], transcytosis through the endoplasmic reticulum [53], and transferrin receptor, secretory IgA-assisted translocation of gluten peptides below the enterocyte monolayer [54]. Paracellularly, following gliadin binding to its CXCR3 receptor, increased zonulin levels compromise tight junction functional integrity by activating the EGFR-PAR2-MyD88-mediated signaling pathways, resulting in increased intestinal permeability and a leaky gut [55].
c. Moreover, gluten-dependent subepithelial deposits involving IgA-tissue transglutaminase (tTG) complexes are a hallmark marker for early celiac disease in seronegative patients and even before histological damage occurs [56], thus, reinforcing the transepithelial transport of gluten peptides [57,58].
d. From an immune perspective: the 33-residue peptide from alpha-2 gliadin is considered the immunogenic celiac disease supramolecule. It can be visualized in gluten-sensitive macaques [59], and gluten-stimulated celiac disease-specific enteric T cells have been shown to increase the transepithelial flux of gluten peptides [60]. tTG-gluten polymeric complexes are potent antigens for tTG-specific mucosal B cells, supported by diverse subepithelial gluten-specific T cells [61].
e. Intriguingly, gluten peptides are presented by subepithelial dendritic cells [62]. Thus, gluten/gliadin peptides located in the lamina propria are presented by local macrophages, activating the adaptive and innate mucosal systems and inducing celiac-specific autoantibodies.

1.5. Gluten Peptides Are Found in Multiple Body Compartments

Traditionally and physiologically, urinary peptide secretion likely originates from the bloodstream by filtration. Recently, Upadhyay et al. [63] reported that the gluten sensitivity metabolic profile expresses itself in potential celiac disease before any intestinal damage occurs. Lower levels of several amino acids and altered levels of six plasma and two urinary metabolites were observed in potential celiac patients compared to controls.

Interestingly, raising the topic of gluten addiction and mental health aspects, gluten metabolites like exorphin B4 and B5 have been reported in normal human blood [64]. Additionally, multiple gluten-dependent circulating miRNAs that appear before IgA-tTG positivity were found to be responsive to gluten withdrawal have been characterized [65].

Urinary gluten metabolites have been extensively reported. Gluten dose escalation, gluten-free diet adherence assessment, urinary gluten intake-dependent miRNAs, urine peptidomics analysis, and urinary metabolic alterations have all been documented [66,67]. Interestingly, since gluten metabolites are circulating systemically and celiac disease autoantigen, namely the tTg enzyme, is ubiquitously distributed, gluten withdrawal might be beneficial in many, non-celiac, ADs [37,38,47].

2. Gluten Is an Abundant Nutritional Adjuvant

Before defining gluten as an abundant adjuvant that fulfills ASIA syndrome criteria, its detrimental and risky capacity and side effects should be enumerated. As mentioned above, the current trend of dietary Westernization induces a surge in gluten consumption, mainly in Africa, Asia-Pacific, and the Far Eastern countries. It appears that the entire world is witnessing a recent evolutionary event that started 10,000 to 14,000 years ago, when wheat was first discovered and domesticated in the Fertile Crescent and diffused through the Middle East worldwide [9,10,43,68]. It seems that the more gluten is scientifically explored, the more side effects are reported.

2.1. Gluten Side Effects

Proinflammatory

The topic has recently been reviewed by us and others [4,6,37,38,47,51,69–71]. There are multiple adverse effects of gluten that have been described to impact human health. These harmful effects are delivered through immunological, inflammatory, and toxic pathways, leading to gut dysfunction or inadequacy that irradiates to the entire body [46].

Many in vitro studies have confirmed the cytotoxicity of various gliadins peptides originating from gluten. The in vitro and ex/in vivo detrimental effects were recently reviewed [37,38,44,69,70]. The major effects include: gluten is pro-inflammatory, pro-apoptotic, pro-oxidative, cytotoxic, immunogenic, decreases cell viability, and alters cell differentiation and epigenetics. It deteriorates the microbiome towards a dysbiotic profile and increases intestinal permeability. Most recently, antibody cross-reactivity and sequence similarity were demonstrated between gluten/wheat and human body antigens, thus substantiating gluten as a risky food additive with potential multiple molecular mimicries repertoire [5,69,72,73].

The potential adjuvant action of gluten can be added to a growing list of harmful food components that express autoimmunogenic capacities. A major pathway by which gluten might increase its adjuvant effect is its role in the leaky gut syndrome. Since enhanced intestinal permeability is frequently associated with a plethora of ADs [37,38,47,74,75], the role of gluten in compromising the tight junction functional integrity needs further detail. Upon binding to its epithelial CXCR3 receptor, gliadin induces zonulin release via a MyD88-dependent pathway, resulting in transactivation of EGFR by PAR2, leading to small intestine tight junction disassembly [4,55]. Gluten affects multiple pathways and systems of the immune apparatus [37,38,47]. It stimulates Th-17 activity, TLR4 signaling, NKG2P expression, and enhances neutrophil migration. Not surprisingly, it affects the innate and reactive immune functions, hence significantly changing Treg performances [37,38,47]. The beneficial avoidance of gluten intake might represent a proof of concept for the "adjuvanity" of gluten. It appears that gluten withdrawal helps patients with various non-celiac ADs, and its elimination may help curtail the adverse effects of gluten [37,38,47,76,77]. Finally, gluten has been shown to increase intestinal permeability not only in celiac patients or those with non-celiac gluten sensitivity but also in normal and disease controls, in both animals and humans [78–81].

2.2. Gluten Depended Autoimmunity

The list of gluten-dependent conditions is expanding. The primary targeted organ is the human small bowel in celiac disease, but gluten allergy, dermatitis herpetiformis, gluten ataxia, and non-celiac gluten sensitivity are additional gluten-dependent diseases [37,82]. Celiac disease is an underdiagnosed condition with a ratio of undiagnosed to diagnosed patients of 7:1, where many patients are asymptomatic or hypo-symptomatic [43,49,83,84]. Since extraintestinal manifestations are more prevalent [48,49], many patients may not realize that gluten could be inducing their symptoms. Irritable bowel disease is an example of this.

2.3. Gluten Fulfils the Diagnostic Criteria of ASIA Syndrome

Taking into account the above information, the food component and additive, gluten, fulfills all the major and minor diagnostic criteria for ASIA syndrome Table 1 [21]. Among the major criteria, gluten acts as a classical external stimulus, induces typical clinical manifestations (whether allergic, intestinal, or extraintestinal), targeting various remote organs and tissues [37,46,48], and its removal in gluten-dependent autoimmune conditions leads to definite improvement [38,47,76,77]. Examining the minor criteria, anti-gluten/anti-gliadin antibodies are prevalent in gluten-related and non-celiac-related ADs and chronic conditions [83,84]. Despite controversy about their specificity and sensitivity [85], when gluten/gliadins are post-translationally modified by tissue or microbial transglutaminases, their cross-linked complexes induce very specific antibodies, namely, anti-neo-epitope tissue transglutaminase and anti-neo-epitope microbial transglutaminase antibodies [86–88]. Celiac disease is a typical HLA-DQ-2/8-dependent condition [89–91], and gluten is a well-documented offending environmental factor [37]. As mentioned above, gluten is related to several Ads, and many of them might respond to gluten-free diet [38,47,92–94]. Thus, gluten joint several other processed food additives that might induce Ads [4–6,72,73,95–98]. In summary, gluten fulfills all the ASIA diagnostic criteria and is a nutritionally based adjuvant.

Table 1. Gluten fulfills all the major and minor criteria for Asia Syndrome.

Major Criteria for ASIA	Gluten	References
Exposure to external stimuli	Yes	[4–7,39–42,45,70,82]
Typical clinical manifestations	Yes	[10,37,38,48,49]
Removal of triggers leads to improvement	Yes	[38,47,76,77]
Minor Criteria for ASIA	**Gluten**	**References**
Autoantibody or antibody to the adjuvant	Yes	[83–88]
Specific HLA	Yes	[89–91]
Autoimmune disease	Yes	[37,38,46,47,53,82,99,100]

3. Conclusions

Based on the above, gluten exhibits immune-stimulation activities, is frequently used as a nutritional processed food adjuvant, and broadly fulfills both the major and minor criteria of ASIA syndrome. Figure 1 schematically describes the place of gluten in ASIA syndrome, and Table 1 outlines its fulfillment of the syndrome's criteria. Gluten should be added to the increasing list of environmental factors that induce inflammation and AD's related to adjuvant exposure. It is not only infectious agents, breast implants, and many other foreign bodies, drugs, metals, or vaccine adjuvants that have this capacity. Nutrients also have adjuvant capacity and should be included on the list of ASIA syndrome environmental factors.

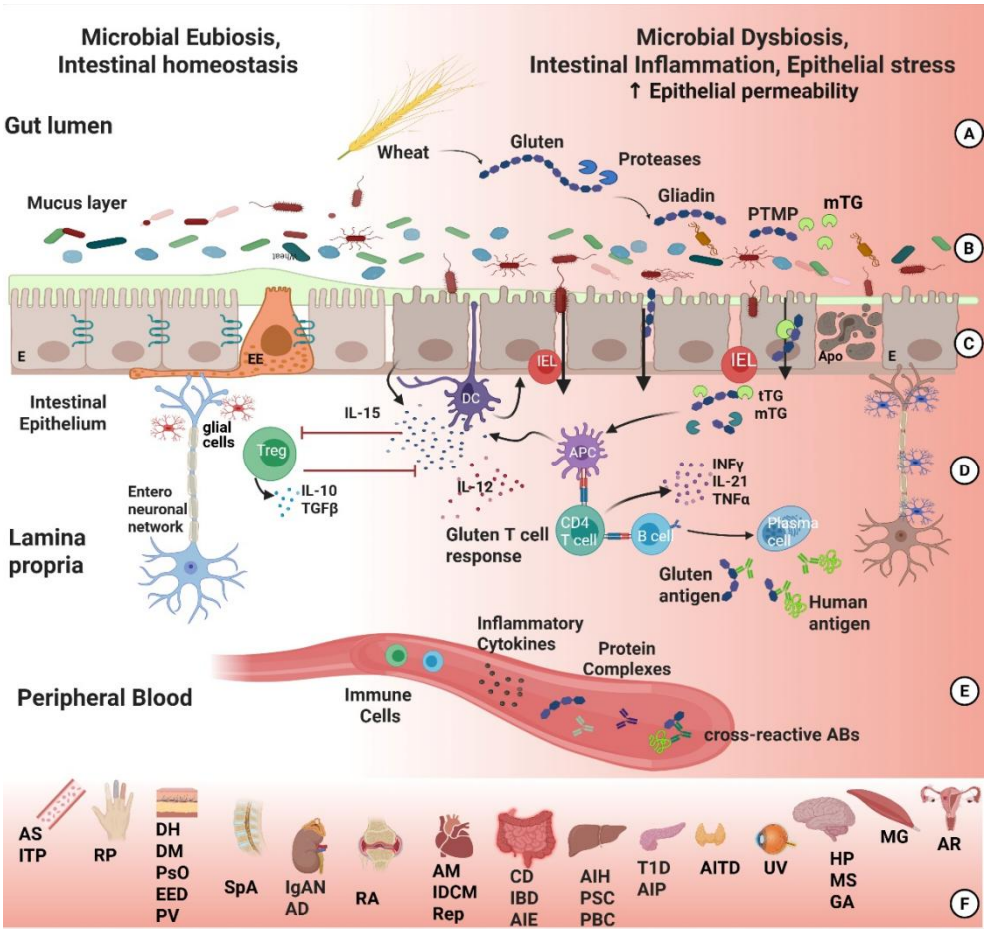

Figure 1. A schematic presentation of gluten's place and role as a nutritional adjuvant in ASIA syndrome. (**A**): Upon gluten ingestion, gliadin peptides reach the gut lumen. (**B**): These peptides act as primary substrates for cross-linking by luminal transglutaminases, forming post-translationally modified proteins (PTMPs) with enhanced immunogenicity. These cross linked, protease resistant, iso-peptide bond complexes trigger an inflammatory cascade that disrupts mucosal integrity, induces dysbiosis, damages the intestinal epithelium, and increases permeability ("leaky gut"). (**C**): Gliadin peptides and transglutaminases may infiltrate the lamina propria either through open junctions or trans-enterocytically, exposing the highly immunoreactive sub-epithelium to foreign antigens or complexes. (**D**): Within the lamina propria, dendritic cells (DCs) encounter gliadin-transglutaminase complexes, acting as antigen-presenting cells, and activating CD4+ T cells. This interaction prompts T cells to secrete proinflammatory

cytokines (IFNγ, IL-21, TNFα), and stimulate B cells to produce anti-tTG, and cross-reactive autoantibodies. (**E**): Mucosal immune cells, immunogenic modified proteins, like gliadin peptides, proinflammatory cytokines, autoantibodies, and small particles that evade immune surveillance, enter the bloodstream. The circulating components may reach remote organs, potentially triggering autoimmune responses. (**F**): The presence of gliadin peptides, transglutaminases, or cross-linked complexes in peripheral organs can exacerbate gluten-dependent autoimmune diseases: celiac disease (CD), dermatitis herpetiformis (DH), gluten ataxia (GA), and non-celiac gluten sensitivity (NCGS). Interestingly, other autoimmune conditions, responding to gluten-free diet (GFD) [47], may benefit from gluten withdrawal: AD: Addison's disease; AIE: autoimmune enteropathy; AIH: autoimmune hepatitis; AIP: autoimmune pancreatitis; AITD: autoimmune thyroiditis; AM: autoimmune myocarditis; APS: antiphospholipid syndrome; AR: amenorrhea; Dm: dermatomyositis; EED: erythema elevatum diutinum; HP: autoimmune hypopituitarism; IBD: inflammatory bowel disease; IDCM: idiopathic dilated cardiomyopathy; IgAN: IgA nephropathy; ITP: idiopathic thrombocytopenic purpura; MG: myasthenia gravis; MS: multiple sclerosis; PBC: primary biliary cholangitis; PSC: primary sclerosing cholangitis; PsO: psoriasis; PV: pemphigus vulgaris; RA: rheumatoid arthritis; ReP: recurrent pericarditis; RP: Raynaud phenomenon; SpA: spondyloarthritis; T1D: type 1 diabetes; Uv: uveitis; V: vitiligo. Designed the figure with BioRender.com.

Author Contributions

A.L.: screened the literature, designed and wrote the manuscript, C.B.: screened the literature, edited and revised the manuscript, designed the figure with BioRender.com permission, A.V.: conventionalized, edited, revised and supervised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

Abbreviations

tTG—tissue transglutaminase, PTMP—post translational modification of proteins, ASIA—The autoimmune/inflammatory syndrome induced by adjuvants, ADs-autoimmune diseases.

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