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Use of cannabidiol in children and adolescents with autism spectrum disorder: a scoping review

Uso de canabidiol em crianças e adolescentes com transtorno do espectro autista: uma revisão de escopo

Uso de cannabidiol en niños y adolescentes con trastorno del espectro autista: una revisión de alcance

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Abstract

Introduction: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that affects social communication and leads to repetitive behaviors. Treatment involves therapeutic and pharmacological approaches, with cannabidiol (CBD) emerging as a promising alternative to reduce disruptive symptoms and improve social interaction. **Objective:** To analyze the effects of cannabidiol in treating behavioral symptoms in children and adolescents with ASD, considering its efficacy, safety, and drug interactions. **Methods:** This review analyzed four studies involving a total of 350 participants, suggesting a

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Authors' contributions:
JVBC: conception and design of the study; methodology; analysis and interpretation of data; writing of the original draft; review and editing of the manuscript; creation of tables and figures.
MTJ: conception and design of the study; methodology; writing of the original draft; review and editing of the manuscript; creation of tables and figures.
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reduction in behavioral symptoms. In addition, there were reports of improved communication and mild adverse effects. **Results:** The studies included in this scoping review suggest that CBD may have potential beneficial effects in ASD, but there was no consensus on the superiority of whole-plant extract compared to isolated CBD compounds. Effects vary depending on formulation and symptom severity, with divergent assessments. The safety of long-term use is not well established, and there are concerns regarding drug interactions and metabolic and cardiovascular risks. **Conclusion:** This scoping review mapped the available scientific evidence on the use of cannabidiol in children and adolescents with Autism Spectrum Disorder. The findings indicate that cannabidiol has therapeutic potential for behavioral symptoms of ASD; however, the heterogeneity of studies and the lack of long-term research limit definitive conclusions about its efficacy and safety. Further research is needed to fill knowledge gaps and support clinical practice.

Keywords: Autism spectrum disorder; Children; Cannabidiol; Efficacy; Safety.

Resumo

Introdução: O transtorno do espectro autista (TEA) é um transtorno do neurodesenvolvimento que afeta a comunicação social e provoca comportamentos repetitivos. O tratamento envolve abordagens terapêuticas e medicamentosas, sendo o canabidiol (CBD) uma alternativa promissora para reduzir sintomas disruptivos e melhorar a interação social. **Objetivo:** Analisar os efeitos do canabidiol no tratamento de sintomas comportamentais em crianças e adolescentes com TEA, considerando sua eficácia, segurança e interações medicamentosas. **Métodos:** Esta revisão analisou quatro estudos com 350 participantes, sugerindo redução de sintomas comportamentais. Além disso, houve relatos de melhora na comunicação e efeitos adversos leves. **Resultados:** Os estudos incluídos nesta revisão de escopo sugerem que o CBD pode apresentar potenciais efeitos benéficos no TEA, mas não houve consenso sobre a superioridade do extrato de planta inteira em relação aos compostos isolados de CBD. Os efeitos variam conforme formulação e gravidade, com avaliações divergentes. A segurança do uso prolongado não está bem estabelecida, e há preocupações sobre interações medicamentosas e riscos metabólicos e cardiovasculares. **Conclusão:** Esta revisão de escopo mapeou as evidências científicas disponíveis sobre o uso de canabidiol em crianças e adolescentes com Transtorno do Espectro Autista. Os achados indicam que o canabidiol apresenta potencial terapêutico para sintomas comportamentais do TEA, porém, a heterogeneidade dos estudos e a ausência de pesquisas de longo prazo limitam conclusões definitivas sobre sua eficácia e segurança. São necessárias mais pesquisas para preencher as lacunas de conhecimento e fornecer subsídios para a prática clínica.

Palavras-chave: Transtorno do espectro autista; Crianças; Canabidiol; Eficácia; Segurança.

Resumen

Introducción: El trastorno del espectro autista (TEA) es un trastorno del neurodesarrollo que afecta la comunicación social y provoca comportamientos repetitivos. El tratamiento incluye enfoques terapéuticos y farmacológicos, siendo el cannabidiol (CBD) una alternativa prometedora para reducir los síntomas disruptivos y mejorar la interacción social. **Objetivo:** Analizar los efectos del cannabidiol en el tratamiento de los síntomas conductuales en niños y adolescentes con TEA, considerando su eficacia, seguridad e interacciones medicamentosas. **Métodos:** Esta revisión analizó cuatro estudios con 350 participantes, sugiriendo una reducción de síntomas conductuales. Además, se informaron mejoras en la comunicación y efectos adversos leves. **Resultados:** Los estudios incluidos en esta revisión de alcance sugieren que el CBD puede tener efectos beneficiosos potenciales en el TEA, pero no hubo consenso sobre la superioridad del extracto de planta entera en comparación con los compuestos aislados de CBD. Los efectos varían según la formulación y la gravedad, con evaluaciones divergentes. La seguridad del uso prolongado no está bien establecida, y existen preocupaciones sobre interacciones medicamentosas y riesgos metabólicos y cardiovasculares. **Conclusión:** Esta revisión de alcance mapeó la evidencia científica disponible sobre el uso de cannabidiol en niños y adolescentes con Trastorno del Espectro Autista. Los hallazgos indican que el cannabidiol presenta un potencial terapéutico para los síntomas conductuales

del TEA; sin embargo, la heterogeneidad de los estudios y la ausencia de investigaciones a largo plazo limitan conclusiones definitivas sobre su eficacia y seguridad. Se necesitan más investigaciones para llenar las lagunas de conocimiento y proporcionar soporte a la práctica clínica.

Palabras clave: Trastorno del espectro autista; Niños; Cannabidiol; Eficacia; Seguridad.

Introduction

Autism spectrum disorder (ASD) is considered a neurodevelopmental disorder characterized by early and persistent impairments in reciprocal social communication and social interaction, as well as restricted and repetitive patterns of behavior, interests, or activities. These impairments may manifest from the earliest stages of neurodevelopmental growth, leading to reduced functionality in children as they develop. The presentation of ASD varies in severity, depending on the patient's limitations and support needs, and can be classified into support levels ranging from Level 1 ("requiring support") to Level 3 ("requiring very substantial support"). Additionally, it is common for other neurodevelopmental disorders and clinical conditions to co-occur, necessitating thorough and individualized clinical investigation, longitudinal follow-up, and multiple sources of information[1].

Estimates of ASD prevalence in Brazil and globally show considerable variation, reflecting methodological and contextual differences regarding the disorder. Global prevalence is estimated at approximately 1% of the population, with variations across different regions[2]. Data from the Burden of Disease Study (2021) indicate a global prevalence of 61.8 million individuals at the time, with an age-standardized prevalence of 788.3 per 100,000 people[3]. For children diagnosed with ASD, recent studies report values close to those without age stratification, with a median prevalence of 100 per 10,000. In Brazil, data are limited but appear to align with global trends[4]. However, awareness campaigns and increased access to specialized care have progressively impacted these figures.

ASD affects the quality of life of both patients and their families or caregivers. This impact, to varying degrees, stems from difficulties in self-regulation and impairments in skills necessary for autonomy[5,6]. Furthermore, families of children with ASD face significant financial and time-related challenges, with considerable impacts on employment and family finances[7]. Thus, the importance of interventions that can clinically manage patients over time, as well as institutional support for families, is evident.

Pharmacological interventions for ASD aim to manage associated maladaptive symptoms (such as emotional dysregulation, irritability, and aggression) and treat comorbidities (such as attention-deficit/hyperactivity disorder). Atypical antipsychotics, such as risperidone and aripiprazole, have proven effective in treating irritability and aggression in patients with ASD and are approved for this purpose by the Food and Drug Administration (FDA)[8,9,10]. Cannabidiol, derived from Cannabis sativa extract, has emerged as a potential alternative to traditional pharmacological treatments, with reported improvements in disruptive symptoms and communication skills, associated with a low incidence of side effects, particularly long-term endocrine-metabolic effects[11,12].

The regulation and approval of cannabidiol have been topics of growing global discussion. For instance, the Food and Drug Administration (FDA) in the United States has approved a cannabidiol-based medication for the treatment of certain forms of refractory epilepsy, such as Lennox-Gastaut syndrome and Dravet syndrome[12]. In Brazil, the National Health Surveillance Agency (ANVISA) has also advanced the regulation of cannabinoid-based products for medicinal purposes, allowing importation and, more recently, the commercialization of certain products in pharmacies with a medical prescription[13]. Beyond epilepsy, cannabidiol has been investigated for other clinical indications, such as anxiety, chronic pain, and multiple sclerosis, although most of these applications remain in the research phase and lack broad regulatory approval[14,15,16].

Previous systematic reviews and scoping reviews have explored the use of cannabinoids in various neurological and psychiatric conditions, including ASD. However, the literature still lacks robust and standardized studies evaluating the efficacy and safety of cannabidiol specifically in children and adolescents with ASD, justifying the need for new reviews to synthesize available evidence[17].

It is believed that the endocannabinoid system (ECS) plays a significant role in organic functions such as sleep, appetite, pain, memory, and mood, with uses for analgesic, anti-inflammatory, and hypnotic purposes dating back to 2,900 BCE in China[18]. Studies in animals and humans suggest dysregulation of the ECS associated with ASD, proposing upregulation of the cannabinoid receptor type 2 (CB2) and alterations in levels of anandamide, 2-arachidonoylglycerol, oleoylethanolamide, and palmitoylethanolamide[19],[20],[21]. Consequently, there is growing interest in neuroscience to elucidate the potential benefits of phytocannabinoids in treating core symptoms of ASD. In this context, this study aims to analyze the scientific evidence regarding the efficacy and tolerability of cannabidiol in children and adolescents with autism spectrum disorder.

Methods

This is a scoping review aimed at identifying, selecting, evaluating, and analyzing scientific evidence on the topic to identify its main concepts, characteristics, and knowledge gaps, thereby establishing goals for future studies. The construction of this scoping review is based on the Joanna Briggs Institute (JBI) methodology.

A scoping review, rather than a systematic review, was chosen due to the scarcity of consolidated clinical studies and the methodological heterogeneity of publications found on the use of cannabidiol in children and adolescents with ASD. This scenario would not allow for robust quantitative synthesis or uniform assessment of bias risk.

The PCC acronym was used to formulate the research question, where P stands for the target population, C for the concept, and C for the context of the study object. In this study, P: children and adolescents, C: cannabidiol, and C: use of cannabidiol in the treatment of autism. Thus, the review's research question was: "Does the use of cannabidiol contribute to the treatment of autism spectrum disorder in children and adolescents?"

Original studies on the topic, published between January 1970 and December 2024, were included. Data collection was conducted in December 2024, with no language restrictions, and studies were required to be available electronically with full text.

Exclusion criteria included dissertations, theses, letters to the editor, editorials, manuals, case reports, and review articles (scoping, integrative, systematic, narrative, and meta-analyses). As this is a scoping review, methodological quality assessment of included studies is not mandatory. The review was developed following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – extension for Scoping Reviews (PRISMA-ScR).

The search was conducted systematically across four electronic databases: PubMed (National Library of Medicine, National Institutes of Health), Embase, Web of Science, and the Virtual Health Library (BVS). Terms were used in accordance with the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH). The search strategies included terminological variations in English, such as "autism" AND "child" AND "adolescent" AND "cannabidiol," to maximize the identification of relevant articles compared to searches using descriptors in other languages. Boolean operators "AND" and "OR" were also employed. Data were extracted from eligible articles included in the scoping review by two independent researchers with expertise in the field, and any inconsistencies were resolved by a third researcher until consensus was reached.

Following the methodological guidelines of PRISMA-ScR, it is recommended to register the review protocol on public platforms such as the Open Science Framework (OSF) to ensure transparency and reproducibility of the study. The protocol for this review was registered on the Open Science Framework (OSF) under the DOI: 10.17605/OSF.IO/GFE4Z.

Results

Of the 142 records identified in the searches, 4 studies were included and form the body of this review (Figure 1). Information was extracted based on the inclusion and exclusion criteria and tabulated in an Excel® database, including details such as identification—title, authors, year of publication, country, objective, study type, sample, results, and conclusion. The studies investigated the use of cannabidiol in the treatment of children and adolescents with ASD, totaling 350 participants of both sexes (Chart 1).

The analysis of the results was conducted descriptively, with the development of a synthesis for each primary study included in this review. The rigor of data extraction and analysis was ensured through in-depth and critical discussions among the researchers involved in the study.

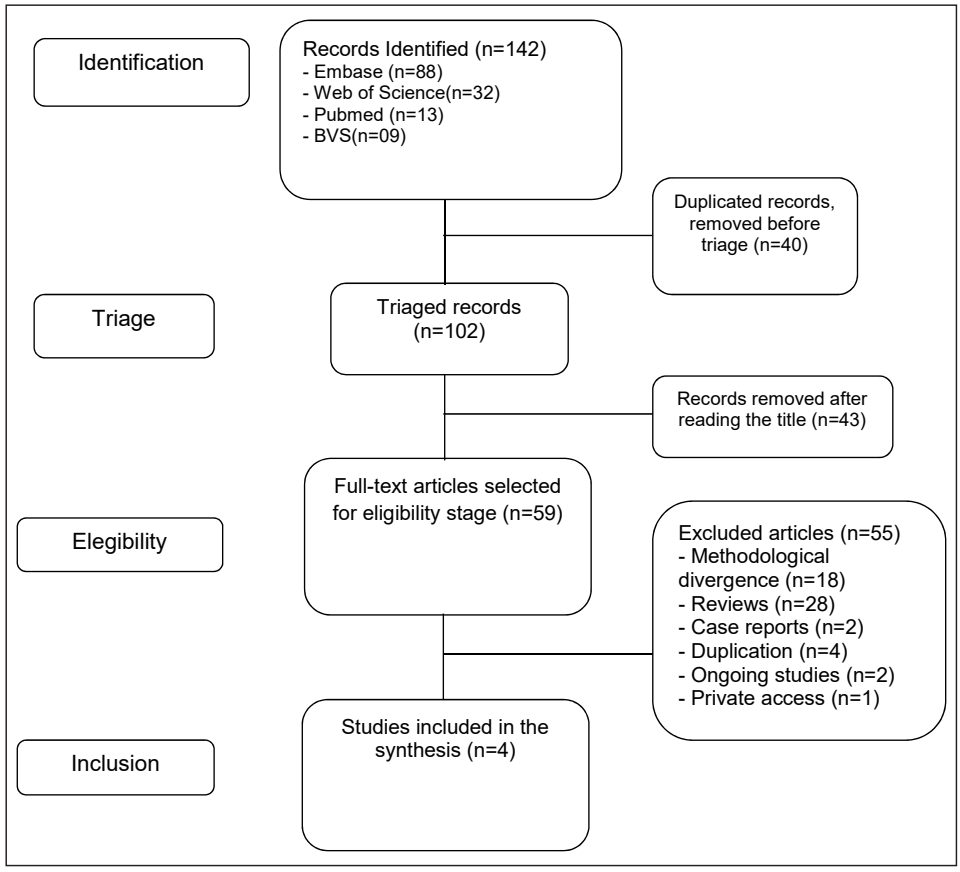

Figure 1. Selection process for the files included in the revision, as per PRISMA-ScR recommendations.

Chart 1. Features of the selected papers

Title, authors, and year	Country	Objective	Type of Study	Sample N	Results	Conclusion
Cannabinoid treatment for autism: a proof-of-concept randomized trial[16] Adi Aran, Moria Harel, Hanoch Cassuto, Lola Polyansky, Aviad Schnapp, Nadia Wattad, Dorit Shmueli, Daphna Golan, F. Xavier Castellanos 2021	Israel	Hypothesize that whole-plant extract (BOL-DP-O-01-W), due to the entourage effect, is more effective than placebo for disruptive behaviors. Evaluate the efficacy of pure cannabinoids, which are more standardizable and reproducible than whole-plant extracts and therefore more suitable for pharmacotherapy.	Single-center, randomized, double-blind, placebo-controlled proof-of-concept trial 12-week follow-up, followed by a 4-week washout, and another 12 weeks of follow-up, with interventions switched in each group (crossover design). Group 1: Oral placebo Group 2: Whole-plant cannabis extract (CBD 20:THC 1) Group 3: Pure CBD and THC, in the same ratio	150 children and adolescents 5.1–20.8 years Mean age 11.8 ± 4.1 years Median age 11.25 years 80% boys DSM-5 diagnosis and CGI-S ≥ 4 (moderate to severe)	Drowsiness was the only statistically significant adverse effect related to cannabidiol use (p-value < 0.001). There was a statistically significant reduction in the Social Responsiveness Scale (SRS-2) when comparing whole-plant extract vs. placebo (p-value < 0.009) and an improvement in disruptive behaviors on the CGI-I scale (p-value = 0.05).	Whole plant extract improves disruptive behaviors in one of two primary outcome measures and in one secondary outcome, with acceptable adverse events (including contributing to BMI reduction)
Children and adolescents with ASD treated with CBD-rich cannabis exhibit significant improvements particularly in social symptoms: an open label study[17] Micha Hacohen, Orit E. Stolar, Matitiahu Berkovitch, Odelia Elkana, Elkana Kohn, Ariela Hazan, Eli Heyman, Yael Sobol, Danel Waissengreen, Eynat Gal, Ilan Dinstein 2022	Israel	Expand existing knowledge by conducting an open-label efficacy study of CBD-rich cannabis treatment. Quantify treatment effects separately for social communication, restricted and repetitive behaviors, adaptive behaviors, and cognitive skills, comparing clinical assessments and parental reports.	Open-label, uncontrolled clinical trial Clinical evaluation (ADOS-2), parental report collection (Vineland), and questionnaire completion (SRS-2) after recruitment Use of whole-plant extract (CBD 20:THC 1) at 400/20 mg/day or 10/0.5 mg/kg/day Biweekly telephone interview New full assessment after 6 months	110 participants 5 to 25 years old Average age 9.2 years old 65 men Expert assessment: DSM-5 diagnosis and disruptive behavior	82 participants completed the study 75 completed the ADOS assessment after recruitment and at 6 months Large improvements in social affect and weak improvements in restrictive and repetitive behavior on the ADOS Calibrated Total Severity Score Participants with more severe initial symptoms (ADOS-2 CSS) exhibited greater improvements Age and final dosage were unrelated to improvement Significant improvement in Vineland Total Scores (communication, daily life, and socialization)	CBD-rich whole-plant cannabis extract demonstrates benefit in social communication skills, particularly in participants with high baseline severity of core ASD symptoms
Clinical and family implications of cannabidiol (CBD)-dominant full-spectrum phytocannabinoid extract in children and adolescents with moderate to severe non-syndromic autism spectrum disorder (ASD): an observational study on neurobehavioral management[18] Jeanne Alves de Souza Mazza, Lisiane Seguti Ferreira, Alice de Faria Martins-Vieira, Doris Day Lopes Beserra, Victor Alves Rodrigues, Renato Malcher-Lopes e Fabio V. Caixeta 2024	Brazil	To evaluate the effects of full-spectrum CBD oil, containing THC in a 33:1 ratio, and its potential therapeutic value for non-syndromic children and adolescents with ASD.	Retrospective, observational, cross-sectional cohort Neuropsychological assessment at baseline Use of full-spectrum cannabidiol extract (CBD 33:THC 1) with an initial dose of 1 mg/kg/day of CBD and individualized titration Clinical assessment of adaptive behavior and restricted and repetitive patterns through questionnaires before treatment, as well as at months 1, 3, and 6 Semi-structured interviews with parents at the end of treatment	30 volunteers 5 to 18 years old Average age 11.2 years old 24 males Patients previously monitored at the University Hospital of the University of Brasília, diagnosed with moderate to severe ASD and using at least one type of prior medication (other than CBD). Patients with suspected or diagnosed genetic or neurometabolic syndromes, as well as epilepsy, were excluded.	Two volunteers discontinued treatment before 6 months due to adverse effects. Overall, more positive effects on social cognition than on repetitive/restricted and dysfunctional patterns. Higher percentage of significant improvements, in the clinical assessment, in expressive language, activities of daily living, aggression toward others, and irritability. In the family assessment, there was a higher percentage of significant improvements in the patient's and family's quality of life, as well as in communication and personal interaction. The most commonly reported adverse effects were irritability (3), agitation (2), and aggression (2).	The findings corroborate that treatment with full-spectrum cannabidiol extract, combined with a gradual and individualized dosing regimen, is safe and effective for the broader treatment of core and comorbid symptoms related to ASD.

Title, authors, and year	Country	Objective	Type of Study	Sample N	Results	Conclusion
Evaluation of the efficacy and safety of cannabidiol-rich cannabis extract in children with autism spectrum disorder: randomized, double-blind, and placebo-controlled clinical trial[19] Estácio Amaro da Silva Junior, Wandersonia Moreira Brito Medeiros, João Paulo Mendes dos Santos, João Marçal Medeiros de Sousa, Filipe Barbosa da Costa, Katiúscia Moreira Pontes, Thaís Cavalcanti Borges, Carlos Espínola Neto Segundo, Ana Hermínia Andrade e Silva, Eliane Lima Guerra Nunes, Nelson Torro Alves, Marine Diniz da Rosa, Katy Lísias Gondim Dias de Albuquerque 2022	Brazil	To evaluate the efficacy and safety of Cannabis extract rich in cannabidiol in children with ASD	Randomized, double-blind, placebo-controlled clinical trial 12-week follow-up Randomization and stratification by severity Initial dose of 3 drops every 12 hours (5 mg/ml CBD, in a 9:1 ratio of THC) up to 70 drops/day Semi-structured interview with caregivers at the beginning and end of the trial, and laboratory evaluation before the start of the study	60 children aged 5 to 11 52 males Average age 7.68 years Recruitment was conducted through advertising at autism support institutions, lectures, and social media posts Sociodemographic assessment and Childhood Autism Rating Scale (CARS) ≥ 15 points Participants with comorbidities or who used cannabis-based products up to 2 months prior to the study were excluded	Four children dropped out of the treatment group (three in the placebo group and one in the treatment group) due to mobility difficulties. Significant improvement in psychomotor agitation, food acceptance, and, above all, social interaction. Reduction in anxiety levels. Improved concentration in patients with mild ASD. Three children in the treatment group experienced side effects (dizziness, insomnia, colic, and weight gain).	CBD-rich cannabis extract has been considered safe up to 70 drops/day. It is also effective in the short term for social interaction, psychomotor agitation, and anxiety. Increasing the number of meals may be related to better anxiety control.

Sample N: number of patients included in the study; "type of study": design, hypothesis, and methodology employed in each study.

Discussion

The studies included in this scoping review suggest potential beneficial effects of cannabidiol (CBD) use in children and adolescents with autism spectrum disorder (ASD), particularly in reducing disruptive symptoms such as irritability, aggression, and difficulties in social interaction. However, these findings should be interpreted with caution, as the heterogeneity of the included studies limits the generalizability of the results.

Among the studies included in this scoping review, the one by Aran and colleagues[22] is the most methodologically robust. It raises questions about the greater efficacy of whole-plant Cannabis extract compared to isolated cannabinoids in controlling disruptive ASD symptoms. It is believed that the combination of cannabidiol, tetrahydrocannabinol, minor cannabinoids, terpenes, and flavonoids has a synergistic and self-regulating effect on the endocannabinoid system, referred to as the "entourage effect." A randomized, double-blind clinical trial was designed, with primary assessments of disruptive symptoms and secondary assessments of social responsiveness, parental stress, and adverse effects.

The groups received two distinct interventions, interspersed with a 4-week washout period. Initial doses of 1 mg/kg/day of cannabidiol, combined with 0.5 mg/kg/day of tetrahydrocannabinol, were used. Doses were progressively increased up to 10 mg/kg/day of cannabidiol for patients weighing 20 to 40 kg, and 7.5 mg/day for those over 40 kg, administered orally in three daily doses. All medications prescribed for the same purpose were maintained in combination. Assessments were conducted periodically using scales applied to patients and their caregivers. The only adverse effect with statistical significance when comparing placebo and cannabinoid use (isolated or in combination) was somnolence. No serious adverse events were reported in any of the study groups. On the other hand, the body mass index (BMI) of patients with higher baseline values showed a significant reduction in the active compound groups. Ultimately, a response was observed in 49% of patients using whole-plant extract, compared to 21% in those using placebo ($p = 0.0005$). Finally, no difference in efficacy was found between the use of whole-plant extract and isolated cannabinoids.

The second Israeli study included in this review, conducted by Micha Hacohen and col-

leagues[23], recruited 110 community participants through advertisements, who were evaluated by a specialist. Patients with ASD-compatible conditions and disruptive behaviors, such as aggression, were included in the study (82 participants). Exclusion criteria aimed to mitigate confounding factors, such as clinical comorbidities and genetic syndromes, and to avoid exposing individuals at higher risk of psychosis to THC. In addition to clinical assessments and standardized caregiver information collection through scales, participants also underwent subtests to quantify intelligence. The intervention follow-up lasted 6 months, with biweekly telephone interviews investigating irritability, aggression, hyperactivity, sleep disturbances, and adverse effects. The initial dose was one drop per day of whole-plant Cannabis extract (5.7 mg of CBD and 0.3 mg of THC), with individualized adjustments up to a maximum dose of 10 mg/kg/day of CBD and 0.5 mg/kg/day of THC. The results concluded that patients with more severe symptoms showed more significant improvement, with age and final dosage not correlated with better response. Parents reported improvements in social responsiveness, communication, autonomy, and socialization, with some discrepancy compared to clinical assessments. This highlights the need for more objective symptom evaluations.

A Brazilian study, published in 2024 and authored by Mazza and colleagues[11], was also included in this review. It is a retrospective cohort study with 30 participants aged 5 to 18 years, with an average follow-up duration of 6.6 months. To ensure greater homogeneity, patients with diagnosed or suspected clinical, genetic, or neurometabolic conditions were excluded. Whole-plant Cannabis extract containing CBD and THC in a 33:1 ratio was used, with an initial dose of 1 mg/kg/day of CBD. Titration was performed progressively and individually based on response and tolerability parameters, with an average final dose of 3.11 mg/kg/day of CBD and 0.09 mg/kg/day of THC. Social interaction, communication, and behavior patterns were assessed using a fixed questionnaire based on DSM-V criteria, applied before treatment and at 1, 3, and 6 months of treatment. At the end of the treatment, parents and caregivers were also interviewed, either in person or by telephone, using a form with multiple-choice and open-ended questions. More positive effects were observed in social cognition compared to repetitive or restricted functioning patterns. Among the identified adverse effects, the most common were related to worsening of disruptive behavior (irritability, agitation, and aggression). Other symptoms related to cannabinoid use included gastrointestinal and sleep disturbances, as well as intensification of compulsive eating and obsessive-compulsive symptoms. However, all of these were resolved after dose reduction. Twenty-seven participants were previously using other psychotropic medications, with dose reduction or discontinuation of at least one medication in 20 cases. In 4 cases, a dose increase was necessary, and in 3 cases, a new medication was introduced. In this study, parental reports corroborated the clinical findings.

Finally, Silva and colleagues[24] conducted a double-blind, randomized, placebo-controlled interventional study in the Brazilian population. In addition to assessing symptomatology, the clinical trial also investigated the sociodemographic conditions of participants and their families, as well as addressing some impacts of the COVID-19 pandemic on the development of patients with ASD. Despite the study being disseminated to the general population without restrictions, the predominant participation of male individuals (86.67%) drew the authors' attention. It is hypothesized that the higher prevalence of the disorder in this population may be due to a "female protective effect" requiring a greater "etiological load" for phenotypic manifestation. Regarding symptomatology, the results indicate significant improvement in social interaction patterns ($p = 0.000268$) in the treatment group, associated with improvements in psychomotor agitation ($p = 0.002$), anxiety ($p = 0.01$), and an increase in the number of daily meals ($p = 0.04$). Concentration was also evaluated, with patients with milder conditions showing improvement, attributed to less cognitive impairment. Adverse effects were considered mild and resolved after dose adjustments in the intervention group.

The cited authors converge on the point that full-spectrum cannabidiol extract, when individually titrated, demonstrated an acceptable safety profile and potential short-term efficacy for ASD symptoms. However, it is important to emphasize that while the study by Aran stands out for its methodological robustness (randomized, double-blind clinical trial), the other studies included in this review are predominantly open-label, observational, or have small sample sizes, which limits the

comparability and generalizability of their findings. This methodological heterogeneity is a significant gap in the current literature on the topic.

Due to methodological differences, there is some divergence in the evaluation of exposures and outcomes. The lack of standardization among cannabinoid formulations results in distinct interventions, and there is still no evidence of the superiority of whole-plant Cannabis extract over isolated components. The studies included in this review evaluated combined formulations of CBD and THC in varying proportions.

Despite a certain level of short-term safety—adverse events were mostly mild—the risks of continuous use over years have not been investigated. This is a significant limitation of the study, given the theoretical higher risk of psychotic episodes with continuous exposure to tetrahydrocannabinol[25,26]. Furthermore, it is not yet possible to determine whether phytocannabinoids pose a lower metabolic and cardiovascular risk compared to traditional treatments with atypical antipsychotics. Although the studies suggest the possibility of dose reduction or discontinuation of medications associated with cannabidiol, its use as monotherapy requires further investigation. This would enable a better understanding of its tolerability and adverse effect profile in isolation.

In the same vein, there are few data on drug interactions with cannabidiol, which may be attributed to its recent commercialization. However, significant drug interactions are known with anticonvulsants such as Clobazam, Diazepam, and Topiramate, as well as opioids and antidepressants. These properties require greater vigilance from clinicians, as these medications are frequently prescribed for comorbidities common in ASD[27,28].

To obtain specific analyses for the use of cannabidiol in children and adolescents with ASD, this review included only studies with participants without any other comorbidities. The use of phytocannabinoids in conditions such as refractory epilepsy is well-established, with its prescription approved by the FDA for genetic syndromes with neurological involvement. It is even hypothesized that epilepsy and autism spectrum disorder share a common neurodevelopmental basis, involving shared biological and molecular mechanisms[29,30]. Thus, studies evaluating populations with such comorbidities suggest satisfactory response rates[31].

This article presents some limitations that should be considered when interpreting the results. First, the methodological heterogeneity among the included studies hinders direct comparisons and the generalizability of findings. The lack of standardization in the cannabidiol formulations used, as well as in doses and administration regimens, poses a challenge to evaluating the true efficacy and safety of the treatment. Additionally, most of the analyzed studies assessed only the short-term use of CBD, making it impossible to determine the effects of its prolonged use, especially in pediatric populations. The lack of consensus on the superiority of whole-plant extracts versus isolated CBD compounds also limits understanding of which formulations would be most suitable. Finally, there is a scarcity of robust studies addressing potential drug interactions between CBD and concomitant treatments, which is particularly relevant given the high prevalence of comorbidities in autism spectrum disorder. Future research with greater methodological rigor, larger samples, and long-term follow-up is essential to elucidate these issues and guide the safe and effective clinical use of cannabidiol in ASD.

Conclusion

This scoping review mapped the available scientific evidence on the use of cannabidiol in children and adolescents with autism spectrum disorder. The findings suggest that cannabidiol has potential therapeutic benefits for behavioral symptoms of ASD, such as irritability, aggression, and difficulties in social interaction. However, the methodological heterogeneity of the studies, the lack of standardization in formulations and dosages, and the absence of long-term research represent significant gaps in current knowledge.

It is critical that future research focus on randomized, controlled clinical trials with larger samples and long-term follow-up to more robustly evaluate the efficacy and safety of cannabidiol in ASD. Furthermore, studies investigating the relationship between different cannabinoid formulations and their specific effects, as well as the safety profile in pediatric populations, are essential to support clinical decision-making and the development of evidence-based guidelines.

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