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Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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NEW PHARMACOLOGICAL THERAPIES FOR CELIAC DISEASE – A SYSTEMATIC REVIEW

Mateusz Myśliwiec *(Corresponding Author, Email: mateusz_mysliwiec@icloud.com)*
Independent Public Health Care Center of the Ministry of the Interior and Administration in Kraków, Kraków, Poland
ORCID ID: 0009-0007-4552-4827

Tytus Tyralik
Stefan Żeromski Specialist Hospital SP ZOZ, Kraków, Poland
ORCID ID: 0009-0001-7370-4610

Maciej Karwat
Independent Public Health Care Center of the Ministry of the Interior and Administration in Kraków, Kraków, Poland
ORCID ID: 0009-0007-5917-977X

Julia Kular
Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0004-6287-2637

Oliwia Malec
Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0002-5391-3148

Justyna Niebylecka
Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0006-8773-3355

Izabella Michalska
Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0007-9030-0603

Natalia Glanc
Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0007-1130-0956

Dominik Sendecki
Independent Public Health Care Center of the Ministry of the Interior and Administration in Kraków, Kraków, Poland
ORCID ID: 0009-0004-4166-2219

Grzegorz Zalewski
Jagiellonian University Medical College in Kraków, Kraków, Poland
ORCID ID: 0009-0004-8161-5951

ABSTRACT

Background: Celiac disease is an immune-mediated condition caused by gluten in genetically susceptible individuals. Although a gluten-free diet is the basis of treatment, it is often difficult to maintain and may not fully prevent symptoms or intestinal damage.
Objective: This systematic review examines emerging non-dietary therapies for celiac disease, with emphasis on their mechanisms, clinical effectiveness, and safety.
Methods: A total of 23 peer-reviewed studies were analyzed, covering enzyme therapies, gluten sequestrants, tight junction modulators, immunotherapies, cytokine inhibitors, transglutaminase blockers, and probiotics.
Results: TAK-062 and ZED1227 emerged as the most promising candidates. TAK-062 showed strong gluten-degrading activity, while ZED1227 consistently reduced mucosal injury. Other enzymes, like latiglutenase, offered partial benefit, especially in seropositive patients. BL-7010 sequestered gliadin effectively in preclinical models. Larazotide acetate improved symptoms at low doses. Immunotherapies showed mixed outcomes—Nexvax2 failed in phase 2, while TAK-101 showed early potential. AMG 714 helped in refractory cases but lacked strong histological effects. Probiotics improved gut symptoms and microbiota balance, supporting their role as adjuncts.
Conclusions: While most therapies remain investigational, several show real potential as supplements to the gluten-free diet. Future research should focus on long-term outcomes and personalized approaches to improve disease management.

KEYWORDS

Celiac Disease, Gluten Degradation, ZED1227, TAK-062, Enzyme Therapy, Larazotide Acetate

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Introduction

Celiac disease is a chronic immune-mediated enteropathy of the small intestine, triggered by the ingestion of gluten—a protein found in wheat, rye, and barley—in genetically predisposed individuals (Ludvigsson et al., 2013). Once regarded as a rare pediatric disorder marked by overt malabsorptive symptoms, CD is now recognized as a widespread condition affecting individuals across all age groups and geographic regions (Catassi & Yachha, 2008). Epidemiological estimates suggest that the global prevalence of biopsy-confirmed CD is approximately 0.7%, with serological screening indicating rates approaching 1.4% (King et al., 2020). Over recent decades, the incidence of CD has increased markedly. A comprehensive systematic review and meta-analysis of population-based studies demonstrated an average annual increase of 7.5% in CD diagnoses (King et al., 2020). These trends may reflect improved awareness and diagnostic practices, but they also point toward evolving environmental or dietary exposures that warrant further investigation. Currently, the cornerstone of CD management is a strict lifelong gluten-free diet. While effective in achieving clinical and histological remission in many patients, the GFD poses several challenges. Adherence is often burdensome due to the high cost and limited availability of gluten-free products, as well as the risk of inadvertent gluten exposure through cross-contamination. Psychosocial burdens and diminished dietary quality are common, and in some patients, persistent intestinal inflammation and symptoms may occur despite reported adherence (Catassi et al., 2007). The Oslo consensus definitions have contributed to diagnostic clarity by distinguishing among classical, non-classical, potential, and refractory forms of CD (Ludvigsson et al., 2013). However, the heterogeneity in patient response to treatment and the limitations of dietary therapy underscore the need for alternative therapeutic strategies. Emerging evidence indicates that even minimal gluten exposure may induce mucosal damage in treated patients. A multicenter, double-blind, placebo-controlled trial demonstrated that daily ingestion of 50 mg of gluten for 90 days led to a significant decrease in the villous height to crypt depth ratio in small-intestinal biopsies—indicative of mucosal injury. Notably, while a 10 mg/day dose did not consistently cause histological changes, variability among patients was substantial, with some showing

deterioration at this lower threshold (Catassi et al., 2007). This interindividual sensitivity complicates the establishment of a universally safe gluten threshold in gluten-free products. International regulatory standards currently vary from 20 to 200 parts per million (ppm). Although in this study it was concluded that the threshold of 20 ppm ensures that the consumption of gluten from "gluten-free food" remains significantly under the threshold of 50 mg/d, thereby providing a safety buffer for the diverse gluten sensitivities and nutritional practices of individuals affected by this condition(Catassi et al., 2007). In addition to the direct effects of gluten exposure, adherence to a GFD has been linked to other health risks. A population-based analysis from the National Health and Nutrition Examination Survey (NHANES) revealed that individuals on a GFD exhibited significantly elevated levels of heavy metals—including mercury, lead, cadmium, and arsenic—compared with those not on the diet. These elevations persisted after adjusting for potential confounders and were attributed to the dietary reliance on rice and fish, staples in many gluten-free diets, which are known to accumulate toxic metals (Raehsler et al., 2018). Although the long-term clinical implications of chronic low-level heavy metal exposure remain unclear, the findings raise concerns about the nutritional safety of the GFD. The combination of residual mucosal inflammation, potential for inadvertent gluten intake, and increased toxic burden underscores the limitations of the GFD as a standalone therapy (Raehsler et al., 2018). Given these limitations and the increasing global burden of CD, there is a critical need to explore and rigorously evaluate novel non-dietary therapies.

Aim of the study

This systematic review aims to synthesize current evidence on emerging therapeutic strategies for CD, with a focus on their safety, efficacy, and potential for integration into clinical practice.

Methods

Protocol and Registration

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The protocol was designed prior to data extraction and adhered to principles of transparency and reproducibility.

Eligibility Criteria

Included 23 studies were original research articles evaluating therapeutic interventions in individuals with celiac disease or relevant in vitro or in vivo models. Eligible designs included randomized controlled trials, controlled clinical trials, observational studies with rigorous analytical methods, and preclinical studies employing validated models of gluten sensitivity. Studies were required to include clear methodological descriptions, appropriate statistical analyses, and outcome assessments relevant to celiac pathology, symptomatology, or gluten degradation. The search covered publications from the last 20 years, prioritizing recent studies (2015–2025).

Information Sources

The analysis included articles published in English, sourced from databases such as PubMed and Google Scholar, as well as websites and textbooks. A total of 35 sources were gathered, of which 23 met methodological criteria and were included in the further analysis.

Study Selection

Articles were screened for eligibility based on study design, participant characteristics, intervention type, and outcome measures. Studies involving adult patients with biopsy-confirmed celiac disease on a gluten-free diet, non-celiacs, gluten challenge protocols, or molecular analyses related to celiac mechanisms were included. Selection was independently verified to ensure adherence to inclusion criteria.

Data Collection Process

Methods data were extracted from each included article and compiled into a structured dataset. Details extracted included study design, participant demographics, intervention protocols, sample collection procedures, statistical tests employed, and regulatory or ethical approvals.

Data Items

Key data items included:

- Study design (e.g., randomized, double-blind, placebo-controlled trials; crossover; parallel-group; prospective; multicenter; in vitro/in vivo)
- Participant characteristics (e.g., GFD adherence, symptom status, gluten exposure)
- Intervention details (e.g., drug doses, gluten challenge protocols, organoid cultures, peptide therapies, enzyme supplementation)

- Biological sample collection (e.g., duodenal biopsies, fecal and urine samples, peripheral blood, organoids)
- Outcome measures (e.g., VH:CrD ratio, IEL density, symptom scores, immunologic markers, pharmacokinetics)
- Statistical methods (e.g., ANOVA, Wilcoxon signed-rank tests, ANCOVA, regression models, Bonferroni corrections)

Risk of Bias and Ethical Considerations

All included studies reported adherence to ethical standards such as the Declaration of Helsinki and Good Clinical Practice guidelines. Institutional review board approvals and informed consent from participants were documented. Several studies were registered with clinical trial registries. While formal risk of bias assessment was not performed, design rigor (e.g., blinding, randomization, control groups) was noted.

Summary Measures and Synthesis

Due to the methodological heterogeneity of interventions and outcome measures, a qualitative synthesis approach was adopted. Quantitative pooling of results was not performed. Data were narratively synthesized to identify methodological patterns, intervention frameworks, and outcome assessment strategies.

Literature review results

Gluten enzymatic degradation

In evaluating the efficacy of Aspergillus niger-derived prolyl endoprotease (AN-PEP) - an oral enzyme proficient in hydrolyzing gluten's antigenic proteins - across multiple clinical trials, findings demonstrated varying levels of effectiveness depending on study design and population. König et al. conducted a placebo-controlled crossover trial in gluten-sensitive individuals, revealing that both low and high doses of AN-PEP significantly degraded gluten in the stomach and duodenum, even within a complex meal matrix (König et al., 2017). Salden et al. corroborated these findings in healthy volunteers using liquid meals with AN-PEP, achieving substantial reductions in α-gliadin in both stomach and duodenum regardless of caloric content (Salden et al., 2015). In contrast, Tack et al.'s pilot study in celiac disease patients found no significant mucosal deterioration upon gluten challenge with or without AN-PEP over two weeks; however, a trend toward reduced IgA-tTG deposits in the AN-PEP group was noted, suggesting potential protective effects that require longer trials for confirmation (Tack et al., 2013). Similarly, Stefanolo et al.'s real-life trial in celiac patients adhering to a gluten-free diet found no significant difference in stool gluten immunogenic peptides (GIP) between AN-PEP and placebo groups, yet the prevalence of severe symptoms was significantly lower in the AN-PEP arm, highlighting its symptomatic benefit despite limited biochemical impact (Stefanolo et al., 2024). Overall, while AN-PEP consistently reduced gluten exposure markers in non-celiac populations and in vitro models, its impact on clinical and histological outcomes in celiac disease patients remains inconclusive and warrants further investigation in larger, longer-duration trials. TAK-062 is a modified endopeptidase derived from kumamolisin, originally obtained from Alicyclobacillus sendaiensis and altered to improve its capacity to decompose proteins. It specifically targets proline-glutamine (P-Q) dipeptide bonds and is designed to remain effective throughout the gastrointestinal tract's fluctuating pH levels and in the presence of digestive protease. In the phase I clinical study, conducted on 24 CD patients who consumed gluten-containing meals, TAK-062 demonstrated potent gluten-degrading activity, favorable pharmacokinetics, and good safety and tolerability profiles in both in vitro models and human participants. In vitro assessments showed that 100–300 mg of TAK-062 degraded over 99% of gluten (up to 9 g) within 10 minutes under simulated gastric conditions. In the dynamic gastric model, 300 mg of TAK-062 achieved more than 99% degradation of 3 g of gluten, with the capsule formulation showing delayed activity due to dissolution kinetics. Clinically, TAK-062 effectively degraded gluten in the stomachs of healthy participants across multiple dosing regimens (100–900 mg, both liquid and capsule), with median degradation exceeding 97% within 20–65 minutes postdose, even in the presence of a proton pump inhibitor. TAK-062 plasma levels were consistently below the quantification threshold, indicating minimal systemic exposure. The enzyme was well tolerated across all cohorts, with no serious adverse events reported; all observed treatment-emergent adverse events were mild and primarily unrelated to the study drug. These findings support TAK-062's potential as a safe and efficacious oral therapeutic for celiac disease by enabling rapid gastric degradation of immunogenic gluten peptides (Pultz et al., 2021). Latiglutenase (also known as ALV003 or IMGX003), a combination of two recombinant gluten-specific proteases, has been investigated in multiple clinical trials for its ability to mitigate gluten-induced effects in patients with celiac disease. In a placebo-controlled phase 2 trial, 900 mg/d of latiglutenase protected

the small intestinalmucosa from damage during a 6-week 2 g/day gluten challenge. Patients in the placebo group experienced a significant reduction in villus height to crypt depth ratio (from 2.8 to 2.0; P = 0.0007) and an increase in CD3+ intraepithelial lymphocytes (from 61 to 91 cells/mm; P = 0.0003). In contrast, those receiving latiglutenase showed no significant deterioration (VH:CrD = 2.7; P = 0.2499), with significant between-group differences for both morphometry and inflammation (P = 0.0133 and P = 0.0152, respectively) (Lähdeaho et al., 2014). In the second, placebo-controlled study conducted on 398 participants, in seropositive patients on a gluten-free diet, latiglutenase reduced symptom severity in a dose-dependent manner. At 900 mg, abdominal pain and bloating severity decreased by 58% and 44%, respectively, compared to placebo (P = 0.008 and P = 0.007). Benefits increased over the 12-week treatment period and were greatest in patients with higher baseline symptom scores (Syage et al., 2017). In a gluten challenge study conducted by Murray et al. using a higher 1200 mg daily dose of latiglutenase again attenuated mucosal injury, showing a smaller mean decrease in villus height to crypt depth ratio (–0.04 vs. –0.35; P = 0.057) and a significantly smaller increase in intraepithelial lymphocytes density (9.8 vs. 24.8 cells/mm; P = 0.018) compared to placebo. In the gluten challenge setting, latiglutenase significantly reduced worsening of abdominal pain, bloating, and tiredness symptoms over time (trend P-values = 0.014, 0.030, and 0.002, respectively). Urinary measurements confirmed the mechanism of action, showing approximately 95% gluten degradation with latiglutenase during gluten exposure (P = 0.001) (Murray et al., 2022). Latiglutenase was well tolerated across all studies, with adverse events comparable to placebo and primarily attributed to gluten ingestion rather than the treatment itself.

Gluten sequestration

BL-7010, a synthetic polymer designed to bind gliadin in the gut, was evaluated in a preclinical model using NOD-DQ8 mice. In this study, the copolymer BL-7010 demonstrated high-affinity and specific binding to gliadin, with dissociation constants (KD) of 1.21×10^{-8} M for Polymer A and 2.44×10^{-9} M for Polymer B, and showed no detectable interaction with digestive enzymes or essential vitamins, suggesting minimal nutritional or enzymatic interference. In a chronic NOD-DQ8 mouse model of gliadin sensitivity, both batches of BL-7010 effectively mitigated gluten-induced intestinal pathology, including significant prevention of villus to crypt ratio reduction and intraepithelial lymphocytosis, as well as normalization of increased intestinal permeability and PAT-1 mRNA expression. The polymers were also found to be non-absorbable, with no detectable systemic exposure in rats even at high doses, and showed no signs of toxicity or mutagenicity in comprehensive in vivo and in vitro assays, including a 14-day repeated-dose toxicology study (McCarville et al., 2014). These findings affirm the therapeutic potential and safety of BL-7010 in counteracting gliadin-induced mucosal damage, supporting its progression to clinical evaluation.

Tight junction modulators

Larazotide acetate (AT-1001) is a synthetic octapeptide derived from the occludin zone toxin of Vibrio cholerae which acts as a zonulin receptor inhibitor, reducing tight junction permeability in the intestinal epithelium. Two randomized, double-blind, placebo-controlled trials evaluated larazotide acetate in celiac disease patients, one during a gluten challenge and the other in individuals with persistent symptoms despite adherence to a gluten-free diet. While the primary endpoint in the gluten challenge trial—reduction in intestinal permeability measured by the lactulose-to-mannitol ratio—was not met due to high inter-patient variability, secondary outcomes indicated that lower doses of larazotide acetate (0.25 mg and 4 mg) significantly reduced gastrointestinal symptom severity (Leffler et al., 2012). In the persistent symptoms study, the 0.5 mg dose met the primary endpoint by significantly reducing average weekly symptom scores (p=0.022) and improving several exploratory outcomes, including reductions in symptomatic days and improvements in both gastrointestinal and extraintestinal symptoms (e.g., headache, tiredness) (Leffler et al., 2015). Higher doses (1 mg and 2 mg) did not demonstrate similar benefits in either trial. Larazotide acetate was well tolerated in both studies, with no serious adverse events and adverse event rates comparable to placebo. These findings suggest that larazotide acetate, particularly at lower doses, may provide symptomatic benefit in CeD patients, although further investigation is needed to confirm efficacy and define optimal dosing.

Transglutaminase inhibition

In a series of investigations examining the efficacy of the transglutaminase 2 inhibitor ZED1227 in patients with celiac disease, robust clinical, histological, and molecular evidence demonstrated the compound's capacity to mitigate gluten-induced intestinal damage. In a randomized, double-blind, placebo-controlled phase 2 trial, daily administration of ZED1227 at doses of 10 mg, 50 mg and 100 mg over a 6-week gluten challenge significantly attenuated duodenal mucosal injury, as evidenced by preserved villus height to crypt depth ratios compared to placebo ($p \leq 0.001$ for all doses), with the 100 mg dose additionally reducing intraepithelial lymphocyte infiltration and improving quality of life indices (Schuppan et al., 2021). Complementary molecular analyses confirmed that ZED1227 accumulated predominantly in villous enterocytes, particularly at the brush border, suggesting its action at the early phase of gliadin peptide modification (Isola et al., 2023). Transcriptomic profiling of duodenal biopsies revealed that ZED1227 treatment preserved gene expression patterns associated with mucosal integrity, nutrient absorption, and enterocyte differentiation, and effectively suppressed gluten-induced interferon-γ responses and downstream inflammatory cascades (Viiri et al., 2024). ZED1227, also referred to as TAK-227, is under development. In October 2022, Takeda Pharmaceutical Company entered a collaborative agreement with Zedira and Dr Falk Pharma for its advancement. Takeda obtained exclusive development and marketing rights in the United States, while Zedira and Dr Falk Pharma maintained rights in Europe, Canada, Australia, and China. A Phase IIb trial, sponsored by Dr Falk Pharma, assessed the efficacy and safety of ZED1227 against a placebo for individuals with celiac disease on a gluten-free diet. This trial concluded in September 2024, with results expected to be published shortly (Santonicola et al., 2025).

Immunotherapy and Immune Modulation

Nexvax2, an investigational peptide-based immunotherapy, was developed to induce antigen-specific tolerance in individuals with celiac disease who carry the HLA-DQ2.5 haplotype. It consists of three synthetic gluten-derived peptides representing key immunodominant T-cell epitopes. The goal of the therapy was to reduce or eliminate the immune response to dietary gluten by targeting pathogenic CD4+ T cells. In multiple randomized, double-blind, placebo-controlled phase 1 trials, Nexvax2 was administered via intradermal or subcutaneous injection. Initial studies showed that low starting doses followed by gradual dose escalation up to 900 µg were generally well tolerated. Early doses caused transient gluten-like symptoms and interleukin-2 (IL-2) elevations, but these effects diminished or were avoided entirely with gradual dose increases (Goel et al., 2017; James et al., 2023). In a subsequent phase 1 study comparing subcutaneous and intradermal delivery, 14 patients (12 with Nexvax2, 2 with placebo) completed the full treatment course, which included a five-week dose escalation phase and two weeks of 900 µg maintenance dosing (Truitt et al., 2019). Most adverse events were mild and self-limited, and no serious safety concerns were identified. Pharmacokinetic analysis showed slightly higher peptide exposure with subcutaneous dosing. IL-2 responses were successfully suppressed during maintenance dosing, indicating the development of immune non-responsiveness (Truitt et al., 2019). Despite these immunologic findings, Nexvax2 failed to demonstrate efficacy in preventing gluten-induced intestinal injury or clinical symptoms in a phase 2 trial (RESET CeD). As a result, the development of Nexvax2 was discontinued. Nonetheless, the program offered key insights into antigen-specific immune modulation in celiac disease and established proof-of-concept for future epitope-targeted therapies (Santonicola et al., 2025). TAK-101, a gliadin-encapsulated nanoparticle therapy, was evaluated in a randomized, double-blind, placebo-controlled study. Following gluten challenge, patients receiving placebo showed a ~10-fold increase in gliadin-specific IFN-γ–producing T cells, while the TAK-101 group had no significant rise. TAK-101 reduced the mean change in IFN-γ spot-forming units by 88% compared to placebo (2.01 vs. 17.58 cells/1×10^6 PBMCs, $P = 0.006$). Villus height to crypt depth ratio significantly worsened in the placebo group but remained stable in TAK-101–treated patients, though the between-group difference was not statistically significant. TAK-101 also suppressed gluten-induced activation of circulating gut-homing effector memory T cells and did not affect systemic immune function. The treatment was well tolerated with no serious adverse events(Kelly et al., 2021).

The other study investigated the effects of the cathepsin S inhibitor RO5459072 in celiac disease patients undergoing a controlled gluten challenge. 19 participants were randomized to receive either RO5459072 or placebo for 28 days, with gluten exposure occurring from Days 8 to 20. The primary endpoint—defined as an increase in gliadin-specific IFNγ-secreting T cells—was not met due to a weak overall response to gluten, with only 11% of the RO5459072 group and 44% of the placebo group responding at Day 13, and no responders detected at Day 21. Serological responses, including anti-tTG and anti-DGP antibodies, were minimal in both

arms, with isolated increases observed only in a small number of participants. RO5459072 treatment was associated with reduced intestinal permeability and decreased circulating B cells, CD4+, and CD8+ T cells compared to baseline, aligning with its proposed mechanism of action. Pharmacodynamic analysis confirmed target engagement through sustained elevation of the p10 fragment in B cells. Although adverse events were common, they were mild and similarly distributed across groups. Despite some immunomodulatory effects, the absence of a robust immune response to gluten challenge suggests that cathepsin S inhibition with RO5459072 may not provide clinically meaningful benefits in celiac disease management under the study conditions. The trial was underpowered and did not meet primary endpoints (Bentley et al., 2025).

Cytokine-Targeted Interventions

In two phase 2a, randomised, double-blind, placebo-controlled studies, AMG 714 - an anti-IL-15 monoclonal antibody, also known as PRV-015 - was evaluated for its efficacy and safety in coeliac disease. In the first study involving 64 adults with well-controlled coeliac disease subjected to a 10-week gluten challenge, AMG 714 did not significantly prevent mucosal damage, as measured by the primary endpoint, change in villous height-to-crypt depth ratio (–2.49% for 150 mg and 6.39% for 300 mg compared with placebo; p=0.73 and p=0.34, respectively). However, the 300 mg dose was associated with a nominally significant reduction in intraepithelial lymphocyte density (–41.24%, p=0.03) and improved clinical outcomes such as fewer episodes of diarrhoea, reduced coeliac disease-specific symptoms, and more favorable physician global assessments (Lähdeaho et al., 2019). In the second study, 28 patients with type 2 refractory coeliac disease received AMG 714 or placebo over 10 weeks. The primary endpoint—the change in aberrant intraepithelial lymphocyte percentage—was not significantly different between groups (–4.85%, p=0.75). Nevertheless, AMG 714 showed a consistent trend towards improvement in multiple secondary endpoints, including reduced progression of T-cell receptor clonality, less histological deterioration, and reduced diarrhoea (Cellier et al., 2019). Across both studies, AMG 714 was well tolerated, with adverse event rates comparable to placebo. These findings suggest that while AMG 714 did not achieve primary histological endpoints, its biological and clinical effects, particularly in symptom reduction and lymphocyte activity, warrant further investigation in non-responsive and refractory coeliac disease.

Gut Microbiota and Probiotics

In two recent randomized, double-blind, placebo-controlled trials, different probiotic strategies were evaluated for their efficacy in managing gluten-related disturbances, with a focus on microbiota modulation and symptom relief. Francavilla et al. investigated the effects of a multispecies probiotic mixture in celiac disease patients experiencing irritable bowel syndrome - like symptoms despite adherence to a strict gluten-free diet. Their study demonstrated that a 6-week supplementation led to significant reductions in IBS Severity Scoring System and Gastrointestinal Symptom Rating Scale scores compared to placebo. The intervention also resulted in a statistically significant improvement in treatment success and was associated with an increased abundance of beneficial gut bacteria, such as Bifidobacterium, without any reported adverse events (Francavilla et al., 2019). Complementarily, Nikoloudaki et al. explored a novel probiotic formulation with demonstrated in vivo gluten-degrading capacity in healthy adults subjected to escalating gluten challenges. Compared to placebo, the probiotic group exhibited markedly lower fecal gluten content across increasing intake levels and higher microbial diversity and richness during the intervention. The probiotic strains persisted transiently in the gut and induced metabolomic shifts associated with immunomodulatory potential, including elevated levels of short-chain fatty acids and indole derivatives (Nikoloudaki et al., 2024). These findings suggest a dual benefit of targeted probiotics in both gluten degradation and modulation of the gut environment, supporting their potential role as adjunctive therapies in gluten-related disorders.

Discussion

This systematic review evaluated emerging therapeutic strategies for celiac disease, reflecting a shift toward targeted, non-dietary interventions. These therapies address different aspects of disease pathophysiology, from enzymatic detoxification of gluten to modulation of immune responses and gut barrier function. While some candidates show encouraging results, most remain investigational, with limited evidence supporting their standalone use. Enzyme therapies such as AN-PEP, TAK-062, and latiglutenase aim to degrade immunogenic gluten peptides before they trigger mucosal damage. AN-PEP demonstrated reliable gluten breakdown in non-celiac populations, with limited impact on mucosal or immunological outcomes in celiac patients. However, some symptomatic relief was noted, suggesting a role in managing accidental gluten

exposures. TAK-062, a more robust enzyme, showed near-complete gluten degradation under gastric conditions and was well tolerated in clinical studies. Its stability and potency position it as a promising candidate for further trials. Latiglutenase yielded mixed results—while some studies reported protection against mucosal injury and symptom improvement during gluten challenge, others showed only modest histological benefits. Its effects were more pronounced in symptomatic, seropositive patients, indicating a potential role as an adjunctive therapy. BL-7010, a synthetic polymer designed to bind gliadin, showed strong efficacy and safety in preclinical models, preventing gluten-induced pathology without affecting nutrient absorption. However, human data are lacking, and clinical trials are needed to validate its potential. Larazotide acetate, a tight junction modulator, improved gastrointestinal symptoms at low doses, though results were inconsistent across endpoints. Its benefits may be dose-dependent and more visible in patients with persistent symptoms, suggesting it could complement dietary management rather than replace it. ZED1227, a transglutaminase 2 inhibitor, emerged as the most promising therapy. Clinical trials demonstrated significant mucosal protection, symptom improvement, and suppression of gluten-induced immune activation. With consistent histological and molecular evidence and a favorable safety profile, ZED1227 appears closest to clinical application. Antigen-specific immunotherapy with Nexvax2 failed to prevent gluten-induced damage in phase 2 trials, despite early signs of immunologic tolerance. Nevertheless, it provided valuable proof-of-concept for future epitope-targeted approaches. TAK-101, a nanoparticle-based therapy, effectively suppressed gluten-specific T-cell responses and prevented histological deterioration during gluten challenge. While still early in development, its targeted mechanism and safety warrant further study. RO5459072, a cathepsin S inhibitor, showed modest immunologic effects without meeting primary endpoints, likely due to limited gluten responsiveness and underpowered design. AMG 714, an anti-IL-15 monoclonal antibody, did not significantly prevent mucosal damage but showed symptomatic and immunological benefits, particularly in refractory celiac disease. These findings support continued exploration in specific patient subgroups. Probiotic therapies demonstrated potential in symptom relief and microbiota modulation. Both multispecies and gluten-degrading formulations improved gastrointestinal outcomes and altered microbial profiles favorably. Although unlikely to replace dietary therapy, probiotics may serve as supportive interventions for symptomatic patients.

Conclusions

Emerging therapies for celiac disease show considerable promise, particularly drugs like: ZED1227, TAK-062, and latiglutenase. However, most interventions remain adjunctive and require further validation and research. Personalized approaches and longer-term studies will be essential to advance these candidates toward clinical use. While compliance with a strict gluten-free diet remains the standard, these therapeutic interventions may serve to address existing treatment deficiencies and enhance the quality of life for individuals with celiac disease.

Authors' Contributions Statement

All authors have read and agreed with the published version of the manuscript.

All authors have reviewed and agreed to the publication of the final version of the manuscript.

Conceptualization and methodology: Julia Kular, Oliwia Malec, Justyna Niebylecka, Izabella Michalska

Software: Mateusz Myśliwiec, Izabella Michalska, Natalia Glanc, Dominik Sendecki, Grzegorz Zalewski

Check: Grzegorz Zalewski

Formal analysis: Tytus Tyralik, Natalia Glanc, Dominik Sendecki, Justyna Niebylecka

Investigation: Tytus Tyralik, Natalia Glanc, Dominik Sendecki

Resources: Mateusz Myśliwiec, Tytus Tyralik, Maciej Karwat,Natalia Glanc, Dominik Sendecki, Grzegorz Zalewski

Writing -rough preparation: Mateusz Myśliwiec, Julia Kular, Oliwia Malec

Writing -review and editing: Maciej Karwat, Oliwia Malec, Justyna Niebylecka

Visualization: Mateusz Myśliwiec, Tytus Tyralik, Maciej Karwat, Izabella Michalska, Natalia Glanc

Supervision: Tytus Tyralik, Maciej Karwat, Julia Kular

Project administration: Mateusz Myśliwiec

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