CBD

What Does the Science Say?

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Preface

The writing of this book has been a labor of love for all three authors, having been drawn together by our keen interest in the science of cannabidiol (CBD). The first paper that Raphael Mechoulam published in the cannabinoid field (among nearly five hundred lifetime publications) was the identification of the structure of the CBD molecule (Mechoulam and Shvo 1963), which allowed its synthesis and an evaluation of its mechanism of action in several biological assays. For the past sixty years, several groups have collaborated with Mechoulam, conducting some of the earliest studies on the potential medicinal benefits of this compound. Among those collaborations was one with Linda Parker's laboratory in Canada, investigating the effects of cannabinoids on nausea, vomiting, anxiety, pain, and addiction in preclinical rodent models (see Mechoulam and Parker 2013). Erin Rock joined in this collaboration, first as an undergraduate at Wilfrid Laurier University (Waterloo, Ontario) and then as a graduate master's and PhD student at the University of Guelph, identifying the mechanism of action of the antinausea and antivomiting effects of CBD for her PhD research (Rock et al. 2012). Rock continued as a postdoctoral fellow/research associate with Parker, continuing to unlock the mysteries of CBD and several other cannabinoids using these models.

People have used the cannabis plant for millennia for its medicinal and mind-altering effects. This complex plant contains over 100 plant cannabinoids, including the most well known, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Of the over 100 cannabinoid compounds in the cannabis plant, THC has been identified as essentially the only psychotropic compound, based on research by Raphael Mechoulam's group in Israel and several others in the 1960s and 1970s. CBD, however, is not mind-altering.

Awareness of the potentially beneficial effects of CBD has grown at an astonishing rate in the mind of the general public, with Google Internet searches doubling in frequency every year for the past five years, and it is continuing to accelerate (Leas et al. 2019). Indeed, CBD has become a trendy ingredient in mass market products that make broad and at times unsubstantiated claims of its ability to treat a myriad of symptoms from skin disorders to chronic pain, as well as cosmetic use—and in many cases, without human clinical trial evidence. Many pet owners are also administering CBD for management of conditions such as pain and anxiety without relevant scientific evidence for these indications.

This current "CBD craze" often generalizes to human health on the basis of findings in cells or in preclinical rodent research. However, human clinical trial research has severely lagged behind the basic cellular and preclinical animal research on the beneficial effects of CBD, with the exception of the use of CBD in rare forms of childhood epilepsy. The lack of clinical trial data is surprising, given that over sixty years ago, small-scale human trials for treatment of epilepsy, addiction, and anxiety showed that CBD may be a promising potential treatment option. However, the regulatory rules governing research with cannabis, a Schedule I drug, prohibited large-scale research with humans on the therapeutic potential of CBD. In recent years with countries such as Canada and several US states legalizing cannabis, one would expect that access to CBD has become much more feasible for large-scale human clinical trials. However, at the time of writing

this book, this has not yet been the case. As consumers have increased access to a variety of cannabis products, US and Canadian scientists face the burden of strict regulatory scrutiny (Haney 2020) and have a limited variety of cannabis and CBD to evaluate in trials. Despite these barriers, a current survey of the National Institutes of Health website, www.clinicaltrials.gov, revealed 276 planned, ongoing, or completed human trials with CBD (the vast majority using oral formulations) for many of the indications that have shown promise in the preclinical research.

It must be emphasized that the standardized, chemically pure CBD available for preclinical research and human clinical trials is not necessarily the consumer CBD available for sale from vendors and the Internet. A 2017 survey (Bonn-Miller, Banks, and Sebree 2017) reported that of eighty-four online CBD and hemp oil products examined, only twenty-six were accurately labeled for CBD and THC content, with CBD often being overlabeled and THC underlabeled, consistent with warnings from the Food and Drug Administration. Buyer beware!

Many drugs used today are natural products or their derivatives. So far, CBD has been approved as a treatment by the US Food and Drug Administration only for some rare forms of childhood epilepsy and seizures associated with tuberous sclerosis complex in patients one year of age or older. In this book, we discuss various aspects of CBD's actions. In many disease states, mostly in animal models, but also some in human studies, positive results have been noted and published. In view of the encouraging animal as well as the limited human clinical data and the relatively low level of toxicity or major side effects, we expect that CBD or, more likely, CBD derivatives with an improved pharmacological profile may be developed as drugs to treat several additional medical conditions in the future.

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Chemical and Pharmacological Aspects

Cannabis contains a mixture of many closely related compounds. These compounds were difficult to identify until recently with the development of modern methods, such as chromatography and spectrometry. Chromatography is needed to isolate the chemical substances in a mixture, and spectrometry is needed to then determine that substance's chemical makeup and structure. Over the past few decades, 554 compounds in cannabis have been identified, including 113 phytocannabinoids and 120 terpenes (aromatic oils that give cannabis strains their distinctive scents; Ahmed et al. 2008; ElSohly and Gul 2014).

Over the past ten years, the concentration of THC has been increasing in the illicit market, but recently more high-CBD products have also been produced. Of interest is a recent report (ElSohly et al. 2021) on the concentration of seven major cannabinoids, including Δ^9-THC and CBD, in illicit herbal cannabis products seized by the Drug Enforcement Agency in the last ten years in the United States. The number of samples seized decreased dramatically over the past five to six years because of legalization of marijuana for either medical or recreational purposes in many states. Of the confiscated samples analyzed, the mean Δ^9-THC concentration increased from 10 percent in 2009 to 14

percent in 2019, with the mean THC:CBD ratio increasing from 25 in 2009 to 105 in 2017. Perhaps because of the evolving interest in the potential benefits of CBD, the THC:CBD ratio in 2019 decreased to 25, suggesting a trend in the production of more high-CBD products.

The therapeutic potential of these cannabis constituents has been mostly limited to the investigation of THC and CBD, leaving many unanswered questions regarding the biological activity of most of the other cannabinoids found in cannabis. Indeed, there has been considerable discussion of "entourage effects" (Mechoulam et al. 2014) among these cannabinoids; that is, the effect of cannabis is more than just the sum of its parts. Synergistic or at times antagonistic effects occur because there are different actions of the various cannabinoids at specific receptors in the body. It is like an orchestra that can blend and mix its components in an almost unlimited fashion. The emphasis of this book, however, is to identify the current state of knowledge about the effects of CBD as one of these components of cannabis. In this chapter, we describe the chemistry and pharmacology of CBD.

Cannabidiol: Chemical Aspects

Cannabidiol (CBD) was isolated in 1940 from marijuana in the laboratory of Roger Adams in the United States (Adams, Hunt, and Clark 1940) and from Indian hemp resin in the laboratory of Alexander Todd in the United Kingdom (Jacobs and Todd 1940). They suggested a tentative partial structure based on chemical degradation and correlation with the known cannabinoid constituent cannabinol. In 1963, the correct full structure was reported by Mechoulam and Shvo (1963) and in 1964 by Santavy (1964), mostly based on nuclear magnetic resonance (NMR) data. The absolute stereochemistry was determined in 1967 (Mechoulam and Gaoni 1967a).

CBD is a crystalline compound with a melting point of 66°C to 67°C. Its NMR spectroscopy and infrared spectra are presented in a review (Mechoulam and Gaoni 1967b). The crystalline structure

of CBD was determined by Jones et al. (1977). The aromatic ring and the terpene ring were found to be almost perpendicular to each other. This is in contrast to the structure of Δ^9-tetrahydrocannabinol (THC), the main psychoactive cannabis constituent, in which the two rings are almost in the same plane. However, the different conformations in the crystalline state may be irrelevant to the difference in activity between CBD and THC, as the two rings in CBD can freely rotate in solution and in the gaseous state.

Synthesis of CBD

Of the several CBD syntheses that have been reported (Jung et al. 2019), the most efficient one seems to be the acid condensation of p-mentha-2,8-dien-1-ol with olivetol, as originally proposed by Petrzilka and colleagues (1967) and later improved (Baek, Srebnik, and Mechoulam 1985; figure 2.1). The yield reported (41 percent) in this one-step reaction makes CBD readily available. In addition to CBD, this reaction also leads to the abnormal CBD (abn-CBD), a relatively unstudied cannabinoid.

Chemical Reactivity of CBD

Acidic Conditions Under strong acidic conditions (heating with p-toluene sulphonic acid; p-TSA) CBD is converted first into Δ^9-THC, which is then isomerized to Δ^8-THC. Under different acidic conditions (with BF_3), CBD is ring closed into Δ^9-THC, as well as into Δ^8-iso-THC (figure 2.2) (Gaoni and Mechoulam 1966a, 1966b). While Δ^9-THC has

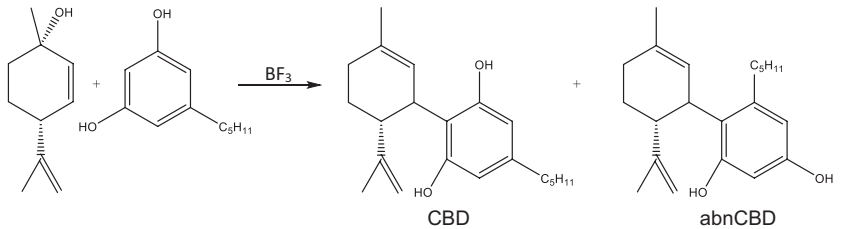

Figure 2.1
The synthesis of CBD

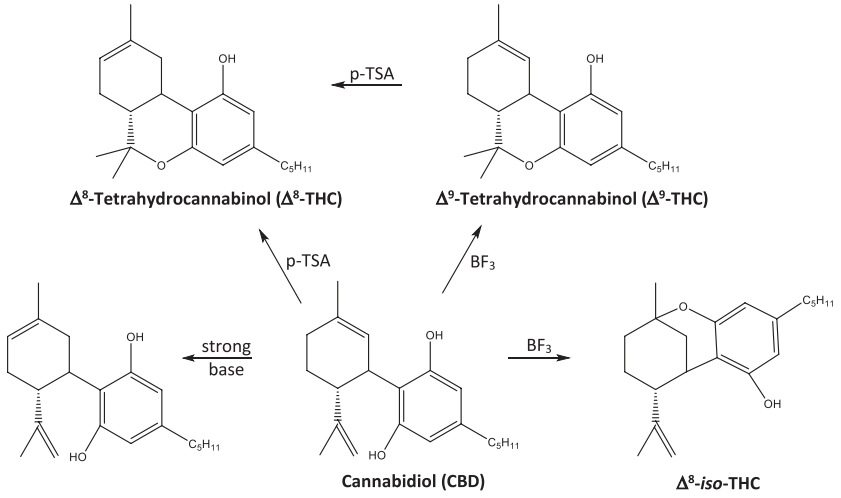

Figure 2.2
Reactions of CBD under acidic and basic conditions

been the subject of hundreds of publications, Δ^8-iso-THC, which is also psychoactive, has been almost totally neglected.

Recently it was claimed that CBD can convert into Δ^9-THC upon prolonged exposure to simulated in vitro acidic gastric conditions (Merrick et al. 2016). This report was strongly opposed by Grotenhermen and colleagues (2017), who claimed that the conversion of CBD into THC does not take place in vivo in the stomach and brought evidence that the in vitro conditions may not be representative of the in vivo gut environment and that this reaction does not seem to be relevant to the actual in vivo conditions that exist in our gut. A main point that Grotenhermen and colleagues stressed is that because CBD does not cause cannabis-type psychoactivity when administered orally to patients, its conversion to the psychoactive THC does not take place. The Grotenhermen opposing report was not accepted by the original authors (Bonn-Miller, Banks, and Sebree 2017); however, several additional publications support the claim that CBD is not converted into THC in the animal body (Nahler et al. 2017; Wray et al. 2017; Crippa et al. 2020).

Basic Conditions Under specific basic conditions (potassium in tert-pentyl alcohol), CBD has been isomerized to its Δ^6 analog (Srebnik et al. 1984), which has received very little investigation (figure 2.2). In order for the isomerization to take place, both phenolic groups have to be free. Apparently the CBD phenolate is involved in this reaction. Contrary to the natural CBD (Δ^1 isomer), the synthetic Δ^6 isomer of CBD showed THC-like activity in rhesus monkeys (Mechoulam and Hanus 2002). Again, as with the Δ^8-iso-THC, mentioned above, while the plant CBD (Δ^1 isomer) has been the topic of many hundreds of publications, its Δ^6 isomer has not received any attention.

Oxidation CBD in base in the presence of oxygen is oxidized to the p-quinone (figure 2.3), a potent topoisomerase II inhibitor (Kogan

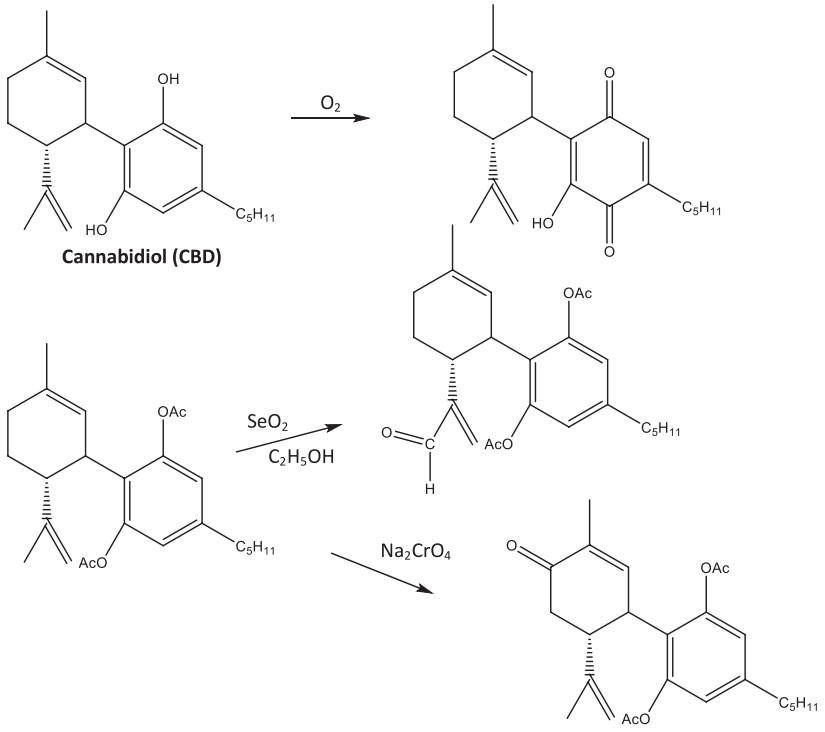

Figure 2.3
Oxidations of CBD and CBD diacetate

et al. 2004; Kogan, Schlesinger, Priel, et al. 2007). A comparative in vivo study in mice has shown that the CBD quinone is less toxic and more effective in reducing tumor growth than the widely used anticancer drug doxorubicin, which is also a topoisomerase II inhibitor (Kogan, Schlesinger, Peters, et al. 2007). Oxidation of CBD diacetate with selenium dioxide leads to the aldehyde on the C-10 position, while oxidation with sodium chromate takes place on the C-6 position (Lander et al. 1976; figure 2.3). In several studies, CBD has been found to possess potent antioxidant activity, which may be the basis of its assumed role in neurodegenerative diseases (Hacke et al. 2019).

Photochemical Reactions of CBD

Irradiation of CBD in methanol with a 450 W lamp gives a mixture from which two 1-methoxy dihydro cannabidiols were isolated. Irradiation in cyclohexane also leads to a mixture from which Δ^9-THC, iso-THC, reduced CBD, and an additional product of cyclohexane to CBD were isolated (Shani and Mechoulam 1971; figure 2.4). The

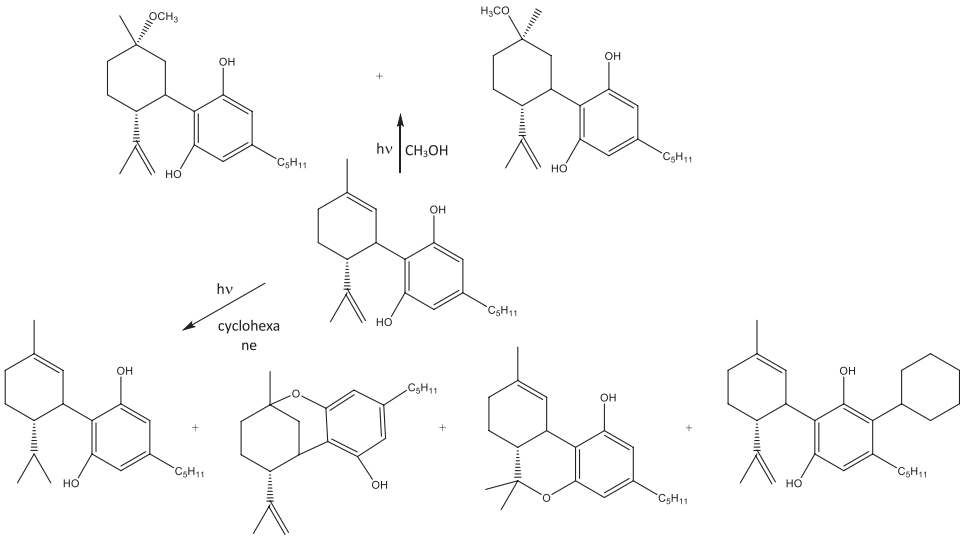

Figure 2.4
Photochemical reactions of CBD

instability of CBD on irradiation (possibly only in solution) should be taken into account in laboratory studies as well as in commercial products.

(+) Cannabidiol

The unnatural (+) CBD enantiomer and some of its derivatives have been reported (Leite et al. 1982; Hanus et al. 2005). Surprisingly, contrary to the compounds in the (–) series, which bind very weakly to the CB_1 receptor, (+) CBD and most of the derivatives in the (+) series bind to the CB_1 receptor in the nanomole range, as well as to the vanilloid receptor type 1 (VR1) (Hanus et al. 2005; Bisogno et al. 2001). Some of these compounds also bind weakly to the CB_2 receptor. A derivative of (+) CBD was reported to be more active than the (–) enantiomer in an ovulation blockage assay in rats (Cordova et al. 1980).

Cannabidiolic Acid

CBD is actually not a natural product. The cannabis plant produces the unstable cannabidiolic acid (CBDA), which is nonenzymatically decarboxylated to CBD (figure 2.5) often by heating or drying of the plant material. Preclinical investigations in rats indicate that CBDA is 100 to 1,000 times more potent than CBD in reducing nausea and vomiting (Bolognini et al. 2013; Rock and Parker 2013), stress-induced anxiety (Bolognini et al. 2013; Rock et al. 2017), and inflammatory pain (Rock, Limebeer, and Parker 2018). At much higher doses, it also seems to parallel CBD in its antiepileptic activity (Anderson et al. 2019). However, CBDA is unstable and may not be optimal as a medicine. Recently it was shown that the methyl ester of CBDA (HU-580) is stable, and several reports on its biological activities have been published. It can cause suppression of nausea and stress-induced anxiety in rats, which is serotonin 1A ($5\text{-}HT_{1A}$) receptor-mediated (Pertwee et al. 2018). In animal models, it also lowers depression-like behavior (Hen-Shoval et al. 2018), as well as neuropathic pain (in male animals only!) (Zhu et al. 2020).

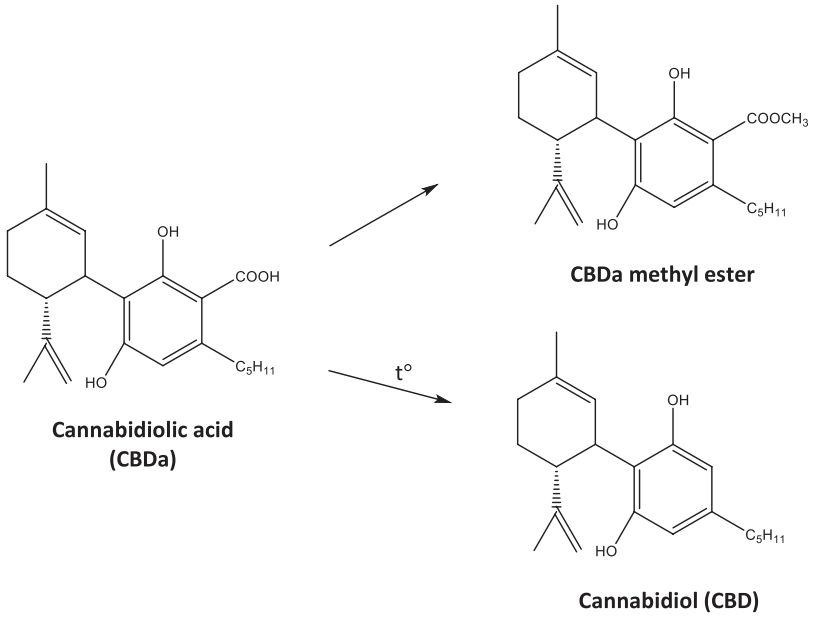

Figure 2.5
Reactions of cannabidiolic acid

Murillo-Rodríguez and colleagues (2020) have recently reported that the methyl ester of CBDA prolonged wakefulness and decreased slow-wave sleep duration. It enhanced extracellular levels of dopamine and serotonin in the nucleus accumbens, while adenosine and acetylcholine were increased in the basal forebrain.

Derivatives of Cannabidiol

Many drugs used today are semisynthetic (made from the synthesis of a natural product) derivatives of natural products, developed in order to enhance the activity of the natural product or to make it more suitable for human use. Derivatives of penicillin and cortisone are typical examples. Derivatives of CBD have also been reported. Thus, 4′-F-CBD, was prepared by direct fluoridation of CBD (Breuer et al. 2016; figure 2.6). It was found to be considerably more potent than CBD in behavioral assays in mice predictive of anxiolytic,

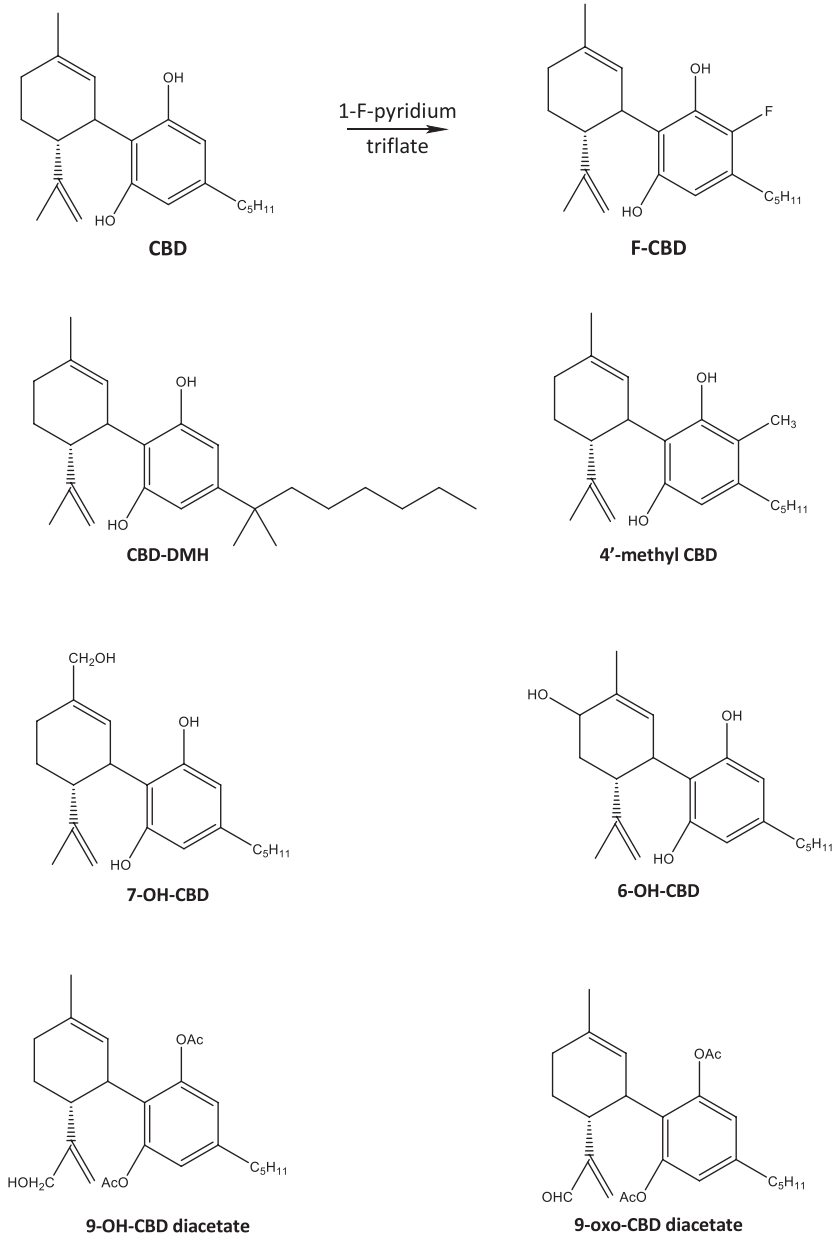

Figure 2.6
CBD derivatives

antidepressant, antipsychotic, and anticompulsive activity. It also lowers pain in mice (Silva et al. 2017).

The exchange of the pentyl side chain in CBD with a dimethyl heptyl side chain leads to a new compound known as CBD-dimethylheptyl, CBD-DMH, which has been shown, like CBD, to downregulate the expression of inflammatory cytokines, decrease the proliferation of pathogenic-activated T_{MOG} cells (Juknat et al. 2016), and inhibit TNF production by targeting NF-kB activity (Silva et al. 2019).

Further known derivatives of CBD are 6-hydroxy-CBD, 7-hydroxy-CBD, 9-hydroxy-CBD, 9-oxo-CBD diacetate (Lander et al. 1976), and 4′-methyl-CBD (Edery et al. 1972; figure 2.6).

Conclusion: CBD Chemistry

The chemistry of CBD is well established, and its facile synthesis makes it easily available. As described below, it acts through several mechanisms of action. It is nontoxic, has numerous therapeutic activities, and as it causes relatively few adverse side effects, it is already widely used as a therapeutic agent, although it has been approved by the FDA only for some seizure conditions.

Cannabidiol: Pharmacological Aspects

Preclinical animal research has revealed that CBD should be evaluated as a therapeutic tool for a large variety of conditions, including epilepsy, analgesia, inflammation, anxiety, psychosis, and addiction. Clinically, a few human studies with CBD have investigated the treatment of multiple disease states, including epilepsy, neurodegeneration, pain, anxiety disorder, schizophrenia, and addiction. A current survey of the NIH website, www.clinicaltrials.gov, revealed 276 planned, ongoing, or completed human trials with CBD (the vast majority using oral formulations) for many of the indications that have shown promise in the preclinical research. Over-the-counter

CBD is also marketed as an unregulated food supplement/medication. It has been reported (Bonn-Miller et al. 2017) that 69 percent of these unregulated products marketed as "CBD-only" were inaccurately labeled (43 percent underlabeled for CBD concentration, 26 percent overlabeled for CBD concentration, and 21 percent contained THC [up to 6.4 mg/L]). Despite the prevalence of CBD use, guidance on dose recommendations has not advanced, mostly because of the lack of pharmacokinetic and bioavailability data for CBD in humans. Only a few published studies report oral bioavailability of CBD in humans. As well, there are few dose-determination studies, limiting our understanding of the desired plasma concentrations to achieve minimum effective doses. There is a lack of information about how different formulations and routes of administration affect absorption into the bloodstream. We review the published data available below.

CBD Bioavailability

The term *bioavailability* refers to the fraction of an administered dose of unchanged drug that reaches the systemic circulation. When a drug is administered directly into the bloodstream intravenously, its bioavailability is 100 percent. When a drug is administered orally, inhaled, or delivered transdermally (by application to the skin), its bioavailability decreases because of incomplete absorption into the blood or by first-pass metabolism by enzymes in the liver. It is clear that the bioavailability of CBD varies with the route of administration.

Bioavailability is assessed by a number of metrics reflecting pharmacokinetic (PK) properties of drugs. C_{max} means the maximum (peak) concentration in the blood recorded, and T_{max} means the time it takes to reach that peak concentration. The area under the plasma-drug concentration-time curve (AUC) is expressed as ng/L for CBD. The AUC reflects that actual body exposure to the drug after administration of a given dose and is dependent on the absorption and elimination of the drug from the body. The elimination half-life of a drug

is defined as the time it takes for the concentration of the drug in the plasma to be reduced by 50 percent; that is, after one-half-life, the concentration of the drug in the body will be half of the starting dose. These metrics are used to reveal the bioavailability of drugs. CBD is generally administered orally as either a capsule or dissolved in an oil solution (e.g., olive or sesame oil) in clinical trials or research studies. It can also be administered through sublingual, intranasal, and transdermal routes; however, the relative plasma absorption of these routes is not well understood.

Smoking/vaporizing. Smoking CBD-rich hemp or a CBD-biased cannabis strain provides a rapid and efficient delivery from the lungs to the body. The bioavailability of aerosolized CBD has been reported to yield rapid peak plasma concentrations in five to ten minutes and higher bioavailability (approximately 31 percent) than oral administration (Grotenhermen 2003; Ohlsson et al. 1986). Because vaporizers (commonly called e-cigarettes) typically operate at temperatures that do not combust the cannabis product being inhaled, they expose cannabis smokers to fewer toxicants (e.g., carbon monoxide) compared to smoked methods (Spindle, Bonn-Miller, and Vandrey 2019). Vaporized cannabis users report fewer respiratory symptoms compared to those who predominantly smoke cannabis, but the long-term health effects of regular users of smoked versus vaporized cannabis remain unclear (Newmeyer et al. 2016). In 2019 there was an outbreak of emergency department visits in the United States related to vaping THC products, but the incidence has declined due to the removal of vitamin E acetate from the products. Laboratory data show that vitamin E acetate, an additive in some THC containing vaping products, was strongly linked to these outbreaks (Blount et al. 2020). However, it is not known if long-term use of vaporizers may be harmful.

Topical formulations. Some of the most popular emerging cannabis products are topical, with formulations including balms, creams, salves, gels, and patches. At this time, there are no controlled clinical

studies or representative surveys with which to assess the pharmacokinetic profile, behavioral effects, and use characteristic of these products (Spindle, Bonn-Miller, and Vandrey 2019). Few data are available about the bioavailability of topical formulations. In dogs, CBD (from Applied Basic Science Corporation) was administered by transdermal cream, oral CBD-infused oil, or oral CBD in microencapsulated beads (Bartner et al. 2018) at doses of 750 mg and 1,500 mg and CBD levels in plasma were measured over the first twelve hours. Over the first twelve hours, bioavailability was eight times higher by oral infused oil than by transdermal cream at a dose of 75 mg and three times higher at a dose of 150 mg. Since CBD is highly lipophilic, it accumulates in the outer layer of the skin (strata corneum) and does not penetrate through the skin layers. New delivery technologies are being developed to enhance permeation approximately three-fold, as tested in guinea pigs (Paudel et al. 2010). New research (described in detail in chapter 11) indicates that transdermal CBD (combined with a permeation enhancer) at twenty-four-hour intervals for seven days reduced relapse to alcohol or cocaine self-administration in rats, a model of addiction, as well as anxiety in an elevated plus maze (Gonzales-Cuevas et al. 2018).

Oral administration. The most common method for administration of CBD is orally or by submucosal spray. The vast majority of clinical trials posted on www.clinicaltrials.gov involve oral administration of CBD. CBD is a highly lipophilic drug, with its solubility in the aqueous environment of the gut being in the range of only several milligrams per liter (Samara, Bialer, and Mechoulam 1988). This low water solubility leads to incomplete absorption. As well, when administered orally, CBD undergoes first-pass metabolism in the liver (Martin, Harvey, and Paton 1977), while a large proportion (33 percent) is excreted unchanged in the feces. The earliest work with humans estimated the bioavailability of oral delivery of 20 mg CBD to be only 6 percent due to significant first-pass metabolism in the liver (Agurell et al. 1981). Subsequently, 900 mg of CBD was administered orally

to a monkey, and extremely low levels of plasma CBD were detected over the entire experiment (Jones et al. 1981). In dogs, oral CBD (180 mg by gelatin capsule) was detected in the blood of only three out of six dogs with bioavailability values of 13 percent, 13 percent, and 19 percent, respectively (Samara, Bialer, and Mechoulam 1988).

GW Pharmaceuticals' plant-derived highly purified oral CBD (Epidiolex, 100 mg/ml) was FDA approved in the United States in June 2018 for seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients two years of age and older. Four randomized, placebo-controlled trials (Devinsky et al. 2017; Devinsky, Patel, Cross, Villanueva, Wirrell, Privitera, Greenwood, Roberts, Checketts, VanLandingham, Zuberi, et al. 2018; Devinsky, Patel, Thiele, et al. 2018; Thiele et al. 2018) demonstrated the efficacy and safety of CBD in these severe and treatment refractory epilepsies. Recently, a phase 2 human clinical trial with both a single ascending dose and multiple-dose pharmacokinetic trial (Taylor et al. 2018) of this oral formulation of CBD (Epidiolex) was reported in healthy adult volunteers. The single ascending dose arm of the study was double-blind, randomized, and placebo controlled. Four groups of healthy participants received single ascending oral doses of 1,500, 3,000, 4,500, or 6,000 mg CBD or matching placebo. Over the course of CBD treatment, the C_{max} of CBD and metabolites increased with a trend to less than dose proportionality; that is, as the dose increased, the C_{max} did not increase representatively. CBD and metabolites appeared rapidly in the plasma, with a T_{max} of four to five hours independent of the dose. The effective half-life of CBD was in the range of ten to seventeen hours, independent of the dose. Given the high lipophilicity of CBD, solubility-limited absorption of higher doses is a likely explanation for the lack of dose-dependent elevation of C_{max}. Lim, Sharan, and Woo (2020) reviewed several studies using single dose (5,000–6,000 mg) oral CBD plasma concentration-time profiles in healthy participants with the conclusion that CBD absorption saturated around 4,000 mg, where the amount absorbed into the body (dose multiplied by bioavailability)

approaches its plateau. When absorption saturation occurs, systemic exposure does not proportionately increase with increasing doses.

In the multiple dose arm of the phase 1 double-blind, randomized, and placebo-controlled trial (Taylor et al. 2018), two groups received multiple oral doses of 750 or 1,500 mg CBD or matching placebo twice daily, under fasted conditions for seven days. Steady-state CBD plasma concentrations were reached at approximately two days. At steady state, there was an almost doubling in exposure for a twofold increase in dose (750–1500 mg) with C_{max} increasing by about 1.6-fold and AUC increasing approximately 1.9-fold. Therefore, unlike single dosing, multiple dosing increased bioavailability in almost a dose-proportional manner, at least at these two lower doses. At steady state, T_{max} of CBD and its metabolites occurred at approximately three hours, independent of the dose. Single doses up to 6,000 mg and multiple doses up to 1,500 mg twice daily were well tolerated, with only mild and moderate aversive effects reported (diarrhea, nausea, headache, and somnolence) during the trial. There were no discontinuations due to aversive effects.

Finally, the phase 1 trial (Taylor et al. 2018) also included a food effect arm, which was randomized to a period (fed [high fat breakfast], then fasted or fasted, then fed). Participants were dosed thirty minutes after starting breakfast and then fasted for four hours. In the fed state, bioavailability of CBD was increased in all groups (4.85-fold increase in C_{max}; 4.2-fold increase in AUC) compared to the fasted state. The bioavailability of CBD is clearly increased by food. However, there was no effect of food on T_{max} or on half-life of CBD or its metabolites. This effect was recently confirmed (Crockett et al. 2020) following a single oral 750 mg dose of CBD (Epidiolex in healthy adults following a high-fat/calorie meal ($n=15$), a low fat/calorie meal ($n=14$), whole milk ($n=15$), or alcohol ($n=15$) relative to a fasted state ($n=29$). Blood samples were collected until ninety-six hours postdose and analyzed by liquid chromatography and tandem mass spectrometry. The bioavailability of CBD administered with a

high fat/calorie meal increased by 5.2-fold versus fasted, low fat/calorie meal by 3.8-fold versus fasted, whole milk by 3.1-fold versus fasted and alcohol by 3.1-fold versus fasted. The meal state did not affect T_{max} of CBD. As well, Birnbaum et al. (2019) evaluated the pharmacokinetics of purified oral CBD capsule with and without food in adults with refractory epilepsy. A single dose of 99 percent pure CBD capsules was taken in fasting (no breakfast) and fed (840–860 calorie high-fat breakfast) conditions. Blood sampling for CBD in plasma concentrations was performed under each condition between 0 and 72 hours postdose and measured by liquid chromatography mass spectrometry assay. Bioavailability of CBD was fourteen times higher in the fed state than in the fasted state. No adverse effects were reported.

Clearly, in a fasted state, oral CBD has poor bioavailability, but in a fed state, bioavailability is significantly improved. One of the current focuses of pharmaceutical research is the development of new vehicles (solutions that CBD is mixed in) for delivery of CBD to increase bioavailability. Such vehicles include capsules in which CBD is suspended in solutions of long-chain fatty acids high in oleic acid (Patrician et al. 2019) or in nano-lipospheres of less than 60 nm in diameter (Atsmon et al. 2018), both showing higher bioavailability relative to generic CBD.

Once in the bloodstream, CBD is rapidly distributed into tissue and, like THC, may preferentially accumulate in adipose tissues due to its high lipophilicity.

CBD Metabolism

CBD is extensively metabolized in the liver (Martin, Harvey, and Paton 1977). The primary route is hydroxylation to 7-OH-CBD, which is then metabolized further, resulting in a number of metabolites that are excreted in feces and urine. In vitro studies with human liver microsomes (Jiang et al. 2013, 2011) demonstrated that seven human cytochrome P450 (CYP) enzymes are capable of metabolizing

CBD, with the two main forms being CYP3A4 and CYP2C19, known to also be involved in the metabolism of various clinically important drugs. This suggests that CBD may interact with other drugs by this mechanism; in fact, there is a report that the metabolism of Δ^9-THC is inhibited by CBD (Jones and Pertwee 1972). A recent report (Taylor et al. 2019) suggests that exposure to CBD metabolites was increased in subjects with moderate and severe hepatic impairment, suggesting that dose modification is necessary in such patients—they should start at a lower dose with slower titration. However, CBD was well tolerated in this population as well. In the recent clinical trials for epilepsy, CBD is given as an adjunct treatment along with the patient's prescribed antiepilepsy medication(s) (typically three medications), which may interfere with drug-drug metabolism. It has been shown that concomitant administration of CBD with clobazam (a common antiepilepsy drug) produced increased plasma concentrations of clobazam's major active metabolite, N-desmethylclobazam, likely the result of CBD inhibition of CYP2C19, which may result in the adverse event of sedation, a common side effect of clobazam administration (Geffrey et al. 2015; Gaston et al. 2017). However, a recently reported clinical trial (Gaston et al. 2019) showed that such drug-drug interactions cannot account for the effects of CBD on reducing seizure frequency and severity in treatment-resistant epilepsy. Interestingly, data suggest that acute treatment with CBD (120 mg/kg, i.p.) inactivated at least one cytochrome P450 isozyme in mice livers, but after repetitive CBD (120 mg/kg, i.p. for four days) treatment, an isozyme was induced that was resistant to further doses of CBD (Bornheim and Correia 1989). This isozyme appears to be similar to the isozyme induced by phenobarbital (a common anticonvulsant medication that controls epileptic seizures) in mice. A comprehensive review (Balachandran, Elsohly, and Hill 2021) describes the interactions between CBD and other medications, illicit substances, and alcohol.

Can CBD Be Converted in Vivo to THC?

In the laboratory using certain methods, CBD can be converted to THC (Mechoulam and Hanus 2002); however, the likelihood that CBD converts to THC in the body of CBD consumers is very low. There were in vitro reports that CBD could be converted to THC spontaneously in the presence of an acid that could occur in the human gut (Merrick et al. 2016); however, subsequent research has indicated that this finding is limited to specific experimental conditions and likely does not occur when oral CBD is consumed by humans. A recent study supported by GW pharmaceuticals, the source of Epidiolex, examined the gastric and plasma concentrations of cannabinoids in mini-pigs (with a GI composite similar to humans) after repeated CBD administration (15 mg/kg/day for five days). No THC or THC metabolites were detected in plasma or gastric fluid after CBD administration (Wray et al. 2017). Generally there is no experimental evidence that this transformation occurs in humans after oral CBD administration. In one human study, 600 mg of CBD was administered to healthy participants. No THC or trace concentrations of THC metabolites (11-OH-THC, THC-COOH) were detected (Martin-Santos et al. 2012). Even chronic administration of CBD does not result in detectable THC concentrations in plasma; for example, in a six-week clinical study with Huntington's disease patients who were administered CBD 10 mg/kg/day (about 700 mg/day), CBD average plasma concentration range was 5.9 to 11.2 ng/ml with no THC detected (Consroe et al. 1991). In addition, a recent study (Kintz 2021) tested the blood of eight volunteers after vaping an e-cigarette containing 100 mg/mL of CBD, and no THC or THC-COOH was detected (at fifteen and forty-five minutes after the last use). This is of importance, as the blood testing was achieved under acidic conditions, suggesting no evidence of in vivo conversion of CBD to THC when CBD was administered by vaporization. Most recently, McCartney et al. (2021) reported that orally administered CBD did not produce false positive tests for THC on standard point

of collection oral fluid testing devices. In a randomized, double-blind, crossover design, healthy participants ($n = 17$) completed four treatment sessions involving administration of placebo, 15 mg, 300 mg, or 1500 mg pure CBD in a high-fat dietary supplement. Oral fluid samples were tested at baseline, 20, 145, and 185 minutes post-treatment. THC was not detected in any samples. Recent reviews have summarized a number of studies involving high doses of CBD consistently failing to demonstrate THC-like effects (psychomotor impairment, increased HR, tachycardia, dry mouth; Nahler et al. 2017; Grotenherman, Russo, and Zuardi 2017). Overall, there is no evidence that oral CBD administration in humans results in clinically relevant THC-like subjective or physiological effects or appreciable plasma concentrations of THC or its metabolites.

Impact of CBD on Drug Testing for THC

The impact of CBD exposure on urine drug testing for THC has not been well studied. Spindle et al. (2020) characterized the urinary pharmacokinetic profile of 100 mg oral and vaporized CBD, vaporized CBD-dominant cannabis (100 mg CBD; 3.7 mg Δ^9-THC), and placebo in six healthy adults using a within-subjects crossover design. Urinary peak concentrations of CBD were higher after oral (mean C_{max}:776 ng/ml) versus vaporized CBD (mean $C_{max:}$ 261 ng/ml). CBD concentrations peaked five hours after oral CBD ingestion and within one hour after inhalation of vaporized CBD.

Due to the increased use of CBD and CBD-dominant cannabis products, there is a need to understand the impact of CBD on urine drug-testing programs commonly used in the workplace, criminal justice, drug treatment, and other settings. Urine is the primary biological choice for drug testing, and the most commonly targeted analyte to evaluate cannabis exposure is 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol (Δ^9-THCOOH), a metabolite of Δ^9-THC. Although drug testing is not aimed at detecting CBD in existing drug-testing procedures, contaminated CBD products could theoretically produce

a positive result for Δ^9-THCOOH on a urine drug test. Indeed, given the nature of the unregulated cannabis industry, products may falsely advertise as containing only CBD but may also contain Δ^9-THC in concentrations ranging from trace levels to those capable of producing intoxication (and detection in drug testing). As well, hemp-derived CBD products can contain up to 0.3 percent Δ^9-THC, and even the FDA-approved CBD medication, Epidiolex, may contain trace levels (less than 0.1 percent) of Δ^9-THC, and possibly increase the risk of testing positive for THC. Acute oral ingestion or inhalation of a 100 mg dose of CBD did not result in positive urine drug test when using screening and confirmatory cutoffs in the mandatory guidelines for federal workplace drug testing in the United States (Spindle et al. 2020). In contrast, inhalation of cannabis containing 100 mg CBD and 3.7 mg Δ^9-THC resulted in positive test results for two of the six participants. Urinary concentrations of CBD were higher and peaked later when CBD was orally ingested compared to when it was inhaled. There was no evidence in this study that CBD converts to Δ^8-THC or Δ^9-THC in the human gut in a fed state. However, it is not known if this would also not occur in a fasted state when the gut is more acidic.

CBD Pharmacodynamics

CBD has been reported to have several molecular sites of action for its various effects. A summary of CBD pharmacodynamics is presented in table 2.1. Some have argued that the myriad potential therapeutic effects of CBD may be related to these varied mechanisms of action.

CBD does not appear to act directly at CB_1 or CB_2 receptors—there is very little measurable response in binding assays; that is, only at high concentrations (greater than 10 μM) has CBD been found to bind with CB_1 receptors or CB_2 receptors (Pertwee 2008). However, using human CB_2 receptors in HEK293A cells, CBD has more recently been reported to act as a partial agonist (in the nM range; Tham et al. 2019). It appears to act indirectly at both cannabinoid receptors. It

Table 2.1
CBD pharmacodynamics

Receptors	Ion Channels	Enzymes	Other
Low CB_1/CB_2 affinity CB_1- or CB_2-negative allosteric modulator $5HT_{1A}$ agonist Peroxisome proliferator-activated receptor gamma (PPAR γ) activator GPR55 antagonist GPR18 agonist Inverse agonist for GPR3, GPR6, and GPR12 Adenosine receptor agonist	Activation of TRPV1, TRPV2, TRPV3, and TRPM8 Calcium channel inhibition	FAAH inhibitor Inhibits CYP1A1, 2B6, 2C19, 3A4, and 3A5 Cyclooxygenase inhibitor/activator	Binds to FABPs (competitive inhibition) Adenosine uptake inhibitor

Abbreviations: $5HT_{1A}$, serotonin1A; CB_1, cannabinoid receptor type 1; CB_2, cannabinoid receptor type 2; CBD, cannabidiol; CYP, cytochrome P450; FAAH, fatty acid amide hydrolase; FABP, fatty acid binding protein; GPR, g- protein coupled receptor; TRPM, melastatin-related transient receptor potential cation channels; TRPV1, transient receptor potential cation channel subfamily V member.

is a negative allosteric modulator of the CB_1 receptor, thereby acting as a noncompetitive antagonist of the actions of THC and other CB_1 agonists (Laprairie et al. 2015). CBD also has been reported to act as a negative allosteric modulator at the CB_2 receptor (Martinez-Pinilla et al. 2017). In rodent studies, CBD may also enhance the action of anandamide, an endogenous ligand of the CB_1 and CB_2 receptors by blocking its degradation by the enzyme, fatty acid amide hydrolase (FAAH) (Bisogno et al. 2001); however, this mechanism may not occur in humans (Criscuolo et al. 2020). CBD dampens nitric oxide (NO) production in animal models of inflammation and the expression of inflammatory cytokines and transcription factors and reactive oxygen species (ROS) production. However, in cancer cells, CBD is capable of generating ROS, thereby inducing cytotoxicity or apoptosis and autophagy (Ligresti et al. 2006).

CBD has also been shown to modulate several non-endocannabinoid neurotransmitter signaling systems that may be responsible for its therapeutic effects. Considerable evidence suggests that CBD enhances serotonergic activity at the 5-HT_{1A} receptor (Rock et al. 2012; Russo, Burnett, and Hall, 2005) which may mediate its antinausea, antiemetic, and anxiolytic effects. It has also been shown to act on several other neurotransmitter systems, including inhibition of the uptake of adenosine, agonism of several channels belonging to the transient receptor potential (TRP) family (TRPV1, TRPV2, TRPA1), enhancement of the activity of glycine receptor subtypes, activation of peroxidase proliferator–activated receptor γ (PPARγ), and blockade of the orphan G-protein coupled receptor GPR55 (Pertwee 2008). It has been suggested that such a multitarget action by CBD is key for its diverse therapeutic potential for several indications. The potential mechanisms of action of CBD for each of the therapeutic end points discussed in this book are reviewed in the relevant chapter.

CBD Safety and Toxicology

Several reviews have evaluated the safety and toxicity of CBD (Iffland and Grotenhermen 2017; Bergamaschi, Queiroz, Zuardi et al. 2011). Generally, in vitro and preclinical animal studies have found CBD to be relatively low in toxicity; however, less is understood about the toxicity of long-term use in humans, especially of the high therapeutic doses used for many indications such as psychosis (see chapter 10). There are also no human data on the effects of CBD in pregnancy and in breastfeeding mothers on fetal and infant development. CBD modifies growth of tumoral cell lines but has no effect on most nontumor cells (Massi et al. 2006). Although the evidence is severely limited, CBD does not appear to affect the development of embryonic cells (Paria, Das, and Dey 1995). In preclinical animal research (Rosenkrantz, Fleischman, and Grant 1981), CBD has generally no effects on a wide range of physiological and biochemical parameters or on animal behavior on its own unless extremely high

doses are given (e.g., in excess of 150 mg/kg i.v. as an acute dose or exceeds 30 mg/kg orally daily for ninety days in monkeys). The effect on the immune system is unclear, with evidence of immune suppression at higher concentrations but immune stimulation at lower concentrations.

There is a potential for CBD to be associated with drug interactions through inhibition of some cytochrome P450 enzymes (Sholler, Schoene, and Spindle 2020; Balachandran, Elsohly, and Hill 2021). The impact of CBD alone, and in combination with other medications, on liver function needs continued monitoring. Specifically, CBD may inhibit metabolic activity of several cytochrome (CYP) P450 drug-metabolizing liver enzymes that are instrumental in the metabolism of many common prescription and over-the-counter drugs. More specifically, administration of CBD in combination with drugs metabolized by certain CYP enzymes (for example, CYP2C9, CYP2D6) may lead to delayed metabolism of these drugs. For example, a study of children with refractory epilepsy found that administration of Epidiolex (5–25 mg/kg/day) in combination with clobazam (antiseizure medication) elicited about a 500 percent increase in plasma concentrations of the active metabolite of clobazam (norclobazam; Geffrey et al. 2015). In a recent review (Balachandran, Elsohly, and Hill 2021), CBD has been reported to interact with antiepileptic drugs, antidepressants, opioid analgesics, and THC, but it surprisingly also interacted with several other common medications, including acetaminophen and alcohol. Continued research is needed in this area.

In contrast to THC, CBD has no effect on heart rate or blood pressure under normal conditions, but in animal models of stress, it reduces heart rate and blood pressure (Sultan et al. 2017). Several clinical trials with humans have assessed safety and toxicology of CBD as a therapy for treatment-resistant epilepsy. A thorough review of these studies (Iffland and Grotenhermen 2017) revealed that the most commonly reported side effects were fatigue, diarrhea, and changes of

weight or appetite. Since CBD is most commonly used as an adjunct therapy, more clinical research on the impact of CBD on hepatic liver enzymes, interactions with other drugs, and effects on embryonic development is needed.

A more recent meta-analysis of randomized clinical trials with CBD (Chesney et al., 2021) suggests that the likelihood of voluntary withdrawal from the study was greater compared with placebo. The likelihood of withdrawal was also a function of CBD dosage, with low-dose CBD (20–400 mg/day) not differing from placebo. Serious adverse effects were only reported at high doses of CBD (1400–3000 mg/day), particularly in studies of epilepsy in children with the participants taking other epilepsy medications that can interact with CBD. The doses of CBD provided by health and food supplements are typically much lower (5–20 mg/day), so incidence of adverse events is likely to be much lower; however, this has yet to be demonstrated. This issue requires more research as some over-the-counter products are poorly labeled or do not contain purified CBD, and may possibly contain other cannabinoids and contaminants.

CBD Dependence and Abuse Potential

Controlled human studies regarding the potential physiological dependence/tolerance effects of CBD in humans have not been reported. In preclinical animal studies, however, CBD does not appear to produce dependence. Male mice were injected with CBD (0.1, 1, or 3 mg/kg) or THC (1, 3, 10 mg/kg) daily for fourteen days to determine tolerance to the neuroprotective effects of these compounds against cerebral ischemia. Tolerance developed to the neuroprotective effects of THC but not CBD over the course of treatment (Hayakawa et al. 2007). As well, tolerance does not develop to the antinausea effects of CBD over seven days of treatment (Rock, Sullivan, Collins, et al. 2020). Several preclinical animal studies have shown that CBD lacks abuse potential, using a variety of animal models, including a reduction in threshold frequency for intracranial

self-stimulation (ICSS), dopamine release in the mesolimbic system, conditioned place preference, and drug discrimination. A low dose (5 mg/kg) of CBD did not modify the threshold frequency required for ICSS; however, high doses of CBD (10 and 20 mg/kg) elevated the threshold frequency for ICSS, opposite to that of drugs of abuse (such as amphetamine, cocaine, and opiates; Katsidoni, Anagnostou, and Panagis 2013). Unlike most drugs of abuse, CBD did not modify the dopamine release in cells of the reward system, consisting of the mesolimbic ventral tegmental area-nucleus accumbens pathway (French, Dillon, and Wu 1997). CBD (10 mg/kg) alone produces neither a conditioned place preference nor a conditioned place aversion. However, rats treated with increasing doses of CBD and THC (1, 3, and 10 mg/kg) showed a trend toward a conditioned place preference not seen with THC alone (Klein et al. 2011), which may represent a pharmacokinetic interaction leading to higher concentration of THC rather than a receptor action change. CBD does not exhibit THC-like discriminative stimulus effects in rats trained to discriminate between THC and vehicle (Vann et al. 2008). CBD clearly does not produce rewarding or aversive effects on its own in preclinical animal models.

Human studies of the abuse potential of CBD are limited. However, a randomized double-blind, placebo-controlled trial study indicated that CBD, unlike THC, did not have abuse potential following a single oral dose of 600 mg of CBD in healthy volunteers (Martin-Santos et al. 2012). Unlike CBD, THC (10 mg oral) was associated with subjective intoxication, euphoria, sedation, hallucinogenic activity, increased psychotic symptoms, and anxiety. As well, although THC increased heart rate, CBD did not. In another randomized double-blind, within-subject laboratory study, CBD (0, 200, 400, 800 mg, oral) combined with inactive (0.01 percent THC) and active (5.3–5.8 percent THC) smoked cannabis, was assessed for abuse potential in healthy cannabis smokers. The participants completed eight outpatient sessions with CBD administered ninety minutes prior to

cannabis self-administration. Among the groups administered 0 mg/kg CBD (placebo conditions), active cannabis was self-administered by significantly more participants and produced time-dependent increases in subjective ratings and heart rate relative to inactive cannabis. CBD produced no significant psychoactive, cardiovascular, or other effects among the inactive cannabis conditions. Active cannabis self-administration, subjective effects, and cannabis ratings did not vary as a function of CBD dose relative to placebo conditions. These findings suggest that oral CBD does not reduce the reinforcing, physiological, or positive subjective effects of smoked cannabis.

Conclusion: Pharmacological Aspects of CBD

CBD has diverse molecular targets including indirect activity at the cannabinoid receptors, agonism of TRPV and 5-HT_{1A} receptors, and additional receptor targets are being investigated. Some argue that the many potential health benefits are related to the widespread action of CBD. The consensus is that pharmaceutical-grade CBD has a favorable safety profile with limited side effects, but this may not generalize across all populations or across all CBD formulations, as unregulated retail products carry inaccurate labels. As well, there are limited reports that daily chronic administration of CBD may inhibit activity of liver CYP 450 drug-metabolizing enzymes. More research on interactions of CBD with other drugs is crucial.

The most common form of CBD treatment is oral administration, which is plagued by low bioavailability because of first-pass metabolism and acidic stomach conditions, requiring considerably high doses to achieve therapeutic levels. Human trials have revealed, however, that repeated treatments with lower doses produce a steady state of CBD availability when it is administered with food. The bioavailability of topically applied CBD has been little studied, whereas bioavailability is higher when CBD is smoked or vaporized. CBD is metabolized in the liver by CYP 450 enzymes, with the most common forms being CYP3A4 and CYP2C19, known to be involved in

the metabolism of various clinically important drugs. This suggests that CBD may produce drug interactions through this mechanism. CBD may also interfere with some effects of THC by this mechanism. CBD, unlike THC, does not appear to have abuse potential and has relatively fewer adverse side effects; it is not intoxicating. CBD acts on several receptors, which we review in the following chapters regarding its mechanism of action for each indication.