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Cannabis Allergy: Medical Use in the Context of Contemporary Issues and Risks

Alergia al cannabis: uso médico en el contexto de problemas y riesgos contemporáneos

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SUMMARY

Legalizing cannabis will increase its use in both recreational and medical contexts, leading to a rise in allergic reactions. Research in this field will help uncover potential risks and provide crucial information to the medical community for improving usage and minimizing adverse outcomes. **Objective:** *This article aimed to provide a comprehensive overview of allergic reactions to cannabis and evaluate its impact on health and society.* **Method:** *This research employed an analytic-synthetic approach. The necessary information for the article was obtained and analyzed from electronic scholarly sources.* **Results:** *As a result of this study, it was identified that healthcare professionals' knowledge regarding the application of cannabis and its compounds in clinical practice is limited, thereby lacking experience in treating cannabis allergies. Active education of medical practitioners regarding the application of cannabinoids and potential allergic reactions is necessary, especially as cannabis consumption continues to rise.*

Keywords: *Sensitization, recreational cannabis, marijuana, cannabinoids, addiction.*

RESUMEN

La legalización del cannabis aumentará su uso tanto en contextos recreativos como médicos, lo que provocará un aumento de las reacciones alérgicas. La investigación en este campo ayudará a descubrir riesgos potenciales y proporcionará información crucial a la comunidad médica para mejorar el uso y minimizar los resultados adversos. **Objetivo:** *El objetivo de este artículo es proporcionar una visión integral de las reacciones alérgicas al cannabis y evaluar su impacto en la salud y la sociedad en general.* **Método:** *Para realizar esta investigación se utilizó un enfoque analítico-sintético. La información necesaria para el artículo se obtuvo y analizó de fuentes electrónicas de literatura académica.* **Resultados:** *Como resultado de este estudio, se identificó que el conocimiento de los profesionales de la salud sobre la aplicación del cannabis y sus compuestos en la práctica clínica es limitado, por lo que carecen de experiencia en el tratamiento de las alergias al cannabis. Es necesaria una educación activa de los médicos sobre la aplicación de cannabinoides y las posibles reacciones alérgicas, especialmente porque el consumo de cannabis sigue aumentando.*

Palabras clave*: Sensibilización, cannabis recreativo, marihuana, cannabinoides, adicción.*

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INTRODUCTION

Cannabis has long been recognized for its medicinal benefits, including its ability to alleviate chronic pain, reduce nausea in chemotherapy patients, control epilepsy, and mitigate symptoms of multiple sclerosis. Its therapeutic potential is primarily attributed to its interaction with the endocannabinoid system, which can produce anti-inflammatory, analgesic, and antiemetic effects. Despite these significant benefits, cannabis remains illegal in many nations due to its status as a readily accessible drug, leading to limited research and understanding of its effects on human health, especially concerning allergic reactions. This legal status has hindered comprehensive studies, making the effects of cannabis, particularly allergies, poorly understood in modern medicine. Therefore, examining cannabis-related allergies is highly relevant, as it addresses a critical gap in the current medical knowledge and can lead to safer usage guidelines and better therapeutic applications.

Cannabis helps reduce the symptoms of a number of illnesses, including multiple sclerosis, chemotherapy-induced nausea, epilepsy, and chronic pain. It can have analgesic, anti-inflammatory, and antiemetic properties through its interaction with the endocannabinoid system. Legalization promotes research into the potential medicinal uses of cannabis while ensuring that patients have access to safe, standardized products. Open communication between patients and healthcare professionals is encouraged, and people are empowered to make decisions without worrying about legal consequences. Moreover, allowing medicinal marijuana use can boost the economy. The use of cannabis for medical purposes has been associated with decreased opiate medication use in patients with chronic pain. It is effective for pain control, particularly for chronic pain, multiple sclerosis-related spasticity, and nerve pain.

Germany, Italy, and the Netherlands were the first European countries to legalize cannabis for medical purposes (1). Germany introduced a regulated system for prescribing and dispensing in 2017, while Italy allowed it for specific medical conditions in 2013. The Netherlands officially legalized medical cannabis in 2003, setting a precedent for other European countries. Over 20 European countries now have legalized cannabis for medical use, with each country having its own regulations. This includes countries like Austria, Belgium, the Czech Republic, Finland, France, Poland, Portugal, Spain, and Switzerland.

Depending on the method of consumption and interaction with various substances, different reactions to cannabis are possible. The similarity of symptoms to other allergies complicates the diagnosis and identification of allergic reactions to cannabis. After the legalization of medical cannabis in Poland in 2017, its role in the treatment of patients has grown significantly (2). Hordowicz et al. (3) found that most Polish doctors were in favor of legalizing medical cannabis but had limited experience prescribing it. Almost 91.3.% of respondents had no clinical experience of using cannabis, although 49.7 % had patients for whom it would be appropriate to use cannabis in the treatment of various pathologies. Most indications for cannabinoids included chronic oncology pain and neuropathic pain, cachexia, and chemotherapy-related symptoms.

Graczyk et al. (4) described the anti-inflammatory, antioxidant, and immuno-modulatory effects of major phytocannabinoids such as Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), synthetic and endogenous cannabinoids like nabilone, ajulemic acid, anandamide, 2-arachidonoylglycerol, and arachidonoylethanolamide. The mechanism of action is related to their influence on cannabinoid CB1 and CB2 receptors located in the central nervous system (CNS) and peripheral nervous system (PNS), gastrointestinal tract, skin, liver, blood vessels, immune system cells, and endothelium. Cannabinoids can increase the synthesis of anti-inflammatory eicosanoids, inhibit leukocyte proliferation, and suppress the release of pro-inflammatory cytokines.

Manthey et al. (5) identified an increase in cannabis consumption, treatment frequency, and risky usage patterns in Europe from 2010 to 2019. Specifically in Poland, the level of THC in cannabis rose from 0.5 % to 1.1 %. The high THC content increases the likelihood of toxic poisoning from consuming the product. Cavalheiro et al. (6) found a positive impact of using *Cannabis sativa*

in the treatment of obesity and related conditions due to its anti-inflammatory properties.

The mechanism of allergy development involves sensitization and the effector phase. After the initial contact with the allergen, CD4 cells, T-helper 2 cells, and IgE antibodies are released, which diffuse and bind to the IgE receptor (FcεR1) on the surface of mast cells and basophils. Upon subsequent contact with the allergen, cross-linking of IgE-FcεR1 complexes occurs, releasing inflammatory mediators (7). The purpose of this study was to provide contemporary insights into cannabis-related allergies and to determine the possibilities and limitations of cannabis use in medical practice.

METHODOLOGY

A comprehensive analysis of scientific sources, publications, medical databases, and information resources on the Internet related to cannabis allergy was conducted—an extensive database covering information from various scientific materials worldwide, including Europe and Poland. Most articles were used from the NCBI source, UpToDate, Medscape, PubMed, Cochrane Library, MDPI, and others were also used. The primary sources of reliable and up-to-date information were scientific articles, review materials, clinical studies, as well as websites of leading medical organizations and universities, which covered information on the use of cannabis for recreational and medical purposes and possible side effects and allergic reactions to its use. The following keywords were used to search for information: sensitization, hypersensitivity, marijuana, cannabinoids, medical use, allergy, Poland, and Europe. The possibility of including all countries in the study was allowed. The article did not consider works unrelated to the research topic and needed reliable information. For the analysis of information on allergic reactions to cannabis and its compounds, relevant studies were selected, which included clinical cases of allergy, previous studies of allergic reactions to plant allergens, as well as studies of the medical use of cannabis. All the necessary ethical norms and principles of using scientific information were observed concerning authorship rights and citation of materials. Fifty-two sources over the last few years of publication were used to conduct research and assess the current state of cannabis use. After the selection of the necessary information and analysis was completed, aspects such as the prevalence of cannabis use, the general properties of cannabinoids, and the current state of the use of cannabis, in particular for medical purposes, were taken into account. The article discloses data on the plant's microbiome and its influence on sensitization and developing other pathological conditions in the body. The study also included information on the professional effects of cannabinoids on the human body. The types of allergic reactions to cannabis, clinical manifestations of allergic and adverse reactions to the use of cannabis, the main allergenic proteins of the plant, the mechanism of the body's interaction with cannabis allergens, and possible ways of diagnosing and treating allergic reactions were considered. The article also delves into the efficacy and safety of cannabinoid use.

GENERAL INFORMATION ABOUT CANNABIS

Annually, about 2.5 % of the world's population uses marijuana, compared to 0.2 % for cocaine and 0.2 % for opiate drugs (7). Among psychoactive substances, cannabis use among young people in the Baltic States and Poland in 2006-2018 ranged from 5 % to 13 % among boys and from 2 % to 8 % among girls (8). In 2014, 44.6 % of all persons diagnosed with drug addiction in Poland for the first time were marijuana users (9). According to the results of Lo et al. (10), the prevalence of cannabis hypersensitivity among active marijuana users was 52.2 %. The acceptance by society and legalization of recreational cannabis usage continues to increase, which will lead to a rise in marijuana consumption and, consequently, elevate the level of sensitization through direct or passive cannabis consumption.

Cannabis is a general term that covers several narcotic substances obtained from the *Cannabis sativa* plant. Cannabis is a plant known for its psychoactive and other medicinal properties. In addition to *Cannabis sativa*, the main species of cannabis include *Cannabis indica* and *Cannabis ruderalis* (13). Today, more than 140 cannabinoids are known, among which Δ9-tetrahydrocannabinol, cannabidiol, cannabinol,

and cannabidivarin (CBDV) are considered the main ones (14-16). The leaves and flowers of *Cannabis sativa* and *Cannabis indica* plants are commonly referred to as marijuana. Hashish, on the other hand, is a concentrated resin derived from the unpollinated female cannabis plant. This resin contains higher concentrations of psychoactive compounds, primarily tetrahydrocannabinol, compared to marijuana. Some new compounds that differ from cannabinoids also have many similar pharmacological properties. Hemp oil is a concentrate of cannabinoids.

In Poland, the area under *Cannabis sativa* cultivation increased by 80 % from 2018 to 2020, reaching about 3,000 hectares (17). Increasing the cultivation area of *Cannabis sativa* may contribute to expanding access to raw materials to produce medicinal preparations based on cannabis. Members of the world's allergy societies have formed the Cannabis Allergy Interest Group (CAIG), which intends to create a biobank to collect samples from Europe, the United States, and Canada. In addition, the CAIG collects information resources on the clinical use and occurrence of allergic reactions to cannabis and plans to create international guidelines for the diagnosis and treatment of cannabis allergy (18).

As of 2023, the Food and Drug Administration (FDA) has not approved the medical use of cannabis for the treatment of disease but has approved the cannabis-based drug Epidiolex and the synthetic agents Marinol (dronabinol), Syndros (dronabinol), Cesamet (nabilone) (19). Pharmacological properties are realized through interaction with the endocannabinoid system, which includes cannabinoid receptors, natural (endogenous) cannabinoids, and enzymes that regulate the formation and degradation of endocannabinoids (20). The effectiveness and side effects of using medical or recreational cannabis depend on the concentration of THC in the substance, the capacity of which is determined by the genetics of the plant and the growing environment (21). The pathway of cannabinoids' entry into the body determines its pharmacokinetics. Absorption of inhaled THC in the lung alveoli leads to an immediate peak plasma concentration within the first few minutes. The psychotropic effect begins after a few minutes and gradually fades over 2-3 hours. Oral consumption triggers psychoactive effects within 30 to 90 minutes and lasts for 4-12 hours (22).

The reaction to synthetic cannabinoids is less predictable and can lead to unforeseen consequences for consumers. The main psychoactive effects of recreational cannabis depend on THC; the primary medical use is to relieve pain and nausea. CBD has no psychoactive effects and is used to reduce pain and inflammation and control epilepsy and other medical conditions (23). Cannabis affects the regulation of metabolism, appetite, blood pressure, blood sugar control, immune responses, altered consciousness, and the perception of pleasure. The binding of Δ^9-THC to neuronal CB1 receptors causes stimulation of G_i signaling that inhibits cAMP synthesis, and N-type Ca^{2+} channel opening. In addition, the CB1 receptor/G_i stimulation activates G protein-gated inward rectifier K^+ (GIRK) channels, resulting in a more negative resting membrane potential and an inhibition of neurotransmitter release. CB1 receptors cannabinoids inhibit neurotransmitter release via specific presynaptic cannabinoid CB1 receptors. Studies using either the CB1 receptor antagonist and inverse agonist SR141716 or CB1-receptor-deficient mice suggest that numerous presynaptic cannabinoid receptors are tonically activated by endogenous cannabinoids and/or are constitutively active. Thus, cannabis influences the release of the neurotransmitters serotonin, dopamine, norepinephrine, and gamma-aminobutyric acid (GABA) (24,25). Through the CB2 receptor, CBD may inhibit the expression of TNF-α, iNOS, and COX-2, which are involved in inflammatory signaling pathways. After interaction with the CB2 receptor, CBD inhibits adenosine uptake via the A2A receptor, thereby inhibiting inflammatory reactions (25). By affecting the CB2 receptor, cannabis can be used in various forms, such as smoking, consuming cannabis-infused food or drinks, possibly injecting, and taking it through the skin or under the tongue in the form of oils and extracts.

Some studies show the potential of cannabis for the treatment of certain medical conditions, such as epilepsy, chronic pain, and appetite disorders, able to reduce inflammation in multiple sclerosis, sepsis, allergies, and inflammatory processes of the respiratory tract and intestine (26). CBD may

be beneficial in treating obesity by regenerating damaged adipose-derived stem cells (ASC) (27). The use of cannabis and cannabinoids in clinical practice has been shown to reduce nausea and vomiting and reduce pain sensations (28). However, some aspects of its medical use remain debated due to limited scientific research and unclear side effects. Orozco et al. (29) found that the presence of sinonasal symptoms was less common among subjects who used cannabis regularly compared to patients who rarely used it. The mechanism of occurrence of this condition requires further research.

The increasing use of cannabis globally, especially in Poland, has led to a high prevalence of hypersensitivity among users, necessitating the development of allergy research. Organizations like CAIG are creating international guidelines and biobanks for allergy research. However, legal and regulatory frameworks have limited comprehensive research on long-term effects and allergy mechanisms. Understanding the pharmacokinetics of cannabinoids is crucial for developing safe, effective treatments. Further research is needed to optimize therapeutic use and mitigate risks.

CLINIC, DIAGNOSIS, AND TREATMENT OF CANNABIS ALLERGY

Cannabinoid allergies usually manifest during the first 30 minutes and are mainly dependent on the manner of contact with the substance. Cannabis's aero-allergenic qualities have the potential to aggravate bronchial asthma, induce allergic rhinitis, and cause keratoconjunctivitis (30). Because marijuana is smoked widely, the respiratory system is more likely to exhibit symptoms. Clinical symptoms include coughing, trouble breathing, itching and burning in the throat, secretions and nasal congestion, and sneezing. Contact dermatitis and potential itching, redness, rashes, and skin swelling are signs of skin symptoms. The gastrointestinal tract can go through diarrhea, vomiting, nausea, and abdominal discomfort. In severe cases, cannabis use can trigger a fatal anaphylactic reaction (31).

Differential diagnosis between side effects from cannabis use and an allergic reaction can be challenging due to the similarity of symptoms. Differences in ophthalmic and nasal symptoms include the presence of pronounced itching of the nose, eyes, palate, and throat in allergic reactions compared to the side effects of cannabis. From other systems, possible manifestations of increased arterial pressure, tachycardia, the development of pneumothorax, pneumomediastinum, and eosinophilic pneumonia can occur with side effects of cannabis use. In contrast, during anaphylaxis, changes include bradycardia, arterial hypotension, and spasmodic abdominal pain (32).

Confirmation of an allergy to cannabis consists of an appropriate history of contact with the substance, determination of quantitative IgE to cannabis, a basophil or mast cell activation test, and a positive prick test result. Negative tests suggest that a diagnosis of cannabis allergy is unlikely (18). Commercial diagnostic tests are unavailable in the clinical setting, making diagnosis difficult. When commercial cannabis extracts become widely available, it is necessary to consider the variety of allergens of this plant. Also, cannabis use is often silenced by patients due to legal implications, social stigma, and the misconception that cannabis use does not affect medical conditions and treatment. Healthcare professionals must create an open and nonjudgmental environment for patients to discuss their cannabis use. Improving methods for diagnosing cannabis allergies and developing effective treatment and management strategies for these allergies is crucial.

Cannabis sativa is known to include allergens such as profilin, non-specific lipid transfer protein (ns-LTP), oxygen-evolving enhancer 2, and pathogenesis-related protein PR-10, which is a homolog of Bet v 1, the identification of which occurred after exposure to the respiratory tract. Nayak et al. (33) found heterogeneous IgE reactivity in various plant parts. The identified allergenic proteins of *Cannabis sativa* included ATP synthase, phosphoglycerate kinase, RuBisCO, and glycerol-3-phosphate dehydrogenase. Potential sources of allergens in hemp seeds are vicilins and elastins; it is also indicated that a cross-reactive allergic reaction to hazelnuts is possible (34).

Cannabis has the ability to cause allergy responses of type 1 and type 4 (35). When cannabis

comes into touch with other plants, whether nearby or far away, allergenic components of thaumatin-like proteins may react, causing allergic responses (36). The term "cannabis-fruit/vegetable syndrome" refers to a possible cross-reactive allergic reaction to foods containing ns-LTP, which is found in many fruits and vegetables (37,38). Peaches, apples, tomatoes, bananas, walnuts, hazelnuts, wheat, cherries, mandarins, wine, and beer are the foods most commonly linked to these relationships. Ns-LTP can cause hypersensitive responses when it comes into contact with the skin, oral cavity, or respiratory system. It is also resistant to heat and digestive processes (35). Armentia et al. (39), showed that pollen allergy did not increase the probability of sensitization to cannabis. Ebo et al. (40) found that allergic reactions to plant foods in patients with cannabis allergy were clinically more severe compared to patients without cannabis allergy. All examined patients, except for one, were sensitized to ns-LTP.

Cysteinyl leukotrienes (CysLT) released by mast cells, eosinophils, and macrophages in nasal tissue after allergen contact are involved in the development of allergic rhinitis (AR) (41). Histamine release contributes to nasal congestion during allergic inflammation (37). Manthey et al. (5) reported that the concentration of THC in cannabis resin extracted from the plant increased in European countries from 2010 to 2019. These changes are associated with a shift towards THC-dominant cannabis plants imported into the European market from Morocco. The increase in THC concentration may lead to a higher likelihood of side effects and allergies in consumers. Further research is necessary to expand the understanding of the molecular mechanisms of allergic reactions to cannabis and their clinical consequences.

Currently, the primary approach to managing cannabis allergies involves allergen avoidance, which includes steering clear of cannabis products and potentially cross-reactive foods. When avoidance is not feasible, treatment focuses on symptom management using a variety of medications. These include systemic and local antihistamines to reduce allergic responses, inhaled and intranasal corticosteroids to decrease inflammation, mast cell stabilizers to prevent the release of allergy mediators, and adrenaline for severe, life-threatening reactions such as anaphylaxis (43).

An emerging treatment option is allergen-specific immunotherapy, which aims to desensitize the immune system to cannabis allergens. However, this approach is still in its early stages and has certain limitations that require further research and refinement. Another promising avenue for preventing allergic reactions involves the development of purified or synthetic cannabis-derived substances that lack the protein components responsible for triggering allergies (18). It's important to note that despite these advancements, there is currently no standardized, approved protocol for treating allergic reactions to cannabis and its derivatives. This underscores the need for continued research and development in this field to establish evidence-based treatment guidelines for cannabis allergies.

TOXICITY, MICROBIOME AND ALLERGIC REACTIONS IN THE CONDITIONS OF PROFESSIONAL PRODUCTION

The use of cannabis for medical purposes is accompanied not only by beneficial properties but also by undesirable side effects. Intensive cannabis consumption can disrupt intellectual and psychomotor functions. Among the anticipated yet unwanted physiological reactions that should be noted when an allergy is suspected, possible symptoms include orthostatic hypotension, sinus tachycardia, conjunctival redness, and panic attacks (44,45). Cannabinoids and their derivatives have the property of inducing acute toxicity, which is associated with excessive stimulation of the endocannabinoid system. In severe cases, the development of rhabdomyolysis and renal failure is possible, especially in pediatric cases. There is an elevated risk of experiencing side effects such as disorientation, drowsiness, hallucinations, confused consciousness, fatigue, and dizziness (27).

In the study of the effectiveness and safety indicators of THC and CBD applications conducted by Olsson et al. (46), it was found that most adverse reactions were mild. The most common side effects throughout the treatment were fatigue, drowsiness, dizziness, headache,

coordination disturbances, and nausea. Women and individuals with no prior cannabis use were more susceptible to experiencing undesirable effects. The tendency for recurrent cases of acute cannabis poisoning may indicate low cannabis tolerance, adulterated or contaminated products, individual reactions, or the development of psychological dependence, which could lead to more negative effects over time (47, 48).

The possibility of reducing the toxicity of cannabinoids has been identified through the modification of the genetic structure of *Cannabis sativa* using *Agrobacterium tumefaciens* (49). The indicated methodology requires further research. Potentiation of the effects of cannabinoids is possible with concurrent use of ketoconazole, macrolides, verapamil, warfarin, and theophylline, along with marijuana. The mechanism of these effects is associated with the shared inhibition of CYP2C9 and liver cytochrome P450. An additive effect of co-administration is possible when combining cannabinoids with sympathomimetics, anticholinergic drugs, alcohol, and opioids (50). The data on interactions of medicinal products with cannabis should be considered when used in clinical practice.

The understudied topic of the cannabis microbiome could pose significant risks to the quality and safety of cannabis, especially as the demand for its production increases. Medical cannabis can contain hazardous levels of fungi, bacteria, and toxic pesticides, which present a health risk to humans (51). Smoking marijuana with a high concentration of mold-producing fungi such as *Aspergillus* can lead to allergic bronchopulmonary aspergillosis (52). Reported cases of eosinophilic pneumonia after consuming cannabis hash oil are likely associated with fungal contamination by *Aspergillus* (53). Mold and mycotoxins can induce allergic immune reactions, precisely type 1, 3, and 4 hypersensitivity reactions (54,55). Mycotoxins act as inflammation initiators by introducing inflammatory triggers and allergens, thereby causing the onset or exacerbation of chronic diseases. Mold can compromise the epithelial barrier of the respiratory and gastrointestinal tracts, becoming systemically bioavailable and capable of affecting multiple organ systems.

Rapidly increasing demand for cannabis in both medical and non-medical sectors has led to a rise in the number of workers engaged in cannabis processing. Throughout the entire process of cultivation, processing, and storage, there is a potential risk of developing allergic sensitization to hemp (56). Occupational exposure to cannabis can result in elevated serum IgE levels specific to hemp (57). Prolonged inhalation of organic cannabis dust and endotoxins can lead to an occupational lung disease known as "byssinosis," characterized by bronchial obstruction, inflammation, and hyperreactivity, mimicking bronchial asthma (58).

In a study investigating the occupational impact of cannabis on workers at a closed cannabis cultivation facility, Sack et al. (59) identified a tendency toward respiratory, ocular, nasal, and cutaneous symptoms among employees associated with job-related activities. Some of these workers exhibited elevated levels of exhaled nitric oxide (FeNO), changes in spirometry, and skin sensitization through skin prick tests. Most of these workers also reported recreational marijuana use, making it challenging to isolate the occupational influence of cannabis definitively. In addition to inhaling organic dust in workplaces, which includes fungi, bacteria, and endotoxins, there is a risk of inhaling volatile organic compounds (VOCs), diacetyl, and 2,3-pentanedione during decarboxylation and grinding of dried cannabis (60).

Cannabis use in medical settings has both positive and negative effects, which range from mild to severe, including fatigue and organ damage. The cannabis microbiome, including fungi and bacteria, poses health risks. Occupational hazards include allergic sensitization and respiratory issues. Further research is needed to reduce cannabinoid toxicity, improve quality control, and develop safety measures. A comprehensive understanding of cannabis's effects and risks is essential for safe and effective use in both medical and non-medical settings.

CONCLUSIONS

An allergic reaction related to cannabinoids is a significant and current issue in modern medicine. Clinical symptoms depend on the method of contact with the substance. More often,

the aeroallergenic properties of cannabis lead to manifestations of keratoconjunctivitis, allergic rhinitis, and bronchial asthma, especially with active marijuana smoking. Skin symptoms can occur after direct contact with the skin, including contact dermatitis, itching, redness, and swelling. Gastrointestinal symptoms are also possible.

Allergic reactions to cannabis can arise from both natural plant compounds and synthetic analogs. It was shown that appropriate testing, such as a history of drug exposure, an assessment of one's IgE level, skin prick testing, and tests for mast cell and basophil activation, are crucial to confirm a cannabis allergy. Shared allergenic compounds with other plants, such as fruits and vegetables, can trigger cross-reactive allergic reactions to cannabis. Reaction to ns-LTP can lead to the "cannabis-fruit/vegetable" syndrome. Increasing the concentration of THC in cannabis products may raise the risk of allergic and adverse reactions in consumers. This is particularly relevant in countries where the concentration of THC in market-available products is on the rise.

Cannabis allergy diagnosis is challenging due to the lack of commercially accessible diagnostics and patients' reluctance to use the drug. Current therapy approaches include corticosteroids, adrenaline, and antihistamines, with the potential for allergen-specific immunotherapy. The study also highlights the risks of the cannabis microbiome, particularly in medicinal cannabis products, which can cause allergic responses and health issues. The most effective treatment is avoidance, with symptomatic relief achieved through antihistamines, corticosteroids, and adrenaline. This research highlighted that professional cannabis production exposes workers to allergic sensitization due to direct and passive contact with cannabinoids, as well as contamination with fungi, bacteria, and toxic pesticides, which can lead to allergic bronchopulmonary aspergillosis and eosinophilic pneumonia.

There is a need to improve the level of education among physicians and patients regarding allergic reactions to cannabis and formulate prospective prevention and treatment strategies for allergic conditions associated with cannabis consumption in the face of its increasing use. Further research needs to expand the understanding of the molecular mechanisms of allergic reactions to cannabis, the potential cross-reactivity with other plant-based allergens, the impact of cannabis cultivation and processing on occupational health and develop effective diagnostic protocols.

REFERENCES

1. Marta M. Legal aspects of the use of medical cannabis in Poland compared to other countries: Comparative legal analysis. Law J Natl Acad Intern Affairs. 2023;13(3):18-25.
2. Act of 7 July 2017 amending the Act on Counteracting Drug Addiction and the Act on Reimbursement of medicines, foodstuffs for particular nutritional uses, and medical devices. 2017.
3. Hordowicz MJ, Jarosz J, Klimkiewicz A, Czaplińska M, Leonhard A, Wysocka M. To treat or not to treat? Polish physicians' opinions about the clinical aspects of cannabinoids – an online survey. Food Res Int. 2022;11(1):236.
4. Graczyk M, Lewandowska A, Dzierzanowski T. The therapeutic potential of cannabis in counteracting oxidative stress and inflammation. Molecules. 2021;26(15):4551.
5. Manthey J, Freeman T, Kilian C, Lopez-Pelayo H, Rehm J. Public health monitoring of cannabis use in Europe: prevalence of use, cannabis potency, and treatment rates. The Lancet Reg Health Eur. 2021;10:100227.
6. Cavalheiro EKFF, Costa AB, Salla DH, Silva MRD, Mendes TF, Silva LED, et al. *Cannabis sativa* as a treatment for obesity: from anti-inflammatory indirect support to a promising metabolic re-establishment target. Cannabis Cannabinoid Res. 2022;7(2):135-151.
7. Angelina A, Perez-Diego M, Lopez-Abente J, Palomares O. The role of cannabinoids in allergic diseases: Collegiums International Allergologicum (CIA) update 2020. Int Arch Allergy Immunol. 2020;181(8):565-584.
8. World Health Organization. Alcohol, drugs, and addictive behaviors unit. 2023. Available at: https://www.who.int/teams/mental-health-and-substance-use/alcohol-drugs-and-addictive-behaviours/drugs-psychoactive/cannabis#:~:text=About%20147 %20million%20people%2C%202.5,than%20cocaine%20and%20opiate%20abuse.
9. Vaiciunas T, Zemaitaitytr M, Lange S, Stelemekas M, Oja L, Petkeviciene J, et al. Trends in adolescent substance use: analysis of HBSC data four eastern European countries, 1994-2018. Int J Environ Res Publ Health. 2022;19(23):15457.

10. Pinkas J, Jabłonski P, Kidawa M, Wierzba W. Use of marijuana for medical purposes. AAEM. 2016;23(3):525-528.
11. Pomohaibo V, Berezan O, Petrushov A. Genetics of cannabis addiction. Psychol Personal. 2023;2(24):290-303.
12. Lo S, Abbaslou M, Abbas K, Kobric D, Silvers W, Sussman G. Cannabis hypersensitivity prevalence and presentation – a survey-based study of an allergic adult population in a Toronto clinic at the onset of Canadian legalization of recreational marijuana. J Allergy Clin Immunol Pract. 2020;145(2):AB129.
13. Pisanti S, Bifulco M. Medical cannabis: Aplurimillennial history of an evergreen. J Cell Physiol. 2019;234(6):8342-8351.
14. Sun X. Research progress on cannabinoids in cannabis (*Cannabis sativa L.*) in China. Molecules. 2023;28(9):3806.
15. Banerjee R, Erridge S, Salazar O, Mangal N, Couch D, Pacchetti B, et al. Real-world evidence in medical cannabis research. Ther Innovation & Regul Sci. 2022;56(1):8-14.
16. Hasiuk OP. Pharmacological and morphological features and socioeconomic aspects of cannabidiol: A literature review. Int J Med Med Res. 2023;9(1):47-59.
17. Telesko M, Zając A, Rusak T. Hemp seeds of the Polish 'Bialobrzeskie' and 'Henola' varieties (*Cannabis sativa L.* var. sativa) as prospective plant sources for food production. Molecules. 2022;27(4):1448.
18. Janeczko L. As more people use cannabis, doctors need to learn how to diagnose and treat cannabis allergies. 2022. Available at: https://www.medscape.com/viewarticle/978697?icd=login_success_email_match_norm#vp_2 .
19. FDA and cannabis: research and drug approval process. 2023. Available at: https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process.
20. Lu H, Mackie K. An introduction to the endogenous cannabinoid system. Biol Psychiatry. 2015;79(7):516-525.
21. Lafaye G, Karila L, Blecha L, Benyamina A. Cannabis, cannabinoids, and health. Dialogues in Clin Neurosci. 2017;19(3):309-316.
22. Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clin Pharmacokinet. 2003;42(4):327-360.
23. Turner A, Agrawal S. Marijuana. 2022. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430801/.
24. Dashi F, Seferi A, Rroji A, Enesi E, Petrela M. Bathing epilepsy: Report of three Caucasian cases. Acta Inform Med. 2015;23(2):113-115.
25. Woerdenbag HJ, Olinga P, Kok EA, Brugman DAP, van Ark UF, Ramcharan AS, et al. Potential, limitations, and risks of cannabis-derived products in cancer treatment. Cancers. 2023;15(7):2119.
26. Klein T. Cannabinoid-based drugs as anti-inflammatory therapeutics. Nat Rev Immunol. 2005;5(5):400-411.
27. Kowalczuk A, Marycz K, Kornicka-Garbowska K, Kornicka J, Bujalska-Zadrożny M, Groborz S. Cannabidiol (CBCs) protects adipose-derived mesenchymal stem cells (ASCs) against endoplasmatic reticulum stress development and its complication. Int J Environ Res Public Health. 2022;19(17):10864.
28. Whiting P, Wolff R, Deshpande S. Cannabinoids for medical use. A systematic review and meta-analysis. JAMA. 2015;313(24):2456-2473.
29. Orozco F, Lin M, Hur K. Cannabis use and sinonasal symptoms in US adults. JAMA Otolaryngol Head Neck Surg. 2022;148(9):854-861.
30. Ismailov I, Kalmatov R, Abdurakhmanov B, Mirza AM, Chaurasia JK. Role of reactive oxygen species in the pathogenesis of bronchial asthma and obstructive pulmonary diseases: Systematic Review. Adv Life Sci. 2024;11(2):286-295.
31. Asaumi T, Ebisawa M. How to manage food-dependent exercise-induced anaphylaxis (FDEIA). Curr Opin Allergy Clin Immunol. 2022;18(3):243-247.
32. Toscano A, Ebo DG, Abbas K, Brucker H, Decuyper II, Naimi D, et al. A review of cannabis allergy in the early days of legalization. Ann Allergy Asthma Immunol. 2023;130(3):288-295.
33. Nayak AP, Green BJ, Sussman G, Berlin N, Lata H, Chandra S, et al. Characterization of cannabis sativa allergens. Ann Allergy Asthma Immunol. 2013;111(1):32-37.
34. Beriziky P, Cherkaoui M, Linxe L, Perrin E, Rogniaux H, Denery-Papini S, et al. Hemp seed: an allergen source with potential cross-reactivity to hazelnut. Food Res Int. 2023;169:112932.
35. Skypala IJ, Jeimy S, Brucker H, Nayak AP, Decuyper II, Bernstein JA, et al. Cannabis-related allergies: An international overview and consensus recommendations. Allergy. 2022;77(7):2038-2052.
36. Larramendi CH, López-Matas MÁ, Ferrer A, Huertas AJ, Pagán JA, Navarro, LÁ, et al. Prevalence of sensitization to cannabis sativa. Lipid-transfer and thaumatin-like proteins are relevant allergens. Int Arch Allergy Immunol. 2013;162(2):115-122.
37. Drouet M, Hoppe A, Mereau A, Boneau J, Leclere J, Sellin J. Cannabis and crossed allergy with food. Rev Pneumol Clin. 2017;73(6):290-293.
38. Van Gasse A, Sabato V, Faber M, Bridts C, Ebo D. Chapter 54 – Cannabis allergy: More than a bad trip.

In: Handbook of Cannabis and Related Pathologies. London: Academic Press. 2017:517-526.

39. Armentia A, Castrodeza J, Ruiz-Muñoz P, Martínez-Quesada J, Postigo I, Herrero M, et al. Allergic hypersensitivity to cannabis in patients with allergy and illicit drug users. Allergol et Immunopathol. 2011;39(5):271-279.
40. Ebo DG, Swerts S, Sabato V, Hagendorens MM, Bridts CH, Jorens PG. et al. New food allergies in European non-mediterranean region: Is *Cannabis sativa* to blame? Int Arch Allergy Immunol. 2013;161(3):220-228.
41. Peters-Golden M Gleason M, Togias A. Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. Clin Exp Allergy. 2006;36(6):689-703.
42. Bachert C. The role of histamine in allergic disease: re-appraisal of its inflammatory potential. Allergy. 2002;57(4):287-296.
43. Parisi GF, Leonardi S, Ciprandi G, Corsico A, Licari A, Miraglia del Giudice M, et al. Antihistamines in children and adolescents: A practical update. Allergol Immunopathol. 2020;48(6):753-762.
44. Ocampo T, Rans T. *Cannabis sativa*: the unconventional "weed" allergen. Ann Allergy Asthma Immunol. 2015;114(3):187-192.
45. Lako AZ, Myderrizi N, Krasniqi M, Kalaja R. Parkinson's disease, early physiotherapeutic rehabilitation during the period January-December 2022 at the Central Polyclinic, Durres. J Adv Pharm Educ Res. 2023;13(4):104-108.
46. Olsson F, Erridge S, Tait J, Holvey C, Coomber R, Beri S, et al. An observation study of safety and clinical outcome measures across patient groups in the United Kingdom Medical Cannabis Registry. Expert Rev Clin Pharmacol. 2023;16(3):257-266.
47. Spytska L. Anxiety and depressive personality disorders in the modern world. Acta Psychol. 2024;246:104285.
48. Spytska L. Forecasts regarding mental disorders in people in the post-war period. Eur J Trauma Dissociation. 2024;8(1):100378.
49. Niaz K, Khan F, Maqbool F, Momtaz S, Ismail Hassan F, Nobakht-Haghighi N, et al. Endo-cannabinoids system and the toxicity of cannabinoids with a biotechnological approach. EXCLI Journal. 2017;16:688-711.
50. Antoniou T, Bodkin J, Ho J. Drug interactions with cannabinoids. CMAJ. 2020;192(9):E206.
51. Vujanovic V, Korber D, Vujanovic S, Vujanovic J, Jabaji S. Scientific prospects for cannabis-microbiome research to ensure quality and safety of products. Microorganisms. 2020;8(2):290.
52. Llamas R, Hart D, Schneider N. Allergic bronchopulmonary aspergillosis associated with smoking moldy marihuana. Chest. 1978;73(6):871-872.
53. Lee M, Cool C, Maloney J. Histopathological correlation of acute on chronic eosinophilic pneumonitis caused by vaporized cannabis oil inhalation. Chest. 2021;159(3):137-139.
54. Kraft S, Buchenauer L, Polte T. Mold, mycotoxins and a dysregulated immune system: a combination of concern? Int J Mol Sci. 2021;22(22):12269.
55. Moller J, Hyldgaard C, Kronborg-White S, Mussen F, Bendstrup E. Hypersensitive pneumonitis among wind musicians – an overlooked disease? Eur Clin Respir J 2017;4(1):1351268.
56. Decuyper I, Green B, Sussman G, Ebo D, Silver W, Pacheco K, et al. Occupational allergies to cannabis. J Allergy Clin Immunol: Pract. 2021;8(10):3331-3338.
57. Sussman G, Beezhold D, Cohn J, Silvers W, Zeiger J, Nayak A. Cannabis: an emerging occupational allergen? Ann Work Exposures Health. 2020;64(7):679-682.
58. Patel P, Yarrarapu S, Anjum F. Byssinosis. Statpearls. 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK519549/.
59. Sack C, Ghodsian N, Jansen K, Silvey B, Simpson C. Allergic and respiratory symptoms in employees of indoor cannabis grow facilities. Ann Work Exposures Health. 2020;64(7):754-764.
60. Couch JR, Grimes GR, Green BJ, Wiegand DM, King B, Methner MM. Review of NIOSH cannabis-related health hazard evaluations and research. Ann Work Exposures Health. 2020;64(7):693-704.