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Review

Beyond CBD and THC: Cannabigerol (CBG) as an Emerging Neuropsychiatric Drug Candidate

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Abstract

Cannabigerol (CBG) is a non-intoxicating phytocannabinoid under investigation as a neuropsychiatric drug candidate. Although historically studied primarily for its role in cannabinoid biosynthesis, CBG has a multitarget pharmacological profile distinct from those of cannabidiol (CBD) and Δ9-tetrahydrocannabinol (Δ9-THC). Experimental studies implicate cannabinoid receptors, α2A-adrenoceptors, 5-HT1A receptors, transient receptor potential channels, peroxisome proliferator-activated receptor-γ, and voltage-gated sodium channels, alongside effects on neuroinflammation, oxidative stress, neuronal survival, and excitability. These findings support investigation across several neuropsychiatric conditions, but their clinical relevance remains uncertain. Human studies have begun to characterize oral pharmacokinetics, the influence of food and formulation on systemic exposure, and acute tolerability. A single-dose controlled study of healthy adults reported preliminary effects on anxiety and stress, whereas a repeated-dose randomized trial in participants with problematic sleep found no superiority over placebo on its primary outcome. Brain exposure, target engagement, exposure–response relationships, drug interactions, therapeutic dosing, and long-term safety remain insufficiently defined. This review critically evaluates the pharmacological, preclinical, and human evidence for CBG and identifies the barriers to clinical translation. Despite a plausible experimental rationale, efficacy has not been established for any neuropsychiatric disorder.

Keywords: cannabigerol; CBG; cannabinoids; neuropsychiatry; anxiety; depression; neuroinflammation; neuroprotection

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1. Introduction

Research on *Cannabis sativa*-derived compounds has focused predominantly on Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), leaving many other phytocannabinoids comparatively unexplored. Among them, cannabigerol (CBG) has attracted interest as a non-intoxicating compound with a pharmacological profile distinct from those of both Δ9-THC and CBD [1–3]. Although CBG occurs at low concentrations in most mature cannabis plants, its scarcity has not diminished interest in its pharmacological properties.

Experimental studies indicate that CBG interacts with cannabinoid receptors, α2A-adrenoceptors, 5-HT1A receptors, transient receptor potential channels, and other systems

implicated in neuronal excitability, inflammation, and cell survival [1–3]. These findings provide a rationale for investigating CBG in neuropsychiatric diseases, but the concentrations and conditions under which many effects have been observed may not reflect achievable exposure in humans. The breadth of its experimental activity therefore raises a more focused question: which of these effects, if any, contribute to clinically meaningful outcomes?

Human studies have begun to address this question without yet establishing therapeutic efficacy. A single 20-mg dose produced preliminary effects on self-reported anxiety and stress in healthy adults, while a dose-escalation study characterized systemic exposure and acute tolerability across doses of 25–200 mg [4,5]. Whether these findings extend to patients with neuropsychiatric disorders remains uncertain. This narrative review critically examines CBG's pharmacology, pharmacokinetics, preclinical findings, and emerging human evidence, with particular attention to the evidence required to translate experimental activity into clinical benefit.

Literature Search and Narrative Review Approach

This article was conducted as a critical narrative review aimed at integrating and interpreting the available evidence on the pharmacological properties, pharmacokinetics, safety, and potential neurological and neuropsychiatric applications of cannabigerol (CBG). A narrative approach was considered appropriate given the emerging nature of the field, the substantial heterogeneity of experimental models and study designs, and the limited availability of controlled human investigations.

A literature search was conducted in PubMed/MEDLINE, Scopus, Web of Science, ClinicalTrials.gov and LILACS, using the keywords "cannabigerol" and "CBG". The search covered publications available through 30 September 2026, and was restricted to articles published in English, Portuguese, or Spanish.

The literature was examined and synthesized according to the main objectives of the review, encompassing molecular pharmacology, experimental neurobiological effects, pharmacokinetics, safety, and evidence from human investigations. Particular attention was given to distinguishing findings involving native CBG from those obtained with chemically modified derivatives or multicomponent cannabinoid formulations, for which the attribution of effects to CBG may be uncertain.

The evidence was critically discussed in relation to study design, experimental conditions, population characteristics, dosing and exposure, outcome measures, methodological limitations, and translational relevance. Findings from in vitro experiments, animal models, and human investigations were interpreted according to their respective levels of evidence, with particular emphasis on distinguishing pharmacological plausibility from demonstrated clinical efficacy.

This review was not designed or conducted as a systematic review. Accordingly, no prespecified systematic review protocol, formal study-selection flowchart, quantitative accounting of included and excluded records, standardized risk-of-bias assessment, or meta-analysis was undertaken. The literature was integrated through a qualitative narrative synthesis intended to identify convergent and conflicting findings, critically examine the limitations of the available evidence, and highlight priorities for future research. Consequently, the review does not claim exhaustive coverage of all relevant publications or provide formal estimates of the certainty of evidence.

2. CBG: From a Minor Phytocannabinoid to a Potential Therapeutic

2.1. Biosynthesis and Phytochemistry

Cannabigerolic acid (CBGA), the acidic precursor of CBG, occupies a central branch point in *Cannabis sativa* biosynthesis. Specific synthases convert CBGA into the acidic pre-

cursors of Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), and cannabichromene (CBC), while decarboxylation of residual CBGA yields CBG [1,3,6]. Because much of the CBGA pool is directed toward these downstream cannabinoids during plant maturation, CBG occurs at relatively low concentrations in most chemovars.

The proportion of CBG in *Cannabis sativa* depends on the extent to which its precursor, CBGA, is converted into downstream cannabinoid acids. In CBG-dominant plants, commonly classified as chemotype IV, reduced conversion allows CBGA and CBG to accumulate. Selective breeding of these plants, together with the increasing availability of purified CBG, has expanded access to the compound for pharmacological research [1,3,7].

2.2. CBG Versus CBD and THC

Although CBG, CBD, and Δ9-THC share a common biosynthetic origin, they differ substantially in their pharmacological actions (Figure 1). The intoxicating effects of Δ9-THC arise predominantly from partial agonism at central CB1 receptors, whereas CBG and CBD are generally considered non-intoxicating. The latter two compounds are both pharmacologically pleiotropic, but their interactions with molecular targets differ in affinity, intrinsic activity, and, in some cases, direction of action [1,2,6].

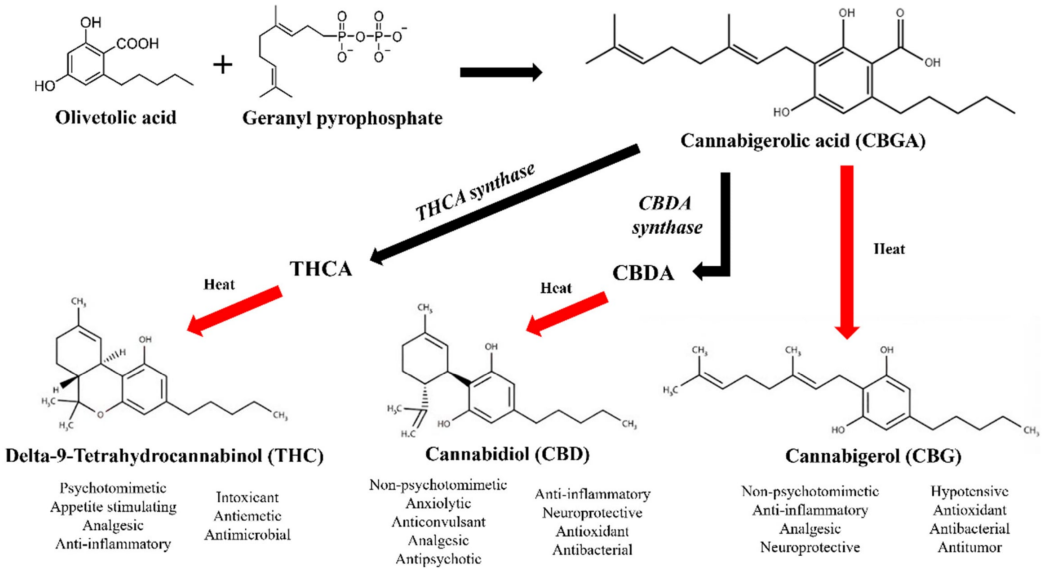


Figure 1. The biosynthetic route of major phytocannabinoids begins with the coupling of olivetolic acid and geranyl pyrophosphate to generate cannabigerolic acid (CBGA). Serving as a central precursor, CBGA is subsequently transformed into Δ9-tetrahydrocannabinolic acid (Δ9-THCA) and cannabidiolic acid (CBDA). Thermal decarboxylation then converts CBGA, Δ9-THCA, and CBDA into their corresponding neutral forms: cannabigerol (CBG), Δ9-tetrahydrocannabinol (Δ9-THC), and cannabidiol (CBD). Due to its rapid utilization as a central precursor in phytocannabinoid biosynthesis, CBGA typically accumulates in only trace concentrations within *Cannabis* sp. plant material.

At cannabinoid receptors, CBG displays measurable but comparatively modest affinity for CB1 and CB2 receptors, with pharmacological behavior that is more complex than a simple agonist/antagonist classification, appearing to depend on receptor subtype, assay system, concentration, and cellular context. This contrasts with the prominent CB1-mediated pharmacology of Δ9-THC and with CBD, whose principal actions are generally considered to extend beyond direct orthosteric activation of CB1 or CB2 receptors. CBG also displays potentially consequential activity outside the canonical endocannabinoid system. Experimental studies have identified interactions with α2A-adrenoceptors, 5-HT1A receptors, several transient receptor potential (TRP) channels, and other molecular targets

involved in neurotransmission, nociception, inflammation, and cellular homeostasis [1–3]. The differences between CBG and CBD extend to targets implicated in neuropsychiatric processes, making it difficult to extrapolate from the pharmacology of one compound to that of the other. In experimental systems, CBG exhibits α2A-adrenoceptor agonism and 5-HT1A receptor antagonism and modulates several TRP channels, acting as an agonist at TRPA1, TRPV1, and TRPV2 and as an antagonist at TRPM8; it also affects endocannabinoid signaling through additional pathways [1,2,8,9]. These findings characterize CBG as a pharmacologically distinct multitarget phytocannabinoid, although its therapeutic effects and adverse-effect profile cannot yet be inferred from its activity in experimental systems or from clinical experience with CBD or Δ9-THC. The principal pharmacological and clinical differences among the three compounds are summarized in Table 1.

Table 1. Comparative Pharmacological Features of CBG, CBD, and Δ^9-THC.

Feature	CBG	CBD	Δ^9-THC
Major biosynthetic precursor	CBGA	CBDA	THCA
Typical abundance in conventional chemovars	Low	Variable/high in CBD-rich chemovars	Variable/high in THC-rich chemovars
Intoxicating effects	No established THC-like intoxication	No	Yes
CB1 receptor	Modest affinity; context-dependent activity	Low direct affinity; complex modulation	Partial agonist
CB2 receptor	Modest binding affinity; context-dependent functional activity	Low direct affinity; complex modulation	Partial agonist
α_2-Adrenoceptor	Prominent agonist activity in experimental systems	Not considered a defining primary target	Not considered a defining primary target
5-HT1A receptor	Antagonist activity reported in experimental systems	Modulatory/agonist-like effects reported; mechanism remains debated	Not a defining pharmacological action
TRP channels	TRPA1, TRPV1, TRPV2, TRPV3 agonism; TRPM8 antagonism reported	Broad TRP modulation, including TRPV1	TRP modulation described but CB1 predominates clinically
Pharmacological profile	Multitarget	Multitarget	Predominantly cannabinoid-receptor mediated
Human clinical evidence	Very limited; early translational stage	Extensive relative to CBG; approved for selected epilepsy syndromes and, with THC, for multiple sclerosis-related spasticity	Extensive; cannabinoid medicines approved/used in selected settings
Current neuropsychiatric status	Emerging investigational candidate	Approved for selected epilepsy syndromes; investigational for most other psychiatric and neurological indications	Therapeutic use constrained by psychoactive and psychiatric effects

Note: The table provides a qualitative comparison rather than an exhaustive receptor-binding profile. Pharmacological effects may vary according to concentration, experimental system, species, receptor expression, and assay conditions.

3. Pharmacodynamics: A Multitarget Neuropsychiatric Profile

The pharmacology of CBG is characterized less by high-affinity engagement of a single molecular target than by activity across several receptor, ion-channel, and signaling systems. This profile distinguishes CBG from Δ9-THC, whose central effects are strongly linked to CB1 receptor activation, while also differentiating it from CBD despite substantial overlap in their non-cannabinoid targets. Available evidence implicates cannabinoid receptors, α2A-adrenoceptors, serotonergic signaling, transient receptor potential (TRP) channels, peroxisome proliferator-activated receptor-γ (PPARγ), voltage-gated sodium channels, and mechanisms regulating endocannabinoid availability [1,8–11]. This pharmacological diversity provides a plausible basis for neuropsychiatric investigation, but it remains unclear which of these targets, if any, are engaged at CBG concentrations attainable in the human brain.

3.1. Cannabinoid Receptors and the Endocannabinoid System

CBG binds to the classical cannabinoid receptors CB1 and CB2, although generally with lower affinity than Δ9-THC. Reported Ki values vary considerably across experimental systems but typically fall within the high-nanomolar to low-micromolar range, while functional potency and intrinsic activity depend on receptor subtype and assay conditions. Recombinant-system studies indicate that CBG can modulate signaling through both receptors, with partial agonist-like activity reported at CB2. CBG has also been shown to influence cAMP signaling, ERK phosphorylation, β-arrestin recruitment, and signaling through CB1–CB2 heteroreceptor complexes [10]. More recent comparative analyses confirm its substantially lower affinity for CB1 and CB2 relative to Δ9-THC, supporting the view that much of its pharmacology involves targets beyond the classical cannabinoid receptors rather than predominant CB1 activation [6].

This relatively weak CB1 engagement is particularly relevant to neuropsychiatry because it provides a pharmacological explanation for the absence of the characteristic THC-like intoxicating profile while preserving the possibility of indirect modulation of the endocannabinoid system. CBG has been reported to inhibit cellular uptake of anandamide (AEA), although at micromolar concentrations, potentially modifying extracellular or intracellular AEA availability [9]. The effect of CBG on AEA signaling should therefore not be attributed to direct inhibition of AEA degradation. In the same comparative study, the fatty acid amide hydrolase enzyme (FAAH) was significantly inhibited by CBD but not by purified CBG. Although some cannabinoid-rich botanical extracts inhibited MAGL, their corresponding purified cannabinoids, including CBG, did not. Thus, CBG may influence endocannabinoid tone, but current evidence does not support describing it simply as a FAAH or MAGL inhibitor.

3.2. α2A-Adrenergic Signaling

Experimental evidence of potent activity at α2A-adrenoceptors makes adrenergic signaling a plausible central component of CBG pharmacology. In the pharmacological study by Cascio and colleagues [8], CBG behaved as a highly potent α2A-adrenoceptor agonist in a [^{35}S]GTPγS binding assay, with activity in the subnanomolar range. This finding distinguishes CBG from both CBD and Δ9-THC and raises the possibility that adrenergic modulation contributes substantially to its pharmacological profile. Notably, this high-affinity interaction has not been independently reproduced and exhibits a potency divergence of over three log units compared to all other reported targets. The relative role of α_2-adrenergic pathways thus warrants measured interpretation until confirmed through systematic verification across independent experimental systems. α2A-adrenoceptors regulate presynaptic neurotransmitter release and central noradrenergic circuits involved in arousal,

attention, stress responses, and autonomic regulation [12]. Their activation may contribute to the effects of CBG on anxiety, stress responses, and arousal observed in experimental settings, but this mechanistic interpretation rests largely on the high potency reported under specific in vitro assay conditions [8]. Evidence of α2A-adrenoceptor-mediated effects in vivo is restricted to a small number of animal studies [12,13], and receptor-subtype selectivity, regional target engagement, and central α2A-adrenoceptor occupancy at clinically attainable CBG concentrations remain unknown.

3.3. Serotonergic Signaling: 5-HT1A Receptors

The interaction between CBG and 5-HT1A receptors is particularly relevant because it illustrates why the pharmacology of CBG should not be inferred from that of CBD. Cascio et al. [8] demonstrated that CBG antagonized 5-HT1A receptor-mediated activation in experimental systems and characterized it as a 5-HT1A receptor antagonist [8]. This finding contrasts with the agonist-like or positive modulatory effects at 5-HT1A receptors frequently proposed to contribute to the anxiolytic, antipsychotic and antidepressant-like properties of CBD. The 5-HT1A receptor antagonism observed with CBG in experimental systems limits the extent to which serotonergic mechanisms proposed for CBD can be extrapolated to CBG. If anxiolytic or stress-modulating effects are confirmed in humans, they may instead arise from interactions among multiple molecular targets. In preclinical models, CBG has also been shown to attenuate the antinausea and antiemetic effects of CBD, potentially through opposing actions at 5-HT1A receptors [14].

3.4. Transient Receptor Potential Channels

CBG also modulates several members of the TRP superfamily, ion channels that integrate thermal, chemical, inflammatory, and nociceptive signals and are increasingly recognized as modulators of neuronal excitability. In heterologous expression systems, CBG activates and subsequently desensitizes TRPV1, activates TRPV2 and TRPV3, displays agonist activity at TRPA1, and antagonizes TRPM8 [9]. Reported potencies differ substantially among channels and experimental systems, ranging from submicromolar to low-micromolar concentrations.

TRPV1 merits particular attention because it is expressed in sensory pathways and several CNS regions and is involved in nociception, synaptic plasticity, neuroinflammatory signaling, and regulation of neuronal excitability. TRPA1 similarly participates in nociceptive and inflammatory signaling, whereas TRPV2 and TRPM8 broaden the potential influence of CBG on sensory processing and cellular homeostasis. These channels may therefore mediate analgesic, anti-inflammatory, and potentially neuroprotective effects of CBG.

Although these findings implicate TRP channels in CBG's effects on sensory and inflammatory signaling, evidence from recombinant and peripheral models does not establish whether they contribute to its central behavioral effects at exposures achievable in humans.

3.5. PPARγ and Nuclear Signaling

Unlike membrane receptors and ion channels, PPARγ is a ligand-activated nuclear receptor capable of altering transcriptional programs related to inflammation, oxidative metabolism, mitochondrial function, cellular differentiation, and survival. CBG and, more prominently, synthetic CBG-derived quinones have been reported to activate PPARγ-dependent signaling [15,16]. Experimental activation by native CBG generally occurs at micromolar concentrations, again raising questions about direct translation to human exposure.

PPARγ signaling offers a candidate mechanism linking CBG activity to neuroprotection. In experimental models of Huntington's disease, CBG reduced neuroinflammatory

markers, enhanced antioxidant defenses, preserved striatal neurons, and partially normalized disease-related alterations in gene expression, including those involving PPARγ, BDNF, and IGF-1 [16]. CBG-derived compounds such as VCE-003 and VCE-003.2 have produced more direct evidence of PPARγ-dependent anti-inflammatory and neuroprotective activity, including attenuation of microglial activation and neuronal loss in experimental neurodegenerative paradigms [15,17]. It is important to emphasize that when evaluating the pharmacodynamic profile of CBG, a clear distinction must be maintained between this native phytocannabinoid and its synthetic derivatives, such as VCE-003.2 [15,18]. VCE-003.2 is a semi-synthetic aminoquinone derivative specifically engineered to enhance the activation of PPARγ and improve metabolic stability relative to the parent molecule [19,20]. Consequently, while positive preclinical outcomes with VCE-003.2 highlight the utility of the CBG chemical scaffold for drug design [21], these findings cannot be directly extrapolated to native CBG, which displays distinct receptor binding affinities, lower PPARγ potency, and differing pharmacokinetic behavior, necessitating an independent evaluation of its therapeutic potential [15,18]. Evidence for PPARγ-mediated effects must be interpreted considering the compound tested, because findings obtained with chemically modified CBG derivatives cannot be directly attributed to native CBG. Structural modifications may alter potency, target selectivity, pharmacokinetics, and tissue exposure. Thus, PPARγ remains a candidate mediator of the anti-inflammatory and neuroprotective effects proposed for CBG, although causal evidence is stronger for selected derivatives than for the parent compound. Furthermore, while preclinical models demonstrate that CBG interacts with pivotal neuroprotective pathways such as PPARγ activation, CB1/CB2 receptor modulation, and attenuation of neuroinflammatory cascades, it is essential to highlight that these findings are currently restricted to cell cultures and animal models. Human clinical evidence evaluating CBG for neurological conditions remains extremely limited. Consequently, mechanistic preclinical data should not be equated with demonstrated therapeutic efficacy in humans, highlighting the urgent need for well-designed, randomized controlled clinical trials.

3.6. Other Emerging Targets and Mechanisms

Electrophysiological studies have identified voltage-gated sodium (NaV) channels as potential targets of CBG, providing a mechanism through which it may modulate neuronal excitability. CBG inhibited NaV channels, including NaV1.7, in a state-dependent manner, with potency varying according to channel state and generally observed at micromolar concentrations. In dorsal root ganglion neurons, channel inhibition was accompanied by reduced excitability, supporting a possible contribution to analgesic effects [22]. These findings derive from peripheral sensory neurons and do not establish whether CBG modulates central neuronal networks at clinically attainable unbound concentrations.

In preclinical models, CBG treatment has been associated with reduced oxidative injury and preservation of endogenous antioxidant defenses, alongside attenuation of pro-inflammatory mediators and changes in Nrf2-, NF-κB-, and related stress-response pathways [11,16]. These findings support investigation into disorders involving neuroinflammation, mitochondrial dysfunction, and oxidative stress, although it remains unclear whether the observed changes reflect direct actions of CBG on these pathways or downstream effects of other pharmacological mechanisms. Moreover, CBG exhibits a complex pharmacological profile that extends beyond canonical cannabinoid receptors (CB_1 and CB_2). Emerging evidence indicates that CBG acts as an antagonist at the orphan G-protein-coupled receptor 55 (GPR55), a receptor closely linked to the regulation of pain, inflammation, and oncogenic cell proliferation [10].

Taken across these systems, the findings describe a pharmacological profile spanning receptor signaling, ion-channel modulation, and cellular responses to inflammatory and

oxidative stress (Figure 2). The contribution of each mechanism to human outcomes remains uncertain and will depend on whether its concentration requirements are met at tolerable exposures. This distinction is particularly important for CBG, whose reported activities arise from experimental systems that differ substantially in assay conditions and biological context.

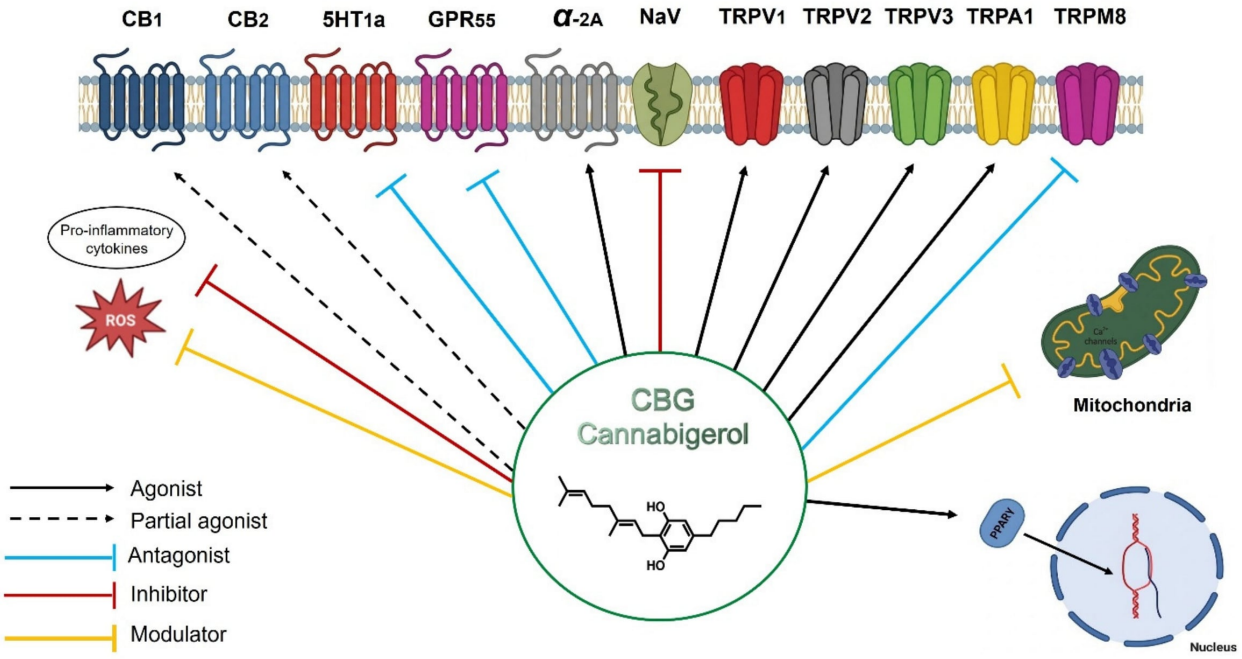


Figure 2. Chemical structure and pharmacodynamic targets of CBG. CBG acts as an agonist at TRPV1, TRPV2, TRPV3, TRPA1, PPARγ, and α2A-adrenoceptors, and as an antagonist at 5-HT1A, GPR55, and TRPM8 receptors. Additionally, CBG is suggested to be a partial agonist at CB1 and CB2 receptors. Moreover, CBG modulates the activity of mitochondrial complexes, exerting antioxidant and anti-inflammatory effects partially mediated by its actions on TRPV1, mitochondria, and the nuclear receptor PPARγ. CBG inhibits NaV channels and pro-inflammatory cytokines, and can modulate ROS levels. CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; GPR55, G-protein-coupled receptor 55; PPARγ, peroxisome proliferator-activated receptor gamma; TRPA1, transient receptor potential ankyrin 1; TRPV, transient receptor potential vanilloid; TRPM, transient receptor potential cation channel subfamily M; 5-HT1A, serotonin receptor 1A; α2A, α2A-adrenoceptor; NaV, voltage-gated sodium channel; ROS, reactive oxygen species.

4. Pharmacokinetics, Brain Exposure, and Safety

Human studies have begun to characterize oral CBG exposure and acute tolerability, while animal experiments provide initial information on brain distribution and metabolite formation. These findings allow a more precise assessment of its proposed central actions, although repeated-dose disposition, unbound brain exposure in humans, and clinically relevant exposure–response relationships remain undefined.

4.1. Absorption and Bioavailability

The lipophilicity of CBG makes its oral exposure sensitive to formulation and administration conditions. In a double-crossover pilot study, Story et al. [23] compared emulsified and non-emulsified preparations after a single 25-mg dose administered with low-fat (<5 g) or high-fat (>30 g) meals. Dietary fat substantially increased peak plasma concentration (C_max) and overall exposure (AUC), while reducing the time to peak concentration (T_max) and its variability. The effect of the meal exceeded that of emulsification. However,

the two formulations did not meet conventional bioequivalence criteria. These findings indicate that identical oral doses may yield different systemic exposures under different dietary conditions. Although the absolute oral bioavailability of CBG has not been determined in humans, animal data indicate that the route of administration substantially affects systemic exposure. In mice given 10 mg/kg CBG, oral administration resulted in a lower peak blood concentration and a later T_max than intraperitoneal administration; however, this comparison does not quantify first-pass loss in humans [24].

4.2. Distribution and Brain Penetration

Animal data offer a preliminary indication of CBG distribution in the brain, although corresponding measurements in humans remain unavailable. After intraperitoneal administration of 10 mg/kg CBG to mice, brain concentrations peaked at approximately 30 min. Total brain exposure was lower than plasma exposure, with a brain-to-plasma AUC ratio of approximately 0.26, whereas the estimated unbound brain-to-plasma partition coefficient ($K_{p,uu}$) was approximately 1.26 after correction for tissue binding [25]. These estimates indicate that lower total brain exposure did not correspond to proportionally lower unbound brain exposure in this model.

Although circulating concentrations of the oxidative metabolite cyclo-CBG were substantially lower than those of CBG, its brain-to-plasma AUC ratio was approximately 7.1, indicating greater relative brain exposure than that observed for the parent compound. Greater conversion of CBG to cyclo-CBG in brain homogenate than in plasma raises the possibility of local formation or preferential retention within the central nervous system [25]. Whether this metabolite contributes to neurobehavioral effects is unknown, and neither its distribution nor the estimated $K_{p,uu}$ of parent CBG can be extrapolated directly from mice to humans.

A critical consideration when evaluating the clinical potential of CBG is the translation between experimentally active concentrations and achievable human systemic exposure. In vitro models often demonstrate target modulation (e.g., receptor agonism or enzyme inhibition) at micromolar (μM) concentrations [26,27]. However, human pharmacokinetic data indicate that standard oral dosing yields peak plasma concentrations (C_max) predominantly in the low nanomolar (nM) range, further constrained by extensive plasma protein binding [28]. Consequently, mechanisms observed strictly at high concentrations in vitro must be interpreted with caution, as they may not represent primary drivers of therapeutic efficacy at clinically tolerated doses unless novel delivery systems (e.g., nanoformulations) are utilized to enhance systemic bioavailability [28].

4.3. Metabolism and Elimination

Studies using human cytochrome P450 enzymes have shown that CYP2J2, CYP3A4, CYP2D6, CYP2C8, and CYP2C9 can form the oxidative metabolite cyclo-CBG, which has also been detected after CBG administration in mice [29]. The relative contribution of these enzymes to CBG metabolism in humans remains undetermined. In mice given 10 mg/kg CBG intraperitoneally, peak concentrations occurred at approximately 15 min in plasma and 30 min in brain, with estimated elimination half-lives of 46 and 57 min, respectively [25]. Because these estimates derive from intraperitoneal dosing in mice, they cannot be used to infer the elimination of orally administered CBG in humans.

Acute oral studies show that CBG remains measurable in human plasma for several hours, but their single-dose designs cannot establish steady-state exposure, accumulation, changes in metabolism over time, or metabolite concentrations during repeated administration [5,23]. These gaps matter because circulating metabolites may contribute to both the

pharmacological effects and the adverse effects of CBG, although their activity in humans remains uncertain.

4.4. Dose–Exposure Relationships

In a within-subject single-ascending-dose study, 12 healthy adults received placebo and isolated CBG at 25, 50, 100, and 200 mg in medium-chain triglyceride oil, with serial plasma sampling for 8 h [5]. Systemic exposure increased with dose but varied substantially between participants. Despite this increase, the study detected no robust dose-dependent subjective, cognitive, or physiological effects. The absence of a clear dose-related gradient in acute pharmacodynamic measures cannot be interpreted as evidence that CBG lacks central activity, because target engagement was not assessed and the selected outcomes may have been insensitive to effects requiring different exposure levels or longer treatment.

4.5. Drug–Drug Interaction Potential

The identification of several CYP enzymes capable of metabolizing CBG suggests that inhibition or induction of these pathways could alter its exposure, although the contribution of each enzyme and the magnitude of any interaction in humans remain unknown [29]. Conversely, evidence that CBG is a substrate for an enzyme does not establish that it inhibits or induces that enzyme. Its effects on drug-metabolizing enzymes and transporters, and hence its capacity to alter exposure to concomitant medications, have not been characterized sufficiently to support clinical predictions. This gap matters especially in neuropsychiatry, where patients commonly receive psychotropic or antiseizure medications. At present, the evidence does not support CBG-specific dose-adjustment recommendations or extrapolation of CBD's interaction profile to CBG. Dedicated enzyme and transporter studies, followed where indicated, by pharmacokinetic modeling and clinical interaction studies, are needed to define its interaction liability.

4.6. Safety and Tolerability

The controlled human studies available to date suggest generally favorable tolerability at the doses and durations examined. No adverse events were reported after a single 25-mg dose in the food-effect study, and a single 20-mg dose in the crossover behavioral study produced no subjective intoxication or measurable cognitive or motor impairment [4,23]. In 12 healthy adults, single doses of isolated CBG from 25 to 200 mg were generally well tolerated, with no drug-related adverse events reported and no clinically significant acute liver-function abnormalities detected after the two highest doses [5]. The principal evidence on repeated-dose tolerability comes from a four-week placebo-controlled trial in 63 veterans with problematic sleep, in which CBG was administered at 25 mg/day for two weeks and 50 mg/day for the subsequent two weeks. Five mild, nonserious adverse events were considered possibly related to CBG: one each of headache, lethargy, gastric upset, nausea, and hypersomnia [30]. The limited sample size and treatment duration preclude reliable estimates of uncommon or delayed adverse effects. Reports from users of CBG-predominant cannabis preparations provide little additional evidence about isolated CBG because product composition and exposure were uncontrolled [31]. Experimental α2A-adrenoceptor agonism raises a theoretical concern about sedation and cardiovascular effects, supported by a reduction in blood pressure observed after acute CBG administration in mice [13]. Clinically significant hypotension or bradycardia has not, however, been demonstrated consistently in the small human studies available, and the lethargy or hypersomnia reported during repeated administration cannot be attributed to α2A-adrenoceptor activity. The current findings support short-term tolerability within the studied exposure range, while

uncommon, cumulative, delayed, and interaction-related risks during prolonged treatment remain undetermined.

5. Neurobiological Properties Relevant to Neuropsychiatry

The pathophysiology of neuropsychiatric disorders generally involves interacting molecular, cellular, and circuit-level processes rather than dysfunction of a single receptor or neurotransmitter system. Across diagnostic boundaries, convergent processes including persistent neuroimmune activation, oxidative and mitochondrial stress, impaired cellular resilience, altered synaptic plasticity, and dysregulated neuronal excitability can contribute to disease expression and progression. The multitarget pharmacology of CBG described above provides several potential points of intersection with these processes. Preclinical studies increasingly suggest that CBG can modulate inflammatory, redox, survival, and excitability pathways rather than acting exclusively through conventional neurotransmitter mechanisms [1,11,16,18]. This broader neurobiological profile is potentially relevant to neuropsychiatry because the same cellular processes may operate across multiple disorders. However, the strength of evidence differs substantially among domains. Neuroinflammatory and neuroprotective effects are supported by several experimental models, whereas direct evidence for mitochondrial restoration, neuroplasticity, or synaptic remodeling remains considerably more limited. Maintaining these distinctions is essential to avoid interpreting pharmacological plausibility as evidence of therapeutic efficacy.

5.1. Neuroinflammation and Microglial Modulation

Neuroinflammation represents one of the most thoroughly explored biological domains in preclinical CBG research. Initial in vitro studies indicated that CBG can modulate key inflammatory pathways including NF-κB, Nrf2, and PPARγ and enhance cell viability in microglial and motor-neuron models [16,18,32,33]. While these cell culture findings provide valuable mechanistic insights, translating in vitro dynamics to intact systems requires accounting for blood–brain barrier permeability, metabolic fate, and complex neuro-glial interactions. In rodent paradigms, such as experimental autoimmune encephalomyelitis and early-life iron overload, systemic CBG administration attenuated glial reactivity, preserved blood–brain barrier integrity markers (such as occludin), and reduced hippocampal IL-1β alongside cognitive recovery [34,35]. To fully contextualize these in vivo observations, certain methodological factors warrant consideration. In vivo support is provided by Kowalski et al. [35], who reported that repeated intraperitoneal CBG treatment (10 mg/kg/day for 21 days) rescued recognition memory, lowered hippocampal IL-1β levels, and restored occludin expression in a rat model of early-life iron overload. These findings, however, must be interpreted within specific experimental parameters: the study evaluated a fixed single-dose protocol via a non-clinical route of administration without dose–response characterization, pharmacokinetic profiling, oral bioavailability assessment, or antagonist-mediated receptor verification. Furthermore, the observation that CBG modestly elevated baseline TNF-α in uninjured control animals underscores the nuanced, state-dependent nature of its immunomodulatory profile and points to potential off-target pro-inflammatory effects in non-pathological tissue. Overall, while these findings offer an encouraging preclinical proof-of-concept, they emphasize the necessity of comprehensive dose-ranging and mechanistic studies to establish the therapeutic scope of CBG.

5.2. Oxidative Stress and Mitochondrial Function

Oxidative stress and imbalance between the generation of reactive species and the capacity of antioxidant defenses to neutralize them have been examined in preclinical studies of CBG. When sustained, this imbalance can damage proteins, lipids, nucleic acids, and

mitochondria, impairing neuronal function and survival. It also interacts with neuroinflammation, as activated immune cells generate reactive species and mitochondrial dysfunction can further amplify inflammatory signaling and oxidative injury.

In cell-free spectrophotometric assays, including ABTS, DPPH, ORAC, CUPRAC, and FRAP, CBG showed free-radical scavenging and reducing activity, with results broadly comparable to those of other phytocannabinoids and, across the assays used, vitamin E [36]. These findings demonstrate antioxidant activity under the conditions tested, but do not establish that CBG reduces oxidative injury in neural tissue or at clinically achievable concentrations.

Evidence from cellular and animal models extends beyond these chemical assays. In NSC-34 motor neuron-like cells exposed to inflammatory and oxidative injury, CBG reduced oxidative stress alongside inflammatory mediators and apoptotic signaling [18]. CBG also attenuated hydrogen peroxide- and rotenone-induced toxicity in neural cell cultures; the 5-HT1A receptor antagonist WAY-100635 reduced protection against rotenone, whereas CB1 and CB2 receptor antagonists did not, suggesting a context-dependent contribution of 5-HT1A signaling [37]. In Huntington's disease models, treatment was associated with preservation of antioxidant defenses and attenuation of changes linked to oxidative injury [16].

Across these systems, the findings support antioxidant and cytoprotective effects in experimental systems, whereas evidence for direct restoration of mitochondrial function is less developed. Protection against rotenone toxicity, for example, does not itself demonstrate improved mitochondrial bioenergetics. Mitochondrial respiration, membrane potential, ATP production, mitophagy, and related functions have not been comprehensively characterized for CBG in relevant neuronal models; claims about mitochondrial restoration should therefore remain more cautious than those concerning its experimental antioxidant effects.

5.3. Neuroprotection and Neuronal Survival

The anti-inflammatory and redox-modulating effects described above may contribute to the neuroprotection observed with CBG in experimental systems. As detailed in Section 5.2, findings in models of Huntington's disease provide in vivo evidence for this possibility [16]. In a separate model of neurotoxic injury, CBG was associated with preservation of cognitive function and blood–brain barrier integrity, although the generalizability of these findings remains uncertain [35].

Cellular studies add evidence of protection against distinct forms of neuronal injury. In motor neuron-like cells exposed to inflammatory toxicity, CBG reduced caspase-3 activation and Bax expression while increasing the anti-apoptotic protein Bcl-2 [18]. CBG also attenuated amyloid-β-induced neurotoxicity and preserved aspects of neuronal morphology in PC12 cells [38].

Studies of synthetic CBG derivatives provide additional mechanistic evidence but require separate interpretation. The quinone derivative VCE-003.2 improved neuronal progenitor survival, reduced caspase-3 activation and neuroinflammation, and protected striatal neurons in Huntington's disease models, with several effects linked to PPARγ signaling [19]. Oral VCE-003.2 also promoted subventricular-zone neurogenesis and attenuated neurodegeneration associated with mutant huntingtin expression [17]. Because chemical modification can alter pharmacodynamics and pharmacokinetics, these results cannot be attributed to native CBG.

5.4. Neuroplasticity and Synaptic Function

The evidence linking native CBG to neuroplasticity is limited to indirect findings, including modest increases in the expression of BDNF and IGF-1 in R6/2 mice, without

direct demonstration of changes in synaptic function or neurogenesis [16]. By contrast, the chemically modified derivative VCE-003.2 promoted neuronal progenitor survival and subventricular-zone neurogenesis in experimental models [17,19]. Those results cannot be attributed to native CBG, for which effects on synaptic structure, activity-dependent plasticity, and circuit remodeling remain undetermined.

5.5. Neurotransmission and Neuronal Excitability

CBG may also influence neuropsychiatric function by altering neurotransmission and the intrinsic excitability of neurons. At the receptor level, the α2A-adrenergic, 5-HT1A, cannabinoid, and TRP interactions discussed above provide multiple potential mechanisms for modifying monoaminergic transmission, presynaptic release, sensory processing, and neuronal firing. However, direct electrophysiological evidence provides an additional mechanism independent of classical neurotransmitter receptors.

CBG inhibits NaV channels in a state-dependent manner. Detailed electrophysiological experiments demonstrated inhibition over an approximately 2–20 μM concentration range, with preferential effects on channels occupying inactivated states. In dorsal root ganglion neurons, these actions reduced excitability, providing a candidate cellular mechanism for some of CBG's proposed analgesic properties [22]. Subsequent analyses have highlighted NaV modulation as an important non-cannabinoid mechanism shared to varying degrees by non-intoxicating phytocannabinoids, including CBD and CBG [39].

Whether this mechanism extends beyond peripheral sensory neurons is particularly relevant to neuropsychiatry. NaV channels govern action-potential initiation and propagation throughout the nervous system, making state-dependent inhibition potentially relevant to hyperexcitable neural networks. Yet the concentration required for substantial NaV inhibition must be reconciled with the human pharmacokinetic data discussed in Section 4. At present, it remains uncertain whether unbound CBG concentrations sufficient to produce meaningful NaV blockade are reached in the human brain after tolerated oral doses.

The available models show that CBG can influence several processes associated with neuronal resilience and excitability, but these effects need not occur together or at equivalent concentrations in vivo. Their value for indication selection will depend on whether a disease-relevant effect can be linked to exposure and to a reproducible functional outcome, rather than on the number of pathways affected.

6. CBG Across Neuropsychiatric and Neurological Conditions

The pharmacological actions of CBG intersect with processes implicated in several neurological and psychiatric conditions, but the strength of the supporting evidence differs substantially by indication. Disease-specific animal models provide more informative grounds for prioritization than activity at a broadly relevant receptor or inflammatory pathway alone. The discussion below therefore focuses on what each experimental contributes to a clinical hypothesis, while the designs and findings of human studies are examined in Section 7. Although antinociceptive effects have also been reported in inflammatory and neuropathic pain models, pain disorders fall outside the principal scope of this review [22,40–43].

6.1. Anxiety and Stress-Related Disorders

Anxiety and stress-related outcomes allow a comparatively focused examination of whether CBG's experimental actions translate into effects relevant to patients. Its interactions with α2A-adrenergic and 5-HT1A signaling provide plausible mechanisms, although neither pathway has been shown to mediate an anxiolytic effect in humans. In rats, CBG altered

receptor-mediated electrophysiological responses in the locus coeruleus and dorsal raphe and produced anxiolytic-like effects in the elevated plus maze and novelty-suppressed feeding test. Blockade of the latter effect by WAY-100635 suggested a contribution from serotonergic signaling despite the complexity of CBG's 5-HT1A pharmacology in vitro [12].

The behavioral evidence is not uniform: oral CBG failed to reduce acoustic startle in a study with effective lorazepam control, while locomotor activity increased at the highest doses tested. These differences caution against treating "anxiolytic-like activity" as a stable property across paradigms, routes, and exposures. As discussed in Section 7.1, the available controlled human finding supports further investigation but has not established efficacy in a diagnosed anxiety disorder.

6.2. Depression and Mood Disorders

The rationale for investigating CBG in depression initially rested on its actions in pathways associated with inflammation, oxidative stress, and monoaminergic function. Disease-relevant experimental evidence remains limited, although a recent study reported an antidepressant-like effect in the forced-swim test and found that repeated CBG administration in a chronic mild-stress model improved cognitive performance alongside increased hippocampal dendritic spine density [44]. These observations extend the hypothesis beyond receptor pharmacology, but behavioral responses in these models cannot establish an antidepressant effect in patients.

6.3. Neurodevelopmental Disorders

CBG's activity at α2A-adrenoceptors suggests a possible connection to attention and executive function, but it does not establish that CBG reproduces the effects of selective α2A-adrenoceptor agonists used in attention-deficit/hyperactivity disorder (ADHD). Indeed, high oral doses impaired sustained attention in female rats, indicating that cognitive effects may depend on exposure, behavioral domain, and biological sex [45]. A registered human study addresses acute cognitive outcomes in ADHD, as described in Section 7.3; its existence does not constitute evidence of efficacy.

For autism spectrum disorder, the attribution problem is more pronounced. Clinical studies of cannabis-derived products in autistic populations generally involve CBD-rich or multicomponent preparations, sometimes containing CBG, and cannot identify a CBG-specific contribution. Neither core nor associated symptoms of autism spectrum disorder currently have a convincing clinical evidence base for isolated CBG.

6.4. Psychotic Disorders

In a recent preclinical evaluation, Pedrazzi et al. [46] assessed acute CBG administration across two distinct rodent models relevant to psychosis: amphetamine-induced dopaminergic hyperactivity and MK-801-induced NMDA receptor hypofunction. While CBG attenuated disruptions in prepulse inhibition across both paradigms, as well as amphetamine-induced hyperlocomotion and MK-801-induced deficits in social interaction and novel-object recognition, several methodological constraints must be noted. As an initial acute investigation, this work establishes a compelling behavioral foundation, though additional studies are warranted to build upon these findings. In particular, examining repeated dosing regimens, potential tolerance, and pharmacokinetic parameters will help clarify whether these acute benefits persist during chronic administration. Furthermore, future studies incorporating direct measures of target engagement and central neurochemical dynamics will be important in delineating the specific receptor-mediated mechanisms underlying these behavioral effects and ruling out non-specific behavioral modulation. Consequently, while cross-model convergence offers preliminary proof-of-concept, acute pharmacological

challenges in rodents fail to capture the neurodevelopmental etiology, chronic progression, or multifaceted symptomatology of clinical schizophrenia.

6.5. Substance Use Disorders

CBG's non-intoxicating profile and experimental effects on adrenergic signaling, stress responses, and neuroinflammation provide a rationale for investigating substance use disorders, although disease-specific evidence remains sparse. In a mouse model of opioid withdrawal, CBG reduced naloxone-precipitated jumping but also attenuated morphine-induced antinociception, indicating that its effects on opioid-related responses may have different clinical implications depending on the outcome assessed [42]. For alcohol, stimulant, cannabis, and nicotine use disorders, the available evidence does not yet support a specific therapeutic hypothesis beyond exploratory investigation.

6.6. Sleep Disorders

The rationale for CBG as a sleep intervention has been shaped largely by consumer reports rather than by a clearly defined sleep-related mechanism or consistent disease-specific preclinical evidence. Surveys of people using CBG-predominant preparations document perceived benefit, but variable product composition and uncontrolled use prevent attribution of those reports to CBG [31,47]. The placebo-controlled study examined in Section 7.2 provides a more rigorous evaluation and did not establish benefit in the population and regimen studied.

6.7. Neurodegenerative Disorders

Among neurodegenerative conditions, Huntington's disease has the most developed disease-specific preclinical evidence for native CBG, as described above [16]. This evidence should be distinguished from studies of VCE-003.2 and other chemically modified CBG derivatives, whose neuroprotective, anti-inflammatory, and proneurogenic effects in models relevant to Huntington's and Parkinson's diseases cannot be attributed to the parent compound [17,19–21].

Evidence for native CBG in other conditions is less developed. Findings relevant to Alzheimer's disease remain largely confined to cellular models, whereas repeated CBG administration attenuated memory impairment, neuronal loss, and glial reactivity in a mouse model of transient global cerebral ischemia [48]. These studies broaden the experimental scope of CBG but do not establish comparable neuroprotective effects across neurodegenerative diseases.

6.8. Epilepsy and Neuronal Hyperexcitability

State-dependent inhibition of NaV channels offers a plausible mechanism through which CBG could affect neuronal hyperexcitability, although channel blockade has not consistently predicted seizure protection across experimental models [49]. In the maximal electroshock model, CBG exhibited intrinsic antiseizure activity, while a combination with CBD produced a predominantly additive rather than synergistic interaction [50]. The divergent relationship between channel inhibition and seizure protection makes exposure–effect testing particularly important for this indication.

7. Preclinical Evidence: Methodological Quality and Limitations

Two critical limitations in the preclinical literature regarding CBG warrant explicit discussion: the systematic lack of methodological quality appraisal and a pronounced sex bias in animal models. The majority of available studies fail to consistently report essential measures to minimize risk of bias, such as randomization, investigator blinding,

and power calculations thereby compromising the internal validity and reproducibility of the findings. Equally concerning is the near-exclusive reliance on male animals, a limitation rarely acknowledged in synthesized literature. This omission is particularly critical given evidence of sex-dependent divergence in CBG's pharmacological profile; notably, the single preclinical study conducted on female subjects reported attentional impairment rather than therapeutic benefit [45]. Future preclinical investigations must rigorously incorporate sex as a biological variable and adhere to standardized reporting frameworks (e.g., ARRIVE guidelines, SYRCLE risk of bias tool) to establish the safety and translational potential of CBG.

7.1. Human Evidence: Current Status and Limitations

Human studies have progressed from characterizing oral exposure to examining acute behavioral outcomes and repeated administration in symptomatic participants. Because these designs answer different questions, their populations, products, doses, and endpoints must be considered before interpreting a pharmacodynamic observation as evidence of therapeutic benefit.

7.2. Healthy Volunteer Studies

As detailed in Section 4, the studies by Story et al. [23] and Wolinsky et al. [5] characterized the influence of administration conditions and dose on systemic exposure. Wolinsky et al. also assessed acute subjective, cognitive, and physiological outcomes across doses of 25–200 mg, finding relatively modest effects despite increasing exposure. These studies establish a pharmacokinetic basis for human investigation without identifying a clear dose-related acute pharmacodynamic response.

In a randomized, double-blind, placebo-controlled crossover study, Cuttler et al. [4] administered a single 20-mg dose of hemp-derived CBG to 34 healthy adults. Participants reported lower anxiety overall and lower stress at one post-administration assessment; verbal memory performance also improved, without subjective intoxication or measurable impairment. These findings provide a preliminary behavioral signal, but the small sample, single-dose design, and absence of a diagnosed anxiety disorder preclude conclusions about sustained anxiolytic efficacy.

7.3. Neuropsychiatric Clinical Studies

In a decentralized, randomized, triple-blind, placebo-controlled trial representing the first published evaluation of repeated CBG administration in a symptomatic population, Emerson et al. [30] evaluated 63 U.S. Veterans reporting sleep issues. Following a two-week run-in phase, participants received oral CBG at 25 mg daily for two weeks, titrated to 50 mg daily for an additional two weeks, or a matching placebo. The primary endpoint was the change in sleep quality assessed via the Medical Outcomes Study Sleep Problems Index II (MOS-SS SPI-II), while secondary endpoints included functional disability measured by the World Health Organization Disability Assessment Schedule (WHODAS-2.0-12), post-traumatic stress disorder symptoms evaluated via the PTSD Checklist for DSM-5 (PCL-5), and actigraphy-derived sleep metrics captured via Fitbit devices.

Although sleep scores improved numerically in both study arms and CBG was generally well tolerated, CBG did not achieve statistically significant superiority over placebo on the primary outcome or on any secondary measures. While the trial offers foundational empirical data on repeated CBG dosing, the interpretation of these negative findings is substantially limited by methodological constraints and potential sources of bias. Notably, of the 63 randomized participants (33 in the CBG group and 30 in the placebo group), only 35 completed the trial without major protocol deviations (18 receiving CBG and 17 placebo).

This reduction in the per-protocol sample size leaves the trial underpowered, markedly elevating the risk of a Type II error and limiting the capacity to detect small-to-moderate therapeutic effects. Furthermore, the substantial numerical improvement observed across both study arms highlights a strong placebo response common in decentralized sleep trials, which, combined with participant heterogeneity in the Veteran population and reliance on self-reported endpoints, substantially reduced the trial's overall assay sensitivity. Consequently, while the study failed to demonstrate superiority under the specific dosing regimen, population, and four-week timeframe evaluated, its statistical and design limitations prevent reaching a definitive conclusion regarding the therapeutic inactivity of CBG.

7.4. Ongoing and Recently Completed Registered Trials

Registered investigations extend to patient populations and routes of administration beyond those in the published studies, although registration alone supplies no efficacy evidence. NCT06115603 [51] is a randomized, double-blind, placebo-controlled study evaluating a single 80-mg dose of CBG in adults with ADHD. Its target enrollment is 76 participants, with acute measures including sustained attention and processing speed. As of September 2026, it was listed as recruiting, without published peer-reviewed efficacy results.

Other registered studies address distinct questions or evaluate mixed products. The ASCENT crossover study (NCT04859296 [52]) examines vaporized CBG at 5 and 15 mg, alone and with THC, for outcomes including analgesia, appetite, subjective effects, and abuse-related measures. A completed single-group study (NCT05743985 [53]) evaluated a full-spectrum CBG-containing hemp preparation in 69 adults, primarily for general health, inflammatory, and safety outcomes; neither its uncontrolled design nor its multicomponent product permits a CBG-specific efficacy conclusion. An open-label study of generalized anxiety disorder (NCT07821840 [54]) similarly evaluates a tincture containing CBD, CBN, and CBG, so any future observed effect will require attribution to the preparation rather than to isolated CBG.

7.5. Current Status of Human Evidence

Across the published studies, CBG administration has produced measurable systemic exposure and generally favorable tolerability under the conditions tested, but the designs support different levels of clinical inference. The controlled anxiety and stress findings concern acute effects in healthy adults, whereas the repeated-dose sleep trial did not meet its primary efficacy endpoint in symptomatic participants. Neither result defines a therapeutic exposure range or can be generalized to other indications. Table 2 summarizes the studies according to the conclusions supported by their designs.

Table 2. Current Human Evidence for Cannabigerol.

Study	Population	CBG Formulation	Dose	Design	Main Outcome	Main Findings	Major Limitations
Story et al., 2024 [23]	Adults	CBG isolate/emulsified oral preparations	25 mg single dose	Double-crossover PK pilot	CBG PK; food/formulation effects	Food markedly increased exposure; no adverse effects reported	Small PK study; no therapeutic outcome; single dose
Cuttler et al., 2024 [4]; NCT05257044	34 healthy adults	Hemp-derived CBG tincture	20 mg single dose	Randomized, double-blind, placebo-controlled crossover	Anxiety, stress, mood, cognition	Reduced overall anxiety and stress at one assessment; improved verbal memory; no intoxication/impairment	Healthy participants; acute dosing; predominantly self-reported outcomes; remote study
Wolinsky et al., 2026 [5]	12 healthy adults	CBG isolate in MCT oil	0, 25, 50, 100, 200 mg	Within-subject single-ascending-dose laboratory study	Safety, PK and PD	Dose-ordered, highly variable exposure; no drug-related adverse events up to 200 mg	Very small sample; single-dose exposure; no patient population
Emerson et al., 2025 [30]; NCT05088018	63 veterans with problematic sleep	Oral CBG tablets	25 mg/day × 2 weeks → 50 mg/day × 2 weeks	Randomized, triple-blind, placebo-controlled	MOS-SS SPI-II sleep score	No efficacy signal; five mild, nonserious, possibly related adverse events	Modest sample; only 35 PP; heterogeneous/self-reported sleep problems; short treatment
NCT06115603	Adults with ADHD; target N = 76	CBG	80 mg single dose	Phase 2 randomized, double-blind, placebo-controlled	Attention/cognitive measures	Ongoing; no efficacy results available	Acute single dose; results unavailable
NCT04859296 (ASCENT)	Healthy occasional cannabis users; target N = 20	Vaporized CBG ± THC	CBG 5 or 15 mg; combinations with THC	Phase 1 randomized, double-blind crossover	Analgesia, appetite, subjective effects	Results not yet posted	Small sample; not a neuropsychiatric efficacy trial; concomitant THC conditions
NCT05743985	Adults; N = 69	Full-spectrum hemp-derived CBG	Registry-defined intervention	Open-label, single-group	Safety, subjective health/inflammatory outcomes	Completed; peer-reviewed efficacy evidence not identified	No placebo; full-spectrum product; attribution to CBG difficult

Note: Studies are categorized according to the population and primary purpose rather than simply the presence of CBG in the intervention. Multicannabinoid formulations are not considered evidence of CBG-specific efficacy unless the design permits attribution of effects to CBG. The trial status reflects information available through September 2026.

8. Translational Challenges and Current Knowledge Gaps

Differences in product composition and administration conditions complicate comparisons across CBG studies. Investigations have used isolated CBG in various oral formulations as well as CBG-predominant botanical preparations containing other potentially active cannabinoids. Formulation and administration conditions can alter CBG exposure, whereas effects observed with mixed preparations cannot be attributed specifically to CBG [31]. Consequently, differences in study findings may reflect variation in the products tested or the exposure achieved, rather than differences in the effects of CBG itself.

Although oral CBG produces measurable systemic exposure, the relationship between plasma concentrations and its proposed central mechanisms remains unresolved. Neither unbound CBG concentrations in the human brain nor engagement of the molecular targets identified in experimental studies has been measured. As these targets differ in their concentration–activity relationships, plasma exposure alone cannot identify which pathways are affected in humans. The absence of measurements linking exposure to pharmacodynamic outcomes also prevents the acute behavioral findings from defining an exposure–response relationship.

The available human studies differ in population, treatment duration, and outcomes, which limits both comparisons between them and the conclusions that can be drawn from each. Acute behavioral findings in healthy volunteers cannot be directly compared with results from repeated administration in participants with sleep problems, and neither can be generalized to other neuropsychiatric indications [4,30]. Similarly, favorable tolerability in small, short-duration studies does not establish the risks of prolonged treatment, uncommon adverse events, or interactions with concomitant medicines.

Consumer use provides another source of interpretive uncertainty. Surveys can identify symptoms that users seek to address, but self-selection, variable product composition, exposure to other cannabinoids, and the absence of placebo controls preclude causal conclusions about CBG [31,47].

A barrier to establishing the therapeutic feasibility of CBG lies in the methodological constraints of available clinical data. Existing human studies are predominantly limited by small sample sizes, single-dose or acute treatment protocols, brief follow-up windows, and highly selective patient cohorts. While these preliminary designs provide proof-of-concept and initial safety signals, they offer limited insight into the viability of long-term treatment. Chronic administration poses unique pharmacodynamic and pharmacokinetic challenges such as receptor desensitization, metabolic enzyme induction/inhibition, and potential delayed adverse effects that cannot be captured in acute settings. Consequently, extrapolating current findings to real-world chronic disease management remains premature. Future clinical research must employ adequately powered, double-blind, placebo-controlled trial designs, incorporating multi-dose regimens and extended longitudinal follow-up to establish both long-term safety and sustained efficacy.

9. Future Directions for Clinical Development

A translational clinical development program for CBG must move beyond generic drug-development paradigms by incorporating the compound's distinct pharmacological, metabolic, and receptor-profile characteristics while ensuring pharmaceutical preparations are reproducible across studies. For isolated CBG preparations, analytical specifications must define stringent purity thresholds, degradation kinetics, stability, excipients, manufacturing standards, and trace phytocannabinoid impurity profiles, such as residual Δ9-THC or CBD. Conversely, botanical CBG extracts must be evaluated as distinct complex mixtures given potential terpene interactions. Due to CBG's high lipophilicity, rapid first-pass clearance, and variable oral bioavailability, early-phase trials must priori-

tize formulation-dependent exposure, comparing lipid-based delivery against crystalline isolates. With formulation and administration conditions controlled, initial single- and multiple-ascending dose (SAD/MAD) studies should characterize exposure variability, steady-state pharmacokinetics, accumulation, active metabolites, and CYP450-mediated drug-interaction potential, evaluating safety during repeated administration in individuals receiving concomitant medications. These studies must include obligatory sex-stratified analyses to account for potential sex-dependent pharmacokinetic variability. Once human exposure profiles for a defined product are established, experimental medicine studies must test whether those concentrations engage proposed pathways and produce anticipated biological effects. Because CBG exhibits a complex polypharmacological profile with differing concentration-activity relationships across targets, biological activity or target engagement established for one receptor pathway cannot be extrapolated to others. Serial pharmacokinetic measurements should be integrated with prospectively selected pharmacodynamic outcomes. When direct measures of target engagement are unavailable, appropriately validated indicators, such as central autonomic tone, blood pressure, sedation to verify α2A-adrenergic activity, cortical excitability, stress reactivity, or systemic and tissue-specific neuroinflammatory markers, provide evidence of downstream activity. Crucially, given preclinical evidence indicating female-specific attentional deficits alongside male-oriented benefits, prospective safety decision criteria must incorporate sex-stratified cognitive testing, specifically measuring sustained attention, as an explicit gate before dose escalation.

Advancement to proof-of-concept testing in target indications, such as anxiety, neuropathic pain, or inflammatory bowel disease, should be contingent upon the convergence of disease-specific experimental findings, clean safety profiles across both sexes, and preliminary human observations aligning with plausible activity at achievable exposures. Furthermore, clinical trials must explicitly confirm that systemic concentrations reach the binding affinity relevant to the candidate mechanism and demonstrate target-biomarker or downstream engagement in human subjects. Phase 2a randomized controlled trials in diagnostically homogeneous populations should assess prespecified clinical and mechanistic outcomes over a clinically relevant treatment period, integrating dense exposure–response modeling to link plasma CBG levels directly with the primary clinical endpoints.. Reproducible signals from these trials will provide the rationale for dose-ranging Phase 2b studies to refine therapeutic windows and identify optimal exposures associated with benefit and acceptable tolerability prior to initiating adequately powered Phase 3 confirmatory trials.

10. Discussion

Although CBG interacts with several molecular systems relevant to neuropsychiatry, which of these targets contribute to its effects in vivo remain uncertain. Findings involving cannabinoid, adrenergic, serotonergic, TRP-channel, PPARγ-related, and sodium-channel pathways were obtained under different experimental conditions and at concentrations of uncertain relevance to human brain exposure [1,8–10]. Identifying the mechanisms relevant to treatment therefore requires a distinction between activity demonstrated in experimental systems and target engagement attainable in patients. This polypharmacological profile introduces significant clinical complexities. Broad receptor activity raises the propensity for off-target adverse effects, such as cardiovascular alterations or central nervous system modulation, depending on dose and tissue-specific receptor density [3]. Furthermore, CBG exhibits non-linear, biphasic (bell-shaped) dose–response relationships in several functional paradigms, where escalating doses may lead to receptor desensitization, pathway cross-inhibition, or diminished therapeutic efficacy [3,55]. Additionally, preliminary metabolic studies indicate potential interactions with cytochrome P450 enzymes (e.g., CYP3A4, CYP2C9) and drug transporters, which could alter the systemic exposure

of co-administered medications [56,57]. Therefore, defining precise therapeutic windows and mapping potential drug–drug interactions will be crucial before polypharmacological benefits can be safely realized in clinical practice. Table 3 lists the therapeutic targets of CBG along with their respective clinical potential.

Table 3. Cannabigerol: Pharmacodynamic Targets and Therapeutic Potential.

Biological Target	Pharmacodynamic Action	Experimental Pharmacological Findings and Translational Relevance
CB1 Receptor	Partial agonist	Neuroprotection, anti-inflammatory, antioxidant, anti-nausea
CB2 Receptor	Low-affinity partial agonist	Anti-inflammatory response, immunomodulation, peripheral neuropathic pain relief
TRPA1 Ion Channel	High-potency agonist and desensitizer	Analgesia, anti-nociception, neuroprotective, cutaneous inflammation reduction
TRPV1 Ion Channel	Agonist/desensitizer	Chronic pain relief, gastrointestinal motility regulation
TRPV2 Ion Channel	Agonist	Gastrointestinal regulation, neuroprotection
TRPV3 Ion Channel	Agonist/desensitizer	Cutaneous inflammation reduction, dermatological health regulation, keratinocyte differentiation control, nociceptive pain management
TRPM8 Ion Channel	Potent antagonist	Cold hypersensitivity treatment
GPR55 Receptor	Antagonist/modulator	Neuropathic and inflammatory pain management, anti-inflammatory response
5-HT1A Receptor	Antagonist	Neuroprotection
α_2-Adrenergic Receptor	High-potency agonist	Analgesia, central sedation, blood pressure regulation, neuroprotection
PPARγ	Nuclear receptor agonist	Neurodegenerative diseases (Huntington's, Parkinson's), neuroinflammation suppression, metabolic syndrome
ROS and Pro-inflammatory cytokines	Modulation/inhibition	Antioxidant and anti-inflammatory actions
Sodium NaV Channels	State-dependent inhibitor/suppressor of peak sodium current	Neuropathic and inflammatory pain management, anticonvulsant activity, neuroprotection against excitotoxicity, visceral pain control

Interpretation of the evidence also depends on distinguishing native CBG from compounds with related structures or overlapping molecular targets. Although CBG and CBD act on some of the same targets, differences in their pharmacological activity do not support extrapolating clinical effects from one to the other. Findings obtained with chemically modified CBG derivatives likewise cannot be attributed to native CBG, particularly in neurodegeneration, where disease-specific results with the parent compound coexist with the larger experimental literature on derivatives [16]. Treating these observations as equivalent would overstate the evidence for native CBG.

The contrast between acute changes in anxiety and stress measures in healthy adults and the absence of superiority on the primary outcome of a repeated-dose sleep trial demon-

strates that the available human findings answer distinct, indication-specific questions [4,30]. The former provide a rationale for testing CBG in patients with anxiety disorders, while the latter constrains claims of benefit for the sleep-related regimen and population studied. Neither result supports a general conclusion about CBG efficacy across neuropsychiatric disorders; together, they underscore the need to test whether a defined preparation produces clinically meaningful effects at exposures consistent with the proposed mechanism in a specified patient population.

11. Conclusions

Translating preclinical observations of CBG into clinically viable therapeutics requires a rigorous, multi-tiered research framework. Initial efforts must focus on the formulation of pharmaceutical-grade, chemically standardized compounds. The integration of advanced drug delivery systems is essential to overcoming poor bioavailability and ensuring reproducible systemic pharmacokinetic profiles across study populations. Systematic dose-ranging protocols are subsequently needed to map potential non-linear or biphasic pharmacodynamic relationships, thereby establishing precise therapeutic windows in humans. To verify central target engagement, early-phase clinical trials should incorporate objective central nervous system pharmacokinetic assessments, including cerebrospinal fluid sampling and positron emission tomography neuroimaging, confirming blood–brain barrier permeability in vivo. In parallel, extended longitudinal evaluations involving multi-week and multi-month regimens are necessary to characterize chronic safety profiles, monitor hepatic and cardiovascular parameters, evaluate potential tolerance development, and delineate cytochrome P450-mediated metabolic interactions. Finally, preliminary proof-of-concept findings must be validated through adequately powered, multi-center, randomized, double-blind, placebo-controlled trials using established disease-specific endpoints in well-defined clinical cohorts.

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