Chapter 9
The Pharmacology and Therapeutic Potential of Plant Cannabinoids

Maria Grazia Cascio, Roger G. Pertwee and Pietro Marini

Abstract The plant *Cannabis sativa* has been widely used by humans over many centuries as a source of fibre, for medicinal purposes, for religious ceremonies and as a recreational drug. Since the discovery of its main psychoactive ingredient, Δ^9-tetrahydrocannabinol (THC), significant progress has been made towards the understanding (1) of the in vitro and in vivo pharmacology both of THC and of certain other cannabis-derived compounds, and (2) of the potential and actual uses of these "phytocannabinoids" as medicines. There is now extensive evidence that the pharmacological effects of some widely-studied phytocannabinoids, are due to their ability to interact with cannabinoid receptors and/or with other kinds of pharmacological targets, including non-cannabinoid receptors, and this makes the pharmacology of the phytocannabinoids rather complex and interesting. In this chapter, we provide an overview of the in vitro pharmacology of five selected phytocannabinoids and report findings that have identified potential new therapeutic uses for these compounds.

Abbreviations

THC	Tetrahydrocannabinol
CBD	Cannabidiol
CBG	Cannabigerol
THCV	Tetrahydrocannabivarin
CBC	Cannabichromene
CBDV	Cannabidivarin
CBDA	Cannabidiolic acid
CBGV	Cannabigerovarin
CBGA	Cannabigerolic acid
THCA	Tetrahydrocannabinolic acid
THCVA	Tetrahydrocannabivarinic acid

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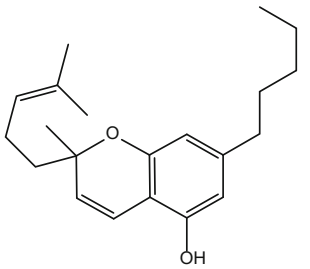
TRP	Transient receptor potential
PPAR	Peroxisome-proliferator activated receptor
GPCR	G-protein coupled receptor
CB	Cannabinoid
HT	Hydroxytryptamine
8-OH-DPAT	8-hydroxy-2-(di-n-propylamino)-tetralin
HU-201	6a*R*,10a*R*)- 9-(Hydroxymethyl)- 6,6-dimethyl- 3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo [c]chromen- 1-ol
WIN55212	[2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-*de*]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate
CP55940	(-)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol
GTPγS	Guanosine 5′-O-[gamma-thio]triphosphate)
AMP	Adenosine monophosphate
ERK	Extracellular signal-regulated kinases
CHO	Chinese hamster ovary
NAM	Negative allosteric modulator
SR141716A	*N*-(Piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide hydrochloride
WAY100135	(*S*)-*N*-*tert*-Butyl-3-(4-(2-methoxyphenyl)-piperazin-1-yl)-2-phenylpropanamide dihydrochloride
WAY100635	*N*-[2-[4-(2-Methoxyphenyl)-1-piperazinyl]ethyl]-*N*-2-pyridinylcyclohexanecarboxamide maleate
AM251	*N*-(Piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide

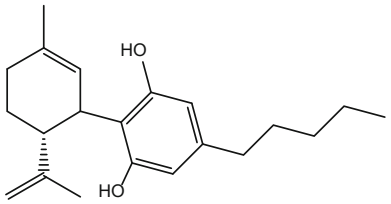
9.1 Introduction

The term “plant cannabinoids” refers not only to the chemical substances isolated from *Cannabis sativa* possessing the typical C21 terpenophenolic skeleton, but also to their derivatives and transformation products.

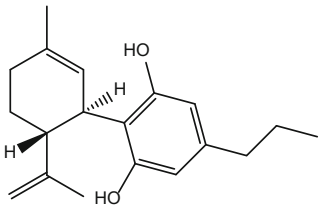
Plant cannabinoids, which are also known as “phytocannabinoids”, are classified into main two types: neutral cannabinoids and cannabinoid acids, based on whether they contain a carboxy group or not. In fresh *Cannabis* plants, cannabinoids are biosynthesized and accumulate as cannabinoid acids. However during the storage of harvested cannabis plants, or when cannabis is smoked, these acids undergo non-enzymatic decarboxylation to their neutral forms (Kimura and Okamoto 1970). So far, 112 phytocannabinoids have been isolated from *Cannabis sativa*, with Δ^9-THC (THC) (Fig. 9.1) being the plant cannabinoid mainly responsible for producing the well-known effects on perception, mood, emotion, and cognition that together constitute the psychotropic effect of cannabis (Pertwee 1988).



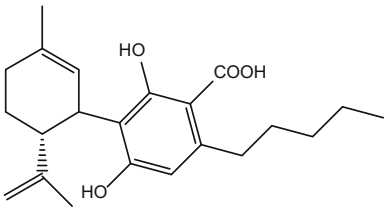
Cannabichromene (CBC)



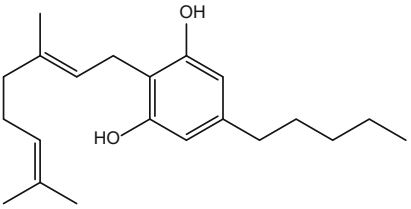
Cannabidiol (CBD)



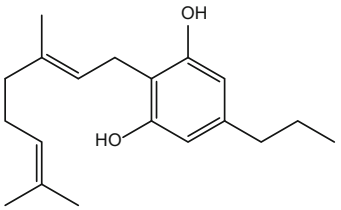
Cannabidivarin (CBDV)



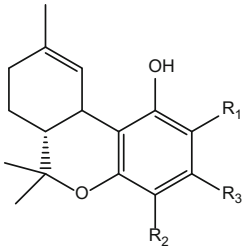
Cannabidiolic acid (CBDA)



Cannabigerol (CBG)

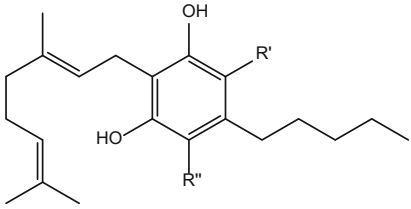


Cannabigevarin (CBGV)



Δ^9-tetrahydrocannabinolic (Δ^9-THCA) acid OR
Δ^9-tetrahydrocannabivarinic acid (Δ^9-THCVA)

R_1= COOH; R_2= H; R_3= $(CH_2)_4CH_3$ Δ^9-THCA-A
R_1= H; R_2= COOH; R_3= $(CH_2)_4CH_3$ Δ^9-THCA-B
R_1= COOH; R_2= H; R_3= $(CH_2)_2CH_3$ Δ^9-THCVA-A
R_1= H; R_2= COOH; R_3= $(CH_2)_2CH_3$ Δ^9-THCVA-B



Cannabigerolic acid (CBGA)

R'= COOH; R"= H CBGA-A
R'= H; R"= COOH CBGA-B

Fig. 9.1 Molecular structures of some, well-known, phytocannabinoids

Originally, because of its hydrophobic nature, it was suggested that the effects of THC were due to a non-specific perturbation of cell membranes. Subsequently, however, after the synthesis of the first THC enantiomers (Mechoulam et al. 1980, 1988) it was observed that the pharmacological actions of THC were stereoselective, leading to the hypothesis that it might be targeting a specific receptor. This hypothesis prompted research that led to the important discoveries (1) of two types of cannabinoid receptors, CB_1 and CB_2 (described in the paragraph below), to which THC is able to bind with high potency (EC_{50} in the nanomolar range), and (2) that the well-known psychotropic effects of THC are mainly due to its ability to interact with CB_1 receptors located in the brain (Howlett et al. 2002; Pertwee 1997, 2005). Importantly, although many of the effects of THC are cannabinoid-receptor mediated, there is now evidence that some plant-derived and synthetic cannabinoids can also target other receptors (Pertwee 2010; Cascio and Pertwee 2014; Pertwee and Cascio 2014). These include the transient receptor potential (TRP) cation channel, TRPV1 (Zygmunt et al. 1999), nuclear peroxisome-proliferator activated receptors (PPARs) (O'Sullivan 2007), certain transmitter-gated channels and ion channels (Oz 2006), and also several G-protein coupled receptors, such as the GPR55 (Ross 2009), and 5-HT_{1A} receptors (Russo et al. 2005; Rock et al. 2011, 2012; Bolognini et al. 2013; Cascio et al. 2015). In this chapter we attempt to provide an overview of what it is currently known about the in vitro pharmacology of selected plant derived cannabinoids, and about their actual or potential uses as medicines.

Our chapter focuses mainly on the following five phytocannabinoids: Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabigerol (CBG), Δ^9-tetrahydrocannabivarin (THCV), and cannabichromene (CBC) (Fig. 9.1). Little is currently known about the in vitro or in vivo pharmacology of the many other cannabinoids that are produced by cannabis, such as cannabidivarin (CBDV), cannabidiolic acid (CBDA), cannabigerovarin (CBGV), cannabigerolic acid (CBGA), Δ^9-tetrahydrocannabinolic acid (THCA), and Δ^9-tetrahydrocannabivarinic acid (THCVA) (Fig. 9.1).

9.2 A Brief Overview of the Cannabinoid Receptors

Cannabinoid CB_1 (Devane et al. 1988; Matsuda et al. 1990) and CB_2 (Munro et al. 1993) receptors are G-protein coupled receptors (GPCRs) that signal through $G_{i/o}$ proteins to inhibit adenylate cyclase and activate mitogen-activated protein kinase (Howlett 2002, 2005). Cannabinoid CB_1 receptors can also mediate inhibition of N-type and P/Q type calcium currents, and activate A-type and inwardly rectifying potassium currents.

These receptors are mainly located in the terminals of central and peripheral neurons, where they mediate inhibition of ongoing release of various neurotransmitters such as acetylcholine, γ-aminobutyric acid, 5-hydroxytryptamine, D-aspartate and cholecystokinin (Howlett 2002; Pertwee and Ross 2002). There is

evidence as well that CB_1 receptors are also present in peripheral organs, tissues and cells such as testis, heart, vascular tissue and immune cells. CB_2 receptors, initially found in immune cells, have also been detected in some brainstem neurons (Van Sickle et al. 2005; Onaivi et al. 2006).

Recently, there has been interest in the possibility that there may be a third type of cannabinoid receptor (reviewed in Pertwee et al. 2010). One possible candidate is GPR55 which shows only 13–14% homology with both CB_1 and CB_2 and is present in the brain at a concentration tenfold lower than that of CB_1 (Ross 2009). THC acts as a high efficacy agonist at GPR55; however, it is not clear what role this receptor plays in mediating the effects of THC in the brain.

In addition to the plant-derived cannabinoids, both endogenously produced cannabinoids (endocannabinoids) and synthetic cannabinoids are able to activate or block CB_1 and/or CB_2 receptors (reviewed in Pertwee et al. 2010; Pertwee 2015).

9.3 The in Vitro Pharmacological Effects of Certain Plant-Derived Cannabinoids

9.3.1 Δ^9-Tetrahydrocannabinol

(−)-*trans*-Δ^9-tetrahydrocannabinol (Fig. 9.1) is a ligand for both cannabinoid CB_1 and CB_2 receptors as shown by the observations that this phytocannabinoid can bind to cannabinoid CB_1 and CB_2 receptors with K_i values in the nanomolar range. Its affinity for both these receptors is higher than that of its corresponding (+)-*cis* (6a*S*, 10a*S*) enantiomer ((+)-Δ^9-THC), but lower than certain synthetic CB_1/CB_2 receptor agonists, such as for example HU-210, CP55940 and *R*-(+)-WIN55212 (Pertwee 2008). However, this affinity does match or exceed that of the phytocannabinoids (−)-Δ^8-THC, Δ^9-THCV, CBD, cannabigerol, and cannabinol (Pertwee 2008). Importantly, (−)-Δ^9-THC exhibits lower CB_1 and CB_2 efficacy than the above synthetic agonists, indicating it to be a partial agonist for both these receptor types (Pertwee 2008).

Interestingly, there are several reports that THC can behave both as a cannabinoid receptor agonist and as an antagonist (Pertwee 2008). Indeed, since THC displays relatively low efficacy as an agonist at CB_1 and CB_2 receptors, it is to be expected that the maximum size of the effect that it can produce when it activates CB_1 or CB_2 receptors will be greatly influenced by the proportion of the receptors that are in the "active state" (Bolognini et al. 2012; Pertwee and Cascio 2014), as well as by the expression level and coupling efficiency of these receptors, and hence that the size of the maximum effect of THC will not be the same in all CB_1 or CB_2 receptor expressing-tissues. In addition, THC has been also found to:

- reduce stimulation of [^{35}S]GTPγS binding to rat cerebellar membranes produced by the synthetic cannabinoid receptor agonist, *R*-(+)-WIN55212 (Sim et al. 1996);

- attenuate inhibition of glutamatergic synaptic transmission induced in rat or mouse cultured hippocampal neurons by *R*-(+)-WIN55212 and by the endocannabinoid, 2-arachidonoylglycerol (Kelley and Thayer 2004; Shen and Thayer 1999; Straiker and Mackie 2005);
- antagonize CB_2 receptor-mediated inhibition of cyclic AMP production in CB_2-transfected cells (Bayewitch et al. 1996);
- inhibit [^{35}S]GTPγS binding to membranes obtained from CB_2-transfected cells, thus behaving as a CB_2 inverse agonist (Govaerts et al. 2004).

Like the other phytocannabinoids described below, THC can exert actions that are not mediated by cannabinoid receptors. These additional actions have been described elsewhere in a recent review by Pertwee and Cascio (2014). Interestingly, in in vitro investigations, it was found that THC can have "opposite" effects on the G-protein coupled receptor, GPR55. Thus, in some studies, THC at submicromolar or micromolar concentrations, showed an ability to activate GPR55 both in a α-arrestin (Yin et al. 2009) and in a [^{35}S]GTPγS binding (Ryberg et al. 2007) assay. In contrast, Anavi-Goffer et al. (2012) found that THC at 1 μM, a concentration per se inactive at GPR55, induced a downward shift in the log concentration-response curve of the endogenous GPR55 agonist, α-lysophosphatidylinositol in ERK1/2 assays.

9.3.2 Cannabidiol

Cannabidiol (or CBD) (Fig. 9.1) is present in *Cannabis sativa* in relatively high concentrations and it has been classified as a non-psychotropic cannabinoid because of its inability to cause cannabis-like psychoactive effects.

It is now well-established that CBD is able to produce both cannabinoid and non-cannabinoid receptor-mediated effects and this makes its pharmacology rather complex.

That CBD can interact with the cannabinoid system is indicated, for example, by findings that it:

- displaces [^{3}H]CP55940 from both CB_1 and CB_2 receptors at μM concentrations (Showalter et al. 1996; Thomas et al. 2004, 2007);
- behaves as a low-potency CB_1 receptor inverse agonist as indicated by its ability at 10 μM to inhibit [^{35}S]GTPγS binding to membranes obtained from C57BL/6 mouse brains, from human CB_1 Chinese Hamster Ovary (CHO) cells (Thomas et al. 2007), or from rat cerebellum (Petitet et al. 1998); it remains likely, however, that this effect is not CB_1 receptor mediated since it is also detectable in $CB_1^{-/-}$ mouse brain membranes (Thomas et al. 2007);
- behaves as a potent CB_1 antagonist as shown by its ability to antagonize CP55940-induced stimulation of [^{35}S]GTPγS binding to rat cerebellar membranes at 10 μM (Petitet et al. 1998), CP55940- and *R*-(+)-WIN55212-induced

inhibition of electrically-evoked contractions of the mouse isolated vas deferens (K_B in the nanomolar range) (Pertwee et al. 2002), and CP-55940- and *R*-(+)-WIN55212-induced stimulation of [^{35}S]GTPγS binding to mouse brain membranes (K_B values = 79 and 138 nM, respectively);

- produces, at submicromolar concentration, a small but significant stimulation of [^{35}S]GTPγS binding to membranes obtained from CHO cells overexpressing human CB_1 receptors without affecting such binding to wild-type CHO cell membranes, thus behaving as a very-low efficacy CB_1 receptor partial agonist (Thomas et al. 2007);
- antagonizes CP55940-induced stimulation of [^{35}S]GTPγS binding to human CB_2-CHO cell membranes, with a K_B value in the nanomolar range (Thomas et al. 2007);
- inhibits [^{35}S]GTPγS binding to human CB_2 CHO cell membranes, thus behaving as a CB_2 receptor inverse agonist (Thomas et al. 2007), an action that may underlie the well-known anti-inflammatory effects of CBD (Izzo et al. 2009; Pertwee 2004a, b) as well as the ability of CBD to inhibit the immune cell migration (Sacerdote et al. 2005; Walter et al. 2003).

Recently CBD has been reported to behave as a cannabinoid CB_1 receptor negative allosteric modulator (NAM) as indicated by its ability to reduce the efficacy and potency of the endocannabinoid, 2-arachidonoylglycerol, and of Δ^9-THC on PLCb3 and ERK1/2-dependent signalling in cells heterologously (HEK293A) or endogenously (ST*Hdh*$^{Q7/Q7}$) expressing CB_1 receptors (Laprairie et al. 2015).

The pharmacology of CBD extends well beyond cannabinoid receptors. Thus, it is now well-established that this non-psychotropic cannabinoid can interact with other kinds of receptor and that these other receptors may mediate some of its pharmacological effects. Indeed, Russo et al. (2005) reported that CBD, at the rather high concentration of 16 μM, can bind to and activate human 5-HT_{1A} receptors (Russo et al. 2005), and more recently, our group reported first, that CBD can enhance the stimulation of [^{35}S]GTPγS binding to rat brainstem membranes induced by the well-known 5-HT_{1A} receptor agonist, 8-hydroxy-2-(di-n-propylamino)-tetralin (8-OH-DPAT), and second that the log concentration-response curve of CBD for its production of this enhancement is bell-shaped (Rock et al. 2012). It is noteworthy that CBD failed to displace 8-[^{3}H]-OH-DPAT from specific binding sites in rat brainstem membranes, prompting the hypothesis that this phytocannabinoid does not interact directly with orthosteric sites on these receptors. It has also been reported that CBD acts as an enhancer of the adenosine signallings (Carrier et al. 2006).

Other non-cannabinoid receptor-mediated effects of CBD have been widely reported. Thus, for example, at submicromolar concentrations, CBD has shown an ability to: (1) antagonize the G-protein-coupled receptor, GPR55 (Anavi-Goffer et al. 2012) as well as the cation channel, TRPM8 (De Petrocellis et al. 2008, 2011); (2) activate TRPA1 and TRPV4 cation channels (De Petrocellis et al. 2011, 2012); (3) cause the desensitization of TRPV1 and TRPV3 cation channels to their activation by an agonist (De Petrocellis et al. 2011, 2012); (4) potentiate the activation

of the cation channel, 5-HT_{3A} (Yang et al. 2010); and (5) inhibit the cytochrome P450 enzyme, CYP1A1 (Yamaori et al. 2010).

9.3.3 Δ^9-Tetrahydrocannabivarin

Δ^9-tetrahydrocannabivarin (THCV) (Fig. 9.1) is the *n-propyl* analogue of Δ^9-THC which was first detected in cannabis by Gill et al. (1970). When investigated in mice in vivo, it has been found to produce signs of CB_1 receptor activation at doses of 10, 30 and/or 56 mg kg^{-1} i.v., but to behave as a CB_1 receptor antagonist at much lower doses (0.3 and/or 3 mg kg^{-1} i.v.) (Pertwee et al. 2007). Evidence has also been obtained from in vitro experiments (Thomas et al. 2005) that THCV is a competitive antagonist at both cannabinoid CB_1 and CB_2 receptors as indicated by the observations that it:

- displaces [^{3}H]CP55940 from specific binding sites on mouse brain and human CB_2 CHO cell membranes (K_i = 75.4 and 62.8 nM, respectively);
- at 1 μM, also antagonizes CP55940-induced stimulation of [^{35}S]GTPγS binding to these brain and cell membranes (apparent K_B = 93.1 and 10.1 nM, respectively);
- antagonizes the ability of Δ^9-THC to inhibit electrically-evoked contractions of the mouse *vas deferens* with an apparent K_B value of 96.7 nM that is very similar to the apparent K_B values for its antagonism of CP55940- and *R*-(+)-WIN55212-induced stimulation of [^{35}S]GTPγS binding to mouse brain membranes;
- antagonizes the cannabinoid receptor agonists, *R*-(+)-WIN55212, anandamide, methanandamide and CP55940, in the *vas deferens*, albeit with lower apparent K_B values (1.5, 1.2, 4.6 and 10.3 nM, respectively) than the apparent K_B value for its antagonism in this bioassay of Δ^9-THC.

More recently, our group demonstrated that THCV can also activate CB_2 receptors in vitro as indicated by its ability (1) to inhibit cyclic AMP production by human CB_2 CHO cells (EC_{50} = 38 nM) but not by human CB_1, by untransfected cells, or by human CB_2 CHO cells pre-incubated with pertussis toxin (100 ng.mL^{-1}) and (2) to stimulate [^{35}S]GTPγS binding to human CB_2 CHO and mouse spleen membranes (Bolognini et al. 2010). However, the mean E_{max} value of THCV was less than that of CP55940 in both these assays, evidence that it activates CB_2 receptors with lower efficacy than CP55940 and that it is, therefore, a CB_2 receptor partial agonist.

Interestingly, THCV also appears to interact with non-cannabinoid receptors. Thus, evidence has emerged suggesting that THCV can activate or block certain TRP cation channels (De Petrocellis et al. 2011) or activate or block/modulate GPR55 receptors (Anavi-Goffer et al. 2012). More recently, our group reported the

interesting in vitro finding that like CBD, THCV can also interact with the serotoninergic 5-HT_{1A} receptor (Cascio et al. 2015). Thus, THCV:

- potently, albeit only partially, displaced 8-[^{3}H]-OH-DPAT from specific binding sites in rat brainstem membranes;
- at 100 nM, significantly enhanced 8-OH-DPAT-induced activation of receptors in these membranes;
- produced concentration-related increases in 8-[^{3}H]-OH-DPAT binding to specific sites in membranes of human 5-HT_{1A} receptor-transfected CHO cells;
- at 100 nM, significantly enhanced 8-OH-DPAT-induced activation of these human 5-HT_{1A} receptors.

9.3.4 Cannabigerol

Cannabigerol (CBG) (Fig. 9.1) is a little investigated phytocannabinoid which, like CBD, does not induce cannabis-like psychoactive effects. Recently, our group carried out an in vitro pharmacological investigation of CBG (Cascio et al. 2010) and found that this phytocannabinoid can displace [^{3}H]CP55940 from specific binding sites on mouse brain membranes with a K_i value of 381 nM, and that it exhibits significant potency both as a stimulator of [^{35}S]GTPγS binding to mouse brain membranes and as an inhibitor of electrically-evoked contractions of the mouse isolated *vas deferens* (Cascio et al. 2010). Neither of these effects appeared to be mediated by cannabinoid CB_1 receptors since they were not attenuated by the CB_1-selective antagonist, rimonabant (100 nM), but were reduced by the selective α_2-adrenoceptor antagonist, yohimbine, suggesting that both the stimulatory effect of CBG on [^{35}S]GTPγS binding to mouse brain membranes and its inhibitory effect on electrically-evoked contractions of the *vas deferens* were mediated by α_2-adrenoceptors. Whether these effects of CBG are mediated by α_{2A}-, α_{2B}- and/or α_{2C}-adrenoceptors remains to be established.

In addition, other results obtained from in vitro experiments indicate that CBG can (a) antagonize (at 1 μM) the 5-HT_{1A} receptor agonist, 8-OH-DPAT (apparent K_B = 51.9 nM) (Cascio et al. 2010) (b) behave (at 10 μM) as a CB_1 receptor competitive antagonist (Cascio et al. 2010); (c) antagonize TRPM8 cation channels (IC_{50} = 160 nM) (De Petrocellis et al. 2011) and (d) activate TRPA1 cation channels (EC_{50} = 700 nM) (De Petrocellis et al. 2011).

9.3.5 Cannabichromene

Cannabichromene (CBC) (Fig. 9.1) has been detected in cannabis in high concentrations (Brown and Harvey 1990). De Petrocellis et al. (2011, 2012) reported

that this phytocannabinoid can target TRP cation channels as indicated by the findings that it:

- activates TRPA1 cation channels at 10 μM (EC_{50} = 90 nM);
- desensitizes TRPA1 cation channels to activation by allyl isothiocyanate (IC_{50} = 370 nM);
- activates TRPV4 and TRPV3 cation channels (EC50 = 600 nM and 1.9 μM, respectively);
- desensitizes TRPV2 and TRPV4 cation channels to their activation by an agonist (IC_{50} = 6.5 and 9.9 μM, respectively);
- activates TRPV1 cation channels (EC_{50} = 24.2 μM);
- desensitizes TRPV3 cation channels to their activation by an agonist (IC_{50} = 200.8 μM);
- blocks the activation of TRPM8 cation channels (IC_{50} = 40.7 μM).

In addition, the same group reported that CBC inhibits both the cellular uptake of anandamide (IC_{50} = 12.3 μM) and the metabolism by monoacyl glycerol lipase of the endocannabinoid, 2-arachidonoylglycerol (IC_{50} = 50.1 μM) (De Petrocellis et al. 2011).

9.4 Potential and Approved Therapeutic Uses of Plant Cannabinoids

Some phytocannabinoids have been reported to exert in vivo effects in animal models that suggest that these cannabinoids are likely to have a number of important therapeutic applications (Pertwee and Cascio 2014; Cascio and Pertwee 2014). Below we present a general overview of the main potential (or established) therapeutic uses of some cannabis-related drugs.

9.4.1 Multiple Sclerosis

This is a disease of the central nervous system, in which the ability of neurons to transmit impulses becomes impaired through the loss of myelin, which normally forms the outer covering of many nerve fibres (Pertwee 2007). As a consequence, people with this disease show a variety of symptoms such as tremor, spasticity and pain, and bladder and sexual dysfunction. Unfortunately, most of the drugs currently used for the treatment of multiple sclerosis are not particularly effective and can cause many side effects. Convincing evidence has emerged, however, suggesting that the activation of cannabinoid receptors can ameliorate these symptoms (Pertwee 2007). Indeed, Sativex®, an oral spray that is licenced in the UK and other

countries, and that contains the two phytocannabinoids THC and CBD, has been reported to be very effective in the treatment of multiple sclerosis, particularly in the amelioration of spasticity (Alexander et al. 2016).

9.4.2 Nausea and Vomiting

Linda Parker's group and others have obtained convincing evidence that CBD can reduce vomiting in *Suncus murinus* (house musk shrew) produced by nicotine, cisplatin or lithium chloride (LiCl, Kwiatkowska et al. 2004; Parker et al. 2004; Rock et al. 2011, 2012), although not by motion (Cluny et al. 2008), and that it can also reduce the establishment of conditioned gaping reactions elicited by a LiCl-paired flavour, a model of nausea-induced behaviour in rats (Parker et al. 2008). In addition, in a rodent model of anticipatory nausea evident in chemotherapy patients returning to the treatment-paired context, CBD (unlike traditional anti-emetics) effectively suppresses the expression of conditioned gaping elicited by LiCl-paired contextual cues (Rock et al. 2008).

It has also been found that in a phase II clinical trial, Sativex® was both effective in reducing the incidence of chemotherapy-induced nausea and vomiting, and well tolerated by patients (Duran et al. 2010). However, the log dose-response curves for the anti-emetic effects produced by CBD in house musk shrews are biphasic, since CBD suppresses acute cisplatin-induced vomiting at 5 mg kg^{-1}, but potentiates it at 40 mg kg^{-1} (Kwiatkowska et al. 2004). Similarly, acute vomiting elicited by LiCl is suppressed by low doses of CBD (5-10 mg kg^{-1}), whereas higher doses (20–40 mg kg^{-1}) of this phytocannabinoid act to facilitate LiCl-induced vomiting, rather than to reduce this effect (Parker et al. 2004). This narrow range of CBD efficacy may limit its clinical use as an anti-emetic. Interestingly, our group in collaboration with Parker's group discovered that the ability of CBD to attenuate toxin-induced vomiting in shrews and signs of nausea in rats was due to indirect agonism by CBD of 5-HT_{1A} receptors located in the brainstem, as indicated by the findings that: (a) these effects of CBD were prevented by the administration of a selective 5-HT_{1A} receptor antagonist, either WAY100135 or WAY100635; (b) CBD displayed significant potency at enhancing the ability of the selective 5-HT_{1A} receptor agonist, 8-OH-DPAT, to stimulate [^{35}S]GTPγS binding to rat brainstem membranes; and (c) when co-administered with 8-OH-DPAT, CBD suppressed LiCl-induced signs of nausea in rats in an apparently synergistic manner. In view of the ability of CBD to interact with CB_1 receptors, it is also noteworthy that its ability to suppress vomiting in house musk shrews is not blocked by the cannabinoid CB_1 receptor-selective antagonist/inverse agonist, SR141716A (Parker et al. 2004).

Interestingly, we have also obtained evidence that the immediate precursor of CBD in the cannabis plant, cannabidiolic acid (CBDA), shares the ability of CBD to produce anti-nausea and ant-emetic effects in vivo (Bolognini et al. 2013). Thus, in shrews, CBDA (0.1 and/or 0.5 mg kg^{-1} i.p.) reduced toxin- and motion-induced

vomiting, and increased the onset latency of the first motion-induced emetic episode, and in rats, CBDA (0.01 and 0.1 mg kg^{-1} i.p.) suppressed LiCl- and context-induced conditioned gaping, effects that were blocked by the 5-HT_{1A} receptor antagonist, WAY100635 (0.1 mg kg^{-1} i.p.). We also found, first, that at 0.01 mg kg^{-1} i.p., CBDA enhanced saccharin palatability, and second, that CBDA-induced suppression of LiCl-induced conditioned gaping in rats was unaffected by the CB_1 receptor antagonist, SR141716A (1 mg kg^{-1} i.p.). It is likely that, as postulated for CBD (see above), CBDA produces these in vivo effects by enhancing the activation of 5-HT_{1A} receptors. Thus, we have found that at concentrations ranging from 0.1 to 100 nM, CBDA shares the ability of CBD (100 nM) to increase the E_{max} of 8-OH-DPAT for its stimulation of [^{35}S]GTPγS binding to rat brainstem membranes (Bolognini et al. 2013).

9.4.3 Cancer

Certain phytocannabinods have been reported to have promising anti-tumoral actions. Thus, for example, in 1975, Munson et al. discovered that Lewis lung adenocarcinoma growth was retarded by oral administration of THC and later on it was found that THC was able to induce apoptosis in C6.9 glioma cells (Sánchez et al. 1998) and could also cause apoptosis in human prostate cancer PC-3 cells (Ruiz et al. 1999). Studies carried out with the aim of elucidating mechanisms underlying the anti-tumoral effects of THC reported that this phytocannabinoid may exert its anti-cancer effects by inducing apoptosis or antiproliferation, as well as by inhibiting tumor angiogenesis and metastasis (Hart et al. 2004; Ramer and Hinz 2008). These effects of THC may be mediated in part by cannabinoid CB_1 and CB_2 receptors (Galve-Roperh et al. 2000). In addition to THC, cannabigerol (CBG) has also been found to exert an anti-cancer effect, in this case in human oral epithelioid carcinoma cells (Baek et al. 1998) with a mechanism as yet to be established. In 2006, Ligresti and coworkers investigated the anti-tumor effects of the plant-cannabinoids, CBD, CBG, cannabichromene (CBC), CBDA and THC acid (THCA), and looked to see whether there was any advantage in using cannabis extracts (enriched in either CBD or THC) rather than pure cannabinoids. Results obtained from experiments with various tumor cell lines clearly indicated that, of the five above phytocannabinoids, cannabidiol was the most potent inhibitor of cancer cell growth (IC_{50} between 6.0 and 10.6 μM), and displayed significantly lower potency in non-cancer cells. A CBD-rich extract was equipotent with pure CBD, whereas CBG and CBC followed in the terms of potency. Both CBD and the CBD-rich extract (1) inhibited the growth of xenograft tumours produced by s.c. injection into athymic mice, of human MDA-MB-231 breast carcinoma or rat v-K-*ras*-transformed thyroid epithelial cells, and (2) reduced lung metastases resulting from intra-paw injection of MDA-MB-231 cells. It is likely, at least for its inhibitory effect on the growth of MDA-MB-231 cells, that CBD induces apoptosis through (1) direct or indirect activation of cannabinoid CB_2 and vanilloid TRPV1

receptors and (2) cannabinoid/vanilloid receptor-independent elevation of intracellular calcium and reactive oxygen species (Ligresti et al. 2006).

In other experiments, CBD was found to cause apoptosis in human myeloblastic leukemia cells. At the highest concentration of CBD tested (8 μg/ml), 61% of the cells underwent apoptosis and this was increased to 93% when the cells were exposed to γ-radiation before CBD treatment. Importantly, CBD with or without irradiation did not cause apoptosis in healthy mononuclear cells (Gallily et al. 2003; McKallip et al. 2006; Vaccani et al. 2005). In 2008, Massi et al. investigated the possibility that 5-lipoxygenase and cyclooxygenase-2 as well the endocannabinoid system, could be modulated by CBD in a manner that suppresses tumor growth. The authors found that CBD exerts its antitumor effects at least in part through modulation of 5-lipoxygenase, and subsequently of the endocannabinoid system (Massi et al. 2008).

Unfortunately, very few clinical trials with cannabinoids and cancer patients have yet been carried out (Kramer 2015), prompting an urgent need for further clinical research directed at assessing the benefits of using cannabinoids as anti-tumor medicines. In 2006, Guzmán et al. reported results from the first clinical study aimed at evaluating the antitumor effect of THC following its intracranial administration (Guzmán et at. 2006). Results from this study indicated that THC delivery by this route was both safe and effective, and did not produce overt psychotropic effects.

9.4.4 Pain

There is now convincing evidence that cannabinoid receptor agonists can reduce various kind of pain, including acute, neuropathic, inflammatory, visceral and cancer pain, by acting on both cannabinoid CB_1 and CB_2 receptors that are located on pain pathways in the brain, spinal cord, peripheral sensory nerves and/or non-neuronal cells in the skin (Pertwee 2001, 2005, 2009; Guindon and Hohmann 2008). In this regard, the THC- and CBD-containing medicine, Sativex®, is already prescribed for the symptomatic relief of neuropathic pain in adults with multiple sclerosis (Perez and Ribera 2008; Rahn and Hohmann 2009) and as an adjunctive-analgesic treatment for adult patients with advanced cancer. Costa et al. (2007) investigated the effect of CBD on chronic inflammatory and neuropathic pain in rats. CBD reversed both thermal and mechanical hyperalgesia on repeated oral treatment in two different models of persistent pain: the sciatic nerve constriction injury model of neuropathic pain, and the complete Freund's adjuvant model of inflammatory pain. The effect was reversed by a transient receptor potential cation channel (TRP) antagonist, but not by a CB_1 antagonist (Costa et al. 2007).

Moreover, results from clinical trials suggest that nabilone, a synthetic cannabinoid receptor agonist, can relieve chronic neuropathic pain, fibromyalgia (diffuse musculoskeletal pain) and headache (Pinsger et al. 2006; Skrabek et al.

2008; Rahn and Hohmann 2009). Finally, in 2010 our group found that THCV is able to activate CB_2 receptors in vitro, and that this action underlies the ability of this plant cannabinoid (0.3 or 1 mg kg^{-1} i.p.) to decrease carrageenan-induced oedema and to suppress carrageenan-induced hyperalgesia in vivo (Bolognini et al. 2010). In the same study, THCV also decreased pain behaviour in phase 2 of the formalin test at 1 mg·kg^{-1} i.p., and in both phases of this test at 5 mg·kg^{-1} i.p.

9.4.5 Schizophrenia

There seems to be an association between schizophrenia and cannabis consumption, particularly for strains with high concentrations of THC. We recently found that in phencyclidine-treated rats, THCV, like clozapine: (a) reduced stereotyped behaviour; (b) decreased time spent immobile in the forced swim test; and (c) normalized hyperlocomotor activity, social behaviour and cognitive performance. Some of these effects were counteracted by the 5-HT_{1A} receptor antagonist, WAY100635, or could be reproduced by the CB_1 antagonist, AM251 (Cascio et al. 2015). Taken together our findings suggest that by both enhancing the activation of 5-HT_{1A} receptors and blocking CB_1 receptors (see also Sect. 4.6), THCV may have therapeutic potential for ameliorating some of the negative, cognitive and positive symptoms of schizophrenia (Cascio et al. 2015).

9.5 Conclusions

Evidence from both in vitro and in vivo studies suggest that *Cannabis* can be considered as a promising source of established and future therapeutic agents particularly for the treatment of certain diseases such as, to mention only a few, pain, multiple sclerosis, cancer and nausea/vomiting. Unfortunately, despite the emergence of a huge amount of preclinical literature that describes the actions and effects of some cannabinoids, there have as yet been relatively few publications describing effects produced by cannabinoids in clinical studies performed with human subjects. Importantly, a cannabis-based medicine, Sativex®, was recently licenced in the UK and many other countries, for example for the treatment of symptoms (tremor, spasticity) associated with multiple sclerosis, and before this, other cannabinoid drugs, Cesamet® (Nabilone) and Marinol® (dronabinol; synthetic THC) successfully entered the clinic, for example for the treatment of vomiting and nausea caused by cancer therapy.

It will now be important to complete the pharmacological characterization of all phytocannabinoids that are known to be present in cannabis. Such research would advance our understanding of the pharmacological effects produced by cannabis when it is used either as a recreational drug or for self-medication, and should also facilitate the discovery of any important new uses for cannabis-based medicines.

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