NATURAL ENZYMES AND ALLERGIES*

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Review paper

Abstract

Enzymes play a crucial role in speeding up chemical reactions in living organisms. Discovered in the late 19th century, these complex proteins are essential for various biological processes. Food allergies are immune responses to specific proteins in food. Common allergens include proteins from eggs, milk, peanuts, tree nuts, and seafood. Allergic reactions can vary from mild to severe and affect different body systems. The prevalence of food allergies is rising, with some estimates suggesting that up to 10% of the population may be affected.
The aim of this paper is to investigate the influence of some natural enzymes on allergies.
Enzymes used in food processing, like lysozyme in wine or alpha amylase in baked goods, can pose risks for those with sensitivities. Lysozyme, an enzyme that breaks down bacterial cell walls, can cause allergic reactions in some people, particularly those allergic to eggs. Similarly, enzymes like enolases and aldolases, which are involved in energy production, can trigger allergies, especially among those sensitive to fish proteins. Alpha-amylase, an enzyme that breaks down starches, is a well-known allergen, particularly in occupational settings like baking. Arginine kinase, found in seafood and insects, can also cause allergic reactions, which is a concern for people handling these products. Chitinase, which breaks down chitin in insects, and papain from papaya, used in meat tenderizers, can lead to allergies as well.
Conclusion: Clearly specifying the natural or synthetic origin of potentially allergenic substances enables the avoidance of allergic reactions and directly contributes to maintaining the health of individuals sensitive to these ingredients.

Keywords: *lysozyme allergy, ɑlpha-amylase, chitinase, aldolase, papain*

INTRODUCTION

The concept of enzymes in nature has been recognized for over a century. The German physiologist Wilhelm Kühne introduced the term enzyme in 1878 to describe yeast's ability to ferment sugar into alcohol. The term originates from the Greek words "en" (within) and "zyme" (yeast) (Robinson, 2015). In 1926, James B. Sumner achieved a

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milestone by isolating the first enzyme, urease, in crystalline form from beans (Sumner, 1926). Enzymes, often referred to as biocatalysts, are specialized biological molecules that speed up biochemical reactions without being consumed. While they are synthesized within living cells, enzymes remain functional outside of their natural environment, enabling their use in industrial applications. Most enzymes are proteins and serve as essential biocatalysts in sustaining life by facilitating vital biochemical processes (Kuddus, 2018).

Allergies are defined in various ways depending on the context. According to the World Health Organization (2003), they involve hypersensitivity reactions initiated by immune mechanisms. Another perspective describes allergies as an overreaction of the immune system to typically harmless environmental substances (Dougherty *et al*., 2023). The term "allergy" was first introduced in 1906 by Clemens von Pirquet, a Viennese pediatrician, who used it to broadly describe alterations in an organism's reactivity, considering factors such as timing, quality, and intensity of the response (Huber, 2006). Substances that provoke allergic reactions are referred to as allergens. These can be biological or chemical agents and often consist of foreign proteins or glycoproteins that stimulate IgE antibody responses in humans (Judith *et al*., 2015; Mekori, 1996). The International Union of Immunological Societies stipulates that a substance must induce IgE-mediated allergic reactions in at least 5% of the population to qualify as an allergen under their nomenclature (Løwenstein, 1996).

Food allergies, a specific category, are defined as adverse health effects stemming from a reproducible immune response triggered by exposure to foods (Boyce *et al*., 2010). These reactions are usually linked to specific proteins within the food, though occasionally chemical haptens may also act as allergens. While some food allergens, particularly those in fruits and vegetables, provoke reactions only when consumed raw, most can still elicit allergic responses even after being cooked or digested (Boyce *et al*., 2010).

Protein-rich foods are common sources of allergens, with most food-induced allergic reactions attributed to specific food proteins (James *et al*., 2012). The distribution of proteins, fats, and carbohydrates varies across food types, but allergens are predominantly associated with the protein fraction.

Food allergies exhibit varying patterns of persistence and resolution. While allergies to eggs, milk, and wheat often diminish during early childhood, allergies to peanuts, tree nuts, sesame seeds, fish, shellfish, and buckwheat are more likely to persist throughout life. However, the likelihood of resolution can differ significantly across studies for a given food allergen (James *et al*., 2012).

According to the World Allergy Organization (WAO), adverse reactions to food are collectively referred to as food hypersensitivity. This term is further divided into immune-mediated responses, known as food allergies, and non-immune-mediated responses, termed food intolerances. Food allergies themselves can be classified into two main categories based on the immune mechanism involved: immunoglobulin E (IgE)-mediated reactions, which occur rapidly, and non-IgE-mediated reactions, which have a delayed onset (James *et al*., 2012).

MATERIALS AND METHODS

This study examines the interrelationships between natural enzymes and allergies. Key terms such as "enzyme" and "allergy" are defined to establish their fundamental meanings. The research focuses on natural enzymes that can stimulate the immune response and lead to adverse reactions in individuals. To conduct this research through literature review, methods classification, description and comparison were used. The most well-known natural enzymes associated with unwanted allergic reactions were identified and described, highlighting their potential to threaten human life through inhalation or consumption.

RESULTS AND DISCUSSION

Over recent decades, researchers have identified over 2,000 allergens, with detailed information available in online databases. Among these, the allergen nomenclature database maintained by the World Health Organization and the International Union of Immunological Societies (WHO/IUIS) is one of the most rigorous and extensively peer-reviewed resources, accessible at www.allergen.org. Another key resource, the Allergen Online database, provided by the Food Allergy Research and Resource Program (FARRP) (www.allergenonline.org), offers valuable data on allergenic proteins (Karnaneedi *et al*., 2021).

Food allergies have become a growing public health issue worldwide. Approximately 2.5% of the global population is estimated to be affected, though prevalence rates vary widely between 1% and 10% depending on the region and study. Applying this percentage to the global population of 8.1 billion suggests that around 202.5 million people could have food allergies (Fiocchi & Fierro, 2017). This issue not only affects individual health but also imposes substantial socioeconomic challenges on patients, families, and society. Although fatalities are rare, the fear of severe outcomes, including death, remains a significant concern for those with food allergies.

Proteins, including some enzymes, are key triggers of allergic sensitization. Despite the vast number of proteins classified in databases, allergenic proteins belong to a relatively small number of protein families. The Pfam protein family database (http://pfam.xfam.org/) identifies 19,632 families, while the Structural Database of Allergenic Proteins (SDAP; http://fermi.utmb.edu/) lists 1,908 allergens and isoallergens, along with 233 novel Pfam classes. SDAP combines an allergenic protein database with bioinformatics tools to study structural features and epitope characterization. The most impactful plant- and animal-derived food allergens are concentrated in eight protein superfamilies (James *et al*., 2012).

Symptoms of allergic reactions can affect the skin, gastrointestinal tract, respiratory system, and cardiovascular system. Common signs include abdominal cramps, vomiting, hives, difficulty breathing, persistent coughing, hoarseness, trouble swallowing, tongue swelling that interferes with speaking or breathing, weak pulse, pallor or bluish skin, dizziness, and fainting. Severe reactions, such as anaphylaxis, can be life-threatening, causing breathing difficulties and potentially leading to shock (American College of Allergy, Asthma and Immunology).

Lysozyme

Lysozyme is a versatile enzyme found across living organisms and viruses, showing considerable diversity in its origin, abundance, and biochemical characteristics (Ferraboschi *et al*., 2021). First identified by Alexander Fleming, lysozyme is recognized for its bacteriolytic properties and classified as a hydrolase under EC 3.2.1.17 (Figure 1). The enzyme's name reflects its function: breaking down bacterial cell walls through hydrolysis of the β-1-4-glycosidic bond between N-acetylglucosamine and N-acetylmuramic acid, a process earning it the alternative name "muramidase" (Daniel *et al*., 2015).

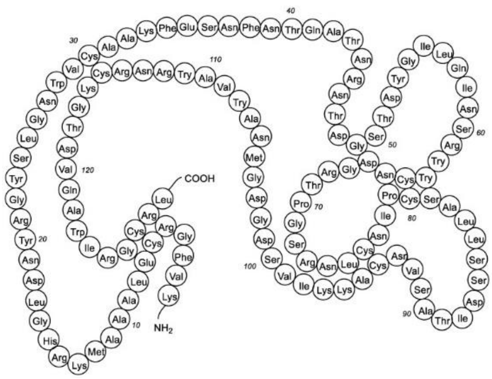

Figure 1. Representation of the lysozyme structure
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Lysozymes are categorized into three primary families: chicken type (c-type), goose type (g-type), and invertebrate type (i-type) with additional varieties, such as phage, bacterial, and plant lysozymes, also identified (Table 1). C-type lysozyme, including the chicken egg white lysozyme (HEWL), plays a significant role in the pharmaceutical industry due to its efficacy against bacterial, viral, and inflammatory conditions (Wu *et al*., 2019).

Egg white is composed of approximately 90% water and 10% protein, with around 40 proteins identified. Among these, lysozyme (Gal d 4) is considered a minor allergen but has been associated with sensitization in roughly one-third of egg-allergic individuals. The allergenicity of Gal d 4 diminishes with heat or enzymatic treatment, making reactions more likely when raw egg is consumed (Lopata, 2013).

Table 1. Overview of some characteristics of lysozyme

Biological function	Glycosyl hydrolase
Allergen code	362
Source	Egg extract
Latin name	*Gallus domesticus*
Other names	Gal d IV, lysozyme,E1105
Molecular weight	14 kDa
Categories	Eggs, food animal-derived food

Source:https://www.thermofisher.com/diagnostic-education/hcp/wo/en/resource-center/allergen-encyclopedia/allergen-component.html?key=k208

The EU Food Safety Authority has found that wines treated with egg-derived lysozyme (used as a microbiological stabilizer or additive) to control lactic acid bacteria can cause undesirable allergic reactions in some individuals. At the request of the European Commission, the Panel on Dietetic Products, Nutrition, and Allergies (NDA) was asked to provide a scientific opinion regarding the labeling of egg lysozyme, where the panel concluded that wines treated with lysozyme may cause undesirable allergic reactions in sensitive individuals (EFSA Journal 2011).

Egg-derived lysozyme is increasingly used as an antibacterial additive to prevent spoilage in cheese, wine, or other foods, as well as in medications for respiratory tract infections and congestion, which usually do not specify the source, posing a risk to consumers allergic to chicken eggs (Benede *et al.*, 2014).

Lysozyme can be used as a preservative in cheese to prevent the late release of gas caused by the genus *Clostridium* (anaerobic Gram-positive bacteria) and represents an alternative to nitrate (Schneider & Pischetsrieder, 2013).

Enolase and Aldolase

Enolases and aldolases, which are part of the lyase enzyme class, play a vital role in glycolysis, a fundamental metabolic process found across all tissues. Glycolysis is a highly conserved pathway comprising ten steps that break down glucose into pyruvate, generating adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NADH) as high-energy molecules (Pirovich *et al*., 2021).

Fish allergies can trigger adverse reactions in sensitive individuals through ingestion, inhalation of cooking vapors, or direct contact. Symptoms range from mild, such as oral itching and hives, to severe manifestations like asthma and systemic anaphylaxis. Around half of individuals with fish allergies may experience cross-reactivity with other fish types (Kuehn *et al*., 2014).

Epidemiological studies highlight the prevalence of fish allergies. In Norway, a survey of 3,623 children revealed nearly 3% of reported food-related reactions by age two were linked to fish. In Spain, a cohort of 355 children with IgE-mediated food allergies showed that fish allergies often began before two years of age. In the United States, approximately 5.9% of 14,948 respondents reported seafood allergies (Sharp & Lopata, 2013). Similarly, in Australia, research at a specialized clinic involving 2,999 children indicated a 5.6% prevalence of fish allergies, with white fish, tuna, and salmon as the most common culprits. In Asian populations, fish allergies are also significant, as shown by a Singaporean study where 13% of 227 children with food hypersensitivity were sensitized to fish, often introduced into diets by seven months of age (Sharp & Lopata, 2013).

While proteins such as enolases and aldolases were initially linked to fish-specific allergies, it has been observed that many individuals allergic to fish with IgE targeting enolase and aldolase also react to parvalbumin. However, there are documented cases where patients with significant sensitization to enolase or aldolase lack IgE specific to parvalbumin. These findings suggest that such sensitizations can lead to species-specific fish allergies. Despite this, cross-reactivity among enolase and aldolase allergens from fish species like cod, salmon, and tuna remains possible (Dijkema *et al*., 2020).

α-Amylase

Amylase, a hydrolase-class enzyme, was first identified in the early 19th century and is among the earliest enzymes to be studied scientifically (Akinfemiwa *et al*., 2023). Its primary role is to break down glycosidic bonds in starch, transforming complex carbohydrates into simpler sugars. There are three primary types of amylase enzymes: alpha-amylase, beta-amylase, and gamma-amylase, each targeting specific parts of carbohydrate structures. Alpha-amylase is found in humans, animals, plants, and microorganisms, while beta-amylase occurs in plants and microbes (Table 2). Gamma-amylase is present in both animals and plants (Akinfemiwa *et al*., 2023).

In the baking industry, amylase is a key enzyme used to enhance and optimize various processes, playing a critical role in improving the quality of baked goods.

Table 2. Overview of some characteristics of fungal α-amylase

Properties	Fungal α-amylase
Physical Appearance	White to gray powder
EC Code	3.2.1.1
Ph	4,5-7.0
Temperature	30 °C -60°C

Source:https://www.foodnetworksolution.com/company/angel-yeast-co-ltd/products/1019/Enzymes-for-baking

In humans, α-amylase is synthesized by the exocrine pancreas and also secreted in saliva. It is a recognized occupational allergen when inhaled. In cases of bakery asthma associated with the flour processing industry, the allergenic α-amylase typically originates from fungal contamination (Pali-Schöll *et al*., 2018).

The enzyme α-amylase (4-α-D-glucan glucanohydrolase; EC 3.2.1.1) is produced using a non-genetically modified strain of *Aspergillus oryzae* (Lambre *et al*., 2023). It is utilized across seven food production processes: starch processing to produce glucose, maltose syrups, and other hydrolysates; brewing, baking, production of distilled alcohol, grain-based processes, manufacturing of milk analog products and processing fruits and

vegetables for juice production. During the production of glucose syrups and distillation, residual total organic solids (TOS) from the enzyme are removed, so dietary exposure is not calculated for these processes. For the other five processes, the estimated dietary exposure in European populations is up to 0.134 mg TOS/kg body weight per day.
Genotoxicity assessments raised no safety concerns, and systemic toxicity was evaluated in a 90-day repeated oral toxicity study in rats. Based on the proposed uses (excluding distilled alcohol production), the risk of allergic reactions due to food exposure cannot be entirely ruled out, although the likelihood is considered low (Lambre *et al*., 2023).

Arginin kinase
Arginine kinase (EC 2.7.3.3) is a transferase enzyme that facilitates the transfer of phosphate groups from high-energy molecules like ATP (adenosine triphosphate) to specific substrate molecules. Specifically, it catalyzes the transfer of a phosphate group from ATP to the amino acid arginine, resulting in the formation of phosphoarginine. Arginine kinases have been identified as allergens in various invertebrates, including food sources such as shrimp, and in cross-reactive species like the Indian meal moth, royal shrimp, lobster, and mussel (Binder *et al*., 2001). This enzyme has a molecular weight of 40-42 kDa and is considered unstable in acidic or basic conditions (Laly & Sankar, 2020).
Inhaled bioaerosols containing seafood allergens can provoke allergic responses, posing a risk to individuals working in seafood-related industries. This includes those involved in seafood processing, food preparation (e.g., chefs and restaurant staff), and collection activities like fishing and aquaculture. While the percentage of shrimp-sensitized individuals recognizing arginine kinase is not definitively established, estimates suggest it ranges between 10 and 51% (Giovannini *et al*., 2023). Additional studies indicate that IgE sensitization to arginine kinase is observed in 21-50% of adults and as much as 67% of children (Kleine-Tebbe & Jakob, 2017).

Chitinase
Chitinases (EC 3.2.1.14), classified under hydrolases, are enzymes that break down β-1,4-N-acetyl-D-glucosamine bonds in chitin polymers. They are produced by various organisms, including bacteria, fungi, insects, plants, and vertebrates, and play roles in nutrition, morphogenesis, and defense against pathogens containing chitin (Rathore *et al*., 2015; Leoni *et al*., 2019).
An allergenic form of chitinase has been identified in the silkworm pupa (*Bombyx mori L.*), which is consumed as food (Zhao *et al*., 2015). This is notable as it is the first allergenic chitinase linked to food that is not plant derived. This finding is significant, particularly given that silkworm pupae are a traditional food in East Asia and may become part of emerging dietary trends in other regions (Leoni *et al*., 2019). Table 3 outlines various food sources of chitinases that could potentially induce allergic reactions.

Table 3. Chitinases identified as food allergens

Source	Molecule	Assay
Class I (GH19, with chitin binding module)		
Kiwi fruit *(Actidinia chinensis)*	I	IR
Papaya *(Carica papaya)*	I	
Chestnut *(Castanea sativa)*	I	
Tomato *(Lycopersicum esculentum)*	I	IR
Banana fruits *(Musa sp.)*	P	IR, SPT
Avocado (*Persea americana*)	P, R	IR
Green bean (*Phaseolus vulgaris*)	I	SPT
Wheat (*Triticum aestivum*)	I	IR
Class II (GH19, without chitin binding module)		
Tomato *(L.esculentum*)		
Wheat (*T. aestivum)*	I	
Rice (*Oryza sativa)*	R	IR
Class III (GH18, without chitin binding module)		
Coffee green beans (*Coffea arabica)*	I, R	IR
Raspberry berries (*Rubus ideaeu*)	I	IR
Indian jujube fruit (*Zizyphus mauritiana*)	P, R	IR
Pomegranate (*Punica granatum*)	I	IR, SPT
Class IV (GH19, with chitin binding module)		
Grape (*Vitis vinifera*)	I, R	IR
Maize (*Zea mays)*	R	IR
Insect chitinases (GH18)		
Silkworm (*Bombyx mori)*	I	IR

Source:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6600546/#:~:text=Chitinases%20are%20a%20group%20of,been%20only%20partially%20carried%20out.

For plant and insect chitinases, it is considered that the allergic reaction may be a result of the so-called cross-reactivity syndrome, meaning the occurrence of a food allergy in individuals who have already been exposed and sensitized to structurally similar non-food allergens. Specifically, for many plant chitinases, structural similarity with hevein (a protein identified as a significant allergen for patients allergic to latex extracted from the rubber tree) was noted in the first descriptions of allergenic chitinases in plants. Furthermore, for the recently identified insect allergenic chitinase, structural similarity with the allergenic chitinase from house dust mites was reported (*Leoni et al*., 2019).

Papain

Papain (EC 3.4.22.2) is a proteolytic enzyme in the hydrolase class, derived from the latex of the papaya plant (*Carica papaya*). It is extensively utilized in various industries, including as a meat tenderizer, beer clarifier, and contact lens cleaner, and plays a significant role in the pharmaceutical and cosmetic sectors. The first IgE-mediated allergic reaction to papain in workers was documented in 1975 (Milne & Brand, 1975). The initial report of papain allergy dates to 1928. Since then, numerous cases of occupational asthma linked to papain exposure have emerged, primarily among workers in the pharmaceutical and cosmetic industries (Soto-Mera *et al*., 2000). Papain adversely affects the skin by impairing its protective barrier. It can quickly increase vascular permeability and attract inflammatory cells to the skin (Medical University of Vienna, 2015).

Structurally, papain shares significant similarities with a major allergen found in house dust mites. Due to these properties, individuals with sensitive skin and young children are advised to avoid papain-containing products and carefully review ingredient labels for consumer items (Medical University of Vienna). Tests are now available to identify allergic reactions to this enzyme (https://www.healthlabs.com/papain-allergy-testing). Papain allergy can arise in both occupational and non-occupational settings, with most cases involving individuals employed in factories where papain is processed, biochemical laboratories, or cosmetic facilities.

Triosephosphate Isomerase

Triosephosphate isomerase (TIM or TPI) is a key enzyme in glycolysis and has been identified as an allergen in saltwater products, belonging to the class of isomerases (Yang *et al.* 2017). TIM (EC 5.3.1.1.) has been described as a new allergen, mainly in marine organisms and certain invertebrates. Some of these species include *Octopus fangsiao* (webfoot octopus), *Blattella germanica* (German cockroach), *Penaeus monodon* (black tiger shrimp), *Procambarus clarkii* (red swamp crayfish), and *Citrullus lanatus* (watermelon) (Yang *et al.,* 2017). Its clinical and immunological relevance and cross-reactivity are still not well researched (Lopata, 2017).

CONCLUSIONS

Food allergies are an important public health issue that affect both children and adults and may be on the rise. An allergy manifests as a hypersensitivity reaction to environmental factors known as antigens or allergens. Despite the significant risk of severe allergic reactions, and even death, there is currently no treatment for food allergies. The symptoms of an allergic reaction vary greatly in terms of onset speed and intensity. The condition can only be managed by avoiding allergens or treating symptoms. Every food or allergen derivative must be clearly labeled and indicated on food, medication, and other product labels that people consume to improve the safety of individuals prone to allergic reactions. Reviews of the literature often focus on egg and milk derivatives. It is essential to clearly state the natural or synthetic origin of potentially allergenic substances, such as lysozyme, casein, lactose, albumin, papain, arginine kinase, and aromatic essences. Providing such information enables the avoidance of allergic reactions and directly contributes to maintaining the health of people who may be at risk when consuming these ingredients.

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PRIRODNI ENZIMI I ALERGIJE

Sažetak

Enzimi igraju ključnu ulogu u ubrzavanju hemijskih reakcija u živim organizmima. Otkriveni krajem 19. stoljeća, ovi složeni proteini su neophodni za različite biološke procese. Alergije na hranu predstavljaju imunološke reakcije na specifične proteine u hrani. Uobičajeni alergeni uključuju proteine iz jaja, mlijeka, kikirikija, orašastih plodova i morskih plodova. Alergijske reakcije mogu varirati od blage do teške i utjecati na različite sisteme tijela. Učestalost alergija na hranu raste, a neka istraživanja sugeriraju da čak do 10% populacije može biti pogođeno.
Cilj ovog rada je istražiti utjecaj nekih prirodnih enzima na alergije. Enzimi korišteni u preradi hrane, poput lizozima u vinu ili alfa-amilaze u pečenim proizvodima, mogu predstavljati rizik za osobe sa senzibilitetom. Lizozim, enzim koji razgrađuje ćelijske zidove bakterija, može izazvati alergijske reakcije kod nekih ljudi, posebno onih alergičnih na jaja. Slično tome, enzimi poput enolaza i aldolaza, koji su uključeni u proizvodnju energije, mogu izazvati alergije, posebno kod osoba osjetljivih na proteine ribe. Alfa-amilaza, enzim koji razgrađuje škrob, poznati je alergen, posebno u radnim okruženjima kao što je pekarstvo. Argininska kinaza, koja se nalazi u morskim plodovima i insektima, također može izazvati alergijske reakcije, što predstavlja zabrinutost za osobe koje se bave ovim proizvodima. Hitinaza, koja razgrađuje hitin u insektima i papain iz papaje, koji se koristi za omekšavanje mesa, također mogu dovesti do alergija.
Zaključak: Jasno specificiranje prirodnog ili sintetičkog porijekla potencijalno alergenih supstanci omogućava izbjegavanje alergijskih reakcija i izravno doprinosi održavanju zdravlja osoba osjetljivih na ove sastojke.

Ključne riječi: *alergija na lizozim, alfa-amilaza, hitinaza, aldolaza, papain*