REVIEW ARTICLE

Cannabis sativa allergy: looking through the fog

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Abstract

IgE-mediated *Cannabis* (*C. sativa*, marihuana) allergy seems to be on the rise. Both active and passive exposure to cannabis allergens may trigger a *C. sativa* sensitization and/or allergy. The clinical presentation of a *C. sativa* allergy varies from mild to life-threatening reactions and often seems to depend on the route of exposure. In addition, sensitization to cannabis allergens can result in various cross-allergies, mostly for plant foods. This clinical entity, designated as the 'cannabis-fruit/vegetable syndrome', might also imply cross-reactivity with tobacco, natural latex and plant-food-derived alcoholic beverages. Hitherto, these cross-allergies are predominantly reported in Europe and appear mainly to rely upon cross-reactivity between nonspecific lipid transfer proteins or thaumatin-like proteins present in *C. sativa* and their homologues, ubiquitously distributed throughout plant kingdom. At present, diagnosis of cannabis-related allergies predominantly rests upon a thorough history completed with skin testing using native extracts from crushed buds and leaves. However, quantification of specific IgE antibodies and basophil activation tests can also be helpful to establish correct diagnosis. In the absence of a cure, treatment comprises absolute avoidance measures. Whether avoidance of further use will halt the extension of related cross-allergies remains uncertain.

Abbreviations
Act d, *Actinidia deliciosa* (kiwi fruit); Ara h, *Arachis hypogaea* (peanut); Art v 3, *Artemisia vulgaris* (mugwort); ATP, adenosine triphosphate; BAT, basophil activation test; Bet v, *Betula verrucosa* (birch); Can s, *Cannabis sativa*; CCD, cross-reactive carbohydrate determinants; Cit s, *Citrus sinensis* (tangerine); Cor a, *Corylus avellana* (hazelnut); CRD, component-resolved diagnosis; Cup a, *Cupressus arizonica* (cypress native to the southwest of North America); Hev b, *Hevea brasiliensis* (natural rubber tree); Jug r 3, Juglans regia (walnut); Lyc e, *Lycopersicom esculentum* (tomato); Mal d, *Malus domestica* (apple); Mus a, *Musa acuminate* (banana); NSAIDs, nonsteroidal anti-inflammatory drugs; Ns-LTP, nonspecific lipid transfer protein; OAS, oral allergy syndrome; Phl p, *Phleum pratense* (Timothy grass); PRP, pathogenesis-related protein; Pru av, *Prunus avium* (cherry); Pru p, *Prunus persica* (peach); RuBisCo, ribulose-1,5-biphosphate carboxylase/oxygenase; sIgE, specific immunoglobulin E; THC, tetrahydrocannabinol; TLP, thaumatin-like protein; Tri a, *Triticum aestivum* (wheat); Vit v, *Vitis vinifera* (grape).

Cannabis sativa (*C. sativa*) is an annual, dioecious and anemophilous flowering plant (order: Rosales, family *Cannabaceae*) that is native to central and southern Asia and the Caucasian region. Different preparations [dried flowering tops, hashish, hashish oil] are obtained from cannabis varieties containing elevated levels of cannabinoids, especially delta-9-tetrahydrocannabinol (THC), several of them being more or less potent psychoactive substances. Although, today, cannabis use is still illegal in most countries, it is widespread for its relaxing and euphoric effects. Furthermore, worldwide the illegal status of the drug has gained more and more resistance recently, resulting in legalization of both sale and possession of marijuana in Colorado, Alaska, Oregan and Washington, for example, both for medicinal and recreational use (1). Different European countries are debating the legalization of cannabis as well. While consumption of cannabis has been legal under certain conditions for a while

in the Netherlands, both Germany's and Belgium's minister of Health plan to legalize certain medicinal cannabis preparations in the near future (2, 3). When used, it can be consumed by smoking, vaporizing or gastrointestinal ingestion. In addition to hempseed and hempseed oil, derivatives of dried flowers or resinous extract can be incorporated in food and ingested (4–6). *C. sativa* in the form of industrial hemp containing lower amounts of THC is commercially used for fibre, cosmetics and clothing. Apart from these various (ab) uses unfortunately, cannabis may elicit some undesirable effects amongst which allergy and the consequential allergic symptoms seem to be an increasing problem. This review aims to summarize the current knowledge on cannabis-related allergy, with a particular focus on clinical manifestations, allergenic components and management of the patients.

Prevalence

Few true IgE-dependent allergic reactions in illicit abusers have been published (7–10) making it hard to determinate the true prevalence of this allergy. Nevertheless, multiple reports on cutaneous and respiratory allergies to different members of the *Cannabaceae* family like industrial hemp and hop (*Humulus lupulus)* have been published (11–15). This under-reporting probably results from the illegal status of cannabis use, which makes the patients reluctant to admit their abuse. Liskow et al. (16) described a 29-year-old housewife who suffered an allergic reaction upon smoking a marihuana cigarette. Diagnosis of cannabis allergy was documented by a positive scratch test and passive transfer studies (16). Today, no information is available about the prevalence of IgE-mediated *C. sativa* allergy but it is likely that cannabis allergy will be an increasing problem in the future, partly in the settings of its evolving legal status (6).

Routes of exposure and sensitization

When cannabis is used for its psychoactive effects, drug (ab) users may become sensitized by inhalation of cannabis allergens through active smoking and/or vaporizing the drug. Cutaneous contact through handling of the drug is another possible route of sensitization. This last route of exposure is not only relevant in drug (ab) users but could be important in cannabis growers and policemen seizing illegal cannabis (plants). Herzinger et al. (15) also reported cannabis allergy in laboratory workers handling cannabis for professional purposes. Cannabis derivatives may be used in food preparations, which can cause allergic sensitization by chewing or ingestion. Intravenous use can also cause both sensitization and elicitation of allergic symptoms. An alternative route of sensitization could be exposure by proxy when allergens become airborne or are transferred via indirect cutaneous contact. Such a second-hand exposure might be particularly relevant in children or bystanders who may become sensitized to cannabis allergens through smoking by relatives or friends (8).

In contrast to a birch pollen sensitization that is known to cause a pollen–food syndrome with secondary food allergies, cannabis seems to be not always the primary allergic source and allergic symptoms on exposure to cannabis might also originate from cross-reactivity with allergenic compounds such as nonspecific lipid transfer proteins (ns-LTPs) or thaumatin-like proteins (TLPs) present in other plants from closely or more distantly related origin (10).Finally, *C. sativa* produces wind-borne pollen easily transported over long distances (17–22). For example, in Nebraska, where industrial *C. sativa* is cultivated, *C. sativa* pollen accounts for 36% of the total pollen count during mid- to late August (18). Similar observations were made in Italy (19) and Spain (21). Multiple reports were published in which allergic symptoms are presumed to result from cannabis pollen sensitization (18, 21, 23). Interestingly, the link with ns-LTPs from plant foods has only been described in relation to cannabis sensitization in drug (ab)users and no studies have been published relating ns-LTPs or TLPs to cannabis pollen. As only female (non-pollinating) plants are cultivated for illicit use, it is less likely for abusers of cannabis, who grow their own plants, to become sensitized to marihuana through pollen exposure. Furthermore, a correlation between ns-LTP sensitization more specifically Can s 3 and cannabis pollen has not been described up till now.

Allergenic components

At present, the allergenic composition of *C. sativa* remains largely unknown. Larramendi et al. (10) described six different bands with a molecular weight varying between 10 and 60-kDa in a *C. sativa* leaf extract that were recognized by the individual patients' sera. The 10-kDa IgE binding band was already described in other reports (10, 24, 25) and corresponds to Can s 3, the nonspecific lipid protein (ns-LTP) of *C. sativa* (10) that belongs to the pathogenesis-related proteins (PR)-14 group (26). Sensitization to the ns-LTP Can s 3 was observed in 124 of 130 patients (95.3%) with a primary cannabis allergy in a Spanish study (27). In our own case–control study, sensitization to ns-LTP was demonstrable in 10 of 12 (83%) patients with cannabis-related food allergies (8). In comparison, in our regions sIgE reactivity towards ns-LTP in patients with pollen and/or plant-derived food allergies is observed in about 25% of the cases (28). Anyhow, it appears that next to peach (24) and mugwort (29) *C. Sativa* might be another source that dominates sensitization to ns-LTP and triggers ns-LTP-related allergies that extend far beyond vegetables and fruits. The 38-kDa band corresponds with a TLP, which belongs to the PR-5 family (10). Although in the study of Larramendi et al. (10) no homology was found between the 14-kDa band and any known allergen, it was speculated that this band could be a profilin (30).

In a study of Nayak et al. (31), multiple IgE binding proteins were observed. The 23-kDa band was identified as 'oxygen-evolving enhancer protein 2', an enzyme involved in the photosynthesis. The 50-kDa band corresponds with the heavy chain subunit of ribulose-1,5-biphosphate carboxylase/oxygenase (RuBisCo). This is a highly abundant protein in nature that catalyses a reaction that is rate-limiting for photosynthesis. Other putative allergens identified by Nayak et al. (31)

are glyceraldehyde-3-phosphate and adenosine triphosphate (ATP) synthase. Finally, the authors observed that ubiquitously distributed cross-reactive carbohydrate determinants (CCDs) might also be the cause of some IgE reactivity. Unlike the European studies, in this American/Canadian proteomics study no IgE binding sequences of the pan-allergen ns-LTP were observed, even though IgE reactivity at approximately 10-kDa was observed in two patients. Moreover, in contrast to the European series, most of the Canadian patients apparently did not suffer from a cannabis-related cross-reactivity syndrome as is described below. Whether this indicates cannabis allergy to display geographically different sensitization profiles with distinct clinical phenotypes remains elusive. The most relevant putative cannabis allergens are displayed in Table 1.

Clinical manifestations

The clinical presentation of an IgE-mediated cannabis allergy can vary considerably from mild to life-threatening reactions and seems to relate to the route of exposure. First, respiratory reactions like rhinitis, conjunctivitis, asthma and palpebral angioedema have been described. These reactions predominantly occur when cannabis is consumed by smoking or vaporizing (for review: (6, 35)) but can also arise from passive second-hand exposure to cannabis smoke, indirect cutaneous transmission (8, 24) or inhalation of *C. sativa* pollen (6, 17–22).

Direct handling of *C. sativa* plants may lead to contact urticaria (13, 33, 36) and contact dermatitis (13). Finally, anaphylaxis can result from ingestion of hempseed (5), drinking marihuana tea (37) and smoking (38).

Patients with IgE-mediated cannabis allergy can display distinct sensitization profiles such as sensitization to the ns-LTP of *C. sativa,* that is Can s 3. Nonspecific lipid transfer proteins are pan-allergens ubiquitously present throughout the plant kingdom including fruits and vegetables (39). Consequently, sensitization to Can s 3 might be an explanation for the high variety of secondary plant-derived food allergies seen in European patients with a cannabis allergy. This, sometimes extensive, cross-reactivity between cannabis and plant-derived food has been described in multiple studies (6, 8, 35, 38) and was recently designated as the 'cannabis-fruit/vegetable syndrome' (8, 40). The foods most commonly implicated in this allergy syndrome are peach, apple, nuts, tomato and occasionally citrus fruit as orange and grapefruit. Figure 1, adapted from (35), gives a nonexhaustive overview of this 'cannabis-fruit/vegetable syndrome'.

It is important to note that the allergic reactions to these plant foods are often triggered or exacerbated by cofactors such as exercise or nonsteroidal anti-inflammatory drugs (NSAIDs) and are therefore variable which can make history taking more complex (42). Furthermore, these reactions are frequently more severe than the classic oral allergy syndrome (OAS) expected in food allergy related to sensitization to Bet v 1, the major allergen from birch pollen (43). This could be explained by the fact that ns-LTPs, unlike Bet v 1 homologues, resist to gastroduodenal proteolysis (44, 45) and thermal processing (46–48). However, it should also be kept in mind that in addition to plant-food allergies, sensitization to Can s 3 might also explain cross-reactions to ns-LTP present in various sources such as *Hevea* latex (49–51), alcoholic beverages such as beer and wine (52, 53) and finally also tobacco (*Nicotinia tabaccum)* (9, 38, 54).

As described in Table 1, thaumatin-like proteins (TLP), belonging to the PR-5 family, constitute another important group of components that might explain extensive cross-reactivity between cannabis and plant-derived food in European patients (10). These TLPs can be found in pollen and different foods such as NP24 from tomato (*Solanum lycopersicon*) (55), Cup a 3 from cypress (*Cupressus arizonica*) (56), Act d 2 kiwi fruit (*Actinidia deliciosa*) (57) and Mal d 2 from apple (*Malus domestica*) (58). For the discussion about the clinical significance of the pan-allergen profilin, the reader is referred elsewhere (59, 60).

Diagnosis

Although a thorough history is absolutely mandatory for correct diagnosis, it appears that it is frequently pieced together from inadequate and incomplete descriptions and recalled by patients reluctant to admit or simply denying

Table 1 (Putative) *Cannabis sativa* allergens

Molecular weight (kDa)	Allergen	Function	Homologues (not exhaustive)	References
9	Can s 3	Ns-LTP (PR-14)	Pru p 3, Mal d 3, Cor a 8, Hev b 12, Ara h 9, Tri a 14, Jug r 3, Art v 3	(8, 10, 24, 27, 29, 30, 32–34)
14	Profilin (?)	Cytoskeleton	Bet v 2, Phl p 12	(30)
23	Oxygen-evolving enhancer protein	Photosynthesis		(31)
38	TLP (thaumatin-like)	PR-5	Act d 2, Mal d 2, Mus a 4, Pru av 2, Cup a 3	(10)
50	Can s RuBisCo	Photosynthesis		(31)

Table updated from Decuyper et al. (35).

Ns-LTP, nonspecific lipid protein; PR, pathogenesis-related.

Except the study published by Larramendi et al. (10), allergens described in the table have been suggested without deep investigation and warrant further studies.

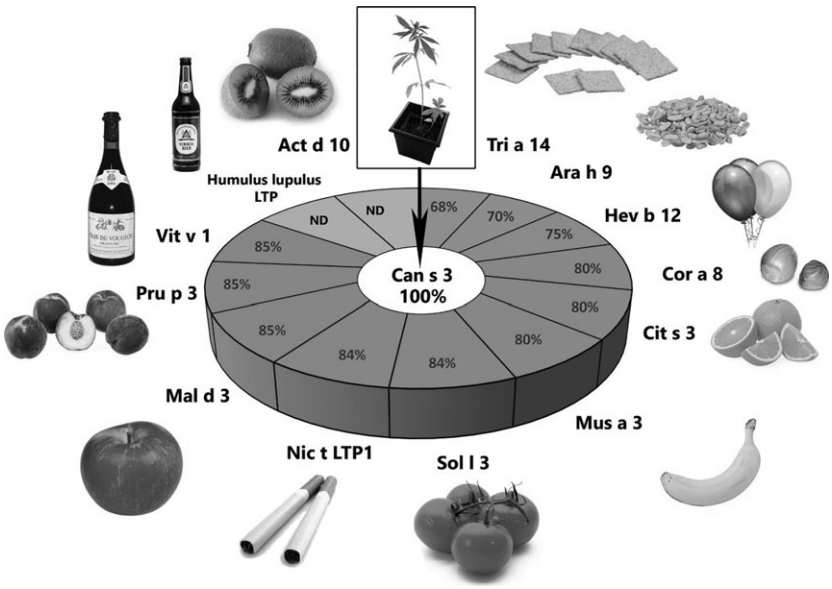

Figure 1 Nonspecific lipid transfer proteins (ns-LTPs) are ubiquitously present in the plant kingdom. Consequently, sensitization to Can s 3, the ns-LTP from *Cannabis sativa*, could lead to a broad variety of cross-reactions. Cross-reactive substances displayed in the figure: cherry (*Prunus avium*), tangerine (*Citrus reticulata*), orange (*Citrus sinensis*), peach (*Prunus persica*), apple (*Malus domestica*), tomato (*Solanum Lycopersicum*), hazelnut (*Corylus avellana*), walnut (*Juglans regia*), banana (*Musa acuminate*), wheat (*Triticum aestivum*), latex (*Hevea brasiliensis*), tobacco (*Nicotiana tabacum*) and alcoholic beverages such as wine (grapes: *Vitis vinifera*) and beer (common hop: *Humulus lupulus*). Percentages represent sequence homology. ND: no data (41).

illicit drug abuse. History might also be misleading because of misinterpretation or misconception of symptoms related to active or passive exposure. Presently, sensitization and allergy to cannabis is almost exclusively studied or documented by prick–prick skin testing. Prick–prick skin tests use a broad variety of raw materials such as macerated *C. sativa* leaves, buds and flowers (5, 8, 10, 14, 15, 17, 18, 22, 24, 27, 30–32, 37). Needless to say that this approach is virtually impossible to standardize, mainly because of unpredictable variations in composition and potential contaminations with other allergens of the raw material.

A second method that can be applied to document cannabis allergy is quantification of serum specific IgE (sIgE) antibodies towards industrial hemp, an assay that can be obtained from Thermo Fisher Scientific (Uppsala, Sweden) but has not been thoroughly clinically validated. In our case–control study, a positive industrial hemp sIgE test result was observed in all 12 cannabis allergic patients but unfortunately also in three of eight pollen-allergic patients without overt cannabis allergy (8). Using a whole protein extract, Larramendi et al. (10) found a positive sIgE result to a native cannabis extract in 21 of 32 individuals who had their cannabis sensitization documented by a positive cannabis skin test. Herzinger et al. (15) found positive sIgE results to marihuana and/or hashish in two patients with professional exposure to cannabis.

During the last two decades, significant advances in biochemistry and molecular biology enabled the characterization, cloning and recombinant synthesis of relevant allergenic components and epitope-emulating peptides enabling quantification of serum sIgE antibodies to these components or sequential epitopes, a method known as component-resolved diagnosis (CRD). In contrast to traditional sIgE tests, CRD does not rely upon whole extract preparations but upon single native or recombinant components (e.g. proteins or peptide components) (61, 62). CRD involves unique marker components to study the sensitization of patients towards a particular allergen and the presence of sIgE antibodies to cross-reactive components (e.g. profilins and CCD) that point to cross-reactivity. CRD not only allows one to discriminate between genuine allergy and cross-reactivity, but also enables to establish individual sensitization profiles, which can be highly relevant in food allergy. In a study by Armentia et al. (27), sIgE antibodies against purified cannabis ns-LTP were demonstrable in over 95% of the patients with a primary cannabis allergy. Recently, Rihs et al. (34) succeeded to clone Can s 3 from *C. sativa L ssp sativa cv Kompolti* and to study its IgE binding properties. Other *in vitro* tests that have been employed to document sensitization to cannabis are histamine release tests (15) and basophil activation tests (BAT) (8). In a preliminary study, we found BAT with a cannabis extract rich in ns-LTP to be absolutely discriminative between food-allergic patients with and without cannabis allergy, larger studies are mandatory to confirm this finding. In healthy control individuals, no basophil responses to this extract were demonstrable (8). Although cannabis challenge tests might add to the diagnosis of cannabis allergy (9, 14), it is highly unlikely this technique to enter mainstream use for obvious practical and ethical reasons.

Treatment

For the time being, there is no cure for IgE-mediated *C. sativa* allergy nor for the cannabis-fruit/vegetable syndrome. Therefore, strict avoidance measures remain of utmost importance. These measures comprise a complete stop of further abuse of the drug, and avoidance of exposures to allergens implicated in the individual cross-reactivity syndrome. As reviewed by Ocampo et al. (6), hemp/cannabis desensitization has been described. However, these cases remain anecdotal and long-term follow-up data are lacking.

Natural history

The natural history of a cannabis allergy is currently unknown. Nevertheless, in our practice we observed several patients in who cannabis-related allergies were still evolving despite any further use of the drug. Longitudinal studies with larger numbers of participants are mandatory to establish whether cannabis allergy might have lighted an eternal flame.

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Author contributions:

Ine I. Decuyper participated in interpretation of data, literature search, data analysis, writing the manuscript; Athina L. Van Gasse participated in proofreading final text; Nathalie Cop participated in proofreading final text; Vito Sabato participated in proofreading final text; Margaretha A. Faber participated in literature search and proofreading final text; Christel Mertens participated in interpretation diagnostic data and proofreading final text; Chris H. Bridts participated in data interpretation and proofreading final text; Margo M. Hagendorens participated in proofreading final text; Luc De Clerck participated in proofreading final text; Hans-Peter Rihs participated in discussion diagnostic techniques and proofreading final text; Didier G. Ebo participated in literature search, data analysis, writing and proofreading final text.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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