Journal of Public Health and Pharmacy
2775-4952 (Online - Elektronik)
Review Articles Open Access

Efficacy and Safety of Cannabidiol for Anxiety: A Bibliometric Analysis and Systematic Review

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ARTICLE INFO

Manuscript Received: 06 Nov, 2024
Revised: 13 Feb, 2025
Accepted: 23 Feb, 2025
Date of publication: 02 Oct, 2025
Volume: 5
Issue: 3
DOI: 10.56338/jphp.v5i3.6807

KEYWORDS

Anxiety;
Anxiolytic;
Cannabidiol;
Pharmacology

ABSTRACT

Introduction: A non-psychoactive substance present in the cannabis plant, cannabidiol (CBD), seems to have potential as an anxiolytic agent. This study systematically reviews the efficacy, safety, dosage, mechanisms, and adverse effects of CBD in treating anxiety.
Methods: The PRISMA guideline was used to conduct the review.
Results: A total of 64 articles were included in the study. It showed that CBD works at the endocannabinoid receptors CB1 and 5-HT1A, which regulate mood and reduce anxiety. In animal models, a range dosage of 5 – 10 mg/kg showed a significant anxiolytic effect in behavioral tests, while in humans, 300 mg/day was proven to be effective in treating various types of anxiety disorders. However, individual responses to CBD showed varying results, and demographic characteristics affect the efficacy of animal and human studies. CBD was also considered safer to be used in the short term compared to diazepam, although the long-term effect remains lacking evidence
Conclusion: This study concludes that CBD has potential as an alternative choice for anxiety. Further research is needed in larger populations with rigorous study design and longer study durations to evaluate its effectiveness and ensure its safety.
Recommendations for Future Research: It is hoped that future research can examine the effects of fly resistance and killing on non-target organisms and control environmental conditions.

Publisher: Pusat Pengembangan Teknologi Informasi dan Jurnal Universitas Muhammadiyah Palu

INTRODUCTION

Cannabidiol (CBD) has been known as a Phyto cannabinoid compound that is non-psychoactive, meaning it has not caused a high effect or dependence like Tetrahydrocannabinol (THC) (1). CBD has featured a dibenzopyran ring with a phenol group, a hydroxyl group, a pentyl side chain, and a chiral center, see Figure 1. In addition to its chemical structure, the pharmacokinetic profile of CBD, including parameters such as Tmax, Cmax, and half-life (t1/2), is summarized in Table 1. Previous research proved that CBD was able to relieve anxiety (2). CBD interacts with the body's endocannabinoid system, especially at Cannabinoid 1 Receptor (CB1), that regulates mood (3). In addition, CBD also interacts with receptors from neurotransmitters such as serotonin (5HT1A receptors) that regulate mood (4). Its interaction with these receptors led to anxiolytic effects.

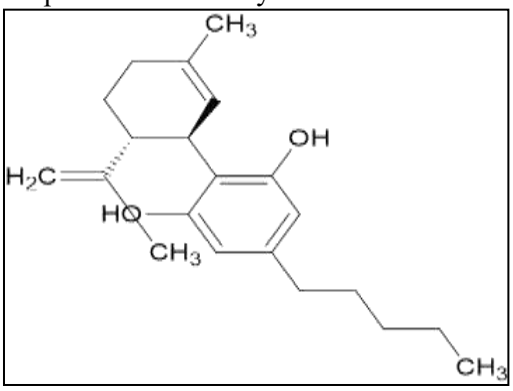

Figure 1. Chemical Structure of Cannabidiol

Research on its anxiolytic effect has grown rapidly, starting from animal studies to clinical trials. Animal studies involved a variety of animals and diverse study designs that were to measure anxiety levels in animals, such as elevated plus maze test and open field test (5–9). These positive findings were then followed by early clinical trials in humans with anxiety disorders (10–14). It has been demonstrated that CBD decreased the level of anxiety in animals and humans.

The legality of CBD as an anxiolytic remains limited due to inconsistent clinical results and varying individual responses. While it has the potential to reduce anxiety, the FDA has only approved *Epidiolex*® for epilepsy (15), with limitations in standardized dosing and large-scale clinical trials. Some studies indicate that the effects of CBD depend on dosage, but its optimal dose and comparative effectiveness with conventional therapies have not been clearly established. Therefore, this study aims to explore its mechanism of action, optimal dosage, long-term safety, and genetic factors influencing individual responses to assess the evidence-based potential of CBD as an anxiety treatment.

Table 1. Pharmacokinetics profile of cannabidiol (CBD)

Parameters	Value	Reference
Cmax	20.5 ng/mL (epidiolex); 17.5 ng/mL (capsule); 2.8 ng/mL (syrup)	(16)
Tmax	3.3 ng/mL (epidiolex); 2.5 ng/mL (capsule); 3.2 ng/mL (syrup)	(16)
$T^1/_2$	1.10-31.00 h (inhalation); 1.44-10.86 h (spray); 1.09-70.3 h (oral)	(17)
Vd	32L/kg (oral)	(18,19)
F	13 – 19% (oral)	(20)
Cl	1111–1909 L/h (oral)	(21)

Cl: clearance; Cmax: maximum concentration; F: bioavailability; Tmax: maximum time; T1/2: half-life; Vd: volume of distribution

METHOD

Search Strategy

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension for systematic review (22). Some databases used in the literature search included PubMed, ScienceDirect, and Scopus. The search was conducted using the following keywords ("CBD" OR "Cannabidiol") AND ("Anxiety"

OR "Anxiolytic") and there were no initial year limits. The reliance on specific databases may limit the inclusion of relevant studies, affecting the completeness of this review.

Inclusion Criteria

The chosen study articles concentrated on the mechanisms of CBD in treating anxiety, appropriate dosage form, dosage or strange, and adverse effects. The main source of this research was in vivo studies written in English. We included animal and human studies written in English. The chosen studies assessed a minimum of two significant points, including cannabidiol and anxiety.

Exclusion Criteria

Conference papers, thesis dissertations, review articles, papers published in conference proceedings, manuscripts without abstracts, gray literature or unpublished studies and those that did not fit the inclusion criteria were all disqualified to proceed with our review. Articles discussing the association of CBD with the diseases not covered in this review were also excluded from the analysis. These exclusion criteria may introduce selection bias, potentially limiting the generalizability of the findings

Data extraction and management

Bibliometric Analysis

We used VOSviewer (v1.6.19, CWTS, Leiden University) to visualize term relationships in scientific literature, aiding conceptual understanding and study selection. By analyzing co-occurring keywords from titles and abstracts, with a minimum threshold of two occurrences, we generated impactful network, overlay, and density visualizations to highlight key interconnections.

Systematic Review

We utilized Zotero (AGPL, USA) to collect and manage relevant articles, ensuring alignment with inclusion criteria for analysis. Studies were categorized into two groups: (1) animal studies and (2) human studies. Key data extracted from animal studies included animal type, intervention, dosage, study design, and outcomes (Table 2 and Table 3).

RESULTS

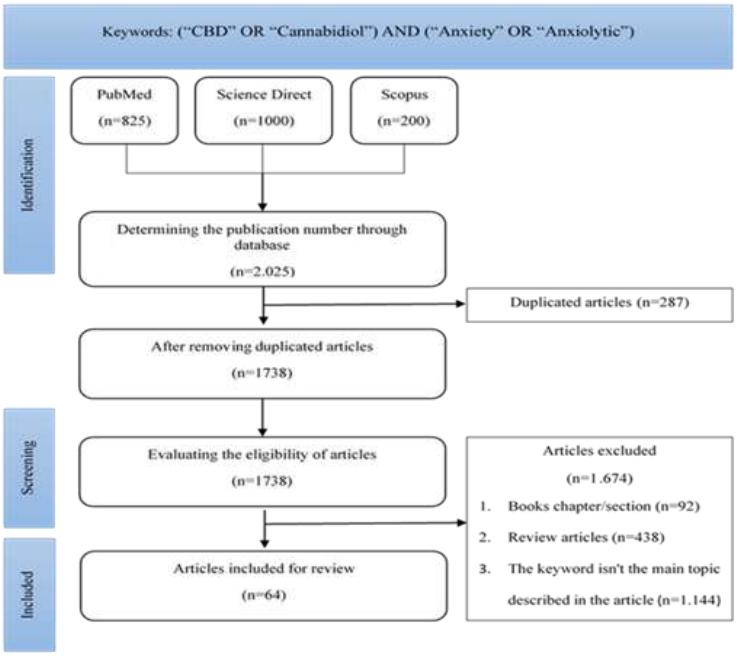

Figure 2. PRISMA diagram [22]

Relevant articles for treating anxiety using cannabidiol were identified through a systematic search according to the PRISMA guidelines.

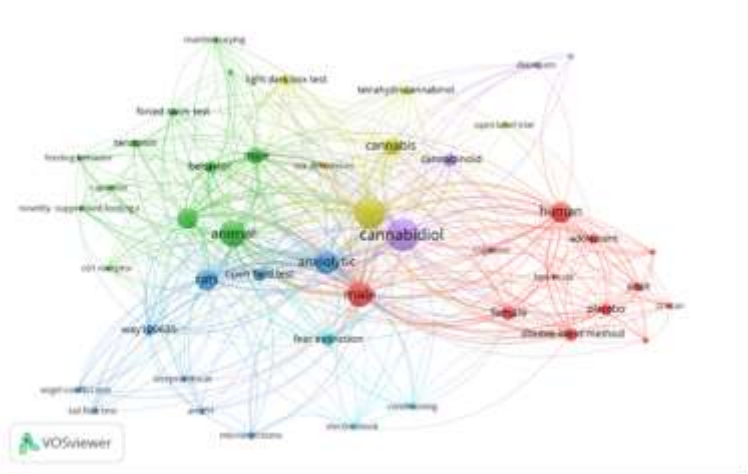

Figure 3. Network Visualization

The network visualization of the studies is shown in Figure 3. Based on the color of the nodes, the VOS viewer groups the keywords into seven distinct clusters.

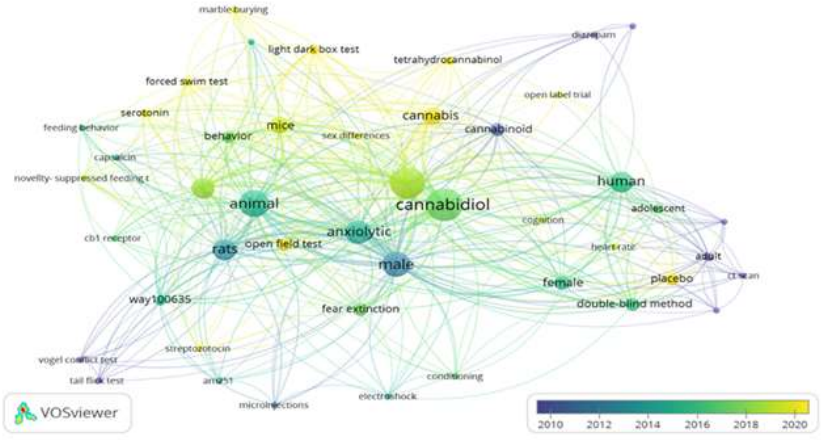

Figure 4. Overlay Visualization

Figure 4 depicts research trends on CBD and anxiety (2012–2022) using an overlay visualization. Keywords are color-coded by publication year in the VOS viewer. Notably, "anxiety" showed peak activity in 2018.

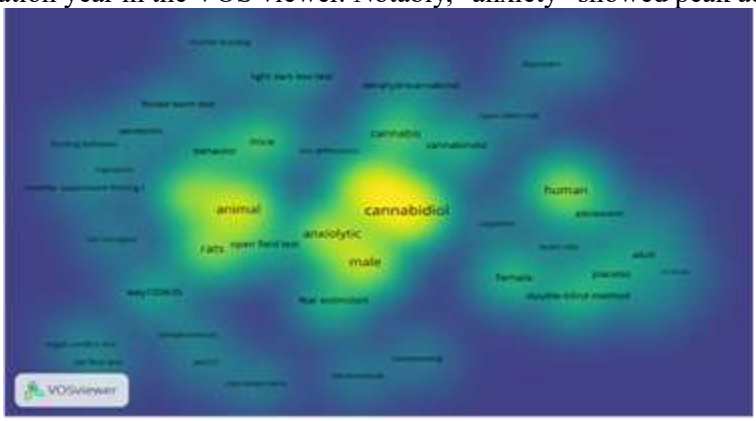

Figure 5. Density Visualization

Figure 5 highlights keyword frequency and intensity related to CBD and anxiety using a heat map. Bright yellow indicates high density (frequent co-occurrence), while dark blue/purple shows lower density. Terms like "cannabidiol" and "anxiety" appeared in 100% of articles, while others, such as "open field test" (12.4%) and "placebo," had lower density, reflecting limited research or emerging topics.

Table 2 shows that CBD has significant anxiolytic effects, particularly in rats, as evidenced by behavioral tests like the elevated plus maze and open field test. Effective doses range from 0.3 to 30 mg/kg, with optimal effects at 5 – 10 mg/kg. Some studies report a biphasic response, where very low or high doses are less effective, suggesting dose-dependent effects influenced by species and experimental conditions**.**

Table 2. Overview of the search for Cannabidiol (CBD) in Animal Models.

Study	Animal	Test	Intervention	Doses and Administration	Results
Uribe - Mariño et al., 2012 (23)	Mice (Male Swiss)	MP	CBD	0.3, 3 and 30 mg/kg; iv	CBD treatment reduced defensive immobility, behavioral index, explosive fleeing, and total fleeing duration.
Guimarães et al., 1990 (24)	Rat (Male Wistar)	EPM	CBD vs Diazepam vs Vehicle	CBD: 2.5, 5.0, 10 and 20 mg/kg Diazepam: 2 mg/kg; i.p	CBD (5 mg/kg) increased open-arm entries but was weaker than diazepam.
Elbatsh et al., 2012 (25)	Rat (Male Lister-hooded)	CER	CBD vs Vehicle	For 14 days, 10 mg/kg. (acute)	Repeated CBD administration significantly increased freezing behavior duration.
Guimarães et al., 1994 (7)	Rat (Male Wistar)	EPM	CBD vs HU-219 vs HU-252 vs HU-261 vs Diazepam	CBD (5 mg/kg), HU-219 (0.03-3.0 mg/kg), HU252 (0.2-5 mg/kg), HU-261 (0.3-10 mg/kg) and Diazepam (2.5 mg/kg); i.p	CBD and HU-219 (0.03–1 mg/kg) increased open-arm entries but were less potent than diazepam.
Moreira, 2006 (26)	Rat (Male Wistar)	VC	CBD vs Diazepam vs CBD + Flumazenil vs Diazepam + Flumazenil	CBD (2.5, 5 or 10 mg/kg), Flumazenil (10 mg/kg), Diazepam (3.0 mg/kg); i.p	Flumazenil did not block CBD's anxiolytic effects; CBD (10 mg/kg) increased both penalized and total licks.
Zieba et al., 2019 (9)	Mice (Male Fmr1 knockout and WT)	OF	CBD vs vehicle	5 and 20 mg/kg; i.p	CBD (5 mg/kg or 10 mg/kg) showed no significant effect on anxiety parameters compared to controls.
		EPM	CBD vs vehicle	5 and 20 mg/kg; i.p	CBD induced anxiolytic effects in both mice, with no differences between genotypes.
Silva-Cardoso et al., 2021 (27)	Rat (Male Wistar)	OF	CBD vs Vehicle	0.3, 3, 10, 30 mg/kg; i.p	CBD (3 mg/kg) effectively reduced anxiety caused by chronic pain.
Almeida et al., 2013 (28)	Rat (Male Wistar)	SI	CBD	1, 5, 15, 30, 60 mg/kg; i.p	CBD (1 mg/kg) increased passive social interactions.
Shu et al., 2024 (29)	Mice (Male ICR)	SIH	CBD vs Diazepam vs CBD with WAY100635	WAY100635 (0,1, 0,3, 1 mg/kg), diazepam (3 mg/kg), CBD (1, 3, 10 mg/kg); i.p	CBD reduces SIH by 55% and 51% at 3 and 10 mg/kg but diazepam at 3 mg/kg shows a stronger 86% reduction.

Study	Animal	Test	Intervention	Doses and Administration	Results
Kaplan et al., 2021 (8)	Mice (Male and Female C57BL/6 J)	EPM	CBD	5, 10 mg/kg; i.p	CBD at 5 mg/kg increased time spent in open vs. closed arms.
Wanner et al., 2021 (30)	Mice (Male and Female Agouti viable yellow (Avy)).	MB	CBD	20 mg/kg/day; oral	F1 female mice treated with CBD during development buried twice as many marbles as controls.
Chaves et al., 2021 (31)	Rat (Male Wistar)	EPM	Experimental design I: vehicle vs CBD vs CBD with WAY100635	WAY 100635: 0.1 mg/kg CBD: 30 mg/kg; i.p	WAY100635 partially reduced CBD's anxiolytic effect.
			Experimental design II: Vehicle vs CBD; vs CBD with AM251; vs CBD with AM630	CBD: 30 mg/kg AM251: 1 mg/kg AM630: 1 mg/kg; i.p	CBD reduces anxiety by increasing time and frequency in open arms, but AM251 diminishes this effect.
Chaves et al., 2023 (32)	Rat (Male Wistar)	EPM	CBD vs Vehicle	30, 60 mg/kg; i.p	CBD increasing open-arm entries, duration, and overall exploratory activity ($p < 0.05$)
De Grogerio et al., 2019 (5)	Rat (Male Wistar)	NSF and EPM	CBD vs CBD with WAY100635, CBD with Capsazepine	CBD: 5 mg/kg, WAY100635: 2 mg/kg, Capsazepine: 10 mg/kg; s.c	CBD increased open-arm duration, but its anxiolytic effects were inhibited by WAY100635.
Alegre-Zurano et al., 2021 (33)	Mice (Male CD1)	EPM	Vehicle vs CBD vs CBD with MDPV	CBD: 20 mg/kg, MDPV: 3 – 4 mg/kg; i.p	Mice given MDPV and CBD spent extra time in the open arm
Austrich-Olivares et al., 2022 (34)	Mice (Male WT)	LDB	CBD	10, 20, 30 mg/kg; i.p	CBD at 10 and 20 mg/kg increased time spent in the light box.
		EPM	CBD	10, 20, 30 mg/kg; i.p	CBD (10, 20 mg/kg) increased open-arm percentage, peaking at 20 mg/kg.
		NSFT	CBD	10, 20, 30 mg/kg; i.p	CBD at 10 mg/kg improved motivation and feeding, while 20 mg/kg showed strong anxiolytic effects.
Hsiao et al.,2012 (35)	Rat (Male Wistar)	EPM OF	CBD	0,5 and 1 mg/kg; inject to CeA	CBD (1 mg/kg) increased exploration in the OF and time spent in the open arm.
Chesworth et al., 2022 (36)	Mice (Female WT) and APPxPS 1)	EPM	CBD	20 mg/kg; oral	CBD showed no effect in both mouse groups.
Rock et al., 2017 (37)	Rat (Male	LDB emergen	CBD vs CBDA	5 mg/kg; i.p	CBD (5 mg/kg) reversed FS stress-induced anxiety and

Study	Animal	Test	Intervention	Doses and Administration	Results
	Sprague-Dawley)	ce test with foot shock stress			increased time spent in the bright room.
			CBDA, CBD, THC	CBDA: 1 µg/mL, CBD: 5 mg/kg, THC: 1 mg/kg; i.p	THC induced anxiety and foot shock stress worsens anxiety.
Melkumnyan et al., 2024 (38)	Mice (Male and Female C57Bl/6)	OF	CBD vs CBD: THC (3:1)	CBD :10 mg/kg, CBD : THC (3:1): 7,5:2,5 mg/kg	At 24-hour alcohol withdrawal, single CBD reduced anxiety.
Marinho et al., 2015 (39)	Rat (Male wistar)	EPM	CBD vs CBD with WAY100635	CBD: 15, 30, and 60 nmol, WAY100635: 0,37 nmol; microinjection to intra-infralimbic	CBD (15 and 30) nmol increased exploration of EPM open arms.
		Restrain stress and EPM			In stress-restricted rats, CBD treatment did not alter open arm exploration in the EPM compared to untreated groups.
Fogaça et al., 2014 (6)	Rat (Male Wistar)	EPM	CBD vs CBD with WAY100635	CBD: 15, 30, and 60 nmol, WAY100635: 0,37 nmol; microinjection to intra-prelimbic	CBD (30nmol) reducing open-arm exploration in the EPM.
		Restrain stress and EPM	CBD vs CBD with WAY100635vs Metyrapone	CBD: 15, 30, and 60 nmol, WAY100635: 0,37 nmol; microinjection to intra-prelimbic. Metyrapone: 75 mg/kg;i.p	CBD's effect on EPM shifted from anxiogenic to anxiolytic-like in rats.
Granjeiro et al., 2011 (40)	Rat (Male Wistar)	EPM	CBD	30 nmol	CBD exhibited increased open-arm entries.
Campos and Guimarães, 2009 (41)	Rat (Male Wistar)	EPM	CBD vs CBD with Capsazepine vs WIN 55,212-2 vs WIN 55,212-2 with Capsazepine	CBD: 30 and 60 nmol, WIN 55,212-2: 3, 10, 30 nmol, Capsazepine: 10 nmol; intra-dlPAG	CBD (30 nmol) and WIN 55,212-2 (3–10 nmol) increased open-arm entries, while higher doses reduced the effect. Capsazepine blocked anxiety from high doses.
Bitencourt et al., 2008 (3)	Rat (Male Wistar)	EPM	CBD vs AM404 vs Diazepam	AM404 (1.0 µg/µl), CBD (2.0 µg/µl), Diazepam (2.85 µg/µl); i.c.v	AM404 and CBD increased open-arm entries in the conditioned group, while diazepam increased entries in both groups.
Salviato et al., 2021 (42)	Rat (Female Wistar)	EPM	CBD	1 mg/kg and 3 mg/kg; i.p	CBD (3 mg/kg) showed increase in %OAT and %OAE compared to control.
	Rat (Male wistar)	EPM	THC: CBD	THC (1 mg/kg): CBD (1 – 3 mg/kg), THC (0,075 mg/kg): CBD (1 mg/kg); i.p	THC's anxiogenic effects were reduced with CBD (1-3 mg/kg). Combining THC (0.075 mg/kg) and CBD (1 mg/kg) enhanced THC's anxiolytic effects.
Breurer et al., 2016 (43)	Mice (Male swiss)	EPM	CBD	30 mg/kg; i.p	Time spent in the open arm (%OAT) and entries into the open arm (%OAE) were increased.
			HUF-101	1, 3, and 10 mg/kg. i.p	The number of entries into the open arm (%OAE) and the

Study	Animal	Test	Intervention	Doses and Administration	Results
					duration in the open arm (%OAT) were increased by 3 mg/kg.
			HUF-102	1, 10 and 60 mg/kg; i.p	HUF-102 showed no increase in open-arm time or entries.
			HUF-103	1, 3 and 10 mg/kg; i.p	Significant increases in open-arm time (%OAT) at 3 and 10 mg/kg.
Campos and Guimarães, 2008 (4)	Rat (Male Wistar)	EPM	CBD	15, 30, and 60 nmol	Rats (30 nmol) spent more time in the open arm, showing a bell-shaped dose-response curve with 30 nmol as the optimal dose.
			CBD with AM251	CBD: 30 nmol, AM251: 100 pmol	Rats given 30 nmol CBD with AM251 showed similar open-arm exploration as with CBD alone.
			CBD with WAY100635	CBD: 30 nmol, WAY100635: 0,37 nmol.	CBD (30 nmol) with WAY100635 didn't increase open-arm exploration.
		VC	CBD	15, 30, dan 60 nmol	Rats given 30 nmol CBD drank more despite electric shocks.
Masataka, 2024 (44)	Cat (Male Domesti)	SB	CBD vs placebo	4 mg/kg	Cats given CBD spent more time near their owner without contact.
Schleicher et al., 2019 (45)	Mice (Male and Female C57BL/6 J)	LDB	CBD (3 months/former group) vs CBD (6 months/current groups)	20 mg/kg	CBD-treated mice showed no increased time in the lighted area, unlike vehicle-treated mice.
		EPM	CBD (3 months/former group) vs CBD (6 months/current group)	20 mg/kg	Former group showed no change, while the current group reduced time in the open arm.
Nazario et al., 2015 (46)	Zebrafish (Male and Female WT)	Time in the top area of the aquarium	CBD	0.1, 0.5, 5.0, and 10 mg/kg	CBD showed a U-shaped dose-response, with 0.5 mg/kg significantly increasing surface time.
Fabris et al., 2022 (47)	Rat (Male and female Wistar)	EPM	CBD	0.3, 3, 30 mg/kg; i.p	In males, CBD (3 mg/kg) increased open-arm entries; in females, effects appeared at 0.3 mg/kg in late diestrus.
Pérez-Valenzuela et al., 2023 (48)	Rat (Male and female Sprague Dawley)	LDB	CBD vs THC: CBD	30 mg/kg, 0.3 mg/kg: 30 mg/kg; oral	CBD alone had little effect; combined treatment reduced anxiety in stressed males.
		EPM	CBD vs THC: CBD	30 mg/kg, 0.3 mg/kg: 30 mg/kg; oral	In males, the combination significantly increased open-arm duration.

Study	Animal	Test	Intervention	Doses and Administration	Results
Huffstetler et al., 2023 (49)	Mice (Male and Female WT C57BL/6 J) and (Kv1.3−/−)	MB	CBD	10 mg/kg and 20 mg/kg; i.p	Male WT mice given CBD (10 mg/kg) buried significantly fewer marbles than controls.
		EPM	CBD	10 mg/kg and 20 mg/kg; i.p	WT mice showed no change, but Kv1.3−/− females (10 mg/kg) spent more time in closed arms.
		LDB	CBD	10 mg/kg and 20 mg/kg;i.p	CBD eased anxiety in WT mice but increased it in female Kv1.3−/− mice at 20 mg/kg.
Campos et al., 2013 (50)	Mice (Male WT C57BL/6 J and GFAP-TK transgenic)	EPM	CBD vs CBD with AM251	CBD: 30 mg/kg (14 days), AM251: 1 mg/kg; i.p	CBD increased open-arm duration, showing anxiolytic effects in stressed WT mice.
		NSF	CBD vs CBD with AM251	CBD: 30 mg/kg (14 days), AM251: 1 mg/kg; i.p	CBD reduced eating latency in stressed WT mice.
Fogaça et al., 2018 (51)	Mice (Male C57BL/6)	EPM	CBD	30 mg/kg; i.p	Repeated CBD intake boosted open-arm exploration in stressed mice.
			CBD with AM251	30 mg/kg, 0.3 mg/kg; i.p	AM251 blocked the CBD's anxiolytic effect.
			CBD with AM630	30 mg/kg, 0.3 mg/kg;i.p	AM630 blocked the CBD's anxiolytic effect.
			CBD with WAY100635	30 mg/kg, (0.05 mg/kg and 0.1 mg/kg); i.p	WAY100635 (0.05 mg/kg) did not block CBD's anxiolytic effect.
		NSF	CBD	30 mg/kg; i.p	CBD decreased the latency to feed in stressed mice.
			CBD with AM251	30 mg/kg 0.3 mg/kg; i.p	AM251 blocked CBD's anxiolytic effect..
			CBD with AM630	30 mg/kg, 0.3 mg/kg;i.p	AM630 blocks CBD's anxiolytic effect.
			CBD with WAY100635	30 mg/kg, (0.05 mg/kg and 0.1 mg/kg); i.p	WAY100635 did not block CBD's anxiolytic effect.
Gomes et al., 2011 (52)	Rat (Male Wistar)	EPM	CBD	15, 30, or 60 nmol; injection into BNST	CBD (60 nmol) significantly increased open-arm entries and duration.
			CBD with WAY100635	CBD: 15, 30, or 60 nmol, WAY100635: 0.37 nmol; injection into BNST	WAY100635 (0.37 nmol) blocked CBD's anxiolytic effects.
		VC	CBD	15, 30, or 60 nmol; injection into BNST	CBD (30–60 nmol) increased punished licks, resembling anxiolytic effects.
			CBD with WAY100635	CBD: 15, 30, or 60 nmol, WAY100635: 0.37 nmol; injection into BNST	WAY100635 blocked CBD's anxiolytic effects.
Shallcross et al., 2019 (53)	Rat (Male Sprague-Dawley)	EPM	CBD	5 mg/kg; i.p	Rats treated with CBD were less frequent in the open arms
			CPPDB	30 mg/kg; s.c	CPPDB did not affect open-arm duration.

Study	Animal	Test	Intervention	Doses and Administration	Results
		LDB	CBD	5 mg/kg; i.p	CBD reduced dark box time and sped up light entry.
			CPPDB	30 mg/kg;s.c	CPPDB had no effect on dark box time or light box latency.
Morris et al., 2020 (54)	Dog (Male and Female)	Noise-induced fear response model	CBD	1.4 mg/kg body	CBD doesn't significantly decrease anxiety.
			CBD with Trazodone	CBD: 1.4 mg/kg, Trazodone: 100 mg for dogs 10-20 kg, 200 mg for dogs 20.1-40 kg	No added benefit over trazodone alone; may reduce its cortisol-lowering effect.
Stern et al., 2015 (55)	Rat (Male Wistar)	EPM	CBD	1, 3 mg/kg; i.p	CBD showed no significant effect on open-arm duration or entries versus controls.
			THC with CBD	THC (0.1 mg/kg) and CBD (1.0 mg/kg); i.p	THC (0.1 mg/kg) and CBD (1.0 mg/kg) reduced freezing and boosted open-arm exploration.
		OF	CBD	1, 3 mg/kg; i.p	CBD (1.0 or 3.0 mg/kg) did not affect center duration in the OF test versus controls.
			THC with CBD	THC (0.1 mg/kg) and CBD (1.0 mg/kg); i.p	The combination treatment increased center duration in the OF test.

BNST: Bed Nucleus of the Stria Terminalis; CBD: Cannabidiol; CBDA: Cannabidiol Acid; CeA: Central Amygdala; CER: Conditioned Emotional Response; CPPDB: *3-Cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide*; dlPAG: Dorsolateral Periaqueductal Gray; EPM: Elevated Plus Maze; i.c.v: intracerebroventricular; i.p: Intraperitoneal; LDB: Light Dark Box; MB: Marble Burying; MDPV: Methylenedioxy pyrovalerone; MP: Mock Predatory; NSF: Novelty-Suppressed Feeding; OF: Open Field; s.c: Subcutaneous; SB: Secure Base; SI: Social Interaction; SIH: Stress-Induced Hyperthermia; THC: Tetrahydrocannabinol; VC: Vogel Conflict; VH: Ventral Hippocampus; vs: versus; WT: Wild Type.

Table 3 presents that CBD reduces anxiety across diverse populations, including individuals with social anxiety disorder and PTSD at doses ranging from 150 to 800 mg/day. It has been found that combining CBD with THC or antidepressants could balance the anxiogenic effects of THC and improved therapeutic outcomes.

Table 3. Overview of the search for Cannabidiol (CBD)

Study	N Participant (condition)	Age (years)	Drug	Doses and administration	Results
Stanley et al., 2023 (56)	32 (Test Anxiety Induction)	18 – 25	CBD vs placebo	150, 300, 600 mg; oral	Patients on 600 mg CBD showed more physical anxiety signs than placebo and lower-dose groups.
Zuardi et al., 1982 (2)	8 (healthy)	20 - 38	CBD	1 mg/kg; oral	CBD had mild anxiolytic effects, weaker than diazepam.
			CBD: THC	1 mg/kg: 0.5 mg/kg; oral	The THC-CBD combination consistently reduced psychological anxiety.

Study	N Participant (condition)	Age (years)	Drug	Doses and administration	Results
Martin et al., 2021 (57)	538 (anxiety)	≥ 18	Medical cannabis product (CBD dominant 82 %)	61 mg; oral	CBD consistently reduced anxiety in both acute and long-term doses without psychoactive effects.
			Medical cannabis product (balanced THC: CBD 7%)	-	CBD can reduce the anxiety-increasing THC's effect.
Masataka, 2019 (58)	37 (SAD)	18-19	CBD vs placebo	300 mg/day for 4 weeks; oral	Significant decrease in social anxiety scores (FNE & LSAS) compared to placebo
Hurd et al., 2019 (13)	42 (heroin use disorder)	21-65	CBD vs placebo	400 mg; oral once daily for 3 consecutive days	Moderate anxiety and craving reductions lasted up to 7 days post-dose.
				800 mg; oral once daily for 3 consecutive days	CBD sharply reduced anxiety and craving, lasting 7 days, beating 400 mg and placebo.
Berger et al., 2022 (59)	31 (anxiety)	12 - 25	CBD	Starting at 200 mg/day, titrated to max 800 mg/day over 12 weeks; oral	Anxiety dropped 42.6% in 12 weeks, with 40% seeing a 50% reduction.
			Antidepressants with CBD		CBD with antidepressants reduced anxiety more than CBD alone.
Bergamaschi et al., 2011 (10)	24 (SAD) and 12 (healthy)	23	CBD vs Placebo	600 mg; oral	CBD significantly reduced anxiety during public speaking.
Laczkovics et al., 2021 [59]	1 (SAD)	16.9	CBD	Cannabidiol (CBD), 100-600 mg/day (over 8 weeks); Sertraline (100 mg/day, discontinued after 3 weeks of CBD); oral	CBD reduced anxiety and depression, lowering depressive symptoms from moderate to minimal in 8 weeks.
Hutten et al., 2022 (60)	26 (cannabis users)	23.1	THC-dominant cannabis	13.75 mg THC, vaporized	Significant increase in state anxiety compared to placebo.
			CBD-dominant cannabis	13.75 mg THC, vaporized	No significant increase in anxiety compared to placebo.
			THC/CBD-equivalent cannabis	13.75 mg THC + 13.75 mg CBD, vaporized	CBD reduced THC-induced anxiety.
Dahlgren et al., 2022 (61)	14 (anxiety)	22 - 64	CBD solution (contains 9.97 mg/mL CBD, 0.23 mg/mL THC)	1 mL sublingually 3x/day (total: 30 mg CBD, <1 mg THC/day)	Anxiety dropped significantly by week 4, evident by week 1.
Ramani et al., 2024 (62)	109 (healthy)	18 - 50	CBD with L - theanine	CBD:30, 60 mg/day; L-theanine: 175–185 mg; oral	Anxiety, cognitive function, exhaustion, and BDNF levels did not significantly change.
Crippa et al., 2004 (11)	10 (healthy)	25 - 42	CBD	400 mg; oral	Reduced anxiety ($p < 0.001$) compared to placebo

Study	N Participant (condition)	Age (years)	Drug	Doses and administration	Results
Kwee et al., 2024 (63)	69 (SAD)	33.8	CBD	300 mg, 2 hours before therapy; oral	CBD reduced subjective shock expectancy under mild/unknown threat.
	69 (antidepressants user)	33.8	CBD with serotonergic antidepressants	300 mg CBD, before therapy sessions; oral	CBD impaired fear re-extinction compared to placebo.
Gundugurti et al., 2024 (64)	178 (anxiety)	37.2	Nano-dispersible CBD and Placebo	150 mg/mL (300-600 mg/day) for 12 weeks; oral	Significant reduction in GAD-7 and HAM-A score.
Zuardi et al., 2017 (65)	60 (healthy)	18 - 35	CBD	100 mg, 300 mg, 900 mg; oral	CBD (300mg) reduced anxiety in the post-speech phase (inverted U-shaped curve).
Souza et al., 2022 (14)	300 (frontline healthcare workers during COVID-19)	34.5	CBD	150 mg twice daily (300 mg/day) for 28 days; oral	CBD group demonstrates significant reduction in anxiety (GAD-7 scores) compared to control.
Crippa et al., 2011 (66)	10 (SAD)	22	CBD	600 mg; oral	CBD significantly reduced anxiety during public speaking tests versus placebo.
Bloomfield et al., 2022 (67)	24 (stress-inducing arithmetic task)	18 – 27	CBD	600 mg; oral	No difference behaviour between CBD and placebo's group
Bolsoni et al., 2022 (68)	14 (PTSD; sexual trauma)	18 – 60	CBD and Placebo	300 mg; oral	CBD did not significantly reduce anxiety compared to placebo.
	19 (PTSD; nonsexual trauma)				CBD significantly reduced anxiety and cognitive impairment.
Stack et al., 2023 (69)	198 (anxiety disorders)	18 – 70	CBD	0 – 100 mg/day; oral	50% of participants improved anxiety. Significant reductions in anxiety ($p < 0.001$)
			CBD (dominant): THC	0-100mg/day; oral	Significant reduction in fatigue and anxiety ($p < 0.001$)
			THC (dominant): CBD	0-38mg/day; oral	61.1% of participants improved anxiety ($p = 0.011$)
			CBD: THC(Balance)	0-100mg/day; oral	Significant anxiety reduction ($p < 0.001$)
Hundal et al., 2018 (12)	32 (high paranoia)	18 – 50	CBD	600mg; oral	CBD increased anxiety slightly (non-significant)
Gournay et al., 2023 (70)	63 (elevated trait worry)	18 – 25	CBD	50, 600mg (twice daily for a week); oral	CBD reduced anxiety symptoms in 2 weeks but did not affect worry severity.

CBD: Cannabidiol; PTSD: Post Traumatic Stress Disorder; SAD: Social Anxiety Disorder; VS: Versus

DISCUSSION

Mechanism Action of Cannabidiol (CBD*)*

According to the results, cannabidiol (CBD) was effective to treat anxiety in both animal and human studies. CBD acts on the 5HT1A receptor, a serotonin receptor, as well as on the endocannabinoid system receptors, namely CB1 and CB2 (4,31,50,51). Research has shown that serotonin has an important role in reducing anxiety. Studies have also found that 5HT1A antagonists (WAY100635), block the CBD's anxiolytic effect, causing anxious behavior in tests such as the Elevated Plus Maze (42,45,47,49,53), Open Field Test (27,35,38,55) and other anxiety assessments (5,30,34,37). Serotonin is a neurotransmitter that regulates mood and is influenced by the Endocannabinoid System (ECS). 5HT1A receptors are distributed in the amygdala, hippocampus, and prefrontal cortex (PFC), all of which regulate anxiety and fear (72). Activation of 5HT1A receptors improves mood, resulting in happiness and calmness (73).

In addition, research has shown the role of CB1 and CB2 receptors in anxiety (4,31,51,55,74). Co-administration of CBD with CB1 antagonist (AM251) and CB2 antagonist (AM630) eliminated the anxiolytic effect in test animals, as AM251 is a CB1 antagonist and AM630 is a CB2 antagonist (4,31,50,51). The ECS impacts the serotonin and GABA systems, with the activation of CB1 receptors has been shown to increase serotonin release in certain parts of the brain, potentially enhancing mood and leading to anxiolytic effects (75).

Optimal Dose of Cannabidiol (CBD)

The dosage (CBD) varied significantly across both types of studies (see Tables 2 and 3). In animal studies, the dosage between 0.3 mg/kg to 30 mg/kg. Various studies have demonstrated an inverted U-shaped curve between dosage and the anxiolytic effect of CBD, indicating that too low a dose might have no effect, while high doses often led to increased anxiety (anxiogenic). The optimal dosage of CBD appeared to be between 5 mg/kg and 10 mg/kg in animal studies (7,8,26,37,49,53). In human clinical studies, the dosage of CBD ranged from 150 mg to 800 mg per day, with varying durations of use and different patient's condition. The 300 mg dose was the one that provided the most optimal anxiolytic effects (58,64,66,69). The 600 mg dose showed anxiolytic effects in studies involving volunteers with anxiety (10,65,71) Stanley (2023) reported increased physical anxiety symptoms at this dose (56). Gradually increasing the CBD dose to 800 mg showed positive results in the treatment of anxiety (59). Variations in optimal dosage can be explained by differences in CBD metabolism among individuals, particularly the role of the CYP3A enzyme, which contributes the most to the metabolic clearance of CBD. High CYP3A activity clears CBD quickly, reducing its levels and necessitating higher doses, while low activity sustains CBD levels longer, allowing for lower doses. Polymorphisms in the CYP3A enzyme can cause differences in metabolic rate (76). This results in variations in drug and metabolite concentrations in the body, which in turn affects the therapeutic response among individuals. This highlights the critical need for personalized dosing in clinical practice.

Sex Differences in Response to Cannabidiol (CBD)

Sex differences indicate varying responses to cannabidiol (CBD). CBD has anxiolytic effects in both sexes (47). However, female rats only reacted to CBD during the LD phase and at a lower dose than male rats. After a short four-day treatment, the response to CBD persisted in female rats at the late diestrus stage but was absent in the proestrus stage (47). This is attributed to a decrease in allopregnanolone (ALLO). The reduction in ALLO increased the sensitivity of extra synaptic neuronal GABA-A receptors, which are associated with the regulation of anxiety behavior, allowing CBD to work more effective (48,77). Gao et al (2023) also reported the differences in response between male and female rats (77). Female rats showed minimal response to the CBD and THC combination in the EPM test, with no significant changes in anxiety-like behavior observed in most trials (77). These results point out the importance of considering sex-specific aspects in the therapeutic application of CBD for anxiety treatment.

Comparison of Cannabidiol (CBD) with Conventional Drugs

Conventional drugs used to treat anxiety often present side effects (78). For example, benzodiazepines can lead to dependence, sedation, and psychomotor disorders, while selective serotonin reuptake inhibitors (SSRIs) may initially increase anxiety before exhibiting anxiolytic effects and can also lead to dependence (79). In contrast, CBD does not appear to cause dependence (80). Research conducted by Masataka (2019) found that administering 300 mg of CBD daily for 4 weeks showed no signs of dependence in patients (58). Additionally, a study by Zuardi et al

(1982) directly compared CBD with diazepam. Diazepam demonstrated a strong anxiolytic effect with dizziness, whereas CBD had no such effects (2). Other studies have also proven the safety of CBD in its long-term use (59,60,65). These findings imply that CBD may become safer for treating anxiety in the future.

Variability of CBD Effects Based on Participant Conditions

The effects of CBD on anxiety are not solely dependent on dosage but also on individual characteristics and psychological conditions of the participants. A 600 mg dose of CBD exhibits varying pharmacological responses depending on the type of anxiety experienced. In individuals with social anxiety disorder (SAD), this dosage significantly reduces anxiety symptoms during public speaking tests (10). In contrast, among individuals experiencing anxiety induced by arithmetic stress tests, academic examinations, or those with high paranoia, CBD does not demonstrate a clear anxiolytic effect and, in some cases, even increases anxiety levels (12,56,68). These findings suggest that the effectiveness of CBD depends on the nature and severity of anxiety, indicating that dosage and administration methods may need to be adjusted for optimal therapeutic outcomes.

CONCLUSION

CBD has been shown to reduce anxiety, but its effectiveness varies based on the type of disorder and individual conditions. Further research is needed to ensure consistent findings. Future studies should conduct large-scale RCTs to evaluate long-term safety and efficacy, investigate CBD's effects on specific anxiety disorders, assess sex-based differences in response, and explore genetic factors influencing individual variability.

AUTHOR'S CONTRIBUTION STATEMENT

All authors contributed to concept and design. Putu Ayu Putri Fajaryani and I Made Agus Gelgel Wirasuta contributed to literature search. Putu Ayu Putri Fajaryani contributed to data analysis and writing. I Made Agus Gelgel Wirasuta, Pande Made Nova Armita Sari, Dyah Kanya Wati, Putu Indah Budi Apsari, Made Ary Sarasmita contributed to critical revision of manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest regarding the publication of this paper.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors used AI-assisted technology (e.g., Grammarly) only for language editing purposes.

SOURCE OF FUNDING STATEMENTS

This study was conducted without financial support from any public, commercial, or non-profit funding agencies.

ACKNOWLEDGMENTS

We would like to express my sincere gratitude to Udayana University for providing the facilities and space necessary to conduct this research. The support in terms of access to workspace was invaluable in completing this study.

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