



ELSEVIER

A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol

Ethan Russo^{a,b,c,*}, Geoffrey W. Guy^a

^a *GW Pharmaceuticals, Porton Down Science Park, Salisbury, Wiltshire SP4 0JQ, UK*

^b *University of Washington School of Medicine, Seattle, WA, USA*

^c *University of Montana Department of Pharmaceutical Sciences, MT, USA*

Received 15 August 2005; accepted 18 August 2005

Summary This study examines the current knowledge of physiological and clinical effects of tetrahydrocannabinol (THC) and cannabidiol (CBD) and presents a rationale for their combination in pharmaceutical preparations. Cannabinoid and vanilloid receptor effects as well as non-receptor mechanisms are explored, such as the capability of THC and CBD to act as anti-inflammatory substances independent of cyclo-oxygenase (COX) inhibition. CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain. Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined. The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported.

© 2005 Elsevier Ltd. All rights reserved.

Introduction

Cannabinoids refer to a heteromorphic group of molecules that demonstrate activity upon cannabinoid receptors and are characterised by three vari-

eties: endogenous or endocannabinoids, synthetic cannabinoids, and phytocannabinoids, which are natural terpenophenolic compounds derived from *Cannabis* spp.

In recent years, scientists have provided elucidation of the mechanisms of action of cannabis and THC with the discovery of an endocannabinoid ligand, arachidonylethanolamide, nicknamed anandamide, from the Sanskrit word *ananda*, or "bliss" [1]. Anandamide inhibits cyclic AMP mediated through G-protein coupling in target cells. Early

* Corresponding author. Present address. 2235 Wylie Avenue, Missoula, MT 59802, USA. Tel.: +1 406 542 0151; fax: +1 406 542 0158.

E-mail addresses: erusso@gwpharm.com, erusso@montanadsl.net (E. Russo).

testing of its pharmacological action and behavioural activity indicate similarity to THC [2], and both are partial agonists on the CB₁ receptor. Pertwee [3] has examined the pharmacology of cannabinoid receptors in detail. CB₁ receptors are most densely demonstrated in the central nervous system, especially in areas subserving nociception, short-term memory, and basal ganglia, but are also found in the peripheral nerves, uterus, testis, bones and most body tissues. CB₂ receptors, in contrast, are mostly found in the periphery, often in conjunction with immune cells, but may appear in the CNS particularly under conditions of inflammation in association with microcytes. Additional non-CB₁ and non-CB₂ receptors in endothelial and other tissues are hypothesised [4], but not yet cloned. Further research has elucidated analgesic mechanisms of cannabinoids, which include effects on numerous neurotransmitter systems and interactions with the endogenous opioid system.

This paper will focus on the biochemical and clinical effects of two phytocannabinoids, Δ^9 -tetrahydrocannabinol (THC) (Fig. 1), the main psychoactive component of cannabis, and its non-psychoactive but highly physiologically relevant isomer, cannabidiol (CBD) (Fig. 1). While it was originally thought that CBD was the metabolic parent to THC in the cannabis plant, rather, they are both biosynthesised as THCA and CBDA from a cannabigerolic acid precursor (Fig. 2) according to genetically determined ratios [5], and then decarboxylated by heat or extraction to produce THC and CBD proper. It is interesting to note that the phytocannabinoids can be considered as half-siblings to the essential oil terpenoids with which they share a geranyl pyrophosphate precursor in the glandular trichomes of the plant where they are produced. It is felt by some authorities that these terpenoids share important modulatory and pharmacological effects with trace cannabinoids [6] in an elegant 'entourage effect' [7] that may account for synergistic activity of can-

nabis extracts over that of isolated components. Therapeutic benefits are thus added, whilst some adverse effects are attenuated. In this regard, Carlini [8] determined that cannabis extracts produced effects two or four times greater than that expected from their THC content, based on animal and human studies. Similarly, Fairbairn and Pickens [9] detected the presence of unidentified 'powerful synergists' in cannabis extracts, causing 330% greater activity in mice than THC alone. An unidentified component of the plant (perhaps linalool?) also showed anticonvulsant properties of equal potency to cannabinoids [10]. Finally, although anecdotal to some degree, extensive surveys in the USA comparing patients' subjective responses with synthetic THC as Marinol[®] supports a preference for whole cannabis products [11]. In most instances, synthetic THC is considered by patients to be more productive of intoxicating and sedative adverse effects [12], characterised by the authors as (p. 95), 'dysphoric and unappealing'.

The effects of THC are well known, and include analgesia, intoxication, short-term memory loss, muscle relaxant and anti-inflammatory effects [3,13] (summarised in Fig. 3, with corresponding references).

The pharmacological profile of CBD has received three recent excellent reviews [14,15]. Briefly stated, CBD has anti-anxiety actions [16], anti-psychotic effects [17], modulates metabolism of THC by blocking its conversion to the more psychoactive 11-hydroxy-THC [18], prevents glutamate excitotoxicity, serves as a powerful anti-oxidant [19], and has notable anti-inflammatory and immunomodulatory effects [20] (summarised in Fig. 3 with corresponding references). Notably, CBD has recently been shown to act as a TRPV1 agonist of potency equivalent to capsaicin, while also inhibiting reuptake of anandamide and its hydrolysis [21]. Thus, CBD may prove to be the first clinical pharmaceutical to modulate endocannabinoid function.

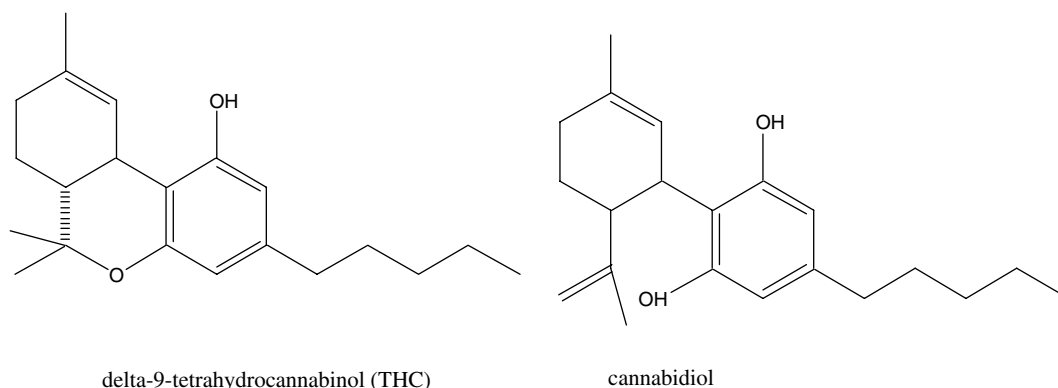


Figure 1 Structures of THC and CBD.

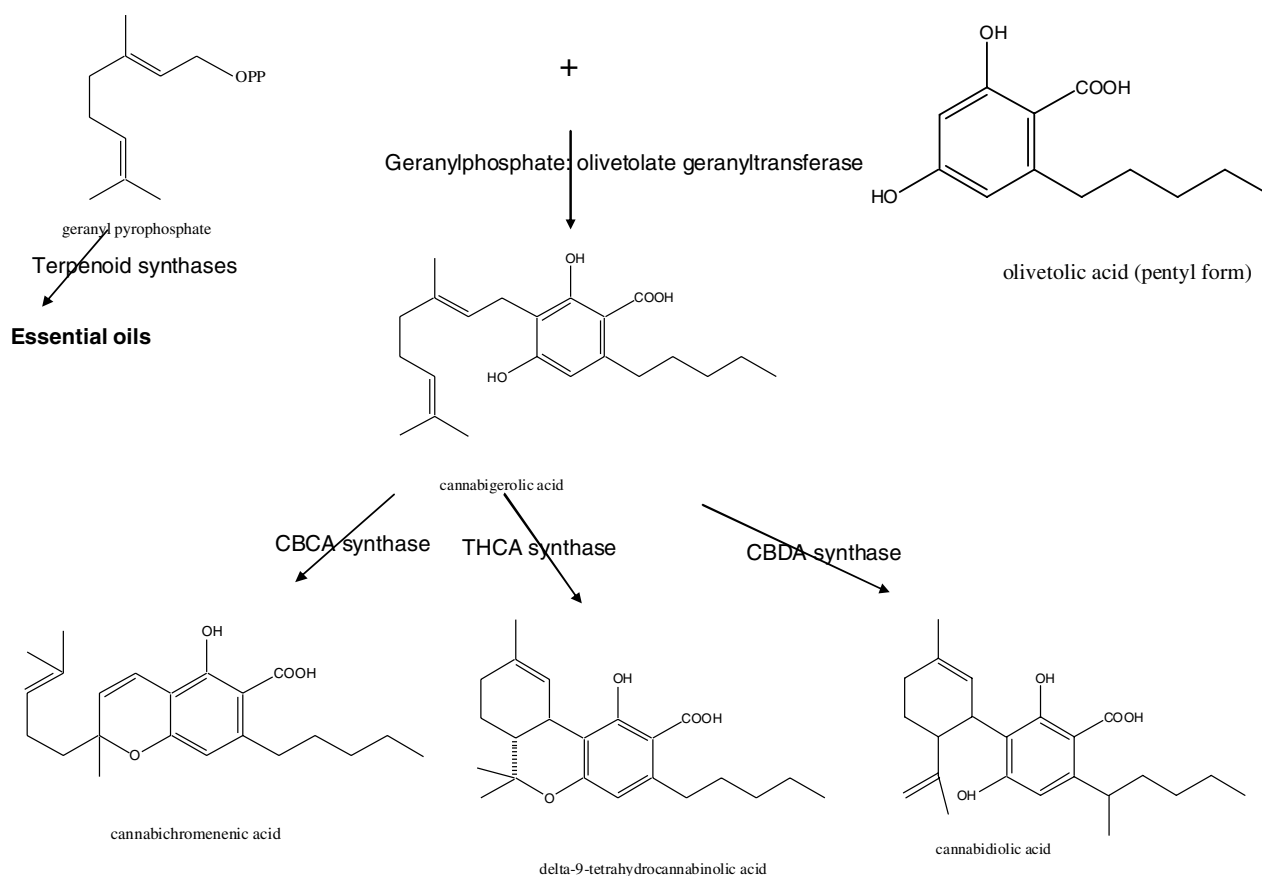


Figure 2 Biosynthetic pathways of pentyl phytocannabinoids (adapted and revised from de Meijer et al. [5]).

The remainder of this paper will focus on the interactions of the two compounds when administered simultaneously and explore the theoretical advantages of so doing in clinical application.

A review of animal studies of simultaneously administered THC and CBD

A great deal of the early research pertaining to interactions of THC with other phytocannabinoids was performed in Brazil in the 1970s. The seminal work was that of Karniol and Carlini [22] who examined various animal species with differing low-moderate doses of THC and CBD administered IP. To summarise, CBD blocked certain effects of THC: catatonia in mice, corneal areflexia in rabbits, increased defaecation and decreased ambulation in rats in the open field after chronic administration, and aggressiveness in rats after REM-sleep deprivation. In contrast, CBD potentiated THC analgesia in mice and the impairment of rope climbing in rats. The authors hypothesised that CBD interacted via a dual mecha-

nism: potentiating the depressant effects of THC while inhibiting its excitatory and emotional effects.

In an Australian study of oral dosing [23], the 'abdominal constriction response' to formic acid in mice, CBD antagonised the analgesic effect of THC. The pertinence of this model to current clinical models in humans is unclear.

In a rat study with implanted brain electrodes [24], CBD 20 mg/kg IP decreased slow-wave sleep latency. The author posited a hypnotic effect, but given the experimental setting, an analgesic response may have been operative.

In a complex protocol assessing variable-interval performance in rats after food deprivation [25], the authors assessed that a 'marijuana extract distillate' depressed performance at most levels of deprivation, but that IP CBD potentiates that depression only at high levels of deprivation. In subsequent related rat experiments [26], a 20-fold CBD:THC ratio antagonised THC effects on variable-interval performance, while fivefold ratios seemed to potentiate THC effects. The implications for therapeutic usage in humans are not clear from these data.

An American group [27] implicated CBD as contributing to mortality and seminiferous tubule degeneration in an usual protocol employing smoke exposure in rats to a Turkish cannabis strain. No separation of CBD vs. CBC (cannabichromene) was achieved, however. These results would not be contrasted to the extremely low-level mortality and histological changes seen in current animal toxicity studies performed with cannabis based medicine (CBM) combining THC and CBD [28].

In a study of rats trained to distinguish THC in a T-maze [29], CBD 40 mg/kg prolonged running time, but did not affect the animals' choices. This high dose was employed because (p. 140), "this dose was the minimum capable of interfering with the discriminative performance of rats that that received 5 mg/kg Δ^9 -THC". This slowing of run time also disappeared within 72 h.

In a recent study in rats [30], a CBD-rich extract containing THC did not affect spatial working mem-

Effect	THC	CBD	References
Receptor/Non-Receptor Effects			
CB ₁ (CNS/PNS receptors)	++	±	Pertwee (104)
CB ₂ (peripheral receptors)	+	±	Showalter (105)
Vanilloid (TRPV ₁) receptors	-	-	Bisogno (21)
Anti-inflammatory	+	+	Hampson (73)
COX-1, COX-2 inhibition	-	-	Stott (106)
Immunomodulatory	+	+	Cabral (107),Malfait (20)
CNS Effects			
Anticonvulsant	+	++	Wallace (42), Carlini (40)
Muscle relaxant	++	+	Collin (61)
Antinociceptive	++	+	Pertwee (13)
Psychotropic	++	-	Russo (108)
Anxiolytic	±	++	Zuardi (109)
Antipsychotic	-	++	Zuardi (17), Moreira (78)
Neuroprotective antioxidant	+	++	Hampson (73)
Antiemetic	++	+	Parker (99)
Sedation	+	-	Nicholson (55)
Agitation (Alzheimer disease)	+	-	Volicer (79)
Tic reduction (Tourette syndrome)	+	?	Müller-Vahl (111)
Opiate withdrawal reduction	+	?	Cichewicz (91), De Vry (36)
Migraine treatment	+	+	Russo (112)
Bipolar disease	+	?	Grinspoon (113)
Dystonia		+	Consroe (85)
Parkinsonian symptoms	+	?	Venderova (51)
Withdrawal symptoms to other drugs (reduction)	+	+	Labigiani (89), Dreher (90), De Vry (36)
Motor neurone disease (ALS) (increased survival, function)	+	+	Raman (81), Abood (82)
Cardiovascular Effects			
Bradycardia	-	+	Weil (114)
Tachycardia	+	-	Karniol (33)
Hypertension	+	-	Weil (114)
Hypotension	-	+	Batkai (115)
Appetite/Gastrointestinal			
Appetite	+	-	Pertwee (14)
GI motility (slowed)	++	+	Pertwee (14)
Anti-Carcinogenesis			
Glioma (apoptosis)	+	+	Sanchez (116), Massi (117)
Glioma cell migration		+	Vaccani (98)
Ophthalmological			
Intra-ocular pressure (reduced)	++	+	Jarvinen (118)
Night vision	+	-	Russo (119)

Figure 3 Effects of tetrahydrocannabinol (THC) and cannabidiol (CBD), adapted and updated from Russo 2003 [52] ([13,14,17,20,21,33,36,40,42,51,55,61,73,78,79,81,82,85,89–91,98,99,104–109,111–119]).

ory or short-term memory, even in doses up to 50 mg/kg.

A review of human studies of THC and CBD simultaneously administered

Administration of CBD orally (up to 300 mg) and IV (up to 30 mg) in volunteers were felt to be inactive in early experiments [31], with similar conclusions after IV infusion by another group [32].

In Brazil in 1974, effects of THC up to 30 mg and CBD up to 60 mg orally were studied in varying ratios in blinded fashion in 40 male subjects [33]. CBD at doses 15–60 mg evidenced few effects of its own, but effectively countered effects of 30 mg of THC including tachycardia, disturbed time tasks and strong psychological reactions. Interestingly, with higher doses of THC (p. 175), ‘‘symptoms appeared in ‘waves’ during which the subjects reported strong feelings of anxiety reaching sometime a near panic state’’. (These complaints are similar to those voiced by Marinol[®] patients currently when the dosage is not tolerated; perhaps enterohepatic circulation is operative.) With addition of CBD, the authors observed (p. 176), ‘‘CBD also changed the symptoms in such a way that the subjects receiving the mixtures showed less anxiety and panic but reported more pleasurable effects’’. Unfortunately, this statement was interpreted in context by the anonymous author(s) of a *US Federal Register* article [34] (p. 20065) as follows, ‘‘Most importantly, CBD appears to potentiate the euphorogenic and reinforcing effects of THC which suggests that the interaction between THC and CBD is synergistic and may actually contribute to the abuse of marijuana’’. This contention is unsupported by any of the cited literature. Furthermore, as the context of the discussion pertains to smoked cannabis in the USA, it is impertinent, as North American drug strains of cannabis are virtually devoid of CBD-content [35]. No epidemiological data are evident in any of the world’s literature that supports the allegation that the presence of CBD contributes or promotes cannabis abuse. In fact, the neutral antagonism of CB₁ receptors by CBD should actually reduce risk of development of tolerance [36] (vide infra).

In 1975, Hollister and Gillespie [37] noted very little THC–CBD interaction clinically in humans, except for a delayed onset and prolongation of THC effects that was so slight as to be felt negligible by the authors, who actually suggested it appropriate to ignore the CBD content of test cannabis.

In a test of smoked placebo cannabis with or without THC and a sixfold higher dose of CBD [38], the ‘high’ of THC was significantly attenuated when CBD was present: 11/15 subjects felt the effects of THC alone as greater than the combination.

In a similar protocol [39], co-administration of smoked CBD with THC attenuated THC effects including tachycardia, impairment on stance stability on a wobble board, and ability to track on a pursuit meter.

In 1981, cannabidiol was tested as an anticonvulsant in Brazil [40]. Fifteen patients with frequent attacks of unresponsive ‘secondarily generalized epilepsy’ (seizures of partial onset with secondary generalisation), aged 14–49, were treated with CBD vs. placebo in double-blind fashion. Three of eight treated patients had complete seizure control with 200 mg of CBD per day, and a fourth with 300 mg per day. One was improving, but was unavailable for follow-up. One other was markedly improved, two somewhat, and one not at all. Neither laboratory changes, nor major adverse effects were noted; merely some somnolence in four subjects. The latter has been misinterpreted in much subsequent literature to support a sedative property of CBD.

As, subsequent recent work has confirmed powerful anticonvulsant effects of THC and the key role of the endocannabinoid system in regulating seizure thresholds [41,42], it is logical to think that THC:CBD combinations may produce effective anticonvulsants.

Additional clinical experimentation in normal subjects [16], THC provoked anxiety that was antagonised by concomitant CBD administration. When given alone, subjective assessments of CBD effects included such terms (p. 249) as, ‘quick witted’ and ‘clear minded’.

Modern clinical trials of cannabis extracts containing THC and CBD

Cannador

A recent small clinical trial of THC and an oral cannabis extract (Cannador) was performed with 16 subjects. Neither was observed to reduce spasticity, and adverse events were reported as greater in the extract group even at low dosages [43]. Numerous criticisms were subsequently voiced in this regard [44] such that the plant extract was poorly categorised, and employed sub-optimal oral administration with no real dose titration. An

additional study in Switzerland [45] with more patients and doses of up to 15 mg THC with 6 mg CBD equivalent PO divided did provided better results with reduction in spasms ($p < 0.05$) and no significant side effects vs. placebo.

A British group examined 667 MS patients taking placebo, Marinol[®] (synthetic THC) or Cannador capsules over 15 weeks, with daily doses up to 25 mg THC equivalent (CAMS Study) [46]. While no change was seen in Ashworth Scales, improvement was observed on 10 m walking time, and subjective pain and spasticity ($p = 0.003$). Interestingly, fewer relapses were noted in the Cannador group during the study course, suggesting possible neuroprotective effects. Data from the same cohort were assessed for benefit on tremor, but no treatment benefit was observed [47]. In follow-up after one year, however, improvement was noted in spasticity for Marinol, but not Cannador [48]. In a recent review, it was suggested that this result points to THC as the active component and even that CBD detracts from therapeutic benefit [49]. Further data presented below will possibly support a different conclusion.

Cannador has also been assessed in treatment of parkinsonian dyskinesia, but without benefit in a four-week trial [50]. Better results were reported in a Czech survey study of Parkinson disease in which oral herbal cannabis with no analysis of cannabinoid content was taken for longer periods of time with improvement in multiple symptoms [51].

Cannador is an ethanolic extract that has not been particularly well characterised as to components or pharmacokinetics in published sources. Although labelled as 'standardised', clear variation in cannabinoid content has been reported in available studies with THC:CBD ratios noted as 2.5:0.9 [45], unspecified [43], or 2.5:1.25 = 2:1 [46,50], or just 2.5 mg of THC with no mention of CBD [47]. It is supplied as oral gelatine capsules in oil.

Experience with oromucosal cannabis based medicines

Sativex[®] is a highly standardised medicinal product composed of liquid carbon dioxide extracts from selected strains of cloned cannabis plants cultivated employing Good Agricultural Practice (GAP), to provide high and reproducible yields of THC and CBD. Sativex is a 1:1 combination from two clonal cannabis cultivars yielding a high THC extract (Tetranabinex[®]) and a high CBD extract (Nabidiolex[®]). The dried of unfertilised female flowers are extracted and refined utilising Good

Manufacturing Practice (GMP) produce a botanical drug substance (BDS) of defined composition with controlled reproducibility batch to batch. THC and CBD comprise some 70% (w/w) of the total BDS, with minor cannabinoids (5–6%), terpenoids (6–7%, most GRAS (Generally Recognized as Safe)), sterols (6%), triglycerides, alkanes, squalene, tocopherol, carotenoids and other minor components (also GRAS) derived from the plant material. BDS is formulated into a spray for oromucosal administration with each 100 μ L pump-action spray providing 2.7 mg of THC and 2.5 mg of CBD, the minor components, plus ethanol:propylene glycol excipients, and 0.05% peppermint as flavouring [52].

Extensive pharmacokinetic and pharmacodynamic studies have been undertaken with the three extracts in normal volunteers. Pertinent observations comparing extracts in context include the following:

- (1) The preparation has onset of activity in 15–40 min, which allows patients to titrate dosing requirements according to symptoms, with a very acceptable profile of adverse events.
- (2) When CBD and THC extracts were co-administered as sublingual drops, the rate of appearance of THC in serum was marginally increased possibly suggesting a stimulation of THC absorption [53].
- (3) The appearance of 11-OH-THC was reduced when CBD was co-administered with THC extracts [53].
- (4) THC T_{max} was later following the 1:1 mixture as compared to high-THC possibly due to CBD delaying THC absorption [54].

Observations (2) and (4) may appear contradictory, but the findings are unlikely to have great clinical significance. While patients differed, sometimes markedly, in pharmacokinetic values, especially with respect to cannabidiol, in all instances, reliable serum levels of THC and CBD were produced via the oromucosal route.

In a Phase I study of sleep and cognitive effects in eight normal volunteers [55], the THC:CBD 1:1 combination produced less sedation than THC-predominant extract and rather, some alerting properties. Although memory impairment was noted the following day after 15 mg THC extract, none was apparent with concomitant administration of CBD. The 1:1 mixture produced therapeutic advantages over effects seen with single components, as CBD counteracted residual effects of THC on daytime sleep latencies and memory.

In a subsequent Phase II clinical trial in 20 patients with intractable neurogenic symptoms [56], significant improvements (all $p < 0.05$) were seen as follows: THC- and CBD-predominant extracts on pain (especially neuropathic), THC- and 1:1 extracts on spasm, THC extract on spasticity, THC extract on appetite, and 1:1 extract on sleep. Post-hoc analysis revealed that overall symptom control was best with THC:CBD 1:1 ($p < 0.0001$), and in a subset of patients with MS ($p < 0.0002$), and intoxication was less than with THC-predominant extract.

In another Phase II study of intractable chronic pain [57], in 24 subjects who did not employ rescue medication, visual analogue scales (VAS) were 5.9 for placebo, 5.45 for CBD, 4.63 for THC and 4.4 for 1:1 THC:CBD extracts ($p < 0.001$). Sleep was also most improved on the latter ($p < 0.001$). Of 28 subjects, 11 preferred THC:CBD overall, while 14 found THC and THC:CBD equally satisfactory. Once more, for pain in the MS patients, THC:CBD produced best results ($p < 0.0042$).

In a Phase II, open label study of THC-predominant and 1:1 THC:CBD extracts vs. placebo in patients with intractable lower urinary tract symptoms, both active groups had significant improvement in urgency, cumber and volume of incontinence episodes, frequency, nocturia, daily total void volume, catheterised and urinary incontinence pad weights [58].

Once again, in a Phase III study of intractable pain associated with brachial plexus injury [59], roughly equivalent benefits were noted in Box Scale-11 pain scores with THC-predominant ($p = 0.002$) and THC:CBD 1:1 extracts ($p = 0.005$).

On the basis of these results with oromucosal cannabis based medicines, Professor Carlini has stated [60] (p. 463), 'However, any possible doubts that might exist on whether or not Δ^9 -THC is an useful medicine for MS symptoms, were removed by the results obtained in four very recent randomized, double-blind, placebo-controlled trials'.

In a study of 189 subjects with clinically definite MS with associated spasticity from 12 European centres, patients were randomised 2:1 to receive self-titrated daily doses of THC:CBD 1:1 ($N = 124$) or placebo ($N = 65$) in a double blind trial of eight weeks duration [61]. The THC:CBD oromucosal cannabis based medicine produced statistically significant objective benefit on spasticity on Motricity Index of lower extremities, as well as subjective improvement in NRS measures of spasticity, and responder analysis with a very acceptable adverse event profile compared to placebo.

In a controlled double-blind clinical trial of intractable central neuropathic pain [62], 66 MS

subjects showed mean Numerical Rating Scale (NRS) analgesia favouring THC:CBD 1:1 extract over placebo ($p = 0.009$), with sleep disturbances scores also positive ($p = 0.003$). There were no major changes in neuropsychological test measures vs. placebo. In marked contrast, results in two articles examining Marinol in central or peripheral neuropathic pain with oral doses up to 25 mg revealed no clear benefit on pain or allodynia, and with poor tolerance to adverse events [63,64]. A study of two subjects with similar doses for 2–5 years showed initial decrements in pain, but with unsustainable temporal improvement [65]. Better results were seen in a Swedish study [66], limiting Marinol doses to 10 mg/d in 24 subjects with central neuropathic pain due to MS. Median numerical pain scale in final week favoured Marinol ($p = 0.02$), as did median pain relief ($p = 0.035$). Authors rated analgesic effect as 'modest'. While number needed to treat (NNT) to attain a 30% decrement in pain were comparable in this study vs. Sativex, the reduction of pain on a numerical rating scale favoured the latter (1.0 vs. 0.6), as did side effect profile particularly for somnolence and headache, despite much higher total doses of THC and the concomitant usage of additional medicines for neuropathic pain. These differences point to either an advantage of oromucosal administration of phytocannabinoids, a reduction of THC adverse events due to inclusion of CBD, or both.

In a Phase III, double-blind placebo-controlled trial of peripheral neuropathic pain characterised by allodynia [67], THC:CBD 1:1 produced highly statistically significant improvements in pain levels with additional benefit on static and dynamic allodynia measures.

In a Phase III, double-blind placebo-controlled trial in 160 subjects with various symptoms of MS [68], THC:CBD 1:1 significantly reduced spasticity over placebo ($p = 0.001$) without significant adverse effects on mood or cognition. In a long-term safety-extension study (SAFEX), some 137 patients elected to continue on THC:CBD 1:1 [69]. On VAS of symptoms, rapid declines were noted over the first 12 weeks in pain ($n = 47$), spasm ($n = 54$), spasticity ($n = 66$), bladder problems ($n = 57$), and tremor ($n = 35$), with slower sustained improvements for more than one year. Interestingly, no tolerance was noted with mean THC:CBD 1:1 doses actually declining over time. Furthermore, VAS of intoxication in the cohort measured in the single digits out of 100 and did not differ significantly from placebo. In a cohort of 18 volunteers who abruptly stopped THC:CBD 1:1, no significant evidence for a withdrawal syndrome was observed. Rather, patients suffered recrudescence of symptoms after 7–10

days, but easily re-titrated to prior dosages with renewed efficacy.

Finally, the recently announced results of a Phase III study comparing THC:CBD 1:1, THC-predominant extract and placebo in intractable pain due to cancer unresponsive to opiates [70] with strong neuropathic pain components, demonstrated that THC:CBD 1:1 produced highly statistically significant improvements in analgesia ($p = 0.0142$), while the THC-predominant extract failed to do so in this trial, confirming the key importance of the inclusion of CBD in the preparation.

Analysis of sleep parameters in seven Phase II and III trials of MS and neuropathic pain and two corresponding SAFEX studies to date demonstrate significant to highly statistically significant and durable benefits of THC:CBD 1:1 on this important clinical symptom [71].

These trials, combined with their safety-extension studies comprise some 1500 subjects and 1000 patient-years of experience, during which no abuse or diversion of THC:CBD 1:1 have occurred, and no tolerance or withdrawal effects have been noted [69,72]. Thus, the fears expressed in the *Federal Register* [34] with respect to CBD–THC interactions appear unfounded.

New horizons in phytocannabinoid therapeutics

Neuroprotection

The seminal work describing the neuroprotective roles of THC and CBD has been that of Hampson et al. [73]. Both phytocannabinoids protected equally against glutamatergic neurotoxicity mediated by NMDA, AMPA, or kainate receptors, and this effect was not antagonized by SR1414716A, thus demonstrating it to be operative independently of cannabinoid receptor activation. The group additionally investigated the effects of THC and CBD on reactive oxygen species (ROS), finding them equal to that of the BHT and HU-211 (dexanabinol). CBD was considerably more potent as an antioxidant than ascorbate or tocopherol. Recent work has also shown that CBD reversed binge ethanol-induced neurotoxicity via a cannabinoid receptor-independent antioxidant mechanism [74], and prevented cerebral infarction via a 5-HT_{1A} receptor dependent mechanism [75]. Activity of CBD at that receptor has been independently confirmed [76], supporting a role in migraine and anxiety treatment.

Cannabidiol was shown to prevent β -amyloid induced toxicity in the PC12 pheochromocytoma

model of Alzheimer disease [77], increasing cell survival, while decreasing reactive oxygen species (ROS) production, lipid peroxidation, caspase 3 levels, DNA fragmentation and intracellular calcium.

A recent study [78] in mice supports the prospect that CBD has antipsychotic properties without extrapyramidal side-effects. Thus, CBD might improve symptoms of agitation and behavioural issues previously treated to advantage with THC alone in a clinical Alzheimer population [79].

One article has described the palliative use of cannabis in motor neurone disease, or amyotrophic lateral sclerosis (ALS) [80]. THC has previously been shown to delay motor deterioration and increase survival in a mouse model of ALS [81]. That work was recently extended to demonstrate that the addition of CBD further slowed disease progression with a 14% improvement in motor performance, and a trend toward extension of survival beyond that previously achieved with THC alone [82].

The intriguing survey supporting symptomatic improvement in Parkinson disease (PD) after prolonged usage was previously mentioned [51]. This finding is lent additional credence by the demonstration that equivalent benefits were observed with THC and CBD in preventing damage produced by injection of 6-hydroxydopamine into the median forebrain bundle of experimental animals [84], a result independent of cannabinoid receptor effects, but more likely due to antioxidant activity and regulation of glial influences upon neurones. This would support a neuroprotective benefit beyond the issue of symptomatic relief that would warrant additional trials, particularly with a mixed THC:CBD preparation.

Dystonic disorders are frequently progressive degenerative diseases, wherein CBD was employed in isolation and demonstrated benefit [85].

CBD treatment was attempted in Huntington's disease [86], but with little benefit seen over the 6-week trial. Perhaps the length of treatment was too short, and may support the concept of additional trials, particularly with a THC:CBD preparation. Such a combination may well prove to effect neuroprotective benefits in MS in the long term, having a strong theoretical basis [87]. Given the failure of various glutamate antagonists in efforts at neuroprotection in this and other conditions, phytocannabinoid approaches certainly appear warranted.

Cannabinoids and dependency

A simple perusal of the medical literature will confirm that considerable concern continues in

context as to the drug abuse liability of THC preparations. However, that substance in isolation has proven to pose little risk [12]. To the extent that rapidly rising serum levels promote reward and addictive potential of a given pharmaceutical [88], it is certainly arguable that the addition of CBD to THC would reduce psychoactive attraction, and that an oromucosal delivery eliminates the steep slope pharmacokinetic profile of cannabis smoking [54]. Additionally, cannabinoid receptor blockade by CBD may well reduce addiction potential [36], and support its usage as an 'anti-addictive' compound [72]. Interestingly, THC and CBD have both been demonstrated to potentiate the extinction of cocaine and amphetamine conditioned incentive learning in rats, supporting clinical studies claiming benefit of cannabis on cocaine addiction in Brazil [89] and Jamaica [90].

The fact that THC potentiates opiate analgesia, eliminates morphine tolerance and reduces withdrawal [91] highlights the rationale of cannabinoid–opiate combinations for treatment of severe and chronic pain. Recently, it was shown that interleukin-1 (IL-1) antagonises morphine and underlies development of tolerance [92]. As THC and CBD both suppress IL-1 secretion in humans in mononuclear cells in vitro [93], it is possible that this mechanism may also play a helpful role in addiction issues with a combined pharmaceutical.

Neoplastic disease

THC has demonstrated cytotoxic benefits and anti-angiogenic effects in a wide variety of cell lines (reviewed in [94,95]). CBD has also proven active as a cytostatic/cytotoxic, especially in gliomas where it inhibits cell migration leading to tumour invasion [96], decreases oxidative mitochondrial metabolism with decrease in cell survival and inducing apoptosis in vitro and in vivo [97], and additionally inhibits cell migration, underlying metastatic mechanisms, independently of CB₁ and CB₂ [98]. Given the analgesic effect of the THC:CBD combination in cancer treatment discussed above [70], the side benefit of THC and CBD [99] in chemotherapy-associated nausea, and these primary effects on tumour growth and spread, a strong rationale is currently present for their application in additional clinical trials.

Conclusion

Various publications have presented the position that THC accounts for the main effects [100], the

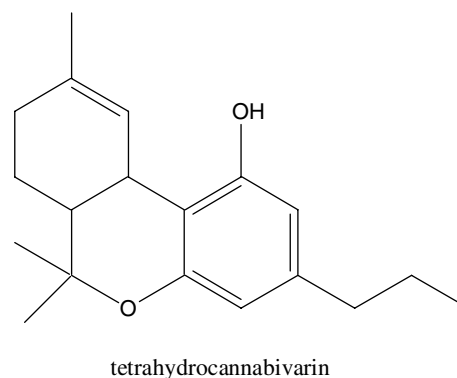


Figure 4 Tetrahydrocannabivarin (THCV), a propyl phytocannabinoids with potent antagonist properties at CB₁ [103].

analgesic and other medicinal benefits [101] of cannabis. This paper supports a distinct view that CBD and perhaps other cannabis components [6] achieve synergy with THC [102] consisting of potentiation of benefits, antagonism of adverse effects, summation (*à la* the entourage effect), pharmacokinetic advantages (in CBD suppression of 11-hydroxylation of THC), and metabolism (e.g., lower toxicity of a 'natural product' as compared to synthetic COX-inhibitor anti-inflammatory). The range of effects of the phytocannabinoids on pathophysiological processes is truly impressive, and suggests broad applicability in their future therapeutic application.

The recent discovery that the propyl phytocannabinoid, tetrahydrocannabivarin (THCV) (Fig. 4), is a potent antagonist at the CB₁ receptor [103] supports the notion that we yet have a great deal to learn about the therapeutic potential of this venerable medicinal plant.

The data herein presented strongly support the therapeutic rationale for combining THC and CBD for therapeutic usage.

Conflict of interest/role of funding Source

The author has been a consultant for GW Pharmaceuticals since 1998, and has received grants-in-aid, travel expenses, research support, stock options and salary in this regard.

Search strategy and selection criteria

References for this review were identified by searches of PubMed/National Library of Medicine

database from 1966 to June 2005 for articles pertinent to cannabidiol and its combination with THC in English, French, Spanish, Portuguese and Italian. Additional sources were identified in the author's extensive personal library of books and files.

Acknowledgements

The author thank Richard Musty for suggesting certain references and Emma Brierley and Alice Mead for suggested revisions.

References

- [1] Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science* 1992;258(5090):1946–9.
- [2] Fride E, Mechoulam R. Pharmacological activity of the cannabinoid receptor agonist, anandamide, a brain constituent. *Eur J Pharmacol* 1993;231(2):313–4.
- [3] Pertwee RG. Cannabis and cannabinoids: pharmacology and rationale for clinical use. *Pharm Sci* 1997;3:539–45.
- [4] Begg M, Pacher P, Batkai S, Osei-Hyiaman D, Offertaler L, Mo FM, et al. Evidence for novel cannabinoid receptors. *Pharmacol Ther* 2005;106(2):133–45.
- [5] de Meijer EP, Bagatta M, Carboni A, Crucitti P, Moliterni VM, Ranalli P, et al. The inheritance of chemical phenotype in *Cannabis sativa* L. *Genetics* 2003;163(1):335–46.
- [6] McPartland JM, Russo EB. Cannabis and cannabis extracts: greater than the sum of their parts? *Journal of Cannabis Therapeutics* 2001;1(3–4):103–32.
- [7] Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: the ongoing story of cannabis. *Nat Prod Rep* 1999;16(2):131–43.
- [8] Carlini EA, Karniol IG, Renault PF, Schuster CR. Effects of marijuana in laboratory animals and in man. *Brit J Pharmacol* 1974;50(2):299–309.
- [9] Fairbairn JW, Pickens JT. Activity of cannabis in relation to its delta'-*trans*-tetrahydro-cannabinol content. *Brit J Pharmacol* 1981;72(3):401–9.
- [10] Whalley BJ, Wilkinson JD, Williamson EM, Constanti A. A novel component of cannabis extract potentiates excitatory synaptic transmission in rat olfactory cortex in vitro. *Neurosci Lett* 2004;365(1):58–63.
- [11] Russo EB. Hemp for headache: an in-depth historical and scientific review of cannabis in migraine treatment. *J Cannabis Ther* 2001;1(2):21–92.
- [12] Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). *J Psychoactive Drugs* 1998;30(2):187–96.
- [13] Pertwee RG. Cannabinoid receptors and pain. *Prog Neurobiol* 2001;63(5):569–611.
- [14] Pertwee RG. The pharmacology and therapeutic potential of cannabidiol. In: DiMarzo V, editor. *Cannabinoids*. Dordrecht (Netherlands): Kluwer Academic Publishers; 2004.
- [15] Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol* 2002;42(Suppl 11):115–9S.
- [16] Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology* 1982;76(3):245–50.
- [17] Zuardi AW, Morais SL, Guimaraes FS, Mechoulam R. Antipsychotic effect of cannabidiol [letter]. *J Clin Psychiatry* 1995;56(10):485–6.
- [18] Bornheim LM, Grillo MP. Characterization of cytochrome P450 3A inactivation by cannabidiol: possible involvement of cannabidiol-hydroxyquinone as a P450 inactivator. *Chem Res Toxicol* 1998;11(10):1209–16.
- [19] Hampson AJ, Grimaldi M, Lolic M, Wink D, Rosenthal R, Axelrod J. Neuroprotective antioxidants from marijuana. *Ann NY Acad Sci* 2000;899:274–82.
- [20] Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreaskos E, Mechoulam R, et al. The non-psychoactive cannabis constituent cannabidiol is an oral anti-arthritis therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA* 2000;97(17):9561–6.
- [21] Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, et al. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Brit J Pharmacol* 2001;134(4):845–52.
- [22] Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia* 1973;33(1):53–70.
- [23] Welburn PJ, Starmer GA, Chesher GB, Jackson DM. Effect of cannabinoids on the abdominal constriction response in mice: within cannabinoid interactions. *Psychopharmacologia* 1976;46(1):83–5.
- [24] Monti JM. Hypnoticlike effects of cannabidiol in the rat. *Psychopharmacology (Berl)* 1977;55(3):263–5.
- [25] Musty RE, Sands R. Effects of marijuana extract distillate and cannabidiol on variable interval performance as a function of food deprivation. *Pharmacology* 1978;16(4):199–205.
- [26] Zuardi AW, Karniol IG. Effects on variable-interval performance in rats of delta 9- tetrahydrocannabinol and cannabidiol, separately and in combination. *Braz J Med Biol Res* 1983;16(2):141–6.
- [27] Rosenkrantz H, Hayden DW. Acute and subacute inhalation toxicity of Turkish marijuana, cannabichromene, and cannabidiol in rats. *Toxicol Appl Pharmacol* 1979;48(3):375–86.
- [28] Stott CG, Guy GW, Wright S, Whittle BA. The genotoxicology of Sativex. In: Conference on the Cannabinoids, 2005 June. Clearwater (FL): International Cannabinoid Research Society; 2005.
- [29] Zuardi AW, Finkelfarb E, Bueno OF, Musty RE, Karniol IG. Characteristics of the stimulus produced by the mixture of cannabidiol with delta 9-tetrahydrocannabinol. *Arch Int Pharmacodyn Ther* 1981;249(1):137–46.
- [30] Fadda P, Robinson L, Fratta W, Pertwee RG, Riedel G. Differential effects of THC- or CBD-rich cannabis extracts on working memory in rats. *Neuropharmacology* 2004;47(8):1170–9.
- [31] Hollister LE. Cannabidiol and cannabinol in man. *Experientia* 1973;29(7):825–6.
- [32] Perez-Reyes M, Timmons MC, Davis KH, Wall EM. A comparison of the pharmacological activity in man of intravenously administered delta9-tetrahydrocannabinol, cannabinol, and cannabidiol. *Experientia* 1973;29(11):1368–9.
- [33] Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta

- 9-tetrahydrocannabinol in man. *Eur J Pharmacol* 1974;28(1):172–7.
- [34] US Government. Additional scientific data considered by the Drug Enforcement Administration in evaluating Jon Gettman's petition to initiate rulemaking proceedings to reschedule marijuana. In: Federal Register, editor. Drug and chemical evaluation section OoDC, Drug Enforcement Administration. Washington (DC): US Government Printing Office; 2001. p. 20053–71.
- [35] ElSohly MA, Ross SA, Mehmedic Z, Arafat R, Yi B, Banahan 3rd BF. Potency trends of delta9-THC and other cannabinoids in confiscated marijuana from 1980–1997. *J Forensic Sci* 2000;45(1):24–30.
- [36] De Vry J, Jentzsch KR, Kuhl E, Eckel G. Behavioral effects of cannabinoids show differential sensitivity to cannabinoid receptor blockade and tolerance development. *Behav Pharmacol* 2004;15(1):1–12.
- [37] Hollister LE, Gillespie H. Interactions in man of delta-9-tetrahydrocannabinol. II. Cannabinol and cannabidiol. *Clin Pharmacol Ther* 1975;18(1):80–3.
- [38] Dalton WS, Martz R, Lemberger L, Rodda BE, Forney RB. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. *Clin Pharmacol Ther* 1976;19(3):300–9.
- [39] Lemberger L, Dalton B, Martz R, Rodda B, Forney R. Clinical studies on the interaction of psychopharmacologic agents with marijuana. *Ann NY Acad Sci* 1976;281:219–28.
- [40] Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol* 1981;21(Suppl. 8–9):417S–27S.
- [41] Wallace MJ, Blair RE, Falenski KW, Martin BR, DeLorenzo RJ. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 2003;307(1):129–37.
- [42] Wallace MJ, Martin BR, DeLorenzo RJ. Evidence for a physiological role of endocannabinoids in the modulation of seizure threshold and severity. *Eur J Pharmacol* 2002;452(3):295–301.
- [43] Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002;58(9):1404–7.
- [44] Russo EB. Safety, tolerability and efficacy of orally administered cannabinoids in MS. *Neurology* 2003;60(4):729–30.
- [45] Vaney C, Heinzl-Gutenbrunner M, Jobin P, Tschopp F, Gattlen B, Hagen U, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult Scler* 2004;10:417–24.
- [46] Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003;362(9395):1517–26.
- [47] Fox P, Bain PG, Glickman S, Carroll C, Zajicek J. The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology* 2004;62(7):1105–9.
- [48] Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. The cannabinoids in MS study – final results from 12 months follow-up. *Mult Scler* 2004;10(Suppl.):S115.
- [49] Pryce G, Baker D. Emerging properties of cannabinoid medicines in management of multiple sclerosis. *Trends Neurosci* 2005;28(5):272–6.
- [50] Carroll CB, Bain PG, Teare L, Liu X, Joint C, Wroath C, et al. Cannabis for dyskinesia in Parkinson disease: a randomized double-blind crossover study. *Neurology* 2004;63(7):1245–50.
- [51] Venderova K, Ruzicka E, Vorisek V, Visnovsky P. Survey on cannabis use in Parkinson's disease: subjective improvement of motor symptoms. *Movement Disord* 2004;19(9):1102.
- [52] Russo EB. Introduction. Cannabis: from pariah to prescription. *J Cannabis Ther* 2003;3(3–4):1–29.
- [53] Guy GW, Flint ME. A single centre, placebo-controlled, four period, crossover, tolerability study assessing pharmacokinetic effects, pharmacokinetic characteristics and cognitive profiles of a single dose of three formulations of cannabis based medicine extracts (CBMEs) (GWPD9901), plus a two period tolerability study comparing pharmacodynamic effects and pharmacokinetic characteristics of a single dose of a cannabis based medicine extract given via two administration routes (GWPD9901 EXT). *J Cannabis Ther* 2003;3(3):35–77.
- [54] Guy GW, Robson P. A Phase I, double blind, three-way crossover study to assess the pharmacokinetic profile of cannabis based medicine extract (CBME) administered sublingually in variant cannabinoid ratios in normal healthy male volunteers (GWPK02125). *J Cannabis Ther* 2003;3(4):121–52.
- [55] Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol* 2004;24(3):305–13.
- [56] Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil* 2003;17:18–26.
- [57] Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmonds S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 "N of 1" studies. *Anaesthesia* 2004;59:440–52.
- [58] Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler* 2004;10:425–33.
- [59] Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. *Pain* 2004;112(3):299–306.
- [60] Carlini EA. The good and the bad effects of (–)trans-delta-9-tetrahydrocannabinol (Delta(9)-THC) on humans. *Toxicol* 2004;44(4):461–7.
- [61] Collin C. A cannabis-based medicine (Sativex) has sustained efficacy in the treatment of spasticity in multiple sclerosis. In: Association of British Neurologists; Belfast, Northern Ireland; 2005 April 1.
- [62] Rog DJ, Nurmiko T, Friede T, Young C. Randomized controlled trial of cannabis based medicine in central neuropathic pain due to multiple sclerosis. *Neurology* 2005;65(6):812–9.
- [63] Attal N, Brasseur L, Guirimand D, Clermont-Gnamien S, Atlami S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? *Eur J Pain* 2004;8(2):173–7.
- [64] Clermont-Gnamien S, Atlami S, Attal N, Le Mercier F, Guirimand F, Brasseur L. Utilisation thérapeutique du delta-9-tétrahydrocannabinol (dronabinol) dans les douleurs neuropathiques réfractaires [The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain]. *Presse Med* 2002;31(39 Pt 1):1840–5.
- [65] Rudich Z, Stinson J, Jeavons M, Brown SC. Treatment of chronic intractable neuropathic pain with dronabinol:

- case report of two adolescents. *Pain Res Manag* 2003;8(4):221–4.
- [66] Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *Brit Med J* 2004;329(7460):253.
- [67] Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ. A multi-center, double-blind, randomized, placebo-controlled trial of oro-mucosal cannabis-based medicine in the treatment of neuropathic pain characterized by allodynia. In: American Academy of Neurology. Miami Beach (FL); 2005 April 14.
- [68] Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler* 2004;10(4):434–41.
- [69] Robson P, Wade D, Makela P, House H, Bateman C. Cannabis-based medicinal extract (Sativex) produced significant improvements in a subjective measure of spasticity which were maintained on long-term treatment with no evidence of tolerance. In: International Association for Cannabis as Medicine; Leiden, Netherlands; 2005 September 9.
- [70] Johnson JR, Potts R. Cannabis-based medicines in the treatment of cancer pain: a randomised, double-blind, parallel group, placebo controlled, comparative study of the efficacy, safety and tolerability of Sativex and Tetranabinex in patients with cancer-related pain. In: British Pain Society. Edinburgh, Scotland; 2005 March 8–11.
- [71] Russo EB. Sativex cannabis based medicine maintains improvements in sleep quality in patients with multiple sclerosis and neuropathic pain. In: American Academy of Neurology. Miami Beach (FL); 2005 April 12.
- [72] Russo EB, Guy GW, Robson PJ, Pertwee RG. Tolerance and THC: cannabis based medicine extracts maintain long-term clinical efficacy without dosage increases. In: 2004 Symposium on the cannabinoids. Paestum (Italy): International Cannabinoid Research Society; 2004. p. 90.
- [73] Hampson AJ, Grimaldi M, Axelrod J, Wink D. Cannabidiol and (–)Delta9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA* 1998;95(14):8268–73.
- [74] Hamelink C, Hampson A, Wink DA, Eiden LE, Eskay RL. Comparison of cannabidiol, antioxidants and diuretics in reversing binge ethanol-induced neurotoxicity. *J Pharmacol Exp Ther* 2005.
- [75] Mishima K, Hayakawa K, Abe K, Ikeda T, Egashira N, Iwasaki K, et al. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. *Stroke* 2005;36(5):1077–82.
- [76] Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT_{1a} receptors. *Neurochem Res* 2005;30(8) [in press].
- [77] Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from *Cannabis sativa*, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem* 2004;89(1):134–41.
- [78] Moreira FA, Guimaraes FS. Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. *Eur J Pharmacol* 2005;512(2–3):199–205.
- [79] Volicer L, Stelly M, Morris J, McLaughlin J, Volicer BJ. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatr* 1997;12(9):913–9.
- [80] Carter GT, Rosen BS. Marijuana in the management of amyotrophic lateral sclerosis. *Am J Hosp Palliat Care* 2001;18(4):264–70.
- [81] Raman C, McAllister SD, Rizvi G, Patel SG, Moore DH, Abood ME. Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid. *ALS and Other Motor Neuron Disorders* 2004;5:33–9.
- [82] Abood ME, Raman C, Kim K, Moore DH. Evaluation of cannabidiol in a mutant SOD1 mouse model of ALS. In: International alliance of ALS/MND associations. Philadelphia; 2004 December 3.
- [84] Lastres-Becker I, Molina-Holgado F, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. *Neurobiol Dis* 2005;19(1–2):96–107.
- [85] Consroe P, Snider SR. Therapeutic potential of cannabinoids in neurological disorders. In: Mechoulam R, editor. *Cannabinoids as therapeutic agents*. Boca Raton (FL): CRC Press; 1986. p. 21–49.
- [86] Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, et al. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav* 1991;40(3):701–8.
- [87] Baker D. Therapeutic potential of cannabis and cannabinoids in experimental models of multiple sclerosis. In: Guy GW, Whittle BA, Robson PJ, editors. *Medicinal uses of cannabis and cannabinoids*. London: Pharmaceutical Press; 2004. p. 141–64.
- [88] Samaha AN, Robinson TE. Why does the rapid delivery of drugs to the brain promote addiction? *Trends Pharmacol Sci* 2005;26(2):82–7.
- [89] Labigalini E, Jr LR, Rodrigues DX. Therapeutic use of cannabis by crack addicts in Brazil. *J Psychoactive Drugs* 1999;31(4):451–5.
- [90] Dreher M. Crack heads and roots daughters: the therapeutic use of cannabis in Jamaica. *J Cannabis Ther* 2002;2(3–4):121–33.
- [91] Cichewicz DL, Welch SP. Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral Delta 9-tetrahydrocannabinol. *J Pharmacol Exp Ther* 2003;305(3):812–7.
- [92] Shavit Y, Wolf G, Goshen I, Livshits D, Yirmiya R. Interleukin-1 antagonizes morphine analgesia and underlies morphine tolerance. *Pain* 2005;115(1–2):50–9.
- [93] Watzl B, Scuderi P, Watson RR. Influence of marijuana components (THC and CBD) on human mononuclear cell cytokine secretion in vitro. *Adv Exp Med Biol* 1991;288:63–70.
- [94] Maccarrone M, Finazzi-Agro A. The endocannabinoid system, anandamide and the regulation of mammalian cell apoptosis. *Cell Death Differ* 2003;10(9):946–55.
- [95] Guzman M, Sanchez C, Galve-Roperh I. Control of the cell survival/death decision by cannabinoids. *J Mol Med* 2001;78(11):613–25.
- [96] Vaccani A, Massi P, Parolaro D. Inhibition of human glioma cell growth by the non-psychoactive cannabidiol. In: First European workshop on cannabinoid research. Madrid; 2003 April 4–5. p. 66.
- [97] Massi P, Vaccani A, Ceruti S, Colombo A, Abbracchio MP, Parolaro D. Antitumor effects of cannabidiol, a non-psychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther* 2004;308(3):838–45.
- [98] Vaccani A, Massi P, Colombo A, Rubino T, Parolaro D. Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism. *Brit J Pharmacol* 2005.

- [99] Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *Neuroreport* 2002;13(5): 567–70.
- [100] Wachtel SR, ElSohly MA, Ross RA, Ambre J, de Wit H. Comparison of the subjective effects of delta9-tetrahydrocannabinol and marijuana in humans. *Psychopharmacology* 2002;161:331–9.
- [101] Varvel SA, Bridgen DT, Tao Q, Thomas B, Martin B, Lichtman A. {Delta}9-Tetrahydrocannabinol accounts for the antinociceptive, hypothermic, and cataleptic effects of marijuana in mice. *J Pharmacol Exp Ther* 2005.
- [102] Whittle BA, Guy GW, Robson P. Prospects for new cannabis-based prescription medicines. *J Cannabis Ther* 2001;1(3–4):183–205.
- [103] Thomas A, Stevenson LA, Wease KN, Price MR, Baillie G, Ross RA, et al. Evidence that the plant cannabinoid delta-9-tetrahydrocannabinol is a cannabinoid CB1 and CB2 antagonist. *Brit J Pharmacol* 2005 [in press].
- [104] Pertwee RG. Advanced in cannabinoid receptor pharmacology in cannabis. In: Brown DT, editor. *Cannabis: The genus Cannabis*. Amsterdam: Harwood Academic Publishers; 1998.
- [105] Showalter VM, Compton DR, Martin BR, Abood ME. Evaluation of binding in a transfected cell line expressing a peripheral cannabinoid receptor (CB2): identification of cannabinoid receptor subtype selective ligands. *J Pharmacol Exp Ther* 1996;278(3):989–99.
- [106] Stott CG, Guy GW, Wright S, Whittle BA. The effects of cannabis extracts Tetranabinex and Nabidiolex on human cyclo-oxygenase (COX) activity. In: *Symposium on the Cannabinoids*, 2005 June. Clearwater (FL): International Cannabinoid Research Society; 2005.
- [107] Cabral G. Immune system. In: Grotenhermen F, Russo EB, editors. *Cannabis and cannabinoids: Pharmacology, toxicology and therapeutic potential*. Binghamton (NY): Haworth Press; 2001. p. 279–87.
- [108] Russo EB. *Handbook of psychotropic herbs: a scientific analysis of herbal remedies for psychiatric conditions*. Binghamton (NY): Haworth Press; 2001.
- [109] Zuardi AW, Guimaraes FS. Cannabidiol as an anxiolytic and antipsychotic. In: Mathre ML, editor. *Cannabis in medical practice: a legal, historical and pharmacological overview of the therapeutic use of marijuana*. Jefferson (NC): McFarland; 1997. p. 133–41.
- [111] Müller-Vahl KR, Schneider U, Prevedel H, Theloe K, Kolbe H, Daldrup T, et al. Delta9-Tetrahydrocannabinol (THC) is effective in the treatment of tics in tourette syndrome: a 6-week randomized trial. *J Clin Psychiat* 2003;64(4): 459–65.
- [112] Russo EB. Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuroendocrinol Lett* 2004;25(1–2):31–9.
- [113] Grinspoon L, Bakalar JB. The use of cannabis as a mood stabilizer in bipolar disorder: anecdotal evidence and the need for clinical research. *J Psychoactive Drugs* 1998;30(2):171–7.
- [114] Weil AT, Zinberg NE, Nelsen JM. Clinical and psychological effects of marijuana in man. *Science* 1968;162(859): 1234–42.
- [115] Batkai S, Pacher P, Osei-Hyiaman D, Radaeva S, Liu J, Harvey-White J, et al. Endocannabinoids acting at cannabinoid-1 receptors regulate cardiovascular function in hypertension. *Circulation* 2004;110(14):1996–2002.
- [116] Sanchez C, Galve-Roperh I, Canova C, Brachet P, Guzman M. Delta9-tetrahydrocannabinol induces apoptosis in C6 glioma cells. *FEBS Lett* 1998;436(1):6–10.
- [117] Massi P, Vaccani A, Ceruti S, Colombo A, Abbraccio MP, Parolaro D. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther* 2004;308(3):838–45.
- [118] Jarvinen T, Pate D, Laine K. Cannabinoids in the treatment of glaucoma. *Pharmacol Ther* 2002;95(2): 203–20.
- [119] Russo EB, Merzouki A, Molero Mesa J, Frey KA, Bach PJ. Cannabis improves night vision: a pilot study of dark adaptometry and scotopic sensitivity in kif smokers of the Rif Mountains of Northern Morocco. *J Ethnopharmacol* 2004;93(1):99–104.

Available online at www.sciencedirect.com

