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Food allergy: From mechanisms to management - a review of pathogenesis, novel diagnosis and dietary regulation strategies

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ABSTRACT: As a global public health challenge, food allergy affects hundreds of millions of individuals worldwide. This review provides a recent advance in the field of food allergy, including developments in diagnostic techniques, allergy evaluation methods, and management strategies. In addition, the modulation of food allergies by natural active substances in foods is also emphasized. Combining bioinformatics diagnostics with regulation of dietary actives holds great promise for allergy prevention. Furthermore, evaluation methods that combine dynamic gastrointestinal digestion modeling with bioinformatics provides new ideas for revealing the structural stability of allergens. Finally, enhanced food allergy management has further improved the effectiveness of allergy prevention. This review provides a better understanding and novel insights into the prevention and control of food allergies, as well as explores the potential applications of natural bioactive substances in food allergy management strategies.

Keywords: food allergy; diagnosis; dietary regulation strategies; management

1. Introduction

Food allergy has been highlighted as an emerging public health concern, as evidenced by recent epidemiological data (Warren et al., 2020). It results from adverse reactions triggered by the consumption of specific foods, which occur due to a lack of appropriate immune tolerance (Bi et al., 2024). According to the statistics from the Food and Agriculture Organization and the World Health Organization (WHO), more than 90% of food allergies are caused by cereals containing gluten, milk, eggs, fish, crustacean shellfish, peanuts, tree nuts (Liu et al., 2022). In recent years, the classification of food allergens has also been expanding. Starting in 2023, the U.S. Food and Drug Administration will require that sesame be listed as the ninth allergen in prepackaged foods (Zeng et al., 2024). Other food sources that are increasingly classified as novel allergens in regulatory frameworks, defined in this review as allergens linked to emerging dietary patterns or newly emphasized exposure contexts, such as pulses, fruits, and insects are summarized in Table S1 (Carrera et al., 2024). Food allergy has emerged as a critical food safety concern that the food industry must urgently address and resolve.

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Depending on the pathogenesis, food allergies can be categorized into immunoglobulin E (IgE)-mediated, non-IgE-mediated, and mixed-mediated reactions. From an epidemiological and clinical perspective, IgE-mediated food allergies are the most relevant immune-mediated disorders triggered by food (Cabanillas et al., 2021). Typical symptoms include skin disturbances, respiratory tract involvement, gastrointestinal tract issues, and cardiovascular abnormalities. Recently, there have been new developments in research and clinical guidelines related to food allergies (Bartha et al., 2024). A better understanding of the immune mechanisms, diagnosis, treatment, and prevention of this condition is crucial for identifying target therapies that can alter the current epidemiological landscape.

The global prevalence of food allergies has increased dramatically, affecting over 220 million people worldwide, according to recent epidemiological reports. This trend carries profound implications for individuals, society, and the economy (Wang et al., 2025; Satitsuksanoa et al., 2021). Food allergies have a profound impact on patients' quality of life, presenting both physical and psychological challenges, while also placing considerable financial strain on their families. Currently, no widely accepted therapeutic approaches exist to completely eliminate food allergies. Recent studies have extensively explored the immunomodulatory functions of natural bioactive substances, which demonstrate anti-allergic effects and show promise for preventing and treating food allergies (Zhang et al., 2022).

Therefore, this review systematically examines recent advances in food allergy research. We outline the characteristics of major and emerging novel food allergens, with emphasis on contemporary diagnostic methods and allergenicity assessment approaches. Furthermore, we highlight the potential of natural anti-allergic substances in preventing and mitigating food allergies, while clarifying current limitations and future prospects for allergy management strategies. Our objective is to advance effective food allergy prevention and control, providing insights for safety management and novel treatment development. This review draws on 587 published studies—including research articles, reports, and reviews—with Fig. 1 illustrating the selection procedure. Keywords included food allergy, allergy pathogenesis, allergy diagnostic methods, allergy evaluation methods, dietary substances, and management.

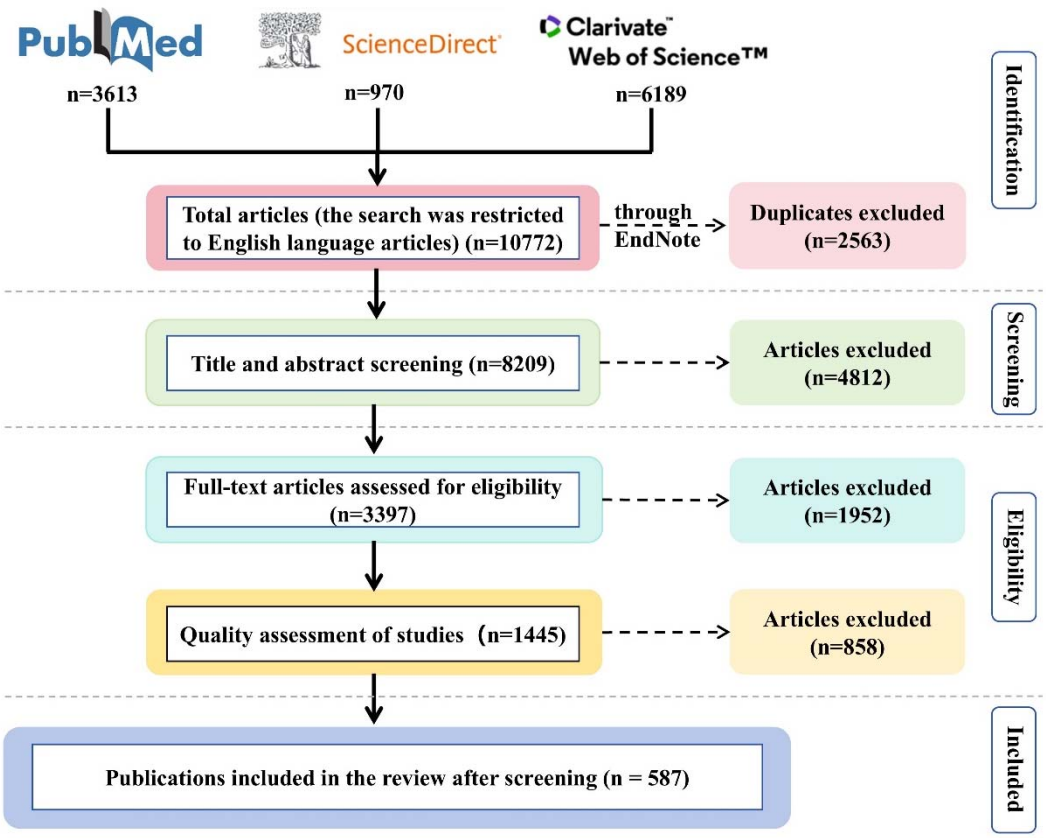

Figure 1 Chart of process of selection studies.

2. Pathogenesis and diagnosis of food allergy

2.1 Pathogenesis

Based on the different immunologic mechanisms, food allergy can be categorized into IgE mediated, non-IgE mediated and mixed mediated types. Among these, IgE mediated hypersensitivity manifests as immediate hypersensitivity, representing the most common type of food allergy (Chinthrajah et al., 2016). This IgE mediated immune response is primarily characterized by two distinct phases: the sensitization phase and the effector phase.

During the sensitization phase, the epithelial barrier is damaged, leading to an increase in the permeability of food protein antigens, which induces epithelial cells to secrete cytokines, such as IL-25, IL-33 and thymic stromal lymphopoietin (Khodoun et al. 2018). Th2 cells secrete IL-4, IL-5, and IL-13, with IL-5 recruiting eosinophils and IL-4 and IL-13 inducing B cells to transform into plasma cells and produce large amounts of allergen-specific IgE antibodies. These IgE antibodies sensitize the body by binding to high-affinity receptors on the surface of mast cells and basophils (León & Ballesteros-Tato, 2021). Upon re-exposure to the same food antigen, allergen-derived epitopes bind to sIgE on the surface of immune effector cells, leading to IgE cross-linking (Figure 2). This process triggers the release of inflammatory mediators, including histamine and leukotrienes, which elicit a range of physiological responses. The primary clinical manifestations include gastrointestinal symptoms (such as nausea, vomiting, and diarrhea), cutaneous symptoms (erythema, urticaria, pruritus, and eczema) and respiratory symptoms

(sneezing, coughing, wheezing, and dyspnea). In cases of severe allergic reactions, patients may experience hypotension, arrhythmias, and potentially progress to anaphylactic shock (Krishnaswamy, 2021).

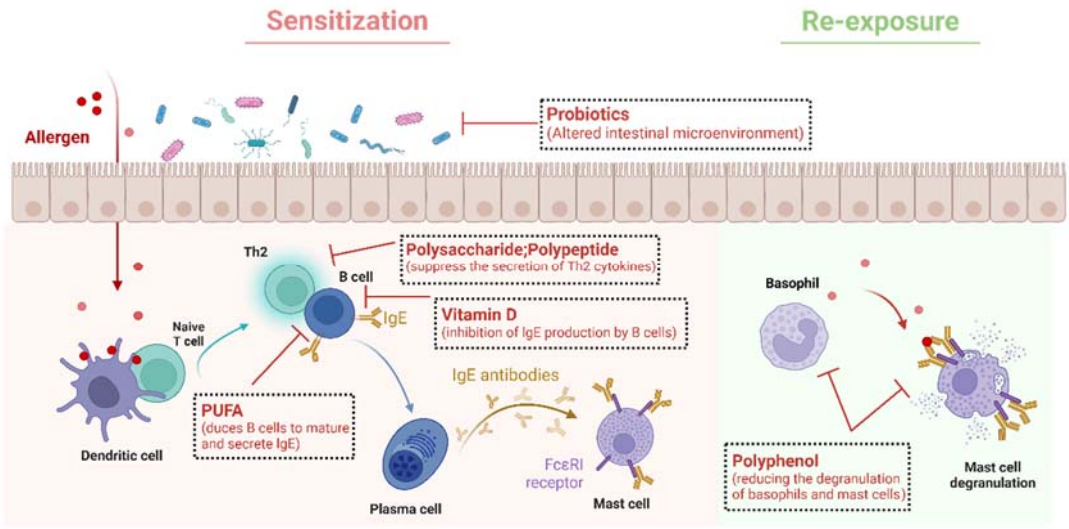

Figure 2 Mechanisms of food allergy.

In recent years, nearly 20% of the population in industrialized countries has reported adverse food-related reactions (Onyimba et al., 2021). In addition to food allergy, food intolerance can also trigger discomfort (Nwaru et al., 2021). Although both conditions can cause post-ingestive symptoms that negatively affect quality of life, particularly in terms of digestive manifestations, they fundamentally differ in the underlying mechanisms (Gargano et al., 2021). Food allergy involves an immune-mediated response, typically with rapid onset and potential for severe reactions like anaphylaxis. Conversely, food intolerance is non-immune in origin, characterized by delayed symptom onset and absence of life-threatening complications (Namazova-Baranova et al., 2024). Given that no comprehensive cure has been documented, the most effective preventive measure is the partial or complete exclusion of such foods from one's daily diet (Muthukumar et al., 2020). Consequently, the accurate identification of allergens and the correct diagnosis of sensitization play a crucial role in allergy prevention, patient dietary guidance and allergy management.

2.2 Diagnosis

2.2.1 Traditional diagnosis methods

There are standardized criteria for the diagnosis of IgE-mediated food allergy (Table 1). The oral food challenge (OFC) is a common diagnostic medical procedure that involves gradually administering the suspected allergenic food to the patient and monitoring for the development of allergic symptoms (Kuźniar et al, 2024). It includes open food challenge, double-blind placebo-controlled food challenge (DBPCFC), stepwise food challenge, single dose food challenge and cross-food challenge. According to Santos et al. (2023), OFC is considered the gold standard for confirming or ruling out food allergies, especially in cases where IgE sensitization test results are unclear.

Table 1 Common and novel allergy diagnostics.

Diagnosis methods	Advantages	Disadvantages	application	references
OFC	It is the “gold standard” for diagnosing food allergies.	Risk of allergic reactions, including anaphylaxis; time-consuming and requires medical supervision.	Identification of food allergens; reassessment of food allergies; screening for nonspecific food reactions.	(Calvani et al., 2019); (Santos et al., 2023)
BAT	High sensitivity and specificity, wide range of diagnostics, high security.	Insufficient standardization, non-IgE-dependent allergy limitation.	Diagnosis of Food Allergy; Evaluation of Drug Allergy; Study and Diagnosis of Allergic Asthma; Supplement to the Diagnosis of Specific IgE.	(Santos et al., 2021); (Santos et al., 2023)
SPT	Fast (usually 15-20 minutes for results). High sensitivity and specificity for common allergens. Multiple allergens can be detected at the same time.	May be irritating to the skin and may cause mild pain or localized reactions. Subject to antihistamine medication and patient's skin condition. Severe allergic reactions may occur (rare). Not suitable for patients with severe eczema or other skin conditions.	Diagnosis of food allergies; inhalant allergen testing; screening for drug allergies; diagnosis of insect venom allergy.	(Ansotegui et al., 2020); (Santos et al., 2023)
ELISA/WB	High sensitivity and specificity; simple and rapid; quantitative; suitable for mass screening.	High sample quality requirements; specific antibodies required; cross-reactivity issues; limited assay range; Limited sensitivity and specificity.	Diagnosis, testing and evaluation of allergic diseases; cytokine testing.	(Elisyutina et al., 2019)
sIgE	Unaffected by skin conditions or medications (e.g. antihistamines) and safer, no allergen exposure required. Can be used in patients who are unable to perform skin prick tests (e.g., patients with severe eczema or infants).	The test is expensive. Results may not be completely accurate and are prone to false positives or false negatives. Less sensitive, especially for low-level allergic reactions.	Diagnosis of food allergies; Detection of common inhalant allergens; Drug allergy assessment; Diagnosis of insect venom allergy.	(Ansotegui et al., 2020)
Epigenomic	Uncovering the genetic basis, precise individualized medicine, early diagnosis and prevention.	Results may not be completely accurate and are prone to false positives or false negatives.	Allergen screening; immune response studies; biomarker development; drug target discovery.	(Dhondalay et al., 2018)
Transcriptomics	Comprehensive and high-throughput; reveals molecular mechanisms; efficient biomarker screening; can be used for different sample types.	Complexity of data interpretation; interference of environmental and genetic factors; influence of technology and experimental conditions; cross-individual differences.	Study of the molecular mechanisms of allergic reactions; allergen recognition; biomarker discovery; regulatory mechanisms of immune responses.	(Zhang et al., 2022)
Proteomics	Directly reveals key proteins in allergic reactions; high-throughput analysis; biomarker screening; protein	Complex gene-environment interactions, difficult data interpretation, diversity and population differences.	Research on molecular mechanisms of allergic reactions; identification of allergens; research on allergic immune tolerance; targeted therapy and	(Goleva et al., 2020)

	modifications can be analyzed simultaneously.		drug development.	
Metabolomics	Systematic and comprehensive; early diagnosis and disease monitoring; reflecting the metabolic state of the immune system; providing new therapeutic targets.	Dynamic changes and time dependence; interference from environmental and genetic factors; difficulty in detecting low-abundance metabolites; experimental conditions and technical limitations.	Biomarker discovery of allergic reactions; molecular mechanism studies of allergic reactions; allergen characterization; assessment of therapeutic response.	(Ho, et al., 2021)
Microbiomics	Reveals biological mechanisms of allergy; allows for non-invasive studies.	Complexity of data analysis; complex relationship between microbes and immune response; high individual variability.	Research on the occurrence mechanism of allergy; research on allergic immune tolerance; allergen identification and diagnosis; prevention and intervention of allergic diseases.	(Shu et al., 2019)

DBPCFC requires blinding of both patients and clinicians to whether the administered substance is the allergen or placebo. Crucially, both must be indistinguishable in appearance and flavor. This design minimizes subjective bias, establishing DBPCFC as the most rigorous diagnostic method. It is reserved for ambiguous open OFC results or research settings requiring objective endpoints. However, DBPCFC entails significant time and resource commitments (6-8 hours of nursing observation) and carries anaphylaxis risk (Wong & Santos, 2024). Additionally, there exists considerable variation across trial design, providers, and academic sites posing substantial challenges to the standardization of DBPCFCs.

Allergen-specific IgE (sIgE) assays are readily available in clinical practice and are commonly used to assess sensitization to specific food allergens. However, elevated sIgE levels primarily reflect sensitization rather than clinical reactivity and do not necessarily correlate with reaction severity or individual threshold (Santos et al., 2023). As a result, it must be evaluated in conjunction with clinical symptoms and other diagnostic test results. Skin prick tests (SPTs) are primary screening tools that are rapid, cost-effective, and widely used in clinical practice. It is capable of detecting multiple allergens simultaneously, but it may cause skin irritation, mild discomfort, or localized reactions. and even trigger severe allergic reactions to those who is sensitive to antihistamines (Ansotegui et al., 2020). OFC is usually used as a reference for predicting allergic reactivity to evaluate the diagnostic effect of SPTs. Clinically, the integration of SPTs results with food sIgE levels has been demonstrated to improve diagnostic accuracy in several studies.

Basophil activation test (BAT) as an in vitro allergen diagnostic test, exhibits high specificity and safety, making it a valuable complement to skin-prick and sIgE tests (Hoffmann-Sommergruber et al., 2016). Studies have shown that using BAT as a second-round diagnostic test following skin-prick and sIgE pre-screening can reduce the number of required diagnostic OFC for peanut, sesame, and cashew by 5-15% (Santos et al., 2021). The BAT can also be used to evaluate the severity of food allergy, monitor the clinical response to immunomodulatory treatments, and detect the release of inflammatory mediators (Santos et al., 2021). Santos et al. (2015) demonstrated that increased basophil activation is associated with a more severe OFC reaction to peanuts. New technologies, particularly those incorporating innovative gating strategies with optimization of storage and automation of measurements and analysis, play an important role in supporting the utility of BAT in predicting and monitoring response to oral immunotherapy (OIT). These advancements also facilitate the potential for routine high-throughput analysis in future applications.

2.2.2 Novel multi-omics approaches

With the advancement of omics technologies, they have become indispensable tools for identifying diagnostic and prognostic markers as well as defining disease endotypes of various diseases and pathologies. In recent years, studies have employed large-scale omics approaches, such as epigenomic and transcriptomics, to identify biomarkers associated with allergic reaction diagnosis, reaction severity, and outcomes during OIT, which bring innovative improvements to standard clinical assays. Importantly, omics technologies are also particularly valuable in identifying patients at risk of developing food allergies in the

future, which will facilitating effective management and potentially enabling the implementation of novel personalized prevention strategies. Novel methods for the diagnosis of food allergy are presented in Table 1.

2.2.2.1 Epigenomic

Epigenomic studies have provided valuable insights into the contribution of gene-environment interactions to disease development. Importantly, epigenetic regulation may influence food allergy development by modulating immune-related gene expression, thereby affecting immune cell differentiation, inflammatory signaling, and immune tolerance (Mijač et al., 2024). At the DNA level, the first retrospective epigenomic association study (EWAS) of food allergy identified differential methylation probes in infant CD4+ T cells diagnosed at 12 months, with pathway analysis indicating enrichment of several genes in mitogen-activated protein kinase signaling pathways (Martino et al., 2014). A cross-sectional EWAS was conducted to investigate the role of epigenetics in the development of milk allergies in children. The study identified significant methylation alterations linked to Th1/Th2 immune regulation. These findings suggest that epigenetic modifications may contribute to food allergy by shaping helper T-cell polarization and downstream immune responses. Notably, the analysis revealed differentially methylated loci not only in classical immune pathways but also in novel biological processes. These included butylamine-related modifications (potentially influencing histamine metabolism) and epigenetic variations in neomycin biosynthesis pathways, which may interact with microbial-derived metabolites. This observation highlights a potential link between epigenetic regulation, metabolic pathways, and host-microbiota interactions in food allergy. EWAS also identified 32 epigenetically significant loci and 14 loci with a false discovery rate (FDR) of less than 10^{-4} associated with epithelial barrier and immune regulation, and most of them overlapped with other allergic diseases such as asthma and atopic dermatitis (Arnau-Soler et al., 2024). Alterations in epithelial barrier-related gene regulation may increase allergen penetration and immune activation, thereby facilitating allergic sensitization. Furthermore, aberrant methylation patterns were observed in genomic regions governing carbohydrate metabolism, suggesting metabolic reprogramming as a potential modulator of allergic responses. Interestingly, several newly identified probes exhibited dual-directional epigenetic changes (hypomethylation and hypermethylation) across distinct genomic regions, highlighting the complexity of epigenetic regulation in food allergy pathogenesis (Martino et al., 2014). Understanding these immunological mechanisms provides a theoretical basis for the development of dietary strategies aimed at modulating allergic responses. Therefore, the study of other epigenetic changes, such as epigenetic changes mediated by histone modification, will help expand our understanding of the molecular evolution of food allergy.

The application of genomics in allergy has greatly enhanced our comprehension of the genetic basis of allergic disease, allowing early identification of allergic risk, personalized treatment strategies and the development of novel therapeutic approaches (Dhondalay et al., 2018). Nevertheless, it faces significant challenges including high costs, intricate data analysis requirements, privacy concerns, and the complex

interplay between genetic information and disease phenotypes. These factors restrict the application of genomics in allergy clinical practice. Therefore, while advancing personalized medicine, it is imperative to carefully address the ethical issues associated with genetic data (Kanchan et al., 2021).

2.2.2.2 Transcriptomics

The main application of transcriptomics in food allergy is on the molecular mechanisms of allergic reactions, including allergen recognition, immune cell activation and regulation of inflammatory responses. Its high-throughput, systematic, and precise features give it a unique advantage in unraveling the molecular basis of allergic reactions. Most importantly, transcriptomics can respond to changes in gene expression over time and space (Xu et al., 2023). By studying the gene expression patterns of cells or tissues under specific conditions, it is possible to reveal key genes associated with food allergy and their regulatory mechanisms and the onset, progression and possible therapeutic targets of allergic diseases. Thus, supporting a comprehensive understanding of the molecular basis of allergic reactions (Daccache et al., 2024). Li et al. (2024) explored the molecular changes in intestinal tissues during the development of cow's milk protein allergy (CMPA) by transcriptomics and quantitative tandem mass spectrometry tagging (TMT)-labeled proteomics analysis, and identified kallikrein B1, a key serine protease in the kallikrein-kinin system involved in inflammatory responses, as a potential therapeutic target. Zhang et al. (2024) utilized transcriptomics to explore the molecular level changes in peanut-allergic children at different reaction thresholds, providing important information to better explore the molecular mechanisms of peanut allergy to develop new therapeutic strategies.

In addition, transcriptomics provides a theoretical basis and practical support for the development of novel therapeutic approaches in food allergy treatment and management. For example, Li et al. (2024) employed transcriptomics to not only elucidate the molecular underpinnings of CMPA, but also to systematically analyze the gene expression profiles of small intestinal tissues in a mouse model of CMPA. Transcriptomics can also provide gene expression data directly related to altered biological functions, as well as in-depth analysis of individual immune cells through single-cell transcriptomics techniques, thereby revealing key biological processes and molecular mechanisms. However, technologies involving possible variability in the correlation between transcriptomic data and other histologic data, as well as the high cost of technologies such as single-cell RNA sequencing, have limited their widespread application (Zhang et al., 2022).

2.2.2.3 Proteomics

Proteomics is the science that studies the expression, modification, interaction and function of all proteins in an organism. In recent years it has played an important role in exploring the disease endotypes and biomarkers in different food allergy populations (Manea et al., 2016). For example, by comparing the protein expression profiles of healthy individuals and allergic patients, researchers can identify key proteins associated with allergy, such as specific allergen-binding proteins, inflammatory factors and

immunoregulatory molecules (Nony et al., 2016). These proteins may not only serve as markers of allergic reactions, but also as potential targets for targeted therapies. Furthermore, the role of post-translational modifications of proteins (e.g. phosphorylation, glycosylation) in allergy has also been elucidated by proteomics (D'Auria et al., 2018). Changes in post-translational modifications often affect the function and stability of proteins and play important regulatory roles in immune cell activation, signal transduction and effector molecule release. For example, mast cells and basophils release histamine by degranulation during allergic reactions, and proteomic analysis can reveal modification changes in key signaling pathways during this process (Goleva et al., 2020).

In the field of allergy treatment, proteomics-based drug target discovery and functional validation can accelerate the development of anti-allergy drugs (Zhang et al., 2022). After screening the signaling pathway proteins or cytokines associated with allergic reactions through proteomics technology, blockers or inhibitors against these targets can be designed to intervene in allergic reactions. Additionally, proteomics can also be used to assess the effectiveness of treatment and monitor drug response, revealing the molecular mechanism of therapeutic intervention and optimizing treatment regimens by analyzing changes in protein expression profiles before and after treatment (López-Pedrouso et al., 2020).

The application of proteomics in allergy research also lays the foundation for the practice of personalized medicine. The occurrence of allergic reactions varies from individual to individual, and proteomics can help reveal the molecular differences between different individuals and provide a basis for individualized treatment (Hoffmann-Sommergruber, 2016). For example, by identifying the allergen profile and inflammatory factor characteristics of a specific patient through proteomic analysis, targeted treatment plans, such as personalized immunotherapy or anti-inflammatory therapy, can be developed.

2.2.2.4 Metabolomics

Metabolomics, as a research method reflecting the composition and content changes of small molecule metabolites in the real-time state of the organism, is an emerging means to find the relative relationship between metabolites and physiological and pathological changes (Spertini et al., 2020). It can reflect the interaction between the immune system and metabolic networks, providing new ideas for the diagnosis and treatment of food allergies (Lee et al., 2024). Spertini (2020) identified serum metabolite profiles in children with food allergies, particularly changes in lipid and amino acid metabolites, by means of metabolomic analysis. These changes may be related to interactions between gut microbiota and may affect immune system functions such as natural killer T cell activity.

Metabolomics has also made outstanding contributions to biomarker discovery and differential diagnosis. Zhang et al. (2024) used metabolomics to reveal metabolic profiles associated with clinical milk allergy and sensitization tolerance, and identified candidate metabolites as phenotypic and diagnostic biomarkers for food allergy. This improves the diagnosis and treatment of milk allergy. Metabolomics may offer new tools for improving food allergy diagnosis in the future, mechanism studies and intervention

strategies by revealing allergy-related metabolic features and pathways, especially in biomarker mining and individualized therapy.

2.2.2.5 Microbiomics

The microbiome refers to the microbial communities colonizing different ecological niches within the human body and their complete genomic information, primarily comprising bacteria, fungi, viruses, and archaea along with their genetic material (Huang et al., 2017). The human gastrointestinal tract represents one of the most complex microbial ecosystems, harboring approximately 10^{14} microbial cells per gram of intestinal contents (Nance et al., 2020). Variations in gut microbiota composition and abundance can markedly influence host metabolic activities, immune homeostasis, and disease susceptibility (Laforest-Lapointe & Arrieta, 2017; Bai et al, 2024). Increasing evidence suggests that gut dysbiosis may elevate the risk of atopic diseases, including food allergies, by disrupting metabolic pathways and immune regulatory networks (Shi et al., 2025).

The gut microbiome undergoes dynamic changes across the lifespan. Microbial diversity generally increases during childhood, particularly before the age of 12, stabilizes in adulthood, and declines in older age (Lynch, 2016). In addition, factors such as pregnancy status, psychological stress, dietary patterns, and medication use (e.g., antibiotics) can substantially shape microbiome composition and function (Gern et al., 2017). Notably, during infancy, early gut microbiota establishment plays a critical role in immune system maturation and is closely associated with the subsequent development of immune tolerance to food allergens (Azad et al., 2015). A three-year follow-up study involving 220 infants with cow's milk allergy reported divergent trajectories of tolerance acquisition in relation to early-life gut microbial features, suggesting an association between microbiome composition and later clinical outcomes (Berni Canani et al., 2016; Canani et al., 2017). In addition, comparative microbiome profiling studies have consistently shown that individuals with food allergy exhibit distinct gut microbial patterns compared with non-allergic controls, including differences in microbial diversity, community structure, and metabolite-associated profiles (Berni Canani et al., 2016).

Collectively, these findings indicate that microbiome signatures are closely linked to food allergy risk, disease phenotype, and immune response status. Microbiomics therefore holds promise as a complementary tool for auxiliary diagnosis, risk stratification, and prognosis evaluation in food allergy research.

Overall, despite the rapid development of multi-omics technologies and their growing application in food allergy research, several challenges remain for their translation from laboratory-based studies to routine clinical practice. These approaches are often associated with high costs, complex data integration, and substantial technical requirements, which currently limit their widespread clinical implementation. In addition, the lack of standardized protocols, reference databases, and validated diagnostic thresholds across different platforms and laboratories poses significant barriers to reproducibility and clinical interpretation. Therefore, further efforts are required to establish standardized workflows and clinically validated

biomarkers before multi-omics approaches can be reliably applied in food allergy diagnosis and management.

3. Food allergenicity evaluation

Based on a clear diagnosis of food allergy, accurate assessment of the sensitization of food proteins is essential for allergen management. In recent years, multidimensional assessment systems based on in vitro digestion models, serological analysis, animal models and bioinformatics analysis have been rapidly developed (Figure 3). These methods provide a scientific basis for food processing optimization and regulatory policy making by resolving protein structural stability, immunogenicity, and cross-reactivity risk.

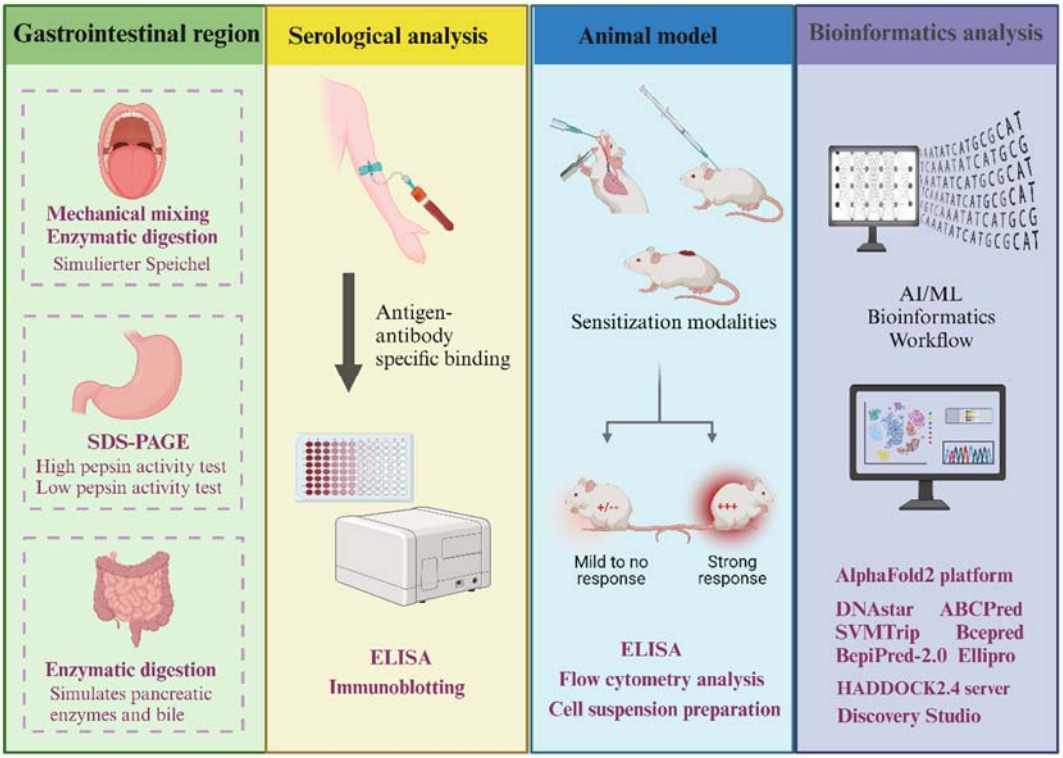

Figure 3 Food allergen assessment methods.

3.1 In vitro gastrointestinal digestive model

The in vitro gastrointestinal digestion test constitutes a critical component of the evaluation system for potential food allergenicity. It enhances the understanding of the characteristics of food allergens and their effects on the human immune system, and has become an indispensable tool in food allergenic risk assessment. In vitro gastrointestinal digestive models are mainly divided into two categories: static digestive models and dynamic digestive models. Static digestion models are favored for their low cost and ease of operation and are suitable for the initial assessment of food allergens (Sensoy et al., 2021). The dynamic digestion model is closer to the digestive environment in human body and is more suitable for studying the digestive process of food allergens (Wang et al., 2023).

3.1.1 Static digestion model

Static digestion model refers to a process that simulate the dynamic changes of food components through the digestive tract and the time changes of enzyme activity under certain conditions (Le Feunteun et al., 2021). The most classical in vitro static digestion methods are the INFOGEST method. Bavaro et al. (2018) investigated the degradation behavior of Ara h 2 under the action of pepsin using a static digestion model and found that the protein has high gastric acid and enzyme stability, suggesting that the digestive stability of Ara h 2 is a key reason for its strong sensitization. Di Stasio et al. (2020) found roasted nuts exhibited enhanced digestibility compared to raw nuts, and also led to the reduction or destruction of known epitopes of more allergens by using a standardized static digestion model in combination with bioinformatics tools.

Despite the important role of static digestion modeling in food allergy research, its limitations cannot be ignored. First, static models cannot simulate the dynamic characteristics of the gastrointestinal tract, such as gastric emptying, peristalsis, and continuous secretion of digestive juices, thus making it difficult to fully reproduce the real digestive process (Brodkorb et al., 2019). Second, static models usually ignore the role of gut microbiota on allergen degradation, which plays an important role in allergen metabolism and immune response. In addition, static models have more fixed settings for digestion time and enzyme concentration, which cannot reflect the physiological differences between individuals (Sensoy et al., 2021). Therefore, future studies can compensate for its shortcomings by incorporating factors such as dynamic modeling or introducing microbiota to more accurately assess the risks and mechanisms of food allergy.

3.1.2 Dynamic digestive model

Although static digestive models are currently widely used in the assessment of food allergens, they oversimplify digestive physiology and fail to simulate the dynamic aspects of digestion. In recent years, researchers have developed a series of dynamic in vitro models order to compensate for the shortcomings of static models. Dynamic digestion models can be computer-controlled during digestion fluid, enzyme, pH, duration, peristalsis, absorption and emptying, etc., closer to the physiological environment in the body (Dixit et al., 2023). Guo et al. (2021) investigated the effects of static and dynamic digestion systems on the digestibility and potential allergenicity of raw shrimp extract. It suggested that the dynamic digestion system may be more accurate in assessing the digestibility and allergenicity of food allergens.

In addition, several studies are employing in vitro digestion models to integrate the target compound with other specific compounds, with the objective of mitigating the induced immune response. A study has demonstrated that phosphorylation treatment combined with in vitro digestion significantly can alleviate allergic reactions to α-lactalbumin, which provides a scientific basis for the development of new strategies to alleviate allergic reactions to milk (Chen et al., 2022). However, it still has some limitations, especially in terms of immune responses, microbiota effects and individual differences, which need to be overcome by further improving the model and experimental design (Wang et al., 2023).

3.2 Serological analysis

The application of serum analytical models in the regulation of food allergy focuses on the characterization of the onset, development, and immune response to food allergy by measuring the levels of specific biomarkers in serum, such as IgE, sIgE and cytokines (Kanagaratham et al., 2018). Due to the complexity of obtaining human allergy serum, most immunoassays are performed using animal allergy serum. Currently, common serological methods include enzyme-linked immunosorbent assay (ELISA) and western blot.

In the research and clinical application of food allergy, ELISA is mainly used to detect IgE antibodies in serum that are associated with allergic reactions, especially specific IgE. sIgE is a key marker in allergic reactions, which usually produce allergic reactions to specific allergens (e.g., peanuts, eggs, milk, etc.) in food allergy patients (Tedner et al, 2022). A study using ELISA to detect specific IgE in peanut allergy patients found a significant correlation between their IgE levels and the onset and severity of allergic symptoms (Datema et al., 2021). Western blotting combines the high resolution of SDS-PAGE with the high specificity and sensitivity of antibodies. Therefore, it is widely used to evaluate antigen-antibody immune activity (Grishina et al., 2017). For example, In an experiment to verify the effectiveness of some non-specific proteases in reducing the allergenicity of raw peanuts, Yu & Mikiashvili, (2020) treated peanut kernels with alkaline protease, papain, neutral sugar and pineapple protease, respectively, and determined the residues of the major peanut allergens, Ara h 1, Ara h 2, and Ara h 6, by sandwich ELISA and SDS-PAGE and compared the allergenicity of treated peanuts with untreated peanuts by western blot. Comparison of the allergenicity of treated and untreated peanuts by western blot showed that these proteases could hydrolyze the major allergens in peanuts and reduce the IgE binding/allergenicity of the soluble and insoluble fractions of peanuts to different degrees.

However, there are individual differences in biomarkers for allergic diseases such as IgE, and some people have low sensitivity to the specific food allergen IgE, thus affecting the accuracy of the test. Moreover, current serologic tests mainly rely on the detection of individual indicators, which cannot fully reflect the body's immune response. Therefore, it must also be combined with other clinical tests to improve the diagnostic accuracy of the disease.

3.3 Animal model

Animal models are extensively utilized to elucidate immune mechanisms, evaluate allergic responses and therapeutic approaches (Nesovic et al., 2024). Researchers can simulate allergic reactions, analyze IgE-mediated immune responses, and study specific responses to different food allergens via animal models. With the rapid development of genetic engineering, mice have been widely used as animal models for the detection of human diseases (Nesovic et al., 2024). Freidl et al. (2017) established a mouse model of fish allergy similar to the human disease and demonstrated that antibodies immunoinduced by hypoallergenic Cyp c 1 mutants prevented allergic reactions in mouse models of fish allergy.

Additionally, animal models provide a pre-validated platform for immunotherapy that can provide detailed data on treatment efficacy, appropriate dosing and side effects, which help optimize immunotherapy regimens and improve the success of clinical treatments to evaluate the efficacy and safety of regimens such as anti-IgE antibodies or desensitization therapies (Kazemi et al., 2023). For example, Shakya et al. (2019) were the first to use peanut protein extract (PE)-coated microneedles to deliver PE into the skin of mice and induced PE-specific immune response, thereby desensitizing the PE allergic immune response in a peanut-allergic mouse model.

However, because of the variability between species, it is not possible to fully apply the results of animal experiments to humans in terms of immune responses and clinical manifestations. (Gonipeta et al., 2015). Moreover, animal experiments are ethically controversial and the high cost and long lead time of animal experiments limits the breadth of their application (Bøgh et al., 2016). Therefore, in order to enhance the reliability and convertibility of studies, it is expected to integrate animal models with complementary approaches such as in vitro experiments and computational modeling in the future.

3.4 Bioinformatics analysis

Bioinformatics is playing an increasing role in the areas of data analysis, genomics research and prediction of allergic diseases, with a wide range of potential applications. High-throughput sequencing technology, data mining technology and bioinformatics are employed to investigate genes associated with food allergies and underlying mechanisms. Bioinformatics technology enables the extraction and analysis of complex biological data to uncover the genetic basis, immune pathways, and environmental interactions associated with food allergies (Wang et al., 2020).

In genomic studies of food allergy, bioinformatic technology reveals genetic markers associated with allergic reactions by comparing genetic differences between allergic and healthy individuals. For example, GWAS have been used to identify susceptibility genes in food allergy, and studies have shown that certain genes, such as IL-4, IL-13 and FCER1A, are closely associated with the development of food allergy (Tamari & Hirota, 2014). In addition, bioinformatics plays a pivotal role in characterizing the molecular structure and sensitization mechanism of food allergens, as well as predicting the allergenic potential of specific proteins, which is essential for advancing the development of novel diagnostic tools and therapeutic approaches for food allergies (López-Pedrouso et al., 2023).

Bioinformatics also plays an important role in the study of immune mechanisms in food allergy. By analyzing the cells and molecules involved in allergic reactions, researchers can elucidate the role of the immune system in food allergy. For example, through RNA-Seq and single-cell sequencing technologies, bioinformatics can help analyze the gene expression profiles of different immune cell types to gain insight into the immunological basis of food allergy (Kumar et al., 2019). These technologies allow researchers to understand the dynamic process of the immune response in a more systematic and precise way, and to explore new therapeutic targets.

However, current analytical tools and platforms still face challenges in data integration and accuracy (Pedrouso et al., 2023). Although bioinformatics can identify potential allergy mechanisms and therapeutic targets, further experimental validation and clinical studies are still needed to translate these theoretical findings into clinical applications (Wang et al., 2020).

4. Dietary immunomodulatory active substances and food allergy

While allergenicity evaluation provides the foundation for understanding and managing food allergy risk, it does not fully explain inter-individual variability in immune responses or disease outcomes. Accordingly, increasing attention has been directed toward dietary factors beyond allergenic proteins themselves. Changes in dietary patterns associated with socioeconomic development and food system modernization have highlighted the potential immunological relevance of non-allergenic food components. Accumulating evidence indicates that specific dietary constituents, such as vitamins, lipids, and antioxidants, can modulate immune function and influence allergic susceptibility and clinical expression, thereby representing potential complementary approaches for food allergy management (Yang et al., 2022). (Table 2)

Table 2 Summary of immunomodulatory active substances modulating food allergy

Dietary Immunomodulatory active substances	Experimental model	Main immunomodulatory mechanisms	References
Phenolic compounds	In vitro allergen-polyphenol interaction studies using peanut allergen Ara h 1 and milk allergen *β*-lactoglobulin	Modify allergen structure and mask IgE-binding epitopes, reducing IgE-binding capacity of allergenic proteins.	(He et al., 2020); (Zhang et al., 2024)
Polysaccharides	OVA-induced BALB/c mouse model of food allergy	Promote Treg differentiation, suppress Th2 responses, inhibit mast-cell degranulation, and modulate gut microbiota.	(Lee et al., 2018); (Li et al., 2023); (Murphy et al., 2020); (Olsthoorn et al., 2021)
Vitamins (vitamin D, vitamin A)	Human observational studies in infants with food allergy; food allergy mouse models	Promote immune tolerance by regulating Tregs and Th1/Th2 balance, reducing IgE production, and maintaining intestinal barrier function.	(Allen et al., 2013); (Maeta et al., 2020)
Dietary immunomodulatory active substances	Experimental model	Main immunomodulatory mechanisms	References
Peptides	Cow's milk allergy mouse model; peptide immunotherapy studies	Induce antigen-specific immune tolerance through Treg activation and suppression of allergen-specific IgE; reduce Th2 cytokines and effector cell activation.	(Meulenbroek et al., 2013); (Lozano-Ojalvo and López-Fandiño, 2018)
Polyunsaturated fatty acids (PUFAs)	Food allergy mouse model (dietary PUFA supplementation studies)	Suppress pro-inflammatory cytokines, reduce Th2 responses, enhance Treg activity, and regulate omega-6/omega-3 lipid mediator balance.	(Sartorio et al., 2021); (Gardner et al., 2020)
Probiotics	Clinical studies in infants with cow's milk allergy; food allergy mouse models	Promote oral tolerance by modulating gut microbiota and enhancing Treg-mediated immune regulation.	(Berni Canani et al., 2016); (Canani et al., 2017); (Kreft et al., 2020); (Gu et al., 2023)

4.1 Phenolic compounds

Phenolic compounds are naturally occurring antioxidants with at least 10,000 chemical constituents that are widespread in the plant kingdom such as fruits, tea, coffee and vegetables (de Araujo et al., 2021). Common polyphenols include epigallocatechin gallate (EGCG), caffeic acid, chlorogenic acid (CHA), proanthocyanidins, quercetin and others (Pi et al., 2023). In the recent years, a large number of studies have shown that phenolic compounds possess a variety of biological activities, including antibacterial, antifungal, anti-inflammatory, antioxidant, immunomodulatory, antidiabetic, anticancer, anticoagulant and neuroprotective properties (Sahraeian et al., 2024).

Zhang et al. (2024) demonstrated that polyphenols can effectively reduce the allergenicity of *β*-lactoglobulin by altering its conformational structure, providing a potential non-thermal treatment strategy for alleviating milk allergy. He et al. (2020) investigated the covalent coupling of EGCG and CHA, with the major peanut allergen Ara h 1. The results showed that this coupling significantly reduced the IgE-binding capacity of Ara h 1 by masking or disrupting IgE epitopes.

Although the ability of polyphenols to modulate the epitopes of sensitized proteins through covalent or non-covalent interactions provides a new strategy for food desensitization technology, its practical application still faces several challenges. The reaction efficiency of polyphenols with proteins is affected by dynamic conditions such as temperature, pH, and oxygen concentration, and there are significant specificities in different polyphenol-protein combinations (e.g., the inhibitory effect of EGCG on the sensitization of *β*-lactoglobulin is superior to that of other systems) (Pi et al., 2023). Non-covalent complexes are susceptible to dissociation by perturbations in the processing environment, whereas covalent modifications, despite their enhanced stability, depend on complex enzyme-catalyzed systems and may retain linear epitope activity (Dai et al., 2023). From a structure–function perspective, the anti-allergic activity of phenolic compounds cannot be generalized across different subclasses (Yun et al., 2010). Polyphenolic and tannic structures, owing to their multiple interaction sites, are more frequently associated with protein aggregation and conformational masking phenomena (Zhou et al., 2023). Such structural differences may contribute to the variability in reported effects on IgE binding and immune modulation observed across studies. It is necessary to systematically construct a theoretical model for targeted polyphenol modification, develop novel stabilization technologies, and promote the industrialization of this technology through molecular mechanism-process optimization-clinical validation (Pi et al., 2023). Moreover, high-dose polyphenol supplementation may interfere with nutrient absorption or drug metabolism (Duda-Chodak & Tarko, 2023), underscoring the importance of safety evaluation and dose standardization alongside molecular mechanism studies and process optimization.

4.2 Polysaccharides

The application of polysaccharides in modulating food allergy is gaining increasing attention, particularly due to their significant role in immunomodulation and the promotion of immune tolerance (Yu et al., 2023). Polysaccharides are natural biomolecules widely found in plants, fungi and microorganisms.

Polysaccharides exhibit considerable structural heterogeneity, with variations in monosaccharide composition, glycosidic linkage patterns, branching degree, and higher-order conformations (Yin et al., 2019). Such structural features critically influence their biological activity, as polysaccharides forming ordered conformations, such as certain *β*-glucans, have been more frequently associated with immune regulation in experimental systems (Ying & Hao, 2023). Murphy et al., (2020) found that *β*-glucan inhibits allergen-specific immune responses and reduces IgE levels by activating dendritic cells and promoting Tregs production. Studies have shown that polysaccharides not only promote the balance of the immune system, but also improve the symptoms of food allergy by regulating intestinal microecology, improving immune tolerance and inhibiting allergic reactions (Zhang et al., 2022). In recent years, plant polysaccharides have become a hotspot in the study of anti-food allergy, which can alleviate food allergy by stabilizing mast cells and regulating intestinal homeostasis (Li et al., 2025). Li et al., (2023) found that sea cucumber chondroitin sulfate polysaccharides could alleviate food allergy symptoms in OVA-induced BALB/c mouse models by altering the structure of the intestinal flora and by increasing secretion of short-chain fatty acids in the feces of the mice. *β*-glucans from mushrooms are a common class of immunomodulatory polysaccharides.

Another group of polysaccharides with immunomodulatory effects are algal polysaccharides such as fucoidan. Studies have shown that algal polysaccharides can alleviate the severity of allergic reactions by regulating the Th1/Th2 immune balance. Fucoidan has been shown to reduce the expression of Th2-type cytokines such as IL-4 and IL-13 and inhibit the degranulation response of mast cells in a mouse model of food allergy (Olsthoorn et al., 2021). Lee et al. (2018) demonstrated that aloe vera gel polysaccharides attenuated OVA-induced food allergy by significantly decreasing MCP-1 levels and histamine concentrations in the serum of ovalbumin-sensitized mice, significantly inhibiting mast cell degranulation, and suppressing Th2-type immune cells and increasing the number of types 1 Tregs in the spleen and mesenteric lymph nodes.

According to previous studies, active oligosaccharides and polysaccharides have positive effects on the regulation of food allergy (Motoyama et al., 2018). However, the specific mechanism by which glycan structures exert anti-allergic effects remains to be fully elucidated, necessitating reasonable extrapolation for the therapeutic application of polysaccharide-based drugs, foods, or materials in treating allergic diseases (Ying & Hao, 2023). In addition, most of the models studied are limited by an insufficient range of food allergens (Yang et al., 2022). More attention should be paid to the interaction of polysaccharides with allergenic structures, modulation of the immune microenvironment of mast cells, and targeted modulation of metabolites in allergic diseases in research (Yu et al., 2023).

4.3 Vitamins

Vitamins in the regulation of food allergy has attracted increasing attention, especially vitamin D and vitamin A, which play key roles in the regulation of the immune system, the suppression of inflammatory responses, and the maintenance of immune tolerance (Costa et al., 2019). Studies have shown that vitamins

may help to alleviate the symptoms of food allergy or even prevent it by directly or indirectly regulating immune cell function, cytokine levels and the balance of immune responses (Yang et al., 2022).

Vitamin D is one of the most widely studied vitamins related to immune response. It plays an important role in the immune system by regulating the function of immune cells through its receptor (VDR), especially in Tregs function and suppression of Th2-type immune responses (Murdaca et al., 2021). Studies have shown that vitamin D promotes the production of Tregs and inhibits the differentiation of Th2 cells, thereby reducing IgE production and alleviating the clinical symptoms of food allergy (Zhang et al., 2024). In addition, vitamin D can alleviate allergic inflammatory reactions by inhibiting the expression of pro-inflammatory cytokines such as IL-4 and IL-5 (Murdaca et al., 2021). In recent years, researchers have proposed a hypothesis, suggesting that there may be a U-shaped relationship between vitamin D and the incidence of food allergies, that is, insufficient or excessive vitamin D levels may increase the risk of food allergies (Neeland et al., 2021). In a study involving 5,276 one-year-old infants, Allen et al. (2013) reported that infants with insufficient serum vitamin D levels were ten times more likely to develop multiple food allergies by the age of one year compared to those with adequate vitamin D levels. However, there is currently no sufficient data to further confirm the hypothesis. In addition, vitamin D supplementation doses typically range from 400 to 2000 IU/day in infants and children, depending on baseline deficiency status and national guidelines. While supplementation is generally considered safe within recommended upper intake levels, excessive intake may lead to hypercalcemia, nephrolithiasis, or vascular calcification (Pludowski et al., 2018). In order to further clarify the potential of vitamin D in the prevention and treatment of food allergies, it is imperative to elucidate the cellular and molecular mechanisms by which vitamin D influences both the innate and adaptive immune systems.

Vitamin A, especially its metabolite retinol, also plays an important role in regulating the immune system (Yang et al., 2022). Studies have shown that vitamin A can alleviate the occurrence of food allergies by regulating the Th1/Th2 balance in the immune system, promoting the development of Tregs, and enhancing immune tolerance (Zakariaeeabkoo et al., 2014). In an animal study, vitamin A supplementation was shown to reduce IgE production in allergic reactions by up-regulating Tregs levels, thereby alleviating allergic symptoms (Oliveira et al., 2018). Maeta et al. (2020) found that continuous intake of retinoic acid (one of the three forms of vitamin A) in response to allergen exposure alleviated the severity of food allergy by increasing levels of IL-10 and IFN-γ in a mouse model of allergy. In addition, vitamin A further alleviates the occurrence of allergic reactions by enhancing the immune function of epithelial cells and maintaining the integrity of the intestinal barrier (Roy & Awasthi, 2019). In nutritional studies, recommended daily intakes generally range from 700-900 μg retinol activity equivalents for adults. However, the benefits of vitamins typically manifest over an extended period, and excessive intake of vitamins can lead to significant toxic effects and severe adverse reactions (Zhang et al., 2020). In-depth

explorations need to be conducted to better understand the mechanisms by which vitamins A and D influence food allergy.

4.4 Peptides

As bioactive molecules, peptides have attracted increasing attention for their potential to alleviate or prevent food allergy through the induction of immune tolerance, immunomodulation, and regulation of specific immune cell functions (Lozano-Ojalvo & López-Fandiño, 2018; Meulenbroek et al., 2013). Studies have shown that specific allergenic peptides in food allergy can play an important role in inducing immune tolerance. By inoculating the immune system with allergenic peptides, the immune system can be induced to produce specific Tregs, which in turn inhibit the production of allergen-specific IgE and alleviate the incidence of allergic reactions (Abril et al., 2022). Another way in which peptides modulate the allergic response through direct action on the immune system is by inhibiting the release of inflammatory mediators. It has been found that some small molecule peptides are able to inhibit the activation of important immune cells (e.g. mast cells, eosinophils) in the allergic response and reduce the release of pro-inflammatory cytokines such as IL-4, IL-5, IL-13, etc (Lozano-Ojalvo & López-Fandiño, 2018). These mechanisms contribute to the alleviation of allergy symptoms, such as pruritic skin and gastrointestinal reactions.

However, peptides are less stable and easily degraded by enzymes in the body, which affects their biological activities. In addition, the specificity of peptides can present certain limitations. As each food allergy has its own specific allergen, peptide therapies for different food allergies need to be customized to the individual's allergy, which undoubtedly increases the complexity and cost of treatment (Chen & Land, 2017).

4.5 Polyunsaturated fatty acids

The use of polyunsaturated fatty acids (PUFAs) in the regulation of food allergy is gaining attention, especially omega-3 and omega-6 fatty acids (López-Fandiño, 2020). Studies have shown that omega-3 fatty acids, specifically docosahexaenoic acid and eicosapentaenoic acid, have a significant effect in attenuating allergic reactions (Sartorio et al., 2021). Omega-3 fatty acids modulate the immune response by inhibiting the production of pro-inflammatory cytokines and by reducing the activity of Th2 cells, which can alleviate clinical symptoms of food allergy (Gardner et al., 2020). One study found that omega-3 fatty acid supplementation reduced IgE levels and allergic symptoms in a mouse model (Sartorio et al., 2021). In addition, omega-3 fatty acids improve the function of Tregs, which are essential for maintaining immune tolerance and reducing allergic symptoms (Sartorio et al., 2021).

The role of omega-6 fatty acids in food allergy is more complex. Studies have found that metabolites of omega-6 fatty acids-such as arachidonic acid and its derivatives, such as leukotrienes and prostaglandins, are often proinflammatory and may promote the development of allergic reactions (Hoppenbrouwers et al., 2019). Thus, regulating the omega-6 to omega-3 ratio may be effective in the prevention and treatment of food allergies.

In view of the above evidence, the effects of PUFAs depend on their type, dose and duration of intake. In the clinical management of food allergy, the effect of PUFAs may take a longer time to show up. Besides, differences in the amount and proportion of PUFAs intake in different populations may lead to individual differences in efficacy. For example, excess omega-6 fatty acids may exacerbate allergic symptoms in some individuals, whereas omega-3 intake acts as a moderator (Yang et al., 2022). Overall, the application of PUFAs, particularly omega-3 fatty acids, in modulating food allergy demonstrates promising potential.

4.6 Probiotics

The composition and functional state of the intestinal microbiota are important factors influencing the development of food allergy (Bai et al, 2024). As beneficial live microorganisms, probiotics have been extensively investigated for their potential to restore microbial homeostasis and regulate local and systemic immune responses associated with food allergy (Zubeldia-Varela et al., 2022; Gu et al, 2023).

Studies have shown that probiotics can inhibit allergic reactions by enhancing Tregs function through interaction with intestinal immune cells (Boonpiyathad et al, 2020). Berni Canani et al. (2016) treated 20 healthy infants and 19 infants with cow's milk allergy (CMA) with a hydrolyzed casein formula (EHCF) containing *Lactobacillus rhamnosus* (LGG). The results suggest that EHCF+LGG promotes tolerance in infants with CMA to some extent by influencing the levels of the strain in the infant's gut. Similarly, Canani et al. (2017) found that infants receiving the formula plus probiotic combination had a higher prevalence of milk tolerance at 12, 24, and 36 months of age. Kreft et al. (2020) verified that orally administered *Clostridia* strains significantly increased the frequency of Tregs in the colon. Some studies have found that *LGG*, *Bifidobacterium bifidum* and complex strains are able to effectively attenuate allergic reactions by promoting the production of Tregs and the secretion of anti-inflammatory factors (Shu et al., 2019). In addition, by inoculating specific allergen-modified strains, the immune system can be induced to produce a tolerant response to allergic diseases (Nance et al., 2020). These immunomodulatory effects provide new strategies for the prevention and treatment of food allergy, especially in the field of immunotherapy.

Although many studies have shown that probiotics play an important role in alleviating food allergy, their impact on clinical application is still controversial. Since food allergy occurs in families with multiple factors such as genetics, dietary structure and environment, and is specific between different patients. Clinical studies have reported that the effective doses of probiotics generally range from 10^8 to 10^{10} colony-forming units per day, depending on the specific strain and study design (Devi, 2025). Although probiotics are widely regarded as safe for healthy populations, caution is warranted in vulnerable groups, including immunocompromised individuals and preterm infants. Moreover, the lack of standardized dosing regimens and strain-specific validation frameworks substantially complicates their clinical translation, thereby presenting significant challenges for both the rational application and the efficient screening of probiotic candidates (Gu et al., 2023).

Overall, current evidence supporting dietary immunomodulatory active substances in food allergy predominantly derives from vitro experiments and animal models, with a limited number of well-designed human trials. These compounds should therefore be viewed as complementary dietary factors rather than established therapeutic interventions. Future research should prioritize dose standardization, safety evaluation, and high-quality randomized controlled trials.

5. Management strategies

In the IgE-mediated food allergy management system, a three-tiered prevention and control model covering preventive dietary interventions, acute reaction response, and patient education needs to be established (Santos et al., 2025). As shown in Figure 4, this model realizes the entire risk control process through the synergistic linkage of each component.

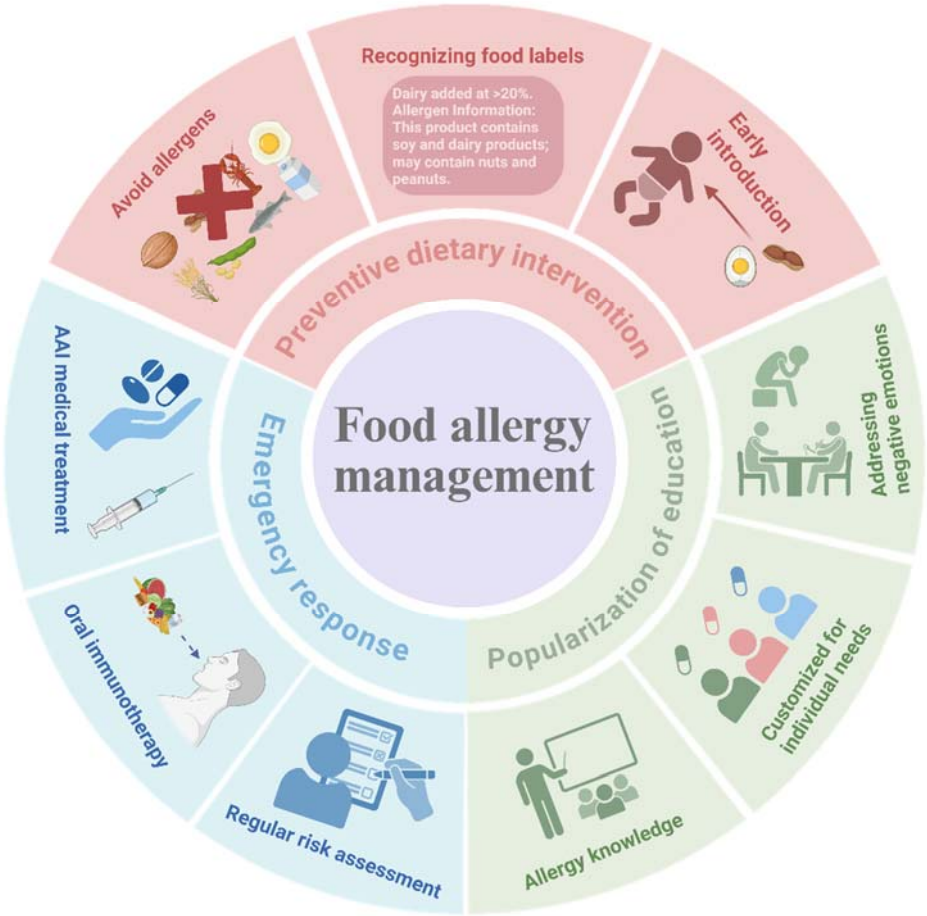

Figure 4 Food allergy management.

Pre-allergy prophylaxis is primary prevention, which focuses on allergen exposure control and precise dietary interventions. Primary prevention emphasizes appropriate allergen exposure rather than absolute avoidance, requiring patients and caregivers to accurately interpret food labeling and to identify and manage the risk of allergen cross-contact during food production, processing, and preparation (Leung et al., 2025; Camus-Ela et al., 2025). In addition, threshold-based action levels have been proposed as a complementary

population-level risk management concept, referring to predefined allergen concentration levels below which unintended exposure is unlikely to trigger reactions in most sensitized individuals (Madsen et al., 2020). Although these thresholds are not intended to define individual safety limits, their application may support labeling decisions and cross-contact control strategies, thereby reducing unnecessary dietary restrictions while maintaining an appropriate level of protection for allergic individuals (Li et al., 2024). For high-risk infants, the Global Allergy and Asthma European Network guidelines contraindicate partially hydrolyzed formulas, alternative animal milks, or soy formulas under six months, recommending extensively hydrolyzed or amino acid-based formulas for cow's milk allergy (Muraro et al., 2022). Beyond avoidance-based strategies, early and sustained introduction of allergenic foods, particularly peanut and egg, during infancy has been recognized as an effective primary prevention approach compared with delayed exposure (Schroer et al., 2021). Evidence indicates that early introduction of peanuts can reduce the risk of peanut allergy by up to 80%, with a sustained impact into early childhood. A similar risk reduction has been observed in studies on early introduction for egg allergy: introducing eggs at 1 year of age reduces the cumulative incidence of egg allergy at 3 years from 2.2% to 0.2% (Yakaboski et al., 2021). Accordingly, controlled and age-appropriate introduction of peanut and egg is now recommended as a key component of primary prevention strategies.

Post-allergy management represents secondary prevention, which should focus on emergency care and disease-modifying treatments, as well as strengthening risk management in high-risk populations. All diagnosed patients should receive individualized emergency action plans that include access to epinephrine autoinjectors (AAIs) (Santos et al., 2025). In addition to prescription, effective management requires adequate education on the recognition of allergic symptoms, timely administration of AAIs, and ensuring their availability in relevant settings, as delayed or inappropriate use remains a major contributor to severe outcomes (Leung et al., 2025). At this stage, allergen immunotherapy is an important intervention. Infancy is the “golden window” for OIT, with a negligible risk of severe reactions, desensitization rates exceeding 80%, and a high potential for immune tolerance induction when appropriately supervised (Soller et al., 2025). However, clinical decision-making should be individualized, and risk stratification should incorporate eliciting doses, reaction severity, and threshold-based action levels rather than relying solely on allergen-specific IgE levels (Muraro et al., 2022).

Education is a three-tiered prevention that must be structured and tailored to different populations' characteristics and scenarios. Educational programs should ensure understanding of disease mechanisms, appropriate use of emergency medications, and the potential benefits and adverse effects of immunotherapy, thereby improving management effectiveness (Santos et al., 2025). Ensuring equitable access to education, diagnostic services, emergency medications, and therapeutic options is essential to reduce disparities in food allergy outcomes. An intelligent food allergy management system can be constructed by integrating the

synergistic measures of prevention, response, and education to achieve comprehensive risk prevention, control, and scientific management throughout the entire supply chain.

6. Conclusions and outlook

Food allergy represents a significant global public health concern, with a reported increase in prevalence in recent years, particularly among pediatric populations. This paper provides a comprehensive and systematic review of recent advances in the field of food allergy, covering the characterization of major and novel food allergens, their pathogenesis, novel diagnostic and allergenicity assessment methods, the potential of dietary active substances for preventive therapy and allergy management strategies. Notably, recent developments in diagnostic and allergenicity assessment methods have expanded upon traditional approaches. Molecular diagnostic techniques facilitate a more comprehensive assessment of the allergic spectrum of patients through the precise detection of specific allergen components. The integration of multi-omics techniques (genomics, proteomics, and metabolomics) with artificial intelligence prediction models has shown promise in improving diagnostic sensitivity and specificity and may provide a basis for the future development of personalized management strategies. In vitro cellular assays and biomarker-based assessment techniques are also being increasingly applied in clinical and research settings, with the potential to reduce reliance on traditional skin prick tests and oral food challenges, thereby contributing to improved safety in selected contexts. In addition, accumulating evidence suggests that dietary actives including polyphenols, polysaccharide and probiotics, may exert immunomodulatory effects by modulating inflammatory responses and influencing allergen sensitization processes. These findings highlight the potential role of functional foods and complementary therapeutic strategies in managing food allergy. The current management of food allergy predominantly focuses on allergen avoidance, aiming to reduce the risk of accidental exposure through dietary control, food labeling systems and improvement of food processing. Emerging technologies, such as precision medicine, may offer opportunities to further refine allergy management strategies in the future. Future research should focus on the clinical validation of multi-omics technologies, the analysis of the synergistic effects of dietary actives, and the construction of artificial intelligence-based allergy risk prediction models, to facilitate the gradual translation of mechanistic insights into clinical applications.

Conflict of interest statement

The authors declare no conflict of interests.

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