Minireview

The Pharmacological Case for Cannabigerol

Rahul Nachnani, Wesley M. Raup-Konsavage, and Kent E. Vrana

Department of Pharmacology, Penn State College of Medicine, Hershey, Pennsylvania

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ABSTRACT

Medical cannabis and individual cannabinoids, such as Δ9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), are receiving growing attention in both the media and the scientific literature. The Cannabis plant, however, produces over 100 different cannabinoids, and cannabigerol (CBG) serves as the precursor molecule for the most abundant phytocannabinoids. CBG exhibits affinity and activity characteristics between Δ9-THC and CBD at the cannabinoid receptors but appears to be unique in its interactions with α-2 adrenoceptors and 5-hydroxytryptamine (5-HT1A). Studies indicate that CBG may have therapeutic potential in treating neurologic disorders (e.g., Huntington disease, Parkinson disease, and multiple sclerosis) and inflammatory bowel disease, as well as having antibacterial activity. There is growing interest in the commercial use of this unregulated phytocannabinoid. This review focuses on the unique pharmacology of CBG, our current knowledge of its possible therapeutic utility, and its potential toxicologic hazards.

SIGNIFICANCE STATEMENT

Cannabigerol is currently being marketed as a dietary supplement, and, as with cannabidiol (CBD) before, many claims are being made about its benefits. Unlike CBD, however, little research has been performed on this unregulated molecule, and much of what is known warrants further investigation to identify potential areas of therapeutic uses and hazards.

Introduction

Cannabinoids as Medicine. The use of Cannabis sativa as a medicine dates back millennia. In ancient China, marijuana was used to treat gout, malaria, digestive disorders, and menstrual pain (Bostwick, 2012; Russo, 2016; Kinghorn et al., 2017; Ryz et al., 2017; Baron, 2018; Ambrose and Simmons, 2019). Cannabis was introduced to Western medicine by William O’Shaughnessy, who proposed its use for the treatment of rheumatism and seizures (Bostwick, 2012; Russo, 2016; Kinghorn et al., 2017; Baron, 2018). However, the use of medicinal marijuana fell out of favor toward the end of the 19th century and continued to decline until it was banned by the Controlled Substances Act of 1970 (Bostwick, 2012; Sacco, 2014; Kinghorn et al., 2017). Since that time, few cannabinoid drugs have been approved for human use. These drugs include nabilone in 1985, dronabinol in 1986, rimonabant in 2006 (in Europe; withdrawn in 2008), Sativex (in Europe) in 2010, and Epidiolex in 2018. A growing number of countries have also approved the use of medical marijuana for treating a variety of medical conditions; however, the data that support the use of marijuana for treatment are often anecdotal or from small studies.

Cannabigerol and Cannabinoid Synthesis. Cannabinoid synthesis begins with the precursor molecules olivetolic acid and geranyl-pyrophosphate, which combine to form cannabigerolic acid (CBGA) (Shoyama et al., 1975; Fellermeier and Zenk, 1998; Fellermeier et al., 2001; Gülck and Møller, 2020). CBGA serves as the precursor to most other cannabinoids and is converted to Δ9-tetrahydrocannabinolic acid (Δ9-THCA), cannabidiolic acid (CBDa), and cannabichromenic acid (Fig. 1). Because CBGA serves as the precursor molecule to the other cannabinoids, it is normally found in very low quantities in Cannabis; however, strains with reduced activity of the three major synthesis enzymes can accumulate higher levels of CBGA (Fellermeier and Zenk, 1998; Fellermeier et al., 2001). All enzymatically produced cannabinoids (including CBG) are produced as their acidic form and are then decarboxylated by heat to create the “active” form.

With the recent deregulation of cannabidiol (CBD) and other hemp-derived cannabinoids, such as CBG, cannabichromene
(CBC), and cannabiol (2018 Farm Bill), there is growing interest in cannabinoid pharmacology (https://www.usda.gov/farmbill). For instance, in spite of having CBG as a common precursor, Δ9-THC, CBD, and CBC have dramatically different physiologic effects. In the case of the two most widely studied compounds, Δ9-THC is known to produce euphoria and appetite stimulation (Volkow et al., 2014), and CBD is noneuphorigenic and is thought to be antiepileptic (Jones et al., 2010) and anti-inflammatory (Carrier et al., 2006). Much less is known about CBG and CBC, but since there are differences in ring structure, it is not surprising that they have differing pharmacological properties; however, cannabinoids other than Δ9-THC and CBD have had little exploration and characterization.

**Interest in Alternative Cannabinoids.** Recent events are prompting increased interest in the pharmaco-therapeutic potential of the 100+ cannabinoid compounds. First, there exists growing belief that the beneficial effects of Cannabis derive from the entourage effect: all of the Cannabis-derived cannabinoids, terpenoids, and flavonoids acting in concert. Although there is little evidence to document this, it does support the notion that the entire plant material needs to be consumed. Then, with the explosion in sales of CBD products, entrepreneurs are searching for the next economic market, and it appears that CBG oil may prove to be that market. Indeed, several commercial outlets are advertising CBG as the “mother of all cannabinoids”—presumably because in Cannabis it is a common precursor. However, CBG will not give rise to the myriad other cannabinoids when taken into the human body because of the lack of necessary conversion pathways.

Work in recent years has garnered interest in other cannabinoids, such as CBC and Δ9-tetrahydrocannabivarin, but more studies are needed. Δ9-Tetrahydrocannabivarin is suggested to induce similar effects as Δ9-THC without excessive appetite stimulation (Tudge et al., 2014), and studies of CBC show it can improve inflammation-related pain (Wirth et al., 1980).
In the present review, we explore potential therapeutic benefits and adverse side effects of CBG. Recent literature on CBG has revealed that its pharmacology addresses therapeutic targets distinct from those of Δ9-THC and CBD. We summarize previous investigations into therapeutic applications and propose new areas of interest for CBG’s medical use. In vitro and in vivo studies suggest a potential future for CBG to address unmet needs in medical therapy, including its actions on adrenergic, serotonergic, peroxisome proliferator-activated receptor (PPAR), and cannabinoid receptor families (Cascio et al., 2010; Rock et al., 2011; O’Sullivan, 2016; Navarro et al., 2018).

Discussion

The Unique Pharmacologic Properties of CBG

CBG is distinct from Δ9-THC and CBD in its pharmacological profile (as summarized in Tables 1 and 2). In a variety of different ways, CBG seems to reside, pharmacologically, in between Δ9-THC and CBD. From the receptor binding data presented in Table 1, CBG is more like Δ9-THC at the CB1/CB2 receptors than CBD, but with a lower affinity (by a factor of between 5-fold and 27-fold) (Pertwee, 2008; Cascio et al., 2010; Pollastro et al., 2011; Rosenthaler et al., 2014; Navarro et al., 2018, 2020). However, a 2012 study of CBG in human cell culture demonstrated negligible binding affinities for CBG at CB1 and CB2 receptors (Granja et al., 2012). More research is required to better understand the effects of CBG in vivo on cannabinoid receptor function and activity. In addition, CBD and CBG are very comparable at six transient receptor potential cation channels (TRPA1, TRPV1, TRPV2, TRPV3, TRPV4, and TRPM8) with relatively minor differences in affinity (generally less than 5-fold differences) (De Petrocellis et al., 2011, 2012; Pollastro et al., 2011; Muller et al., 2019). Important differences or gaps in our knowledge, however, exist for three key players. First, for GPR55 (the potential nonhomologous CB3 receptor), there is no information on CBG binding (Ryberg et al., 2007). Second, CBG appears to be a very potent (nanomolar to sub-nanomolar affinity) agonist at the α-2 adrenoceptor (Cascio et al., 2010). Physiologically, this is so potentially important that it is the subject of extensive discussion below. At the present time, there are no data on this receptor for CBD and Δ9-THC. Finally, there is a clear differentiation of CBG and CBD at the 5-HT1A receptor, in which the former is reported to be an antagonist, whereas the latter is an indirect agonist (with an unreported affinity) (Russo et al., 2005; Cascio et al., 2010; Rock et al., 2011, 2012). There are currently no data in this regard for Δ9-THC.

Table 2 provides a more detailed analysis of the physiologic activities that are exhibited by CBG (whether in intact animals, whole cells, or subcellular preparations). CBG appears to act as an agonist at the α-2 receptor (with varying EC50 values reported) and all of the Transient Receptor Potential Cation Channel (TRP) family channels (except TRPM8, at which it is reported to act as an antagonist). Together, these data suggest that the physiologic effects of CBG tend toward Gi-mediated inhibition, autoregulatory activity, and calcium-based signaling by both ion channels and protein kinase C (PKC). Given the differential pharmacological profiles, there are a number of important concerns to consider concerning the therapeutic potentials and potential adverse outcomes for the widespread and unregulated use of CBG.

The α-2 Adrenergic Receptor (the α-2 Adrenoceptor)

The observation that CBG is a potent agonist at the α-2 receptor has significant implications for potential therapeutic uses and adverse side effects (Cascio et al., 2010). Catecholamines (dopamine, norepinephrine, and epinephrine), produced by the nervous system, use a variety of methods to exert different physiologic effects. The main receptor families that mediate these functions are the adrenergic receptors [alpha (α-1 and α-2) and beta (β-1, β-2, and β-3) families] and the dopamine receptors (D1 through D5 receptors) (Molinoff, 1984). Using the norepinephrine system as an exemplar, these receptors almost all act in the following way: vesicles containing norepinephrine are released from the presynaptic neuron, and synaptic norepinephrine activates postsynaptic G protein–coupled receptors (GPCRs) to create a unique downstream effect. Although the catecholamine receptor families are all GPCRs of varying functions, the α-2 receptor class is best known as a presynaptic receptor (Saunders and Limbird, 1999); however, it also functions in peripheral tissues and cells. Extensive study of this autoregulatory receptor has shown its ability to dampen sympathetic nervous system activity through its Gi (inhibitory) activity that is triggered when synaptic norepinephrine binds to the presynaptic receptor. Additionally, α-2 receptor activation demonstrates

### Table 1

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Affinity</th>
<th>Function</th>
<th>Assay</th>
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</thead>
<tbody>
<tr>
<td>CB1</td>
<td>5.1–80.3 (Ki)</td>
<td>Partial agonist</td>
<td>nM</td>
</tr>
<tr>
<td>CB2</td>
<td>3.1–75.3 (Ki)</td>
<td>Agonist</td>
<td>nM</td>
</tr>
<tr>
<td>GPR55</td>
<td>8 (EC50)</td>
<td>Agonist</td>
<td>nM</td>
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<tr>
<th></th>
<th>Δ9-THC</th>
<th>CBD</th>
<th>CBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>CB1</td>
<td>5.1–80.3 (Ki)</td>
<td>Partial agonist</td>
<td>nM</td>
</tr>
<tr>
<td>CB2</td>
<td>3.1–75.3 (Ki)</td>
<td>Agonist</td>
<td>nM</td>
</tr>
<tr>
<td>GPR55</td>
<td>8 (EC50)</td>
<td>Agonist</td>
<td>nM</td>
</tr>
</tbody>
</table>

N.T., not tested.

aPertwee (2008).
bRosenhaler et al. (2014).
cCascio et al. (2010).
dPollastro et al. (2011).
eNavarro et al. (2018).
fRyberg et al. (2007).
other mechanisms of reduced sympathetic activity such as opening receptor operated K+ channels and inhibiting voltage-gated calcium channels (Cotecchia et al., 1990; Saunders and Limbird, 1999). The family of α-2 receptors has its own further classification into three receptor subtypes—α-2A, α-2B, and α-2C—the genes for which are found on chromosomes 10, 2, and 4, respectively (Saunders and Limbird, 1999).

Although highly related, the different subtypes of the α-2 receptor are distinct in their sequence, structure, and receptor distribution in the body (Saunders and Limbird, 1999). Structural differences between subtypes arise from the intracellular and extracellular regions of the receptor structure, as well as differential post-translational modifications. Anatomic differences are well characterized for the three subtypes in the brain and in the periphery through in situ hybridization of receptor mRNA and through immunochemical analysis of rodent receptor locations (Saunders and Limbird, 1999). In the brain, 2A receptors are widely distributed and abundant in the locus coeruleus and in brainstem regions with homeostatic functions. The α-2B receptors are found in the thalamic nuclei, whereas 2C is found in the basal ganglia, olfactory tubercle, hippocampus, and cerebral cortex (Molinoff, 1984; Arnsten et al., 1988; Saunders and Limbird, 1999). The 2A and 2C receptors are the primary contributors of α-2 receptor function in the central nervous system. Although all three subtypes are found in the nervous system, each subtype has a unique peripheral tissue distribution. In the periphery, 2A is found in platelets, beta cells of the pancreas, adrenal glands, intestinal epithelia, vascular endothelium, and smooth muscle cells (Molinoff, 1984; Saunders and Limbird, 1999); α-2B is found in rat neonatal lung and liver, the adult kidney, vascular endothelium, and smooth muscle cells, whereas 2C is only found in the adult kidney (Molinoff, 1984; Saunders and Limbird, 1999).

Table 2 presents the binding affinities for Δ9-THC, CBD, and CBG at noncannabinoid receptors. Binding affinities for Δ9-THC, CBD, and CBG at TRP ion channels, α-2 adrenoceptors, the serotonin receptor 5-HT1A, and PPARγ are presented. Values are all EC50 for agonists and IC50 for antagonists. Follow-up analysis of the receptor classification into three receptor subtypes—α-2A, α-2B, and α-2C—has revealed that the α-2A, α-2B, and α-2C receptors are the primary contributors of α-2 receptor function in the central nervous system.

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Affinity (nM)</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ9-THC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPA1</td>
<td>2300</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV1</td>
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<td>Unknown</td>
</tr>
<tr>
<td>TRPV2</td>
<td>6500</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV3</td>
<td>9500</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV4</td>
<td>8500</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPM8</td>
<td>1600</td>
<td>Agonist</td>
</tr>
<tr>
<td>α-2 adrenoceptor</td>
<td>N.T.</td>
<td>Unknown</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>N.T.</td>
<td>Unknown</td>
</tr>
<tr>
<td>PPARγ</td>
<td>2120h</td>
<td>Agonist</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CBD</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPA1</td>
<td>1100</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV1</td>
<td>1000</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV2</td>
<td>1250</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV3</td>
<td>3700</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV4</td>
<td>800</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPM8</td>
<td>1400</td>
<td>Antagonist</td>
</tr>
<tr>
<td>α-2 adrenoceptor</td>
<td>N.T.</td>
<td>Unknown</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>N.D.Fg</td>
<td>Indirect agonist</td>
</tr>
<tr>
<td>PPARγ</td>
<td>2010h</td>
<td>Agonist</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>CBG</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPA1</td>
<td>700h</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV1</td>
<td>1300h</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV2</td>
<td>1720h</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV3</td>
<td>1000h</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV4</td>
<td>5100h</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPM8</td>
<td>160h</td>
<td>Agonist</td>
</tr>
<tr>
<td>α-2 adrenoceptor</td>
<td>N.T.</td>
<td>Unknown</td>
</tr>
<tr>
<td>5-HT1A</td>
<td>0–72,5e</td>
<td>Antagonist</td>
</tr>
<tr>
<td>PPARγ</td>
<td>1270h</td>
<td>Agonist</td>
</tr>
</tbody>
</table>

N.D., not detected; N.T., not tested.
• De Petrocellis et al., 2011.
• Muller et al., 2010.
• Pollastro et al., 2011.
• Rock et al., 2011.
• Cascio et al., 2010.
• Russo et al., 2005.
• Rock et al., 2012.
• Granja et al., 2012.
• De Petrocellis et al., 2011.
psychiatric disorders and are another example of \( \alpha-2 \) subtype specificity determining functionality; guanfacine has less intense hypotensive and sedative side effects than clonidine while boasting increased activity at the PFC (Arnst, 2010). Researchers believe that this is due to its specificity at \( \alpha-2A \). Interestingly, whereas agonism of \( \alpha-2A \) receptors has shown benefits in selected psychiatric disorders, antagonism of \( \alpha-2C \) receptors may be beneficial in other psychiatric disorders, such as psychosis and schizophrenia (Uys et al., 2017). This diversity in receptor distribution and potential function indicates a major need for further research into subtype-specific actions and functions of the \( \alpha-2 \) adrenergic receptors.

Although \( \alpha-2 \) agonists have considerable therapeutic applications, the current knowledge of CBG activity at \( \alpha-2 \) receptor subtype and location is lacking. From the potency of CBG at this adrenergic receptor, ingestion may unpredictably change blood pressure, induce sedation, and interact with other cardiovascular medications. Later in this review, we discuss the imperatives for further research into these physiologic effects of CBG administration.

**The Serotonin 5-HT\(_{1A}\) Receptor**

Serotonin, or 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter produced throughout the body for a variety of physiologic and neurologic functions. It plays a central role in maintaining homeostatic functions (e.g., in the enteric gastrointestinal nervous system) (Coates et al., 2017). In the central nervous system, it is a target of antidepressant medications. Serotonin binds to different receptor families (Nichols and Nichols, 2008); here, we will focus on the 5-HT\(_{1A}\) receptor, which has previously been shown to interact with endogenous and exogenous cannabinoid ligands. The 5-HT\(_{1A}\) receptor is a G\(\alpha/o\) GPCR that inhibits adenylate cyclase, but the receptor has also been shown to interact with other growth factor pathways (Rojas and Fiedler, 2016). The receptor is located both pre- and postsynaptically, and the downstream functions of receptor activation vary based on neuronal identity and location. Inhibition of 5-HT\(_{1A}\) autoreceptor (presynaptic) activity is suggested to significantly affect the speed and efficacy of other serotonin-modulating drugs, such as selective serotonin reuptake inhibitors (Artigas et al., 1996). A selective 5-HT\(_{1A}\) antagonist, WAY100635, has potentiated the effects of fluoxetine, a selective serotonin reuptake inhibitor, in vivo. Additionally, the \( \beta \)-adrenergic/5-HT\(_{1A}\) antagonist pindolol was found to enhance the effects of several different classes of serotoninergic antidepressants in patients with major depressive disorder (Artigas et al., 1994). One possible mechanism for these effects is that 5-HT\(_{1A}\) antagonists reduce the increase in 5-HT\(_{1A}\) autoreceptor activity created by antidepressants, which increases synaptic serotonin availability.

In the present context, we note that CBG has been reported to be a potent (50 nM) 5-HT\(_{1A}\) antagonist. Given this pharmacological characteristic, it may have unpredictable potentiating effects on concurrently administered psychiatric medications and serotonin-modulating substances. Recently, Echeverry et al. (2020) reported that CBG and CBD have neuroprotective effects against oxidative neurotoxicity through a 5-HT\(_{1A}\) receptor–mediated mechanism. The effects of CBG on serotonin signaling or availability have not yet been thoroughly studied, and more research is needed to understand the impact of CBG-mediated 5-HT\(_{1A}\) antagonism before it is made widely available in an unregulated commercial environment.

**The Peroxisome Proliferator–Activated Receptors**

The PPAR family is a collection of nuclear receptor transcription factors; there are three isoforms: PPAR\(\alpha\), PPAR\(\beta\), and PPAR\(\gamma\). PPAR nuclear activation induces conformational changes and binding to PPAR response elements of DNA to modulate gene transcription (O’Sullivan and Kendall, 2010; O’Sullivan, 2016). These receptors transcriptionally regulate lipid metabolism, hepatic metabolic functions, and inflammation. PPARs accept a wide variety of ligands because of their large binding domains, and many cannabinoids and their metabolites are reported to interact with the various isoforms (O’Sullivan and Kendall, 2010; O’Sullivan, 2016). In the reviewed studies, CBG exhibits stronger affinity to the PPAR\(\gamma\) receptor than \( \Delta ^9 \)-THC and CBD.

PPAR\(\gamma\) will regulate adipocyte differentiation, insulin sensitivity, and inflammatory states. This is the therapeutic mechanism of thiazolidinediones, like rosiglitazone, commonly used in patients with type 2 diabetes to improve adipocyte functioning and increase insulin sensitivity (O’Sullivan and Kendall, 2010; O’Sullivan, 2016). Cannabinoid compounds display varying affinities at PPAR isoforms, and the effects of CBG on these receptors are being studied in the regulation of inflammation and metabolic functioning; these potential therapeutic effects are reviewed in the next section.

**Potential Therapeutic Potentials for CBG**

Based on the receptor signaling of the \( \alpha-2 \), 5-HT\(_{1A}\), and PPAR\(\gamma\) receptors and the reported affinities of CBG at these receptors (in the tens of nanomolars to sub-nanomolar range), there are many reasons to believe that CBG will have therapeutic potential (Cascio et al., 2010; Rock et al., 2011; Granja et al., 2012). Similarly, however, there are reasons to monitor high-dose CBG for untoward side effects beyond drug-drug interactions.

**Neuroprotection and Neuromodulation.** A number of studies have shown that CBG and a second-generation synthetic quinone derivative, VCE-003.2, have neuroprotective potential in vitro and in animal models to reduce the severity of neurologic illnesses, such as Huntington disease (HD), amyotrophic lateral sclerosis, Parkinson disease, and multiple sclerosis; this seems to largely be mediated through PPAR\(\gamma\) (Granja et al., 2012; Carrillo-Salinas et al., 2014; Díaz-Alonso et al., 2016; Mammana et al., 2019). VCE-003.2 is distinct from the first-generation CBG quinone derivative VCE-003 because it retains neuroprotective activity through dose-dependent PPAR\(\gamma\) activation but does so without the cytotoxicity and thiophilic properties of VCE-003 (Díaz-Alonso et al., 2016). These properties lend some pharmacological explanation to its beneficial effects on various models of neurotoxicity. Indeed, VCE-003.2 is reported to have negligible affinity at either CB1 or CB2 (>40 \( \mu \)M). CBG and VCE-003.2 have been shown to reduce the inflammatory molecules TNF-\(\alpha\), IL-1\(\beta\), IL-6, Macrophage Inflammatory Protein (MIP-1\(\alpha\)), and Prostaglandin E2 (PGE2) in rat microglial cells treated with lipopolysaccharide (LPS), and both compounds reduce glutamate-induced oxidative cell death in mouse hippocampal cells (Granja et al., 2012).
Using two mouse models of HD, Valdeolivas et al. (2015) reported improvement of HD symptoms. In particular, in 3-nitropropionate–treated mice, CBG prevented striatal neuron death, reduced markers of inflammation, and improved motor deficits (Valdeolivas et al., 2015). The results in a transgenic R6/2 mouse model of HD were not as robust. Treatment with CBG did not reduce the weight loss observed in this model, but it did moderately improve Rotarod performance and reduced the number of huntingtin aggregates (Valdeolivas et al., 2015). A study using VCE-003.2 found a similar improvement in HD symptoms in the murine model of HD (Díaz-Alonso et al., 2016). In the quinolinic acid murine model of HD, treatment with VCE-003.2 improved Rotarod performance (Díaz-Alonso et al., 2016). VCE-003.2 also improved motor deficits in the 3-nitropropionate (NP3) model of HD, and this was found to be dependent upon PPARγ activity in that inhibition of PPARγ by T0070907 blocked the effect of VCE-003.2 treatment (Díaz-Alonso et al., 2016).

Experiments using the SOD<sup>G93A</sup> mouse model of amyotrophic lateral sclerosis found that VCE-003.2 improved the neuropathological symptoms, including attenuating weight loss, improving clinical scores, and preserving motor neurons in the spinal cord (Rodríguez-Cueto et al., 2018). Additionally, astrocytes cultured from SOD<sup>G93A</sup>, when treated with VCE-003.2, exhibited a morphology close to wild-type astrocytes (Rodríguez-Cueto et al., 2018). Using an lipopolysaccharide (LPS)-induced inflammatory model of Parkinson disease, VCE-003.2 reduced the inflammatory markers TNF-α, IL-1β, and inducible nitric oxide synthase (iNOS), and this response was mediated through PPARγ (García et al., 2018). Finally, VCE-003.2 has also been shown to improve motor activity, reduce vascular cell adhesion molecule (VCAM-1) expression, and decrease microglia activity in the Thelier murine encephalomyelitis virus model of multiple sclerosis (Granja et al., 2012).

Another area of interest is the therapeutic potential of CBG involving 5-HT<sub>1A</sub> receptor activity. In 2020, Echeverry et al. (2020) studied the effects of CBG and CBD on neurotoxicity as assessed in neural cell cultures. The neuroprotective qualities of CBD and CBG were distinct at two different models of oxidative damage (the H<sub>2</sub>O<sub>2</sub> model and the rotenone model) (Echeverry et al., 2020). The authors found that the protective effects were lost when CBG and CBD were administered with a 5-HT<sub>1A</sub> antagonist, WAY-100635, but were unchanged with CB1 and CB2 receptor antagonists (Echeverry et al., 2020). This suggests that the protective effects of CBG and CBD against oxidative neurotoxicity are derived from a 5-HT<sub>1A</sub> receptor–mediated process (Echeverry et al., 2020).

Finally, a relatively unexplored area of CBG neuromodulation is its effect on neurotransmission. Recently, transcriptomic changes by administration of CBD and CBG on motor neuron–like cells has shown an insight into this neuromodulatory effect. In NSC-34 motor neuron–like cells, authors Gugliandolo et al. (2020) compared the transcriptomic changes from CBD and CBG. The two compounds similarly changed transcription in the dopamine, GABA, and glutamate pathways. This was from, generally, reduced expression of glutamate release genes, enhanced expression of GABA release genes, and upregulated dopamine D4 receptor and its downstream effectors (Gugliandolo et al., 2020). Characterization of these changes on behavior and neuronal signaling through translational research is necessary to better understand the context of CBG in psychopharmacology. However, the results do speak to the need to monitor untoward side effects.

**Gastrointestinal Disease.** Cannabigerol has been explored as a therapeutic for gastrointestinal diseases such as colorectal cancer and colitis using mouse models. In the dinitrobenzene sulfuric acid model of colitis, treatment with CBG increased the rate of tissue recovery in the colon as measured by histologic structure, the ratio of colon weight to length, colonic permeability, and reduced inflammation (Borrelli et al., 2013). The authors also found that CBG was also effective as a treatment to prevent colitis-associated damage (Borrelli et al., 2013). In a follow-up study, it was found that cannabigerol reduced tumor formation in the azoxymethane model of colorectal cancer and reduced xenograft tumor growth (Borrelli et al., 2014). Although the authors conclude that this reduction was mediated by TRPM8, these studies were performed in cell culture rather than in the murine model. In 2020, Pagano et al. (2020) used a mouse model of dinitrobenzene sulfuric acid–induced colitis to study the effects of CBG on inflammatory activity. Orally administered CBG reduced colonic inflammation as measured by significantly reducing myeloperoxidase (MPO) activity, IL-1β levels, and serum fluorescein isothiocyanate (FITC)-dextran concentration. In contrast, CBD on its own did not induce significant changes to these metrics. Adding fish oil to the treatment paradigm increased the CBG-induced reduction in myeloperoxidase activity, IL-1β levels, and serum FITC-dextran concentration (Pagano et al., 2020).

CBG has also been shown to increase feeding in rats and to reduce weight loss associated with cisplatin chemotherapy (Brierley et al., 2016, 2017, 2019). However, an earlier study found no impact of CBG on feeding behavior (Farrimond et al., 2012). Unlike Δ<sup>9</sup>-THC and CBD, CBG has not been found to have antiemetic effects and appears to oppose the antiemetic effects of CBD (Rock et al., 2011). Taken together, these studies indicate that there may be a role for cannabigerol in chemotherapy–associated weight loss and loss of appetite, although Δ<sup>9</sup>-THC (dronabinol) and nabilone have already been proven efficacious, CBG lacks the potential euphoric side effect of these medications.

**Metabolic Syndrome.** Metabolic syndrome affects millions of Americans and contributes to the highest burden of healthcare costs and preventable mortality in the country. A clinical diagnosis, metabolic syndrome is a combination of insulin resistance, obesity, hypertension, high levels of low-density lipoprotein, and reduced levels of high-density lipoprotein. Although a wide array of medications and surgical interventions are available for metabolic syndrome, few treatments are effective enough to serve as monotherapy, and many patients need multiple medications with harsh side effects to keep this chronic illness at bay.

Recent studies on CBG provide promise for its use as part of a multifactorial pharmacotherapy for metabolic syndrome and its components. Hypertension, one component of metabolic syndrome, can be modestly reduced with α-2 agonist therapy, which reduces synaptic norepinephrine levels to reduce vasoconstriction and improve blood pressure. CBG is currently the only known cannabinoid that is an agonist at the adrenergic receptor (Cascio et al., 2010). In addition, as previously mentioned, CBG and its derivatives are shown to act on PPARγ receptors in its role on neuroinflammation. In
agonists, which appears to be mediated by the CB2 receptor, and this unique property could also induce unintended cardiovascular consequences such as hypotension, bradycardia, and xerostomia. Additionally, some investigators have reported hypertension as a counterintuitive adverse effect in high doses of α-2 agonists, which appears to be mediated by the α-2B receptor subtype (Philipp et al., 2002). The potential for this adverse effect is unclear in the case of CBG, since its activity at different α-2 receptor subtypes has yet to be studied. Although we surmise that CBG may have therapeutic potential among neurologic, gastrointestinal, and metabolic disorders, there must be more research to ensure that unintended cardiovascular effects do not reduce the utility of CBG. In addition, in this era of unregulated CBD preparations, companies are making unsubstantiated claims and overselling the benefits and underselling the risks. Indeed, companies are already touting CBG as the “mother of all cannabinoids,” presumably because it is the immediate precursor of CBD and Δ9-THC. What they fail to point out, however, is that only the Cannabis plant goes on to convert CBG to the other molecules—the human body does not. This is problematic because very few Cannabis strains actually harbor large concentrations of CBG, so there is not much prior reporting (and virtually no documentation) of human side effects of CBG.

Several recent cautionary situations come to mind. In a couple of recent reports on CBD oil, it has been reported that not all CBD oil preparations had concentrations of CBD close to what the manufacturer claimed (Bonn-Miller et al., 2017; Pavlovic et al., 2018; Raup-Konsavage et al., 2020; Urasaki et al., 2020). Moreover, the U.S. Food and Drug Administration had to prompt recalls for CBD preparations that contained unacceptable concentrations of lead (https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/inhe-manufacturing-llc-and-mhr-brands-issues-voluntary-nationwide-recall-several-products-due-utm_campaign=FDA%20MedWatch%20-%20Several%20Hemp%20Oil%20Products%20from%20InHe%20Manufacturing%20and%20MHR%20Brands%3A%20Recall&utm_medium=email&utm_source=Eloqua; https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/summitt-labs-issues-voluntary-nationwide-recall-kore-organic-watermelon-cbd-oil-due-high-lead). We have reported that, even when the different CBD oil preparations contain the reported levels of this phytocannabinoid, they had very different activities in suppressing cancer cell growth in vitro, and only one approximated the activity of pure CBD (Raup-Konsavage et al., 2020). Finally, there is also the very real risk of inducing drug-drug interactions when over-the-counter preparations like CBD oil or CBD oil are taken by a patient on other (prescription) medications (Kocis and Vrana, 2020). This may lead to unintended adverse consequences when not appropriately monitored.

**Future Imperatives**

Research into cannabigerol is in its infancy but has shown promise for addressing a diverse array of therapeutic needs. Based on its pharmacodynamics, here we highlight potential indications for CBG and its derivatives to improve available drug treatment regimens for selected diseases and medical conditions. However, these applications will rely on additional research studies to further understand how CBG can be used safely and effectively.

First, there is potential for CBG as a major player in the treatment of metabolic disease as described by its action on the PPAR family of receptors to improve insulin sensitivity and adipogenesis. A supplementary effect is its antihypertensive properties at α-2 receptors. Patients with diabetes frequently have hypertension, hyperlipidemia, and insulin resistance stemming from glucose dysregulation and vascular endothelial dysfunction. CBG may improve this profile as an adjunct to the mainstay of treatment, metformin, or potentially serve as its own regimen. In current practice, α-2 agonists such as clonidine are infrequently used as antihypertensive agents, largely because these effects of clonidine...
are enhanced with imidazoline receptor activity; this rendered clonidine too powerful as an antihypertensive drug and unreliable in practice. To our knowledge, the sympatholytic effect of CBG is limited to $\alpha$-2 action, which makes it more useful for this indication than clonidine, but more studies are needed.

Second, several studies have described the neuroprotective effects of CBG through action on the PPAR family of receptors. Other sources have reported reduction in age-related cognitive decline in patients with neurodegenerative disease with the addition of $\alpha$-2 agonists to their treatment regimens. Although CBG’s effect on cognition has yet to be studied, it may play a role for improving quality of life in these vulnerable populations, as the few drugs currently available for neurodegenerative diseases also carry uncomfortable and disabling side effects.

Third, similar to other phytocannabinoid derivatives, CBG may play an important role for improving the drug cocktails of patients who struggle with disorders of executive function, such as schizophrenia and ADHD. Two current $\alpha$-2 agonists, clonidine and guanfacine, are indicated for their $\alpha$-2-mediated action on the human prefrontal cortex to improve executive function and self-regulation; however, clonidine is less safely prescribed because of its potent antihypertensive properties and generalized action on $\alpha$-2 receptor subtypes. Guanfacine is well studied as an adjunct therapy with stimulants in ADHD because of its $\alpha$-2A subtype specificity. The $\alpha$-2A specificity of CBG has yet to be elucidated; therefore, it cannot be predicted how CBG will improve executive dysfunction compared with guanfacine. Finally, researchers have studied the effects of CBG as a safe appetite stimulant in chemotherapy-related appetite suppression in vivo and as an agent that reduces in vitro signs of pathology in colitis and colorectal cancer.

In closing, although there is much to suggest that CBG may provide alternative therapeutics for a number of disorders, much is left to learn. In particular, given the potent bioactivity CBG displays in a number of settings, we should be very cautious about releasing it in an unregulated retail environment. There is simply insufficient experience with this relatively rare phytocannabinoid, and the potential for adverse effects is high. Given the dramatic increase in unregulated CBD oil use following deregulation of hemp, it behooves the pharmaceutical community to undertake CBG research before its use explodes as well.

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Wrote or contributed to the writing of the manuscript: Nachmani, Raup-Konsavage, Vrana.

References


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