Chapter 11
Sensitization and Allergies of Herbal Products

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Abstract The most common example for an allergy to herbal material is rhinoconjunctivitis, better known as "hay fever." It is estimated that between 10 and 40 % of the world's population suffers from allergic rhinoconjunctivitis (Bachert et al., Allergy 65 (Suppl 93): 1–13, 2010). But food allergies, which are estimated to affect 1–10 % of the world's population, including allergies to plant-derived materials such as wheat, soy, peanuts and tree nuts, are also prevalent (Quake and Nadeau, Semin Cell Dev Biol, 43: 125–130, 2015). While most of the cases will also refer to animal proteins (milk, egg, fish), separate numbers for plant food allergy are not available. Also, medicinal products containing herbal substances/preparations may provoke allergies. Not only can the processed forms trigger allergies, the starting material (plants) may provoke allergic reactions as well, either in individuals involved in harvesting or processing, or in persons concocting preparations (Sticher et al., Hänsel/Sticher – Pharmakognosier Phytopharmazie. Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, 2015), such as pharmacists or nurses; this has in particular been reported for *Psyllium*.

Beside these facts, it should not be forgotten that a "food/plant allergy" is inferred by patients or consumers, whereas signs of allergy have effectively been triggered by food additives (i.e., artificial coloring), excipients, fungal spores, or contaminants. Therefore, in most cases, it is not, or at least hardly ever, possible to pinpoint the triggering agent and to confirm or exclude herbal preparations as allergic agents. This chapter will focus mainly on herbal preparations found in food supplements or medicinal products; however, there are flowing transitions to food, cosmetics, and environmental herbal products such as pollen.

Keywords Adverse effects • Allergy • Cosmetics • Food • Food supplements • Herbal medicinal products • Labelling • Plant allergens • Test systems

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Sensitization and Allergy: A Brief Introduction

It is not the objective of this chapter to describe the immunological processes of sensitization and allergy in detail (textbooks on immunology are more appropriate for this purpose); however, the effort should be made here to at least grasp the basic principles.

Today, allergy is defined as any exaggerated immune response to a foreign antigen, regardless of the mechanism of response, with the antigen being harmless for most people. Therefore sensitization is seen as the induction of allergic responses, and it can be long-lasting due to the immunologic memory. However, it is useful to note that sensitization will not always lead to symptoms or clinical disease (Rosenstreich et al. 2016). The substances that provoke allergic reaction (antigens) are called "allergens," and in most cases they are small (5–100 kDa), water-soluble proteins, often with carbohydrate side chains. However, in addition, other smaller molecules, pure carbohydrates or hydrophobic proteins, might act as allergens (Scheurer et al. 2015). But also "haptens" might provoke allergic reactions; these are defined as small organic compounds (also reactive secondary metabolites, such as quinones, aldehydes, sesquiterpenic lactones, etc.) that are susceptible to electrophilic additions to proteins (so-called "haptenization") and therefore generating allergens (Dudeck et al. 2011).

Different Types of Hypersensitivity Reactions

Gell and Coombs (1963) proposed a subdivision of hypersensitivity reactions that classifies those reactions based on the underlying immune mechanisms (Fig. 11.1). It is still used today as a general basis although with current information, additions/corrections are often made by various authors.

In the context of herbal material, all types of hypersensibility are possible. Usually most plant allergy reactions belong to type I (approximately 48 %), followed by type IV (approximately 18 %), and types III and II (10 % and 6 %, respectively) (Żukiewicz-Sobczak et al. 2013). Type I and type IV reactions seem significant and will therefore be highlighted, even though none of the reactions may occur in isolation; rather, mixed responses are conceivable (Descotes and Choquet-Kastylevsky 2001).

Type I Reaction

Type I hypersensitivity is the form of hypersensitivity that is often simply called "allergy." The reaction occurs "immediately," which means within seconds or minutes, and, in most cases, IgE antibodies are responsible for such allergic reactions. With "atopy" or "atopic," the predisposition to become IgE-sensitized to allergens

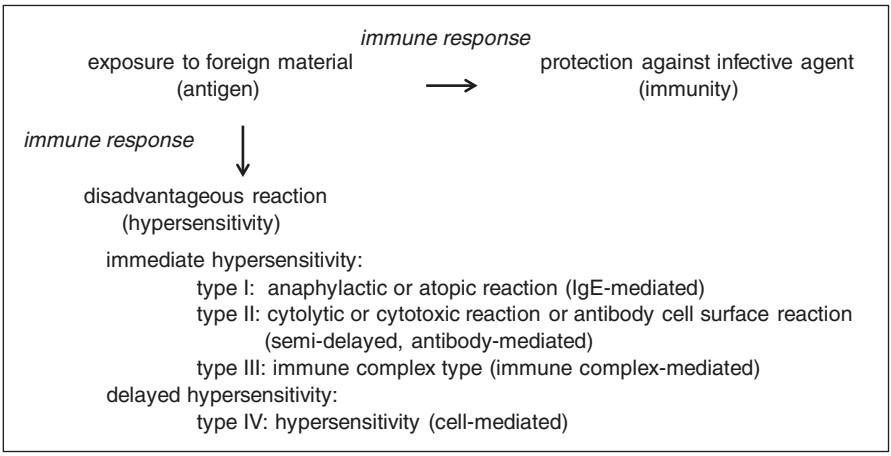

Fig. 11.1 Hypersensitivity reactions to foreign material according to the Gell and Coombs classification (Reprinted from *Toxicology*, Vol. 158, nos. 1-2, Jacques Descotes and Geneviève Choquet-Kastylevsky, "Gell and Coombs's Classification: Is It Still Valid?," Fig. 1, Copyright 2001, with permission from Elsevier)

is described. In predisposed people, the first contact with an allergen will lead to sensitization, and those individuals can develop typical symptoms of allergy. Unfortunately, there is no adequate understanding as to why allergens promote allergic responses or what the mechanisms behind the complex cascade are.

The prerequisite for developing an allergy seems to be the ability of allergens to penetrate mucosal tissue. It is presumed that a genetic basis underlies the development of allergies, but epigenetic and environmental factors are also probably involved (De Swert 1999; Sabounchi et al. 2015).

It seems to be a given that sensitization begins with antigen-presenting cells that present the processed antigen to naïve T-helper cells (Th-cells), via a major histocompatibility class II (MHC-II) complex and co-stimulating and soluble factors. After stimulation by these three signals, the naïve Th-cells will polarize into Th2-cells in atopic patients, while in non-atopic patients there will be no such change due to poorly understood genetic and environmental factors (Grammatikos 2008; van Ree et al. 2014). The activation of Th2-cells and their interaction with B-cells will lead to isotype switching of B-cells to IgE-producing cells. While the majority of activated B-cells are short-lived, there are also long-lived resident plasma cells that might survive up to several months or even an entire lifetime, mainly in the spleen, bone marrow, and inflamed tissue. IgE antibodies secreted from activated B-cells bind to specific high-affinity Fc receptors on the surface of mast cells and basophils. The IgE-coated cells, at this stage, are sensitized to the allergen, since the coating makes those cells sensitive to activation by subsequent encounters with that antigen. IgE antibodies also stimulate the activation and proliferation of mast cells and eosinophils.

In sensitized subjects, at later exposure, the allergen can bind to the IgE molecules held on the surface of the mast cells or basophils. Those cells are activated by the cross-linking of IgE and high-affinity Fc receptors (FcεRI) if the allergen binds to two or more IgE antibodies on the cell. The cross-linking of IgE and FcεRI triggers biochemical signal cascades that lead to the rapid release of granule content (degranulation) (e.g.,, histamine, serine proteases, carboxypeptidase A, proteoglycans, sulfatases) and synthesis and secretion of lipid mediators (e.g., prostaglandins, thromboxanes, leukotrienes) and cytokines (e.g., TNF-α, IL-1α, IL-4, IL-6, IL-13) (Paul 2003).

There are various categories of allergic disorders, describing the anatomical site where the disease is seen: atopic dermatitis, atopic rhinitis, atopic asthma, (food) allergy, and anaphylaxis (see Table 11.1). The effector cascade for all these forms will be more or less the same; however, the route and dosage of allergen exposure, and the site of initial sensitization, etc., might be different. Some patients will experience even two or more forms.

For food allergens – and here herbal preparations used in medicinal products or food supplements will be covered as well – two types are described. Class I food allergens will cause allergic reactions via primary sensitization (ingestion via the gut). They are called "classical," "true," or "complete" food allergens. Sensitization with class I food allergens is often associated with severe (sometimes anaphylactic) reactions. Class II food allergens produce sensitization via various routes (mainly inhalation). A reaction represents cross-reactivity of IgE antibodies with food proteins from the same protein family as the primary allergen; mostly mild to moderate reactions are seen (Lorenz et al. 2015).

Type IV Reaction

Type IV reactions are called "delayed hypersensitivity," since clinical symptoms peak 48–72 h after contact with the allergen in sensitized persons. Type IV reactions can be subdivided either by time of onset, clinical manifestation and cells involved, or by effector cells and mediators involved, leading to three or four sub-categories, respectively. Antigen-specific Th1 and cytotoxic T-lymphocytes, but also Th2- and T-cells, are mediators of such delayed hypersensitivity reactions.

Allergens for type IV reactions might be pathogens such as bacteria, fungi, or viruses, but also proteins and low-molecular-weight-chemicals. Such smaller molecules may act as haptens, which mean that they become allergens only after conjugation with proteins (prohaptens). But there are also substances that act as prehaptens, meaning that the components act as haptens only after external activation. An example of this is linalool, a substance occurring in the essential oil of many plants, which acts as an allergen after autoxidation. For other substances, such as geraniol (also in essential oils of plants), both activation ways are known (Peiser et al. 2012). Such substances (essential oils) are often used in flavoring agents, which might contribute to the allergenicity of the finished product.

Table 11.1 Manifestations of type I hypersensitivity

Organ system	Clinical features	Remarks
Eyes	Allergic conjunctivitis	Often associated with rhinitis, but not always
		As reaction to food mainly in pollen-sensitized individuals, but less frequently than asthma
Respiratory tract	Allergic rhinitis; allergic sinusitis	As reaction to food, less frequently than asthma
	Cough; stridor; asthma	As manifestation of a food-allergic reaction, sometimes the dominating symptom, but often associated with eczema, urticaria or gastrointestinal symptoms
		Deaths from anaphylactic reactions more often caused by respiratory problems than by circulatory failure
Gastrointestinal tract	Oral allergy syndrome (OAS); nausea/vomiting; gastro-oesophageal reflux disease; abdominal pain; diarrhea; enteropathies; infantile colic; constipation; failure to thrive	While OAS is IgE-mediated, all other forms are mainly mixed forms
		OAS can be restricted to the mouth/pharynx but may also involve several organs even reaching anaphylaxis
		Some of the conditions mainly occur in childhood and often cows' milk seems to be responsible
Skin	Atopic dermatitis; pruritus; angioedema; urticaria; erythema	Atopic dermatitis usually occurs in early infancy and persists sometimes in adulthood; children with atopic dermatitis often develop allergic rhinitis and asthma later
		Urticaria (synonyms are hives or nettle rush) due to food ingestion generally occurs within hours and fades within 3 h
Generalized (systemic)	Anaphylaxis	Involves cardiovascular symptoms (e.g., tachycardia, hypotension, cardiovascular collapse); respiratory involvement (e.g., bronchospasm, dyspnea, wheezing); cutaneous symptoms (e.g., urticaria, erythema, pruritus); edema of the pharynx (inducing difficulties in talking, breathing, swallowing); gastrointestinal symptoms (e.g., abdominal pain), singly or in combination
		In fatal cases, initial symptoms develop within 3-30 min and severe respiratory symptoms between 20 and 150 min of exposure

According to EFSA (2014)

The first step in the initiation of such a reaction is the internalization of the antigen by antigen-presenting cells (e.g., Langerhans cells and dermal dendritic cells), the presentation of the antigen together with MHC-class II molecules, and the secretion of interleukins. Naïve CD4-T-cells will therefore be activated, and memory cells will be formed. This phase will last 1–2 weeks. Also, for type IV reactions, microbial triggers and reactive oxygen species (ROS) may possibly be involved in the development of sensitization (Martin 2015).

The subsequent exposure of the antigen-activated cells will lead to the secretion of several cytokines. These will induce blood monocytes to adhere to vascular endothelial cells and to migrate to surrounding tissues. Lytic enzymes are excreted by macrophages and will lead to nonspecific destruction of host cells and tissue damage; the growth factor produced by macrophages will stimulate the proliferation and differentiation of fibroblasts that lead to the formation of fibrotic tissues.

Type IV reactions are generally confined to the contact site, but generalized reactions may occur (Baldo and Pham 2013). Furthermore – at least on the basis of animal studies – it is known that cutaneous sensitization may predispose to intestinal allergy (Ashley et al. 2015). On the other hand, there are known cases in which an allergic dermatitis reaction may develop after systemic exposure to a hapten that reaches the skin through hematogenous transport. While this condition has traditionally been described following topical exposure, it can also be observed without previous cutaneous sensitization to the hapten (Thyssen and Maibach 2008).

It is estimated that 15–20 % of the general population suffer from contact dermatitis to at least one allergen. Acquired risk factors, such as inflammatory skin diseases and hereditary risk factors such as genes, age, gender, and ethnicity, have been described (Peiser et al. 2012).

A special case of type IV reaction is photoallergy. Contact (mostly dermal) with photoallergens leads to allergic reactions, whereby photoallergens are often haptens that form reactive species under UV radiation; they then covalently bind to proteins (human serum albumins) to develop into full allergens. Other classes of photoallergens may be activated by radiant energy and transform chemically when returning to a resting state; the released energy then promotes conjugation of this new chemical entity to a carrier protein, forming a completely new antigen (Stein and Scheinfeld 2007).

Finally, there are terms used in (lay) literature that sometimes cause confusion. These terms should not be confused with hypersensitivity reactions, which always require the involvement of the immune system:

Pseudoallergy/anaphylactoid intolerance:

Terms such as “pseudoallergy,” “anaphylactoid reactions,” and “intolerance” describe non-immune responses that do not require a sensitization step; their definitions are not consistent among authors. Symptoms may occur mainly because of absent or defective enzymes (enzymopathy), activation of complement, unstable cell membranes of mast cells, or basophile granulocytes or metabolic disorders of the arachidonic acid pathway. Such symptoms often resemble type I-hypersensitivity reactions, but without proof of IgE antibodies

involvement. Allergy-like symptoms can also mirror pharmacological effects of herbal material, for instance by its histamine or vasoactive amines content, which might lead to symptoms comparable to an allergic reaction (e.g.,, rash or abdominal pain). It is sometimes claimed that such reactions are as frequent as true IgE-mediated reactions (Pichler 2007).

Irritation:

According to the U.S. Occupational Safety and Health Administration (OSHA 1994), "…Irritants are noncorrosive substances that cause a temporary inflammation on direct contact with the skin, eyes, nose, or respiratory system by a chemical action at the point of contact," It is questionable whether the irritant effects (of contact allergens) may trigger the development of type IV hypersensitivity (Martin 2015).

Phototoxicity:

Phototoxicity may arise from systemically administered agents or from direct contact, and a sufficient dose will be needed. Such compounds will cause harm, either by the formation of free radicals or by the formation of stable phototoxic products after absorption of photons (energy). Erythema that is limited to sun-exposed skin will appear (Stein and Scheinfeld 2007).

Non-clinical Test Methods

Several test methods and international guidance documents cover medicinal products, food/food supplements, and cosmetics. As for most other toxicological methods, these tests describe methods that have been developed for single substances rather than for mixtures of substances (extracts) that may vary in composition. The tests mentioned here do not aim for completeness; rather, they are proposed as examples. It is also acknowledged that recent guidelines for assessing the genetically modified food and feed have been published (EFSA 2011) but they are not discussed here.

Systemic Hypersensitivity

Usually it is expected to find signs of hypersensitivity in chronic toxicity studies (e.g., microscopic findings of lymphoid tissue, hematology, lymphocyte subsets, or pathology at administration site). Concerning specific methods, standard hypersensitivity tests that have proven useful for detecting contact sensitization (see the section on ____) are not very useful for the identification of systemic sensitizers (Hastings 2001; Bala et al. 2005). It is quite likely that methods that exist for well-defined and known proteins (such as IgE-binding studies with human sera from individuals known to be allergic to the identified allergen source, which notably

require standardization of test materials and stability to in vitro pepsin digestion) will not be applicable for multi-component mixtures, especially if no information about the triggering structure(s) is available.

However, three in vivo methods are described to detect substance-induced specific antibodies (FDA 2002):

- Passive cutaneous anaphylaxis assay (PCA-assay), which represents a localized cutaneous allergic response as a consequence of allergen-induced vascular permeability and plasma extravazation;
- Active cutaneous anaphylaxis test (ACA-assay), which is performed similarly to PCA, but without dye; instead, ear swelling, skin lesions, or severity of symptoms of anaphylactic reactions such as respiratory distress, increased respiratory rate, dyspnea, cyanosis, and mortality can be measured;
- Active systemic anaphylaxis assay (ASA-assay), which represents a generalized allergic reaction that manifests as hypotension, bronchoconstriction, or hypothermia.

Usually the tests are performed on guinea pigs, but since not only IgE-triggered reactions occur in guinea pigs but IgG-triggered reactions as well, all three tests are considered limited for safety assessment and consequently are not recommended for routine testing. Furthermore, the testing of small molecular weight compounds remains challenging, especially if biotransformation is important for the production of potential haptens (FDA 2002; Luebke et al. 2006; Gad 2009).

Over the last few years, a number of experimental mouse models of oral antigen-induced anaphylaxis have been described (Hogan et al. 2012), but (as with guinea pigs) questions about the human relevance of these studies remain, due to the differences in anaphylaxis between both animal species and humans (Verdier et al. 1994; Finkelman 2007). *In vitro* (ex-vivo) models have also been proposed to evaluate the allergic potential of orally administered compounds (Berin and Mayer 2009). Neither approach (mouse or ex-vivo models) has been developed into a guideline so far.

Respiratory Hypersensitivity

These mainly consist of adaptions of assays, such as the Local Lymph Node Assay (LLNA) for the detection of type IV hypersensitivity but with exposure via inhalation (FDA 2002; Derelanko and Auletta 2014), or the ACA-assay, performing the sensitization via the respiratory tract (Muller and Healy 1973).

Allergic Contact Dermatitis

From the numerous assays to detect a dermal sensitizing potential, the most common methods are Local Lymph Node Assays (LLNA) (OECD 2010a, b, c) in mice and guinea pigs, notably the Guinea Pig Maximization Test (GPMT – adjuvant test

in which the acquisition of sensitization is potentiated by the use of Freund's Complete Adjuvant) and the Buehler test (OECD 1992). The Organisation for Economic Co-operation and Development (OECD) Guidelines (OECD 2010b, c) propose non-radioactive modifications of the LLNA. Other techniques, such as the mouse ear swelling test (MEST) (Gad et al. 1986; Auttachoat et al. 2011) or the Draize test (Draize et al. 1944), have also been described. While the goal of the LLNA is the afferent phase of the hypersensitivity (initial exposure through clonal expansion and release of memory cells), all other tests on guinea pigs and mice describe the efferent phase (local recognition of the antigen by the memory cells, release of lymphokines and activity of the inflammatory mediators) (Hayes and Kruger 2014).

The mouse ear swelling test (MEST) and variations on it were developed in the early 1980s (Gad et al. 1986), but it was shown to be unreliable for detecting weak to moderate sensitizers (Cornacoff et al. 1988). A modified test procedure has been described (Auttachoat et al. 2011) that increases the explanatory power. Even if no standardized guideline is available, the MEST is currently listed as an accepted test system under OECD guidance (OECD 1992).

The OECD published a guideline on acute eye irritation/corrosion (OECD 2012) that is based on the original idea behind the Draize test. However, it is clearly suggested that before performing this test, a weight-of-evidence analysis be performed on the existing data and that validated and accepted in vitro tests (e.g., OECD 2013, 2015a) be preferred; furthermore, the Draize test can also be performed on animal trunks (Hayes and Kruger 2014).

The four biological key events accounting for a skin sensitization process are well known and have been summarized in OECD (2014b): (1) the covalent binding of the chemical to skin proteins (haptenation); (2) the release of pro-inflammatory cytokines and the induction of cyto-protective pathways in keratinocytes; (3) the maturation and mobilization of dendritic cells; and (4) the antigen presentation to naïve T-cells and proliferation of memory T-cells. Over the past few years, efforts have been made to develop alternative (non-animal) methods to address these key elements. Until now, two in chemico/*in vitro* methods have been integrated into the evaluation of skin sensitization: the Direct Peptide Reactivity Assay (DPRA), which addresses reactivity towards peptides (key event 1) (OECD 2015b), and the ARE-Nrf2 Luciferase Test Method, which addresses the keratinocyte induction of cyto-protective gene pathways (key event 2) (OECD 2015c). Furthermore, a draft proposal for the human Cell Line Activation Test (h-CLAT), which measures the activation of dendritic cells (key event 3) was published by the OECD (2014a). It is acknowledged that only the combination of information from such alternative test methods could replace animal testing in future. Further mechanism-based methods are being developed and will likely contribute to risk assessment.

Therefore it seems that – especially in the field of allergic contact dermatitis – there are advanced efforts under way to replace animal testing. This was notably seen in the 7th Amendment to the Cosmetic Guideline (Guideline 2003/15/EC) (EU 2003) that banned animal tests for cosmetic finished products (implemented in 2004) and for cosmetic ingredients (implemented in 2009) throughout the European Union.

Photoallergenicity

While there is no valid assay that predicts photoallergenicity, some in vitro (e.g., Lovell 1993; Karschuk et al. 2010) and in vivo models (e.g., Scholes et al. 1991; Ulrich et al. 1998; Descotes 2004) have been developed for this purpose. For herbal preparations containing compounds with a molar extinction coefficient value greater than 1,000 l mol^{-1} cm^{-1} at any wavelength between 290 and 700 nm, a photoallergy assessment would be crucial. However, as the predictability of nonclinical photoallergy tests is not known, clinical testing, using the to-be-marketed formulation and conducted during phase 3 of the clinical trials (ICH S10 2013), would be needed.

Pseudoallergy

Even though predicting the potential to induce pseudoallergic reactions are limited in animal models, biochemical markers of an anaphylactoid reaction can be observed in non-clinical toxicology studies (e.g., detection of serum anaphylactic complement products in animals showing signs of anaphylaxis; measurement of histamine plasma levels) (Descotes 2004). Mostly, it is pointed out that in vitro assays using human cells or peripheral blood may be more valuable; histamine release, basophil degranulation, or complement activation can be easily tested using increasing concentrations of the test article (FDA 2002; Descotes 2004).

Herbal Preparations and Herbal Substances with Sensitizing/Allergic Reactions

Allergies After Oral Intake of Herbal Preparations

In theory, all foods/plants can cause Allergic Reactions, but in reality only a small part is responsible for allergies to food or plants. However, in some publications, soy, some fruits (especially cherries, peaches, plums, and apricots), as well as oleaginous fruits (nuts, seeds), and peanuts are most often associated with allergic reactions (Żukiewicz-Sobczak et al. 2013), although in most cases there is no proof of the basic involvement of these materials in the allergic reaction.

While there are plants/plant parts that are used as food supplements (regulated as foods), cosmetics (regulated as cosmetics) as well as herbal medicinal products (regulated as medicinal products), there are also cases where plant/plant parts are only or mainly used in one category. Especially in the field of food supplements/cosmetics, new (at least to Europe) ingredients can be easily used, so that the number of plant preparations used in all fields cannot be calculated to a reasonable amount.

Reliable information on the allergenicity of herbal medicinal products and herbal food supplements is scarce and available only for some major preparations or components thereof. It might be debated whether excipients, which are also often found within such industrial products, are involved in such allergenic reactions. The literature indicates that IgE-related reactions to excipients (such as coloring agents or benzoate derivatives) are rare, and most reactions are described as non-IgE-mediated histamine release. For other excipients, such as soy, guar, tragacanth, and gum arabic allergic reactions are conceivable. While such excipients are often used in smaller amounts, they may be present in many food supplements/industrially prepared food, so that daily exposure may be relevant.

Furthermore, it also has to be kept in mind that plant material with a natural content of allergens, such as nickel or salicylic acid, might lead to (pseudo)allergic reactions due to the presence of this component (de Medeiros et al. 2008; Baenkler 2008).

The pollen-food-allergy syndrome is a situation in which food allergy develops in relation to inhalant allergens. The incidence is highest in patients with pollen allergy, and the symptoms occur mainly after ingestion of raw herbal materials such as fruits, nuts, vegetables, and spices. Even for processed dosage forms, this may be applicable as raw material (such as herbal powders) may have been used for production. For instance, such association with aeroallergens have been described for fennel, soybean, caraway seeds, aniseed, or dandelion (Price et al. 2015).

Both food supplements and herbal medicinal products might contain fragrances or herbal components that are used also in fragrances, implying a problem common with the fragrance field. In the general population, fragrance allergy is among the most frequently detected allergies and has a prevalence ranging from 1.0 to 4.2 % (Carlsen et al. 2007). In the "Opinion on Fragrance Allergens in Cosmetic Products" (SCCS 2012), a number of established contact allergens in humans were published; indeed, several natural compounds known as "fragrance allergens" are most frequently reported and well recognized consumer allergens: amyl cinnamal, amyl cinnamyl alcohol, benzyl alcohol, benzyl salicylate, cinnamal, cinnamyl alcohol, citral, coumarin, eugenol, geraniol, hydroxycitronnellal, and isoeugenol. Furthermore, substances that are less frequently reported and thus less documented were listed; these include anisyl alcohol, benzyl benzoate, benzyl cinnamate, citronellol, farnesol, hexyl cinnamaldehyde, d-limonene or linalool. It should be pointed out that for the oxidized forms of limonene and linalool, a significant rate of allergies (approximately 5 % of the patients tested) could be shown (Audrain et al. 2014). Additionally, extracts are also mentioned in the SCCS paper (2012) (Table 11.2). Even if it were possible to completely avoid these fragrances (which appears to be virtually impossible), the main problem will be that the same substances/extracts might be taken orally via food, herbal supplements, or herbal medicinal products. Other plants, such as *Ocimum basilicum* or *Pimenta racemosa,* are also mentioned because of their content of established human allergens, although publications regarding human data are lacking.

Table 11.2 Natural extracts, which are established as contact allergens in humans or for which at least positive human data exist, but which are, however, not sufficient to be categorized as established contact allergens in humans

Extract/preparation	Category
Acorus calamus (root oil)	Positive results
Cananga odorata and *Ylang-ylang* (oil)	Established contact allergen in humans
Cedrus atlantica (bark oil)	Established contact allergen in humans
Cedrus deodara (wood oil)	Positive results
Cinnamomum cassia (leaf oil)	Established contact allergen in humans
Cinnamomum zeylanicum (bark oil)	Established contact allergen in humans
Citrus aurantium amara (flower/peel oil)	Established contact allergen in humans
Citrus aurantium amara (leaf oil)	Positive results
Citrus bergamia (peel oil expressed)	Established contact allergen in humans
Citrus limonum (peel oil expressed)	Established contact allergen in humans
Citrus sinensis (peel oil expressed)	Established contact allergen in humans
Citrus tangerina	Positive results
Cymbopogon citratus/schoenanthus (oils)	Established contact allergen in humans
Cymbopogon nardus winterianus (herb oil)	Positive results
Eucalyptus ssp. (leaf oil)	Established contact allergen in humans
Eugenia caryophyllus (leaf/flower oil)	Established contact allergen in humans
Evernia furfuracea (extract)	Established contact allergen in humans
Evernia prunastri (extract)	Established contact allergen in humans
Illicium verum (fruit oil)	Positive results
Jasminum grandiflorum/officinale	Established contact allergen in humans
Juniperus virginiana	Established contact allergen in humans
Laurus nobilis	Established contact allergen in humans
Lavandula hybrida	Established contact allergen in humans
Lavandula officinalis	Established contact allergen in humans
Lavandula spica	Positive results
Litsea cubeba	Positive results
Mentha piperita	Established contact allergen in humans
Mentha spicata	Established contact allergen in humans
Myroxylon pereirae (balsam of Peru)	Established contact allergen in humans
Narcissus ssp.	Established contact allergen in humans
Pelargonium graveolens	Established contact allergen in humans
Pelargonium roseum	Positive results
Pinus mugo/pumila	Established contact allergen in humans
Pogostemon cablin	Established contact allergen in humans
Rosa ssp. (flower oil)	Established contact allergen in humans
Rosmarinus officinalis	Positive results
Santalum album	Established contact allergen in humans
Salvia ssp.	Positive results
Tagetes patula	Positive results
Thymus ssp.	Positive results
Turpentine (oil)	Established contact allergen in humans
Verbena absolute	Established contact allergen in humans
Vetiveria zizanoides	Positive results

According to SCCS (2012)

Herbal Food Supplements

According to the Commission to the Council and the European Parliament (COM 2008) "Food supplements containing substances other than vitamins or minerals are foodstuffs within the meaning of Article 2 of Regulation (EC) No 178/2002 of the European Parliament and of the Council, which states that "foodstuff" (or "food") means any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans;" therefore such food supplements containing herbal preparations are regarded as "food."

In the field of food/food supplements, in 2014 the European Food Safety Agency (EFSA) published a document that deals with the most common allergens found in food. Table 11.3 summarizes the information given concerning plant-derived allergens; it should be pointed out that the EFSA document refers only to immune-mediated adverse reactions and covers only the most important food allergens. The minimum dosages taken from EFSA (2014) should be interpreted carefully, since (1) in the underlying literature, it is often not stated whether the values refer to discrete or cumulative doses; and (2) in some studies, the allergenic food was not administered in the form in which it is usually eaten (e.g., freeze-dried). So EFSA declares that these values do not represent a scientific based NOAEL, nor might they be taken to recommend an acceptable level of intake for individuals.

EFSA (2014) refers to a publication of Hompes et al. (2011), which maintains that most cases of anaphylactic reaction (defined as severe systemic allergic reactions with concomitant pulmonary and/or cardiovascular symptoms) registered between 2006 and 2009 in the anaphylaxis registry of German-speaking countries in children and adolescents, were traced to legumes – in particular peanuts, followed by tree nuts. Most important plant allergens belong to one of four main families on

Table 11.3 The most common allergens derived from plants found in food/food supplements according to the EFSA (2014) (it should be mentioned that the minimal dosages for sensitized persons might be much lower, since persons who are known to have severe reactions are mostly excluded from challenge studies)

Herbal substance/ plant material	Plant family	Min. dosages triggering allergic reactions	Cross-reactivity
Apium graveolens (celery)	Apiaceae (Umbellifereae)	~0.7 g (raw celery root) ~0.16 g (celery spice)	Parsley, peach, olive, timothy grass, bermuda grass, sunflower, soy, peanut, pear, cherry Pollen-allergy: Birch-mugwort-celery syndrome Celery-carrot-mugwort-spice syndrome
Arachis hypogea (peanut)	Fabacea	~0.1 mg (protein)	Extensive serological cross-reactivity with members of the legume family Tree nut

(continued)

Table 11.3 (continued)

Herbal substance/ plant material	Plant family	Min. dosages triggering allergic reactions	Cross-reactivity
Brassica junca (brown/oriental mustard) *Brassica nigra* (black mustard) *Sinapis alba* (white/ yellow mustard) (Or mixtures out of them)	Brassicaceaea	~1 mg (protein)	*Brassica napus* (rapeseed), turnip rape; *Brassica rapa* subsp. *oleifera* (turnip rape), *Brassica napus* subsp. *oleifera* (oilseed rape) Almond, walnut, pistachio, hazelnut, tree nut, peanut, fruits of the Rosaceae family Pollen allergy: Celery-mugwort-birch-spice syndrome Mugwort-mustard allergy syndrome
Glycine max (soy, soybean)	Fabacea	~0.2 mg (protein) (To be taken into account also for residual proteins in lecithin and soybean oil)	Members of the legume family (peanut, green pea, lima bean, string bean), wheat flour, casein Pollen-allergy: Birch pollen allergy
Lupin species (lupin)	Leguminosaea	~50 mg (protein) Subjective symptoms from ~0.5 mg (lupin flour)	Members of the legume family (peanut, soybean, lentils, beans, chickpeas, peas)
Nuts Such as hazelnut, Brazil nut, walnut, almond, cashew, macadamia, pecan, chestnut	Several e.g., Betulaceae, Juglandaceae, Rosaceae, Anacardiaceae	<1 mg (protein)	If allergy to a single nut is demonstrated, the nuts of the entire nut group should be avoided (often associated with botanical family but also cross-reactivity among nuts not showing taxonomic relationship is reported) Hazelnut: birch (pollen) Chestnut: latex Nuts: peach
Sesamum indicum (sesame)	Pedialaceae	6 mg (seed) 1 ml (oil) Few mg (protein)	Peanut, hazelnut, egg, walnut, almond, tree nut
Wheat and other cereals (e.g., barley, rye, oats) Gluten and similar cereal storage proteins (not IgE- but IgA-mediated) Non-gluten proteins	Mostly Gramineae	Gluten intake of <50 mg/day is considered safe for most patients with celiac disease Children: ~2.6 mg (wheat protein) Adults: ~100 mg wheat flour	Within members of the Graminaea family Grass pollen

the basis of sequence homology, conserved 3-D structures, and function: the prolamin, cupin, profilins, and Bet v 1 superfamilies (Radauer and Breitender 2007; Wang and Sampson 2011; EFSA 2014; Lorenz et al. 2015).

The largest number of plant food allergens contain the prolamin superfamily: 2S seed storage albumins; cereal seed storage proteins; cereal α-amylase/trypsin inhibitors; and non-specific lipid transfer proteins (nsLTPs). Most of the proteins have a defensive/protective role against pathogens, or they are needed to provide proteins to the developing seed. While major allergens in tree nuts, sesame, and mustard seeds belong to the 2S seed storage albumins, allergens present in wheat, barley, rice, and maize belong to the α-amylase/trypsin inhibitors family. Lipid transfer proteins are frequent and potentially severe allergens; they are responsible for most of the severe allergic reactions to fruits from the Rosaceae family (EFSA 2014), but also for allergies to vegetables such as asparagus, cabbage, and lettuce (James et al. 2012).

The proteins of the cupin superfamily are the cause of most allergic reactions to legumes and nuts, while profilins are cytosolic proteins, which are exclusively found in flowering plants, such as peanut, apple, and celery, and which account for a strong serological cross-reactivity with other plant foods, pollens and *Hevea* latex, which may be of clinical significance (EFSA 2014). Eight families are counted within the Bet v 1 superfamily, among which are the "pathogenesis-related proteins 10," the major latex proteins. These allergens are homologous to the major birch pollen allergen and are present in fruits of the Rosaceae family (e.g., apple, cherry, apricot, and pear) and Apiaceae vegetables (e.g., celery and carrot) (EFSA 2014). Bet v 1 is reported to act as an inhalant allergen and, only after sensitization, individuals develop allergies to a variety of fresh fruits, vegetables, nuts, and seeds.

Taking into account the information from EFSA (2014) (see Table 11.2), consequently within the Annex II of the Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011, the following plant-derived substances or products may cause allergies or intolerances, which are mandatory to label to protect vulnerable consumers from inadvertent consumption:

- Cereals containing gluten – namely, wheat, rye, barley, oats, spelt, kamut, or their hybridized strains, and products thereof (with some exceptions, e.g., wheat-based glucose syrups including dextrose or cereals used for making alcoholic distillates including ethyl alcohol of agricultural origin);
- Peanuts and products thereof;
- Soybeans and products thereof (with some exceptions, e.g., fully refined soybean oil and fat or vegetable oil-derived phytosterols and phytosterol esters from soybean sources);
- Nuts, namely almonds, hazelnuts, walnuts, cashews, pecans, Brazil nuts, pistachios, macadamia, or Queensland nuts, and products thereof (exception: nuts used for making alcoholic distillates including ethyl alcohol of agricultural origin);
- Celery and products thereof;
- Mustard and products thereof;
- Sesame seeds and products thereof;
- Lupin and products thereof (EU 2011).

Food-associated, exercise-induced anaphylaxis is a particular case of food-induced anaphylaxis. It was reported for the first time only in 1979 but its incidence seems to be increasing over the past few decades. In affected individuals, the ingestion of causal food(s) followed by exercise leads to a rapid onset of anaphylaxis, while food and exercise are independently tolerated (James et al. 2012). It is assumed, although the pathogenesis is poorly understood, that during exercise the gut permeability increases so that larger amounts of allergenic proteins might reach the host's gut-associated immune system.

Some countries have implemented national measures, such as the Allergy Vigilance Network in France, to record severe adverse allergic effects (anaphylactic reactions) of food/food supplements or medicinal products. In the evaluation of the time frame of January 2001 until December 2004, the most important plant allergens in France were peanuts and other legumes (20 %), nuts (14 %), the latex group (7 %), wheat (6 %), and celery (5 %). From previous publications it was known that also rarer allergens, such as chamomile, boldo, caffeine ,and gum arabic, can cause severe anaphylaxis (Moneret-Vautrin et al. 2005). Such a network can also be used to conduct studies, for instance on sensitization prevalence; it was reported that among atopic patients, 11.8 % were sensitized against oilseed rape pollen, 26 % against maize pollen, 7.7 % against oilseed rape seeds, and 8.3 % against corn seeds (out of 5,372 subjects studied) (Moneret-Vautrin et al. 2012).

Besides the major allergens (see above), cases have been described that concern less frequently reported plant allergens, some of which should be mentioned here. A patient sensitized to grasses had allergic reactions to foods containing oregano or thyme; his skin prick test also revealed positive results for basil, lavender, hyssop, marjoram, peppermint, and sage, and in vitro testing of serum IgE revealed specific IgE levels for almost all these herbs. The authors concluded a cross-sensitivity involving plants of the Labiatae family (Benito et al. 1996). Armentia et al. (2014) report allergy to cannabis; the most important allergens seem to be lipid transfer proteins, which also provoked positive responses to lipid transfer proteins, mainly from tomato, mugwort and tobacco. Hence, cannabis lipid transfer proteins may act as primary sensitizers and can therefore be responsible for the induction of further food allergies.

It is worth pointing out that various EFSA panels and their cohorts are working on the assessment of preparations/substances, such as gums and food additives from natural sources. Such assessments will be published in the EFSA Journal and will include the known data on allergenicity, hypersensitivity, and intolerance, if available.

It should not be forgotten that "health food products" (often advertised as "all natural") might be adulterated by other substances, also including potent chemical medicines, such as phosphodiesterase type 5 inhibitors or synthetic corticosteroids (Ramsay et al. 2003; Lee et al. 2013). Such chemicals might be responsible for possible allergic reactions, although it will be attributed to the herbal preparations.

Herbal Medicinal Products

When discussing food/food supplements the question of allergy focuses mainly on proteins, but the situation is unclear for herbal medicinal products. Non-protein structures (secondary metabolites) are often discussed as sources for allergenicity, but proteins (possibly present as trace amounts in extracts) cannot be excluded as potential agents for adverse reactions.

The monographs of the Committee of Herbal Medicinal Products (HMPC) of the European Medicines Agency (EMA) certainly present the most condensed information on (traditional) herbal medicinal products. This committee is responsible for assessing the efficacy and safety of herbal substances/preparations marketed within the European Union (EU); data from the literature as well as pharmacovigilance data, are taken into account, and more than 150 monographs have been published. Table 11.4 lists all the undesirable effects associated with allergic reactions (including gastrointestinal disturbances). While the monographs typically cover several preparations (e.g., aqueous extracts and a high percentages of ethanol extracts), the undesirable effects are generally not split for the various extracts; it is possible, however, that chemical or thermal influences modify the composition in potential allergic structures and therefore influence the allergenicity of the various preparations.

Unfortunately, for different reasons, some assessments of the HMPC lead to "public statements" rather than monographs, which means that no recommendation could be given for the use of certain plants or plant parts. In such cases, the risk assessment did not always take place; therefore it might be that some allergenic plants are missing in the overview (such as *Adhatoda vasica*, *Withania somnifera*). For other herbal materials, for which allergenicity is probable (e.g., lecithin), an assessment has not yet been published. In addition, it is of course also questionable whether the plants for which no allergic potential was described, in fact exhibit very low allergenicity; if their usage is marginal compared to other plants, allergic reactions are not reported or correctly attributed. On the other hand, especially for effects related to the gastrointestinal tract, it cannot be taken for granted that these correspond to true allergic events. Also intolerances, irritations, or even the worsening of symptoms of the disease might be possible. For example, *Gentiana lutea* is traditionally taken in cases of mild dyspeptic/gastrointestinal disorders; the described undesirable effects called "gastrointestinal disorders" might reflect a "failure of therapy."

Not only patients taking herbal medicinal products develop allergic reactions. A study by Bernedo et al. (2008) in a sample of healthcare workers in geriatric care homes repeatedly exposed to *Plantago ovata* seed (ispaghula seeds) products revealed that about 9 % suffered allergic reactions confirmed by allergy tests. Furthermore, pharmacovigilance data on allergic reactions (respiratory symptoms such as rhinitis and asthma) have been described in persons who inadvertently

inhale a powder while preparing it for administration. Such cases have been reported in pharmaceutical industry workers who work with ispaghula seeds during their preparation (HMPC 2012).

Preparations/substances derived from plants are also used as excipients in herbal medicinal products. These might be either comminuted herbal substances – in herbal teas, for example – or herbal preparations, such as tinctures, to improve the flavor of the finished product. As required by medicinal products regulation, all the ingredients of the finished product must be indicated in the package leaflet, but a case-by-case decision is needed regarding eventual allergenicity warnings related to such excipients. In the Volume 3B of the Annex of the Notice to Applicants, several plant-derived preparations are mentioned, which in any case require special labeling due to their allergenic properties (Table 11.5) (EC 2003).

Contact Dermatitis Due to Herbal Preparations

In Tables 11.3, 11.5, and 11.6, examples of cases of contact allergy are shown. Mainly molecules with a molecular weight between 100 and 1,000 are considered to be responsible for such effects (Merfort 2002). It is estimated that 80 % of contact dermatitis cases are due to irritant events, while only 20 % correspond to allergenic reactions. Pharmaceutical products (or cosmetics) might be applied on diseased, inflamed, or dry skin. Therefore it can be anticipated that the barrier function of the skin might be disturbed and even weak allergens – either active principles or excipients/vehicle components – could thus induce sensitization.

Data of the HMPC mirror the data from other publications; mainly, Asteraceae (Compositae) are known for their allergic potential, followed by Primulaceae, Apiaceae, and a few other plant families (Aberer 2008). This is especially noteworthy since the Asteraceae family comprises some of the oldest and most valued medicinal plants, sometimes also used for their anti-inflammatory activity, such as *Calendula officinalis* (marigold). At least 15 species, including *Arnica montana* (arnica), *Chamomilla recutita* (German chamomile) or *Echinacea* sp. are associated with sensitization and/or allergies. On the basis of case reports and testing described in the literature, Paulsen (2002) remarked that only a few species, such as arnica, are associated with a high frequency of sensitization while for the majority of species, frequency is rare. Other authors claim a low incidence, even concerning contact allergy to arnica or chamomile (Merfort 2002; Aberer 2008), and discussions on the responsible allergens are ongoing. While sesquiterpene lactones are seen as very important allergens from Asteraceae, in addition, sensitization cases due to a coumarin, a sesquiterpene alcohol, epoxythymol-derivatives, polyacetylenes and thiophenes are known (Merfort 2002). Also vanillic acid, cinnamic acid, ferulic acid, caffeic acid and a variety of mono-caffeyl and di-caffeyl esters of quinic acid are discussed (Olennikov and Kashchenko 2013). As some of the plants are also taken orally, the question of allergy-triggering substances arises for this usage as well.

Table 11.4 Plant/plant extracts or preparations for which hypersensitivity reactions after oral intake are reported according to the monographs of the HMPC (positive assessment)

Herbal substance	Plant family	Undesirable effect noticed
Achillea millefolium (flos + herba)	Asteraceae (Compositae)	Hypersensitivity reactions of the skin
Aesculus hippocastanum (semen)	Sapindaceae	Itching and allergic reactions; gastrointestinal complaints
Aloe [various species], folium	Xanthorrhoeaceae	Hypersensitivity reactions; abdominal pain and spasms
Arctium lappa (radix)	Asteraceae (Compositae)	Anaphylactic reactions
Arctostaphylos uva-ursi (folium) (bearberry leaf)	Ericaceae	Nausea, vomiting, stomachache
Betula pendula and/or *Betula pubescens* as well as hybrids of both species (folium)	Betulaceae	Allergic reactions (itching, rash, urticaria, allergic rhinitis); gastrointestinal complaints (nausea, vomiting, diarrhea)
Cassia senna and *Cassia angustifolia* (fructus + folium)	Fabaceae	Hypersensitivity reactions (pruritus, urticaria, local or generalized exanthema); abdominal pain and spasms
Cimicifuga racemosa (rhizome)	Ranunculaceae	Skin reactions (urticaria, itching, exanthema), facial edema, peripheral edema; gastrointestinal symptoms (i.e., dyspeptic disorders, diarrhea)
Cinnamomum verum (corticis aetheroleum)	Lauraceae	Local irritation of the oral mucosa
Cucurbita pepo (semen)	Cucurbitaceae	Mild gastrointestinal complaints
Curcuma longa (rhizome)	Zingiberaceae	Mild symptoms of flatulence and gastric irritation
Curcuma xanthorrhiza (rhizome)	Zingiberaceae	Mild gastrointestinal symptoms such as dry mouth, flatulence, and gastric irritation
Cynara scolymus (folium)	Asteraceae (Compositae)	Slight diarrhea with abdominal spasm, epigastric complaints such as nausea and heartburn; allergic reactions
Echinacea angustifolia (radix)	Asteraceae (Compositae)	Hypersensitivity reactions (skin reactions)
Echinacea pallida (radix)	Asteraceae (Compositae)	Hypersensitivity reactions (skin reactions)
Echinacea purpurea (herba recens)	Asteraceae (Compositae)	Hypersensitive reactions in the form of rash, urticaria, itching, swelling of the face; cases of severe hypersensitivity reactions, such as Stevens-Johnson syndrome, angioedema of the skin, Quincke edema, bronchospasm with airway obstruction, asthma and anaphylactic shock

(continued)

Table 11.4 (continued)

Herbal substance	Plant family	Undesirable effect noticed
Echinacea purpurea (radix)	Asteraceae (Compositae)	Hypersensitivity reactions (skin reactions)
Equisetum arvense (herba)	Equisetaceae	Allergic reactions (e.g., rash); mild gastrointestinal complaints
Foeniculum vulgare subsp. vulgare var. vulgare (aetheroleum)	Apiaceae (Umbelliferae)	Allergic reactions affecting the skin or the respiratory system
Foeniculum vulgare subsp. vulgare var. dulce (fructus)	Apiaceae (Umbelliferae)	Allergic reactions affecting the skin or the respiratory system
Foeniculum vulgare subsp. vulgare var. vulgare (fructus)	Apiaceae (Umbelliferae)	Allergic reactions affecting the skin or the respiratory system
Gentiana lutea (radix)	Gentianaceae	Pruritus; gastrointestinal disorders
Ginkgo biloba (folium)	Ginkgoaceae	Hypersensitivity reactions (allergic shock); allergic skin reactions (erythema, edema, itching and rash); gastrointestinal disorders (diarrhea, abdominal pain, nausea, vomiting)
Harpagophytum procumbens and/or *Harpagophytum zeyheri* (radix)	Pedaliaceae	Allergic skin reactions; gastrointestinal disorders: (diarrhea, nausea, vomiting, abdominal pain)
Hedera helix (folium)	Araliaceae	Allergic reactions (urticaria, skin rash, couperoses, dyspnea); gastrointestinal reactions (nausea, vomiting, diarrhea)
Hypericum perforatum (herba)	Hypericaceae	Allergic skin reactions; fair-skinned individuals may react with intensified sunburn-like symptoms under intense sunlight; gastrointestinal disorders
Juniperus communis (aetheroleum)	Cupressaceae	Allergic skin reactions
Juniperus communis (pseudo-fructus)	Cupressaceae	Allergic skin reactions
Linum usitatissimum (semen)	Linaceae	Hypersensitivity including anaphylaxis-like reactions
Matricaria recutita (flos)	Asteraceae (Compositae)	Hypersensitivity reactions including severe allergic reaction (dyspnea, Quincke's disease, vascular collapse, anaphylactic shock)
Melilotus officinalis (herba)	Fabaceae	Allergic reactions; gastrointestinal disorders
Mentha x piperita (aetheroleum)	Lamiaceae (Labiatae)	Allergic reactions with headache, bradycardia, muscle tremor, ataxia, anaphylactic shock and erythematous skin rash; nausea and vomiting

Table 11.4 (continued)

Herbal substance	Plant family	Undesirable effect noticed
Oenothera biennis; *Oenothera lamarckiana* (oleum)	Onagraceae	Hypersensitive reactions such as exanthema and headache; gastrointestinal effects, indigestion, nausea, softening of the stool
Olea europaea (folium)	Oleaceae	Pollinosis in the form of rhinitis or bronchial asthma
Panax ginseng (radix)	Araliaceae	Hypersensitivity reactions (urticaria, itching); gastrointestinal disorders such as abdominal discomfort, nausea, vomiting, diarrhea, constipation
Pelargonium sidoides and/or *Pelargonium reniforme* (radix)	Geraniaceae	Allergic reactions; mild gastrointestinal complaints (diarrhea, epigastric discomfort, nausea or vomiting, dysphagia)
Peumus boldus (folium)	Monimiaceae	Hypersensitivity (anaphylaxis)
Pimpinella anisum (aetheroleum)	Apiaceae (Umbelliferae)	Allergic reactions affecting the skin or the respiratory system
Pimpinella anisum (fructus)	Apiaceae (Umbelliferae)	Allergic reactions affecting the skin or the respiratory system
Plantago afra or *Plantago indica* (semen)	Plantaginaceae	Hypersensitivity reactions such as rhinitis, conjunctivitis, bronchospasm, and in some cases, anaphylaxis
		Cutaneous symptoms such as exanthema and/or pruritus [*also contact with skin or cases of inhalation of the powder*]
Plantago ovata (semen + seminis tegumentum)	Plantaginaceae	Hypersensitivity reactions such as rhinitis, conjunctivitis, bronchospasm, and in some cases, anaphylaxis
		Cutaneous symptoms such as exanthema and/or pruritus [also contact with skin or cases of inhalation of the powder]
Potentilla erecta (rhizome)	Rosaceae	mild gastrointestinal complaints such as nausea and vomiting
Primula veris and/or *Primula elatior* (flos)	Primulaceae	Allergic reactions
Quercus robur, *Quercus petraea*, *Quercus pubescens* (cortex)	Fagaceae	Allergic reactions
Rhamnus purshianus (cortex)	Rhamnaceae	Hypersensitivity reactions; abdominal pain and spasm and passage of liquid stools
Rhamnus frangula (cortex)	Rhamnaceae	Hypersensitivity reactions; abdominal pain and spasm and passage of liquid stools

(continued)

Table 11.4 (continued)

Herbal substance	Plant family	Undesirable effect noticed
Rheum palmatum or *Rheum officinale* or their hybrids, or a mixture of these two species and/or their hybrids (radix)	Polygonaceae	Hypersensitivity reactions; abdominal pain and spasm and passage of liquid stools
Rosmarinus officinalis (folium)	Lamiaceae (Labiatae)	Hypersensitivity (contact dermatitis and occupational asthma)
Rosmarinus officinalis (aetheroleum)	Lamiaceae (Labiatae)	Hypersensitivity (contact dermatitis and asthma)
Ruscus aculeatus (rhizome)	Asparagaceae	Nausea, gastrointestinal complaints, diarrhea, lymphocytic colitis
Salix [various species including *S. purpurea*, *S. daphnoides*, *S. fragilis*] (cortex)	Salicaceae	Allergic reactions such as rash, pruritis, urticaria, asthma, exanthema; gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea, dyspepsia, heartburn
Serenoa repens (fructus)	Aracaceae	Gastrointestinal disorders (abdominal pain, nausea, vomiting, diarrhea); skin and subcutaneous tissue disorders (skin rash); nervous system disorders (headache); allergic or hypersensitivity reactions
Solidago virgaurea (herba)	Asteraceae (Compositae)	Hypersensitivity reactions; gastrointestinal disorders
Tanacetum parthenium (herba)	Asteraceae (Compositae)	Gastrointestinal disturbances
Taraxacum officinale (folium)	Asteraceae (Compositae)	Allergic reactions
Taraxacum officinale (radix cum herba)	Asteraceae (Compositae)	Allergic reactions; epigastric pain
Thymus vulgaris or *Thymus zygis* or a mixture of both species (aetheroleum)	Lamiaceae (Labiatae)	Hypersensitivity reactions
Thymus vulgaris and *Thymus zygis* or a mixture of both species (herba)	Lamiaceae (Labiatae)	Gastric disorders
Trigonella foenum-graecum (semen)	Fabaceae	Allergic reactions (facial angioedema, wheezing) or ingestion (asthma, allergic rhinitis); gastrointestinal disorders: flatulence, diarrhea
Urtica dioica or *Urtica urens*, their hybrids or mixtures (radix)	Urticaceae	Allergic reactions, i.e., pruritus, rash, urticaria; gastrointestinal complaints such as nausea, heartburn, feeling of fullness, flatulence, diarrhea

Table 11.4 (continued)

Herbal substance	Plant family	Undesirable effect noticed
Urtica dioica or *Urtica urens* or a mixtures of the two species (folium)	Urticaceae	Skin reactions (e.g., itching, exanthema, hives); mild gastrointestinal complaints (e.g., nausea, vomiting, diarrhea)
Urtica dioica or *Urtica urens*, their hybrids or mixtures (herba)	Urticaceae	Skin reactions (e.g., itching, exanthema, hives); mild gastrointestinal complaints (e.g., nausea, vomiting, diarrhea)
Valeriana officinalis (radix)	Caprifoliaceae	Gastrointestinal symptoms (e.g., nausea, abdominal cramps)
Vitex agnus-castus (fructus)	Lamiaceae (Labiatae)	Severe allergic reactions with facial swelling, dyspnea and swallowing difficulties; (allergic) skin reactions (rash and urticaria); gastrointestinal disorders (such as nausea, abdominal pain)
Vitis vinifera (folium)	Vitaceae	Contact allergy and/or hypersensitivity reactions of the skin (itching and erythema, urticaria); nausea, gastrointestinal complaints
Zingiber officinale (rhizome)	Zingiberaceae	Minor gastrointestinal complaints (stomach upset, eructation, dyspepsia, nausea)

Some plants commonly used in Chinese topical medicinal products show positive reactions in patch tests in patients. Examples of such plants are *Syzygium aromaticum* (flos), *Angelica pubescens* (radix), *Cinnamomum verum* (cortex), *Cnidium monnieri* (fructus), *Gentiana macrophylla* (radix) and *Eleutherococcus senticosus* (cortex radix). In most of these positive reactions, a concomitant allergy to colophonium was also found (Chen et al. 2003).

Strong contact sensitizers such as alk(en)yl catechols (urushiols), from the Anarcardiaceae plant family, e.g., poison ivy (*Toxicodendron rydbergii*), poison oak (*Toxicodendron toxicarium*), poison sumac (*Toxicodendron striatum*) and lacquer tree (*Toxicodendron vernicifluum*), and alk(en)yl resorcinols, which were identified in different plants, such as cashew nut (*Anacardium occidentale*), mango (*Mangifera indica*) or *Philodendron* ssp. (Christensen 2014) should not be used in products applied to skin. However, lacquer allergy (due to the usage of lacquer tree products) is a serious occupational skin disease of lacquerware workers, especially in East Asia (Christensen 2014). Similarly, this might be true for a couple of other substances such as primin, a benzoquinone found in some *Primula* spp., which might be important mainly for gardeners, florists or herbalists.

Table 11.5 Excipients and information for the package leaflet taken from the notice to applicants in Volume 3B concerning plant-derived products connected to allergies (EC 2003)

Name	Route of administration	Threshold	Information for the package leaflet
Arachis oil (peanut oil)	All	Zero	(Medicinal product) contains arachis oil (peanut oil). *If you are allergic to peanuts or soy, do not use this medicinal product*
Balsam of Peru	Topical	Zero	May cause skin reactions
Bergamot oil Bergapten	Topical	Zero	May increase sensitivity to UV light (natural and artificial sunlight). [*Does not apply when bergapten is shown to be absent from the oil!*]
Castor oil polyoxyl and hydrogenated castor oil polyoxyl hydrogenated	Parenteral		May cause severe allergic reactions
	Oral		May cause stomach upset and diarrhea
	Topical		May cause skin reactions
Latex natural rubber (latex)	All	Zero	The container of this medicinal product contains latex rubber. May cause severe allergic reactions
Sesame oil	All	Zero	May rarely cause severe allergic reactions
Soy oil (and hydrogenated soya oil)	All	Zero	(Medicinal product) contains soy oil. *If you are allergic to peanut or soy, do not use this medicinal product*
Wheat starch	Oral	Zero	Suitable for people with celiac disease. *Patients with wheat allergy (different from celiac disease) should not take this medicine*. [*Wheat starch may contain gluten, but only in trace amounts, and is therefore considered safe for people with celiac disease*. (*Gluten in wheat starch is limited by the test for total protein described in the PhEur monograph*)]

Not only direct contact may induce allergic contact dermatitis; also aerogenic contact dermatitis is described. Here, plant parts that are transferred by air (e.g., plant hairs, small fruits, or withered plant particles) may reach the skin and lead to responses.

Photoallergy

Cases of real photoallergy due to herbal material is rare; most cases will include phototoxic reactions. Very rare cases of photoallergy after exposition to furanocoumarins have been described (Hausen and Vieluf 1997), but such a sensitization possibility remains to be confirmed.

Table 11.6 Plant/plant extracts or preparations for which hypersensitivity reactions after cutaneous use have been reported according to the monographs of the HMPC (positive assessment)

Herbal substance	Plant family	Undesirable effect noticed
Achillea millefolium (flos + herba)	Asteraceae (Compositae)	Hypersensitivity reactions of the skin
Aesculus hippocastanum (semen)	Sapindaceae	Hypersensitivity reactions of the skin (itching and erythema)
Arnica montana (flos)	Asteraceae (Compositae)	Itching, redness of the skin and eczema
Avena sativa (fructus)	Poaceae	Skin reactions
Calendula officinalis (flos)	Asteraceae (Compositae)	Skin sensitization [*also oromucosal use*]
Capsicum annuum var. minimum and small fruited varieties of *Capsicum frutescens* (fructus)	Solanaceae	Skin hypersensitivity and allergic reactions (e.g., urticaria, blisters or vesiculation)
Commiphora molmol (gummi-resina)	Burseraceae	Allergic skin reactions [*also oromucosal use*]
Echinacea purpurea (herba recens)	Asteraceae (Compositae)	Hypersensitive reactions (local rash, contact dermatitis, eczema and angioedema of the lips)
Echinacea purpurea (radix)	Asteraceae (Compositae)	Hypersensitivity reactions (skin reactions) [oromucosal use]
Hamamelis virginiana (cortex + folium)	Hamamelidaceae	Allergic contact dermatitis [also oromucosal, rectal, anorectal use]
Hamamelis virginiana (folium et cortex aut ramunculus)	Hamamelidaceae	Allergic contact dermatitis conjunctivitis [ocular use]
Hypericum perforatum (herba)	Hypericaceae	Allergic skin reactions
Juniperus communis (aetheroleum)	Cupressaceae	Allergic skin reactions
Matricaria recutita (aetheroleum)	Asteraceae (Compositae)	Hypersensitivity reactions including severe allergic reaction (dyspnea, Quincke's disease, vascular collapse, anaphylactic shock) [bath additive]
Matricaria recutita (flos)	Asteraceae (Compositae)	Hypersensitivity reactions including severe allergic reaction (dyspnea, Quincke's disease, vascular collapse, anaphylactic shock) [inhalative; oromucosal]
Melaleuca alternifolia, *Melaleuca linariifolia*, *Melaleuca dissitiflora* and/or other species of Melaleuca, (aetheroleum)	Myrtaceae	Adverse skin reactions, including smarting pain, mild pruritus, burning sensation, irritation, itching, stinging, erythema, edema (contact dermatitis) or other allergic reactions [also oromucosal use]
Melilotus officinalis (herba)	Fabaceae	Allergic reactions

(continued)

Table 11.6 (continued)

Herbal substance	Plant family	Undesirable effect noticed
Mentha x piperita (aetheroleum)	Lamiaceae (Labiatae)	Hypersensitivity reactions such as skin rash, contact dermatitis, and eye irritation [also transdermal use]
		Apnea, broncho- and laryngoconstriction [inhalative use]
		Contact sensitivity with intra-oral symptoms in association with burning mouth syndrome, recurrent oral ulceration or a lichenoid reaction [oromucosal use]
Quercus robur, *Quercus petraea*, *Quercus pubescens* (cortex)	Fagaceae	Allergic reactions [also oromucosal; anorectal]
Rosmarinus officinalis (folium)	Lamiaceae (Labiatae)	Hypersensitivity (contact dermatitis and occupational asthma) [bath additive]
Rosmarinus officinalis (aetheroleum)	Lamiaceae (Labiatae)	Hypersensitivity (contact dermatitis and asthma) [also as bath additive]
Syzygium aromaticum (floris aetheroleum)	Myrtaceae	Allergic reactions [oromucosal; dental]
Thymus vulgaris or *Thymus zygis* or a mixture of both species (aetheroleum)	Lamiaceae (Labiatae)	Hypersensitivity reactions and skin irritation [also as bath additive]
Trigonella foenum-graecum (semen)	Fabaceae	Allergic reactions (facial angioedema, wheezing) or ingestion (asthma, allergic rhinitis)
Vitis vinifera (folium)	Vitaceae	Contact allergy and/or hypersensitivity reactions of the skin (itching and erythema, urticaria)

Other ways in addition to cutaneous use – other than oral and cutaneous – are italics

Herbal Preparations Used in Inflammation and Allergic Reactions

Natural preparations able to regulate allergic responses, via various mechanisms, including inhibition of allergen diffusion into epithelial cells, are discussed, as are the suppression of Th2-related cytokine production, the inhibition of T-cell differentiation, and/or the inhibition of degranulation of mast cells. For each mechanism, non-clinical data exist for herbal preparations or their compounds. For instance, (1) an extract of *Scutellaria baicalensis* could be shown to inhibit ovalbumin permeation via Caco-2 cells monolayers; (2) *Trigonella foenum-graecum* is known to increase Th-1 response and decrease Th-2 response; and (3) compounds such as curcumin or resveratrol are able to suppress the Th-2 cell response (Shin and Shon 2015). Although clinical proof for such actions is still lacking, the fact that part of our diet can show antiallergic effects should not be ignored.

Some examples of in vitro or in vivo anti-allergenic activity of herbal preparations have been well documented:

Food Allergy Herbal Formula-2

A product called Food Allergy Herbal Formula-2 (FAHF-2) (an extract of nine herbs: *Prunus mume* fruit, *Zanthoxylum schinifolium* fruit skin, *Angelica sinensis* root, *Zingiber officinale* rhizome, *Cinnamomum cassia* twigs, *Phellodendron chinense* bark, *Coptis chinensis* rhizome, *Panax ginseng* root and *Ganoderma lucidum* fruiting body) was tested in a peanut allergic murine model. The protection against peanut-induced anaphylactic symptoms persisted for at least 6 months post-therapy following a single 7 week course of treatment. A reduction of Th2-cytokines and serum IgE-levels and an increase of IFN-γ and IgG2a could be seen. Also, a reduction in basophil and mast cell numbers and mast cell activation was demonstrated (Wang and Li 2012). After an acute, 1 week, randomized double-blind placebo-controlled, dose escalation phase I trial in subjects with peanut and/or tree nut, fish and shellfish allergies, an extended phase I clinical trial (open-label study) was performed for 6 months in 14 patients. During the course of the study, basophil activation and basophil and eosinophil numbers were evaluated. While no significant drug-associated differences in laboratory parameters, pulmonary function studies, or electrocardiographic findings before and after treatment were found, there was a significant reduction in basophil expression in response to *ex vivo* stimulation at month 6. There was also a trend towards a reduction of eosinophil and basophil numbers after treatment (Patil et al. 2011); however, although clinical safety could be proven, clinical data on efficacy are still lacking.

Petasites hybridus leaves

A CO_2 supercritical fluid extract of the leaves of *Petasites hybridus* (petasin chemovariety), given intranasally in mice, showed leukotriene-inhibiting properties that led to a reduced allergic airway inflammation (Brattström et al. 2010). It was suggested that petasin (a sesquiterpene) inhibits L-type Ca^{2+}-channels. The same extract has been studied in three placebo-controlled clinical studies showing that it may be effective for the relief of symptoms or improved peak nasal inspiratory flow (Guo et al. 2007). An oral product containing this extract was authorized in Switzerland for the treatment of allergic rhinitis (Zeller Medical 2012).

Urtica dioica

In vitro, an *Urtica dioica* extract inhibited several key inflammatory events (antagonist activity against the Histamine-1 receptor and inhibition of mast cell tryptase; inhibition of cyclooxygenase-1, cyclooxygenase-2 and hematopoietic prostaglandin D(2) synthase) that cause the symptoms of seasonal allergies (Roschek et al. 2009). These might justify, at least in part, the folk medicine use of *Urtica dioica* in such cases of seasonal rhinitis.

The use of herbal preparations in cases of cutaneous allergy

While a couple of herbal preparations are used cutaneously in cases of dry or inflamed skin, nothing is really known about the use of herbal preparations in

cases of allergy. Of course it can be assumed that some cases of "inflamed skin" might also mirror allergic skin conditions, but this is only speculation.

Some non-clinical results concerning plants of traditional Chinese medicine have been published. In various models (in vivo, in vitro, or ex vivo), the ethanol extract of the radix of *Achyranthis bidentata*, methanol extract of *Schisandra chinensis* fruits, methanol extract of radix of *Sanguisorba officinalis*, ethanol extract of the defatted radix of *Scutellaria baicalensis*, ethanol extract of *Zizyphus jujube* fruits, extracts of *Rubia cordifolia* and *Dianthus superbus*, demonstrated anti-allergic activity (Jung et al. 2015; Lee et al. 2015; Jo et al. 2015; Li et al. 2014; Naik et al. 2013; Wang and Li 2012). The same applies for artesunate, a semisynthetic derivative of artemisinin, an active component of *Artemisia annua* (Cheng et al. 2013), or for Δ^9-tetrahydrocannabinol, an active constituent of *Cannabis sativa* (Gaffal et al. 2013).

Future Considerations

Allergies due to herbal preparations or substances isolated from plants (and later manufactured synthetically) are described, and it often seems that the main structures responsible for it are known – or at least suspected to be known. While it seems that the majority of allergies are associated with a manageable number of plant allergens, a few rare cases of allergies associated with different structures have also been reported.

It would be desirable to establish surveillance systems in the fields of food (supplements)/herbal medicinal products/cosmetics to improve information on potential allergens, since this is the basis of the prevention of allergies; this means, however, that for all product categories, an accurate diagnosis of IgE-mediated allergy should be performed by specialists who have been educated to interpret the results of such testing in an appropriate way and to use standardized allergen extracts.

For a long time, strict avoidance of specific antigen/herbal preparations was seen as the only possible way to avoid allergic reactions. A strict labelling of antigens/herbal preparations (considering the main/active ingredient, excipient, and possible contaminations) is a prerequisite for the patient. In food regulation, there is an ongoing discussion about the labelling of food/food supplements that *could* contain allergenic substances such as nuts, etc., as contamination (e.g., "May contain traces of …"). A regulatory standardized system is lacking in Europe, leading to inadequate labelling, and therefore to misinformation and/or an erroneous feeling of safety. Some countries, such as Australia and New Zealand, have undertaken to improve precautionary allergen labeling. The establishment of appropriate parameters (reference doses) is discussed, to label only the relevant level of allergens to avoid "overuse" of precautionary labeling, and to ensure the protection of most of the food-allergic population. But therefore, of course, manufacturers should quantitatively determine the degree of contamination – which may present a huge analytical problem as the level of detection of analytical methods can be too high, compared

to the level of immunoreactivity in sensitized patients. The most sensitive methods, based on DNA (qPCR) or protein (immunoassays) detection, may also be impossible in cooked foods (heat denaturation). Furthermore, technical steps are desirable to prevent contamination as much as possible.

During the last years, immunotherapeutic strategies were developed to avoid serious adverse effects, such as standard subcutaneous immunotherapy or oral immunotherapy. Final conclusions are still lacking on the induction of short-term desensitization or even long-term tolerance by these treatments, and more meaningful clinical trials are needed. Furthermore, innovative drugs need to be developed, which may take into account some promising plant extracts or plant-derived compounds. There is some information on herbal preparations that might be useful in the treatment of allergies, but until now, mainly in vitro or animal data indicate that such activities and clinical data are missing in most cases.

Food, its preparation and the use of food supplements might change in the future, or may have changed already. There are bound to be changes not only in eating behaviors, but also in changes in production processes/technologies and the introduction of product innovations. Changes in allergenic properties or in hypersensibility patterns that arise from these altered conditions are not really known so far. Further research is definitely needed.

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