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CME Review

Cannabis sativa: the unconventional "weed" allergen

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- Describe diagnostic and therapeutic methods that have been used in *Cannabis sativa* associated allergies

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Introduction

Passage of legislation in Washington, Colorado, Oregon, Alaska, and the District of Columbia allowing recreational use of marijuana, despite federal regulation to the contrary, highlights the continued debate surrounding this unconventional plant. Allergies to marijuana are not commonly reported in the medical literature despite

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being the most widely used illicit drug in the world.[1–3] However, especially in the setting of an evolving legal status, marijuana might become an increasingly relevant "weed" for the allergist. This article aims to review the literature pertaining to *Cannabis sativa* in the context of allergic disease and its potential clinical implications.

Legal Background

Used for 5 millennia for spiritual, medicinal, and recreational use and even routinely by American physicians in the late 19th century, marijuana was first prohibited in the United States under the 1937 Marijuana Tax Act.[2,4] Further restriction followed in 1970, when the federal government passed the Controlled Substances Abuse Act classifying marijuana as a Schedule I substance.[5] This federal mandate was reinforced in June 2011, when the Drug Enforcement Administration denied a petition to reschedule marijuana by reiterating a lack of scientific or medical evidence to warrant such a change.[5] Nevertheless, 21 states (and the District of Columbia) currently approve the use of medical marijuana.[4,6]

Cannabis sativa

Cannabis sativa is an annual, dioecious, and anemophilous flowering plant that belongs to the Cannabaceae family and is native to Central and South Asia.[7] Its pollen is typically 23 to 28 μ in diameter, triporate, isopolar, and spheroidal.[8] Typically shed during the late summer to early autumn, *Cannabis* pollen grains are very buoyant, allowing for distribution across many miles.[9] Wild growth occurs in some geographic regions and it is a relevant pollen in the aerobiology of central India, urban Pakistan, southern Europe, and parts of the United States.[8,10–14]

Cannabis sativa contains more than 400 compounds, including more than 60 cannabinoids. Delta-9-tetrahydrocannabinol (THC) is of particular interest as the primary psychoactive component of *Cannabis*.[3] There are different preparations of *C sativa*. These include marijuana (dried flowering tops and leaves), hashish (dried resin surrounding leaves), and hashish oil (hashish distillate). Marijuana and hashish are typically smoked, vaporized, or chewed.[2] However, in addition to other forms, including hemp seed and hempseed oil, they can be incorporated into foods and ingested.[15] *Cannabis sativa* in the form of hemp, with a lower THC content, is used commercially for fiber, cosmetics, and clothing. In addition to its growing popularity as a "health food," hemp seed is commercially found in bird feed and fishing bait.[16]

The often illicit nature of marijuana growth involves unique harvesting techniques. Intentional isolation of female flowering plants aims to prevent pollination and increase the plant's psychoactive properties by its THC content (referred to as *sinsemilla*).[3,17] The potency of *C sativa,* often measured by THC content, has increased over the years, with some Japanese strains of sinsemilla containing as much as 22.6% THC.[2] This could play a role in allergic disease because THC has been suggested as a pertinent *Cannabis* allergen.[18] Some marijuana growers implement indoor cultivation techniques that allow for robust year-round and clandestine growth in climates and environments that would otherwise be unhospitable. Cross-breeding and hybridization of different strains of marijuana aimed at developing new "highs" and accessibility of seed purchases through the Internet add yet another dimension to *Cannabis* exposure throughout the world.[19]

Cannabis Physiologic Effects

The physiologic effects of *Cannabis* consumption include orthostatic hypotension with reflex tachycardia, fatigue, dizziness, dry mouth, decreased lacrimation, muscle relaxation, increased appetite, and decreased intraocular pressure.[4,20,21] Desired psychoactive properties of *Cannabis* species, such as relaxation and euphoria, can yield to associated dysphoria, anxiety, memory impairment, psychomotor or cognitive decreases, altered time perception, and the induction of psychosis in vulnerable individuals.[20] Exposure to *Cannabis* smoke has been known to cause conjunctival injection, nasopharyngeal irritation, pharyngitis, sinusitis, and symptoms of bronchitis (Table 1).[2]

Table 1
Allergies reportedly associated with *Cannabis sativa*

Allergic rhinitis[9,14,18,43]
Allergic conjunctivitis[9,14]
Asthma[42,43]
Food allergy[15]
Eczema[17]
Drug eruption[37]
Contact urticaria[31,38,39]
Anaphylaxis[15,33,35,51]

Regular *Cannabis* smokers have reported wheezing, sputum production, and chronic coughing.[3] The often deep inhalation with prolonged breath holding that creates a Valsalva maneuver in *Cannabis* smoking also has been speculated as a factor in rare cases of pneumothorax and bullous lung disease.[22,23] Studies have shown marijuana causes acute bronchodilation and even reversal of methacholine- and exercise-induced bronchospasm.[24,25] Marijuana smoking also has been reportedly associated with increases in forced vital capacity and airway resistance,[23,26] but most of the evidence in this area has not supported a significant association between its use and specific measurements of airway obstruction.[21,24,25,27] Debate remains regarding the long-term effects of marijuana on cancer and chronic lung disease (ie, chronic obstructive pulmonary disease).[23,24]

Cannabis Allergy

Case reports in the medical literature have described episodes of allergic reactions, hypersensitivity, and even anaphylaxis to *C sativa* in its various forms.

As expected with most plant aeroallergens, *Cannabis* pollen inhalation has been noted to cause symptoms of allergic rhinitis, conjunctivitis, and asthma. *Cannabis* pollen or smoke exposure has resulted in nasal congestion, rhinitis, sneezing, conjunctival injection, pharyngeal pruritus, coughing, wheezing, and dyspnea.[2,18,28–36] A case of erythema multiforme-like recurrent drug eruption thought to be associated with *Cannabis* use also has been described.[37] Cutaneous contact through personal handling of plant material or occupational exposure has been associated with urticaria, generalized pruritus, and periorbital angioedema.[16,30,31,33,38,39] Anaphylaxis associated with ocular symptoms, urticaria, angioedema, dyspnea, and dysphonia has been reported with hemp seed ingestion.[15] This patient ate hemp seed–encrusted seafood (and tolerated a subsequent oral seafood challenge) and required antihistamine and epinephrine treatment.

Industrial hemp dust exposure has been implicated in byssinosis, an occupational obstructive (small airway) lung disease associated with organic textile dust exposure in work environments.[40,41] Allergic asthma triggered by seasonal and occupational exposure to *C sativa* also has been reported.[42,43] *Cannabis* use has even been speculated as an etiologic factor in a few cases of eosinophilic pneumonia, although tobacco use also was present in most of these cases.[44–46] The presence of fungal contamination (*Aspergillus* and *Penicillium* species) in marijuana samples has been demonstrated, at times putting immunocompromised patients at risk for invasive disease.[47–49] A case of allergic bronchopulmonary aspergillosis attributed to fungal contamination of the patient's marijuana supply has been described.[50]

Anaphylaxis after intravenous use of marijuana has been reported.[51] Although supportive allergy testing was not performed in this case, the patient's history was strongly suggestive with the development of facial edema, truncal urticaria, pruritus, dyspnea, and wheezing within minutes of intravenous exposure. In addition, the

patient responded to administration of epinephrine, antihistamine, and corticosteroids, clinically suggesting an IgE-mediated reaction.[51]

Environmental Exposure

Like other aeroallergens, *C sativa* sensitization can be influenced by aerobiology, varying geographically and even temporally within the same area.

Positive *Cannabis* pollen skin prick test reactions were seen in 8.3% of 48 Indian patients with allergic rhinitis or bronchial asthma.[52] Of those with a positive skin test reaction, none had a reaction larger than 50% of the positive histamine control wheal. In addition, a specific correlation between clinical allergic symptoms and *Cannabis* exposure or other aeroallergen sensitizations was not addressed. In Islamabad, Pakistan, 22% of 1,000 patients demonstrated a positive skin test reaction to *C sativa* pollen defined by a wheal larger than 2 mm.[10] Many patients had additional aeroallergen sensitivities, but a specific association between skin test results and related clinical symptoms to *Cannabis* was not elaborated.

In the American Southwest, Freeman[11] studied 129 unselected patients presenting to an allergy clinic. In an area where *Cannabis* pollen was noted to be a minor aeroallergen, 70% of these patients found to be atopic demonstrated *Cannabis* sensitization by pollen skin prick or intradermal testing. However, all patients also demonstrated other aeroallergen sensitivities and no data were collected regarding marijuana use or specific *Cannabis* pollen exposures, making it challenging to clarify a specific mode of sensitization or clinical relevance.

In Omaha, Nebraska, where *Cannabis* reportedly grows wildly and commercially, 2 studies looked at *Cannabis* sensitization.[14,36] During a 3-year period in the late 1930s, Maloney and Brodkey[36] reported hemp sensitivity by scratch tests using "pollen dollar diagnostic sets" in 22% of 119 patients with hay fever. Most patients developed symptoms during the typical summer pollination season and 11 patients demonstrated sensitivity to hemp alone, suggesting clinical relevance of the skin test results. In 2000, Stokes et al[14] noted that 61% of 127 patients in Omaha with allergic rhinoconjunctivitis and/or asthma symptoms had a positive *Cannabis* pollen skin prick test reaction. Twenty-two of 30 (73%) randomly selected patients in a *Cannabis*-sensitive subgroup reported respiratory symptoms during the *Cannabis* pollination season, although all these patients also were found to have additional aeroallergen sensitivities.

Cannabis Use

Sensitization associated with *Cannabis* use also has been suggested. Larramendi et al[7] noted an 8.1% prevalence of positive skin prick test reactions to *Cannabis* leaf extracts in 545 patients with atopy. A higher prevalence of skin test reaction positivity was seen in marijuana smokers (14.6%) and even more so in those who reported frequent and/or regular use (18.2%) compared with nonsmokers (5%). A positive association also was noted between *Cannabis* smoking, plant handling, and sensitization. However, only 2 patients reported symptoms and 13 sensitized patients (29.5%) denied any previous exposure, highlighting the challenge of correlating diagnostic results with allergic disease.

In a cohort of 140 patients with atopy and users of illicit drugs reporting asthma symptoms, patients underwent in vivo and in vitro testing to evaluate *Cannabis* sensitivity.[28] In this study, Armentia et al[28] showed that, overall, 74 patients (53.2%) had a positive skin prick test reaction to *Cannabis* leaf extract and 48 patients (34.4%) demonstrated positive serum specific IgE. Patients also underwent a direct inhalation challenge to *Cannabis* and tobacco, with 42 (30%) of those tested demonstrating a decrease (>20% decrease in forced expiratory volume in 1 second) in lung function compared with baseline spirometric findings. This study suggested the highest level of positive *Cannabis* skin prick and serum testing results in self-reported "habitual and dependent users" compared with "experimental or occasional users."

More recently, Tessmer et al[33] reported on a cohort of 17 patients with symptoms of hypersensitivity reactions associated with *Cannabis* inhalation, contact, and ingestion. These patients demonstrated sensitivity by skin prick tests to a crude nonstandardized marijuana extract from macerated buds and flowers.

Allergen Cross-reactivity

Some European studies have investigated cross-reactivity between *Cannabis* and other plants. Gamboa et al[31] reported on a case of a 28-year-old *Cannabis* smoker with progressive allergic symptoms of contact urticaria, sneezing, rhinorrhea, palpebral edema, itching, and eye redness with *Cannabis* use. Without previous food allergies, the patient went on to develop urticaria to peach peel, food pollen syndrome to several foods (apple, almonds, eggplant, and chestnut), and anaphylaxis to tomato, pepper, and fig. Immunoblotting identified a 9-kDa lipid transfer protein (LTP), speculated as the reason for cross-reactivity and development of his food allergies.

De Larramendi et al[29] suggested a high degree of cross-reactivity between tomato and *C sativa* leaf extract. In this study, 24 tomato-sensitized patients with and without allergic symptoms associated with *Cannabis* use had positive prick-prick (*Cannabis* leaves) skin test reactions. All those with *Cannabis*-related symptoms and most without *Cannabis*-related symptoms also demonstrated measurable IgE levels. Only 1 of 8 control patients also had a positive skin prick test reaction to *Cannabis* extract. Inhibition immunoblot testing demonstrated cross-reactivity of *Cannabis* extracts with fruit (peach and tomato) and pollens (mugwort and plane tree).

Ebo et al[30] further suggested allergic cross-reactivity to fruits, vegetables, and nuts and the possibility of a "cannabis–plant food syndrome" in a group of Belgian patients. In this study, *Cannabis*-sensitive patients frequently demonstrated allergies to foods (banana, tomato, citrus, and grapefruit) not typically associated with Bet v 1–related food pollen syndrome, as would otherwise be expected in this and other areas of northern Europe. Although a food pollen syndrome owing to other cross-reactive pollens (seen in 10 of 12 *Cannabis*-allergic patients) is possible, the investigators suggested that the degree of food allergy in these patients was more severe than would be expected in typical food pollen syndrome and might represent cross-reactivity resulting from *Cannabis* sensitization.

In the study of *Cannabis* sensitivity in patients with asthma and users of illicit drugs mentioned earlier, Armentia et al[28] also noted that patients sensitive to tomato had the highest prevalence of *Cannabis* sensitization by skin (92%) and serum IgE (68%) testing compared with patients not sensitized to tomato regardless of *Cannabis* use. Tomato and tobacco sensitivities also were suggested as risk factors for *Cannabis* allergy because 52% and 61% of these patients, respectively, had a positive bronchial challenge reaction to nebulized *Cannabis* extract.

A 2013 study by Larramendi et al[7] suggested the possibility of primary and cross-reactive sensitizations in their study population. Primary sensitization was speculated based on a higher relative rate of sensitization seen in regular *Cannabis* users and a positive association with skin test reaction positivity and exposure (smoking and handling). Secondary sensitization was suggested by high percentage of *Cannabis* sensitization (73.7%) in patients sensitive to peach and tomato.[7]

Occupational Exposure

Although uncommon, allergic reactions associated with occupational exposure to *C sativa* have been reported. It has been suggested that symptoms of nonoccupational use might be mild,

tempered by user titration, and/or the illicit nature of *Cannabis* use could limit patient reporting.[29]

Occupational asthma was described in a bird breeder who developed rhinorrhea, chest tightness, dyspnea, cough, and wheezing with hemp seed exposure.[42] Positive skin prick and intradermal test reactions to *Cannabis* seed extract, reverse enzyme immunoassay, and histamine release tests supported an IgE-mediated response. A bronchial challenge also showed a significant decrease (31%) in forced expiratory volume in 1 second with aerosolized *Cannabis* inhalation. No changes were seen in 5 control patients with asthma who also underwent bronchial challenge.

A medical marijuana grower without atopy who previously tolerated personal recreational marijuana use developed contact urticaria and pruritus with subsequent handling of the plant. The patient demonstrated positive *Cannabis* leaf prick-prick skin testing reactions and elevated serum specific IgE. A negative patch test result further supported the presence of an IgE-mediated reaction in this case.[38]

Laboratory workers also have been reported to develop allergic rhinitis, asthma, and cutaneous symptoms with occupational *Cannabis* exposure.[9,16,17,39] Allergic rhinoconjunctivitis was described in a researcher with direct contact with *Cannabis* pollen.[9] The patient denied previous *Cannabis* use but had lived in a region of Spain dedicated to hemp cultivation, which highlights the possibility of occupational exacerbation vs sensitization in this patient.

Two patients who did not use *Cannabis* noted nasal and respiratory symptoms to hashish and marijuana after several years of work in a forensic laboratory.[17] Serum specific IgE and basophil histamine release assays confirmed *Cannabis* sensitivity in these patients. One patient had more pronounced symptoms with handling of the sinsemilla variant, known for its higher THC content, suggesting the possible allergenic role of THC in this case.[17] In a separate case, a forensic laboratory employee with urticaria within minutes of handling marijuana was found to have positive skin prick test reactions to extracts from the *Cannabis* leaf (4-mm wheal), immature flowering material (13-mm wheal), and female flowering material (15-mm wheal).[39] The variability of these results could suggest differences in the allergens and/or allergen concentrations in different parts of the *Cannabis* plant. Yet another laboratory worker with *Cannabis*-induced urticaria had a positive patch test reaction, suggesting a case of a non–IgE-mediated cutaneous reaction (although no controls or other testing was reported).[16]

Cannabis sensitivity also has been demonstrated in the commercial hemp industry. In a study of 42 Croatian hemp factory workers, there was a 64.2% prevalence of positive skin prick test reactions to a 1:10 w/v aqueous extract of hemp dust collected from various areas of their work site. These patients also were shown to have a higher prevalence of reported nasal symptoms and occupational asthma (manifested as dyspnea, chest tightness, and abnormal spirometric results) compared with coworkers with negative skin test reactions.[53] Although a higher total serum IgE level was seen in hemp workers compared with controls, researchers were unable to link measured lung function with total IgE levels or skin test results. No serum specific IgE to hemp was analyzed.[53]

Allergen Identification

There have been efforts to identify specific allergens for *C sativa* (Table 2). After the first reported case of marijuana hypersensitivity in 1971, Liskow et al[18] suggested cannabinoids as relevant allergens based on positive skin prick test reactions in the case patient. THC was more specifically suspected as a significant allergen from localized skin sensitivity seen on passive transfer studies in a control subject without atopy. This also has been suggested clinically in a case of a forensic laboratory worker with more pronounced allergic rhinitis symptoms when handling sinsemilla variants of *C sativa*, known to have higher THC content.[17] Anibarro and Fontela[34] later presented a case of marijuana allergy suggesting a water-soluble allergen, instead of the lipophilic THC, based on the use of an aqueous extract of *Cannabis* that resulted in positive skin test reactions.

Table 2
Potential allergens of *Cannabis sativa*

Delta-9-tetrahydrocannabinol (THC)[17,18]
Nonspecific lipid transfer protein[7,29,30,38](Can s 3)[31]
Thaumatin-like protein[7]
Ribulose-1,5-biphosphonate carboxylase/oxygenase (RuBisCO)[55]
Oxygen-evolving enhancer protein 2[55]

Immunoblotting has shown a wide range of IgE reactive bands.[9,15,54] Nevertheless, a single unifying allergen among reported cases has not been discovered. Early work at specifically identifying *Cannabis* allergens by Tanaka et al[54] demonstrated several reactive IgE bands on immunoblotting to an allergic patient's serum at 10, 14, 45, 60, and 68 kDa. However, it was only relatively recently that Gamboa et al[31] identified a nonspecific LTP (ns-LTP) relevant to *C sativa* and named it Can s 3. Additional studies evaluating *Cannabis* sensitization have found ns-LTPs on immunoblotting.[7,29,30,38] Two studies by Larramendi et al[7,29] supported these findings with the isolation of 9- and 10-kDa bands. Ebo et al[30] used multiplexed component-resolved diagnostics to support the potential of Can s 3 as a major allergen in *Cannabis* allergy.

In addition to confirming the presence of ns-LTP by immunoblotting in sensitized patients, de Larramendi et al[29] speculated on the presence of other specific allergens based on reactive bands discovered by in vitro testing in the previously mentioned studies. Suggested allergens included profilins (panallergen) and polygalacturonase (a common allergen in pollen extracts).

Rojas Perez-Ezquerra et al[38] described a corresponding ns-LTP in a patient without atopy with cutaneous symptoms upon handling marijuana plants. Unlike previous studies, cross-reactivity with peach (Pru p 3, a representative LTP) was not found. It was suggested that the variable homology of ns-LTPs between botanically unrelated plants (35–95%) likely explains this difference in findings. Also, unlike the findings of de Larremendi et al, skin prick testing in this study did not confirm a role of panallergens.

A more recent study by Larramendi et al[7] also identified a 38-kDa band noted to be a thaumatin-like protein (previously seen in fruit allergens with cross-reactivity to apple, tomato, gold kiwi, and cypress). This was not typically recognized in subjects sensitized to tomato and *Cannabis* species, suggesting it is an alternative allergen of sensitization. Additional bands also were identified, although with more sparse and varied episodes.

In a study aimed to define *Cannabis* allergens, Nayak et al[55] showed that only 2 in a cohort of 23 *Cannabis*-sensitive patients had a reactive band in the area of ns-LTPs. Instead, the more notable identified allergens included a 50-kDa protein identified as a photosynthetic enzyme called ribulose-1,5-biphosphonate carboxylase/oxygenase (RuBisCO) and a 23-kDa oxygen-evolving enhancer protein 2. Other less consistently demonstrated allergens (and alternative sources) included adenosine triphosphate synthase (bovine), phosphoglycerate kinase (candida), glyceralderhyde-3-phosphate dehydrogenase (wheat, fungi, and rambutan), luminal binding protein in root (hazel pollen and fungi), and carbohydrate determinants.

Diagnosis

Evaluation of *Cannabis* allergy is dependent largely on skin testing. Extracts are typically created with crushed buds, leaves, and flowers of the *Cannabis* plant.[15,18,29–33,42] Differences in source material and extraction techniques can introduce significant variability. Contaminants, additives, and inherent variability in the

native allergen extracts might lead to irrelevant IgE binding components that can cloud diagnostic evaluation.[56] Some studies have demonstrated skin test reaction positivity in atopic controls and those without prior exposure or clinical symptoms, thus emphasizing that further study is needed to establish skin test sensitivity and specificity.[17,29]

One study suggested promising sensitivity and specificity of skin tests (92.7% and 63.3% respectively) and serum IgE (88.1% and 88% respectively) used in its reviewed population.[28] However, the study's unique demographic and lack of standardized extracts limit its use for comparative testing and widespread applicability.

Some studies also have demonstrated *Cannabis* allergy with in vitro tests such as serum IgE antibodies,[17,29,30,32,42] histamine release assays,[17,42] and basophil activation tests.[30] However, these tests often require advanced technologies or assistance from research or specialized laboratories. Bronchial challenge has been used to correlate *Cannabis* exposure with clinical symptoms.[34] Nevertheless, all these tests have not been extensively validated and face the same challenges that remain from a lack of standardized extracts.

Without reliable standardized diagnostic testing options and often poor correlation between testing and true clinical allergy, the importance of the history in evaluating patients remains vital. Nonetheless, it should be realized that the illicit nature of *Cannabis* use can create barriers for accurate and clear patient reporting. In addition, legal limitations to obtaining, preparing, and using extracts can pose diagnostic challenges. The allergist should take this into consideration because the only federally approved source of *Cannabis* species in the United States is located at the University of Mississippi and is strictly limited to research use.[4]

Treatment

As with other allergens, avoidance is recommended. However, factors such as local aerobiology, occupational exposures, and compliance with the added layer of substance abuse and addiction should be taken into consideration. Symptomatic treatment with antihistamines, intranasal steroids, and nasal decongestants can be used to treat symptoms of allergic rhinoconjunctivitis. Asthma should be treated with β-agonists and consideration of an inhaled corticosteroid if indicated. Epinephrine auto-injectors should be prescribed for patients with a history of anaphylaxis.

Rare cases of treatment with immunotherapy have been described in the literature. As far back as the 1930s, Maloney and Brodkey[36] reported hemp desensitization in 2 patients. Although clinical improvement was reported, no details regarding extract, regimen, or long-term follow-up were described. In 1980, Gupta et al[57] noted clinical improvement (reported respiratory symptoms and statistically significant changes in forced vital capacity and forced expiratory volume in 1 second) in a cohort of hemp workers who received immunotherapy to hemp (dust and fiber) extract twice a week for a year compared with control patients. Kumar and Gupta[43] more recently reported subcutaneous immunotherapy to treat a *Cannabis*-monosensitized patient with corresponding asthma and allergic rhinitis during the *Cannabis* pollination season in India. Clinical improvement was noted after 1 year of maintenance immunotherapy. Further study to establish the major *Cannabis* allergens and the development of a standardized extract could help clarify the potential role of immunotherapy in other *Cannabis*-allergic patients.

A published abstract described a case of using omalizumab to treat a patient with recurrent episodes of anaphylaxis (dyspnea, throat symptoms, urticaria, and hypotension) owing to occupational *Cannabis* exposure as a police detective.[35] Although the patient was able to tolerate subsequent exposures without anaphylaxis, long-term follow-up was not elaborated.

Conclusions

Although still relatively uncommon, allergic disease associated with *C sativa* exposure and use has been reported with increased frequency. Allergic reactions and even anaphylaxis attributed to *C sativa* have been noted with sensitization associated with pollinosis, *Cannabis* use, potential plant cross-reactivity, and occupational exposure. With state laws allowing medical and in some cases recreational use of marijuana, there is a growing potential for legitimate personal and commercial exposure. The evolving legal status of *C sativa*, its highly prevalent use throughout the world, and the varied forms in which it is used could translate into its growing role as a clinically relevant allergen that might be encountered.

Crude extracts have been used in different in vivo and in vitro testing methods to demonstrate the immunologic nature of these cases. However, the lack of standardized extracts limits validation and widespread applicability of such diagnostic testing. Much research is still needed to more definitively define pertinent allergens, develop a standardized extract, establish diagnostic sensitivity and specificity, and clarify treatment options for clinically affected *Cannabis*-allergic patients.

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