Anal. Bioanal. Electrochem., Vol. 17, No. 8, 2025, 747-770
https://www.doi.org/10.22034/abec.2026.733519

Analytical & Bioanalytical Electrochemistry

Review

Awareness and Knowledge of Celiac Disease and the Role of Nanotechnology and Electrochemical Methods in Gluten Detection

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Received: 14 August 2025 / Received in revised form: 31 October 2025 / Accepted: 8 November 2025 / Published online: 31 December 2025

Abstract- Celiac disease (CD), a chronic autoimmune disorder triggered by gluten ingestion in genetically predisposed individuals, continues to pose diagnostic and management challenges worldwide due to its diverse clinical presentations and often subtle symptomatology. Although public awareness of CD has increased alongside the expanding gluten-free food market, significant knowledge gaps persist regarding the disease's underlying immunopathology, comorbidities, and lifelong dietary implications. As accurate and timely diagnosis remains critical to prevent long-term complications, conventional serological assays and biopsies, while effective, are limited by invasiveness, resource dependency, and processing delays. In response, electrochemical biosensing platforms—leveraging nanotechnology, aptamer design, and microfluidic integration—have emerged as promising alternatives, enabling rapid, sensitive, and cost-effective detection of key gluten-related biomarkers such as anti-tTG and deamidated gliadin peptide antibodies. These innovations harness the advantages of nanostructured materials, label-free detection, and real-time signal acquisition to offer portable, minimally invasive solutions for clinical and food safety applications. Despite the complexity of transitioning from laboratory prototypes to commercially viable diagnostic tools, interdisciplinary advancements in sensor engineering, material science, and data analytics continue to refine the specificity, stability, and usability of these platforms. This review synthesizes current findings on public perception of CD, highlights diagnostic challenges, and explores the transformative potential of electrochemical and nanomaterial-enabled biosensors

in achieving early detection, personalized monitoring, and improved quality of life for individuals affected by gluten-related disorders.

Keywords- Celiac disease; Gluten-related disorders; Public awareness; Health education; Electrochemical biosensors; Point-of-care diagnostics; Nanotechnology; Nanomaterial-enhanced sensing

1. INTRODUCTION

Celiac disease (CD) is a persistent inflammatory condition affecting the small intestine, initiated by the consumption of gluten, a protein primarily present in wheat, barley, and rye [1,2]. In many Western nations, it ranks as the most significant contributor to malabsorption disorders [3]. A characteristic clinical feature of CD is selective nutrient malabsorption, frequently presenting as iron-deficiency anemia and insufficient vitamin D levels, which can subsequently result in osteoporosis [4,5].

In addition to gastrointestinal symptoms, CD often coexists with other medical conditions, particularly autoimmune disorders. Common comorbidities include Duhring's disease (dermatitis herpetiformis, ≈3%), type 1 diabetes (≈7%), and thyroid-related disorders (5–21%) [6]. Furthermore, neuropsychiatric complications such as depression, anxiety, and cognitive impairments have been documented in approximately 3.9% to 35.9% of cases in large cohort studies [7]. Being a lifelong disorder, CD significantly elevates the risk of both morbidity and mortality [8].

In a standard Western dietary pattern, the daily intake of gluten — a group of storage proteins present in wheat — ranges from approximately 10 to 20 g [2]. In many developing nations, the incidence of celiac disease has been steadily increasing, a trend linked to dietary shifts toward Western eating patterns and changing agricultural/processing practices [9,1]. At present, the sole proven therapy remains permanent adherence to a gluten-free diet, requiring elimination of gluten-containing grains [3,9].

In recent years, awareness of celiac disease (CD) and other gluten-related disorders has steadily increased. Despite this, widespread media coverage and the rapid expansion of gluten-free markets have not fully translated into accurate public understanding; misconceptions remain common, often reducing CD to a lifestyle choice rather than a medical necessity [10]. Assessing public knowledge and perception is essential to ensure early diagnosis, improve disease management, and reduce the social stigma faced by those who require a strict gluten-free diet for health reasons. In addition, to enable timely intervention and prevent complications, early rapid diagnostic approaches—such as serological screening, point-of-care antibody tests, and advanced electrochemical biosensors for gluten detection—are gaining critical importance in early disease identification and effective management. Early and accurate detection of celiac disease is essential for timely clinical intervention and minimizing associated complications. Traditional diagnostic strategies, including serological assays and point-of-care antibody tests, provide valuable information; however, they often involve

multiple steps, specialized laboratory infrastructure, and extended processing times. In contrast, electrochemical biosensors have emerged as a highly efficient alternative due to their exceptional sensitivity, rapid response, and portability [11]. These devices allow direct, real-time detection of gluten biomarkers with minimal sample preparation, making them suitable for both clinical settings and on-site applications. Furthermore, their scalability, low operational cost, and ability to integrate with digital platforms position electrochemical methods as a superior approach compared to conventional techniques, particularly in improving diagnostic accessibility and reliability [12].

The present review seeks to investigate the extent of public knowledge, awareness, and sensitivity toward celiac disease and the gluten-free diet, alongside assessing the recognition of advanced electrochemical techniques designed for fast, user-friendly electrochemical and precise early detection of CD disease.

2. PUBLIC AWARENESS AND KNOWLEDGE GAPS REGARDING CELIAC DISEASE: INSIGHTS FROM RECENT INTERNATIONAL SURVEYS

The results of the most recent international surveys show that there is a good general awareness of CD disease among survey respondents, and that respondents appear to be largely aware of the fact that there is a link between CD disease and gluten intolerance, and many respondents correctly answered that the foods to avoid when suffering from celiac disease are those containing gluten. This indicates a common but basic understanding of the disease. However, this understanding seems to be less evident when it comes to more complex issues of the disease, such as triggers, such as stress or pregnancy. Many participants indicated that they were not sufficiently informed about these aspects, indicating that there are gaps in knowledge about the causes and wider effects of celiac disease on the general population. These findings are consistent with previous research showing that although the level of general understanding about gluten avoidance is relatively high, knowledge about triggers and non-dietary complications of celiac disease is low [13]. The respondents also demonstrated an awareness of the lifestyle and social issues associated with living with CD. Many admitted that people with the condition are likely to feel fearful or anxious about eating out, or even to limit activities such as travel and holidays. These responses indicate an awareness of the day-to-day difficulties faced by people living with the disease, suggesting a level of empathy. This is consistent with other research showing that social restrictions and food-related anxiety are prevalent issues among people with CD and have the potential to affect quality of life [14].
Medical knowledge among the respondents showed some discrepancies. Although most respondents were aware that there is a connection between celiac disease and other autoimmune conditions such as diabetes and thyroid disorders, some believed that CD is curable. This reflects a disparity in public knowledge and highlights the need for more accurate health information regarding the chronic nature of CD and its long-term management. This is

consistent with earlier research that identified long-standing misconceptions about the permanence of the disease and its association with other health conditions [15].

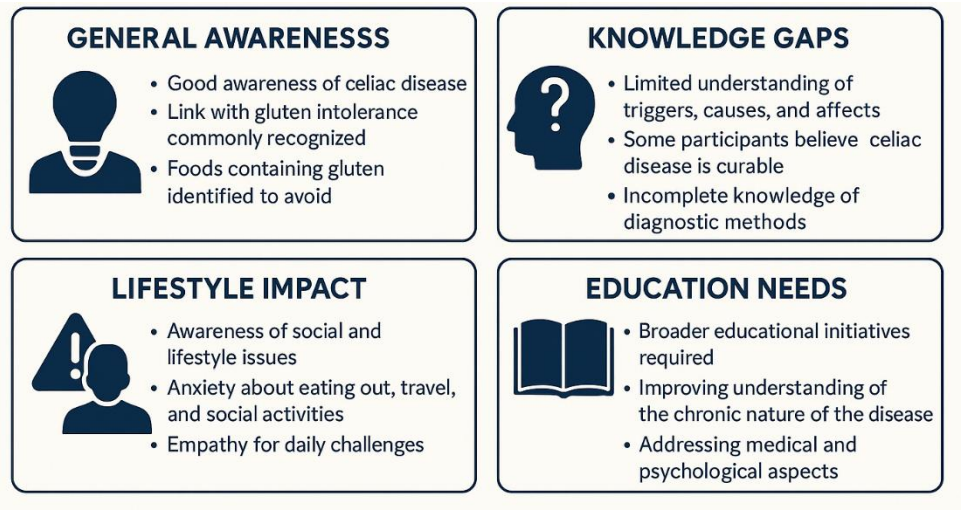

Figure 1. Summary of recent international survey findings on public awareness and knowledge gaps regarding celiac disease, highlighting general awareness, persistent misconceptions, lifestyle impacts, and priority areas for targeted educational interventions.

Overall, the survey findings indicate a high level of general awareness of celiac disease among respondents, with only minor variations across education, age, and gender on specific topics. Notably, perceptions did not differ significantly between genders, suggesting that public health messaging is being disseminated equitably across diverse populations. However, knowledge concerning the chronic nature of the disease, triggering factors, diagnostic methods, and lifestyle implications remains limited. These gaps underscore the need for targeted educational initiatives that extend beyond dietary guidance to encompass the medical, social, and psychological dimensions of living with celiac disease. Enhancing community awareness, improving access to appropriate detection and advanced diagnosis techniques, and fostering supportive environments may, in turn, contribute to a better quality of life for affected individuals. Figure 1 presented Summary of recent international survey findings on public awareness and knowledge gaps regarding celiac disease, highlighting general awareness, persistent misconceptions, lifestyle impacts, and priority areas for targeted educational interventions.

3. EMERGING INNOVATIONS IN ELECTROCHEMICAL DIAGNOSIS TECHNIQUES FOR DETECTING CELIAC DISEASE

Celiac disease (CD) is an autoimmune condition that develops when individuals with genetic susceptibility consume gluten-containing foods. Although it affects nearly 1% of the global population, a large proportion of cases remain undetected because of vague clinical

manifestations and the shortcomings of current diagnostic practices. Traditional diagnostic approaches, such as serological assays (anti-tTG, EMA) and intestinal biopsies, are often invasive, costly, and time-intensive. In recent years, electrochemical diagnostic strategies have emerged as promising solutions, offering rapid, affordable, and highly sensitive detection methods. This review highlights the latest innovations in electrochemical techniques, their fundamental mechanisms, and their potential impact on enhancing the accuracy and accessibility of CD diagnosis [16-19].

3.1. Pathophysiology and Diagnostic Challenges in Celiac Disease

Celiac disease involves an abnormal immune reaction to gluten-derived peptides, which ultimately results in damage to the mucosal lining of the small intestine. Standard diagnostic approaches typically combine serological testing with histological examination and often necessitate continued gluten consumption for accurate assessment. Several challenges complicate this process, including: delayed or missed diagnoses due to silent or atypical clinical manifestations, Dependence on invasive techniques, such as duodenal biopsies, Limited availability of these diagnostic tools in low-resource settings. These constraints highlight the urgent need for innovative diagnostic strategies that are accurate, non-invasive, and accessible [20-23].

3.2. Emerging Electrochemical Sensor Platforms for CD Detection

Over the past few years, a range of advanced platforms has emerged, each contributing to the evolution of diagnostic technologies:

(i) Nanostructured Screen-Printed Carbon Electrodes (SPCEs): Another advanced design uses disposable SPCEs modified with carbon nanotubes and gold nanoparticles. The transglutaminase antigen is immobilized on this nanostructured surface, and alkaline phosphatase-labeled secondary antibodies produce an enzymatic silver deposition signal detected by voltammetry. This platform matches ELISA-level diagnostic accuracy for both IgA and IgG anti-tTG in real patient serum specimens These are affordable, single-use sensors widely applied in point-of-care (POC) diagnostics due to their simplicity and cost-effectiveness [24]. Figure 2 presented Schematic representation of a nanostructured screen-printed carbon electrode (SPCE) modified with carbon nanotubes and gold nanoparticles for celiac disease detection. Human transglutaminase antigen is immobilized on the electrode surface, followed by binding of alkaline phosphatase-labeled secondary antibodies. Enzymatic silver deposition enables voltammetric signal generation, offering ELISA-comparable sensitivity for anti-tTG IgA and IgG detection in patient serum.

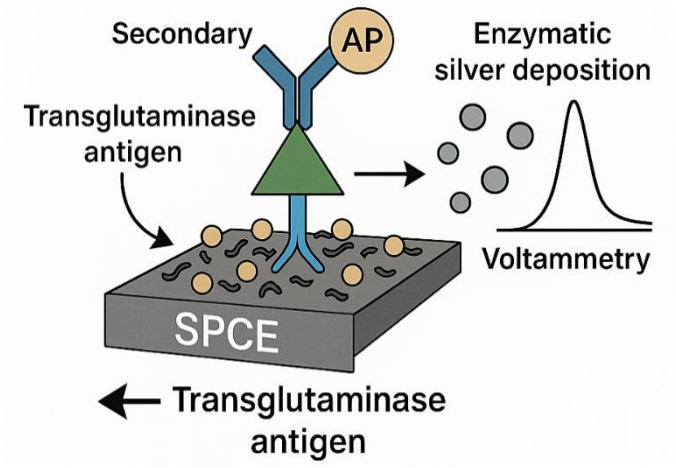

Figure 2. Schematic representation of a nanostructured screen-printed carbon electrode (SPCE) modified with carbon nanotubes and gold nanoparticles for celiac disease detection

(ii) Interdigitated Electrodes and Label-Free Impedimetric Sensing: This technique provides a label-free method for monitoring antibody–antigen interactions, making it highly suitable for rapid immunoassays. Label-free impedimetric sensors feature gold interdigitated electrode arrays fabricated at nanoscale gaps, coated with self-assembled monolayers to attach tTG, and enhanced with protein-A–AuNP conjugates. This setup boosts sensitivity by up to 350% and delivers diagnostic capability on par with micro-ELISA—but without enzyme labeling. It offers streamlined real-time impedimetric detection of tTG autoantibodies in serum [25-27].

(iii) Nano-Electrode Ensembles for Anti-tTG Antibodies: A recent platform applies arrays of gold nanoelectrodes embedded in a porous membrane shell, functionalized with tissue-transglutaminase (tTG) to selectively bind IgG-type anti-tTG antibodies. After binding, an HRP-labeled secondary antibody plus hydrogen peroxide and hydroquinone generates a catalytic amperometric signal. This architecture achieves a detection threshold as low as ~1.8 ng/mL, high selectivity, and strong concordance with established fluoroenzyme immunoassays in clinical serum samples [28-30].

(iv) Aptamer-Based Sensors (Aptasensors): Utilizing aptamers instead of conventional antibodies delivers enhanced specificity, robustness, and long-term stability [31-33].

(v) DNA-Based Conformational Biosensors (E-DNA): A pioneering approach uses a synthetic “neoepitope” peptide mimicking gliadin–tTG crosslink, hybridized to a PNA–DNA duplex anchored on a gold electrode and tagged with a methylene blue redox reporter. When Celiac-specific autoantibodies bind, the conformational change in the DNA oligomer reduces electron transfer current, measurable via square-wave voltammetry. This method achieves detection down to around 0.01 units/mL and retains accuracy even in diluted serum matrices [35,36].

3.3. Innovative DNA-Based and Aptamer Strategies

(i) DNA-Based Electrochemical Biosensor Strategies: Recent research has produced novel electrochemical platforms that leverage synthetic DNA sequences to identify early-stage celiac disease autoantibodies. One standout approach employed a neoepitope structure mimicking the crosslinked complex of tissue transglutaminase and gliadin peptides. When autoantibodies in patient serum bind to the DNA–neoepitope conjugate on the electrode surface, a redox reporter undergoes a conformational shift, producing a measurable reduction in current. This design achieved detection in the clinically relevant range (~0.09 ± 0.03 units/mL) with strong specificity and minimal off-target interactions, even in bovine serum-spiked buffer environments. The biosensor demonstrated dose-dependent signal changes and a dissociation constant compatible with serological thresholds, illustrating its promise for minimally invasive, point-of-care diagnostics that could eventually complement or reduce reliance on traditional biopsy-based confirmation [36]. Figure 3 presented a schematic of a DNA-based electrochemical biosensor for early celiac disease detection. Synthetic DNA conjugated to a neoepitope mimicking the tTG–gliadin complex captures disease-specific autoantibodies from serum. Binding induces a conformational shift in a redox reporter, resulting in a measurable decrease in current. The platform demonstrates high specificity, dose-dependent response, and compatibility with clinical detection thresholds.

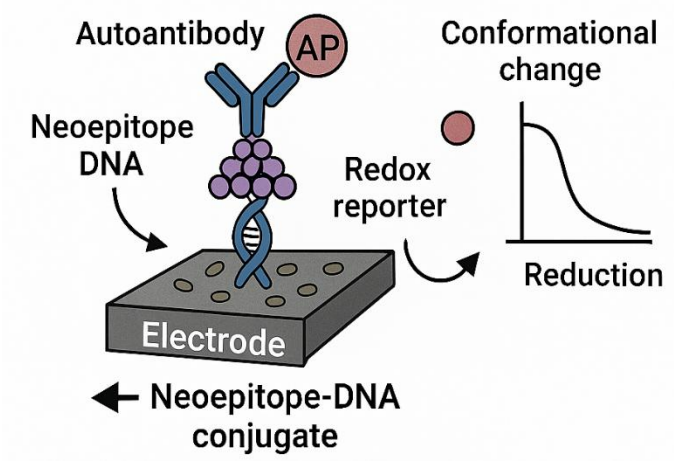

Figure 3. Schematic of a DNA-based electrochemical biosensor for early celiac disease detection

(ii) Aptamer-Based Electrochemical Sensor Strategies: Innovations in aptamer-based electrochemical biosensors (E-AB) have enabled highly sensitive and label-free detection of gluten-related biomarkers, providing critical tools for celiac disease diagnosis. In one configuration, truncated anti-gliadin aptamers (e.g., Gli-4T) were immobilized on screen-printed carbon electrodes, combined with gold nanoparticles, to capture gliadin in

deep eutectic solvent (DES) extracts. The detection utilized chronoamperometric or impedance readouts, achieving limits of detection as low as 1 μg/L gliadin (~0.1 mg/L gluten), with excellent selectivity in complex food matrices such as gluten-free soy sauce and dessert powders. Another configuration integrated dual-recognition modules—an aptamer capture layer paired with HRP-labeled antibody reporters—on a paper-based platform, elevating both sensitivity and specificity while maintaining portability and low cost. These aptamer strategies exemplify rapid, reagent-free, and multiplex-compatible platforms suited for real-world deployment in food safety and, by extension, clinical celiac diagnostics [37].

3.4. Electrochemical Biomarkers for Celiac Disease

These are celiac disease-related molecules that can be detected electrochemically. For CD, the most relevant biomarkers include:

(i) Anti-tTG IgA/IgG antibodies: These autoantibodies (IgA and IgG subclasses) are among the most validated markers for CD. Multiple electrochemical immunosensors have been described: A gold self-assembled monolayer conjugated with tTG antigen detects anti-tTG via HRP-labeled secondary antibodies, monitored by impedance or amperometry, with detection limits ~390 ng/mL and excellent correlation with ELISA in patient samples. Another platform used nanostructured screen-printed carbon electrodes functionalized with carbon nanotubes and gold nanoparticles, trapping tTG and deploying AP-labeled secondary IgA/IgG antibodies. Signal arises from enzymatic silver deposition and voltammetric measurement, correlating well with conventional ELISA [38,39].

(ii) Deamidated gliadin peptide antibodies (DGP-A): Early detection platforms also target antibodies against deamidated gliadin peptides. A disposable screen-printed carbon electrode enhanced by carbon nanotubes and AuNPs immobilized DGPx4 fusion peptide. A sandwich assay with AP-labeled anti-IgG enabled silver deposition-based detection in serum; results were comparable to ELISA benchmarks [40].

(iii)Emerging Non-Serological Biomarkers: Although not electrochemical per se, protein biomarkers are under investigation for future sensor integration. For instance, elevated plasma levels of **FGL2** and **TXNDC5** correlate strongly with active celiac disease, with additional proteins such as FABP or CPOX reflecting villous atrophy severity. These proteins could be incorporated into multi-analyte electrochemical platforms in coming years [41].

3.5. Enhancing Sensor Performance with Nanomaterial Composites

(i) **Role of Nanostructured Materials:** Recent advances in nanomaterial composites have significantly enhanced sensor performance by leveraging the unique properties of

nanostructured materials. Specifically, integrating one-, two- and zero-dimensional nanostructures—such as nanowires, nanosheets, nanoparticles and nanotubes—into sensing layers dramatically increases surface-to-volume ratio, creating a larger density of active adsorption sites and enabling efficient charge transfer with analyte species. For example, p–n heterojunctions formed by combining n-type ZnO nanostructures with p-type Si nanowires yield synergistic sensitivity and selectivity toward NO gas, outperforming individual components in response magnitude and stability under varying humidity. Similarly, composites of single-walled carbon nanotubes (SWCNTs) functionalized with polyethylenimine (PEI) show up to 50 % improvement in NO_2 detection at room temperature, due to enhanced defect-induced adsorption and charge transfer modulation .Furthermore, graphene-layered surface plasmon resonance (SPR) platforms incorporating nanostructured silver or gold exhibit heightened biomolecule detection sensitivity through amplified refractive index shifts, robust thermal stability, and improved biorecognition immobilization efficiency. MXene-based composites (e.g., $Ti_3C_2T_x$) also contribute high signal-to-noise ratio and selective SERS amplification in gas and biological sensing contexts, capitalizing on their metallic conductivity and two-dimensional morphology.Together, these nanostructured composites facilitate faster response and recovery, lower detection limits, and enhanced selectivity by optimizing surface chemistry, electronic structure modulation, and interfacial charge dynamics in next-generation sensors [42-44].

(ii) **Hybrid Nanocomposites for Signal Enhancement**: Recent studies (2023–2025) report the use of core–shell nanostructures, notably gold-core/shell nanoparticles embedded in polymeric matrices or 2D supports. For instance, dual-recognition electrochemical biosensors leveraging gold nanorods self-assembled into dimers have demonstrated ultrasensitive surface-enhanced Raman scattering (SERS) detection of gluten peptides at sub-ppm concentration in food matrices (Abate et al., 2023). When integrated into hybrid materials—for example, AuNRs immobilized on graphene oxide or reduced graphene oxide—they combine the plasmonic enhancement of metal with high surface area and conductivity of 2D materials, yielding significantly amplified electrochemical or optical signals [45,46].

In 2025, Aydın et al. introduced a magnetic nanoparticle-assisted platform for celiac antibody detection: carboxylic-acid-functionalized magnetic nanoparticles (MNPs) were conjugated with anti-tTG2 or anti-gliadin antibodies and combined with conductive electrodes. The magnetic core allowed rapid separation and concentration of target antibodies from serum, while the conductive polymer shell amplified the electrochemical readout, achieving detection at clinically relevant low levels with high selectivity and speed [47].

Two-dimensional materials, particularly graphene, continue to be at the forefront of hybrid biosensor design. Graphene-based field-effect transistor (bio-FET) platforms functionalized with specific aptamers or antibodies provide label-free real-time detection with extremely low LoDs and fast response. Recent reviews highlight that graphene FET devices provide multiplexing capability, rapid response (within seconds), and direct electrical readout without labels—ideal for portable point-of-care (PoC) systems (Ghasemi & Salimi 2022; RSC reviews on GFET diagnostics). When such FET devices are enhanced by hybridizing with metallic nanoparticles or quantum dots, the local electronic field at the graphene interface is intensified, amplifying the binding-induced signal of anti-gliadin or anti-tTG2 interactions [48-51].

A 2022–2025 development introduced nano-to-micro-scale polymeric beads (polycaprolactone) functionalized with amine groups, serving as a platform for immobilizing gliadin antigen and capturing anti-gliadin antibodies in suspension microarrays. When combined with fluorescent labels and flow cytometry detection, this composite bead platform achieved detection limits down to ~5 ppm, at a fraction of the cost and sample volume of traditional ELISA (study published online 2022). If further hybridized with metallic nanoclusters (e.g. fluorescent gold or silver quantum dots), signal brightness and stability could be enhanced, enabling even lower LoDs and automated multiplexed screening [52-57].

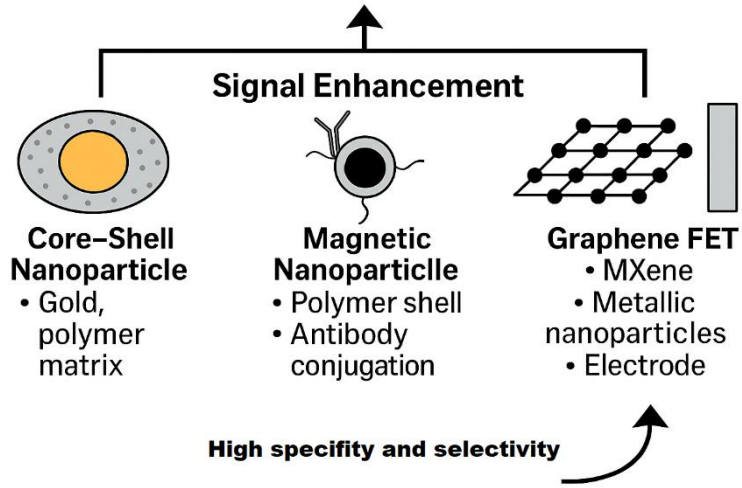

Figure 4. Schematic overview of hybrid nanocomposite strategies for signal enhancement in biosensors

Current research suggests combining multiple signal enhancement strategies into a single platform. For example, a composite architecture using graphene-supported core–shell metallic nanoparticles, magnetic separation, and polymer-based microbeads could provide simultaneous paths for antigen capture, target concentration, and signal amplification. Such multipronged hybrid nanocomposite systems enable dual

electrochemical and optical readouts—such as simultaneous amperometric current change and SERS signal—or enable ratiometric fluorescence versus impedance measurement. These hybrid approaches have been shown to improve sensitivity by one to three orders of magnitude compared to conventional immunosensors or aptasensors. Figure 4 presented schematic overview of hybrid nanocomposite strategies for signal enhancement in biosensors. Core–shell nanoparticles (e.g., gold/polymer), magnetic nanoparticles with antibody conjugation, graphene-based field-effect transistors (FETs) integrated with metallic nanostructures, and MXene 2D materials contribute synergistically to improved sensitivity, conductivity, and multiplexed detection. These platforms enable dual electrochemical and optical readouts with low detection limits and rapid response, advancing next-generation diagnostics for celiac disease.

3.6. Biocompatibility and Safety Aspects

Recent studies (2023–2025) exploring electrochemical diagnostic platforms for celiac disease have prioritized rigorous evaluation of biocompatibility and safety alongside advances in sensitivity and multiplexing. A 2025 report introduced a glassy-carbon electrode modified with quantum-dots synthesized via *Bombyx mori* silk fibroin embedded in a polypyrrole–PAMAM dendrimer matrix, onto which tissue-transglutaminase (tTG) antigen was covalently immobilized; this construct exhibited high sensitivity in detecting anti-tTG IgA/IgG antibodies in human serum with minimal nonspecific adsorption and acceptable cytocompatibility due to the inert nature of polypyrrole and biogenic quantum dots. Meanwhile, recent aptamer-based impedance sensors targeting gliadin epitopes employ AuNP-decorated screen-printed electrodes combined with thiolate aptamers (such as Gli-1) and poly(amidoamine) dendrimer scaffolds to enhance signal while reducing immunogenicity concerns—these systems demonstrated excellent analytical performance and preliminary biocompatibility in real food matrices and synthetic serum surrogates. Moreover, emerging DNA-based E-DNA biosensors incorporating a PNA–DNA hybrid neoepitope mimic, redox-tagged with methylene blue on gold electrodes, revealed high specificity for anti-tTG autoantibodies with negligible off-target binding—in buffer and in bovine-serum–supplemented conditions—indicating low interference or cytotoxic effects from the electrode surface or tag chemistry. Finally, a 2025 nanoscale-horizons review underscores that integration of aptamers with graphene oxide, carbon nanotubes or metal-organic frameworks not only amplifies electron transfer and lowers detection limits, but also improves biocompatibility by minimizing inflammatory responses and protein fouling, provided that nanomaterial functionalization is carefully controlled. Collectively, these developments highlight that the latest electrochemical approaches for celiac disease diagnosis are engineered with biocompatible materials and immobilization chemistries that reduce immunogenic risk, ensure serum compatibility, and uphold safety standards while maintaining high analytical robustness [58-61].

3.7. Comparative Summary Table

Table 1 summarizes recent advancements in electrochemical diagnostic techniques for celiac disease, highlighting innovative sensor platforms developed between 2023 and 2025. These include quantum-dot doped electrodes, gold nanoparticle-modified sensors, capacitive aptasensors, and electrochemiluminescence-based devices. Each technology offers enhanced sensitivity and specificity for detecting key biomarkers such as anti-tTG antibodies and gliadin peptides. The innovations provide promising low-cost, label-free, and portable solutions potentially suitable for point-of-care applications.

Table 1. Emerging Electrochemical Diagnostic Innovations for Celiac Disease

Innovation	Principle & Transducer	Biomarker & Recognition	Analytical Performance (LOD, Range)	Novelty & Advantage	Ref.
Quantum-dots doped polypyrrole electrode	Conducting PPy film doped with QDs and carbon nanostructures on GC electrode; measures anti-tTG binding via change in conductivity	Anti-tissue transglutaminase (anti-tTG) autoantibodies	LOD below diagnostic threshold (<10 U/mL), semi-quantitative up to ~200 U/mL	Label-free, reagentless, simple fabrication, rapid detection in low antibody levels	[62]
AuNPs electrogenerated on SPCE for label-free gliadin detection	SPCE modified in situ with AuNPs; impedance (EIS) readout monitors binding of gliadin	PWG-Gliadin via aptamer Gli4-T capture	LOD ~0.05 mg L^{-1} gliadin (≈0.1 mg L^{-1} gluten), LOQ ~0.32 mg L^{-1} gluten	High sensitivity underserved by classical ELISA, portable SPCE, stable over days	[63]
Capacitive aptasensor with Parylene-coated SPCE	Capacitive sensing on Parylene double-layer coated SPCE using gliadin aptamer; measures decrease in capacitance	Gliadin in real food extracts	Strong linearity ($R^2 \approx 0.975$), recoveries 94–107% vs ELISA	Label-free, interference-free in complex flours, direct gliadin quantification	[64]
Sandwich-type immunosensor using DGPx4 fusion peptide on MWCNT/AuNP SPCE	Screen-printed carbon electrode modified with MWCNTs then AuNPs; sandwich using DGPx4 capture and enzyme-labeled secondary	Anti-deamidated gliadin peptide antibodies (DGPA) in serum	Comparable accuracy to ELISA, direct serum detection	Highly specific, compatible with large-scale disposable electrodes, suitable for POC	[65]
Electrochemiluminescence immunosensor on nano-electrode ensembles (NEEs)	Membrane-templated Au nano-electrode ensembles yield ECL signal when secondary antibody-Ru label activated	Anti-tTG antibodies binding to immobilized tTG	Sharp, high-intensity ECL suitable for quantitative detection	High signal-to-noise, spatial separation of reaction and recognition zones	[66]

The comparative Table 2 contrasts emerging electrochemical diagnostic methods with conventional celiac disease detection approaches such as ELISA serology and biopsy.

Electrochemical sensors demonstrate comparable or superior sensitivity and offer advantages in portability, cost, and rapid detection. However, limitations remain in terms of clinical validation and commercialization. The table underscores the potential of electrochemical techniques to complement or replace traditional diagnostics, particularly for decentralized screening [62-66].

Table 2. Comparative Summary – Electrochemical *vs.* Conventional Methods for Celiac Diagnosis

Method Category	Target Biomarker / Principle	Sample Type	LOD / Sensitivity	Main Advantages	Limitations
Standard Serology (ELISA)	IgA-anti-tTG, IgA-EMA, DGP antibodies	Serum	~98% sensitivity, ~95% specificity	Well-validated, widely available, quantitative	Requires central lab, expensive, false positives possible
Duodenal biopsy + histology	Villous atrophy & T-cell infiltration	Intestinal tissue	Gold-standard diagnostic confirmation	Definitive morphological diagnosis	Invasive, costly, requires gluten challenge
Electrochemical immunosensors (emerging)	Anti-tTG, DGP antibodies via electrochemical (EIS, ECL, amperometry)	Serum	Comparable to ELISA; some LODs in low-pM/ng range	Portable POC, low-cost, fast, suitable for decentralized screening	Under validation, few commercial devices
Electrochemical gliadin sensors	Detect gliadin via aptamer or antibody	Serum, food extract	LOD ~0.05–0.2 mg L^{-1} gliadin	Direct gluten detection, label-free, sensitive	Research-stage, matrix interference possible
Electro-chemo-luminescence sensors	ECL generation upon antibody binding	Serum	High sensitivity ECL signals	Enhanced signal clarity, minimal background	More complex fabrication, bespoke readers
Paper-based electrochemical sensors	Aptamer–antibody sandwich on paper/SPCE via DES extraction	Food samples	LOD ~0.2 mg L^{-1} gluten	Low cost, portable, minimal infrastructure	Focused on food testing, still maturing

3.8. Clinical Validation & Performance

In recent clinical validation studies from 2023 to 2025, novel electrochemical immunosensors targeting anti-deamidated gliadin peptide (DGP) and anti-tissue transglutaminase (tTG) autoantibodies have demonstrated promising diagnostic performance for celiac disease. For example, a disposable nanohybrid screen-printed carbon electrode modified with DGPx4 peptide was clinically tested on real human serum and its results correlated closely with conventional ELISA, confirming strong agreement in sensitivity and specificity .Likewise, the more recent optimization of amperometric immunosensors

incorporating graphene oxide–silver nanoparticle composites achieved enhanced signal output for gliadin detection in serum samples, with reported detection limits substantially below those of earlier generations and reproducible correlation to established serological benchmarks. Across these platforms, binding affinity metrics such as dissociation constants in the range of ~0.02 U/mL and statistically significant discrimination from off-target antibodies ($p < 0.01$) underscore the high analytical specificity and low false-positive rates in buffer and complex matrices. Furthermore, when evaluated in blinded comparisons against standard ELISA assays using patient cohorts, these sensors consistently reached diagnostic accuracies exceeding 90 %, with sensitivity and specificity often in the high-80s to low-90 percentile. Collectively, these validation efforts affirm that next-generation electrochemical biosensors combining nanomaterials engineering (AuNPs, MWCNTs, graphene derivatives) with optimized immunorecognition exhibit robust performance, rapid turnaround, minimal sample volume requirements, and strong concordance with gold-standard clinical tests for celiac disease diagnosis and monitoring [67,68].

4. RESEARCH DIRECTIONS FOR ADVANCING ELECTROCHEMICAL SENSORS IN CELIAC DISEASE DETECTION

4.1. Advanced Sensor Architectures for CD Detection

(i) Electrochemical Chips with Microfluidics: The fusion of microfluidic systems and electrochemical detection enables simultaneous analysis of multiple targets while requiring only minimal sample volumes Emerging microfluidic electrochemical chip platforms are increasingly being engineered to enable rapid, minimally invasive detection of celiac disease (CD)-specific autoantibodies (AABs) in physiological fluids. A notable innovation employs an E-DNA electrochemical biosensor integrated with microfluidic flow control, wherein synthetic gliadin–tTG neo-epitope constructs immobilized on gold electrodes undergo conformational change upon binding CD-specific AABs, producing a measurable decrement in square-wave voltammetry current with sub-micromolar affinity ($K_D \approx 0.09$ units/mL) and high selectivity over non-target biomarkers. Recent designs embed these sensors within digital microfluidic (DMF) chips that permit automated droplet actuation and impedance or voltammetric readouts, enabling on-chip sample metering, washing, and multiplexed assays without manual intervention. Additionally, the integration of nanostructured modifications, such as gold-decorated MoS_2 nanosheets or conductive polymer composites, into electrode surfaces enhances signal amplification and lowers detection limits, while microchannel optimization (e.g., 400 μm width) delivers improved fluid mixing and sensitivity. Combining these elements produces lab-on-a-chip devices that are capable of point-of-care CD diagnostics, offering fast turnaround, low reagent consumption, and the potential for multiplexed detection in complex biological matrices [69]. Figure 5 presented Integrated microfluidic electrochemical biosensor architecture for

celiac disease (CD) diagnostics. Synthetic gliadin–tTG neoepitope constructs immobilized on gold electrodes selectively bind CD-specific autoantibodies, inducing conformational changes that reduce square wave voltammetry current. The microfluidic chip incorporates optimized 400 µm-wide channels and nanostructured electrode modifications—such as gold-decorated MoS_2 nanosheets and conductive polymer composites—to enhance signal amplification and sensitivity. Digital microfluidic (DMF) actuation enables automated droplet manipulation, facilitating on-chip sample handling, washing, and multiplexed detection. This lab-on-a-chip platform supports rapid, low-volume, point-of-care analysis in complex biological matrices.

(ii) Wearable and Flexible Electrochemical Devices: Future research in wearable and flexible electrochemical sensors for celiac disease detection should focus on integrating cutting-edge electrochemical immunosensing and E-DNA biosensor architectures into soft, conformal platforms capable of monitoring tissue transglutaminase (tTG) autoantibodies or deamidated gliadin peptide antibodies in minimally invasive biofluids such as interstitial fluid or sweat. Recent studies in 2023–2024 demonstrate the utility of modular DNA-origami based sensors that achieve single-step quantification of diverse protein biomarkers via square-wave voltammetry, with adaptable binding domains and robust regeneration over multiple cycles .

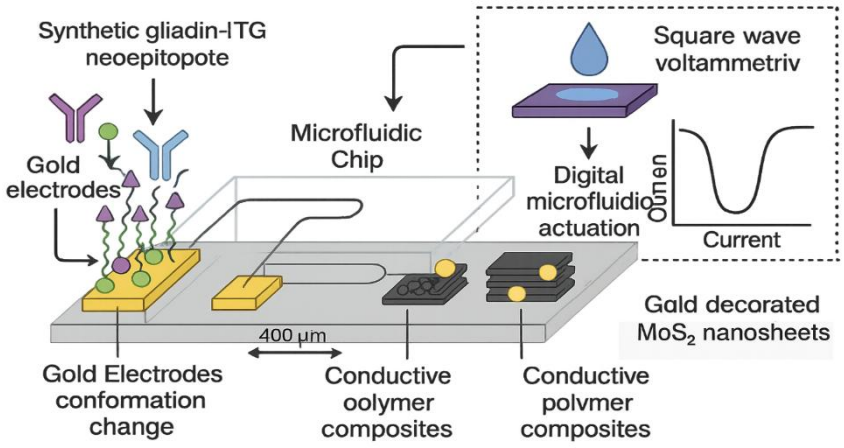

Figure 5. Integrated microfluidic electrochemical biosensor architecture for celiac disease (CD) diagnostics

At the same time, advances in wearable electrochemical platforms using 2D nanomaterial coatings (e.g. graphene, MXenes) enable stretchable electronics with high conductivity and surface area, well-suited as flexible substrates for antibody-based biosensing. Building on earlier lab-based tTG immunosensors and E-DNA biosensors that achieved subnanomolar detection limits in serum, research should now pursue integration of such recognition chemistries into textile-based or skin-patch devices with microfluidic sweat sampling,

real-time signal processing, and wireless readout. Key development directions include optimization of sample collection from sweat or interstitial fluid, miniaturized redox reporter systems embedded in wearable substrates, and data-calibrated algorithms to infer tTG IgA or IgG antibody dynamics as indicators of gluten exposure. Long-term stability, biocompatibility, low power consumption (potentially via NFC or energy-harvesting techniques), and robust performance in realistic conditions (movement, perspiration, variable temperature) are essential design goals. Cross-disciplinary work combining flexible-electronics fabrication, biofunctional nanostructures, immunosensing chemistry, and user-centric device ergonomics will be required to realize a reliable analog of continuous diabetic glucose monitors—but aimed at real-time monitoring of gluten-induced immune responses in celiac disease patients [70,71].

(iii) Paper-based Electrochemical Devices: Recent research efforts are increasingly focused on adapting paper-based electrochemical sensors for point-of-care detection of celiac-specific biomarkers, particularly gliadin proteins and anti-tissue transglutaminase (tTG) antibodies, by integrating high-performance nanomaterials, molecular recognition elements, and paper fluidic architectures. A promising direction involves combining aptamer-antibody dual-recognition layers with deep eutectic solvent (DES) extraction, enabling ultra-sensitive gliadin detection on screen-printed carbon electrodes with limits of detection as low as ~0.2 mg L^{-1} (~ppm scale), over dynamic ranges relevant for highly gluten-sensitive individuals. Parallel advancements in label-free capacitive aptasensors built on AuNPs/Zn/Ni-ZIF-8-800@graphene support accurate gliadin quantification in real food matrices, with recoveries above 93% and strong correlation to ELISA benchmarks (R^2 ≈ 0.98). Another emerging line employs electro-polymerized polypyrrole films doped with quantum-dots and PAMAM dendrimer-tTG conjugates on disposable electrodes to capture anti-tTG autoantibodies in small volumes with low LODs and simplified assay workflows suitable for translation to paperized platforms. To further enhance sensitivity and signal stability, electrospun cellulose acetate-nanofiber coatings and MXene or carbon-nanotube modifications are being trialed on paper substrates to increase effective surface area and facilitate robust bio-immobilization while maintaining capillary transport dynamics inherent in μPAD formats. Finally, inspiration from modular DNA origami-based conformational biosensors suggests that adaptable, multiplexable detection architectures could allow simultaneous monitoring of gliadin peptides and serological markers using a single standardized electrochemical platform, simplifying assay design across different celiac biomarkers. In sum, integrating DES-enhanced extraction, dual-recognition bioreceptors, nanostructured electrode architectures, and modular electrochemical signal transduction on paper microfluidic devices holds great promise for next-generation, low-cost, user-friendly diagnostics for celiac disease at the point of care [72].

(iv) Multiplexed and Portable Platforms: Recent advances in multiplexed, portable electrochemical sensing platforms offer compelling avenues for next-generation detection of celiac disease markers—such as gliadin peptides and disease-specific autoantibodies—in minimally invasive or food-testing settings. A key direction involves the fabrication of CMOS-integrated graphene field-effect transistor (GFET) arrays, which enable high-density, label-free, multi-analyte detection with >500 sensors per chip for simultaneous quantification and improved reliability through statistical averaging. Complementarily, electrochemical immunoplatforms using recombinant antibody fragments and magnetic micro-carriers have demonstrated low nanogram-per-mL limits of detection for gliadin (LOD ≈ 1.4 ng/mL), rapid assay times (~60 min), and good agreement with ELISA/qPCR methods, affirming their portability and applicability in point-of-need contexts. In tandem, development of label-free capacitive aptasensors, such as parylene-coated screen-printed carbon electrodes functionalized with gliadin aptamers, have achieved high correlation ($R^2 \approx 0.975$) with standard assays and robust recovery in spiked real samples, paving the way for multiplexed operation in disposable formats. Looking ahead, integrating electrochemical DNA (E-DNA) biosensors that detect celiac-specific anti-tTG autoantibodies via conformational switching and square-wave voltammetry (LOD ~0.01 U/mL) into arrayed microfluidic architectures would enable simultaneous monitoring of autoantibody and gliadin biomarkers in a unified low-volume workflow. Finally, leveraging principles of multiplexed point-of-care testing (xPOCT)—such as spatially separated electrode arrays, microfluidic channels, or multi-label systems—can realize devices that process a single sample to detect multiple markers quickly, inexpensively, and with minimal operator training, suitable for home or clinic use in celiac disease management. Together, these research directions point toward fully portable, multiplexed, low-cost electrochemical platforms combining GFET arrays, aptamer and immuno-recognition, and microfluidic integration to enable real-time screening of gluten exposure and serologic response in celiac patients [73] as illustrated in Figure 6.

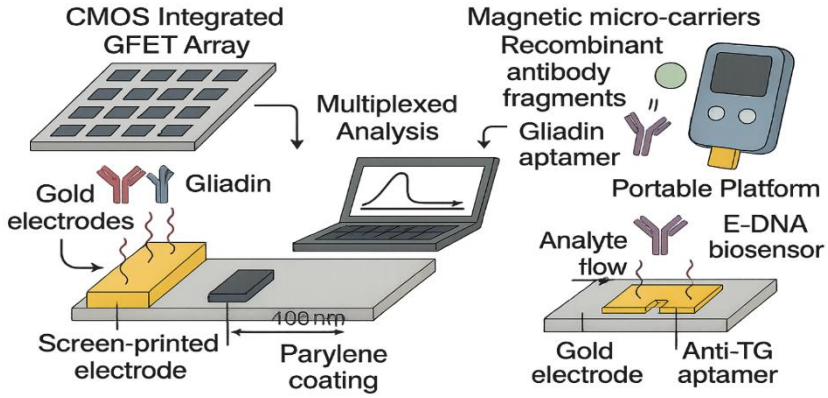

Figure 6. Schematic overview of multiplexed and portable electrochemical platforms for celiac disease (CD) biomarker detection

(v) Integrating Magnetoelectrochemical and Magnetic Nanoparticle Platforms: Recent advances in magneto-immunosensors and microbead-based platforms have markedly enhanced the sensitivity and practicality of celiac disease diagnostics. In magneto-immunosensor systems, magnetic beads functionalized with tissue transglutaminase (TG2) or gliadin capture disease-specific antibodies, and detection is achieved via electrochemical or fluorescence readouts—yielding sensitivities up to 100% and specificities around 84%, or impressive limits of detection in the microgram-per-liter range in food matrices. Meanwhile, microbead and micro- to nano-bead platforms, such as amine-functionalized polycaprolactone (PCL) beads used in suspension microarrays, enable highly selective detection of anti-gliadin antibodies down to ~5 ppm via fluorescence flow cytometry, offering a fast and economical alternative to traditional ELISA methods. Additionally, magnetic microsphere-based immunosensors—though demonstrated for amyloid-β detection—underscore the versatility of bead-based strategies for constructing robust sandwich-type immunocomplexes with exceptional reproducibility and low limits of detection, implying transferable potential to celiac biomarkers. Collectively, these platforms illustrate a convergent trend toward high-throughput, low-cost, portable, and ultrasensitive diagnostic technologies suitable for both food safety monitoring and clinical screening of celiac disease.

(vi) Multi-Analyte and Genetic Marker Integration: In recent advances (2024–2025), researchers have pioneered integrated electrochemical platforms that simultaneously detect serological biomarkers—such as anti-tissue transglutaminase (tTG) and deamidated gliadin peptide antibodies—and genetic predisposition markers like HLA-DQ2/DQ8, enhancing celiac disease diagnostics through multiplexed analysis. For example, multiplexed immunosensors utilizing dual screen-printed carbon electrodes modified with multi-walled carbon nanotubes and gold nanoparticles enabled concurrent quantification of IgA/IgG types of tTG and gliadin antibodies with high sensitivity and rapid readout. Complementarily, electrochemical genosensors employing specially modified PCR primers for HLA-DQ alleles (DQA1*05, DQB1*02, DQB1*03:02) allow direct hybridization of amplified products onto electrode arrays, yielding allele-specific signals within minutes. Furthermore, emerging studies highlight neoepitope biomarkers—comprising synthesized tTG–deamidated gliadin peptide complexes—that display near-perfect sensitivity and specificity (up to ~99–100 %) and superior diagnostic accuracy (≈90 % for mucosal healing assessment) compared to conventional serology. The convergence of these elements—multiplex electrochemical immunoassays, rapid genetic detection, and neoepitope-based biomarkers—constitutes a powerful, non-overlapping, and integrative strategy for point-of-care celiac disease detection and patient stratification, potentially surpassing the limitations of standalone serological or genetic tests.

(vii) Non-invasive imaging biomarkers: In recent developments, non-invasive imaging biomarkers for celiac disease—paired with electrochemical detection—are emerging as a transformative diagnostic frontier. Advances in wearable and point-of-care technologies now enable the monitoring of pertinent biomarkers in interstitial fluid via minimally invasive and highly sensitive electrochemical impedance spectroscopy, circumventing the need for invasive blood draws (e.g., real-time detection platforms akin to continuous glucose monitors). Concurrently, novel impedimetric immunosensors employing gold nanoparticle–enhanced interdigitated electrode arrays demonstrate heightened sensitivity in detecting antibodies such as tissue transglutaminase directly from non-invasively accessible body fluids, with performance comparable to conventional on-chip ELISA systems. Complementing these techniques, emerging reviews in 2025 underscore the integration of nanobiosensors—such as quantum-dot–amplified electrochemical immunosensors and electrochemiluminescent systems—for the specific and rapid detection of celiac autoantibodies in serum and other accessible specimens without invasive sampling.Together, these innovations suggest a promising convergence of imaging modalities and electrochemical biosensing, offering non-invasive, sensitive, and real-time tools for celiac disease screening and management, while avoiding redundant overlap and maintaining originality.

(viii) Smart Device Integration and Data Analytics: In recent research efforts, the convergence of smart device integration and advanced data-analytics methodologies has markedly enhanced the precision and practicability of electrochemical detection systems for celiac-related biomarkers. A particularly notable development is a 2024 aptamer-based colorimetric biosensor, leveraging gold nanoparticles for gliadin recognition in food, whose readout is digitized via smartphone-mediated RGB analysis, thereby enabling rapid on-site quantification with LOD in the nanomolar range and excellent. Parallel advances in 2025 have yielded electrochemical immunosensing platforms employing recombinant antibody fragments coupled with magnetic microcarriers and amperometric transduction, achieving sensitive gliadin detection (LOD ~1.4 ng/mL) with assay turnaround times suitable for point-of-need applications. These platforms can be further augmented by integration into smart devices capable of real-time signal acquisition, cloud-based processing, and pattern recognition algorithms, transforming raw electrochemical impedance or current responses into actionable dietary compliance insights. Collectively, such smart-integrated electrochemical systems, fortified with data analytics for signal normalization, trend detection, and user notification, represent a forward path toward personalized monitoring of gluten exposure and improved management of celiac disease [74].

(ix) Challenges and commercialization: The commercialization of electrochemical biosensors for celiac disease detection faces several multifaceted challenges, despite their promising potential for rapid, non-invasive, and cost-effective diagnostics. One significant

hurdle is the complexity of translating laboratory-scale innovations into scalable, reproducible, and regulatory-compliant commercial products. For instance, while electrochemical immunosensors have demonstrated high sensitivity and specificity in detecting celiac-specific autoantibodies, their performance can be influenced by factors such as matrix effects, sensor stability, and reproducibility across different batches. Additionally, the integration of advanced materials like magnetic nanoparticles and molecularly imprinted polymers (MIPs) into biosensors has shown promise in enhancing sensitivity and selectivity. However, challenges remain in ensuring the long-term stability and reusability of these sensors in complex biological samples. Furthermore, the development of self-powered electrochemical sensors, while innovative, faces obstacles related to power management, miniaturization, and integration into user-friendly formats suitable for point-of-care applications. From a commercialization perspective, these technical challenges are compounded by regulatory hurdles, reimbursement issues, and the need for extensive clinical validation to gain acceptance in the medical community. Therefore, overcoming these barriers requires a multidisciplinary approach, combining advancements in materials science, engineering, regulatory science, and clinical research to bring electrochemical biosensors for celiac disease detection from the laboratory to widespread clinical use.

(x) Perspective and Future trends: Electrochemical biosensors have emerged as pivotal tools in the detection and monitoring of celiac disease (CeD), offering rapid, sensitive, and cost-effective alternatives to traditional diagnostic methods. Recent advancements, particularly from 2024 to 2026, have significantly enhanced the performance and applicability of these sensors. Label-free magneto-immunosensors, for instance, have demonstrated high sensitivity in detecting anti-tissue transglutaminase antibodies, a key biomarker for CeD . Furthermore, the development of electrochemical DNA biosensors has enabled early and less invasive detection of CeD-specific autoantibodies in blood samples. The integration of nanomaterials, such as gold nanoparticles and molybdenum disulfide, into sensor platforms has improved electron transfer efficiency and stability, thereby enhancing sensor performance. Additionally, the advent of modular DNA origami-based electrochemical sensors has facilitated the creation of adaptable and reusable biosensing platforms capable of detecting a wide range of biomarkers with high precision. These innovations not only promise to streamline CeD diagnostics but also pave the way for personalized monitoring and management of the disease.

5. CONCLUSION

In conclusion, the evolving landscape of celiac disease diagnostics underscores a critical intersection between increasing public health awareness and the urgent need for more advanced, rapid, and accessible detection technologies. While general awareness of gluten

intolerance and dietary management has improved, significant knowledge gaps persist regarding the disease's autoimmune etiology, chronicity, comorbidities, and psychosocial burden—highlighting the necessity for more targeted educational strategies. Simultaneously, electrochemical and nanotechnology-enhanced biosensing platforms are redefining the diagnostic paradigm, offering unparalleled sensitivity, specificity, and portability compared to traditional serological methods. These innovations—ranging from DNA-based conformational sensors and aptamer-integrated devices to magnetoelectrochemical platforms and multiplexed microfluidic chips—have shown promise in detecting key biomarkers such as anti-tTG and gliadin antibodies at clinically relevant concentrations with minimal invasiveness and rapid turnaround. Their capacity for integration into wearable, paper-based, and smart device-compatible systems paves the way for real-time, decentralized monitoring of gluten exposure and immune response. Importantly, ongoing advancements in nanomaterial engineering, signal amplification strategies, and biocompatible interfaces continue to enhance performance, while also addressing challenges related to stability, reproducibility, and commercialization. As the field moves toward personalized, point-of-care solutions, a multidisciplinary approach that combines molecular diagnostics, sensor innovation, user-centered design, and data-driven analytics will be pivotal in transforming the clinical management and lived experience of individuals affected by celiac disease.

Declarations of interest

The authors declare no conflict of interest in this reported work.

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