

PLANT LIPID TRANSFER PROTEINS (LTPs): BIOCHEMICAL ASPECT IN PANALLERGEN - STRUCTURAL AND FUNCTIONAL FEATURES, AND ALLERGENICITY

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SUMMARY: Lipid transfer proteins (LTPs) are highly conserved and widely distributed throughout the plant kingdom. Several members of LTP family have been identified as relevant allergens in food and pollens. Because of their high resistance to heat treatments and enzymatic digestion, these proteins are allergenic candidates for oral route sensitisation. This review presents biochemical features, allergenicities and cross reactivities of fruit, cereal and pollen LTPs.

Key-words: Lipid transfer proteins - Rosaceae - Parietaria pollen, wheat, food and respiratory allergy.

INTRODUCTION

Plant non-specific lipid transfer proteins (LTPs) are ubiquitous proteins widely distributed throughout the plant kingdom. Several members of the plant LTPs family have been identified as relevant allergens in foods and pollens. LTPs are now classified as plant panallergens. Food allergy to fruit LTPs of the *Rosaceae* family is well-known in the Mediterranean area. LTPs are also identified as major allergens for *Rosaceae* allergy. Moreover, LTPs have been identified as relevant allergens in other plant foods as fruits not belonging to the *Rosaceae* family or cereals and also in pollens. The physicochemical properties and structural stability to both heat treatment and proteolytic digestion of plant LTPs are intrinsically linked to their allergenicity. These share properties could let imagine strong cross-reactivity between different plant LTPs. We focus, here, our attention on these share properties and analysed recent works in cross reactivity of plant LTPs. The analysis of recent findings on the biochemical and allergenic properties of LTPs will allow to better apprehend the "LTP syndrome" and to understand the interest of many scientists on the study of this model of plant panallergen.

Functions and structures of plant LTPs

LTPs are ubiquitous proteins in the plant kingdom and form a very homogeneous class of proteins. Plant LTPs are small, abundant and soluble extracellular

proteins that are able *in vitro* to bind and transfer between membranes a variety of lipids (1). Nevertheless, their biological function *in vivo* remains unclear. LTPs expression pattern is complex and characterised by strong developmental and tissue specificity and modulated by environmental and stress conditions (2). Consequently, different hypothesis have been suggested. LTPs could be involved in the transfer of the hydrophobic monomer of cutin or in the defence response against pathogens (3-5). LTPs have been suspected to be involved in the transfer of phospholipids from their synthesis site to membrane and thus to play a role in managing the flux of lipids essential for the genesis and renewal of cellular membranes (6). They can be divided into two types: those that are specific for certain classes of phospholipids, and those (called "nsLTPs" for non specific LTPs) that are able to accommodate several varieties of lipids. They have been proposed that LTPs could act as systemic signalling molecules. LTPs may interact with specific cellular membrane receptor of elicitor, a 10 kDa protein able to bind to lipid and secreted by a fungus (7, 8). Recently, they have been described that the localisation of LTPs in the pollen grains of *Parietaria judaica* changes during the process of hydration (9). The localisation of LTPs in cytoplasm and lipid bodies associated with vacuoles showed that LTPs of *Parietaria judaica* pollen represent primarily intracellular proteins. These authors suggest that these LTPs may be cytoplasmic proteins secreted for the pollen-stigma interactions.

Plant LTPs are encoded by a multigenic family (up to 30 genes in *A. thaliana*) and form a big family of little basic monomers (pI ~ 9), with sequences between 90 to 95 amino acids (8, 10). On the basis of molecular

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mass, LTPs are subdivided into two subfamilies: LTP1 (Mr ~ 9 kDa) and LTP2 (Mr ~ 7 kDa), except for LTPs of *Parietaria* and *Artemisia* pollen which sequences are comprised between 12 to 15 kDa (1, 11-14). The degree of sequence homology between LTPs of different species differs largely between less or no sequence homology to strong sequence homology (22 to 65%) (Fig. 1). LTPs had strong intra-species homologies in their primary sequences (80 to 95 %) justified frequent clinical observations of cross allergy between members of the same species (15, 16). On the other hand, plants LTPs show no sequence homology with mammals LTPs (1).

Moreover, LTPs are members of the prolamin superfamily characterised by the presence of a conserved skeleton of eight cysteine residues within the protein sequence; this superfamily includes a range of important plant allergens (17, 18). Plants LTPs are characterised by the presence of eight conserved cysteines forming four intramolecular disulphides bridges, called: "The cysteine signature of LTPs" (Fig. 2), which are responsible of their compact folding and their strong stability to the various heat or enzymatic treatments (1, 19). Resolution of three-dimensional structures of the cereals LTP1 by X-ray crystallography

allows establishment of three-dimensional models of plants LTPs folding (Fig. 3) (20-22). These proteins are characterized by only one compact domain with four α -helices connected by flexible loops and a C-terminal fragment having the original shape of saxophone (19). The folding of these α -helices allows formation of hydrophobic tunnel covered by the side chain of the hydrophobic residues of the amphipathic helices and the C-terminal region. This hydrophobic cavity is partially closed by a flexible C-terminal region. Tunnel size seems to be different with isoforms comparing folding of different LTPs, thus conferring less or more lipid binding and transfer properties (23). Interestingly, other plant allergens, such as soybean Gly m 1, the α -amylase/trypsin inhibitors from cereal flours and some 2S storage proteins, show 3-D structures close to the LTP fold (19, 24). Crystal structure of the major peach allergen, Pru p 3, has been resolved recently by Pasquato *et al.* (Fig. 4) (25). These data may validate 3D models of plants LTPs folding and may localise epitopes on the folding of these proteins. Plants LTPs share little size (between 7 and 16 kDa) and common function, a role in plant defence mechanisms against pathogen, at least in some species and tissue (24). Consequently, LTPs are now classified in

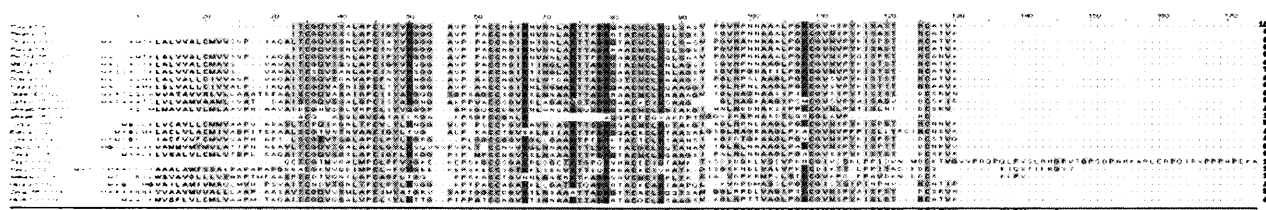


Fig. 1: Multiple alignment of various LTPs by CLUSTALW. Identity percent with Pru p 3 was indicated on the right column. Conserved Cys residues are indicated by pink box.

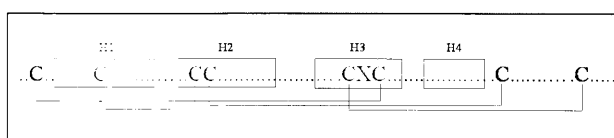


Fig. 2: The Cysteine signature of LTPs. Distribution and binding of Cysteine residues in primary sequence of LTPs. "H1-4" showing the four α -hélices (19).

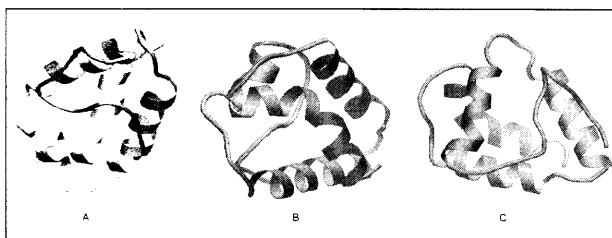


Fig 3: Three dimensional structures of three LTP1 of cereals: maize (A), rice (B) and wheat (C) showing the four α -helices (111-113).

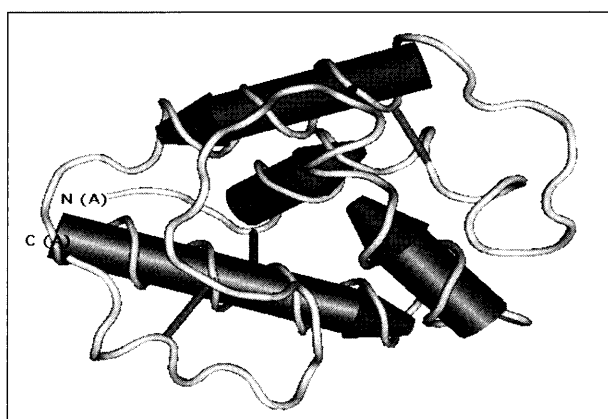


Fig 4: Crystal structure of peach Pru p 3. Ribbon diagram of the modelled Pru p 3 showing the three α -helices (pink) connected by turns and loops (blue); Red sticks correspond to the disulfides bridges; N(A) and C(A) correspond to the N- and C-terminal amino-acid of the polypeptide chain, respectively (25).

the pathogenesis-related (PR) protein families as PR-14 (26). Two properties that seem in general to be shared by plant protein allergens are abundance coupled with structural stability (27). While LTP are not very abundant in the whole plant tissues, levels of LTPs are relatively abundant in skin and peel, being around 7-fold higher in these tissues compared with pulp in fruits such as peach (28, 29). Indeed, LTPs are localised in the plant aerial organs (1, 4, 19, 30-32). LTPs are accumulated in the epidermal tissues of exposed surface like fruit skin. This why, the skin fruits belonging particularly to the *Rosaceae* family are considered more allergenic than the peel of these fruits (33). Indeed, except for plum and apricot, other *Rosaceae* fruits, especially apple, concentrate LTPs in the skin (29). Moreover, the localisation and distribution of LTPs in tissues of *Rosaceae* fruits could be also provide information for diagnostic and therapeutic applications. Indeed, the subcellular localisation of LTPs in *Rosaceae* fruits shed new lights on the availability of these allergens for triggering an anaphylactic response in susceptible individuals (29). The localisation of secreted LTPs as components of the cell wall of epidermal/hypodermal cells ensure the exposition of these allergens at the surface of these fruits. Recent results suggest that the fuzzy hairy cover of peach might account for the high prevalence of sensitisation to peach in people from Mediterranean countries (34). As a consequence Borges *et al.* recommended a consumption of peeled-off fruits to reduce the risk of severe allergic reactions in individuals sensitised to *Rosaceae* fruits (29). The chemical peeling treatment, if appropriately added in an industrial process, could lead to hypoallergenic derivatives by successfully removed Pru av 3 (LTP of cherry), such as jams and fillings, suitable for people sensitised exclusively to LTP (35). Furthermore, the syruping process removed almost all allergenic proteins to whom patients with pollinosis are responsive. However, discrepancies were observed among the different commercially available apple varieties. Similar differences were shown among the fruits from various peach and apple varieties (36, 37).

Plants LTPs Allergenicity

The broad distribution of LTPs among the plants suggests a potential role of vegetable panallergen (Table 1) (16, 38). Nevertheless, in Northern Europe and Central Europe, plants food allergy is mainly due to sensitisation by birch pollen (39). Indeed, up to 80% of patients of these areas, suffering from plants food allergy, show pollinosis associated with birch (40). The patients sensitised by birch showed an important reactivity with the fruits of *Rosaceae* family (apple, peach, cherry,...), but also with other plants (carrots,

celery, hazelnut,...). The immunological base of this phenomenon is the cross reactivity of IgE due to the strong homologies of primary sequences between allergens of pollen and some allergens of vegetable food (41, 42). The major allergen of the birch, Bet v 1, and its homologues as food proteins (Mal d1 for apple, Pru av 1 for cherry and Cor a 1 for hazelnut) are important mediators of cross reactivities (43-45). Bet v 2, Bet v 6 and Bet v 8 are also involved in the same type of cross reactions (46-48). Most of the time, patients suffering from this type of food allergy have presented restricted mild symptoms with oral allergy syndromes (39, 49). In this case, the allergens responsible for the primary sensitisation are pollen and not food fruits allergens. However, systemic reactions like anaphylaxis or urticaria were also described for this allergy (50, 51).

This traditional diagram of plants food allergy mainly due to birch pollen in the areas of Northern and

Common name	Species	Allergen	Reference
Rosaceae			
Almond	<i>Prunus dulcis</i>	Pru du LTP	(74)
Apple	<i>Malus domestica</i>	Mal d 3	(15)
Apricot	<i>Prunus armeniaca</i>	Pru ar 3	(56)
Cherry	<i>Prunus avium</i>	Pru av 3	(104)
Peach	<i>Prunus persica</i>	Pru p 3	(54)
Pear	<i>Pyrus communis</i>	Pyr c 3	(72)
Plum	<i>Prunus domestica</i>	Pru d 3	(57)
Raspberry	<i>Rubus idaeus</i>	Rub i 3	(114)
Strawberry	<i>Fragaria ananassa</i>	Fra a 3	(76)
Nuts			
Chestnut	<i>Castanea sativa</i>	Cas s 8	(80)
Hazelnut	<i>Corylus avellana</i>	Cor a 8	(79)
Peanut	<i>Arachis hypogaea</i>	Ara h LTP	(74)
Walnut	<i>Juglans regia</i>	Jug r 3	(82)
Cereal			
Barley	<i>Hordeum vulgare</i>	Hor v LTP	(63)
Maize	<i>Zea mays</i>	Zea m 14	(84)
Wheat	<i>Triticum aestivum</i>	Tri a LTP	(86)
Rice	<i>Oryza sativa</i>	Ory s LTP	(30)
Pollens			
Short ragweed	<i>Ambrosia artemisiifolia</i>	Amb a 6	(115)
Mugwort	<i>Artemisia vulgaris</i>	Art v 3	(75)
Sunflower	<i>Helianthus annuus</i>	Hel a 3	(99)
Olive	<i>Olea europea</i>	Ole e 7	(92)
Wall Pellitory	<i>Parietaria judaica</i>	Par j 1	(91)
Wall Pellitory	<i>Parietaria judaica</i>	Par j 2	(90)
Others			
Asparagus	<i>Asparagus officinalis</i>	Asp o 1	(99)
Cabbage	<i>Brassica oleracea</i>	Bra o 3	(102)
Carrot	<i>Daucus carota</i>	Dau c LTP	(101)
Grape	<i>Vitis vinifera</i>	Vit v 1	(69)
Latex	<i>Hevea brasiliensis</i>	Hev b 12	(97)
Lemon	<i>Citrus limon</i>	Cit l 3	(83)
Lettuce	<i>Lactuca sativa</i>	Lac s 1	(100)
Onion	<i>Allium cepa</i>	All c LTP	(98)
Orange	<i>Citrus sinensis</i>	Cit s 3	(83)
Tomato	<i>Lycopersicon esculentum</i>	Lyc e 3	(61)

Table 1: Allergenic LTPs of plants.

Central Europe is different for allergic populations of the Mediterranean areas. Ten years ago, major allergen for individuals sensitised to fruits of *Prunoideae* subfamily and who, moreover did not present cross reactivity with birch and grass pollens, was identified as a 8-10 kDa protein (33, 52, 53). This allergen is a member of LTPs family and many cases of food allergy were described among members of this fruits (15, 54-57). The patterns of sensitisation and clinical symptoms are different for patients suffering from food allergy without associated pollinosis. Indeed, systemic reactions are frequently observed (20 to 30 %), even in absence of oral allergic syndrome (58, 59). LTPs were identified as the major allergens for this population. High stability of these allergens to proteolytic digestion and heat treatment highlighted the hypothesis that LTPs were the proteins responsible of the primary sensitisation by ingestion and this why LTPs were described as a true food allergen (60-65). They were known to induce severe reactions in many patients (16). LTP of maize (*Zea m 14*) always presents IgE-binding sites of serums of allergic patients even after heat treatment going until 100°C, which altering in an irreversible way the secondary structure of this protein (66). In the same way, the recombinant major allergen of cherry (*rPru av 3*) had shown strong stability to peptic digestion confirming the results observed on the peach major allergen (*Pru p 3*) (64, 67). LTP of grape (*Vit v 1*) has been used as model of plant LTPs (68). *Vit v 1* is a major allergen for patients allergic to grape in Mediterranean area (69, 70). These authors have studied the resistance of *Vit v 1* allergenicity with *in vitro* model of gastroduodenal digestion including evaluation of digestion effect with or without a physiological phospholipid (phosphatidylcholine) linked to LTP. They confirmed that grape LTP, like other plants LTPs, is also very stable during gastric digestion and showed no significant change in IgE-binding capacity on immunoblotting or in ability to trigger histamine release. Digests also retained their capacity to induce a positive skin prick test response. Gastroduodenal digestion with ratios of enzymes relatively close to the physiologic conditions of human gastrointestinal tract rapidly gave rise to a stable fragment of approximately 6 kDa that had lost the C-terminal portion of the LTP. This fragment then remained intact during 2 hour of digestion and kept its IgE-binding potency. This is probably why the LTP digests retained their biologic activity *in vitro* and *in vivo*. Furthermore, it is interestingly to observe that addition of phosphatidylcholine during gastric digestion protected LTP to a limited extent against digestion. This result confirmed that the presence of ligand can increase stability by reducing polypeptide backbone mobility, and many proteases require flexibility in substrate proteins for optimal activity (42).

In brief, the allergenic activity of plant LTPs is highly resistant to *in vitro* digestion. This property, their abundance in the plant, also their high resistance to heat treatment and their classification as panallergen confirm that plant LTPs could be model allergens of true food allergy which are of high importance to atopics in Mediterranean countries (71). These properties might facilitate sensitisation via the gastrointestinal tract and might also potentiate the ability of LTPs to elicit severe allergic reactions in sensitised patients (42).

■ **Fruits LTPs.** - Several members of the *Rosaceae* family induce food allergic reactions, particularly, fruits of the *Prunoideae* (peach, apricot, plum, cherry, almond...) and the *Pomoideae* (apple, pear...) subfamilies (15, 33, 53, 59, 72, 73). Peach is one of the *Rosaceae* fruits, which is the more eaten in Mediterranean area and responsible of many food allergic cases (54, 58, 74). In 1999, major peach allergen (*Pru p 3*), a 9 kDa protein of the LTP family has been identified and sequenced (54). Since then, a lot of proteins between 8 to 13 kDa have been identified by IgE-binding of allergic patient sera to *Rosaceae* fruits in Mediterranean area (52-55, 57, 64, 72). Moreover, various studies have shown that IgE-binding of patient sera were not inhibited by grass or birch pollen extracts in immunoblot inhibition assay, highlighted sensitisation without associated pollinosis (52, 53, 75). The last years, number of data about *Rosaceae* LTPs, involved in food allergy cases, has increased continually (16, 42). Besides *Pru p 3* and *Mal d 3* (LTP of apple), closely related allergens (80 % of sequence identity) have been found in apricot (*Prunus armeniaca*, *Pru ar 3*), cherry (*Prunus avium*, *Pru av 3*), plum (*Prunus domestica*, *Pru d 3*) and strawberry (*Fragaria ananassa*, *Fra a 3*) (Fig. 1) (56, 57, 64, 76). Moreover, allergenic LTPs have also been identified in other fruits, such as grape (*Vitis vinifera*, *Vit v 1*), pear (*Pyrus communis*, *Pyr c 3*), raspberry (*Rubus idaeus*, *Rub i 3*), almond (*Prunus dulcis*, *Pru du LTP*) and tomato (*Lycopersicon esculentum*, *Lyc e 3*), and in nuts, such as chestnut (*Castanea sativa*, *Cas s 8*), peanut (*Arachis hypogaea*, *Ara h LTP*) and hazelnut

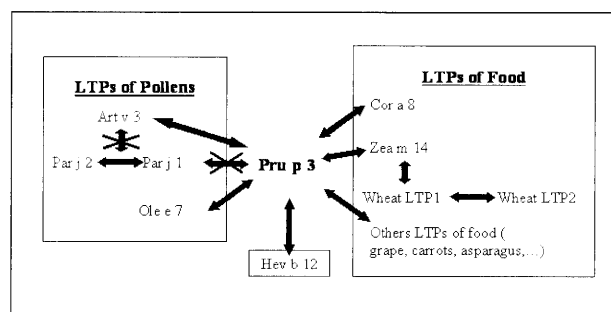


Fig. 5: Schematic representation of cross reactivities between different plant LTPs.

(*Corylus avellana*, Cor a 8) (69, 70, 77-80). Cross reactions among allergens (LTPs) from Rosacea fruits, and between these and allergens from other foods have been demonstrated *in vitro* and *in vivo*. Major peach allergen, Pru p 3, is used as reference allergen in the most cases to study cross reactivity between plants LTPs (Fig. 5). Cross reactivities were observed between different *Rosacea* LTPs, but also to LTPs of grape, nuts and citrus fruits (69, 74, 76, 80-83).

■ **Cereals LTPs.** - Some isoforms of cereals LTPs were isolated from soluble extract, where they represented approximately 5 to 10 % of total soluble proteins (1). Presence of these isoforms suggest that cereals LTPs, like others plants LTPs, belong to a multigenic family comprising the two groups: LTP1 and LTP2 (11, 12, 77). Currently, there is less case of food allergy associated with cereals LTPs compared with *Rosaceae* LTPs. Nevertheless, LTP1s have also been identified as major allergens for patients with food allergy to maize, Zea m 14 (84). Indeed, among 22 subjects presenting systemic symptoms after maize ingestion, 86 % of these sera had specific IgE binding to Zea m 14. Maize LTP1 presented no cross reaction with pollen allergens, indicating that sensitisation occurs probably by ingestion and not by a primary sensitisation with homologous of pollen allergens (84). Heat resistance have been demonstrated on maize LTP but also on barley LTP (*Hordeum vulgare*, LTP1) that have still found in beer after technologic processes as brewing and malting (63, 66, 85). Indeed, beer has been implicated as the causative agent of contact urticaria and severe IgE-mediated anaphylaxis. In a previous study, we reported, for the first time, the presence of specific IgE to wheat LTP1 in about 30% of 60 patients suffering from food allergy to wheat (86). Cross reactivities between different cereals LTPs have been also studied by ELISA using several LTPs purified from wheat (LTP1 and LTP2), maize (LTP1) and barley (LTP1) seeds (87). These results highlighted the diversity of IgE responses to cereals LTPs. The cross reactivities could be explain by sequence homologies between wheat and barley LTPs1 (72% of homologies) and to a lesser extent between these proteins and maize LTP1 (around 55 %). On the other hand, cross reactivities between wheat LTP1 and LTP2 (18% of sequence homologies) could be probably explained by homologies in their folding. Linear and conformational common epitopes binding to IgE of patients suffering from food allergy to wheat could probably explain cross reactivities observed (87). Cross reactivity between maize LTP1 and peach major allergen (Pru p 3) have been also shown, but only *in vitro*, by immunoblotting (84).

■ **Pollens LTPs.** - In the Mediterranean area, food allergy to *Rosaceae* fruits, mainly peach and cherry, were clearly associated to LTPs sensitisation and

were markers of severe symptoms (38, 59). LTPs were regarded as food allergens, however, major peach allergen could also probably acted as respiratory allergen and cause occupational rhinoconjunctivitis and asthma (88).

LTPs were identified as allergens in several pollens. *Parietaria judaica* pollen is the main cause of allergy in the Mediterranean area (89). Main allergens in *Parietaria judaica* pollen are Par j 1 and Par j 2, belonging both to the LTPs family, and were known as diagnosis markers for *Parietaria* pollen sensitisation (90, 91). Recently, other allergens, members of the LTPs family, were also described in others pollens like *Helianthus annuus* (Hel a 3), *Artemisia vulgaris* (Art v 3) or *Olea europea* (Ole e 7) pollens (77, 92, 93). High presence of these plants in the Mediterranean area had open some debate as to whether allergies triggered by LTPs in plant foods are actually the result of primary sensitisation to pollen LTPs. So, cross reactivities between pollen and food LTPs could justified a primary sensitisation by respiratory route and then a food sensitisation by cross reaction. Several studies have attempted to elucidate the cross reactivity between foods and pollen LTPs from different sources. An Italian group reported on partial cross reactivity between *Rosaceae* LTPs (peach, apple, apricot) and those from different plant sources (mugwort, chestnut) due to common epitopes shared by LTPs from theses foods and pollens (77). Nevertheless, IgE reactivity of patients suffering from *Rosaceae* allergy remains weak against *Artemisia* LTP. The higher percentage of inhibition is obtained for *Artemisia* LTP against peach or apple. Mains allergens of *Parietaria* pollen were LTPs and they presented no cross reactivity with grass and birch pollen LTPs and peach LTPs (77, 94-96).

■ **Other plants LTPs.** - Allergens belonging to the LTP family have also been identified in other plant sources. Thus, a basic protein of 9,3 kDa have been identified as allergen in latex (*Hevea brasiliensis*, Hev b 12). Hev b 12 have shown around 65% of sequence identity with Pru p 3 (Fig. 1) (97). Allergens belonging to the LTP family have been identified in asparagus (*Asparagus officinalis*, Asp o 1.01 and Asp o 1.02), lettuce (*Lactuca sativa*, Lac s 1), carrot (*Daucus carota*, Dau c LTP), onion (*Allium cepa*) and cabbage (*Brassica oleracea*, Bra o 3) (98-102).

CONCLUSION

Wide distribution and biochemical features of plants LTPs justified their designation as true vegetal pan-allergens involved as food and/or respiratory allergens. The frequency of sensitisation to plants LTPs in

the southern European populations to multiple vegetables foods that might or might not be botanically related, such as *Rosaceae* fruits, nuts, cereals and others foods but also to several pollens of different plants could be defined by the common term "LTP Syndrome".

Figure 5 presents a synthesis of the different cross reactions described in studies. The majority of these studies have used major peach allergen, Pru p 3, as reference allergen for the cross reactivities studies. These cross reactivities observed *in vitro* did not systematically involve clinical symptoms. Nevertheless, the knowledge of common epitopes between LTPs of different plants is important for biochemists but also for clinicians in prescription of a diet with avoidance of any products. A recent study on the IgE reactivity of peach LTPs allergic patients, against bean extract, has shown no *in vitro* reactivity (103). Authors have concluded on the absence of common epitopes between these organisms or on the absence of LTPs in beans. This study concludes of the *in vitro* safety of this food for allergic patients to LTPs.

Moreover, cDNA clones encoding several LTPs allergens have been obtained, allowing not only to deduce the full amino acid sequence of the protein, but also to express it in heterologous systems, either prokaryotic (*Escherichia coli*) or eukaryotic (*Pichia pastoris*) (76, 79, 94, 97, 101, 104). The recombinant LTPs of different plants could allow, in a first step, the identification of epitopes binding to the specific IgE of allergic patients *in vitro*, as described earlier for *Parietaria* and peach LTPs (14, 105, 106). Three-dimensional crystal structures of maize and peach LTP have been described (22, 25). These data could allow the validation of 3D models suggested for plants LTPs and allow the localisation of specific IgE epitopes identified on the structure. These informations could be useful for the development of allergen mutants with reduced IgE reactivity for therapeutic applications (76, 107, 108). However, certain data still remains to be determined. Particularly, none epitope binding to T lymphocytes have ever been identified for these allergens. These knowledges are also important to well understand plants LTPs allergenicity. LTP sensitisation shows a surprisingly, and not yet fully explained, geographical distribution pattern in northern and southern European populations. Several hypothesis could explain this difference: genetic pattern of these populations, food consumption, environment of the plants culture (stress, pathogens), type and/or localisation of culture, storage and/or transport conditions, influence of the ripening, influence of technological treatments... Certain groups started to work on one or other of these problems, but it remains still much of point to solve to understand clearly this "LTP Syndrome" (34, 109, 110).

References

1. Kader J.-C. - Lipid-transfer proteins in plants. *Annu. Rev. Plant Physiol. Plant Mol. Biol.* 1996;47:627-54.
2. Kader J. - Lipid-transfer proteins: a puzzling family of plant proteins. *Trends in plant science* 1997;2:66-70.
3. Sterk P., Booij H., Schellekens G.-A., Van Kammen A. *et al.* - Cell-specific expression of the carrot EP2 lipid transfer protein gene. *Plant Cell* 1991; 3:907-21.
4. Garcia-Olmedo F., Molina A., Segura A., Moreno M. - The defensive role of nonspecific lipid-transfer proteins in plants. *Trends Microbiol* 1995;3:72-4.
5. Cheng C.-S., Samuel D., Liu Y.-J., Shyu J.-C. *et al.* - Binding mechanism of nonspecific lipid transfer proteins and their role in plant defense. *Biochemistry* 2004;43:13628-36.
6. Guerbette J.F., Grosbois M., Jolliot-Croquin A., Kader J.-C. *et al.* - Lipid-transfer proteins from plants: structure and binding properties. *Mol Cell Biochem* 1999;192:157-61.
7. Blein J.-P., Coutos-Thevenot P., Marion D., Ponchet M. - From elicitors to lipid-transfer proteins: a new insight in cell signalling involved in plant defence mechanisms. *Trends Plant Sci* 2002;7:293-6.
8. Da Silva P., Landon C., Industri B., Marais A. *et al.* - Solution structure of a tobacco lipid transfer protein exhibiting new biophysical and biological features. *Proteins* 2005;59:356-67.
9. Vega-Maray A.-M., Fernandez-Gonzalez D., Valencia-Barrera R., Polo F. *et al.* - Lipid transfer proteins in *Parietaria judaica* L. pollen grains: immunocytochemical localization and function. *Eur J Cell Biol* 2004;83:493-7.
10. Arondel VV., Vergnolle C., Cantrel C., Kader J. - Lipid transfer proteins are encoded by a small multigene family in *Arabidopsis thaliana*. *Plant Science* 2000;157:1-12.
11. Doulliez J.-P., Jegou S., Pato C., Larre C. *et al.* - Identification of a new form of lipid transfer protein (LTP1) in wheat seeds. *J Agric Food Chem* 2001;49:1805-8.
12. Doulliez J.-P., Pato C., Rabesona H., Molle D. *et al.* - Disulfide bond assignment, lipid transfer activity and secondary structure of a 7-kDa plant lipid transfer protein, LTP2. *Eur J Biochem* 2001;268:1400-3.
13. Liu Y.-J., Samuel D., Lin C.-H., Lyu P.-C. - Purification and characterization of a novel 7-kDa non-specific lipid transfer protein-2 from rice (*Oryza sativa*). *Biochem Biophys Res Commun* 2002;294:535-40.
14. Asturias J.-A., Gomez-Bayon N., Eseverri J.-L., Martinez A. - Par j 1 and Par j 2, the major allergens from *Parietaria judaica* pollen, have similar immunoglobulin E epitopes. *Clin Exp Allergy* 2003;33:518-24.
15. Sanchez-Monge R., Lombardero M., Garcia-Selles F.-J., Barber D. *et al.* - Lipid-transfer proteins are relevant allergens in fruit allergy. *J Allergy Clin Immunol* 1999;103:514-9.
16. Salcedo G., Sanchez-Monge R., Diaz-Perales A., Garcia-Casado G. *et al.* - Plant non-specific lipid transfer proteins as food and pollen allergens. *Clin Exp Allergy* 2004;34:1336-41.
17. Shewry P.-R., Beaudoin F., Jenkins J., Griffiths-Jones S. *et al.* - Plant protein families and their relationships to food allergy. *Biochem Soc Trans* 2002;30:906-10.
18. Breiteneder H., Radauer C. - A classification of plant food allergens. *J Allergy Clin Immunol* 2004;113:821-30;quiz 31.
19. Doulliez J., Michon T., Elmorjani K., Marion D. - Structure, biological and technological functions of Lipid Transfer Proteins and Indolines, the major lipid binding proteins from cereal kernels. *Journal of Cereal Science* 2000;32:1-20.
20. Gincel E., Simorre J.-P., Caille A., Marion D. *et al.* - Three-dimensional structure in solution of a wheat lipid-transfer protein from multidimensional 1H-NMR data. A new folding for lipid carriers. *Eur J Biochem* 1994;226:413-22.
21. Shin D.-H., Lee J.-Y., Hwang K.-Y., Kim K.-K. *et al.* - High-resolution crystal structure of the non-specific lipid-transfer protein from maize seedlings. *Structure* 1995;3:189-99.
22. Han G.-W., Lee J.-Y., Song H.-K., Chang C. *et al.* - Structural basis of non-specific lipid binding in maize lipid-transfer protein complexes revealed by high-resolution X-ray crystallography. *J Mol Biol* 2001;308:263-78.
23. Lee J.-Y., Min K., Cha H., Shin D.-H. *et al.* - Rice non-specific lipid transfer protein: the 1.6 Å crystal structure in the

unliganded state reveals a small hydrophobic cavity. *J Mol Biol* 1998;276:437-48.

24. Mills ENC., Madsen C., Shewry P.-R., Wichers H.-J. - Food allergens of plant origin - their molecular and evolutionary relationships. *Trends in Food Science & Technology* 2003;14:145-56.
25. Pasquato N., Berni R., Folli C., Folloni S. *et al.* - Crystal structure of peach Pru p 3, the prototypic member of the family of plant non-specific lipid transfer protein pan-allergens. *J Mol Biol* 2006;356:684-94.
26. Van Loon L., van Strien E. - The families of pathogenesis-related proteins, their activities, and comparative analysis of PR-1 type proteins. *Physiol Mol Plant Pathol* 1999;55:85-97.
27. Mills E.-N., Jenkins J.-A., Alcocer M.-J., Shewry P.-R. - Structural, biological, and evolutionary relationships of plant food allergens sensitizing via the gastrointestinal tract. *Crit Rev Food Sci Nutr* 2004;44:379-407.
28. Carnes J., Fernandez-Caldas E., Boluda L., Casanovas M. *et al.* - Rapid release of Ole e 1 from olive pollen using different solvents. *Allergy* 2002;57:798-804.
29. Borges J.-P., Jauneau A., Brule C., Culerrier R. *et al.* - The lipid transfer proteins (LTP) essentially concentrate in the skin of *Rosaceae* fruits as cell surface exposed allergens. *Plant Physiol Biochem* 2006;44:535-42.
30. Vignols F., Wigger M., Garcia-Garrido J.-M., Grellet F. *et al.* - Rice lipid transfer protein (LTP) genes belong to a complex multigene family and are differentially regulated. *Gene* 1997;195:177-86.
31. Botton A., Begheldo M., Rasori A., Bonghi C. *et al.* - Differential expression of two lipid transfer protein genes in reproductive organs of peach (*Prunus persica* L. Batsch). *Plant Sci.* 2002;163:993-1000.
32. Chardin H., Mayer C., Senechal H., Wal J.-M. *et al.* - Lipid transfer protein 1 is a possible allergen in *Arabidopsis thaliana*. *Int Arch Allergy Immunol* 2003;131:85-90.
33. Fernandez-Rivas M., van Ree R., Cuevas M. - Allergy to *Rosaceae* fruits without related pollinosis. *J Allergy Clin Immunol* 1997;100:728-33.
34. Asero R., Mistrello G., Amato S., Roncarolo D. *et al.* - Peach fuzz contains large amounts of lipid transfer protein: is this the cause of the high prevalence of sensitization to LTP in Mediterranean countries? *Allerg Immunol (Paris)* 2006;38:118-21.
35. Primavesi L., Brenna O., Pompei C., Pravettoni V. *et al.* - Influence of cultivar and processing on cherry (*Prunus avium*) allergenicity. *J Agric Food Chem* 2006;54:9930-5.
36. Carnes J., Fernandez-Caldas E., Gallego M.-T., Ferrer A. *et al.* - Pru p 3 (LTP) content in peach extracts. *Allergy* 2002;57:1071-5.
37. Marzban G., Puerhinger H., Dey R., Brynda S. *et al.* - Localisation and distribution of the major allergens in apple fruits. *Plant Sci.* 2005;169:387-94.
38. Ballmer-Weber B.-K. - Lipid transfer protein as a potential panallergen? *Allergy* 2002;57:873-5.
39. Ma S., Sicherer S.-H., Nowak-Wegrzyn A. - A survey on the management of pollen-food allergy syndrome in allergy practices. *J Allergy Clin Immunol* 2003;112:784-8.
40. Johansson S.-G., Hourihane J.-O., Bousquet J., Buijnzeel-Koomen C. *et al.* - A revised nomenclature for allergy. An EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813-24.
41. Breiteneder H., Ebner C. - Molecular and biochemical classification of plant-derived food allergens. *J Allergy Clin Immunol* 2000;106:27-36.
42. Breiteneder H., Mills C. - Nonspecific lipid-transfer proteins in plant foods and pollens: an important allergen class. *Curr Opin Allergy Clin Immunol* 2005;5:275-9.
43. Vanek-Krebitz M., Hoffmann-Sommergruber K., Laimer da Camara Machado M., Susani M. *et al.* - Cloning and sequencing of Mal d 1, the major allergen from apple (*Malus domestica*), and its immunological relationship to Bet v 1, the major birch pollen allergen. *Biochem Biophys Res Commun* 1995;214:538-51.
44. Scheurer S., Metzner K., Hausteiner D., Vieths S. - Molecular cloning, expression and characterization of Pru a 1, the major cherry allergen. *Mol Immunol* 1997;34:619-29.

45. Luttkopf D., Muller U., Skov P.-S., Ballmer-Weber B.-K. *et al.* - Comparison of four variants of a major allergen in hazelnut (*Corylus avellana*) Cor a 1.04 with the major hazel pollen allergen Cor a 1.01. *Mol Immunol* 2002; 8:515-25.
46. Valenta R., Duchene M., Ebner C., Valent P. *et al.* - Profilins constitute a novel family of functional plant pan-allergens. *J Exp Med* 1992;175:377-85.
47. Karamloo F., Wangorsch A., Kasahara H., Davin L.-B. *et al.* - Phenylcoumaran benzylic ether and isoflavonoid reductases are a new class of cross-reactive allergens in birch pollen, fruits and vegetables. *Eur J Biochem* 2001;268:5310-20.
48. Mahler V., Fischer S., Heiss S., Duchene M. *et al.* - cDNA cloning and characterization of a cross-reactive birch pollen allergen: identification as a pectin esterase. *Int Arch Allergy Immunol* 2001;124:64-6.
49. Ebner C., Hirschewehr R., Bauer L., Breiteneder H. *et al.* - Identification of allergens in fruits and vegetables: IgE cross-reactivities with the important birch pollen allergens Bet v 1 and Bet v 2 (birch profilin). *J Allergy Clin Immunol* 1995;95:962-9.
50. Kleine-Tebbe J., Vogel L., Crowell D.-N., Hausteiner U.-F. *et al.* - Severe oral allergy syndrome and anaphylactic reactions caused by a Bet v 1-related PR-10 protein in soybean, SAM22. *J Allergy Clin Immunol* 2002;110:797-804.
51. Mittag D., Vieths S., Vogel L., Becker W.-M. *et al.* - Soybean allergy in patients allergic to birch pollen: clinical investigation and molecular characterization of allergens. *J Allergy Clin Immunol* 2004;113:148-54.
52. Leonart R., Cistero A., Carreira J., Batista A. *et al.* - Food allergy: identification of the major IgE-binding component of peach (*Prunus persica*). *Ann Allergy* 1992;69:128-30.
53. Pastorello E.-A., Ortolani C., Farioli L., Pravettoni V. *et al.* - Allergic cross-reactivity among peach, apricot, plum, and cherry in patients with oral allergy syndrome: an *in vivo* and *in vitro* study. *J Allergy Clin Immunol* 1994;94:699-707.
54. Pastorello E.-A., Farioli L., Pravettoni V., Ortolani C. *et al.* - The major allergen of peach (*Prunus persica*) is a lipid transfer protein. *J Allergy Clin Immunol* 1999;103:520-6.
55. Pastorello E.-A., Pravettoni V., Farioli L., Ispano M. *et al.* - Clinical role of a lipid transfer protein that acts as a new apple-specific allergen. *J Allergy Clin Immunol* 1999;104:1099-106.
56. Pastorello E.-A., D'Ambrosio F.-P., Pravettoni V., Farioli L. *et al.* - Evidence for a lipid transfer protein as the major allergen of apricot. *J Allergy Clin Immunol* 2000;105:371-7.
57. Pastorello E.-A., Farioli L., Pravettoni V., Giuffrida M.-G. *et al.* - Characterization of the major allergen of plum as a lipid transfer protein. *J Chromatogr B Biomed Sci Appl* 2001;756:95-103.
58. Cuesta-Herranz J., Lazaro M., de las Heras M., Lluch M. *et al.* - Peach allergy pattern: experience in 70 patients. *Allergy* 1998;53:78-82.
59. Fernandez-Rivas M., Gonzalez-Mancebo E., Rodriguez-Perez R., Benito C. *et al.* - Clinically relevant peach allergy is related to peach lipid transfer protein, Pru p 3, in the Spanish population. *J Allergy Clin Immunol* 2003;112:789-95.
60. Brenna O., Pompei C., Ortolani C., Pravettoni V. *et al.* - Technological processes to decrease the allergenicity of peach juice and nectar. *J Agric Food Chem* 2000;48:493-7.
61. Asero R., Mistrello G., Roncarolo D., de Vries S.-C. *et al.* - Lipid transfer protein: a pan-allergen in plant-derived foods that is highly resistant to pepsin digestion. *Int Arch Allergy Immunol* 2000;122:20-32.
62. Lindorff-Larsen K., Winther J.-R. - Surprisingly high stability of barley lipid transfer protein, LTP1, towards denaturation, heat and proteases. *FEBS Lett* 2001;488:145-8.
63. Garcia-Casado G., Crespo J.-F., Rodriguez J., Salcedo G. - Isolation and characterization of barley lipid transfer protein and protein Z as beer allergens. *J Allergy Clin Immunol* 2001;108:647-9.
64. Scheurer S., Lauer I., Foetisch K., Moncin M.-S. *et al.* - Strong allergenicity of Pru av 3, the lipid transfer protein from cherry, is related to high stability against thermal processing and digestion. *J Allergy Clin Immunol* 2004;114:900-7.

65. Sancho A.-I., Rigby N.-M., Zuidmeer L., Asero R. *et al.* - The effect of thermal processing on the IgE reactivity of the non-specific lipid transfer protein from apple, Mal d 3. *Allergy* 2005;60:1262-8.
66. Pastorello E.-A., Pompei C., Pravettoni V., Farioli L. *et al.* - Lipid-transfer protein is the major maize allergen maintaining IgE-binding activity after cooking at 100 degrees C, as demonstrated in anaphylactic patients and patients with positive double-blind, placebo-controlled food challenge results. *J Allergy Clin Immunol* 2003;112:775-83.
67. Duffort O.-A., Polo F., Lombardero M., Diaz-Perales A. *et al.* - Immunoassay to quantify the major peach allergen Pru p 3 in foodstuffs. Differential allergen release and stability under physiological conditions. *J Agric Food Chem* 2002;50:7738-41.
68. Vassilopoulou E., Rigby N., Moreno F.-J., Zuidmeer L. *et al.* - Effect of *in vitro* gastric and duodenal digestion on the allergenicity of grape lipid transfer protein. *J Allergy Clin Immunol* 2006;118:473-80.
69. Pastorello E.-A., Farioli L., Pravettoni V., Ortolani C. *et al.* - Identification of grape and wine allergens as an endochitinase 4, a lipid-transfer protein, and a thaumatin. *J Allergy Clin Immunol* 2003;111:350-9.
70. Schad S.-G., Trcka J., Vieths S., Scheurer S. *et al.* - Wine anaphylaxis in a German patient: IgE-mediated allergy against a lipid transfer protein of grapes. *Int Arch Allergy Immunol* 2005;136:159-64.
71. van Ree R. - Clinical importance of non-specific lipid transfer proteins as food allergens. *Biochem Soc Trans* 2002;30:910-3.
72. Asero R., Mistrello G., Roncarolo D., Casarini M. *et al.* - Allergy to nonspecific lipid transfer proteins in *Rosaceae*: a comparative study of different *in vivo* diagnostic methods. *Ann Allergy Asthma Immunol* 2001;87:68-71.
73. Fernandez-Rivas M., Bolhaar S., Gonzalez-Mancebo E., Asero R. *et al.* - Apple allergy across Europe: how allergen sensitization profiles determine the clinical expression of allergies to plant foods. *J Allergy Clin Immunol* 2006;118:481-8.
74. Asero R., Mistrello G., Roncarolo D., Amato S. - Relationship between peach lipid transfer protein specific IgE levels and hypersensitivity to non-*Rosaceae* vegetable foods in patients allergic to lipid transfer protein. *Ann Allergy Asthma Immunol* 2004;92:268-72.
75. Pastorello E.-A., Pravettoni V., Farioli L., Rivolta F. *et al.* - Hypersensitivity to mugwort (*Artemisia vulgaris*) in patients with peach allergy is due to a common lipid transfer protein allergen and is often without clinical expression. *J Allergy Clin Immunol* 2002;110:310-7.
76. Zuidmeer L., Salentijn E., Rivas M.-F., Mancebo E.-G. *et al.* - The role of profilin and lipid transfer protein in strawberry allergy in the Mediterranean area. *Clin Exp Allergy* 2006;36:666-75.
77. Diaz-Perales A., Lombardero M., Sanchez-Monge R., Garcia-Selles F.-J. *et al.* - Lipid-transfer proteins as potential plant panallergens: cross-reactivity among proteins of *Artemisia* pollen, *Castanea* nut and *Rosaceae* fruits, with different IgE-binding capacities. *Clin Exp Allergy* 2000;30:1403-10.
78. Pastorello E.-A., Vieths S., Pravettoni V., Farioli L. *et al.* - Identification of hazelnut major allergens in sensitive patients with positive double-blind, placebo-controlled food challenge results. *J Allergy Clin Immunol* 2002;109:563-70.
79. Schocker F., Luttkopf D., Scheurer S., Petersen A. *et al.* - Recombinant lipid transfer protein Cor a 8 from hazelnut: a new tool for *in vitro* diagnosis of potentially severe hazelnut allergy. *J Allergy Clin Immunol* 2004;113:141-7.
80. Sanchez-Monge R., Blanco C., Lopez-Torrejon G., Cumplido J. *et al.* - Differential allergen sensitization patterns in chestnut allergy with or without associated latex-fruit syndrome. *J Allergy Clin Immunol* 2006;118:705-10.
81. Crespo J.-F., Rodriguez J., James J.-M., Daroca P. *et al.* - Reactivity to potential cross-reactive foods in fruit-allergic patients: implications for prescribing food avoidance. *Allergy* 2002;57:946-9.
82. Pastorello E.-A., Farioli L., Pravettoni V., Robino A.-M. *et al.* - Lipid transfer protein and vicilin are important walnut allergens in patients not allergic to pollen. *J Allergy Clin Immunol* 2004;114:908-14.
83. Ahrazem O., Ibanez M.-D., Lopez-Torrejon G., Sanchez-Monge R. *et al.* - Lipid transfer proteins and allergy to oranges. *Int Arch Allergy Immunol* 2005;137:201-10.
84. Pastorello E.-A., Farioli L., Pravettoni V., Ispano M. *et al.* - The maize major allergen, which is responsible for food-induced allergic reactions, is a lipid transfer protein. *J Allergy Clin Immunol* 2000;106:744-51.
85. Asero R., Mistrello G., Roncarolo D., Amato S. *et al.* - A case of allergy to beer showing cross-reactivity between lipid transfer proteins. *Ann Allergy Asthma Immunol* 2001;87:65-7.
86. Battais F., Courcoux P., Popineau Y., Kanny G. *et al.* - Food allergy to wheat: differences in immunoglobulin E binding proteins as function of age or symptoms. *Journal of Cereal Science* 2005;2:109-17.
87. Battais F., Doulliez J.-P., Marion D., Popineau Y. *et al.* - Involvement of Lipid Transfer Proteins in food allergy to wheat. In: *Gluten proteins*. Cambridge, UK: The Royal Society of Chemistry; 2004.
88. Garcia B.-E., Lombardero M., Echechipia S., Olaguibel J.-M. *et al.* - Respiratory allergy to peach leaves and lipid-transfer proteins. *Clin Exp Allergy* 2004;34:291-5.
89. Masullo M., Mariotta S., Torrelli L., Graziani E. *et al.* - Respiratory allergy to *Parietaria* pollen in 348 subjects. *Allergol Immunopathol (Madr)* 1996;24:3-6.
90. Duro G., Colombo P., Costa M.-A., Izzo V. *et al.* - cDNA cloning, sequence analysis and allergological characterization of Par j 2.0101, a new major allergen of the *Parietaria judaica* pollen. *FEBS Lett* 1996;399:295-8.
91. Stumvoll S., Westritschnig K., Lidholm J., Spitzauer S. *et al.* - Identification of cross-reactive and genuine *Parietaria judaica* pollen allergens. *J Allergy Clin Immunol* 2003;111:974-9.
92. Tejera M.-L., Villalba M., Batanero E., Rodriguez R. - Identification, isolation, and characterization of Ole e 7, a new allergen of olive tree pollen. *J Allergy Clin Immunol* 1999;104:797-802.
93. Rodriguez R., Villalba M., Batanero E., Gonzalez E.-M. *et al.* - Allergenic diversity of the olive pollen. *Allergy* 2002;57Suppl 71:6-16.
94. Costa M.-A., Colombo P., Izzo V., Kennedy H. *et al.* - cDNA cloning, expression and primary structure of Par j1, a major allergen of *Parietaria judaica* pollen. *FEBS Lett* 1994;341:182-6.
95. Duro G., Colombo P., Assunta Costa M., Izzo V. *et al.* - Isolation and characterization of two cDNA clones coding for isoforms of the *Parietaria judaica* major allergen Par j 1.0101. *Int Arch Allergy Immunol* 1997;112:348-55.
96. Lombardero M., Garcia-Selles F.-J., Polo F., Jimeno L. *et al.* - Prevalence of sensitization to *Artemisia* allergens Art v 1, Art v 3 and Art v 60 kDa. Cross-reactivity among Art v 3 and other relevant lipid-transfer protein allergens. *Clin Exp Allergy* 2004;34:1415-21.
97. Beezhold D.-H., Hickey V.-L., Kostyal D.-A., Puhl H. *et al.* - Lipid transfer protein from *Hevea brasiliensis* (Hev b 12), a cross-reactive latex protein. *Ann Allergy Asthma Immunol* 2003;90:439-45.
98. Asero R., Mistrello G., Roncarolo D., Amato S. - A case of onion allergy. *J Allergy Clin Immunol* 2001;108:309-10.
99. Diaz-Perales A., Tabar A.-I., Sanchez-Monge R., Garcia B.-E. *et al.* - Characterization of asparagus allergens: a relevant role of lipid transfer proteins. *J Allergy Clin Immunol* 2002;110:790-6.
100. San Miguel-Moncin M., Krail M., Scheurer S., Enrique E. *et al.* - Lettuce anaphylaxis: identification of a lipid transfer protein as the major allergen. *Allergy* 2003;58:511-7.
101. Ballmer-Weber B.-K., Wangorsch A., Bohle B., Kaul S. *et al.* - Component-resolved *in vitro* diagnosis in carrot allergy: does the use of recombinant carrot allergens improve the reliability of the diagnostic procedure? *Clin Exp Allergy* 2005;35:970-8.

102. Palacin A., Cumplido J., Figueroa J., Ahrazem O. *et al.* - Cabbage lipid transfer protein Bra o 3 is a major allergen responsible for cross-reactivity between plant foods and pollens. *J Allergy Clin Immunol* 2006;117:1423-9.
103. Asero R., Mistrello G., Roncarolo D., Amato S. *et al.* - Why do lipid transfer protein-hypersensitive patients tolerate bean (and other legumes)? *Int Arch Allergy Immunol* 2005;137:236-40.
104. Scheurer S., Pastorello E.-A., Wangorsch A., Kastner M. *et al.* - Recombinant allergens Pru av 1 and Pru av 4 and a newly identified lipid transfer protein in the *in vitro* diagnosis of cherry allergy. *J Allergy Clin Immunol* 2001;107:724-31.
105. Colombo P., Kennedy D., Ramsdale T., Costa M.-A. *et al.* - Identification of an immunodominant IgE epitope of the *Parietaria judaica* major allergen. *J Immunol* 1998;160:2780-5.
106. Garcia-Casado G., Pacios L.-F., Diaz-Perales A., Sanchez-Monge R. *et al.* - Identification of IgE-binding epitopes of the major peach allergen Pru p 3. *J Allergy Clin Immunol* 2003;112:599-605.
107. Zuidmeer L., van Leeuwen W.-A., Budde I.-K., Cornelissen J. *et al.* - Lipid transfer proteins from fruit: cloning, expression and quantification. *Int Arch Allergy Immunol* 2005;137:273-81.
108. Reuter A., Lidholm J., Andersson K., Ostling J. *et al.* - A critical assessment of allergen component-based *in vitro* diagnosis in cherry allergy across Europe. *Clin Exp Allergy* 2006;36:815-23.
109. Giovannini L., Bourrier T., Noormahomed M.-T., Albertini M. *et al.* - *Rosaceae* allergy in children about twenty-two cases. *Rev Fr Allergol* 2004;44:625-33.
110. Sancho A.-I., Foxall R., Rigby N.-M., Browne T. *et al.* - Maturity and storage influence on the apple (*Malus domestica*) allergen Mal d 3, a nonspecific lipid transfer protein. *J Agric Food Chem* 2006;54:5098-104.
111. Gomar J., Petit M.-C., Sodano P., Sy D. *et al.* - Solution structure and lipid binding of a nonspecific lipid transfer protein extracted from maize seeds. *Protein Sci* 1996;5:565-77.
112. Poznanski J., Sodano P., Suh S.-W., Lee J.-Y. *et al.* - Solution structure of a lipid transfer protein extracted from rice seeds. Comparison with homologous proteins. *Eur J Biochem* 1999;259:692-708.
113. Tassin-Moindrot S., Caille A., Douliez J.-P., Marion D. *et al.* - The wide binding properties of a wheat nonspecific lipid transfer protein. Solution structure of a complex with prostaglandin B2. *Eur J Biochem* 2000;267:1117-24.
114. Marzban G., Mansfeld A., Hemmer W., Stoyanova E. *et al.* - Fruit cross-reactive allergens: a theme of uprising interest for consumers' health. *Biofactors* 2005;23:235-41.
115. Roebber M., Hussain R., Klapper D.-G., Marsh D.-G. - Isolation and properties of a new short ragweed pollen allergen, Ra6. *J Immunol* 1983;131:706-11.

