JOURNAL OF FOOD QUALITY & HAZARDS CONTROL
SHAHID SADOUGHI UNIVERSITY OF MEDICAL SCIENCES & HEALTH SERVICES

Journal of Food Quality and Hazards Control 3 (2016) 3-9

If There Is Really a Notable Concern about Allergenicity of Genetically Modified Foods?

B. Yavari[1], S. Sarami[2], S. Shahgaldi[2], S.S. Athari[2*], A. Sharma[3]

1. Department of Plant Biology and Halophytes Biotechnology Center, Azarbaijan Shahid Madani University, Tabriz, Iran
2. Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran
3. College of Health Sciences, Qatar University, Qatar

Article type
Review article

Keywords
Food, Genetically Modified
Hypersensitivity
Allergens
Food Safety

Received: 27 Sep 2015
Revised: 30 Oct 2015
Accepted: 29 Nov 2015

Abstract

In recent decades, biotechnologists have striven to improve the quantity and quality of food supply. Producing genetically modified (GM) foods is one of the main goals and many countries all over the world have approved the distribution and consumption of the labeled GM foods in their own regions. However, there are still few groups having concerns about allergenicity of GM foods. This review highlights the pathways to ensure food safety of GM foods from view point of absence of allergens and also describes the risk assessment procedures, including bioinformatics assays, biochemical procedures, immunological assessments and animal models. According to present published database, there are few studies demonstrated that GM foods have some slight allergic effects. In this regard, the authors concluded that, at the present, producing GM foods in response to the enormous need of the universal population could be a good solution; yet assessing the allergenicity of these foods is an approach to ensure the highest safety of GM foods. On the other hand, considering important role of GM foods in decreasing hunger and achieving food security in the world, possible allergenicity of GM foods is preventable by strict regulation and extensive laboratory testing before distribution in local and global markets. Finally, according to literature review, it seems probably that there is no serious risk about allergenicity of GM foods produced and consumed until now in the world.

Introduction

As the population increasing, food production is considered as a difficult task due to climate changes, population growth, decreasing in arable lands, and increasing pesticide resistance. These are the main challenges for the governments all over the world. Therefore, it seems to be necessary to make effective approaches for production of safe and adequate food from renewable resources with minimal hazardous effects for health and environment. Genetically engineered (GE) or genetically modified (GM) foods could be one of the important solutions to this scenario. In these kinds of foods, in order to increasing the quality or quantity, one or more genes are manipulated (Ezzaher, 2015; Livermore, 2003; Prakash, 2014). Nowadays, the evidences show that GM food are distributed and consumed in many countries (Arun et al., 2013; Chaouachi et al., 2013; Elsanhoty et al., 2013; Fernandes et al., 2014; Herzallah, 2012; Premanandh et al., 2012; Rabiei et al., 2013).

*Corresponding author
E-mail: ss.athari@gmail.com

In order to ensure that GM foods are safe, they should be tested carefully and extensively for screening, reducing potential risks and giving products with vast humanitarian benefits. On the other words, after GM food production, the risk assessment procedures should be done. There are few controversies about allergy against the new proteins produced by GM foods (Nordlee et al., 1996; Prescott and Hogan, 2006). The aim of this review is to provide information on the allergenicity risk of GM foods and to describe the methods that are used to assess their probable allergenicity. Potential shortcomings in the process of these foods will be also scrutinized.

What is allergy?

The word 'allergy' is used to describe an improper immune response disorder which occurs in only a portion of the population exposed to what typically is a non-harmful substance such as pollen or food. Furthermore, hypersensitivity reactions can be either antibody-mediated or cell-mediated (Athari, 2014; Athari and Omidi, 2014). According to Coombs and Gell (1963), such reactions can be classified as type I – IV. Type I comprises reactions between antigens (antigens of this type are often termed 'allergens') and IgE antibodies attached to mast cells that are pivotal in this type of hypersensitivity. In addition to mast cells, eosinophils and T helper 2 cells (Th2) are also involved. Allergic asthma, hay fever (allergic rhinitis) and some food reactions (for example peanut hypersensitivity) are the classic examples of type I. Type II comprises acytotoxic interactions between cell-surface antigens and IgG or IgM antibodies binding to Ig receptors on cytotoxic cells that are pivotal in this type of hypersensitivity. Typical examples of type II are immune cytopenias including autoimmune hemolytic anemia and immune thrombocytopenia. In this type, antibodies bind to antigens or cell membranes and form cytotoxic antibodies, which eventually leads to the destruction of these antigens or cells. It is called Ab-dependant cell cytotoxicity (Athari, 2014; Athari and Omidi, 2014; Athayi et al., 2015; Nikaein et al., 2015). Type III is consisted of interactions between circulating antigens and IgG antibodies (like immune-complex reactions), which leads to the subsequent deposition of these immune complexes in the walls of kidneys, skin, blood vessels, and joints (for example serum sickness). Type IV is mediated by sensitized lymphocytes (like cellular immune responses), which cause local immune responses. In this problem, phagocytes accumulate around pathogens and try to uptake and kill them. Consequently, this reaction leads to cell inflammation and granuloma (examples of this type are any granulomatous diseases such as leprosy and tuberculosis). Newly, auto-immune diseases are classified as type V hypersensitivity (systemic lupus erythematosus, Grave's disease, celiac disease). Nowadays the term 'allergy', or 'atopy', as it is called, is restricted to IgE-mediated reactions since most allergies belong to type I hypersensitivity; other types are simply called hypersensitivity. Before development of various biotechnology assays, some compatible plants were selected and reproduced by natural or selective breeding (Coombes and Gell, 1963; Lehrer et al., 1996; Nikaein et al., 2015; Rajan, 2003).

Some opinions about allergenicity of GM foods

At present, in order to produce GM plants, DNA of mitochondrion, chloroplast or genome is directly modified and by methods such as particle bombardment, electroporation or infection with recombinant vectors (such as *Agrobacterium tumefaciens*), scientists are able to produce desirable products. Essentially, the aim of GM plants is giving ability to particular plants to express the desired proteins through the insertion of a gene sequence encoding a desirable protein into the genome of plant (Goodyear-Smith, 2001; Livermore, 2003; Nicolia et al., 2014). Now, common GM foods, which their productivity and yield is improved, include soybean, cocoa beans, canola, maize, potato, and cottonseed oil (Bachas-Daunert and Deo, 2008). Some studies made doubts that eight foods or food groups caused food allergy in 2-8% of the population (Lehrer and Bannon, 2005). Peanuts, eggs, fish, shrimps, walnuts, and cashews have the suspicious food allergens, which can significantly elicit IgE responses. Allergenic foods approximately contain up to 20000 proteins, of which only about 20 ones may cause allergy. In spite of this, the chance of getting exposed to allergenic food proteins is considerably low (Burks and Sampson, 1993; Lehrer and Bannon, 2005; Sampson, 1999; Sicherer et al., 2000). The primary allergy risks of foods for consumers can be categorized into three main groups. In the first group, a specific allergen or a cross-reactive allergen is transferred into a crop (such as peanut allergen into corn). Therefore, the foods in this group are considered to have the highest risk of allergenicity for consumers. In second group, the levels of endogenous allergenic proteins alter due to the transformation process, especially for already allergic patients. This occurrence may exhibit a mediocre risk to allergic consumers. Third group, in which the expression of new proteins may become allergens, exhibits a low risk to allergic consumers (Burks and Fuchsb, 1995; Nordlee et al., 1996; Park et al., 2001). Also, IgE sensitivity caused by consumption of GM peas has been previously reported. A protein, named kidney bean protein, was taken from kidney beans and inserted to peas. Although, this protein, in kidney beans, is denatured during cooking and is digestible, but both cooked and uncooked GM peas show

an allergic response (Bachas-Daunert and Deo, 2008; Prescott et al., 2005). Another study presented its doubt as giving rise of allergenicity or trigger asthma with new produced proteins with transgenic alteration foods (Jank and Haslberger, 2003).

It has been stated that allergenic responses which are induced by GM foods could range from extremely mild to extremely severe and could be divided into two main classes including, food intolerance and food hypersensitivity. Patients with food intolerance have a negative reaction to food such as lacking the essential enzyme to digest the allergen (celiac disease), and also patients with food hypersensitivity manifest elevated immunological responses via IgE mechanism such as hives, asthma, gastrointestinal problems, and anaphylaxis. Scientists believe that glycoproteins are responsible for IgE mediated allergic responses; thus, glycosylation process can be a cause of transforming a benign protein into a severe allergen. The allergenicity of GM peas, for example, stems from a slight alteration in the glycosylation process of kidney bean protein (Bachas-Daunert and Deo, 2008; Prescott et al., 2005). Although standard scientific tests have shown that GM foods, in developmental stages, could provoke allergic responses, no allergenic effects relative to these foods have been reported in the markets. In addition, the actual occurrence of this allergenicity is rare (Bachas-Daunert and Deo, 2008). On the other hand, a recent study by Sheng et al. (2014) have shown that there is no evidence of potential allergenicity of the GM rice. Also, a comperhensive 10-year overview about safety of GM crops highlithed that there is no risk in regard to allergenicity of these products (Nicolia et al., 2014).

Allergenicity assessment procedures for GM foods

In order to reduce the potential risk of allergy associated with biotech foods in the three groups mentioned above, a series of tests should be designed. Comparing the sequence of introduced proteins with allergens that are already known to elicit allergenic reactions is the first step in evaluating whether a novel protein is an allergen or not. This step is significant since suspected individuals might be sensitized to an allergen which can cause cross-reaction in those contacting to the novel protein. The stability of all biotech proteins to protease digestion is also assessed (Astwood et al., 1996a; Metcalfe et al., 1996). Therefore, the procedures employed for assessing allergenicity in various kinds of GM foods, include evaluating the gene source, serum IgE binding studies, bioinformatics analysis, and investigating the stability of new proteins to pepsin digestion (Goodman et al., 2008; Holzhauser et al., 2008; Taylor, 2006; Young et al., 2012).

Bioinformatics analysis (amino acid sequence comparison)

In order to determining the allergenicity of introduced genes/proteins, bioinformatics analysis, which has long been considered a core part in the safety assessment of GM foods, is the first step. Bioinformatics analysis is carried out to ensure that a known allergen is not transferred from an allergenic organism and the novel protein does not contain significant sequence similarity to a known allergen. Bioinformatics analysis is a partly simple procedure that can give rapid results (Young et al., 2012). Thus, it is not assumed that bioinformatics can alone determine whether a novel protein will ‘‘become’’ an allergen or not. Essentially, bioinformatics analysis answers the primary question if the novel protein is a known allergen or likely elicits IgE responses in the manner that cross-reacting antibodies do? In this regard, the sequence of the transferred protein is compared with the amino acid sequences of all known allergens. There are several useful databases that can help to achieve the best comparisons, but a few partially comprehensive lists of allergens can be found on the internet. So, it is not easy to approximate the total number of allergenic sources. The applicable databases like Allergen database and Allergome database are critical in this analysis. Allergome database roughly catalogues 800 species of allergenic proteins, for which no individual allergenic protein has been identified, yet. Additionally, Allergen database approximately catalogues 210 species, including 620 allergenic proteins, in which the sequence of at least one allergen is known. The other appropriate electronic database resources such as PubMed are used to obtain recent reports on potential allergenicity (Goodman et al., 2005; Ladics et al., 2007).

Serum IgE binding assay

IgE binding assay, which is used as a screening tool for proving the allergenicity of foods, airway, and contact sensitizers, is an antigen-specific serum test. Although, at the present time, the reagents used in this assay are common and the methods are routine, the validation of the assay and the explanation of its results can be a little challenging and complicated (Goodman et al., 2008). IgE binding assay is performed when the source of our desired gene/protein is a food generally known to be allergenic or the similarity between the sequence of our transferred protein and the sequences of known allergens is greater than 35% (over an 80 amino acid segment). However, this evaluation may be affected by several factors such as gender, age, demographic information and the prevalence of allergy (Holzhauser et al., 2008). Additionally, this test, along with western blotting and ELISA

methods, plays a critical role when the source of our desired gene is known to be allergenic (Aas and Johansson, 1971; Goodman et al., 2005; Ishizaka and Ishizaka, 1966; Singh et al., 2006; Sten et al., 2004). This evaluation needs appropriate positive and negative controls, but it should be considered that false positives do not affect the interpretations of this test (Astwood et al., 1996b; Nakajima et al., 2007). However, for beside IgE binding methods to evaluate safety of GM foods, some other tests should be done for ensuring ignoring any doubts regarding to false positive or false negative data (Holzhauser et al., 2008).

Digestion with pepsin assay

Digestion with pepsin, like any other simple assays, can be carried out *in vitro*. In general, the majority of dietary intake proteins is degraded and digested into small non-immunogenic peptides by proteolytic enzymes and thus their allergenicity is neutralized. Many important food allergens are stable at pH 1.2 in the presence of pepsin; therefore, this test can be appropriate for risk assessment, but it is not 100% predictive. Findings suggest that further evaluation of the quantity of a protein with unknown function in potential food products is indispensable, because a stable non-abundant food can become allergenic if consumed in high quantities (Fig. 1). As an international collaborative study, pepsin digestion assay has relatively good predictive value for food allergens (Asero et al., 2000; Bannon et al., 2002; Chehade and Mayer, 2005; Goodman et al., 2008).

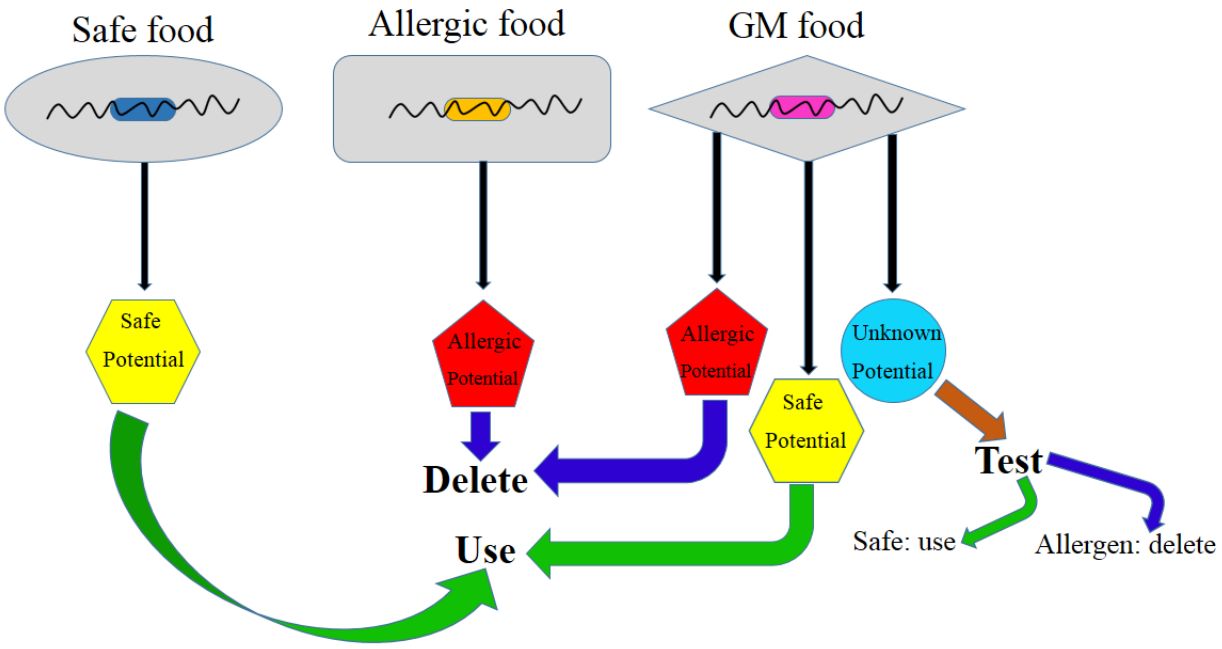

Fig. 1: Food production and using cycle. If a food is safe along with its components and yields safe products, it can be used in people's diets. Allergenic foods, which produce allergenic products, should not be consumed. When GM foods are known to be safe and produce safe products, they can be included in people's diets; when GM foods are known to be allergenic and produce allergenic products, they should be abstained. If it is learned that the new GM foods are allergenic and therefore not safe, they should be abstained; otherwise they are safe for consumption.

Heat-stable protein assay

Heat-stable protein assay is another simple assay used to perform food allergy identification. Generally, after boiling or roasting, some of the allergens in major allergenic foods remain unchanged (Bannon et al., 2002; Scheurer et al., 2004; Sheng et al., 2014). Ordinarily, the heat-stable allergen proteins of vegetables as well as fruits, e.g. non-specific lipid transfer proteins, are strictly cross-linked by disulfide bonds, which cause structural preservation. However, if an allergen is heat-stable, it is unlikely that the protein either unfolds by heating at fairly low temperatures (e.g. less than 70 $^{\circ}$C) or loses enzymatic or biological activity at low temperatures. In short, if a novel protein is unstable against heat and digestion, its potential allergenicity risk is at a low level, whereas heat stable proteins may have higher risks (Goodman et al., 2005; Wensing et al., 2002).

Animal models

Nowadays the application of animal models to assess the potential allergenicity of GM foods is well developed and is appropriated by the active areas of research. Basically, specific animal models such as rodents, mice, rats, pigs and dogs are employed for allergenicity assessment (Atherton et al., 2002). All of these models have various advantages and disadvantages; therefore, they can provide us with important information. The mechanism of food allergy in mammalians, especially humans, has a complex process and depends on different factors to trigger allergic sensitization. One of these factors is diversity in translational and post-translational modification routs between species that could change the molecular architecture of an expressed protein and subsequently may change its antigenicity. The different in protein glycosylation between plants, animals and humans is another important factor. A slight variation in the same glycoproteins may potentially lead to the allergenicity of modified foods. On the other hand, it is unlikely that a single animal model will be able to clearly predict the potential allergenicity of new foods' antigens (Atherton et al., 2002; Goodman et al., 2005; Nordlee et al., 1996; Prescott and Hogan, 2006; Prescott et al., 2005; Rang et al., 2005; Windels et al., 2001). Currently, there are no available validated and generally accepted models which can completely predict the allergenic potential of specific proteins, but scientists suggest that mice may respond to foods released through the oral route the same way humans do. Also, the BN (Brown Norway) rat as a high-immunoglobulin (particularly IgE) responder strain, preferentially produces an antigen-specific IgE isotype (Akiyama et al., 2001; Knippels et al., 1998; Lehrer and Bannon, 2005). Additionally, efforts to reduce the allergenicity of foods led scientists to use genetic engineering methods such as manipulation of the primary amino acid sequence of genes encoding allergens, modification of an allergen's secondary or tertiary structure and post-transcriptional gene silencing (Goodman et al., 2005). Additionally, further procedures include potential asparagine-linked glycan test in different plants, baculoviruses and yeast, molecular weight of heterologous proteins test, and any biological or biochemical activity (Goodman et al., 2005).

Monitoring organizations

Some governmental organizations, as well as several European Union agencies within the EU countries, have addressed the issue of GM foods and their allergenicity risk. Several organizations impose a number of world-wide standards which provide a universal set of rigid guidelines for the standardization of testing GM foods. Three major organizations are responsible for GM foods include, food and drug administration (FDA), food and agriculture organization (FAO) and world health organization (WHO) (Konig et al., 2004; Lehrer and Bannon, 2005; Ortiz et al., 2007).

Conclusion

The possible advantages of GM foods are boundless and through the biotechnological improvement of both foods and the environment, GM foods can serve a variety of humanitarian purposes. The production of GM foods is progressing and the future of these products holds much promise. It is assumed that the combined application of appropriate animal models and standard assessment methods enables us to recognize the safety of GM foods to a greater degree. It seems that the post-market monitoring of these products may be useful to manage pre-market exposure assessments or dietary intake patterns and it should be conducted in scientific testable methods which allow us to confirm the high safety of GM foods. Also, many worldwide organizations are engaged in supervising the quality of GM foods produced. According to literature review, it seems probably that there is no serious risk about allergenicity of GM foods produced and consumed until now in the world. However, current assessment procedures are robust, but the knowledge of allergy and allergens is still improving and new information and technologies will aid us in further developing and refining these procedures.

Conflicts of interest

None.

Acknowledgements

We thank sincerely Dr. A. Hasanzade for scientific review and edition of the manuscript.

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