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Cannabis-related allergies: an international overview and consensus recommendations

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Cannabis Allergy: an international review

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The following authors wrote specific sections of the document; Isabel Skypala, Samira Jeimy Hannelore Brucker, Ajay Nayak, Lori Connors, Amin Kanani, Ludger Klimek, Ryan Lo, Kevin Murphy, Anil Nanda, Jill Poole, Jolanta Walusiak-Skorupa, William Silvers and Didier Ebo. The figures were created by Ine Decuyper and Didier Ebo. All the sections of the paper were merged and edited into one cohesive document by Isabel Skypala, supported by Hannelore Brucker and Samira Jeimy. The final version of the paper was created after the input of expert opinion and extensive critique from Jonathan Bernstein, Gordon Sussman, Joanna Zeiger, Richard Goodman and Anne Ellis, and all of the contributing authors. Anne Ellis, William Silvers and Isabel Skypala as representatives of the three allergy societies involved in the Cannabis Allergy Interest Group (Canadian Society of Allergy & Clinical Immunology, American College of Asthma, Allergy and Immunology, and European Academy of Allergy & Clinical Immunology), ensured the paper was reviewed by each of these organisations prior to submission.

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Abbreviations

BAT: basophil activation test

Bet v: *Betula verrucosa*

CAIG: Cannabis Allergy Interest Group

CBD: Cannabidiol

CCDs: cross-reactive carbohydrate determinants

CRD: component resolved diagnosis

MAT: mast cell activation test

pMAT: passive MAT

nCan s: native *Cannabis sativa* component

NPV: negative predictive value

nsLTP: nonspecific lipid transfer protein

PPV: positive predictive value

rCan s: recombinant *Cannabis sativa* component

rPru p 3: recombinant ns-LTP from peach (*Prunus persica*)

THC: Tetrahydrocannabinol

sIgE: specific IgE antibody

SPTs: skin prick tests

WE: whole extract

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Abstract

Cannabis is the most widely used recreational drug in the world. *Cannabis sativa* and *Cannabis indica* have been selectively bred to develop their psycho-active properties. The increasing use in many countries has been accelerated by the COVID-19 pandemic. Cannabis can provoke both type 1 and type 4 allergic reactions. Officially recognised allergens include a pathogenesis-related class 10 allergen, profilin and a non-specific Lipid Transfer Protein. Other allergens may also be relevant, and recognition of allergens may vary between countries and continents. Cannabis also has the potential to provoke allergic cross-reactions to plant foods. Since cannabis is an illegal substance in many countries, research has been hampered, leading to challenges in diagnosis since no commercial extracts are available for testing. Even in countries such as Canada, where cannabis is legalized, diagnosis may rely solely on the purchase of cannabis for prick-to-prick skin tests. Management consists of avoidance, with legal issues hindering the development of other treatments such as immunotherapy. Education of healthcare professionals is similarly lacking. This review aims to summarise the current status of cannabis allergy and proposes recommendations for the future management of this global issue.

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Introduction

Approximately 192 million people, 3.9% of the global population use *Cannabis sativa* (Can s) for medical and/or recreational purposes.[1-4] The legal status of cannabis varies, but one recent key driver of consumption is the COVID 19 pandemic, with rising intakes during lockdown, especially when self-isolating.[5-7] Adverse effects associated with cannabis use include respiratory, dermatologic, gastrointestinal and cardiovascular symptoms and mental health issues.[8] These effects are often ignored or overlooked in favor of the positive benefits of reduced anxiety, improved sleep, pain relief, and decreased nausea.[9] First described 50 years ago, allergic reactions to cannabis can present with symptoms of rhinitis, conjunctivitis, asthma, cutaneous reactions due to industrial contact and anaphylaxis to hemp seed.[10-12]. As well as exposure through ingestion, inhalation, or skin contact, cannabis can also provoke occupational allergies.[13]

Rising consumption underlines the need for greater awareness of the spectrum of cannabis allergy, its diagnosis and management. In recognition of this unmet need, members of the American College of Asthma Allergy and Immunology (ACAAI), the European Academy of Allergy and Clinical Immunology (EAACI) and the Canadian Society of Allergy and Clinical Immunology (CSACI) formed a joint Cannabis Allergy Interest Group (CAIG) (Appendix I). This group developed a plan of action, which includes a survey of the membership of the three societies, the development of an international registry and biobank, and the publication of this joint paper on cannabis allergy (Figure 1).

Background and Epidemiology of Cannabis Use

Cannabis has been used for five millennia for spiritual, medicinal and recreational purposes, with recent archaeological evidence of ritualized consumption dating from 500 BC.[14,15] Cannabis use varies worldwide and rates of consumption do always correlate with legalization status; the illicit use of cannabis can be similar to that reported in countries where it has been decriminalized or fully legalized. Although there is some variation between countries and continents, the highest use is in young adults, although the age range of cannabis users is increasing and is projected to continue to do so.[16-18]

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United States

Cannabis was prohibited in the United States by the 1937 Marijuana Tax Act, and further restricted in 1970 following its classification as a Schedule I substance.[19] In 1996 medical cannabis was legalized in California, with recreational cannabis legalized in Colorado and Washington states in 2012, Colorado being the first to roll out commercial sales for adult non-medical use in 2014. Currently, 36 states, and the District of Columbia (DC), have moved to legalize medical cannabis, 15 states, and DC, legalizing recreational cannabis, and 16 states decriminalizing its use.[20] However, cannabis remains illegal under US Federal Law.[21] In the United States, roughly one in 7-8 individuals has engaged in medical cannabis use.[22] Since the early 2000s, there has been little change in adolescent use, but an increase in adult cannabis use, especially in those aged 50 years and over.[23] Cannabis use across most sociodemographic groups is more common in states where it has been fully legalized, whereas the effect of medical legalization is heterogeneous by age and socioeconomic status[24]. A study evaluating cannabis attitudes and patterns of use among followers of the Allergy & Asthma Network, reported that 88/489 (18%) of respondents used cannabis, 66% for medical reasons[9]. Just over half (58%) of these individuals reported asthma, especially uncontrolled asthma, but asthma control, quality of life, and frequency of exacerbations were no different in respondents with asthma who did and did not report cannabis use. Of the non-cannabis users, 2.5% reported cannabis allergy.

Canada

In Canada, the Cannabis Act of 2018 legalised cannabis, giving it a similar status to that of alcohol.[25] Cannabis use has been assessed since 1989 by the annual Canadian Cannabis Survey (Health Canada), and the quarterly National Cannabis Survey (Statistics Canada).[26-35] The prevalence of lifetime cannabis use has gradually increased from 23.2% (1989) to 45.3% (2019).[16,26] At the end of 2020, 20% of Canadians reported Cannabis use within the past 3 months, compared with 14% immediately preceding its legalization.[35,36] Surveys suggest 25% of Canadians consumed cannabis in 2020, mainly those aged 18-44 years with 7.9% reporting almost daily use.[9,36] Most Canadians consume cannabis via smoking (79%), followed by ingestion (52%), with the use of edible cannabis products increasing, and dried flower or leaf use decreasing.[34,36] It is reported that 14% of Canadians used cannabis for medical purposes in the

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249 past year, with 321,539 active medical cannabis federal license holders in Canada as of December
250 2020.[34,37] A cross-sectional survey of adults in a Canadian allergy clinic found that 107/179 had a
251 lifetime past use of cannabis, with 42/107 reporting symptoms upon exposure that may be
252 explained by cannabis allergy[38].
253
254 *Europe*
255 Cannabis is the most widely used illicit drug in Europe, with a higher prevalence in
256 Mediterranean and Central-Western European countries.[39] Some cannabinoids are approved for
257 medicinal use in some European countries, while in others the recreational use of cannabis has
258 been decriminalized.[40] In the 15-64 age group, approximately 90.2 million people (27%) in the
259 European Union have used cannabis at least once in their lifetime, ranging from over 33% of
260 adults in Denmark, France and the United Kingdom, to 8% or less in Bulgaria, Romania, Turkey
261 and Malta.[41 37] Long term trends show that, apart from Sweden, many countries have a modest
262 increase in prevalence, although only a small percentage (1.8%) of adults in the EU are
263 daily/almost daily users.[42,43] The lifetime prevalence of cannabis use in Europe is projected to
264 grow from 28.3% in 2015 to 42.0% in 2045, but 30 day use is projected to only increase slightly
265 (2.7% to 3.4%) accompanied by an increase in the age of users.[17]
266
267 **Medical Cannabis Use**
268 Medical cannabis generally refers to the use of cannabis to treat disease or alleviate symptoms.[44]
269 In ancient Chinese, Greek and Middle Eastern culture, cannabis was used for its psychoactive and
270 medical effects.[45] In western culture, there was more disease targeted treatment beginning in
271 the 19th century and cannabis was utilised by physicians world-wide in the pharmacopeia of the
272 time.[46,47] Regulation of the medical use of cannabis started in the 20th century, and the
273 widespread use and acceptance of medical cannabis often depends on its legal status in the
274 nation or state.[44] Medical cannabis is used in various preparations, including smoking, vaporizing,
275 ingestion of raw plant products, or consumption of capsules or oils in manufactured extracts. In
276 the US, 3 cannabinoids, dronabinol, nabilone, and cannabidiol (CBD) are approved for medical use
277 by the US Food and Drug Administration.[48] In Europe, some countries have introduced specific
278 laws to permit the use of cannabis preparations to treat the symptoms of severe diseases.[49] The

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extent of the possible medical uses of cannabis is quite exhaustive and include , multiple sclerosis, arthritis, epilepsy, some psychiatric conditions, and chemotherapy-induced nausea and vomiting in cancer patients.[50] The highest quality of evidence exists for its use in chronic pain spasticity and the anti-epileptic activity in the therapy resistant Dravet and Lennox-Gastaut syndromes.[44,51] The use of cannabis for pain relief may also be common; in one survey, over one third of Danish patients with spinal cord injury had tried cannabis at least once and 9% were current users, although most of these patients also used cannabis before their injury.[52]

Botany of Cannabis and proposed allergens

Cannabis belongs to the *Cannabaceae* family, can grow in diverse climates, and is found in most parts of the world. Cannabis is an annual herb, largely dioecious with separate male and female plants. It is easily recognized by the distinctive arrangement of leaves. The plant is marked by hair-like glandular projections called trichomes, which serve as a rich source of cannabinoids. *Cannabis sativa* and *Cannabis indica* (and to a lesser extent *Cannabis ruderalis*) are the most common botanical varieties, but there is significant diversity in the biological and vernacular use of terms to identify different strains.[53,54] This is largely due to the fact that since the 1970s, the plant has undergone significant selective hybridization and crossbreeding, leading to the development of strains with poorly characterized botanical backgrounds. Consequently, a wide variety of cannabis strains are in circulation, selected for their unique biochemical and mood-altering profile. However, genetic studies have shown that there is a merging of *Cannabis sativa* and *Cannabis indica* and that the separation of the two is becoming less common.[55] Another class of *Cannabis sativa* is hemp, the cultivars of which are grown specifically for industrial or medicinal use. It is unrelated to water hemp (*Amaranthus tuberculatus*) which is a dioecious plant native to North America.

Over 140 phytocannabinoids have been identified in cannabis, although only those with a terpenyl residue including geranyl (CBG-type), menthyl (CBD-type and THC-type), or prenylchromanyl (CBC-type) are present in any significant amount.[56-58] Delta-9-Tetrahydrocannabinol (THC) is the most well-known cannabinoid that leads to psychoactive effects and, due to selective cross-breeding, the proportion of THC in cannabis has risen from 5%

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to 15% or more, leading to increases in psycho-activity and adverse effects.[59,60] The US federal government defines cannabis with more than 0.3% THC as a Class I Controlled Substance. However, derivatives of cannabis containing less than 0.3% THC, such as CBD oil and hemp may be legal in some states or countries.[61]

Cannabis proteins can act as high-molecular weight allergens and contribute to type I allergic reactions.[62] Multiple cannabis allergens have been sequenced, four of which are accepted by the WHO/IUIS Allergen Nomenclature Subcommittee (www.allergen.org). (Table 1). Molecular analysis has suggested the presence of other diverse allergenic proteins in cannabis including ribulose-1,5-bisphosphate carboxylase-oxygenase (RuBisCo), adenosine triphosphate synthase, glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase, heat shock protein 70,[63] thaumatin-like protein,[64] peptinesterases and polygalactouranases.[65] Plant carbohydrates may also play a role in IgE-binding and perceived allergy, and glycoproteins that cross-react with other carbohydrates, known as cross-reactive carbohydrate domains (CCDs) may partly explain cross-reactivity.[63,66] Additional studies are needed to clarify the relative contribution of glycosylation sites on cannabis proteins to the allergic sensitization potential of the plant.

Links between Cannabis allergy and food allergy

The relevance of different cannabis allergens may vary, depending on geographical location, prior sensitization to food or/pollen, and other factors.[67] Non-specific Lipid transfer proteins are a common food allergen in Europe, and are stable to heat and digestion, thus provoking reactions to both raw and cooked plant foods.[68-74] Sensitisation to Can s 3, the nsLTP in cannabis, is a feature of European patients with cannabis allergy.[75,76] It was first shown in 2007 that a patient sensitized to the peach nsLTP Pru p 3 reacted to *Cannabis sativa*; further research confirmed that Can s 3 was a relevant cause of sensitization and reactions to other nsLTP, even via passive inhalation.[64,75,77-79] Thus *Cannabis sativa* could act as a primary sensitizing allergen, with a significant percentage of those allergic to cannabis reporting severe allergy to plant foods.[75,80-83] Due to cross-reactivity between nsLTPs, patients sensitized to Can s 3 may develop sensitization and relevant clinical symptoms to a wide range of fruits, vegetables and cereals, and also to wine, beer, *Hevea* latex and tobacco (Figure 2) .[68,81,82,84,85] A feature of reactions to nsLTP

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is that they can occur in combination with co-factors (exercise, non-steroidal anti-inflammatory drugs or alcohol).[72,83,86] *Cannabis sativa* may also act as a co-factor of reactions to foods in cannabis-allergic individuals.[87] Sensitization to the Bet v 1 homologous cannabis allergen Can s 5 occurs in European individuals with cannabis allergy, but it is not clear whether these patients also have Bet v 1-related food allergy, otherwise known as Pollen Food Syndrome (PFS) or Oral Allergy Syndrome (OAS). Similarly, it is also unknown how prevalent sensitisation is to other *Cannabis sativa* allergens such as the profilin Can s 2, the Oxygen-evolving enhancer protein Can s 4, or the Thaumatin-like protein, and whether they are relevant allergens in relation to food cross-reactions.[63,64,67]

Clinical manifestations of Cannabis allergy

Cannabis hypersensitivity spans the spectrum of allergic response and can provoke both type 1 and type 4 reactions.[38,88] Cannabis pollen and/or cannabis smoke has been implicated in allergic rhinoconjunctivitis, allergic keratoconjunctivitis, hypersensitivity pneumonitis, and exacerbations of asthma symptoms.[11,89] Additionally, patients may experience cutaneous reactions in the form of generalized pruritus, contact urticaria, angioedema, upper and lower respiratory tract symptoms and anaphylaxis from cannabis use. Early reports of allergic reactions were of contact dermatitis after touching cannabis leaves or flowers, and toxico-dermatitis after smoking hemp.[90,91] More recently, contact dermatitis has been described in a patient harvesting *Cannabis sativa* and *Cannabis indica*, which was proven by positive skin patch testing to the involved cannabis species.[88] A case report detailed the development of sensitization and occupational contact urticaria to cannabis in a forensic sciences technician due to regular and repeated handling of cannabis.[92] Erythema multiforme has also been associated with recreational consumption.[93] Anaphylaxis to *Cannabis sativa* with hemp seed ingestion, smoking, and injection have also been reported.[10,94,95] It is not only users or those at high occupational risk who may be affected by cannabis exposure; there are case reports of cannabis allergy, or allergies to foods which cross-react with cannabis, due to passive inhalation of cannabis smoke at home.[96,97] Exposure to cannabis has expected, but undesirable physiologic effects including conjunctival injection, sinus tachycardia, orthostatic hypotension, anxiety or panic reactions, and dysphoria. If

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reported, such symptoms should not be ignored or misattributed if the index of suspicion for a serious reaction or anaphylaxis to cannabis is high.[11]

Occupational Cannabis allergy

Cannabis varieties such as hemp contain very low or undetectable levels of THC and have been used for many years as an agricultural commodity and source of fiber, with the seeds used in food products. In recent years, occupational sensitization to cannabis has mostly centered on the cannabis exposures of law enforcement officers and forensic investigators.[92,98-100] However, increased access to cannabis for medicinal and recreational use has led to an emerging cannabis industry, currently valued at $11 billion, with a projected growth rate of approximately 15% through the next 5 years .[101] Consequently, a considerable workforce is now engaged in growing, processing and distributing cannabis for commercial use, thus allergic sensitization to cannabis is an emerging topic of interest.[12,13] However, little is known of the potential for occupational allergic reactions in those with close contact and prolonged exposure to the plant and its derived materials. The Colorado Department of Public Health and Environment (CDPHE), and the National Institute for Occupational Safety and Health (NIOSH), have identified multiple biological hazards in cannabis work environments with potential to drive allergic reactions.[102,103]

Most allergic symptoms observed from direct handling of cannabis are typically marked by respiratory symptoms, ranging from rhino-conjunctivitis to bronchial hyperresponsiveness and chest tightness.[13] Prolonged occupational exposure to hemp dust results in respiratory irritation, airflow obstruction and inflammation called 'byssinosis'.[104-106] Byssinosis is marked by severe bronchial hyperresponsiveness, but occurs in absence of any specific IgE antibodies, suggesting lack of allergic sensitization. High levels of endotoxin in occupational hemp dust exposures have been consistently associated with adverse respiratory outcomes in exposed workers.[107] Cutaneous reactions such as urticaria and angioedema are also commonly reported through occupational exposure.[88] Although these symptoms resemble those observed in symptomatic recreational cannabis users, cross-reactivity does not appear to be a driver of symptoms. For example, Can s 3, a mediator of cross-reactive allergies related to cannabis, has not been established as a relevant allergen in the context of occupational exposures.[13] Detailed studies

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into occupational cohorts are needed, including whether specific strains are more likely to provoke allergic reactions or if those with a previous allergic history have a higher rate of cannabis allergy.[108]

Other risks associated with Cannabis Consumption

Cannabis consumption presents a risk to immunosuppressed patients via exposure to microbiological contaminants, particularly when inhaled. Aspergillus has been isolated from cannabis samples.[109,110] In one observational study, the majority of cannabis users had antibody evidence of Aspergillus exposure, compared to a minority of controls.[111] There is also an association between cannabis use and sensitization to Alternaria. [112,113] Regarding the pulmonary effects of cannabis smoking on respiratory symptoms, a recent review found that, prevalence of chronic cough, sputum and wheeze were similar to those who smoke tobacco but the effects from habitual cannabis use on progressive obstructive lung disease and emphysema are less clear.[114]

Diagnosis

The most important test for diagnosing IgE-dependent cannabis allergy is the clinical history, although patients may be reluctant to admit consumption where cannabis use is legally restricted. Determining whether symptoms are attributable to cannabis is challenging, especially in pollen allergic individuals.[115] An example is a birch pollen allergic patient who experiences pronounced seasonal rhino-conjunctivitis while smoking cannabis outdoors during the pollen season. New-onset reactions to plant foods in teens and adults could also be linked to a cannabis allergy but establishing whether a food allergy represents cross-reactivity with a pollen allergen (e.g., the Bet v 1 homologue) or cannabis allergen (e.g., the cannabis ns-LTP Can s 3) may be difficult. Although younger patients may also be potentially exposed, cannabis allergy should be considered in those aged 16 years and over, presenting with symptoms of cough and wheeze indicating a new onset of asthma, or difficult to control existing asthma despite medication adherence.[116] The creation of a standardized intake form on cannabis-related questions can further guide the physician/healthcare professional, such as the one developed by the ACAAI.[117]

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After establishing the clinical history, it may not always be possible to undertake standard allergy tests. There are no commercially available extracts, so unstandardized prick-prick tests (PPT) with the buds, leaves or seeds of the cannabis plant is usually the only option, if available.[63,118] If possible, several different strains of the cannabis plant (sativa, indica and hybrid) should be used to ensure a wide variety of potential allergens are included.[108] Unfortunately, those sensitized to pollens or plant foods can have clinically insignificant positive results, due to ubiquitous plant proteins such as profilins, decreasing the specificity of the cannabis PPT test. An alternative option is to perform SPTs with pre-prepared cannabis extracts, which can be better standardized, and designed to concentrate known allergen components such as Can s 3.[75,82,115] Such extracts can achieve a negative predictive value (NPV) of 91%, but the positive predictive value (PPV) is low, around 50%, increasing to 80% in those reporting anaphylaxis and/or respiratory symptoms although the NPV is reduced to 58% (Table 2).[75] Unfortunately such extracts may not be available in routine clinical practice, and also the same issue of cross-sensitization may occur in those individuals sensitized to ns-LTP allergens.

Currently, there are no commercial sIgE tests for *Cannabis sativa* or *Cannabis indica,* and a possible alternative, the sIgE hemp assay using a crude industrial hemp extract (FEIA ImmunoCAP® Phadia Thermofisher Scientific, Uppsala, Sweden), is only available for research purposes (Table 2). Although the sensitivity exceeds 80% (Table 2), sIgE hemp is not a reliable diagnostic tool, because a significant proportion of positive results occur in cannabis-tolerant individuals due to sensitization to pollen and/or ns-LTPs. Although CCDs rarely trigger clinically irrelevant SPT results, they can decrease the specificity of sIgE tests due to their structural similarity to allergens originating from both taxonomically related and distant plants, e.g., cannabis, pollen, plant-derived foods, *Hevea* latex and Hymenoptera venom.[75,115,119] However, the specificity of sIgE hemp can be improved; using a cut-off of 0.02 for sIgE hemp-to-total IgE, achieves a specificity of 93% (95% confidence interval (CI), 85-98%).[120]

Molecular diagnostics using purified and/or recombinant (non-glycosylated) species-specific allergen components could be useful. However, a single component rarely covers the entire sensitization profile, and test results are influenced by age and/or population.[121] Although four

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cannabis allergens are officially recognized (Table 1), only Can s 3 merits the status of a major allergen. In some European regions, Can s 3 covers approximately 70% of the sensitization profile, but its value in the US or Canada is unknown.[75] Thus, Can s 3 tests cannot be used as a sole substitute for a whole extract test (Table 2), if component allergens are utilized. Unfortunately, sIgE to rPru p 3 from peach (*Prunus persica*), a biomarker often used to depict sensitization to ns-LTP, frequently fails to detect sIgE to rCan s 3.[75] It is unknown whether further studies with the more recently identified cannabis allergens Can s 2, Can s 4 and Can s 5,[63,67,122] or allergens such as ribulose-1,5-bisphospate carboxylase/oxygenase[63] and thaumatin-like protein[64] will advance the molecular diagnosis of cannabis allergy. It is also unknown whether ratios between whole extract sIgE/total IgE and/or component sIgE/whole extract sIgE might benefit the diagnosis, as might be achieved for hemp.[120] Should all component tests be negative, sensitization to CCDs can be detected with commercially available assays.[119]

Cellular tests such as *ex vivo* Basophil Activation Tests (BAT), and mast cell activation tests (pMAT) may also be useful (see Appendix II).[67,123,124] Unlike, traditional sIgE binding assays, they more closely reflect the *in vivo* situation, and in addition to SPTs, can help to detect sensitization to CCDs, and enable safe evaluation of recombinant components (Figure ~~2 and~~ 3).[75,115] BAT using rCan s 3 has predictive values similar to SPTs with a Can s 3-rich extract (Table 2). Thus, a negative SPT or BAT with a crude extract, and negative sIgE to hemp, have a good negative predictive value, but a positive result for one of these tests warrants complementary diagnostics (Figure 4). This is especially important when diagnosis is complicated by PR-10, profilin, ns-LTP or CCD sensitization, resulting in cross-reactivity between cannabis and other allergens. BAT and pMAT have also been used to study other cannabis allergens, but larger collaborative studies are needed to verify whether these tests could enter mainstream application.

Where there is clinical suspicion of a cannabis allergy, our diagnostic algorithm (Figure 4) proposes starting the work-up with SPTs using a native extract and/or quantification of sIgE hemp. In difficult cases, diagnosis can be complemented by calculation of the sIgE/total IgE ratio, molecular diagnostics and/or BAT/pMAT if available. If the results are negative, cannabis allergy is highly unlikely. Given the lack of standardized extracts, and non-availability of commercial BAT

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and pMAT tests, it is currently not possible to optimize the process. A provocation challenge with inhaled cannabis is not recommended, as apart from the legal issues this may cause in many countries, inhalation of cannabis fumes can trigger nonspecific hyperresponsiveness without confirming allergy.[125] It is unknown whether an oral challenge to edible cannabis products or hemp seed would be useful. As with any allergy diagnostic work-up, establishing sensitization to other relevant allergens including molds, pollens, and foods may be helpful, utilizing the most appropriate country-specific tests.

Management Strategies

Currently, the only available treatment for cannabis allergy is avoidance. When avoidance is difficult or impossible, such as occupational exposure, treatment of symptoms is identical to that of other allergens and based on the clinical phenotype upon exposure. Medications could include non-sedating, second generation antihistamines, intranasal and inhaled corticosteroids, and ophthalmic antihistamine/mast cell stabilizers.[11,126] Patients with a history of severe systemic symptoms or anaphylaxis to cannabis should be supplied with auto-injectable epinephrine. For occupational exposure, while a combination of administrative, engineering, and protective controls may mitigate some of the exposures, most occupational settings have limited options to remedy the situation. Treatment with omalizumab has been tried successfully in one case of unavoidable occupational allergy with anaphylaxis.[127]

In established cannabis allergy it is important to understand the cross-reactivity profile to foods. Treatment for cannabis-related cross-reactivity to fruits, vegetables and latex (due either to pollens or nsLTP) entails avoidance, not only of cannabis, but also of the reported food triggers.[128,129] The history of those presenting with more severe reactions needs to be analyzed for the presence of co-factors such as exercise, non-steroidal inflammatory drugs (NSAIDs) and alcohol.

Besides avoidance and symptomatic treatments, there is limited evidence for other therapeutic approaches. The seminal paper on the potential of immunotherapy in cannabis allergy, published in a veterinary journal, described an dog successfully desensitized with cannabis pollen extract.[130]

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Kumar et al. successfully adopted subcutaneous immunotherapy to reduce a patient's symptoms of allergic rhinitis and asthma.[131] With increasing legalization likely to entail a rise of cannabis sativa use, and consequent increasing occupational exposure, safe desensitization and/or tolerance induction protocols need to be developed.[12,13,126]

Educational needs of patients and healthcare professionals

For many allergy healthcare professionals, determining cannabis use is not part of routine history-taking. Initiating such a discussion is vital, and questions should address cannabis exposure in a non-judgmental manner.[132] Confidential discussions on issues surrounding cannabis allergy, within a medical facility, can ease concerns of patients. Patient-oriented information, both web-based, and written handouts can supplement the patient consultation. Healthcare professionals who see allergy patients would benefit from continuous professional development initiatives on cannabis allergy; for example, the development of competencies addressing practical approaches to its diagnosis and management. These could be adapted by individual countries to link in with existing competencies such as the Canadian Medical Education Directives for Specialists (CanMEDs) that address Communicator, Advocate and Medical Expert roles in Canada.[133] While the viewpoints and regulations pertaining to cannabis vary globally, it is important to recognize the issues surrounding its use. Continued education can increase the clinician's understanding and comfort level and improve the chances of them initiating an open discussion on cannabis use with each patient. Furthermore, it gives the clinician the opportunity to discuss the potential harm of recreational or non-evidence based medical use of cannabis.

Conclusion

The global use of cannabis, either for medical reasons, and/or where legalized for recreational purposes, is only likely to increase, and with it the prevalence of cannabis allergy. The diagnosis of any allergy can be problematic, and there are added difficulties with cannabis allergy, not least due to legal issues. There are currently no commercial allergy tests for the diagnosis of cannabis allergy in a clinical setting. Whole cannabis extracts could be purchased for SPT, depending on the legal status of cannabis in that area. Specific IgE to hemp is another option, but usually only available for use in research settings. Where possible, a connection should be made with

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548 laboratories that can perform IgE, molecular and cellular tests. Where cannabis is allowed for
549 medical/recreational use, there needs to be recognition of cannabis allergy and support from
550 allergy organizations, to address what might become a significant public health issue. A large
551 survey demonstrated that people with asthma or allergies may not wish to discuss cannabis use
552 with their physicians, but also physicians often did not inquire about cannabis use.[9] This
553 highlights the need to raise awareness and improve communication between patient and
554 physician on cannabis use and/or exposure.
555
556 The CAIG aims to emphasise the need for more data to establish the significance of cannabis
557 allergies in context of increasing access. Current projects include a survey of knowledge,
558 attitudes and practices related to cannabis allergy amongst members of the three CAIG societies
559 (ACAAI, CSACI and EAACI). This collaboration also plans to identify challenges that currently limit
560 studies on cannabis allergy e.g., Schedule I drug limitations, access to patients, lack of guidance
561 on management, poor validation of diagnostic assays. Another goal is to clarify the importance of
562 the context of exposures and the need to collect details on strain diversity, and complexity of
563 use. Key aspects of cannabis allergy need to be addressed, including the relevant allergens,
564 diagnostic workup, surveillance programs for occupational and environmental exposures and the
565 prevention of cannabis allergy. To collect more real-world data, the CAIG seeks to establish a
566 registry and biobank to collect samples from Europe, USA and Canada. The intention is that these
567 workstreams lead to the development of international guidelines on the diagnosis and
568 management of cannabis allergy.
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573 **Figures and Tables**

574 **Table 1 – Cannabis allergens**

Allergen	**IUIS ID**
Profilin[67]	Can s 2
Non-specific lipid transfer protein[75,76]	Can s 3
Oxygen-evolving enhancer protein 2[63,122]	Can s 4
Pathogenesis related protein 10 homologue[67]	Can s 5

575 Details sourced from WHO/IUIS Allergen Nomenclature Subcommittee (www.allergen.org).

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Table 2 – Performance of different tests in Cannabis-sensitized and Cannabis allergic patients

	SPT nCan s 3-rich extract		sIgE hemp (ImmunoCAP)		sIgE rCan s 3 (CBA)		CD63-BAT crude CS extract		CD63-BAT Can S 3	
	A	B	A	B	A	B	A	B	A	B
Sensitivity	72% (51-89)	58% (49-67)	86% (66-97)	82% (74-89)	63% (41-81)	47% (38-56)	63% (38-84)	49% (37-60)	71% (48-89)	45% (35-55)
Specificity	81% (71-88)	81% (71-88)	32% (20-45)	32% (20-45)	87% (78-93)	87% (78-93)	67% (55-78)	67% (55-78)	85% (76-92)	85% (76-92)
PPV	51% (39-63)	80% (72-86)	33% (28-38)	70% (66-74)	56% (40-70)	82% (72-89)	35% (25-47)	64% (54-73)	54% (39-67)	78% (67-86)
NPV	91% (84-95)	58% (53-64)	86% (66-95)	47% (34-61)	90% (84-94)	56% (51-60)	87% (78-92)	52% (46-59)	93% (86-96)	57% (52-62)
LHR+	3.7 (2.3-6.0)	3.0 (1.9-4.7)	1.3 (1.0-1.6)	1.2 (1.0-1.5)	4.7 (2.6-8.7)	3.5 (2.0-6.2)	1.9 (1.2-3.1)	1.5 (1.0-2.2)	4.8 (2.7-8.6)	3.0 (1.8-5.2)
LHR-	0.4 (0.2-0.7)	0.5 (0.4-0.7)	0.4 (0.1-1.3)	0.6 (0.3-1.0)	0.40 (0.3-0.7)	0.60 (0.5-0.7)	0.6 (0.3-1.0)	0.8 (0.6-1.0)	0.3 (0.2-0.7)	0.7 (0.5-0.8)

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A: Cannabis-anaphylaxis group *vs.* cannabis tolerant individuals sensitized to either pollen alone, or to pollen and nsLTP

B: Complete cannabis allergy group (both anaphylaxis and/or cutaneous symptoms) *vs.* cannabis tolerant individuals sensitized to either pollen alone, or to pollen and nsLTP

Test performance for both CD63-BAT's was calculated by considering both responders and non-responders to anti-IgE (positive control).

PPV and NPV= positive and negative predictive values, respectively. LHR+ and LHR-= positive and negative likelihood ratio's, respectively.

SPT: skin prick test, sIgE: specific IgE, CBA: cytometric bead assay, CD63: lysosomal membrane protein used as basophil degranulation marker.

Adapted from:[75]

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Figure 1 **Current status of cannabis allergy**

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Figure 2 Cannabis Allergens and homologous plant proteins

Legend

There is proven cross-reactivity between Can s 3 and other nsLTP, whereas for the other sequenced cannabis allergens, this has not been investigated. However, there are protein amino acid identity matches across species suggesting possible IgE cross-reactivity.

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Figure 3: Basophil activation plots of a patient with CSA with sIgE reactivity to Can s 3, Can s 4 and Can s 5

Legend

Cells are responsive to a raw extract, Can s 3, Can s 4, Can s 5, but not to Can s 2. The percentages in the plots denote the net percentages of $CD63^+$ basophils after stimulation with relevant allergen.

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Figure 4: Diagnostic algorithm for Cannabis Allergy[13,87]

Legend

Molecular diagnostics – the Can s allergens have all been sequenced except for TLP (Thaumatin-like protein), a potential new cannabis allergen

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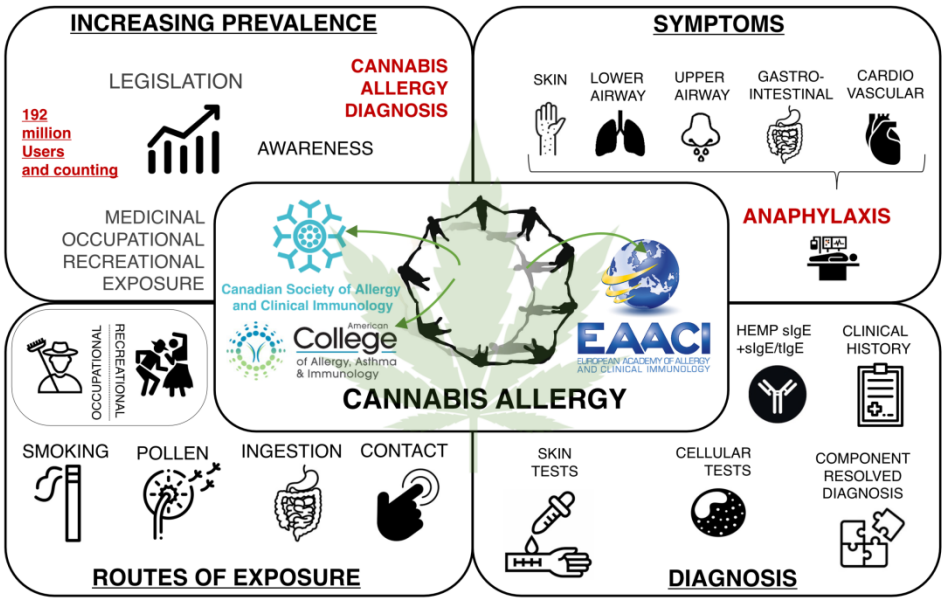


Figure 1_Skypala et al.

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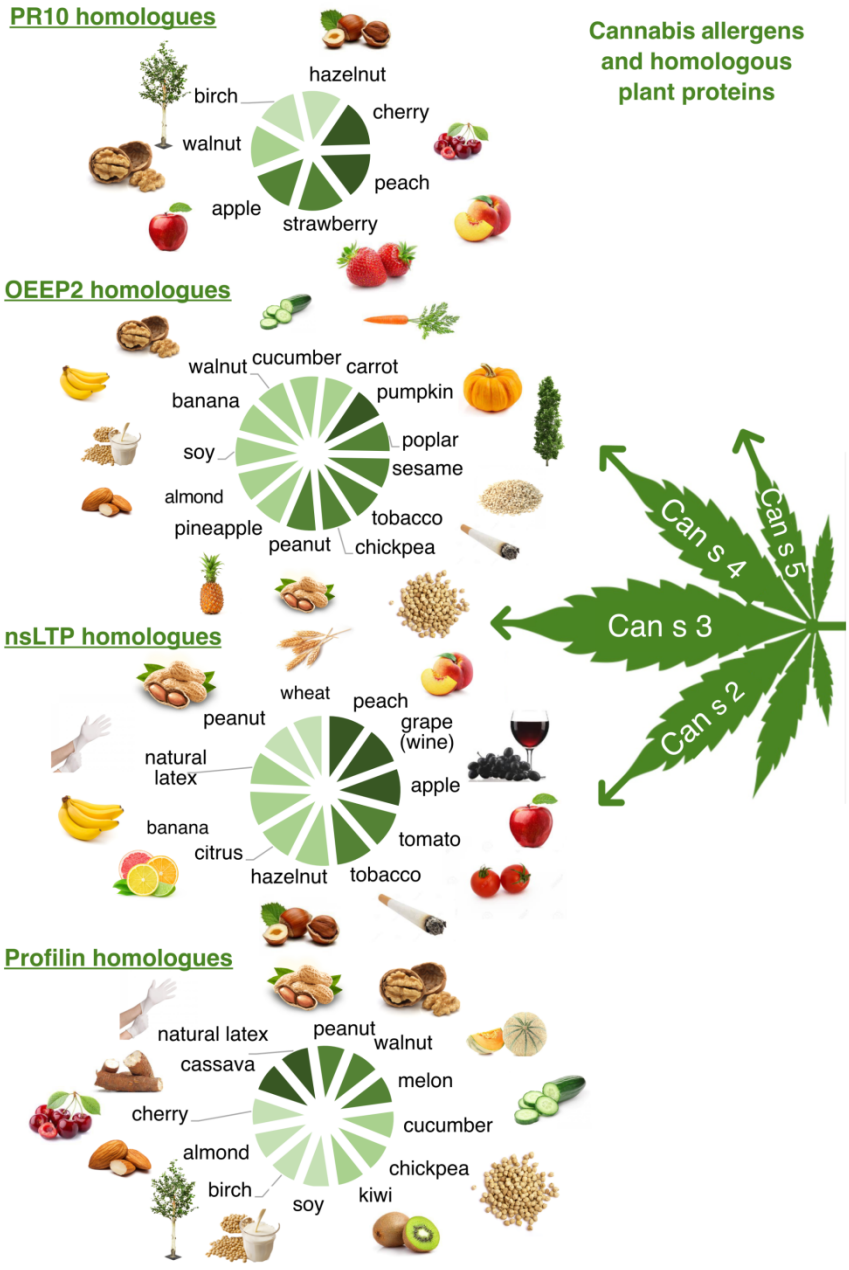


Figure 2_Skypala et al.

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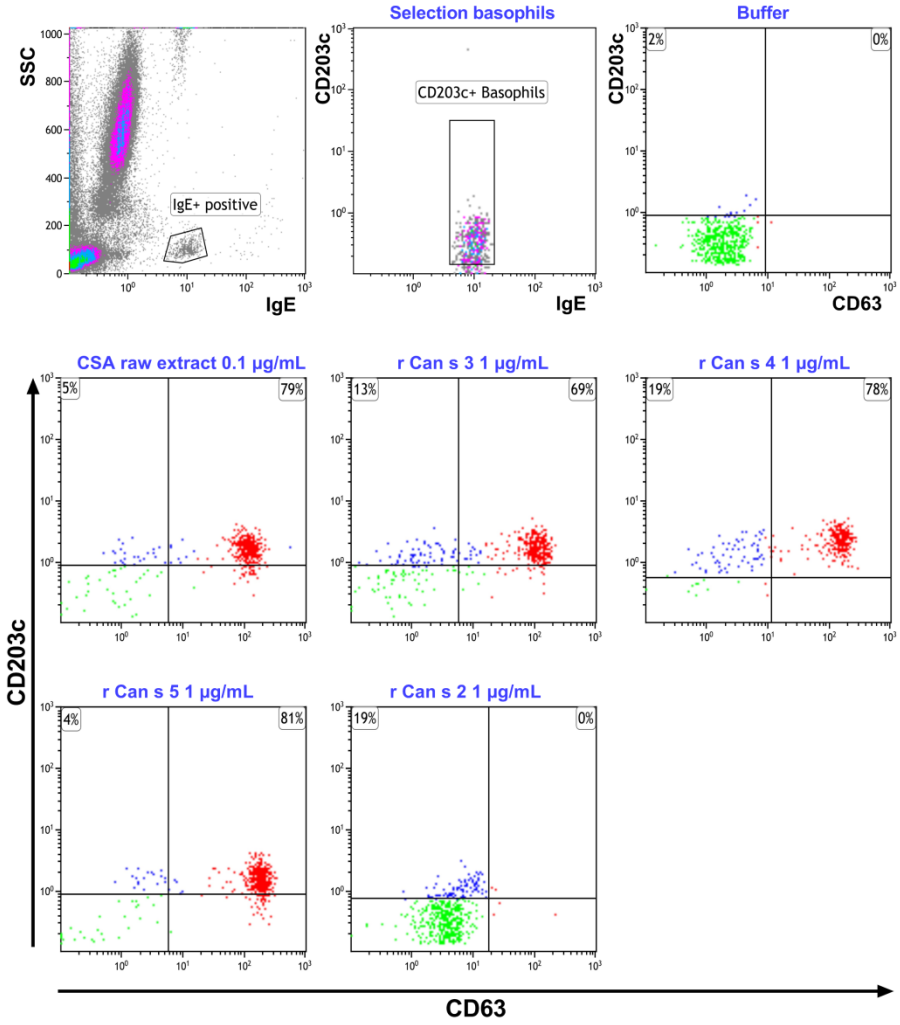


Figure 3_Skypala et al.

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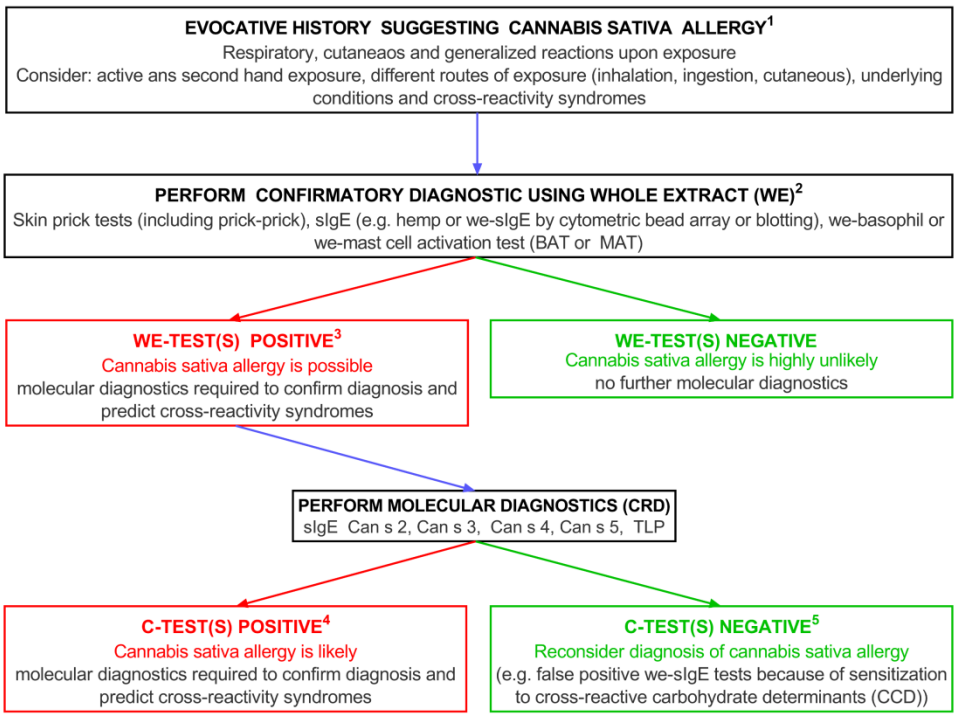
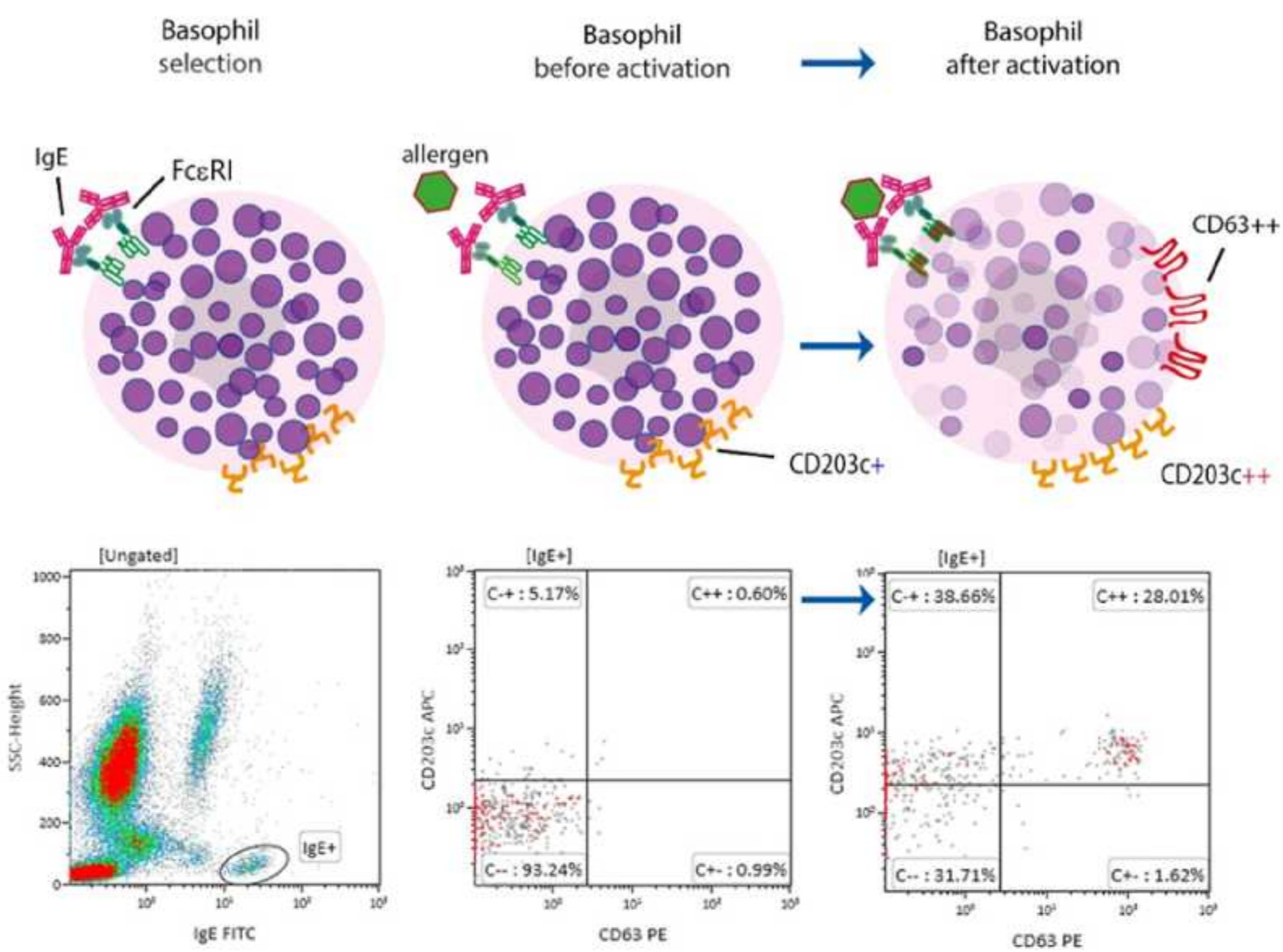


Figure 4_Skypala et al.

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Basophil
selection
Basophil
before activation
Basophil
after activation
IgE
FcεRI
allergen
CD63++
CD203c+
CD203c++
[Ungated]
SSC-Height
IgE FITC
IgE+
[IgE+]
CD203c APC
CD63 PE
C-+ : 5.17%
C++ : 0.60%
C-- : 93.24%
C+- : 0.99%
[IgE+]
CD203c APC
CD63 PE
C-+ : 38.66%
C++ : 28.01%
C-- : 31.71%
C+- : 1.62%

Appendix 1 International Cannabis Allergy Collaboration Membership

Full Name	Organization and Location	Representing
Donald H Beezhold, PhD	Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Morgantown, West Virginia, United States.	Observer
Jonathan A. Bernstein, MD	Department of Internal Medicine, Division of Immunology/Allergy Section, University of Cincinnati College of Medicine and Bernstein Allergy Group; Bernstein Clinical Research Center, Ohio, USA	ACAAI
Leonard Bielory, MD	Center for Environmental Prediction, Rutgers University, New Brunswick, Environmental and Occupational Health Science Institute, Rutgers University, Piscataway, Medicine, Allergy, Immunology and Ophthalmology Department, Hackensack Meridian School of Medicine, Nutley, New Jersey Center of Science, Technology and Mathematics, Kean University, Union, New Jersey, USA	ACAAI
Michael S. Blaiss, MD	Department of Pediatrics, Medical College of Georgia, Augusta University, Augusta, Georgia, USA	ACAAI
Hannelore A. Brucker, MD	Southdale Allergy and Asthma Clinic, Minneapolis, Minnesota, USA	ACAAI
Rick Goodman, PhD	Food Allergy Research and Resource Program, University of Nebraska-Lincoln. Lincoln, Nebraska, USA	ACAAI
Rohit K. Katial, MD	Division of Allergy & Clinical Immunology, National Jewish Health, Denver, Colorado, USA	ACAAI
Kevin Murphy, MD	Division of Allergy, Asthma and Pediatric Pulmonology, Department of Pediatrics, Boys Town National Research Hospital, Omaha, Nebraska, USA	ACAAI
David R. Naimi, DO	Naval Hospital Camp Pendleton, Oceanside, California, USA	ACAAI
Anil Nanda, MD	Asthma and Allergy Center, Lewisville and Flower Mound, Texas, and Division of Allergy and Immunology, University of Texas Southwestern Medical Center, Dallas, Texas, USA	ACAAI
Ajay Nayak, PhD	Department of Medicine, Center for Translational Medicine and Division of Pulmonary Allergy and Critical Care Medicine; Jane and Leonard Korman Respiratory Institute, Thomas Jefferson University, Philadelphia, Pennsylvania, USA	ACAAI
Jill A. Poole, MD	Division of Allergy and Immunology, Department of Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA	ACAAI
William S. Silvers, MD (Co-chair)	Division of Allergy Clinical Immunology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colorado, USA	ACAAI
Robert S. Zeiger, MD, PhD	Kaiser Permanente Southern California, San Diego, California and Canna Research Foundation, Boulder, Colorado, USA	ACAAI
Mina Abbaslou, MD	Department of Medicine and Division of Clinical Immunology & Allergy, University of Toronto, Ontario, Canada	CSACI
Lori Connors, MD, MEd, FRCPC	Dept of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada	CSACI
Anne K. Ellis, MD (Co-Chair)	Division of Allergy & Immunology, Department of Medicine, Queen's University, Kingston, Ontario, Canada	CSACI

Samira Jeimy, MD, PhD, FRCPC	Division of Clinical Immunology and Allergy, Department of Medicine, Western University, London, Ontario, Canada	CSACI
Amin Kanani, MD, FRCPC	Division of Allergy and Immunology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada	CSACI
Harold Kim, MD, FRCPC	Division of Clinical Immunology and Allergy, Department of Medicine, Western University, London, and Department of Medicine, McMaster University, Hamilton, Ontario, Canada.	CSACI
Gordon L. Sussman, MD	Department of Medicine and Division of Clinical Immunology & Allergy, University of Toronto, Ontario, Canada	CSACI
Shun Chi Ryan Lo, MD	Division of Allergy and Immunology, Department of Medicine, University of British Columbia, Vancouver, British Columbia, Canada	CSCAI
Matteo Bonini, MD, PhD	Department of Cardiovascular and Thoracic Sciences, Fondazione Policlinico Universitario A. Gemelli, IRCCS, Catholic University of Rome, Rome, Italy.	EAACI
Ine Decuyper, MD, PhD	Department of Pediatrics, University Hospital of Antwerp, Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium	EAACI
Didier Ebo, MD, PhD	University of Antwerp, Faculty of Medicine and Health Sciences, Department of Immunology, Allergology, Rheumatology and the Infla-Med Centre of Excellence, Antwerp (Belgium) and Immunology, Allergology, Rheumatology, Antwerp University Hospital, Antwerp (Belgium) and Department of Immunology and Allergology, AZ Jan Palfijn Gent, Ghent, Belgium	EAACI
Francisca (Paqui) Gómez	Allergy Clinical Unit, Hospital Regional Universitario de Málaga, Málaga, Spain.	EAACI
Ludger Klimek MD, PhD	Center for Rhinology and Allergy, Wiesbaden, Germany	EAACI
Oscar Palomares Gracia, PhD	Department of Biochemistry and Molecular Biology, Chemistry School, Complutense University of Madrid, Madrid, Spain.	EAACI
Hans Peter Rihs, PhD	Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), Institute of the Ruhr-University Bochum, Bochum, Germany.	EAACI
Jolanta Walusiak-Skorupa, MD, PhD	Department of Occupational Medicine and Environmental Health, Nofer Institute of Occupational Medicine, Łódź, Poland	EAACI
Isabel J. Skypala, PhD, RD (Co-chair)	Department of Allergy & Clinical Immunology, Royal Brompton & Harefield Hospitals, and Imperial College, London, UK	EAACI
Joanna Zeiger MS PhD	Canna Research Foundation, Boulder, Colorado, USA	Canna Research Foundation
Khaldon Abbas, BSc	University of British Columbia, Faculty of Medicine and Department of Medicine and Division of Clinical Immunology & Allergy, University of Toronto, Ontario, Canada	Other
Martin Chapman, PhD	Indoor Biotechnologies, Inc, Charlottesville, Virginia, USA	Other
Tara Croston	Allergy and Clinical Immunology Branch, Health Effects Laboratory Division, National Institute for Occupational	CDC/NIOSH/ HELD/ACIB

	Safety and Health, Centers for Disease Control and Prevention, Morgantown, West Virginia, USA	
Sylvie Franken	Urticaria Center of Reference and Excellence (UCARE), Department of Dermatology, Amsterdam UMC, Amsterdam, The Netherlands.	Other
Shmuel Kivity	The Tel Aviv Medical Center, Tel Aviv, Israel.	Other
Christel Mertens	Faculty of Medicine and Health Sciences, Department of Immunology, Allergology, Rheumatology and Infla-Med Centre of Excellence, University of Antwerp and Antwerp University Hospital, Antwerp (Belgium).	Other
Karin Pacheco, MD, MSPH.	Division of Environmental and Occupational Health Sciences, Department of Medicine, National Jewish Health, Denver, Colorado, USA	Other
Thomas Rustemeyer, MD, PhD	Department of Dermatology, Amsterdam University Medical Centre location AMC, Amsterdam, The Netherlands.	Other
Umesh Singh	Bernstein Clinical Research Center, Ohio, USA	Other

Appendix II: Principles of the basophil activation test (BAT) using whole blood.

Legend

Circulating basophils are identified based on scatter characteristics and surface expression of IgE and the lineage specific marker CD203c. Before stimulation basophils barely express the lysosomal degranulation marker CD63 (left and mid panel). After cross-linking of surface-bound IgE by relevant allergen, basophils quickly up-regulate surface expression of CD203c and CD63. Resting basophils are frequently designated as CD203c+CD63-. Degranulating cells as CD203c++CD63++. For a more detailed description on the principles and readouts of basophil degranulation see:[121]