

Review Article

The Use of Components of *Cannabis sativa* in Autism Spectrum Disorder

O uso de Componentes da Cannabis sativa no Transtorno do Espectro Autista

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ABSTRACT:

Autism Spectrum Disorder (ASD) is defined as a neurodevelopmental disorder that manifests in childhood, characterized by impairments in social interaction, communication, and behavior. ASD is often accompanied by various comorbidities such as sleep disorders, attention deficit, hyperactivity, and even epilepsy. Therefore, the importance of appropriate therapeutic treatments targeting the symptoms of the disorder is emphasized. The objective of this research is to analyze studies regarding the effectiveness and adverse effects of *Cannabis sativa* extract in ASD. The contributions of this research aim to provide information that may support the use of these psychopharmaceuticals in the treatment of the disorder and possibly their pediatric use for medicinal purposes, considering that the sooner therapeutic intervention is initiated, the better the prognosis. This is a systematic review conducted from February to June 2022, utilizing databases such as SciELO, PubMed, Biblioteca Virtual em Saúde (BVS), Lilacs, WorldCat, as well as official websites such as ANVISA. From the databases used, 17 articles were found, of which 8 were selected, published between 2019 and 2021. The reviewed literature agrees that Cannabis-based interventions are effective in treating the primary symptoms and secondary aspects of ASD.

RESUMO

O Transtorno do Espectro Autista (TEA) é definido como um transtorno neuropsiquiátrico desenvolvido na infância, no qual ocorre prejuízo na interação social, comunicação e comportamento. O TEA possui várias comorbidades associadas, tais como distúrbios do sono, déficit de atenção, hiperatividade e até mesmo epilepsia. Diante disso, destaca-se a importância de tratamentos terapêuticos adequados que atuem nos sintomas da doença. O objetivo desta pesquisa é analisar estudos sobre a efetividade e os efeitos adversos do uso de extrato da *Cannabis sativa* no TEA. As contribuições da pesquisa visam a disponibilizar informações que possam dar suporte para o uso desses psicofármacos no tratamento do transtorno e, possivelmente, seu uso pediátrico para uma abordagem medicamentosa, visto que, quanto mais rápida a instituição terapêutica, melhor o prognóstico. Trata-se de uma revisão sistemática, realizada nos meses de fevereiro a junho de 2022, nas bases de dados SciELO, PubMed, Biblioteca Virtual em Saúde (BVS), Lilacs, WorldCat e em sites oficiais como ANVISA. Nas bases de dados utilizadas foram encontrados 17 artigos e, desses, selecionados 8, publicados entre os anos de 2019 e 2021. As revisões analisadas concordam que procedimentos à base de Cannabis são eficazes para o tratamento dos principais sintomas e nos aspectos secundários do TEA.

Keywords:

Autism Spectrum
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Autistic Disorder.
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Palavras-chave:

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INTRODUCTION

Autism Spectrum Disorder (ASD), commonly known as autism, is a neurodevelopmental disorder, diagnosed by impairments in three domains: social interaction, communication, and behavior. Social interaction is affected by difficulties in verbal and non-verbal communication or by a lack of interest in communicating. Deficits in these domains can lead to incapacitation of the affected individual. Symptoms typically appear between 12 and 24 months of age, affecting patients' quality of life. Furthermore, the prevalence of cases has increased in recent years, and most autistic individuals have conditions that interfere with their quality of life and autonomy, such as sleep disorders, aggression, epilepsy, anxiety, and irritability¹. ASD is considered a global disorder, with estimates suggesting that 1 in 88 live births worldwide are affected. In Brazil, it is estimated that two million people are affected, with males being more commonly affected².

Caregivers of individuals with ASD should be guided immediately after diagnosis regarding treatment to reduce characteristic symptoms of the disorder. Early identification allows caregivers to manage crises and social and communication deficits. Medications may also be prescribed to treat ASD symptoms and aid in the child's educational progress. However, conventional medications can cause severe long-term adverse effects. Consequently, researchers are exploring alternative therapeutic options, such as substances derived from *Cannabis sativa*³.

PHARMACOLOGICAL USE OF *CANNABIS SATIVA*

Plants have long been used medicinally for treating various diseases due to their healing potential. The World Health Organization (WHO) has reported that approximately 80% of the population in developing countries rely on medicinal plants for disease prevention, treatment, and basic health care⁴.

Cannabis sativa, commonly known as marijuana in Brazil, is a herb originating from Central

Asia, adaptable to various climates, altitudes, and soils⁵. Historically, oils, extracts, and parts of the plant have been used as analgesics, anticonvulsants, anxiolytics, and remedies for migraines, asthma, and muscle spasms by many cultures, though they were unaware of the plant's chemical and pharmacological properties or mechanisms of action on the brain. Today, some of these mechanisms are recognized even by the American Academy of Neurology (AAN), acknowledging the efficacy and safety of therapeutic use of marijuana and its derivatives for various diseases⁶.

The treatment of ASD symptoms through the administration of *Cannabis sativa* extracts is being studied and could be revolutionary, potentially improving patient quality of life, reducing the frequency of psychotic episodes, and causing fewer undesirable effects. The two phytocannabinoids being tested are delta-9-tetrahydrocannabinol (Δ 9-THC) and cannabidiol (CBD). Δ 9-THC is the main component associated with the plant's psychotic effects, while CBD has anti-inflammatory effects³. Notably, cannabidiol, a component of *Cannabis sativa*, is effective in improving irritability, aggression, anxiety, and emotional phobia, thereby enhancing social interaction and quality of life for patients and their families⁷.

For the prescription of *Cannabis* as a medication, patient authorization and clear consent are required. Similar to analgesics, *Cannabis* is administered in small doses to assess the body's acceptance, with dosages gradually increased to ensure greater effects⁸. *Cannabis* consists of various chemical components, with the four most abundant being delta-9-tetrahydrocannabinol (Δ 9-THC), cannabidiol (CBD), delta-8-tetrahydrocannabinol (Δ 8-THC), and cannabinol (CBN)⁹.

Cannabidiol and delta-9-tetrahydrocannabinol are gaining attention for treating ASD. Each acts differently and complementarily concerning the desired therapeutic effect. In pharmacological use, THC interacts directly with CB1 and CB2 receptors: CB1 has psychoactive effects, while CB2 enhances immunomodulation. The psychoactive effect of THC occurs through higher doses than CBD, which acts as an allosteric

inhibitor of these receptors, regulating psychotic effects¹⁰. Studies demonstrate that Δ^9 -THC interacts with CB1 and CB2 endocannabinoid receptors. Cannabidiol functions as an agonist for G-protein coupled receptors, which are not cannabinoids, such as serotonergic receptors, reducing irritability, aggression, and anxiety¹¹.

For medicinal use of *Cannabis*, it is essential to understand the two endocannabinoid receptors, CB1 and CB2. CB1 receptors are found in cortical areas regulating cognitive, motor, and sensory functions, predominantly in the cingulate gyrus, medial prefrontal gyrus, hippocampus, caudate nuclei, putamen, *globus pallidus*, and cerebellum. CB2 is associated with dopaminergic action in the ventral tegmental area¹².

ENDOCANNABINOID SYSTEM AND MECHANISM OF ACTION

The endocannabinoid system is a biological system composed of enzymes responsible for synthesizing and degrading neuromodulators, metabotropic receptors, and endocannabinoids (anandamide and 2-arachidonoylglycerol (2-AG)). Anandamide and 2-AG are endogenous lipid-based retrograde neurotransmitters that bind to cannabinoid receptors and receptor proteins expressed throughout the central nervous system (CNS), playing a significant role in regulating physiological processes and modulating emotional responses and behavioral reactivity¹³. The endocannabinoid system is often affected in patients with ASD comorbidities such as seizures, anxiety, sleep disorders, and cognitive impairments. Approximately 40% of children with ASD exhibit disruptive behavior and do not respond well to standard behavioral therapy and medical treatment¹⁴.

The effects of phytocannabinoids on the endocannabinoid system in patients with ASD have been analyzed, showing that CBD can alter specific functional properties of the brain, focusing on regions typically damaged in individuals with ASD¹⁵. Therefore, the pharmacological potential of cannabinoids is highly relevant when discussing alternative therapies for treating ASD patients.

Endocannabinoid mechanisms at the pre-

synaptic terminal involve anandamide and 2-AG activating CB1 receptors coupled to G-proteins, modulating neuronal membrane permeability to Ca^{2+} and K^{+} ions and adenylate cyclase (AC) activity, altering neurotransmitter release, action, or both, and affecting slow and fast neurotransmission. When released by neuron depolarization, these lipid-soluble compounds can behave like other arachidonic acid (AA) derivatives, acting as autocrine and paracrine signals in the originating neuron or neighboring neurons or astrocytes. In the hippocampus, AC inhibition and subsequent protein kinase A (PKA) inhibition, dependent on cAMP, can modulate synaptic plasticity, for example, by increasing tyrosine phosphorylation and subsequent activation of focal adhesion kinase (FAK)¹⁶.

Cannabidiol use in ASD patients is being studied due to its effect on basal neural hyperexcitability. The therapeutic effects of a 20:1 CBD ratio medication include inhibiting the metabolic degradation of anandamide, as cannabidiol prevents the enzyme fatty acid amide hydrolase (FAAH) from metabolizing this endogenous cannabinoid, leading to its accumulation. This effect reduces ASD deficits and neural hyperexcitability due to low anandamide levels, stimulating synaptic modulation¹⁷.

The main risks associated with early recreational and chronic uncontrolled cannabidiol use include cognitive decline, schizophrenia, and reduced motivation, stemming from high THC levels in the medication. Conversely, there is limited information on anticipated chronic medicinal use in controlled doses, as it is a recent therapeutic option¹⁰.

Inappropriately used cannabinoids can cause renal dysfunction and other adverse effects, confirmed by increased serum creatinine levels in patients without pre-existing renal injury. This dysfunction occurs due to increased bioavailability of unmetabolized drugs excreted via the kidneys. An example is lithium, a mood stabilizer commonly used in autism patients for aggression, which, when combined with cannabinoids, has elevated serum levels. If not initially addressed, this can lead to epileptic seizures, loss of consciousness, and even death¹⁸.

There is resistance from traditional med-

ical organizations, but some countries have legalized marijuana for medicinal and recreational use. Examples include Argentina and Uruguay in South America, while the United States, which led prohibition campaigns, now accepts medicinal use in various states and recreational use in at least two¹⁹.

LEGISLATION IN BRAZIL FOR THE USE OF *CANNABIS SATIVA*

In 2017, was proposed to amend Article 28 of Law No. 11.343 of August 23, 2006, to decriminalize the cultivation of *Cannabis sativa* for personal therapeutic use. If previously law cited is approved, many patients unable to afford treatment costs will have access to the plant and an improved quality of life.

In December 2018, ANVISA approved the registration of the specific medication Mevatyl (tetrahydrocannabinol (THC) 27 mg/ml + cannabidiol (CBD) 25 mg/ml). This medication, derived from *Cannabis sativa*, is the first registered Cannabis-based medication. It is registered in other countries under the commercial name Sativex²⁰.

Resolution RDC No. 327/2019 establishes requirements for the importation and manufacture of medication, stipulating requirements for commercialization, prescription, dispensing, monitoring, and supervision of industrialized products containing *Cannabis sativa* derivatives or phytopharmaceuticals²¹.

On April 22, 2020, the first Cannabis-based product for commercialization and production in Brazil was authorized. This phytopharmaceutical contains up to 2% THC in oral solution form, with 200 mg/ml of cannabidiol, and must be prescribed using type B prescriptions²².

On May 6, 2022, ANVISA authorized another Cannabis-based medicinal product, Green-care 16032 mg/ml. On May 11, 2022, two additional products were approved: Mantecorp Farmasa 16032 mg/ml and Mantecorp Farmasa 7914 mg/ml. Two of these products are the first to be approved by the agency with THC content above 2%. These products contain 96 mg/ml of CBD and 0.24% THC. Approval is based on RDC No. 327/2019, allowing *Cannabis* products with THC

content above 2% for palliative care only for patients without therapeutic alternatives and in irreversible or terminal clinical situations. Dispensing of *Cannabis* products with THC content above 2% is done by a pharmacist in pharmacies and drugstores upon medical prescription accompanied by a special type A (yellow) prescription. The third approved product contains 475 mg/ml of CBD and no more than 2% THC. This product should be dispensed by medical prescription using a special type B (blue) prescription. These products will be manufactured in Colombia and commercialized in Brazil as oral drop solutions²³.

Currently, in Brazil, it is possible to acquire cannabidiol-based medication, but access is difficult, expensive, and involves various bureaucratic procedures. If *Cannabis sativa* were cultivated in Brazil for medication production and research, treatment would be more accessible for patients. Leandro Ramires, a doctor and director of the Brazilian Association of Medical *Cannabis* Patients (AMA+ME), states that access is difficult even for financially able patients. He notes that monthly treatment with imported products costs at least R\$ 1,000, but if produced in Brazil, it would cost R\$ 40 per month, allowing for export as well²⁴.

The bureaucratic process for importation, as established by ANVISA, involves submitting a request to ANVISA with the following documents: a medical prescription including the patient's and medication's name, dosage, required quantity, treatment duration, date, signature, and stamp of the doctor; a medical report with the disease code in the International Classification of Diseases, pathology description, case justification, and responsibility term signed by the doctor and patient or legal guardian; and the exceptional importation request form for special control medications filled and signed by the patient or legal guardian²⁵.

Health professionals have diverse opinions. Those with children are more likely to support marijuana use for treating various diseases. Professionals who have used drugs appear more "liberal" and favorable. Experienced, often married, and religiously practicing doctors tend to have more conservative views on the plant's use²⁶.

The objective of this research is to analyze available studies on treating ASD symptoms using *Cannabis sativa* medicinal extracts.

MATERIAL AND METHODS

The study is a systematic review based on electronic searches in scientific publications from the following databases: SciELO, PubMed, Biblioteca Virtual em Saúde (BVS), Lilacs, WorldCat, and official sites like ANVISA, considering the period from 2019 to 2021.

The descriptors used were "Autism Spectrum Disorder," "Cannabis sativa," "Autism," "Cannabidiol," "Tetrahydrocannabinol" in Portuguese and their English equivalents, specifying the publication year.

Inclusion criteria included the availability of full-text national and international articles, the specified publication period, human studies

related to characteristic ASD symptoms. Exclusion criteria included articles not available in full, animal studies, and articles before the specified publication period. The bibliographic survey was conducted from February to June 2022.

This manuscript was translated with the assistance of ChatGPT, an AI language model developed by OpenAI.

RESULTS AND DISCUSSION

A total of seventeen articles were found in the databases, with nine excluded due to the publication period and animal studies. Eight articles published between 2019 and 2021 were selected, with four conducted in Israel, two in Canada, one in Turkey, and one in Brazil (**Table 1**).

In all included studies, cannabinoid use showed effectiveness in at least one ASD symptom, primarily social communication, behavior,

Table 1: Articles on the use of Cannabis sativa components for treating ASD symptoms – 2019-2021

Author and Year	Substance Used	Effectiveness	Adverse Effects
ARAN et al., 2021 ²⁷	20:1 CBD and THC	Improved disruptive behavior.	Adverse effects included drowsiness and decreased appetite.
BILGE; EKICI, 2021 ²⁸	0.7 mg/kg/day CBD and THC below 3%	Improved behavioral symptoms, increased expressive language, and improved cognition.	No adverse effects observed.
ARAN; RAND, 2020 ¹⁰	20:1 CBD and THC	Improved behavior disorder, communication, and anxiety.	Decreased appetite, fatigue, sleep disturbance, and irritability.
PONTON et al., 2020 ²⁹	Cannabidiol-based extract (1:20 – THC 0.0001% and CBD 0.02%)	Improved behavioral and social symptoms like anxiety, sleep disorders, and weight.	No adverse effects observed.
ARAN et al., 2019 ³⁰	20:1 CBD and THC dissolved in olive oil	Significant improvement in behavioral symptoms.	Sleep disturbance, irritability, and decreased appetite.
BARCHEL et al., 2018 ³¹	Cannabinoid oil solution with 30% concentration and 20:1 CBD and THC ratio	Improved aggression, hyperactivity, and anxiety.	Most frequent adverse effects were drowsiness and appetite changes.
SCHLEIDER et al., 2019 ³²	20:1 CBD and THC oil	Improved behavioral symptoms, aggression, and agitation.	Restlessness, drowsiness, psychoactive effect, reflux, and decreased appetite.
TEIXEIRA et al., 2019 ¹⁷	CBD-enriched extract with 75:1 CBD to THC ratio	Improved ADHD symptoms, social interaction, and communication.	Drowsiness, irritability, increased heart rate, and behavioral crises.

and anxiety. Of the eight selected articles, six reported significant side effects with higher THC levels. The other two articles, with the highest CBD purity, reported no significant side effects. Thus, THC is associated with side effects. The results and side effects are directly linked to the administered CBD/THC ratio, but the exact ratio remains uncertain.

Comparing clinical studies^{10, 27, 30-32}, it is noted that the authors used the same 20:1 dosage of CBD and THC. The most common effectiveness after cannabinoid use was improved communication, with the two main adverse effects being drowsiness and decreased appetite. Other authors used different dosages^{17, 28, 29}. In one study, a dosage of 0.7 mg/kg/day of CBD and THC below 3% showed improved behavioral symptoms, increased expressive language, improved cognition, and no adverse effects²⁸. In another study²⁹, a 1:20 THC and CBD dosage was effective for behavioral and social symptoms such as anxiety and sleep disorders, with no adverse effects observed. In a third study¹⁷, a 75:1 CBD-enriched extract dosage improved ADHD symptoms, social interaction, and communication, with adverse effects like drowsiness, irritability, increased heart rate, and behavioral crises.

Regarding *Cannabis sativa* components' use, ethical considerations must be emphasized. Prejudice against its components hinders the broad approval of cannabinoids as medications. Another issue is the lack of authorization, leading many to acquire and use them inappropriately and in inadequate doses with higher THC proportions relative to CBD¹⁰. Moreover, its use for treatment, even if beneficial, can be impeded by parental or caregiver prejudice³³.

Up to 70% of autism patients have symptoms of anxiety, epilepsy, and sleep disorders. However, treatment for these conditions involves medications like anxiolytics, antiepileptics, and mood stabilizers. This increases medication interactions, affecting therapeutic efficacy and bioavailability¹. Therefore, studying cannabinoids' use for treating ASD symptoms shows improvements, especially in associated conditions.

The eight clinical test-based articles in this review indicated improvements in behavioral symptoms, aggression, and anxiety, with good acceptance of *Cannabis sativa* use in ASD patients, demonstrating higher CBD dosage efficacy relative to THC. Cannabinoids were intended to address primary symptoms and were effective for associated conditions like sleep disorders, anxiety, and hyperactivity. However, some side effects were notable in five studies, including appetite loss, irritability, and sleep disorders.

Despite unresolved dosage and long-term prognosis questions, prescribing doctors should be aware of the risks and benefits of medication interactions and provide adequate support to parents and caregivers of patients using psychopharmaceuticals. The trend is for more studies to investigate unresolved issues regarding the drug, using existing studies as a starting point. Although some clinical trials are ongoing, more long-term studies are needed.

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