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Dr. Sussman is a Professor of Medicine in the Division of Clinical Immunology and Allergy at University of Toronto. His research includes the characterization of marijuana allergy and allergens, which has become more relevant in recent years with its legalization and increased medicinal use. His previous research focused on natural rubber latex allergy. Dr. Sussman recognized and reported some of the first cases of latex allergy, which eventually lead to widespread declines in latex allergy

AN OVERVIEW OF CANNABIS ALLERGY

INTRODUCTION

Cannabis refers to a genus of annual, herbaceous, dioecious flowering plants that are members of the family *Cannabaceae*, which include about 102 plant species.[1] Although there is much debate, the most common taxonomy is that the genus *Cannabis* comprises one species, *Cannabis sativa* L (*C. sativa*)., which includes the highly polymorphic subspecies *sativa,* and *indica*.[22]

Hemp and cannabis both refer to the same species *C. sativa*; however, there is important distinction between the two. Whereas hemp (fiber-type) is grown for its cellulose-rich fiber in the stem, cannabis (drug-type) is cultivated for its flowers where the glandular trichomes produce the psychoactive delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC provides the analgesic and relaxing effects of cannabis, whereas CBD produces other effects such as antiemetic and soporific properties. Researchers have used the THC content to define *C. sativa* subspecies *sativa* as containing less than 0.3% THC in dried flowering tops of female plants and *C. sativa* subspecies *indica* as containing ≥0.3% THC.[3] This threshold has been used by regulatory bodies to legally differentiate hemp plants (<0.3% THC) and cannabis plants (≥0.3% THC).

Canada legalized the production, distribution, sale and non-medical use of cannabis for adults in October 2018. Recent data from nation-wide surveys show that approximately 6.2 million people aged 15 or older, or 20% in this age group, reported using cannabis in the past 3 months.[4] which represents an increase from 14% before legalization. Cannabis can be used and/or ingested in a variety of forms including capsules, oils, dried flower, vaporization and through the consumption of edibles. With the increased use of recreational cannabis in Canada, it is expected that there will be a concomitant increase in cases of cannabis hypersensitivity.

CLINICAL MANIFESTATIONS OF CANNABIS ALLERGY

Since the first description of reactions to cannabis-containing cigarettes in 1971, there have been numerous reports of cannabis hypersensitivity associated with different routes of exposure and a wide-range of symptoms.[5-11] Most case reports described an immediate onset of upper airway symptoms such as rhinitis and conjunctivitis after smoking cannabis in recreational users.[6-10] There has also been evidence suggesting that long-term use of cannabis can result in chronic airway inflammation and exacerbate existing asthma, despite its mild and short bronchodilator effect.[12] Indeed, there are several reports of patients experiencing the immediate onset of lower respiratory symptoms such as dyspnea, coughing, wheezing and chest tightness with recreational cannabis use. Gastrointestinal symptoms such as vomiting and abdominal cramps can also occur especially after ingestion of marijuana edibles.[7] In regions where *C. sativa* is cultivated or wild cannabis plants exist, environmental exposure to *C. sativa* pollen, which typically peak in summer months, has also been implicated in seasonal allergic rhinoconjunctivitis.[11] Contact urticaria has also been described in patients who have repeated direct contact with the plant.[6,13,14] In general, the symptoms of cannabis allergy can be variable and are not limited by the route of exposure. Not surprisingly, anaphylactic reactions from recreational cannabis use have been reported.[7,15] There is also one report of cannabis-dependent exercise-induced anaphylaxis where the patient reported allergic reaction only when he engaged in rigorous activity after smoking cannabis.[9] Hemp seed ingestion can result in anaphylaxis in patients sensitized to cannabis from recreational cannabis use.[16] It is important for patients who have a history of cannabis allergy to be educated on the risk of hemp seed as a potential food allergy.

Occupational exposure has also been recognized as a risk of sensitization to cannabis.[17,18] There also have been several reports of workers in cannabis facilities and forensic laboratory personnel developing allergic symptoms including rhinitis, urticaria and angioedema from cannabis exposure in the work environment despite having no history of recreational cannabis use.[13,14,19] A recent study involving law enforcement officers with a reported history of cutaneous or respiratory symptoms from work-related cannabis exposure was unable to establish a causal relationship between cannabis allergy and symptomology.[20] This potentially suggests that a non-immune mechanism exists for some of the symptoms experienced with cannabis exposure or that the relevant cannabis allergens implicated in occupational exposure remain yet to be identified.

CANNABIS ALLERGENS AND CROSS-REACTIVITY

Although cannabis allergy has long been recognized, it is only recently that investigations into the allergenic component have been reported. Can s 3, a non-specific lipid transfer protein (ns-LTP) that belongs to the pathogenesis-related (PR)-14 group, is the first IgE-binding allergenic protein identified (**Table 1**).[6,8,21]

This protein is believed to be the major allergen in the European population. In a Spanish study, sensitization to Can s 3 was observed in 124 of 130 patients with primary cannabis allergy and a similar trend was also observed in another European study.[22,23] Since ns-LTP is ubiquitous throughout the plant kingdom, sensitization to Can s 3 could lead to secondary plant-derived food allergies as reported in the literature. This pattern of cross-reactivity has been termed "cannabis-fruit/vegetable syndrome".[23,24] The foods most commonly implicated are allergies to peach, banana, apple, nuts, grapes, cherry, and tomato (**Figure 1**).

The symptoms due to cannabis-fruit/vegetable syndrome

Allergen	WHO/IUIS allergen nomenclature	Examples of homologues	Reference Source
Profilin	Can s 2	Bet v 2, Pru p 4, Sola i 1	21
Non-specific lipid transfer protein	Can s 3	Pru p 3, Cor a 8, Hev b 12, Ara h 9, Sola i 3, Vit v 1	6, 8, 21
Oxygen-evolving enhancing protein 2	Can s 4	-	27
Pathogenesis-related protein 10	Can s 5	Bet v 1, Mal d 1, Ara h 8	26
Ribulose-1,5-bisphosphate carboxylase/oxygenase	-	-	27

Table 1. Cannabis allergens. Adapted from Decuyper et al.[24]

are typically more severe as compared to those observed in Bet v 1-related pollen food syndrome. This is likely because ns-LTPs are resistant to gastroduodenal proteolysis and thermal processing. Cross-reactivity with Can s 3 has also been shown to extend to latex and tobacco (**Figure 1**).[25] The cannabis homologue of Bet v 1 and *C. sativa* profilin, now termed Can s 5 and Can s 2 respectively, have also been demonstrated to play a role in cannabis allergy.[26]

Unlike the European investigations, the first study on *C. sativa* allergen in the North American population did not show the same pattern of sensitization.[27] Rather than Can s 3, the predominant IgE-binding allergens were found to be ribulose-1,5-bisphosphate carboxylase oxygenase (RuBisCO) and oxygen evolving enhancer protein 2 (Can s 4), both of which are involved in photosynthesis.[27] Interestingly, in line with the different pattern of sensitization, there is also a lack of association between cannabis allergy and plant-food allergies in the North American population.[7,27,28] Whether this is related to geographical differences in *C. sativa* resulting in different clinical phenotypes is unknown. A more recent study did detect Can s 3 sensitization in a small number of Canadian patients with cannabis allergy although the exact prevalence remains to be eludicated.[29]

DIAGNOSTICS AND MANAGEMENT

As with other allergies, the diagnosis of cannabis allergy relies mainly on an accurate history of the allergic reaction. However, several important factors can make this challenging. Although cannabis is now legalized in Canada, patients may not be forthcoming about their cannabis use due to social stigma and taboos. Another challenge is that cannabis smoking or ingestion can result in side effects such as conjunctival injection and panic attacks that can be misattributed as allergic reaction. For workers in cannabis facilities or law enforcement officers, occupational exposure to pesticide, organic dusts or fungi from handling or processing cannabis can also elicit or mimic allergic symptoms.

Currently, there is no standardized or commercially available diagnostic test for cannabis allergy. Even direct provocation testing, which is the gold standard in allergy diagnosis, has unclear reliability given the paradoxical short-term bronchodilator effect of cannabis. For skin prick

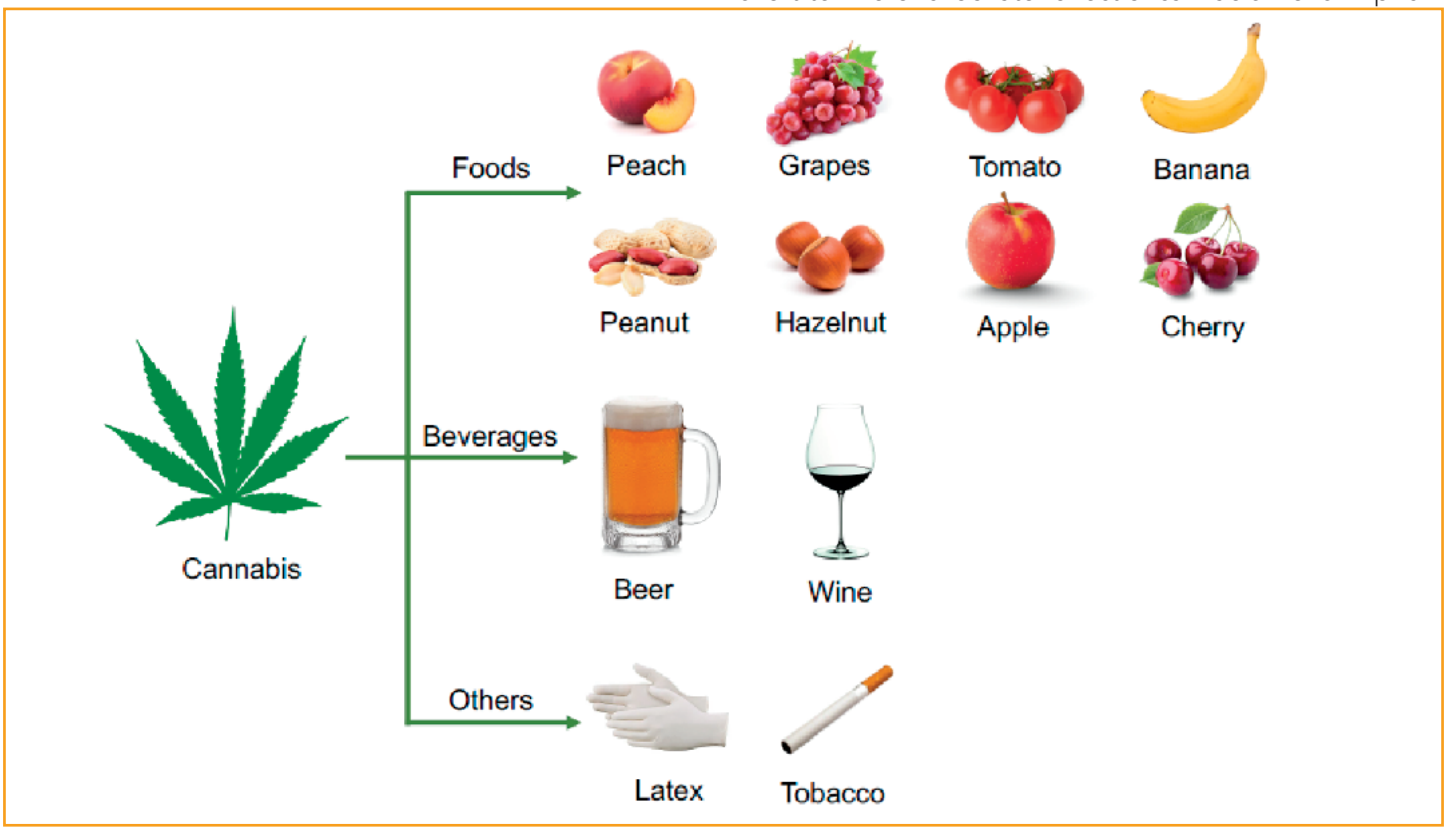

Figure 1. Sensitization to C. sativa can lead to cross-reactivity with a vaierty of foods, beverages, latex and tobacco due to the ubiquitous non-specific lipid transfer protein. This is termed "cannabis-fruit/vegetable syndrome". Adapted from Decuyper et al.[24]

testing, most case reports in the literature use prick-prick tests with crude cannabis or non-standardized cannabis extracts for diagnosis.[30] This approach could potentially be confounded by variable results depending on the composition of the source material or varieties of *C. sativa* used. A recent European study showed that Can s 3-based testing is the most effective and reliable.[30] Although not commercially available, skin prick testing with a Can s 3 enriched extract and specific IgE testing to recombinant Can s 3 were both demonstrated to have positive and negative predictive value of around 80% and 60%, respectively.[30] However, whether these results apply to the North American population, which seems to have different pattern of sensitization, remains unknown. Specific IgE testing to hemp, which is commercially available, can be considered a proxy although it lacks specificity (32%).[30] Certainly, more research in the development of diagnostic testing, targeted towards the North American population is needed.

With regards to management of cannabis allergy, strict avoidance when feasible is the only available treatment. There is one case report in the literature describing the use of omalizumab for the treatment of cannabis allergy in a patient who had regular occupational exposure to cannabis resulting in anaphylactic reactions.[31] After 4 months of therapy, the patient was able to tolerate exposure to large amounts of cannabis with only mild cutaneous symptoms. Successful immunotherapy treatment for cannabis allergy has also been previously reported.[32] However, the lack of a standardized extract along with uncertain efficacy and safety data make it challenging to foresee broad application particularly for recreational cannabis users.

CONCLUSION

With the legalization of cannabis, there is likely to be a continuing trend of increased numbers of recreational users and an increased prevalence of cannabis allergy. Occupational exposure is also recognized as a risk for cannabis sensitization. Diagnosing cannabis allergy remains challenging due to a lack of standardized testing, however, there is hope that commercially available testing will be available in the near future with a better understanding of the allergenic components. An important question to answer concerns the role that geographical differences may play in cannabis allergy as shown by the distinct sensitization and clinical phenotypes between North American and European populations, which will most certainly impact the diagnosis and management of cannabis allergy. As there are numerous strains and varieties of *C. sativa.*, it is unclear whether the various strains have different allergenicity and more research is needed in this regard. Component-specific cannabis extracts including Can s 3 are not yet available as allergen extracts. Research is ongoing using component-specific diagnostics.

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