Chapter 62

An Overview of Major and Minor Phytocannabinoids

Jahan P. Marcu

Americans for Safe Access, Washington, DC, USA; Green Standard Diagnostics, Inc., Las Vegas, NV, USA

Abbreviations

BCP β-Caryophyllene
CBC Cannabichromene
CBG Cannabigerol
ECS Endocannabinoid system
THC Δ^9-tetrahydrocannabinol
THCA Tetrahydrocannabinol acid
THCV Tetracannabivarin
TRP Transient receptor potential
TRPV Transient receptor potential vanilloid type

INTRODUCTION

For nearly five millennia, *Cannabis* has been documented as a medicine with unmatched applicability (Russo, 2011). The mechanism of action of *Cannabis* remained a mystery until fairly recently, with the discovery of phytocannabinoids, or plant cannabinoids, and the receptor system known as the endocannabinoid system (ECS). Phytocannabinoids are terpenophenolic compounds associated with the effects of the *Cannabis* plant and mimic the effects of endogenous cannabinoids. These phytocannabinoids are biosynthesized and secreted by glandular trichomes found on the flower tops of the *Cannabis* plant (Figure 1). In the 1960s a host of cannabinoids were discovered, including cannabigerol (CBG), tetracannabivarin (THCV), and cannabichromene (CBC) (Figure 2). More than 100 cannabinoids have been identified in *Cannabis* and reports are emerging of their occurrence in other plants (Appendino, Chianese, & Taglialatela-Scafati, 2011; Pertwee, 2014). The great bulk of clinical cannabinoid research focuses on the psychotropic Δ^9-tetrahydrocannabinol (THC), inadvertently marginalizing the roles of other cannabinoids in altering the pharmacological activities of *Cannabis* compounds. Many compounds in the plant can enhance or inhibit various aspects of THC pharmacology, for example, the inhibition of unwanted side effects such as with the coadministration of cannabidiol (CBD) (Russo & Guy, 2006). Major and minor phytocannabinoids can have remarkably positive effects in mammalian behavior related to anxiety and drug acquisition and may offer novel drug abuse treatment options.

The ratios of these major and minor compounds can vary greatly and some compounds are not often detected or tested for or reported. Furthermore, the *Cannabis* plant is not the only source of phytocannabinoids. Excellent in-depth reviews of the phytocannabinoids have been published (Pertwee, 2014; Pharmacopoeia, 2013). The following is an overview of the major and minor phytocannabinoids that can be found in *Cannabis*.

TETRAHYDROCANNABINOL ACID, TETRAHYDROCANNABIVARINIC ACID, AND CANNABIGEROL ACID

Cannabinoid acids are found as primary metabolites in *Cannabis* plants. For example, tetrahydrocannabinol acid (THCA) is synthesized in glandular trichomes of the *Cannabis* plant and forms THC after the parent compound is decarboxylated by UV exposure, prolonged storage, or heat (Figure 3). The cannabinoid acids do not produce any significant or documented psychotropic effects. THCA, tetrahydrocannabivarinic acid, and cannabigerol acid (CBGA) are the immediate natural precursors of THC, THCV, and CBG. THCA and CBGA are the primary phytocannabinoid metabolites and can cause apoptosis of insect cells (Figure 3) (Sirikantaramas, 2004)

Basic research has shown that these acidic compounds can efficiently activate TRPM8 channels and stimulate or desensitize a range of other transient receptor potential (TRP) cation channels. THCA and CBGA have been found to inhibit enzymes responsible for the breakdown of endocannabinoids, as well as cyclooxygenase-1 and -2, thus stimulating the ECS by increasing levels of endogenous cannabinoids.

CANNABIGEROL

This compound was the first cannabinoid purified from *Cannabis* (Gaoni & Mechoulam, 1964). CBG lacks the psychotropic effects of THC (Grunfeld & Edery, 1969a, 1969b, 1969c). This compound does not have a significant subjective psychotropic effect in humans but CBG may stimulate a range of receptors important for pain, inflammation, and heat sensitization. This compound can antagonize transient receptor potential vanilloid type (TRPV) 8 receptors and stimulates TRPV1, TRPV2, TRPA1, TRPV3, TRPV4, and α_2-adrenoceptor activity (Cascio, Gauson, Stevenson, Ross, & Pertwee, 2010; De Petrocellis & Di Marzo, 2009; De Petrocellis &

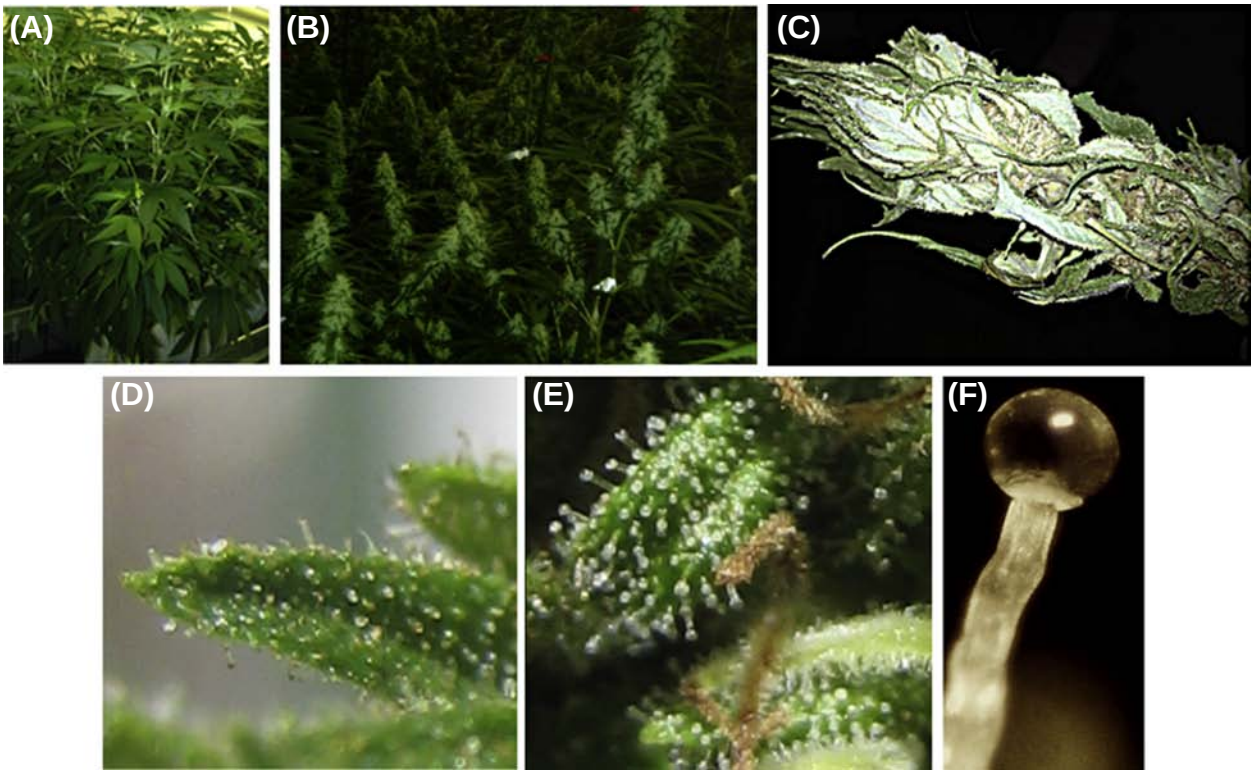

FIGURE 1 **The *Cannabis* plant and its trichomes.** Immature *Cannabis* plants are seen in (A), while in (B) there is an example of flowering plants. An example of a harvested and dried flower from a *Cannabis* plant is shown in (C), while (D and E) display close-ups of the trichomes, visible as pale stalks. A glandular cystolic trichome can be seen in (F); these are found in *Cannabis* flowers and biosynthesize cannabinoids. A cannabinoid-rich oil is secreted out of the top of trichomes in a waxy layer. *Photos A–C, courtesy of J.P.M., photos D–F, courtesy of E.R.*

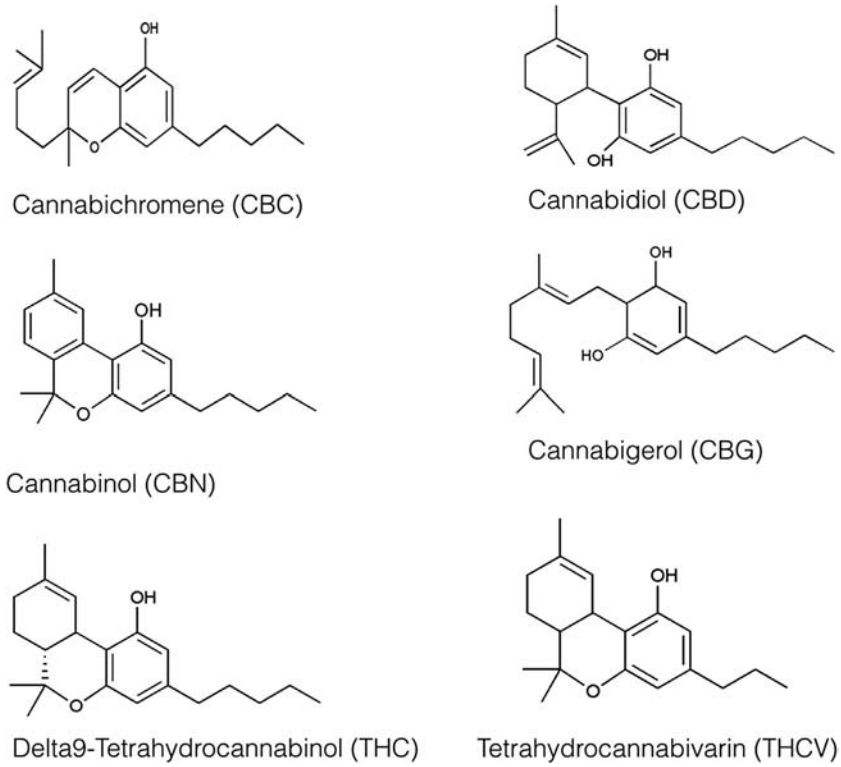

FIGURE 2 **Structures of cannabinoids found in the *Cannabis* plant.** These compounds are the secondary metabolites of *Cannabis*. These compounds are synthesized as acidic versions and decarboxylate over time or when heat is applied. *All images generated by J.P.M. using ChemDraw software.*

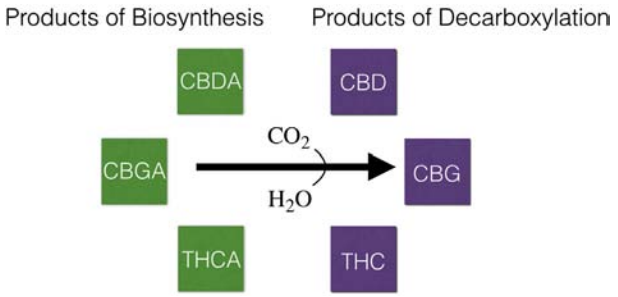

FIGURE 3 Products of biosynthesis and decarboxylation. Phytocannabinoids are biosynthesized as acidic precursors, such as THCA. Acidic phytocannabinoids are decarboxylated to form neutral cannabinoids. The conversion of acidic to neutral cannabinoid can occur from prolonged storage and when heat is applied, generating carbon dioxide and water. CBDA, cannabidiolic acid.

Di Marzo, 2010; De Petrocellis et al., 2011, 2012). CBG can also antagonize the stimulation of serotonin 5-HT1A and cannabinoid type 1 (CB1) receptors with significant efficiency.

Δ^9-TETRAHYDROCANNABINOL

THC is the degradation product of nonpsychotropic THCA, which is synthesized from CBGA by THCA synthase. THC is a partial agonist at CB1 and CB2 receptors with a high affinity for both receptors. Stimulation of CB1 receptors by THC can lead to a tetrad of effects in assays with laboratory animals; these effects are documented as suppression of locomotor activity, hypothermia, catalepsy (ring test), and antinociceptive effects in tail flick test (Martin et al., 1991). THC can stimulate CB2 receptors, which may decrease the growth of some cancers and reduce arthritic pain and edema in models of arthritis. Perhaps most surprising is that direct stimulation of CB2 receptors can result in significantly reducing cocaine self-administration in animals (Gardner, 2013). Stimulation of CB2 receptors is not associated with the psychotropic effects of *Cannabis* use.

THC also has several non-CB receptor mechanisms that have been reported; these include inhibiting the 5-HT3A receptor, enhancing glycine receptor activation by allosteric modification, elevating calcium levels via TRPA1 or TRPV2, reducing elevated intracellular calcium levels from TRPM8 activity, stimulating nuclear receptors, and stimulating G Protein Receptor 18 (Barann et al., 2002; De Petrocellis et al., 2012, 2008; Hejazi et al., 2006; McHugh, Page, Dunn, & Bradshaw, 2012; O'Sullivan, Tarling, Bennett, Kendall, & Randall, 2005).

Oral THC administration can have significant effects on anxiety, depression, and mood. The effects of THC in humans can vary depending on the experience of the subject. The oral administration of pure THC to naïve subjects can induce anxiety but this is not reported with experienced users, and use of the drug is not significantly associated with developing anxiety and depressive disorders later in life (Bahi et al., 2014; Ballard, Bedi, & de Wit, 2012; Campos et al., 2013; Crippa et al., 2009). Oral administration of THC results in its metabolism to 11-hydroxy-THC, which possesses up to10 times greater potency. This metabolism can explain some discrepancies between the observed effects in groups administered oral or inhaled forms of THC.

THC-predominant *Cannabis* is reported to be a commonly abused or misused substance. Street *Cannabis* can be contaminated or adulterated and this may underlie the negative health aspects of lifelong use. THC can cause temporary impairments to neuropsychomotor performance. All observable negative effects of THC administration on neurocognitive tasks disappear within 30 days regardless of the amount or length of use (Pope, Gruber, Hudson, Huestis, & Yurgelun-Todd, 2001). The proposed treatment for so-called *Cannabis* addiction or withdrawal is oral THC (Lichtman & Martin, 2005). CBD may also be considered an antidote for THC, as CBD and compounds in the plant tame or inhibit the psychotropic effects of THC (Russo, 2011). Excellent reviews are available covering numerous clinical trials with oral and inhaled THC for the treatment of over 10 pathologies (Ben Amar, 2006; Hazekamp & Grotenhermen, 2010; Pacher et al., 2006).

THC, the ECS, and the endorphin/opiate system can interact in remarkable ways (Table 1). Animal research has demonstrated a potential prophylactic effect on developing opiate dependence, as adolescent exposure to chronic THC blocks opiate dependence in maternally deprived rats (Morel, Giros, & Daugé, 2009). The ECS is proposed to interact with endorphins, through the release of opioid peptides from CB receptor activation and the synthesis of endocannabinoids induced by opiate receptor stimulation

TABLE 1 The ECS Is Proposed to Interact with Opioids through a Few Mechanisms

References	Finding
Morel et al. (2009)	Adolescent exposure to THC may impart resistance to opiate dependence in maternally deprived animals.
Abrams et al. (2011) and Russo et al. (2008)	CB receptor stimulation can result in endorphin release, and opioid receptor stimulation may increase synthesis of endogenous cannabinoids.
Abrams et al. (2011)	Clinical research demonstrates that THC can enhance the pain-relieving effects of suboptimal doses of opiates.
Bachhuber et al. (2014)	The state of Colorado has experienced a significant decrease in opiate-related deaths since the implementation of medical and commercial *Cannabis* laws.

The release of opioid peptides by CBs and the release of endocannabinoids by opioids may be one mechanism (Abrams et al., 2011; Russo, 2008). Clinically, THC may enhance the pain-relieving effects of opiates, lowering the amount of an opiate necessary for relief. Drug abuse studies demonstrate that adolescent exposure to chronic THC blocks opiate dependence in maternally deprived rats. There is evidence of the existence of a direct receptor–receptor interaction and cellular pathways, such as via allosteric modification of heterodimers.

(Abrams, Couey, Shade, Kelly, & Benowitz, 2011; Russo et al., 2008). Clinically, THC may enhance the pain-relieving effects of opiates, lowering the amount of an opiate necessary for relief. Surveys suggest *Cannabis* is used to decrease the use of other drugs (alcohol, nicotine, and opiates) (Reiman, 2009). In the United States, the state governments that have passed commercial *Cannabis*/marijuana laws report lower opiate overdose and related death statistics; these populations may reflect what has been observed in surveys and clinical studies of THC and opiates (Bachhuber, Saloner, Cunningham, & Barry, 2014).

TETRAHYDROCANNABIVARIN

THCV is a propyl analogue of THC and most often occurs as a small percentage of dried plant material, and THCV-rich plants that are 16% THCV by dry weight have been developed by a pharmaceutical company (Pharmacopoeia, 2013). Mechanistically speaking, THCV can behave as both an agonist and an antagonist at CB receptors depending on the concentration (Pertwee, 2008).

Antagonizing CB receptors can suppress appetite and the intoxicating effects of THC. However, caution must be emphasized when developing CB1 receptor antagonists. Clinical studies in human populations studying the antagonists of CB receptors with the drug rimonabant (SR141716A) led to depressive episodes and potentially worsened neurodegenerative disease outcomes, and ultimately this drug was withdrawn from the market (McLaughlin, 2012). Despite this setback, SR141716A remains a very important research tool for unlocking potential medical treatments targeting the CB receptors and deepening the understanding of the ECS.

CANNABIDIOL

The main nonpsychotropic phytocannabinoids are CBD and its acidic precursor cannabidiolic acid. These are the most abundant phytocannabinoids in European hemp (Pharmacopoeia, 2013). CBD has a very low affinity for CB receptors but may have significant CB1- and CB2-independent mechanisms of action. CBD is reported to be an agonist at TRPV1 and 5-HT1A receptors and to enhance adenosine receptor signaling (Russo, Burnett, Hall, & Parker, 2005). Exceptional tolerability of CBD in humans has been demonstrated (Mechoulam, Parker, & Gallily, 2002). CBD can produce a wide range of pharmacological activity including anticonvulsive, anti-inflammatory, antioxidant, and antipsychotic effects. These effects underlie the neuroprotective properties of this CB and support its role in the treatment of a number of neurological and neurodegenerative disorders, including epilepsy, seizures, Parkinson disease, amyotrophic lateral sclerosis, Huntington disease, Alzheimer disease, and multiple sclerosis (Hofmann & Frazier, 2013; de Lago & Fernández-Ruiz, 2007; Martin-Moreno et al., 2011; Scuderi et al., 2009).

CBD possesses the unique ability to counteract the intoxicating effects of *Cannabis* (Russo & Guy, 2006). The benefits of CBD include reducing the unwanted side effects of THC, a dynamic pharmacological effect that has been fairly well studied in clinical trials. CBD is included in a specific ratio of 1/1 in the medicinal *Cannabis* preparation and licensed pharmaceutical known as Sativex®, which has been studied in numerous properly controlled clinical trials representing some 30,000 patient years (Flachenecker, Henze, & Zettl, 2014; Rog, 2010; Sastre-Garriga, Vila, Clissold, & Montalban, 2014; Wade, Collin, Stott, & Duncombe, 2010).

CANNABICHROMENE

CBC can be one of the most abundant nonpsychotropic CBs found in strains or varieties of *Cannabis* (Brown & Harvey, 1990; Holley, Hadley, & Turner, 1975). CBC can cause strong anti-inflammatory effects in animal models of edema through non-CB receptor mechanisms (DeLong, Wolf, Poklis, & Lichtman, 2010). CBC has been shown to significantly interact with TRP cation channels, including TRPA1, TRPV1–4, and TRPV8 (Pertwee, 2014). CBC can also produce behavioral activity in the Billy Martin tetrad assay for the effects of CB administration. The effects of CBC can be augmented for additive results when THC is coadministered. CBC administration can induce nociception by itself and can potentiate the nociceptive effects of THC in animal models.

CANNABINOL

CBN is a degradation product of THC and its presence in the *Cannabis* plant may indicate the relative age of the harvested plant material or how well the material was stored. CBN binds less efficiently than THC to CB1 and CB2 receptors. CBN binds more tightly to CB2 receptors than to CB1 receptors. The metabolite of CBN is 11-hydroxy-CBN, which is reported to be more potent at CB1 receptors (Yamamoto et al., 2003).

A recent review of phytocannabinoids summarized the ability of CBN to inhibit the activity of a number of enzymes, including cyclooxygenase, lipoxygenase, and a host of cytochrome P450 (CYP) enzymes (e.g., CYP1A1, CYP1A2, CYP2B6, CYP2C9, CYP3A4, CYP3A5, CYP2A6, CYP2D6, CYP1B1, and CYP3A7) (Pertwee & Cascio, 2014). CBN may also stimulate the activity of phospholipases.

β-CARYOPHYLLENE

BCP is a volatile terpene with CB receptor activity, found ubiquitously throughout nature and in great abundance in *Cannabis*, cloves, and black pepper (Figure 4). This terpene is an efficient CB2 receptor agonist, is generally regarded as safe by the US Food and Drug Administration, and is available commercially (Gertsch et al., 2008). BCP binds and stimulates CB2 receptors, causing analgesic and anti-inflammatory activity without psychotropic effects. BCP has also been shown to reduce drug administration,

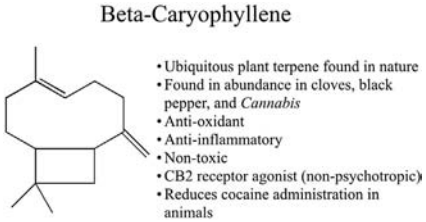

FIGURE 4 Structure and key facts regarding BCP. BCP is a volatile terpene that activates CB2 receptors and may be a useful therapeutic compound. *Structure generated with ChemDraw by J.P.M.*

improving scores of depression and anxiety in mammals (Bahi et al., 2014; Onaivi et al., 2008; Xi et al., 2011).

APPLICATIONS TO OTHER ADDICTIONS AND SUBSTANCE MISUSE

Medical *Cannabis* and *Cannabis*-based medicines could potentially be developed as drug addiction disorder treatments or used as a substitute for alcohol and other drugs such as opiates and cocaine (Aggarwal, 2008; Otto, 2012; Reiman, 2009; Subbaraman, 2014). BCP and other CBs that activate the CB2 receptor may provide a safe treatment for drug addiction and withdrawal symptoms by providing anti-inflammatory effects and pain relief and improving mood, but without any intoxicating effects. CB1 receptor-based therapies may be appropriate for patients who have previous experience with *Cannabis*, as naïve patients have been shown to be less tolerant of the side effects of CB1 activation compared to experienced users in clinical settings.

DEFINITION OF TERMS

- Cannabinoids: This is a group of closely related compounds, similar to THC or other compounds found in plants.
- CB1 receptor: This is a G-protein-coupled receptor densely located in the brain and nervous tissue.
- CB2 receptor: This is a G-protein-coupled receptor densely located in immune tissue and also found in the brain.
- Endocannabinoid system: This is a mammalian biological system consisting of receptors (i.e., CB1, CB2), endogenously produced compounds (i.e., anandamide, 2-arachidonoylglycerol), and proteins responsible for the synthesis, breakdown, and transport of endogenous CBs.
- Phytocannabinoid: These are CB compounds that are found in plants.

SUMMARY

This chapter focuses on a group of terpenophenolic compounds found in the *Cannabis* plant (Table 2). *Cannabis* is a plant that has been documented as a medicine for millennia. Neurocognitive deficits related to *Cannabis* use are reversible regardless of the amount or duration of use over a lifetime. CBs such as BCP and CBD may offer novel therapeutic strategies to develop treatments for drug abuse-related disorders. BCP, CBD, and other phytocannabinoids are nonpsychotropic and do not cause intoxication. CBD is well tolerated in humans and can reduce anxiety. Furthermore, the administration of CB2 agonists reduces anxiety and depression in animal models, with supporting, but limited, evidence in humans.

THC and the ECS can interact with the opiate system. Clinically coadministration of THC with opiates allows the administration of significantly less opiate to reach the desired analgesic effects. Additionally, administration of CB2 agonists reduces drug-seeking behavior and signs of withdrawal in animal models. *Cannabis* and its pharmacological agents may have a potential role in drug abuse treatment programs; evidence exists from animal and human research suggesting clinical benefits related to cocaine and opiate pharmacodynamics.

TABLE 2 Chemical Types and Numbers of Cannabinoids

Chemical Class or Type	Number of Compounds
THC	18
CBG	17
Cannabidiol (CBD)	8
Other CBs	61
Non-CBs	>400

This table represents a simple breakdown of compounds found in *Cannabis*. There are several isomers of each class or type, as well as hundreds of non-CB components, including terpenes, flavonoids, vitamin K, fatty acids, nitrogenous compounds, etc.

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