Review Article

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Review Article

Celiac disease: Pathogenesis, disease management and new insights into the herbal-based treatments

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Abstract

Celiac disease (CD) is a gluten intolerance autoimmune disorder which its symptoms involve the gastrointestinal tract and sometimes the other organs. It is one of the most prevalent health problems rising in many populations as statistics show that in every 100 people about one person is suffering from CD. It has been observed that the persons who genetically contain the human leukocyte antigen (HLA) DQ2 and HLA DQ8 genes involved in the immune system haplotypes are more prone to develop an allergy to gluten. The only treatment currently available for CD is a strict gluten-free diet. However, recent research has shown promising new insights into the herbal-based treatments of CD. New insight on CD is now offering various prospects to manage its treatment, diagnosis, and serving in the development of advanced therapies. Several herbs and botanical extracts have demonstrated anti-inflammatory, immunomodulatory, and gut-healing properties that make them potential candidates for the management of CD. Here, we provide an updated review on pathogeneses and managements of CD. In particular, we summarize the current understandings of herbal-based treatments for CD and highlights their potential benefits.

Keywords: Celiac disease, autoimmune disorder, gluten, human leukocyte antigen, genetic

Introduction

Celiac disease (CD) (gluten-sensitive enteropathy) is a genetic, multisystemic autoimmune-mediated enteropathy that grounds inflammation of the small intestine due to the intake of gluten and restricts the absorption of dietary nutrients [1-3]. People suffering from CD are permanently gluten intolerant [4]. It was mentioned that polygenic predisposition, high pervasiveness (1%) and widely assorted expressions are responsible for other autoimmune disorders. The basis of the disease observed by diagnosis is characteristic or symptomless inflammation of the small intestinal mucosa which can be treated by a gluten-free diet [4-6].

At the time of World War II, Professor Dicke reported much less improvement in children with CD and later he described the involvement of wheat and rye in CD [1]. In the early 1950s, when it was first identified that gluten is responsible for CD, it has been advisable to the patients suffering from CD to follow the strict gluten-free diet (GFD). Elevated morbidity, mortality, and impaired quality of life are the result due to symptomatic and untreated CD.

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Charlotte Anderson also identified gluten as an aberrant component extracted from wheat. Later in the 1960s, physicians started to diagnose CD by small intestinal biopsies and further transglutaminase was recognized as the autoantigen in CD in 1997 [7, 8]. Earlier in the twentieth century, a new high-banana diet was recommended to reduce the high mortality rate of this disease. This diet specifically became the foundation stone of treatment for CD in which bread and cereals were excluded from this diet [6, 9]. European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) diagnostic instructions claims the diagnosis of autoantibodies in CD and suggested the use of GFD until the exact results are out. Patients with HLA-DQ2.5 and HLA-DQB1*02 genes show more severe histological damage when diagnosed [10, 11].

Pathogenesis

Pathogenesis of CD includes various crucial steps where T-cell epitopes peptides of gluten retaliate degradation of gastrointestinal. Gluten peptide deamidation is catalyzed by the tTG enzyme, which then easily gets attached to the predisposing HLA-DQ gene on intestinal antigen-presenting cells (APCs) [10]. When gluten-specific $CD4^+$ T cells get activated, IFN-γ and IL-21 type cytokines are released which further activate B-cell and intraepithelial lymphocytes (IELs) that result in gastrointestinal lesions [12]. Giving a stress signal activated, IELs get converted into cytolytic NK-type cells which results in enterocytes damages. Interleukin-15 (IL-15) secretes effector T cells that do not get affected by the effect of regulatory T cells (Tregs). IL-15 provides mucosal specialized dendritic cells (DCs), encourages inflammatory reactions and inhibits differentiation of Tregs [13] (see **Figure 1**). The pathogenesis of CD is associated with an interaction between genes, gluten, and environmental influences.

Genetics

Patients suffering from CD mainly have two predisposing genes human leukocyte antigen (HLA) class II genes which are HLA-DQ2 and HLA-DQ8 [4]. Both genes exist primarily in all patients with CD but many other non-HLA genes were also assumed to cause CD in different populations [6]. It is found that about 40% of people have at least one of these predisposing genes so the diagnosis of these genes is not sufficient to identify CD. However, if the presence of HLA-DQ2 and DQ8 are the same predictive value for CD, then there is a chance to get a negative predictive value for the CD when diagnosed [14, 15].

Gluten

The development of CD depends on the presence of predisposing genes and in addition, it also depends on exposure to gluten in the diet. Gliadins and glutenins are both types of protein that are present in gluten. Gliadins are monomeric proteins, whereas glutenins are defined as polymeric aggregated proteins. These proteins are not processed by the gastrointestinal tract since they contain proline and glutamine peptides which are alcohol soluble as they oppose deprivation by luminal border endopeptidases [16].

An essential step in the pathogenesis of CD takes place in lamina propria due to the activation of the tissue transglutaminase (tTG) enzyme. tTG enzyme deamidates gliadin with deamidase enzyme, which makes it immunogenic and affects the adaptive immune system. Gliadin activates adaptive immune response which encompasses antigen-depicting cells, such as macrophages, dendritic cells, and B cells [17]. These gliadin-specific CD41 TH1 cells and antigen-depicting cell interaction produce inflammatory cytokines, for example, IFN-g [18].

In addition, due to presence of gliadin, innate immune response increases the production of cytokines, macrophages, enterocytes, and dendritic cells in the epithelial constituent of the intestinal mucosa [19]. As a result, intraepithelial lymphocytes differentiate into NK-G2D markers represented as cytotoxic CD81 T cells. Direct ligands on the epithelial surface for NK-G2D are promoted by IL-15. This cascade of inflammatory mediators at last causes collective intestinal mucosa damage illustrated by crypt hyperplasia and villous atrophy [9, 17].

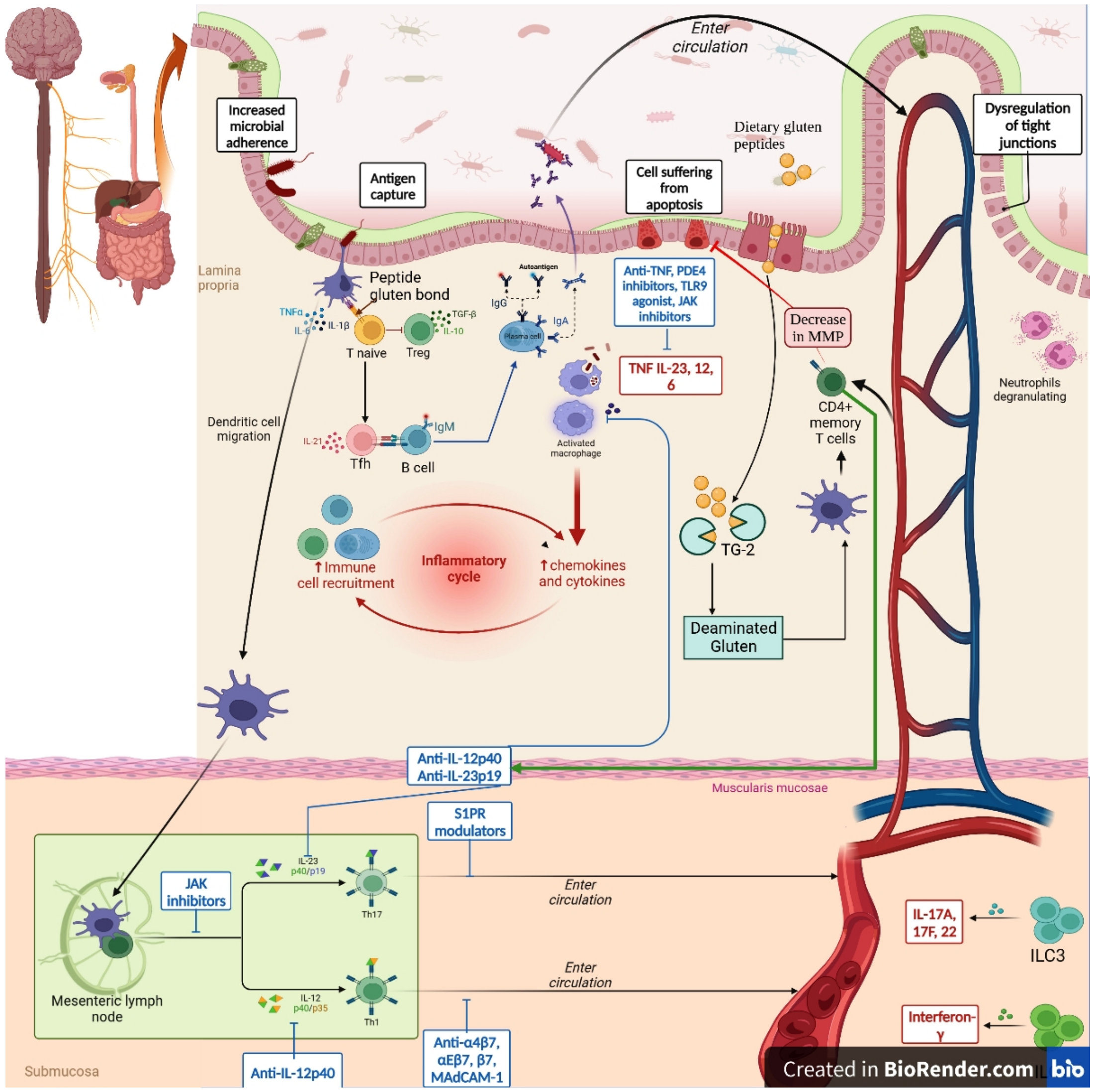

Figure 1. Key steps in the pathogenesis of celiac disease. Peptides originating from gluten undergo modification by TG2 and are presented by antigen-presenting cells in the mesenteric lymph nodes (MLN) to CD4+ T cells within the context of HLA-DQ2. This interaction triggers a TH1 type response, resulting in the production of IFNγ and intestinal inflammation. The chronic inflammation further leads to the expansion and persistence of Vδ1+γδ T cells, which also contributes to IFNγ production. The expression of IL-15 and stress molecules on enterocytes is induced by gluten peptides. The increased levels of IL-15 promote a NK-like phenotype in CD8+ T cells, contributing directly to enterocyte death. A subset of CD8+γδ+ T cells is believed to have a regulatory role through the secretion of TGF-β. Plasma cells are also abundant in the lesion and express the immunodominant gluten peptide DQ2.5-glia-α1a. They are induced to secrete antibodies that bind to TG2 and other targets.

Environmental factors

Various environmental components add to the pathogenesis of CD. Earlier, in the 1950s, factors like breastfeeding, infection, and modifications in the intestinal microbiota were taken into consideration. It was also considered that intestinal infection in infants and adults increases the risk for the future development of CD. The fundamental principle behind these factors was that an augmented permeability of epithelial enterocytes increases the entrance of gluten protein like gliadin, which further activates tTG enzyme in lamina propria and these infections increase the production of interferon [12, 20]. Recently, some data also recommended that breastfeeding may have a defensive effect against the progression of CD at 4 to 6 months of age, especially if gluten is also provided in the diet. Infants at this age acquire immune tolerance against CD through breastfeeding [7].

Another environmental factor that is known to influence CD development is the intestinal microbiome which is also widely studied and investigated. It was found in some duodenal biopsy samples of children with the CD (with or without GFD) that there is an altered microbiome [21]. Further in this study, it was found that subjects who were not given a GFD show increased proportions of *Bacteroides* species and reduced *Bifidobacterium* species compared to those subjects who were provided with GFD and control subjects without CD. Then likewise, the *Bacteroides* versus *Bifidobacterium* species proportions were normalized in the subjects by recommending GFD. As concluded that the intestinal microbiome is a potential marker and has a pathogenic role in CD [22]. In a placebo-controlled trial study, patients with CD on GFD administered daily with *Bifidobacterium* species and their intestinal microbiome, cytokine, and secretory IgA profile were studied. It was concluded that *Bacteroides* species and secretory IgA levels decrease in stools. Although these findings reported promising results, more advanced research is needed before concluding immunopathogenic role of the intestinal microbiome in CD patients [21, 23].

Diagnosis

Various methods are used for diagnosis of CD including small intestinal biopsy and serologic screening which are extremely profound and specific for antibodies. With the invention of quick screening techniques and knowledge of CD, many individuals are diagnosed including those who are asymptomatic [24-26].

Small intestinal biopsy

Histologic analysis in small intestinal biopsy indicates villous atrophy, intraepithelial lymphocytosis, and crypt hyperplasia. It also shows the presence of tissue transglutaminase enzyme (tTG), deamidated gliadin peptides (DGP), CD-specific antibodies, and endomysial antibodies (EMA) [24].

Serologic tests

In the CD, gluten presence causes intestinal injury because of the antibodies produced by the autoimmune system. These specific antibodies are tested in serological tests [27]. The preliminary screening tests for CD are (1) Quantitative immunoglobulin A (IgA) test; (2) IgA anti-tissue transglutaminase antibodies (tTG-IgA); and (c) IgA anti-endomysial antibody test. There is an additional test IgA anti-EMA test for CD patients, especially for those who are suffering from diabetes mellitus (type 1). IgA anti-endomysial antibodies are present in about 90% of patients [28, 29].

Genetic testing

A quick specific test to diagnose CD is not available yet. However, commonly the presence of two pre-disposing genes, HLA-DQ2 and DQ8 alleles, are studied for diagnosis. Notably, the presence of one or both alleles are certain in a patient with CD, but about 50% of the general population shows the presence of these alleles as well, so these tests are not fully helpful in CD diagnosis. However, if genetic testing shows that both genes are negative in a patient, then the possibility of CD is very low [20, 29, 30].

Symptoms of celiac disease

The signs of CD differ amongst various patients and have different effects on the human body. For example, a patient may have symptoms like severe diarrhea with stomach pain while other patients may show liver, neurological, skin, or dental problems. The most common characteristic of CD symptoms are gastrointestinal, behavioral/psychiatric, and autoimmune symptoms [31].

Some of gastrointestinal symptoms includes diarrhea, vomiting, lactose intolerant, abdominal distention, malabsorption, alteration in appetite, constipation, bacterial infection, flatulence, reflux heartburn, hepatitis, bloating, ulcers (mouth, esophageal and stomach), dyspepsia, irritable bowel syndrome, and inflammatory bowel disease (IBD) [3-34]. However, the behavior symptoms include hypochondria, incapability to concentrate, brain fog, anxiety, neurosis irritability, depression, attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and autism spectrum disorder [35-37]. Hashimoto's disease, Grave's disease, Sjogren's syndrome, hyperparathyroidism, dilated (congestive) cardiomyopathy, fibromyalgia, alopecia areata, rheumatoid arthritis, multiple sclerosis and systemic lupus erythema are some of the autoimmune response-based symptoms [38-40].

Treatment strategies of celiac disease

Medical nutrition therapy is the only established method for CD treatment [41]. Treatment of CD primarily includes a gluten-free diet (GFD) and it is compulsorily recommended to all those patients who are diagnosed to be suffering from CD. GFD includes avoiding all foods made from wheat, barley, and rye. The safe range for CD patients is 50-100 mg per day of gluten in the diet. Fish, plain meat, fruits, and various vegetables are free from gluten, so patients with CD can consume this type of diet. Also, CD patients are instructed to take multivitamins that are gluten-free [42-45]. Examples of various herbs that can be used for the management of CD are mentioned in **Table 1** and their chemical structures are described in **Figure 2**.

Table 1. Examples of various herbs for the management of celiac disease [46]

Name of the herbs	Role played
Chamomile	Carminative
Meadowsweet	Antacid and anti-inflammatory
Lemon balm	Reduce bloating
Liquorice	Antispasmodic
Peppermint	Carminative and antispasmodic
Fennel	Carminative and antispasmodic
Slippery elm	Demulcent action

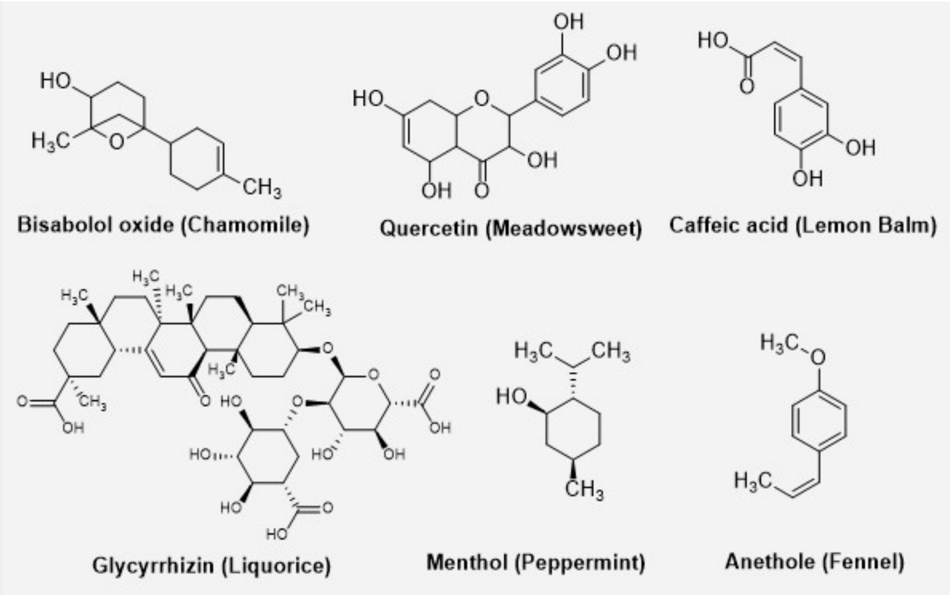

Figure 2. The chemical structures of herbal plants constituents used in the treatment of celiac disease based on previous studies [47-49].

Chamomile (*Matricaria chamomilla* L.) that belongs to the Asteraceae family is a well-known therapeutic plant. It has been used in herbal treatment for thousands of years. Chamomile is used mainly as an antiseptic, anti-inflammatory, and antispasmodic, and very effectively for urinary tract swelling and menstrual pain. The other therapeutic properties include carminative, healing, and sedative activity [50-53].

Meadowsweet (*Filipendula ulmaria* L.) is used as a diuretic, anti-hemorrhoid, sedative, anti-inflammatory, wound-healing, analgesic, antiulcerogenic, hypoglycemic, and astringent in some European countries. Conventionally, it has been used for rheumatic pains, dyspepsia with hyperacidity and heartburn, and diarrhea (children) and specifically for the prevention and management of peptic ulcers [47-49, 54, 55].

Lemon balm (*Melissa officinalis* L.) has its place in the mint family. Lemon balm has medicinal properties like flatus relieving, digestion promotion, antidepressant, antioxidant, and antiviral activity. According to the German Commission E monograph, it is also prescribed in the gastrointestinal complaints especially cramps in the digestive tract and flatulent dyspepsia [56-59].

Liquorice (*Glycyrrhiza glabra* L.) is known for its ethnopharmacological value in traditional medicine across the world. Liquorice has been recommended as a preventive agent for duodenal and gastric ulcers. During allergy, it is used in dyspepsia as an anti-inflammatory agent. It is also employed as an emmenagogue, contraceptive, anti-asthmatic, laxative, galactagogue, and antiviral agent in folk therapy [60-62].

Peppermint *(Mentha piperita* L.) that belongs to the family Lamiaceae (Labiatae) is an interminable herb and is a combination of two plants viz. spearmint (*Mentha spicata* L.) and water mint (*Mentha aquatica* L). The plant is extensively used in folk or traditional medicine for the management of digestive and nervous system disorders. The herb also has antitumor and antimicrobial properties, chemopreventive potential, renal actions, antiallergenic effects, and is for lessening cramps, digestive complaints, anorexia, nausea, and diarrhea [63-65].

Fennel (*Foeniculum vulgare* Mill) is a therapeutic plant belonging to the Umbelliferae (Apiaceae) family. As a traditional medicine, it is used for many types of ailments like diseases related to digestive, respiratory, reproductive, and endocrine systems. In various countries, it is used to stimulate appetite, and treat abdominal pain, antiemetic, arthritis, cancer, stomach pain in children, irritable colon, constipation, depurative, emmenagogue, conjunctivitis, fever, gastritis, flatulence, insomnia, kidney ailments, laxative, liver pain, leucorrhea, and mouth ulcer [66-69].

Slippery elm (*Ulmus rubra*) is an herbal medicine obtained from its inner bark. According to the Natural Medicines Comprehensive Database, it is used for the treatment of sore throat, dysphasia, colic, loose motions, hemorrhoids, irritable bowel syndrome, septicemia of the urinary tract, syphilis, tapeworm expulsion, as well as protecting against stomach and duodenal ulcers, swelling of the colon, GI inflammation, and acidity [70-72].

Adjuvant therapies for the management of celiac disease

Oral enzyme supplementation

It has been reported that *in vitro* T cell toxicity is decreased by admixtures of purified prolyl endopeptidases (PEPs) and sprouting wheat proteases, by hydrolyzing gluten [59, 73]. PEPs obtained from various bacterial species like *Flavobacterium meningosepticum*, *Myxococcusxanthus*, and *Sphingomonascapsulata*, and some from fungal species like *Aspergillus niger* are widely reviewed [47, 63].

Anti-inflammatory therapy

Many proinflammatory cytokines and lymphocytes (e.g., TNFα, IFNγ, IL-15, CCL25, CXCL10) were found to have a significant contribution to the CD. Considering these as molecular targets, scientists had already developed the drugs for these inflammatory mediators and some research is still being carried out. Infliximab Remicade® (Janssen Biotech, Titusville NJ, USA), a monoclonal antibody blocking TNFα used in RA and Crohn's disease, had positive effects on a patient with refractory CD [38, 54, 74].

Desensitization

A desensitizing immunization with Nexvax2 as an immune therapy and preventive drug to regain gluten resistance to three immunostimulatory gluten peptides from wheat and barley were synthesized [43, 68, 75, 76].

The paracellular permeability modulator

The gliadin-mediated opening of tight junction contributes to the increased permeability of the mucosa in active CD. The reliability of lactulose as a marker for increased paracellular leakage of gliadins was contested concerning the molecular weight of lactulose (342 Da) compared to immunogenic gliadin peptides such as p31-49 and 33mer (2,245 and 3,900 Da, respectively). A fluorescently labeled gliadin fragment may be of higher relevance [38, 77-79].

Polymeric binders

In the gastrointestinal tract, polymeric binders are considered to sequester gluten. Poly(hydroxyethyl methacrylate-*co*-styrene sulfonate) (P(HEMA-*co*-SS), BL-7010, BioLineRx) is responsible to formulate gliadin complex and it can decrease the production of the immune stimulatory complex in digestive fluid. It can sequester gluten presence in the stomach, which is a significant benefit of this polymeric binder [77-79].

Modified grains

Modified grains are developed using various techniques like breeding of selective wheat species or by using the small interfering RNA (siRNA) technology to mutate or silence immunostimulatory sequences [56, 58].

Preventing gluten entry through the intestinal epithelium

Zonulin inhibitor larazotide (AT-1001) is studied in the animal model and is capable of treating intestinal barrier defects. AT-1001 undertaken in phase II clinical trials is presently the best pharmacological agent to treat CD patients [67, 74-76].

Molecular targets of celiac disease

Consideration of the best possible aims of therapy and the techniques to evaluate effectiveness is an evolving area. Molecular targets for CD are mentioned in **Table 2.**

Table 2. Molecular targets of celiac disease

Approach	Proposed mechanism	Reference(s)
Endopeptidases	Enzymatic degradation of gluten	[68]
Tight junction regulators	Reduce paracellular passage of gluten across the mucosa	[57, 59]
Gluten binding agents	Sequester gluten in the intestinal lumen	[56, 57, 59]
Endorphin-based therapeutic vaccine	Gluten-specific $CD4^+$ T cells are targeted by epitope-specific immunotherapy	[79]
Inflammatory proteases inhibition	Anti-inflammatory effects and improved barrier function	[68]
HLA DQ2 blockers	Gliadin antagonist blocks the binding grooves of HLA molecules and peptides might suppress the antigen presentation process and block the cascade of T cell stimulation	[57, 59]
Immune modulation to induce tolerance to gluten	Protein-based desensitization therapy- Nexvax2 vaccine	[63, 78, 79]

Therapies under clinical trials

Various drugs that are under clinical trials for the treatment of CD are represented in **Table 3**. Some drugs such as anokion, KAN-101, CALY-002, DONQ52, EQ102 and others have been developed from different companies and have been entered to phase 1 to phase 2 clinical trials.

Table 3. Various investigational drug molecules under clinical trials for celiac disease treatment

Drug name	Innovator company/ sponsor	Target	Phases of clinical trials
Anokion, KAN-101	Subsidiary Kanyos Bio, Inc.	Target immune CD cells	Phase 1b clinical trial
CALY-002	Calypso Biotech	Inhibit the cytokine interleukin role in the immune system	Phase 1b clinical trial for safety and tolerability

Drug name	Innovator company/ sponsor	Target	Phases of clinical trials
DONQ52	Chugai pharmaceutical	Target immune complex causing CD	Conducting phase 1 clinical trial
EQ102	Equillium biotechnology company	Inhibit cytokines lL-15 and lL-21 that drive cytotoxic T cell and optimal approach CD	February 2022 conducting phase 1 clinical trial
GSK2915393	GlaxoSmithKline (GSK)	Inhibit TG2 enzyme for inflammatory action response to gluten exposure in CD	Completion on phase 1 clinical trial study in 2021
IMU-856	Immunic Therapeutic biopharmaceutical company	Restore intestinal barrier, compromise immune function, treat gastrointestinal disease, and treat CD	In September 2022, Immunic announced positive results part A and B of its phase 1 clinical trial and part C on-going
HU-Mik-Beta-1	National Cancer Institute and Mayo Clinic	Monoclonal antibody targets the cytokine receptor subunit IL-2/IL-15RBETA tested for CD	Phase 1 trial
Immunogenx	IMGX003 Alvine Pharmaceutical	Break gluten protein down to relieve CD symptoms	The technology has extensively studied in phase 1 and phase 2
TAK-062	Takeda Pharmaceuticals	TAK-062 is a highly potent enzyme for gluten breakdown in CD with GFD	Currently conducting phase 2 clinical trial

Conclusion and future perspectives

CD is an autoimmune allergy to dietary gluten and is very common nowadays. It can have typical intestinal manifestations. The therapy to treat this disease is to keep a patient on a GFD which lacks patient compliance. Novel therapeutic targets have been found from deep insights into the pathophysiology of CD. The new research on the molecular targets of CD has resulted in various new therapies like the engineering of gluten-free grains, reducing intestinal permeability by blocking the various receptors, formulation of new vaccines, and the use of probiotics for the degradation of immunodominant gliadin peptides. These therapies boosted the efficacy of CD management and helped in the improvement of patient conformity. However, while a GFD diet is the main key for CD therapy for the immediate foreseeable future, these treatment options are expected to get US Food and Drug Administration soon.

In CD, comprehension of severe gluten intolerance is a primary issue that needs more study. Enzyme supplementation therapy is a very assuring approach as a forthcoming treatment for CD patients which is already established to have both preclinical and clinical potentials. Recently many investigations are ongoing and recommended as various treatment strategies, but the studies are still in their initial days and their Phase III clinical trials are yet to be reached. The novel therapies for CD are still not studied for children. Hopefully, it is believed that soon we will be able to develop a good disease prevention therapy for CD with the evolving studies on the role of the microbiome and environmental factors and in what way they may influence gluten immunity.

Ethics approval

Not required.

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Conflict of interest

All the authors declare that there are no conflicts of interest.

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Underlying data

All data underlying the results are available as part of the article and no additional source data are required.

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