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The pharmacological properties of cannabis

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Abstract

The efforts to understand the nature of how the consumption of cannabis affects the human body are ongoing, complex, and multifaceted. Documentation on the use of cannabis dates back thousands of years; however, it is only now with the recent softening of legal restrictions that modern research approaches have been able to initiate an appropriate level of detailed investigations. For clinicians, researchers and policy makers, this chapter reviews the general structure of cannabinoids, the current understanding of cannabinoids on cellular systems, the difference between inhalation and oral consumption on cannabinoid bioavailability, the variance among purified cannabinoids versus whole plant extract, and the potential activities of another prominent family of secondary metabolites found in cannabis, the terpenes.

Keywords: Cannabis, cannabinoids, terpenes

Introduction

The efforts to understand the nature of how the consumption of cannabis affects the human body is an ongoing and complex process. Although documentation of cannabis' use dates back thousands of years, it was only the recent amelioration of legal restrictions that allowed modern research approaches to initiate an appropriate level of detailed investigations, as with other plant species. For clinicians, researchers and policy makers, this chapter reviews the general structure of cannabinoids, the current understanding of cannabinoids within cellular systems, the differences of inhalation and oral consumption on cannabinoid bioavailability, the therapeutic efficacy of purified cannabinoids versus whole plant extract, and the potential activities of another prominent family of secondary metabolites found in cannabis, the terpenes.

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Structure, expression and production of known cannabinoids

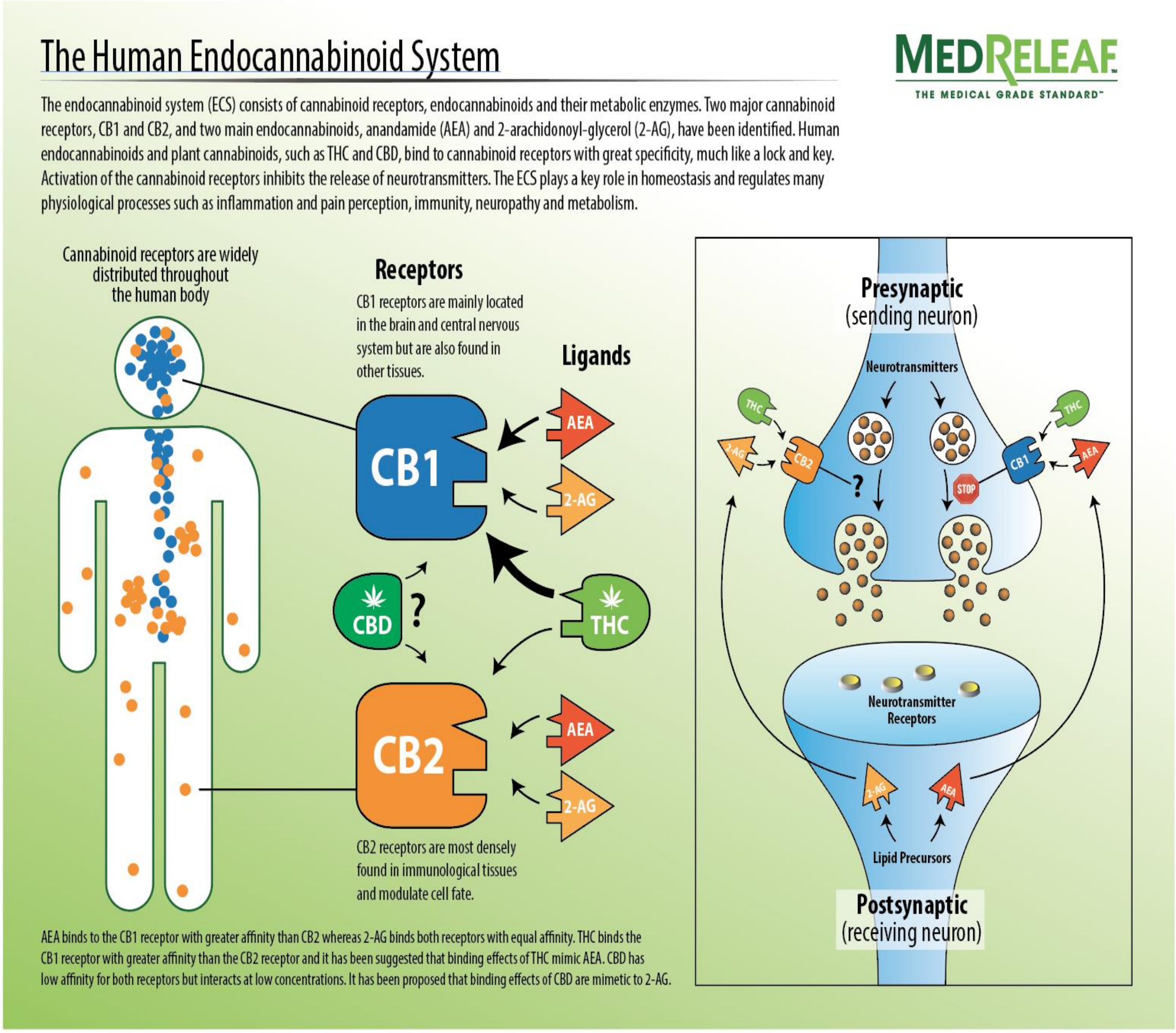
Phytocannabinoids are represented by a number of compounds that exhibit potent bioactivities on human physiology (1) and make up the most studied group of chemicals from the *Cannabis sativa* plant (see Table 1 for a list of predominant cannabinoids). Phytocannabinoids have also been discovered in plants from the genus Radula (liverworts) and Helichrysum (sunflower family) (2). Notwithstanding the long history of cannabis use and research, the cannabinoid biosynthesis pathways have only been recently elucidated. Cannabigerol type compounds (CBG, CBGa) were the first cannabinoids identified (3), and it is CBGa that is converted into THCa, CBDa and CBCa via the action of oxidocyclase THCa-, CBDa- or CBCa-synthase (4). Cannabigerol is synthesized from olivetolic acid (OLA) and geranyl diphosphate (GPP), products of the polyketide and non-mevalonate pathways, respectively. The cannabinoids THC, CBD and CBC possess a C_5 side chain, and versions also exist wherein a C_3 group is substituted and the compounds are otherwise identical. These analogous cannabinoids are THCVa, CBDVa and CBCVa, whose precursors are divarinolic acid (DVA) and GPP.

Cannabinoids are not present plant-wide. They are produced and primarily localized to specialized structures called trichomes. Trichomes are epidermal protuberances that cover the flower, leaves and parts of the stem (1, 5). The cannabinoids are synthesized in secretory cells and translocated to a storage cavity within the trichome (6). Compartmentalization is necessary due to the cytotoxic nature of cannabinoids. It is from these trichomes that the cannabinoids are harvested or vaporized, depending on the end use or mode of consumption. The natural form of the cannabinoids as they exist in the trichome are the acid forms, however, neutral cannabinoids are the pharmacologically active forms responsible for the partial agonistic effects on both the CB1 and CB2 type receptors. Consequently, moderate heating is required to drive a decarboxylation reaction where the carboxylic acid moiety of the acid cannabinoids is removed, leaving the neutral forms (7).

Known cannabinoids and their effects on cellular and system physiology

Cannabis sativa produces a wide range of secondary metabolites, with the total number of identified and reported compounds increasing steadily since Gaoni and Mechoulam first isolated (-)-*trans*-delta-9-tetrahydrocannabinol (Δ^9-THC) in 1964 (8). In total, 545 different compounds have been isolated, of which 104 belong to a group of compounds unique to *Cannabis sativa*, referred to as cannabinoids (9-17) (see Table 1). However, this number is considered by many researchers to be dynamic and is a subject of debate, with the number of cannabinoid-like compounds possibly exceeding 130 (18). Most of these compounds are typically present only in trace quantities, and the pharmacological value of only a small number has been researched. The focus of this paper is the pharmacological action of Δ^9-THC and cannabidiol (CBD).

The primary cannabinoid that is responsible for the psychotropic effects of *Cannabis sativa* is Δ^9-THC (19) (see figure 1). Similar to endogenous post-synaptic released endocannabinoids anandamide and 2-arachidonoylglycerol, Δ^9-THC interacts with and activates G protein-coupled CB_1 and CB_2 cannabinoid receptors (20-22). CB_1 receptors are found in a high concentration in many tissue types throughout the body, including most brain regions and the peripheral nervous system (23), as well as some non-neuronal tissues such as the liver, stomach, heart, testes, and fat tissue (24-28). Presynaptic activation of CB_1 receptors in neuronal tissue inhibits release of neurotransmitters such as *gamma*-Aminobutyric acid and glutamate by releasing βγ-subunits from the G protein complex, leading to inhibition of voltage-gated calcium channels and vesicle release (29-30). However, while activation of CB_1 receptors typically inhibits release of neuronal transmitters, *in vivo* activation of CB_1 with Δ^9-THC has been observed to occasionally increase release of acetylcholine, dopamine and glutamate in various regions of the brain in rats (31-34). It is likely that this is due to selective antagonism by Δ^9-THC of endocannabinoids, as reported by Patel and Hillard (35) when observing anti-anxiolytic effects of Δ^9-THC administration in mice. It is this inhibitory-stimulation modulation of neurotransmitter release mediated by Δ^9-THC that is thought to be responsible for the psychotropic effects of Cannabis, both depressant and excitatory in nature. Cannabidiol, however, does not share psychotropic activity with Δ^9-THC, instead acting as a CB_1 inverse agonist or even antagonist, thereby attenuating *in vivo* response to Δ^9-THC in multiple model species (36). Cannabinoid CB_2 receptors, on the other hand, are more typically located on organs related to the immune system, and when activated attenuate pro-inflammatory responses such as cytokine release and immune cell response (37-38) (see Figure 1). There is evidence that CBD interacts with CB_2 receptors as an inverse agonist, leading to the well-documented reduction of clinical pro-inflammatory markers such as TNF-α, iNOS and COX-2 expression (39). In addition to the effects on CB_2, CBD has also been reported to interact with additional receptors related to the immune system. For example, CBD has been found to potently inhibit uptake of adenosine at A2A receptors, the mechanism by which adenosine signaling terminates, thereby enhancing the anti-inflammatory effects of adenosine agonists (40). CB_2 receptors are also found in both brain and peripheral neuronal tissue in a lower concentration relative to CB1 receptors, however their role has yet to be elucidated (41).



The Human Endocannabinoid System

The endocannabinoid system (ECS) consists of cannabinoid receptors, endocannabinoids and their metabolic enzymes. Two major cannabinoid receptors, CB1 and CB2, and two main endocannabinoids, anandamide (AEA) and 2-arachidonoyl-glycerol (2-AG), have been identified. Human endocannabinoids and plant cannabinoids, such as THC and CBD, bind to cannabinoid receptors with great specificity, much like a lock and key. Activation of the cannabinoid receptors inhibits the release of neurotransmitters. The ECS plays a key role in homeostasis and regulates many physiological processes such as inflammation and pain perception, immunity, neuropathy and metabolism.

Cannabinoid receptors are widely distributed throughout the human body

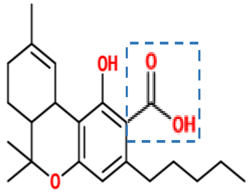
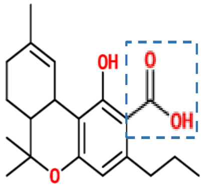
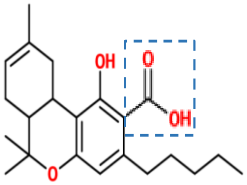
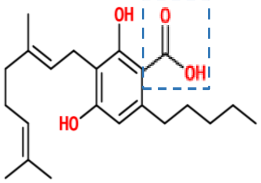
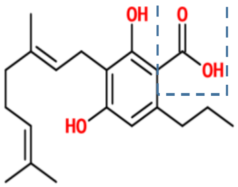
CB1 receptors are mainly located in the brain and central nervous system but are also found in other tissues.

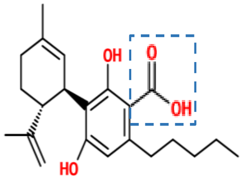
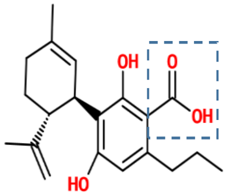
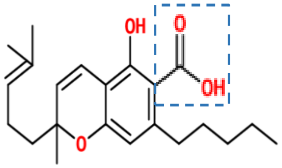
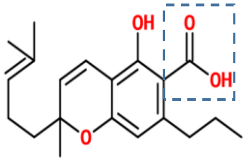
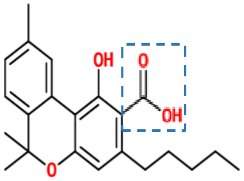
CB2 receptors are most densely found in immunological tissues and modulate cell fate.

AEA binds to the CB1 receptor with greater affinity than CB2 whereas 2-AG binds both receptors with equal affinity. THC binds the CB1 receptor with greater affinity than the CB2 receptor and it has been suggested that binding effects of THC mimic AEA. CBD has low affinity for both receptors but interacts at low concentrations. It has been proposed that binding effects of CBD are mimetic to 2-AG.

Figure 1. The human endocannabinoid system.

Table 1. Predominant cannabinoids with clinical relevance

	Molecule	Clinical Relavance
Δ^9-THCA $C_{21}H_{30}O_2$ 314.47 g/mol **Acidic Form** **$C_{22}H_{30}O_4$** **358.47 g/mol**		Antiemetic (Hernandez *et al.* 2015) Treatment of PTSD (Roitman *et al.* 2014) Treatment of Sleep Disorders (Gorelick *et al.* 2013) Palliative Treatment of Dementia (Woodward *et al. 2014)* Treatment of IBS (Wong *et al.* 2011) Appetite Stimulant (Costiniuk *et al.* 2008)
Δ^9-THCVA $C_{19}H_{26}O_2$ 286.41 g/mol **Acidic Form** **$C_{20}H_{26}O_4$** **330.41 g/mol**		Treatment of Obesity (Tudge *et al.* 2014) Anti-Inflammatory/Anti-nociceptive (Bolognini *et al.* 2010) Treatment of Epilepsy (Hill *et al.* 2010) Treatment of Insulin Sensitivity (Wargent *et al.* 2013)
Δ^8-THCA $C_{21}H_{30}O_2$ 314.47 g/mol **Acidic Form** **$C_{22}H_{30}O_4$** **358.47 g/mol**		Improvement of Appetite (Avraham *et al.* 2004) Antineoplastic Activity (Munson *et al.* 1975) Antiemetic (Abrahamov *et al.* 1995)
CBGA $C_{21}H_{32}O_2$ 316.48 g/mol **Acidic Form** **$C_{22}H_{32}O_4$** **360.48 g/mol**		Appetite Stimulant (Brierley *et al.* 2016) Treatment of Huntington's Disease (Diaz-Alonso *et al.* 2016) Reduction of Intraocular Pressure (Szczesniak *et al.* 2011) Treatment of Dry-Skin Syndrome (Olah *et al.* 2016) Anti-Cancer (Scott *et al.* 2013)
CBGVA $C_{19}H_{28}O_2$ 288.42 g/mol **Acidic Form** **$C_{21}H_{28}O_4$** **332.42 g/mol**		Treatment of Dry-Skin Syndrome (Olah *et al.* 2016) Anti-Cancer (Scott *et al.* 2013)

	Molecule	Clinical Relavance
CBDA $C_{21}H_{30}O_2$ 314.46 g/mol **Acidic Form** **$C_{22}H_{30}O_4$** **358.46 g/mol**		Antipsychotic (Leweke *et al.* 2012) Palliative Care of Parkinson's (Chagas *et al.* 2014) Anxiolytic (Bergamaschi *et al.* 2011) Treatment of PTSD (Das *et al.* 2013) Treatment of Epilepsy (Pelliccia *et al.* 2005) Anti-Inflammatory/Anti-nociceptive (Gallily *et al.* 2015)
CBDVA $C_{19}H_{26}O_2$ 286.40 g/mol **Acidic Form** **$C_{20}H_{28}O_4$** **330.40 g/mol**		Antiemetic (Rock *et al.* 2013) Anticonvulsant in Mice (Hill *et al.* 2012) Treatment of Epilepsy (Amada *et al.* 2013) Anti-Acne (Olah *et al.* 2016) Treatment of Bladder Dysfunctions (Pagano *et al.* 2015)
CBCA $C_{21}H_{30}O_2$ 314.46 g/mol **Acidic Form** **$C_{22}H_{30}O_4$** **358.46 g/mol**		Anti-Acne (Olah *et al.* 2016) Anti-Inflammatory (Wirth *et al.* 1980) Treatment of Colitis (Romano *et al.* 2013) Treatment of Hypertension (O'Neil *et al.* 1979) Treatment of Hypermotility (Izzo *et al.* 2012) Reduction of Intraocular Pressure (Colasanti *et al.* 1984)
CBCVA $C_{19}H_{26}O_2$ 286.40 g/mol **Acidic Form** **$C_{20}H_{30}O_4$** **330.40 g/mol**		No Clinical Research Preformed
CBNA $C_{21}H_{26}O_2$ 310.43 g/mol **Acidic Form** **$C_{21}H_{26}O_2$** **354.43 g/mol**		Analgesia (Sofia *et al.* 1975) Reduction of Intraocular Pressure (Colasanti et al. 1984) Appetite Stimulant (Farrimond *et al.* 2012)

Inhalation versus oral consumption and bioavailability

As with all drugs, the pharmacokinetics (PK) of cannabis are dependent on the route of administration. To date, most human clinical trials have evaluated the PK activity of cannabis after inhalation or ingestion. While different studies report a wide range of PK parameters due to differences in dosing, it is still clear that the onset, rate of absorption, and bioavailability of THC and CBD are significantly higher after inhalation than after ingestion or oral administration (42, 43) (see Table 2).

Table 2. Pharmacokinectics of cannabis based on route of administration

Route of Administration	Inhalation	Oral
% Dose Consumed	~ 50% (loss due to pyrolysis)	100%
Trajectory to Circulation	Lungs – Bronchi-Bronchiole - Alveoli	Stomach – Small Intestines – Portal Vein - Liver
Other Factors Affecting Uptake	Intake upon inhalation (puff duration, intake volume, holding time)	Absorption (stomach contents, metabolic rate, genetic variants in CYP 450 enzyme activity, enzyme regulation by other drugs)
First-Pass Hepatic Metabolism	Bypassed	First-Pass Hepatic Metabolism by CYP450 enzymes
Bioavailability	2 – 56%	<20%
Onset	Immediate	30 – 90 minutes
Time of Peak Plasma	5 – 10 minutes	1 – 6 hours
Duration	2 - 4 hours	4 – 8 hours

THC is detectable in blood almost immediately after smoking, with peak plasma concentrations measurable after 5 – 10 minutes (42, 44-46). Reported peak values vary with administered dose. For instance, one study reported that inhalation of cigarettes containing 1.75% THC (equivalent to 16 mg THC) and 3.55% THC (34 mg THC) resulted in mean peak plasma concentrations of 84.3 ng/ml and 162.2 ng/ml, respectively (42). However, the range of measured peak plasma concentrations for the low dose cigarette was 50-129 ng/ml and 76-267 ng/ml for the high dose cigarette.

Such wide ranges are also found when comparing reported bioavailability values. Some studies have reported the bioavailability of inhaled THC as 30% (46), 10–35% (43), and 18% (47). One study comparing the pharmacokinetics of THC between frequent and occasional users concluded that the bioavailability was 23–27% for frequent users, and 10–14% for occasional users (45). These differences arise from variances in smoking technique, with factors such as puff duration, intake volume, and holding time determining drug intake (42, 43, 48). Furthermore, up to 30% of THC has been shown to be lost during the pyrolysis process, with additional loss occurring in the side stream smoke and incomplete absorption in the lungs (43, 45, 49). As a conservative calculation, the bioavailability of THC after smoking is reported as 2-56% (42, 48).

Fewer studies have focused exclusively on the PK activity of CBD. One study reported that the bioavailability of CBD after inhalation was 31%, while others remark on the similarity in PK activity between THC and CBD (43, 50). However, it has been reported that CBD may alter the PK activity of THC and can mediate some of its adverse effects, such as paranoia and anxiety (42, 50-53). The exact reason for this modulatory effect is unknown, but current scientific opinion is that CBD inhibits the activity of cytochrome P450 enzymes, which in turn effects THC metabolism, particularly after oral administration (42, 48, 51).

The PK activity of cannabis after oral administration is rather different. Absorption is much slower and irreproducible, with the onset of action ranging between 30–90 minutes. Peak THC plasma concentrations may be reached as early as 1-2 hours after ingestion or as late as 4–6 hours (42, 45). Also, the duration of effects is noticeably longer after oral administration than after inhalation (48).

Oral administration is known to diminish the bioavailability of both THC and CBD compared to inhalation. Several studies have reported that the bioavailability of THC after ingestion is 4-20% (42), 4-12% (43), 3-14% (50), and 6% (52). Similarly, the oral bioavailability of CBD has been reported as 13–19% (54) and 6% (55).

The major explanation for this reduction in oral bioavailability is that cannabinoids undergo extensive first pass hepatic metabolism by CYP 450 genes prior to reaching systemic circulation (42, 43, 50). Oxidation into 11-OH-THC and other metabolites diminishes the amount of THC that reaches systemic circulation, thereby reducing oral bioavailability. For the same reason, plasma levels of 11-OH-THC are significantly higher after oral administration compared to inhalation (43). With inhalation, first pass hepatic metabolism is avoided since the cannabinoids enter system circulation via the lungs. Overall, these differences in PK activity allow patients to customize their treatment based on their therapeutic needs. For example, a patient in need of instant pain relief may prefer to smoke or vape cannabis. Conversely, a patient with insomnia may be less interested in instant effects, and instead may prefer to ingest cannabis and experience its effects throughout the night.

The cocktail versus the individual compounds

The use and efficacy of herbal drugs in traditional medicine has been documented for centuries among many cultures. Recently published data has presented evidence for the therapeutic benefits of whole botanical extracts over single isolated constituents, as well as their bioequivalence with synthetic chemotherapeutics (56, 57).

Different molecules and metabolic pathway components such as enzymes, substrates, receptors, ion channels, transport proteins, DNA/RNA, ribosomes, monoclonal antibodies and physico-chemical mechanisms are the possible targets for different bio-chemical molecules that are present in a plant extract (59). Synergistic effects of plant extracts result in the following ways: (i) Constituents of a plant extract affect different targets. (ii) Constituents interact with one another to improve their solubility, thereby enhancing the bioavailability of one or several substances of an extract. (iii) Compounds may also have their efficacy enhanced with agents that antagonize mechanisms of resistance (58).

A given synergistic effect can be tested by comparing the pharmacological effects of the mono-substances versus the combination of substances by analyzing isobole curves based on data from several dose combinations (60). This analysis enables one to discriminate effects between simple additive, antagonistic interactions or real synergism with potentiated or over-additive effects (56).

However, other compounds in plant extracts could enhance the overall efficacy if negative symptoms or ‘‘lateral damages’’ have developed during a disease. Many plant extracts are rich in other secondary metabolites, such as polyphenols and terpenoids. These have an important role in this way, specifically when their bioavailability is high. Polyphenols possess a strong ability to bind with proteins or glycoproteins, and terpenoids have great affinities for cell membranes because of their lipophilicity and thus a high potential to permeate through cell walls of the body or bacteria (56).

For example, a study clearly illustrated that cannabis plant extracts are superior to pure cannabidiol for the treatment of inflammatory disease. This higher efficiency might be explained by additive or synergistic interactions between CBD and minor phytocannabinoids or non-cannabinoids presented in the extracts (61). A study of efficacy of the whole plant *Artemisia annua* and pure artemisinin (the active compound) in the treatment of malaria showed the whole plant to be clinically efficacious, well tolerated, and oftentimes more effective than purified compounds used to reduce malaria morbidity and mortality (62). While the synergism between compounds in the whole plant extract increases the extract’s efficacy, there are also concerns about adverse drug reactions (ADRs). Adverse drug reactions tend to be more apparent with combinations of prescribed synthetic medicines, but clinical manifestations of ADRs do not seem to be common for botanical extracts. This may be due, in part, to a lack of reporting of adverse reactions for herbal medicines (63).

Terpene biochemistry and free radical scavenging

Terpenes comprise a diverse class of organic compounds which are produced by a variety of plants. Their functions range from plant protection by deterring herbivores to attracting predators and pollinating insects. In addition to their roles as end-products or secondary metabolites, terpenes are biosynthetic building blocks within nearly every living creature. Steroids, as an example, are derived from the terpene squalene.

When terpenes are modified chemically through oxidation or structural rearrangement, the resulting compounds are generally referred to as terpenoids. More often than not, the term terpene is used to include all terpenoids. The difference between terpenes and terpenoids is that terpenes are hydrocarbons, whereas terpenoids contain additional functional groups such as oxygen moieties or branching methyl groups. Terpenes and terpenoids are the primary constituents of the essential oils of plants and flowers (64). They are a chief constituent of the *Cannabis sativa* plant; as of 2011, more than 200 terpenoids have been identified in cannabis, with little being known about how they affect the pharmacological properties (65). The synergistic relationship between terpenes and cannabinoids can occur through four different mechanisms: (i) multi-target physiological effects, (ii) pharmacokinetics, (iii) bacterial resistance, and (iv) side-effect modulation. The synergistic potential of terpenes adds weight to the idea that plants can be better drugs than singular compounds derived from them (65).

Terpenoids are pharmacologically versatile due to their lipophilic nature, enabling interaction with cell membranes, neuronal and muscle ion channels, neurotransmitter receptors, G-protein coupled receptors, second messenger systems and enzymes (66). These substances have immensely broad biochemical effects, influencing some of the most critical enzyme systems, while affecting neurotransmitter levels and other fundamental processes. These effects are exactly what pharmaceutical drugs are designed to do. One of the most important and captivating aspects of these novel compounds is that they are pharmacologically active in extremely minute quantities well below toxic levels. Terpenoids are bioavailable in high percentages due to their lipophilic properties, permitting passive migration across biological membranes and entrance into the blood stream, influencing activities of the brain, heart or other organs.

Some of the most commonly found terpenes in *Cannabis sativa* are:

- D-limonene: Studies using citrus oils in mice and humans showed profound anxiolytic and antidepressant effects (67, 68).
- β-Myrcene: anti-inflammatory, analgesic and sedative properties (69).
- α-Pinene: anti-inflammatory, antibacterial and a bronchodilator, as well as being able to counteract short-term memory deficits induced by THC intoxication (65, 68).
- D-Linalool: anxiolytic activity (68, 70).
- β-Caryophyllene: is the most common sesquiterpenoid encountered in cannabis.

While these compounds are the major representatives by mass, it is important to note that there are significantly more chemical species present in small quantities each with its own and compounded effects.

Plant antioxidants are composed of a broad variety of compounds, such as ascorbic acid, polyphenolic compounds, and terpenoids. Terpenes are the main components of essential oils, their anti-oxidative capacity contributing to the beneficial properties of fruits and vegetables. Three main modes of antioxidant action have been detected to date: (i) quenching of singlet oxygen, (i) hydrogen transfer, and (iii) electron transfer. Several investigations have studied reactive oxygen species and the antioxidant activity of monoterpenes and diterpenes or essential oils in vitro (71). Reactive oxygen species (ROS) are created from free radicals generated during energy metabolism and by environmental deterioration, inadequate nutrition, exposure to irradiation and stress involved in the pathological development of many human diseases such as neurodegeneration, cardiovascular deterioration, diabetes and others. The most promising strategy to avert oxidative damage caused by these reactive species is the use of antioxidant molecules. Antioxidants play an important role in defending the body against free radical attack by delaying or inhibiting the oxidation of lipids or other biomolecules, preventing, or facilitating the repairing of the damage to cells (72). These compounds can act as direct antioxidants through free radical scavenging mechanisms and/or as indirect antioxidants by enhancing the antioxidant status (enzymatic and non-enzymatic). Terpenes, one of the most extensive and varied structural compounds occurring in nature, display a wide range of biological and pharmacological activities. Due to their antioxidant behaviour, terpenes have been shown to provide relevant protection under oxidative stress conditions in different diseases including liver, renal, neurodegenerative and cardiovascular diseases, cancer and diabetes, as well as in aging processes (73).

Conclusion

Cannabis is a plant rich with diverse compounds that exhibits a range of effects on human physiology. These effects are primarily attributed to cannabinoids and terpenes, large families of metabolites that can interact with many cellular and physiological systems in the body. Although much research still needs to be done, the effects of these metabolites provide an important tool in managing a range of clinical symptoms. Among cultivars of the plant, varying levels of these compounds create different physiological effects and, depending on how the plant is administered to patients, can alter the clinical utility.

Conflict of interest

The authors are all employees of MedReleaf, an authorized grower and distributor of medical cannabis in Canada. The authors report no other conflicts of interest.

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