การทบทวนอย่างเป็นระบบเกี่ยวกับผลของสารแคนนาบิไดออล (Cannabidiol) ต่อความจำประเภทต่างๆ

ศิวพร ปราณีนิจ

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรวิทยาศาสตรมหาบัณฑิต
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A SYSTEMATIC REVIEW ON THE EFFECTS OF CANNABIDIOL ON DIFFERENT TYPES OF MEMORIES

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science
Department of Anti-aging and Regenerative Medicine,
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ภาษาไทย การทบทวนอย่างเป็นระบบเกี่ยวกับผลของสารแคนนาบิไดออล (Cannabidiol) ต่อความจำประเภทต่างๆ

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หัวข้อวิทยานิพนธ์	การทบทวนอย่างเป็นระบบเกี่ยวกับผลของสารแคนนาบิไดออล (Cannabidiol) ต่อความจำประเภทต่างๆ
ชื่อผู้เขียน	ศิวพร ปราณีนิจ
อาจารย์ที่ปรึกษา	ผู้ช่วยศาสตราจารย์ ดร.เอกราช บำรุงพืชน์
หลักสูตร	วิทยาการชะลอวัย และฟื้นฟูสุขภาพ
ปีการศึกษา	2565

บทคัดย่อ

ความเป็นมา: การเปลี่ยนแปลงล่าสุดในการลดทอนความเป็นอาชญากรรมและการทำให้กัญชาถูกกฎหมายในประเทศไทยส่งผลกระทบการเข้าถึงและได้มาของกัญชาต่อประชากรสำหรับการใช้ทั้งทางการแพทย์และสันทนาการ กัญชามีสารไฟโตแคนนาบินอยด์ เทอร์ปีน และสารประกอบอื่นๆ จำนวนมากที่มีฤทธิ์ทางชีววิทยา กายภาพ และจิตวิทยาที่หลากหลาย หลักฐานใหม่สนับสนุนคุณสมบัติทางยาที่เป็นไปได้ของ "กัญชาทางการแพทย์" ในการรักษาโรคทางพยาธิวิทยา ระบบประสาท และทางจิตเวช แต่ก็สามารถส่งผลเสียต่อความปลอดภัยของผู้บริโภคและสุขภาพของประชาชนได้เช่นกัน นักวิทยาศาสตร์ได้แยกสารประกอบในกัญชาเพื่อศึกษาผลการรักษาและผลข้างเคียง CBD ซึ่งเป็นสารประกอบที่ไม่ออกฤทธิ์ต่อจิตประสาท ได้รับความสนใจจากศักยภาพในการบรรเทาผลกระทบที่เป็นอันตรายของ THC ในขณะเดียวกันก็ส่งเสริมผลลัพธ์ด้านสุขภาพในเชิงบวกและส่งเสริมความเป็นอยู่ที่ดีโดยรวม หน่วยความจำเป็นสิ่งจำเป็นสำหรับชีวิตประจำวัน การตัดสินใจ และการเรียนรู้ และ CBD ได้รับการศึกษาถึงผลกระทบต่อหน่วยความจำประเภทต่างๆ การทบทวนอย่างเป็นระบบนี้มีจุดมุ่งหมายเพื่อเน้นย้ำถึงผลกระทบของ CBD ต่อความทรงจำประเภทต่างๆ เพื่อให้มีหลักฐานเพิ่มเติมในการสนับสนุนการใช้ CBD เป็นตัวกระตุ้นประสิทธิภาพที่เกี่ยวข้องกับความจำและความเป็นอยู่ที่ดี และอาจเป็นมาตรการป้องกันผลกระทบของ THC

วัตถุประสงค์: วัตถุประสงค์หลักของการทบทวนอย่างเป็นระบบนี้คือการประเมินวรรณกรรมปัจจุบันเกี่ยวกับผลกระทบของ CBD ต่อความทรงจำประเภทต่างๆ และเพื่อเป็นหลักฐานล่าสุดสำหรับการนำ CBD ไปใช้ทางคลินิกในด้านที่เกี่ยวข้องกับการปรับหน่วยความจำ วัตถุประสงค์รองคือการให้ข้อมูลเชิงลึกเพิ่มเติมเกี่ยวกับประเด็นแนวคิดและวิธีการของการใช้ CBD เพื่อการปรับปรุงในอนาคต

วิธีการ: ค้นหาอย่างเป็นระบบเพื่อระบุการศึกษาที่เกี่ยวข้องโดยใช้แนวทาง Systematic Review and Meta-Analysis (PRISMA), Medical Subject Heading (MeSH) word และเกณฑ์ที่กำหนดไว้ล่วงหน้าสำหรับการเลือกบทความ การค้นหานี้ดำเนินการในฐานข้อมูลต่างๆ รวมถึง EMBASE, MedLine, PubMed, PsychINFO และ Sciencedirect โดยใช้คำค้นหาที่เกี่ยวข้องกับ CBD และหน่วยความจำร่วมกัน การค้นหาจำกัดเฉพาะบทความที่ตีพิมพ์ระหว่างปี 2010 ถึงมกราคมปี2023 (ปัจจุบัน)

ผลลัพธ์: การค้นหาให้ผลการศึกษาพรีคลินิกในสัตว์ทดลอง 48 งาน และการทดลองในมนุษย์ที่มีกลุ่มควบคุมแบบสุ่ม (RCTs) 12 งานที่เข้าเกณฑ์การคัดเลือก ประชากรทั้งสัตว์และมนุษย์เป็นประชากรที่มีสุขภาพดีและผู้ที่มีความบกพร่องทางสติปัญญา เช่น ภาวะสมองเสื่อมและอาการคล้ายโรคจิตเภท มีการใช้การทดสอบพฤติกรรมและการรับรู้หลายอย่างเพื่อประเมินประเภทและขั้นตอนต่างๆ ของการประมวลผลหน่วยความจำ และใช้ปริมาณ CBD และมีวิธีการให้ที่แตกต่างกัน การศึกษาในสัตว์แสดงให้เห็นถึงการปรับปรุงในความจำอาศัยเหตุการณ์ ความจำการทำงานเชิงพื้นที่ ความจำที่เกี่ยวข้องกับความกลัว และความจำที่เกี่ยวข้องกับยา การศึกษาในมนุษย์แสดงให้เห็นการปรับปรุงในความจำที่เกี่ยวข้องกับความกลัว แต่มีผลลัพธ์ที่ไม่แน่นอนในความจำอาศัยเหตุการณ์ และความจำเพื่อใช้งานผลกระทบของ CBD ต่อความจำเสื่อมที่เกิดจาก THC นั้นยังไม่สามารถสรุปได้ พบว่า CBD ส่งผลกระทบต่อขั้นตอนต่าง ๆ ของการประมวลผลหน่วยความจำ รวมถึงการรวม การรวมใหม่ การสูญพันธุ์ และการคืนสถานะในลักษณะที่ขึ้นกับปริมาณ นอกจากนี้ CBD ยังลดการแสดงออกของโปรตีนและปรับระดับการกระตุ้นสมองในบริเวณสมองที่เกี่ยวข้องกับความจำ มีรายงานผลข้างเคียงเล็กน้อย แต่สามารถหายได้เอง คุณภาพโดยรวมของหลักฐานถูกจำกัดเนื่องจากประชากรที่แตกต่างกัน ความแตกต่างของระเบียบวิธี และอคติที่อาจเกิดขึ้น

สรุป: การทบทวนอย่างเป็นระบบนี้ชี้ให้เห็นว่า CBD อาจปรับเปลี่ยนความทรงจำประเภทต่างๆ โดยมีผลดีต่อความจำที่เกี่ยวข้องกับความกลัว และอาจมีผลกระทบในเชิงบวกต่อความจำอาศัยเหตุการณ์ ความจำการทำงานเชิงพื้นที่ และความจำที่เกี่ยวข้องกับยา อย่างไรก็ตาม จำเป็นต้องมีการวิจัยเพิ่มเติมเพื่อหาผลกระทบของ CBD ต่อความบกพร่องของความจำที่เกิดจาก THC และเพื่อให้เข้าใจอย่างถ่องแท้ถึงผลกระทบของขนาดยา วิธีการให้ และวิธีการทดสอบพฤติกรรม ดังนั้น จึงจำเป็นต้องมีแนวทางที่มีลักษณะเป็นพหุวิทยาการ ในการกำหนดขนาดยา วิธีการให้ และผลระยะยาวที่เหมาะสม โดยรวมแล้ว การค้นพบนี้สนับสนุน CBD ในฐานะตัวเลือกการรักษาที่มีแนวโน้มสำหรับการปรับปรุงการทำงานของหน่วยความจำในประชากรทางคลินิกและไม่ใช่ทางคลินิก

คำสำคัญ: แคนนาบิไดออล, CBD, กัญชา, หน่วยความจำ, การประมวลผลหน่วยความจำ, การทบทวนอย่างเป็นระบบ

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Thesis Title	A SYSTEMATIC REVIEW ON THE EFFECTS OF CANNABIDIOL ON DIFFERENT TYPES OF MEMORIES
Author	Siwaporn Praneenij
Thesis Advisor	Assistant Professor Dr. Akkarach Bumrungpert
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ABSTRACT

Background: The recent changes in decriminalization and legalization of cannabis in Thailand has impacted the population's exposure to cannabis and availability for both medical and recreational use. Cannabis contains numerous phytocannabinoids, terpenes, and other compounds that have diverse biological, physical, and psychological actions. Emerging evidence supports the potential medicinal properties of "medical cannabis" in treating various pathological, neurological, and psychiatric disorders, but it can also have adverse effects on consumer safety and public health. Scientists have isolated compounds in cannabis to study their therapeutic and side effects. CBD, a non-psychoactive compound, has gathered attention for its potential to mitigate the deleterious effects of THC while simultaneously promoting positive health outcomes and enhancing overall well-being. Memory is essential for daily life, decision-making, and learning, and CBD has been studied for its effects on different types of memory. This systematic review aims to highlight the effects of CBD on different types of memories to provide further evidence to support the use of CBD as a performance booster in relation to memory and well-being, and perhaps as a protective measure against the effects of THC.

Objective: The primary objective of this systematic review is to evaluate the current literature on the effects of CBD on different types of memories and to provide up-to-date critical evidence for the clinical implications of CBD in its relations to memory modulation. The secondary objective is to provide further insight into the conceptual and methodological issues of CBD usage for future improvement.

Methods: A systematic search was conducted to identify relevant studies using the Systematic Review and Meta-Analysis (PRISMA) guideline, Medical Subject Heading (MeSH) words, and a predetermined set of criteria for article selection. This search was performed across a range of databases, including EMBASE, MedLine, PubMed, PsychINFO, and Sciencedirect, utilizing a combination of search terms related to CBD and memory. The search was limited to articles published between 2010 and January 2023 (present).

Results: The search yielded 48 preclinical animal studies and 12 human randomized controlled trials (RCTs) that met the inclusion criteria. Both animal and human populations included healthy individuals and those with cognitive impairments such as dementia and schizophrenia-like conditions. Multiple behavioral and cognitive tests were utilized to assess various types and stages of memory processing, and different CBD dosages and administration routes were employed. Animal studies demonstrated improvements in episodic memory, spatial working memory, fear-associated memory, and drug-associated memory. Human studies showed improvements in fear-associated memory, but mixed results in episodic and working memory. The effects of CBD on THC-induced memory impairment remain inconclusive. CBD was found to affect different phases of memory processing, including consolidation, reconsolidation, extinction, and reinstatement, in a dose-dependent manner. Furthermore, CBD decreased protein expression and modulated brain activation levels in memory-related brain regions. Mild adverse effects were reported but resolved on their own. The overall quality of evidence was limited due to the heterogeneous populations, methodological differences, and some potential biases.

Conclusion: This systematic review suggests that CBD may modulate different types of memories, with a beneficial effect on fear-associated memory and potential positive effects on episodic, spatial working memory, and drug-associated memory. However, more research is needed to determine the effects of CBD on THC-induced memory impairment and to fully understand the impact of dosage, administration route, and cognitive tasks. Thus, a multidisciplinary approach is required to establish optimal dosage, administration, and long-term effects. Overall, these findings support CBD as a promising therapeutic option for improving memory function in clinical and non-clinical populations.

Keywords: Cannabidiol, CBD, cannabis, memory, memory processing, systematic review

(Assistant Professor Dr. Akkarach Bumrungpert)

Thesis Advisor

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Siwaporn Praneenij

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CHAPTER 1
INTRODUCTION

1.1 Background and significance of the problem / Rationale

2022 has been an interesting year in terms of how Thailand has decriminalized and legalized the use of cannabis. The changes in the legal status of cannabis had significant impact on the general population of cannabis exposure and increased the availability of acquiring cannabis for both medical and recreational usage, in which there are currently 200 million cannabis users or more worldwide[1]. Cannabis contained numerous phytocannabinoids, terpenes and other compounds which can bind and have certain affinity to specific receptors in the human body known as the endocannabinoid system. Currently there are approximately 560 compounds and 120 phytocannabinoids that are primarily produced in the trichomes identified[2] in which these compounds and phytocannabinoids have diverse biological, physical and psychological actions that are sometime opposing to one another.

There are emerging evidences supporting the potential medicinal properties of "medical cannabis". In the review by Fraguas-Sánchez and Torres-Suárez[3], cannabinoids showed promising results in many pathological, neurological and psychiatric disorders, in terms of how the endocannabinoid system played an important role in energy balance, stimulating appetite, modulating pain, nausea and vomiting control, immunological response as well as anti-inflammatory effect, memory, recall and learning. Evidence from studies including randomized control trial and systematic review suggested that cannabinoids are effective in treating Multiple Sclerosis[4–6], Epilepsy[7], Parkinson's Disease[8,9], Alzheimer's Disease[10], Chronic Pain[11], Post-Traumatic Stress Disorder[12], Anxiety[13] and Insomnia[14]. Due to the positive effects cannabinoids had on attenuating psychological and cognitive-like behaviors[15]; therefore, it can be arguably said that cannabinoids not only played a therapeutic role in several disorder but in roles of well-being as well. Although not all studies support the therapeutic uses of cannabinoids and found that adverse effects may not outweigh the benefits[16] and thus these adverse effects may complicate consumer safety and public health expenditures.

With the development of technology, increasing numbers of phytocannabinoids are being isolated and identified in which studies are now more focused on individual compounds. The most frequent studied phytocannabinoids are $\Delta 9$ - tetrahydrocannabinol (THC) and

cannabidiol (CBD). THC is recognized as the main psychoactive cannabis compound[17] that is found to have several detrimental cognitive effects such as declining in executive function, decision making, attention and the most impaired was memory[18]. In contrast to its counterpart, CBD is a non-intoxicating phytocannabinoid and is shown to have more positive health sequalae and wellbeing. Batalla and colleagues[19] found that CBD had opposite effects to THC and is shown to modulate brain areas that are involved in cognitive processes including emotional processing and memory. It has been suggested that pre-dosing with CBD may provide some protective mechanism against the detrimental effects of THC[18]. In this regard, CBD consumption has been on the rise and many used CBD for its calming effects and to enhance performances.

It is undeniable that memory plays a vital part in our daily life, humans depend on their working memory in order to execute decision making, learning and daily operational tasks. Impairment of memory can affect our cognitive capabilities and therefore affect quality of life and development[20]. With many studies, including systematic reviews, focusing on neuroimaging[21] and overall cognitive function[19,22], this systematic review highlights the effects of CBD on different types of memories to bridge the gap of knowledge and provide further evidence to support the use of CBD as performance booster and wellbeing, and perhaps a protective measure against the effects of THC.

1.2 Research question

The research question focused on whether CBD has any effects on memory and if it does which types of memories are affected.

1.3 Objective of Study

The primary aim of the review focused on the effects of CBD on different types of memories and to provide up-to-date critical evidence for the clinical implication of CBD in its relations to memory modulation. The secondary objective is to provide further insight in the conceptual and methodological issues of CBD usage for future improvement.

1.4 Scope of research

This research focused on the effects of CBD on different types of memories. The research was conducted using different online databases for preclinical studies done in animal and randomized controlled trials (RCTs) done in human, where eligible studies were selected in terms of relevancy and or if the studies and RCTs included results on any memory performance or task. All forms and administration of CBD and dosage such as pills, vaporized or solution were included. Participants were not limited to species, nationality, age, sex, underlying illness and status of cannabis usage. The time-period between 2010 and January 2023 was chosen to include newer and more recent studies.

1.5 Research Design

The research is a systematic review with the purpose 'to identify, appraise and synthesize all the empirical evidence that meets pre-specified eligibility criteria to answer a given research question'[22] in which qualified animal's preclinical studies and human's randomized control trials were selected for this systematic review.

1.6 Expected Benefits and Applications

1. The research will be able to determine the effect of CBD has on memory and if such effects were to be concluded in a positive outcome, CBD may be used as agent that boost cognitive performance in terms of memories' function and types, and possible therapeutic agent in illnesses that involve memory impairment.

2. Direction of use associated with memory boost can be conceptualized to provide standardized consumer's protocol.

3. Methodological issues in practice and research can be acknowledged for future improvement.

4. Evidence to support health and safety of recreational CBD usage.

1.7 Definition of Terms

1. Cannabis is a flowering plant where three species have been recognized Cannabis sativa, Cannabis indica and Cannabis ruderalis. They contain active phytochemicals called cannabinoids that have various physical and neurological effects on the human endocannabinoid system.

2. Cannabinoid is a common term used to described compounds that are psychoactive and found in both cannabis plant (phytocannabinoids) and the human body (endocannabinoid).

3. Phytocannabinoids are phytochemicals found naturally in cannabis plant. The most concentrated phytocannabinoids are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) found in the trichrome of the female plant.

4. Endocannabinoid system (ECS) refers to the biological system in the human body that encompass the endocannabinoids, the endocannabinoid receptors that are expressed throughout the body and their synthetic and degradative enzymes.

5. Cannabinoid receptor 1 (CB1) is a G protein-coupled cannabinoid receptor found mostly in the central nervous system and the peripheral nervous system. The binding site has affinity for the endocannabinoid (anandamide and 2-arachidonoylglycerol (2-AG)) and the phytocannabinoids such as THC.

6. Cannabinoid receptor 2 (CB2) is a G protein-coupled cannabinoid receptor found mostly in cells associated with immune system.

7. Cannabidiol (CBD) is a phytocannabinoid that doesn't have psychoactive activity.

8. **Δ**9- tetrahydrocannabinol (THC) is a phytocannabinoid that has psychoactive effect.

CHAPTER 2

CONCEPTS, THEEORIED AND RELATED RESEARCH

2.1 Endocannabinoid System

The endocannabinoid system referred to the endogenous signaling system[23] that is characterized by endocannabinoids, which are the endogenous cannabinoid neurotransmitters or ligands, their receptors, transporters and enzymes responsible for their synthesis or metabolism[24,25]. The system is established throughout the body and thus control various physiologic, metabolic and neurological networks. The modulation of these networks included working at a central networks of regulating brain homeostasis, brain plasticity, neurogenesis, and even higher cognitive function such as learning and memory[26]; and at peripheral networks involving inflammation and immune responses[27]. While there are more components of the endocannabinoid system being discovered, this systematic review will focus on the most studied endogenous endocannabinoids and receptors.

2.1.1 Endocannabinoids

The most studied endogenous endocannabinoids (ligands) are arachidonyle-thanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG). Both AEA and 2-AG are bioactive phospholipid that have a very short half-life, hydrophobic in nature and are unstable to uptake and stored into vesicles, therefore the endocannabinoids are synthesized and released “on demand” from stimuli such as depolarization of neurons[28]. The endocannabinoids are said to exhibit control on excitatory and inhibitory signaling through the regulation of the neurotransmitters, glutamine and gamma-aminobutyric acid (GABA), in a retrograde manner which are in contrast to the usual electrochemical synaptic connection and communication[29]. While anandamide acts as a partial agonist at cannabinoid receptors, 2-AG acts as an agonist at cannabinoid receptors with a much higher intrinsic efficacy[30].

(1) Anandamide (AEA)

In 1992, Devane and colleagues were successful in the isolation and the discovery of the first endocannabinoid which was named as Anadamide (AEA). AEA are arachidonic acid derivatives conjugated with ethanolamine which are biosynthesized via a phospholipid dependent pathway[31]. The phospholipid derivative N-arachidonoyl

phosphatidylethanolamine (NAPE) is hydrolyzed by a phospholipase D (PLD) selective for NAPE called the NAPE-PLD to form AEA and phosphatidic acid[23,31]. However, studies done in mice showed that there are alternative pathways, and perhaps is an evolutionarily conservative mechanism, to the biosynthesis of AEA[32]. AEA can be synthesized through the hydrolysis of other enzymes such as a lysophospholipase-D (lyso-PLD), α/β-hydrolase 4 and phospholipase C (PLC)[33]. The deactivation and degradation of AEA is done after cellular uptake from the extracellular space through transporters, by fatty acid amide hydrolase (FAAH) which breaks down AEA into arachidonic acid and ethanolamine[34,35]. In addition to FAAH's degradation, AEA can also be deactivated through N-acylethanolamine acid amidase (NAAA), oxygenated by cyclooxygenase-2 (COX-2), lipoxygenase (LOX) isoenzymes, and by cytochrome P-540 [34].

(2) 2-arachidonoylglycerol (2-AG)

2-AG and AEA are structurally similar and differs in the length and the unsaturation of acyl chains, with 2-AG as arachidonic acid derivatives conjugated with glycerol[31]. Through the phospholipase C (PLC)/DAG lipase pathway, 2-AG is synthesized from the conversion of diacylglycerols (DAG) with additional alternative pathways via PI-specific phospholipase A1 (PLA1) and PI-selective phospholipase C (PI-PLC)[31,36]. The primary enzyme responsible for the degradation of 2-AG is monoacylglycerol lipase (MAGL) and to a lesser degree FAAH, hydrolase α-β-hydrolase domain 6 (ABHD6) and hydrolase α-β-hydrolase domain 12 (ABHD12)[37]. Similar to the deactivation of AEA, 2-AG can also be deactivated via COX-2, LOX isoenzymes, and by cytochrome P-450[38]. Thus, giving the product of arachidonic acid and glycerol.

2.1.2 Cannabinoid Receptors

The cannabinoid receptors, CB1 and CB2 receptors, are G protein-coupled receptors (GPCRs)[39], the receptors are differentiated by their amino acid numbers and sequences, their signaling pathway and distribution in the body[40,41]. In accordance with the retrograde released on the endocannabinoids, the activation of cannabinoid receptors was described as a "circuit-breaker" [29]. The cannabinoids receptors are presented at the presynaptic cleft where activation will subdue the release of neurotransmitter onto the synaptic junction and depending on the types of neurotransmitters will either suppress the excitation (glutamine) or inhibition (GABA) depolarization.

(1) Cannabinoid Receptor 1 (CB1)

Even though CB1 receptors are found throughout the body, they are most abundantly found in the central and to a lesser extent peripheral nervous system[40]. CB1 receptors are highly expressed in the cerebral cortex, hippocampus, cerebellum and brainstem[41,42] where there are expressed more in GABAergic neurons than glutamatergic neurons[43]. It is in this regard that stimulation of CB1 receptors affect cognitive function, memory and motor control, and therefore translated into behavioral and psychological outcomes as well. In addition, stimulation of CB1 receptors in astrocytes or glia cells responsible for neurogenesis and synaptogenesis are revealed to modulate neuroplasticity[29,44]. As a GPCR, the binding of CB1 receptor stimulate Gi/o leading to inhibition of adenyl cyclase and decrease of cyclic adenosine monophosphate (cAMP) levels which results in decreased of Ca2+ influx[31,41]. Other pathway includes interaction with β- arrestins which mediated signal transduction for cellular effects at extracellular-signal-regulated kinase (ERK), and c-jun terminal kinase (JNK)[31].

(2) Cannabinoid Receptor 2 (CB2)

Predominantly, CB2 receptors are generally expressed in the immune tissues and cells[40,45] such as leukocytes, spleen, tonsils, thymus, as well as the lung and testes[39]. The expression of receptors in the immune system gave rise to the medicinal potential in modulating the immune function and inflammatory cytokines. Like CB1, CB2 is a GPCRs receptors that when activated causes a chain reaction involving adenyl cyclase, cAMP, β-arrestin and protein kinase[31].

2.2 The Phytocannabinoids: THC and CBD

There are approximately 560 compounds and 120 phytocannabinoids identified[2], they are found in the flowering plant Cannabis sativa and most abundantly in the glandular trichomes of the female flowers[46]. The term phytocannabinoid refers to a group of natural cannabinoids that have similar biochemical structures and is said to contribute to 24% of the compounds found in Cannabis sativa[47,48]. The most studied phytocannabinoids are THC and CBD. They both are able to bind to the CB1 and CB2 receptors, and have a profound effect on the endocannabinoids.

2.2.1 9- tetrahydrocannabinol (THC)

THC made up the most of the phytocannabinoid components in a plant[3] and is a known psychoactive compound[28]. THC is described as partial agonist of CB1 and CB2 receptor, sharing this effect with the endocannabinoids AEA and 2-AG that act on presynaptic receptors [49]. Due to its partial agonist nature, from its low receptor affinity, THC can show mixed agonist-antagonist effect depending on the numbers of cannabinoid receptors present at the site of activation[48]. For example, downregulation of receptors may produce antagonism effect whereas upregulation may enhance the partial agonist activity[49]. The mixed agonist-antagonist effect may attenuate and fine tune the level of endocannabinoid that are full agonist and thus mediate neuromodulator functions[50]. THC's effects include dysphoria, pain control, anti-emesis, tolerance, and dependence[46].

2.2.2 Cannabidiol (CBD)

The second most abundant phytocannabinoid is the non-psychoactive CBD[47]. In contrast to the THC, CBD expressed an antagonistic effect on both CB1 and CB2 receptors [49]. However, recent studies revealed that CBD is complexed and uniquely acted as negative modulator of CB1 and showed inverse agonism at CB2 receptors, as well as inhibiting enzymatic degradation of endogenous cannabinoid[50]. CBD is proposed to have a counter or a protective effect to THC due to the antagonistic and modulator effects[18]. According to these properties, CBD has been therapeutically used as anxiolytic, antipsychotic, anticonvulsive and anti-inflammatory agent[46].

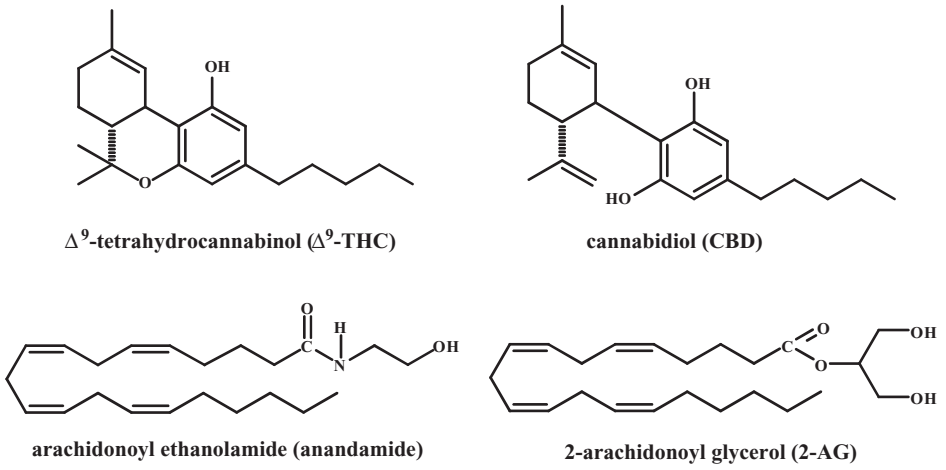

Figure 2.1 Structures of plant cannabinoids and endocannabinoids [51].

2.3 Memory

Memory is a cognitive phenomenon that refers to the process of encoding, storing, and retrieving information over time, it can be categorized roughly into sensory, short-term, and long-term memory[52]. In 1968, Atkinson and Shiffrin have proposed a foundational framework that paved way into the understanding and research of human memory in their Multi Store Model of Memory. In their concept, memories are compartmentalized into storage unit according to time. Once an event is perceived (as sensory input), it is stored as Sensory Memory (SM) which is transferred into Short-Term Memory (STM) and through rehearsal it is stored as Long-Term Memory (LTM). STM can be defined as the capability to remember seven plus or minus two items lasting for a few minutes to hours, while LTM has "unlimited" capacity that can be retained and revisited over a long period of time[53]. However due to the oversimplification criticism, The Multi Store Model of Memory has been through significant modifications over the past few decades. Working memory is a more recent term that has more or less replaced STM in many literature reviews. LTM can be subdivided into explicit and implicit memory where explicit memory is defined as a conscious memory content such as facts and events (semantic and episodic memory), and implicit memory as unconscious memory content referring to skills, habits and reflex (procedural memory) that guided performance[54].

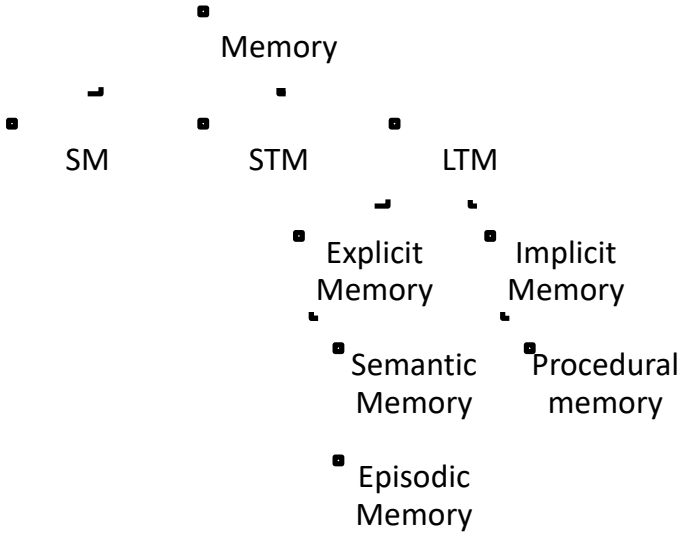

Figure 2.2 Memory Structure. SM = Sensory Memory, STM = Short-Term Memory, LTM = Long-Term Memory.

The study of memory remains a challenged to psychologist and neuroscientist as there are many theories and domains of the brain involved in terms of how memory is encoded, stored and retrieved. It is vital that memories are viewed as a dynamic process instead of a fixed and linear entity[55]. A sensory memory input is comprised of different senses depending on what the memory represents and therefore networks of neural activation composing of several regions of the brain is responsible for memory processing instead of one modularity. It was found that the medial temporal cortex, consisting of hippocampus, amygdala and parahippocampal lobe, prefrontal cortex and cerebellum are involved in memory processing[54] and these regions overlap with one another during STM and LTM memory tasks[56]. Another fascinating feature that demonstrates the dynamicity of memory is the modulation of memory where memories are not all created and stored equally and thus influences other memory processes such as memory extinction and recall[57]. The strength of memory traces is theorized to be dependable on the strength of the synapses in which various cellular mechanism such as synaptic tagging, protein synthesis and protein kinase-based cascades are responsible for synaptic plasticity[20]. Memory that involved multiple sensory input systems also demonstrate stronger retention of new information[53].

The difference in the strength of memory modulation can be further explain by the physical and emotional state of the host. Emotional significant experience or stressful event are bounded to be remembered more strongly[58]. Memory consolidation is regulated through the activation of adrenergic neurotransmitters and stress hormones interacting with related brain regions. During high arousal or stressful situation, the sensory input is perceived through the primary pathway to the thalamus and then to the amygdala[53] where the amygdala is connected to the caudate nucleus and the hippocampus[57]. As a result of stress, there is an upregulation of dopaminergic and noradrenergic activity through the sympathetic-adrenal-medullary (SAM) axis[59,60]. However, contradicting effects of stress were reported in which some studies found that stress can both impair and improve memory.

These contradictions concluded that while stress enhanced memory consolidation, it impairs recall and retrieval in a dose dependent manner in which extremely stressful stimulation and excess norepinephrine or dopamine's level will impair memory[57–59,61].

2.4 Memory and (Endo)cannabinoids

There are supporting evidences that demonstrated the involvement of the endocannabinoid system in learning and memory. While the exact mechanism is currently being studied, it is suggested that the endocannabinoid modulated consolidation, destabilization and extinction of memories by controlling the neural and adrenergic responses. The effects, both enhancement and diminishment, is dependent on the types of neurons and synaptic location[62]. This is due to the retrograde signaling of the endocannabinoids that attenuate the presynaptic release of GABA, glutamate and other neurotransmitters[19].

In regards to CB1 receptors, they are found in memory related brain areas such as the cerebral cortex, amygdala and with the highest density at the hippocampus[51,63]. It is found that the stimulation of CB1 receptors will impair acquisition of memory and promotes memory extinction[50,64]. This may be the results of suppressed hippocampal presynaptic release of glutamate which is responsible for synaptic plasticity[51] in memory tracing. Additionally, stimulation of CB2 receptors will also promote synaptic plasticity[65]

Administration of phytocannabinoids was also found to affect memory processes. It was found that THC can induced memory impairment as both humans and animal participants were found to perform poorer at memory tasks[51,64,66]. Whereas CBD was found to have opposing effects to THC and may improve attention, working memory, and episodic memory especially in THC induced memory impaired participants[67,68]. A systematic review on neuroimaging studies by Batalla and colleagues[19] found that CBD enhanced fronto-striatal connectivity and decrease limbic activity during resting state and modulated brain activity in the hippocampus, insula, midtemporal gyrus, lingual gyrus, precuneus and precentral gyrus. The mechanism behind this is thought to be due to the antagonistic effect of CBD on cannabinoid receptors as well as how CBD can act as negative modulator of CB1 and upregulates endogenous cannabinoid by inhibiting enzymatic degradation.

There are evidences that support CBD's role in restoring homeostasis of neurotransmitters and growth factors such as brain-derived neurotropic factor (BDNF) levels that appears to also stimulate synaptic plasticity and neurogenesis[69] where considerable effects on synaptic plasticity in the hippocampus and amygdala was found in a dendritic spine data[70]. Furthermore, the modulation of endogenous cannabinoid and restoring the balance of neurotransmitters could potentially play a role in the signaling of stress pathway in the

amygdala by decreasing the activity of the primary pathway and alleviate stress as a result[43,71]. The change in aversive state could therefore improve memory recall and retrieval.

In conclusion, the endocannabinoids and phytocannabinoids can both improve and impair memory functions and different memory processes. This is dependent to the types and locations of cannabinoid receptors in the brain where the mechanism is through stimulations of receptors and modulation of neurotransmitters in neural plasticity and stress pathway.

2.5 Related Systematic Review

Batalla and colleagues did a systematic review in 2021[19] on the impact of CBD on human brain function. The aim of this review is to provide supporting evidence using neuroimaging studies that examined the effects of CBD on human brain function. The review was conducted using PubMed as the database using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline where studies until May 2020 were included. The following search terms or PubMed search syntax were used: ("magnetic resonance imaging"[MeSH Terms] OR "neuroimaging"[MeSH Terms]) OR "fMRI"[Title/Abstract]) OR "magnetic resonance"[Title/Abstract]) OR "blood oxygen level"[Title/Abstract]) OR "BOLD"[Title/Abstract]) OR "neuroimaging"[Title/Abstract]) OR "brain imaging"[Title/Abstract]) OR "MRI"[Title/Abstract]) OR "single photon emission tomography"[Title/Abstract]) OR "SPECT"[Title/Abstract]) OR "positron emission tomography"[Title/Abstract]) OR "PET"[Title/Abstract]) OR "MRS"[Title/Abstract]) AND "humans"[MeSH Terms]) AND (("cannabinoids"[MeSH Terms] OR "cannabidiol"[Title/Abstract]) AND "humans"[MeSH Terms]).

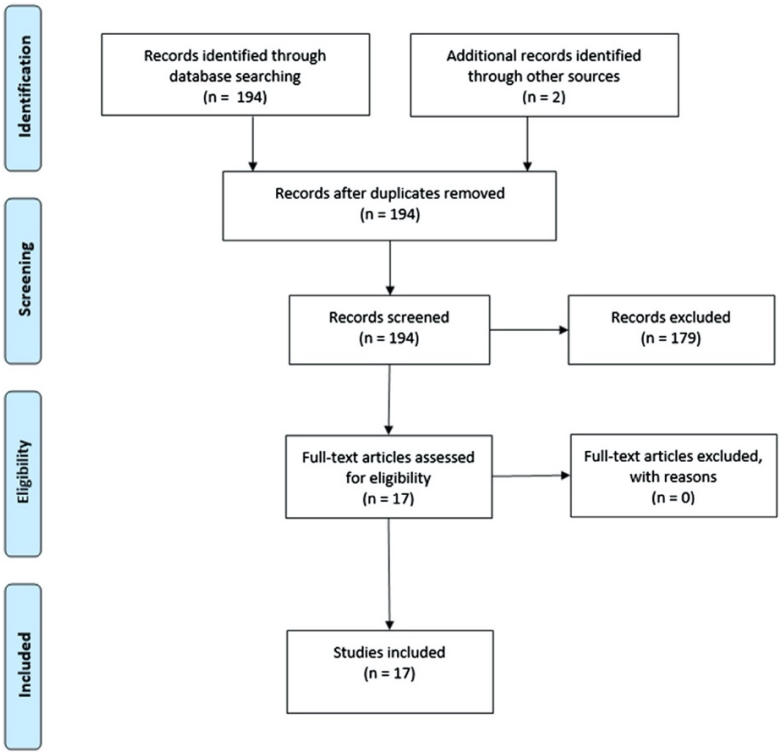

Figure 2.3 PRISMA Flow Diagram of The Impact of Cannabidiol on Human Brain Function: A Systematic Review [19].

Two authors screened the titles and abstracts for eligibility using the inclusion criteria of: 1). use of neuroimaging techniques and 2). administration of CBD to human subjects, in which any discrepancies were settled by the third author. 17 out of 194 studies were eligible in concordance to the inclusion criteria. The data extracted were: study information, sample characteristics, cannabinoid dose and administration route, time interval between administration and imaging, imaging modality, cognitive task and degree of sample overlap.

Population: A total of 118 participants were reported. 115 were healthy participants while 33 participants were with clinical high risk for psychosis, 13 participants with psychotic disorder, 10 with anxiety disorder and 13 with autism spectrum disorder. Both male and female were included but some studies did not report the proportion of gender. The mean and standard deviation of the age ranged from 22.4(5.0), 22.7 (5.1), 23.9 (4.2), 24.1 (4.5), 25.4 (5.2), 26.7 (5.7), 26.2 (7.1), 26.3 (7.4), 27.7 (4.6), 28.5 (6.6), 29.8 (5.1) to 31.3 (9.9) years old. Their cannabis usage status includes those who use less than 5 times in their life time to less than 3 times per week, more than 4 times per year and more than once per week.

Intervention: 13 studies used 600 mg of CBD in oral form, 1 study used 400 mg of CBD in oral form and 2 used 10 mg of CBD in inhalation form.

Comparison: 10 studies compared the effects of CBD to a placebo whereas 7 studies compared the effects of CBD to THC. The THC route of administration in 2 studies were in the form of inhalation using 8 mg of THC and 5 studies used 10 mg of THC in oral form.

Outcome: The studies used different types of cognitive tasks to measure the outcomes. 3 studies used the Go-no go salience task, 6 used visual and auditory processing tasks, 2 used fearful face processing task, 3 used verbal learning memory task and 1 used monetary incentive task, while 6 reported CBD effects of brain function during resting state. All studies reported effects of CBD on brain function which the outcome can be categorized into three domains.

2.5.1 Effects of CBD vs. placebo on brain function in healthy participants.

During the resting state of healthy participants, CBD was found to enhanced the connectivity between the frontal lobe and striatum as well as decreasing the activity of the limbic system. The effects of CBD compared to the placebo in healthy participants was shown to modulate brain activity during cognitive tasks that processed fearful face by decreasing the connectivity between the frontal and limbic cortex, and increased the connectivity between the frontal, limbic and striatal cortex. In verbal learning task that involved memory encoding and recall, CBD was reported to modulate the activity of the insula, midtemporal gyrus, lingual gyrus, precuneus, precentral gyrus and hippocampus. However, the findings of the verbal learning task were not significant.

2.5.2 Effects of CBD vs. THC on brain function in healthy participants

CBD and THC were reported to have opposite effects during the verbal memory task (frontal lobe to striatum activity), response inhibition task and tasks involving the processing of emotion (frontal to temporal lobe activity), auditory and visual stimuli (temporal to occipital lobe activity).

2.5.3 Effects of CBD vs. placebo in participants with psychiatric disorder

Compared to healthy participants, administration of CBD in participants with Psychiatric disorder were shown to have intermediate activity in the areas of the brain involving memory and reward processing, as well as the modulation of the activity in the limbic system during cognitive tasks.

CHAPTER 3

METHODOLOGY

3.1 Eligibility criteria

To be eligible for inclusion in the reviews, the studies had to meet several criteria. Specifically, they needed to be peer-reviewed journal articles, written in English, and evaluated using the Population, Intervention, Comparison, and Outcome (PICO) framework.

3.1.1 Inclusion Criteria

(1) Population:

The participants will not be limited to species (for preclinical animal studies), race, age, gender and status of cannabis usage. The participants can be healthy individuals or those with underlying disease.

(2) Intervention:

The intervention will be administration of CBD where there is no restriction regarding the types and durations of CBD given in which this includes the types, forms of administration and dosage of CBD.

(3) Comparison:

The control group may be given a placebo, no drugs and/or THC.

(4) Outcome:

Randomized controlled trials (RCTs) with statical outcomes and analyses were to be included in this review where the outcome's measure would include or demonstrate memory performances or tasks in which types of memory will also be mentioned.

3.1.2 Exclusion Criteria

The exclusion criteria were to exclude studies with no control intervention, study protocol, case study, review, naturalistic study and discussion or review article

3.2 Information sources

A systematic search for relevant studies was performed on a range of database composing of EMBASE, MedLine, PubMed, PsychINFO and Sciencedirect. Search was done separately on each database using the same search terms from the time-period between 2010 and January 2023 (present). Authors of the chosen articles were contacted personally for any missing or more relevant data.

3.3 Search strategy

Separate searches were done with individual database's using the same time-period and search terms to validate the numbers of articles obtained and thus improving replicability. The time-period between 2010 and January 2023 (present) was chosen to include newer and more recent studies. The time-period chosen was filtered using the database's own filter tool.

The systematic review was done in two parts: a preclinical study done in animals and the review of the RCTs done in human. The search used MeSH (Medical Search Heading) terms and following keywords for the preclinical study which are "CBD" OR "cannabidiol" OR "cannabis" OR "marijuana" AND "memory" OR "recall" OR "cognition" AND "animal". Whereas, the search terms "CBD" OR "cannabidiol" OR "cannabis" OR "marijuana" AND "memory" OR "recall" OR "cognition" AND "Randomized Control Trial" or "RCT" were chosen for the human studies. The searched studies were reviewed one by one from the title and abstract by the author and selected using the eligible criteria stated above.

3.4 Selection process and data collection process

Each record was assessed independently by two reviewers (the author and Miss Lauren Rose Rowntree), who screened the title and abstract of all retrieved articles according to the eligible criteria for article selection. In cases where discrepancies arose between the reviewers, a third reviewer (Miss Sujaree Kuenghakit) was consulted for input. After the preliminary screening, the author reviewed the full text of the chosen articles and selected those that met the criteria for inclusion in the systematic review.

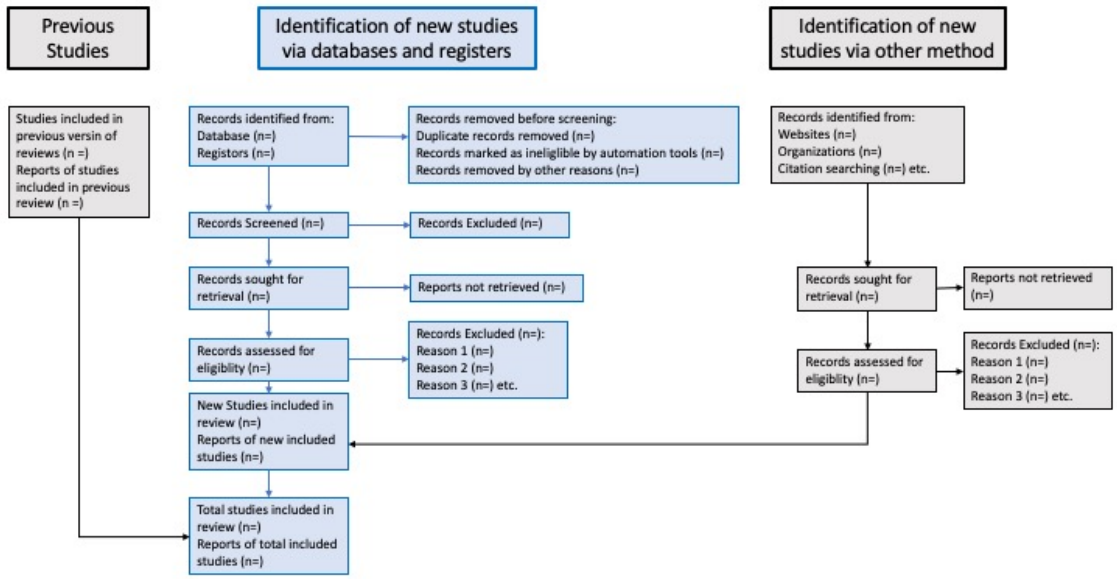

Figure 3.1 PRISMA 2020 flow diagram[72].

3.5 Data collection process

Two reviewers conducted the data collection, which involved inputting the extracted data into a table designed by the author. The articles were meticulously reviewed multiple times to address any discrepancies in the data and to identify any data that may have been missed during the initial review. Additionally, the authors of the selected articles were contacted to obtain any missing data or clarify any information that was unclear.

3.6 Data items and effects measure

The data items included all the relevant outcomes for which the data retrieved will answer the aim and objectives for this systematic review. The data collected was entered into a table comprising the following data: Author / Year, Country, Study Design, Study Population, Characteristics and Size, Cannabis use and frequency, Duration of Study, Intervention and Control, Clinical Test (Memory Task) and Types of Memory (Outcome measures) and Results. The results were statistical outcomes obtained from the clinical test and memory task which would be the mean difference of the accuracy of recall and performance on the cognitive clinical test compared between the intervention and the control group. In cases where data was missing, it was recorded as "not mentioned".

3.7 Study risk of bias assessment and reporting bias assessment

The quality of the RCT studies were assessed and reported using the Cochrane's Risk of Bias taken from chapter 8 Assessing risk of bias in included studies of Cochrane Handbook for Systematic Reviews of Interventions[22]. The studies were also checked for any conflict of interest.

Table 3.1 Cochrane's Risk of Bias [22]

Bias	Author's Judgment
Random sequence generation (selection bias)	Low Risk / Unclear Risk / High Risk
Allocation concealment (selection bias)	Low Risk / Unclear Risk / High Risk
Binding of participants and personnel (performance bias)	Low Risk / Unclear Risk / High Risk
Blinding of outcome assessment (detection bias) Self-reported outcomes	Low Risk / Unclear Risk / High Risk
Blinding of outcome assessment (detection bias) Reaction time	Low Risk / Unclear Risk / High Risk
Incomplete outcome data (attrition bias)	Low Risk / Unclear Risk / High Risk
Selective reporting (reporting bias)	Low Risk / Unclear Risk / High Risk
Other bias	Low Risk / Unclear Risk / High Risk

3.8 Ethics approval

Ethics approval was done through the office of Human Research Ethics Dhurakij Pundit University. See appendix for ethics exemption document.

CHAPTER 4

RESULTS

4.1 Preclinical Animal Studies

4.1.1 Study selection

The initial search across five databases found a combined total of 5,848 studies. This included 579 studies found in Embase, 426 in Medline, 152 in PsycINFO, 563 in PubMed, and the highest number of 4,128 in ScienceDirect. After screening the titles and abstracts, a total of 5,795 studies were excluded as duplicates and studies that were not relatable based on their title and abstract. Full-text articles of 53 potential studies were assessed for their eligibility and the total of 48 preclinical studies were eligible and included in this review (see figure 4.1 for flow of studies). Two studies with no memory as outcome measures were excluded[73,74]. Three were excluded as they were commentary article[75], review article[76] and poster presentation[77].

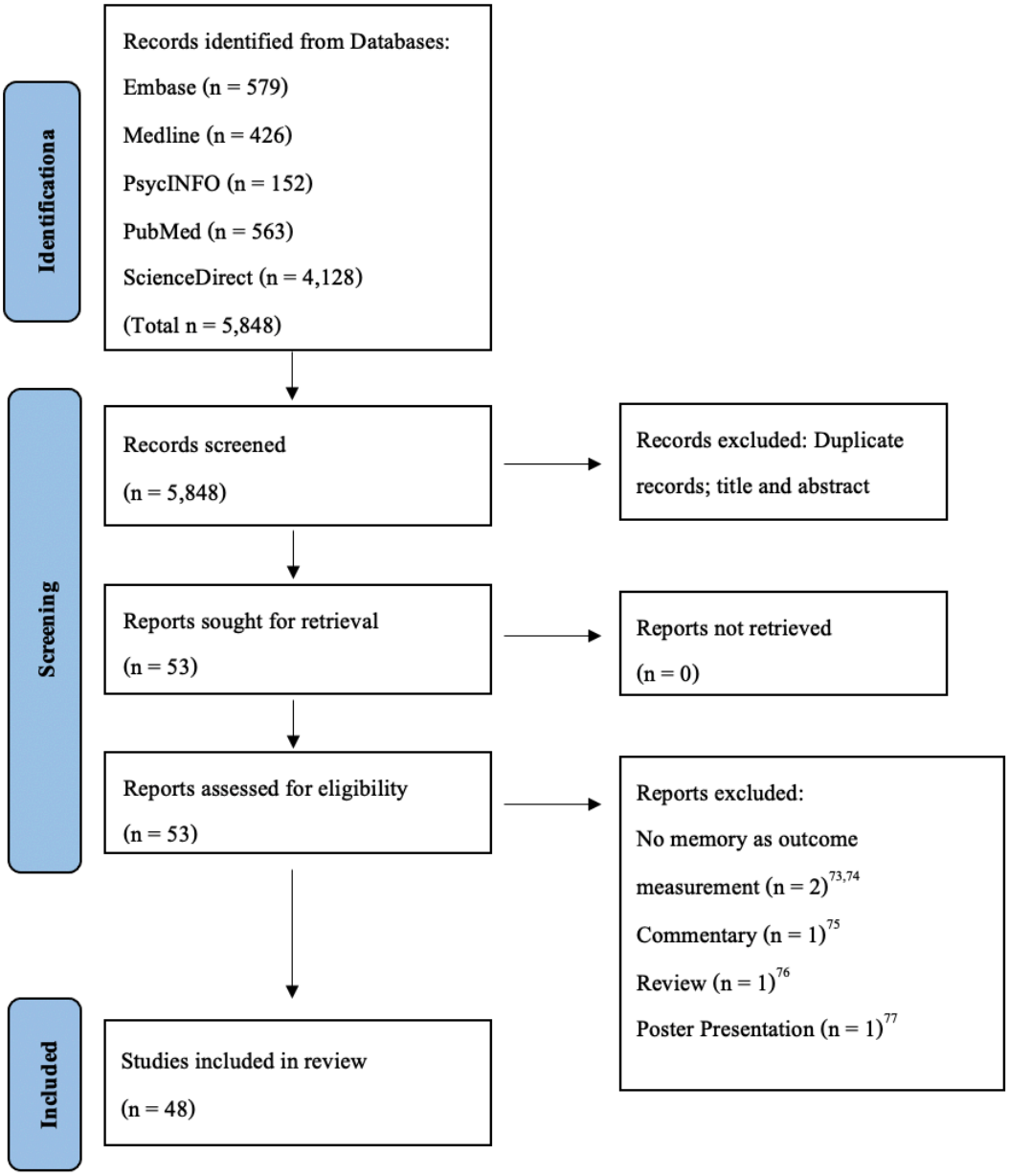

Figure 4.1 Flow of Studies for Preclinical Animal Studies.

4.1.2 Study characteristics

The animal models consisted of a few different species ranging from rodent to mammals which are mice, rats and monkeys. Nineteen studies[70,78–95]used mice as study models and two studies[96,97] used offspring of mice bred together to represent developmental exposure conditions. Fifteen studies[8,81,89,98–109] used Wistar rats as their model. Sprague Dawley rat models were used in seven studies[110–116] and two studies[117,118]

used offspring of Sprague Dawley rats. One study[119] used Squirrel Monkey while one study[120] used Rhesus Monkey as their model. The animal models represented various cognitive impairment conditions which were induced by gene mutations or introduction of causative agents. Nine studies modeled dementia with Alzheimer (AD)'s disease and Frontotemporal Dementia (FTD) induced by mutations that expressed pathology in amyloid accumulation and plaque formation (APPxPS1 model, n = 6)[86–88,90,93,95], tau protein hyperphosphorylation and neurofibrillary tangles (NFTs) formation (n = 2)[91,94]; and impairment caused by intracerebroventricular injection of Streptomycin (n = 1)[8]. One study[89] applied ovariectomy to model memory impairment caused by estrogen depletion. Neurodegenerative condition of one study was modeled using iron ingestion[121].

Schizophrenia-like condition and Psychotomimetic behavior were induced by N-methyl-D-aspartate (NMDA) receptor antagonist (n = 3)[82,92,116], ketamine injection (n = 1)[114] and prenatal injection of polyinosinic-polycytidilic acid (poly I:C; n = 2)[117,118]. Fetal Alcohol Spectrum Disorder (FASD) model was used one study[96]. Transient Global Cerebral Ischemia (TGCI) model, by four vessels occlusion, represent ischemia-induced memory deficit in one study[98]. A model of Status Epilepticus-Spontaneous Recurrent Seizure (RISE-SRS) of chronic temporal lobe epilepsy (TLE) in one study[99] was induced by using a modified version of the lithium-low dose pilocarpine.

A long-term cognitive impairment model from chronic drug use of methamphetamine (METH) was used in one study[100], while three[79,83,102] studies represent drug addiction memory processes using cocaine and morphine. One study[80] modeled the mice with post-traumatic stress disorder (PTSD) and one study[122] used Fragile X syndrome to represent cognitive impairment.

One study[85] modeled Adenosine (A_{2A}) receptor deficiency in mice to further demonstrate the mechanism and receptor involved in CBD activity. Twenty-one studies[70,78,81,83,84,101,103–113,115,119,120,123] used non-disease animal models while one study[97] also used non-disease animal models but the intervention was exposed during developmental period. The study characteristics of the animal models and their conditions are summarized in table 4.1.

4.1.3 Routes of administrations and dosage of CBD and duration of intervention

Many studies used more than one dosage and route of administration of CBD to compare its effects in memory and cognitive performance. The most common route of administration was intraperitoneal injection with thirty-six[8,70,78–86,89–98,101,103–105,107–110,113,114,117,118,121–123] studies using this method and the dosage of CBD used ranged between 1 to 120 mg/kg with 10 mg/kg as the most common dosage (1 mg/dl, n = 5; 1.875 mg/dl, n = 1; 2.5 mg/dl, n = 1; 3 mg/dl, n = 5; 3.75 mg/dl, n = 1; 5 mg/dl, n = 6; 7.5 mg/dl, n = 1; 10 mg/dl, n = 18; 15 mg/dl, n = 1; 20 mg/dl, n = 6; 30 mg/dl, n = 7; 50 mg/dl, n = 4; 60 mg/dl, n = 1; 100 mg/dl, n = 2; 120 mg/dl, n = 1). The second most common route is intracranial administration, although the locations of injection were different among studies. Intra-cerebroventricular injection was done in one study[100] with the dosage of 32 and 160 nmol (converted to 10.063 and 50.315 μg using the molecular weight of 314.47 g/mol for CBD). One study[116] injected 10, 100, 500 ng/0.5μl (0.02, 0.2 and 1μg/μl) of CBD into the prefrontal cortex (intra-PFC), while two other studies injected 100 ng/0.5μl[115] (0.2 μg/μl) and 2 μg/μl[106] of CBD. Three studies[103–105] studied the effects of intra-dorsal hippocampus (DH)'s injection of CBD using the dosage of 9.4 μg/side, 30 nmol (9.4341 μg), and 10 or 30 pmol (3.1447 and 9.4341 μg) respectively. Intra-ventral hippocampal injection of 10 and 100 ng (0.01 - 0.1 μg) of CBD was examined in one study[110].

Injection of CBD into the shell region of the mesolimbic nucleus accumbens (intra-NASh) was studied in one study[112] using the dosage of 1, 10, 100 ng/0.5 μl (0.002, 0.02, 0.2μg/μl). Four studies[87,88,99,111] administered CBD orally using 20 mg gel pellet (n = 2), 200 mg mixed with drinking water (n = 1) and 50 mg/kg of CBD's extraction from Strawberry Kush (*Cannabis indica* and *Cannabis sativa* hybrid; n =1). Two studies[119,120] injected CBD muscularly using the dosage of 0.5 and 3 mg/kg, and one[102] subcutaneously at 5 and 10 mg/kg. There were twenty-six studies[70,78,79,81–85,101–113,115,116,120,122,123] testing acute effects of CBD as CBD was given for the duration of one day but with different time frame to either before or after memory conditioning and/or cognitive tests to test different stages of memory. Eight studies studied subacute effects of CBD from six (n = 1)[114], seven (n = 1)[8], ten (n = 2)[96,100] and fourteen days (n = 4)[89,90,98,121]. Chronic effects of CBD were studied in fourteen studies with the duration of intervention ranging from three weeks (n =

7)[80,86,92,95,97,117,118], five weeks (n = 1)[94], seven weeks (n = 2)[91,93], ten weeks (n = 1)[99], four months (n = 1)[119] to eight months (n = 2)[87,88].

The CBD were supplied by THC Pharma GmbH (Germany, n = 19) [78,79,83,86–88,91,92,94,95,98,101,105–107,117,118,121,123], Biosynthesis Pharma Group (UK; n = 5)[8,89,101,103,104], Tocris Bioscience (UK & USA, n = 7) [82,85,102,110,112,115,116], STI Pharmaceuticals (UK, n = 1)[80], HPLC (China, n = 1) [81], Phytoplant Research Ltd. (Spain, n = 2)[96,105], Cayman Chemical Company (USA, n = 2)[97,120], Cannabidiol Ltd. (Ireland, n = 1)[90], National Institute on Drug Abuse (NIDA) of USA (n = 2)[113,119], GW Pharmaceuticals Ltd. (UK, n = 2)[93,99], National Measurement Institute of Australia (n = 1)[122], combination of THC Pharma GmbH and STI Pharmaceuticals (n = 1)[121] and University of Ottawa (Canada, n = 1)[111]. Three studies[70,84,100] did not mention their source of CBD.

4.1.4 Outcome measures used and types of Memories

Multiple behavioral and cognitive tests were used in the animal studies to assess various types and stages of memory processing. The tests employed to assess object recognition memory included the Novel Object Recognition Test (NORT; n = 13)[8,85,86,88,90,93,95,96,100,114,117,118,121], Novel Object Location Task (NOLT; n = 2) [96,98], Spontaneous Oddity Discrimination (SOD) test (n = 1)[115], and a Touch Screen Based Cognitive Test (n = 1)[119]. While social recognition memory was tested using Social Preference Test (SPT; n = 5)[86,87,91,94,122]. Spatial memory was tested using Cheeseboard (CB) test (n = 4)[88,91,93,95], 8-arm Aversive Radial Maze (n = 1)[98], rewarded T Maze (n = 2)[117,118], Y-Maze (n = 5)[92,96,100,116,122], Barnes Maze (n = 1)[97], Hole-Board Apparatus (n = 1)[99], Visuospatial Paired Associates Learning (vsPAL; n = 1)[120] and Self-Ordered Spatial Search (SOSS) Task (n = 1)[120].

Attention Test Shifting was used to test for working memory (n = 1)[116]. Fear associated memory was conditioned and tested using Fear Conditioning (FC) paradigm (n = 24)[70,78,80,81,84,86–88,91,93,94,101,103–113,123], Avoidance Task (n = 5)[82,89,92,121,122] and Latent Inhibition procedure (n = 1)[115]. Conditioned Place Preference (CPP; n = 4)[79,83,102,110] and Conditioned Place Aversion (CPA; n = 1)[102] were used to test drug associated memory and addiction.

4.1.5 Results of individual studies

(1) Effects of CBD on Object and Social Recognition Memory

Eight studies showed improvement and reversal of both object[8,86,90,95,121] and social[86,87,91,94] recognition memory, as well as a protective effect when mice and rats modeled for dementia (Alzheimer's disease (AD) and frontotemporal dementia (FTD)) were given CBD treatment; with the study done by Fagherazzi and colleagues[121] demonstrating a dose dependent effect of CBD where CBD treatment at a higher dose of 10 mg/kg is able to recover recognition memory deficit in rats with iron-induced dementia. However, Watt and colleagues[93] found no significant difference in memory performance, all of their AD's model mice demonstrated intact sociability and social recognition memory. Chestworth et al.[88] arrived at a similar conclusion, but in reverse, their control mice failed to demonstrate novel object recognition, thus comparison of groups cannot be concluded. CBD treatment in animals modeled with schizophrenia-like cognitive deficit resulted in improvement of object recognition memory[117,118] where animals were shown to spend more time with a novel object instead of a familiar object.

Kozela and colleagues[114] did further test to demonstrate that acute CBD treatment prevented object recognition memory deficit in schizophrenia-like model, while sub-chronic treatment reversed object recognition memory deficit. CBD treatment were also found to reduced object recognition memory deficit in ischemia-induced[92] and drug-induced (Cocaine and Meth) cognitive impairment models[83,100], with Razavi and colleagues'[100] study also demonstrating the dose dependent mechanism of CBD where CBD at a higher dosage of 160 nmol were shown to be effective in reversing the deficit but not at 32 nmol. However, CBD treatments were found to have no effect on recognition memory in studies done by García-Baos and colleagues[96] and Zieba colleagues[122] where their animals were modeled for FASD and Fragile X syndromes. Two studies with non-disease animal models compared the memory performance of CBD when co-administered with THC and found contradicting results with Aso and colleagues[85] showed that CBD diminished Δ9-THC-induced cognitive impairment, whereas, Withey and colleagues[119] found that CBD did not modulate THC effects on object recognition memory in their animals. Furthermore, Aso et al.[85] also noted in their findings that CBD alone in non-diseased animals did not have a significant effect on

memory. Interestingly, Szkudlarek and colleagues[115] found that intra-PFC injection of CBD impaired object recognition memory in comparison to systematic injection.

(2) Effects of CBD on Spatial Memory and Working Memory

Four studies showed preventive and restoration effect of CBD treatment on spatial memory deficit in animals modeled for dementia[88,91,94,95]. CBD treatment also showed improvement in spatial memory in animals with cognitive deficit induced by FASD-like[96], Schizophrenia-like[117], TGCI[92], SRS[99] and Meth[100]. Further evaluation from Razavi and colleagues[100] demonstrated dose dependent mechanism of CBD where 160 nmol was found to be more effective than 32 nmol in improving spatial memory deficit. CBD treatment was shown to increase the rate of spatial learning in a study done by Kaplan and colleague[97]. Wright and colleagues[120] had found contradicting results in their study with CBD co-administered with THC was effective in improving memory performance in one task (vsPAL) but not the other (SOSS) where both tasks tested for spatial memory. Two studies showed failure of CBD treatment to improve spatial memory deficit in schizophrenia-like model[118] and mice modeled for Fragile X syndrome[122]. However, Szkudlarek and colleagues[116] found deteriorating effect of CBD treatment on both spatial and working memory when injected into the intra-PFC.

(3) Effects of CBD on Fear Associated Memory

Five studies have reported positive outcomes of CBD treatment in reducing the formation and expression of fear memory, leading to a decrease in freezing behavior. These studies include Assare et al.[78], Kreilaus et al.[91], Montaya et al.[84], Norris et al.[112], and Szkudlarek et al.[115]. Notably, Norris et al.[112] demonstrated a dose-dependent effect of intra-NASH injection of CBD, with a dosage of more than 10 ng showing efficacy. Additionally, CBD treatments have shown to improve long-lasting fear-related memory and anxiety-like behaviors in PTSD modeled mice[80] and were found to counteract THC's effect in increasing fear associated memory and behaviors[110].

Several other studies explored the effects of CBD on fear associated memory deeper in regard to the different phrases of memory and timing of CBD administration. The different phrases of memory included memory consolidation, reconsolidation, extinction and reinstatement. In terms of memory consolidation, three studies demonstrated impairment of memory consolidation when CBD was administered[105,106,109].

Raymundi et al.[105] found the effect of window period where intra-DH CBD treatment shown to be effective when given immediately and at 1 hour after conditioning but no effect on consolidation when given at 3 hours after conditioning. Additionally, they found decreased expression of Arc protein in DH and the effect of CBD were dependent on different receptors where the effect was disrupted by blocking CB1 and CB2 receptors, partly disrupted by 5-HT_{1A} and A_{2A} antagonist and unaffected by PPARγ receptor antagonist. In their study, Rossignoli and colleagues[106] also demonstrated the effect of window period but their study show the effective period of 3 to 6 hours which is in contrast to Raymundi et al.'s[105] study. However, their study showed similar effect of protein expression where there was a decreased in the expression of c-fos and zif-268 protein in the hippocampus, PFC, and thalamus, as well as a reduction in dopamine (DA) released in the cortico-limbic circuits.

Similarly, Stern et al.[109] found the effective period of CBD administration to be less than six hours and that the effect was mediated by activation of CB1 and CB2 receptors. Six studies found that CBD treatment impaired memory reconsolidation[101,103,104,107,108,111]. Franzen and colleagues[103] found the effect of CBD to be dose dependent (3.0 and 10 mg/kg) where local (intra-DH) and systematic (intraperitoneal) administration produced the same effect in impairing memory reconsolidation. Additionally, Franzen and colleagues[104] found that the impairment of memory reconsolidation was through CB1 receptors where local (intra-DH) and systematic (intraperitoneal) administration produced the same effect. The finding of CB1 receptor dependent mechanism was also found in the study done by Bayer and colleagues[101]. In their study, Murkar and colleagues[111] found the effect of CBD to be long lasting (7 days) and combination of CBD and THC in Plant BM also reduced fear memory reconsolidation. Stern et al.[107] also demonstrated dose dependent effect where 10 mg/kg was most effective in disrupting memory reconsolidation and CB1 receptor dependent mechanism, moreover their study revealed a window period effect of less than 6 hours.

Regarding fear memory extinction and reinstatement, the study done by Song et al.[123] and Montaya et al.[84] showed that extinction was enhanced from reduced fear memory expression, on the other hand Franzen et al.'s[104] study fear associated memory did not show reinstatement. Song et al.[123] also found that even though extinction was enhanced, it was enhanced with strong conditioning and weaker conditioning showed that

CBD treatment impaired extinction with increased freezing expression. Two studies demonstrated CBD treatment improved all phases of fear associated memory where Han et al.[81] found that CBD treatment was effective at 10 mg/kg and 30 mg/kg was found from the study done by Kruk-Slomka and Biala[82].

In contrast to the studies above, seven studies found that CBD treatment had no effect on fear associated memory[86,87,93,94,113,121,122] and one study revealed increased freezing behavior and enhanced fear memory[70]. A study done by Corre and colleagues[89] found that CBD treatment can restore fear memory that was impaired by ovariectomy in mice modeled for dementia from estrogen depletion.

(4) Effects of CBD on Drug Associated Memory and Addiction

CBD treatment was shown to reduce context preference in drug associated memory in two studies[79,102] where the study done by Chesworth and Karl[79] demonstrated a lasting effect at 20 days after CBD treatment cessation. Hudson and colleagues[110] found that that coadministration of CBD and THC counteracted the morphine preference that was increased by THC. Diverse results were shown in regards to the consolidation, reconsolidation, extinction and reinstatement of drug associated memory. Ledesma and colleagues[83] found that while CBD treatment prevent reinstatement of drug associated memory, it did not affect the acquisition, expression or extinction of CPP.

de Carvalho and Naoto Takahashi[102] demonstrated that CBD treatment can impaired reconsolidation and prevent reinstatement of drug associated memory. Whereas, Chesworth and Karl[79] found that while CBD treatment impaired consolidation, it did not affect reconsolidation, extinction, or reinstatement of drug associated memory.

4.2 Human's RCT studies

4.2.1 Study selection

The initial search across five databases found a combined total of 5,433 studies. There were 145 studies from Embase, 98 studies from Medline, 46 studies from PsycINFO, 258 studies from PubMed and 4,886 studies from ScienceDirect. After screening the titles and abstracts, a total of 5,419 studies were excluded as duplicates and studies that were not relatable based on their title and abstract. Full-text articles of 14 potential studies were assessed for their eligibility and the total of 12 RCT studies were eligible and included in this review (see figure 4.2 for flow of studies). One study with no memory as outcome measures were excluded[124] and one study were excluded as it was a pseudorandomized study[125].

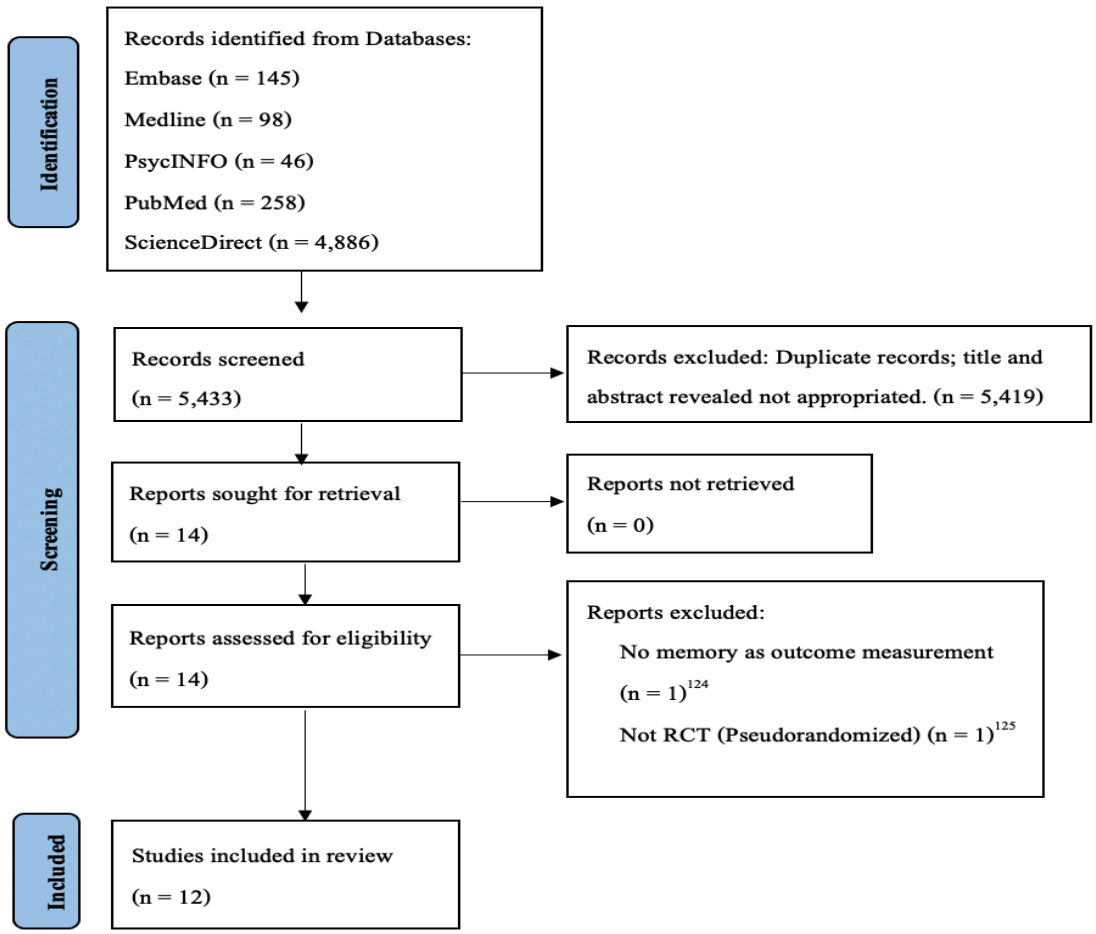

Figure 4.2 Flow of Studies for Human's RCT Studies.

4.2.2 Study characteristics

There was a total of 570 patients, aged between 18 and 48 years old. The twelve studies originated from UK (n = 6)[67,126–130], Germany (n =2)[131,132], USA (n = 1)[133], Switzerland (n = 1)[134], Canada (n = 1)[135] and a collaboration between UK, Romania and Poland (n =1)[136]. The study population in five studies were classified healthy participants[67,127,128,132,134]. Participants with psychological disorder were recruited in seven studies where the phycological disorders were medication-naïve Clinical High-Risk (CHR) of Psychosis[126], Chronic Schizophrenia[133], Acute paranoid Schizophrenia[131], Schizophrenia or related psychotic disorder defined by DSM-IV[136], Psychosis defined by DSM-IV[130], Schizotypal Personality Disorder[129] and Cocaine Use Disorder (CUD)[135]. The majority of the studied population were male with (68% of population) with one study consisted of only male participants[132].

A characteristic of the population that was worth mentioning was history of cannabis usage and frequency. There was only one study[127] with cannabis and CBD naïve participants and only two studies with no information on cannabis status[131,133]. In the study done by Bhattacharyya and colleague[126], the majority of their participants were lifetime users in the CBD (94%) and placebo group (100%) and are still current users in the CBD (44%) and placebo group (41%). There were about 29% cannabis users from Das et al.'s [128] study, in which the mean and standard deviation of cannabis days ranged from 0.75 ± 0.5, 1.75 ± 2.22 and 3.17 ± 3.82 days. In Englund and colleagues' [67] study, the previous cannabis episodes of CBD group and placebo group were 137 ± 234 and 118 ± 218 respectively. The frequency of annual cannabis consumption for Hotz et al.'s[134] participants were 2.24 ± 3.2 and with the range 0 –12 times. In their study, McGuire and colleague[136] did not mention the frequency of CBD usage but there were 3.4% participants with positive baseline urine THC test. Morgan et al.[129] recruited cannabis users as their participants and categorized their participants into light (1 – 24 days per month, n = 50%) and heavy user (25+ days per month, n = 50%). In the study done by O'neil and colleague[130], 15 of their participants in PSY group were lifetime users and 9 were current regular users but there was no information on the healthy control group.

While there was no information provided on the participants' cannabis status in Rizkallah et al.'s[135] study, there were 12.8% of participants that had a cannabis use disorder. In their study, Woelfl et al.[132] reported the cannabis lifetime use as median and 0, 25, 75,

100 percentiles of number of participants with: PLA/PLA = 3 (1, 2, 4, 5), CBD/PLA = 6 (2, 4, 8, 10), PLA/THC = 6 (6, 6, 6, 7) and CBD/THC = 5 (4, 4, 5, 6). The characteristics and size of the participants and the cannabis status of the included studies are summarized in table 4.2.

4.2.3 Routes of administrations and dosage of CBD and duration of intervention

Nine studies used oral form of CBD as their intervention with six studies used 600 mg capsule[67,126,127,130,131,133], two studies used 800 mg capsule[132,135], and one study used 1,000 mg of CBD in oral solution[136]. The other alternative route of administration was inhalation of vaporized CBD where three studies employed this technique[128,129,134]. Eight studies compared the effect of CBD with placebo[126–128,130,133–136] and one study tested the effect of CBD and placebo on THC[67]. One study compared the effect of CBD with the antipsychotic, Amisulpride (AMI)[131]. Lastly, two studies had four intervention groups which are CBD, THC, CBD + THC and placebo control[129,132].

Five studies administered CBD one time before cognitive test where CBD was given three hours prior in three studies[126,127,130], 205 mins (3.42 hours) prior in one study[132] and 210 mins (3.5 hours) in one study[67]. For studies that employed vaporization of CBD as route of administration, CBD was inhaled before cognitive test in one study[129], before and after conditioning in one study[128], and 15 mins after words learning and immediate recall in one study[134]. Four studies examined a more long-term effect of CBD where CBD was administered for 4 weeks[131], 6 weeks[133,136] and 92 days (13.15 weeks)[135].

The CBD were supplied by STI Pharmaceuticals (UK, n = 5)[67,127,128,132,133], THC Pharma (Germany, n = 2)[126,130], PharmaHemp (Slovenia, n = 1)[134]. Four studies did not mention their source of CBD[129,131,135,136].

4.2.4 Outcome measures used and types of Memories

Each RCT study employed several cognitive tasks to test different types of memory. Episodic memory was tested using: Verbal Paired Associate (VPA) learning tasks (verbal memory; n = 2)[126,130], Rivermead Behavioural Memory Test (prose recall; n = 1)[127], Verbal Learning Task (verbal memory; n = 2)[67,134], Auditory Verbal Learning Test (AVLT; verbal memory; n = 1)[131], The Rey-Osterrieth Complex Figure Test (ROFT; visual memory; n = 1)[131] and Delayed Prose Recall (n = 1)[129]. Working memory was tested using: N-back task (spatial memory; n = 3)[127,129,134], The Digit Span task (n = 2)[67,127], MATRICS Consensus Cognitive Battery (MCCB, n = 1)[133], The Letter Number Sequencing (STM capacity; n = 2)[131,132], Subject

Ordered Pointing Task (n = 1)[131], Delayed Response Task (spatial memory; n = 1)[131], and Cambridge Neuropsychological Test Automated Battery (CANTAB): Pattern Recognition Memory (n = 1)[135]. One study[136] used Brief Assessment of Cognition in Schizophrenia (BACS) composite score which tested both episodic and working memory. One study[128] employed Fear Conditioning (FC) paradigm to test for fear associated memory.

4.2.5 Risk of bias in studies

This study employed the Cochrane risk of bias tool (ROBIN-II;)[137] to examine the risk of bias of each RCT studies included in the systematic review. The analysis was divided into five different domains that assessed: Bias arising from the randomization process (D1), Bias due to deviation from intended intervention (D2), Bias due to missing outcome data (D3), Bias in measurement of the outcome (D4) and Bias in selection of the reported result (D5). Seven studies were classified as low risk[126,129,130,132,134–136], three studies revealed some concern[67,127,133] and two studies were considered as high risk[131]. See figure 4.3 for traffic light plot and figure 4.4 for summary plot.

The concern in bias was raised from the D5 domain in the study done by and colleague[127] which was due to the multiple outcome measurements (different cognitive tests) to test memory performance. However, because the different tests measured different types of memory which was in accordance with the secondary objective in determining the associations of cerebral blood flow with different memory tasks, the bias was considered as some concern in how the results would be reported. In Boggs et al.'s[133] study, there were some concerns in the D2 domain where a participant withdrew from experiencing side effects that were specific to CBD treatment. Nevertheless, preliminary considerations were not breached and could not have influenced intervention group assignment. There was some concern in the study done by Englund and colleagues[67] as their study revealed three subjects that failed to follow the protocol (failure of IV cannulation) but appropriate analysis was used.

The high risk in bias for Das et al.'s[128] study was due to several different domains. There was some concern from a baseline difference between intervention group with participants in the pre-extinction group having more recent tobacco use in which the difference could have an effect on the pharmacology of CBD. There was also a failure to implement the protocol which could have affected the outcome where some data were

lost due to equipment failure and failure of participants to make response during tasks. The post hoc power calculation was used to assess the impact of missing data. The missing data in some intervention groups exceed 95% which was excluded from the analysis. There was no evidence that the result would not be biased and the power was stated to be compromised but not too overly. While there were multiple outcome measurements, the objective of the study was to examine the fear conditioning paradigm and different phases of memories involved.

In Leweke and colleagues'[131] research, there were several concerns raised that \resulted in a suggestion for high risk in bias. The total amount of intervention was reduced from 800 to 600 mg per day in some participants due to unwanted side effects which resulted in unstandardized total amount of intervention used. While the reduction of the dosage was justified for clinical and safety reasons, this raised a notion of awareness in the participants and researcher of assigned intervention and assert a risk of bias in this domain. Thirty-three participants out of forty-two completed the protocol, thus the availability of data was below 95%.

There was no information about the missingness and how the true value was affected. It was also noted the type I error (alpha) was not adjusted for multiplicity due to the explorative nature of the study and that the results needed to be interpreted carefully by the researcher.

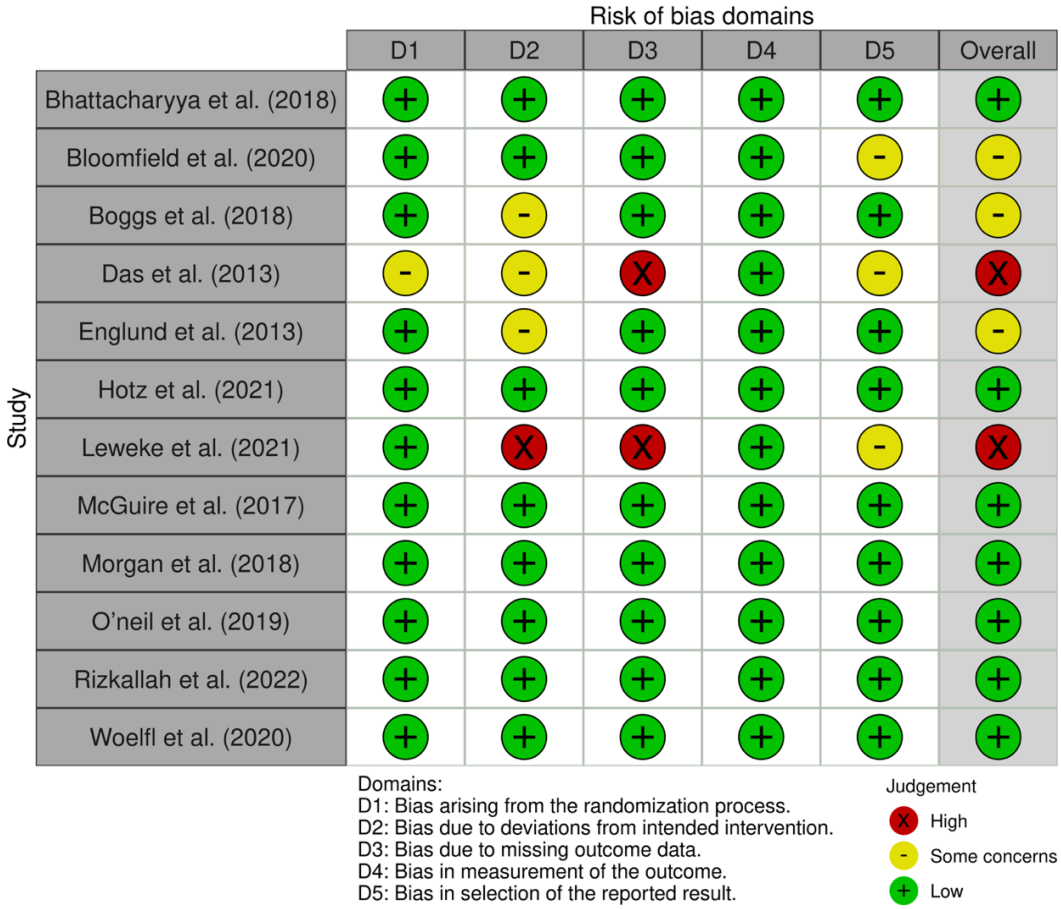

Figure 4.3 Risk of Bias Traffic light Plot.

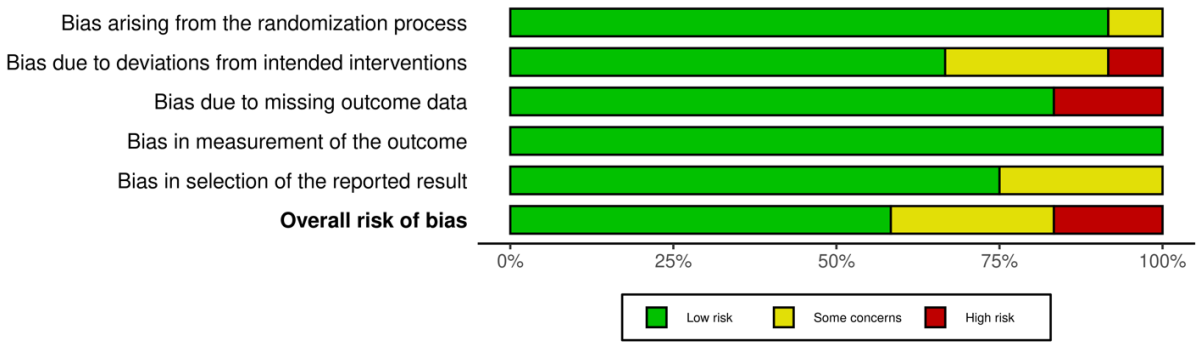

Figure 4.4 Risk of Bias Summary Plot.

4.2.6 Results of individual studies

(1) Effects of CBD on Episodic Memory

In regards to episodic memory, Hotz and colleague[134] found a significant effect of CBD treatment in verbal episodic memory (words recall) using Verbal Learning Task when compared to the placebo. The positive effect of CBD on episodic memory was also supported by a study done by Leweke and colleagues[131] which found improvement in visual episodic memory recall using ROFT, however, their study also demonstrated no effect of CBD treatment on auditory verbal memory recall through AVLT. Even though there was an improvement in overall composite score of BACS utilized by McGuire et al.[136], the difference was not significant and there was no effect in verbal episodic memory. Similarly, the studies done by Bhattacharyya et al.[126], Bloomfield et al.[127] and O'neil et al.[130] also found no effect on episodic memory performance. However, it is important to note that while there was no effect on the task performance in the later three studies, there were correlations between CBD treatment and brain activities.

There was a significant correlation between total recall and the level of left parahippocampal activation, as well as an intermediate level of activation in brain areas involved in memory (parahippocampal gyrus/midbrain) in healthy participants[126]. In participants with psychosis or related disorder, CBD treatment showed significant increase in CBF in the hippocampus[127] and attenuation of dysfunctionality in prefrontal activation and hippocampal-striatal functional connectivity[130].

(2) Effects of CBD on Working Memory

Bloomfield and colleagues[127] demonstrated decreased reaction time in working memory task and increased CBF in orbitofrontal cortex (ORF) which suggested that CBD may have an effect in working memory performance. Nevertheless, most of the studies found no effect of CBD treatment on working memory of both spatial and non-spatial domains where CBD treated groups did not have better performance compared to their control[131,133–136].

(3) Effects of CBD on Fear Associated Memory

There was only one study by Das and colleague[128] which also claimed to be the first study that examined the effect of CBD on fear associated memory in Human's RCT. CBD treatment showed decreased fear expression during recall and reinstatement, and enhanced extinction of fear memory. It was found that CBD treatment given at post-extinction demonstrated lower response to extinction context which led to generalized attenuation of explicit fearful response during recall and reinstatement. There was also a trend level reduction in reinstatement of autonomic contextual responding when given pre- and post-extinction, suggesting potential CBD effect in the potentiation of extinction memory consolidation.

(4) Effects of CBD on THC induced memory impairment

Three studies[67,129,132] examined the effect of CBD on THC induced memory impairment. All three studies showed detrimental effects of THC where THC impaired cognitive performance on both working and episodic memory but found contradicting results for CBD. Englund and colleagues[67] found that pre-treatment with CBD had a protective effect against THC on episodic memory but not on working memory where participants had better delayed recall in Verbal Learning Task, but no significant difference in Digit-Span task. Both studies done by Morgan et al.[129] and Woelfl et al.[132] revealed that CBD treatment did not improve the cognitive impairment induced by THC.

(4) Adverse events

Seven studies out of twelve reported adverse events from their participants [67,126,129,132–134,136] . There was no serious adverse event or side effect that was resolved without intervention where the CBD and placebo group showed similar rate of occurrence and events. Reported adverse events were: sedation[133], mild headache and abdominal pain[134], diarrhea and nauseas[136]. Additionally, pre-treatment with CBD decreased the proportion of participants experiencing psychosis induced by THC[67]. There was one case of exacerbation of Schizophrenia but it was reported in the placebo group[136].

Table 4.1 Summary Table of the Characteristics of Preclinical Animal Studies.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Aso et al. (2019)[85], Spain	Mice, C57BL/6J with A_{2A} receptor ($A_{2A}R$) deficient ($A_{2A}R^{-/-}$).	23 male mice were randomly assigned n = 5–8 per group. - Vehicle group - CBD group - THC group - CBD + THC group	- Memory task was done in 24 hours after intervention.	Intraperitoneal injection of: - CBD: 3 mg/kg (from Tocris 9 BioScience; Bristol, UK). Dissolved in 5% ethanol, 5% Tween and 90% saline. - THC: 1 and 3 mg/kg, (from Sigma-Aldrich Química SL; Madrid, Spain). Dissolved in 5% ethanol, 5%	- Two-Object Recognition Test.	- Object recognition memory.	- CBD diminished THC-induced impairment through adenosine receptor dependent mechanism. - THC (3 mg/kg) significantly reduced recognition memory ($p < 0.01$) and was reversed with the selective CB_1R antagonist SR141716A (1 mg/kg; $p < 0.05$). - Co-administration of CBD with THC diminished memory impairment.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
				Tween and 90% saline. - CB_1R antagonist SR141716A: 1 mg/kg (from Tocris 9 BioScience; Bristol, UK). Dissolved in 5% ethanol, 5% Tween and 90% saline. - Selective $A_{2A}R$ antagonists SCH442416: 0.1 mg/kg, and KW-6002: 0.1 mg/kg (from Tocris			Two-way ANOVA [$F(1,25) = 11.09$, $p < 0.01$] & Three-way ANOVA with antagonist and THC + CBD [$F(1,98) = 16.81$, $p < 0.001$]. - CBD was still able to diminished THC induced impairment when administered with KW-6002 (0.1 mg/kg; $p < 0.05$), while administering with SCH442416 (0.1 mg/kg) significantly reduced CBD effect on THC-induced memory

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
				9 BioScience; Bristol, UK). Dissolved in 1% DMSO. - In all cases, the volume administered was 10 ml/kg body weight.			impairment ($p < 0.01$). Thus, suggesting the involvement of $A_{2A}R$. - CBD alone did not have significant effect on memory.
Assare et al. (2020)[78], Australia	- Male C57BL/6J mice.	Mice were randomly assigned into treatment group. (N =	- CBD or CBDA was injected 24 hours after conditioni	Intraperitoneal injection of: - CBD: 1, 10, 30, and 100 mg/kg (from THC Pharma GmbH; Germany).	- Fear conditioning.	- Aversive memory (Fear associated memory).	- CBD treatment disrupted cued fear memory's expression while CBDA did not. Additionally, CBD did not affect generalized

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		10 –17 per group) - Nonshock-vehicle (NS-VEH) group - Shock-vehicle (S-VEH) group - S-CBD1 group - S-CBD10 group - S-CBD30 group - S-CBD100 group	ng and prior to assessment.	Dissolved in ethanol, Tween 80 and 0.9% NaCl. The ratio by volume of 1:1:18 of Tween 80:ethanol:saline was used. - CBDA: 0.1, 1, 10, and 30 mg/kg. (purified from hemp extract). Dissolved in ethanol, Tween 80 and 0.9% NaCl. The ratio by volume of 1:1:18 of Tween			anxiety-related behavior induced by trauma, while CBDA did. Therefore, CBD and CBDA demonstrated opposing effects. - There was a main effect of CBD on freezing behaviour [$F(4,45) = 3.23$, $p = 0.025$]. Dunnett's post-hoc analyses showed that S-CBD30 group had significantly reduced freezing time compared to S-VEH ($p < 0.01$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- S-CBDA0.1 group - S-CBDA1 group - S-CBDA10 group - S-CBDA30 group		80:ethanol:saline was used. (Cannabidiolic acid (CBDA) is the acidic precursor to CBD) - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 10 ml/kg body weight.			- CBD or CBDA had no effects on the expression of contextual fear memory when re-exposed to conditioned stimuli ($p > 0.05$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Bayer et al. (2022)[10][1], Brazil	- Male Wistar rats.	Mice were assigned into groups according to different experiment. Experiment 1: - Non-reactivated (neutral exposure) group, N = 3 - Vehicle-activated (vehicle treated and	Intervention was given after reactivation session.	Intraperitoneal injection of: - CBD: 10 mg/kg (99.9% purified from BSPG Pharm, Sanwich, UK). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate - In all cases, the volume administered was 1.0 ml/kg body weight.	- Fear conditioning.	- Aversive memory (Fear associated memory).	- CBD has the potential to impair reconsolidation of destabilized aversive memories specifically in the dorso-ventral axis of the medial prefrontal cortex and this effect relies on the activation of CB1 receptors. Experiment 1: Intraperitoneal injection of CBD reduced the activity-associated plasticity in the AC [$F(2,10) = 18.7$; $p = 0.0004$; $\eta^2 = 0.79$] and PL

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		conditioned exposure) group, N = 5 - CBD-reactivated (CBD treated and conditioned exposure) group, N = 5 Experiment 2: four groups (N = 9 – 12/group) - Intra-AC-Vehicle group	Infused intracranially into the mPFC: - CBD: 30 pmol (99.9% purified from BSPG Pharm, Sanwich, UK). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate - AM251 (CB1 receptor antagonism/inverse agonist *N*-				cortex [$F(2,10) = 51.9$; $p = 0.00001$; $\eta^2 = 0.91$] during the reconsolidation of contextual fear memory. Reactivation of fear memory increased the expression of cells in the AC and PL cortex, but the CBD group showed lower expression in AC ($p = 0.03$) and PL cortex ($p = 0.00002$) compared to the vehicle group. - Experiment 2: CBD disruption of fear

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Intra-AC-AM251 group - Systemic (intraperitoneal)-Vehicle group - Systemic (intraperitoneal)-CBD group Experiment 3: four groups (N = 8 – 9/group) - Intra-PL-Vehicle group		(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carbox-amide): 50 pmol (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate. - In all cases, the volume administered was 0.2 μl/hemisphere.			memory reconsolidation depended on the activation of CB1 receptors in the AC cortex.VEH-CBD group showed lower freezing time than the VEH-VEH ($p = 0.002$), AM251-VEH and AM251-CBD groups ($p = 0.001$ in both case). However, VEH-VEH, AM251-VEH and AM251-CBD groups did not differ. - Experiment 3: CBD disruption of fear

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Intra-PL-AM251 group - Systemic (intraperitoneal)-Vehicle group - Systemic (intraperitoneal)-CBD group Experiment 4: four groups (N = 8 – 9/group) - Intra-IL-Vehicle group					memory reconsolidation depended on the activation of CB1 receptors in PL cortex. VEH-CBD group showed lower freezing time than the VEH-VEH group ($p = 0.0005$), AM251-VEH and AM251-CBD groups ($p = 0.002$ in both case). However, VEH-VEH, AM251-VEH and AM251-CBD groups did not differ. - Experiment 4: CBD disruption of fear

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Intra-IL-AM251 group - Systemic (intraperitoneal)-Vehicle group Experiment 5: two groups (n = 7 – 9/group) - Intra-AC-Vehicle group - Intra-AC-CBD group Experiment 6: two groups (n					memory reconsolidation depended on the activation of CB1 receptors in IL cortex. VEH-CBD group showed lower freezing time than the VEH-VEH group (p = 0.002), AM251-VEH and AM251-CBD groups (p = 0.0003 and 0.003, respectively). However, VEH-VEH, AM251-VEH and AM251-CBD groups did not differ. - Experiment 5: CBD disruption of fear

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		= 9 – 11/group) - Intra-PL-Vehicle group - Intra-PL-CBD group Experiment 7: two groups (n = 8/group) - Intra-IL-Vehicle group - Intra-IL-CBD group					memory reconsolidation when infused directly into the AC cortex. CBD group showed lower freezing time than controls (p = 0.01). - Experiment 6: CBD disruption of fear memory reconsolidation depended on the activation of CB1 when infused directly into the PL cortex. CBD group showed lower freezing time than controls (p = 0.001).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- Experiment 7: CBD disruption of fear memory reconsolidation depended on the activation of CB1 when infused directly into the IL cortex ($p < 0.05$).
Cheng et al. (2014)[86], Australia	- Mice carrying double transgenes expressing chimeri	45 mice were assigned to vehicle or CBD groups. Treatments were quasi-randomized.	The total duration of treatment was 3 weeks.	Intraperitoneal injection of: - CBD: 20 mg/kg (from CAS: 13956-29-1 THC Pharma GmbH; Frankfurt/Main, Germany).	- Social preference test (SPT). - Novel object recognition test (NORT).	- Social recognition memory. - Object recognition memory.	- Chronic CBD treatment reversed cognitive impairment in APPxPS1 mice with no effects on aversive memory (fear associated memory) and anxiety-related behaviours.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	c mouse/ human mutations of amyloid precursor protein (APP) and presenilin 1(PS1/ ΔE9) =	- Vehicle (Control): Wild type-like (WT), N = 11 APPxPS1, N = 11 - CBD: WT, N = 11 APPxPS1, N = 12		Dissolved in equal amounts of Tween 80 and 100% ethanol, diluted with 0.9% NaCl. Ethanol and Tween 80 comprised 10 % of the total volume. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was	- Fear conditioning.	- Aversive memory (Fear associated memory).	- One-sample t test showed that all groups, except APPxPS1-VEH, spent significantly more time with the novel (unfamiliar) mouse than the familiar mouse [WT-VEH, $t(7) = 3.7$, $p < 0.01$; APPxPS1- VEH, $t(8) = 0.8$, $p = 0.4$; WT-CBD, $t(9) = 2.8$, $p < 0.05$; APPxPS1-CBD, $t(10)=3.4$, $p<0.01$]. - The effect of 'treatment' was found between APPxPS1-VEH and APPxPS1- CBD

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	(APPxPS 1). - The mice modeled for Alzheimer's disease (AD).			10 ml/kg body weight.			groups [F(1,17) = 4.7, p < 0.05]. Thus, CBD treatment restored object recognition. - APPxPS1 mice did not develop impairment in fear-associated memory as all mice have similar freezing time (p > 0.05). Thus, CBD has no impact on aversive memory (fear associated memory).
Cheng et al. (2014)[87]	- Mice carrying double	Mice were either given CBD or	The total duration of	Oral administration of gel pellet of:	- Social preference test (SPT).	- Social recognition memory.	- CBD prevented social recognition deficit in AβPP × PS1 mice

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
, Australia	transgenes expressing chimeric mouse/ human mutations of amyloid -β precursor protein (AβPP)	vehicle gel pellet. Treatments were quasi-randomized. - WT-vehicle, N = 8 - AβPP × PS1-vehicle, N = 10 - WT-CBD, N = 10	treatment were 8 months: - WT-vehicle = 241.6 ± 38.9 days - AβPP × PS1-vehicle = 247.9 ± 31.6 days - WT-CBD = 239.3 ± 33.4 days	- CBD: 20 mg/kg (from CAS: 13956-29-1 THC Pharma GmbH; Frankfurt/Main, Germany). Dissolved in equal amounts of Tween 80 and 100% ethanol in gel pellet with the composition of 2.0% ethanol, 2.0% Tween 80, 15.2% sweetener (Splenda), 8.7%	- Fear conditioning.	- Aversive memory (Fear associated memory).	without affecting aversive memory (fear associated memory) and anxiety-related behaviours. - RM ANOVA showed that vehicle-treated APPxPS1 mice showed impairments in social recognition [$F(1,41) = 4.8$, $p < 0.05$]. - T-test showed that all groups, except APPxPS1 mice, spent significantly more time with the novel mouse [WT-VEH: $t(7) = 2.5$, $p < 0.05$; AβPP

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	and presenilin 1(PS1/ ΔE9) = (APPxPS1). - The mice modeled for AD.	- AβPP × PS1-CBD, N = 10	- AβPP × PS1-CBD = 251.2 ± 35.8 days	gelatine, 20.1% chocolate flavoring and 52.0% water for irrigation. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 8 ml/kg body weight.			× PS1-VEH: t(13) = 0.3, 469 p = 0.8; WT-CBD: t(9) = 3.3, p < 0.01; AβPP × PS1- 470 CBD: t(12) = 3.7, p < 0.01]. - Two-way ANOVA showed a trend toward an effect of CBD treatment [F(1,41) = 3.1, p = 0.09]. - ANOVA showed that CBD had positive effect on social recognition memory in AβPP × PS1 [F(1,25) = 5.0, p < 0.05], but showed no effect in

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							WT mice [F(1,16) = 0.2, p = 0.7]. - Two-way ANOVA showed all mice have similar freezing time and intact context memory regardless of treatment (p>0.05), demonstrating that CBD has no impact on aversive memory (fear associated memory).
Chesworth and Karl (2020)[79]	- Male C57BL/6J mice.	Mice were randomly assigned into groups	Intervention was administered 30	Intraperitoneal injection of: - CBD: 10 mg/kg (from THC Pharma	Conditioned place preference (CPP).	Drug-associated memory.	- CBD treatment reduced preference for cocaine context and a long-lasting effect at 20 days

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
, Australia	- The mice modeled cocaine - memory processes.	according to different experiment in an unbiased allocation manner. Experiment 1- 5: N = 9 – 15 /drug treatment condition in each experiment.	mins prior to different phrases of CPP.	GmbH; Germany). Suspended in 100% ethanol, Tween 80 and 0.9% NaCl. The ratio by volume of 1:1:18 was used. - Cocaine hydrochloride: 15 mg/kg (From National Measurements Institute, Australia). Dissolved in 0.9% saline.			after treatment cessation. CBD treatment reduced consolidation of cocaine memory. CBD did not affect reconsolidation, extinction, or reinstatement. Experiment 1: effect of CBD on acquisition of cocaine CPP. - CBD treatment reduce preference for cocaine when given prior to conditioning across the test period with

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Vehicle group - CBD group		- Control for cocaine was 0.9% saline. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 10 ml/kg body weight.			significant days x CBD treatment interaction [F(3,48) = 4.1, p = 0.01]. Bonferonni post-hoc tests confirmed the reduction in preference at 20 days after conditioning s ($p < 0.01$). Experiment 2: effect of CBD on consolidation of cocaine CPP. - There was a main effect on treatment on % time spent in the cocaine paired compartment at 1 day after CBD cessation

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							[F(1,28) = 4.34, p = 0.04] and there was a significant treatment x time interaction [F(5,140) = 3.2, p = 0.001]. Bonferonni post-hoc tests showed that CBD group had weaker preference ($p < 0.05$) Thus, CBD reduced consolidation of cocaine memory. Experiment 3: effect of CBD on reconsolidation of cocaine CPP

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- CBD was given after reactivation of memory with no effect on reconsolidation of cocaine memory. There was no effect on treatment [F(1,22) = 0.4, p = 0.5] and no interaction between day x CBD treatment [F(4,88) = 0.1, p = 0.9]. Experiment 4: effect of CBD on extinction of cocaine CPP - CBD was given prior extinction conditioning

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							and showed no effect on the preference [‘days’ F(5,80) = 3.1, p = 0.01; no days x CBD treatment interaction: F(5,80) = 0.9, p = 0.5]. Experiment 5: effect of CBD on drug-primed reinstatement of cocaine CPP - CBD was given prior to drug-primed reinstatement and showed no effect on relapse-like behaviour. CBD treatment showed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							no effect on reinstatement [no interaction of CBD treatment x days: F(1,16) = 0.1, p = .9].
Chestworth et al. (2022)[88], Australia	- Female mice carrying double transgenes expressing chimeric	Mice were either given CBD or vehicle gel pellet. Treatments were quasi-randomized. - WT-vehicle, N = 14, - APPxPS1-	The total duration of treatment was 8 months.	Oral administration of gel pellet of: - CBD: 20 mg/kg (from CAS: 13956-29-1 THC Pharma GmbH; Frankfurt/Main, Germany). Composition of the gel pellets were 2.0% ethanol, 2.0%	- Cheeseboard (CB). - NORT. - Fear conditioning.	- Spatial memory. - Object recognition memory.	- CBD showed moderate preventive effect on spatial learning in APPxPS1 mice but limited effects on fear memory. - Two-way ANOVA of CB experiment showed longer time to find food in VEH-treated APPxPS1 mice than CBD-treated

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	mouse/ human mutations of amyloid precursor protein (APP) and presenilin 1(PSEN 1dE9) = (APPxPS1).	vehicle, N = 16 - WT-CBD, N = 14 - APPxPS1-CBD, N = 12		Tween 80, 15.2% sweetener (Splenda), 8.7% gelatine, 20.1% chocolate flavoring and 52.0% water for irrigation. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 8 ml/kg body weight.		- Aversive memory (Fear associated memory).	APPxPS1 mice [F(1,24) = 5.1, p = 0.03] but not in WT mice [F(1,25) = 0.1, p = 0.9]. - Two-way ANOVA CB experiment showed CBD reduced intermediate-term memory in APPxPS1 mice [F(1,24) = 4.6, p = 0.04] but not in WT mice [F (1,25) = 0.1, p = 0.9] - There is no difference for long-term memory (p>0.05). - In NORT experiment, WT VEH-treated mice

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	- The mice modeled for AD.						failed to demonstrate novel object recognition therefore cannot be concluded. - All mice have similar freezing time ($p > 0.05$), demonstrating that CBD has no impact on aversive memory (fear associated memory).
Coles et al. (2022)[95], Australia	- Female mice carrying double transge	50 mice were assigned to vehicle or CBD group - WT-VEH, N = 15	The total duration of treatment prior cognitive	Intraperitoneal injection of: - CBD: 5 mg/kg (from CAS: 13956-29-1 THC Pharma GmbH;	- CB. - NORT.	- Spatial memory.	- CBD treatment showed a reversal effect of object recognition deficits and delayed spatial learning in APPxPS1 mice.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	nes expressing chimeric mouse/ human mutations of amyloid precursor protein (APP_{Swe}) and presenil	- WT-CBD, N = 13 - APPxPS1-VEH, N = 10 - APPxPS1-CBD, N = 12	assessment was 3 weeks.	Frankfurt/Main, Germany). Dissolved in 0.5 mg/ml equal amounts of Tween 80 and 100% ethanol, diluted with 0.9% NaCl. Ethanol and Tween 80 comprised 10 % of the total volume. The ratio by volume of 1:1:18 of ethanol:Tween 80:saline was used.		- Object recognition memory.	- One-sample t-tests of NORT showed that all groups except for vehicle-treated APPxPS1 mice had a significant preference for the novel object [WT-VEH: $t(13) = 4.5$ and $p = 0.001$; APPxPS1-VEH: $t(9) = 0.5$ and $p = 0.6$; WT-CBD: $t(12) = 2.8$ and $p = 0.02$; APPxPS1-CBD: $t(9) = 2.6$ and $p = 0.03$]. - APPxPS1 mice were slower on the CB during reversal training [$F(1,45)$

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	in 1(PS1Δ E9) = (APPxPS 1). - The mice modeled for AD.			- Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 10 ml/kg body weight.			= 17.2; p < .001] and they took longer to find reward [F(1,45) = 17.9; p < 0.001] compared to WT groups. There was also a significant interaction between time x genotype x treatment [F(3,135) = 3.6; p = 0.02] with CBD treated group showing increased average speed than the VEH treated groups (p < 0.001).
Corre et al.	- Female	Rats were assigned into	The total duration	Intraperitoneal injection of:	- Inhibitory avoidance	- Aversive memory	- CBD treatment was able to reverse the

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
(2022)[89], Brazil	Wistar rat. - The rat modeled memory impairment due to estrogen depletion induce	ovariectomy group (OVX, N = 28) and false-operated (sham, N = 25) group. - Vehicle-Sham group, N = 10 - Vehicle-OVX group, N = 14	of treatment was 14 days.	- CBD: 10 mg/kg (from BSPG-Pharm, UK). Suspended in 100% ethanol, Tween 80 and 0.9% NaCl. The ratio by volume of 1:1:18 was used. - Vehicle solution: Tween 80 and saline solution in the ration of 1:16 v/v.	(IA) conditioning. (Step down = shock)	(Fear associated memory).	aversive memory impairment caused by estrogen depletion. - Two-way ANOVA showed significant main effect of treatment [F(1, 49) = 6.21, p = 0.016] and significant interaction [F(1, 49) = 4.37, p = 0.042] in comparison of reaction time to step down. - CBD-OVX group showed longer time to step-down than Vehicle-OVX group [F(1, 49) = 11.38, p =

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	d by ovariectomy.	- CBD-Sham group, N = 15 - CBD-OVX group, N = 14					0.001] suggesting the reversal effect of fear memory deficit. - Sham groups showed no significant simple effect of treatment (p = 0.785), main effects of surgery [F(1, 49) = 0.99, p = 0.325] and treatment [F(1, 49) = 0.062, p = 0.805], and no interactions [F(1, 49) = 0.053, p = 0.819].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
de Carvalho and Naoto Takahashi (2016)[10][2], Brazil	- Male Wistar rats. - The mice modeled cocaine and morphine memory processes.	Rats were assigned into groups according to different experiment. Experiment 1: effects of CBD on reconsolidation, N = 10–11/group For MOR-trained group:	Intervention was given immediately after reconsolidation.	Subcutaneous injection of: - CBD: 5 and 10 mg/kg (from Tocris Bioscience, USA). Dissolved in vehicle solution of 10% dimethyl sulfoxide, 0.1% Tween 80 in saline. Given at the volume of 2 ml/kg body weight. - Morphine hydrochloride: 2.5mg/kg (from	- Conditioned place preference (CPP). - Conditioned place aversion (CPA).	Drug-associated memory.	- CBD treatment reduced environmental preference for morphine and cocaine and impaired reconsolidation of drug-associated memory by blocking reactivated memory. - Moreover, CBD treatment resulted in a notable decrease in both morphine- CPP and CPA induced by naltrexone in the same context. Experiment 1: CBD group showed disrupted

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Saline group - MOR-VEH group - MOR-CBD5 group - MOR-CBD10 group For COC-trained group: - Saline group - COC-VEH group		Merck, Germany). Dissolved in 0.9% sodium chloride. Given at the volume of 1 ml/kg body weight. Intraperitoneal injection of: - Cocaine: 10 mg/kg (from Sigma-Aldrich, USA). Dissolved in 0.9% sodium chloride. Given at 1 ml/kg. Given at the			reconsolidation of place preference. - Two-way ANOVA showed significant effect on treatment [$F_{2, 108} = 32.09$, $p < 0.00001$] and trials [$F_{3,108} = 4.50$; $p < 0.005$], with significant interaction between treatment x trials [$F_{6,108} = 5.48$; $p < 0.0001$]. CBD10 groups showed significant disruption of morphine CPP which persisted at 7 ($p < 0.003$) and 14 ($p < 0.01$) days.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- COC-CBD10 group Experiment 2: effects of CBD on reinstatement of MOR-trained rats (N = 8–10/group) - MOR-VEH-Non-Stress group		volume of 1 ml/kg body weight. Cocaine (Sigma-Aldrich, Missouri, USA) and morphine hydrochloride (Merck, Darmstadt, Germany) were both dissolved in 0.9 percent sodium chloride (saline) and given at a volume of 1 ml/kg to a final concentration of 10mg/kg for initial			- Two-way ANOVA of COC-trained groups showed significant effect on treatment [$F_{1, 60}$ = 33.28; $p < 0.00001$] and trials [$F_{2, 60}$ = 3.76; $p < 0.03$], with significant interaction between treatment x trials [$F_{2, 60}$ = 5.38; $p < 0.008$]. CBD10 groups showed significant disruption of morphine CPP which persisted at 7 ($p < 0.01$) and 14 ($p < 0.03$) days.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- MOR-VEH-Stress group - MOR-CBD-Non-Stress group - MOR-CBD-Stress group Experiment 3: effects of CBD on development of naltrexone-precipitated		CPP training and at 2.5mg/kg as the priming drug for reinstatement of MOR-CPP.			Experiment 2: CBD groups showed prevention of spontaneous recovery and the reinstatement of morphine-reward memory. - Two-way RM ANOVA of MOR-trained rats showed significant main effects of treatment [$F_{1, 37}$ = 153.48; $p < 0.00001$], repetition [$F_{4, 148}$ = 137.49; $p < 0.00001$], interaction between treatment x trials [F4,

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		withdrawal (N = 8–9/group) - MOR-VEH-VEH group - MOR-CBD-VEH group - MOR-VEH-NTX group - MOR-CBD-NTX group					148 = 47.68; p < 0.00001] and interaction between stress x trials [$F_{4, 148}$ = 3.21; p < 0.02]. - Bonferroni's test showed that CBD treated group had less time spent in MOR-paired chamber (p < 0.0001). CBD treatment prevented spontaneous recovery where MOR-CBD-non-stress and MOR-CBD-stress (both p's < 0.00001) groups showed significant decrease in

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							CPP scores which lasted until 21 days. - MOR-CBD-non-stress and MOR-CBD-stress groups also maintained lower CPP compared to VEH groups (both $p < 0.00001$), thus showing the prevention of stress-induced reinstatement of MOR-CPP. Experiment 3: CBD group showed disruption of reconsolidation of MOR-CPP and suppression of

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							subsequent naltrexone-precipitated CPA. - Two-way RM ANOVA for MOR-trained rats showed main effects of post-treatment [$F_{1, 31}$ = 135.51; $p < 0.00001$], repetition [$F_{2, 62}$ = 217.13; $p < 0.0001$], pre-treatment x post-treatment interaction [$F_{1, 31}$ = 52.51; $p < 0.0001$] and pre-treatment vs. post-treatment vs. repetition interaction [$F_{2, 62}$ = 27.38; $p < 0.0001$].

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							- Post-hoc tests showed CBD treatment significantly reduced place preference in MOR-VEH-VEH vs. MOR-CBD-VEH and aversion in MOR-VEH-NTX vs. MOR-CBD-NTX to MOR-paired chamber ($p < 0.001$) in which the effect lasted at 7 days ($p < 0.001$). - Groups treated with CBD also showed decrease in CPP scores after treatment ($p < 0.0001$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
de Paula Faria et al. (2022)[8], Brazil	- Male, outbred Charles River Wistar rats. - The rat modeled for AD induced by strepto	12 rats were randomly assigned into 2 groups - STZ, N = 6 - STZ + CBD, N = 6	The total duration of treatment was 1 week.	Intraperitoneal injection of: - CBD: 20 mg/kg (from Biosynthesis Pharma Group Limited-BSPG, UK). Diluted in 2% Tween 80 and 98% saline.	- NORT.	- Object recognition memory.	- CBD showed a protective effect on STZ-induced AD, preserving STM and LTM. - STZ group showed worse memory index for NORT in both STM (53.83 ± 3.12, −20%) and LTM (39.17 ± 14.43, −53%) compared to STZ + CBD group (STM: 67.33 ± 5.13, $p = 0.0003$; LTM: 83.67 ± 4.13, $p < 0.0001$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	zotocin (STZ).						
Faghera zzi et al. (2012)[10] [1], Brazil	- Male, Wistar rats. - The rat modeled Neurodegenerative disorder using iron-	60 rats were randomly assigned to treatment groups - Vehicle, N = 15 - CBD 2.5 mg/kg, N = 15 - CBD 5 mg/kg, N = 15	The total duration of treatment was 2 weeks.	Intraperitoneal injection of: - CBD: 2.5, 5.0 and 10 mg/kg (99.9% pure from THC-Pharm, Germany and STI-Pharm, UK). Dissolved in Tween 80 1:16 v/v.	- NORT. - Inhibitory avoidance task	- Object recognition memory. - Aversive memory (Fear associated memory).	- Acute CBD at the highest dose (10 mg/kg) was able to recover memory in iron-treated rats. - Chronic CBD showed improvement in recognition memory in iron-treated rats. CBD does not show any effect on memory in control rats. CBD showed no

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	induced (oral) impairment.	- CBD 10 mg/kg, N = 15					effect on memory for inhibitory avoidance task. - Iron given during neonatal period induced severe recognition memory impairment ($p < 0.0001$). - Two-way ANOVA showed significant interaction between the effects treatment x acute CBD [$F = 20.30$; $df = 2$; $p < 0.0001$]. - Tukey's post hoc showed that acute administration of CBD at

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							2.5 mg/kg and 5.0 mg/kg showed no significant effect ($p < 0.0001$). Whereas, 10 mg/kg showed significantly higher recognition ($p < 0.0001$). - Two-way ANOVA showed a significant interaction between the effects of treatment x chronic CBD [$F = 34.87$; $df = 2$; $p < 0.0001$]. - Tukey's post hoc showed chronic administration of CBD at

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							2.5, 5.0 and 10 mg/kg showed significantly higher recognition indexes ($p<0.0001$) where 10 mg/kg was able to reverse the memory deficit ($p < 0.0001$). - Chronic CBD in control rats showed no effect on recognition memory.
Franzen et al. (2022)[10][3], Brazil	- Female Wistar rats.	Rats were randomly assigned into groups according to	Exp. 1: Intervention was administered 45	Intraperitoneal injection of: - CBD: 1.0, 3.0 and 10 mg/kg (99.9% purified from BSPG	- Fear conditioning.	- Aversive memory (Fear	- Higher doses of CBD treatment (3.0 and 10 mg/kg) reduced freezing time through DH 5-HT1A receptors, regardless of

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		different experiment. Experiment 1: effects of CBD on contextual fear memory (N = 9–11/group). - VEH group - CBD1 group - CBD3 group - CBD10 group Experiment 2: effects of	mins before testing. Exp. 2: Interventio n was administer ed 24 hours before testing. Exp. 3: Interventio n was	Pharm, Sanwich, UK). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate. - In all cases, the volume administered was 1.0 ml/kg body weight. Infused intracranially into the DH (Dorsal		associated memory).	estrous cycle. CBD treatment impaired reconsolidation and lowered fear expression during early extinction. Local administration (DH) produced the same effects of systematic (intraperitoneal). Experiment 1: CBD reduced contextual fear memory. - CBD treatment (intraperitoneal) showed an effect of freezing time during exposure [F(3,37)

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		early CBD treatment on contextual fear memory (N = 9/group). - VEH group - CBD10 group Experiment 3: effects of the estrous cycle on CBD and contextual fear memory retrieval/expr	administered 45 mins before testing. Exp. 4: Intervention was administered 45 mins (intraperitoneal) and 55 mins (intracrania	Hippocampus) of interest: - CBD: 9.4 μg (99.9% purified from BSPG Pharm, Sanwich, UK). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate. - AM251 (CB1 receptor antagonism/inverse agonist: 0.2 ng (Tocris, USA).			= 8.8, p = 0.0002; η^2 = 0.42] where CBD 3 (p = 0.04) and CBD10 (p = 0.001) groups showed lower freezing time compared to VEH group. Experiment 2: early CBD administration did not affect contextual fear memory suggesting that the effects of CBD was acute. - CBD 10 and VEH groups showed similar scores when test was done 24

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		ession (N = 9–11/group) - Proestrus-VEH - Proestrus-CBD10 - Estrous-VEH - Estrous-CBD10 - Diestrus - VEH - Diestrus - CBD10 Experiment 4: effects of DH CB1, CB2, or	l) before testing. Exp. 5: Intervention was administered 45 mins before testing. Exp. 6: Intervention was administered 10	Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate. - AM630 (CB2 receptor antagonism/inverse agonist: 1.0 ng (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate and			hours later [$t_{16} = 0.33$; $p = 0.74$]. Experiment3: the effects of CBD on contextual fear memory were similar across different phase of the estrous cycle. - There was no main effect on the estrous cycle [$F(2,56) = 0.80$, $p = 0.45$; $\eta^2_p = 0.03$] and no significant interaction between treatment x estrous cycle [$F(2,56) = 0.72$, $p = 0.49$; $\eta^2_p = 0.02$].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		5-HT1A receptor antagonism and CBD on contextual fear memory (N = 10–12/group). - VEH-VEH group - CBD-VEH group - VEH-AM251 0.2 group - CBD-AM251 0.2 group	mins before testing. Exp. 7: Intervention was administered 45 mins before testing.	5% dimethyl sulfoxide. - WAY100635 (a selective 5-HT1A receptor antagonis): 0.1 ng (Tocris, USA). Dissolved in NaCl 0.9%. - In all cases, the volume administered was 0.5 μl/hemisphere.			Experiment 4: antagonism of DH 5-HT$_1$A but not CB1 or CB2 receptors prevented CBD effects on contextual fear memory. - There was an effect on DH treatment [F(1,81) = 33.2, p = 0.000001; η^2_p = 0.29] and interaction between treatment x freezing time [F(3,81) = 4.2, p = 0.008; η^2_p = 0.13] where VEH-CBD (p = 0.0002) and AM251-CBD groups (p = 0.0004)

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH-AM630 1.0 group - CBD-AM630 1.0 group - VEH-WAY100635 0.1group - CBD-WAY100635 0.1group Experiment 5: effects of systemic CBD of contextual fear memory					showed lower scores than control groups. WAY100635-CBD and AM630-CBD groups did not show any significant difference, suggesting that CBD reduced the fear memory through activation of DH 5-HT_1A receptor. Experiment 5: intraperitoneal CBD treatment impaired memory reconsolidation resulting in lower fear

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		on extinction (N = 8/group). - VEH group - CBD10 group Experiment 6: effects of intra-DH CBD infusion on contextual fear memory extinction (N = 7/group). - VEH group - CBD10 group					expression during early extinction. - There was an effect of treatment [$F(1,14) = 8.6$, $p = 0.01$; $\eta^2_p = 0.38$] and repeated testing [$F(1,14) = 35.9$, $p = 0.00003$; $\eta^2_p = 0.72$] on freezing time but there was no significant interaction [$F(1,14) = 2.3$, $p = 0.15$; $\eta^2_p = 0.14$]. CBD groups showed lower scores than VEH group during test ($p = 0.004$) but not at the retest period. Both

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		Experiment 7: effects of CBD on anxiety-related behaviors (N = 8–15/group) - VEH group - CBD1 group - CBD3 group - CBD10 group					VEH ($p = 0.00005$) and CBD ($p = 0.02$) groups showed lower freezing times after extinction session. - During the extinction session, there was an effect on treatment [$F(1,14) = 13.0$, $p = 0.003$; $\eta^2_p = 0.48$], time bin [$F(4,56) = 49.1$, $p = 0.00001$; $\eta^2_p = 0.78$] and significant interaction on freezing time [$F(4,56) = 11.0$, $p = 0.00001$; $\eta^2_p = 0.44$]. Both VEH and CBD

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							group showed lower scores from the 2^{nd} – 5^{th} extinction session ($p \leq 0.01$) where CBD group showed accelerated extinction rate in the first two session ($p \leq 0.0003$). Experiment 6: Intra-DH CBD infusion reduced contextual fear memory and impaired reconsolidation resulting in lower fear during early extinction. - There was an effect of treatment [$F(1,12) = 24.7$,

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							p = 0.0003; η^2_p = 0.67] and repeated testing [F(1,12) = 132.2, p = 0.000001; η^2_p = 0.92] on freezing time but there was no significant interaction [F(1,12) = 29.6, p = 0.0002; η^2_p = 0.71]. CBD group showed lower score than VEH group during the test (p = 0.0002) but not the retest session. Both VEH (p = 0.0002) and CBD (p = 0.003) groups showed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							lower freezing times after the extinction session. - During the extinction session, there was an effect on treatment [$F(1,12) = 4.6$, $p = 0.05$; $\eta^2_p = 0.28$], time bin [$F(4,48) = 66.4$, $p = 0.00001$; $\eta^2_p = 0.85$] and significant interaction on freezing time [$F(4,48) = 10.0$, $p = 0.00001$; $\eta^2_p = 0.45$]. Both VEH and CBD group showed lower scores from the 2^{nd} – 5^{th} extinction session ($p \leq$

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							0.005) where CBD group showed accelerated extinction rate in the first two session ($p \leq 0.0002$). Experiment 7: CBD reduced anxiety-related behaviors.
Franzen et al. (2022)[10] [4], Brazil	- Female Wistar rats.	Rats were randomly assigned into groups according to different experiment.	Exp. 1: Intervention was given immediately after reactivation.	Intraperitoneal injection of: - CBD: 10 mg/kg (99.9% purified from BSPG Pharm, Sanwich, UK). Dissolved in NaCl 0.9% containing 5%	- Fear conditioning.	- Aversive memory (Fear associated memory).	- CBD treatment impaired the reconsolidation process and resulted in reduced freezing time for more than a week, thought the activation of CB1 receptor (but not CB2) located on DH. The

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		Experiment 1: Effects of systematic CBD on contextual fear memory reconsolidation (N = 9–10/group) - VEH group - CBD10 group Experiment 2: Effects of delayed systemic CBD	Exp. 2: Intervention was given 6 hours after reactivation. Exp. 3: Intervention was given immediately after non-	of polyoxyethylene sorbitan monooleate. - In all cases, the volume administered was 1.0 ml/kg body weight. Infused intracranially into the DH (Dorsal Hippocampus) of interest: - CBD: 30 nmol (99.9% purified			action was restricted to time and on reactivation and destabilization. Local administration (DH) produced the same effects of systematic (intraperitoneal). Fear associated memories reduced by CBD did not show reinstatement. Experiment 1: CBD impaired contextual fear memory reconsolidation. - There was an effect on treatment [$F(1,17) = 8.8$; $p = 0.0009$; $\eta 2 = 0.34$],

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		treatment on contextual fear memory reconsolidation (N = 9/group) - VEH group - CBD10 group Experiment 3: Effects of systematic CBD in the absence of reactivation and	reactivation. Exp. 4: Intervention was given 10 mins after antagonists. Exp. 5: Intervention was given immediately after	from BSPG Pharm, Sanwich, UK). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate. - AM251 (CB1 receptor antagonism/inverse agonist: 0.0002 μg (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene			repeated testing [F(2,34) = 14.8; p = 0.00002; η2 = 0.46], and interaction between treatment x repeated testing [F(2,34) = 5.6; p = 0.008; η2 = 0.25] on freezing time. CBD group showed lower score compared to VEH group at 1 day (p = 0.002) and 7 days after reactivation (p = 0.01). Experiment 2: Delayed CBD treatment had no effect on memory reconsolidation.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		destabilization of contextual fear memory (N = 9/group) - VEH group - CBD10 group Experiment 4: Effects of CB1 or CB2 receptor antagonism in the DH CA1 on CBD and contextual	reactivation.	sorbitan monooleate. - AM630 (CB2 receptor antagonism/inverse agonist: 0.001 μg (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate and 5% dimethyl sulfoxide.			- There was an effect repeated testing [$F(2,32) = 23.7$; $p = 0.000001$; $\eta 2 = 0.60$] but no effect on treatment [$F(1,16) = 0.2$; $p = 0.67$; $\eta 2 = 0.01$] and interaction [$F(2,32) = 1.0$; $p = 0.38$; $\eta 2 = 0.06$] on freezing time, suggesting that CBD did not impair memory. Experiment 3: CBD induced reconsolidation's impairments required

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		fear memory reconsolidation (N = 9–12/group) - VEH-VEH group - CBD-VEH group - VEH-AM251group - CBD-AM251 group - VEH-AM630 group - CBD-AM630 group		- In all cases, the volume administered was 0.5 μl/hemisphere.			destabilization of memory. - There was on effect of treatment on freezing time [t16 = 0.33; p = 0.74]. Experiment 4: Antagonism at CB1 receptors, (not CB2) in the DH prevented the impairments in reconsolidation caused by systemic CBD treatment. - There was an effect on pre-treatment [F(2,54) =

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		Experiment 5: Effects of CBD on DH on contextual fear memory reconsolidation (N = 8/group) - VEH group - CBD30 nmol group					3.3; p = 0.04; $\eta 2$ = 0.11], treatment [F(1,54) = 14.7; p = 0.0003; $\eta 2$ = 0.21], and repeated testing [F(2108) = 51.7; p = 0.000001; $\eta 2$ = 0.49] on freezing time. There was also significant interaction between effects of pretreatment x repeated testing [F(4108) = 7.2; p = 0.00003; $\eta 2$ = 0.21] and treatment x repeated testing interactions [F(2108) = 11.3; p = 0.04; $\eta 2$ = 0.17,

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							respec- tively]. CBD group showed lower score compared to VEH group at 1 day (p = 0.001) and 7 days after reactivation (p = 0.003). - Co-administration of CB1 antagonist (AM251) diminished the impairing effect of CBD on reconsolidation, indicating that CBD's impact is mediated through CB1 receptor. - However, co-administration of CB2

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							antagonist (AM630) showed significant difference between AM630-CBD and AM630-VEH groups (p = 0.002). Experiment 5: CBD infused directly into the DH impaired memory reconsolidation. - There was an effect on treatment [F(1,14) = 27.0; p = 0.0001; $\eta 2$ = 0.66], repeated testing [F(2,28) = 12.2; p = 0.0002; $\eta 2$ = 0.46], and an interaction between treatment x

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							repeated testing [F(2,28) = 3.7; p = 0.04; $\eta 2$ = 0.21] on freezing time. CBD group showed lower score compared to VEH group at 1 day (p = 0.0002) and 7 days after reactivation (p = 0.002).
García-Baos et al. (2021)[96], Spain	- Male and female C57BL/6 were bred togethe	- Offspring mice were used as a whole population and balanced for numbers	The total duration of treatment was 10 days.	Intraperitoneal injection of: - CBD: 20 mg/kg (from Phytoplant Research S.L., Spain). Mixed in 2% Tween 80 and	- Y-maze. - NORT. - Novel Object Location (NOL) task.	- Spatial memory. - Object recognitio n memory.	- CBD treatment improved reference memory, object location memory and partially improved spatial working memory deficits in

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	r for offsprin g mice. - Pregnan t females were random ly assigne d to 20% (v/v) alcohol or	of male and female. - Offspring were randomly distributed where N = 10–14 per group. - PLAE-CBD - PLAE-VEH		added with 0.9% NaCl. - Ethyl alcohol (from Merck Chemicals, Germany) diluted in tap water to obtain 20% (v/v) alcohol solution.			FASD-like mice model. - Two-way ANOVA showed that CBD counteracted the PLAE-induced reference memory deficit as there was significant interaction between group x treatment [$F(1,45) = 4.906$, $p < 0.05$]. PLAE-CBD group showed significantly higher score compared to PLAE-VEH ($p < 0.05$). - Two-way ANOVA showed that CBD has no

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	water (control) to induced early alcohol exposure for Foetal alcohol spectrum disorder (FASD) mice model.						effect on recognition memory ($p > 0.05$). - Two-way ANOVA showed that CBD improves deficit in object location memory where there was significant interaction between group x treatment [$F(1,46) = 7.598$, $p < 0.01$]. Bonferroni's multiple comparisons revealed that PLAE-CBD animals showed greater score when compared to PLAE-VEH ($p < 0.05$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- Two-way ANOVA showed that CBD partially improved spatial working memory deficits where group [$F(1,46) = 5.605$, $p < 0.05$] and interaction [$F(1,46) = 4.379$, $p < 0.05$] effect were significant. Bonferroni's post-hoc analyses showed that PLAE-VEH mice have lower correct score than Water-VEH group ($p < 0.01$) and the PLAE-CBD group showed no

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							significant difference compared to PLAE-VEH and to Water-VEH.
Gasparyan et al. (2021)[80], Spain	- Male C57BL/6J mice. - The mice modeled post-traumatic stress disorde	Mice were randomly assigned into groups according to different experiment. - PTSD-VEH group, N = 10 - PTSD-CBD group, N = 10	The total duration of treatment was 3 weeks.	Intraperitoneal injection of: - CBD: 20 mg/kg (from STI Pharmaceuticals; UK). Dissolved in ethanol, cremophor and saline. The ratio by volume of 1:1:18 of ethanol:cremophor : saline was used.	- Fear conditioning.	- Aversive memory (Fear associated memory).	- CBD treatment improved long-lasting fear memory and anxiety-like behaviors in mice modeled for PTSD in which the improvement was enhanced when combined with STR. - Student's t-test showed PTSD modeled mice had increased freezing time (t

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	r (PTSD).	- PTSD-STR group, N = 9 - PTSD-CBD+STR group, N = 10 - Control-VEH group, N = 10 - Control-CBD group, N = 9 - Control-STR group, N = 9		- In all cases, the volume administered was 10 ml/kg body weight. Oral administration of: - Sertraline (STR): 10 mg/kg (from Pfizer laboratories; Spain). Dissolved in water. - Vehicle group was administered similarly without addition of CBD.			-13.738, $p < 0.001$, 14 d.f.), startled response (t -3.002, $p < 0.01$, 14 d.f.) and latency time (t -6.824, $p < 0.001$, 14 d.f.). - Student's t-test showed PTSD modeled mice had increased gene expression of corticotropin releasing factor (Crf; t -9.349, $p < 0.001$, 14 d.f.) and proopiomelanocortin (Pomc; t -5.565, $p < 0.001$, 14 d.f.), relative expression of

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Control-CBD+STR group, N = 10		- In all cases, the volume administered was 10 ml/kg body weight.			paraventricular nucleus (PVN) and arcuate nucleus (ARC), and decreased expression of glucocorticoid receptor (GCr) in the hippocampus (HIPP; t 5.734, $p < 0.001$, 14 d.f.). The mice hair also showed increased concentration of corticosterone (t -3.943, $p < 0.01$, 14 d.f.). - Student's t-test showed PTSD modeled mice had

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							decreased CB1 receptor (t 5.647, p < 0.001, 14 d.f.), increased CB2 receptor (t −3.604, p = 0.003, 14 d.f.) and enhanced gene expression on serotonin transporter (Slc6a4; t −3.337, p = 0.005, 14 d.f.) - PTSD-CBD and PTSD-STR groups showed reduced freezing time but PTSD-CBD+STR group showed no significant differences (Two-way ANOVA, CBD: $F_{(1,37)}$

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							4.794, $p < 0.05$; STR: $F_{(1,37)}$ 4.712, $p < 0.05$; CBD x STR: $F_{(1,37)}$ 1.140, $p = 0.293$). - CBD + STR showed a superior effect in reducing freezing time compared to PTSD-CBD and PTSD-STR treatments, although the difference was not statistically significant.
Han et al. (2022)[81], China	- Male C57BL/6 J mice.	Mice were randomly assigned into groups	Exp. 1: Intervention was administer	Intraperitoneal injection of: - CBD: 10 and 30 mg/kg (from HPLC;	- Fear conditioning.	- Aversive memory (Fear	- CBD treatment (10 mg/kg) reduced fear associated memory, anxiety-like behavior and

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		according to different experiment Experiment 1: Alleviation of responses by CBD and sertraline in PTSD model (N = 6–8/group) - Control (no shock) group - VEH + Shock group	ed 30 mins before test from day 3 to 15. Exp. 2: Interventio n was administer ed during the interval period immediate ly after re-	China). Dissolved in saline containing 2% ethanol and 2% Tween 80. Oral (intragastric) administration of: - Sertraline (STR): 15 mg/kg (from Sigma Chemical; USA). Dissolved in saline.		associated memory).	increased social interaction behavior. - CBD treatment also reduced consolidation, retrieval and reconsolidation of fear associated memory. - Two-way RM ANOVA of daily administration of CBD and STR showed significant effect of treatment ($F [4, 31] = 54.56$, $P < 0.001$), time ($F [3.176, 98.44] = 78.28$, $P < 0.001$) and interaction between time x

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- STR + Shock group - CBD10 + Shock group - CBD30 + Shock group Experiment 2: Alleviation of PTSD-like symptoms by CBD and sertraline during the interval period (N = 8–12/group)	exposure from day 3 to 7. Exp. 3: Intervention was administered during before foot shock at day 1 and 2. Exp. 4: Intervention was				treatment (F [16, 124] = 9.331, P < 0.001) on freezing time. Bonferroni's post-hoc tests showed daily administration of STR and CBD (10 mg/kg) had reduced freezing time from days 3 to 15 (all p's < 0.05) but CBD at 30 mg/kg showed no significant effect. - Two-way RM ANOVA of daily administration of CBD and STR during the interval period after

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Control group - VEH + Shock group - STR + Shock group - CBD10 + Shock group Experiment 3: Effects of CBD and sertraline on fear memory acquisition (N = 9–12/group)	administered 30 mins before test on day 3, 8, and 15. Exp. 5: Intervention was administered after test at reconsolidation then 24 hours				shock showed significant effect of treatment (F [3, 42] = 57.62, P < 0.001), time (F [2.829, 118.8] = 67.58, P < 0.001) and interaction between time x treatment (F [12, 168] = 6.608, P < 0.001) on freezing time. Bonferroni's post-hoc tests showed CBD10 group had lower freezing time in day 8 and 15 (all p's < 0.05). Further testing at day 25, after extinction, showed CBD

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Control group - VEH + Shock group - STR + Shock group - CBD10 + Shock group Experiment 4: Effects of CBD and sertraline on fear memory retrieval (N = 8–10/group)	after re-exposure at days 4 to 7 and 9 to 14. Interventio n was also given at day 3, 8 and 15 to test the effect of absence.				group with lower freezing time ($p < 0.01$). - CBD and STR treatments did not significantly affect the acquisition of fear-associated memory when administered prior to foot shock. While Two-way RM ANOVA showed significant effect of treatment ($F[3, 39] = 50.58$, $P < 0.001$), time ($F[2.446, 95.38] = 102.8$, $P < 0.001$) and interaction between time x

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Control group - VEH + Shock group - STR + Shock group - CBD10 + Shock group Experiment 5: Effects of CBD and sertraline on fear memory reconsolidation (N = 8–10/group)					treatment (F[12, 156] = 6.347, P < 0.001) on freezing time, post hoc analyses indicated that PTSD model group was the one with significant higher freezing time compared to control. - Both CBD and STR showed decreased retrieval of fear associated memory. Two-way RM ANOVA of CBD and STR before retrieval showed significant effect of

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Control group - VEH + Shock group - STR + Shock group - CBD10 + Shock group - CBD10 (24 hours after exposure) + Shock group - Naïve + Shock group - Naïve CBD + Shock group					treatment (F [3, 34] = 103.9, P < 0.001), time ((F [3.218, 109.4] = 51.86, P < 0.001) and interaction between time x treatment (F [12, 136] = 17.56, P < 0.001) on freezing time. Bonferroni's post-hoc tests showed STR and CBD10 group had lower freezing time (Day 3, STR: P < 0.001, CBD: P = 0.04; Day 8, STR: P<0.001, CBD: P=0.002; Day 15, STR: P=0.009, CBD: P=0.03).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- Two-way RM ANOVA of daily administration of CBD and STR after freezing test showed significant effect of treatment ($F [3, 34] = 76.65$, $P < 0.001$), time ($F [3.309, 112.5] = 100.1$, $P < 0.001$) and interaction between time x treatment ($F [12, 136] = 9.777$, $P < 0.001$) on freezing time. Bonferroni's post-hoc tests showed CBD10 group had lower freezing

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							time in day 8 (P = 0.05) and 15 (P = 0.02). Thus, suggesting that CBD disrupted reconsolidation of fear associated memory.
Hudson et al. (2019)[110], Canada	Male Sprague Dawley rats.	Rats were randomly assigned into groups according to different experiment and counterbalan	Injectors/infusions were removed after 1 min and were done immediate ly before	Intra-vHipp (ventral hippocampus) microinfusions of: - CBD: 10 and 100 ng (from Tocris Bioscience; USA). Dissolved in ethanol cremophor and saline. The ratio by volume of	- Context-dependent fear conditioning. - Context-independent fear conditioning.	- Aversive memory (Fear associated memory).	- Co-administration with CBD prevented THC effect in increasing fear associated memory and drug associated memory through blockade of extracellular signal-regulated kinase (ERK) phosphorylation.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		ced within groups. - VEH group, N =11 - THC 10 group, N = 8 - THC 100 group, N = 9 - CBD 10 group, N = 7 - CBD 100 group, N = 8	cognitive testing.	1:1:18, ethanol:cremophor :saline was used. - THC: 10 and 100 ng (from Cayman Chemical; USA). Dissolved in cremophor and saline. The ratio by volume of 1:18, cremophor: saline was used. - U0126 (selective MEK1/MEK2 inhibitor): 1 μg (from Tocris	- Conditioned place preference (CPP).	- Drug-associated memory	Context-dependent fear conditioning: - One-way ANOVA showed significant main effect of group [F(5,45) = 3.09, p = 0.018]. Fisher's LSD Post-hoc comparisons showed THC 100 group had elevate freezing time compared to VEH (p = 0.003), CBD 100 (p = 0.038), THC 100 + CBD 100 group (p = 0.001). Thus, suggesting that co-administration with CBD

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- THC 100 + CBD 100 group, N = 8 - THC 100 + U0126 group, N = 9 - THC 100 + CBD 100 + EPA group, N = 10 - U0126 group, N = 8 - EPA group, N = 8		Bioscience; USA). Dissolved in DMSO and diluted in saline to achieve a 25% DMSO concentration. - EPA (ω-3 fatty acid eicosapentaenoic acid): 1 mM (from Tocris Bioscience; USA). Dissolved in cremophor and saline. The ratio by volume of 1:18,			diminished the increase fear associated memory induced by THC. - Further testing showed THC 100 + U0126 group had reduced freezing time compared to THC 100 group ($p = 0.034$). Thus, suggesting that blockade of MEK1-2 disrupt the potentiate effect of THC. - THC 100 + CBD 100 + EPA group showed increased freezing time

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
				cremophor: saline was used. - Vehicle solution of cremophor and saline (1:18) was used as control. - In all cases, the volume administered was 0.5 μl/hemisphere. Intraperitoneal injection of: - Morphine sulfate: 0.05 mg/kg.			compared to THC 100 + CBD 100 group [t(16) = -2.19, p = 0.043]. Thus, suggesting upregulation of pERK1–2 diminished the effect of THC and CBD in reducing fear associated memory. Context-independent fear conditioning: - Mixed-measures ANOVA showed significant effect of group group [F(3,28) = 13.36, p = 0.001], conditioned stimulus factor (F(1,28) = 24.67, p

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
				Dissolved in saline.			= 0.001) but no interaction between group x conditioned stimulus factor. Post-hoc comparisons showed THC 100 group had elevate freezing time to CS^- and CS^+ compared to VEH (p = 0.022; p =0.001), CBD 100 (p = 0.007; p = 0.001), THC 100 + CBD 100 group (p = 0.007; p = 0.001). Thus, suggesting that co-administration with CBD diminished the

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							potentiate effect from intra-vHipp THC. - Further testing showed THC 100 + U0126 group had reduced freezing time to CS^+ compared to THC 100 group (p = 0.004) but not to CS^-. Thus, suggesting that inhibition of pERK1–2 disrupt the effect of THC. - THC 100 + CBD 100 + EPA group showed increased freezing time to CS^- and CS^+ compared to THC 100 + CBD 100

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							group (p = 0.026; p = 0.001). Thus, suggesting co-administration with CBD counteract the effect of THC through inhibition of vHipp pERK1–2 activation. Conditioned place preference (CPP): - Mixed-measures ANOVA showed significant interaction between group x context factor [F(3,24) = 3.38, p = 0.035] but no effect of group and context factor. Post-

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							hoc comparisons showed THC 100 group spent more time in morphine context compared to VEH (p = 0.035), CBD 100 (p = 0.028), THC 100 + CBD 100 group (p = 0.007). Thus, suggesting that co-administration with CBD counteracted the enhanced preference for morphine from THC. - Further testing showed THC 100 + U0126 group compared to VEH group did not differ in the time

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							spent in the morphine context. This suggested that THC's modulation of the reward process in response to morphine may occur through local pERK1-2 signaling. - VEH group showed increased time spent in the morphine context compared to THC 100 + CBD 100 + EPA group, suggesting that CBD counteract THC potentiation effect

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							through local pERK1–2 inhibition.
Kaplan et al. (2021)[97], USA	- Male and female C57BL/6J were bred together for offspring mice. - The mice modele	- 26 mice were assigned to treatment groups in a between-subjects experimental design. - Vehicle group, N = 13 (M:F = 8:5)	The total duration of treatment was 21 days.	Intraperitoneal injection of: - CBD: 20 mg/kg (isolated CBD with >98% purity from Cayman Chemical Company; Michigan, USA). Dissolved in a solution of 1:1:18, ethanol: cremophor: 0.9% saline.	- Barnes Maze.	- Spatial memory.	- CBD treatment improved the rate of learning in the Barnes Maze. Prolonged CBD exposure during adolescence did not have any negative effects on anxiety behavior or spatial memory - Three-way ANOVA showed significant interaction between the exposure condition x

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	d for develo pmenta l exposur e studies.	- CBD group, N = 13 (M:F = 8:5)		- Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 3 ml/kg body weight.			acquisition day for the latency to the escape box [$F(2,66) = 5.14$, $p < 0.01$] and the distance to the escape box [$F(2,66) = 3.60$, $p = 0.04$] - Tukey's post hoc showed that CBD group had a shorter mean latency and distance to the escape box on second training day ($p < 0.05$), suggesting faster rate of the spatial learning task.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- There was significant main effect of exposure condition on mean latency to the escape box [F(1,66) = 6.01, p = 0.02] and number of errors, [F(1,66) = 4.04, p < 0.05]. - Tukey's post hoc showed CBD group had shorter mean latency to the escape box and made fewer errors.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Khodadadi et al. (2021)[90], USA	- Mice carrying double transgenes of 5xFAD expressing APP and PSEN1 transgenes - The mice modele	- Mice were randomly assigned N = 6–10 per group in blind experimental conditions. - 5xFAD-Vehicle group, N = 6–10 - 5xFAD-CBD group, N = 6–10	The total duration of treatment was 2 weeks.	Intraperitoneal injection of: - CBD: 10 mg/kg (CBD isolate from Canabidiol Ltd.; Dublin, Ireland). Mixed in 2% Tween 80 and added with 0.9% NaCl. - Placebo group was administered similarly without addition of CBD.	- NORT.	- Object recognition memory.	- CBD treatment improved symptoms of AD and decrease cognitive decline. - CBD treatment improved cognitive function (Discrimination Index increased to 0.5 ± 0.9 from –0.2 ± 0.8, p = 0.04).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	d for AD.	- WT group, N = 6					
Kozela et al. (2019)[11][4], Israel and Poland	- Male Sprague - Dawley rats. - The rat modeled schizophrenia-like	- Rats were assigned into treatment groups. For acute administration of CBD - Vehicles only treated (V-V), N = 7 - KET-only treated (KET-V), N = 8	The total duration of treatment was 6 days for sub-chronic experiment.	Intraperitoneal injection of: - CBD: 1.875, 3.75, 7.5, 15, and 30 mg/kg (from THC Pharma GmbH; Frankfurt/Main, Germany). Dissolved in 10% aqueous solution of mixture of 1:1 ethanol.	- NORT.	- Object recognition memory.	- CBD treatment prevented (acute) and reversed (sub-chronic) KET-induced object recognition deficit. - Acute administration of CBD before KET injection prevented deficit [$F(6,56) = 24.25$; $p < 0.001$]. - The effect can be observed in a dose dependent manner

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	cognitive deficits using intraperitoneal administration of 20 mg/kg of ketamine (KET from 115.34 mg/ml	- KET+ CBD 1.875 mg/kg (KET-CBD), N = 9 - KET+ CBD 3.75 mg/kg (KET-CBD), N = 10 - KET+ CBD 7.5 mg/kg (KET-CBD), N = 10 - KET+ CBD 15 mg/kg (KET-CBD), N = 9		- In all cases, the volume administered was 1 ml/kg body weight.			where 7.5 and 30 mg/kg showed effectiveness. - Two-way mixed design ANOVA showed significant effects of CBD treatment [$F(3,33) = 61.561$; $p < 0.001$]. Thus, showed that CBD reversed KET-induced deficit.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	of an aqueous solution, Vetoquinol Biowet, Gorzow Wielkopolski, Poland diluted in distilled water).	- KET+ CBD 30 mg/kg (KET-CBD), N = 10 For sub-chronic administration of CBD - Vehicles only treated (V-V), N = 9 - 7.5 mg/kg CBD only treated (V-CBD) N = 9					

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- KET-only treated (KET-V), N = 10 - KET+ CBD 7.5 mg/kg (KET-CBD), N = 9					
Kreilaus et a. (2022)[91], Australia	- Female mice carrying heterozygous transgenes of TAU58/	- Mice were assigned into treatment groups. - WT-vehicle group, N = 11 - TAU58/2-vehicle group, N = 11	The total duration of treatment was 7 weeks.	Intraperitoneal injection of: - CBD: 100 mg/kg (from CAS: 13956-29-1 THC Pharma GmbH; Frankfurt/Main, Germany). Dissolved in 100%	- SPT. - CB.	- Social recognition memory. - Spatial memory.	- Chronic CBD treatment restored social and spatial reference memory deficit and decreased contextual fear-associated memory. - In SPT, single sample t-tests showed CBD treatment reversed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	2 expressing the human 0N4R tau isoform with the P301S mutation. - The mice modeled for	- WT-CBD group, N = 11 - TAU58/2 CBD group, N = 9		ethanol andTween 80, diluted with 0.9% NaCl with final volume of 5% ethanol and 5% Tween80. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 10 ml/kg body weight.	- Fear conditioning.	- Aversive memory (Fear associated memory).	deficit [Sociability of TAU58/2-CBD, t(8) = 4.32; p = 0.003; Social recognition memory of TAU58/2-CBD group, t(8) = 4.48; p = 0.002]. - In CB training, two-way ANOVA showed CBD restored spatial memory by reducing the overall latency to find reward [F(1,18) = 5.77; p = 0.027], and increasing the speed of trial compared [F(1,36) = 5.44; p = 0.025].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	Frontotemporal dementia (FTD) and AD.						- In CB probe trial, single sample t-tests showed CBD group having higher preference to reward zone compared to TAU58/2-vehicle group [TAU58/2-vehicle group $t(10) = 1.78$; $p = 0.11$; TAU58/2-CBD group $t(8) = 4.65$; $p = 0.002$] with two-way ANOVA comparison showing significant genotype x ‘reatment interaction [$F(1,35) = 5.2$; $p = 0.029$].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- In reversal probe trial, TAU58/2-vehicle group spent longer in the reward zone while CBD treated group did not. [TAU58/2-vehicle group t(10) = 2.63; p = 0.025; TAU58/2-CBD group t(7) = 1.30; p = 0.23]. - CBD treatment reduced freezing time [F(1,37) = 4.46; p = 0.042].
Kruk-Slomka and	- Male Swiss mice.	Mice were assigned into groups.	For acute administra	Intraperitoneal injection of:	- Passive avoidance	- Aversive memory (Fear	- CBD treatment at 30 mg/kg improved all phases of fear associated

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Biala (2021)[82], Poland	- The rat modeled Schizophrenia's pathology and cognition impairment using intraperitoneal injectio	Acute administration of CBD (N = 8-10): - VEH group - CBD 1 group - CBD 5 group - CBD 30 group Acute co-administration of CBD and	tion of CBD: - Memory acquisition: intervention was given 30 mins prior. - LTM consolidation: intervention was given	- CBD: 1, 5, and 30 mg/kg (from Tocris, USA). Suspended in 1% Tween 80 and 0.9% NaCl. - MK-801: 0.6 mg/kg (Tocris, Bristol, UK). Dissolved in 0.9% NaCl. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was	(PA) learning task.	associated memory).	memory where CBD at 1 or 5 mg/kg reduced memory impairment in the consolidation and retrieval stage. Acute administration of CBD: - For memory acquisition: one-way ANOVA showed effect of CBD doses on latency index [LI; $F(3.33) = 15.99$; $p < 0.0001$]. Post-hoc Tukey's test showed CBD at 30 mg/kg increased LI scores compared to VEH group

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	n of N-methyl-D-aspartate (NMDA) receptor antagonist, MK-801.	MK-801 (N = 8-9): - VEH-VEH group - VEH-MK-801 group - CBD1-VEH group - CBD5-VEH group - CBD1-MK-801 group	immediately after trial - Retrieval: intervention was given 30 minutes before retrieval. For co-administration of CBD and MK-801:	10 ml/kg body weight.			($p < 0.001$). Thus, suggesting that CBD treatment improved memory acquisition. - For consolidation: one-way ANOVA showed effect of CBD doses on LI [$F(3.31) = 6.105$; $p = 0.0025$]. Post-hoc Tukey's test showed CBD at 30 mg/kg increased LI scores compared to VEH group ($p < 0.05$). Thus, suggesting that CBD treatment improved memory consolidation.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD5-MK-801 group	- Memory acquisition : intervention was given 15 mins prior trial before MK-801 or VEH. - LTM consolidation: intervention was				- For memory retrieval: one-way ANOVA showed effect of CBD doses on LI [F (3.31) = 5.473; p = 0.0043]. Post-hoc Tukey's test showed CBD at 30 mg/kg increased LI scores compared to VEH group ($p < 0.01$). Thus, suggesting that CBD treatment improved memory retrieval. Acute co-administration of CBD and MK-801:

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
			given 15 mins prior trial before MK-801 or VEH where test was 24 hours later. - Retrieval: intervention was given 24 hours after test and 15 mins				- For memory acquisition: two-way ANOVA showed significant effect of MK-801 on LI [$F(1.42) = 134.8$; $p < 0.0001$] and interaction [$F(2.42) = 3.784$; $p = 0.0308$] but no significant effect of pretreating with CBD [$F(2.42) = 3.207$; $p = 0.0505$]. Post-hoc Tukey's test showed MK-801 decrease LI scores compared to VEH group ($p < 0.001$) but CBD

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
			prior trial before MK-801 or VEH.				showed no effect against MK-801 ($p > 0.05$). - For memory consolidation: two-way ANOVA showed significant effect of MK-801 on LI [$F(1.44) = 13,77$; $p = 0.0006$] and interaction [$F(2.44) = 4.643$; $p = 0.0148$] but no significant effect of pretreating with CBD [$F(2.44) = 2.571$; $p = 0.0879$]. Post-hoc Tukey's test showed MK-801 decrease LI scores

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							compared to VEH group ($p < 0.001$) and that CBD (1 and 5 mg/kg) showed effect against MK-801 ($p < 0.05$). - For memory retrieval: two-way ANOVA showed significant effect of MK-801 on LI [F(1.42) = 20,27; p < 0,0001], interaction [F(2.42) = 6.581; p = 0.033] and effect of pretreating with CBD [F(2.42) = 13.19; p < 0.0001]. Post-hoc Tukey's test showed MK-801

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							decrease LI scores compared to VEH group ($p < 0.001$) and that CBD (1 and 5 mg/kg) showed effect against MK-801 ($p < 0.001$).
Ledesma et al. (2021)[83], Spain	- Male C57BL/6 J mice.	Mice were assigned into groups. Experiment 1: effects of CBD on CPP acquisition.	Exp 1. Intervention was given prior conditioning. Exp 2. Intervention was	Intraperitoneal injection of: - CBD: 30, 60 and 120 mg/kg (from THC Pharm GmbH; Germany). Dissolved in vehicle solution of saline and 4% of	- Cocaine-induced CPP. - NORT.	- Drug-associated memory. - Object recognition memory.	- CBD treatment at 30 and 60 mg/kg prevented reinstatement of CPP while at 120 mg/kg improved memory deficits induced by cocaine withdrawal. However, there was no effect on acquisition,

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 0 + Coc group, N = 12 - CBD 30 + Coc group, N = 10 - CBD 60 + Coc group, N = 12 - CBD 30 + Sal group, N = 11	given post conditioning and 60 mins before test. Exp 3. Intervention was given 60 mins before extinction. Exp. 4 Interventio	dimethyl sulfoxide (DMSO). - Cocaine hydrochloride: 5, 10, 15, 20 and 25 mg/kg. Dissolved in 0.9% NaCl.			expression or extinction of cocaine-induced CPP. Experiment 1: effects of CBD on CPP acquisition. - CBD treatment had no effect on acquisition. - ANOVA showed significant effects on Days [$F(1, 50) = 10.67$; $p < 0.01$], Treatment [$F(4, 50) = 3.65$; $p < 0.05$] and Days x Treatment interaction [$F(4, 50) = 9.01$; $p < 0.01$]. Post-hoc tests showed cocaine treated mice spent more

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 60 + Sal group, N = 10 Experiment 2: effects of CBD on the CPP expression. - Coc + CBD 0 group, N = 10 - Coc + CBD 30 group, N = 12	n was given before Coc/Sal administration Exp. 5 – 7 Intervention was given during withdrawal period and 60 mins				time in drug-paired context during post-conditioning compared (CBD 0 + Coc group, $p < 0.001$; CBD 30 + Coc group, $p < 0.05$; CBD 60 + Coc group, $p < 0.001$). While CBD + Sal groups showed no significant change in time spent in the compartment. Experiment 2: effects of CBD on CPP expression. - CBD treatment had no effect on CPP expression.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Coc + CBD 60 group, N = 10 Experiment 3: effects of CBD on CPP during extinction and reinstatement. - CBD 0 + RCoc group, N = 8	before test.				- ANOVA showed significant effects on Days [F (1, 29) = 33.8; p < 0.01] but not on Treatment nor interaction. Post-hoc tests showed cocaine treated mice spent more time in drug-paired context during post-conditioning (Coc + CBD 0 group, p < 0.01; Coc + CBD 30 group, p < 0.01; Coc + CBD 60 group, p < 0.05).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 30 + RCoc group, N = 10 - CBD 60 + RCoc group, N = 9 Experiment 4: effects of CBD on locomotor stimulation. - CBD 0 + Coc group, N = 12					Experiment 3: effects of CBD on CPP during extinction and reinstatement. - ANOVA showed significant effects on Days [$F(1, 24) = 58$; $p < 0.001$] but not on Treatment nor interaction with only CBD 0 + RCoc group showed reinstatement of CPP ($p < 0.05$). Thus, suggesting CBD had blocking effect on reinstatement.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 30 + Coc group, N = 12 - CBD 60 + Coc group, N = 11 - CBD 0 + Sal group, N = 12 - CBD 30 + Sal group, N = 12 - CBD 60 + Sal group, N = 12					Experiment 4: effects of CBD on locomotor stimulation. - Pre-treatment with CBD at 30 mg/kg reduced the locomotor stimulating effects of Coc. Experiment 5: effects of CBD on the open field after withdrawal. - All the groups showed similar activities. Experiment 6: effects of CBD on object recognition after withdrawal.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		Experiment 5: effects of CBD on the open field after withdrawal (N = 12–15/group). - Sal + CBD 0 group - Sal + CBD 60 group - Sal + CBD 120 group - Coc + CBD 0 group					- CBD treatment at 120 mg/kg prior to exposure showed improvement in memory impairment induced by withdrawal. - ANOVA showed significant effects on treatment [$F(1, 82) = 108.48$, $p < 0.01$] and Treatment x CBD interaction [$F(2, 82) = 13.51$, $p < 0.01$]. Post-hoc tests showed Coc + CBD 120 group had significantly higher DI than both Coc + CBD 0

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Coc + CBD 60 group - Coc + CBD 120 group Experiment 6: effects of CBD on the object recognition test after withdrawal (N = 12–15/group). - Sal + CBD 0 group					and Coc + CBD 60 groups ($p < 0.01$). Experiment 7: effects of CBD on the Tail Suspension Test after withdrawal. - CBD treatment showed no effect on depressive-like symptoms.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Sal + CBD 60 group - Sal + CBD 120 group - Coc + CBD 0 group - Coc + CBD 60 group - Coc + CBD 120 group Experiment 7: effects of CBD on the Tail Suspension Test after					

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		withdrawal (N = 12–15/group). - Sal + CBD 0 group - Sal + CBD 60 group - Sal + CBD 120 group - Coc + CBD 0 group - Coc + CBD 60 group - Coc + CBD 120 group					

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Long et al. (2010)[92], Australia	- Male C57BL/6JArc mice. - Drug-induced psychotomimetic behaviour were done with non-	- Mice were randomly assigned and counterbalances across groups, N = 8–10. Per group. - Vehicle group - Δ^9-THC 0.3 mg/kg group - Δ^9-THC 1 mg/kg group - Δ^9-THC 3 mg/kg group	The total duration of treatment was 21 days for chronic experiment.	Intraperitoneal injection of: - CBD: 1, 5, 10 and 50 mg/kg (from THC Pharma GmbH; Frankfurt/Main, Germany). Suspended in a 1:1:18 mixture of ethanol: Tween-80: saline. - Δ^9-THC: 0.3, 1, 3 and 10 mg/kg (from THC Pharma GmbH; Frankfurt/Main, Germany).	- Y-maze. - PA Test.	- Spatial memory. - Aversive memory (Fear associated memory).	- CBD treatment had no effect on spatial and aversive memory. There was no difference Y-maze tasks and PA test.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	competitive NMDA antagonist MK-801 and the catecholaminergic stimulant dexamphetamine (Dex).	- Δ^9-THC 10 mg/kg group - CBD 1 mg/kg group - CBD 5 mg/kg group - CBD 10 mg/kg group - CBD 50 mg/kg group		Suspended in a 1:1:18 mixture of ethanol: Tween-80: saline. - In all cases, the volume administered was 10 ml/kg body weight.			

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Meyer et al. (2021)[98], Brazil	- Male Wistar rats - The rat modeled Transient global cerebral ischemia (TGCI) induce	- Rats were randomly assigned into treatment groups. For 8-arm Aversive Radial Maze: - Sham + vehicle, N = 14 - Sham + CBD, N = 17 - TGCI + vehicle, N = 12	The total duration of treatment was 14 days.	Intraperitoneal injection of: - CBD: 10 mg/kg (from THC Pharma GmbH; Frankfurt/Main, Germany). Dissolved in 2% Tween 80 in sterile isotonic saline (vehicle).	- 8-arm Aversive Radial Maze (AvRM). - Object Location Test (OLT).	- Spatial memory. - Object recognition memory.	- CBD treatment reduced ischemia-induced memory deficits. - Analysis showed that both latency and number of errors significantly decreased in the TGCI + CDB group ($p < 0.0001–0.01$). - CBD treatment improved impairment in discrimination ability [student's t-test, $t_{26} = 2.60$, $p < 0.05$]. - One-way ANOVA showed significant

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	d by four-vessel occlusion (4-VO) model.	- TGCI+CBD, N = 13 For Object Location Test: - Sham + vehicle, N = 21 - TGCI + vehicle, N = 20 - TGCI+CBD, N = 21					differences in discrimination index among groups [$F_{2, 46}$ = 4.67, $p < 0.05$] where Duncan's post hoc analyses showed TGCI + vehicle group having lower score than the sham + vehicle group ($p < 0.05$). But TGCI + CBD group showed significant decrease in spatial memory impairment ($p = 0.05$). - TGCI + CBD group showed discrimination

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							score that was significant [Student's t-test, t_{26} = 2.87, $p < 0.01$], showing that CBD treatment prevented TGCI-induced spatial memory deficits.
Montaya et al. (2020)[84], USA	Female C57BL/6 mice.	Mice were assigned in different conditioning group. Paired-conditioned group:	Intervention was given 30 mins (CBD) and 60 mins (CIT) prior fear conditioning.	Intraperitoneal injection of: - CBD: 10 mg/kg. Dissolved in 2% ethanol, 2% Tween 80 and 0.9% NaCl. - Citalopram (CIT; SSRI): 10 mg/kg. Dissolved in 2%	- Fear Conditioning.	- Aversive memory (Fear associated memory).	- CBD treatment showed reduced contextual and generalized fear memory while extinction of fear was enhanced. CBD treatment had no effect on auditory cue-associated fear memory.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH-Pair group (N = 12) - CBD-Pair group (N = 12) - CIT-Pair group (N = 12) Unpaired-conditioned group: - VEH-UP group (N = 12)		ethanol, 2% Tween 80 and 0.9% NaCl. - Vehicle group was administered similarly without addition of CBD or CIT.			CBD and CIT showed no effect on auditory cue-associated fear memory: - There was no significant difference in freezing behavior between different conditioning and treatment groups compared to control. Thus, suggesting that both CBD and CIT showed no effect on auditory cue-associated fear memory. CBD reduced contextual fear memory but not CIT:

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD-UP group (N = 12) - CIT-UP group (N = 12) Non-conditioned group: - VEH-NC group (N = 12) - CBD-NC group (N = 12)					- CBD treated groups showed reduced freezing time by 11% compared to VEH groups ($p < 0.05$). But CIT treated group showed similar results. CBD and CIT reduced generalized fear memory: - CBD treated groups showed reduction in freezing time by 20% and CIT treated groups showed reduction by 22% compared to VEH groups (both: $p < 0.05$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CIT-NC group (N = 12)					CBD and CIT showed enhanced extinction: - For auditory cued memory extinction, both CBD and CIT treated groups showed significant reduction in freezing time (both: $p < 0.05$). - For contextual memory extinction, CBD treated groups showed significantly lower freezing time compared to control groups ($p = 0.001$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- For generalized fear memory extinction, CBD treated group showed reduced freezing time ($p < 0.05$). Effects of estrous cycle on fear memory: - There was no effect of estrous cycle phase on fear memory or extinction.
Murkar et al. (2015)[11]	- Male Sprague -Dawley rats.	Rats were randomly assigned into different	Intervention was given immediate	Oral administration of: - CBD: 50 mg/kg (extracted from	- Fear Conditioning.	- Aversive memory (Fear	- CBD treatment reduced fear memory reconsolidation in which the effect lasted for 7

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
[1], Canada		experiment groups (N = 7–10/group). For Experiment 1 and 2: - 50 THC + 21.5 BM group - 50 CBD + 21.5 BM group - 5 THC + 2 BM group	ly after memory retrieval.	Strawberry Kush, *Cannabis indica* and *Cannabis sativa* hybrid; University of Ottawa, Canada). - THC: 5 and 50 mg/kg (extracted from Strawberry Kush ; University of Ottawa, Canada). - Plant background material (BM): 2, 21.5, 24 and 43 mg/kg (extracted		associated memory).	days. THC combined with CBD or plant BM reduced reconsolidation of fear memory but not when given as monotherapy. Plant BM reduced fear memory reconsolidation alone and in combination with THC and CBD. Experiment 1: Effects of CBD, THC and plant BM on short-term fear memory reconsolidation. - Mixed measure ANOVA showed significant main

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- 50 THC + 50 CBD + 43 BM group - 50 CBD + 5 THC + 24 BM group - 43 BM group - VEH group For Experiments 3, 4 and 5: - 5 THC group - 50 CBD group		from Strawberry Kush containing less than 3 ± 0.5% THC and less than 0.6% of CBD; University of Ottawa, Canada). Total amount of compounds contained 30% of BM and 70% cannabinoids.			effect of treatment on freezing time [$F(6,53) = 5.509$, $p < 0.001$]. Further analyses showed 5 THC + 2 BM group, 50 THC + 50 CBD + 43 BM group, 50 CBD + 21.5 BM group and 43 BM group showed significant reduction in freezing time (all p's < 0.05). However, 50 THC + 21.5 BM group and 50 CBD + 5 THC + 24 BM group did not ($p > 0.05$). Experiment 2: Effects of CBD, THC and plant BM

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- 50 THC + 50 CBD group - 43 BM group - VEH group					on long-term fear memory reconsolidation. - Mixed measure ANOVA showed significant main effect of treatment on freezing time [$F(6,53) = 4.974$, $p < 0.001$]. Further analyses showed 5 THC + 2 BM group, 50 THC + 50 CBD + 43 BM group, 50 CBD + 5 THC + 24 BM group, 50 CBD + 21.5 BM group and 43 BM group showed significant reduction in freezing time (all p's < 0.01).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							However, 50 THC + 21.5 BM group did not ($p > 0.05$). Experiment 3: Effects of CBD, THC without plant BM on short-term fear memory reconsolidation. - Mixed measure ANOVA showed significant main effect of treatment on freezing time [$F(4,40) = 7.517$, $p < 0.001$]. Further analyses showed 43 BM group, 50 THC + 50 CBD group, 50 CBD group showed significant

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							reduction in freezing time (all p's < 0.05). However, 5 THC group did not (p > 0.05). Experiment 4: Effects of CBD, THC without plant BM on long-term fear memory reconsolidation. - Mixed measure ANOVA showed significant main effect of treatment on freezing time [F(4,40) = 6.670, p < 0.001]. Further analyses showed 43 BM group, 50 THC + 50 CBD group, 50 CBD group

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							showed significant reduction in freezing time (all p's < 0.05). However, 5 THC group did not (p > 0.05). Experiment 5: Effects of CBD, THC and plant BM on memory recall. - There was no significant main effects of group [F(4,40) = 0.919, p > 0.05].
Norris et al. (2016)[11]	Male Sprague –	Rats were assigned into different	Injections/infusions were	Infused intracranially into intra-shell region of	- Olfactory Fear	- Aversive memory (Fear	- Intra-NASh CBD treatment disrupted formation of conditioned

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
[2], Canada	Dawley rats.	treatment and experimental groups. For olfactory fear conditioning: - VEH group, N = 6 - CBD 1 group, N = 7 - CBD 10 group, N = 8	removed after 1 min and were done immediately before test.	the mesolimbic nucleus accumbens (NASh): - CBD: 1, 10 and 100 ng/0.5 μl (from Tocris, USA). Dissolved in DMSO and diluted in PBS to form 1% DMSO in PBS vehicle (VEH) solution. - RIM: 50 and 500 ng/0.5 μl (SR141716A; CB1R antagonist; Tocris, USA). Dissolved in	Conditioning. - Footshock Sensitivity Tests.	associated memory).	freezing behaviors in a dose dependent manner. This occurred through a mechanism dependent on 5-HT1A and GABAergic transmission substrates, acting via the NASh and VTA neuronal pathway. - ANOVA of % freezing time showed significant main effect of group [F(7,287) = 5.75, p = 0.0001] with post-hoc analyses showing treatment with higher doses of CBD (10 and

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 100 group, N = 6 - CBD 100 + NAD299 10 group, N = 7 - CBD 100 + NAD299 100 group, N = 6 - CBD 100 + α-flu 100 group, N = 6 - CBD 100 + α-flu 1000 group, N = 8		DMSO and diluted in PBS to form 1% DMSO in PBS vehicle (VEH) solution. - NAD 299: 10, 100 and 500 ng/0.5 μl (5-HT_{1A} receptor antagonist; Tocris, USA). Dissolved in DMSO and diluted in PBS to form 1% DMSO in PBS vehicle (VEH) solution.			100 ng) reduced freezing response to CS+ compared to control (both p's < 0.001). - Co-administration of CBD and NAD 299: ANOVA of % freezing time showed significant main effect of treatment group [$F(1,37) = 13.9$; $p < 0.001$] with post-hoc analyses showing co-administration of CBD with NAD 299 (10 and 100 ng) significantly increased freezing

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 100 + RIM 50 group, N = 9 - CBD 100 + RIM 500 group, N = 10 - NAD299 100 group, N = 8 - α-flu 1000 group, N = 8 For Footshock Sensitivity Test:		- α-flu: 100 and 1000 ng/0.5 μl (α-flupenthixol; DA receptor antagonist; Tocris; USA). Dissolved in saline. - Bicuculline: 50 ng/0.5 μl ($GABA_A$ antagonist; Tocris; USA). Dissolved in saline. - Saclofen: 50 ng/0.5 μl ($GABA_B$ antagonist; Tocris;			response to CS+ compared to control (both p's < 0.01). Thus, suggesting 5-HT_{1A} dependent mechanism in which blockade of 5-HT_{1A} counteracted CBD's effect. - Co-administration of CBD and α-flu: ANOVA of % freezing time showed significant main effect of treatment group [F(3,50) = 5.65; p < 0.001] with post-hoc analyses showing coadministration

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH group, N = 8 - CBD 100 group, N = 7 - α-flu 1000 group, N = 8 - NAD299 100 group, N = 8 For ventral tegmental area (VTA) recordings on DAergic and		USA). Dissolved in saline.			of CBD with α-flu (100 and 1000) showed no effect on associative freezing during exposure to CS+ ($p's > 0.05$). Thus, suggesting that blockade of DA receptor had no effect on fear memory acquisition. - Coadministration of CBD and RIM: ANOVA of % freezing time showed significant main effect of treatment group [$F(2,47) = 10.53$; $p < 0.001$] with post-hoc analyses

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		non-DAergic neuronal activity: - CBD 100 group, N = 15 For ventral VTA recordings on serotonergic/ dopaminergic antagonists activity: - VEH group, N = 10					showing coadministration of CBD with RIM (50 and 500 ng) showed no reversal of CBD's disruption on fear memory acquisition (p's > 0.05). - For footshock sensitivity tests: ANOVA showed no effect on freezing behavior [F(3,29) = 1.10; p > 0.05], total distanced traveled [F(3,29) = 0.92; p > 0.05] and average number of jumping

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 100 group, N = 15 - CBD 100 + NAD299 100 group, N = 10 - CBD 100 + α-flu 1000 group, N = 9 For NASh–VTA Functional Disconnection Studies:					events [F(3,29) = 0.25; p > 0.05]. - Analysis of VTA recordings on DAergic neuronal activity showed that 60% of DA neurons had decreased activity and CBD increased neuronal activity. - Analysis of VTA recordings on GABAergic neuronal activity showed that 40% of non-DA neurons had increased activity and CBD

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH + VEH group, N = 6 - VEH + CBD 100 group, N = 6 - Saclofen + Bicuculline + CBD 100 group, N = 6 - Saclofen + Bicuculline + VEH group, N = 6					increased neuronal activity. - VTA recordings of DAergic neuronal activity showed the following: ● Intra-NASh VEH showed 30% increased and 20% decreased neuronal activity. ● Intra-NASh CBD showed 60% decreased neuronal activity. ● Intra-NASh CBD + NAD 299 showed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							60% decreased neuronal activity. ● Intra-NASh CBD + α-flu showed 78% decreased neuronal activity. ● Comparison of activity rate of pre- and post-infusion showed -27% in CBD, +3% in CBD + NAD 299, and - 23% CBD + α-flu group.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- ANOVA of VTA DA neuron activity showed significant main effect of treatment [$F(3,43) = 3.57$, $p < 0.05$] with post-hoc analysis showing intra-NASh CBD and CBD + α-flu had decreased activity (p's < 0.05), while CBD + NAD 299 group had increased activity ($p < 0.05$). Thus, suggesting that coadministration with NAD 299 may reversed the reduction effect of CBD.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- Disconnecting the NASh-VTA pathway reversed the blocking effect of intra-NASh CBD on fear memory formation [$F(3,38) = 3.261$; $p \leq 0.05$]. Post-hoc analysis showed that administering $GABA_{A/B}$ antagonists in the VTA before intra-NASh CBD significantly increased freezing behaviors in response to the CS+ stimulus ($p < 0.05$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Osbourne et al. (2017)[117], Australia	- Offspring of Sprague-Dawley rats. - The rat modeled schizophrenia-like phenotype induce	Offspring were grouped as offspring of control (saline injection) or offspring of poly I:C. - CONT+VEH, N = 12 - CONT+CBD, N = 12 - POLY+VEH, N = 12 - POLY+CBD, N = 12	The total duration of treatment was 3 weeks.	Intraperitoneal injection of: - CBD: 10 mg/kg (from THC Pharma GmbH; Frankfurt/Main, Germany). Dissolved in 1:16 (v/v), Tween 80:saline. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume	- NORT. - Rewarded T-maze alternation test.	- Object recognition memory. - Spatial memory (reference and working memory).	- CBD treatment improved deficits in recognition and working memory as well as social interaction in rat model. - In NORT, CBD treatment significantly improved discrimination ratio of poly I:C offspring (POLY+CBD vs POLY+VEH, p = 0.003). But there was no significant difference between CONT+VEH and CONT+CBD group (p = 0.205).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	d by polyino sinic-polycyti dilic acid (poly I:C) injectio n (4 mg/kg).			administered was 5 ml/kg body weight.			- In Rewarded T-Maze Alternation Test, CBD treatment improved working memory deficits in poly I:C offspring (POLY+VEH vs POLY+CBD, p = 0.009) and restored performance to control levels (POLY+CBD vs CONT+VEH, p = 0.561). - However, CBD treatment did not affect working memory performance of control groups (CONT+VEH vs

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							CONT+CBD, p = 0.686) showing no effect in healthy rats.
Osbourne et al. (2019)[118], Australia	- Offspring of Sprague-Dawley rats. - The rat modeled maternal immun	Offspring were grouped as control (saline injection) or poly I:C. - CONT+VEH, N = 12 - CONT+CBD, N = 12 - POLY+VEH, N = 12	The total duration of treatment was 3 weeks.	Intraperitoneal injection of: - CBD: 10 mg/kg (from CAS: 13956-29-1, THC Pharma GmbH; Frankfurt/Main, Germany). Dissolved in 1:16 (v/v), Tween 80:saline. - Vehicle group was administered	- NORT. - Rewarded T-maze alternation test.	- Object recognition memory - Spatial memory (reference and working memory)	- CBD treatment improved deficits in recognition memory and social interaction in rat model, while there was no difference in working memory. - In NORT, CBD treatment improved discrimination index in poly I:C offspring (POLY+VEH vs POLY+CBD, p = 0.036) and restored

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	e activation (MIA) to produce offspring with schizophrenia-like symptoms induced by	- POLY+CBD, N = 12		similarly without addition of CBD. - In all cases, the volume administered was 5 ml/kg body weight.			performance to control level (POLY+CBD vs CONT+VEH, p = 0.578). - However, CBD treatment showed no effect in NORT of control groups (CONT+VEH vs CONT+CBD, p = 0.280). - Mann-Whitney tests showed no significant difference in Rewarded T-Maze Alternation Test (CONT + VEH vs. POLY+VEH, p = 0.950; POLY+VEH vs. POLY+CBD, p = 0.724;

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	poly I:Cinjection (4 mg/kg).						CONT + VEH vs. CONT + CBD, p = 0.519).
Patra et al. (2018)[99], UK	- Wistar rat. - The rat modeled Status Epilepticus-Spontaneous	Rats were assigned into treatment groups. - Naive vehicle-treated, N = 15 - Epileptic vehicle-	- CBD was administered for 10 weeks.	Oral administration of: - CBD: 200 mg/kg (from GW Pharmaceuticals Ltd.; Cambridge, UK) and vehicle (3.5% Kolliphor® HS, Sigma-Aldrich, Poole, UK). All drugs were	A hole-board apparatus.	Spatial learning and memory. (Reference-memory error; RME and Working-memory	- Chronic CBD treatment improved spatial learning and memory in rat model for RISE-SRS of TLE. - One-way ANOVA showed significant difference in RMEs [$F_{2, 42} = 15.06$, $p < 0.0001$] where Holm-Sidak post hoc test showed naïve

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	Recurrent Seizure (RISE-SRS) of chronic temporal lobe epilepsy (TLE) induced using lithium-low dose pilocar	treated, N = 15 - Epileptic CBD-treated groups, N = 15 N = 15 mean trial/group		administered in drinking water		error; WME)	vehicle ($p < 0.0001$) and CBD group ($p < 0.05$) made significant lower errors. - However, CBD group made significantly more RMEs compared to the naïve vehicle group ($p < 0.05$) showing that CBD failed to completely restore reference memory. - One-way ANOVA showed significant difference in WMEs [$F_{2, 42} = 35.72$, $p < 0.0001$]

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	pine model.						where Holm-Sidak post hoc test showed chronic CBD group made fewer errors ($p < 0.0001$). - Additionally, working memory in epileptic CBD group was superior to the naïve vehicle group ($p < 0.05$).
Raymundi et al. (2019)[10][5], Brazil	- Male Wistar rats.	Rats were assigned into different treatment and	Exp.1A-1B: Intervention was given immediate	Intraperitoneal injection of: - CBD: 10 mg/kg (from Phytoplant, Spain). Dissolved in NaCl 0.9%	- Fear Conditioning.	- Aversive memory (Fear associated memory).	- CBD treatment impaired memory consolidation when administered immediately or 1 hour after conditioning. Additionally, systematic

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		experimental groups. Experiment 1A: intra-DH CBD effects on contextual fear memory consolidation. - VEH group, N = 7 - CBD 10 group, N = 7 - CBD 30 group, N = 7	ly after paring. Exp.2A-2B: Intervention was given immediately 1 hour after paring. Exp. 3: Intervention was given immediate	containing 5% of Tween 80. - In all cases, the volume administered was 1.0 ml/kg body weight. - Vehicle group was administered similarly using NaCl 0.9% containing 5% of Tween 80 Infused intracranially into the DH (Dorsal			CBD treatment reduced the expression of Arc protein in the DH. - CBD's effects on memory consolidation were disrupted by CB1 and CB2 receptor antagonists, partially disrupted by 5-HT1A and A2A antagonists, and unaffected by a PPARγ receptor antagonist. However, when administered 1 hour after conditioning, the PPARγ receptor antagonist

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		Experiment 1B: systemic CBD effects on DH's Arc protein expression. - VEH group, N = 8 - CBD 10 group, N =10 - Naïve group, N = 8 Experiment 2A: intra-DH CBD effects on	ly 3 hours after paring. Exp. 4: Interventio n was given immediate ly after paring. Exp. 5: Interventio n was given 1 hour	Hippocampus) of interest: - CBD: 10 or 30 pmol (from Phytoplant, Spain). Dissolved in NaCl 0.9% containing 5% of Tween 80. - AM251 (CB1 receptor antagonist): 0.5 nmol (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80.			prevented CBD's effect. Inhibiting FAAH impaired memory consolidation immediately after conditioning but not at 1 hour. Experiment 1A: intra-DH CBD impaired contextual fear memory consolidation. - One-way RM ANOVA showed significant main effects of treatment but no interaction between treatment x re-exposure. Post-hoc analyses

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		contextual fear memory consolidation at 1 hour. - VEH group, N = 11 - CBD 30 group, N = 9 Experiment 1B: systemic CBD effects on DH's Arc protein expression at 1 hour.	immediately after paring. Exp. 6A: Intervention was given immediately after paring. Exp. 6B: Intervention was given immediate	- AM630 (CB2 receptor antagonist): 0.1 nmol (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80. - ZM241385 (A_{2A} receptor antagonist): 10 nM (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80. - URB597 (FAAH inhibitor): 0.1 μg			showed CBD 30 group had less freezing time ($p < 0.05$). Experiment 1B: systemic CBD reduced DH's Arc protein expression. - One-way ANOVA showed significant main effects of treatment groups on Arc protein expression. Post-hoc analyses showed CBD 30 group had reduced expression ($p < 0.05$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH group, N = 9 - CBD 10 group, N =11 - Naïve group, N = 7 Experiment 3: intra-DH CBD effects on contextual fear memory consolidation at 3 hours. - VEH group, N = 7	ly 1 hour after paring.	(Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80. - WAY100635 (5-HT_{1A} receptor antagonist): 0.14 nmol (Sigma-Aldrich, USA). Dissolved in NaCl 0.9%. - GW9662 (PPARγ receptor antagonist): 32 pmol (Sigma-Aldrich, USA).			Experiment 2A: intra-DH CBD impaired contextual fear memory consolidation when administered at 1 hour. - One-way RM ANOVA showed significant main effects of treatment but no interaction between treatment x re-exposure. Post-hoc analyses showed CBD 30 group had less freezing time ($p < 0.05$). Experiment 2B: systemic CBD reduced DH's Arc

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 30 group, N = 7 Experiment 4: intra-DH CBD effects on consolidation and different types of receptors. - VEH-VEH group, N = 9 - VEH-CBD group, N = 11 - AM251-VEH group, N = 10		Dissolved in NaCl 0.9% containing 5.0% DMSO. - In all cases, the volume administered was 0.5 μl/hemisphere. - Vehicle group was administered similarly using NaCl 0.9% containing 5% of Tween 80			protein expression when administered at 1 hour. - One-way ANOVA showed significant main effects of treatment groups on Arc protein expression. Post-hoc analyses showed CBD 30 group had reduced expression ($p < 0.05$). Experiment 3: intra-DH CBD had no effect on contextual fear memory consolidation at 3 hours. - One-way RM ANOVA showed no significant

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- AM251-CBD group, N = 8 - AM630-VEH group, N = 9 - AM630-CBD group, N = 9 - WAY-VEH group, N = 10 - WAY-CBD group, N = 10 - ZM-VEH group, N = 7 - ZM-CBD group, N = 8 - GW-VEH group, N = 10					main effects of treatment, exposure and interaction between treatment x re-exposure. Thus, suggesting the effect of window period. Experiment 4: intra-DH CBD effects on contextual fear memory consolidation was dependent to CB1 and CB2 receptors. - Two-way ANOVA showed significant effects of the interaction between pretreatment x

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- GW-CBD group, N = 10 Experiment 5: intra-DH CBD effects consolidation and different types of receptors at 1 hour. - VEH-VEH group, N = 8 - VEH-CBD group, N = 8 - AM251-VEH group, N = 8					treatment on freezing time. Post-hoc analyses showed AM251-CBD and AM630-CBD groups had similar freezing time to control group and higher freezing time compared to VEH-CBD group ($p < 0.05$). VEH-CBD and GW9662-CBD showed less freezing time compared to control ($p's < 0.05$). WAY100635-CBD, ZM241385-CBD, and GW9662-CBD groups showed similar freezing

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- AM251-CBD group, N = 10 - AM630-VEH group, N = 7 - AM630-CBD group, N = 9 - WAY-VEH group, N = 8 - WAY-CBD group, N = 9 - ZM-VEH group, N = 7 - ZM-CBD group, N = 9 - GW-VEH group, N = 10					time to VEH-CBD group. Thus, suggesting that the effect of CBD was through the activation of CB1 and CB2 receptors. Experiment 5: intra-DH CBD effects on contextual fear memory consolidation was dependent on activation of PPARγ receptors. - Two-way ANOVA showed significant effects of the interaction between pretreatment x treatment on freezing

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- GW-CBD group, N = 11 Experiment 6A: intra-DH URB597 effects on contextual fear memory consolidation . - VEH group, N = 9 - URB597 group, N =10 Experiment 6B: intra-DH					time. GW9662-CBD group showed increased freezing times ($p < 0.05$). VEH-CBD group showed less freezing time compared to control ($p < 0.05$) and showed similar freezing time to AM251-CBD, AM630-CBD, WAY100635-CBD, and ZM241385-CBD groups. Thus, suggesting that the effect of CBD was through PPARγ receptor activation.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		URB597 effects on contextual fear memory consolidation at 1 hour. - VEH group, N = 9 - URB597 group, N =10					Experiment 6A–1B: immediate administration of intra-DH URB597 impaired contextual fear memory consolidation. - Unpaired Student's t test showed significant effects of treatment where URB597 group showed less freezing time than control. However, the effect was not significant at 1 hour after conditioning.
Razavi et al.	- Male albino	62 mice were randomly	The total duration	Intracerebroventricular injection of:	- Spontaneou	- Spatial memory.	- CBD treatment improved spatial

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
(2019)[10][0], Iran	Wistar rats. - The rat modeled METH-induced memory impairment by subcutaneous	assigned into groups. - METH group - CBD 32 nmol group - CBD 160nmol group - Sham group (free drug during abstinence period)	of treatment was 10 days during abstinence period.	- CBD: 32 and 160nmol - Vehicle group was administered similarly with solvent (DMSO 10%)	s alternation Y-Maze test. - NORT.	- Object recognition memory.	memory and reversed long-term METH induced memory deficit where higher dose (160 nmol) was found to be more effective. - One-way ANOVA followed by Dunnett's multiple comparison test show that CBD could improve the deficit of spatial memory, induced during abstinence period [$F(4, 37) = 7.12$; $p < 0.001$] where 160 nmol dose was more effective

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	injection of Methampheta mine (2 mg/kg).	- Vehicle (DMSO) control group					than 32 nmol [(F(2, 21) = 11.45; p < 0.001]. - One-way ANOVA followed by Dunnett's multiple comparisons showed that the preference index increased in both CBD group [F(4, 40) = 3.472; p < 0.005]. - One-way ANOVA followed by Dunnett's multiple comparisons showed a significant reduction in LTM in METH group compared

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							with CBD groups. (F [4,40] = 3.907; P = 0.0098). While only CBD at 160 nmol dose could improve LTM [F(2, 22) = 5.36; p < 0.025].
Rossignoli et al. (2017)[10][6], Brazil	- Male Wistar Rats.	Rats were assigned into different treatment groups. CBD infusion at 0 hour on % freezing:	Intervention was given immediately (0 h) or 5 h after conditioning.	Intra-PFC (prefrontal cortex) microinfusions of: - CBD: 2 μg/μl (from THC-Pharm; Germany). Dissolved in grape seed oil.	- Fear Conditioning.	- Aversive memory (Fear associated memory).	- Bilateral intra-PFC CBD treatment impaired contextual fear memory consolidation at 5 hours post-conditioning but not immediately after. This effect may be attributed to reduced dopamine levels and decreased

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH group, N = 10 - CBD group, N = 10 CBD infusion at 5 hours on % freezing: - VEH group, N = 16 - CBD group, N = 19		- Vehicle group was administered similarly without addition of CBD: grape seed oil 2 μg/μl. - In all cases, the volume administered was 0.2 μl/hemisphere.			expression of c-fos and zif-268 protein in the hippocampus, PFC, and thalamus, indicating diminished PFC influence on cortico-limbic circuits. - Intra-PFC CBD treatment impaired consolidation at 5 hours post conditioning by showing a 12% reduction in % freezing [two-way RM ANOVA; $F(2,66) = 3.328$; $p < 0.05$; treatment x time interaction; $p < 0.001$].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		CBD on 5-HT and 5-HIAA level: - VEH group, N = 5 - CBD group, N = 5 CBD on DOPAC/DA ratio: - VEH group, N = 5					While CBD treatment at 0 hour showed no significant difference in % freezing [two-way RM ANOVA; $F(1,36) = 0.278$; $p > 0.05$]. Thus, suggesting a window period of 3 to 6 hours. - Intra-PFC CBD treatment at 5 hours post conditioning decreased cortical DA released. T-test showed significant decreased in DOPAC/DA ratio by 38% ($p < 0.05$). While 5-HT

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD group, N = 6 CBD on immunopositive area for c-fos: - VEH group, N = 7-9 - CBD group, N = 7-9 CBD on area for zif-268:					and 5-HIAA levels were not affected ($p > 0.05$). - T-tests showed CBD treatment had decreased the c-fos protein expression at PL of the mPFC, midline thalamic structures and hippocampal regions ($p < 0.05$) and zif-268 protein expression at midline thalamus and hippocampal structures ($p < 0.05$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH group, N = 4-7 - CBD group, N = 4-8					
Shallcross et al. (2019)[113], USA	- Male Sprague-Dawley rats.	Rats were assigned into different treatment and experiment groups. Experiment 1:	Intervention was given 20 mins before each session.	Intraperitoneal injection of: - CBD: 5 mg/kg (NIDA controlled substances program, RTI, Research Triangle; USA). Dissolved in 100% ethanol, Cremophor, and	- Fear conditioning (Contextual Fear Extinction).	- Aversive memory (Fear associated memory).	- CBD treatment had no effect on freezing time but reduced anxiety in susceptible rats. It also decreased unconditioned fear but did not affect conditioned fear. - CDPBB (mGlu5 positive allosteric modulator)

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Sus-Veh group, N = 7 - Sus-CDPP group, N = 7 Experiment 2: - Sus-Veh group, N = 8 - Sus-CDPP group, N = 8 - Sus-CBD group, N = 8 - Res-Veh group, N = 8		0.9% NaCl to 5 mg/ml. Subcutaneous injection of: - CDPPB (3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)-benzamide): 30 mg/kg (from Abcam Biochemical; USA). Suspended in 10% Tween 80 and phosphate-buffered saline to 30 mg/ml.			treatment reduced freezing time but had no effect on anxiety in susceptible rats. This indicates that enhancing mGlu5 signaling in stress-prone rats may promote resistance to fear memory extinction. Experiment 1 –Effects of CDPPB on Extinction and Fos Protein Expression. - Two-way RM ANOVA on freezing behavior showed main effect of treatment [F(1,11) = 6.803, p =

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							0.024], days [F(2,22) = 3.905, p = 0.035] and interaction between Treatment × Day [F(2,22) = 5.134, p = 0.015]. Post-hoc test showed CDPPB treated group had less freezing time on day 2 (p < 0.05). - CDPPB treated group showed increased Fos expression in the prelimbic cortex [t(10) = 2.80, p = 0.02], infralimbic cortex [t(10) = 3.03, p = 0.01] and trend

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							in basal lateral amygdala (p = 0.054). Experiment 2 –Effects of CDPPB and CBD on Anxiety and Extinction. - One-way ANOVA showed differences in time spent in the dark [F(3,27) = 4.686, p = 0.0092]. Post-hoc tests showed susceptible CBD treated group spent less time in the dark box (p = 0.023) but susceptible CDPPB treated group did not (p = 0.692). Thus,

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							showing anxiolytic effect of CBD. - Two-way RM ANOVA showed main effect of freezing time on treatment groups in light-dark box test [F(2,20) = 4.106, p = 0.032] where both susceptible groups (vehicle and CBD) showed increased freezing.
Song et al. (2016)[12][3], UK	- Male Lister Hooded Rats.	Rats were assigned into different treatment	Intervention was given 30 min prior	Intraperitoneal injection of: - CBD: 10 mg/kg (from THC pharm,	- Fear Conditioning FC.	- Aversive memory (Fear	- CBD treatment reduced contextual fear memory expression during extinction and retention

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		and experimental group. Mild/weak conditioning (N = 6–8/group): - VEH-No Ext group - VEH-Ext group - CBD-No Ext group	to extinction.	Germany). Dissolved in DMSO and diluted in saline to a final vehicle solution of 20% DMSO with 0.1% Tween 80. - MK-801 (NMDA receptor antagonist): 0.1 mg/kg (Sigma, Bristol, UK). Dissolved in saline vehicle. - DCS (D-cycloserine; NMDA		associated memory).	tests in response to strong fear conditioning. However, it impaired extinction and increased freezing expression for weaker conditioning. DCS treatment enhanced extinction for strong conditioning but had no effect on weaker conditioning. MK-801 treatment increased freezing behavior for both strong and weaker conditioning.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD-Ext group - Saline group - MK-801 group - DCS group Strong conditioning (N = 7–8/group): - VEH-No Ext group	receptor partial agonist): 15 mg/kg (Sigma, Bristol, UK). Dissolved in saline vehicle. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was 1 ml/kg body weight.				Mild/weak conditioning: - ANOVA showed significant main effect of extinction session [$F_{(1, 23)} = 14.1$, $p = 0.001$, $\eta^2_p = 0.38$, $BF_{10} = 37.7$] but no effect of CBD [$F_{(1, 23)} = 2.4$, $p = 0.14$, $\eta^2_p = 0.09$, $BF_{10} = 0.91$] and no interaction between CBD x extinction [$F_{(1, 23)} = 1.8$, $p = 0.19$, $\eta^2_p = 0.07$, $BF_{10} = 0.84$]. Planned comparison of extinction condition showed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH-Ext group - CBD-No Ext group - CBD-Ext group - Saline group - MK-801 group - DCS group					significant effect of CBD on elevate freezing [$F(1, 12) = 7.1$, $p = 0.02$, $\eta^2_p = 0.37$, $BF_{10} = 3.2$] but not on freezing during the extinction session [CBD: $F(1, 12) = 0.11$, $p = 0.74$, $\eta^2_p = 0.009$, $BF_{10} = 0.43$; CBD x bin (extinction sessions): $F(3,36) = 0.28$, $p = 0.84$, $\eta^2_p = 0.02$, $BF_{10} = 0.23$] and no difference for within-session extinction [$F(3,$

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							36) = 1.7, p = 0.19, η^2_p = 0.12, BF_{10} = 0.69]. - MK-801 impaired extinction while DCS had no effect. ANOVA showed significant difference between groups [$F(2, 17)$ = 14.6, p < 0.001, η^2_p = 0.63, BF_{10} = 125] with post-hoc analyses showing that MK-801 group had increased freezing time (p < 0.05). Strong conditioning:

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- ANOVA showed significant main effect of extinction session [$F_{(1, 24)} = 47.4$, $p < 0.001$, $\eta^2_p = 0.66$, $BF_{10} = 27.5 \times 10^3$] but no effect of CBD [$F_{(1, 24)} = 1.1$, $p = 0.30$, $\eta^2_p = 0.05$, $BF_{10} = 0.52$] and no interaction between CBD x extinction [$F_{(1, 24)} = 3.0$, $p = 0.10$, $\eta^2_p = 0.11$, $BF_{10} = 1.2$]. Planned comparison of extinction condition showed significant effect of CBD

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							on reducing freezing [$F(1, 12) = 7.3$, $p = 0.02$, $\eta^2_p = 0.38$, $BF10 = 3.3$] and acute impairment of freezing during extinction session [CBD: $F(1, 12) = 5.4$, $p = 0.04$, $\eta^2_p = 0.31$, $BF10 = 1.1$; CBD x bin: $F(3,36) = 1.9$, $p = 0.15$, $\eta^2_p = 0.16$, $BF10 = 0.90$]. There was also significant reduction in freezing throughout extinction session [$F(3, 36) = 5.2$, $p = 0.004$, $\eta^2_p = 0.30$, $BF10$

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							= 18.3]. Thus, suggesting that CBD enhanced extinction with stronger conditioning of fear. - DCS treatment increased extinction while MK-801 had no effect. ANOVA showed significant difference between groups [$F_{(2, 21)}$ = 5.31, p = 0.014, η^2_p = 0.34, BF_{10} = 4.5] with post-hoc analyses showing that DCS group had decreased freezing time ($p < 0.05$).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Stern et al. (2012)[10][7], Brazil	- Male Wistar rats.	Rats were randomly assigned into groups per experiments. Experiment 1: Immediate CBD and Midazolam (MDZ) treatment on reconsolidation of 1-day-old memory	Intervention was given immediately and 6 hours after memory retrieval.	Intraperitoneal injection of: - CBD: 3, 10 and 30 mg/kg (from THC-Pharma, Germany). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene sorbitan monooleate. - AM251: 1.0 mg/kg (from Tocris, USA). Dissolved in NaCl 0.9% containing 5% of polyoxyethylene	- Fear Conditioning (FC).	- Aversive memory (Fear associated memory).	CBD treatment at 10 mg/kg effectively disrupted memory reconsolidation for memories that were 1 and 7 days old. This effect lasted for at least 1 week. The disruption of CBD on reconsolidation was blocked by CB1 receptor antagonist but not by 5-HT_{1A} receptor antagonist. These findings suggest that older memories are more

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		(N = 7-12/group). - VEH group - CBD 3 group - CBD 10 group - CBD 30 group - MDZ group Experiment 2: Delayed (6 hours) CBD and MDZ on reconsolidation of 1-day-		sorbitan monooleate. - WAY100635 (5-HT_{1A} receptor antagonist): 0.1 mg/kg (from Sigma, USA). Dissolved in NaCl 0.9%. - Midazolam: 1.5mg/kg (from Tocris, USA). Dissolved in NaCl 0.9%. - In all cases, the volume			susceptible to the effect of CBD and that the effect has a window period of less than 6 hours. Experiment 1: CBD and MDZ treatment disrupted reconsolidation of 1-day-old memory dependent to memory reactivation. - RM ANOVA showed significant Treatment x Context A re-exposure (reactivation) interaction [$F(4,46) = 3.9$; $p < 0.01$] with CBD and MDZ

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		old memory (N = 7/group). - VEH group - CBD 10 group - MDZ group Experiment 3: CBD on recovery of memory reconsolidation (N = 6-7/group). - VEH group - CBD 10 group		administered was 1 ml/kg body weight.			treated groups showing decreased freezing time ($p's < 0.05$), where CBD at 10 mg/kg was most effective. - However, without prior reactivation there was no difference in freezing behavior. Experiment 2: Delayed CBD and MDZ treatment did not disrupt reconsolidation of 1-day-old memory. - RM ANOVA showed no main effect of treatment

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		Experiment 4: CBD on memory reinstatement and extinction (N = 9-10/group). - VEH group - CBD 10 group Experiment 5: Long lasting CBD treatment					[F(2, 18) = 0.32; P = 0.73] and Context A re-exposure [F(1, 18) = 1.61; p = 0.22] and no significant Treatment x Context A re-exposure (reactivation) interaction [F(2,18) = 40.72; p > 0.50] with CBD and MDZ treated groups at 6 hours after retrieval showing similar freezing time. Thus, suggesting the window period effect. Experiment 3: CBD treatment disrupted

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		effect (N = 8-11/group). - VEH group - CBD 10 group Experiment 6: CBD on older memory (N = 8-9/group). - VEH group - CBD 10 group Experiment 7: CBD on reconsolidation and CB1					reconsolidation did not show recovery over 22 days. - RM ANOVA showed main effect of treatment when test was performed 21 days after [$F(1,10) = 11.4$; $p < 0.01$] with CBD group showing less freezing ($p < 0.05$). Experiment 4: CBD treatment disrupted reconsolidation but does not show reinstatement. - RM ANOVA showed significant Treatment x

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		receptors (N = 8-9/group). - VEH-VEH group - VEH-CBD group - WAY-VEH group - WAY-CBD group - AM-VEH group - AM-CBD group					Context A re-exposure (reactivation) interaction [$F(3,51) = 3.6$; $p < 0.05$]. However, while CBD treated group showed less freezing time during test A, the effect was not presented with fear extinction session ($p = 0.28$). Thus, suggesting that CBD treatment did not show reinstatement. Experiment 5: CBD treatment disrupted memory reconsolidation

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							was long lasting (1 week later). - RM ANOVA showed significant Treatment x Context A re-exposure (reactivation) interaction [$F(1, 17) = 24.5$; $p < 0.001$] with CBD treated group showed significant less freezing time compared to control when re-exposed to context A 1 week after ($p < 0.05$). Experiment 6: CBD treatment disrupted

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							older memory reconsolidation. - RM ANOVA showed significant Treatment x Context A re-exposure (reactivation) interaction [$F(2, 28) = 10.5$; $p < 0.001$]. CBD treated group showed significant lesser freezing time when test was performed 1 week after ($p < 0.05$). Experiment 7: CBD treatment disrupted memory reconsolidation

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							was dependent to CB1 receptors. - RM ANOVA showed significant Pre-treatment x Treatment interaction [$F(2, 46) = 3.3$; $p < 0.05$]. VEH-CBD and WAY-CBD group showed less freezing time (p's < 0.05) but AM-CBD group showed no reduction. CB1 receptor blockade counteracted the effects of CBD on memory reconsolidation, while 5-

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							HT1A receptor blockade did not.
Stern et al. (2015)[10][8], Brazil	- Male Wistar rats.	Rats were randomly assigned into groups per experiments. Experiment 1: THC on fear memory reconsolidation (N = 7–8/group) - VEH group - THC 0.1 mg/kg group	Intervention was given immediately after retrieval.	Intraperitoneal injection of: - CBD: 1.0 and 3.0 mg/kg (THC-Pharma, Germany). Dissolved in NaCl 0.9% containing 5% of Tween 80. - AM251: 1.0 mg/kg (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80.	- Fear Conditioning.	- Aversive memory (Fear associated memory).	- THC treatment disrupted fear memory reconsolidation through CB1 receptor activation in the prelimbic cortex, while CBD treatment also effectively disrupted memory reconsolidation. Experiment 1– 4: THC treatment disrupted fear memory reconsolidation required memory reactivation. The effect was long lasting (22 days)

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- THC 0.3 mg/kg group - THC 1.0 mg/kg group - THC 10 mg/kg group Experiment 2: Memory reactivation and THC on reconsolidation (N = 6–7/group) - VEH group - THC 0.3 mg/kg group	- THC: 0.1, 0.3, 1.0 and 10.0 mg/kg (THC-Pharma, Germany). Dried and suspended in5% of DMSO and dissolved in PBS solution containing 0.1% of bovine serum albumin. - In all cases, the volume administered was 1 ml/kg body weight.			and relied on activation CB1 receptors. - RM ANOVA of Experiment 1 showed significant Treatment x Context A re-exposure (reactivation) interaction [$F(4,34) = 8.6$; $p = 0.00007$] with THC treated group at dose 0.3 to 10.0 mg/kg showed significantly less freezing time ($p's < 0.05$). - One- ANOVA of Experiment 2 showed no significant treatment on

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		Experiment 3: Long lasting effect THC on reconsolidation (N = 8/group) - VEH group - THC 0.3 mg/kg group Experiment 4: THC effects on reconsolidation and CB1 receptors (N		Infused intracranially bilaterally into the mPFC subregion of interest: - AM251: 50pmol (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80.			freezing time in Test A [$F(1,11) = 0.21$; $p = 0.66$] when memory was not reactivated. - RM ANOVA of Experiment 3 showed significant Treatment x Context A re-exposure (reactivation) interaction at 22 days [$F(2,28) = 5.1$; $p = 0.013$] with THC treated group showed significantly less freezing time ($p < 0.05$). - RM ANOVA of Experiment 4 showed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		= 8–10/group) - VEH-VEH group - VEH-THC group - AM251-VEH group - AM251-THC group Experiment 5: THC and CBD effect on reconsolidation (N = 8–9/group)					significant Pre-treatment x Treatment interaction [F(3,34) = 3.8; p = 0.01]. VEH-THC group showed less freezing time (p < 0.05) but AM251-THC group showed no reduction. Thus, suggesting that CB1 receptors blockade counteracted effects of THC. Experiment 5: THC and CBD treatment disrupted reconsolidation.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH-VEH group - VEH-THC 0.1 group - VEH-CBD 1.0 group - THC 0.1-CBD 1.0 group Experiment 6: THC and CBD on anxiety-like behavior. - VEH group - THC 0.3 group					- RM ANOVA showed significant interaction between treatment and re-exposure for freezing time [F(3,29)=5.1; P=0.005] where THC 0.1-CBD 1.0 group had significantly less freezing time ($p < 0.05$). - One-way ANOVA followed by Newman–Keuls test, showed THC 0.3 group, CBD 3 group and THC 0.1- CBD 1.0 group had significant susceptibility for

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- THC 0.1-CBD 1.0 group					reconsolidation disruption (p's < 0.05). - THC+CBD did not show a statistically significant difference compared to the individual effects of THC and CBD alone, indicating an additive interaction. Experiment 6: THC nor THC + CBD showed interference with anxiety behavior.
Stern et al.	- Male Wistar rats.	Rats were randomly assigned into	Intervention was given	Intraperitoneal injection of:	- Fear Conditioning.	- Aversive memory (Fear	- Immediate CBD treatment disrupted fear memory consolidation,

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
(2017)[10] [9], Brazil		groups per experiments. Experiment 1: CBD effects on fear memory consolidation (N = 7–8/group). - VEH group - CBD 3.0 group - CBD 10 group Experiment 2: CBD effects	immediately and 6 hours after conditioning.	- CBD: 3.0 and 30 mg/kg (THC-Pharma, Germany). Dissolved in NaCl 0.9% containing 5% of Tween 80. - AM251: 1.0 mg/kg (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80. - AM630: 0.3 mg/kg (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80.		associated memory).	both specific and generalized, but not when administered with a 6-hour delay. The effect was mediated by CB1 and CB2 receptor activation. However, CBD had no impact on short-term fear memory. Experiment 1: CBD treatment disrupted consolidation of specific contextual fear memory. - RM ANOVA showed significant freezing time on main effect of

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		on short-term consolidation (N = 7/group). - VEH group - CBD 10 group Experiment 3: Delayed (6 hours) CBD effects on fear memory consolidation (N = 7–9/group). - VEH group		- URB597: 0.5 to 1.0 mg/kg (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80. Infused intracranially bilaterally into the DH subregion of interest: - AM251: 0.5 nmol (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80.			treatment [$F(2,20) = 4.8$; $p = 0.02$], Context A re-exposure [$F(1,20) = 29.6$; $p = 0.0004$] but not interaction between treatment x Context A re-exposure [$F(2,20) = 0.53$; $p = 0.60$] with CBD treated group at 10 mg/kg showing less freezing time ($p < 0.05$). Experiment 2: CBD treatment had no effect on short-term fear memory.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 10 group Experiment 4: CBD effects on generalized fear memory consolidation (N = 9–11/group). - VEH group - CBD 3.0 group - CBD 10 group		- AM630: 0.1 nmol (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80. - URB597: 0.01 nmol (Tocris, USA). Dissolved in NaCl 0.9% containing 5% of Tween 80. - In all cases, the volume administered was 0.5 μl/hemisphere.			- One-way ANOVA showed no significant of treatment on freezing time [F(1,12) = 0.002; p = 0.97] with CBD and VEH group showed similar freezing time. Experiment 3: Delayed CBD treatment (at 6 hours) had no effect on fear memory consolidation. - One-way ANOVA showed no significant of treatment on freezing time on Test A [F(1,14) =

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD 30 group Experiment 5: CBD effects on generalized fear memory consolidation and 22-kHz USVs (N = 12–13/group). - VEH group - CBD 10 group Experiment 6: systemic CBD					0.56; p =0.47] and Test B [F(1,14) = 0.02; p = 0.90] with CBD and VEH group showed similar freezing time. Experiment 4: CBD treatment disrupted consolidation of generalized contextual fear memory. - RM ANOVA showed significant main effect of treatment [F(3,37) = 12.1; p = 0.00001] and the Context B re-exposures [F(1,37) = 5.5; p = 0.02]

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		with CB1 or CB2 receptor antagonist effects on generalized fear memory consolidation (N = 8–10/group). - VEH-VEH group - VEH-CBD group - AM251-VEH group					but not interaction between treatment x Context B re-exposure [F(3,37) = 0.01; p = 0.99] with CBD treated group at 10 and 30 mg/kg showing less freezing time (p's < 0.05). - RM ANOVA of fear ratio Context B vs. Context A showed significant main effect of treatment [F(3,37) = 6.1; p = 0.002], repetition [F(1,37) = 8.7; p = 0.005] and interaction between

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- AM251-CBD group - AM630-VEH group - AM630-CBD group Experiment 7: intra-DH CBD with CB1 or CB2 receptor antagonist effects on generalized fear memory consolidation					treatment x repetition [F(3,37) = 0.42; p = 0.74]. CBD treated group (10 and 30 mg/kg) showed lower fear ratio. Experiment 5: CBD interference during generalized fear consolidation on 22-kHz USVs. - Unpaired student's t tests showed significant effects of treatment for 22-kHz USVs during Test A1 (t_{23} = 2.3; p = 0.02) and Test B1 (t_{23} = 2.5; p

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		(N = 7–8/group). - VEH-VEH group - VEH-CBD group - AM251-VEH group - AM251-CBD group - AM630-VEH group - AM630-CBD group Experiment 8: systemic					= 0.02) with CBD treated groups showed less freezing time in Test B1 (t_{23} = 4.7; p = 0.0001). Experiment 6: CBD effects on consolidation was blocked by systemic CB1 or CB2 receptor antagonists. - Two-way ANOVA of Test B1 showed significant effects of pretreatment x treatment factors interaction for freezing time [F(2,46) = 3.6; p =

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		URB597 effects on generalized fear memory consolidation (N = 8–10/group). - VEH group - URB 0.5 group - URB 1.0 group Experiment 9: intra-DH URB597 effects on					0.03] with CBD treated groups had less freezing time. However, the effect was no presented when the groups were pretreated with AM251 and AM630. Experiment 7: CBD effects on consolidation was blocked by intra-DH of CB1 or CB2 receptor antagonists. - Two-way ANOVA of Test B1 showed significant effects pretreatment and

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		generalized fear memory consolidation (N = 8–10/group). - VEH group - URB 0.01 group Experiment 10: CBD effects on generalized fear memory consolidation and					treatment factors interaction for freezing time [F(2,39) = 3.3; p = 0.04] with CBD treated groups had less freezing time. However, the effect was no presented when the groups were pretreated with AM251 and AM630. Experiment 8: systemic URB597 treatment disrupted the generalized fear memory consolidation.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		extinction (N = 8/group). - VEH group - CBD 10 group					- One-way ANOVA of Test B1 showed significant effects of treatment on freezing time [F(2,24) = 9.9; p = 0.001] with URB597 treated group at 1.0 mg/kg had less freezing time. Experiment 9: intra-DH URB597 treatment disrupted the generalized fear memory consolidation. - One-way ANOVA of Test B1 showed significant effects of treatment on

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							freezing time [F(1,16) = 5.3; p = 0.04] with URB597 treated group at 1.0 mg/kg had less freezing time. Experiment 10: CBD treatment enhanced extinction. - RM ANOVA during extinction showed significant interaction between treatment x time-bin factors for freezing time [F(4,56) = 5.2; p = 0.001]. CBD treated group showed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							significant less freezing time with accelerated extinction rate during the 3rd and 4th session (p's < 0.05). The freezing time of CBD group was lesser during extinction test (t_{14} = 2.5; P 1/4 0.03) and Test B1 (t_{14} = 2.5; p = 0.02).
Szkudlarek et al. (2019)[11]	- Male Sprague Dawley rats.	Rats were assigned into treatment groups.	Intervention was removed after 1 min and	Intra prefrontal cortex (PFC) injection of: - CBD: 10, 100 and 500 ng/500 nl	- Spontaneous alternation Y-Maze test.	- Spatial memory.	- Intra-PFC CBD treatment reversed acute glutamatergic antagonist induced cognitive impairment.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
[6], Canada	- The rat modeled induced cognitive flexibility deficit by NMDAR antagonist (MK801).	For attentional set-shifting task: - VEH group, N = 9 - CBD10 group, N = 8 - CBD100 group, N = 9 - CBD500 group, N = 8 - CBD100/THC1	behavioral testing began 5min later.	(from Tocris 9 BioScience; Bristol, UK). - 5-HT1a receptor antagonist; NAD299 hydrochloride: 100 ng/500 nl from Tocris 9 BioScience; Bristol, UK). - CB1 receptor antagonist; AM251: 100 and 200 ng/500 nl (from Tocris 9 BioScience; Bristol, UK).	- Attentional set-shifting.	- Working memory	- Intra-PFC CBD impaired spatial working memory with no effects on anxiety or sociability behaviors. - Intra-PFC CBD impaired attentional flexibility in rats in a dose-dependent manner, there was a significant effect of treatment on number of trials [K–W test: $X^2_{(6)}$ = 15.468, p = 0.017], where rats treated with CBD100 (p = 0.004) and CBD 500 (p = 0.015) required

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		00 group, N = 7 - CBD100/NAD 299 100 group, N = 8 - NAD299 100 group, N = 7 For attentional set shifting task with MK801:		- NMDA-receptor antagonism; MK801 maleate: 3 and 6 μg/500 nl (from Tocris 9 BioScience; Bristol, UK). - THC: 10, 50, 100 or 500 ng/500 (from Cayman Chemical Company; Michigan, USA) - All drugs were dissolved in dimethyl sulfoxide (DMSO) and diluted			more trials but CBD10 did not induce impairment. CBD 100 showed significantly more errors (p = 0.019). CBD treatment increased the number of errors [one-way ANOVA: F(6,55) = 3.324, p = 0.008] with CBD100 being the affected dose (p = 0.014). - Intra-PFC CBD was able to reverse MK801-induced impairments. There was significant

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- VEH group, N = 9 - MK801 3 group, N = 7 - MK801 6 group, N = 7 - MK801 6/CBD100 group, N = 6 - MK801 6/CBD500 group, N = 7 For Spontaneous		to final DMSO 5% in saline containing 5% cremophor EL. - All microinfusions were 500 nl/hemisphere. - Drugs were injected as co-mixture when two drugs were tested simultaneously.			effect of treatment on number of trials [K–W test: $X^2_{(4)}$ =14.796, p = 0.005], total error [one-way ANOVA: F(4,35) = 4.938, p = 0.003] and perseverance [one-way ANOVA: F(4,35) = 4.621, p = 0.005]. Post-hoc analyses revealed that MK801 treated rats required significantly more trials (p = 0.002), had more errors (p = 0.002) and displayed increased perseverance

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		alternation Y-Maze test: - VEH group, N = 8 - THC100 group, N = 7 - CBD100 group, N = 8 - CBD100/THC100 group, N = 8 - CBD100/NAD					(p = 0.003). The deficit was reversed by CBD100 and CBD500 (p = 0.035 and p = 0.004, respectively). - Intra-PFC CBD impaired spontaneous alternation behavior/spatial memory. There was a significant effect of drug treatment on spontaneous alternation behavior [one-way ANOVA: F(6,52) = 2.432, p = 0.040] with CBD100 rats showed reduced alternation (p =

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		299 100 group, N = 8 - NAD299 100 group, N = 7 - MK801 6 group, N = 7					0.004). There was also significant returning score on drug treatment [one-way ANOVA: $F(6,52) = 2.968$, $p = 0.016$] with CBD100 rats displaying significantly higher score ($p = 0.001$). Co-administration of CBD100 with THC100 or NAD299 100 restored alternation behavior showing the involvement of 5-HT_{1A} transmission suggesting that activation of CB1R at

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							PFC can prevent CBD-induced deficits.
Szkudlarek et al. (2021)[115], Canada	- Male Sprague Dawley rats.	Rats were assigned into treatment groups. For LI procedure: - Non-pre-exposed (NPE) group, N = 8	Intervention was removed after 1 min and behavioral testing began 5min later.	Intra prefrontal cortex (PFC) injection of: - CBD: 100 ng/500 nl (from Tocris 9 BioScience; Bristol, UK). - 5-HT_{1A} receptor antagonist; NAD299 hydrochloride: 100 ng/500 nl from Tocris 9 BioScience; Bristol, UK).	- Spontaneous oddity discrimination (SOD) task. - Latent inhibition (LI) procedure.	- Object recognition memory. - Aversive memory (Fear associated memory).	- CBD treatment blocked formation of fear associated memory with no effect on panic-like behaviors. - Intra-PFC CBD treatment impaired LI. NPE rats froze significantly more than PE rats [NPE = 62.22 ± 3.73%, PE = 30.96 ± 4.03%; t-test: t = 5.63, p < 0.001] showing

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Pre-exposed (PE) group, N = 9 - NPE-CBD group, N = 9 - PE-CBD group, N = 9 - NPE-THC group, N = 9 - PE-THC group, N = 8		- THC: 100 ng/500 (from Cayman Chemical Company; Michigan, USA) - All drugs were dissolved in dimethyl sulfoxide (DMSO) and diluted to final DMSO 5% in saline containing 5% cremophor EL. - All microinfusions were 500 nl/1 min/side			inhibition effect of control. However, there was no difference with intra-PFC CBD, suggesting impaired LI [NPE-CBD = 37.41 ± 4.35, PE-CBD = 34.71 ± 5.13%; t-test: t = 0.40, p = 0.69]. CBD effect was prevented with 5-HT_{1A}R antagonist NAD299 [NPE-CBD/NAD = 52.54 ± 7.06%, PE-CBD/NAD = 35.10 ± 5.62%; t-test: t = 1.89, p = 0.03]. NPE-CBD rats froze significantly less

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- NPE-CBD/NAD group, N = 9 - PE-CBD/NAD group, N = 8 - NPE-NAD group, N =8 - PE-NAD group, N = 8 - NPE-CBD/THC group, N = 8		- Drugs were injected as co-mixture when two drugs were tested simultaneously.			than NPE-CBD/NAD rats (p = 0.045). - Intra-PFC CBD treatment impaired SOD. One-way ANOVA showed significant treatment effect on SOD scores [F(5,84) = 3.795, p = 0.004] where Gabriel post-hoc comparisons showed intra-PFC CBD having significant SOD scores [VEH = 0.49 ± 0.03, CBD = 0.31 ± 0.02; p = 0.003]. One-way ANOVA showed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- PE-CBD/THC group, N = 9 For SOD task: - VEH group, N =17 - CBD group, N =15 - THC group, N = 14 - CBD/NAD, N = 15 - CBD/THC, N = 16					significant effect of drug on total exploration time [F(5,84) = 4.601, p = 0.001], but only the CBD/THC group showed significantly lowered exploration [VEH = 64.46 ± 6.07 s, CBD/THC = 37.30 ± 3.52 s, Gabriel post-hoc comparison, p = 0.002].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- NAD group, N = 13					
Ukernik at al. (2018)[70], USA	- Male C57BL/6 mice.	Mice were assigned in different conditioning group. Paired-conditioned group: - CON-Pair group (N = 12)	Intervention was given 30 mins prior fear conditioning.	Intraperitoneal injection of: - CBD: 10 mg/kg. Dissolved in 2% ethanol, 2% Tween 80 and 0.9% NaCl. - Vehicle group was administered similarly without CBD.	- Fear Conditioning.	- Aversive memory (Fear associated memory).	- CBD treatment increased freezing behavior during conditioning, generalized fear, and inhibited cue-dependent extinction. It also enhanced contextual fear memory and mildly increased freezing behavior during memory cues. CBD treatment also resulted

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CBD-Pair group (N = 12) Unpaired-conditioned group: - CON-UP group (N = 12) - CBD-UP group (N = 12) Non-conditioned group:					in synaptic plasticity alterations, with increased density in the amygdala and reversed density in the hippocampus. - CBD treated groups showed increased freezing time. T-test showed CBD-Pair group (p = 0.05) and CBD-UP group (p = 0.007) had increased freezing during conditioning. Thus, CBD treated group were more responsive to

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- CON-NC group (N = 12) - CBD-NC group (N = 12)					unconditional stimuli (US). - During trace-conditioning, one-way RM ANOVA showed CBD treated group froze more [F(1, 11) = 11.5, p = 0.006]. Thus, suggesting CBD treatment increased expression of generalized fear. - Freezing time increased during auditory fear cue after conditioning with CBD treated group froze more 49 ± 8% than

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							vehicle group but the difference was not significant. CBD group showed a trend in increasing freezing time during the first half of the 3rd inter-trial interval [F(1, 11) = 11.5, p = 0.058] but it was not significant. - CBD treated group showed more resistant to extinction (p = 0.1) toward reduced freezing time compared to vehicle group (p = 0.009).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							- CBD treated group froze more than vehicle groups during contextual (conditioned chamber) cues exposure. One-way RM ANOVA showed significant difference between CBD and vehicle group [F(1, 11) = 5.1, p = 0.044]. Thus, suggesting the CBD enhanced contextual memory. - CBD treatment showed synaptic plasticity effect in amygdala and

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							hippocampus. Spine density was increased in lateral amygdala (p = 0.004) but not in the hippocampus (p = 0.194) where the density was reduced. However, these effects were independent of fear conditioning.
Watt et al. (2020)[93],	- Mice carrying double transgenes	Mice were assigned to vehicle or CBD groups. Treatments	The total duration of treatment	Intraperitoneal injection of: - CBD: 50 mg/kg (from CAS: 13956-29-1 THC Pharma	- SPT.	- Social recognition memory.	- CBD treatment showed no effect on cognitive changes in TAU58/2 mice where all mice showed intact fear memory,

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Australia	expressing chimeric mouse/human mutations of *0N4R* tau isoform and *P301S*= TAU58/2.	were quasi-randomized. - Vehicle-WT group, N = 14 - Vehicle-TAU58/2, N = 12 - CBD-WT, N = 14 - CBD-TAU58/2, N = 14	was 5 weeks.	GmbH; Frankfurt/Main, Germany). Dissolved in equal amounts of Tween 80 and 100% ethanol, diluted with 0.9% NaCl. Ethanol and Tween 80 comprised 10 % of the total volume. - Vehicle group was administered similarly without addition of CBD.	- Fear conditioning.	- Aversive memory (Fear associated memory).	sociability and social recognition. - All mice including TAU58/2 mice showed intact sociability and social recognition in SPT with no significant interactions between chamber x genotype x CBD ($p > 0.05$). - In FC, while there was a significant interaction of freezing time x genotype with TAU58/2 mice freezing more [$F(6,300) = 3.5$, $p = 0.003$]. Two-way

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	- The mice modeled AD's disease (AD)'s.			- In all cases, the volume administered was 10 ml/kg body weight.			ANOVA for total freezing time showed a 'genotype' effect [F(1,50) = 6.9, p = 0.012] with increased freezing time in TAU58/2 transgenic mice. CBD had no effect on freezing time to the context or the genotype (all p's > 0.05).
Watt et al. (2020)[94],	- Mice carrying double transgenes	Mice were assigned to vehicle or CBD groups.	The total duration of treatment	Intraperitoneal injection of: - CBD: 50 mg/kg (from GW Pharmaceuticals	- SPT. - NORT.	- Social recognition memory.	- CBD treatment restored social recognition memory and reversed spatial learning deficit in AD modeled mice. No

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
Australia	expressing chimeric mouse/ human mutations of amyloid precursor protein (AβPP) and presenilin	- WT-VEH group, N = 10 - AβPPxPS1-VEH, N = 10 - WT-CBD, N = 11 - AβPPxPS1-CBD, N = 18	was 7 weeks.	Ltd.; Cambridge, UK). Dissolved in equal amounts (5% of the volume) of Tween 80 and 100% ethanol, diluted with 0.9% NaCl. The ratio by volume of 1:1:18 of ethanol:Tween 80:saline was used. - Vehicle group was administered similarly without addition of CBD.	- CB. - Fear conditioning.	- Object recognition memory. - Spatial memory. - Aversive memory (Fear associated memory).	significant effect was found for fear associated memory. - Single sample t-tests showed all group has a preference for novel mouse except AβPPxPS1-VEH group which was restored in AβPPxPS1-CBD mice [WT-VEH t(8) = 5.2, p = 0.001; AβPPxPS1-VEH t(9) = 0.7, p = 0.5; WT-CBD t(9) = 3.8, p = 0.004; AβPPxPS1 - CBD t(6) = 3.5, p = 0.013].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	1(PS1/ ΔE9) = (AβPPx PS1). - The mice modeled AD's disease.			- In all cases, the volume administered was 10 ml/kg body weight.			- In reversal spatial learning, there was a significant interaction between days x genotype x treatment [F(3,105) = 2.8, p = 0.044] where AβPPxPS1-VEH group took longer in learning the location of food reward while this deficit was not found in CBD group. - Two-way ANOVA for time spent in the target zone in CB task showed main effect of CBD,

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							where CBD group spend more time in the target zone [F(1,35) = 5.522, p = 0.025]. - Three-way RM ANOVA of NORT showed significant object x genotype interaction with only WT mice showing preference for the novel object [F(1,33) = 5.190, p = 0.029]. - Three-way RM ANOVA for freezing time showed no main effects of

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
							genotype, treatment or interactions with time (all p's > 0.05).
Withey et al. (2021)[119], USA	- Male squirrel monkeys.	- Animals were randomly assigned into different treatment groups. - Vehicle group, N = 4 - High THC group, N = 4	The total duration of treatment was 4 months.	Intramuscular injection of: - CBD: 3 mg/kg (from National Institute on Drug Abuse Drug Supply Program; Rockville, USA). Mixed in 20:20:60 mixture of 95% ethanol, polysorbate-80 (Tween-80), and	- Touchscreen - Based Cognitive Tests for novel discrimination	- Object recognition memory.	- CBD treatment had no effect on THC's impairment of cognitive performance, activity or tolerance. - The rate of acquisition and median reaction times of task was not statistically different between groups (p > 0.05).

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- THC + CBD group, N = 4		0.9% saline solution. - THC: 1 mg/kg (from National Institute on Drug Abuse Drug Supply Program; Rockville, USA). Mixed in 20:20:60 mixture of 95% ethanol, polysorbate-80 (Tween-80), and 0.9% saline solution. - In all cases, the volume			

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
				administered was 0.3 ml/kg body weight.			
Wright et al. (2012)[120], USA	- Male rhesus monkeys.	Animals were assigned to treatment groups where treatment order was pseudo-randomized. For vsPAL, N = 8: - Veh-Veh group	- CBD was administered either 30 min prior to THC or at the same time in two separate injections.	Intramuscular injection of: - CBD: 0.5 mg/kg (from Cayman Chemical Company; Michigan, USA). Mixed in a vehicle of 95% ethanol, Cremophor EL and saline in a 1:1:18 ratio	- Visuospatial Paired Associates Learning (vsPAL). - Self-Ordered Spatial Search (SOSS) tasks.	- Spatial memory.	- CBD improved the effects of THC on vsPAL without affecting SOSS task of working memory. - In vsPAL task, THC impaired overall performance. Three-way ANOVA showed interaction between trial difficulty x THC condition x pretreatment of CBD [$F_{6,42} = 2.72$; $p < 0.05$].

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- 0.5 CBD-Veh group - Veh-0.2 THC group - 0.5 CBD-0.2 THC group - Veh-0.5 THC group - 0.5 CBD-0.5 THC group For SOSS tasks, N = 6: - Veh-Veh group - 0.5 CBD-Veh group		- THC: 0.2 and 0.5 mg/kg (from National Institute on Drug Abuse; USA). Mixed in a vehicle of 95% ethanol, Cremophor EL and saline in a 1:1:18 ratio			Post hoc test confirmed protective effect of CBD (0.5 mg/kg) where accuracy was significantly higher in 0.5 CBD-0.5 THC group compared ($p < 0.05$). - In SOSS task, ANOVA showed that overall completion accuracy is dependent on THC treatment condition [$F_{5,25} = 3.87$; $p < 0.01$] and trial difficulty [$F_{2,10} = 25.52$; $p < 0.0005$]. Post-hoc test confirmed

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
		- Veh-0.2 THC group - Veh-0.5 THC group - 0.5 CBD-0.5 THC group					lower performance with THC regardless of CBD.
Zieba et al. (2019)[12], Australia	- Mice with Fmr1 knockout (KO) gene. - The mice modele	Animals were assigned to treatment groups. - WT-VEH group, N = 12	- CBD was given 30 min prior test.	Intraperitoneal injection of: - CBD: 5 and 20 mg/kg (from National Measurement Institute, NSW, Australia). Dissolved in equal	- Continuous Spontaneous alternation Y-Maze test (SA).	- Spatial memory.	- CBD treatment did not affect cognitive performance of Fragile X modeled mice but CBD showed reduction in anxiety behavior. - In SA test, there was no difference in % correct entries between groups

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
	d Fragile X Syndrome.	- Fmr1-VEH group, N = 12 - WT-CBD 5 group, N = 12 - Fmr1-CBD 5 group, N = 12 - WT-CBD 20 group, N = 12 - Fmr1-CBD 20 group, N = 12		amounts (10% of the total volume) of Tween 80 and 100% ethanol, diluted with 0.9% NaCl. The ratio by volume of 1:1:18 of ethanol:Tween 80:saline was used. - Vehicle group was administered similarly without addition of CBD. - In all cases, the volume administered was	- Passive avoidance. - SPT.	- Aversive memory (Fear associated memory). - Social recognition memory.	[(F(1,66) = 2.7, p > 0.05], nor CBD's effect [(F(2,66) = 0.1, p > 0.05]. - In PA task, there were no differences between genotype groups [F(1,66) = 0.8, p > .05] nor between CBD treatment groups [F(2,66) = 1.6, p > .05]. Three-way RM ANOVA showed no interaction of latency x genotype x CBD (both p > 0.05). Thus, all mice learned equally in PA task.

Author, Year & Country	Animal Model	Study Allocation and Size	Duration of Intervention	Intervention and Control	Memory Test	Types of Memory	Results
				10 ml/kg body weight.			- In SPT, there was no significant effect of chamber [$F(1,66) = 6.2$, $p < 0.05$], no interaction between chamber x genotype ($p > 0.05$) nor chamber x CBD interaction $p > 0.05$).

Table 4.2 Summary Table of the Characteristics of Randomized Controlled Trial Studies.

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
Bhattacharyya et al. (2018)[12][6]; UK	Parallel-group, double-blind, placebo-controlled randomized clinical trial.	- Medication-naive participants at clinical high risk (CHR) of psychosis randomized into 3 groups: - CBD group: N = 16, Age =	CBD Group: - Life time user = 15 - Current user = 7 [> once a week = 11, once/twice monthly = 1, few times a year = 2, Only	- Intervention was given 3 hours before scanning and cognitive task.	Oral form of: - CBD: 600 mg (from THC-Pharm; Germany). - Placebo capsule. - Control group were not	- Verbal Paired Associate (VPA) learning tasks. - Brain activation indexed using fMRI signal.	- Episodic memory.	- CBD treatment showed intermediate brain activity compared to placebo and control group in areas involved in memory (para-hippocampal gyrus / midbrain: CBD: median, -0.013; IQR, - 0.027 to 0.002; placebo:

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		22.43±4.95 years, F:M = 6:10 - Placebo: N = 17, Age = 25.35±5.24 years, F:M = 10:7 - Control group: N = 19 participants, Age = 23.89	once/twice lifetime = 1] Placebo Group: - Life time user = 17 - Current user = 7 [> once a week = 12, Once/twice monthly = 3, Few times a year		given any drug.			median, - 0.007; IQR, - 0.019 to 0.008; control: median, 0.034; IQR, 0.005 to 0.059). - Total recall score was directly correlated with the level of left para-hippocampal activation (r = 0.28; p = 0.046). But no significant group differences

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		±4.14 years, F:M = 8:11	= 0, Only once/twice lifetime = 2] Control Group: - Life time user = NA - Current user = NA					in task performance was found. - There were no significant group differences in demographic and clinical variables. - No adverse or serious adverse events were observed.

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
Bloomfield et al. (2020)[12][7]; UK	Within-subjects, randomized, double-blind, placebo-controlled design.	- Healthy participants: N = 15; Age = 24.1±4.95 years, F:M = 9:6	Cannabis and CBD naïve participants.	Intervention was given 3 hours before scanning and cognitive task. - Two sessions separated by ≥ one week.	Oral form of: - CBD: 600 mg (99.9% purity, from STI Pharmaceuticals; UK). - Placebo capsule.	- Rivermead Behavioural Memory test - N-back task - The digit span task - Regional cerebral blood flow.	- Episodic memory. - Spatial working memory. - Working memory.	- CBD treatment showed significant increase in CBF in the hippocampus. There was no difference in memory task performance. - Decreased reaction time was found in N-back task which suggested that CBD may have an effect in working

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								memory performance. - CBD increased CBF in the hippocampus (mean (95% CI) = 15.00 (5.78–24.21) mL/100g/min, t_{14} = 3.489, Cohen's d = 0.75, p = 0.004). Prose recall task: - There was no main effect of drug ($F_{1,14}$ = 3.701,

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								η^2 = 0.184, p = 0.075, mean difference −0.517, 95% CI −1.126–0.092), task ($F_{1,14}$ = 3.311 η^2 = 0.014, p = 0.090) and no significant interaction between drug x task ($F_{1,14}$ = 0.037, η^2 = 0.000, p = 0.850). Digit Span Task:

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								- There was no main effect of drug ($F_{1,14}$ = 0.312, η^2 = 0.007, p = 0.585), but significant effect on task ($F_{1,14}$ = 9.333, η^2 = 0.182. p = 0.009). But the interaction between drug x task was not significant ($F_{1,14}$ = 0.497, η^2 = 0.007, p = 0.492).

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								N-back task's accuracy: - There was no main effect of drug ($F_{1,12}$ = 0.026, η^2 = 0.000, p = 0.875), but significant effect on task ($F_{2,24}$ = 10.180, η^2 = 0.305, p = 0.001). However, the interaction between drug x task was not

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								significant ($F_{2,24}$ = 0.693, η^2 = 0.016, p = 0.510). N-back task's reaction time: - There was no main effect of drug ($F_{1,12}$ = 0.168, η^2 = 0.000, p = 0.689), but significant effect on task ($F_{1,12}$ = 25.642, η^2 = 0.619, p < 0.001).

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								But the interaction between drug x task was not significant ($F_{2,24}$ = 1.420, η^2 = 0.006, p = 0.261). - Correlational analysis of OFC CBF: CBF was associated with decreased reaction time which suggested better working

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								memory performance (r_{11} = −0.73, p = 0.005).
Boggs et al. (2018)[13][3]; USA	Randomized, placebo-controlled, double-blind, parallel group.	- 36 stable antipsychotic-treated patients diagnosed with chronic schizophrenia. - CBD group: N = 18, Age	Not mentioned.	Intervention was given daily for 6 weeks.	Oral form of: - CBD: 300 mg BID = 600 mg/day (from STI Pharmace	- MATRICS Consensus Cognitive Battery (MCCB)	- Working memory.	- CBD treatment showed no improvement in the MCCB sores. - There was no main effect of Drug and Time on MCCB score (p's > 0.05) and the group with

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		= 48.4±9.3, F:M = 6:12 - Placebo group: N = 18, Age = 46.4±9.5, F:M = 5:13			uticals; UK). - Placebo capsule.			improved score was placebo treated group [F(1, 32) = 4.84; p = 0.03]. - For MCCB subscale on working memory composite, there was no main effect of Drug [F(1,34) = 2.25, p = 0.62], Time [F(1,33) = 1.47, p = 0.23] and drug x

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								time interaction [F(1,33) = 1.37, p = 0.25]. - Side effects were similar between CBD and placebo group.
Das et al. (2013)[12][8]; UK	Double-blind, placebo-controlled between	- 48 Healthy participants: 18-35 years old. - CBD pre-extinction	Numbers of Cannabis users per group:	The drugs were inhaled every 10 seconds either before	Vaporized form of: - CBD: 32 mg (from STI Pharmace	- Fear Conditioning.	- Fear associated memory.	- CBD treatment after extinction improved the process of extinction, leading to reduced fear expression during

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
	n-subjects design.	group: N = 16, F:M = 8:8 - CBD post-extinction group: N = 16, F:M = 6:10 - Placebo group: N = 16, F:M = 4:12	- CBD pre-extinction group: 4 - CBD post-extinction group: 6 - Placebo group: 4 Cannabis days per month:	extinction or after extinction session.	uticals; UK). Vaporized at 210 °C with 0.08 mg ethanol vehicle and via a Volcano Medic vaporiser. - Placebo: 0.08 mg			recall and reinstatement. - CBD treatment showed potential for enhancing the consolidation of extinction memory, as indicated by a trend towards decreased reinstatement of contextual responding when CBD was given

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
			- CBD pre-extinction group: 3.17 ± 3.82 - CBD post-extinction group: 1.75 ± 2.22 - Placebo group: 0.75 ± 0.5 Cannabis time to smoke		ethanol vehicle.			before and after extinction. - There was a trend indicating a group difference in the response to conditioned stimuli (p = 0.062), with the CBD post-extinction group showing lower ratings compared to the placebo group (p = 0.047).

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
			eighth (3.5g): - CBD pre-extinction group: 4.5 ± 3.54 - CBD post-extinction group: 12.33 ± 6.81 - Placebo group: 5.75 ± 1.5					However, there was no significant difference between the placebo and CBD pre-extinction group. - In terms of skin conduction responses during reinstatement, there was a significant interaction between the

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								context x group [F(2,35) = 2.545, p = 0.097, η_p^2 = 0.132]. CBD post-extinction group showed lower response to the extinction context compared to the placebo group. But post-hoc test was not significant. - There was a significant main

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								effect of group on conditioned stimuli during reinstatement [F(1,40) = 4.76, p = 0.014, η_p^2 = 0.192], with the CBD post-extinction group rating the stimuli lower than both the placebo group (p = 0.036) and the CBD pre-

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								extinction group (p = 0.005). - In terms of prose recall, the placebo group had better recall than the CBD pre-extinction group [t(30) = 2.456, p = 0.02; t(30) = 2.2946, p = 0.029].

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
Englund et al. (2013)[67]; UK	2×3 mixed, randomized, double-blind, placebo-controlled design.	- 48 Healthy participants completed the protocol. - CBD group: N = 22, Age = 25±3, F:M = 9:13 - Placebo group: N = 26, Age 26±4, F:M = 12:14	- Previous cannabis episodes: - CBD group = 137±234 - Placebo group = 118±218	- Oral intervention was given 210 mins prior intravenous administration of THC.	Oral form of: - CBD: 600 mg (from STI Pharmaceuticals; UK). - Placebo capsule. Intravenous administration of:	- The Hopkins Verbal Learning Task-Revised. - Digit-span forward and reverse.	- Episodic Memory. - Working Memory.	- Pre-treatment with CBD had a protective effect against THC on episodic memory but not on working memory. Whereas, THC impaired both memories. The Hopkins Verbal Learning Task: - For immediate recall there was

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
					- THC: 1.5 mg (from THC-Pharm GmbH; Germany). Diluted in normal saline and contained 1.5% (v/v) ethanol absolute.			main effect of condition (F = 22.64, p < 0.000) but not group (F = 0.079, p = 0.78) and no significant interaction between condition x group (F = 0.92, p = 0.88). Post-hoc analysis showed post THC treatment had poorer immediate

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								recall ($p < 0.005$) and trend toward the CBD group ($p = 0.06$). - Further analysis showed poorer recall post THC by 10.6% in the placebo group and only 0.4% in the CBD pre-treated group ($t = 2.39$, $p < 0.05$). Digit-span forward:

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								- There was main effect of condition (F = 7.38, p < 0.005) but not group (F = 0.44, p = 0.51) and no significant interaction between condition x group (F = 1.24, p = 0.30). Post-hoc analysis showed poorer performance post

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								THC in the placebo group ($p < 0.05$) but no significant difference in the CBD group ($p > 0.05$). Digit-span reverse: - There was main effect of condition ($F = 9.46$, $p < 0.000$) but not group ($F = 0.000$, $p = 0.99$) and no significant

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								interaction between condition x group (F = 1.53, p = 0.86). Post-hoc analysis showed no significance different for both placebo (p = 0.08) and CBD group (p = 0.5). - Pre-treatment with CBD reduced the occurrence of

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								acute THC psychosis.
Hotz et al. (2021)[13][4]; Switzerland	Double-blind, placebo-controlled, randomized, crossover trial.	- Healthy 34 participants completed final analyses: Age = 22.26±3.04, F:M = 17/17. - CBD group: N = 17	- Frequency of annual cannabis consumption = 2.24±3.2 - Cannabis consumption per year/number of participants:	Drugs were administered for 15 mins after word learning and immediate recall.	Vaporized form of: - CBD: 12.5 mg (e-liquid of 0.25 ml and 5% CBD from PharmaHemp; Slovenia).	- Verbal Learning Task (VLT) - N-Back Performance Test.	- Episodic memory. - Spatial Working memory.	- CBD treatment enhanced verbal episodic memory but not on working memory. VLT: - There was a significant main effect of medication [$F(1,33) = 11.12$, $p = 0.048$, $R_2\beta$=

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		- Placebo group: N = 17	0/15, 1/6, 2/1, 3/4, 4/2, 5/2, 6/1, 10/2, 12/1		- Placebo e-liquid: 0.25 ml.			.028] with CBD treated group showing better performance in recall compared to placebo [adjusted group difference 0.68, 95% CI 0.01 to 1.35; $R_2\beta$ = 0.028, p = 0.048]. N-Back Performance Test: - For 0-back performance,

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								there was no significant effect of medication [accuracy: F(1,33) = 1.3, p = 0.26]. - For 2-back performance, there was no significant effect of medication [accuracy: accuracy: F(1,33) = 0.05, p = 0.83]. - There was no serious adverse

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								event occurred, with two cases of headache for CBD and abdominal pain for placebo
Leweke et al. (2021)[13][1]; Germany	Parallel-group, active-controlled, mono-therapeutic, double-	- 29 acute paranoid schizophrenic patients completed the protocol and two cognitive	Not mentioned.	Intervention was given for the duration of 4 weeks.	Oral form of: - CBD: 200 mg TID = total of 600 mg/day.	- The Letter Number Sequencing - Subject Ordered Pointing Task	- Working memory. - Working memory. - Spatial Working memory.	- CBD treatment showed improvement in visual episodic memory. - t-tests showed improvements in visual memory (ROFT: $t_{(13)}$ = -

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
	blind, randomized clinical trial.	assessments. - CBD group: N = 15, Age 28.8±7.7, F:M = 3:12 - AMI group: N = 14, Age = 30.3±9.7, F:M = 1:13			- AMI (Amisulpride; antipsychotic): 200 mg TID = total of 600 mg/day.	- Delayed Response Task - The Auditory Verbal Learning Test (AVLT) - The Rey-Osterrieth Complex Figure Test (ROFT)	- Episodic memory. - Visual Episodic memory.	2.80, p = 0.015 [p_{corr} = 1] [-6.27, -0.80]). - However, there was no difference in working memory (Letter Number Sequencing Test: $t_{(12)}$ = 0.32, p = 0.755 [p_{corr} = 1] [-1.80, 2.41] and Subject Ordered Point Task: $t_{(11)}$ = 0.09, p = 0.932

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								[p_{corr} = 1] [-2.02, 2.19]), spatial working memory (DRT: $t_{(14)}$ = 0.60, p = 0.563 [p_{corr} = 1] [-8.49, 14.98]) and verbal memory recall (AVLT: $t_{(14)}$ = 0.15, p = 0.881 [p_{corr} = 1] [-1.75, 2.02]).
McGuire et al. (2017)[13]	Multicenter, double-	- Participants with	Positive baseline	Intervention was given for the	Oral form of:	- Brief Assessment of Cognition	- Episodic memory	- CBD treatment showed no improvement in

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
[6]; U.K., Romania, and Poland.	blind, randomized, placebo-controlled, parallel-group trial.	schizophrenia or a related psychotic disorder (DSM-IV). - CBD group: N = 43, Age = 40.9±12.49, F:M = 15:28 - Placebo group: N = 45, Age =	urine THC test: - CBD group, N = 1 - Placebo group, N = 2	duration of 6 weeks.	- CBD: 1,000 mg/day as 10 mL of a 100 mg/mL solution. - Placebo: excipients alone.	in Schizophrenia (BACS): composite score.	- Working memory.	episodic and working memory. - Although there was an improvement in the overall composite score of BACS, the difference between the treatment groups was not significant (treatment difference = 1.31,

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		40.8±11.00, F:M = 22:23						95% CI = -0.10 to 2.72, p = 0.068). - There was no improvement in episodic memory (treatment difference = 0.0, 95% CI = -2.9 to 2.9, p = 0.993) and working memory (treatment difference = 1.0, 95% CI = -0.3 to 2.3, p = 0.141).

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								- The groups had a similar rate of adverse events with. Most events were mild and resolved without any intervention. Diarrhea and nausea were the most commonly reported. One serious event was exacerbation of schizophrenia in

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								the placebo group.
Morgan et al. (2018)[12][9]; UK	Randomized, double-blind crossover design.	- 48 cannabis users categorized into (1) schizotypal personality (low, high) and (2) frequency of cannabis	- Cannabis users were categorized into light and heavy user. - Light user = 1–24 days per month	The drugs were inhaled every 10 seconds before tests on four occasions, with a one-week was-	Vaporized form via Volcano Medic vaporiser: - CBD: 16 mg. Dissolved in ethanol. - THC: 8 mg.	- Delayed Prose Recall. - Spatial N-back memory task.	- Episodic memory. - Spatial working memory.	- CBD treatment had no effect on THC induced memory impairment. Prose recall Task: - There was significant main effect of drug [$F(3,132)= 4.458$, $p = 0.005$, η_p^2 =

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		use (light, heavy). - Light and Low group: N = 12, Age = 21±2.13, F:M = 3:9 - Light and High group: N = 12, Age = 22.90±2.02, F:M = 5:7	- Heavy user = 25+ days per month	out period break.	Dissolved in ethanol. - THC 8mg + CBD 16 mg. Dissolved in ethanol. - Placebo: ethanol.			0.092] with THC (p = 0.031) and THC + CBD (p = 0.024) group showing poorer recall. - CBD showed no effect on recall performance. Spatial N-back Task: - There was significant main effect of drug [F(3,129) = 3.421,

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		- Heavy and low group: N = 12, Age = 21.42±1.62, F:M = 1:11 - Heavy and high group: N = 12, Age = 21.50±1.38, F:M = 5:7						p = 0.019, η_p^2 = 0.074] with THC (p = 0.012) and THC + CBD (p = 0.020) group showing poorer performance. - CBD showed no effect on recall performance. - CBD treatment did not exhibit any distinct occurrence rate in the drug effects

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								to symptoms such as anhedonia, delusory thinking, mania, and paranoia when compared to the placebo.
O'neil et al. (2019)[130]; UK	Double-blind, placebo controlled, repeate	Participants with psychosis (DSM-IV). - Psychosis (PSY) group: N = 15, Age	- 15 in PSY group were lifetime users and 9 were current	- Oral intervention was given 180 mins prior task.	Oral form of: - CBD: 600 mg (99.9% pure from THC-	- Verbal Paired Associate (VPA) learning tasks. - fMRI.	- Episodic memory.	- CBD treatment showed no effect on episodic memory. - CBD treatment reduced dysfunction in the

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
	d-measures, within-subject, crossover design.	= 27.73±4.61, Male = 66.7% (13 participants completed the study where 2 participants requested to end the study) - PSY-PLB: N = 7	regular users. - Frequency of cannabis use (past/present) of PSY group: - Daily, N = 6 - More than once a week, N = 4		Pharm; Germany). - Placebo capsule.			prefrontal activation during encoding and mediotemporal and prefrontal activation, as well as mediotemporal-striatal functional connectivity during recall in PSY participants. CBD also resulted in a decrease in hippocampal-

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		- PSY-CBD: N = 8 - Healthy control group (HC): N = 19, Age = 23.89±4.15, Male = 57.9% PSY-PLB, psychosis participants under placebo	- Once/twice monthly, N = 0 - Few times a year, N = 1 - Only once/twice lifetime, N = 4 - No current regular user in HC group.					striatal functional connectivity in PSY participants. During encoding task: - There was no significant difference between PSY-PLB and PSY-CBD group (p = 0.42). - HC group performed better at semantic

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		condition; PSY-CBD, psychosis participants under cannabidiol condition.						relatedness than PSY-PLB group (p = 0.042). During recall task: - There was no significant difference between PSY-PLB and PSY-CBD group (p = 0.71). - There was no significant difference between PSY-PLB

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
								and HC group (p = 0.15).
Rizkallah et al. (2022)[13][5]; Canada	Randomized, double-blind, placebo-controlled.	- 78 Participants with cocaine use disorder (CUD). - Participants were matched in age, sex and CUD severity,	- 10/78 (12.8%) of participants had a cannabis use disorder.	Intervention was given for the duration of 92 days.	Oral form of: - CBD: 800 mg/day. - Placebo capsule.	Cambridge Neuropsychological Test Automated Battery (CANTAB).	- Working memory.	- CBD treatment showed no improvement in working memory. - CBD and placebo groups performed similarly (Wald $\chi 2$ = 3.070; 95% CI = – 4.81 to 5.21: p = 0.080).

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		ethnicity, education level, and other substance use disorders. - Age was not mentioned but F:M = 14:64. - CBD group, N = 40						

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		- Placebo group, N = 38						
Woelfl et al. (2020)[13][2]; Germany	Double-blind, randomized, parallel-group, placebo-controlled experi	- 60 healthy volunteers completed the protocol. - PLA/PLA (Placebo/Placebo) N = 15, Age = 26 (21, 25,	Cannabis lifetime uses: - PLA/PLA = 3 (1, 2, 4, 5) - CBD/PLA = 6 (2, 4, 8, 10) - PLA/THC = 6 (6, 6, 6, 7)	- Oral intervention was given 205 mins prior test.	Oral form of: - CBD: 800 mg (>99.8% pure, from STI Pharmaceuticals; UK).	- Letter Number Sequencing Test.	- Working memory	- Pre-treatment with CBD did not reduce THC induced memory impairment. - CBD/THC group showed poorer performance compared to CBD/PLA (p = 0.005).

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
	mental trial.	28, 29), F:M= 0:15 - CBD/PLA N = 15, Age = 25 (20, 24, 26, 37), F:M= 0:15 - PLA/THC N = 15, Age = 24 (20, 22, 26, 27), F:M= 0:15 - CBD/THC N = 15, Age = 27 (21, 23,	- CBD/THC = 5 (4, 4, 5, 6) Data are presented as median (0, 25, 75, 100 percentiles).		- THC: 20 mg (98.8% pure from THC-Pharm; Germany). - Placebo capsule.			- CBD showed no detrimental effects on emotion, cognition, and attention.

Author, Year & Country	Study Type	Population, Characteristics and Size	Cannabis use and frequency	Duration of Intervention	Intervention and Control	Clinical Test	Types of Memory	Results
		29, 23), F:M= 0:15 Data were median (0, 25, 75, 100 percentiles).						

Chapter 5
Discussion

This current review provides a systematic overview and interpretative analysis of studies that investigated the effects of CBD on memory. It is the first systematic review that attempts to examine different types and aspects of memory processing as well as combining both animal and human studies together.

5.1 Episodic Memory

In animal studies, episodic memory was tested under recognition memory paradigm. Recognition memory is an explicit or declarative memory that falls under the subcategory of episodic memory as it is an ability to recognize previous information of events, objects or people/animals[54]. Animals has the innate preference for novelty and thus would spend more time with novel objects/animals than familiar ones.

Overall, preclinical animal studies revealed a promising result where CBD treatment were shown to improve and reversed deficits in episodic memory in cognitive impaired mice modeled for dementia[8,86,87,90,91,94,95,121]. It was also suggested that higher dosage of CBD was more effective in reversing the deficits. However, the cognitive impaired model of FAAD and Fragile X syndromes [96,122] showed no improvement which suggest the difference in the underlying pathological mechanism. FAAD and Fragile X syndromes were both responsible for various congenital abnormalities, whereas the impairment above were more chronic degenerative diseases/disorders.

One of the possible mechanisms to explain this is the anti-inflammatory effect of CBD[27] where inflammation, in response to amyloid β plaques and neurofibrillary tangles, is one of the central mechanisms of dementia like Alzheimer's disease[138]. It is also possible that the improvement in episodic memory deficit in schizophrenia-like animal models might be due to the antipsychotic effect of CBD[15,46] that causes an alleviate in the overall cognitive function that is reflected in memory. Furthermore, the pathological mechanisms for Schizophrenia were theorized to be due to dopamine's hyperactivity, disruption of brain

connectivity, reduction of dendritic spines on cortical pyramidal neurons and NMDA receptor hypofunction which results in an imbalance of excitation and inhibition signaling[139].

Thus, CBD's role in restoring homeostasis of neurotransmitter[43,69,71] as "circuit-breaker"[29] and synaptic plasticity[18,21] would offer an explanation to why there was an improvement in cognitive functions of animals modeled with schizophrenia-like symptoms. While there was one animal study that examined the effect of CBD alone in non-disease model, it is worth to note that CBD alone did not have significant effect on memory in a non-disease animal model. Thus, the improvement in episodic memory in mice modeled for dementia and schizophrenia-like symptoms has further support the potential therapeutic use of CBD to improve the cognitive performance in Alzheimer's[3,10] and psychological disorder[3,15] in humans.

Even though the preclinical animal studies provided strong positive evidence on the effects of CBD on episodic memory, the results from human RCT studies were not as promising. Two[131,134] out of six studies[126,127,130,136] showed enhancement in episodic memory recall in which only the study done by Hotz and colleagues[134] was of low risk in bias. While the studies that found no effect of CBD on task performance, their results in the neuroimaging part were significant. The three studies[126,127,130] that collaborated neuroimaging investigation found correlations between CBD treatment and brain activities, where there was intermediate level of activation in the brain area of healthy participants involved in memory such as parahippocampal gyrus/midbrain in comparison to placebo and control[126]. CBD treatment were also found to increase CBF in the hippocampus[127] and attenuation of dysfunctionality in prefrontal activation and hippocampal-striatal functional connectivity[130] of participants with psychosis or related disorder. This is in lined with the preclinical evidence provided from mice modeled for schizophrenia-like symptoms mentioned above as a possible explanation of the mechanism why there was an improvement in episodic memory performance. The results from the neuroimaging assays were further supported by previous systematic review on neuroimaging studies[19].

The effects of both enhancement and diminishment of memories are supported by previous evidence[62] where it is dependent to the types of neurons and synaptic location, as well as the retrograde nature of the endocannabinoid system's signaling that attenuate the presynaptic release of both excitatory and inhibitory neurotransmitter[19]. These

contradicting results could be further explained through the emotional state of the participants. It is possible that additional stress was induced during task performance due to experimental setting which could enhanced memory consolidation but impair recall[58–61,140] which might be why there were activations of various memory brain regions but did not reflect in the memory performance.

5.2 Spatial and Working Memory

Spatial memory is a type of memory that operates in both short-term (working memory) and long-term memory (episodic memory), whereas, working memory is information stored in the STM capacity that is used to execute daily cognitive function[54]. Similar to episodic memory, preclinical animal studies showed overall improvement in spatial working memory in regards to preventive and restorative effects of CBD treatment in mice modeled for dementia[88,91,94,95], and other disorders such as FASD[96], Schizophrenia-like[117], TGCI[92], SRS[99] and Meth addiction[100]. Additionally, CBD treatment was shown to increase the rate of spatial learning in non-disease animal model[97]. The dose dependent relationship was also found for spatial working memory. The possible mechanisms of action were consistent with the explanation in episodic memory of anti-inflammatory[138], antipsychotic[15,46], circuit breaking[29,139], restoring the homeostasis of neurotransmitters[43,69,71] and synaptic plasticity [18,21]. The findings reinforced the potential use of CBD to improve the cognitive performance in disorders such as neurodegenerative disorder[10], psychological disorder[3,15] and epilepsy[7,141].

There was only one[127] out of five[131,133–136] studies that showed improvement of working memory. However, the improvement was reported as reaction time in working memory task not the accuracy of memory. Similar to the neuroimaging reports in episodic memory, Bloomfield et al.[127] found that there was an increased CBD in ORF which is in lined with previous evidence[19]. Another similarity to the results from the episodic memory part was that the studies done in human shown no effect of CBD treatment on working memory which again could be explained through the similar mechanism in episodic memory[58–62,140].

5.3 Fear Associated Memory

Traditionally, fear associate memory is classified as implicit or nondeclarative memory due to its classical conditioning nature, however, explicit or declarative memory can also be formed during intense emotional experience[54,142,143]. Therefore, fear associated memory represent both crossing over of implicit and explicit memory domains.

The different phrases of fear memory can be compartmentalized into memory consolidation, reconsolidation, extinction and reinstatement. Memory consolidation refers to stabilization of newly acquired labile memory that was vulnerable to disruption from interference and distraction[144], while memory reconsolidation is a process where stabilized memory is reactivated and retrieved in response to a memory trace[55]. Fear extinction is defined as a decreased in conditioned fear response following exposure to a nonreinforced feared conditioned stimulus[145] and reinstatement refers to the triggering of fear response after extinction[146].

Overall, fear memory's expression was decreased and CBD treatment was shown to block the formation of fear memory in eighteen[78,80–82,84,91,101,103–109,111,112,115,123] out of twenty-five preclinical animal studies. Memory consolidation and reconsolidation were impaired, while memory extinction was enhanced and reinstatement was blocked. There was an effect of window period, although the duration was different between each study[105–107]. Dose dependent mechanism was also found with higher dosage are more effective[81,82,103,112] and that CBD effect on memory was dependent to the activation of CB1 receptors[103,105,109]. This is in accordance to previous studies that demonstrated the dependency of CBD on CB1 receptors on memory performance[50,51,63,64,147]. Additionally, protein expression was decreased in memory related brain area and a reduction in dopamine released in the cortico-limbic system[105,106]. The increased in the dopamine aligned with the stress induced upregulation of dopaminergic and noradrenergic activity through the sympathetic-adrenal-medullary (SAM) axis[59,60,140] where it should enhance memory consolidation and perhaps reinstatement, however the anxiolytic effect[3,15,46] of CBD and modulation of neurotransmitter[43,71] were suggested to counteract this enhancement

resulting in the blocking of fear memory formation. The blocking of fear memory formation would sequentially enhance memory extinction.

There was only one human's RCT study[128] that examined fear associated memory where CBD treatments were shown to impair recall and reinstatement of fear memory, while extinction of fear memory was enhanced. This is in accordance with the results from the preclinical animal studies. The mechanisms behind the similarity in findings were proposed to be the same as for the animal studies. Thus, CBD treatment could be a potential therapeutic agent in treating patients with PTSD as referred to previous evidence[12]. However, it is vital to note that the study by Das and colleagues[128] had a high risk of bias.

5.4 Drug Associated Memory

Drug associated memory was tested using Conditioned place preference (CPP) which demonstrated Pavlovian learning, memory, and reinforcing effects of drugs where classical conditioning and context associations intertwined with one another in a complex relationship[148]. Classical conditioning is a form of implicit or nondeclarative memory while contextual (context-dependent) memory is a form of episodic memory which is a subset of explicit or declarative memory. CPP includes phrases of acquisition, expression, extinction, and reinstatement of memory[148]. Acquisition referred to the pairing of conditioned stimulus to an unconditioned stimulus that resulted in conditioned response, whereas the expression phrase is referred to how the conditioning was expressed and stabilized[149]. The extinction phrase is when there was a decreased in the conditioned response when the conditioned stimulus was repeatedly present without the unconditioned stimulus[149]. The reinstatement (relapse) is defined as the reacquisition of extinct conditioned response in the presence of unconditioned stimuli[149]. The acquisition of memory can be expressed as consolidation and reconsolidation of memory

Regarding drug associated memory, this systematic review only includes animal studies, as no human RCT studies were available. Different phrases of memory provided diverse results but overall, CBD treatment improved drug associated memory in regards to context preference, prevention of reinstatement and impair consolidation as well as reconsolidation[79,83,102]. Thus, demonstration diversity of effects in relations to the different

phrases of memory[62]. These findings provide a potential therapeutic use of CBD treatment in drug associated memory and addiction in human depending on the timing of when CBD was given during different phrases of memory.

5.5 CBD and THC

For both animal and human studies, detrimental effect of THC was found in all studies[67,85,110,119,120,129,132]. This is in accordance to evidence provided by previous studies[17,28,46,51,66,147]. However, it cannot be concluded that CBD treatment can counteracted THC induced memory impairment as stated by preceding studies[18,19,47,68,125] as there were similar numbers of studies that counterbalance both sides of the arguments. Although, the studies used different cognitive tasks and tested different types of memories which could therefore cause a disarray of results[62].

5.6 Adverse events

Overall, CBD was well tolerated in all studies that provided information on side effects and adverse events[67,126,129,132–134,136]. The adverse events were mild such as sedation, mild headache, abdominal pain, diarrhea and nauseas which resolved without intervention. Thus, suggesting that CBD is generally safe to use in participants that has no severe physical illness.

5.7 Strengths

This is the first systematic review that has attempted to critically analyze a combination of animal and human studies specifically to memory paradigm and CBD treatment. While animals and humans are qualitatively different in relations to brain functions, the “quantitative” similarities offered additional insight where limitations and restrictions in human studies were evident. This systematic review includes newer and more current studies, therefore providing a more up-to-date evidence and analysis in CBD studies.

5.8 Limitations

Due to a broad eligible criterion where the search was not limited to conditions of population (underlying disease and cannabis status), intervention (CBD’s dosage, types and routes of administration) and cognitive tasks, there was a lack of homogeneity amongst the

included studies. The original plan for this systematic review was to incorporate a meta-analysis as part of the analysis but due to the heterogeneity among the included studies, this approach was not deemed feasible or appropriate. However, it can be arguable that the research question focused on different types of memories and there were limiting numbers of cannabis or CBD related studies due to ethical and legality issues so broader eligible criteria were needed to get a sense of overall picture and included as many relevant studies as much as possible. The nature of the included studies was experimental study where there was a lack ecological validity and generalization to everyday cognitive performance task. Another generalizability drawback is from the difference in the populations of each study (healthy vs. diseased models) in which results from participants with underlying diseases may not be applicable to general healthy population. The overall risk of bias assessment of included studies had some concerns and high risk in bias (60% low risk, 25% some concerns and 15% high risk) which could affect the internal validity of the results.

In regards to the limitations of the review process, only five databases were chosen for this systematic review which consisted of English language studies. Thus, other valuable studies might be overlooked from the review process. There were two reviewers for the selection process and a third reviewer included in case of any discrepancy. The lesser number of reviewers can give raise to subjectivity and bias which could affect the integrity of the review processes. Thus, this systematic review must be read with consideration of these limitations.

5.9 Implications and future directions

In accordance to previous evidence[19,62], this systematic review does answer the research question and provided evidence that CBD treatment does affect memory where CBD can both have positive and negative impact on memory performance through the modulation of neurotransmitters and activation of cannabinoid receptors which effects physical and emotional status of the users. The results from animal studies were more conclusive in determining that CBD improve episodic (declarative/explicit) memory, spatial memory, working memory, fear and drug associated memory in diseased animal models which provides evidence in the potential therapeutic use of CBD treatment for memory impairment in dementia, schizophrenia-like disorder and PTSD. Additionally, in terms of

memory processing, CBD treatment affects consolidation, reconsolidation, extinction and reinstatement of memory. CBD is also considered generally safe with self-resolving adverse effects suggesting that CBD can be use therapeutically and recreationally.

Although the human studies provided limiting support and were not as conclusive as the results from animal studies, the neurological data offered physiological evidence of CBD's impact on memory related brain regions. The notion of how memory performance was not in concordance with the brain's activity in response to CBD offered a better understanding of memory paradigms and processes. Memory must be viewed as a dynamic phenomenon where present cognitive tasks may not be the true measurement of memory. Different cognitive tasks represent different types of memories and also provoke different elements of memories in relation to recruitment of brain areas, synaptic plasticity, strength of memory tracing and even emotional status. Thus, it can be arguably said that cognitive tasks are a reductionist method in measuring and capturing memory. Future human studies involving a multidisciplinary test such as combining memory task, neuroimaging apparatus, neurotransmitter activity and biological markers at different stages of memory processing might provide a better insight and conclusion in how CBD dynamically effects memory.

Additionally, this systematic review highlights the difference in the dosage and how CBD was administered in each study. It was also suggested a dose dependent mechanism where higher dosage was more effective, however the effective dosage was not consistent among studies. Animal studies mostly used intraperitoneal injection as preferred route of administration which bypass first-pass metabolism and have better drug distribution while human studies used oral administration. Therefore, more studies are needed to determine the therapeutic index (pharmacodynamic) and route of administration (pharmacokinetics) to establish standardized protocol of CBD usage.

Another factor to consider when evaluating the cognitive and brain effects of CBD is that these effects may vary based on the diversity of animal and participants which include the underlying condition, cannabis status and whether they are taking other medications or drugs. Further research for profiling, involving larger and diverse populations and their biological markers is necessary to comprehend the individual variations and to identify those whose memory performance could potentially benefit from CBD.

One other aspect to address the contradicting effects of CBD is to take into account of how CBD interacts with other compounds in the cannabis plant to produce an entourage effect which may enhance its therapeutic potential. Perhaps, a different approach in using cannabinoids should be considered where synergy of compounds is used instead of isolated single compound and RCT studies on strain specific cannabis may shed light into these controversial results. However, this approach for future studies may be challenging due to legal restriction of using the whole cannabis in many countries.

5.10 Conclusion

Overall, the results of this systematic review suggest that CBD may play a potential role in modulating different types of memories. Based on available evidence from both animal and human studies, CBD appears to have a beneficial effect on fear-associated memory. Furthermore, animal studies suggest that CBD may also positively affect episodic, spatial working memory and drug associated memory. However, additional research involving human participants is necessary to provide more conclusive evidence in this regard.

The effects of CBD on THC-induced memory impairment are, however, less clear and require further investigation. The results also suggest that the effects of CBD on memory function may depend on physiobiological status, cognitive tasks, dosage, and route of administration. The studies included in this review indicate that CBD may have potential as a therapeutic agent for memory-related disorders, although further multidisciplinary research is needed to determine the profile, optimal dosage, route of administration, and long-term effects of CBD on memory function. In conclusion, these findings support the potential of CBD as a promising therapeutic option for improving memory function in various clinical and non-clinical populations.

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Appendix

Appendix A

Ethics Approval

DPU DHURAKIJ PUNDIT UNIVERSITY มหาวิทยาลัยธุรกิจบัณฑิตย์

บันทึก
Memorandum

ที่ DPUHREC 0202/2566 วันที่ 2 กุมภาพันธ์ 2566
จาก สำนักงานคณะกรรมการจริยธรรมการวิจัยในมนุษย์ มหาวิทยาลัยธุรกิจบัณฑิตย์
เรียน แพทย์หญิงศิวพร ปราณีนิจ

เรื่อง แจ้งผลการประเมินตนเองเกี่ยวกับจริยธรรมการวิจัยในมนุษย์

ตามที่ วิทยาลัยการแพทย์และบูรณาการ มหาวิทยาลัยธุรกิจบัณฑิตย์ ได้ขอความอนุเคราะห์ให้ทางสำนักงานคณะกรรมการจริยธรรมการวิจัยในมนุษย์ฯ พิจารณาผลการประเมินตนเองเกี่ยวกับจริยธรรมการวิจัยในมนุษย์ ของ **แพทย์หญิงศิวพร ปราณีนิจ วิทยาลัยการแพทย์และบูรณาการ มหาวิทยาลัยธุรกิจบัณฑิตย์** โครงการวิจัยเรื่อง การทบทวนอย่างเป็นระบบและการวิเคราะห์อภิมาณเกี่ยวกับผลของสารแคนนาบิไดออล (Cannabidiol) ต่อความจำประเภทต่างๆ

จากการตรวจสอบเบื้องต้นโดยพิจารณาจาก แบบตรวจสอบ IRB Checklist DPUHRECs และโครงร่างการวิจัย ทางคณะกรรมการจริยธรรมการวิจัยในมนุษย์ฯ ได้พิจารณาแล้วเห็นว่า การดำเนินงานวิจัยของโครงการวิจัยดังกล่าว **ไม่เข้าข่ายจริยธรรมการวิจัยในมนุษย์**

ทั้งนี้ผลการพิจารณาเอกสารดังกล่าวข้างต้น ไม่ถือเป็นการรับรองจริยธรรมการวิจัยในมนุษย์

จึงเรียนมาเพื่อโปรดทราบ

(รองศาสตราจารย์ ดร.พยงค์ วณิเกียรติ)
ประธานคณะกรรมการจริยธรรมการวิจัยในมนุษย์

มหาวิทยาลัยธุรกิจบัณฑิตย์

โทร. 128, 632
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BIOGRAPHY

Name Siwaporn Praneenij, M.D.

Educational Background

2016 – 2017 - Master of Science in Psychology with Merit, University of Westminster

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Work Experiences

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