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 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; Ambrose and Simmons, 2019). 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; Russo, 2016; Kinghorn et al., 2017; Baron, 2018). Since that time, few cannabinoids 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 These drugs include nabilone in 1985, dronabinol in 1986, rimonabant in 2006 (in Europe; withdrawn in 2008), Sativex (in Europe) in 2010, and Epidiolex in 2018.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; Gulck and Møller, 2020). CBGA serves as the precursor to most other cannabinoids and is converted to 9-tetrahydrocannabinolic acid (9-THCA), cannabidiolic acid (CBD), 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 cannabinol (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 pharmacotherapeutic 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). 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 adrenergic receptor (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)] (Molino, 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

Pharmacodynamic properties of Δ9-THC, CBD, and CBG at cannabinoid receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Δ9-THC</th>
<th>CBD</th>
<th>CBG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affinity</td>
<td>Function</td>
<td>Affinity</td>
</tr>
<tr>
<td>CB1</td>
<td>5.1–80.3 (Kiₜₐ,b)</td>
<td>Partial agonist</td>
<td>1458.5–4900 (Kiₜₐ,b)</td>
</tr>
<tr>
<td>CB2</td>
<td>3.1–75.3 (Kiₜₐ,b)</td>
<td>Agonist</td>
<td>372.4–4200 (Kiₜₐ,b)</td>
</tr>
<tr>
<td>GPR55</td>
<td>8 (EC₅₀)</td>
<td>Agonist</td>
<td>445 (IC₅₀)</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).

**TABLE 2**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Δ9-THC</th>
<th>CBD</th>
<th>CBG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Affinity</td>
<td>Function</td>
<td>Affinity</td>
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<td>GPR55</td>
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<td>Agonist</td>
<td>445 (IC₅₀)</td>
</tr>
<tr>
<td>nM</td>
<td>nM</td>
<td>nM</td>
<td>nM</td>
</tr>
</tbody>
</table>

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aPertwee (2008).
bRosenhaler et al. (2014).
cCascio et al. (2010).
dPollastro et al. (2011).
eNavarro et al. (2018).
fRyberg et al. (2007).
TABLE 2
Pharmacodynamic properties of ∆9-THC, CBD, and CBG at noncannabinoid receptors

<table>
<thead>
<tr>
<th>Receptor</th>
<th>∆9-THC Affinity</th>
<th>Function</th>
<th>δ9-THC Function</th>
<th>CBD Affinity</th>
<th>Function</th>
<th>CBD Function</th>
<th>CBG Affinity</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPA1</td>
<td>280a,b</td>
<td>Agonist</td>
<td>N.D.</td>
<td>700a,b,c</td>
<td>Agonist</td>
<td>N.D.</td>
<td>1200h,c</td>
<td>Agonist</td>
</tr>
<tr>
<td>TRPV1</td>
<td>N.D.a,b</td>
<td>Unknown</td>
<td>1100a,b</td>
<td>700a,b,c</td>
<td>Agonist</td>
<td>1300a,b,c</td>
<td>Agonist</td>
<td></td>
</tr>
<tr>
<td>TRPV2</td>
<td>650a,b</td>
<td>Agonist</td>
<td>1250a,b</td>
<td>1720a,b,c</td>
<td>Agonist</td>
<td>1000a,b,d</td>
<td>Agonist</td>
<td></td>
</tr>
<tr>
<td>TRPV3</td>
<td>9500b,d</td>
<td>Agonist</td>
<td>3700b,d</td>
<td>5100b,d</td>
<td>Agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPV4</td>
<td>8506,d</td>
<td>Agonist</td>
<td>800b,d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRPM8</td>
<td>160a,b</td>
<td>Agonist</td>
<td>140a,b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>α2 adrenoceptor</td>
<td>N.T.</td>
<td>Unknown</td>
<td>N.T.</td>
<td>160a,b,c</td>
<td>Agonist</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-HT1A</td>
<td>N.D.fg</td>
<td>Indirect agonist</td>
<td>0.2–72.6e</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPARγ</td>
<td>2120h</td>
<td>Agonist</td>
<td>2010h</td>
<td>51.9d,e</td>
<td>Agonist</td>
<td>1270h</td>
<td>Agonist</td>
<td></td>
</tr>
</tbody>
</table>

Values are all EC50 for agonists and IC50 for antagonists.

- TRPA1 is located on the neuronal plasma membranes and in the periphery through in situ hybridization of receptor mRNA and through immunohistochemical analysis of rodent receptor locations (Saunders and Limbird, 1999).
- TRPV1 receptors are distinct in their sequence, structure, and receptor distribution in the body (Saunders and Limbird, 1999).
- TRPV2 receptors are widely distributed and abundant in the locus coeruleus and in brainstem regions with homeostatic functions. The α2B receptors are found in the thalamic nuclei, whereas α2C 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 α2 receptor function in the central nervous system. Although all three subtypes are found in the nervous system, each subtype has a unique receptor location (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 α2B receptors are found in the thalamic nuclei, whereas α2C 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 α2 receptor function in the central nervous system. Although all three subtypes are found in the nervous system, each subtype has a unique receptor location (Saunders and Limbird, 1999).
- α2B receptors are found in the thalamic nuclei, whereas α2C 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 α2 receptor function in the central nervous system. Although all three subtypes are found in the nervous system, each subtype has a unique receptor location (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 α2B receptors are found in the thalamic nuclei, whereas α2C is found in the basal ganglia, olfactory tubercle, hippocampus, and cerebral cortex (Molinoff, 1984; Arnsten et al., 1988; Saunders and Limbird, 1999).
- 5-HT1A receptors are distinct in their sequence, structure, and receptor distribution in the body (Saunders and Limbird, 1999).
- PPARγ receptors are distinct in their sequence, structure, and receptor distribution in the body (Saunders and Limbird, 1999).
psychiatric disorders and are another example of α-2 subtype specificity determining functionality; guanfacine has less intense hypotensive and sedative side effects than clonidine while boosting increased activity at the PFC (Arnsten, 2010). Researchers believe that this is due to its specificity at α-2A. Interestingly, whereas agonism of α-2A receptors has shown benefits in selected psychiatric disorders, antagonism of α-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 α-2 adrenergic receptors. Although α-2 agonists have considerable therapeutic applications, the current knowledge of CBG activity at α-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<sub>1A</sub> 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<sub>1A</sub> receptor, which has previously been shown to interact with endogenous and exogenous cannabinoid ligands. The 5-HT<sub>1A</sub> receptor is a G/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<sub>1A</sub> 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<sub>1A</sub> antagonist, WAY100635, has potentiated the effects of fluoxetine, a selective serotonin reuptake inhibitor, in vivo. Additionally, the β-adrenergic/5-HT<sub>1A</sub> antagonist pinadolol 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<sub>1A</sub> antagonists reduce the increase in 5-HT<sub>1A</sub> 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<sub>1A</sub> 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<sub>1A</sub> 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<sub>1A</sub> 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<sub>α</sub>, PPAR<sub>β</sub>, and PPAR<sub>γ</sub>. 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<sub>γ</sub> receptor than Δ9-THC and CBD.

PPAR<sub>γ</sub> 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 α-2, 5-HT<sub>1A</sub>, and PPAR<sub>γ</sub> 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<sub>γ</sub> (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<sub>γ</sub> 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 μM). CBG and VCE-003.2 have been shown to reduce the inflammatory molecules TNF-α, IL-1β, IL-6, Macrophage Inflammatory Protein (MIP-1α), 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, Valdeolivias 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 (Valdeolivias 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 (Valdeolivias et al., 2015). A study using VCE-003.2 found a similar improvement in HD symptoms in the murine model of HD (Diaz-Alonso et al., 2016). In the quinolinic acid murine model of HD, treatment with VCE-003.2 improved Rotarod performance (Diaz-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 (Diaz-Alonso et al., 2016).

Experiments using the SOD^{G93A} 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 (Rodriguez-Cueto et al., 2018). Additionally, astrocytes cultured from SOD^{G93A}, when treated with VCE-003.2, exhibited a morphology close to wild-type astrocytes (Rodriguez-Cueto et al., 2018). Using a 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 Theiler murine encephalomyelitis virus model of multiple sclerosis (Granja et al., 2012).

Another area of interest is the therapeutic potential of CBG involving 5-HT1A 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 H2O2 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-HT1A 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-HT1A 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 have 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 Δ9-THC and CBD, CBG has not been found to have anxiolytic effects and appears to oppose the anxiolytic effects of CBD (Rock et al., 2011). Taken together, these studies indicate that there may be a role for cannabigerol in chemotheraphy-associated weight loss and loss of appetite, although Δ9-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.
2019, in vitro modeling of phytocannabinoids suggested CBG as a dual PPARα/γ agonist, first through computer modeling and prediction and then confirmation in HepG2 (human liver epithelial-like) and 3T3L1 (mouse embryo fibroblast) cell lines (D’Aniello et al., 2019).

More support for PPARα/γ agonism of CBG came in 2020 from researchers who tested PPARα/γ-dependent differentiation in bone marrow mesenchymal stem cell lines (Fellous et al., 2020). This effect was enhanced when combined with CBD and had a similar effect as a commonly prescribed drug for metabolic syndrome, rosiglitazone (Fellous et al., 2020). Rosiglitazone is known to act as an agonist at PPARγ receptors and to increase expression of glucose transporter type 4 (GLUT4) glucose channels; both of these effects increase insulin sensitivity. CBG and the CBG/CBD combinations provided similar effects in vivo as rosiglitazone and additive effects to improve adipogenesis (Fellous et al., 2020). Renewed adipogenesis and insulin sensitization improve both symptoms and pathology of metabolic syndrome; therefore, CBG could be explored as a potential therapeutic for this devastating disease.

**Antibacterial Agent.** A number of cannabinoids have been reported to have antibacterial activity; however, CBG was found to be among the most potent cannabinoids tested against antibiotic resistant strains of *Staphylococcus aureus* (Appendino et al., 2008). In comparison with conventional antibiotics, CBG had a lower minimum inhibitory concentration than norfloxacin in five of the six strains tested and was more potent than erythromycin, tetracycline, and oxacillin in at least one resistant strain (Appendino et al., 2008). Using a systemic *S. aureus* infection model in mice, Farha et al. (2020) showed that CBG was as effective at reducing colony forming units as vancomycin. This study also found that CBG was effective against Gram negative bacteria only when the outer membrane was first permeabilized, suggesting that the outer membrane of Gram negative bacteria presents a permeability problem for cannabinoids (Farha et al., 2020). Using in silico modeling, Pinzi et al. (2019) found that CBG acts as an inhibitor of enoyl acyl carrier protein reductase (Gene Name; InhA), and they verified their model with in vitro testing and found that CBG inhibits enoyl acyl carrier, with an IC₅₀ value in the low micromolar range. These data are encouraging because there is a need to develop novel therapeutics, as antibiotic resistance in bacteria is a continuing healthcare issue.

**Potential Arguments against CBG as a Therapeutic**

We have highlighted the potential of cannabigerol as a therapeutic and in medical research; however, for it to be seriously considered as a potential therapeutic, it must be rigorously tested for safety and unintended effects.

CBG has potent activity at the α-2 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 claims (Bonn-Miller et al., 2017; Pavlović 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 CBG 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...
Potential Clinical Uses of CBG
