



Plant food allergy: Influence of chemicals on plant allergens

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ABSTRACT

Plant-derived foods are the most common allergenic sources in adulthood. Owing to the rapidly increasing prevalence of plant food allergies in industrialized countries, the environmental factors are suspected to play a key role in development of allergic sensitization. The present article provides an overview of ways by which chemicals may influence the development and severity of allergic reactions to plant foods, with especial focus on plant allergens up-regulated under chemical stress. In plants, a substantial part of allergens have defense-related function and their expression is highly influenced by environmental stress and diseases. Pathogenesis-related proteins (PR) account for about 25% of plant food allergens and some are responsible for extensive cross-reactions between plant-derived foods, pollen and latex allergens. Chemicals released by anthropogenic sources such as agriculture, industrial activities and traffic-related air pollutants are potential drivers of the increasing sensitization to allergenic PRs by elevating their expression and by altering their immunogenicity through post-translational modifications. In addition, some orally-taken chemicals may act as immune adjuvants or directly trigger non-IgE mediated food allergy. Taken together, the current literature provides an overwhelming body of evidence supporting the fact that plant chemical exposure and chemicals in diet may enhance the allergenic properties of certain plant-derived foods.

1. Introduction

Food allergies represent a major health concern in industrialized countries. The prevalence of food allergy is estimated to reach 6% in children and 4% in adult, with a higher incidence in urban populations (Boye, 2012). Among 170 known allergy-causing foods, only a small portion (e.g. peanuts, nuts, wheat, soybeans, milk, eggs, fish and shellfish) are responsible for about 90% of adverse allergic manifestations (Alonso et al., 2015). The majority of food allergies are the result of the production and subsequent reaction of allergen-specific immunoglobulin E (IgE) against allergenic proteins (IgE-mediated type 1 allergy) and a limited number of them are non-IgE mediated. Food allergens are responsible for a variety of clinical symptoms which mainly affect the gastrointestinal tract, the skin, the respiratory tract and the cardiovascular system. The ingestion of some food allergens may even provoke a systemic and potentially life-threatening reaction referred to as anaphylaxis. Recent studies have reported a 5–7 fold increase in the anaphylaxis prevalence worldwide, with higher incidences in children under 4 years of age (Mills et al., 2004). The rapid increase in both prevalence and severity of food allergies suggest the important contribution of the environment in the allergic susceptibility, especially at the allergen sensitization level (Benedé et al., 2016). Food allergy is thus the result of a complex interplay between genetic and

environmental factors such as diet, microbiota composition and environmental chemical exposure, all contributing to the rising prevalence of food allergies in industrialized countries. In the present review, special attention has been paid to the issue of chemical contaminations affecting plant foods and their potential influence on plant food allergens.

Among food allergenic proteins, plant food allergens show a high life-threatening significance, potentially affecting 1 in 100 adults and 1 in 10 children (Mills and Shewry, 2004). Various plant foods including peanuts, tree nuts, seeds, celery, fresh fruits and legumes may trigger severe anaphylactic reactions when ingested by allergic patients. It is noteworthy that food allergies in children should be considered as the first step in the atopic march, with a strong genetic component and mainly involving allergens resistant to digestion and proteolytic degradations. In contrast, food sensitizations arising in adult age are mainly the consequence of IgE cross-reactivity between raw plant foods and pollen and/or latex inhalant allergens, thereby implicating a broader range of proteins (Muraro et al., 2014; Werfel et al., 2015). With the increasing trend of respiratory allergies over the last two decades (Pawankar, 2014) raw vegetables have become the most prevalent food allergens in adulthood (Ma et al., 2003). It is now estimated that 5% of the central Europe population suffer from pollen-food-allergy syndrome (PFAS) (Popescu, 2015) and 30–70% of patients

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Table 1
Plant protein families with known allergenic members showing elevated expression under chemical stress.

Primary role	Protein family	Function/allergenic plant food	Referenced allergens	Allergenic relevance	Cross-reactivity	Polluting agents (reference)
Plant defense-related proteins	β-1,3-Glucanases (PR-2)	Cleaves β-1,3-glucans/banana fruit, tomato fruit, bell pepper, grape fruit	Mus a 5 (banana)	Barre et al., 2009	Pollen-latex- food (Palomares et al., 2005)	Cd (Lee et al., 2010; Pócs et al., 2011)
	Chitinases class I to IV (PR-3)	Endochitinase/Helianthus spp., Maize, Pea and Fava bean root, cabbages flower and bud, walnut, avocado, banana and grape fruits,	Mus a 2 (banana), Cas s 5 (chestnut), Pers a 1 (avocado), Zea m 8 (maize)	Diaz-Perales et al., 1998	Latex-fruit (Diaz-Perales et al., 1999; Chelmifiska et al., 2016)	Hg (Didierjean et al., 1996) Cd, Hg, Ag (Béková et al., 2008) Cd (Pócs et al., 2011; Metwally et al., 2004) Hg (Didierjean et al., 1996) Pb (Walliwagedara et al., 2010) Cd (Pócs et al., 2011)
	Hevein-like PR-4 (Chitinase class I and II)	Chitin binding, antifungal/turnip, elderberry, caper fruit and bud, Acerola and passion fruit,	Bra r 2 (turnip),	Hänninen et al., 1999	Latex-fruit (Raulf-Heimsoth et al., 2007)	
	Thaumatin-like proteins (PR-5)	Antifungal/Food allergens in bell pepper, apple, cherry, peach, kiwifruit and banana fruits	Pru av 2 (cherry), Mal d 2 (apple), Cap a 1 (bell pepper), Act d 2 (kiwi), Mus a 4 (banana)	Palacin et al., 2008	Pollen-food (Palacin et al., 2008)	mercuric chloride 46; Hg (Didierjean et al., 1996); Cu, Cd, Hg (Pócs et al., 2011); Hg, Li, Zn (Hajduduch et al., 2001); Pb (Walliwagedara et al., 2010); Copper chloride (Rakwal et al., 1999) methyl methane sulfonate (Ahn et al., 2009) post-anthesis fertilizer (N,P,K) (Altenbach et al., 2011)
	Serpin, serine protease inhibitors (PR-6)	Trypsin inhibitors/endopeptidase inhibitors/wheat, barley, tomato, Chinese ginseng	Tri a 33 (wheat), Hor v 33 (barley), Sola t 4 (potato), Tri a 39 (Wheat)	Constantin et al., 2009	-	
	Cucurbit chitinase (PR-8)	Chitinase III/Jujube fruit, coffee beans	Ziz m 1 (Indian jujube), Cof a 1 (coffee)	Lee et al., 2012 Manavski et al., 2012	Latex-fruit (Lee et al., 2012)	Cd (Ge et al., 2009)
	Peroxidases (PR-9)	Catalytic activity/wheat, small spelt, bell pepper, tomato and banana fruits	Mus a 6 (banana)	Wagner and Breiteneder, 2002	Latex-fruit (Wagner and Breiteneder, 2002)	Zn, Cu, Pb (Macfarlane and Burchett, 2001); Al (Sharma and Dubey, 2007); Cu, Cd (Cailin et al., 2008; Metwally et al., 2004)
	Bet v 1-like (PR-10)	Ribonuclease-like/carrot, celery, tomato, hazelnut, peanut, soybean, mung bean as well as apple, cherry, apricot, pear, peach, raspberry, strawberry, yellow and green kiwi fruits, Chinese ginseng (root), etc.	Pru av 1 (cherry), Mal d 1 (apple), Api g 1 (celery), and Dau c 1 (carrot), Gly m 4 (soy), Vig r 1 (mung bean), Cor a 1 (hazelnut), and Cas s 1 (chestnut), Pan g 1 (ginseng)	Blankstijn et al., 2017 Scala et al., 2017	Panallergen Pollen-food (Sinha et al., 2014)	Cd (Ge et al., 2009) Cu, Cd, Hg, Li, Zn (Hajduduch et al., 2001) 1,2,4-trichlorobenzene (Cailin et al., 2008.)
	Lipid transfer proteins PR-14	Shutting of phospholipids and fatty acids/Food allergens in peach, apricot, cherry, pear, apple, strawberry, plum, grape, mulberry, raspberry, orange, lemon, tangerine, kiwi, banana, celery, tomato, asparagus, lettuce, cauliflower, kidney bean, mustard, hazelnut, walnut, almond, sunflower seeds, peanut, maize, wheat, chestnut, etc.	Mus a 3 (banana), Ara h 9 (peanut) Pru p 3 (peach), Pru av 3 (cherry), Pru ar 3 (apricot), Cor a 8 (hazelnut), Cas s 8 (chestnut), and Zea m 14 (maize), Pun g 1, pomegranate, Act c 10 (kiwi), Hel a 3 (sunflower), Sola 1 3 (Tomato)	Asero et al., 2018	Pan-allergen Food-food (Asero et al., 2002) Food-pollen (Popescu, 2015)	Cd (Hollenbach et al., 1997) Ethylene, ABA (Jung et al., 2003) Pb, Cd (Seregin and Ivanov 2001)
	Snakin/Gibberlin regulated protein	Anti-Microbial Peptides/Prunus fruit, Citrus fruit	Cit s 7 (sweet orange), Pru p 7 (peach)	Sénéchal et al., 2017 Inomata et al., 2017	Pollen-food (Sénéchal et al., 2017) Inomata et al., 2017, Charpin et al., 2017)	Cd (Zhang et al., 2015, 2016)
Storage proteins	Isoflavone reductase	Catalytic activity/pear, lemon, litchi, Sharon fruits, carrot root	Dau c 5 (carrot), Pyr c 5 (pear)	Karambo et al., 2001	Pollen food (Karamloo et al., 2001)	Al (Duressa et al., 2011)
	Heat Shock protein	Intra-cellular chaperones/food allergen in chickpea, chestnut	Cic a 10 (chickpea), Cor a 10 (hazelnut), Cas s 9 (chestnut)	Gruehn et al., 2003	Pollen-food (Gruehn et al., 2003)	Cd (D'Alessandro et al., 2013; Rodríguez-Serrano et al., 2009) Ozone (Eckey-Kaltenbach et al., 1997) Cd, Cu, As, Zn, Al, Cr, Ni, Hg (Hasan et al., 2017) post-anthesis fertilizer (N,P,K) (Altenbach et al., 2011)
	Gladians	Nutrient reservoir/food allergen in wheat and barley	Tri a 19, Tri a 20, Tri a 21 (Wheat), Hor v 20 (barley)	Battais et al., 2005	Food-food (among grains) (Vojdani and Tarash (2013)	post-anthesis fertilizer (N,P,K) (Altenbach et al., 2011)
	high and low molecular weight glutenin subunits,	Nutrient reservoir/food allergen in wheat, barley, Tausch's goat grass, oat, rye, rice and maize	Aeg ta 26 (goat grass), Tri a 26 (Wheat), Tri s 26 (spelt), Tri tp 26 (kamut), Ave s 36 (oat), Hor v 36 (barley), Ory s 36 (rice), Pha ca 36 (canary grass), Sec c 36 (rye), Tri a 36 (wheat)	Pastorello et al., 2007	Food-food (among cereals) (Pastorello et al., 2007)	post-anthesis fertilizer (N,P,K) (Altenbach et al., 2011)

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suffering from pollinosis present cross-reactive syndromes to plant food allergens (Ma et al., 2017). These cross-reactions occur because a variety of nuts, spices, fruits and vegetables share similar allergenic structures to those found in pollen and latex (Popescu, 2015). The most widely reported associations causing pollen-food syndrome are with birch, cypress-cedar, grass, ragweed and mugwort pollen (Kleine-Tebbe and Herold, 2003; Maeda et al., 2010; Sénéchal et al., 2017). Clinical manifestations strongly depend on the exposure and geographical factors. The most common symptoms are oropharyngeal and manifest as pruritus, erythema, tingling, and angioedema of the lips, soft palate, oral mucosa and throat (Sampson et al., 2014). The term “oral allergy syndrome” (OAS) is used to describe these reactions as they are mainly limited to the mouth and throat area. Besides oropharyngeal manifestations, the skin is also frequently affected by systemic allergic reactions to food allergens, urticaria being particularly frequent among food allergic patients (Worm et al., 2014). Although the frequency of severe systemic reactions shall not exceed 10%, their occurrence is increasing substantially (Muraro et al., 2014) and certain fruits and vegetables such as peanuts, celery, tree nuts, peaches, and mustard are associated with more systemic reactions than other foods (Pałgan et al., 2012; Popescu, 2015; Worm et al., 2014). The latex–fruit syndrome present numerous analogies with the PFAS and a variety of plant foods, such as chestnut, potato, kiwi, tomato, peach, bell pepper, avocado and banana have been linked to this syndrome (Wagner and Breiteneder, 2002). Up to 50% of latex allergic patients are allergic to cross-reactive plant foods (Radauer et al., 2011). Based on synthesis of the current knowledge (Table 1), the great majority of panallergens eliciting allergic cross-reaction between plant-derived foods, pollen and/or natural rubber latex are plant-defense related proteins.

2. Allergens involved in the plant defense mechanism: influence of chemicals

Plant food allergens belong to a relatively limited number of protein families representing less than 0.3% of the total number of families. According to the WHO/IUIS nomenclature (Radauer et al., 2014) and Allergome databases (www.allergome.org), the majority of plant allergens belong to protein families with seed storage, structural or plant-defense functions. One of the most widespread groups of plant allergens are pathogenesis-related proteins (PR) accounting for about 25% of already referenced food allergens. These proteins are part of the first defense line of the plants, particularly against invading pathogens, but also in case of a variety of other biotic and abiotic stresses (Sinha et al., 2014). PR proteins are now distributed into 17 different groups, among which groups 2, 3, 4, 5, 6, 8, 9, 10 and 14 contain plant food allergens officially named by WHO/IUIS (International Union of the Immunological Societies) allergen nomenclature (Table 1). PR are grouped according to their degree of sequence similarity and their biological function (Sinha et al., 2014). Since different PR structures have been highly conserved through plant evolution, their well-conserved and potentially allergenic structures could elicit IgE cross-reactivity between different PR members in food and inhalant allergens (Midoro-Horiuti et al., 2001). Thus, allergic individuals who are sensitized to PR proteins from a specific plant tissue may exhibit cross-reactive IgE to homologous proteins present in other plants. For instance, PR-10/Bet v 1-like allergens are responsible of extensive cross-reactivity among different pollen and plant-derived food, affecting the quality of life of more than 70% birch allergic patients (Popescu, 2015). Similar cross-reactive syndromes involving a broad variety of plants and tissues have been reported for patients sensitized to PR of groups 2, 3, 5 and 14 (Table 1). In view of the overwhelming importance of PR in the plant defense mechanism, their expression is highly influenced by environmental stresses and plants growing under different conditions may have differential PR expression. Numerous studies have demonstrated that alterations in environmental conditions may enhance the expression of allergenic PR proteins, thereby potentially increasing the

Table 1 (continued)

Primary role	Protein family	Function/allergenic plant food	Referenced allergens	Allergenic relevance	Cross-reactivity	Polluting agents (reference)
Structural proteins	Profilin	Actin-binding protein/Food allergens in apples, sweet cherry, peach, pear, strawberry, orange, pineapple, kiwi, banana, melon, litchi, carrot, celery, tomato, bell pepper, mustard, peanut, te in soybean, hazelnut, almond, wheat, barley, rice, etc.	24 plant food allergens already referenced by the WHO/IUIS allergen nomenclature (www.allergen.org)	Alvarado et al., 2014	Panallergen Food, pollen, latex (Casquete-Román et al., 2012; Ganglberger et al., 2001)	Ozone (Eckl-Dorna et al., 2010); Industrial pollution (cement plant) (Ražná et al., 2014)
	Oleosins	Structural oleosins/peanut, hazelnut, Sesame, soybean, peach, Brazil nut	Ara h 10, Ara h 11, Ara h 14, Ara h 15, Cor a 12, Cor a 13 Ses i 4, Ses i 5	Leduc et al., 2006; Schwager et al., 2017	Food-food (diverse seeds) (Kobayashi et al., 2012)	Cadmium sulfide (Marmiroli et al., 2015) Sulfur dioxide, traffic exhaust (Schiavoni et al., 2017)

allergenicity of different plants. For example, LTPs from pepper and peach were differentially activated by biotic and abiotic environmental stresses (Botton et al., 2002; Jung et al., 2003). Another study revealed that the amount of IgE-reactive antigens increased up to 10 times in *Brassica rapa* plants exposed to salicylic acid and ethephon, representative chemicals stimulating the plant defense response (Hänninen et al., 1999). As depicted in Table 1, the expression of allergenic PR families has proved to be influenced by various chemical pollutants including heavy metals, air pollution and pesticides.

2.1. Cadmium stress

Cadmium stress represents one of the most documented chemical stress factors increasing the PR protein concentrations in a variety of plant derived-tissues and foods. This metal is a bio-persistent and frequently occurring source of environmental contamination in industrialized countries affecting agricultural soils through Cd-containing fertilizers, pesticides and sewage sludge (Wuana and Okieimen, 2011). Food plants growing on Cd-contaminated soil and the meat of ruminants consuming them represent more than 98% of the cadmium intake in human (Van Assche, 1998). Thus, Cd-contaminated plant foods present a dual threat to humans and animals, directly as a source of heavy metal and indirectly by being themselves subjected to serious stresses which could modify their nutritive value and their allergenic composition.

In leaves of cadmium-treated barley, an accumulation of apoplastic PR proteins (belonging to groups 2, 3, 4, 5 and 17) has been reported (Pós et al., 2011). Other studies on rice varieties revealed that cadmium stress enhanced the expression of PRs of groups 2, 3, 8, 5 and 10 (Ge et al., 2009; Hajdúch et al., 2001; Lee et al., 2010). Similarly, accumulation of PR5 and PR16 (a germin-like protein) proteins following cadmium exposure has been reported in Arabidopsis (Semane et al., 2010). Cadmium induced the expression of a PR3 chitinase among different pea genotypes as a consequence of an increased defense response in more sensitive plants (Metwally et al., 2004). In wheat cultures, a low molecular weight protein showing a strong homology to parsley PR2s was elicited as a response to Cu and Cd stresses (Cruz-Ortega and Ownby, 1993). Moreover, Aina et al. (2010) revealed that pollen grains of *Poa* plants exposed to Cd released a higher amount of allergens and a protein belonging to the PR3 panallergen family (class I chitinases) was detected in Cd-exposed plants (Aina et al., 2010).

Besides PR, other plant defense-related proteins identified as potential cross-reactive food allergen sources such as snakin/gibberellin regulated proteins (GRP) and heat shock proteins (Hsp) were upregulated through cadmium treatment. Recently, snakin/GRPs have been associated to at least two pollen-fruit/vegetables syndromes involving cypress pollen and raw fruits (cypress/peach and cypress/citrus) (Charpin et al., 2017; Sénéchal et al., 2017). Snakin/GRPs share high amino-acid sequence identity and common IgE epitopes among fruits and vegetables (Inomata et al., 2017; Sénéchal et al., 2017). In cypress pollen, the cross-reactive allergen exhibits a molecular mass of about 14 kD and displays heat-stable conformational epitopes (Shahali et al., 2012). The expression pattern of the snakin gene in potato (StSN1) suggests their active participation in constitutive defense barriers against both biotic and abiotic stresses in storage and reproductive plant organs (Segura et al., 1999). In *Viola baoshanensis*, the Cd accumulation following Cd treatment induced two snakin cDNAs encoding proteins playing a protective role through heavy metal detoxification increasing the plant tolerance against cadmium pollution (Zhang et al., 2015). Hsp70 chaperons constitute another group of ubiquitous proteins able to sensitize allergic individuals. The high degree of sequence identity between members of this well-conserved family increase the risk of IgE cross-reactivity among HSP70 kD allergens present in pollen and different plant-derived foods (Gruehn et al., 2003). Upregulation of Hsp70 expression is often observed as a tolerance mechanism against various abiotic stresses such as desiccation and heavy metal

contamination. For instance, in *Brassica juncea*, the gene encoding a heat shock protein (BjCdR57) is part of the Cd-regulated genes detected in times of cellular stress caused by Cd stress (D'Alessandro et al., 2013).

In Cd-treated pea plants, an Hsp71 was induced to protect cells against damages caused by the metal stress (Rodríguez-Serrano et al., 2009). As recently reviewed by (Hasan et al., 2017), the expression of all five major classes of heat shock proteins (HSPs) is promoted in response to heavy metal stress and members of the Hsp70 family appeared to be particularly upregulated following arsenic, cadmium, copper and mercury contaminations. Besides cadmium, other man-made pollutants are able to activate the expression of proteins associated to the plant defense/tolerance system and potentially influence the allergenic composition of plant-derived foods. Important groups of chemical pollutants are metals such as lead or mercury, which are regularly found in some plant foods. These contaminations result from background levels of these toxic compounds in the plant environment.

2.2. Mercury pollution

Mercury (Hg) is an odorless, very toxic and naturally occurring metal, particularly impacting the water environment (Björklund et al., 2017). Major sources of mercury pollution include oil and gas industries, agriculture, mining, discharges of industrial wastewater and waste incinerations (Chen et al., 2012). The annual level of Hg emission into the environment has been estimated at 2200 metric tons (Ferrara et al., 2000). Mercury has the ability to damage the protein structures altering by this way the plant cellular structure (Jaishankar et al., 2014). Hg-induced PRs have been identified in many plant foods (Table 1). Frendo et al. (1992) demonstrated that a TLP-homologous protein (PR5) is induced in mercuric chloride-treated maize (Frendo et al., 1992). Similarly, a PR5 protein was highly upregulated in rice following exposure to mercuric chloride (Hajdúch et al., 2001). Besides PR5s, other Hg-induced PR proteins belonging to groups 2 and 3 have been also identified in maize (Didierjean et al., 1996). Accumulation of chitinase isoforms (PR3) have been reported in Hg-contaminated maize and sunflower tissues (Békésiová et al., 2008).

2.3. Lead contamination

Lead (Pb) is another widespread and highly toxic metal causing extensive environmental and health problems worldwide. This heavy metal is taken up by plants through fixation to soil and contaminated waters. Lead is highly toxic for plants by affecting various physiological processes without playing any biological functions. Human Pb exposure is mainly due to plant-derived foods or drinking water (Goyer, 1990). PR3 and PR5 have been found to be induced by Pb in sunflower (Walliwagedara et al., 2010). In Pb-contaminated plants, the expression of *ltp* gene encoding PR14 proteins is promoted as a defense mechanism leading to the accumulation of non-specific LTPs in epidermal plant tissues (Seregin and Ivanov, 2001).

2.4. Copper accumulation

Copper (Cu) is one of the most commonly found metals in the environment. This element is an essential metal for normal plant growth and development. Although Cu participates in numerous physiological processes as an important cofactor for various metalloproteins, excess Cu is potentially toxic for plant cells (Wuana and Okieimen, 2011). Copper has been widely used in the composition of fungicides which led to the accumulation of Cu in agricultural soils in many regions worldwide. It has been shown that in Cu-contaminated soils, excess copper inhibits plant development and promotes the accumulation of PRs in plant tissues (Ferreira et al., 2014). For example, copper promotes the expression of the OsPR5 protein presenting sequence homology to some PR5 panallergens (Hajdúch et al., 2001; Rakwal et al., 1999).

2.5. Sulfur-rich soils

Sulfur (S) is essential for plants. Some sulfur-containing compounds such as phytochelatin, glutathione and the GSH polymers represent vital components in plants that can eliminate heavy metal stress and play an important role in the non-hyperaccumulation of heavy metals in resistant plant (DalCorso et al., 2013). Thus, application of heavy metals in crops contributes to the increase of sulfur concentrations in contaminated plant tissues (Zhong et al., 2011). Furthermore, sulfur is involved in several redox reactions and is crucial for synthesis of cysteine and methionine amino acids, iron-sulfur clusters as well as several proteins and co-enzymes. Since ancient times, sulfur is a component of many agrochemicals and Sumerians from 4500 years ago used sulfur compounds as insecticides (Pogăcean et al., 2013).

Studies on peanut varieties have shown that external sulfur application may enhance the amount of sulfur-containing proteins in seeds, changing seed protein profiles (Sexton et al., 1998). Interestingly, a molecular study on peanut crops revealed that high levels of sulfur in soils differentially influenced sulfur-rich (Ara h 2, Ara h 3, and Ara h 6) and sulfur-poor (Ara h 1) allergen content in peanut seeds (Chandran et al., 2015).

2.6. Air pollution: ozone and dioxide nitrogen

Air pollution is considered to be a potential factor responsible for the increasing prevalence of allergic diseases worldwide. It has been shown that environmental effects caused by major air pollutants such as ozone and nitrogen dioxide may increase the allergenic potency of many pollen species (Chassard et al., 2015; Frank and Ernst, 2016; Ribeiro et al., 2014; Sénéchal et al., 2015). Amongst others, the expression of some cross-reactive pollen allergens associated to PFAS appeared to be significantly upregulated. For example, Beck et al. (2013) showed that the concentration of the Bet v 1 panallergen in birch pollen extracts is positively correlated with increasing ozone levels. These extracts induced significantly larger wheal and flare diameters in allergic patients because of their higher Bet v 1 content (Beck et al., 2013). In cypress pollen, a thaumatin-like protein (Cup a 3) belonging to the PR5 panallergen family is upregulated under polluted air conditions (Cortegano et al., 2004; Suárez-Cervera et al., 2008). Enhanced allergen expressions due to elevated ozone have also been reported for allergenic grass species such as *Lolium perenne* and *Secale cereale* (Eckl-Dorna et al., 2010; Masuch et al., 1997). In parsley, ozone exposure is responsible of an increased induction of parsley pathogenesis-related proteins at the transcript level (Eckey-Kaltenbach et al., 1997). In rice seedlings exposed to elevated ozone, the expression of a PR5 and two PR10 proteins was significantly upregulated and their concentration gradually increased throughout the 2-day exposure period (Feng et al., 2008). Therefore, variability in plant PR expression levels not only results from genetic differences but also from the influence of a variety of agricultural practices and environmental contaminants that play a central role in the expression of many plant defense-related proteins belonging to well-known panallergen families (Table 1).

3. Panallergens and chemical stress

Some proteins are responsible for extensive cross-recognition among unrelated-plant species. These well-conserved allergenic structures are referred to as “panallergen”, which comprise a restricted number of ubiquitous proteins shared by various allergenic sources throughout nature (Hauser et al., 2010). In plants, the majority of panallergens are involved in the plant defense system and represent structurally related and well conserved proteins in the course of evolution. For example, homologous molecules of the birch pollen panallergen Bet v 1 (PR-10) are induced and accumulated in a large variety of taxonomically unrelated and distant fruits and vegetables

(Table 1). This explains why the majority of allergic patients are polysensitized and display allergic reactions upon exposure to a variety of allergen sources.

Despite the vital role of these panallergens in the plant resistance to different stresses, from an allergenic point of view and given the remarkable number of individuals which are exposed and sensitized to these allergens, their increased expression and accumulation in plants represent a threat for general population. The most clinically relevant plant food panallergens belong to PR14s (non-specific lipid transfer proteins, nsLTP), profilins, PR10s (Bet v 1-like proteins), PR5s (Thaumatin-like proteins or TLPs) and PR3s (Chitinases) families. The expression of all these protein families appeared to be influenced by chemical contaminations.

3.1. PR14s (non-specific lipid transfer proteins)

LTPs constitute a group of well-conserved proteins able to transfer phospholipids and other fatty acid groups across cell membranes. Non-specific LTPs (nsLTPs) constitute the group 14 of PR proteins which are strongly abundant in higher plants and exhibit molecular masses ranging from 9 to 12 kDa. Because of their high resistance to heat, proteolytic digestion and gastric fluids, they are responsible for severe clinical symptoms, especially in patients sensitized to Rosaceae-fruits (Van Ree, 2002). PR14s are mainly involved in plant defense to abiotic stress and embryogenesis. In peach, nsLTP is an important fruit allergen and showed different expression levels in response to abiotic stress (Botton et al., 2002). In Cd-exposed seedlings of barley, an elevated amounts of nsLTP has been reported with a potential function in the transfer of wax monomers to the plant cuticle (Hollenbach et al., 1997). Cadmium stress by stimulating the ABA metabolism in higher plants, promotes the expression of the gene encoding for the LTPs in the epidermal tissues (Seregin and Ivanov, 2001).

3.2. PR10s (Bet v 1-like)

Proteins belonging to the PR-10 family are responsible for an important part of OAS in patients suffering from pollen-food allergy syndrome. The members of the PR10 family are resistant to protease, mostly intracellular and cytosolic and have low molecular masses (around 15–18 kDa) (Ekramoddoullah, 2004). The allergens of this family have an unusual quaternary protein structure displaying a seven-stranded β -sheet with a long α -helix harboring a metal binding site (Hurlburt et al., 2013). PR-10 proteins are involved in general stress defense mechanism and certain physiological changes during developmental stages (Fernandes et al., 2013). Several studies have demonstrated that PR10-type proteins are differentially expressed in pollen and plant-derived foods under environmental stresses and chemical contaminations (Table 1). In rice, cadmium stress enhanced the expression of a PR10-type RNases (Ge et al., 2009). Likewise, a PR10-type protein was recently found to be upregulated in the leaves of saffron (*Crocus sativa*) under Cd stress (Rao et al., 2017). Increased levels of a 16 kDa protein related to PR-10s was also found in roots of *Lupinus luteus* exposed to salicylic acid, hydrogen peroxide and ethylene representing the major transducers of the stress response in plants (Przymusiński et al., 2004).

3.3. PR5s (thaumatin-like proteins)

The proteins of the thaumatin-like family have molecular masses of 20–30 kDa and include eight disulphide bridges that give them a very stable three-dimensional structure (Sinha et al., 2014). Because of their high amino-acid sequence homology to a sweet thaumatin protein (Cornelissen et al., 1986), they are known as thaumatin-like proteins (TLPs). TLPs are involved in plant defense against pathogen attacks, particularly in response to fungal infections. TLPs are glycoproteins and harbor cross-reactive carbohydrate determinants (CCDs) which could

be responsible for clinically irrelevant cross-reactivity in *in vitro* studies (Palacin et al., 2008; Shahali et al., 2017). It has been shown that TLPs were produced and accumulated in high amounts in leaves of young plants upon biotic or abiotic stress (Hoffmann-Sommergruber, 2002).

Because the expression of PR5 proteins is inducible by environmental stress, plants growing under different conditions may express different levels of the allergenic PR5 proteins. For example, PR5 proteins have been induced by mercury in maize (Didierjean et al., 1996) and by lead (Pb) in sunflower (Walliwalagedara et al., 2010). Moreover, as part of the cadmium stress response, a thaumatin-like proteins (PR5) and some other PRs were shown to be part of the plant defense response in rice (Hajdúch et al., 2001). Similarly, following cadmium treatment a PR5 was upregulated in *Arabidopsis* (Semane et al., 2010) and at least three PR5 proteins were shown to accumulate in barley leaves (Pós et al., 2011). High level expression in TLP proteins was also found in the roots of *Medicago sativa* after exposure to the atrazine herbicide (Song et al., 2016). In cypress-cedar pollen grains, the amount of PR5 allergens vary extensively in polluted regions. Two cross-reactive PR5 allergens, Jun a 3 in mountain cedar (*Juniperus ashei*) and Cup a 3 from Arizona cypress, were shown to be upregulated under polluted air conditions (Cortegano et al., 2004; Midoro-Horiuti et al., 2000; Suárez-Cervera et al., 2008).

3.4. PR3s (Chitinases)

PR-3 family proteins comprise chitinases of classes I, II, and IV (Sinha et al., 2014). Chitinases are able to hydrolyze the chitin constituting fungal cell walls and the exoskeleton of some animals (Hamid et al., 2013). PR-3 proteins are mostly endochitinases with molecular masses ranging from 25 to 35 kDa. Class I chitinases have been identified as the major panallergen in fruits involved in the latex-fruit syndrome, such as avocado, banana, and chestnut (Wagner and Breiteneder, 2002). A survey on 20 different food extracts revealed that putative class I chitinases were highly cross-reactive and were linked to latex-fruit allergy in cherimoya, passion fruit, kiwi, papaya, mango, tomato, and wheat (Díaz-Perales et al., 1999). Chitinases should also be included among defense components that are responsible for inter- as well as intra-species differences in heavy metal tolerance of plants. In response to metal ion contaminations, 2–5 different chitinase isoforms were significantly upregulated in sunflower, pea, maize and bean cultivars (Békésiová et al., 2008). The total number of chitinase isoforms increased in samples treated with arsenic and cadmium (Gálusová et al., 2015). A coincidence between metal sensitivity and chitinase expression of a variety of pea genotypes have been also observed by (Metwally et al., 2004) as a consequence of enhanced defense response in more sensitive genotypes. This study reported up to 1.3-fold activity increase in chitinase activity in roots and up to 4 fold increase in leaves for more sensitive pea genotypes. In Cd-treated pea plants and barley, chitinases were up-regulated, probably to protect cells against toxic damages (Cao et al., 2014; Rodríguez-Serrano et al., 2009). Interestingly, the amount of the class I chitinase panallergen appeared to be strongly upregulated by ethylene treatment (Sánchez-Monge et al., 2000). This fact can be particularly relevant in fruit allergy because ethylene is widely used to accelerate post-harvest ripening in some fruits such as banana, avocado, apple and tomato.

It is important to emphasize that chitinase genes alone or in combination with β -1,3-glucanase genes have been transferred to numerous transgenic plant species to improve their resistance to certain pathogens (Ebrahim et al., 2011). Hence, most transgenic plants exhibit enhanced chitinase expression. For example in some transgenic plants, the level of chitinase activity showed a 20–40 fold-increase when compared to non-transgenic plants (Broglie and Chet, 1991). Non-plant chitinases from fungal species have also been transferred to model plants to increase the resistance of susceptible varieties (Lorito et al., 1998).

3.5. Profilins

Profilins are ubiquitous proteins that control the polymerization of actin in all eukaryotic cells. Plant profilins present a highly conserved structure provoking cross-reactive specific IgE responses in sensitized patients (Barber et al., 2009). Patients with allergy to plant-derived foods and associated latex allergy show a high frequency of IgE reactivity to the profilin panallergen (Wagner and Breiteneder, 2002). Because of their low thermal and proteolytic resistance, profilins were considered as mild food allergens causing local symptoms such as OAS. However, recent molecular studies (Alvarado et al., 2014) demonstrated that high inhaled exposure to cross-reactive grass allergens promotes severe profilin food mediated reactions. Furthermore, the prevalence of profilin sensitization is positively correlated with the grass pollen gradients. The pollen profilin allergen concentration could be influenced by some environmental chemical factors. For example, exposure to high ozone levels during the growth phase resulted in heightened content of profilin allergen in rye grass cultivars (Eckl-Dorna et al., 2010). Razna et al. (2014) also revealed that among all hazelnut pollen allergens, profilin was the most significantly affected by the industrial pollution of a cement plant with rates almost 52 times higher than those obtained in non-polluted areas (Ražná et al., 2014).

4. Post-translational modifications of plant allergens: role of nitration

Nitration of proteins, resulting from the addition of a nitro group to the tyrosine aromatic ring, has been shown to increase allergenicity (Ackaert et al., 2014; Karle et al., 2012). Air pollutants such as NO_x and ozone were reported to chemically affect allergenic proteins by nitration (Liu et al., 2017), leading to the alteration of both T-cell and B-cell epitopes (Gruijthuijsen et al., 2006; Untersmayr et al., 2010). Franze et al. (2005) showed that the major birch allergen (Bet v 1) is nitrated more effectively in the presence of a combination of nitrogen dioxide and ozone than when proteins were exposed to nitrogen dioxide alone (Franze et al., 2005). The nitration resulting from this interaction altered the allergenic potential of Bet v 1 and led to a stronger proliferation of allergen-specific T cell lines. Moreover, nitrated Bet v 1 appeared to be more IgE reactive (Gruijthuijsen et al., 2006; Karle et al., 2012). An oligomerization of Bet v 1 due to nitration was also observed, which resulted in lower sensitivity to endolysosomal degradation (Ackaert et al., 2014). With regard to food allergens, diet-derived nitrating substances such as nitrate and nitrite have been suggested to be a source of nitration in the gastrointestinal tract (Oldreive and Rice-Evans, 2001). In the stomach, the formation of various nitrating species are facilitated due to the acidic environment which favors the protonation of nitrite (Rocha et al., 2012). Hence, the formation of nitrotyrosine (3-NT) could be both exogenous and endogenous and may have an impact on food allergy. It has been revealed that nitrated antigens resulted in enhanced humoral immunity and may even provide additional epitopes to allergenic proteins. This hypothesis was strengthened by the study of Gruijthuijsen et al. (2006) revealing that the nitrated form of two unrelated proteins (Ovalbumin and Bet v 1) are recognized by the same cross-reactive antibodies (Gruijthuijsen et al., 2006). Moreover, this study revealed the formation of new epitopes (neo-epitopes) following the Bet v 1 nitration inducing specific IgE in murine models. The nitrated form of Bet v 1 also enhanced the presentation of allergen derived peptides through antigen presenting cells (APC). The results of another study (Diesner et al., 2015) suggested that food allergens are differentially altered by nitration. For example, nitrated B-lactoglobulin (BLG) showed a strong tendency to dimerize which led to increased allergenicity and anaphylactic reactions in animals sensitized to BLG.

5. Chemicals as allergens

Food allergies are typically IgE-mediated, but certain reactions result from different immunologic mechanisms. Among them, allergy to metals is part of a cell-mediated (type IV) hypersensitization affecting 10%–15% of the human population (Saito et al., 2016). Metals such as nickel, aluminum, gold and mercury are potential sources of allergic and autoimmune diseases (Björklund et al., 2018). Specific responses to metals are mediated by sensitized T cells and strongly depend on the genetic predispositions of the individual. Allergenic metals are able to bind autologous proteins and may act as active haptens with immunomodulating properties (Stejskal, 2015).

Nickel allergy is the most common type of metal allergy worldwide and represent a public health concern (Yoshihisa and Shimizu, 2012). Nickel is an essential nutrient in mammals (Stangl and Kirchgessner, 1996) and 90% of the total dietary intake comes from plant foods and plant-derived beverages (Björklund et al., 2018). The level of nickel in foods varies greatly among different plant species and varieties as well as with the nickel content of the soils. A half-part of the daily nickel intake is provided by cereals and pulses (Tsoumbaris and Tsoukali-Papadopoulou, 1994). In most studies, plant-derived foods such as nuts, dried peas and beans, whole grains, and chocolate were reported as the richest sources of dietary nickel. Moreover, different parts of the same plant contain different nickel concentrations and the highest nickel contents are found in young leaves (Boyd et al., 1999). The level of nickel in plant foods may vary substantially from place to place. This is due to the variability of the nickel content in different soils. The major sources of nickel contamination in the soil are combustion of fossil fuels, nickel mining and industrial metal plating (Khodadoust et al., 2004). Nickel could also be introduced during some food processing from various sources such as metal containers, metal grinders used to produce flour or cooking utensils.

Food allergy caused by nickel could be suspected when dermatitis is observed on skin surfaces of patients which were not exposed to any known causative allergens. Moreover, patients suffering from systemic lupus erythematosus, rheumatoid arthritis and Sjögren's syndrome appeared to have an elevated frequency of metal and nickel hypersensitivity (Björklund et al., 2018). The consumption of nickel-rich plant foods may elicit systemic contact dermatitis (SCD) in nickel-sensitive individuals. For example, SCD can be provoked from the ingestion of foods with a high nickel content, such as cocoa (Krecisz et al., 2011). In nickel-hypersensitive patients, a low-nickel diet often lead to the resolution of skin symptoms. For example, in the case of an allergic patient suffering from pruritus with high resistance to symptomatic treatments, the skin lesions were resolved following the restrictive consumption of a peanut butter containing high levels of nickel (Silvestri and Barmettler, 2011). Thus, a low-nickel diet is highly recommended for nickel-sensitive patients, particularly in the case of iron deficiency, pregnancy and lactation because of the increased nickel absorption in the human tissues (Tallkvist et al., 2003).

6. Chemicals as potential adjuvants in food allergy

It is now well established that the Th2 immune response is actively promoted by an array of molecules with intrinsic or associated Th2-skewing adjuvant activity (Berin and Shreffler, 2008). Some chemicals such as aluminum may substantially influence the development of food allergy by contributing to the shift toward a Th2-type response. Aluminum and some other metals such as mercury are well-known immunomodulators that may act as immune adjuvants or immunosuppressors. It has the ability to modify the cytokine production and to enhance the immune response to some food allergens (Berin and Mayer, 2009). Plant food intake and food additives constitute an appreciable portion of the human aluminum consumption (Rossi, 2012). Some plant foods such as soy accumulate elevated amounts of aluminum and orally-taken aluminum compounds such as soy-fed,

sucralfate or anti-acid drugs may promote Th2 sensitization to food proteins (Brunner et al., 2009). Moreover, aluminum-rich compounds such as sucralfate may facilitate allergic sensitization through the inhibition of the gastric acid (Brunner et al., 2007; Untersmayr et al., 2003). Psychological stress has also been shown to enhance aluminum-induced sensitization to luminal antigens by facilitating the passage of macromolecules throughout the small and large intestine and across the epithelial barrier (Yang et al., 2006). Autoimmune/inflammatory syndrome induced by adjuvants (ASIA) have recently been associated with aluminum intake and is responsible of chronic fatigue syndrome and autoimmune diseases in susceptible individuals (Rosenblum et al., 2011). Patients with allergy along with those with a previous history of autoimmunity have higher risks to develop ASIA in response to adjuvants (Soriano et al., 2015).

Recent studies suggest that chemicals able to alter the human microflora may also contribute to the increasing prevalence of food allergies in industrial countries. For instance, an epidemiological study on 2211 persons (aged 6 years and older) demonstrated that high urine levels of dichlorophenols, a chemical with strong bactericidal properties found in pesticides and chlorinate water, positively correlated with food allergies (Jerschow et al., 2012).

7. Conclusion

An overwhelming body of evidence now demonstrates that plant chemical exposure and chemicals in diet may contribute to the increase in both prevalence and severity of plant food allergies. Based on the present knowledge, chemicals may influence allergic sensitization to plant-derived foods in different manners. They are able to act I) as chemical adjuvants facilitating IgE-mediated allergic sensitization to plant food allergens; II) as active haptens responsible of non-IgE mediated (type IV) food allergy; III) as elicitors of post-translational modifications in plant allergens leading to an increased allergenic potency; and IV) as potent upregulators of allergenic protein expression. Furthermore, the increased production of some pollen panallergens under chemical stress such as Bet v 1 in birch and Cup a 3 in cypress, indirectly influences the incidence of food allergy since more allergy to cross-reactive pollen allergens may lead to more pollen-food allergic syndromes. This article especially focus on the influence of chemicals on plant food proteins with allergenic potential and their homologues. Considering the fact that a substantial number of plant-derived allergens are defense-related proteins, a better understanding of plant defense system and modifications occurring at both transcriptome and proteome levels during chemical stress may contribute to a better risk assessment in food allergy. Among defense-related proteins induced by chemical stress, PR and PR-like proteins are responsible for extensive cross-reactivities between different inhalant and food allergen sources and play a central role in the high prevalence of cross-reactive food syndromes such as pollen-food allergic syndrome and latex-fruit syndrome. The wide range of chemical stress factors promoting PR expression such as agrochemicals and other anthropogenic pollutants may thus lead to the natural selection and survival of plant strains expressing higher amounts of certain defense-related and PR proteins. Elevated PR induction may also arise from transgenic strains through the insertion of PR-encoding genes or by increasing PR-expression levels to improve their resistance to a variety of environmental stresses and diseases. Although the allergenic features of genetically-modified plants need to be carefully evaluated, a recent study revealed that environmental stress induces far more proteomic and transcriptomic alterations than transgenesis in plants (Batista et al., 2017). Interestingly, these modifications could potentially be memorized throughout generations and may influence the protein content of plants crops intended to human and animal consumption. These recent findings stress the need to consolidate monitoring networks combining environmental and epidemiological data to better evaluate the effects of chemical contaminations on allergic sensitization to plant-derived food allergens.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2018.03.032>.

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