



# Immunological Analysis of Different Food Allergens - A Review

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**Abstract:** Food allergy (FA) is one of the most common health problems worldwide and immunologically it has many aspects to be studied. Mechanism of Tolerance and Sensitization against food antigens are the main factors studied under the immunological basis of allergy. A better understanding of these responses is vital for development of new therapies. In this review, we have focused on the prominent types of FA and its immunological mechanisms along with a statistical comparison of these allergies. Most of the types of food allergies are IgE mediated and is also the main cause of anaphylaxis, diagnosis of which is by careful analysis of history and diagnostic tests, such as skin prick tests, serum-specific IgE and, if indicated, an oral food challenge. Once the allergen is identified, strict elimination of the offending food allergen from the diet is necessary, followed by identification of cross reactive food materials. This report emphasis on allergens from peanut, wheat, cow milk, soy, egg and shellfish; and their pathophysiology, diagnosis, and management.

**Index Terms** -Food allergy, tolerance, sensitization, IgE, Immunological mechanisms.

## I.INTRODUCTION

Food allergy is a set of immune reaction triggered by normally innocuous food protein antigens. It represents increasingly prevalent human health problem, with limited therapeutic options. Better understanding of the crucial immunological mechanisms involved in such responses will help in development of new therapies [1]. There are many forms of food allergy, the most common of which are IgE mediated, others show mechanisms independent of IgE and some are having mixed mechanisms. Common IgE-mediated food allergies include those to peanuts, tree nuts, cow's milk, egg, soy, wheat, shellfish and fish [2]. Generally, tolerance developed to food proteins, at least in part due to the actions of CD4<sup>+</sup> regulatory T cells. But allergic reaction develops when the immune system mounts a T helper 2 (TH2) cell-mediated responses against food epitopes and IgE antibody reactions [3].

As shown in Figure1, IgE mediated responses begin with 'Sensitization' to food consumption of the allergenic food protein stimulates production of food-specific IgE antibodies. These antibodies later bind to and activate effector immune cells which releases molecules like histamine, prostaglandins and leukotrienes, causing "clinical reactivity" (allergic symptoms) [4,5].

Food Allergy differs from pathogenic infections or food toxins, as well as from the so-called food intolerances, which exhibit the same symptoms but recognize different pathogenic mechanisms. Food intolerances are non-immune reactions, mediated by toxic, pharmacological, metabolic, and undefined mechanisms. For example, milk intolerance is due to the deficiency of the enzyme lactase [6].

Food allergies include a wide spectrum of clinical manifestations, from mild forms with skin or organ localization, to serious and potentially fatal forms with systemic involvement [7]. This review describes the immunological basis of some common food allergies with some of their clinical manifestations.

Table 1: Allergen Protein in common food allergies

| Peanut [9]                          | Wheat[18,21,27]   | Cow milk[39-41]   | Soy[50]                             | Egg[57]                       | Shellfish[64]                        |
|-------------------------------------|---|---|-------------------------------------|-------------------------------|--------------------------------------|
| Cupin superfamily (Ara h1,3)        | $\alpha$ -, $\beta$ -, $\gamma$ -, and $\omega$ -gliadins                   | casein (Bos d 8)<br>$\alpha$ S1-(Bos d 9),<br>$\alpha$ S2-(Bos d 10),<br>$\beta$ -(Bos d 11),<br>and $\kappa$ -(Bos d 12) | Gly m 1, a hydrophobic protein,     | ovomucoid (Gal d 1, 11%)      | Tropomyosin                          |
| Prolaminsuperfamily (Ara h2,6,7,9), | Wheat $\alpha$ -amylase inhibitors( Tri a 15, Tri a 28, Tri a 29, Tri a 30) | $\beta$ -lacto-globulin (Bos d 5)   | Gly m 2, Defensin                   | Ovalbumin(OVA) (Gal d 2, 54%) | Arginine kinase                      |
| Profilin family (Ara h5)            | Thioredoxin (Tri a 25)  |   | Gly m 3, profilin                   | Ovotransferrin (Gal d 3, 12%) | Myosin light chain                   |
| Bet v-1-related proteins (Ara h 8)  | Peroxiredoxines (Tri a 32)  |   | Gly m 4, PR-10                      | Lysozyme (Gal d 4, 3.4%)      | Sarcoplasmic calcium binding protein |
| Oleolin (Ara h 10,11)               | $\alpha$ -purothionin, trypsin inhibitors (Tri a 33)                        |   | Gly m 5, vicilin, a cupin           |                               | Troponin C                           |
| Defensin (Ara h 12, 13)             | Thiolreductase (Tri a 27)   |   | Gly m 6, legumin, a cupin,          |                               | Triosephosphate isomerase            |
|                                     | Peroxidase, Serine protease inhibitors                                      |   | Gly m 7, seed biotinylated protein, |                               |                                      |
|                                     |   |   | Gly m 8, 2S albumin                 |                               |                                      |

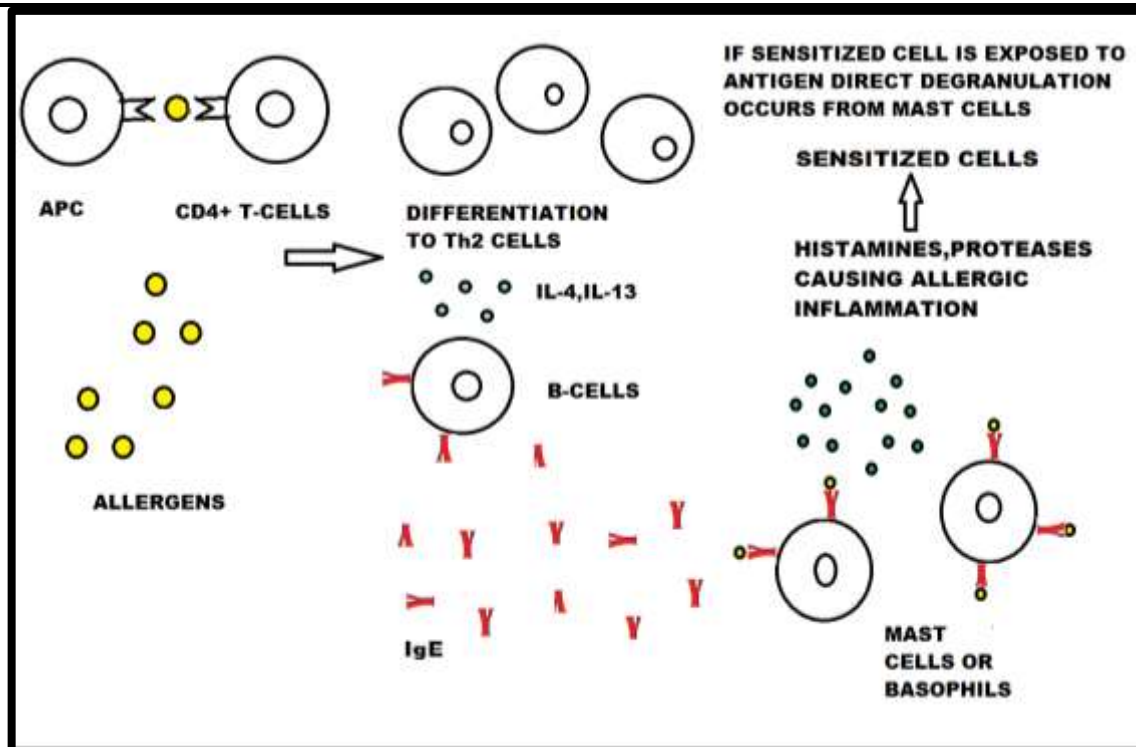


Figure 1: General Mechanism of IgE mediated allergic response [10, 27, 43, 51, and 58]

## 1. PEANUT ALLERGY

Peanut (*Arachis hypogaea*) is an edible seed of the legume family. They are an important food crop known for their high protein and oil. Prevalence of peanut allergy in the United States is about 0.6% of the population. And France, Germany, Israel, Sweden, and the United Kingdom vary between 0.06% and 5.9% [8]. Peanut allergy is IgE mediated and has received significant attention because of high sensitization rate, increased in allergy and severity of the reaction.

Allergens in peanuts can be categorized into the four most common food allergen families: the Cupin superfamily (Ara h 1, 3), the Prolamin superfamily (Ara h 2, 6, 7, 9), the Profilin family (Ara h 5), and Bet v-1-related proteins (Ara h 8), as well as two additional families, Oleosin (Ara h 10, 11) and Defensin (Ara h 12, 13). Currently, structural data exist for Ara h 1, 2, 3, 5, 6, and 8 [9].

The innate immune system includes cells (macrophages, neutrophils, and dendritic cells) that ingest foreign antigens and receptors that are activated by bacterial products (e.g., from microorganisms in the gut) and modulate cellular function. The adaptive immune system includes cells (T and B lymphocytes) along with circulating antibodies such as IgG and IgE that specifically recognize foreign molecules. Specific cytokines (e.g., IL-4 and IL-13) produced by immune cells direct the adaptive immune system to generate T cells called T helper 2 (Th2) cells that mount an IgE response [10]. Dendritic cells in the intestinal mucosal expressing low levels of co-stimulatory molecules such as B7 required for T-cell activation become activated by increased exposure to bacterial toxins and enable activation of food antigens-specific T cells in the mesenteric lymph nodes. Activation of B lymphocytes and their maturation into plasma cells leads to increased levels of peanut allergen-specific IgG and IgE that characterize peanut allergy. An IgG response is evidence of loss of tolerance to peanut allergens and an IgE response is pathophysiologic as discussed above [11]. The factors involved in the activation of Th2 cells and the development of peanut allergy still remains unclear.

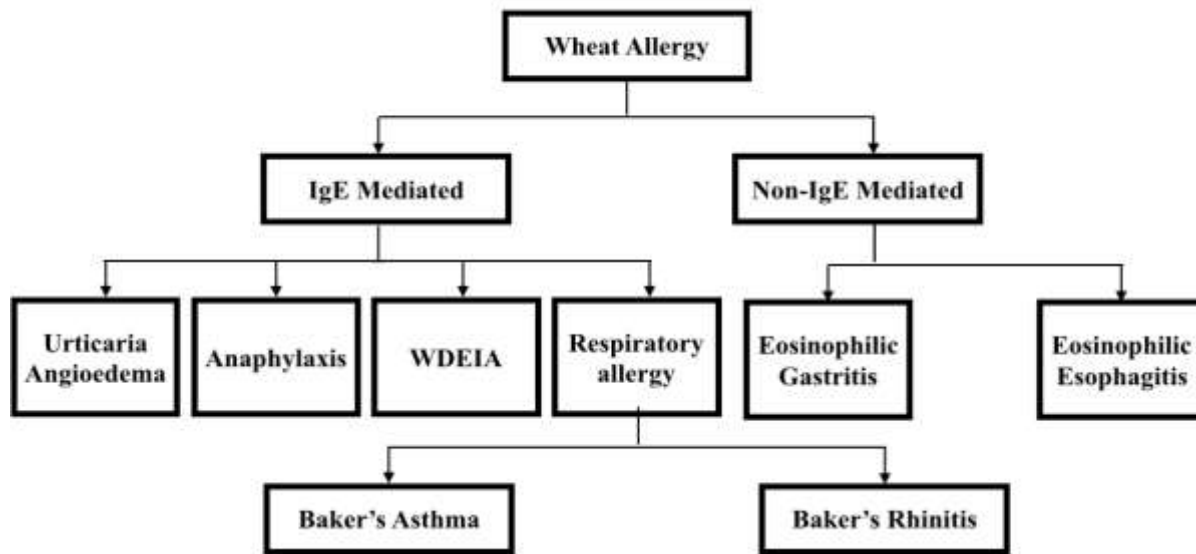
In addition to primary sensitization, secondary sensitization to peanut allergens can occur as a result of exposure to cross-reactive allergens. For example, the birch pollen allergen, Bet v 1, is a homologue to Ara h 8, and the peach allergen, Pru p 3, is a homologue to Ara h 9. In this scenario, patients primarily affected with birch pollen allergy or allergy to peaches can develop a secondary allergy to peanuts [12].

The characteristics of an allergic response depend predominantly on the tissues affected and the cytokines produced, which, in turn, determine inflammatory cell and non-immune cell involvement. Of all of the allergic disorders, anaphylaxis is probably the most dramatic. In this disease, rapid production of large quantities of vasoactive mediators, including histamine, platelet-activating factor (PAF), leukotriene and serotonin, as well as Th2 and inflammatory cytokines and proteolytic enzymes by mast cells, basophils and macrophages causes increases in vascular permeability and smooth muscle contraction that can cause urticaria (hives), swelling of the face, mouth, tongue and pharynx (angioedema), diarrhea, asthma, decreased myocardial function, hypotension. This causes death of approximately 1,500 Americans a year [13, 14]

Prick skin test is commonly used clinical method while fluoroenzyme immunoassay (Pharmacia ImmunoCAP-FEIA) is a common laboratory method. The accuracy of PST positive result is less than 50% but accuracy of negative result is greater than 95%. ImmunoCAP-FEIA is less sensitive than PST, but accuracy is 100%. In case where conclusive diagnosis is impossible oral peanut challenge is required [15].

## 2. WHEAT ALLERGY

Wheat (*Triticumaestivum*) is one of the widely grown crops worldwide which is used as a staple food in many countries and is an important component for bakery and brewed products. But it has been identified as a growing concern with respect to food allergy development in a wide population, including IgE mediated and non-IgE mediated responses [16]. Figure 2 summaries the types of allergic reactions in Wheat. It is observed that wheat allergy is more common in children than in adults, especially if wheat was introduced after 6 months of age [17].



**Figure 2: Types of Wheat Allergy Reactions**

According to Osborne classification (1924), there are four types of wheat proteins depending on solubility-Albumins, Globulins, Gliadins and Glutenins (Gluten proteins). Gluten or prolamins, having high content of proline and glutamine and are the major proteins that cause intolerances and food allergies in individuals [18, 19].  $\omega$ -5gliadin (Tri a 19) is a significant allergen in young children with immediate allergic reactions to ingested wheat. The same allergen causes anaphylaxis and WDEIA. Wheat  $\alpha$ -amylase inhibitors (Tri a 15, Tri a 28, Tri a 29, Tri a 30), thioredoxin (Tri a 25), Peroxiredoxines (Tri a 32) on ingestion or inhalation cause Baker's asthma [18, 21, 27]. The other commonly known allergens causing these reactions include  $\alpha$ -purothionin, trypsin inhibitors (Tri a 33), Peroxidase, Serine protease inhibitors, Thioreductase (Tri a 27) and  $\alpha$ -,  $\beta$ -,  $\gamma$ -, and  $\omega$ -gliadins [22-25]. When the symptoms occur within 1-3 hours of wheat exposure, the allergy is confirmed by measuring IgE specific to wheat by Skin prick test (SPT) or in the serum IgE (sIgE) [26].

IgE mediated response is seen associated with activation of B cell in response to wheat ingestion or TH2 dependent activation of B cell which produces IgE antibody. The allergic condition manifests with different symptoms including urticaria, anaphylaxis, angioedema, asthma, allergic rhinitis and also exercise induced anaphylaxis (EIA) [28, 29].

When wheat allergens come in contact with damaged epithelial lining, cytokines (IL-25, IL-33) are produced by the epithelial cells that trigger innate immune cells (ILC2s, DCs, and basophils) thereby contributing to a Th2 cell response. The response produces cytokines (IL-4, IL-5, and IL-13) that help in IgE class-switching in B cells. This occurs during first time exposure of wheat allergen. On successive exposure, specific allergens interact with two specific IgE antibodies released by memory B-cells that are bound to their high-affinity IgE receptor (Fc $\epsilon$ RI). They induce the cross linking of the Fc $\epsilon$ RI and cause the activation of mast cell and basophils, which further elevates the inflammatory reactions [27,30,31]. Wheat dependent exercise-induced anaphylaxis (WDEIA) has also been reported in many cases (type of anaphylaxis that occurs while performing intense exercise, in close relationship with the timing of wheat based food ingestion) [32].

Wheat also induces non-IgE mediated allergic reactions, which depend on TH2 activation and cause eosinophilic infiltration in the gastrointestinal (GI) tract, and are called eosinophilic gastrointestinal diseases (EGIDs) [33]. EoE (eosinophilic esophagitis) is the most common form of EGID (symptoms of gastro esophageal reflux disease [GERD], vomiting, abdominal pain, dysphagia, and food impaction). These are more commonly seen in adults than in children [33, 34]. In EoE intrinsic and extrinsic factors result in increased esophageal permeability which on exposure to food antigens causes Th2 activation [36].

Studies reveal the active involvement of Th2 dependent cytokines IL-4, IL-5 and IL-13 in inflammation, eosinophilia and fibrotic changes. In this type of IgE-independent allergic reactions in EoE, the Th2 inflammation appears to be driven by a dysfunctional epithelium due to Thymic Stromal Lymphopoietin produced by the esophageal epithelium in genetically predisposed individuals and is considered as one of the major initial driver of the Th2 inflammation [35].

At present, the main treatment of a wheat allergy (both IgE dependent and IgE independent) is based on avoidance of wheat altogether [38]. Immunotherapy based methods like sublingual (SLIT) or epicutaneous (EPIT) or oral (OIT) are a way to treat IgE mediated reactions to wheat. OIT gives the most promising results among all [37].



### 3. COW MILK ALLERGY

Cow Milk (*Bos domesticus*) allergy is an immune mediated response to proteins present in cow milk and is considered as most complex disorder in infants and early childhood. The protein involved in CMA and identified as allergens are casein (Bos d 8) and  $\beta$ -lacto-globulin (Bos d 5) of which casein constitutes 80% of total protein. Casein composed of  $\alpha$ S1-(Bos d 9),  $\alpha$ S2-(Bos d 10),  $\beta$ -(Bos d 11), and  $\kappa$ -(Bos d 12) casein from which  $\alpha$ S1-casein seems to be major allergen according to IgE and T-cell recognition data [39-41]. Cow milk is also a member of "Big-8" food allergen ranking along with egg, soy, wheat and peanut in terms of prevalence [42].

Allergies to milk are often Immunoglobulin E (IgE)-mediated allergy and non-IgE-mediated allergy. The immunological mechanism of IgE-mediated allergy is better understood compared to non-IgE-mediated reaction and is easily treated [43]. IgE-Mediated CMA consists of Sensitization phase and Activation phase. In "sensitization phase", the immune system is programmed to produce IgE antibodies to milk protein which are ingested and internalized by antigen presenting cells (APC) and peptides epitopes are presented to T-cell. The Th2 effector T-cells signals B-cell by means of interleukin-4 (IL-4) which causes class switching from antibody production to allergenic milk protein specific IgE sited on mast-cells surface. Milk proteins cross-linking the IgE sited on mast cells promotes an intracellular signaling process with cell degranulation and release of histamine and other inflammatory mediators that produces local tissue responses of allergic reaction triggers the "activation phase". Non- IgE-mediated CMA involves activation of inflammatory cells by means of interferon-gamma (IFN- $\gamma$ ) mediated by Th1. Whereas, Oral tolerance is achieved by action of regulatory T-cells (Treg) that suppress the action of Th1 and Th2 by interleukin-10 (IL-10) and by transforming growth factor-beta (TGF- $\beta$ ) [42,43].

As CMA is mainly present in early childhood the affected infants usually develop symptoms within 1 week after consumption of milk protein from their diet. The affected children shows more than one symptoms involving organ system mainly gastrointestinal tract and skin [45]. Symptoms associated with IgE-mediated includes Cutaneous (eczema; urticaria; angioedema), gastrointestinal (oral allergy syndrome; nausea; vomiting; diarrhea) or respiratory infection (rhino conjunctivitis; asthma). These symptoms can be diagnosed by skin-prick test (SPT) and Radioallergosorbent test (RAST) [44]. It also causes a life threatening anaphylactic reaction that narrows the airways and can block breathing which can be treated by epinephrine (adrenaline) shot [47]. In non-IgE mediated CMA development of symptoms varies from 1 hour to several days after ingestion of milk. It causes enterocolitis where child develops severe vomiting and diarrhea. Child can also have gastro esophageal reflux, constipation and may also cause Heiner syndrome which is a pulmonary disease that presents child with cough, fever, wheezing and nasal congestion. The only way to treat non-IgE mediated symptoms is self-diagnosis which is avoiding the diet containing milk protein [42,46].

### 4. SOY ALLERGY

Soy is a popular vegetarian alternative to meats, and many processed foods contain soy. Therefore soy avoidance is challenging for the patient with soy allergy. Soy is also an important source of nutrition for infants with milk allergy. Soy allergy also is a common type of allergy in children, and affects approximately 0.4% of children in European countries [48, 49].

The common allergen proteins in Soy has been identified as Gly m 1, a hydrophobic protein, Gly m 2, defensin, Gly m 3, profilin, Gly m 4, PR-10, Gly m 5, vicilin, a cupin, Gly m 6, legumin, a cupin, Gly m 7, seed biotinylated protein, Gly m 8, 2S albumin [50].

The entry and recognition of these soy proteins in allergic individuals generate activated antigen-specific B cells and a special set of helper T cells that direct B cells to differentiate into IgE-producing plasma cells. Once secreted, IgE is quickly bound by high-affinity IgE receptors mainly on the surface of mast cells which contain large amounts of histamine and other allergic reaction mediators and are the main inducers of symptoms of allergy. This results in sensitization and the presence of large numbers of mast cells armed by allergen-specific IgE antibodies on the cell surface in circulation [51]. Post sensitization, IgE antibodies on mast cells binds the allergen so that the allergen cross-links at least 2 receptor-bound IgE molecules. This creates a signal causing the mast cell to release histamine and other inflammatory mediators (degranulation). Timing and magnitude of the release is defined by allergen dose and a number of poorly understood host factors [50,51].

The diagnosis of Soy allergy is generally done by Skin prick test (SPT) or Oral food challenge. In SPT, after introduction of the soy product into the skin, whealing and flaring is observed by the allergic patient. In oral food challenge, the patient is fed with soy product and symptoms such as symptoms of atopic dermatitis wheezing, episodes of diarrhea, persistent rhinorrhea and significant change in blood pressure is analyzed [52]. Soy allergy can be tested using different methods like - Radioallergosorbent Test (RAST) which is a serology test that measures IgE antibodies specific to soy-allergens with the use of radioisotopes [53]; ELISA, where antibody conjugated enzymes and chromatic substrates are used and allergen-bound antibodies are quantified [54]; Immunoblotting, where separated proteins in soy from polyacrylamide gel electrophoresis exposes IgE-allergen binding [54]. The overall human clinical and animal model data indicates that soy proteins tend to be less immunologically reactive than many other food proteins. Further biochemical methods and immunochemical reagents for identifying allergic mechanisms will be required to better characterize and understand soy protein's unique immunological properties [51].

### 5. EGG ALLERGY

Egg allergy is a set of adverse immunological responses to exposure to allergens found in egg white or egg yolk. It is the second most common food allergy in the United States after milk allergy [55]. The reaction includes IgE antibody-mediated allergy as well as other allergic syndromes such as atopic dermatitis and eosinophilic esophagitis, which are mixed IgE- and cell-mediated disorders [56]. The major allergic proteins identified from the egg of the domestic chicken (*Gallus domesticus*) -are ovomucoid (Gal d 1, 11%), ovalbumin (OVA) (Gal d 2, 54%), ovotransferrin (Gal d 3, 12%) and lysozyme (Gal d 4, 3.4%), out of which Ovomuroid (OVM) has been the dominant allergen [57].

IgE mediated reaction has initial sensitization of mast cells, basophils and other effector cells. The re-exposure to egg allergen will cause activation and degranulation of effector cells with subsequent release of pharmacologically active mediators including heparin, histamine, leukocyte chemotactic factors, and leukotrienes [58]. IgE responses have a TH2 dependency. While TH2-derived cytokines promote

IgE response, it is balanced by TH1-derived cytokine down regulation of IgE. Egg allergy can result from a failure of this balance, leading to an overproduction of IL-4 by TH2 cells [58].

Other two immune response related to egg allergy are eosinophilic esophagitis and food protein-induced enterocolitis syndrome (FPIES). Eosinophilic esophagitis is an inflammatory disorder associated with the accumulation of intraepithelial eosinophil, and it is mediated by both IgE and non-IgE processes and egg protein being a major trigger for it. FPIES is also an inflammatory disorder characterized by vomiting, lethargy, and diarrhea. Typically symptomatic presentation in FPIES occurs 2 - 6 hours after ingestion of egg protein [59,60]. Diagnostic evaluation for suspected hen egg allergy includes skin testing, egg-specific serum IgE levels, and oral food challenges. Immunoassay diagnostics include radioallergosorbent tests (RASTs) and fluorescent enzyme immunoassay (FEIA) [61].

Avoidance of egg exposure is the most effective form of egg allergy management but is not equivalent to cure and may not always be feasible since hen's egg is a versatile ingredient used in food from many cultures, including a wide range of manufactured food product. The dietary avoidance of egg can thus be challenging [62].

## 6. SHELL FISH ALLERGY

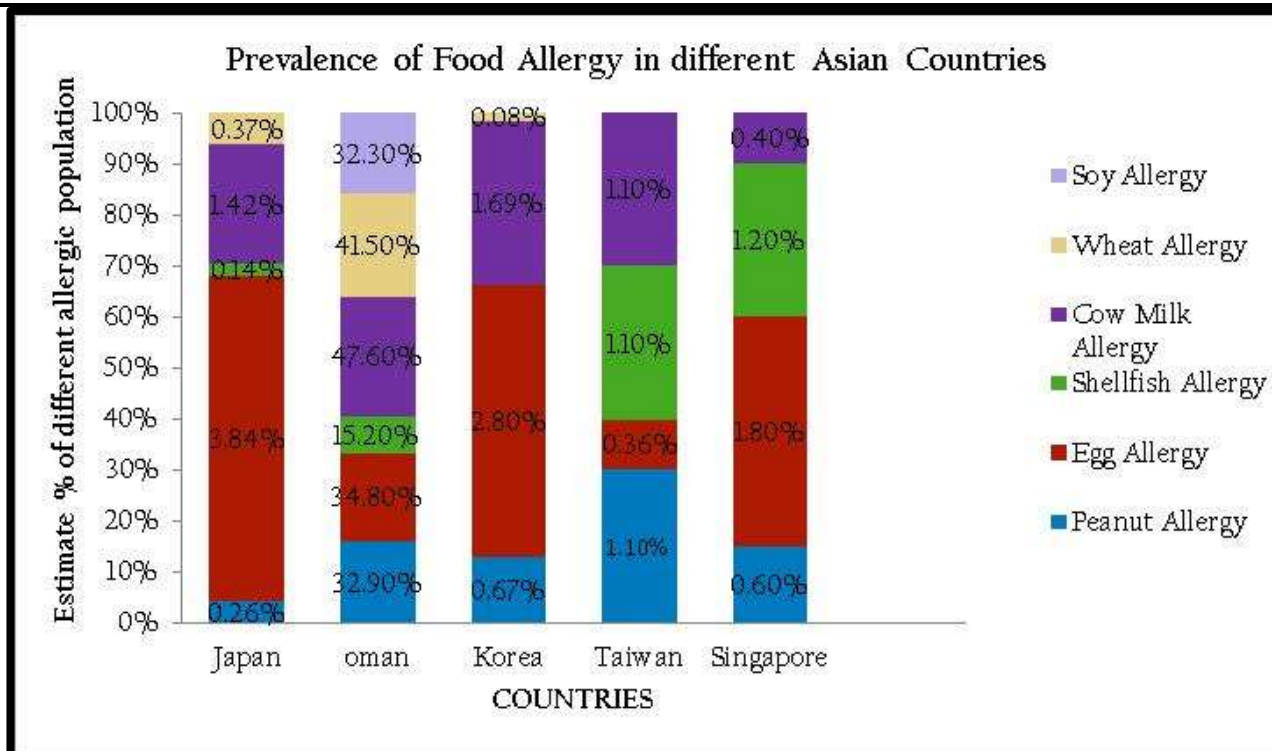
The two invertebrate phyla of arthropods and mollusks are generally referred to as "shellfish". They include mussels, oysters, abalone, snails, squid, prawn, crab, lobster, etc. Shellfish is one of the main food allergens in adults and unlike other food allergies, most shellfish allergy persists for life in the affected individual [63]. Currently, 2 % of the general world population is affected by shellfish allergy, with much higher rates in countries with high seafood consumption.

In shellfish species, 34 allergens have been identified and characterized which belong to the family of Tropomyosin, Arginine kinase, Myosin light chain, Sarcoplasmic calcium binding protein, Troponin C and Triosephosphate isomerase [64]. Diagnosis involves skin prick testing, oral challenge testing, clinical history and in vitro quantification of IgE by immunoCAP assays [66].

The clinical pathology involves similar mechanisms of IgE mediated reactions against shellfish allergen proteins. It is observed that the intensity of IgE binding is greater in children than adults [66]. The main sensitization to shellfish specific allergens can be hampered due the highly cross-reactive nature of some allergenic proteins especially Tropomyosin. It is known that tropomyosin has mainly linear IgE epitopes and is of great importance in determining the degree of cross-reactivity between different shellfish species. Therefore, IgE cross-reactivity is very frequent among crustacean species [65]. Increased analytical specificity of TM in molecular-based serological tests will help to identify patients at risk for severe allergic reactions and, in addition, indicate broad cross-reactivity to TM from other shellfish species and perhaps insects and mites [63]. Due to the often long-lasting nature of IgE-mediated allergies to shellfish species patients with proven allergic reactions should avoid shellfish permanently, unless subsequent controlled challenges have ruled out a still present clinical reactivity.

## II. STATISTICAL ANALYSIS

According to the prevalence carried out on the basis of self-reported cases, questionnaire based and by measuring specific IgE-mediated level, food allergy is the major growing concern in Asian Countries and is mostly detected in young children's in age group of 0-7 years. Allergies that were studied are Peanut, Egg, Shellfish, Cow Milk, Wheat and Soy allergy. In Taiwan region Peanut allergy 1.1%, seemed to be the common trigger followed by Shellfish 1.1% and Milk allergy 1.1% and predominates the Egg allergy 0.36%. The Korea region was more prevalent to Egg allergy with recognition of 2.8% along with Cow Milk rates 1.69% whereas Peanut allergy was reported to be 0.67% and Wheat allergy was less than 0.08%. However the disparity in prevalence of Wheat allergy in Asian region is still unknown. In case of Oman, the most reported allergen cases were found to be associated by Wheat 41.5%, Egg 34.8%, Milk 47.6%, Peanut 32.9% and Soy allergy 32.3% whereas Shellfish was less reported with rate of 15.2%. Allergy to Shellfish and Cow Milk is comparatively lower in Singapore despite of their high consumption and were recognized to be 1.2% and 0.4% respectively. Egg allergy was considered being most common in children below 3 years and was demonstrated to be 1.8% whereas the less detected was Peanut allergy 0.64%. In Japan Egg, Cow Milk and Wheat were the most causative food in children's and the allergies caused by them was estimated to be 3.84%, 1.42% and 0.37%. However Shellfish and Peanut allergy is less reported and were found to be 0.26% and 0.14% respectively. Figure 3 give statistical representation of prevalence of food allergies in different Asian countries [67-69].



**Figure 3: Prevalence Of Food Allergy in different Asian Countries [67-69]**

### III. CONCLUSION

Food allergy is common in many parts of world and is fatal as it affects individuals and families. Although the care for food allergy is avoidance of food itself, but recent advancement in medical technology has made it possible to detect the food allergens and its specific IgE binding epitope which can control the sensitization. Basic studies have identified immune mediated pathways that are helpful in designing therapeutics. Furthermore, sensitization patterns that facilitate specific immunotherapy are often temporary, and recurrence of the food allergy is observed. This happens after regular intake of the maintenance dose of the food allergen is stopped. Although there are number of allergen that still remain unidentified due to conformation changes and other factors. So as an alternative the food market is trying to develop food products that are free from allergens.

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