Cannabis allergy : what the clinician needs to know in 2019

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ABSTRACT

Introduction

Although the use of cannabis dates back millennia, the first description of cannabis allergy is relatively recent (1971). Recent larger-scale data shows that cannabis allergy can manifest severe and generalized symptoms with extensive cross-reactions. Thus, it is essential to become familiarized with its clinical presentation, diagnostic aids and adequate therapeutic guidance.

Area's covered

Here we provide a hands-on overview on cannabis allergy focusing on symptomatology and the reliability of diagnostic options. Recent advances in proteomics are discussed in detail elucidating on the link with nsLTP-related allergies. The proteomics advancements have paved the way for more reliable diagnostics, especially component-based tools. Finally, the current experience in treatment options are highlighted.

Expert commentaries

Cannabis allergy is an allergy entity which can significantly impact the quality of life. For optimal diagnosis, we advise to start with a validated and standardized crude-extract based test such as sIgE hemp complemented by component-based diagnostics such as sIgE Can s 3 quantifications where available. Future research should lift the veil on the true prevalence of cannabis allergy and the importance of other cannabis allergens to further guide our practice.

HIGHLIGHTS BOX

- Cannabis allergy can elicit a variety of symptoms from mild rhinoconjunctivitis to life-threatening anaphylaxis
- Crude extract-based diagnostics show a very high sensitivity albeit a low specificity
- Can s 3, the nsLTP of Cannabis *sativa,* is a major allergen with Can s 3 based diagnostics showing the highest performance
- Reports suggests that symptoms can occur after smoking, cutaneous contact but also ingestion of spacecake, cannabis tea, oil or hemp seeds.
- A significant number of patients even report symptoms on indirect smoke exposure or cutaneous contact
- Cannabis allergy has been described following both recreational use and occupational cannabis exposure

1. INTRODUCTION

The first indication of cannabis use dates back to prehistoric Eurasia and Africa. The plant has been used ever since for its psychoactive properties but it has long been an important source for fiber, rope, food and medicine as well (1). In Western civilization, cannabis became notorious for its psychoactive properties and its use has been restricted since the 19th century. For example, in the United States (US) cannabis was promoted till the 1937 tax act, but now use is confined by its classification as DEA Class I drug. In recent years, numerous nations have debated the illegal status of cannabis resulting in legalization in the Netherlands and Canada. Cannabis for medicinal and/or recreational use has also been decriminalized to some extend in Spain, Portugal, Belgium, Italy, Uruguay and several American States.

According to the United Nations' World Drug Report cannabis is the world's most seized substance, with 4% of the world's population using cannabis recreationally and steadily increasing (2).

Apart from the growing recreational use, it seems that recent trends promoting ecological consciousness and healthy foods have caused a rise in the availability and consumption of hemp seeds, hemp or cannabis oil and other cannabis derived products as well. All these factors together with the increased awareness of cannabis allergy might play a role in the apparent rise of cannabis allergy reports. These reports indicate that cannabis allergy might manifest severe and generalized symptoms with extensive cross-reactions, mainly, but not exclusively, to fruits and vegetables. So, it is likely that the augmented cannabis availability and exposure (both as a drug and as food) coincides with a rise in adverse events including cannabis-related allergies with detrimental effects on health and quality of life. Therefore, it becomes important to become familiarized with the signs of cannabis allergy, be aware of the available diagnostic options, treatment perspectives and patient guidance.

This review aims to be a hands-on synopsis of the current knowledge using findings from both case-reports as well as the most recent larger-scale studies on cannabis allergy.

2. SYMPTOMS & EXPOSURE

2.1 Cannabis exposure and related symptoms

The first description of cannabis allergy dates back to 1971 in which a young housewife experienced an anaphylactic reaction after smoking a cannabis-containing cigarette (3). Since that time, the odd report, mostly cases and small case series, on cannabis allergy was published elucidating on allergic symptoms both after recreational cannabis and work-related exposure.

Most reports describe immediate type hypersensitivity reactions, typically with a rapid-onset of symptoms starting within 20 to 30 minutes after cannabis exposure as shown in figure 1.

Upper airway complaints such as nasal and pharyngeal pruritus, lacrimation, nasal congestion and rhinitis are reported most often (3-20). Then again, several reports also mention more severe lower respiratory symptoms such as cough, mild to severe dyspnea, wheezing and chest tightness (3, 4, 6, 8-10, 12-22). Another organ system oftentimes involved is the skin with patients reporting localized but also generalized pruritus and urticaria, angioedema and sometimes flairs of eczema (7, 8, 10-23). Alternatively, gastro-intestinal and cardiovascular symptoms seem to be rather rare (10, 12-14, 17-20, 24).

The cannabis-related symptoms described above can be isolated or coincide sometimes resulting in generalized, severe reactions and anaphylaxis (9, 10, 12-15, 17-22, 24). These symptoms have often been reported in relation to cannabis smoking but might also occur on cutaneous contact (7, 8, 11-15, 17, 19).

Although some reports describe symptoms only on respiratory exposure, it should be questioned whether cannabis smokers aren't also cutaneously exposed while preparing and handling their cannabis cigarettes. On the other hand, some cases express allergic symptoms on cannabis ingestion either as space cake but also cannabis tea, hemp seeds and oil (8, 12, 13, 19, 20, 22). Two cases presented anaphylaxis on intravenous cannabis use (21, 24). Interestingly, some cases also report elicitation of allergic symptoms on passive smoke exposure or indirect skin contact (7, 14-19). In general, symptoms are not limited to the route of exposure, for example, cannabis smoking can induce respiratory symptoms but can also trigger cutaneous and gastro-

intestinal symptoms. Although the majority of reports on cannabis allergy comprise recreational cannabis users, there is evidence that work-related cannabis contact such as seen in in laboratory and police personnel (15, 25-28), hemp and cannabis factory workers (29, 30) could also elicit type 1 hypersensitivity reactions going from mild local reactions to life-threatening anaphylaxis.

Finally, some Indian (31), Japanese (32), American (33, 34) and southern European (6, 35) research focused on possible cannabis pollen related allergy_indicating that cannabis pollen exposure can also manifest an hay fever-like syndrome. Although many different exposure routes have been known to illicit allergic symptoms, little to nothing is known about the sensitization routes of cannabis allergy. It could be speculated that respiratory and cutaneous contact might both be important as the majority of recreational cannabis users smoke and roll their joints.

Concerning the prevalence of immediate type hypersensitivity reactions to cannabis, only one study explored this feature; Larramendi et al. (9) found that around 0.3% of 544 patients attending their allergy clinics for respiratory or cutaneous symptoms were sensitized to cannabis (skin prick test positive for a crude cannabis extract) and had allergic symptoms on cannabis exposure. Whether this can be extrapolated to other populations in other regions remains elusive.

Some reports also speculate on delayed type hypersensitivity reactions to cannabis. Watson et al. found that cannabis, especially the cannabinoids, can induce nonimmediate contact dermatitis in an experimental animal-model (36). Nevertheless, contact dermatitis has also been described in an in vivo setting (10, 37).

Aside from the above described hypersensitivity reactions it is important to stress that cannabis smoking can, often done without the use of a filter, also induce non-specific bronchial hyperresponsiveness and other respiratory symptoms like tobacco smoking (38). In addition, one of the biochemical consequences of cannabis ingestion either by smoking or eating is a conjunctival injection mimicking conjunctivitis (39). On the other hand, cannabis farms and plantations often use a large number of pesticides and other irritable substances and are often

147 located in poorly ventilated, hot and humid environments which are ideal for fungal
148 proliferation and in itself are also likely to cause both respiratory and cutaneous irritability not
149 always linked to an allergic cause (40-44). Thus, it can be highly challenging to differentiate
150 symptoms mediated by allergy from nonspecific irritability in these instances.
151
152 Finally, cannabis-related symptoms due to byssinosis (29, 45-50) fungal sensitizations but also
153 infections have been reported (51-53) but are outside of the scope of this article.
154
155
156 *2.2 Plant-food cross-reactivity and the cannabis allergy profile*
157
158 Apart from the symptoms reported on direct or indirect cannabis exposure, an increasing
159 number of reports outline mild to severe plant-derived food allergies associated with cannabis
160 allergy, see figure 2. The first reports of alleged cannabis associated allergies originate from
161 southern Europe; Gamboa et al. (7), described this putative association in a 28-year-old male
162 cannabis smoker who, following a cannabis allergy, experienced anaphylaxis on ingestion of
163 pepper, fig and tomato, contact urticaria with peach peel and an oral allergy syndrome with
164 almond, eggplant and chestnut. Later on, Larramendi et al. (8) also reported an association
165 with tomato allergy. Armentia et al. confirmed this association with tomato and suggested an
166 association with tobacco allergy as well (54). Subsequently, cannabis allergy appeared to be
167 associated with symptoms on ingestion of hazelnuts, walnut, peanut, maize, nectarines,
168 cherries, kiwi, avocado, apples but also wine, beer and on latex exposure (11, 14, 16, 55).
169

170 An interesting observation is that virtually all reports relating cannabis allergy and plant-food
171 allergies mainly stem from European research. The most frequent cause of plant-food allergy
172 in north-western Europe is the pollen-food syndrome, mostly eliciting symptoms limited to the
173 oropharyngeal cavity (Oral allergy syndrome (OAS)) (56). However, the reported symptoms
174 after cannabis related plant-food ingestion are often more severe, generalized and comprise
175 different food sources then traditionally seen in the pollen-food syndrome. We found that
176 almost half (45%) of our cannabis allergic population (n=120) reported severe and generalized
177 plant-food allergies going up to 71% in patients suffering anaphylaxis to cannabis (19). At this

time, it appears that the majority of cannabis related plant-derived food allergies could be due to nonspecific lipid transfer proteins (nsLTPs) allergy, as these proteins are highly allergenic and cross-reactive and as it has been demonstrated that nsLTPs can elicit both a cannabis allergy (Can s 3, the nsLTP present in *Cannabis sativa*) and multiple food allergies (Pru p 3-the nsLTP present in peach, Mal d 3-the nsLTP present in apple etc.) (7, 19, 54, 57). The topic of nsLTP-allergy and Can s 3 will be further elucidated in the proteomics section below. Additionally, one in three cannabis allergic patients reported cofactor mediated reactions to plant-foods with cofactors defined as use of non-steroidal inflammatory drugs (NSAIDs), alcohol intake or physical exercise. On the other hand, de Silva et al. (58) report on a case in which cannabis itself is put forward as a possible cofactor in a history of wheat-mediated anaphylaxis.

The fact that the overseas reports like Tessmer et al. (12) and Nayak et al. (13) did not observe an association between cannabis allergy and plant-food allergies as found in the European studies raises the interesting question whether this difference is due to a reporting bias or indicates that cannabis allergy can express distinct allergy profiles in different geographical regions.

Finally, we were the first to look deeper into the profile of cannabis allergy showing that in a northwestern European population, the majority (84%) of cannabis allergic individuals are sensitized to pollen (mostly birch, to a lesser extend also timothy grass) but 72% is also sensitized to nsLTPs. These nsLTP-sensitizations have been linked to Can s 3, the nsLTP of *Cannabis sativa*, and thus are a possible cause and explanation for the reported plant-food cross-reactivity (19).

3. PROTEOMICS

Due to the growing social, medical and occupational exposure to cannabis, the frequency of allergic reactions increased and also the responsible allergens are coming more and more in focus. The best studied and characterized cannabis protein in this context is the 9-kDa heat- and acid-stable non-specific (ns) lipid transfer protein (LTP), which is responsible for dissolving, binding and shuttling of monomeric lipids between cell membranes. The nsLTPs are present in

the whole plant kingdom and belong together with chitinases and pathogenesis related (PR)-10 proteins to the group of defense-related proteins. The nsLTP of cannabis was initially identified and named Can s 3 by Gamboa et al. (7). Further studies described several cross-reactivities i.e. especially with latex (54, 59), tomato (8, 9, 14, 54), peach, apple, banana (14, 18) and tobacco (54). At least with the identification of the complete mature Can s 3 sequence it was possible to produce a recombinant Can s 3 (rCan s 3) in *E.coli* (57). The purified protein allowed sIgE-measurements in sera after binding of the expressed protein to streptavidin-ImmunoCAP. Cross-reactivity between rCan s 3 and the nsLTP of peach (Pru p 3) was confirmed with IgE-inhibiton experiments (57). At the moment this variant (Can s 3.0101) is the solely cannabis allergen in the official WHO/IUIS Allergen nomenclature list.

Although the knowledge about potential cannabis allergens is still in its infancy, a recent study by Nayak et al. (13) shed some light on the matter. With the help of several IgE-immunoblot experiments they identified two promising allergen candidates. The first one was the 23-kDa oxygen evolving enhancer protein 2 (OEEP2) which displayed IgE-reactivity in eight out of their 23 skin prick test-positive patient sera (34.8%) tested. The second one was a 50-kDa ribulose-1,5-bisphosphate carboxylase oxygenase (RuBisCO) which displayed IgE-reactivity with a frequency of 56.5% in these sera. In contrast to OEEP2 where no additional knowledge about its allergic function exists so far, further studies have already suggested that RuBisCO is an allergen in spinach and tomato (60), in chickpea (61) and also in cashew nut, pistachio and pink peppercorn (62). Due to the many observed cross-reactivities between cannabis and fruits and latex as well evidence for the involvement of a “Bet v 1-like” allergen or a pan allergen like profilin is also possible but still needs confirmation when more recombinant cannabis protein components will be available for IgE-binding tests.

4. DIAGNOSTICS

As for other allergies, the diagnosis of cannabis allergy starts with a precise and thorough anamnesis focusing on the symptoms experienced during exposure, the type of exposure, the timeframe during which symptoms appear and subsequently disappear but also the presence of other environmental factors with the potential of eliciting allergic symptoms. When a suspicion of a cannabis allergy arises from the patient’s history, different in vitro and in vivo diagnostics can be used to support a cannabis allergy diagnosis.

4.1 in vivo diagnostic tests

The golden standard in allergy diagnosis remains the challenge test in which the perceived culprit, in our case cannabis, is given to the patient in a controlled setting. However, cannabis challenges are hampered by several factors. First of all, the majority of countries has a strict policy making the possession and use of cannabis products illegal. It goes without saying that performing challenges, in these cases, is impossible. On the other hand, multiple studies have addressed the issue of cannabis induced bronchial hyperresponsiveness/bronchodilation. Although there is some conflicting data, multiple studies suggest (63-65) that inhalation of cannabinoids can induce a short-term bronchodilation but cannabis smoking (with or without tobacco) is associated with both acute and chronic bronchoconstriction resulting in a decreased ratio of forced expiratory volume and forced vital capacity (FEV_1/FVC) (38, 65). These factors indicate that, even when the legal issues are put aside, the reliability of a cannabis challenge remains uncertain, fueling the need for other more accessible and reliable diagnostics.

Most initial reports on an immediate type cannabis hypersensitivity used non-standardized diagnostic techniques such as prick-prick tests with crude cannabis products such as leaves, seeds and buds to verify the presence of a cannabis allergy (4, 8-11, 22, 23). Although easily performable and accessible, this technique is not validated, very difficult, if not impossible, to standardize and therefore not reliable. Another possibility is to perform skin prick tests with prepared cannabis extracts (5, 7, 12, 13, 20, 34, 54, 66). These extracts can be better standardized and one can either choose to use a crude extract (of flower, bud, leave or a combination of the latter) or to concentrate allergenic components such as Can s 3 (14, 17-19). Yet other reports focused on skin tests using specific cannabis pollen extracts (33, 35).

4.2 In vitro diagnostic tests

Another easily performed diagnostic is a specific IgE assay. Hence, multiple reports have described the use of specific IgE quantifications for cannabis using either crude cannabis/hemp extracts or purified/recombinant components (4, 7, 9, 13, 14, 17, 19, 22, 23, 35, 54, 57). The

advantage of a sIgE assay is that it's safe, easily accessible, can be performed on stored patients' sera and is relatively cheap.

An additional *in vitro* technique is the basophil activation test (BAT). It has been suggested that the BAT exhibits better specificity than the sIgE assays as it is an ex vivo technique that needs cross-linking on the basophil membrane to produce a positive result whereas sIgE assays only detect IgE without looking at its function. BATs for cannabis allergy have been used successfully in a number of reports (4, 7, 14, 17, 19).

So, it appears that different diagnostic techniques have been developed and implemented for cannabis allergy but the test availability and performance often remain a question to be resolved. Firstly, the only test which is presently available on the market is the specific IgE (industrial) hemp assay. This test uses a crude hemp extract with the ImmunoCAP technique and is provided by Thermofisher Scientific (Uppsala, Sweden) but is available for research purposes only (RUO). Secondly, only a handful of studies explored diagnostic performances showing that the sIgE hemp is a sensitive test (82%) but its use is limited by a poor specificity (32%) (19). Rihs et al. found a similar performance for a streptavidin ImmunoCAP assay with a crude cannabis extract (54, 57) and both Larramendi and Armentia et al. found a significant number of clinically irrelevant positive skin prick tests i.e. a lower specificity for a crude cannabis extract as well (9, 54). Then again, the sIgE rCan s 3 assay has a better specificity (87%) but is less sensitive then the above-mentioned tests based on crude extracts. BAT with rCan s 3 and the SPT with a Can s 3 rich extract seem equally performant to the sIgE rCan s 3 (17, 19).

Overall, it is important to realize that all diagnostics based on crude cannabis products or extracts, whether it is a skin prick test, sIgE or BAT, can yield clinically irrelevant results, irrespective of the methodology used. Consequently, their specificity is rather low with positive test results in a significant number of cannabis tolerant individuals (9, 54), especially in multi-sensitized individuals (17, 19). On the other hand, the use of component-based diagnostics entails a risk of false negative results (in other words a lower sensitivity) as it is unlikely all cannabis allergic individuals are sensitized to a single component. Pragmatically, to circumvent these issues, Decuyper et al. propose to use a highly sensitive diagnostic based on a crude extract (such as the sIgE hemp) to screen for cannabis allergy where there is a clinical suspicion. In the case of a negative result, cannabis allergy seems highly unlikely. Nevertheless, each

positive result should be complemented by validated component-based diagnostics (such as the BAT, sIgE or SPT based on the Can s 3 component) to further assess the cannabis allergy risks. Figure 3 proposes a diagnostic algorithm based on our population's findings (19) which can be used in the setting of clinical symptoms suspicious of a cannabis allergy.

5. TREATMENT

Most reports advice avoidance of cannabis and all foods implicated in clinical cross-reactivity. There is however, increasing evidence of successful desensitization with and without the use of omalizumab for different nsLTP-mediated food allergies (67-69). Only a single case-report describes a successful desensitization for cannabis with the help of the anti-IgE agent, omalizumab (15). The patient involved is a young asthmatic police woman with regular occupational cannabis exposure resulting in anaphylaxis. After four months of omalizumab therapy no more anaphylaxis episodes were seen, only some cutaneous tingle remained on direct cannabis contact.

As there is a growing body of evidence to assume that at least part of the cannabis allergies and related food allergies are due to nsLTP sensitizations (7, 19, 70), there is hope that immunotherapy with cannabis/Can s 3 could prove to be an interesting therapeutic in the future.

6. FUTURE

What will the future hold? It would be interesting to further elucidate possible geographical differences in cannabis allergy profile as the question remains whether the association with Can s 3 and severe plant-food allergies is an isolated European phenomenon. Additional information on the routes of sensitization and possible allergic implications could also enhance our knowledge on the physiopathology of this type of allergy and subsequently help with patient guidance.

As challenges remain the golden standard of allergy diagnosis, another interesting question remains: what is the value of cannabis challenges? This could be explored in regions where

cannabis use is legalized. In addition, it would be valuable to see whether oral challenges with hemp seeds could serve as a good substitute in regions where cannabis is still illegal.

In addition, it would be interesting to explore which specific plant-food allergies are most common in cannabis allergic individuals. At the same time, it is clear that Can s 3 is an important cannabis allergen but most likely not the only one. Further exploration of the IgE-reactivity profile of cannabis allergy should give an interesting insight into the symptomatology and cross-reactive allergies reported.

7. EXPERT OPINION

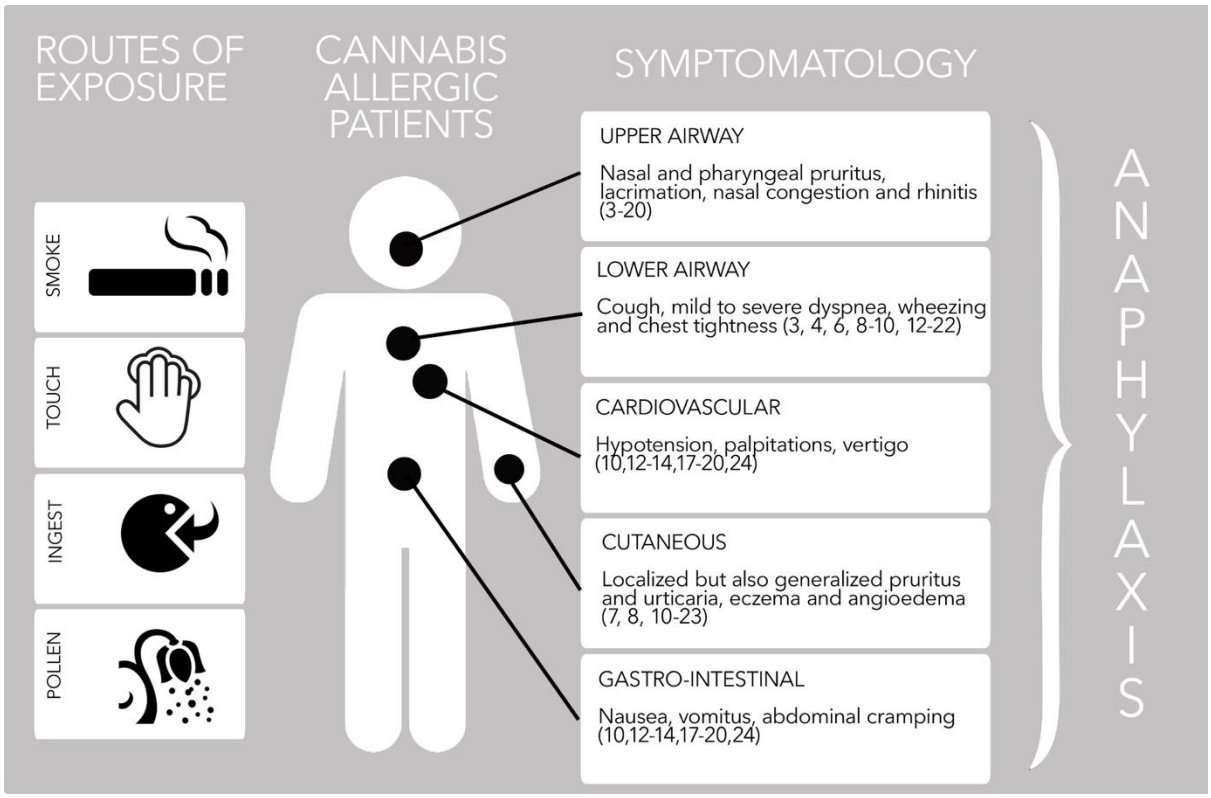
In conclusion, we feel that cannabis allergy is an allergy entity which might be more important than initially suspected. Although the current trend towards cannabis legalization as seen in Canada, the US but also different European countries, might improve the dialogue between cannabis user and their health care provider. On the other side, legalization is likely to induce a rise in the number of users and cause an increasing prevalence of cannabis allergy. This expected increase in frequency together with the severity of symptoms both on cannabis exposure and plant-foods, indicates that the quality of life of patients with a cannabis allergy can be significantly compromised. Hence, we feel it is of vital importance to become aware of the signs of cannabis allergy, the possible relation with nsLTP-related allergies as well as the reliability of the available cannabis diagnostics. As current research shows, the most accessible tests such as prick-prick tests and other crude-extract based techniques often have a very good sensitivity but the disadvantage of a low specificity. On the other hand, component-based techniques show good results but might not be readily available in each center. Therefore, we would advise the combined use of a standardized crude-extract based test such as sIgE hemp or a SPT (extract of flower, bud, leave or combination of the latter) together with component-based diagnostics such as a sIgE or SPT Can s 3 where available. Currently, the only treatment option for confirmed cannabis allergy is the avoidance of all cannabis and cannabis-containing products as well as avoidance of the plant-food products which have been known to elicit allergic symptoms in that specific patient.

Future research should lift the veil on the true prevalence and clinical profile of cannabis allergy as these features will give insight to the magnitude of the problem and are likely to impact the performance of diagnostic testing. More and more, cannabis is also incorporated in medical

products such as CBD oil and others. It would be interesting to look at the allergy potential of these types of products as well. Finally, elucidation of the importance of new cannabis allergens and the prospect of new treatment options such as immunotherapy for both the cannabis and associated plant-food allergies could also significantly improve the quality of life of patients implicated.

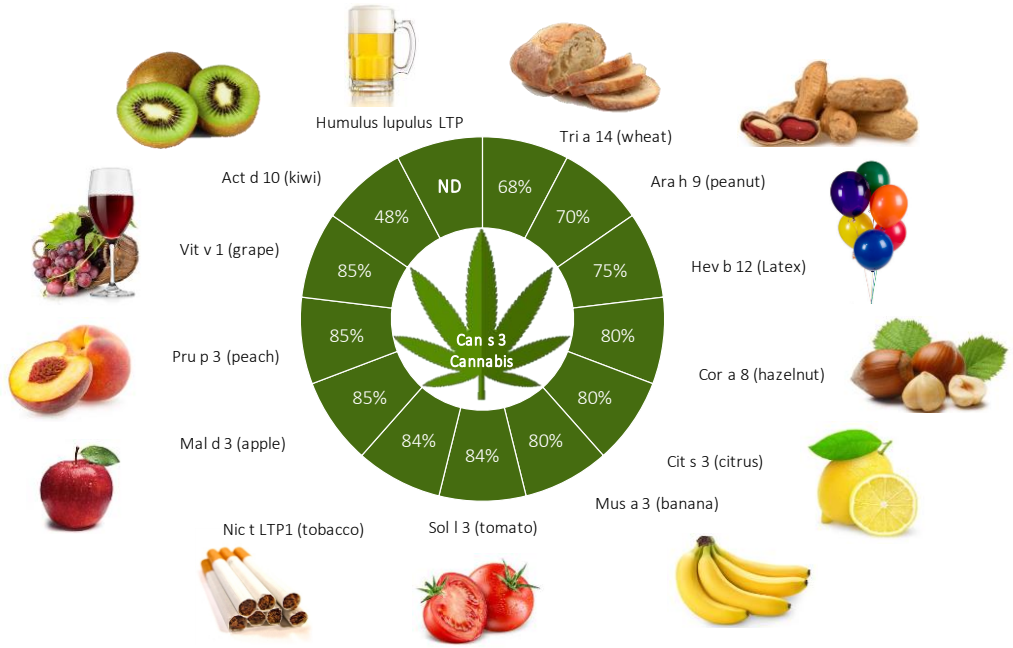
FIGURES

FIGURE 1



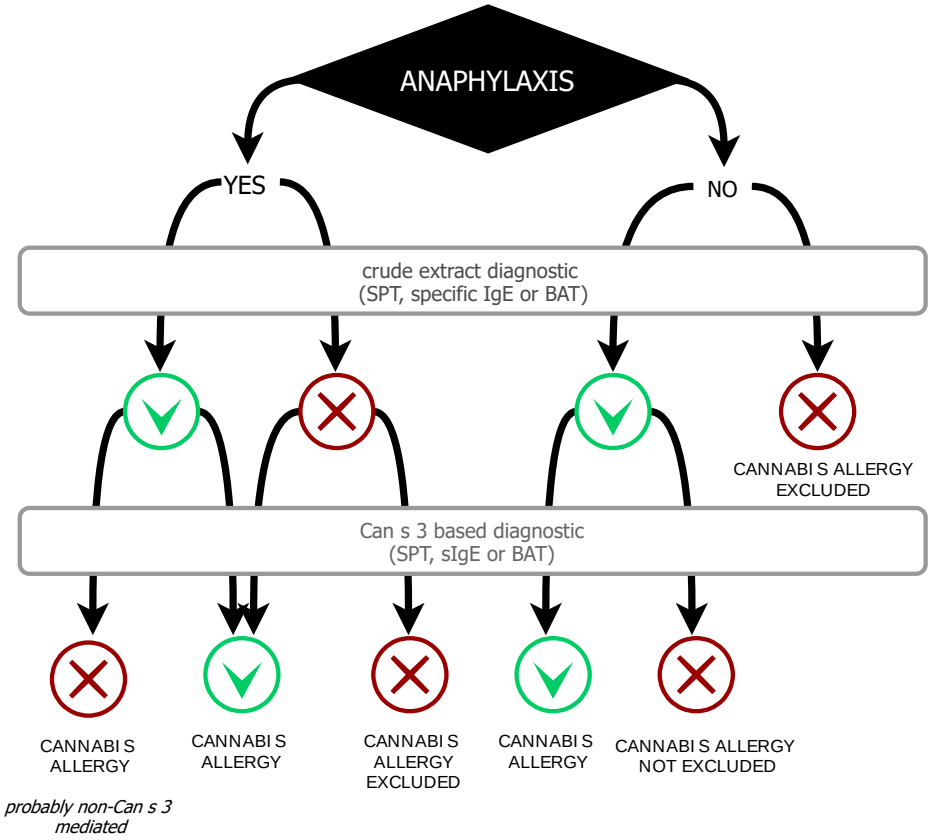
Overview of cannabis allergy symptomatology and possible routes of exposure. Numbers correspond to reference numbers in reference list.

FIGURE 2



Adapted from (71) Tri a from Triticum aestivum, Ara h from Arachis hypogeae, Hev b from Hevea brasiliensis, Cor a from Corylus avellane, Cit s from Citrus sinensis, Mus a from Musa acuminate, Sol l from Solanum lycopersicum, Nic t from Nicotinia tabacum, Mal d from malus domestica, Pru p from prunus persicae, Vit v from Vitis vinifera, Act d from Actinia deliciosa and Can s from Cannabis sativa. ND= no data.

FIGURE 3



Diagnostic algorithm based on findings from (19) SPT= skin prick test, BAT= basophil activation test, Can s= Cannabis sativa.

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