Chapter 5

The United Chemicals of Cannabis: Beneficial Effects of Cannabis Phytochemicals on the Brain and Cognition

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Abstract

'Medicinal cannabis' can be defined as pharmaceutical grade cannabis-based products used for the treatment of illness. Beneficial treatment effects of cannabidiol (CBD), a major non-intoxicating compound isolated from the cannabis plant, have been shown in multiple states of cognitive impairment, including neurodegenerative (Alzheimer's, Huntington's and Parkinson's disease), neuroinflammatory (sepsis-induced encephalopathy) and neurological disorders (ischemic brain injury). CBD can also treat some of the symptoms of schizophrenia, including cognitive deficits (impairments in learning and memory), which is a major symptom domain of the illness that is largely resistant to existing antipsychotic medications. However, empirical evidence suggests the presence of an 'entourage effect' in cannabis; that is, observations that medicinal cannabis seems to work better in some instances when administered as a whole-plant extract. While scientific evidence highlights isolated CBD as a strong candidate for treating cognitive impairment, the entourage effect suggests that the co-operation of other plant molecules could provide further benefits. This chapter explores the scientific evidence surrounding the benefits of CBD and other specific key phytochemicals in cannabis: linalool, α-pinene, β-caryophyllene, flavonoids and anthocyanin, on brain health and cognition.

Keywords: medicinal cannabis, entourage effect, synergy, cannabidiol, CBD, terpenes, linalool, alpha-pinene, beta-caryophyllene, phenol, flavonoid, anthocyanins, purple cannabis, marijuana, cognition, learning, memory, brain, therapeutics, neuroprotection, inflammation

1. Introduction

Research shows that certain molecules identified in the cannabis plant are able to improve aspects of cognition. Cognition encompasses multiple aspects of thought processing including

decision-making, processing speed, attention span, learning and memory. Cognitive dysfunction can occur in a range of illnesses and disease states, for example Alzheimer's disease, dementia, Parkinson's disease, schizophrenia, hypoxic ischemia, stroke and meningitis. There is particularly strong evidence in the existing literature to support the pro-cognitive effects of the cannabinoid, cannabidiol (CBD) in disease states. There is also evidence that other phytochemicals in cannabis provide benefits for brain health and cognitive function. Furthermore, the suggested presence of an 'entourage effect' may mean that the therapeutic potential of CBD could be boosted through synergistic interactions with other phytochemicals. Therefore, certain cannabis strains may confer greater benefits for particular clinical indications, presenting unique opportunities for the discovery of novel personalised therapeutics. Identifying specific beneficial compounds could underpin selective breeding of plant cultivars with phytochemical profiles optimised towards restoring brain function in diseases associated with cognitive dysfunction.

2. Cannabidiol (CBD) and the brain

CBD is a major cannabinoid of *C. sativa*, considered a metabolic by-product rather than a biosynthetic product of the plant [1]. There has been a recent burst of studies showing beneficial effects of CBD in the brain, with evidence pointing to CBD as a promising novel therapy for a range of disorders. Based on its ability to change brain function and behaviour, it is, by definition 'psychoactive', but CBD is non-intoxicating and there is currently no evidence that it causes the deleterious hallucinogenic, paranoia and anxiety-inducing effects of the delta-tetrahydrocannabinol (Δ-THC) type chemicals, particularly Δ9-THC that is primarily responsible for the 'high' induced by recreational cannabis [2]. Instead, CBD has a broad spectrum of therapeutic properties, including antipsychotic, anxiolytic, immunomodulatory, anti-inflammatory, neuroprotective and pro-cognitive benefits in humans and preclinical disease models. Although its mechanisms of action are currently unclear, studies show that CBD is a cannabinoid 1 receptor (CB1) negative allosteric modulator [3], is a partial agonist of the dopamine D2 high receptor sub-type [4] and increases anandamide (AEA) signalling [5], possibly through inhibition of the AEA catabolic enzyme, fatty acid amide hydrolase (FAAH) [6].

2.1. Cannabidiol protects against cognitive harms of high-THC Cannabis

In terms of cognition, our recent systematic review by Osborne et al. [7] revealed a body of clinical and pre-clinical evidence supporting the pro-cognitive effects of CBD. We identified reports demonstrating that CBD can protect against cognitive harms of cannabis. For example, recreational users of cannabis containing higher (>0.75%) CBD performed better in verbal memory testing during acute intoxication compared to users of cannabis with the same Δ9-THC levels but low (<0.14%) CBD [reviewed in 7]. CBD pre-treatment (600 mg oral) also protected against deficits in verbal learning and memory, and aspects of working memory during a Δ9-THC (1.5 mg/kg intravenous (i.v.)) challenge in healthy participants (n = 22) [reviewed in 7].

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Imaging studies over the past decade have revealed altered brain morphology in key regions of the brain implicated in cognition in cannabis users. For example, chronic heavy cannabis users (n = 15) exhibit reduced brain volume in the hippocampus and amygdala compared to matched non-using controls (n = 16) [8], and hippocampal shape aberrations were detected in cannabis users (n = 15 male chronic heavy users) that were exacerbated in people with co-morbid schizophrenia (n = 8 males) compared to healthy controls [9]. Interestingly, regular users of low CBD cannabis had reduced hippocampal volumes compared to non-users; a reduction that was not observed in the participants either using cannabis containing CBD or in former users [10]. The authors of that study concluded that CBD could reduce harm to brain health caused by cannabis use, while periods of abstinence could recover damage in the parameters examined [10]. Recently, it was reported that 10-weeks of oral CBD treatment (200 mg) increased the volume of discrete hippocampal regions in cannabis users (n = 18), with higher growth observed in heavy compared to light cannabis users [11]. Overall, these studies point to a protective effect of CBD on cognitive regions of the brain during canabis use in humans; however, larger scale placebo-controlled trials are required. A potential mechanism for these benefits may relate to the neuroprotective characteristics of CBD, particularly its ability to stimulate neurogenesis, synaptic formation and neurite outgrowth (reveiwed in [12]).

Similar results supporting a protective role of CBD have been reported in pre-clinical studies. For example, CBD (0.5 mg/kg) increased visual learning and memory, and procedural learning in Rhesus monkeys co-administered Δ9-THC (0.2 or 0.5 mg/kg) compared to those administered Δ9-THC alone; however, spatial working memory was further impaired by combined treatment (reviewed in [7]). Chronic Δ9-THC exposure in adolescent mice (3 mg/kg daily) reduced recognition memory that persisted into adulthood, but this was not apparent in the group receiving CBD (3 mg/kg CBD) co-treatment during Δ9-THC exposure [13]. On the other hand, research shows that there are no beneficial effects of CBD on cognition, including verbal learning and memory, social recognition, executive function, spatial memory or conditioned learning, when administered to healthy subjects (humans or rodents) (reviewed in [7, 13]).

2.2. Cannabidiol treatment for neurological disorders and inflammatory disease states

2.2.1. Alzheimer's disease

Alzheimer's disease is the most common form of dementia. It is a progressive neurological disorder characterised by the presence of plaques and neurofibrillary tangles in the brain. Amyloid β peptides form densely packed extracellular filaments (plaques) that block cell signalling and trigger neuroinflammation. Neurofibrillary tangles are caused by transport-associated proteins called tau that form twisted structures during oxidative stress and block transport of nutrients and other essentials for neuronal function [14]. The progressive disruption and destruction of synapses results in memory loss and cognitive dysfunction. A role for cannabinoids as a therapy for Alzheimer's disease has been proposed, in part due to

the neuroprotective, anti-inflammatory and anti-oxidant properties of cannabinoids, as well as the role of the endocannabinoid system in memory and Alzheimer's disease pathology (reviewed in [15]). One study found that Sativex®, containing Δ9-THC and CBD, reduced tau and amyloid deposition in the hippocampus and cortex in a mouse model of tauopathy [16]. In addition, Δ9-THC and CBD administration improved memory deficits in AβPP/PS1 transgenic mice with an Alzheimer-like phenotype, but not in mice with cognitive decline associated with healthy ageing [17]. Another study attributed CBD treatment (20 mg/kg oral, daily for 8 months) of social recognition deficits in AβPP/PS1 mice with the prevention of neuroinflammation and cholesterol homeostasis rather than a reduction in amyloid load [18]. Clinical studies are required to confirm whether CBD/Δ9-THC therapies can improve brain health and function in people with Alzheimer's disease or dementia.

2.2.2. Huntington's disease

Huntington's disease is a progressive neurodegenerative disease of genetic origins, manifesting in motor impairment, cognitive decline and behavioural symptoms. In a double-blinded, placebo-controlled, cross-over clinical trial, Sativex® (orally administered in 12 sprays/day) was unable to improve cognitive, motor or behavioural scores in a cohort of patients with Huntington's disease (n = 24) compared to placebo-treated controls after 12-weeks of treatment [19]. In a smaller double-blinded, randomised cross-over study, CBD alone (10 mg/kg/day, oral) also yielded no symptom efficacy, including recall memory, in 15 patients Huntington's disease after 6-weeks of treatment [20]. However, large cohort studies of CBD administration in people with Huntington's disease are required.

2.2.3. Parkinson's disease

Parkinson's disease occurs through the progressive degeneration of dopaminergic neurons in the midbrain, resulting in severe motor impairment and loss of motor control. CBD is a prime novel therapeutic candidate for the treatment of Parkinson's disease due to its neuroprotective properties. However, one clinical study reported no improvement in motor or general symptoms scores in patients treated with CBD (75 or 300 mg/day) compared to placebo-treated controls (n = 7/group), although, overall quality of life was significantly improved in the 300 mg CBD treatment group compared to placebo-treated controls [21]. Another clinical study (open-label pilot study, n = 6) of Parkinson's disease patients with psychosis revealed significant improvements to psychiatric scores, but not motor function following CBD (>150 mg/day oral CBD) administration for 4-weeks in combination with existing L-dopa medication [22]. On the other hand, CBD (0.5 or 5 mg/kg CBD administered in four injections) prevented cognition and motor dysfunction when administered prior to reserpine treatment in a rodent model of Parkinson's disease [23].

2.2.4. Ischemic brain injury

Brain injury due to blood flow impediment and hypoxic damage can result in immediate and progressive cognitive decline. Ischemic brain injury can occur following events such as a stroke, cardiac arrest, near drowning or birth complications resulting in perinatal asphyxia.

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Rats exposed to hypoxic ischemia at birth exhibited recognition memory deficits that were attenuated by CBD (1 mg/kg) administered subcutaneously 10 min post-ischemia, while CBD treatment (3, 10 or 30 mg/kg 30 min pre- and 3, 24 and 48 h post-ischemic insult) increased spatial memory compared to placebo-treated ischemic rats (reviewed in [7]). In a subsequent study, acute CBD treatment (5 mg/kg, intraperitoneal (i.p.)) reduced apoptosis, neuronal loss and neuroinflammation in ischemic in neonatal rats [24], providing mechanistic clues about the behavioural restorative effects of CBD during hypoxic brain damage. A clinical trial investigating THC:CBD efficacy on spasticity following a stroke has been registered [25]; however, cognitive testing has not been proposed as a treatment outcome.

2.2.5. Sepsis-induced encephalopathy

Sepsis is a potentially life-threatening systemic inflammatory state that occurs as the body attempts to eliminate a pathogen. It can cause rapid cognitive impairment, particularly memory decline that was initially considered a transient state restored through the destruction of the pathogen and attenuation of the inflammatory response. However, sepsis is also associated with encephalopathy, a disease state of the brain that can manifest symptoms ranging from mild personality changes to cognitive and motor impairment, lethargy and coma. Sepsis-induced encephalopathy can be caused by increased permeability of the blood brain barrier and neuroinflammation that can lead to permanent functional impairment and enhance susceptibility to subsequent neurodegenerative disorders post-recovery [26]. Sub-chronic CBD treatment improved associative learning in a rodent model of sepsis (CBD administered either 2.5, 5 or 10 mg/kg daily for 9 days) compared to vehicle-treated controls (reviewed in [7]). CBD (single acute dose 3 mg/kg, i.v.) treatment also preserved blood–brain barrier integrity, restored normal vascular endothelial function and reduced inflammation in the mouse brain during endotoxic shock induced by administration of lipopolysaccharide (LPS) [27], a cell wall component of Gram-negative bacteria that can be used to model an excessive pro-inflammatory response in the host.

2.2.6. Schizophrenia

Schizophrenia is a chronic neurodevelopmental disorder characterised by three main symptom domains: positive (e.g., hallucinations, delusions and paranoia), negative (e.g., social withdrawal, flattened emotional expression, lack of motivation) and cognitive deficits. Existing antipsychotic medications confer minimal to no cognitive benefits (in some instances can further impair cognition) [28], and can cause serious weight gain and diabetes side-effects [29, 30]. We recently discovered that chronic CBD (10 mg/kg CBD, i.p., twice daily (b.i.d.)) treated cognitive impairment (learning, working and recognition memory) and social interaction deficits in a rat prenatal infection (poly I:C) model of schizophrenia-like phenotypes [31]. No behavioural changes were observed in healthy rats administered CBD and CBD did not cause weight gain side-effects [31]. An earlier clinical study (phase II, single-centred, double-blinded, randomised parallel-group controlled clinical trial of CBD vs. amisulpride) had reported improved positive and negative symptoms in people with schizophrenia following 4 weeks of CBD treatment, with therapeutic efficacy similar to the commercial antipsychotic, amisulpride; however, cognitive function was not examined [5]. More recently, a multi-centre

double-blinded parallel-group clinical trial examined the efficacy of CBD co-treatment with the patient's existing antipsychotic medication on a range of endpoints, including positive, negative and cognitive scores and Clinical Global Impression scales (CGI, measuring illness severity, improvement and response to treatment) [32]. Results showed significant improvements in positive (not negative) symptoms and CGI scores, as well as some improvement in cognitive performance (did not reach statistical significance, $p = 0.068$ CBD vs. placebo) when CBD was combined with the patient's existing antipsychotic medications [32].

2.3. Conclusions on the use of CBD in neurological disease

There is substantial scientific evidence to show the beneficial effects of CBD in the brain, with protection and treatment efficacy for various cognitive behaviours conferred in multiple disease states. Overall, there seems to be a general requirement for further placebo-controlled clinical trials, as well as investigation of long-term efficacy and safety in different populations of people. Evidence for illness-specific optimal dosing regimens (dose, route of administration, timing and number of daily doses, effect of concurrent medications, etc.) is also required. In addition, similar to our rodent study of CBD effects on cognition in schizophrenia [31], most studies use either isolated CBD or combined THC and CBD. While this methodology enables investigators to attribute results to a specific compound, it may not be the optimal therapeutic approach as cannabis-derived plant molecules are thought to interact and produce a synergy that enhances therapeutic effects—termed the 'entourage effect'.

3. The entourage effect

The entourage effect is defined as the act by which compounds (both cannabis phytochemicals and compounds from the endogenous cannabinoid system) augment or support the effects of major cannabinoids, for example, Δ9-THC, CBD, 2-arachidonoyl-glycerol (2-AG) [33, 34]. This phenomenon has been likened to an orchestra where 'many musicians support and harmonise the melody provided by the soloists' [34]. Compounds can exert synergistic effects through several mechanisms, for example by interacting with each other to improve bioavailability of beneficial compounds, or through combined actions on different therapeutic targets [35].

The concept of a cannabis entourage effect is largely based on anecdotal evidence from medicinal and recreational users attesting to the notion that cannabis 'works better' as a whole plant extract and its existence has been argued back and forth over time. However, there is evidence to suggest that the cannabis plant contains active ingredients as well as 'synergists' that boost drug effects above that of the isolated compound. Indeed, early description of a potential synergy between molecules in the cannabis plant came from a study in the 1970s that reported a 2–4 times greater deficits in parameters such as processing tasks and motor function in subjects administered Brazilian cannabis samples compared to Δ9-THC [36]. The phrase 'entourage effect' was first described in 1998 in response to the finding that certain

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endogenous molecules (2-linoleoyl-glycerol (2-LG) and 2-palmitoyl-glycerol (2-PG)) potentiated the effects of the endocannabinoid, 2-AG [33]. Interestingly, cultured hippocampal neurons exposed to CBD-rich plant extracts exhibit a significantly greater intracellular signalling response compared to CBD alone [37]. This provides preliminary (*in-vitro*) evidence that CBD-rich plant extracts exert greater effects on cells of the hippocampus (a region of the brain highly implicated in learning and memory) than isolated CBD. Overall, it may be possible to boost the pro-cognitive therapeutic efficacy of CBD through a synergistic approach. Studies show that cannabinoids other than CBD could confer beneficial effects on the brain through synergistic mechanisms, for example, the parent phytocannabinoid cannabigerol (CBG) exerted greater analgesic effects on mice than Δ9-THC alone, while CBG and cannabichromene (CBC) both have anti-depressant effects in rodents (reviewed in [38]) and CBG is neuroprotective in a mouse model of Huntington's Disease [39]. However, section 4 will focus on several key non-cannabinoid cannabis phytochemicals with promising evidence of positive effects on brain function.

4. Non-cannabinoid phytochemicals of Cannabis: terpenes, flavonoids and anthocyanins

The cannabis plant contains hundreds of phytochemicals, with new compounds and metabolites frequently identified. The concentration of chemicals in a cannabis plant can be influenced by multiple factors including nutrition, humidity, temperature, age of plant, strain, harvest time, plant stress, organ and storage conditions [1, 40]. Therefore, plant phytochemical composition is highly variable. Variability identified even within the same strain has led some authors to conclude that the name of a plant strain does not necessarily indicate potency or chemical composition [41]. However, others found that when grown under standardised conditions, certain cannabis strains can provide reproducible terpene and phytocannabinoid profiles that have been considered chemotaxonomic markers [42]. Furthermore, cannabinoid content can be used to classify plants into chemovars (plants with distinct photochemical profiles): Type I Δ9-THC-dominant, Type II Δ9-THC and CBD, Type III CBD-dominant and distinctions can be made outside these classes based on specific terpene profiles [43]. Therefore, it is possible to optimise plants to reproduce a distinct chemical composition and, potentially, specific medicinal characteristics.

4.1. Terpenes: linalool, alpha-pinene and beta-caryophyllene

Terpenes have been described as the most abundant class of small natural molecules by mass on Earth, undertaking innumerable structural and functional roles in most life forms on the planet (e.g., cholesterols for structural and signalling components of cell membranes, retinal in the eye for vision, carotenoids in photosynthesis) [44]. In cannabis, they create fragrances and flavours, but are also found in other plants and commonly used as safe food additives [38]. Terpenes can cross the blood brain barrier due to their lipophilic nature and studies have demonstrated a range of health benefits for some terpenes found in cannabis.

4.1.1. Linalool

Linalool is a monoterpene abundant in aromatic plants, such as lavender and purple basil [45]. Evidence shows that chronic administration of linalool reverses deficits in spatial memory and learning, with reduced amyloid plaque deposition and tau dysfunction in the hippocampus in rodent models of Alzheimer's disease [46, 47], using 25 mg/kg and 100 mg/kg linalool, respectively. Linalool also prevented deficits in spatial memory, motor function, neuroinflammation and post-ischemic neurodegeneration in a rat model of global cerebral ischemia, following oral daily administration (25 mg/kg) for 1 month [48]. However, reduced short and long-term recognition memory (50 and 100 mg/kg linalool, i.p.) [49] and memory acquisition (3% preparation for inhalation) [50] were found when linalool was administered as a single dose to healthy rats. This apparent contradiction in findings could be attributed to the administration of linalool to healthy vs. cognitively impaired rats, suggesting that the compound exerts benefits in a disease state but is detrimental when not patho physiologically required; however, further investigation is necessary to confirm.

4.1.2. Alpha-pinene

Alpha-pinene (α-pinene) is a highly abundant monoterpene found in coniferous trees (e.g., pine and fir) and cannabis [51] that, according to cannabis culture, provides pine-needle fragrances and tastes to cannabis. In mice with cognitive deficits caused by scopolamine-induced blockade of acetylcholine neurotransmission (apparent in advanced stages of Alzheimer's disease [52]), α-pinene (10 mg/kg, i.p.) improved working and spatial memory, and increased markers of acetylcholine synthesis in the cortex [53]. Inhalation of α-pinene can also influence major neurotransmitter signalling in the brain, for example it improved quality and duration of sleep in mice by modulating the major inhibitory neurotransmitter signalling system, gamma-aminobutyric acid (γ-aminobutyric acid, GABA)) [54], and decreased anxiety-like behaviour that was associated with increased tyrosine hydroxylase (the rate limiting enzyme for dopamine synthesis) in the midbrain [55]. Another study reported significant improvements in avoidance memory of cognitively impaired mice following administration of an essential oil obtained from a Korean fir tree containing α-pinene [56]; however, the results cannot be entirely attributed to this terpene due to the use of whole-plant extract containing other constituents.

4.1.3. Beta-caryophyllene

Beta-caryophyllene (β-caryophyllene) is a sesquiterpene that has a weak woody-spicy characteristic, abundant in cloves, black pepper, cinnamon and thyme [57, 58]. In a mouse model of Alzheimer's disease, β-caryophyllene reversed spatial memory deficits, reduced β-amyloid deposition in the hippocampus and cortex, and reduced neuroinflammation when administered for 10 weeks (48 mg/kg, oral) [59]. In rats with chronic cerebral ischemia resembling vascular dementia, β-caryophyllene (administered in a hydroxypropyl-β-cyclodextrin inclusion complex delivery system to enhance its bioavailability) attenuated cognitive deficits and increased cerebral blood flow [60]. β-caryophyllene also prevented oxidative stress in the cortex of rats following transient global cerebral hypoperfusion/reperfusion [61].

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Neurological scores were improved in mice administered β-caryophyllene (24 and 72 mg/kg, i.p.) following an induced stroke [62] and anti-depressant-like behaviour was reported in healthy mice following β-caryophyllene, through mechanisms involving catecholamine (adrenergic) neurotransmission [63]. Overall, the studies provide some evidence to support the role of β-caryophyllene as pro-cognitive, with anti-inflammatory, neuroprotective and anti-depressant effects.

4.2. Phenolic acids: flavonoids and anthocyanins

In addition to terpenes, cannabis plants contain phenolic compounds, including flavonoids and anthocyanins [40, 64–66]. Flavonoids are commonly consumed by humans through dietary fruit, vegetable, tea and wine intake. Anthocyanins are a group of flavonoids responsible for the blue-violet and red-orange colours of plant organs. Certain strains of cannabis plants exhibit a purple phenotype (**Figure 1**), which is widely attributed to anthocyanin content in recreational cannabis culture; however, experimental data showing anthocyanin levels of purple compared to non-purple strains appear to be lacking.

Flavonoids and anthocyanins are extensively researched due to their neuroprotective, anti-inflammatory and pro-cognitive characteristics and can pass the blood brain barrier [67]. For example, one study found that anthocyanin pre-treatment (200 mg/kg orally for 7 days) prevented cognitive deficits in a rat model of dementia [68]. Flavonoids improve working memory, processing speed, executive function and episodic memory in humans (reviewed in [69, 70]) and stimulate neurogenesis, synaptic plasticity and reduced neuroinflammation in the hippocampus (reviewed in [71]). Anthocyanin-rich cherry juice improved verbal fluency and short- and long-term memory performance in people with mild-to-moderate dementia during a 12 week randomised, controlled clinical trial of older people (+70 years) with mild to moderate dementia (200 ml/day cherry juice vs. control juice lacking anthocyanin) [72]. Interestingly, both cherries and cannabis plants contain phenolic acids related to flavonoid and anthocyanin biosynthesis pathways [65, 73]. Indeed, hemp seed extract can contain phenolic compound levels that are comparable to Japanese plums [74, 75]. Japanese plums are an important source of

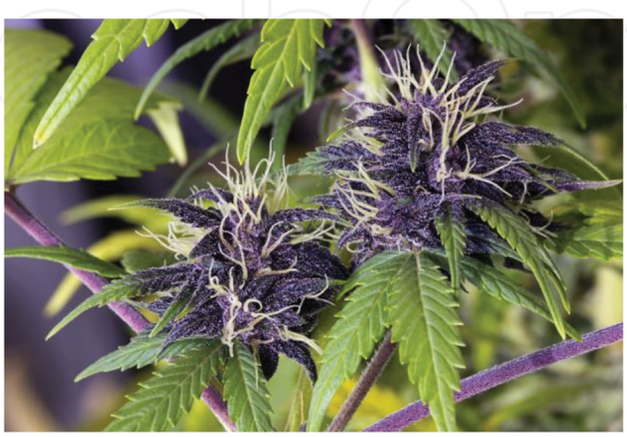

Figure 1. Inflorescence of purple cannabidiol (CBD)-rich, low Δ9-tetrahydrocannabinol (Δ9-THC) medicinal cannabis cultivar, GHM Genetic Development, Amsterdam, The Netherlands (2018).

anthocyanins, with particularly high levels in darker purple, blue and black coloured fruits [75]. Similar to cannabis plants, the phytochemical profile of Japanese plum varieties is influenced by horticultural practices, processing and storage conditions [75]. Other commercial plants, such as violet cauliflower and Thai purple basil, gain their unusual purple colouring through modifications to anthocyanin regulatory genes [76, 77]. Therefore, it is possible that plants can be manipulated naturally and artificially (i.e., genetically) to maximise anthocyanin content.

4.3. Conclusions on the effects of terpenes and flavonoids on the brain

The terpenes linalool, α-pinene and β-caryophyllene, as well as flavonoids and anthocyanins confer pro-cognitive, neuroprotective and anti-inflammatory effects in models of cerebral ischemia and Alzheimer's disease, as well as some anxiolytic effects. Most studies have been conducted in pre-clinical (rodent) models; however, pro-cognitive effects of flavonoids and anthocyanins have been shown in human clinical studies of dementia. Overall, combinations of CBD with other key phytochemicals found in cannabis could confer benefits on brain health through a multi-target synergy (entourage effect); however, further research is required.

5. Overall conclusion

This chapter has identified a consensus in the scientific literature that specific phytochemicals (CBD, linalool, α-pinene, β-caryophyllene, flavonoids and anthocyanins) found in cannabis plants are beneficial for cognition and brain health in a number of disease states. These compounds are psychoactive as they alter the brain to effect behaviour, and there is some evidence that they can differentially affect healthy individuals (e.g., CBD has no cognitive benefits and linalool has detrimental effects on cognition in healthy subjects). Therefore, societal consideration of 'medicinal cannabis' as a true medicine is necessary, that is, prescribed for patients who require treatment of a clinically diagnosed illness. Further research is needed to inform optimal prescription for treating specific illnesses, including dose, route of administration, long-term clinical efficacy, safety and side effects. There is some evidence to support the existence of an 'entourage effect'—such synergism could arise from a multi-target approach. The united benefits of specific terpenes and flavonoids could boost the therapeutic potential of CBD to improve cognition in disease states that manifest impairment; we are currently investigating these synergies in my laboratory. An other exciting future area of investigation is the identification of select cannabis phytochemical profiles that will treat specific illnesses with optimal efficacy. Following this, efforts towards standardising horticultural and cannabis plant processing practices to ensure optimal and reproducible medicines can be directed towards a proven goal—a translational interface between medical science and horticulture.

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Conflict of interest

There are no conflicts of interest to declare.

Notes/Thanks/Other declarations

I dedicate this book chapter to my husband, M. Green, for his tireless support.

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