

Therapeutic potential of minor cannabinoids in psychiatric disorders: A systematic review

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ABSTRACT

Interest in cannabinoids' therapeutic potential in mental health is growing, supported by evidence of the involvement of the endocannabinoid system in psychiatric disorders such as anxiety, depression, and addiction. While the major cannabinoids cannabidiol (CBD) and Δ^9 -tetrahydrocannabinol (Δ^9 -THC) have been more extensively researched, approximately 120 minor cannabinoids from the cannabis plant have been identified. Although some displayed promising pharmacological profiles, research on their application for psychiatric disorders is fragmented. This systematic review evaluates, for the first time, both preclinical and clinical studies exploring minor cannabinoids' therapeutic potential in psychiatric disorders.

22 preclinical studies and one clinical study were included, investigating various minor cannabinoids in substance use disorders, anxiety disorders, depressive disorders, trauma and stressor-related disorders, psychotic disorders, neurodevelopmental disorders, and eating disorders. Despite the heterogeneous results and the moderate to high risk of bias in several articles, certain compounds demonstrate promise for further investigation. Δ^8 -tetrahydrocannabidivarin (Δ^8 -THCV) exhibited potential for nicotine addiction; Δ^9 -tetrahydrocannabidivarin (Δ^9 -THCV) for psychotic-like symptoms; cannabidiolic acid methyl ester (CBDA-ME) alleviated anxiety and depression-like symptoms, and cannabidivarin (CBDV) autism spectrum disorder-like symptoms.

1. Introduction

Cannabis sativa plant has been used for millennia for both medicinal and recreational purposes, but it is only in recent times that it drew the interest of modern medicine for its therapeutic and psychoactive properties (Merlin, 2003). An important advancement in cannabis research was the isolation and biochemical characterization of its two major components, the cannabinoids Δ^9 -tetrahydrocannabinol (Δ^9 -THC) (Gaoni & Mechoulam, 1971) and cannabidiol (CBD) (Adams et al., 1940), (Mechoulam & Shvo, 1963). This paved the way for the identification of the endocannabinoid system, which comprises cannabinoid receptors (CB1 and CB2), endogenous ligands (endocannabinoids), and the enzymes responsible for their synthesis and breakdown (Zou &

Kumar, 2018). Cannabinoids exert their effects primarily by binding to cannabinoid receptors CB1 and CB2 or by influencing the signaling pathways of the endocannabinoid system (Joshi & Onaivi, 2019), which is involved in a wide range of physiological functions. These functions include pain regulation, immune function, appetite, and metabolism, as well as mood and stress regulation (Zou & Kumar, 2018).

Δ^9 -THC is the most abundant phytocannabinoid (cannabinoid derived from the cannabis plant) and is responsible for the majority of the cannabis plant's psychoactive effects. These occur through the binding and activation of CB1 receptors, which are predominantly present in the central nervous system (Pertwee, 2008). CBD, although sharing with Δ^9 -THC a similar chemical structure, does not induce psychomimetic effects because of its lower affinity for the central CB1

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receptors (Russo & Marcu, 2017).

Research on both rodents and humans has provided substantial evidence for the efficacy of CBD, either alone or in combination with Δ^9 -THC, in treating a plethora of different conditions, including epilepsy, nausea post-chemotherapy, and spasticity in multiple sclerosis (National Academies of Sciences, Engineering, and Medicine, 2017). Driven by the need for alternative and more effective treatments in psychiatry, interest has also grown in the potential use of cannabinoids for mental health (Joshi & Onaivi, 2021; Sarris et al., 2020). In 2023, more than 100 trials assessing the effects of CBD as a treatment for various psychiatric disorders were registered at clinicaltrials.gov. In fact, both animal and human studies have shown that CBD may have anxiolytic, antidepressant, and antipsychotic properties (Batalla et al., 2019; Iseger & Bossong, 2015; Rohleder et al., 2016). Converging evidence suggests the involvement of the endocannabinoid system in the etiology of several mental illnesses, such as depressive disorders (Hill & Gorzalka, 2005), anxiety disorders (Patel et al., 2014), psychotic disorders (Bossong & Niesink, 2010; Leweke & Koethe, 2008), and substance use disorders (Maldonado et al., 2006). As a result, the endocannabinoid system emerges as a highly promising target for intervention (Bright & Akirav, 2022; Sarris et al., 2020).

While most of the research on the application of cannabinoids in mental health has focused on Δ^9 -THC and CBD, to date about 120 other phytocannabinoids have been identified (ElSohly & Gul, 2014). These are often referred to as “minor cannabinoids” due to their less investigated biological profile (Caprioglio et al., 2022; Stone et al., 2020). Examples include cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), Δ^8 -tetrahydrocannabinol (Δ^8 -THC), along with acidic cannabinoids such as Δ^9 -tetrahydrocannabinolic acid (Δ^9 -THCA) and cannabidiolic acid (CBDA), as well as propyl phytocannabinoids (varinoids) such as Δ^9 -tetrahydrocannabinoldivarin (Δ^9 -THCV) and cannabidivarin (CBDV) (Hanuš et al., 2016; Walsh et al., 2021).

A reason for these compounds being relatively overlooked is the challenge of isolating sufficient amounts (El-Alfy et al., 2010). However, recent cutting-edge preclinical research has made significant strides in characterizing their pharmacological profile and investigating their therapeutic potential (Stone et al., 2020; Walsh et al., 2021; Zagzoog et al., 2020). Some minor cannabinoids have already exhibited promising preclinical profiles, while being devoid of the psychomimetic effects of Δ^9 -THC (Walsh et al., 2021).

A better understanding of the behavioral pharmacology of the less studied components of cannabis is needed to validate their therapeutic potential and reject misleading information derived from subjective reports only. Some recent reviews have provided a general overview of the possible therapeutic uses of minor cannabinoids (Caprioglio et al., 2022; Stone et al., 2020; Walsh et al., 2021), whereas others have summarized the medicinal effects of cannabinoids (Black et al., 2019; McKee et al., 2021; Sarris et al., 2020), and CBD in particular (Batalla et al., 2019; García-Gutiérrez et al., 2020; Kwee et al., 2023), in neuropsychiatric disorders. To our knowledge, this is the first systematic review to critically assess preclinical and clinical studies that have investigated the therapeutic potential of minor cannabinoids in psychiatric disorders. With this work, we aim to shed light on which therapeutic applications are the most promising and which compounds are worth further investigation.

2. Material and methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 statement (Page et al., 2021), and it was registered on Open Science Framework (OSF) Registries on May 3, 2023.

2.1. Search strategy

Literature searches were performed up to April 3, 2023, using

PubMed/MEDLINE, Scopus, EMBASE, and PsycINFO databases. No restrictions on language or year of publication were applied. In addition, the registers “animalstudyregistry.com” and “preclinicaltrials.eu” were consulted. The search was based on a combination of search terms referring to “minor cannabinoids” and “psychiatric disorders”. MeSH terms, keywords, text words, and search strings were used appropriately for each database. The full search strings for each database are provided in the Supplementary File (see S1). Reference sections of the included articles were also screened to identify additional relevant studies.

2.2. Inclusion and exclusion criteria

This systematic review has a broad scope, focusing on the effects of minor cannabinoids in both humans, and animal models of any psychiatric indication. The following inclusion and exclusion criteria were applied, in accordance with the PICO (Population, Intervention, Comparison and Outcome) framework.

Population type: Studies with humans and animal models of any psychiatric condition and any sample size were included. Not in-vivo studies were excluded.

Intervention type: Studies in which any minor cannabinoid was administered were included, regardless of the modality of administration and doses. Studies involving synthetic cannabinoids were also included if the abstract explicitly mentioned that they were analogues of minor cannabinoids with a similar biological profile. Studies exclusively investigating major cannabinoids (CBD and Δ^9 -THC), studies focusing on endocannabinoids, and studies involving synthetic compounds that act on the endocannabinoid system but are not specifically analogues of minor phytocannabinoids were excluded.

Comparison type: Studies comparing the effects of minor cannabinoids vs. placebo were included. Reviews, case reports, observational studies, and commentary articles were excluded.

Outcome type: Included studies explored the differences between the effects of the investigated cannabinoids and placebo conditions, with respect to the disease-related symptoms under study and/or the respective clinical or preclinical tests used for a specific condition. Studies reporting outcomes not related to psychiatric symptoms or conditions were also excluded.

2.3. Data collection

2.3.1. Data selection

Retrieved articles were imported into the web-based software tool for systematic reviews, Rayyan, where duplicates were removed. Two reviewers (GC and MV) independently screened the articles by title and abstract. Thereafter, the full texts of potentially relevant articles were reviewed for inclusion. Disagreements were resolved through discussion between the two reviewers. In cases where consensus could not be reached, other reviewers (LG and AB) were consulted.

2.3.2. Data extraction

Relevant data from the included articles was extracted by one of the two reviewers (GC or MV) and cross-checked by the other. The extracted data included the following: study information (title, name of the authors, year of publication); psychiatric condition under study; cannabinoid under study (with respective doses, administration route, and number of administrations); sample characteristics (sample size, sex, and, for preclinical studies, animal strain and housing); tests performed; and outcomes.

The outcomes included descriptive results based on the author's conclusions (significant increase/decrease/no significant effect compared to the control group) and quantitative outcomes (mean effects and standard deviations of the experimental and control groups). Since most preclinical studies reported quantitative outcomes only graphically, mean effects and standard error measures for both experimental and control groups were extracted from figures by two reviewers (GC,

MV) using a digital ruler (Universal Desktop Ruler). Subsequently, standard deviations were calculated based on mean effects, sample sizes, and standard error measures. When sample sizes were reported as a range, the lowest sample size was utilized for calculations. If upper and lower confidence limits were reported instead of the standard error measures, the limit representing the largest deviation from the mean was used to calculate the standard deviation. Tests with missing or unclear information regarding sample size and error measures were excluded from further data synthesis steps.

As some of the included studies assessed the effects of a compound using different tests with multiple outcomes, information to extract was selected upfront. Two experienced preclinical researchers (LG, MV) identified a primary test and primary outcome for each experimental group. These were defined as the most representative to explore the specific psychiatric disorder under study. Multiple tests assessing the same compound could be selected when different groups of animals were used. Thereafter, a psychiatrist and a resident in psychiatry (AB, PvdM) were consulted to confirm the translational relevance of the selected outcomes to human psychiatric disorders. If multiple doses of cannabinoids were tested, the dose yielding the largest effect was extracted.

2.4. Data synthesis

Due to the heterogeneity of the retrieved data regarding the conditions under study, the compounds examined, and the tests performed, conducting a meta-analysis was not feasible. Therefore, we opted for a qualitative data synthesis approach. This involved organizing and structuring the data separately based on the psychiatric condition and the specific minor cannabinoids under investigation.

Furthermore, to visualize the effect sizes of the most effective doses for the previously selected outcomes, we created a forest plot based on standardized mean difference (SMD) and 95% confidence intervals (95% CI). Hedge's *g* was used as a standardized measure of effect size, and it was calculated based on sample sizes and the extracted group means and standard deviation.

All statistical analyses were performed using RStudio (R Core Team, 2024).

2.5. Risk of Bias (RoB)

The SYRCLE tool was used to assess the risk of bias (RoB) in preclinical studies (Hooijmans et al., 2014). This tool employs a set of signaling questions, addressing six different types of bias (selection, performance, detection, attrition, reporting, and “other sources of bias”), to categorize the articles into low, high, or unclear (moderate) risk of bias. Two additional items, pertaining to any process of blinding and any randomization mentioned in the study, were assessed, and reported separately. The “revised Cochrane risk-of-bias tool for randomized trials” (RoB 2) was used to evaluate RoB in the single randomized clinical study included (Sterne et al., 2019). RoB 2 encompasses questions related to five domains, including randomization process, intervention deviation, missing outcome data, outcome measurement, and result reporting. The RoB assessment was independently performed by two reviewers (GC, MV). Any disagreements were resolved through discussion, and when consensus could not be reached, reviewers (AB, LG) were consulted.

3. Results

The search strategy retrieved a total of 1612 articles, which was reduced to 1308 after removing duplicates. Thirty-five publications underwent full-text screening, leading to the exclusion of thirteen other articles. One additional article was identified by screening the reference lists of relevant studies. This process yielded a total of 23 articles for inclusion in this systematic review (see Fig. 1).

3.1. Description of the included studies

Twenty-two articles explored the effects of minor cannabinoids on various proxies for psychiatric disorders in animal models. While some authors used specific disorder terms to refer to proxies for the conditions under study, we organized the retrieved studies according to the categories used in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM 5) (American Psychiatric Association, 2013). i) nine studies focused on substance-related and addictive disorders; ii) eight studies on anxiety disorders; iii) three studies on trauma- and stressor-related disorders; iv) three studies on depressive disorders; v) two studies on schizophrenia spectrum and other psychotic disorders; vi) one study on neurodevelopmental disorders. Only one human study, which focused on psychotic disorders, met the inclusion criteria and was included in this systematic review.

Regarding the most studied minor cannabinoids: i) nine articles assessed the properties of CBDA; ii) five studies Δ 8-THC; iii) four studies CBG; iv) four studies CBN; v) four studies Δ 9-THCV; v) three studies CBDA synthetic analogue, cannabidiolic acid methyl ester (CBDA-ME or HU-580). While some authors have referred to CBDA-ME by its other name, HU-580, in this article we will refer to it only as CBDA-ME. Other assessed compounds included CBC (two studies), CBDV (two studies), 11-OH- Δ 8-THC, a metabolite of Δ 8-THC (two studies), Δ 8-THCV (one study), and Δ 9-THCA (one study). Some of the included articles examined the properties of multiple cannabinoids, compared them to one another and to the major cannabinoids Δ 9-THC and CBD. Details about the characteristics of the included articles can be found in Table 1. Effect sizes for the most effective doses of the compounds under study for the previously selected outcomes are presented in the forest plot (Fig. 3). Three studies did not report information on sample size and/or error measures and thus were excluded from the forest plot (Chesher et al., 1985; Rock et al., 2014; Yamaguchi et al., 2001).

3.2. RoB of the included studies

An overview of the results of the RoB assessment for preclinical studies is presented in Fig. 2. The detailed results of individual studies can be found in Supplementary Table S2.1. Overall, the reporting quality was moderate to poor, with a prevailing unclear risk of bias across all six categories. The most common form of bias observed was attrition bias, with 39% of the studies inadequately addressing the data (see Fig. 2). Regarding the two additional items assessed, 43% of the studies mentioned some form of blinding, while 52% of the studies reported randomization practices. The single human study included in the review had an overall low risk of bias according to the RoB-2 tool. Detailed results for this study are shown in Supplementary Table S2.2.

3.3. Preclinical studies

3.3.1. Substance-related and addictive disorders

Five studies examined the effects of minor cannabinoids on naloxone-precipitated withdrawal symptoms in morphine-dependent rats. Behavioral signs of morphine withdrawal, such as repeated jumping behavior and forepaw tremors, were used as outcome measures. (Bhargava, 1976, 1978) observed an effect of Δ 8-THC and 11-OH- Δ 8-THC in reducing jumping withdrawal syndrome, defecation, and rearing behavior in Swiss Webster mice. This effect was present at doses of 5 and 10 mg/kg, but only when administered no earlier than 30 minutes before naloxone administration. Yamaguchi et al. (2001) also found Δ 8-THC to reduce the number of jumps and forepaw tremors at a dose of 10 mg/kg in a different mouse strain. Two studies explored the effects of CBN on morphine withdrawal signs in Sprague-Dawley rats. Chesher et al. (1985) found that CBN was effective in reducing several behavioral signs, collectively regarded as quasi morphine withdrawal syndrome (Collier et al., 1974), at doses of 5, 20, and 80 mg/kg. Hine et al. (1975) did not find any effect in similar experimental conditions at

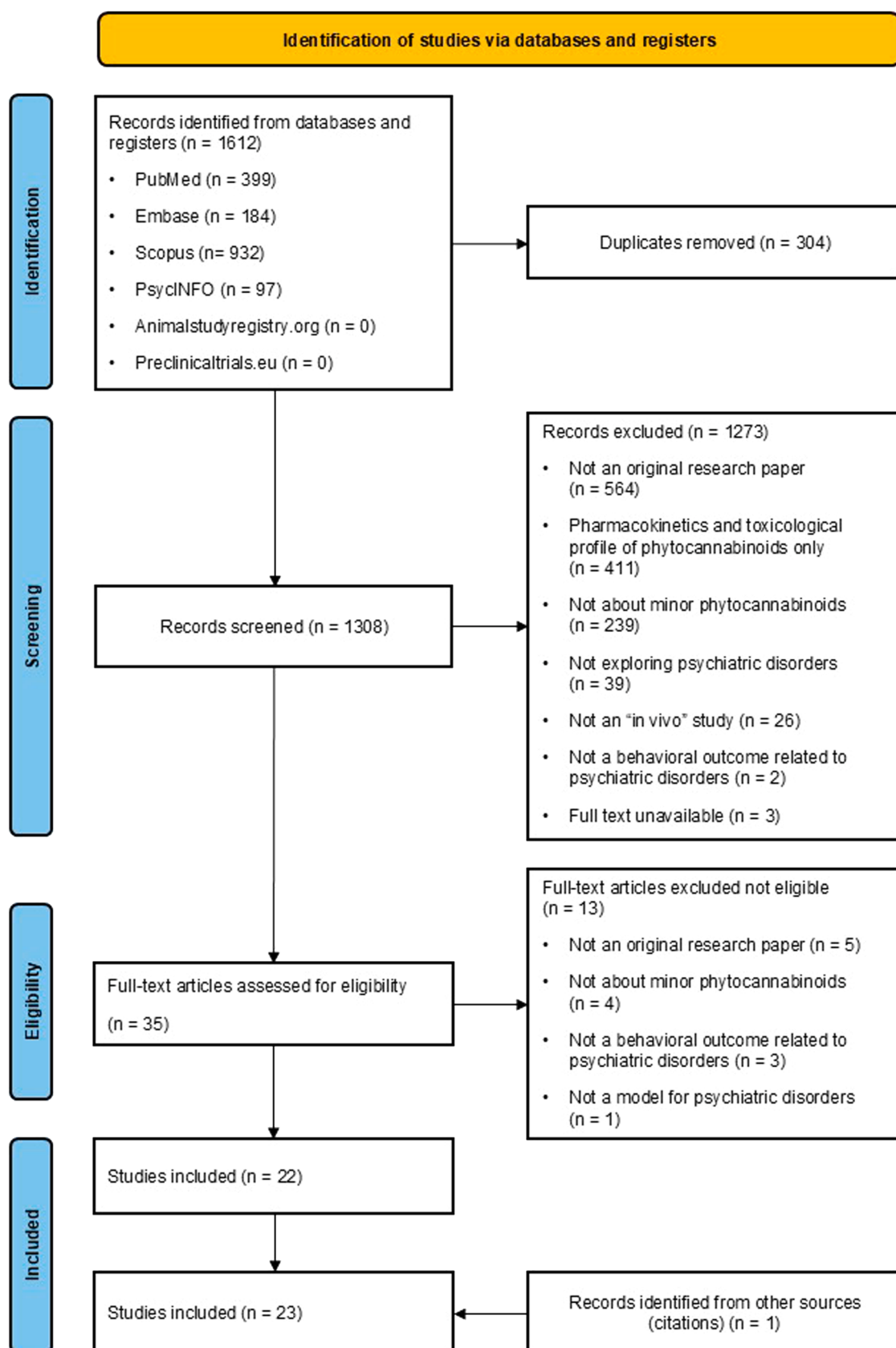


Fig. 1. PRISMA Flowchart.

Table 1
Characteristics of preclinical studies.

Condition under study	First author	Compounds	Animal characteristics (strain; sex; housing)	Sample per group	Route; n of administration	Doses	Test	Outcomes	Results	Conclusion
Substance-related and addictive disorders										
Morphine addiction	Bhargava (1976)	CBN, $\Delta 8$ -THC, 11-OH- $\Delta 8$ -THC	SW mice; male; group	7–10	IP; 1x (30 min before naloxone)	2.5, 5, 10, 20 mg/kg	Naloxone-precipitated withdrawal	Dose of naloxone to precipitate jumping in 50% of mice (ED50)	- $\Delta 8$ -THC: $\uparrow$ of naloxone dose needed at 5 and 10 mg/kg - 11-OH- $\Delta 8$ -THC: $\uparrow$ of naloxone dose needed at 5 and 10 mg/kg - CBN: $\uparrow$ of naloxone dose needed at 5, 10 and 20 mg/kg	$\Delta 8$ -THC, 11-OH- $\Delta 8$ -THC and CBN are effective in inhibiting naloxone-precipitated morphine withdrawal symptoms when administered 30 min before naloxone
	Bhargava (1978)	$\Delta 8$ -THC, 11-OH- $\Delta 8$ -THC	SW mice; male; group	8–10	IP; 1x (2, 4, 6, 24h before naloxone)	10 mg/kg	Naloxone-precipitated withdrawal	Dose of naloxone to precipitate jumping in 50% of mice (ED50)	No significant effect	$\Delta 8$ -THC and 11-OH- $\Delta 8$ -THC are not effective against naloxone-precipitated morphine withdrawal when administered earlier than 30 min before naloxone
	Hine et al. (1975)	CBN	SD rats; male; nr	6–7	IP; 1x	10 mg/kg	Naloxone-precipitated withdrawal	Abstinence signs; n of turns in 15 and 30 min	No significant effect	CBN alone does not modify abstinence signs
	Chesher et al. (1985)	CBN	SD rats; male; group	4	IP; 1x	5, 20, 80 mg/kg	Administration of phosphodiesterase inhibitor IBMX and Naloxone to induce signs of QMWS	Mean withdrawal score from signs of QMWS: rearing, grooming, wet-dog shakes, head shakes, chewing, paw licks, diarrhea, rapid respiration	$\downarrow$ of the mean withdrawal score at all doses tested	CBN is effective in reducing signs of QMWS
	Yamaguchi et al. (2001)	$\Delta 8$ -THC	ddY mice; male; nr	nr	IP; 1x	1, 3.2, 10 mg/kg	Naloxone-precipitated withdrawal	- n of jumps in 20 min - n of forepaw tremors in 20 min - n of lever presses in 120 min (METH-priming) - n of lever presses in 60 min (cue-associated) - n of lever presses in 120 min (METH-priming)	- $\downarrow$ n of jumps at 10 mg/kg - $\downarrow$ n forepaw tremors at 10 mg/kg $\Delta 8$ -THC administered on reinstatement phase: - $\downarrow$ lever presses at 0.32 mg/kg after METH-priming - $\uparrow$ lever presses at 1 mg/kg after cue $\Delta 8$ -THC administered on extinction phase: - $\downarrow$ lever presses at 3.2 mg/kg (after 5x administration; after 1x on day 5, still	$\Delta 8$ -THC shows reduction of opiate withdrawal symptoms
METH addiction	Anggadiredja et al. (2004)	$\Delta 8$ -THC	Wistar/ST rats; male; nr	5–8 (on reinstatement phase) 5–8 (on extinction phase)	IP; 1x (on reinstatement phase) 5x (1/die on extinction phase); 1x (on day 5 of extinction phase)	0.1, 0.32 mg/kg (METH-priming) 1 mg/kg (cue induced) 3.2 mg/kg (extinction phase)	- Effect of $\Delta 8$ -THC on reinstatement of METH-seeking behavior induced by METH-priming - After re-exposure with METH-associated cues - Effect of $\Delta 8$ -THC administered during the extinction phase on reinstatement of METH-seeking behavior	- Effect of $\Delta 8$ -THC on reinstatement of METH-seeking behavior	- $\downarrow$ lever presses at 3.2 mg/kg (after 5x administration; after 1x on day 5, still	$\Delta 8$ -THC is effective in maintaining drug abstinence (extinction phase)

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Table 1 (continued)

Condition under study	First author	Compounds	Animal characteristics (strain; sex; housing)	Sample per group	Route; n of administration	Doses	Test	Outcomes	Results	Conclusion
Nicotine addiction	Umpierrez et al. (2022)	CBDA	SD rats; male; group	12	IP; 1x	0.1, 10, 1000 mg/kg	OFT	Locomotion (n of beam breaks in 60 min)	significant on day 12) No significant effect	METH effect on locomotion is not normalized by CBDA
	Xi et al. (2019)	$\Delta 8$ -THCV	Alcohol preferring rats (self-administration and relapse) or ICR mice (CPP and withdrawal); male; single (P rats) or group (ICR mice)	8–12	IP; 1x	3, 10 mg/kg 10, 20 mg/kg 10, 20 mg/kg 0.03, 0.3, 3, 30 mg/kg 0.3 mg/kg 0.3 mg/kg	- Nicotine self-administration - Relapse after cued conditioning - Relapse with reinstatement - CPP - EPM - Somatic signs of withdrawal	- n active lever pressing (self-administration) - n active lever pressing (cued-conditioned relapse) - n active lever pressing (relapse after reinstatement) - Time in the nicotine-paired chamber (CPP) - Time in the open arms of the maze - Average n of somatic signs	- $\downarrow$ active lever pressing (self-administration) - $\downarrow$ lever pressing (cued-conditioned relapse) - $\downarrow$ lever pressing (relapse after reinstatement) - $\downarrow$ time in the nicotine-paired chamber (CPP) - $\uparrow$ time in the open arms of the maze - $\downarrow$ n somatic signs of withdrawal	$\Delta 8$ -THCV showed anti-nicotine-dependence effects in several different preclinical models
Cocaine addiction	Alegre-Zurano et al. (2020)	CBDA	CD1 mice; male; nr	8–10	IP; 1x	0.01, 0.1 mg/kg	CPP	Time in the cocaine-paired chamber	No significant effect	CBDA does not alter rewarding effect of cocaine
Anxiety disorders	Alegre-Zurano et al. (2020)	CBDA	CD1 mice; male; nr	10	IP; 1x and 10x (1/die)	0.001, 0.01, 0.1, 1.0 mg/kg	- Social interaction test - EPM	- Sociability/social novelty (time in the intruder/ new intruder compartment) - % of time in open arms; entries in open and closed arms	- No significant effect - No significant effect	- Limited effects on anxiety-like behavior
	Assareh et al. (2020)	CBDA	C57BL/6J mice; male; group	10–17	IP; 1x	0.1, 1, 10, 30 mg/kg	LD after FS	% time in the light compartment	$\uparrow$ % time in the light compartment after FS at 1 mg/kg	CBDA can reverse shock-induced increased anxiety in LD test
	Brierley et al. (2016)	CBDA	LH rats; male; group	10	Per orem; 1x	5 mg/kg	- OFT - LD - NSF	- Time in the central sector of the open field - Time in the light compartment - Latency to onset of feeding	- No significant effect - No significant effect - No significant effect	Administration of CBDA alone does not have a significant anxiolytic-like effect
	O'Brien et al. (2013)	$\Delta 9$ -THCV, CBG	SD rats; male; single	8	ip; 1x and 14x (1/die)	2.5 mg/kg	LD	Time in the light compartment	$\Delta 9$ -THCV: no significant effect CBG: no significant effect	Limited effects of acute and chronically administered $\Delta 9$ -THCV and CBG on anxiety-like behaviors

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Table 1 (continued)

Condition under study	First author	Compounds	Animal characteristics (strain; sex; housing)	Sample per group	Route; n of administration	Doses	Test	Outcomes	Results	Conclusion
Trauma- and stressor-related disorders	Pertwee et al. (2018)	CBDA, CBDA-ME	SD rats; male; group	8–12	IP; 1x	0.01 ug/kg	LD no FS LD after FS	Time in the light compartment	- CBDA: No significant effect with no FS; no significant effect after FS - CBDA-ME: no significant effect with no FS; ↑ of time in the light compartment after FS	CBDA-ME can reduce FS enhancement of anxiogenic-like behavior in the LD test at 0.01 ug/kg
	Rock et al. (2017)	CBDA	SD rats; male; group	6–10	IP; 1x and 21x (1/die)	0.1–100 ug/kg	LD no FS (acute and chronic); LD after FS (acute)	Time in the light compartment	No significant effect with no FS; ↑ of time in the light compartment after FS	CBDA acutely or chronically does not modify anxiety-like behavior in the LD emergence test under low-stress conditions; it prevents stress-induced enhancement of anxiogenic-like behavior in previously stressed (FS) rats
	Zagzoog et al. (2020)	CBG, CBC, Δ9-THCA, CBDA, Δ9-THCV, CBDV	C57BL/6J mice; male; group	≥ 6	IP; 1x	0.1–10 mg/kg	OFT	Time in the central sector of open field	- CBG: ↑ at 10 mg/kg - CBC: no significant effect - Δ9-THCA: ↑ at 10 mg/kg - CBDA: ↑ at 3 mg/kg - Δ9-THCV: ↑ at 1 and 10 mg/kg - CBDV: no significant effect	CBG, CBDA, Δ9-THCA and Δ9-THCV show some anxiolytic-like properties
	Zhou et al. (2022)	CBG	C57BL/6J mice; male; group	19–20	IP; 1x	10, 30 mg/kg	LD after FS	Time in the light compartment; distance travelled in the light box; n entries in the dark box; latency to enter the dark box	No significant effect	No effects of CBG on trauma-induced anxiety-related behavior
	Assareh et al. (2020)	CBDA	C57BL/6J mice; male; group	10–16	IP	0.1, 1, 10, 30 mg/kg	Cued fear conditioning with FS; contextual fear conditioning with FS	% of time in freezing behavior	No significant effect	No effects of CBDA on cued fear expression
	Rock et al. (2014)	CBDA	SD rats; male; group	8	IP	0.001, 0.01, 0.1, 1 mg/kg	Cued fear conditioning with FS	% of time in freezing behavior	No significant effect	CBDA does not modify the expression of conditioned freezing to a shock-paired tone
	Zhou et al. (2022)	CBG	C57BL/6J mice; male; group	10 10 8	IP 20x (1/die) 1x	10, 30 mg/kg 30 mg/kg 1 mg/kg	Contextual fear conditioning with FS: - Alteration of long-	% of time in freezing behavior	No significant effect	Repeated CBG exposure does not influence long-term

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Table 1 (continued)

Condition under study	First author	Compounds	Animal characteristics (strain; sex; housing)	Sample per group	Route; n of administration	Doses	Test	Outcomes	Results	Conclusion
				8–10	1x	1, 10, 30 mg/kg	term contextual fear memory			fear memory; acute CBG administration does not reduce the acquisition, expression, consolidation, or reconsolidation of contextual fear
				8–18	1x					
					1x	3, 10, 30, 60 mg/kg	- Alteration of expression - Alteration of acquisition - Alteration of consolidation - Alteration of reconsolidation			
Depressive disorders										
	El-Alfy et al. (2010)	CBC, CBG, CBN, $\Delta 8$ -THC	SW mice (for FST) and DBA/2 mice (for TST); male; group	7–10	IP; 1x	CBG, CBC, CBN: 20–80 mg/kg $\Delta 8$ -THC: 1.25–5 mg/kg	FST, TST	Immobility time and escape attempts (FST); immobility time (TST)	- CBC: ↓ immobility time at 20 mg/kg (FST) and 40–80 mg/kg (TST) - CBG: no significant effect - CBN: no significant effect - $\Delta 8$ -THC: no significant effect	CBC determines significant dose-dependent reduction in immobility indicative of antidepressant-like action.
	Hen-Shoval et al. (2018)	CBDA-ME	WKY rats and FSL rats; male; group	8–12	Per ore; 1x	0.1, 1, 5 mg/kg (WKY) 1 mg/kg (FSL)	FST	Immobility time; swimming time	↓ in immobility time and ↑ swimming time at 1 mg/kg for both WKY and FSL	CBDA-ME reduces depression-like behavior in two different genetic animal models of depression at doses of 1 mg/kg. Biphasic effect
	Hen-Shoval et al. (2023)	CBDA-ME	WKY rats; male and female; group	12–13	Per ore; 1x	1, 5, 10 mg/kg	FST	Immobility time; swimming time	- Female: ↓ in immobility time and ↑ swimming time at 5 and 10 mg/kg 1 mg/kg ineffective - Male: ↓ immobility at 1 mg/kg	CBDA-ME reduces depression-like behavior. Sexually diverse response to the drug treatment
Schizophrenia spectrum and other psychotic disorders										
(PCP-induced)	Cascio et al. (2015)	$\Delta 9$ -THCV	SD rats; male; group	6	IP; 1x (After administration of PCP)	2 mg/kg	- Spontaneous locomotor activity - Stereotyped behaviors - NOR test (classic and spatial) - Social interaction test - FST	- n of movements - n of stereotyped behaviors - Time exploring familiar and novel objects - Time of social behaviors/ aggressive episodes - Immobility time/ swimming time	- ↓ hyperlocomotion - ↓ stereotyped behaviors - ↑ recognition memory - ↑ social behavior and ↓ aggressive episodes - ↓ of time in immobility and ↑ swimming time	THCV is as effective as clozapine in reverting both positive- and negative-like signs of schizophrenia, and cognitive impairments.
(METH-induced)	Umpierrez et al. (2022)	CBDA	SD rats; male; group	12	IP; 1x	0.1, 10, 1000 mg/kg	OFT	Locomotion (n of beam breaks in 60 min)	No significant effect	METH effect on locomotion is not normalized by CBDA
Neurodevelopmental disorders										

(continued on next page)

Table 1 (continued)

Condition under study	First author	Compounds	Animal characteristics (strain; sex; housing)	Sample per group	Route; n of administration	Doses	Test	Outcomes	Results	Conclusion
(induced with valproic acid prenatally)	Zamberletti et al. (2019)	CBDV	SD rats; male; group	5–15	IP; <u>Symptomatic treatment</u> : 22x, 23x, 24x (1/die from postnatal day 34) <u>Preventive treatment</u> : 11x, 12x, 13x (1/die from postnatal day 19)	<u>Symptomatic treatment</u> : 0.2, 2, 20, 100 mg/kg <u>Preventive treatment</u> : 2, 20 mg/kg	<u>Symptomatic treatment</u> : - Three-chamber test (sociability) - Three chamber test (social novelty) - NOR (short-term memory) - Stereotyped behaviors - Locomotion <u>Preventive treatment</u> : - Three-chamber test (sociability) - Three chamber test (social novelty) - NOR (short-term memory) - Stereotyped behaviors - Locomotion	<u>Symptomatic treatment</u> : - % time exploring stranger rat - % time exploring unknown rat - Discrimination index - Time of compulsive self-grooming - Meters of locomotor activity <u>Preventive treatment</u> : - % time exploring stranger rat - % time exploring unknown rat - Discrimination index - Time of compulsive self-grooming - Meters of locomotor activity	<u>Symptomatic treatment</u> : - ↑ time exploring stranger rat at 20 and 200 mg/kg - ↑ time exploring unknown rat at 20 mg/kg - ↑ discrimination index at 2, 20 and 100 mg/kg - ↓ compulsive self-grooming at 20 mg/kg - ↓ hyperlocomotion at 2, 20 and 100 mg/kg <u>Preventive treatment</u> : - ↑ time exploring stranger rat at 2 and 20 mg/kg - ↑ time exploring unknown rat at 20 mg/kg - ↑ discrimination index at 20 mg/kg - No significant effect - ↓ hyperlocomotion at 20 mg/kg	CBDV could ameliorate behavioral abnormalities resembling the core and associated symptoms of autism spectrum disorder

11-OH-Δ8-THC, 11-Hydroxy-Δ8-tetrahydrocannabinol; Δ8-THC, Δ8-tetrahydrocannabinol; Δ8-THCV, Δ8-tetrahydrocannabidivarin; Δ9-THCA, Δ9-tetrahydrocannabinolic acid; Δ9-THCV, Δ9-tetrahydrocannabidivarin; CBC, cannabichromene; CBDA, cannabidiolic acid; CBDV, cannabidivarin; CBN, cannabinol; CPP, conditioned place preference; EPM, elevated plus maze test; FS, foot-shock; FSL, Flinders Sensitive Line; HU-580, cannabidiolic acid methyl ester; IBMX, 3-isobutyl-1-methylxanthine; ICR, Institute of Cancer Research; IP, Intraperitoneal; LD, light-dark emergence test; LH, Lister-Hooded; METH, methamphetamine; NOR, novel object recognition test; NSF, novelty-suppressed feeding; OFT, open field test; PCP, phencyclidine; QMWS, quasi-morphine withdrawal syndrome; SD, Sprague-Dawley; SUD, substance use disorder; SW, Swiss-Webster; TST, tail suspension test; WKY, Wistar-Kyoto

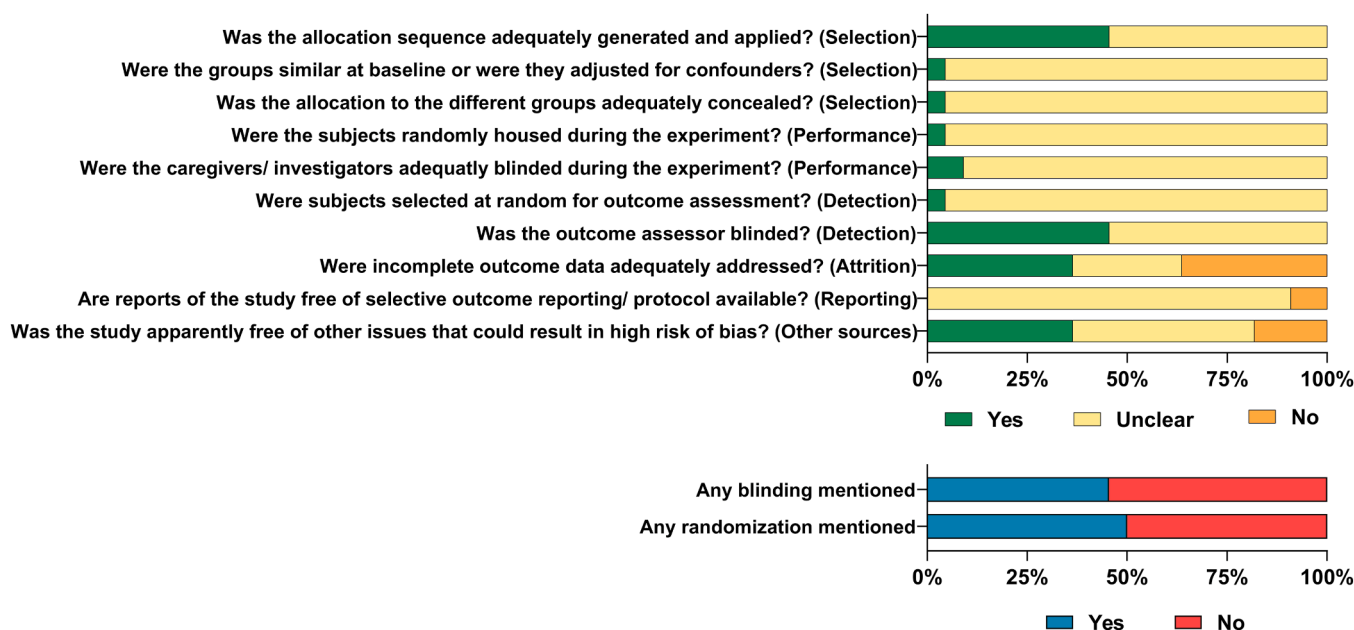


Fig. 2. Risk of Bias assessment of the included preclinical studies.

a dose of 10 mg/kg.

Anggadiredja et al. (2004) investigated the effects of $\Delta 8$ -THC on the extinction phase of methamphetamine (METH)-seeking behavior and the reinstatement phase after METH priming and after METH-associated cues. 3.2 mg/kg $\Delta 8$ -THC suppressed the reinstatement of METH-seeking behavior when administered repeatedly during the extinction phase or as a single dose 24 hours before the first METH-priming or cue challenge. Conversely, Umpierrez et al. (2022) found no efficacy of CBDA in normalizing changes in locomotor activity induced by METH administration, measured as the number of beam breaks in 60 minutes.

One study reported significant and dose-related anti-nicotine-dependence properties of $\Delta 8$ -THCV in several different preclinical models of nicotine addiction (Xi et al., 2019). $\Delta 8$ -THCV proved effective in reducing nicotine self-administration, inhibiting cue-conditioned relapse, and preventing relapse after reinstatement at doses ranging from 3 to 20 mg/kg. Pretreatment of drug-naïve rats with $\Delta 8$ -THCV led to a reduction in context-induced nicotine-seeking behavior compared to a control group in a conditioned place preference experiment. Furthermore, pretreatment with 0.3 mg/kg of $\Delta 8$ -THCV resulted in a significant reduction in nicotine-induced anxiety behaviors and somatic withdrawal symptoms, including paw and body tremors, head shakes, retrograde locomotion, jumps, curls, and ptosis. The only study on cocaine addiction did not find any significant effect of CBDA in reducing cocaine-seeking behaviors in a conditioned place preference experiment (Alegre-Zurano et al., 2020).

In summary, most studies on animal models for substance use disorders reported some beneficial effects for the cannabinoids under investigation, except for CBDA (see Fig. 3). $\Delta 8$ -THCV showed anti-nicotine-dependence properties, while CBN, $\Delta 8$ -THC, and 11-OH- $\Delta 8$ -THC appeared to reduce morphine-withdrawal symptoms. $\Delta 8$ -THC also seemed to have some capacity to inhibit the reinstatement of METH-seeking behavior. CBDA was not effective in reducing METH-induced or cocaine-seeking behaviors.

3.3.2. Anxiety disorders

In a study by Rock et al. (2017), CBDA, administered at doses ranging from 0.1 to 100 μ g/kg intraperitoneally, prevented the enhancement of anxiogenic-like behavior in rats exposed to prior stress induced by foot shock during a light-dark emergence test. This test is a commonly used paradigm in which rodents' preference for a dark area over a brightly lit

area is measured as an indicator of anxiety-like behavior. However, CBDA did not modify anxiety-like behavior in the light-dark emergence test under low-stress conditions. A study by Assareh et al. (2020), also found CBDA to be effective in reversing shock-induced anxiety with doses of 0.1–30 mg/kg intraperitoneally. However, Pertwee et al. (2018) did not obtain similar results with a lower dose of 0.01 μ g/kg, either at baseline or after foot shock. In contrast, the CBDA synthetic analogue, CBDA-ME, effectively reduced the enhancement of anxiogenic-like behavior after foot shock in the light-dark test at a dose of 0.01 μ g/kg. Other authors did not report any significant effects of CBDA in various behavioral tests. These included: 1) the open field test, where the rodent's exploratory behavior as a proxy of anxiety levels is assessed in a novel environment; 2) the elevated plus maze test, which measures approach-avoidance behavior based on the exploration of open and enclosed arms and 3) the novelty-suppressed feeding test, which evaluates conflict behavior by measuring the latency to feed in a novel environment. CBDA was administered acutely at doses of 0.001–1.0 mg/kg intraperitoneally (Alegre-Zurano et al., 2020) or at a dose of 5 mg/kg orally (Brierley et al., 2016).

The anxiolytic properties of CBDA were also tested by Zagzoog et al. (2020), together with those of other minor cannabinoids such as CBG, $\Delta 9$ -THCA, $\Delta 9$ -THCV, CBDV, and CBC. The authors used the open field test to measure anxiety-like behaviors and found increases in the time spent by mice in the central quadrant when pretreated with the following compounds at the following doses: CBDA (3 mg/kg), CBG (10 mg/kg), $\Delta 9$ -THCA (10 mg/kg), and $\Delta 9$ -THCV (1 and 10 mg/kg). The latter compound was also tested in another study (O'Brien et al., 2013) but showed no significant effects on the light-dark test.

Two studies explored the anxiolytic properties of the minor cannabinoid CBG (O'Brien et al., 2013; Zhou et al., 2022). O'Brien et al. (2013) found no significant increase in the time spent in the lit box during the light-dark test, following acute or chronic exposure to 2.5 mg/kg of CBG. Similarly, Zhou et al. (2022) found no effects of CBG (10 and 30 mg/kg) on trauma-induced anxiety behaviors in the light-dark test.

In summary, mixed results emerged on the efficacy of the minor cannabinoids under study on animal models for anxiety (see Fig. 3). CBDA prevented anxiogenic-like responses to foot shock in the light-dark test at doses between 0.1 μ g/kg and 1 mg/kg intraperitoneally but had no effects on unstressed rats. No consistent results were

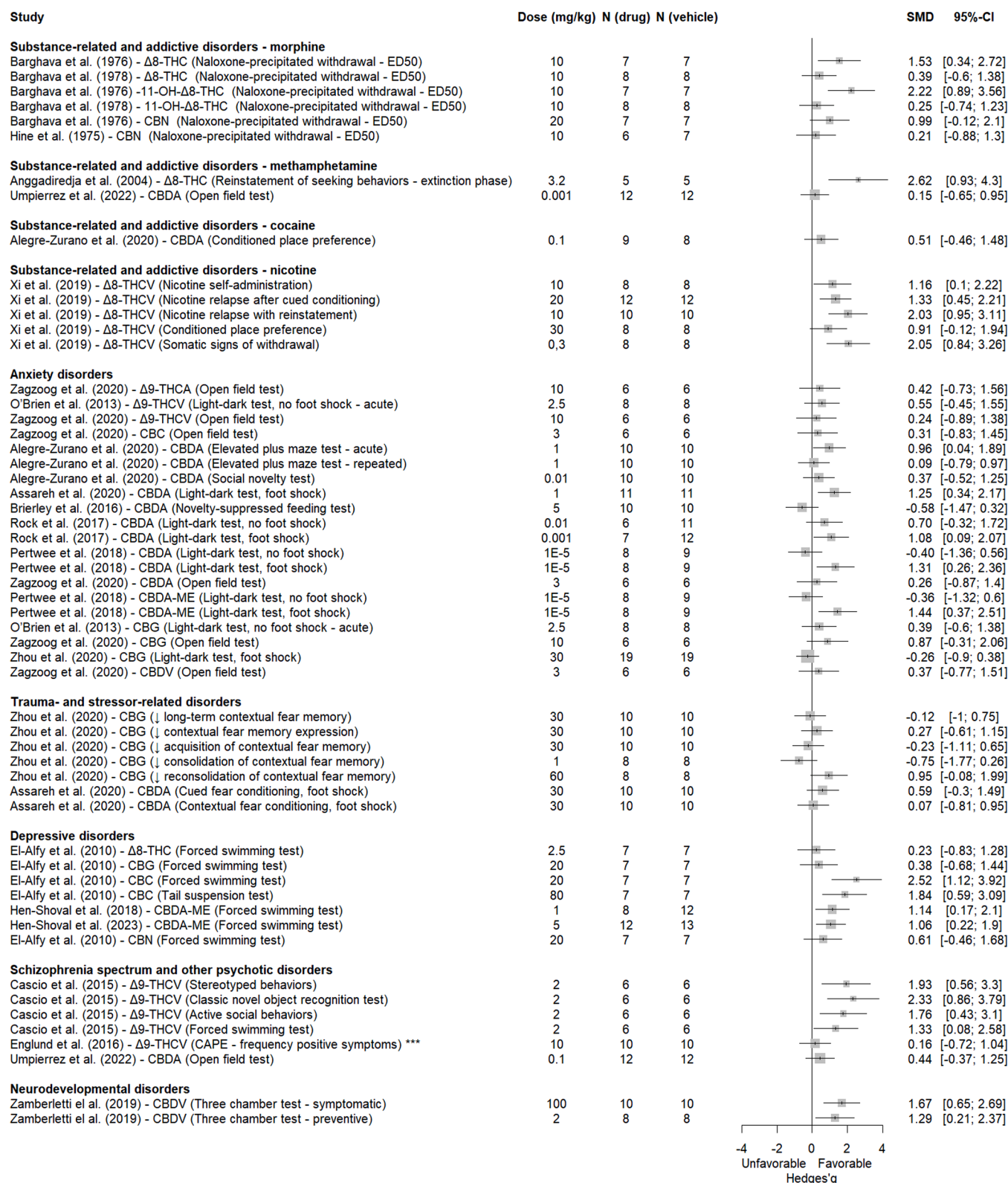


Fig. 3. Forest plot of standardized mean difference (SMD) and confidence interval (CI) for the most effective doses of the compounds under study across selected outcomes. Tests are in round brackets. CAPE, Community Assessment of Psychic Experiences; ***Human study.

observed for CBDA in other behavioral tests like the elevated plus maze test, novelty-suppressed feeding test, and open field test. CBDA-ME appeared to reverse stress-induced anxiety behaviors in the light-dark test at doses as low as 0.01 μ g/kg. The second most studied minor cannabinoid, CBG, did not exhibit any anxiolytic properties.

3.3.3. Trauma- and stressor-related disorders

Rock et al. (2014) assessed the effects of CBDA on the expression of conditioned freezing to a shock-paired tone (cue). CBDA administered at doses of 0.001–1 mg/kg was ineffective in modifying the expression of cue conditioned fear. Another more recent study also investigated the

effects of CBDA on cued fear conditioning, as well as on contextual fear conditioning, whereby foot shocks were delivered without being paired with tones (Assareh et al., 2020). Similarly, the authors did not find any significant reduction in cued or contextual fear expression after the administration of CBDA in doses up to 30 mg/kg. Zhou et al. (2022) explored whether doses of CBG between 1 and 60 mg/kg could affect various contextual fear conditioning processes in a rodent model of post-traumatic stress disorder. CBG neither altered long-term fear memories nor reduced the acquisition, consolidation, reconsolidation, or expression of contextual fear. The effect sizes associated with these studies are shown in Fig. 3.

To summarize, neither CBDA nor CBG proved effective in altering fear memory processes in rodents.

3.3.4. Depressive disorders

Hen-Shoval et al. (2018) investigated the properties of CBDA-ME in two genetic rat models for depression: Wistar-Kyoto and Flinders Sensitive Line rats. These models exhibit inherent behavioral characteristics resembling some aspects of human depression, such as increased immobility, which is often assessed in rodents using the forced swimming test and the tail suspension test. The authors observed a significant reduction in immobility and an increase in swimming behaviors in the forced swimming test when a dose of 1 mg/kg of CBDA-ME was administered orally to male rats. These findings were confirmed in another study, where similar experimental conditions were employed to assess the efficacy of CBDA-ME on a sample of female rats. A reduction in immobility and increased swimming in the forced swimming test were also observed in females, but only at higher doses of 5 and 10 mg/kg (Hen-Shoval et al., 2023).

El-Alfy et al. (2010) used the forced swimming test and the tail suspension test to investigate whether the minor cannabinoids $\Delta 8$ -THC, CBG, CBC, and CBN exhibit any antidepressant-like effect. CBC determined a significant overall reduction in immobility at 20 mg/kg in the forced swimming test and at 40 and 80 mg/kg in the tail suspension test. The other tested compounds did not produce any significant effects.

In summary, CBDA-ME and CBC showed some antidepressant-like properties by reducing immobility time in the forced swimming test and tail suspension test, and by increasing swimming behavior in the forced swimming test. $\Delta 8$ -THC, CBG, and CBN did not exhibit similar properties.

3.3.5. Schizophrenia spectrum and other psychotic disorders

$\Delta 9$ -THCV significantly counteracted schizophrenia-like psychotic symptoms induced by the administration of the dissociative drug phencyclidine (Cascio et al., 2015). A dose of 2 mg/kg of $\Delta 9$ -THCV intraperitoneally was effective in reverting both positive (hyperlocomotion, stereotypies) and negative (social withdrawal, immobility) schizophrenia-like symptoms, as assessed with the social interaction test and forced swimming test. The same dose of $\Delta 9$ -THCV also improved the cognitive deficits induced by phencyclidine, especially recognition memory and spatial memory, as tested with the novel object recognition test.

In another study, Umpierrez et al. (2022) examined the effects of CBDA on METH-induced psychosis. Doses of 0.1, 10, 1000 mg/kg were not effective in reducing the METH-induced hyperlocomotion, as assessed with the open field test. Fig. 3 shows the effect sizes of the studies described above.

3.3.6. Neurodevelopmental disorders

One study tested whether CBDV may prevent and/or reverse autism spectrum disorder-like behaviors in the offspring of rats prenatally exposed to valproic acid (Zamberletti et al., 2019). CBDV was repeatedly administered following two different protocols: preventive (2, 20 mg/kg intraperitoneally, postnatal days 19–32) or symptomatic (0.2, 2, 20, 100 mg/kg intraperitoneally, postnatal days 34–58). Different tests demonstrated that CBDV may ameliorate behavioral abnormalities resembling

the core and associated symptoms of autism spectrum disorder, such as impaired sociability and stereotyped behaviors (see Fig. 3).

3.4. Human studies

The only human study included in this systematic review investigated the potential of $\Delta 9$ -THCV in reversing psychotic-like symptoms induced by the administration of $\Delta 9$ -THC (Englund et al., 2016). Participants received 10 mg of $\Delta 9$ -THCV orally for 5 days in a placebo-controlled cross-over design. Cognitive functioning and psychiatric symptoms such as anxiety and psychotic-like symptoms were assessed using various tasks and psychological scales. $\Delta 9$ -THCV showed some signs of improved performance in a working-memory task, while also resulting in a slight increase in anxiety symptoms. No statistically significant changes were observed in other outcomes. Hedges'g for the selected outcome, "frequency of positive-like symptoms", assessed with the Community Assessment of Psychic Experiences (CAPE), is also reported in the forest plot (see Fig. 3). This allows comparison with the results obtained from other tests in preclinical studies that focused on proxies of psychotic-like disorders.

4. Discussion

To our knowledge, this is the first review systematically evaluating both preclinical and clinical studies that investigated the potential of minor cannabinoids in psychiatric disorders. Despite considerable heterogeneity in compounds and methods, some relatively consistent findings emerged. A comparison via forest plot of the most effective doses of the compounds under study across selected outcomes confirmed relatively small but consistent effects of the most promising potential therapeutic applications. However, the risk of bias in most studies was either unclear or relatively high, meaning findings need to be interpreted with caution.

The type of minor cannabinoids under study has evolved over time, likely influenced by factors such as their availability and the clinical findings associated with major cannabinoids. For instance, it is significant to note that four out of five studies on opioid withdrawal symptoms were conducted in the '70s and '80s, when CBN and $\Delta 8$ -THC were among the most available and studied cannabinoids, along with $\Delta 9$ -THC and CBD. Similarly, included studies involving CBDA were only initiated from the early 2010s onward, specifically after research on the potential anxiolytic effects of its more widely renowned metabolite, CBD, began receiving attention. While CBD is considered to have a favorable safety profile in both animals and humans (Iffland & Grotenhermen, 2017), the safety of minor cannabinoids was only sparsely addressed in the included articles, none of which reported any significant adverse effects. Furthermore, like CBD, the oral bioavailability of minor cannabinoids is generally thought to be low (Moore et al., 2023), which is an important consideration when developing new drugs based on these compounds.

In the next sections, we will discuss the key findings of this review organized by models for categories of psychiatric disorders.

4.1. Substance-related and addictive disorders

The cannabinoids CBN, $\Delta 8$ -THC, and 11-OH- $\Delta 8$ -THC were shown to reduce opioid withdrawal symptoms in morphine-dependent rats. However, concerns have arisen regarding the lack of thorough descriptions of randomization and blinding procedures, especially in historical studies from the '70s and '80s that tested these three compounds. Notably, one of the included studies did not report any measure of standard error (Chesher et al., 1985), and another did not report sample sizes (Yamaguchi et al., 2001). Such omissions cast doubt on the validity of the results obtained. Furthermore, as no effect sizes could be calculated for these studies, they were excluded from the forest plot. The overall small sample sizes of many of these studies may have contributed to the mixed outcomes observed across studies that utilized the same

experimental conditions and rat strains. In addition, studies on $\Delta 8$ -THC and 11-OH- $\Delta 8$ -THC demonstrated effectiveness by reducing naloxone-precipitated withdrawal symptoms, but only when administered no earlier than 30 minutes before the test. The short duration of action may pose a limitation on their practical utility. Taken as a whole, these factors could have discouraged researchers from further testing these compounds for opioid withdrawal symptoms in recent years, both in animals and in humans.

While one study suggested some efficacy of high doses of $\Delta 8$ -THC in animal models for METH addiction (Anggadiredja et al., 2004), caution is warranted in interpreting the results due to experimental iteration and seemingly incomplete reported outcome data. On the other hand, the only study on nicotine dependence, which exhibited a relatively low risk of bias, yielded rather robust evidence of the efficacy of $\Delta 8$ -THCV. This synthetic and more stable analogue of $\Delta 9$ -THCV demonstrated effectiveness in mitigating nicotine addiction behaviors and withdrawal symptoms in rodent models across various experimental conditions (Xi et al., 2019). Crucially, recent research in healthy humans showed a favorable safety profile of this compound at doses of 12.5, 25 and 50 mg (Peters et al., 2023). These findings suggest that $\Delta 8$ -THCV could be a promising candidate for further research on nicotine addiction.

4.2. Anxiety disorders

Most of the included studies on anxiety focused on the minor cannabinoid CBDA. The growing interest in CBDA as a potential treatment for anxiety disorders stemmed from some promising results obtained with CBD. In fact, preclinical studies suggest that CBD holds anxiolytic properties, which seem to be mostly mediated by CB1 and 5-HT1A receptors in different brain regions (Blessing et al., 2015; García-Gutiérrez et al., 2020). Importantly, a recent systematic review and meta-analysis on the anxiolytic effects of endocannabinoid-enhancing compounds suggests that larger effects of CBD on unconditioned anxiety in animals are observed when anxiety pre-exists (Kwee et al., 2023). Research with CBD on humans supported the animal findings, while also indicating a favorable safety profile and minimal sedation effects (Blessing et al., 2015; Rehman et al., 2021).

The six included studies involving CBDA showed that this compound shares some anxiolytic properties with CBD. In fact, it seems to prevent the enhancement of anxiogenic-like behavior in previously stressed rats with effective doses lower than those of CBD (Assareh et al., 2020; Rock et al., 2017). Overall, although possible differences in the effects of CBDA compared to CBD on anxiety still need to be clarified, the current state of research suggests that assessing CBDA in future studies in humans could prove to be a worthwhile pursuit. One potential limitation to its use may lie in its instability to heat. This is why some authors tested CBDA's more stable methyl analogue, CBDA-ME, which showed efficacy in preventing anxiety-like responses in previously stressed mice, even at a lower dose than those of CBDA (Pertwee et al., 2018).

On the other hand, other tested substances, particularly CBG, administered both acutely and chronically in stressed and unstressed rats, did not appear to be effective against anxiety-like symptoms (O'Brien et al., 2013; Zhou et al., 2022). This discrepancy with the effects of CBD and CBDA likely points to underlying differences in the molecular mechanisms of action of these compounds. In fact, the anxiolytic effects of CBD and CBDA seem to be, at least partly, attributed to the enhancement of 5-HT1A receptor activation (Bolognini et al., 2013; Gomes et al., 2011, 2012; Pertwee et al., 2018), whereas CBG appears to act on these receptors as a moderately potent antagonist (Cascio et al., 2010).

4.3. Trauma- and stressor-related disorders

Cannabis is often reported to be used by patients with a history of trauma, and in particular with post-traumatic stress disorder (PTSD), to cope with intrusive memories, flashbacks and nightmares, and alleviate

feelings of stress, anxiety, and tension (Bitencourt & Takahashi, 2018; Rehman et al., 2021). Evidence of the involvement of the endocannabinoid system in the regulation of emotional responses related to traumatic events (Castillo et al., 2012; Riebe et al., 2012) and the low efficacy of current available pharmacological treatments (Bernardy & Friedman, 2015) prompted research on the potential of cannabinoids for treating PTSD. Studies employed cued and contextual fear conditioning paradigms, testing whether different compounds could impact the fear memory processes of acquisition, consolidation, retrieval, reconsolidation, and extinction of aversive memories. However, the results of this review showed that neither CBDA, nor CBG, seem to influence conditioned fear memory in mice, expressed as time spent in freezing behaviors. These results are in contrast with the decrease in acquisition, expression, consolidation, and reconsolidation of contextual fear memory observed in similar rodent studies that employed CBD (Assareh et al., 2020; Raymundi et al., 2020; Stern et al., 2012, 2017).

4.4. Depressive disorders

Two studies reported promising effects of CBDA-ME on antidepressant-like behaviors in two rodent genetic models for depression (Hen-Shoval et al., 2018, 2023). In the forced swimming test, the authors consistently observed a reduction in immobility and an increase in swimming behaviors that served as outcome measures, in the treated animals. CBDA-ME demonstrated efficacy in reducing these behaviors at doses even lower than those required to achieve a similar effect with CBD (Linge et al., 2016; Shoval et al., 2016). Importantly, one of the studies included female rats, whose behavior in the forced swimming test was also significantly modified by CBDA-ME, albeit at higher doses than those needed in males. The inclusion of female rats bears particular significance, as epidemiological studies in humans report a prevalence of major depressive disorder in women almost double that in men (Ferrari et al., 2013).

In another study, the minor cannabinoid CBG also appeared to significantly reduce immobility in the forced swimming test in a dose-dependent manner, although decreased locomotion occurred as a side effect at higher doses (El-Alfy et al., 2010). While the authors demonstrated that safe oral doses of CBDA-ME influence some acute outcomes associated with antidepressant-like behavior in rats, it is crucial to bear in mind that depression, as well as most neuropsychiatric disorders, is a highly heterogeneous condition, encompassing a range of symptoms beyond those specifically examined in these studies (American Psychiatric Association, 2013). As a history of adverse or traumatic events is an established risk factor contributing to its development, further studies should also focus on the aspect of chronic stress related to depression (Bale et al., 2019). Hedonic or reward-seeking experimental conditions could be investigated in animal models with tests such as the sucrose preference and the social interaction test.

4.5. Schizophrenia spectrum and other psychotic disorders

Similar to depression, investigating psychotic disorders poses a significant challenge. Among the reasons are the wide range of different symptoms that characterize these disorders and their subjective nature, which is difficult to fully replicate, especially in animal models. To induce psychotic-like symptoms in rodents, some authors administered phencyclidine, a dissociative molecule often used to test the efficacy of antipsychotic drugs (Bubeníková-Valešová et al., 2008). One of the included studies reported that the minor cannabinoid $\Delta 9$ -THCV was as effective as the routinely used antipsychotic drug clozapine in preventing positive, negative-like symptoms, and cognitive deficits induced by phencyclidine (Cascio et al., 2015). Another study attempted to translate these promising results with $\Delta 9$ -THCV to humans (Englund et al., 2016). Instead of using phencyclidine, the authors administered intravenously 1mg of $\Delta 9$ -THC to the participants, a dose that prior research had indicated could induce psychotic-like symptoms and

cognitive impairment in about 50% of healthy volunteers (D'Souza et al., 2004; Morrison et al., 2009). Despite the minimal effect found in this crossover pilot trial, possibly also influenced by the small sample size, this molecule exhibited an overall safe profile with no serious adverse effects observed. As Δ^9 -THCV can be naturally found in high amounts in the cannabis plant (ElSohly et al., 2017), and recent studies in both animals and humans have confirmed a favorable safety profile, conducting additional human studies with larger sample sizes could prove valuable in shedding light on the effects of this compound (Kulpa et al., 2023; Peters et al., 2023).

4.6. Neurodevelopmental disorders

In this review, only one study tested the minor cannabinoid CBDV in rodent models simulating symptoms of autism spectrum disorder. Autism spectrum disorder encompasses a wide range of symptoms, including difficulties in social interaction, communication, and repetitive behaviors (Lai et al., 2014). Recent studies have suggested a potential link between autism spectrum disorder and the endocannabinoid system, leading to an increased interest in investigating cannabinoids as potential treatment options (Kerr et al., 2013; Schultz & Siniscalco, 2019; Zamberletti et al., 2017). Zamberletti et al. demonstrated that CBDV could be effective in both preventing and treating core symptoms of autism spectrum disorder, such as impaired sociability, repetitive behaviors, hyperactivity, and recognition memory impairments, in rats prenatally exposed to the teratogenic antiseizure medication valproic acid (Zamberletti et al., 2019). Furthermore, CBDV displayed a favorable safety profile, with no significant adverse effects emerging in the tested animals.

Although no studies with minor cannabinoids in humans were retrieved by our systematic search, a clinical trial is ongoing at the time of writing this review, aiming to study the efficacy and safety of CBDV in children with autism spectrum disorder (Hollander, 2019). In addition, several clinical studies have tested cannabinoid compounds, especially formulations with high ratios of CBD on individuals with autism spectrum disorder. These studies mostly suggested some potential for alleviating symptoms such as anxiety, irritability, hyperactivity, bouts of anger, and sleep problems, as well as improvements in cognition, sensitivity, attention, social interaction, and language (Babayeva et al., 2022; Silva Junior et al., 2022).

Given the first preclinical evidence and the encouraging results obtained with other cannabinoid formulations, CBDV stands as a valid candidate for future studies on potential treatments for autism spectrum disorder. It is crucial to better characterize CBDV mechanisms of action in vitro and expand the evidence of the efficacy of this compound, both in animals and in humans.

4.7. Limitations and Strengths

In conducting this systematic review, several strengths and limitations were identified. A major strength lies in the comprehensive review process, which adhered to current guidelines and involved thorough searches across multiple databases and registries. This approach ensured a robust examination of the existing literature. Another strength is the broad scope of psychiatric disorders explored, including substance-related and addictive disorders, and neurodevelopmental disorders. Furthermore, the specific focus on minor cannabinoids represents a novelty compared to previous reviews on cannabinoids in psychiatric disorders, which predominantly focused on Δ^9 -THC and CBD.

This review also has some limitations. First, the heterogeneity of compounds, disorders, and outcomes across studies prevented us from conducting a meta-analysis, thereby limiting our ability to draw quantitative conclusions. However, by calculating the standardized mean differences for selected outcomes, we were able to visualize and compare the effect sizes of the most effective doses in different tests via a forest plot. Furthermore, this allowed us to confirm the results of

preclinical studies, which were otherwise reported by the authors only descriptively. Second, several preclinical studies exhibited a relatively high or unclear risk of bias, stressing the need for cautious interpretation of the findings. Third, the inclusion of only one study on human subjects emphasizes the need for more translational research to bridge the gap between preclinical findings and clinical applications. This is particularly relevant when trying to draw conclusions from preclinical models for psychiatric disorders, as these models can only replicate certain behavioral aspects of complex human mental and neurodevelopmental disorders. They often overlook the multifactorial nature of these conditions, in which social, genetic and environmental factors also play crucial roles.

5. Conclusion and future directions

In summary, despite the paucity of studies and the acknowledged limitations, this systematic review provides an initial exploration of the therapeutic potential of minor cannabinoids in psychiatric disorders. Certain compounds have emerged as promising candidates for further investigation, considering the findings from existing studies, their safety profiles, and the precautionary measures taken by researchers to minimize bias. For instance, Δ^8 -THCV emerged as a candidate for nicotine addiction, and Δ^9 -THCV showed some promise for psychotic disorders by addressing positive, negative-like, and cognitive symptoms. CBDV could be further explored for its potential to reduce symptoms associated with autism spectrum disorder. CBDA-ME exhibited potential in alleviating anxiety and depression-like symptoms, suggesting a possible role in mood disorders. While recognizing the preliminary nature of these findings, the identification of these compounds may open doors for targeted investigations. A common issue in animal research is the low translatability to humans, leading to the failure of most novel drugs that show promise in preclinical trials during clinical trials, particularly for neuropsychiatric disorders (Ineichen et al., 2024). Opportunities to advance research on minor cannabinoids lie in bridging these translational gaps. Future studies should address several critical aspects, including incorporating models that better represent human psychiatric disorders by accounting for social, environmental, and genetic factors. This would improve the predictive validity of preclinical findings. Researchers should aim for larger sample sizes and address sex disparities in the prevalence of psychiatric disorders, a factor often underexplored in preclinical studies. Furthermore, reporting effect sizes and confidence intervals would provide a clearer understanding of the magnitude and reliability of cannabinoid effects. Finally, providing detailed information on safety and adverse effects, as well as considering the bioavailability of these compounds, is crucial for streamlining the drug development process.

Author contributions

Conceptualization: AB, GC, LG; Literature search: GC, MV; Data extraction and data synthesis: GC, MV; Writing – original draft preparation: GC; Writing – review and editing: AB, LG, MV, PvdM.

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None.

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Supplementary materials

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