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REVIEW ARTICLE

Cannabis and Cannabinoids use in Children and Adolescents with Autism Spectrum Disorder: a systematic review

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Autism Spectrum Disorder, Cannabis, Cannabinoids, Cannabidiol.

Abstract

Introduction: Autism spectrum disorders (ASD) are characterized by DSM-5 as persistent deficits in social interaction and communication. Studies suggest cannabidiol may help treat ASD symptoms in children, though the full mechanism remains unclear. **Objective:** Report clinical data on cannabinoid use in treating ASD in children. **Methods:** PubMed, Cochrane, and Embase platforms were searched. A total of 288 articles were identified, screened by title, abstract, and full text (n=6). **Results:** According to Aran et al., ASD participants (n=22) treated with cannabis extract showed improvement in the Clinical Global Impression (p=0.005) and Social Responsiveness Scale (p=0.009) compared with placebo. As reported by Hacohen et al., children (n=75) treated with cannabis showed significant improvements on the Autism Diagnostic Observation Schedule (p=0.003), particularly in social affect (p=0.001). Additionally, some patients (n=61) improved on the Social Responsiveness Scale-2 (p=0.043), while others (n=76) demonstrated enhancements in communication (p=0.008), daily living (p=0.007) and socialization based on Vineland scores (p<0.001). Common adverse events in two studies were somnolence and decreased appetite. No significant difference was found between conventional and cannabidiol treatments for sleep problems and anxiety in two studies. **Conclusion:** Cannabinoid treatment appears safe and may alleviate ASD symptoms but caution is advised with THC use in children due to potential impacts on brain development and other effects.

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INTRODUCTION

Autism spectrum disorders (ASD) are characterized by The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)[1], as persistent deficits in social interaction and communication across multiple contexts, with atypical patterns of behavior, interests, or activities. Children with ASD can experience symptoms such as hyperactivity, self-injury, aggressiveness, restlessness, anxiety, sleep disorders and sensory sensitivity, and manifestations of over or under-sensitivity, along with reactions over specific sights and sounds, can cause distress and discomfort for the child and severe negative impact on the family and social environment[2].

Symptoms can vary based on the severity of the disorder, which involves social communication impairments and restricted repetitive behaviors. Greater impairment in these areas necessitates more support and indicates a more severe disorder[1].

Usually, the diagnosis of ASD is made during the preschool period, in children exhibiting generalized developmental delay[3]. The American Academy of Pediatrics recommends that all children be screened with autism-specific screening tests at 18 and 24 months, but the diagnosis can be made even earlier, in children who meet the diagnostic criteria.[2] An earlier diagnosis allows for sooner intervention services, which can influence outcomes in a child's social and emotional development and quality of life[2].

Until this date, the treatment involves a multi-sensory and multi-disciplinary approach, focusing on the functional independence and quality of life of the children. The non-pharmacological treatments aim to minimize the atypical patterns of behavior and improve social and emotional development, by working on the children's skills and sensory integration through occupational therapy, educational assistance, speech therapy and cognitive behavioral therapy and promoting positive reinforcement with the family[4].

Pharmacological treatments are individualized and symptomatic, including antipsychotics, antidepressants, mood stabilizers, antianxiety agents, benzodiazepines, and sleep medications. These medications are commonly used to reduce symptoms such as irritability, stereotypy, and psychomotor agitation. None of those medications can be considered a cure for the disorder, even though they can be effective in reducing the majority of the symptoms, but the side effects they can present are considerable and can result in the noncompliance to the treatment by the parents[5].

Recent studies have indicated that cannabidiol can be beneficial in managing ASD symptoms in children. Cannabis contains several chemically active compounds, including Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), and terpenoids, which interact with the endocannabinoid system (ECS) in the central nervous system, affecting appetite, anxiety, cognitive function, and memory[6].

The ECS has been studied for its capacity in regulating emotion and social behaviors, which involves the cannabinoid receptors (CB1 and CB2) and their endocannabinoids, as well as the enzymes involved in their biosynthesis and inactivation. The role of the endocannabinoid system is to act on presynaptic cannabinoid receptors to reduce the release of neurotransmitters such as GABA, glutamate, and acetylcholine. Dysfunction in this system's components may contribute to the behavioral deficits and neuroinflammation observed in autism[7].

The ECS plays an important role in the development of the central nervous system (CNS). Its receptors CB1 are located in the CNS, concentrated in the cerebellum, hippocampus, and the basal ganglia, which are areas of dysfunction in autism. Furthermore, autism is associated with dysregulation of the immune system, which has CB2 receptors located in immune cells, and might be critical to ASD-related neuroinflammation[7].

OBJECTIVE

This systematic review of studies aims to report the available clinical data regarding the use of cannabis and cannabinoid in the treatment of the behavioral symptoms and co-morbidities of ASD in children, and potential effectiveness, tolerability and safety of CBD, considering the evolution of symptoms and clinical improvement of the participants in the studies.

METHODS

The review question defined by the PECOTT acronym was "Is cannabidiol effective and safe in the treatment of children with autism spectrum disorder?", and it is represented in Table 1 below.

To answer the review question, we used the "Autism Spectrum Disorder", "treatment", "cannabinoids" and "cannabidiol" entry terms associated by the Boolean Operator "AND" and their associated terms, available on the Medical Subjects Headings (MeSH) website, associated by the Boolean operator "OR". We used the terms to run a search on PubMed, Cochrane Database of Systematic Reviews and Embase, being downloaded researches available on those database.

The inclusion criteria were studies with children and adolescents with Autism Spectrum Disorder and age between 4 and 25 years. We included articles published in the last 10 years that were observational or experimental studies with humans. We excluded articles which didn't focus on the treatment of ASD with cannabidiol and were reviews.

We aim to investigate whether cannabidiol or cannabis are effective in the treatment and management of the symptoms of ASD in children and adolescents. As secondary outcomes, we seek to correlate the effects of cannabidiol in the prognosis of the disorder and its safety.

Through a screening, by applying the PICO question, we selected articles by title, resume and complete article reading, respectively. We used the Rayyan website for the screening, to organize the reasons for inclusion and exclusion of articles more easily, without accounting for selection errors. The process was double-blinded and done by two authors, and disabilities at the second phase were verified by a third author. After the screening, we extracted the data which answered our main outcome. We distributed the articles selected by the full article to two different authors, which selected data from each article and saved it in a Google Docs file. One author looked through every article to assure that unimportant information was left out.

RESULTS

At the beginning of the search, there were 288 articles, including 56 duplicates, resulting in 232 articles. After the first screening, 216 articles were excluded for not meeting the inclusion criteria or meeting the exclusion criteria. Furthermore, 16 articles were included by title and full reading analysis, but 9 of them were excluded for not availability of full reading, resulting in 7 articles from PubMed, Cochrane and Embase database. The screening can be seen on Figure 1 below.

The main origin country of the included articles was Israel (6 studies), and there is one from California. Most of them used DSM-5 as ASD diagnosis criteria. On the other hand, the symptoms were screened by differents scores, such as Home Situations Questionnaire-ASD (HSQ-ASD); CGI-Improvement (CGI-I); Social Responsiveness Scale-2nd edition (SRS-2) and Autism Parenting Stress Index (APSI).

Two randomized controlled trial studies compared placebo to whole-plant cannabis extract containing CBD and THC at a 20:1 ratio and to pure CBD and pure THC at the same ratio and concentration. One prospective cohort study analyzed the results between additional medications and medical cannabis extract infused in MCT oil with a CBD:THC ratio of 20:1. One retrospective study used only cannabinoid oil solution at a concentration of 30% and 1:20 ratio of CBD and THC and another used the olive oil dissolved with the whole plant extracts that contain CBD and THC in a 20:1 ratio. One observational study compared THC (dosing range 0.05–50 mg per dose) to CBD (dosing range 7.5–200 mg per dose). Finally, the last prospective study analyzed the whole-plant extract infused in medium-chain triglyceride (MCT) oil with a CBD:THC ratio of 20:1.

The selected studies are represented in the Table 2 below, with respective author, publication year, study type and follow-up time, study country and sample, ASD diagnosis criteria, symptoms score, intervention and main results.

DISCUSSION

Some studies recognize neurodevelopmental disorders as a cause of morbidity in children, affecting cognitive impairment, quality of life, suffering for patients and their families, and also a lot of costs for society[15]. For this reason, the choice of treatment must take into account the children's performance in social, physical, verbal, and behavioral areas.

The standard treatment includes atypical antipsychotics, selective serotonin reuptake inhibitors, stimulants and anxiolytics, which aim to eliminate the symptoms, not treating the disease properly. In Europe, the approved therapeutic options are aripiprazole and risperidone, drugs with suboptimal efficacy and tolerability in many ASD children[6]. Unfortunately, just 60% of the patients respond well to conventional medical and behavioral treatment[16].

Moreover, aripiprazole and risperidone are atypical antipsychotic medications with similar side effects in ASD children, including fatigue, increased appetite, GI symptoms, hyperprolactinemia, weight gain and sedation. Also, these medications involve some serious side effects, such as dyslipidemia, hyperglycemia, metabolic syndrome and extrapyramidal symptoms[17]. Therefore, the necessity for innovative therapeutic approaches encouraged researchers to explore other alternatives, such as *Cannabis sativa* substances, specialy Cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC).

Table 1. PECOTT acronym, meaning and application in this systematic review.

Acronym	Meaning	Application
P	Population	Children and adolescents with ASD
E	Exposure	Use of cannabis or cannabidiol
C	Control	Other methods of treatment (symptoms control/management)
O	Outcome	Improvement of the symptoms;
T	Type of question and type of study	Effectiveness of the treatment in children; Experimental and Observational studies with humans
T	Time	Unspecified

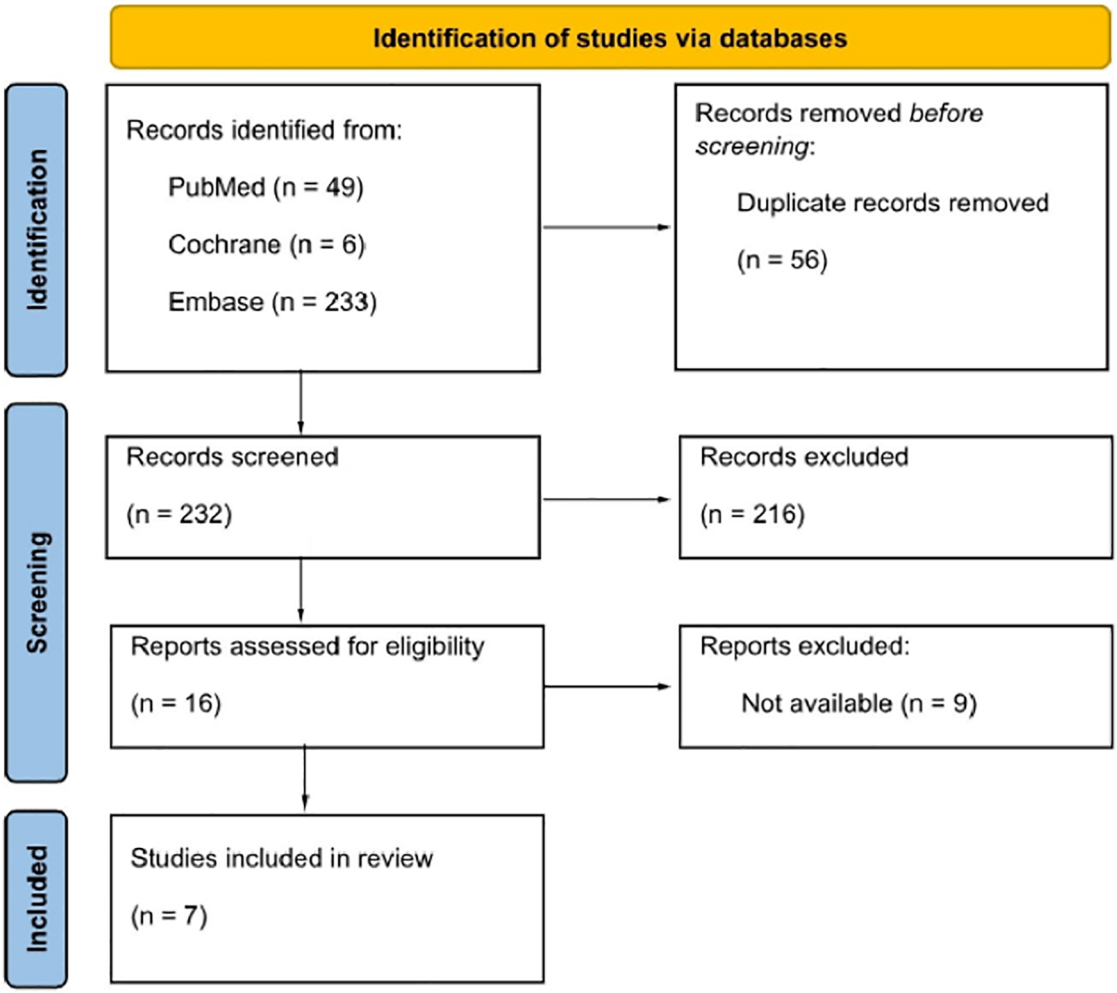

Figure 1. Screening applying PRISMA 2020 diagram for this systematic review. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases only From: Page et al.[18]

A randomized study was conducted in Israel with 150 children and adolescents (5-21 years old) diagnosed with Autism spectrum disorder (ASD), submitted to treatments with oral placebo, whole-plant cannabis extract containing CBD and THC, and pure CBD and pure THC. ASD symptoms were 'severe' in 78.7% per Autism Diagnostic Observation Schedule (ADOS-2) and adaptive level was 'low' (Standard Score ≤ 70) in 88% per Vineland Behavior Scales. Behavior and symptoms were monitored using Home Situations Questionnaire-ASD (HSQ-ASD), Autism Parenting Stress Index (APSI), Clinical Global Impression (CGI-I) and Social Responsiveness Scale-2nd edition (SRS-2). The study showed that HSQ-ASD total scores and APSI total scores did not differ significantly between participants who received cannabinoids and participants who received placebo. However, 49% of 45 participants who received whole-plant cannabinoids responded on CGI-I compared with 21% of 47 on placebo (p=0.005). Also, there was a significant improvement in SRS-2 total score following treatment with whole-plant extract compared with placebo (p=0.009). There were no treatment-related severe or serious adverse events (AEs) monitored with a modified Liverpool Adverse Events Profile (LAEP). Nonetheless, a mild AEs significantly relevant was somnolence (p<0.001)[8].

The same participants in the previous study were analyzed for sleep disorders with Children's Sleep Habits Questionnaire (CSHQ). Among the 146 participants, 86% (n=125) had a sleep disorder (score ≥ 41). Besides, higher CSHQ scores were correlated with a younger age (p<0.001) and with higher SRS total scores (p=0.036) representing more severe core autistic traits. In spite of this, the CSHQ total scores did not differ significantly between the participants who received cannabinoids and the participants who received the placebo. Likewise, there was no significant difference between the participants who received the whole-plant extract versus the pure cannabinoids[9].

In addition, a prospective cohort were conducted with 59 children and young adults (ages 5–25 years), diagnosed with Autism spectrum disorder (ASD) by DSM-5 and carried with

Table 2. Selected studies for analysis in this systematic review.

Author/ year	Title	Study type and follow-up time	Country and sample	ASD diagnosis criteria	Symptoms score	Intervention	Main results
Aran et al., 2021[8]	Cannabinoid treatment for autism: a proof-of-concept randomized trial	RCT with 15 months	Israel; 132 children and adolescents (5–21 years old)	DSM-5 criteria; ADOS-2; (CGI)-Severity scale; rating ≥ 4	HSQ-ASD: scores of 0 to 9; CGI-I: scores of 1 to 7; SRS-2: scores of 0 to 195; APSI: core social disability, difficult-to-manage behavior, and physical issues.	(1) oral placebo; (2) whole-plant cannabis extract containing CBD and THC at a 20:1 ratio; (3) pure CBD and pure THC at the same ratio and concentration	Disruptive behavior on the CGI-I was either much or very much improved in 49% on whole-plant extract (n=45) *versus* 21% on placebo (n=47; *p*=0.005)
Schnapp et al., 2022[9]	A Placebo-Controlled Trial of Cannabinoid Treatment for Disruptive Behavior in Children and Adolescents with Autism Spectrum Disorder: Effects on Sleep Parameters as Measured by the CSHQ	RCT with 15 months	Israel; 132 children and adolescents (5–21 years old)	DSM-5 criteria; ADOS-2; (CGI)-Severity scale; rating ≥ 4	CSHQ: scores of 33 to 99; CGI-I: scores of 1 to 7; SRS-2: scores of 0 to 195.	(1) a whole-plant cannabis extract containing CBD and THC at a 20:1 ratio; (2) purified CBD and THC at the same ratio; (3) placebo.	The CBD-rich cannabinoid treatment was not superior to the placebo treatment in all aspects of sleep measured by the CSHQ.
Stolar et al., 2022[10]	Medical cannabis for the treatment of comorbid symptoms in children with autism spectrum disorder: An interim analysis of biochemical safety	Prospective cohort with 18±8 weeks	Israel; 59 children and young adults (ages 5–25 years)	DSM-5 and DSM-4 criteria	ADOS; Cognitive and Vineland adaptive behavior scales; at least one severe co-morbidity that existed for 6 months	(1) only medical cannabis extract infused in MCT oil with a CBD:THC ratio of 20:1; (2) additional medications	No clinical or statistically significant differences were found in any of the analytes between baseline after 3 months of treatment.
Barchel et al., 2019[11]	Oral Cannabidiol Use in Children With Autism Spectrum Disorder to Treat Related Symptoms and Co-morbidities	Retrospective study with 30–588 days	Israel; 53 children and young adults (ages 4–22 years)	DSM-5 and DSM-4 criteria	Four ASD comorbidity symptoms were evaluated: (a) hyperactivity symptoms (b) sleep problems, (c) self-injury and (d) anxiety.	(1) the cannabinoid oil solution at a concentration of 30% and 1:20 ratio of CBD and THC	There was no statistically difference between the conventional treatment and cannabidiol treatment.
Aran et al., 2019[12]	Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems-A Retrospective Feasibility Study	Retrospective study with 7–13 months	Israel; 60 children and adolescents (ages 5-18 years)	DSM-5 criteria	CGI-S: score of 6 to 7.	(1) whole plant extracts that contain CBD and THC in a 20:1 ratio, dissolved in olive oil	Considerable improvement in behavior problems (61%), anxiety (39%) and communication problems (47%) was reported.

Siani-Rose et al., 2023[13]	Cannabis--Responsive Biomarkers: A Pharmacometabolomics-Based Application to Evaluate the Impact of Medical Cannabis Treatment on Children with Autism Spectrum Disorder	Observational study with at least 01 year	California; 15 children (ages 6-12 years)	ASD diagnosed by a qualified medical or behavioral health clinician	ABAS-3; BASC-3 and SRS-2.	(1) THC (dosing range 0.05–50 mg per dose) in 40% of children; (2) CBD (dosing range 7.5–200 mg per dose) in 60% of children	Sixty-five potential cannabis-responsive biomarkers were identified in children with ASD after medical cannabis treatment
Hacohen et al., 2022[14]	Children and adolescents with ASD treated with CBD-rich cannabis exhibit significant improvements particularly in social symptoms: an open label study	Prospective study with 06 months	Israel; 62 children and adolescents (ages 5-25 years)	DSM-5 criteria	ADOS-2: scores of 0 to 10; Vineland-3; SRS-2; PSI; VCI; POI.	(1) Whole-plant extract infused in medium-chain triglyceride (MCT) oil with a CBD:THC ratio of 20:1	There was significant improvements in overall ADOS-2, SRS, and Vineland scores of the ASD participants who completed the 6-month treatment protocol with CBD-rich cannabis.

Legend: Randomized Clinical Trial (RCT); Autism spectrum disorder (ASD); Diagnostic and Statistical Manual of Mental Disorders (DSM); Autism Diagnostic Observation Schedule (ADOS-2); Clinical Global Impression (CGI)-Severity scale; Δ9-tetrahydrocannabinol (THC); Cannabidiol (CBD); Home Situations Questionnaire-ASD (HSQ-ASD); CGI-Improvement (CGI-I); Social Responsiveness Scale-2nd edition (SRS-2); Autism Parenting Stress Index (APSI); Children's Sleep Habits Questionnaire (CSHQ); Clinical Global Impression Scale- Severity (CGI-S); Adaptive Behavior Assessment System, Third Edition15 (ABAS-3); Behavior Assessment System for Children, Third Edition16 (BASC-3); Vineland adaptive behaviors scale, 3rd edition (Vineland-3); Block design and Matrix subtests from the Perceptual Organization Index (POI); Vocabulary and Similarities subtests from the Verbal Comprehension Index (VCI); Digit symbol-coding subtest from the Processing Speed Index (PSI).

severe co-morbidity, such as problems with sleep, aggression/self-injury behaviors, anxiety, or irritability that existed for at least 6 months. The main aim was to assess the safety-related blood tests of them taking a CBD-rich cannabis oil-based product. No significant change was observed in complete blood count, in urea or creatinine, in liver enzymes (AST, ALT, ALP), thyroid hormones, thyroid antibodies, prolactin, or other hormones, before and after 3 months of treatment. On the other hand, LDH was significantly higher before 3 months of treatment as compared to its level after treatment (p=0.003). Despite the normal ranges, FT4 was significantly higher after the treatment (p=0.03), whereas TSH was higher before treatment (p=0.01). There was a change in potassium level (p=0.04) between the group with additional medications, such as Aripiprazole and Methylphenidate, and the group with only medical cannabis. Finally, comparing a group with low dose of CBD and those who received a high dose of CBD, total protein was significantly higher among patients with high dose of CBD (p=0.01), but the number of platelets was lower among them (p=0.0007). All these changes had no clinical significance[10].

Besides, a retrospective study with 53 patients between 3 and 25 years of age, diagnosed with ASD based on DSM IV, was conducted for one month with cannabidiol treatment. They were evaluated by four ASD comorbidity symptoms: (a) hyperactivity symptoms (b) sleep problems, (c) self-injury and (d) anxiety. The most frequent adverse effects were somnolence (n=12) and decreased appetite (n=6). After cannabidiol administration, self-injury and rage attacks (n=34) improved in 67.6%, hyperactivity symptoms (n=38) improved in 68.4%, sleep problems (n=21) improved in 71.4% and anxiety (n=17) improved in 47.1%. Nevertheless, there was no statistically significant difference between the conventional treatment and cannabidiol treatment in self-injury (p=0.063), hyperactivity symptoms (p=0.125), sleep problems (p=0.4) and anxiety (p=0.232)[11].

Moreover, another study was conducted in Israel with 60 children between 5 and 18 years of age who were diagnosed with ASD by DSM-5 criteria. All children were prescribed cannabidiol treatment and assessed using a modified Liverpool Adverse Events Profile, the Caregiver Global Impression of Change (CGIC) scale, the Home Situations Questionnaire–Autism Spectrum Disorder (HSQ-ASD) and the Autism Parenting Stress Index (APSI). Some adverse events were reported by parents, such as hypervigilance, restlessness, irritability and

loss of appetite**.** In brief, considerable improvement in behavior problems (61%), anxiety (39%) and communication problems (47%) was reported. Also, for those who were treated with medications and cannabis concomitantly, (33%) received fewer medications or lower dosage, 12 (24%) stopped taking medications and 4 (8%) received more medications or higher dose[12].

In addition, 24 children between 6 and 12 years of age previously diagnosed with ASD were recruited in California in an observational study design. They were treated with medical cannabis (n=15) and compared with an age-matched group of typically developing (n=9) children. The study goal was to identify highly abundant potential cannabis-responsive biomarkers and potential cannabis-responsive biomarkers that respond differently to different medical cannabis treatments. After all, 65 potential ASD cannabis-responsive biomarkers were identified in 8–15 children with ASD. Also, 31 (48%) metabolites were detected in all the participants and 21 (32%) exhibited significant change (p<0.05)[13].

Finally, another prospective study in Israel analyzed data from 82 participants between 5 and 25 years of age who received CBD-rich cannabis treatment. All of them fulfilled the DSM-5 criteria for ASD and reported disruptive behavioral problems over the duration of the preceding 6 months. There was a significant improvement in the ADOS total calibrated severity scores (CSS) of 75 participants who completed ADOS assessments before and after 6 months of treatment (p=0.003), specially in social affect (p=0.001). Besides, children with more severe initial symptoms exhibited larger improvements (p=0.002). In the same way, 61 patients that completed the SRS-2 questionnaire before and after treatment reported a significant improvement in core ASD symptoms (p=0.043). Likewise, there was a significant improvement in total Vineland scores in 76 children who completed treatment and completed the Vineland questionnaire, mainly in communication (p=0.008), daily living (p=0.007) and socialization (p<0,001)[14].

CONCLUSION

The studies demonstrate that cannabis and cannabinoids show promise in alleviating symptoms associated with autism spectrum disorder and seem to be safe. However, common side effects include somnolence, hypervigilance, restlessness, irritability, and loss of appetite. While these side effects are generally considered minimal compared to those of traditional medications used for the same purpose, such as dyslipidemia, hyperglycemia, metabolic syndrome, and extrapyramidal symptoms, the long-term effects of continuous cannabis and cannabinoid use in children remain unclear. Despite potential benefits, caution is warranted, particularly in pediatric populations. Further studies involving larger cohorts are necessary to provide clearer guidance for clinical decision-making.

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DISCLOSURE

The authors declare no conflict of interest.

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