A Review of Naturally Occuring Food Allergens and Their Impact on Health

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Allergic reactions to foods influence a remarkable amount of population and are related with significant wellbeing results. It is one of the most significant issues that have expanding consideration. Current comprehension of the turn of events and utilization of allergenic capability of certain types of food proteins is restricted. In spite of the fact that there is a selection of in vivo models for assessing hypersensitivity, none of the current models has been approved, is prescient, or generally acknowledged with respect to their allergen explicit inhibitors. Hence, there is a proceeded with enthusiasm on the knowledge recovery based on food allergy so as to give more enlightening way to the current research field. In this paper, the current status of purification, characterization, and types of food allergens and their impacts is thoroughly reviewed. The present available methods for the allergen assessment (in view of animal, cell and clinical methodologies) are emphasized.

Keywords: Characterization; Food Allergens; in vivo; in vitro; Mechanism.

Food sensitivity is a most common medical issue of both developed and developing countries causes critical anaphylactic reactions consequently leads to notable morbidity. It affects personal satisfaction and makes a substantial economic burden[1]. The pace of food allergy differs by age, local diet, chemical nature of food and numerous other factors[2], and different quantities of clinical highlights impacts the common history of food hypersensitivity[3]. Studies conducted in the western countries based on nut hypersensitivity, recommended that the prevalence rates have expanded, virtually duplicating, and outperform 1 % in children those who are school aged[4]. The report from Centres for Disease Control and Prevention indicated that, youth food sensitivity raised around 18 % with the direct influence of 3.9 % of youngsters are happens from 1997 to 2007[5]. In westernized nations, harmful safe reactions to food items influence around 5 % of young children and in case of grown-upsis around 3 to 4 %, seem to have more predominance[2].

India is the second most crowded nation, having rate of population nearly 1.3 billion. Recent reports revealed that there are an expected 37.5 million instances of asthma and a rise in predominance of hypersensitive rhinitis[6]. A food specific sensitization study conducted on children aged 7 - 10 years indicated that food allergy appears to be less common when compared with developed nations[7].

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A survey conducted by EuroPrevall - INCO in Indian kids revealed, food hypersensitivity to be 0.14 % among youngsters with rate of sensitization was high (around 19.1 %) to food allergens. Considering the case of nut hypersensitivity, it was discovered to be low (around 0.03%) in Indian kids, although the sensitization rate was high at 6.3%[7]. Therefore, further examination is expected to explore why predominance of clinically applicable food sensitivity is low in India in spite of high sensitisation rate.

The function of food related proteins

Hypersensitive responses to milk, egg, fish, peanut, shellfish, wheat, tree nuts and soy represent most important food sensitivities in the worldwide[17].Majority food allergens having atomic weight varying from 10 to 70 kDa and are water dissolvable glycoproteins moderately stable to acid, proteases, and temperature.

Furthermore, food preparation, and manner of food ingestion also affect allergenicity. The studies conducted on pea nut indicate that Millard reaction due to high temperature roasting (180 [0]c) and emulsification due to adjuvant effect are the example which describes how the food preparation methods affect the food allergenicity[4],[18]. The Meta - analysis study conducted on fruits and vegetables accounts that allergic reactions shifted from 0.1 - 1.4 for tree nuts, fruits about 0.1 - 4.3 % and for vegetables under1 %. Food initiated hypersensitivity are normally connected with severe reactions. Certain foods like nuts and seafood activates anaphylactic reactions among children and adults. For example: In the case of young children, cow milk and egg are very common culprits[19].

Common food allergies

Food allergy affects over 200 million people in worldwide. The prevalence rate is mainly raised in developed nations[20]. An investigation of government schools in Australia (>550,000 students) taking a gander at those in danger of hypersensitivity mentioned around 41 % expansion from 2009 to 2014 (0.98 - 1.38 %)[21]. The US Centres for Disease Control and Prevention, utilizing information from one inquiry in the US National Health Interview Survey, disclosed that the commonness of food sensitivities expanded among kids from 3.4% in 1997 to 1999 and 5.1% in 2009 to 2011[22]. AUS overview depending on

parental report of youngster nut hypersensitivity utilizing comparable approach over time exhibit a rate of 0.4 % in 1997 expanding to 1.4% in 2008 [2]. As per National Institute of Allergy and Infectious Diseases, sensitivity of the food item is characterized as "an antagonistic wellbeing impact emerging from a particular resistant response that happens reproducibly on introduction to given nourishment". This reaction incorporates essentially a wide range of safe intervened responses[23].

The term sensitivity was named by the Austrian paediatrician *Clemens von Pirquet*in 1906, who explained instances of serum affliction in kids treated with immunizer arrangements[24]. The common hypersensitivities are fluctuates relying upon the nation. There are many types of allergies. We have given a brief overview of some of the most common food allergies.

Milk allergy

Milk allergy is common among paediatric population. *Carlos & Hania* summarizes the dairy animals' milk sensitivity for its better analysis and risk management[25]. The occurrence of cow's milk sensitivity in kids living in the created world is roughly 2 to 3 %, and lower predominance rate is only observed in breastfed new - born infants (0.5 %)[26],[27].

The significant allergens seen in bovines milk are belongs to casein fraction of proteins and to whey proteins [28].The two fundamental systems which clarify unfavourably susceptible reaction of cow's milk hypersensitivity just as other food sources are: IgE intervened and non-IgE interceded.

IgE mediated manifestation includes acute urticaria and angioedema. Non IgE mediated mechanism involves indications on epidermis and the digestive tract. At the level of digestive tract incorporates: bovine's milk – promptedenterocolitis, bovine's milk –incite denteropathy and bovine's milk - initiated proctitis and proctocolitis[29]. The indications may make before multi month mature enough, and as frequently as conceivable inside multi week after the associate of dairy creatures' milk proteins with their eating routine[26].

In case of non - IgE mediated response; symptoms are delayed and typically happen in no time and up to 2 h of ingestion. The epidermis is

normally included and followed by gastrointestinal plot and, marginally the respiratory and additionally cardiovascular frameworks. The seriousness related with the responses may fluctuate from mild to moderate, and sometimes leads to critical anaphylaxis [30],[31]. The diagnosis of cow's milk allergy includes certain routine work-up like skin prick tests (SPTs), direct IgE (sIgE) estimations, and feeding tests[29],[31],[32],[33],[34].

Egg allergy

Egg allergy most commonly IgE-mediated, and is seen in childhood. It has been reported that prevalence rate is of 1.3 to 10.1 %[35]. This may develops in the main year of life creating, and it is the second most basic reason for food sensitivities in kids[36],[37].

Egg white contains in excess of 20 distinct glycoproteins and proteins. The significant allergens seen in hen's egg are Ovomucoid (Gal d 1), ovalbumin (Gal d 2), conalbumin (Gal d 3), and lysozyme (Gal d 4). The principle allergen found in egg yolk is Alpha - livetin (Gal d 5) [38]. Clinical responses are basically IgE and non - IgE intervened or a combination of the two kinds.

The diagnosis of egg sensitivity mainly depending on history taking, *in vitro* allergen-explicit blood IgE tests, skin prick test, histamine discharge test, and feeding tests[39]. Among this, SPT shows a decent affectability yet a helpless particularity. Currently, oral immunotherapy (OIT) provides better results to egg allergy. It had mild to severe side effects. Additionally, there is a need to develop safer OIT for novel modified food antigens[40].

Peanut allergy

Peanut allergy affects 1 to 4.5 % of children, with severe reactions[41]. *Chiara & Heimo* reviewed about certain peanut allergens [42]. Bicupin seed storage proteins contain Ara h 1 and Ara h 3[43]. Ara h 2, Ara h 6, and Ara h 7 are seed stockpiling proteins, which are included in the prolamin superfamily. Ara h 5 is said to be an individual from the profilin family[8].

Diagnostic investigations of nut allergens incorporate skin prick tests, nut explicit IgE (sIgE), and absolute IgE[44]. Thermal processing like boiling, frying, or roasting appears to have impact on event of nut hypersensitivity. Among these cooking methods, boiling of peanuts has lesser prevalence[45]. Recently, researchers have mainly focussed on the deep immunological characterization of nut allergens and the utilization of decontaminated allergens symptomatic field. *Kelly Bruton* & his colleagues were discussed about the current state of oral immune therapy in the field of peanut allergy [46].

Tree nut hypersensitivity

Tree nut hypersensitivity predominantly creates by age of 2 years, and the sensitization to allergen exposure naturally increases with age[47]. Most of proteins engaged with tree nut hypersensitivity have a place with protein groups ofvicilins, nsLTPs, 2S albumins, and legumins. Of these, dust related tree nut hypersensitivity mediated by Bet v 1 - homologues and profilins. Moreover, oleosins and thaumatin - like proteins were demonstrated to be noteworthy allergens[14],[48]. *Andrzej KuŸmiñski* & his colleague's reviewed about the different nut allergies [49]. Individual tree nut components and their allergic factors are given in table 2.

The analysis of tree nut sensitivity is performed with detailed clinical history, skin prick testing, serum - explicit IgE, and oral food challenges (OFCs) [50],[51],[52]. Dietary management is the only prevention method recommended for tree nut allergy.

Soy allergy

Soy allergy typically happens in the beginning of early stage; with announced pinnacle rate of soy sharpening occur in the age of 2 years[53]. Generally, soy sensitivity is not common as other food hypersensitivities.

International Union of Immunological Societies Allergen Sub - Committee acknowledged birch dust - related proteins, soybean hull proteins (Gly m 1 and Gly m 2), a profiling (Gly m 3), and a PR-10 protein (Gly m 4), are the significant allergenic proteins found in soy (*http://www.allergen.org?Allergen.aspx*). Additionally, certain storage proteins b-conglycinin and glycinin (Gly m 5 and Gly m 6), the thiol protease (Gly m Bd 30 k), the 2S albumin soy protein, and the soybean Kunitz trypsin inhibitor are also have been described[54],[55],[56],[57],[58].

Patients suffering from soy sensitivity present a scope of clinical disorder like IgE - interceded and non - IgE - intervened. *Kattan et al.,* discussed briefly about the clinical manifestation behind soy allergy[59]. The finding of soy sensitivity

is mainly involves by taking the clinical history and allergy testing. Now a days, oral food challenge and oral immunotherapy are the methods used in the field of management of soy allergy.

Wheat allergy

Wheat allergy is very common in paediatric population. The prevalence rate of wheat allergy differs based on age and region [60]. Wheat allergens are belonging to the grass family *Poaceae* and contain numerous allergenic proteins, which are partitioned in four classes dependent on the extraction solvents. American chemist *T. B. Osborne* standardized this classification[61]. Important wheat allergens responsible for wheat allergy are given below (Table: 3):

The clinical sign of wheat hypersensitivity relies upon the course of allergen introduction. Usually, it is liable for IgE - intervened responses, with the event of urticaria, angioedema, bronchial impediment, queasiness, stomach torment, or fundamental hypersensitivity[63]. Non –IgE-intervened indication incorporates food protein-incited enterocolitis condition. The prognosis involves SPT and serum IgE tests. The current management of patients suffering from wheat sensitivity is dietary shirking. Recently, feeding tests has been announced for wheat hypersensitivity with positive outcomes, regardless of whether further investigations are requires for building up the best convention so as to advance resistance in wheat - allergic youngsters[64,65,66,67,68].

Meat allergy

Meat allergy is varied according to region basis, and is accompanied with local dietary habits and environmental factors. This is mainly occurs during the primary long stretches of life, therefore it is uncommon in grown-ups[69]. The major allergens found in meat are serum albumins and immunoglobulin. Important allergens seen in meat are listed below (Table 4).

Several studies shown that activity of this antigenic peptide can be destructed by domestic cooking and some other technological treatments. Certain treatments like warming can adjust or inactivate the epitopic spaces liable for the IgE holding by changing the conformation of the epitopes; or by the denaturation of the three dimensional structure of a protein can create new epitopes and improve the availability of the allergenic determinant to explicit antibodies.

Likewise, freeze - drying, homogenization and mechanical cycles are generally employed to meat during the creation of infant nourishments, can altogether diminish the allergenic capability of beef [71].

Cooking methods frequently destroys heat- sensitive allergens. Conversely, *Fiocchi et al.,* shown that a couple of patients will regardless react to cooked nourishments[72]. Apart from this, researchers reported that allergenic potential of the antigen can be tested through cross reactions, and this can be used in the diagnostic field[73].

Fruit allergy

Literature reports confirmed that the prevalence rate of fruit allergy was ~5-8% children and 2 – 3% adults. Mostly 12 - 15 fruits are associated with fruit allergy, commonly market available fruits and vegetables. Fruit allergic reactions are in relation with oral allergy syndrome (OAS) together with pollen - fruit-vegetable syndrome[74,75].

Classification, mechanism of pathogenesis, and clinical features of food allergy

The epidemic of food sensitivity has expanded over the previous decade. Despite the fact that the innermost processes involved in food related sensitive responses are cleared, yet the ideal molecular events food allergen - instigated hypersensitive showings are not definitely perceived[76]. Recently, researchers evaluated the food allergens mainly through bioinformatics examination, and clinical studies like model tests, cell model creature tests, serological examination, and mimicked gastric assimilation. The studies revealed that using of cell models is more convenient and flexible method instead of using animal models. Yet, *in vivo* test is the most immediate and instructive strategy to assess the possible sensitivity of the food item. *Sampson et al.* provide a detailed review of mechanism of food allergy. They described the factors which effects tissue and immune responses to food antigens, the recent findings with respect to the advancement of invulnerable resilience, the role microbiota in the GI tract and the immunologic response of desensitization system [77].

Food hypersensitivity is generally IgE - mediated type I hypersensitivity, non - IgE-mediated, and mixed type.

IgE mediated

When the food allergens initially enter the body, the initiated cells were emitted interleukin (IL)- 4,5,13, and different cytokines which prompt antibody (IgE) creation in B cells. The communication between IgE and the objective cells (granulocyte cells, basophil, and mast cells) leads the body overly sensitive. Again a similar allergen enters the body once more, it communicates with the IgE molecules on the objective cells mediates the spanning response, activating the underlying pathway, brings about the degranulation of target cells, and deliveries the mediators like 5-hydroxytryptamine, histamine, and leukotriene. This leads to unfavorably susceptible response. This enhances the permeability of intestinal epithelial cells to the allergenic protein, and accordingly influencing the pathway of specific cytokines, and creating a Th2 - type provocative reaction. This is the mechanism behind IgE - mediated food allergy [73].

Mixed type food allergies

This class of food hypersensitivity is intervened by both IgE - dependent and IgE - free pathways. This is delayed type, and the allergy - associated atopic dermatitis seen after 6– 48 hours. This is caused by T helper 2 cells. Apart from this eosinophilic gastrointestinal disorders like eosinophilicoesophagitis (EoE), brought about by the eosinophilic penetration of tissues [78],[79],*,[81]. Further examination is required in this sort of food sensitivity.

Non-IgE-mediated food sensitivity

Mostly Non -IgE-interceded hypersensitivities principally affects digestive tract, as opposed to the skin and respiratory system [82],[83]. At this moment, the framework behind the food sensitivity is very clear and we show it in the figure 2. Major features associated with both type of mechanism are given in the table 6.

Coombs and Gells proposed four types of allergy induction pathways by considering the system of pathogenesis [24].

It isn't surely known to what extent the mechanism behind food allergy; hence there is a need to discuss about the extraction and purification of food allergens from various food sources for the detection and diagnosis of its allergenicity. In this communication, the current status of purification and characterization of food allergens

and evaluation of food hypersensitivity is briefly reviewed, and the present available methods for the allergen assessment (in light of creature, cell and clinical methodologies) are listed. In addition to this, we presented some related examination on food allergen specific inhibitors, and want to have some motivation in the field of food hypersensitivity.

Plant and animal food allergens

Normally, all food allergens are proteins, yet not all food proteins are allergens [85]. There are in excess of 170 nourishments have been accounted to had hypersensitive responses. Of these, the most widely recognized foods with investigated food sensitivities are peanuts, soyabeans, wheat, fish, eggs, crustacea, tree nuts, and dairy animals' milk [86]. To assess the relative allergenicity of novel proteins, it is fundamental to utilize the regular food allergens as reference proteins like cereals containing gluten, crustaceans, eggs, pea nut, soya, milk etc., [3].

The main reason behind the advancement of new food hypersensitivities is to the introduction of new proteins into the eating regimen. Hence, it is needed to elucidate the development and allergenic capability of existing and new food proteins (plants as well as animal sources) for evaluating their safety assessment on clinical studies. Current comprehension of this is deficient and has set number of prescient strategies dependent on *in vivo* examination of food allergens, and *in vitro* techniques. Thus, there is a proceeded with enthusiasm for the improvement of appropriate cell models as well as animal models that give an essential way to deal with the appraisal of hypersensitive capability of proteins [87],[88].

Extraction, purification, and characterization of food allergens

Dietary inclinations for the noteworthy people in an area accept a critical part in the improvement of food hypersensitivity. That is, increased utilization of certain foods may prompt increased sensitization to it, for e.g., sensitivity to soy in Japan, nut hypersensitivity in the France, UK, and North America and sesame sensitivity in Israel [89].Evidences of IgE-mediated hypersensitive responses incited by legumes in Asian and Mediterranean nations have been accounted as legumes are the major source of dietary protein in these nations [90].

Astwood et al. described different types of extraction methods for allergen proteins from various plant sources[91]. Phosphate buffer of different salt concentrations at pH 7.0 were used for the extraction. With the improvement of molecular biology, genomics, and immunology, numerous allergens and allergenic sources are presently revealed from various sources[92]. *RamkrashanKasera et al.* were purified the kidney bean allergen using anion exchanger Q sepharose column. Its characterization was done with immunochemical methods, and the results showed that the molecular weight of the purified protein was found to be 31 kDa[93]. *Pastorello & Trambaioli* reviewed concerning to the field of isolation of allergens from various food sources[94].

Usually food allergens have been distinguished by immunetests, utilizing serum tests from unfavorably susceptible patients. Enzyme-linked immunosorbent assay (ELISA) was the basic strategy utilized for their detection. Currently, there are mainly three methods accessible for the detection and measurement of food allergen, namely: DNA based techniques, protein based methods and cell based methods. In addition, these methods can likewise be utilized in food sensitivity diagnostics[103],[104105]

• DNA based strategy: Methods for estimating allergen coding genes (e.g.: PCR).
• Protein based strategy: Methods for measuring allergenic protein levels (e.g.: ELISA, Protein microarray, Mass spectrometric methods).
• Cell based strategy (otherwise called basophil activation test (BAT): Methods for measuring effector cell activation levels.

Literature reports underlined that there is a correlation between quantitative and subjective advancement of allergen extraction and the protein recovery. *Hocine et al.* constructed a D - optimal plan to advance allergen extraction proficiency at the same time from non - roasted, roasted, non - defatted and defatted pea nut, almond, pistachio flours and hazel nut utilizing three denaturing aqueous buffers at different states of, buffer - to - protein ratio, ionic strength, extraction time duration and temperature. Statistical examination demonstrated that the protein recovery varied by depending on the extraction condition with respect to the samples [9].

Currently, there is also an improved procedure for the extraction of allergenic proteins in fish was developed [106],[107]. The reports revealed that parvalbumin was the major allergen found in various fish species, cause 95 % of patients allergic to fish. Now day, at least 7 different allergens from shellfish have been identified, mostly from crustaceans[108].

The method of purification and characterization of food allergen is an important criterion in diagnostic field. Commonly, chromatographic techniques are used for their purification like gel-filtration, ion - exchange, and affinity chromatography.*Barbara Cases et al.* explained with respect to the chromatographic columns, packing materials, buffers, and methods for extract preparation[103].*Clare Mills et al.* clarified the analytical tools used in food hypersensitivity for the identification and management of numerous food allergens in the food sources. This approach mainly focussed on the quantitative MS - based method [109].

Immunoelectrophoresis was the major technique used for the identification of individual allergens from the sample extracts. This can be used to analyze single protein from a complex mixture. The basic disadvantage of this technique is the dependence on rabbit antisera as reagents[110]. Tandem mass spectrometry can also be used for the identification of purified allergen[93].

Natalia Gasilova and Hubert H Girault summarized the recent advances in food hypersensitivity determination, allergen identification from food items as well as disclosure of the latest allergenic particles *via in vitro* methods. The review pointed on the new symptomatic strategies under lab advancement includes various aptamer and immune based tests. Furthermore, combination of allergenomic techniques with peptide sequencing by the Edman degradation is the powerful apparatuses for the revelation and study of new allergens[111].

In vitro studies

Cell models are mainly defined to explain the molecular basis of an illness and to describe the cell pathways included. These can be taken as a tool for recognizable proof of medication targets, and for the screening of inherited, environmental or pharmacological threat factors related with the infections. In line with this, there are various cell models have been introduced to explain the

allergenicity and sensitization processes, including human basophil granulocyte models, mast cell models, and so forth.

Literature reviews revealed that the most ordinarily utilized cell line assigned as RBL - 2H3, is commonly considered as mast cell line. Particularly, these cell lines are mainly used for the investigations on binding of IgE to receptors (i.e., Fc€RI) and further underlying events[112],[113]. Mast cells and basophils are the two distinct cell

Table 1. List of known food allergens and their classification

S No.	Food source	Identified allergens	Allergen family	Molecular weight (kDa)
1	Peanut [8]	Ara h 1	Cupin superfamily	64
		Ara h 2	Prolamin superfamily	17
		Ara h 3	Cupin superfamily	60.37
		Ara h 4	Cupin superfamily	60
		Ara h 5	Profilin family	15
		Ara h 6	Prolamin superfamily	15
		Ara h 7	Prolamin superfamily	15
		Ara h 8	Bct v 1-related protein family	17
		Ara h 9	Prolamin superfamily	11
		Ara h 10	Olcosin family	16
		Ara h 11	Olcosin family	14
2	Soybean [9]	Gly m 5	Cupin superfamily	140~180
		Gly m 6	Cupin superfamily	320~360
		Gly m Bd 28K	Cupin superfamily	26
		Gly m Bd 30K	Papaya proteinase superfamily	30~34
		Gly m T1	Kunitz soybean trypsin inhibitor family	20
3	Egg [10]	Gal d 1	Kazal-type serine protease inhibitor family	28
		Gal d 2	Serpin serine protease inhibitor family	44.5
		Gal d 3	Transferrin family	76
		Gal d 4	Bet v 1-related protein family	14.3
4	Crustacea[11]	Pen a 1	Tropomyosin family	36
5	Milk [12]	Bos d 4	C-type lysozyme/alpha-lactalbumin family	14.2
		Bos d 5	Lipocalin family	18.3
		Bos d 8		20~30
6	Nut [13],[14]	Jug r 1	Prolamin superfamily	15~16
		Jug r 2	Cupin superfamily	44
		Jug r 3	Prolamin superfamily	9
		Jug n 1	Prolamin superfamily	19
		Jug n 2	Cupin superfamily	56
		Ana o 1	Cupin superfamily	50
		Ana o 2	Cupin superfamily	55
		Ana o 3	Prolamin superfamily	14
		2S albumins	prolamin superfamily	15
		NsLTP	prolamin superfamily	6.038~9.922
		Vicilins	cupin superfamily	150–190
		legumins	cupin superfamily	150–190
		Oleosins	oleosin superfamily	<"15–26
7	Wheat [15]	Tri a gliadin	Prolamin superfamily	30~80
		Tri a 26	Prolamin superfamily	80~120
		Tri a 36	Prolamin superfamily	30~75
8	Fish [16]	Parvalbumin	EF hand domain family	12

(Abbreviation used:Ara h- Arachishypogaea, Gly m - *Glycine* max, Gal d -Gallus domesticus, Pen a - Penaeusaztecus, Bos d - *Bos* domesticus , Jug r - Juglansregia, Jug n -Juglansnigra, Ana o – Anacardium occidentale, NsLTP - Non-specific lipid transfer proteins, Tri a - Triticumaestivum)

types that assume vital roles in inception and advancement of type I hypersensitivity responses. Granulocyte basophils represent less than 1 % of the WBC population, while developed mast cells can be seen in tissues and specifically situated at interfaces with the outer environment like skin, lungs, and mucosal surfaces[114].

Eccleston and co – workers were found Rat basophilic cellsin 1973, when one of the rats was treated with strong cancer- causing agent (2-(a-chlor-b- isopropylamine)ethylnaphthalene), an uncommon type of granulocytic leukemia marked

by a significant peripheral blood basophilia[115].It is the usually utilized histamine - releasing cell line in immunological exploration, inûammation, and hypersensitivity. It has been extensively reviewed that the behavior of cells in regard of their reaction to immunological boosts.

RBL-2H3 cells, similar to basophils and mast cells, react with degranulation by cross linking of their IgE - bound Fc€RI by multivalent allergens, with the appearance of a preformed and newly synthesized mediators that brings a powerful immune allergic responses [116].*EglePassante& Neil*

Table 2. Individual tree nuts and their allergic components[13]

Tree nut	Allergic component	Protein family	Protein type
Hazelnut	Corylusavellana		
	Cor a 1	Pan-allergens	PR-10
	Cor a 2		Profilin
	Cor a 8	Storage proteins	LTP
	Cor a 9		11S globulin
	Cor a 11		7S globulin
	Cor a 14		2S albumin
Cashew	Anacardiumoccidentale		
	Ana o 1	Storage proteins	7S globulin
	Ana o 2		11S globulin
	Ana o 3		2S albumin
Pistachio	Pistaciavera		
	Pis v 1	Storage proteins	2S albumin
	Pis v 2		11S globulin
	Pis v 3		7S globulin
	Pis v 5		11S globulin
Walnut	Juglansregia		
	Jug r 1	Storage proteins	2S albumin
	Jug r 2		7S globulin
	Jug r 4	Pan-allergens	11S globulin
	Jug r 3		LTP
	Jug r 5		Profilin
Pecan	Caryaillinoinensis		
	Car i 1	Storage proteins	2S albumin
	Car i 2		7S globulin
	Car i 4		11S globulin
Almond	Prunusdulcis		
	Pru du 6	Storage proteins	11S globulin
	Pru du 3	Pan-allergens	LTP
	Pru du 4		Profilin
Pine nut	Pinuspinea		
	Pin p 1	Storage proteins	2S albumin
Brazil nut	Bertholletiaexcelsa		
	Ber e 1	Storage proteins	2S albumin
	Ber e 2		11S globulin

Abbreviation used: LTP, lipid transfer protein.

Frankish were also reviewed the provenance and suitability of RBL - 2H3 cells[113]. Subsequently, it has been broadly utilized as the mast cell model in *in vitro* studies, due to their large amount of growth in culture, and its responsiveness to FcåRI-mediated triggers[117].*Bing-Hung Chen et al.* were studied the anti - hypersensitive activity of grape seed extract on RBL - 2H3 cells. They investigated the effect of grape seed extract on the activation and degranulation of these cells [118].

The broadly utilized cell model for molecular and practical examination of intestinal epithelium is Human colon adeno carcinoma cell line (Caco-2 cells).These are profoundly spellbound with a well - shaped brush border and tight intersection[119]. *Eun-Ju Lee et al.* researched the inhibitory impacts of quercetin and kaempferol on the concealment of hypersensitive reactions mediated by IgE in RBL - 2H3 and Caco-2 cells lines. The outcomes were showed that certain flavonols have anti - oxidant and anti - inflammatory activities, hindered the secretion of sensitive mediators in RBL-2H3 cells and terminated the expression of CD23 mRNA and

mitogen - activated protein kinase (p38 MAPK) enactment in IL - 4 stimulated Caco - 2 cells [120]. Obviously, human basophil cells, mast cells, and Caco - 2 cells, RBL - 2H3 cells were commonly used in food sensitivity assessment.

In vivo studies

Animal models are also utilized as useful asset in food sensitivities to clear out the chance of troublesome, life- threatening activities and ethical impediments in clinical trials. This has been useful in permitting more fast and broad examinations to the mechanism behind the hypersensitive pathway, which helps to answer some of the troublesome inquiries still associating with the food sensitivity pandemic[88].

Laure Castan et al. explained the *In vivo* and *ex vivo* methodological endpoints utilized in murine food sensitivity models. The methods relied on the measurement of activity, anaphylaxis, physiological as well as skin response. But still, there is a need to set up validated and effective methods to assist the researchers working with animal model of food allergy[121]. Similarly, *Babu Gonipeta* and colleagues concluded the mechanism, sensitization and elicitation reactions of food allergens in both humans and mice is partially understood and therefore further research is mandatory [122].

Animal models are mainly categorised into two: small animal models and large animal models. Murine species (like BALB/ c, C3H/HeJ, DBA/2, and C57/BL6), rodents (with the Brown Norway (BN) strain, , Hooded Lister, Wistar, and

Table 3. Important wheat allergens [62]

S No.	Allergen component	Common name
1	Tri a 12	Profilin
2	Tri a 14	Lipid Transfer Proteins
3	Tri a 15	alpha-Amylase Inhibitors
4	Tri a 18	Agglutinins
5	Tri a 19	ω-5 gliadins
6	Tri a 20	γ-gliadins
7	Tri a 21	α-β-gliadins
8	Tri a 25	Thioredoxin
9	Tri a 26	Glutenins
10	Tri a 27	ThiolReductase
11	Tri a 28	α -amylase Inhibitor
12	Tri a 29	α -amylase Inhibitor
13	Tri a 30	α- amylase Inhibitor
14	Tri a 31	TriosephosphateIsomerases
15	Tri a 32	Peroxiredoxines
16	Tri a 33	Trypsin Inhibitors
17	Tri a 34	Glyceraldehyde-3-phosphate dehydrogenases
18	Tri a 35	Dehydrins
19	Tri a 36	Glutenins
20	Tri a 37	Thionins

(Abbreviation used: Tri a - Triticumaestivum)

Table 4. Common allergens found in meat[69,70]

Species	Allergen component	Molecular weight (kDa)
Domestic cattle	Bos d 6	67
	Bos d 7	160
Chicken	Gal d 5	69
Dog	Can f 3	69
Guinea pig	Cav p 4	66
Domestic horse	Equ c 3	67
Cat	Fel d 2	69
Domestic pig	Sus s 1	60

(Abbreviation used: Bos d - *Bos* domesticus, Gal d - Gallus domesticus, Can f - Canisfamiliaris, Cav p - Caviaporcellus, Equ c - Equuscaballus, Fel d - Felisdomesticus, Sus s - Sus scrofa)

Piebald Virol Glaxo (PVG) rats, and guinea pig were considered as small animal models, while dogs, pigs and sheep are the significant instances of enormous animal models that have been reported in food sensitivity [88],[123].

Commonly, mice are the important laboratory animal used to examine the advancement of numerous sicknesses, because of their breeding cycle, size, and sensible housekeeping when

Table 5. List of allergens found in fruits

S No.	Fruits	Allergen	Molecular weight (kDa)
1	Apple (*Malusdomestica*)	TLP (Mal d 2)	23
		Bet v 1 homolog (Mal d 1)	17.5
		Profilin (Mal d 4)	14
		LTP (Mal d 3)	9
2	Peach (*Prunuspersica*	TLP (Pru p 2)	23
		Bet v 1 homolog (Pru p 1)	17.5
		Profilin (Pru p 4)	14
		LTP (Pru p 3)	9
3	Musk melon (*Cucumismelo*)	serine protease (Cuc m 1.01)	67
		serine protease (Cuc m 1.02)	54
		serine protease (Cuc m 1.03)	36
		PR-1 protein (Cuc m 3)	16
		Profilin (Cuc m 2)	14
4	Gold kiwi, green kiwi (*Actinidiachinensis*, *A. deliciosa*)	Chitinase (Act d 3)	43
		Actinidin (Act d 1)	30
		Kiwellin (Act d 5)	28
		TLP (Act d 2)	23
		Cystatin (Act d 4)	11
5	Sweet cherry (*Prunusavium*)	TLP (Pruav 2)	23
		Bet v 1 homolog (Pruav 1)	17.5
		Profilin (Pruav 4)	14
		LTP (Pruav 3)	9
6	Grape (*Vitisvinifera*)	Chitinase, hevein-like (Vit v 5)	30
		TLP (Vit v TLP)	23
		Bet v 1 homolog (Vit v 8)	17.5
		Profilin (Vit v 4)	14
		LTP (Vit v 1)	9
7	Strawberry (*Fragaria ananassa*)	Bet v 6 homolog (isoflavonereductase)	35
		Bet v 1 homolog (Fra a 1)	17.5
		Profilin (Fra a 4)	14
		LTP (Fra a 3)	9
8	Banana (*Musa acuminata*)	^{2}-1,3-glucanase (Mus a 5)	33
		Class I chitinase (Mus a 2)	31
		TLP (Mus a 4)	21
9	Custard apple (*Annonacherimola*)	Class I chitinase(Ann c Chitinase)	45
10	Mango (*Anacardiumoccidentale*)	Bet v 1-like (Man i 14kD)	14
		Class I chitinase (Man i Chitinase)	30-45
11	Pomegranate (*Punicagranatum*)	PR-4 protein (Barwin family)	28
		PR-4 protein	17
		PR-4 protein	16
		LTP (Pun g 1)	9

Abbreviations used: LTP - lipid transfer protein; PR - pathogenesis-related; TLP - thaumatin - like protein.

compared to larger models[124],[125].Literature reports suggest that different murine species have the ability to deliver IgE and additionally IgG1 anaphylactic antibodies[126]. One of the challenges involved in developing murine models of food sensitivity is the propensity of the immune system to form oral tolerance to ingested antigens[127],[128].As an option in contrast to mice Brown Norway (BN) had moderate size, and strong IgE antibody responses, therefore, the screening of serum specific antibody reactions inside individual animals can be done effectively. Compared with mice, another advantage of this model is that test antigen without adjuvant can be conveyed day by day over a time of weeks[129].

Alternatively dogs are spontaneously susceptible to sensitivities, when compared with murine models, and it is a decent animal variety for assessing food hypersensitivity. In any case, it is difficult to utilize dogs as model for safety assessment. Moreover, their maintenance is expensive, predetermined number of strains, more noteworthy inter - animal concerning rodents, and lack of availability of immunological reagents. Similarly, this requires long dosing time for sensitization[130],[129].

Published reports suggest that there is a momentous advancement with the use of animal models has been made a better comprehension of

Table 6. Highlights of IgE and non - IgE - mediated hypersensitivity[25]

Factors	IgE mediated	Non - IgE mediated
Time of exposure to allergen	Minutes to 2 hr	Several hours to days
Intensity	Mild to anaphylaxis	Mild to moderate
Time span	May continue beyond 1 year of age	Usually resolved by 1 year
Detection	Specific serum IgE, skin prick test (SPT)	Oral challenge
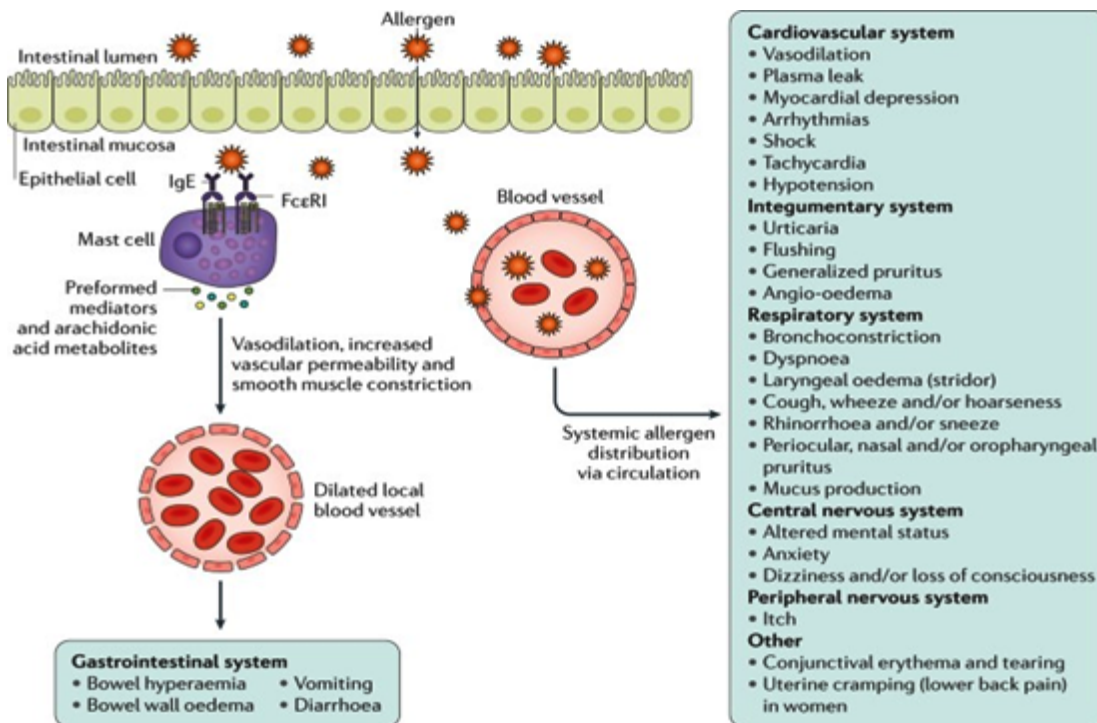
Fig. 1. Pathogenesis and clinical manifestation of food allergy

(Source: https://www.google.com/url?sa=i&url=https%3A%2F%2Fwww.nature.com%2Farti cles%2Fnrdp201798 &psig=AOvVaw09XIbBRkd02thaIXb0CApG&ust=1597914508945000&source=images&cd=vfe&ved =0CAIQjRxqFwoTC Oisw7H1pusCFQAAAAAdAAAAABAx)

the essential mechanisms of food hypersensitivity and the allergen refinement. Considering the current state of food allergy animal model, a single model cannot be satisfactory for all research purposes. The objectives, experiment design, data interpretation are the factors which determine the selection of animal model for experimental purposes. For example, murine models are acceptable for determining the food allergy mechanism, alternatively, swine or dog is acceptable for the studies with a focus on clinical symptoms of allergic disease[88].

Food allergy assessment based on clinical trials

Now days, food allergy assessment have mainly pointed on the better diagnosis and treatment of reactions [131]. *Stefano Luccioli* reviewed the guidelines for food allergy assessment and its treatment based on clinical aspects. His review suggested that, it is necessary to use a better tool for the management of food allergenicity in order to reduce the risk in human beings[132].

Similarlly, *F.Estelle. R. et al*. summarize the key points, which are underlying in the anaphylactic management of food allergy. Based on research articles, they validated the clinical strategies involved in food induced anaphylaxis. The proposed review documented that, there is a need to develop a method for allergen specific inhibitors, which will help to reduce the clinical risk

Table 7. Disorders associated with food allergy[84]

Types	Gastrointestinal	Cutaneous	Respiratory
IgE mediated	Oral allergy syndrome, gastrointestinal anaphylaxis	Urticaria, angioedema, morbilliform rashes and Flushing	Acute rhinoconjunctivitis, bronchospasm (wheezing)
Mixed IgE and cell mediated	Allergic eosinophilic esophagitis, allergic eosinophilic gastroenteritis	Atopic dermatitis	Asthma
Cell mediated	Food protein inducedent erocolitis, food Proteine induced proctocolitis, food Protein induced enteropathy syndromes, celiac disease	Contact dermatitis, dermatitis herpetiformis	Food-induced pulmonary hemosiderosis (Heiner syndrome)
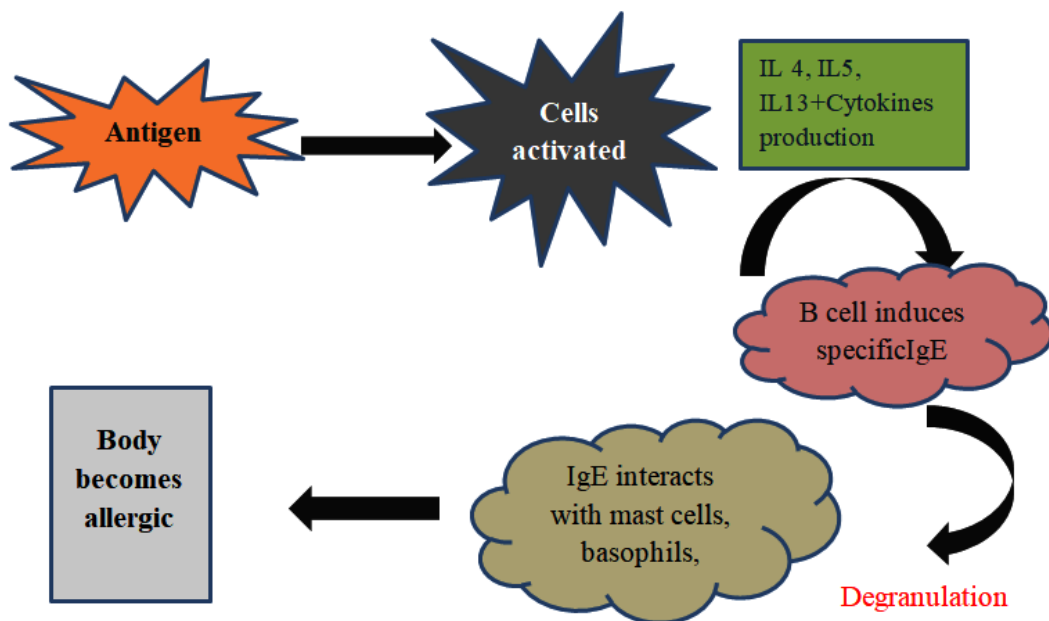
**Fig. 2.** System of food sensitivity development

of food allergenicity, and hence its management can be done easily[133].

    ThaKarrin Hoffman et al. studied the applications of molecular tools in food allergy. They validated allergen specific tests associated with food allergy, which will enable easy diagnosis.

• Skin prick testing (SPK)
• Serum IgEtesting
• Basophil activation test
• Atopy patch testing (APT)
• Immunotherapy

Table 8. Different types of extraction methods used in common food sources

No.	Food source	Method of extraction	References
1	Fruits & vegetable sources	10 mmol/l potassium phosphate buffer (pH 7.0) + 2% polyvinylpolypyrrolidone + 2 mmol/l EDTA + 10 mmol/1sodium diethyldithiocarbamate (DIECA) + 3 mmoI/1 sodium azide (NaN_3)	*Bjorksten et al.* [95], *Vassilopoulou et al.* [96]
2	Cereals	01 M Ammonium Hydrogen Carbonate(AHC) (pH 7-65)	*Shewry et al.* [97], *Qi et al.* [98], *Sandiford et al.* [99]
3	Raw & cooked fish	Phosphate buffered saline (PBS) (pH 8)	*Crespo et al.* [100], *Pastorello&Trambaioli* [94]
4	Egg	Physiological saline solution	*Langeland* [101] *Pastorello&Trambaioli* [94]
5	Milk	Precipitation at pH 4.65 + titration with 1 M HCl + precipitated fraction is to be dissolved in water at pH 7 by slow addition of 1 M NH_4OH.	*Makinen&Sorva* [102], *Pastorello&Trambaioli* [94]
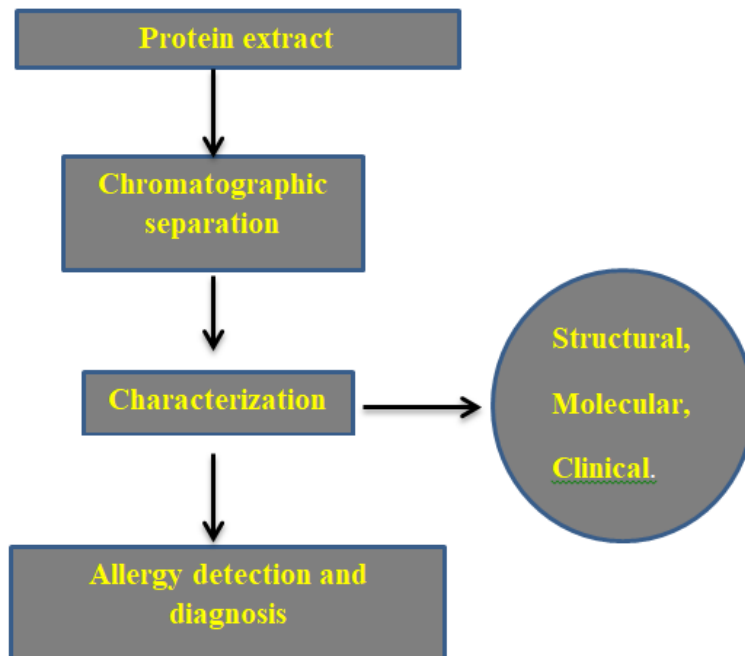
Fig. 3. General strategies involved in the purification and characterization of allergens from natural sources

Skin prick test (SPK)

Skin prick testing (SPK) widely used in plant food allergens (fresh fruits, vegetables, and nuts). In line with, several studies have been performed on the plant sources. *S. Bolhar et al.* carried out these test with apple extracts, and the results showed that, this method is highly reproducible and reliable for assessing food allergy[134]. Likewise, *Garcia et al.* carried out SPKs in peach extracts[135]. *Peeters a*nd his coworker's isolated natural allergens from pea nut are Ara h 1, Ara h 2, Ara h 3, and Ara h 6, and are applied in SPK. Recently, *Kollman et al.* practiced a purified recombinant Bet v 1, Mal d 1 (birch dust allergen) and birch pollen extract (BPE) in skin prick testing[136]. Literature reviews reported that SPK is an easy and reproducible method for the assessment of plan food allergens

Serum IgE testing

Serum IgE testing is the currently used, extract based strategy, and this is an *in vitro* testing for specific IgE antibodies. Research articles shows that this may be a predictive method due to the advanced knowledge and increased applications in molecular biology [137].

Basophil activation tests (BATs)

This test utilizes entire bloodto recognize the capacity of allergens to activate basophils. To distinguish the expression of basophil activation markers (CD63, CD203c) after stimulation with allergens, flow cytometry are used. This reflects cell degranulation, which confirms that CD63 is a key biomarker for hypersensitive responses. Furthermore, this test can also be used in immunotherapy to reflect the desensitized condition of the person[138].

Others

Likewise, cell tests are accessible to get out the presence of patients with antigen specific IgE sera, and their ability to enact basophils. The test is mainly centered on the measurement of cell activation accompanied with determination of histamine or sulfidoleukotriene release[139].Atopy patch testing is rarely used in clinical studies[140].

Ru Xin Foong and co - workers led a pilot study to assess the clinical identification of sensitivity in atopic children using a microarray technique in addition with SPK and serum IgE testing. Their findings showed that serum specific IgE testing produces more positive results rather than others[141].Consequently, the risk of allergic reactions cannot be effectively managed without understanding the associated risk factors. This can be reduced through the confined diets.

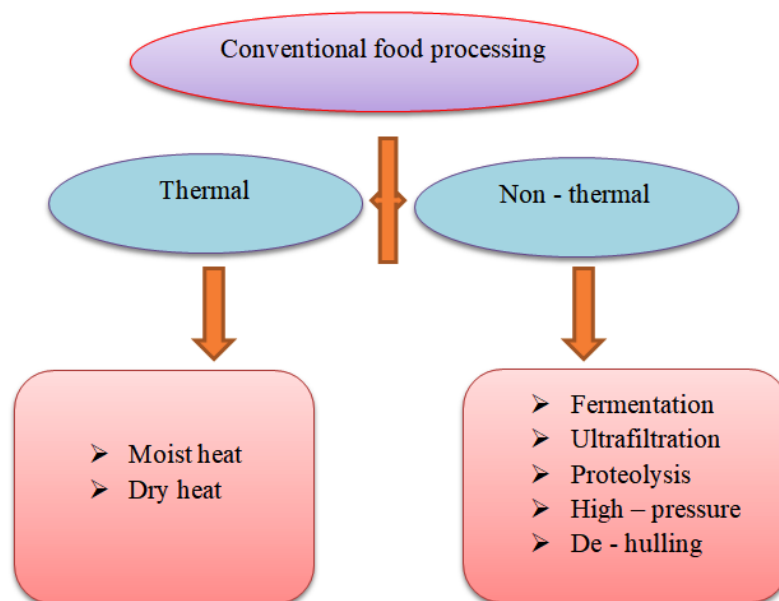*Keet et al.* proposed another theory that how to forestall food hypersensitivity in most

Fig. 4. Categorization of conventional food processing methods

ideal manner. They explored the advances in food sensitivity that was distributed in 2017 and beyond. The review highlights the published standardized treatment for food hypersensitivity. Finally, concluding that there was an increased attention to non - IgE-mediated food sensitivities[142].

Impacts of food preparing techniques on food allergens

Currently, food exposed to various kinds of processing treatments like conventional methods to enhance the shelf life of the food, by inactivating the toxins. It has been mentioned that the processing of foods can also alter the stability of allergenic compounds. This is mainly due to the alteration of amino acids or small linear stretch that occurs in the epitopes. Now days, the clinical symptoms associated with the nature of allergenic epitopes and its severity is not well clear. By understanding these features, the targeted allergen can easily be eliminated[143] .

Food processing affects physical, chemical, and biochemical changes of food, which leads to the alteration of different parts including protein and allergenicity of the particular protein epitope. During this process, new epitopes are formed, referred to as 'neoallergens'[144].

Conventional food processing methods are classified mainly into two types: thermal and non - thermal (figure: 4) [145].*Sathe et al.,* and *vanga et al.*, explained the foood processing methods and the effects of allergens during these processes.

Evidently, food processing aids to inactivate or removes the epitopes present on allergens. Based on the quality and acceptability of food products, enzymatic hydrolysis results in unwanted changes in the food structure. Consequently, to develop robust, dependable, sensitive, and exact allergen identification techniques is the crucial thing inthe field of food sensitivity.

Modern trends in food allergy

Modern trends in food hypersensitivity are primarily connected with the utilization of new strategies in analysis and detection of food
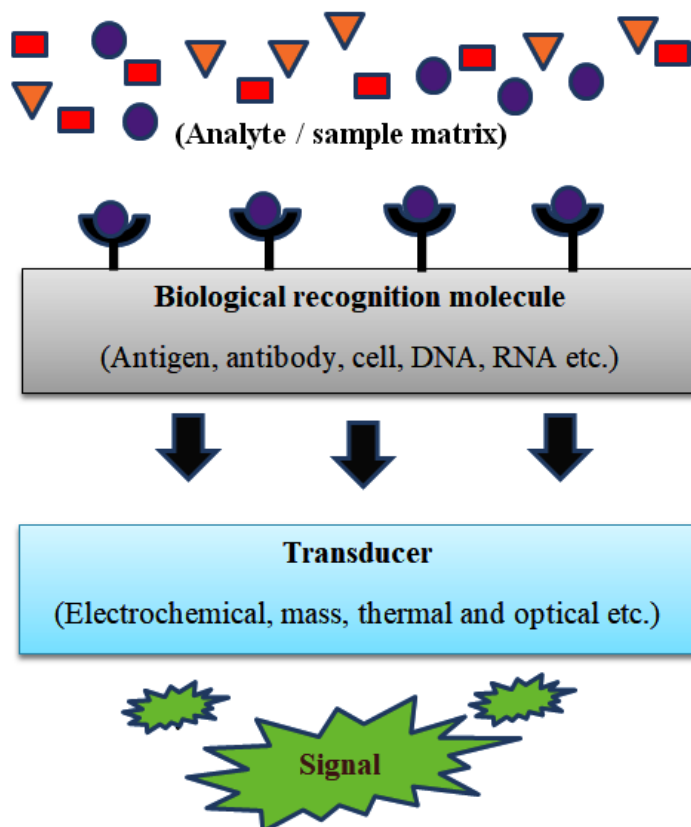

Fig. 5. Working plan of a biosensor

allergens. *Rita c. alves et al.* reviewed the latest detection method for food allergens. They mainly focussed on the use of biosensors as tool for food allergen detection. It has been mentioned that immunological tests and the DNA - based measures, mass spectrometry are the classical available methods used for the confirmation of food allergens. Compared to those tools, biosensors have innovative, sensitive, specific, natural friendly, less expensive and quick methods (particularly when computerized as well as on-going investigation). Therefore, this method easily replaces the earlier ones [146].

Various sorts of biosensors are created, and they set for various objectives in food safety assessment. Literature reviews suggest that for the purpose of food allergen detection, three major groups of biosensors are used, namely: optical, electrochemical, and piezoelectric biosensors [147]. Immunosensors are the identification element used here. The allergenic proteins are immobilized on the outside of these gadgets, and the coupling action between the particles can be estimated by utilizing transducers. General schematic diagram of biosensors is given in the figure 5[146].

Stefanie and colleagues developed the sensitive and specific primers used for the identification of soy allergens (Glycine max) with Loop-mediated isothermal amplification (LAMP). This is simple and rapid detection involved in the DNA - based assays, mainly applicable in the manufacturing of foods. Notably in field - like applications and on - site screening. The study suggests that ORF160b gene was exceptionally explicit for the soybean. Furthermore, LAMP joined with LFD (Lateral Flow Dipstick) -like detection facilitates a simple, highly selective and sensitive recognition of the soybean without the requirement for costly scientific equipment [148].

Overall, additional method validations like to resolve the limit of detection and the performance testing versus established immunoassays for different kind of food matrices are needed for the better detection of allergens. As a next step, the effect of food handling strategies on recognition of allergens and the enhancement of this protocol is need to be validated.

Biomarkers in food allergy

Food allergy is a complex and diverse disease. Therefore it is essential to develop specific and sensitive markers for its proper management. However, many progresses have been made in this way, but further ways are needed for the better comprehension of the reason and system of food sensitivity, giving a remedial methodology focused to the patient.

Currently, biomarkers are used in food allergy, especially on investigations related with allergen immunotherapies (AITs) including epicutaneous immunotherapy (EPIT), sublingual immunotherapy (SLIT), and oral immunotherapy (OIT). The studies associated with reliable biomarkers to foresee treatment results are extremely low in number. Therapeutic benefit of AIT(Investigational allergen immunotherapies) includes different cell types like basophils, T cells, mast cells and B cells. *LaKeya C. Hardy* and colleagues reviewed biomarkers that are at presently being researched for AIT[138].

Numerous endeavours have been created to describe reliable biomarkers in order to recognize specific endotypes and phenotypes in food hypersensitivity. Eventually, sIgE/total IgE ratios, T cell tests, and Specific IgE (sIgE) tests are only a few that have been examined. *Muraro & Arasi* summarizes the currently using biomarkers in food hypersensitivity[149].

Various *in vitro* biomarkers have been assessed to evaluate clinical viability of allergen immunotherapy. Recognizing singular patient responders and nonresponders are the primary issue behind with this concept. Several intermediate steps like the degree, dose, the circumstance of allergen introduction corresponding to manifestations, and the utilization of rescue medication, all of which may jumble the connection between IgE - Fab and clinical indications and reaction to immunotherapy[150]. However many progress has been made in the finding and management of food hypersensitivity, the future strategy seeks the underlying immunologic mechanism and tolerance.

Summary and Conclusion

This review summarizes the basic key objectives regarding to food hypersensitivity. It is an anomalous invulnerable reaction to food. The indications of the unfavorably susceptible response may extend from gentle to extreme, and is regularly happens inside minutes to a few hours of presentation. By understanding about particular methods of extraction and optimisation of those

allergens from common food source improves the diagnosis of its allergenicity. The extraction, purification, and characterization of food allergens from various sources are simultaneously reviewed. The improvement of animal models to test different food hypersensitivities has been gainful for more quick and broad examination about the component behind the unfavorably susceptible pathway. Researchers had continued interest on experimental models (animal as well as plant), in order to explain the mechanism of food induced allergy. Therefore, currently available and existing models of food allergy are briefly discussed. Now days, allergen specific inhibition is a great challenge faced by researchers. It is a key problem involved in food allergy. So, there is a need to look at the current techniques for the evaluation of clinical finding of food hypersensitivity. The effect of food handling techniques on the recognition of allergens is likewise significantly affected. Optimisation of this objective is the key element regarding to the future aspect of food allergen detection. The clarification of these issues will help the researchers to design the experiments with various models (both *in vivo* and *in vitro*), so as to assist further findings of food allergy.

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