# Exploring the Potential of Therapeutic Use of Cannabis in ASD Patients: A Systematic Review

By

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## Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing a degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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## Approval

The project titled "Exploring the Potential of Therapeutic Use of Cannabis in ASD Patients: A Systematic Review" submitted by Jannatul Ferdous Munni (19346049) of Summer, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on July, 2023.

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## Ethics Statement

The project does not involve any clinical trial or human participants, no animals were used or harmed.

## Abstract

Autism Spectrum Disorder (ASD), a complex neurological illness, causes social impairment, communication issues, and repetitive conduct. Traditional ASD treatments include behavioural interventions and symptom-specific drugs. New evidence suggests cannabis therapy may ease some ASD symptoms. This comprehensive analysis evaluates cannabis's medicinal potential for ASD patients. The endocannabinoid system (ECS) and its dysregulation in ASD set the stage for cannabis treatment in this review. We evaluate preclinical and clinical studies on the effects of cannabinoids like THC and CBD on ASD symptoms. In animal models of ASD, cannabinoids improved social interaction, repetitive behaviour, anxiety, and cognition. Preliminary clinical trials and observational research show cannabis-based drugs improve social communication, repetitive behaviour, and quality of life in ASD patients. However, cannabis-based ASD therapy has certain considerations and constraints. There are no dosing guidelines or long-term safety data. Cannabis' moral and legal consequences, especially for youth, must be considered.



**Keywords:** ASD; Autism; Autism Spectrum Disorder; Cannabis Treatment; Systematic Review; Social Communication.

# Dedication

*Dedicated to my faculty members, family and friends*

## Acknowledgement

I would like to begin by expressing my gratitude towards Almighty Allah for providing me with the strength during this whole period; I am indebted and would like to express my sincere gratefulness and gratitude towards Dr. Mesbah Talukder, Associate Professor, School of Pharmacy, Brac University for being a constant guiding spirit throughout my study and for being so supportive, kind and motivating throughout the journey.

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## List of Acronyms

| | |
|---|---|
| ASD | Autism Spectrum Disorder |
| SRS-2 | The Social Responsiveness Scale |
| APSI | Autism Parenting Stress Index |
| THC | Delta-9-Tetrahydrocannabinol |
| CBD | Cannabidiol |
| ADI-R | Autism Diagnostic Interview-Revised |
| ADOS | Diagnostic Observational Schedule |

# Chapter: 1

## Introduction

Autism spectrum disorder is the abbreviation used to describe it. Social contact, communication, and behavior are all negatively impacted by this neurodevelopmental impairment. Although most people with autism are diagnosed during childhood, some may have to wait much longer. A spectrum of symptoms, some more severe than others, define autism (Hyman, 2020). Some symptoms that are often seen in those with ASD are:

- Impairments in social interaction: People with ASD may have trouble reading social signs, understanding nonverbal communication, and establishing and maintaining friendships and romantic connections. It's possible they have difficulty reading and reacting to the emotions of others and finding common ground when it comes to hobbies and life experiences.
- Communication difficulties: Atypical development of language is a common symptom of autism spectrum disorder. Some people may have trouble starting or maintaining conversations, grasping metaphors or sarcasm, or expressing themselves through body language.
- Restricted interests and repetitive behaviors: Repetitive actions, such as hand-flapping, rocking, or lining up objects, are common among people with autism spectrum disorder (ASD), as are limited interests. They could become fixated on one thing or have a hard time breaking out of a rut. They may have a hard time adjusting to shifts in their usual routine.
- Sensory sensitivities: People with ASD may have either increased or decreased sensitivity to sensory stimuli like noise, light, texture, or scent. Some sounds or textures may be too much for them, or they may have other preferences for sensory stimulation (Höfer, 2017, p. 227).

## 1.1 The class of drugs

The term "class of cannabis" is used to describe a more generalised classification of the cannabis plant and its many varieties. There are three main types of cannabis, all of which are in the family Cannabaceae: Cannabis sativa, Cannabis indica, and Cannabis ruderalis. Based on their hereditary qualities, cannabinoid profiles, and other physical characteristics, these species are further divided into subspecies, hybrids, and individual strains.

- **Cannabis sativa:** Cannabis sativa, or a sativa strain, is characterised by a tall, lean body and narrow leaves. Originating in the tropics, they are known for their energising and inspiring qualities. Higher concentrations of THC (tetrahydrocannabinol), the psychoactive ingredient responsible for the "high" associated with cannabis usage, are characteristic of sativa strains. Sativas are known to have a more cerebral and stimulating effect, elevating mood and encouraging mental clarity, concentration, and social interaction. People who want more energy and a better mood may find them helpful to take during the day (Hillig, June 2004).

*Figure 1 : Cannabis Sativa*

- **Cannabis indica:** Cannabis indica has a shorter, bushier plant structure and wider leaves than

Sativa strains. It is theorised that they came from the Hindu Kush mountains in the Indian subcontinent. Higher concentrations of CBD (cannabidiol) and other non-psychoactive cannabinoids in indica strains are responsible for its calming and sedative effects. Indicas are commonly used for their "body high," which includes sedation, pain relief, and increased relaxation. In order to relax, relieve stress, or help one fall asleep, they are typically used in the evening or at night (al, 2011).

*Figure 2 : Cannabis Indica*

- **Ruderalis:** Ruderalis, or "scratchy marijuana," is a type of cannabis that is less popular for both recreational and medical use. Its genesis can be traced back to areas of Eastern Europe and Russia with shorter growing seasons. Autoflowering is a common feature of rudderalis strains; this means that the transition from vegetative to flowering stage is age-dependent rather than time-dependent. Despite their low THC content, Ruderalis strains can be employed in cannabis breeding for their autoflowering abilities (JR, 2001).

*Figure 3 : Ruderali*

## 1.2 Focused drugs

There is still much that is unknown about the complexities of the pharmacokinetics of cannabis and its active ingredients like THC (tetrahydrocannabinol) and CBD (cannabidiol). Furthermore, there is a dearth of studies examining the effects of cannabis on Autism Spectrum Disorder (ASD). On the other hand, I can tell you a little bit about the pharmacokinetics of cannabis and its possible effects on ASD in general.

Absorption: Cannabis can be smoked, vaporized, eaten (edibles), or administered sublingually (under the tongue). Cannabinoids' absorption is also varied depending on how they're taken. Cannabinoids enter the circulation immediately through the lungs during smoking and vaporization, allowing for quick absorption. When cannabinoids are taken orally, they must first travel through the digestive system and be processed by the liver, which slows absorption.

Distribution: Cannabinoids, once absorbed, are transported by the circulatory system to all parts of the body. Both THC and CBD are capable of penetrating the blood-brain barrier and interacting with CNS receptors. However, it is still not well understood how cannabinoids are distributed throughout

the brain and other organs (Ramsay, 2001).

Metabolism: The liver is heavily involved in the metabolism of both THC and CBD. 11-hydroxy-THC is the main metabolite of THC and is also psychoactive. These metabolites are subsequently metabolised into inert substances. Genetics, liver function, and other medications taken at the same time can all affect how a person metabolises cannabis.

Elimination: Cannabinoids and their metabolites are largely excreted in the urine and feces during the fourth phase of elimination. Depending on the circumstances, THC's half-life might be anywhere from a few hours to several days. Cannabinoids may build up in the body with long-term cannabis use.

There has been a scant scientific inquiry into the effectiveness of cannabis for ASD; instead, the evidence that exists is primarily anecdotal or based on small-scale studies. There is anecdotal evidence that the use of cannabis products can help some people with ASD and their carers manage symptoms such as anxiety, aggression, sleep difficulties, and repetitive behaviors. The long-term effects and safety of cannabis usage in ASD are not yet well-established, thus it is important to approach these statements with caution.

Always get the advice of a doctor before using cannabis-based products for Autism Spectrum Disorder or any other medical condition. Individualised advice, risk/benefit analysis, and discussion of potentially more evidence-based treatments and therapies are all within their purview.

Cannabis for Autism Spectrum Disorder (ASD) is complex and changing. Anecdotal evidence suggests cannabis may benefit ASD, but additional research is needed. The most famous cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). These cannabinoids affect the endocannabinoid system, which regulates mood, hunger, pain perception, and immunological function. Cannabis pharmacodynamics generally involve cannabinoids and brain and

body receptors. THC binds to central nervous system CB1 receptors. Cannabis causes pleasure, altered perception, and cognitive impairment due to this interaction. CBD does not affect CB1 receptors or cause psychoactivity. CBD interacts with various receptors, including mood-regulating serotonin receptors. CBD is neuroprotective and anti-inflammatory (Dietert, 2011).

The possible benefits of cannabis for people with Autism Spectrum Disorder (ASD) are the subject of continuous study and interest. The use of cannabis for ASD remains contentious and is not commonly accepted by medical professionals, however it is crucial to highlight that there is some scientific research in this field. Some essential considerations are as follows:

Symptom management: Anxiety, anger, sleep problems, and self-injurious behaviours are all hallmarks of autism spectrum disorder (ASD), and some anecdotal evidence suggests that cannabis's cannabidiol (CBD) may help alleviate these issues. However, further study is required to determine cannabis's safety and effectiveness for these applications.

Epilepsy: People with ASD have an increased risk of developing certain types of epilepsy. CBD, a non-psychoactive component of cannabis, has been licenced by the FDA for the management of some types of epilepsy. As a result, CBD may be evaluated as a therapy option for people with epilepsy and ASD (Ashton, 1998).

Risks and side effects: THC (tetrahydrocannabinol), the main psychoactive ingredient in cannabis, can cause sleepiness, appetite changes, and mood swings, among other things. Furthermore, the long-term consequences and drug interactions are not fully recognised. All of these things make it clear that we need more information before we can safely consider cannabis as a treatment.

It's crucial to remember that research on the impact of cannabis usage on people with Autism Spectrum Disorder (ASD) is currently limited and inconclusive, and that these effects can vary. Cannabis has been linked to therapeutic benefits in treating some ASD symptoms, but there are also

hazards and harmful consequences, according to some research. Here are a few things to think about.

Potentially beneficial results:

1. Cannabis may help lessen the symptoms of anxiety and stress in some people with ASD.
2. Cannabis use has been linked to a decrease in aggressive and self-injurious behaviour in certain people with autism spectrum disorder.
3. The quality of sleep and the treatment of sleep disturbances are common complaints of people with ASD. Cannabis may help with both of these issues (Dietert, 2011).

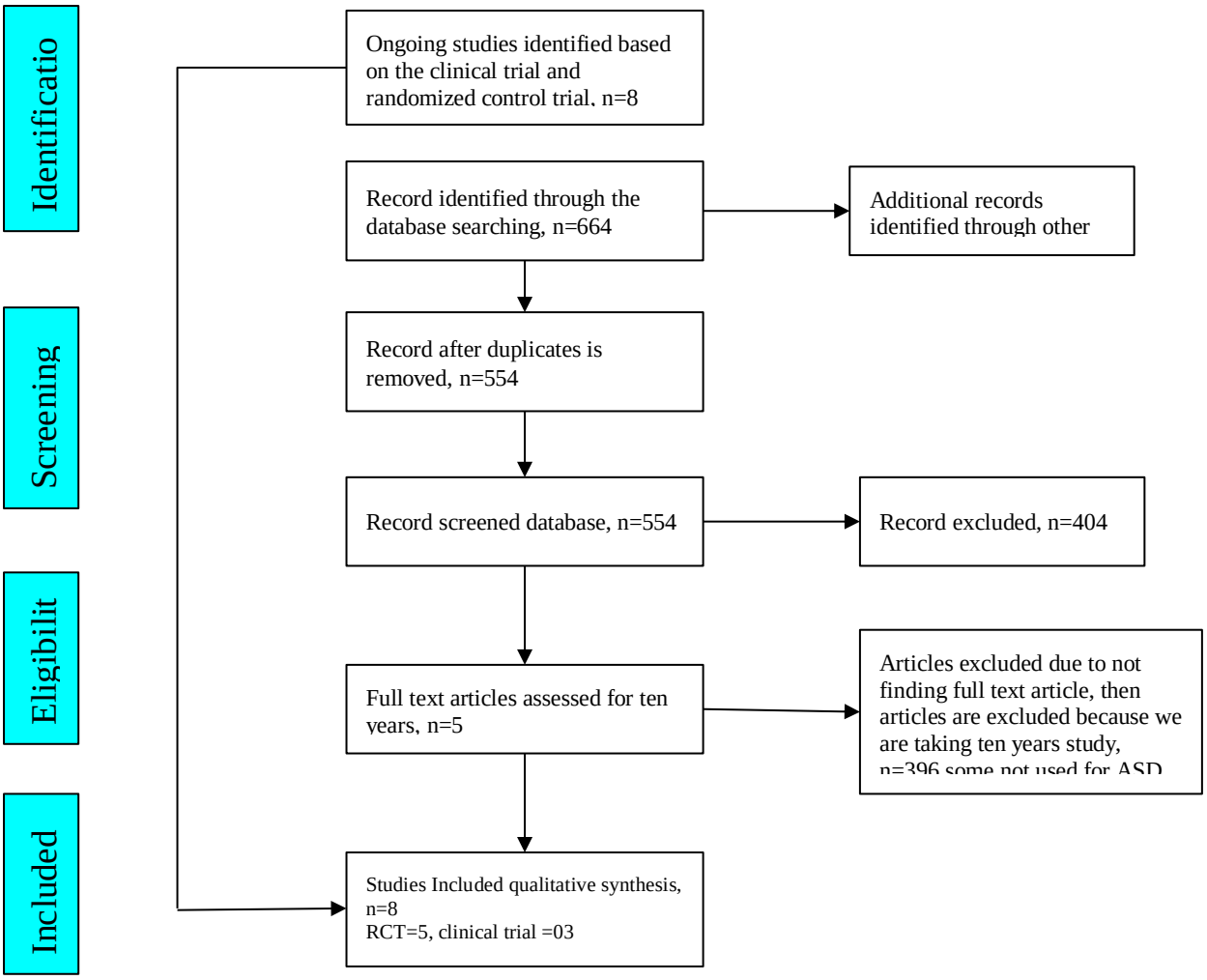
Negative effects (potential risks):

1. Cannabinoids in marijuana have been shown to have negative impacts on memory, thinking, and other cognitive processes. This can exacerbate the cognitive difficulties that some people with ASD may already be experiencing.
2. In some people cannabis has a calming effect, but in others it can cause anxiety, paranoia, and even panic attacks.
3. Cannabis usage may increase the already present issues with executive functioning that are characteristic of autism spectrum disorder.
4. Individuals with ASD may be more susceptible to the risks of dependency and addiction associated with cannabis use, as is the case with any psychoactive substance.

## Chapter: 2

## Materials and Methods

We were able to locate 664 studies from our search and an additional nine publications from other sources. We reviewed 554 titles and abstracts after deleting duplicates. We studied the entire texts of eight studies before deciding to include five studies in our systematic review. In addition, five controlled experiments were located in the PubMed database. Figure depicts the selection process used to determine which research will be included



## 2.1. Search strategy

From 2013 (on January 1) to 2023 (on May 25), the author used multiple keywords and keyword combinations (table 1) to conduct an electronic search on PubMed. In order to find and incorporate the most studies, the author set and chose the key phrases carefully. The following are the search terms:

(Autism OR autism spectrum disorder OR asd OR asd syndrom) AND (Cannbis OR Cannbidiol OR Cannab OR ) AND

(predictor OR predicting outcome OR outcome)

*Table 1: Details about search strategy*

| **Software which is used** | **Research system** | **Taking of years** | **Filter** |
|---|---|---|---|
| Pubmed | (Cannabis or cannabidol or THC) AND (ASD) | 2019-2023 | • RCT<br>• 10 Years<br>• Free Full test |
| Pubmed | Cannabis or ASD | 2019-2023 | • RCT<br>• 10 Years<br>• Free Full test |
| Pubmed | (cannab or cannabidiol or THC) AND (ASD) | 2019-2023 | • Clinical trial<br>• 10 Years<br>• Free Full test |

| | | | |
|---|---|---|---|
| Google scholars | Cannabis or cannabidiol AND ASD | | |

## 2.2 Study Selection and management

All of the first recognized studies were entered into Rayyan software to perform initial title and abstract screening, deduplication, and eligibility determination for full text screening (figure 1). Title and abstract screening, which has allowed the author to at least two or more keywords in their abstract or title.

## 2.3 Table of inclusion-exclusion criteria:

*Table 2: Details about inclusion and exclusion criteria*

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| ● Experimental studies which give effective outcomes of the drug<br>● Randomized control trials are included in these studies<br>● Only 10 years of studies are included<br>● CBD is used for ASD patients | ● In most of the experiments, CBD is not used only for ASD but also other disease<br>● The level of evidence is not rated properly<br>● Some of the studies did not do RCT<br>● Some of the studies did not do single or double-binding design |

## 2.4 Types of Studies

The systematic review was only thought to be meaningful if it contained all relevant level-I randomized control trials (table 4). The RCTs were assessor-blinded and single-blinded, and there were a few non-blinded trials that needed to be included in the evaluation because of their importance and the constraints of collaborating with a parent and therapist to deliver therapy. Computer-generated randomizations, random number tables, or coin tosses must be used to generate randomizations. To be taken into consideration for the evaluation, the patient count must be greater than 10 ($n>10$). Finally, only research that had been published in English was thought to be relevant.

# Chapter: 3

# Results

## 3.1. Characteristic of studies and participants

We included five studies were everything is randomized control trial studies. All papers were published within last ten years. Many patients joined the studies and the results were taken from those studies. Studies characteristics are reported in table 3(three):

| Reference | Study design | Number of participants with ASD | Age range (years) | dosage | Duration | outcome |
|---|---|---|---|---|---|---|
| Pretzsch, Voinescu, Mendez, et al., 2019 | RCT, Double binding, Cross over | 17 (Nurotypicale)<br>13 ASD | 28 years<br>30 years | 600mg | 13 days | CBD 'shifts' fALFF and FC in the adult human brain, and this effect has been documented for the first time. We discovered that CBD considerably raised fALFF in the right fusiform gyrus and cerebellar vermis VI. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Aran et al., 2021 | RCT<br><br>Double blinding | 150 participants | 5-21 years | 165 mg/ml CBD, 8.35 mg/ml THC, 1mg/kg/d first dosage, 10 mg/kg Depend on the body weight, Maximum can give 420mg per day | 12 weeks | Cannabis therapy has the ability to reduce disruptive behaviors linked to for the first time in a placebo-controlled trial tolerable for those with an autism spectrum disorder. The response rate for those given the whole-plant extract was 49%, while it was 21% for those given a placebo. |
| Hacohen et al., 2022 | RCT<br><br>Double blinding | 110 participants<br><br>65 males | 5-25 years Old<br><br>Mean age 9.24 | 5.7mg CBD, 0.3MG THC, 10mg/kg/day, Or 400mg/day, 0.5mg/kg/day, Or 20g/day Of THC | 6 months | Decreased irritability Aggressiveness Hyperreactivitor Sleep disorder<br><br>ADOS-2 Social Communication Improvements Revealed by Autism Diagnostic Observation Schedule Severity scores with a calibrated CSS Only when parents used the SRS did, they notice a significant reduction in RRB symptoms. |

| | | | | | | |
|---|---|---|---|---|---|---|
| Pretzsch, Freyberg, et al., 2019 | RCT | 34 healthy men | Adult | 600mg | 13 days | CBD enhanced GABA+ in healthy subjects, but lowered it in ASD subjects, in both frontal and subcortical regions. |
| Pretzsch, Voinescu, Lythgoe, et al., 2019 | RCT Double blinding | 34 participants | 5-21 years | Single dose 600mg CBDV and placebo | 13 days | Established a single, high-dose injection of CBDV 'shifts' Glx levels in the subcortical regions of the living adult human brain, proving that this neurotransmitter is the principal source of excitatory neuronal activity. |

The study by (Pretzsch, Voinescu, Mendez, et al., 2019) examined 32 patients their age was 28-30 years old with ASD. In this study, they used a randomized control trial, double blinding study design to identify the outcome of the patients. Through this study, they found that CBD shifts fALFF (Fractional amplitude of low-frequency fluctuations) and FC in the adult human brain. In particular, we discovered that CBD dramatically elevated fALFF in the right fusiform gyrus and cerebellar vermis VI by using 600mg of cannabis for 13 days.

Secondly, the study by (Aran et al., 2021) examined 150 patients their age was 5-21 years old with ASD. In this study, they used a randomized control trial, double blinding study design to identify the outcome of the patients. They used 165 mg/ml CBD, 8.35 mg/ml THC, 1mg/kg/d first dosage, 10 mg/kg depending on the body weight, Maximum can give 420mg per day of cannabis and placebo. In this study, they found for the first time Cannabinoid therapy has the potential to reduce disruptive behaviors linked to ASD in a placebo-controlled trial, with acceptable tolerability. In contrast to 21% of people receiving a placebo, we discovered that 49% of participants receiving a whole-plant extract responded.

After that, the study by (Hacohen et al., 2022) examined 110 patients their age was 5-25 years old with ASD. In this study, they used a randomized control trial, double blinding study design to identify the outcome of the patients. They used ADOS, and CSS to check the significant effect on the patients. They measure the outcome of the patients when they used 5.7mg CBD, 0.3MG THC, 10mg/kg/day, Or 400mg/day, 0.5mg/kg/day, Or 20g/day Of THC f cannabis for the 6 months. They found improvements in RRB symptoms were apparent only in parent reports with the SRS. This study had some limitations These findings are supported by information from 82 of the initial 110 study participants. Twelve people, or 11% of the initial sample, discontinued therapy because of negative side effects the 28 participants did not complete the research for various reasons.

Then the study by (Pretzsch, Freyberg, et al., 2019) examined 32 healthy adult men with ASD. In this study, they used a randomized control trial study design to identify the outcome of the patients. They used 600mg of cannabis for 13 days. They found CBD raised GABA+ in the prefrontal and subcortical regions of the controls, but GABA+ was reduced in ASD.

In the last study from our table (Pretzsch, Voinescu, Lythgoe, et al., 2019) examined 32 healthy adult men with ASD. In this study, they used a randomized control trial study design to identify the outcome of the patients. They used a Single dose 600mg CBDV and a placebo for 13 days. In this study, they used a randomized control trial, double blinding study design to identify the outcome of the patients. They revealed that a single acute dose of CBDV 'shifts' the subcortical levels of Glx, the brain's main excitatory neurotransmitter, in the living adult human brain.

## 3.2. Types of participants

The study includes RCTs done on kids and adults with ASD using the Autism Diagnostic Observational Schedule (ADOS), CSS, and fALFF Autism Diagnostic Interview-Revised (ADI-R). Participants had to never get CBD treatments or placebos.

## 3.3. Types of Intervention

The patients must receive regular CBD treatments. Depending on the protocol, the session design could change. The intervention may be compared to a "placebo" group, a treated group, a group receiving conventional care.

## 3.4. Outcome measurement

The main focus was on the broad spectrum of social communicational development in ASD patients, which includes communicative skills, social interaction, adverse effects of social-emotional reciprocity, initiating behavior, social adaptation skills (including outcomes such as behavioral problems, quality of life in environments such as school and home, quality of family relationships, cognitive ability), and changes in receptor

# Chapter: 4

# Risk of bias

The Cochrane risk of bias tool (ROB 2) was used to evaluate the methodological quality. I've added one of the ROB evaluation tool's figures.

The author assessed the following items:

- Random sequence generation;
- Allocation concealment;
- Blinding of participants and personnel
- Blinding of outcome assessment;
- Completeness of outcome data;
- Selective reporting;
- Other sources of bias.

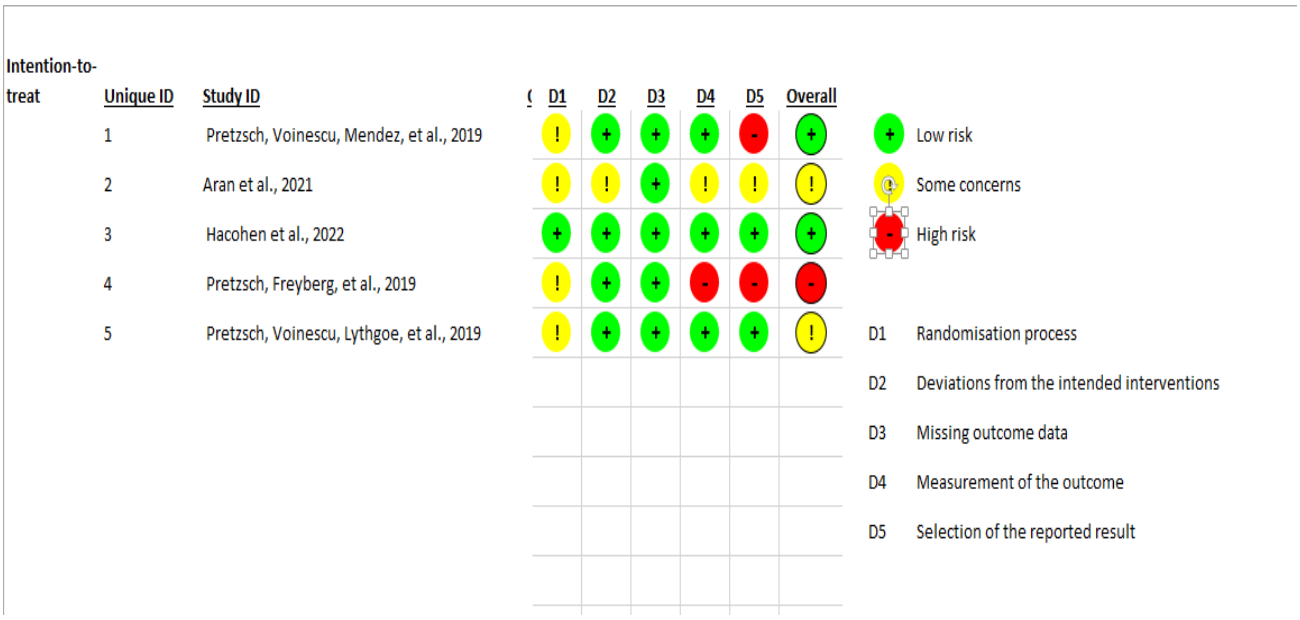



*Figure 4 : Risk of bias*

# Chapter: 5

# Discussion

In ASD (Pretzsch, Voinescu, Mendez, et al., 2019), they predicted that there would be an altered fMRI response to CBD. In the study (Aran et al., 2021) improvements in behavioral issues were measured using the Clinical Global Impression-Improvement scale with disruptive behavior anchor points (CGI-I) and the Home Situation Questionnaire-ASD (differences between whole-plant extract and placebo). SRS-2 and the APSI served as secondary measures. The (Pretzsch, Freyberg, et al., 2019) study before beginning extensive clinical trials, a deeper comprehension of CBD's effects on the brain would be preferable. According to preclinical research, CBD regulates brain excitatory glutamate and inhibitory GABA levels, especially in areas of the brain associated with ASD, like the basal ganglia and the dorsomedial prefrontal cortex (DMPFC). The reaction to CBD in individuals with and without ASD may differ, however, due to variations in glutamate and GABA pathways in ASD. We employed magnetic resonance spectroscopy to determine whether CBD "shifts" glutamate and GABA levels and to look at potential changes in this response in Asian (Pretzsch, Voinescu, Lythgoe, et al., 2019) study that is unclear how CBDV impacts the human brain. CBDV may modify brain excitatory-inhibitory circuits, which are linked to ASD, according to prior (pre)clinical research. Our main goal was to determine whether CBDV affects glutamate and/or GABA metabolites, which are indicators of the brain's fundamental excitatory and inhibitory systems in both the 'normal' and autistic brains, for the first time. Our secondary goal was to examine the relationship between biological phenotype and brain responsiveness to CBDV challenge in ASD. In our study we identify the whole outcome those they done in their studies. We show all result by a table. more studies will do in future for the actor solution of this diseases.

# Chapter: 6

# Level of evidence

***Table 4: details the level of evidence***

| **level** | **Description** |
|---|---|
| Level I | Systematic reviews, RCTS |
| Level II | Two groups (case-control and cohort) |
| Level III | One groups (before and after effect) |
| Level IV | Descriptive studies which analysis of outcome |
| Level V | Expert opinion |
| Strong evidence | Giving the consistent result with RCTs |
| Insufficient evidence | Some studies have limitation to make any clear effectiveness. |

# Chapter: 7

# Conclusion

Our research shows that an effective method for treating ASD is cannabis medication or cannabis extract. Our findings provide stronger support for the effectiveness of this medication in terms of behavioral changes, general social communication improvement, and certain receptor modifications. Cannabis has been shown in our study to be more beneficial for patients with ASD. Additionally, our research on cannabis treatment shows logical advancement and involves self-interest. To find the most accurate and efficient results, clinical trials and randomized control trials should be conducted more frequently.

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