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Neurobiological and Molecular Mechanisms of Cannabidiol in Depressive Disorders: A Preclinical Systematic Review

Mecanismos neurobiológicos e moleculares do canabidiol no transtorno depressivo: Uma revisão sistemática pré-clínica

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SUMMARY **Purpose:** This review aims evaluated preclinical studies published in the last five years investi gating the antidepressant-like effects of CBD and related cannabinoids. **Methods:** This work is a systematic review. The entire process of selecting and choosing the studies for the review was carried out according to the PRISMA protocol. The descriptors used were "Depressive Disorder", "Cannabidiol", and "Phytotherapy". Seven experimental studies met the inclusion criteria. **Results:** The reviewed evidence demonstrates that CBD reduces immobility in the forced swim test, increases sucrose preference, and modulates molecular pathways associated with neuroplasticity and inflammation. Key mechanisms include activation of AMPA receptors, modulation of serotonergic and noradrenergic transmission, reduction of NF-κB and IL-6 expression, and regulation of the kynurenine pathway. Additionally, CBD influences hippocampal neurogenesis and exhibits anti-inflammatory and anti-apoptotic effects through BDNF/TRPC6 signaling. **Conclusion:** Collectively, these findings highlight the multifactorial antidepressant potential of CBD and its analogs, suggesting a role as adjunctive or alternative therapies for mood disorders. However, further randomized controlled trials in humans are essential to confirm efficacy, safety, and optimal dosing parameters for clinical use.

Keywords: cannabidiol; depressive disorder; endocannabinoids; phytotherapy; neuroplasticity.

RESUMO **Objetivo:** Esta revisão teve como objetivo avaliar estudos pré-clínicos publicados nos últimos cinco anos que investigaram os e feitos do tipo antidepressivo do CBD e de canabinoides relacionados. **Método:** Trata-se de uma revisão sistemática. Todo o processo de seleção e elegibilidade dos estudos foi conduzido de acordo com o protocolo PRISMA. Os descritores utilizados foram "Depressive Disorder", "Cannabidiol" e "Phytotherapy". Sete estudos experimentais atenderam aos critérios de inclusão. **Resultados:** As evidências analisadas demonstram que o CBD reduz a imobilidade no teste do nado forçado, aumenta a preferência por sacarose e modula vias moleculares associadas à neuroplasticidade e à inflamação. Entre os principais mecanismos envolvidos destacam-se a ativação de receptores AMPA, a modulação da transmissão serotoninérgica e noradrenérgica, a redução da expressão de NF-κB e IL-6 e a regulação da via da quinurenina. Adicionalmente, o CBD influencia a neurogênese hipocampal e apresenta efeitos anti-inflamatórios e antiapoptóticos por meio da sinalização BDNF/TRPC6. **Conclusão:** Em conjunto, esses achados evidenciam o potencial antidepressivo multifatorial do CBD e de seus análogos, sugerindo um possível papel como terapias adjuvantes ou alternativas nos transtornos do humor. Contudo, são necessários ensaios clínicos randomizados em humanos para confirmar a eficácia, a segurança e os parâmetros.

Palavras-chave: canabidiol; transtorno depressivo; endocanabinoides; fitoterapia; neuroplasticidade.

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Introduction

Cannabidiol (CBD) is a non-psychotomimetic phytocannabinoid derived from *Cannabis sativa*, with broad therapeutic potential in a variety of central nervous system disorders[1].

Cannabinoids are secondary metabolites found in the *Cannabis sativa* plant and play a key role in the therapeutic properties attributed to it. They are produced in the resinous glands of female flowers and exhibit variable concentrations influenced by genetic, environmental, and cultivation factors[2]. These compounds act primarily through the endocannabinoid system, modulating functions such as memory, pain, appetite, and immune response via CB1 and CB2 receptors[3].

Tetrahydrocannabinol (THC) is the most well-known cannabinoid, responsible for the plant's psychoactive effects due to its direct interaction with CB1 receptors, mainly within the central nervous system[4]. In contrast, cannabidiol (CBD), which does not present typical psychoactive properties, stands out for its therapeutic actions, including anti-inflammatory, anxiolytic, and neuroprotective effects. Another cannabinoid of interest is cannabigerol (CBG), the precursor of other cannabinoids such as THC and CBD, which exhibits anti-inflammatory and antibacterial properties[5,6].

Among the various cannabinoids present in *Cannabis sativa*, cannabidiol (CBD) is noteworthy as the earliest to be recognized, the most frequently prescribed, and the one with which the medical community is most familiar. CBD interacts with CB1 receptors in distinct ways, functioning as a neutral antagonist—that is, it does not directly activate the receptor but blocks the action of agonists, preventing their binding. This characteristic is fundamental for modulating the potentially toxic effects of tetrahydrocannabinol (THC)[7].

Additionally, CBD acts as an allosteric modulator, adjusting the effects of agonists on the CB1 receptor, either enhancing or attenuating them. It induces a conformational change in the receptor structure, which can increase or reduce its activation by the agonist. In this way, CBD not only modulates the adverse effects of THC but also enhances therapeutic effects associated with receptor interaction[7].

The endocannabinoid system is a biological signaling mechanism composed of cannabinoid receptors (CB1 and CB2), their endogenous ligands (endocannabinoids), and the enzymes responsible for the metabolism of these ligands. CB1 receptors are found predominantly in the central nervous system, where they modulate motor, emotional, cognitive, and appetite-related functions, whereas CB2 receptors are primarily associated with the immune system but also play roles within the central nervous system[3].

The endocannabinoid system has a protective role in conditions of neurotoxic stress, pain, and psychological trauma, with significant therapeutic implications. Research highlights the use of phytocannabinoids such as CBD, as well as CB1 receptor allosteric modulators, metabolic enzyme inhibitors, and CB1 antagonists, as potential therapeutic approaches for neurological, psychiatric, and metabolic disorders[3].

Abnormal levels of norepinephrine (NE), serotonin (5-HT), and dopamine (DA) in the central nervous system (CNS) are closely associated with depression. These abnormalities may arise from alterations in neurotransmitter content within the CNS or from modifications in receptor number or sensitivity[8]. Furthermore, mutual interactions among neurotransmitters exist, such that impairment in one system can trigger anomalies in another[9]. Disturbances in intracellular cascades may also contribute to the onset of depression[10].

Depression results from the interaction between psychological, physiological, and social factors. This mood disorder affects multiple brain regions, including the hippocampus, prefrontal cortex, and amygdala[9,11,12].

Multiple factors may contribute to the development of depression, including adverse external stimuli or internal conflicts, smoking, alcohol and drug abuse, inadequate diet, genetic predisposition, and chronic illnesses[13]. Stressful life events often precede episodes of mood disorders, apparently due to the consequences that stress imposes on brain biology[10]. The impact of external stressors on the regulation of neuronal plasticity may influence the occurrence of the disorder through the expression of specific genes that determine changes in second messengers (intracellular cascades) and in neurotransmitter activity[14].

The neurobiological link between the endocannabinoid system (ECS), through both CB1 and CB2 receptors, and target conditions such as major depressive disorder (MDD), sclerosis, dementia, Huntington's

disease, affective disorders, fear, anxiety, stress, and other processes related to emotional regulation was reported by *Chadwick et al.*[15]. In *in vitro* environments, CBD is regarded as a microglial stabilizer, with an action comparable to lithium, which may be highly valuable in the treatment of depression as well as in mood stabilization[16].

The possible mechanisms associated with the antidepressant effect of cannabidiol (CBD) include hippocampal neurogenesis[17], epigenetic modulation through DNA methylation[18], alteration of neurotransmitter pathways such as increased serotonin and norepinephrine[19], reduction of NF-κB expression[19], activation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors[20], and modulation of specific endocannabinoid signaling pathways[21]. Furthermore, CBD demonstrates antipsychotic, anorexigenic, and prohedonic effects[22,23].

In *in vitro* settings, CBD is considered a microglial stabilizer, with lithium-like activity, which may prove useful in the treatment of depression as well as in mood stabilization. The clinical indications for cannabidiol may include depression, anxiety, seizures, nausea, loss of appetite, anti-inflammatory purposes, pain management, and even in disorders related to opioid and other substance use[24-26].

Therefore, this review aims evaluated preclinical studies published in the last five years investigating the antidepressant-like effects of CBD and related cannabinoids.

Methods

This study is a systematic review conducted in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020)[27], which are widely adopted to ensure transparency, reproducibility, and methodological rigor in systematic reviews.

The review was guided by the following research question: What are the antidepressant-like effects of cannabidiol and related cannabinoids in experimental models of depressive disorders?

A systematic literature search was performed in multiple databases in order to identify the widest possible range of available scientific evidence. The database consulted were ScienceDirect. The descriptors used in the search strategy were selected and verified according to the Descriptors in Health Sciences (DeCS) and the Medical Subject Headings (MeSH). The following terms were applied: "Depressive Disorder", "Cannabidiol", and "Phytotherapy", combined using the Boolean operator AND and adapted to the specific requirements of each database.

The inclusion criteria comprised primary experimental studies conducted in animal models or humans that investigated altered mood states related to depressive disorders, published within the last five years, written in English or Portuguese, and available in full text, regardless of whether access was free or paid. Exclusion criteria included review articles, in vitro studies, publications that did not directly address the antidepressant-like effects of cannabidiol or related cannabinoids, and studies without full-text availability.

The study selection process was carried out in sequential stages. Initially, 129 records were identified across the selected databases. After the removal of duplicate and clearly irrelevant records, 57 studies remained for initial screening. Title screening led to the exclusion of 44 studies that did not meet the predefined inclusion criteria. Subsequently, 13 articles were assessed in full text. After detailed evaluation of abstracts, methods, and conclusions, 5 studies were excluded for failing to meet the established eligibility criteria. Ultimately, 7 studies were included in the final sample of this systematic review.

Results and discussion

All selected articles were published in the English language. A total of seven studies were included in the final analysis. In all studies, rats were used as the experimental model, and depressive-like states were experimentally induced. In five studies, chronic stress paradigms were employed to induce depressive-like behavior, whereas one study utilized a genetic model of depression.

All stages of study identification, screening, eligibility, and inclusion are presented in the PRISMA flow diagram (Figure 1).

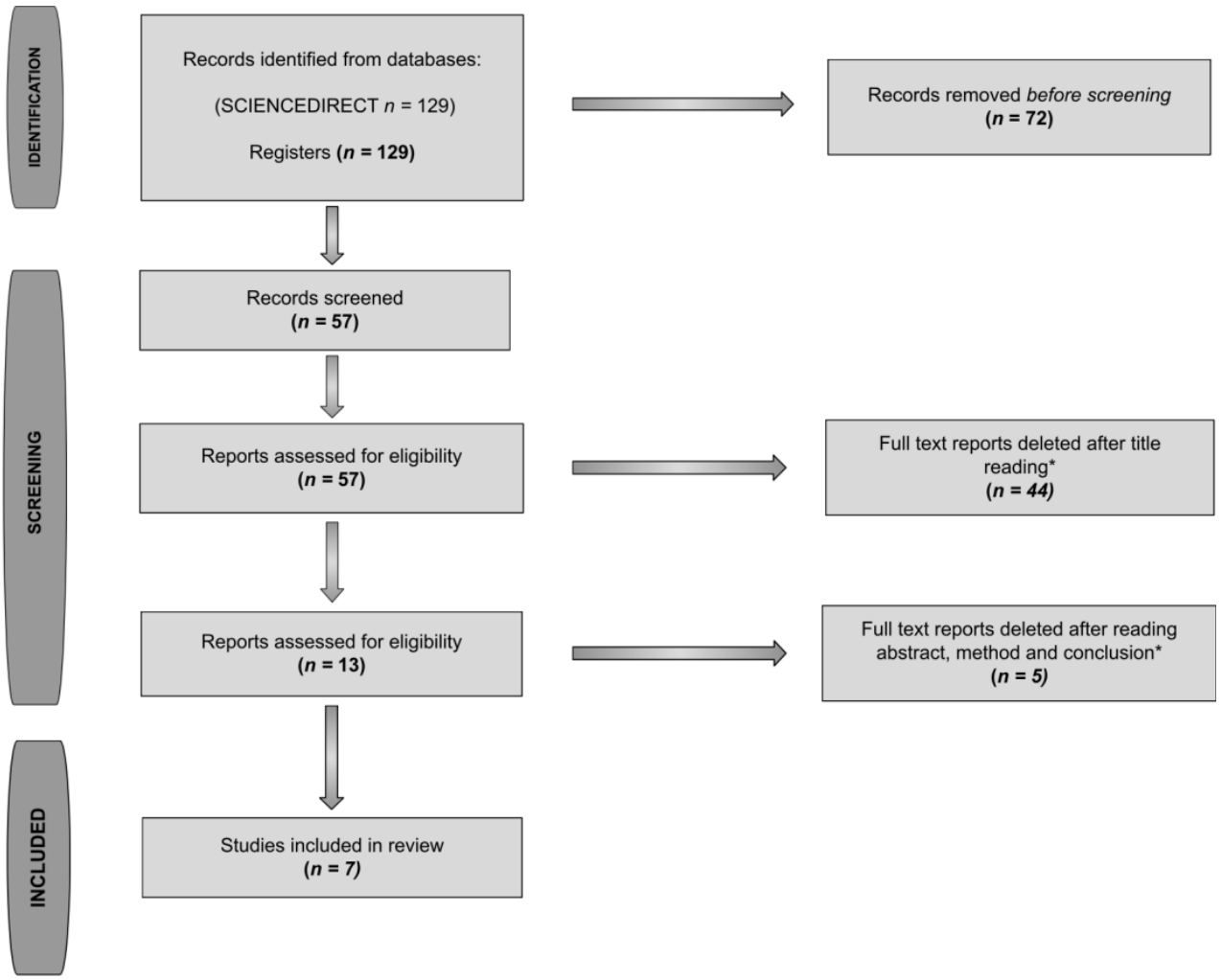

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for studies retrieved through the searching and selection process.

The results of the review are summarized in Table 1.

CBD is the main non-psychotropic psychomimetic component of *Cannabis*, which exhibits antidepressant properties and acts on the kynurenine pathway. According to Florensa-Zanuy *et al.*, CBD reduced immobility time in the tail suspension test and increased sucrose preference in the neuroinflammatory model induced by lipopolysaccharide (LPS) administration, without affecting locomotion or central activity in the open field test. CBD decreased cortical NF-κB and IL-6 levels in both plasma and brain, as well as the increased KYN/TRP and KYN/5-HT ratios in the hippocampus and cortex in the LPS model[25].

These findings demonstrate that CBD produced antidepressant-like effects in the LPS-induced neuroinflammatory model, associated with a reduction in kynurenine pathway activation, IL-6 levels, and NF-κB activity. Given its promising profile as an antidepressant drug, further research is necessary to fully elucidate its mechanisms of action in inflammation-related depression[25].

According to Domingos LB *et al.*, CBD attenuated the increase in immobility observed in FSL rats compared to FRL rats in the forced swim test (FST), without altering locomotor behavior in the open field test (OFT). In synaptosomes, CBD increased ERK1, mGluR5, and synaptophysin expression, but did not restore the reduced CB1 and CB2 levels in FSL rats. In the cytosolic fraction, CBD increased ERK2 expression and decreased mGluR5 in FSL rats. No significant changes in eCB levels were observed in response to CBD treatment[26].

Table 1. Table presenting the author, experimental model, intervention and results observed in the studies analyzed by this review.

Author	Experimental Model	Intervention	Results
Florensa-Zanuy et al.[25]	Mice with LPS-induced inflammation	CBD (cannabidiol)	Reduced immobility time (FST) and increased sucrose preference; no locomotor changes. Reduced NF-κB and IL-6, and lower KYN/TRP and KYN/5-HT ratios in the hippocampus and cortex.
Domingos LB et al.[26]	FSL rats (genetic model of depression)	CBD 10 mg/kg, for 7 days	Reduced immobility (FST) without affecting locomotion. Increased ERK1, mGluR5, and synaptophysin in synaptosomes. Reduced mGluR5 in the cytosolic fraction. There was no change in BDNF or TrkB levels..
Hen-Shoval D et al.[28]	WKY rats (resistant depression model)	CBDA-ME (methylated cannabidiolic acid), oral route	Reduced immobility and increased swimming (FST). Reduced corticosterone and upregulated CB1, FAAH, and CRHR1. Downregulated SERT and BDNF in the medial prefrontal cortex..
Silote GP et al.[29]	C57BL/6 J mice subjected to FST and OFT	Synthetic CBD (10, 30, 100 mg/kg for 7 days, i.p.)	The 100 mg/kg group had an antidepressant effect (FST), without hyperlocation. Increased 5-HT and NA in the hippocampus, reduced 5-HIAA. Reduced NF-κB. No changes in BDNF, mTOR, eEF2, PSD95, and GluA1..
Sartim AG et al.[20]	Swiss mice subjected to FST and OFT	CBD (3–30 mg/kg) + S-ketamine (2.5–30 mg/kg); NBQX (AMPA antagonist)	CBD (10 mg/kg) and ketamine (10–30 mg/kg) reduced immobility (FST). High-dose ketamine caused hyperlocomotion, which was blocked by coadministration with CBD. NBQX blocked the antidepressant effects, suggesting involvement of AMPA receptors..
Shen B et al.[31]	Murine model of PTSD induced by chronic complex stress (CCS)	Medicinal cannabis oil (0.5–2 mg/mL), oral; control group with sertraline	Reversal of anxious/depressive behaviors (OFT, EPMT, FST, TST), without cognitive impairment. Reduction of necrosis/histological changes in the hippocampus. Restoration of BDNF, TRPC6, and antiapoptotic profile (↑ Bcl-2, ↓ Bax).
Ribeiro MA et al.[32]	Mice subjected to chronic unpredictable stress (CUS)	Escitalopram, venlafaxine, with/without AM251 (CB1 antagonist)	ESC and VFX reduced depressive-like behavior independently of CB1 blockade. ESC increased CB1, neurogenesis, and synaptophysin in the hippocampus, but without functional dependence on CB1. It is suggested that the CB1 pathway is not necessary for the antidepressant effects of the drugs tested..

Source: Own authorship.

Repeated CBD treatment at 10 mg/kg for 7 days induced an antidepressant effect in FSL rats, along with specific changes in synaptic plasticity markers in the prefrontal cortex. Thus, the use of CBD for depression appears promising, as it demonstrates relevant properties for reducing depressive behavior. The behavioral results indicated that CBD's antidepressant effects did not involve alterations in BDNF or TrkB levels[26].

Behavioral results of treatment with CBDA-ME, according to Hen-Shoval D *et al.*, indicated an antidepressant effect similar to imipramine, as oral intake reduced immobility and increased swimming duration in the forced swim test. Neither treatment affected locomotion in the open field test or preference in the saccharin preference test. In WKY rats, behavioral improvements coincided with reduced serum corticosterone levels, upregulation of mRNA expression of cannabinoid receptor 1, fatty acid amide hydrolase, and corticotropin-releasing hormone receptor 1, alongside downregulation of serotonin transporter expression in the hippocampus. Additionally, CBDA-ME upregulated CB1 mRNA expression and downregulated brain-derived neurotrophic factor (BDNF) expression in the medial prefrontal cortex (mPFC)[28].

Both CBDA-ME and imipramine reduced corticosterone levels compared to untreated rats. In the hippocampus, significant differences were observed in CNR1 mRNA expression between groups ($F(2,21)=9.934$, $p<0.001$), with CBDA-ME-treated rats showing significantly higher hippocampal CNR1 mRNA levels compared to imipramine ($p<0.01$) or vehicle-treated rats ($p<0.01$). A significant group effect was also observed

for FAAH expression, with CBDA-ME treatment upregulating FAAH compared to both imipramine ($p<0.05$) and vehicle ($p<0.05$)[28].

In a preclinical study, chronic administration of synthetic cannabidiol (CBD), with 99.8% purity and THC-free, induced significant antidepressant effects in C57BL/6J mice, particularly at a dose of 100 mg/kg. Animals were subjected to the forced swim test (FST) and the open field test (OFT), showing reduced immobility time in the FST without locomotor impairment in the OFT. At the molecular level, CBD administration at doses of 30 mg/kg and 100 mg/kg significantly reduced hippocampal expression of the pro-inflammatory protein NF-κB, suggesting a possible anti-inflammatory mechanism underlying its antidepressant effects. No relevant changes were observed in BDNF, PSD95, mTOR, eEF2, or GluA1 expression. The 100 mg/kg dose also increased hippocampal serotonin (5-HT) and norepinephrine (NA) levels while reducing 5-HIAA, the main serotonin metabolite, indicating modulation of monoamine metabolism and availability. These findings point to a synergistic mechanism of CBD involving both monoaminergic modulation and inflammatory pathways, reinforcing its antidepressant potential in animal models of depression[30].

Sartim AG *et al*. investigated the effects of co-administration of cannabidiol (CBD) and S-ketamine in Swiss mice to assess combined antidepressant potential and adverse effects, particularly hyperlocomotion. Using the forced swim test (FST) and open field test (OFT), they found that CBD alone, at 10 mg/kg, induced significant antidepressant effects without altering locomotion. S-ketamine at 10 mg/kg and 30 mg/kg also reduced immobility in the FST; however, the 30 mg/kg dose induced hyperlocomotion in the OFT. Notably, co-administration of CBD (10 mg/kg) with S-ketamine preserved the antidepressant effects of ketamine but inhibited its locomotor-stimulating action, suggesting a modulatory role of CBD against the psychomimetic side effects of ketamine. Moreover, prior administration of NBQX, an AMPA receptor antagonist, blocked the antidepressant effects of both substances, indicating that AMPA receptor activation is essential for the observed therapeutic response. Although the combination of CBD and S-ketamine did not produce additive antidepressant effects, these findings underscore the clinical relevance of CBD as an adjunct in ketamine therapy, enhancing treatment safety for resistant depression by mitigating adverse effects without compromising efficacy[20].

Shen B *et al.* evaluated the therapeutic effects of medicinal cannabis oil, with high cannabidiol (CBD) content and minimal THC (<0.3%), in a murine model of post-traumatic stress disorder (PTSD) induced by complex chronic stress (CCS). Mice were exposed to daily sessions of physical restraint, vibration, noise, and artificial light for four weeks and treated for 14 days with different concentrations of cannabis oil (0.5, 1, and 2 mg/mL) via intragastric administration, alongside a control group treated with sertraline. Behavioral testing showed that CCS induced anxiety- and depression-like behaviors, evidenced by alterations in the OFT, EPMT, FST, and TST, which were significantly reversed by cannabis oil treatment. Cognitive performance, assessed by the Morris water maze, showed no significant changes. Histologically, treatment reduced neuronal necrosis and cellular disorganization in the hippocampus. At the molecular level, CCS increased expression of the pro-apoptotic protein Bax and decreased Bcl-2, effects reversed by cannabis oil. Furthermore, CCS-induced reductions in BDNF and TRPC6 at both mRNA and protein levels were restored with treatment, implicating the BDNF/TRPC6 pathway as a mediator of therapeutic effects. These results support CBD's potential as an antidepressant and neuroprotective agent in chronic stress contexts, particularly through modulation of synaptic plasticity and hippocampal neuronal apoptosis[31].

Ribeiro MA *et al.* investigated the role of the CB1 cannabinoid receptor in the behavioral and neuroplastic effects of two widely used antidepressants — escitalopram (ESC) and venlafaxine (VFX) — in mice subjected to the chronic unpredictable stress (CUS) model, which simulates varied and random environmental stressors closer to human reality. Animals were treated with ESC or VFX alone or in combination with AM251, a selective CB1 receptor inverse agonist/antagonist. Behavioral tests showed that both antidepressants significantly reduced CUS-induced depressive behaviors, and these effects persisted even with CB1 blockade, indicating that CB1 activation is not required for the antidepressant response in this model. Moreover, ESC increased CB1 expression in the hippocampus, as well as neurogenesis and synaptophysin

levels, indicating neurotrophic effects. However, AM251 did not prevent these changes, reinforcing that CB1-mediated signaling is not essential for the observed cellular and molecular outcomes. These findings challenge the hypothesis that antidepressant efficacy depends on CB1 activation, suggesting the possibility of developing therapies that maintain antidepressant effectiveness without engaging cannabinoid pathways, thereby potentially reducing associated risks[32].

Conclusion

The findings of this review reinforce the potential of cannabidiol (CBD) and other *Cannabis*-derived compounds as therapeutic agents in the treatment of depressive disorders, particularly in animal models subjected to chronic or neuroinflammatory stress. Thus, CBD emerges as a promising and safe alternative with multifactorial mechanisms of action. However, translating these findings into clinical practice still requires controlled human studies to confirm its efficacy, safety, and applicability across different patient profiles with depression.

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