CHAPTER

99

Potential Medical Uses of Cannabigerol: A Brief Overview

S. Deiana

CNS Diseases Research Department, Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer straße, Biberach an der Riss, Germany

SUMMARY POINTS

- This chapter focuses on medical uses of cannabigerol (CBG), a phytocannabinoid present in the *Cannabis* plant.
- CBG is a short-life precursor of tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabichromene (CBC), which explains its low concentration in the plant.
- CBG acts on serotoninergic, cannabinoid, peroxisome proliferator-activated receptors, α2-adrenoceptors, vanilloid, melastatin, and ankyrin channels.
- CBG modulates enzymes activity including monoacylglycerol lipase (MAGL), *N*-acylethanolamine acid amide (NAAA) hydrolase, cyclooxygenase (COX), phospholipase-A2 (PLA2), prostaglandin-E2 production (PGE2), and inhibits dopamine, norepinephrine, GABA, and serotonin reuptake.
- By inhibiting prostaglandin production at different levels, CBG owns antinflammatory and analgesic properties.
- CBG possesses antiproliferative effects and it has been suggested for cancer therapy.
- Its effects on preclinical models of mood disorders granted the filing of a patent for CBG use to treat mood disorders, particularly depression.
- CBG has been suggested for skin conditions, glaucoma, sex hormonal dysregulations, eating disorders, and bone healing.
- Due to its difficult availability, CBG has received attention only recently, and further research is required before its clinical efficacy can be demonstrated.

KEY FACTS OF CANNABIGEROL CONTENTS IN CANNABIS PLANT

- Cannabigerol (CBG) concentrations in the *Cannabis* plant are usually extremely low.
- This is due to its rapid conversion into tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabichromene (CBC).
- Recent genetic techniques allowed the inactivation of the devoted synthases to prevent the natural conversion of CBG into its metabolites.
- This permitted the selection of *Cannabis* plant strains with high CBG contents.

KEY FACTS OF FIRST MEDICAL USES OF CANNABIS

- First *Cannabis* uses are documented in the Chinese herbarium Pen-ts'ao (2800 BC), a pharmacopeia describing several drugs.
- Pen-ts'ao described *Cannabis* as *"ma,' meaning* chaotic.
- *Cannabis* pain-relieving, stupefying, hallucinogenic properties were described together with its use for malaria, menstrual irregularities, constipation, gout and rheumatism.

Handbook of Cannabis and Related Pathologies. http://dx.doi.org/10.1016/B978-0-12-800756-3.00115-0

LIST OF ABBREVIATIONS

$5HT_{1A}R$	5-Hydroxytryptamine-1A Receptors
BBB	Blood–brain barrier
BDS	Botanical drug substance
CB_1R, CB_2R	Cannabinoid receptors type 1 and 2
CBC	Cannabichromene
CBD	Cannabidiol
CBG	Cannabigerol
COX	Cyclooxygenase
DNBS	Dinitrobenzene sulfonic acid
EAE	Experimental autoimmune encephalomyelitis
IBD	Inflammatory bowel disease
iNOS	Inducible nitric oxide synthase
IOP	Intra ocular pressure
MAGL	Monoacyl glycerol lipase
MS	Multiple sclerosis
MSCs	Mesenchymal stem cells
NAAA	*N*-acylethanolamine acid amidase
NSAIDs	Nonsteroidal antiinflammatory drugs
PCCs	Prostate cancer cells
PGE2	Prostaglandin-E2
PLA2	Phospholipase-A2
PPARs	Peroxisome proliferator-activated receptors
THC	Tetrahydrocannabinol
TLM	Testosterone lowering medicaments
TMEV	Theiler's murine encephalomyelitis virus
TRP	Transient receptor potential
TRPA	Transient teceptor potential ankyrin
TRPM	Transient receptor potential melastatin
TRPV	Transient receptor potential vanilloid

INTRODUCTION

Medicinal use of *Cannabis* dates back to 2800 BC, with suggested use in treating constipation, malaria, gout, rheumatism, pain, asthma, and menstrual anomalies (Iversen, 2007).

The main constituent of the *Cannabis* plant, tetrahydrocannabinol (THC), possesses psychotropic effects, thus limiting its therapeutic use; attention now focuses on nonpsychotropic phytocannabinoids, such as cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG) as potential therapeutic agents for conditions ranging from cancer to inflammation and to mental disorders. For instance, CBD has been suggested to be beneficial for schizophrenia (Deiana, 2013; Zuardi et al., 2012), while the oromucosal spray Sativex (THC and CBD) is approved for the treatment of spasticity in multiple sclerosis (MS) (GW Pharmaceuticals, 2014).

Described for the first time in 1964 (Gaoni & Mechoulam, 1964), CBG is the least studied among phytocannabinoids (a Pubmed search using keyword "cannabigerol" results in 69 publications only), primarily due to its low availability in the *Cannabis* plant (~10% of the cannabinoid fraction) (de Meijer & Hammond, 2005). Specific synthases rapidly metabolize CBG into THC (Taura, Morimoto, Shoyama, & Mechoulam, 1995), CBD (Taura, Morimoto, & Shoyama, 1996) and CBC (Gaoni & Mechoulam, 1966) thus reducing CBG availability in the plant (Fig 99.1). Plants carrying a recessive allele which reduces the efficacy of these synthases contain higher CBG concentration (94% of the cannabinoid fraction) and genetic engineering allows the generation of CBG-predominant *Cannabis* plants (de Meijer, 2004; GW Pharmaceuticals, 2014), facilitating research into CBG pharmacology, and hence fostering the knowledge on its potentials as a therapeutic agent.

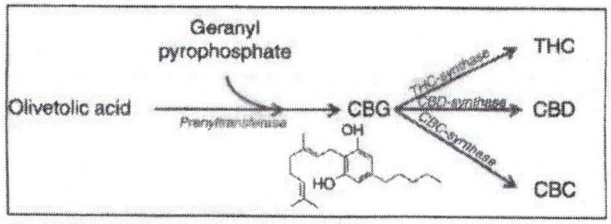

FIGURE 99.1 **Biosynthesis and metabolism of cannabigerol.** A prenyltransferase catalyzes the conversion of olivetolic acid into CBG, which is then converted into THC, CBD, or CBC by specific synthases. *Source: Information collected from Hill, Williams, Whalley, and Stephens (2012) and Marks et al. (2009).*

PHARMACOKINETICS AND PHARMACOLOGY OF CANNABIGEROL

The mechanism of action of CBG was until recently unknown. In recent times, novel studies revealed its polypharmacological profile, making it an interesting molecule for direct use as medicament itself or as a possible starting molecular structure for the development of more selective/potent chemical entities.

Pharmacodynamics and pharmacokinetic figures are fundamental for profiling and selecting a drug for medical use. Human CBG exposure and bioavailability are still unknown, but its pharmacokinetics in rodents have been described (Deiana et al., 2012). Plasma and brain pharmacokinetics of CBG (120 mg/kg) were studied in rats and mice, following acute oral and intraperitoneal administration (Table 99.1).

CBG readily crossed the blood–brain barrier (BBB) and, in general, in both species, intraperitoneal administration provided higher plasma and brain concentration being the difference only marginal in rats. Indeed, C_{max} values were similar in rats receiving oral or intraperitoneal CBG administration, whereas in mice, C_{max} values

TABLE 99.1 Pharmacokinetics of Cannabigerol

	Mouse				Rat			
	Plasma		Brain		Plasma		Brain	
Measure	po	ip	po	ip	po	ip	po	ip
C_{max} (μg/mL)	0.67	40.8	0.42	3.48	1.05	0.81	0.97	1.23
T_{max} (min)	30	120	60	120	30	60	120	60
Apparent elimination half-life (min)	193	176	≤121	252	100	560	96	447
$AUC_{0-6\,h}$ (μg/mL, g min)	57	4324	≤44	679	98	≤199	181	335
$AUC_{0-24\,h}$ (μg/mL, g min)	ID	5563	≤65	1103	ID	≤514	ID	884
$AUC_{0-\infty}$ (μg/mL, g min)	67	5571	≤86	1117	106	≤617	205	992

$n = 4$; po, *per os*; ip, intraperitoneal; ID, insufficient data available for analysis; C_{max}, maximal drug concentration in tissue; T_{max}, time to reach C_{max}; AUC, area under the curve. Mouse and rat pharmacokinetic values in plasma and brain following 0.5, 1, 2, 4, 6, and 24 h oral and intraperitoneal CBG (120 mg/kg) administration. Apparent elimination half-life (minutes) 2–6 h for po; 4–24 h for ip.
Data from Deiana et al. (2012).

were higher after CBG intraperitoneal compared to oral administration. Mice brain/plasma ratios were 0.77 and 0.15 for oral and intraperitoneal treatments, respectively, and in rats ratios were similar in the two administration routes (1.84 oral and 1.68 intraperitoneal).

Considerably broadening the knowledge of CBG pharmacology, Cascio, Gauson, Stevenson, Ross, and Pertwee (2010) conducted a set of experiments elucidating CBG ability to produce G-protein-coupled-receptor activation or blockade. CBG demonstrated partial agonism/antagonism at cannabinoid type-1 (CB_1R) and type-2 (CB_2R) receptors (Cascio et al., 2010; Gauson et al., 2007). Additionally, CBG has been demonstrated to act as an agonist for α2-adrenoceptors, but receptor subtypes selectivity awaits further elucidation. Like other α2-adrenoceptor ligands, CBG also binds at 5-hydroxytryptamine-1A receptors ($5HT_{1A}R$), acting as a neutral antagonist (Cascio et al., 2010).

At transient receptor potential (TRP) channels, CBG induced a TRPA1- but not TRPM8-mediated Ca^{++} elevation; however, it antagonized the menthol- or icilin-induced Ca^{++} elevation TRPM8-mediated (De Petrocellis et al., 2008). This effect was confirmed and expanded by pharmacological experiments using the botanical drug substance (BDS) CBG (De Petrocellis et al., 2011), derived from CBG-predominant genetically selected *Cannabis* plants. Notably, "CBG-free-CBG-BDS" was inactive, but when added to pure CBG, it became more potent and efficacious at antagonizing TRPM8 than CBG alone. This suggests a synergistic effect between CBG and noncannabinoids contained in its BDS. In cells overexpressing recombinant rat TRPV2 or human TRPV1, CBG also stimulated and then desensitized TRPV1 and TRPV2 (De Petrocellis et al., 2011).

CBG acts on several enzymes involved in prostaglandin production pathways. In an in vitro enzyme based cyclooxygenases (COX)-inhibition assay, it showed full inhibition of COX-1 and ~70% of COX-2. In tumor-necrosis-factor-α-stimulated human colon adenocarcinoma cell line HT29, CBG barely decreased prostaglandine-2 (PGE2) production (~5%) (Ruhaak et al., 2011). More potent activity has been seen in human rheumatoid synovial cells stimulated by the proinflammatory agent 12-0-tetradecanoylphorbol-13-acetate where CBG caused 90% inhibition of PGE2 release (Barrett, Gordon, & Evans, 1985).

CBG further modulates the inflammatory pathway by acting on phospholipase-A2 (PLA2), with high doses reducing its activity and low doses enhancing it (Evans, Formukong, & Evans, 1987). It is, therefore, hypothesized that CBG-mediated activation of PLA2, triggers the hydrolysis of phospholipids, inducing increase in arachidonic acid and subsequent inflammatory cascade (Fig 99.3). Vice versa, high doses of CBG may decrease the lipids metabolites, and hence PGE2 synthesis.

CBG-BDS was also shown to inhibit *N*-acylethanolamine acid amidase (NAAA), which hydrolyzes fatty-acid ethanolamides, such as *N*-palmitoylethanolamine (an endogenous antinociceptive and antiinflammatory fatty acid), anandamide cellular uptake, and monoacyl glycerol lipase (MAGL), which hydrolyze the endocannabinoid 2-arachidonoylglycerol and intracellular triglycerides to fatty-acids and glycerol. Pure CBG and the "CBG-free-CBG-BDS" were less potent than CBG-BDS, indicating that both cannabinoid and noncannabinoid substances present in the BDS might synergistically contribute to MAGL inhibition (De Petrocellis et al., 2011).

CBG was found to be active at L-type Ca^{++} and Na^{+} channels (Duncan et al., 2014), it demonstrated partial agonism at peroxisome proliferator-activated receptors (PPARγ), (Granja et al., 2012), and it inhibited the uptake of dopamine (Duncan et al., 2014), 5HT, norepinephrine (in rat hypothalamic synaptosomes) and GABA (in cerebrocortical synaptosomes) (Banerjee, Snyder, & Mechoulam, 1975); all these effects are not fully elucidated so far.

TABLE 99.2 Pharmacological Targets and Actions of Cannabigerol

Target	Action	Pharmacology	References
5HT uptake	Inhibition	K_i = 50 μM	Banerjee et al. (1975)
5HT1A	Antagonism	K_i = 50 μM	Cascio et al. (2010)
Anandamide cellular uptake	Inhibition	*(CBG-BDS)* IC50 = 11.3 μM	De Petrocellis et al. (2011)
CB1R	Partial agonism/antagonism	K_i = 440 nM; 381 nM	Gauson et al. (2007); Cascio et al. (2010)
CB2R	Partial agonism/antagonism	K_i = 337 nM; 2.6 μM	Gauson et al. (2007); Cascio et al. (2010)
COX1	Inhibition	*Not determined*	Ruhaak et al. (2011)
COX2	Inhibition	IC50 = $2.7 \cdot 10^{-4}$ M	Ruhaak et al. (2011)
Dopamine uptake	Inhibition		Duncan et al. (2014)
GABA uptake	Inhibition	K_i = 50 μM	Banerjee et al. (1975)
L Type Ca^{++} channels	Block	*Dihydropyridine site:* IC50 = 3.8 μM; K_i = 1.3 μM *Diltiazem site:* IC50 = 5.1 μM; K_i = 4.7 μM	Duncan et al. (2014)
MAGL	Inhibition	*(CBG-BDS)* IC50 = 24.6 μM	De Petrocellis et al. (2011)
Na^{++} channels	Block	*Site 2:* IC50 = 500 nM; K_i = 450 nM	Duncan et al. (2014)
NAAA	Inhibition	*(CBG-BDS)* IC50 = 18.3 μM	De Petrocellis et al. (2011)
NE uptake	Inhibition	K_i = 67 μM	Banerjee et al. (1975)
PGE2	Release inhibition	*Not determined*	Ruhaak et al. (2011); Barrett et al. (1985)
PLA2	High doses reduce activity; low doses enhance it	EC50 = 9.5 μM, IC50 = 55 μM	Evans et al. (1987)
PPARγ	Partial agonism	EC50 = 12.7 μM	Granja et al. (2012)
TRPA1	Stimulation + desensitization	EC50 = 0.7 μM; IC50 = 13 μM	De Petrocellis et al. (2011)
TRPM8	Antagonism	IC50 (against icilin 0.25 mM = 0.16 μM	De Petrocellis et al. (2011)
TRPV1	Stimulation + desensitization	EC50 = 1.3 μM; IC50 = 2.6 μM	De Petrocellis et al. (2011)
TRPV2	Stimulation + desensitization	EC50 = 1.72 μM; IC50 = 1.5 μM	De Petrocellis et al. (2011)
TRPV3	Stimulation + desensitization	EC50 = 1 μM; IC50 = 66.7 μM	De Petrocellis et al. (2012)
TRPV4	Stimulation + desensitization	EC50 = 5.1 μM; IC50 = 1.3 μM	De Petrocellis et al. (2012)
α2-Adrenoceptors	Agonism	EC50 = 0.2 nM	Cascio et al. (2010)

Cellular target, pharmacological action and values of CBG and/or CBG-BDS. BDS, Botanical drug substance; CBG, cannabigerol; CBR, cannabinoid receptor; EC50, half maximal effective concentration; IC50, half maximal inhibitory concentration; COX, cyclooxygenase; K_i, receptor-ligand inhibition constant; MAGL, monoacyl glycerol lipase; NAAA, *N*-acylethanolamine acid amidase; NE, norpinephrine; PPARs, peroxisome proliferator-activated receptors; PLA2, phospholipase-A2; PGE2, prostaglandin-E2; TRPA, transient receptor potential ankyrin; TRPM, transient receptor potential melastatin; TRPV, transient receptor potential vanilloid.
Data collected from several publications (see references in the table).

Table 99.2 summarizes CBG in vitro pharmacology as determined via different methodological approaches, which suggests caution in the direct comparison of individual data.

POTENTIAL MEDICAL USES OF CANNABIGEROL

Medical use of *Cannabis* has been recognized for millennia for the treatment of a multitude of conditions. Intrigued by its complex and diverse pharmacology, scientists are currently addressing renewed attention on CBG's therapeutic uses (Fig. 99.2).

Analgesia and Inflammation

There exists an increasing body of evidence from in vivo experiments showing that cannabinoids reduce sensitivity to pain.

Acting through inhibition of COX, nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely used drugs for the treatment of pain and inflammation. COXs catalyze the conversion of arachidonic acid into prostaglandins, hormone-like lipids responsible for homeostatic regulation of pathogenic mechanisms, including inflammatory response (Fig. 99.3). In this context, CBG may hold potential as an antiinflammatory agent by acting at different levels of

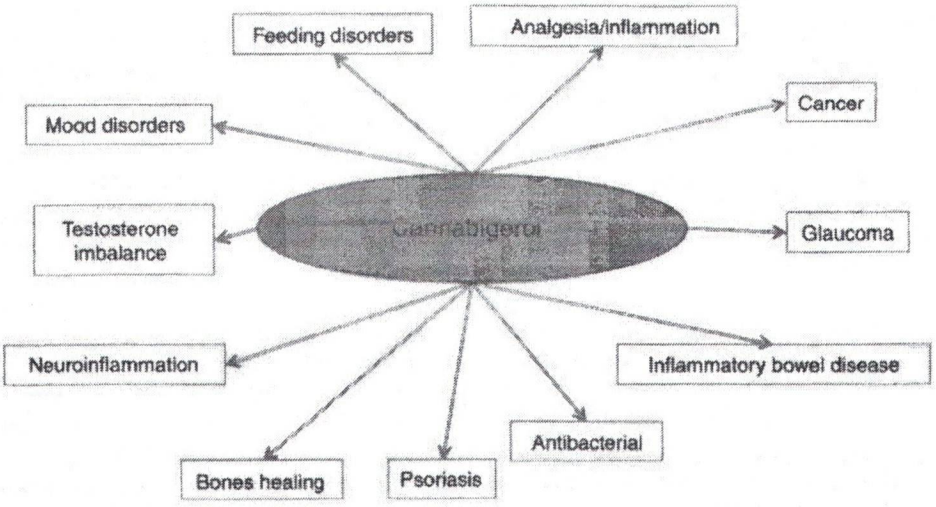

FIGURE 99.2 **Possible therapeutic applications of cannabigerol.** Cannabigerol has been suggested as a possible therapeutic agent for several conditions. To date, for most of these the exact mechanism of action awaits elucidation.

the prostaglandin synthesis pathway: by direct inhibition of PGE2 production, by inhibition of the upstream enzyme PLA2 and by unselective inhibition of the COX enzymes. Its inhibitory activity on MAGL, could also result in reduced prostaglandin synthesis by inhibiting 2-arachidonilglycerol conversion into arachidonic acid.

Data from in vivo experiments showed that CBG was more potent, although less maximally effective, than THC and aspirin in the phenyl benzoquinone (PBQ) model of peripheral inflammatory pain (Formukong, Evans, & Evans, 1988). CBG showed 61% maximum percent inhibition of PBQ-induced writhing behavior in mice with an ED50 = 1.26 mg/kg, a remarkable effect especially in comparison with Aspirin (65%, ED50 = 15 mg/kg) or THC (100%, ED50 = 25 mg/kg).

CBG agonism at α2-adrenoceptor triggered in vivo investigations of its analgesic effects. Comelli et al. (2012) integrated computational and pharmacological studies where the three-dimensional structures of α2A, α2B, and α2C isoforms of murine and human adrenoceptors were modeled by comparative techniques and molecular dynamics simulations. In this computational model, CBG affinity for the receptor appeared higher than that of the α2-adrenoceptor-agonist clonidine. Measured in behavioral models of acute inflammatory pain, CBG dose-dependently reduced the first and second nocifensive phases associated with intraplantar-injection of formalin and reduced λ-carrageenan-evoked hypersensitivity. Both models are α2-adrenoceptor-mediated, as they are blocked by the α2-adrenoceptor-antagonist yohimbine.

Although, to date, there are no supportive in vivo studies, it is interesting to note that CBG is active at the analgesic targets: $5HT_{1A}$Rs, TRPVA1, TRPM8, TRPV2, NAAA, and MAGL. Definitive analgesic efficacy of CBG through these pathways has not yet been reported (Fig. 99.3).

Notably, in 2012, at the 14th World Congress on Pain, CBG was highlighted as one of the phytocannabinoids that may have therapeutic effects on pain (Canadian Consortium for the Investigation of Cannabinoids, 2012).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) describes a group of inflammatory conditions of the colon and intestine caused by dysregulated immune response. It primarily includes ulcerative colitis limited to the colon, and Crohn disease, which can affect any section of the gastrointestinal tract.

TRP channels play a role in gastrointestinal inflammation as they function as sensors of innocuous and noxious chemical/physical stimuli; indeed, they are involved in the antiinflammatory effects of phytocannabinoids in in vivo models of intestinal inflammation (De Petrocellis et al., 2012). In a model of intestinal inflammation induced by the irritant croton oil, CBG exerted a significant TRPV3-mediated elevation of intracellular Ca^{++} with an efficacy (determined by comparing its effect with the analogous effect observed with 4 μM ionomycin, a Ca^{2+} ionophore that mobilizes intracellular calcium stores), lower (18%) and a potency higher (EC50 = 1 μM) than that of typical TRPV3 agonist carvacrol (41.4% and EC50 = 547 μM). When administered 5 min earlier, CBG also desensitized TRPV3 to carvacrol-mediated cell stimulation (IC50 = 66.7 μM).

CBG induced a significant TRPV4-mediated elevation of intracellular Ca^{++} with low efficacy (23.7% of the effect of ionomycin) and medium-low potency (5.1 μM). Despite its low efficacy, CBG desensitized TRPV4 to the action of its agonist 4αPDD with an EC50 value lower than that at which it activates it at low efficacy (De Petrocellis et al., 2012).

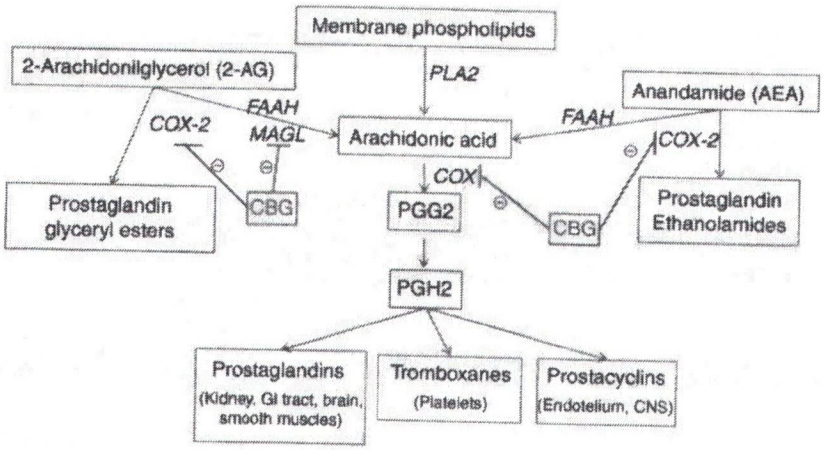

FIGURE 99.3 **Cannabigerol in prostaglandin biosynthesis.** In inflammatory processes arachidonic acid is produced by phospolipase-A2 (PLA2) from membrane phospholipids and it is then metabolized by COX into the instable prostaglandine-G2 (PGG2) which is then converted into prostaglandin-H2 (PGH2). Depending on the tissue, PGH2 is converted into prostaglandins, tromboxanes and prostacyclines. 2-Arachidonilglycerol and anandamide are also substrates of the COX-2, and are metabolized into prostaglandin-glycerol ester and prostaglandin-ethanolamide, respectively. Nonsteroidal antiinflammatory drugs (NSAIDs) and cannabigerol (CBG) inhibit COX and MAGL thereby reducing prostaglandin production. *GI*, gastrointestinal tract; *CNS*, central nervous system. *Source: Information collected from Alhouayek and Muccioli (2014).*

If also in vivo CBG desensitizes TRPV to endogenous stimuli and at doses lower than that required to activate them, its use as a TRPV desensitizer might be employed to develop novel therapies for diseases associated to altered TRPV activity.

In a dinitrobenzene sulfonic acid (DNBS) model of murine colitis, CBG showed protective and curative effects by reducing colon weight/length ratio (an indicator of the inflammatory response severity), it reduced DNBS-induced overexpression of the inducible nitric oxide synthase (iNOS), but not of COX-2. In lipopolysaccharide-activated macrophages, it inhibited nitric oxide production and iNOS protein overexpression. DNBS induced an increase in colonic interleukin-1β and interferon-γ and a decrease in interleukin-10 levels; these alterations were all counteracted by CBG. Finally, CBG restored the DNBS-induced decrease of superoxide-dismutases thus restoring antioxidant protection in intestinal epithelial cells (Borrelli et al., 2013).

Neuroinflammation in Multiple Sclerosis

Neuroinflammation is a component of disorders, such as multiple sclerosis (MS), Alzheimer and Parkinson diseases. It can be initiated as a response to traumatic brain injury, infections, aging, toxic metabolites, or autoimmunity. Acute neuroinflammation involves a rapid activation of microglia and no peripheral immunoresponse. In chronic inflammation, the microglia induces a sustained production of inflammatory modulators that may alter the integrity of the BBB, and recruit peripheral immune cells for inflammatory responses, leading to neuronal dysfunction/neurodegeneration.

In MS, a chronic inflammatory demyelinating disease, microglial activation contributes to the pathology through secretion of proinflammatory mediators.

Effects of CBG and its quinone derivate, VCE-003 (obtained by CBG oxidation), on neuroinflammation have been investigated and they both revealed neuroprotective action by preventing glutamate-induced cell viability decline. In the Theiler's murine encephalomyelitis virus (TMEV) model of MS, VCE-003 improved the motor functions, and locomotor activity was restored to normal levels. VCE-003 also reduced microglia reactivity in the spinal cord of TMEV-infected mice, it outperformed CBG in terms of capacity to inhibit cytokine release, and was as efficient as CBG at inhibiting the release of PGE2 (Granja et al., 2012).

Extending the studies on VCE-003, recently, the same group reported that in the autoimmune model of MS (EAE), VCE-003 attenuated EAE by activating CBR_2 and PPARs. A reduction of CD4+ and T cells infiltrates, inhibition of Th1 and Th17 (T-helper cells involved in different stages of the pathogenesis of autoimmune diseases, including MS) responses in the spinal cord of VCE-003-treated mice, a decreased microglial activation, a structural protection of myelin sheets and reduced axonal damage were reported (Carrillo-Salinas et al., 2014).

Taken together, these data support a potential therapeutic use of quinone derivate of CBG for the treatment of human immune diseases with inflammatory and autoimmune components, such as MS.

Cancer

Cannabinoids are used in the treatment of nausea and vomiting associated with chemotherapy. Their use in oncology is currently receiving increasing interest

as they inhibit the growth of various cancer cell types, inducing apoptosis, cell-cycle arrest, cell growth inhibition, and affecting angiogenesis, and cell migration (Guzman, 2003).

Like other phytocannabinoids, CBG was reported to reduce cell proliferation in several cancer cell lines, including human breast, prostate, colorectal carcinoma, gastric adenocarcinoma, C6-rat glioma, rat basophilic leukemia, and transformed thyroid cells (Ligresti et al., 2006). Interestingly, prostate carcinoma cells were found to be unresponsive to most phytocannabinoids, only CBD and CBG elicited antiproliferative effects.

Although the exact mechanism of action is not fully elucidated, TRPV1, TRPV2, and TRPM8 are involved in prostate cancer, all being CBG-sensitive channels. Specifically, TRPV1 agonist capsaicin induces antiproliferative and proapoptotic effects on prostate cancer cells (PCCs) (Diaz-Laviada, 2010), TRPV2 activation stimulates PCCs migration (Gkika & Prevarskaya, 2011), whereas TRPM8 is overexpressed in androgen-dependent PCCs, and TRPM8 antagonists have been suggested as being effective during the early androgen–responsive stage of prostate cancers (Liu & Qin, 2011). These findings suggest CBG as a relevant agent for prostate cancer since it antagonizes TRPM8 channels and activates/desensitize TRPV2 and TRPV1 (De Petrocellis et al., 2011). In line with this, together with other phytocannabinoids, CBG showed to inhibit PCCs viability in androgen receptors-positive and receptors-negative PCC lines (De Petrocellis et al., 2013). Moreover, CBG activated the proapoptotic proteases caspase3/7 under conditions of serum deprivation and it increased intracellular Ca^{++} (indicating endoplasmic reticulum stress) in PCC lines. It is therefore suggested that phytocannabinoids and, albeit at lower potency/efficacy, CBG can retard PCC proliferation, and cause apoptosis.

CBG showed the greatest growth-inhibitory activity against human oral epitheloid carcinoma cell lines and fibroblasts, when compared to olivetol, geraniol, and cannabinol-methyl-ether (Baek et al., 1998). Although CBG was not the most potent phytocannabinoid, it demonstrated antiproliferative action in human breast cancer cells (McAllister, Christian, Horowitz, Garcia, & Desprez, 2007) and mouse skin melanoma cells (Baek, Han, Yook, Kim, & Kwak, 1996).

The exact mechanism by which CBG acts against cancer remains to be elucidated, and further research is required; however, mounting evidence suggests that this phytocannabinoid possesses several properties, which may counteract cancer cell proliferation.

Mood Disorders

The endocannabinoid system has bidirectional influence on anxiety; its inhibition results in anxiogenic responses, while a moderate increase leads to anxiolytic effects. Anandamide itself possesses a bidirectional profile, acting as an anxiolytic agent at CB_1R, and an anxiogenic at TRPV1 (Rubino et al., 2008).

The CB_1R inverse agonist/antagonist, rimonabant, marketed in the past as an antiobesity drug, was withdrawn as chronic administration induced undesirable anxious and depressive-like states along with suicide (Janero & Makriyannis, 2009).

This discovery sparked interest in the role of cannabinoids in anxiety/depression and a number of studies addressed this subject.

O'Brien et al. (2013) recently investigated acute and chronic effects of CGB in rats in the light/dark immersion model of anxiety-like behavior and in a test of palatability processing for depression-like behavior, that is, the saccharin hedonic reactions in the taste reactivity test. While CBG revealed no effects in the light/dark test, its acute administration produced a slight enhancement of saccharin palatability, indicative of possible antidepressant effect.

El-Alfy et al. (2010) found 20 and 80 mg/kg CBG ineffective in mice locomotor activity, catalepsy, body temperature, and nociception and in the forced swimming test (assessing depression-like behavior). However, in a different study performed in mouse the tail suspension test, CBG (40 mg/kg) reduced the time spent immobile (which in this test is interpreted as a predictor of antidepressant activity), with effects comparable to the antidepressant imipramine (Musty & Deyo, 2006).

Following this finding, the same authors filed several US patents (the latest in 2014: *US20,140,039,043-A1*) claiming the use of CBG for mood disorders, preferably in depression.

Other Potential Medical Uses of Cannabigerol

Further expanding the knowledge on its potential medical uses, CBG effects on rats' feeding behavior have been investigated, revealing to be ineffective when tested at doses up to 17.6 mg/kg (Farrimond, Whalley, & Williams, 2012). In a later study, higher doses of CBG (120 and 240 mg/kg) induced a dose-dependent increase of food intake, number of meals, a decrease of latency to first meal and an enhanced locomotor activity suggesting that at higher doses, CBG stimulates appetite, and enhances consummatory feeding behavior (Brierley, Whalley, & Williams, 2013). Preliminary results also indicate that pure CBG (120 mg/kg) can attenuate weight loss induced by the chemotherapy agent cisplatin (Brierley et al., 2015). Given these findings, CBG was suggested to be useful for feeding disorders associated with chemotherapy but also for the treatment of weight loss in cancer anorexia-cachexia syndrome.

CBG was found to inhibit testosterone synthesis in rat testis Leydig cells more potently than THC (Jakubovic, McGeer, & McGeer, 1979; Burstein, Hunter, & Sedor, 1980). Testosterone lowering medicaments (TLM) are often prescribed for men with prostate cancer, hypersexuality, male contraception, gender reassignment. For women, TLM are prescribed for severe cases of acne, amenorrhea, seborrhea, hirsutism, androgenic alopecia, and hyperandrogenism. TLM are also administered in sex offender treatment, in addition to psychotherapy (Turner, Basdekis-Jozsa, & Briken, 2013).

CBG effects on skin conditions have also been explored. Psoriasis is an inflammatory skin disease characterized by epidermal keratinocyte hyperproliferation paralleled by increased expression of skin proinflammatory mediators. CBG inhibited keratinocyte proliferation in a CB_1/CB_2-receptors-independent manner, and with a greater potency than THC, suggesting a possible therapeutic use for psoriasis (Wilkinson & Williamson, 2007). Effects of CBG on the epigenetic regulation of epidermal differentiation genes have been investigated and CBG acted as transcriptional repressors controlling cell proliferation and differentiation by increasing DNA methylation of keratin-10 gene in a CBR-independent mechanism (Pucci et al., 2013).

Acting through an indirect mechanism regulated by accessory cells, CBG stimulated recruitment of quiescent mesenchymal stem cells (MSCs) in bone marrow (Scutt & Williamson, 2007). The induction of MSC migration by suitable agents, such as in this example CBG, could represent an attractive cell-based therapy to treat osteoporosis and bone regeneration issues by accelerating healing and/or regeneration.

A number of cannabinoids have been shown to reduce intra ocular pressure (IOP) in a CBR-mediated mechanism (Oltmanns et al., 2008). CBG's chronic and, although to a lesser extent, acute administration reduced ocular tension in cats such that IOP of CBG-treated eyes resulted in 4–8 mmHg lower than untreated contralateral eyes (Colasanti, Craig, & Allara, 1984). Additionally, CBG was devoid of ocular toxicity and neurotoxicity, it did not change overall brain electrical activity, but it prolonged the onset of sleep/REM sleep. Possessing such IOP lowering action, CBG may be a possible candidate for the treatment of glaucoma.

CBG possesses antibacterial properties (Mechoulam & Gaoni, 1965) with activity against gram-positive bacteria, mycobacteria, and fungi superior to that of THC, CBD, and CBC (Eisohly, Turner, Clark, & Eisohly, 1982). Additionally, CBG has potent activity against various methicillin-resistant *Staphylococcus aureus* strains of current clinical relevance (Appendino et al., 2008). Finally, and importantly, CBG (1, 3, 10 mg/kg) showed low potential abuse when assessed in a rat model of drug discrimination (Duncan et al., 2014).

CONCLUSIONS

CBG owns a broad pharmacological profile stimulating interest on this nonpsychotropic phytocannabinoid as a potential polydrug or as a starting molecular structure for chemical engineering aimed at developing more selective/potent drugs.

The expanding knowledge on its multifaceted pharmacology allowed intercepting numerous possible medical uses inspiring several attempts to patent its pharmaceutical use for a number of conditions. Among all, its antiinflammatory and anticancer properties stimulated tremendous interest pointing CBG as a possible candidate in the development of novel drugs to prevent, control, and treat conditions where pathological inflammatory responses and abnormal cell proliferation represent a threat.

While the recent research finding summarized in this chapter highlighted the vast potentials of CBG, it is clear that extensive work is needed before its clinical benefits can be definitively stated. Decisive is the fact that, currently, there is no material on CBG pharmacokinetics/pharmacodynamics in humans, and clinicians should remain cautious until more definite studies demonstrate the safety and efficacy of CBG. Further pharmacological and preclinical experiments, together with human toxicological and proof of concept studies, should be performed to confirm the number of reports suggesting CBG value in medical practice.

MINI-DICTIONARY

Botanical drug substance (BDS) Botanical unrefined material from the *Cannabis* plant where a specific cannabinoid, in this case CBG, has at least 95% purity. The amount of the main cannabinoid in the corresponding BDS, expressed as a %w/w of extract, is used to calculate the amount of BDS necessary to achieve the equimolar amount of the corresponding pure cannabinoid. Cannabinoid and noncannabinoid components of the BDS are always identified, and vary between different BDS. "CBG-free CBG BDS" is a BDS extracted from a CBG-predominant *Cannabis* plant virtually devoid (but it may still contain traces) of CBG.

Cyclooxygenase (COX) The enzyme that catalyzes the biosynthesis of prostaglandins from arachidonic acid, produced on demand from arachidonate through PLA2. Two isoforms of the COX exist: COX-1 is constitutively expressed in the gastrointestinal tract, kidneys, and platelets, and it regulates the prostaglandins responsible for the integrity of the gastric mucosa, for the normal platelet function and for the regulation of renal blood flow. COX-2 is expressed in immune system cells, and is inducible by inflammatory stimuli, thereby producing prostaglandins mediating inflammation, pain, and fever.

Transient receptor potential (TRP) Ligand-gated cation channels are a group of ion channels found in the plasma membrane of several cell types mediating a multiplicity of sensations including hotness, pain, warmth or coldness, tastes, pressure, and vision. Endogenous lipids modulate TRP channel activity by direct binding, acting as endogenous ligands. Endocannabinoids interact with several types of TRP channels.

TRP ankyrin 1 (TRPA1) Expressed in trigeminal and dorsal root ganglia neurons. It is activated by low temperatures (17°C), mustard oil, and environmental irritants, such as unsaturated aldehydes, causing painful burning sensation. Its function in cold transduction is still debated; it contributes to inflammatory hypersensitivity, vasodilation, and nociception to irritants.
TRP melastatin 8 (TRPM8) Expressed in nociceptive and nonnociceptive neurons and it is gated by medium–low (25°C) temperatures, as well as chemical cooling agents, such as spearmint, menthol, and eucalyptol. Anandamide binds to TRPM8. Above its role in nociception, which is to date still under discussion, TRPM8 channel has been linked with cancer cell proliferation.
TRP vanilloid type 1 (TRPV1) Activated by heat temperatures (42°C) and basic pH (5.9). Anandamide binds this channel, and CBG activates and desensitizes TRPV1 being this responsible for some of CBG analgesic and antiinflammatory actions.
TRPV type 2 Shares nearly 50% DNA sequence identity with TRPV1, but unlike TRPV1, it is not modulated by vanilloids. It is activated by high temperatures (~52°C), physical stimuli, such as mechanical stretch, osmotic swelling, and modulators, such as hormones, growth factors, chemotactic peptides, lysophospholipids, and cannabinoids. Its physiological role remains one of the most controversial. It has been proposed to be involved in the transduction of high-temperature heat responses in sensory ganglia and to function as a noxious heat thermosensor. However, TRPV2-knockout mice show normal sensory transduction, suggesting that TRPV2 does not function as a noxious heat and mechanical sensor and that it has other, as yet unknown, functions. *Cannabis* derivatives are the most potent TRPV2 activators.

References

Alhouayek, M., & Muccioli, G. G. (2014). COX-2-derived endocannabinoid metabolites as novel inflammatory mediators. *Trends in Pharmacological Sciences, 35*, 284–292.

Appendino, G., Gibbons, S., Giana, A., Pagani, A., Grassi, G., Stavri, M., Smith, E., & Rahman, M. M. (2008). Antibacterial cannabinoids from *Cannabis sativa*: a structure-activity study. *Journal of Natural Products, 71*, 1427–1430.

Baek, S. H., Han, D. S., Yook, C. N., Kim, Y. C., & Kwak, J. S. (1996). Synthesis and antitumor activity of cannabigerol. *Archives of Pharmacal Research, 19*(3), 228–230.

Baek, S. H., Kim, Y. O., Kwag, J. S., Choi, K. E., Jung, W. Y., & Han, D. S. (1998). Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII). Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells. *Archives of Pharmacal Research, 21*, 353–356.

Banerjee, S. P., Snyder, S. H., & Mechoulam, R. (1975). Cannabinoids: influence on neurotransmitter uptake in rat brain synaptosomes. *Journal of Pharmacology and Experimental Therapeutics, 194*, 74–81.

Barrett, M. L., Gordon, D., & Evans, F. J. (1985). Isolation from *Cannabis* sativa L. of cannflavin—a novel inhibitor of prostaglandin production. *Biochemical Pharmacology, 34*, 2019–2024.

Borrelli, F., Fasolino, I., Romano, B., Capasso, R., Maiello, F., Coppola, D., Orlando, P., Battista, G., Pagano, E., Di Marzo, V., & Izzo, A. A. (2013). Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. *Biochemical Pharmacology, 85*, 1306–1316.

Brierley, D. I., Whalley, B. J., & Williams, C. M. (2013). Modulation of feeding behaviour by the non-psychoactive phytocannabinoid cannabigerol. *Proceedings of Pharmacology 2013*. London: British Pharmacological Society. Available from: http://www.pa2online.org/abstracts/vol11issue3abst067p.pdf

Brierley, D. I., Harman, J. R., Giallourou, N., Swann, J. R., Patel, K., Whalley, B. J., & Williams C. M. (2015). Cannabigerol attenuates muscle catabolism and anorexia In a pre-clinical model of chemotherapy-induced cachexia. *Twenty-fifth annual symposium of the international cannabinoid research society*. June 28 – July 3, 2015. P 10. Wolfville, Nova Scotia.

Burstein, S., Hunter, S. A., & Sedor, C. (1980). Further studies on the inhibition of Leydig cell testosterone production by cannabinoids. *Biochemical Pharmacology, 29*, 2153–2154.

Canadian Consortium for the Investigation of Cannabinoids (2012). Cannabinoids & pain. The state of the art, the state of the science White Paper. *Official satellite symposium of the fourteenth world congress on pain*, August 25, 2012. Milan, Italy.

Carrillo-Salinas, F. J., Navarrete, C., Mecha, M., Feliu, A., Collado, J. A., Cantarero, I., Bellido, M. L., Muñoz, E., & Guaza, C. (2014). A cannabigerol derivative suppresses immune responses and protects mice from experimental autoimmune encephalomyelitis. *PLoS One, 9*, e94733.

Cascio, M. G., Gauson, L. A., Stevenson, L. A., Ross, R. A., & Pertwee, R. G. (2010). Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent $5HT_{1A}$ receptor antagonist. *British Journal of Pharmacology, 159*, 129–141.

Colasanti, B. K., Craig, C. R., & Allara, R. D. (1984). Intraocular pressure, ocular toxicity and neurotoxicity after administration of cannabinol or cannabigerol. *Experimental Eye Research, 39*, 251–259.

Comelli, F., Filippi, F., Papaleo, E., De Gioia, L., Pertwee, R. G., & Costa, B. (2012). Evidence that the phytocannabinoid cannabigerol can induce antinociception by activating α2-adrenoreceptors: a computational and a pharmacological study. *Twenty-second annual symposium of the international cannabinoid research society* (p. 44), July 22–27, 2012. Freiburg im Breisgau, Germany.

de Meijer, E. P. (2004). The breeding of Cannabis cultivars for pharmaceutical end-uses. In G. W. Guy, B. A. Whittle, & P. J. Robson (Eds.), *The medicinal uses of Cannabis and cannabinoids* (pp. 55–69). London, UK: Pharmaceutical Press.

de Meijer, E. P., & Hammond, K. M. (2005). The inheritance of chemical phenotype in *Cannabis sativa* L. (II): cannabigerol predominant plants. *Euphytica, 145*, 189–198.

De Petrocellis, L., Vellani, V., Schiano-Moriello, A., Marini, P., Magherini, P. C., Orlando, P., & Di Marzo, V. (2008). Plant-derived cannabinoids modulate the activity of transient receptor potential channels of ankyrin type-1 and melastatin type-8. *Journal of Pharmacology and Experimental Therapeutics, 325*, 1007–1015.

De Petrocellis, L., Ligresti, A., Moriello, A. S., Allara, M., Bisogno, T., Petrosino, S., Stott, C. G., & Di Marzo, V. (2011). Effects of cannabinoids and cannabinoid-enriched *Cannabis* extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology, 163*, 1479–1494.

De Petrocellis, L., Orlando, P., Moriello, A. S., Aviello, G., Stott, C., Izzo, A. A., & Di Marzo, V. (2012). Cannabinoid actions at TRPV channels: effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. *Acta Physiologica (Oxford), 204*, 255–266.

De Petrocellis, L., Ligresti, A., Schiano, M. A., Iappelli, M., Verde, R., Stott, C. G., Cristino, L., Orlando, P., & Di Marzo, V. (2013). Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. *British Journal of Pharmacology, 168*, 79–102.

Deiana, S. (2013). Medical use of *Cannabis*. Cannabidiol: a new light for schizophrenia? *Drug Testing and Analysis, 5*, 46–51.

Deiana, S., Watanabe, A., Yamasaki, Y., Amada, N., Arthur, M., Fleming, S., Woodcock, H., Dorward, P., Pigliacampo, B., Close, S., Platt, B., & Riedel, G. (2012). Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Δ^9-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behaviour. *Psychopharmacology (Berlin), 219*(3), 859–873.

Díaz-Laviada, I. (2010). Effect of capsaicin on prostate cancer cells. *Future Oncology, 6*, 1545–1550.

Duncan, M., Cascio, M. G., Pertwee, R. G., Riedel, G., Amada, N., & Yamasaki, Y. (2014). Pharmacological properties of pure cannabigerol and botanical drug substance. *Twenty-fourth annual symposium*

of the international cannabinoid research society, 28 June–3 July 2014 (pp. P3–36). Baveno, Italy.

Eisohly, H. N., Turner, C. E., Clark, A. M., & Eisohly, M. A. (1982). Synthesis and antimicrobial activities of certain cannabichromene and cannabigerol related compounds. *Journal of Pharmaceutical Sciences, 71*, 1319–1323.

El-Alfy, A. T., Ivey, K., Robinson, K., Ahmed, S., Radwan, M., Slade, D., Khan, I., ElSohly, M., & Ross, S. (2010). Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from *Cannabis sativa* L. *Pharmacology Biochemistry and Behavior, 95*, 434–442.

Evans, A. T., Formukong, E., & Evans, F. J. (1987). Activation of phospholipase A2 by cannabinoids. Lack of correlation with CNS effects. *FEBS Letters, 211*, 119–122.

Farrimond, J. A., Whalley, B. J., & Williams, C. M. (2012). Cannabinol and cannabidiol exert opposing effects on rat feeding patterns. *Psychopharmacology (Berlin), 223*, 117–129.

Formukong, E. A., Evans, A. T., & Evans, F. J. (1988). Analgesic and antiinflammatory activity of constituents of *Cannabis sativa* L. *Inflammation, 12*, 361–371.

Gaoni, Y., & Mechoulam, R. (1964). The structure and synthesis of cannabigerol, a new hashish constituent. *Proceedings of the Chemical Society*, 82–83.

Gaoni, Y., & Mechoulam, R. (1966). Cannabichromene, a new active principle in hashish. *Chemical Communications, 1*, 20–21.

Gauson, L. A., Stevenson, L. A., Thomas, A., Baille, G. L., Ross, R. A., & Pertwee, R. G. (2007). Cannabigerol behaves as a partial agonist at both CB1 and CB2 receptors. *Symposium on the Cannabinoids*, 26 June–1 July, 2007 (pp. 206). St-Sauveur, Canada: International Cannabinoid Research Society.

Gkika, D., & Prevarskaya, N. (2011). TRP channels in prostate cancer: the good, the bad and the ugly? *Asian Journal of Andrology, 13*, 673–676.

Granja, A. G., Carrillo-Salinas, F., Pagani, A., Gomez-Canas, M., Negri, R., Navarrete, C., Mecha, M., Mestre, L., Fiebich, B. L., Cantarero, I., Calzado, M. A., Bellido, M. L., Fernandez-Ruiz, J., Appendino, G., Guaza, C., & Muñoz, E. (2012). A cannabigerol quinone alleviates neuroinflammation in a chronic model of multiple sclerosis. *Journal of Neuroimmune Pharmacology, 7*, 1002–1016.

Guzman, M. (2003). Cannabinoids: potential anticancer agents. *Nature Reviews Cancer, 3*, 745–755.

GW Pharmaceuticals (2014). *GW Breeding programme*. http://www.gwpharm.com/cultivation.aspx

Hill, A. J., Williams, C. M., Whalley, B. J., & Stephens, G. J. (2012). Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacology and Therapeutics, 133*, 79–97.

Iversen, L. (2007). *The science of* Cannabis (2nd ed.). Oxford, UK: Oxford University Press.

Jakubovic, A., McGeer, E. G., & McGeer, P. L. (1979). Effects of cannabinoids on testosterone and protein synthesis in rat testis Leydig cells in vitro. *Molecular and Cellular Endocrinology, 15*, 41–50.

Janero, D. R., & Makriyannis, A. (2009). Cannabinoid receptor antagonists: pharmacological opportunities, clinical experience, and translational prognosis. *Expert Opinion on Emerging Drugs, 14*, 43–65.

Ligresti, A., Moriello, A. S., Starowicz, K., Matias, I., Pisanti, S., De Petrocellis, L., Laezza, C., Portella, G., Bifulco, M., & Di Marzo, V. (2006). Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *Journal of Pharmacology and Experimental Therapeutics, 318*, 1375–1387.

Liu, Y., & Qin, N. (2011). TRPM8 in health and disease: cold sensing and beyond. *Advances in Experimental Medicine and Biology, 704*, 185–208.

Marks, M. D., Tian, L., Wenger, J. P., Omburo, S. N., Soto-Fuentes, W., He, J., Gang, D. R., Weiblen, G. D., & Dixon, R. A. (2009). Identification of candidate genes affecting Delta9-tetrahydrocannabinol biosynthesis in *Cannabis sativa*. *Journal of Experimental Botany, 60*, 3715–3726.

McAllister, S. D., Christian, R. T., Horowitz, M. P., Garcia, A., & Desprez, P. Y. (2007). Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. *Molecular Cancer Therapeutics, 6*, 2921–2927.

Mechoulam, R., & Gaoni, Y. (1965). Hashish. IV. The isolation and structure of cannabinolic, cannabidiolic, and cannabigerolic acids. *Tetrahedron, 21*, 1223–1229.

Musty, R. & Deyo, R. (2006). A cannabigerol extract alters behavioral dispair in an animal model of depression. *In Sixteenth annual symposium of the international cannabinoid research society*, (p. 32), 24–28. Tihany, Hungary.

O'Brien, L. D., Wills, K. L., Segsworth, B., Dashney, B., Rock, E. M., Limebeer, C. L., & Parker, L. A. (2013). Effect of chronic exposure to rimonabant and phytocannabinoids on anxiety-like behavior and saccharin palatability. *Pharmacology Biochemistry and Behavior, 103*, 597–602.

Oltmanns, M. H., Samudre, S. S., Castillo, I. G., Hosseini, A., Lichtman, A. H., Allen, R. C., Lattanzio, F. A., & Williams, P. B. (2008). Topical WIN55212-2 alleviates intraocular hypertension in rats through a CB1 receptor mediated mechanism of action. *Journal of Ocular Pharmacology and Therapeutics, 24*, 104–115.

Pucci, M., Rapino, C., Di, F. A., Dainese, E., D'Addario, C., & Maccarrone, M. (2013). Epigenetic control of skin differentiation genes by phytocannabinoids. *British Journal of Pharmacology, 170*, 581–591.

Rubino, T., Realini, N., Castiglioni, C., Guidali, C., Vigano, D., Marras, E., Petrosino, S., Perletti, G., Maccarrone, M., Di Marzo, V., & Parolaro, D. (2008). Role in anxiety behavior of the endocannabinoid system in the prefrontal cortex. *Cerebral Cortex, 18*, 1292–1301.

Ruhaak, L. R., Felth, J., Karlsson, P. C., Rafter, J. J., Verpoorte, R., & Bohlin, L. (2011). Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from *Cannabis sativa*. *Biological and Pharmaceutical Bulletin, 34*, 774–778.

Scutt, A., & Williamson, E. M. (2007). Cannabinoids stimulate fibroblastic colony formation by bone marrow cells indirectly via CB2 receptors. *Calcified Tissue International, 80*, 50–59.

Taura, F., Morimoto, Y., Shoyama, Y., & Mechoulam, R. (1995). First direct evidence for the mechanism of delta-1-tetrahydrocannabinolic acid biosynthesis. *Journal of the American Chemical Society, 38*, 9766–9767.

Taura, F., Morimoto, S., & Shoyama, Y. (1996). Purification and characterization of cannabidiolic-acid synthase from *Cannabis sativa* L. Biochemical analysis of a novel enzyme that catalyzes the oxidocyclization of cannabigerolic acid to cannabidiolic acid. *Journal of Biological Chemistry, 271*, 17411–17416.

Turner, D., Basdekis-Jozsa, R., & Briken, P. (2013). Prescription of testosterone-lowering medications for sex offender treatment in German forensic-psychiatric institutions. *Journal of Sexual Medicine, 10*, 570–578.

Wilkinson, J. D., & Williamson, E. M. (2007). Cannabinoids inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and have a potential therapeutic value in the treatment of psoriasis. *Journal of Dermatological Science, 45*, 87–92.

Zuardi, A. W., Crippa, J. A., Hallak, J. E., Bhattacharyya, S., Atakan, Z., Martin-Santos, R., McGuire, P. K., & Guimarães, F. S. (2012). A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation. *Current Pharmaceutical Design, 18*(32), 5131–5140.