

Evidence Check

Pharmacological actions and associated therapeutic levels of phytocannabinoids

An **Evidence Check** rapid review brokered by the Sax Institute for the NSW Ministry of Health. January 2016.

This report was prepared by:

Jonathon C. Arnold, David J. Allsop, Nicholas Lintzeris, Iain S. McGregor

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Addendum: This report was finalised in January 2016. In 2017, the Food Standards Code was amended to permit the sale of low THC hemp seed products. The final report and standard by Food Standards Australia New Zealand (FSANZ) are available [here](#).

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LAMBERT INITIATIVE
FOR CANNABINOID THERAPEUTICS



THE UNIVERSITY OF
SYDNEY

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1 Executive summary

Pharmacological actions and associated therapeutic levels of phytocannabinoids

A systematic review of the clinical and preclinical literature was conducted to examine the pharmacological and possible therapeutic effects of various plant-derived cannabinoids (phytocannabinoids) that are found in street cannabis and industrial hemp. Some of these phytocannabinoids may also be present from time to time in hemp seed oil and related products.

The phytocannabinoids of interest were:

- Cannabidiol (CBD)
- Cannabidiolic acid (CBDA)
- Cannabidivarin (CBDV)
- Delta-8-tetrahydrocannabinolic acid (THCA)
- Delta-9-tetrahydrocannabivarin (THCV)
- Delta-9-tetrahydrocannabivarinic acid (THCVA)
- Cannabigerol (CBG)
- Cannabigerolic acid (CBGA)
- Cannabinol (CBN)
- Cannabichromene (CBC).

The specific research questions posed to be addressed were:

1. What are the pharmacological characteristics of individual cannabinoids; and
2. What therapeutic levels of individual cannabinoids are required to elicit the pharmacological characteristic in adults and children?

The therapeutic effects of Delta-9-tetrahydrocannabinol (THC) are well described and Food Standards Australia New Zealand (FSANZ) has already proposed a maximum allowable level of THC in hemp seed and oil added to food or offered for sale as food in their proposal in response to Application A1039¹. The review therefore did not include THC.

Evidence from human trials was considered of greatest relevance. Where this was not available evidence from in vitro and animal studies was reviewed and included.

¹ A1039 proposes a variation to Standards in the Australia New Zealand Food Standards Code that would allow:

- Cannabis sativa seeds to be added to food or offered for sale as food if the seeds contain not more than 5 mg/kg delta 9-tetrahydrocannabinol, each seed is a non-viable seed and each seed is a hulled seed.
- All or any of the following seed products may be added to food or offered for sale as food: oil extracted from Cannabis sativa seeds if the oil contains not more than 10 mg/kg delta 9-tetrahydrocannabinol; a beverage derived from Cannabis sativa seeds if the beverage contains not more than 0.2 mg/kg/ delta 9- tetrahydrocannabinol and any other substance extracted or derived from Cannabis sativa seeds if the substance contains not more than 5 mg/kg delta 9-tetrahydrocannabinol.

Introduction

Cannabis sativa has been used for millennia for its myriad therapeutic effects. Following a few decades of prohibition, recent times have seen resurgent interest in the therapeutic potential of cannabis as well as the legalisation of medicinal cannabis in various countries.

This new interest has coincided with a dramatic increase in our knowledge of the cannabis plant, which is now known to contain more than 100 terpenophenolic compounds that are known as *phytocannabinoids* (plant-derived cannabinoids) in addition to several hundred other compounds including monoterpenoids, sesquiterpenoids and flavonoids.

It is generally accepted that the characteristic intoxicating effects of cannabis are almost exclusively due to the action of the phytocannabinoid *delta-9-tetrahydrocannabinol* (THC). THC acts at cannabinoid CB1 receptors (CB1Rs) in the brain to produce intoxicating effects that are reversible by CB1R antagonist drugs. Administration of pure THC to humans or non-human primates produces intoxication that is very similar to cannabis itself.

Only a few phytocannabinoids other than THC have been administered in purified form to humans. These include *cannabidiol* (CBD), *tetrahydrocannabivarin* (THCV), *cannabichromene* (CBC), *cannabidivarin* (CBDV), *tetrahydrocannabinolic acid* (THCA) and *cannabinol* (CBN). For CBD, a reasonable number of human studies exist, but for THCV, CBC, CBDV and CBN there are very few studies and they are generally of poor quality. Overall, it appears that none of these five phytocannabinoids appear to have THC-like intoxicating properties, although there is some evidence of mild intoxication with CBN and THCV following intravenous dosing, and there may be some mild sedation or somnolence with high oral doses of CBD, although the data are inconclusive on this point.

With the other phytocannabinoids, where human data are scarce or non-existent, intoxicating properties (or lack thereof) can only be inferred from either (1) studies of CB1R binding *in vitro*, in which CB1R binding can predict THC-like intoxicating effects, and (2) studies of THC-like effects in laboratory animals, which when carefully conducted can be broadly predictive of *cannabimimetic* (cannabis-like) intoxicating effects in humans.

Phytocannabinoid content of cannabis plant material and other hemp preparations

The flowering heads of typical street cannabis in Australia contain a mean of 15% THC which is mostly in the form of non-psychoactive *delta-9-tetrahydrocannabinolic acid* (THCA) (approximately 13.5%) with only 1.5% actual THC content. Heating the plant material to 160°C or greater causes the conversion of plant based THCA to THC, a process known as *decarboxylation*. This explains why cannabis is typically smoked, baked or vaporised by recreational users to obtain intoxicating effects. The levels of other phytocannabinoids in the flowering heads of Australian street cannabis is very low, typically <0.2%, suggesting that very large amounts of cannabis would need to be consumed to obtain any relevant pharmacological actions from these compounds.

Fibre hemp varieties of cannabis display an entirely different cannabinoid profile, with very low levels of THC (<0.5%) and THCA (<0.5%) but correspondingly high levels of CBD (approximately 3.5%) and its acidic form *cannabidiolic acid* (CBDA) (approximately 10.5%). There is no evidence of intoxicating effects of CBDA. There is some evidence of mildly sedating and anxiolytic effects of CBD, but no evidence of THC-like intoxication. Other phytocannabinoids such as *cannabidivarin* (CBDV) and *cannabigerol* (CBG) may be present in hemp varieties at levels of 0.5% or less.

Hemp seed oils prepared by the cold pressing of cannabis seeds are acclaimed for their high levels of omega-6 and omega-3 polyunsaturated fatty acids, and also for containing a diverse array of essential amino acids. Cannabinoids are apparently not synthesised within the hemp seed. However traces of cannabinoid contamination may result from the pressing of hemp seed oil probably due to residual contamination from the hull.

Comprehensive reports of the cannabinoid content of hemp seed oils are not readily available. It has generally been assumed that if made from the seeds of low THC hemp fibre varieties then only miniscule, trace levels of CBD, CBDA and sometimes THC will be present, typically at a range of 1-10 parts per million (ppm). However, one very recent analysis from Croatia [1] that included a diverse array of hempseed products, found CBD present at a range of 3-250 ppm, THC at a range of 4-243 ppm and CBN at a range of 2-8 ppm. More data are clearly needed relating to possible cannabinoid content of local Australian hemp seed products.

Diverse pharmacological targets of phytocannabinoids

In considering the possible *therapeutic* actions of phytocannabinoids it is important to consider their pharmacological effects at multiple targets in the brain and body other than the CB1R. These include:

- a) *The cannabinoid CB2 Receptor*: The cannabinoid CB2 receptor (CB2R) is located largely in the immune system and this is an important therapeutic target related to neuropathic pain and inflammation. The CB2R is also an emerging target for novel therapeutics in the addictions field
- b) *The endocannabinoid system*: The brain and body contain at least 2 endogenous cannabinoids called *anandamide* and *2-AG*. Some phytocannabinoids can modulate levels of these endocannabinoids by acting on endocannabinoid synthetic enzymes (NAPE-PLD and DAGL) or degradative enzymes (FAAH and DAGL). Such actions could theoretically produce a range of THC-like effects, although research on this topic is still at an elementary stage
- c) *Transient Receptor Potential (TRP) Channels*. There are more than 28 different TRP channel types in the human brain and body and these have a diverse range of functions relating to pain, inflammation, temperature sensing, taste and visceral function. Endocannabinoids, and some phytocannabinoids, act at TRP channels and this may underlie some therapeutic actions, particularly analgesic and anti-inflammatory effects
- d) *Miscellaneous other receptors*. There is evidence for an action of some phytocannabinoids on a range of other receptors including serotonin (e.g. 5-HT_{1A}), noradrenaline (e.g. α 2) and peroxisome-proliferator activated receptors (e.g. PPAR- α).

Pharmacological actions and possible therapeutic effects of individual phytocannabinoids

The relevant pharmacological and therapeutic actions of various phytocannabinoids, excluding THC, are summarised as follows. However it should be noted that the majority of phytocannabinoids reviewed have no demonstrated action in humans at this stage. We therefore estimated the lowest therapeutic dose (mg) in humans by extrapolating from the lowest dose effective in treating the disease in an *in vivo* animal model. While this dose may be instructive to the reader's consideration of what future limits might be, we do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies at this point in time. Future human studies would be required for this given major limitations in the translatability of animal research.

CBC (Cannabichromene)

CBC is a relatively common phytocannabinoid that is produced from CBG in the cannabis plant. There is little evidence for THC-like effects of CBC at CB1Rs, although there is evidence of sedation and catalepsy in laboratory animals at very high intravenous doses. CBC has a range of intriguing *in vitro* and *in vivo* actions in preclinical models that imply therapeutic efficacy as an anti-inflammatory agent and also perhaps as a mild sedative, analgesic and antibiotic. However, further confirmation in human studies is required.

CBC has no demonstrated therapeutic actions in humans. We therefore estimated the lowest therapeutic dose (mg) in humans by extrapolating from the lowest dose effective in treating disease in an *in vivo* animal model. The lowest therapeutic dose we found in the scientific literature was 1 mg/kg administered intraperitoneally (IP) which was effective in reducing inflammation of the colon (colitis) in mice [2]. As IP phytocannabinoid doses achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels might be as high as 7 mg/kg in mice. Applying calculations relating to interspecies comparison to this dose (see footnote²), the estimated therapeutic oral dose for CBC in a 60 kg human to produce anti-inflammatory effects is calculated at around 35 mg. Given the major limitations of animal to human dose extrapolation, this estimated dose should not be used to set a limit of CBC in hemp food products. To produce sedative, hypothermic or analgesic effects 20-80 fold higher doses are required, namely 0.7 - 3.0 grams. It is very implausible that such dose would be achieved with even excessive consumption of any current hemp seed or hemp oil preparations.

CBDA (Cannabidiolic acid)

CBDA has never been administered to a human as a pure substance. However, the preclinical evidence described above suggests that CBDA is unlikely to have intoxicating effects in humans. CBDA only binds to CB1Rs at relatively high concentrations and does not activate the receptor. It does not appear to produce THC-like cannabimimetic effects in laboratory animals.

CBDA has various pharmacological actions that might be clinically relevant based on the effective concentrations and doses used in cell systems and animal studies respectively. Some effects have been shown at very low concentrations, including antiemetic effects and the potentiation of 5-HT_{1A} receptor activity.

The lowest CBDA dose we identified in the literature to be effective in an animal model of disease was 0.001 mg/kg (IP). This dose inhibited lithium-induced conditioned gaping (an animal model of anticipatory nausea) in rats [4]. As IP phytocannabinoid doses achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels might be 0.007 mg/kg in rats. Applying interspecies calculations to this dose, the estimated therapeutic oral dose of CBDA for this anticipatory nausea therapeutic effect in a 60 kg human would be approximately 0.07 mg². However, we do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.

CBDA is the precursor to CBD in the cannabis plant and is converted to CBD by heat. Given this fact, it is likely prudent to set a similar limit with CBDA as to that set for CBD, as heating CBDA produces CBD.

²Please refer to the Introduction to the Review section under “*Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans*” in the full report for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in *in vitro* and *in vivo* animal models may not translate to humans. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

CBD (Cannabidiol)

CBD has numerous pharmacological actions and is already showing strong clinical promise in the treatment of epilepsy, anxiety and psychosis. Complications may arise with pharmacokinetic interactions when CBD is combined with other medications such as opioids or anticonvulsants.

CBD appears to lack significant intoxicating effects in animals or humans, although some studies indicate the possibility of mild sedative effects of CBD at oral doses ranging from 200 – 800 mg [5-7]. However, the majority of studies in which evidence was presented suggest no sedative effects, even with oral doses as high as 1280 mg.

Across the many human studies performed with CBD, the lowest oral dose at which a therapeutically relevant effect was observed was 800 mg administered daily, which reduced psychotic symptoms in schizophrenia patients [8]. We used this study to obtain our lowest therapeutic dose (800 mg) on the basis of it being in a clinical population (i.e. not in healthy humans), being of robust experimental design and that it reported a clearly defined therapeutic effect. Please note though that this study is a Phase 2 RCT and thus cannot provide sufficient evidence for CBD to be formally approved as a therapeutic agent. Larger scale Phase 3 RCT trials are necessary for this, some of which are being conducted now with results forthcoming in 2016. We therefore conclude that a human oral dose of 800 mg of CBD constitutes a threshold therapeutic dose based on the best available evidence. This dose estimation might be subject to change when results of Phase 3 trials become available.

CBDV (Cannabivarin)

CBDV is the propyl homologue of CBD and has very low affinity for human CB1Rs or CB2Rs. It has powerful effects on various TRP channels, perhaps the most potent TRP effects of any of the phytocannabinoids. CBDV is clearly of major therapeutic interest as an anticonvulsant, given its current investigation in human clinical trials. Although comparatively little work has been done with CBDV, there is nothing to suggest CB1 affinity or intoxicating effects. Evidence for inflammatory and antiemetic actions are preliminary and reflect individual preclinical studies. Anticonvulsant effects may reflect actions of CBDV at TRPV1 channels.

The lowest CBDV dose we identified in the literature to be effective in an animal model of disease was 50 mg/kg IP which inhibited tonic convulsions induced by audiogenic seizures in rats [9]. As IP doses of CBDV achieve 1.6 times higher brain concentrations (the site of anticonvulsant drug action) than oral doses in rats [3], the oral dose needed to achieve equivalent plasma levels would likely be around 80 mg/kg. Applying interspecies conversion calculations to this dose, the estimated human oral therapeutic dose in a 60 kg human would be approximately 774 mg².

CBGA (Cannabigerolic acid)

CBGA is the precursor to both CBDA and THCA in the cannabis plant and is found at low levels in street cannabis. CBGA has never been administered to humans as a pure substance. It is unlikely to have intoxicating effects in humans given its lack of affinity at CB1Rs. However, appropriate preclinical and human studies would be required to rule this out definitively. CBGA has various pharmacological actions that may or may not be clinically relevant given the relatively high concentrations and doses needed to affect cell systems. In the absence of clinical evidence it is difficult to determine what constitutes a therapeutic dose of CBGA. Extrapolation from animals to humans is also not possible, as CBGA has never been tested in an *in vivo* animal study.

CBG (Cannabigerol)

Cannabigerol (CBG) is formed by non-enzymatic decarboxylation from CBGA. CBG has never been administered to a human as a pure substance. It binds to the CB1Rs only at relatively high concentrations and does not activate the receptor. It does not produce THC-like cannabimimetic effects in animals. It is therefore unlikely to have intoxicating effects in humans based on preclinical evidence.

CBG has various pharmacological actions that might be clinically relevant based on the effective concentrations and doses used in cell systems and animal studies respectively. Some effects have been shown at nanomolar concentrations such as α_2 -adrenoceptor agonism and CB1R antagonism.

The lowest CBG dose we identified in the literature to be effective in an animal model of disease was 3 mg/kg IP which inhibited the size of colon tumors in a mouse xenograft model [10]. As IP phytocannabinoid doses achieve 60.9 times higher plasma concentrations than oral doses in mice [3], the oral dose needed to achieve equivalent plasma levels might be as high as 183 mg. Applying interspecies conversion calculations to this dose, the estimated therapeutic oral dose in a 60 kg human would be approximately 892 mg².

CBN (Cannabinol)

CBN was the first cannabinoid to be isolated from the cannabis plant (in 1895) and many studies have examined its pharmacological activity. CBN may have mild psychoactivity when large quantities of the drug are administered intravenously to humans. This presumably reflects lower efficacy of CBN at CB1Rs than THC, despite its higher affinity. In the absence of good quality clinical studies, it is difficult to determine a therapeutic dose of CBN.

The lowest CBN dose we identified in the literature to be effective in an animal model of disease was 5 mg/kg which delayed the onset of symptoms in a mouse model of ALS when administered subcutaneously [11]. A subcutaneous phytocannabinoid dose would achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels would be around 35 mg/kg. Applying interspecies conversion calculations to this dose, the estimated therapeutic oral dose in a 60 kg human for this indication would be 171 mg².

In a recent analysis of hempseed oils, CBN was present in some preparations at a concentration approaching 10 mg/kg [1]. This would suggest that consuming 5 kg (5.5 L) of such hemp seed oil would be necessary to obtain a non-psychoactive dose of 50 mg CBN.

THCA (Delta-9-tetrahydrocannabinolic acid)

THCA is the chemical precursor of THC in the cannabis plant. THCA is formed from cannabigerolic acid (CBGA) by the enzyme THCA synthase. Heating cannabis plant material to around 160°C causes the decarboxylation of THCA to THC by a non-enzymatic reaction. Overall the weight of evidence suggests that THCA is unlikely to have intoxicating effects in humans. This includes a single study in which THCA was administered to human participants.

The lowest THCA dose we identified in the literature to be effective in an animal model of disease was 0.05 mg/kg IP which had anti-nausea effects in rats [12]. As IP phytocannabinoid doses achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels would be around 0.35 mg/kg. Applying interspecies conversion calculations to this dose, the estimated therapeutic oral dose in a 60 kg human for this indication would be 3.5 mg².

It should be noted however that THCA is readily converted to THC by heating plant material. At 100° Celsius it is reported that 80% of THCA is converted to THC [13]. THCA is quite stable in the short term (24 hours) even at high temperatures such as 50°C, although there is a relatively small but significant conversion to THC at room temperature (e.g. a 2% THC content can increase to 5.6% THC across a year of measurement [13]).

Thus THCA content should be measured in hemp food products and maintained at low levels given that it could be readily converted to THC *via* heating by knowledgeable consumers. Similar concentrations of THCA in seed, oil, and beverages might be adopted to that proposed for THC in FSANZ Application A1039.

THCVA (Delta-9-tetrahydrocannabivarinic acid)

THCVA is formed in the cannabis plant from cannabigerovarinic acid (CBGVA). There is extremely limited evidence available with which to form an opinion about the psychopharmacological, therapeutic and intoxicating actions of THCVA. THCVA has cytotoxic effects in prostate cancer cells at medium micromolar concentrations. Without more evidence it is impossible to estimate a human therapeutic dose.

THCV (Delta-9-tetrahydrocannabivarin)

THCV is the propyl homologue of THC differing only in its slightly shortened alkyl side chain. The literature on THCV is very limited, with only a handful of human studies of very limited quality. It is generally thought that THCV has antagonist effects at the CB1R which oppose the intoxicating effects of THC. This forms the basis of current interest in the appetite-suppressant effects of THCV as a treatment for obesity and metabolic disorders.

Nonetheless, there is an absence of good quality clinical evidence to determine a therapeutic dose of THCV. When administered to humans at a dose of 7 mg intravenously there were some mild to moderate subjective effects in a small number of participants that were approximately 25% the potency of THC. A more recent brain imaging study administering 10 mg oral THCV did not assess any therapeutic outcomes, although it did report no significant differences between the THCV dose and placebo on scores for mood, energy and affect.

The lowest THCV dose we identified in the literature to be effective in an animal model of disease was 0.25 mg/kg IP which reduced seizure severity in a rat model of epilepsy [14]. As IP doses of THCV achieve 5.4 times higher brain concentrations (the site of anticonvulsant drug action) than oral doses in rats [3], the oral dose required would be around high 1.35 mg/kg. Applying the FDA calculation to this dose, the estimated therapeutic oral dose in a 60 kg human is 13 mg². We list this dose as our estimated lowest therapeutic dose owing to the human studies listed not quantifying any therapeutic effect, although it is reassuring that the animal calculation closely matches the maximum dose recorded in humans (10 mg oral), which yielded no noticeable intoxication or mood effects.

Conclusions

This review demonstrates a paucity of good quality evidence for many of the phytocannabinoids. For most there are no published studies involving human administration, and therapeutic plasma levels in humans are undefined. Available studies are limited to *in vitro* cellular or *in vivo* rodent preclinical studies and some qualified inferences can be made from such data regarding possible therapeutic levels in humans. Such information provides some clues regarding effective therapeutic doses in humans, but extrapolation from these preclinical *in vitro* concentrations and *in vivo* rodent doses to humans can only be made with caution. Drawing conclusions on therapeutic oral doses in humans from animal studies has major limitations. What appears to be a potent therapeutic action in an animal may not translate to humans, or even if it does, the therapeutic doses achieved in humans may be radically different to those observed in animal studies.

There is reasonably good evidence of the therapeutic effects of CBD in humans at 800 mg (absolute dose). There is the possibility of mild sedation at such doses of CBD, although the current literature is ambiguous on

this point with the balance being in favour of no sedative effects. There is no evidence of THC-like intoxication with CBD.

Evidence relating to potential therapeutic effects of the remaining phytocannabinoids mostly comes from preclinical studies involving cellular models and laboratory animals. Some evidence is available relating to effects arising from the consumption of THCA, THCV, CBDV, CBC and CBN in humans. In general, there is little evidence of intoxication with these phytocannabinoids following an oral route of administration. However, CBN and THCV may be mildly intoxicating following intravenous administration of relatively high doses. Only limited preclinical evidence is available for CBDA, THCVA, CBG and CBGA. None of these phytocannabinoids appear to have intoxicating properties although human studies are required to definitively rule this out.

The specific conclusions for setting limits in hemp-derived products are:

1. **A limit could be set for CBD** given that it has therapeutic effects in humans (lowest human therapeutic absolute dose is 800 mg).
2. **The same limit might also be set for CBDA** (ie. 800 mg) given it is almost completely converted to CBD upon heating.
3. **A limit could be set for THCA** identical to that already set by FSANZ for THC. THCA is almost completely converted to THC when it is heated and so might be heated by some consumers seeking intoxication
4. **At this stage limits may not be required for the remaining phytocannabinoids CBC, CBDV, CBN, CBGA, CBG, THCV and THCVA.** No strong evidence supports these compounds having intoxicating effects following oral administration. The evidence for therapeutic potential comes only from animal studies and so the estimated human doses calculated from animal studies may not be relevant to human consumption.

Addendum: This report was finalised in January 2016. In 2017, the Food Standards Code was amended to permit the sale of low THC hemp seed products. The final report and standard by the Food Standards Australia New Zealand (FSANZ) are available [here](#).

2 Introduction to the review

Cannabis sativa has been used for millennia for its myriad therapeutic effects. Following a few decades of prohibition, recent times have seen resurgent interest in the therapeutic potential of cannabis as well as the legalisation of medicinal cannabis in various countries.

This new interest has coincided with a dramatic increase in our knowledge of the cannabis plant, which is now known to contain more than 100 terpenophenolic compounds that are known as *phytocannabinoids* (plant-derived cannabinoids).

The best-known phytocannabinoid is *delta-9-tetrahydrocannabinol* (THC), which was first reported by Raphael Mechoulam in 1964. THC is the main psychoactive (or intoxicating) ingredient of cannabis, and produces its characteristic intoxicating effects primarily through an action at brain *CB1 cannabinoid receptors* (CB1Rs).

THC is available in Australia in purified capsule form as an S8 medication (*Dronabinol*) for the relief of chemotherapy-induced nausea and vomiting. It is also available as an oromucosal spray (in combination with the non-psychoactive phytocannabinoid *cannabidiol* (CBD) in the S8 medication Nabiximols (*Sativex*). Nabiximols is currently approved in more than 25 countries, primarily for the relief of spasticity in multiple sclerosis.

Phytocannabinoids other than THC and CBD are generally not well characterised for their pharmacological effects. Few have been administered in purified form to humans under controlled conditions. Nonetheless, it is inferred from receptor binding characteristics, and various preclinical animal studies, that these phytocannabinoids lack the distinctive intoxicating and psychoactive effects of THC. Indeed, as early as 1970, Raphael Mechoulam had separated hashish into various purified cannabinoids (including CBG, CBC and CBN), reporting that only a THC-containing extract produced intoxicating like behavioural effects in monkeys (these included akinesia, apathy, reddening of the eyes, drowsiness and tameness) [15].

However, the non-intoxicating phytocannabinoids can have other pharmacological effects that may imbue them with therapeutic potential in disease states such as cancer, inflammation, pain and epilepsy. These include subtle actions on the endocannabinoid system of the brain and body via interactions with specific enzymes, as well as a range of actions at diverse receptor targets such as transient receptor potential (TRP) channels and serotonin (5-HT) receptors. These are outlined in detail in the current review.

In cannabis plants, the phytocannabinoids that tend to dominate are either THC and its acid precursor THCA (in Australian street cannabis these represent on average 15% of weight of flowering heads), or CBD and its acid precursor CBDA (which in industrial hemp can represent around 15% of weight of flowering heads). The other phytocannabinoids such as CBG, CBC, CBN and THCV are typically present in much lower quantities (0-0.5%), meaning that their pharmacological effects will tend to be of lesser significance in plant material, extracts or oils.

The phytocannabinoids of interest in the current review are shown in Table 1 alongside their typical concentration in (a) Australian street cannabis, and (b) Industrial hemp.

Table 1: Phytocannabinoids of interest and their concentration in street cannabis and industrial hemp

	Abbreviation	Name	Australian Street Cannabis (%) ¹	Industrial Hemp (%) ²
1.	THC	Delta-9-tetrahydrocannabinol	1.45	0.52
2.	THCA	Delta-9-tetrahydrocannabinolic acid	12.95	0.42
3.	THCV	Delta-9-tetrahydrocannabivarin	0	0
4.	THCVA	Delta-9-tetrahydrocannabivarinic acid	-	-
5.	CBD	Cannabidiol	0	3.56
6.	CBDA	Cannabidiolic acid	0.04	10.62
7.	CBDV	Cannabidivarin	-	0.35
8.	CBG	Cannabigerol	0.08	0.22
9.	CBGA	Cannabigerolic acid	0.13	0
10.	CBN	Cannabinol	0.03	0
11.	CBC	Cannabichromene	0.03	0.43

¹ Mean content of phytocannabinoids in police seized cannabis in NSW Australia as reported by Swift et al (2013).

² Mean content of an industrial hemp cultivar grown by Australian company *Ecofibre* in Kentucky (USA) and analysed by Bill Arnold at the University of Colorado (personal communication).

CB1 and CB2 cannabinoid receptors

As noted above, the distinctive intoxicating effects of THC are largely, and perhaps exclusively, due to the action of THC as a partial agonist at CB1 cannabinoid receptors (CB1Rs) in the brain.

When given to rats and mice, THC causes four distinctive behavioural and physiological changes that are commonly known as the *tetrad*. These are (1) lowered body temperature (hypothermia), (2) analgesia, (3) an inhibition of locomotor activity (sedation), and (4) a characteristic waxy immobility known as "catalepsy". The CB1R dependence of these effects is shown by the ability of CB1R antagonist drugs to reverse these tetrad effects [16], and the absence of such effects in mice genetically engineered to lack the CB1R [17].

Additionally, a wide range of novel *synthetic cannabinoid* drugs, such as those found in recreational products like *Spice* and *Kronik*, are invariably found to be CB1R agonists, and have potent THC-like (sometimes called "cannabimimetic") subjective effects in humans, and characteristic behavioural and physiological effects in the tetrad test battery in rodents [18].

In 1992, a second cannabinoid receptor was reported, the *CB2 receptor* (CB2R) [19]. The CB2R is mostly found in the periphery in immune organs such as the spleen and thymus, and in white blood cells and macrophages. Although the CB2R is found in the brain, this often reflects induced expression on activated microglia following brain damage or neuroinflammation, with only sparse expression on neurons [20]. Although THC is an agonist at CB2Rs as well as CB1Rs, stimulation of the CB2R not lead to intoxication. A range of selective CB2R agonists have been developed and are under Phase 2 and Phase 3 human clinical trials in the treatment of pain and inflammation [21].

In considering the pharmacological actions of drugs acting at CB1Rs and CB2Rs it is important to consider both *affinity* and *efficacy*.

Affinity refers to the extent to which a drug binds to a receptor, and is usually expressed as a drug concentration (nanomolar > micromolar > millimolar). A drug with high affinity at a receptor requires very low concentrations to competitively bind to that receptor, and this is expressed by pharmacologists in terms of it having *nanomolar* or *micromolar affinity*.

Efficacy refers to the extent to which a drug causes a functional effect in a cell: so a drug can bind to a receptor with nanomolar affinity while causing minimal biochemical changes within that cell (e.g. the firing of a neuron). This is referred to as *low efficacy*. Antagonist drugs tend to have high affinity and no efficacy (they occupy the receptor without causing a functional effect) while agonists have high affinity and high efficacy.

THC is generally found to have nanomolar affinity but only moderate efficacy at both CB1Rs and CB2Rs and consequently is considered to be a *partial agonist* at these receptors.

The endocannabinoid system

The human brain and body contain two major endocannabinoid substances that bind to CB1Rs and CB2Rs under natural conditions and in doing so influence a diverse range of physiological processes. These two ligands are the fatty acid amide substances *2-arachidonyl glycerol* (2-AG) and *arachidonylethanolamide* (anandamide). When administered in high doses to laboratory animals both anandamide and 2-AG produce THC-like behavioural and physiological effects that are CB1R mediated [22, 23].

Most phytocannabinoids are neither CB1R nor CB2R agonists, but some have modulatory effects on endogenous levels of 2-AG and anandamide and these might conceivably lead to indirect cannabis-like (*cannabimimetic*) effects. For example, anandamide is broken down by the enzyme *fatty acid amide hydrolase* (**FAAH**) and drugs that inhibit FAAH can increase endocannabinoid levels, sometimes causing subtle THC-like effects [24]. Similarly 2-AG is broken down by monoacylglycerol lipase (**MAGL**) such that inhibiting this enzyme causes 2-AG levels to rise and may also cause cannabimimetic effects [25, 26].

Other important endocannabinoid related enzymes are diacylglycerol-alpha (**DAGLα**) and diacylglycerol-beta (**DAGLβ**) that play key roles in the synthesis of 2-AG. The main enzyme involved in anandamide synthesis is *N-acylphosphatidylethanolamine-phospholipase D* (**NAPE-PLD**). Interfering with the synthetic enzymes (DAGLα, DAGLβ and NAPE-PLD) can reduce levels of endocannabinoids.

Thus, to better understand the pharmacological actions of phytocannabinoids, it is important to consider that some of them have indirect actions on the endocannabinoid system via FAAH, MAGL, DAGL and NAPE-PLD.

Transient Receptor Potential (TRP) Ion Channels

There is accumulating evidence that both endocannabinoids and phytocannabinoids exert important therapeutically relevant pharmacological actions upon targets other than CB1Rs, CB2Rs, and the endocannabinoid system.

An important set of targets are the transient receptor potential (TRP) ion channels, a total of 28 different types of which have been characterized in the brain and body [27-29]. These channels have an important and diverse range of functions, including sensing noxious and thermal stimuli, involvement in inflammatory, gustatory and gastrointestinal function, and many other physiological processes.

Some of the therapeutic effects of phytocannabinoids outlined in this review are thought to involve actions at these TRP channels, although evidence is still at a formative stage. Of particular importance is the ability of endocannabinoids and phytocannabinoids to activate and desensitize some of these TRP channels. This action may be critical to their analgesic and anti-inflammatory therapeutic effects.

Accordingly, these actions are reported for each phytocannabinoid in the current review. The major TRP ion channels of interest are:

- **TRPA1.** This receptor plays an important role in pain caused by mechanical stress and perhaps noxious cold. The TRPA1 receptor is also sensitive to pungent stimuli such as mustard oil, wasabi, wintergreen and cinnamon. TRPA1 plays an important role in inflammatory processes
- **TRPV1.** This receptor plays a key role in sensing noxious heat and acidity. It is responsible for the burning sensation of chili peppers (capsaicin). Activation of TRPV1 leads to a painful, burning sensation and a compensatory reduction in body temperature. Overexpression and overactivation of TRPV1 is observed in various painful conditions
- **TRPV2.** This receptor is a homologue of TRPV1 and is similarly sensitive to high temperatures (> 52°C)
- **TRPV3.** This receptor is activated by pleasant warm temperatures, but not by noxious heat. TRPV3 has been recently implicated in pruritic dermatitis and skin inflammation and is also widely expressed in the gastrointestinal tract
- **TRPV4.** This receptor plays a variety of roles in growth and development and in vascular and osmotic regulation. It is sensitive to a wide range of osmotic, mechanical and chemical cues
- **TRPM8.** This receptor is the primary sensor of cold in humans and has sensitivity to substances such as menthol, eucalyptol and geraniol. The activation of TRPM8 sends a cool and soothing sensation that alleviates pain.

Investigating the intoxicating effects of phytocannabinoids

As noted above, very few studies have administered individual phytocannabinoids to humans under controlled laboratory or clinical conditions.

Indeed, the current review could only find studies of acceptable quality that involved human administration of cannabidiol (CBD) and tetrahydrocannabivarin (THCV). In addition there were a few early human studies involving administration of cannabinol (CBN) or cannabichromene (CBC) and a single unpublished German study involving administration of tetrahydrocannabinolic acid (THCA). There were no published studies apparent in relation to, THCVA, CBG, CBGA, CBDA and CBDV. In cases where no human studies are available the possible intoxicating (or lack of) effects can be inferred from two principle sources. These are:

- **Tetrad effects in laboratory animals.** As noted above, when THC is administered to rats or mice it produces characteristic physiological and behavioural changes sometimes known as the “tetrad”. These four key indicators are hypothermia, analgesia, sedation, and catalepsy. An absence of such effects at high doses of a phytocannabinoid strongly implies a lack of THC-like CB1R agonist or intoxicating effects
- **CB1 receptor affinity and efficacy.** Further evidence that a compound either possesses or lacks THC-like effects comes from the standard pharmacological method of *competitive radioligand binding assays*. This tests whether a compound competes for CB1R binding in vitro against a known ligand for the CB1R such as THC, CP 55,940 or WIN 55,212-2, which is usually tagged with a radioactive label. If a substance fails to compete with THC at CB1Rs in this assay then it will be very unlikely to have THC-like psychoactive effects.

In interpreting the pharmacological actions of individual phytocannabinoids, it is also important to bear in mind several caveats that are described in detail below. These include:

1. possible additive and subtractive interactions between phytocannabinoids when present in a mixture;
2. the transformation of acid phytocannabinoids by heating, when cannabis plant material or extracts are smoked or vaporized; and
3. hazards in extrapolating from preclinical research outcomes in laboratory animals to humans.

Caveat 1: Interactions between phytocannabinoids

Cannabis plant material and cannabis extracts contain numerous different phytocannabinoids and there is emerging evidence of pharmacologically relevant interactions between these individual components, including supra-additive (synergistic) interactions, inhibitory interactions and a variety of other “entourage effects” [30, 31]. Such effects are the subject of much speculation, particularly in considering whether therapeutic effects are best obtained with purified individual cannabinoids, or broad-spectrum “artisanal” plant material and extracts.

For example, both CBD and CBG diminished the proliferation of human leukemia cells when applied individually to these cells [32]. However, the combination of a lower concentrations of each of these cannabinoids promoted a significantly greater anti-proliferative effect. Supra-additive effects were also observed in this study between CBD and CBDA, and CBGV and CBGA.

Alternatively, CBG may inhibit some of the therapeutic actions of CBD. For example, CBG was found to prevent the antiemetic actions on CBD in rats [33]. In this instance, a cannabinoid extract may then be sub-optimal as an antiemetic agent.

Perhaps the greatest attention in the literature has been focused on the interaction between THC and CBD. In humans there is evidence that consumption of cannabis containing CBD leads to fewer psychosis-inducing and memory-impairing effects than cannabis containing only high THC with no CBD. A number of recent studies support this contention [30, 34-36].

Caveat 2: The effects of heat

It is also important to realise that heating cannabis plant material causes the conversion of acid phytocannabinoids to non-acid varieties. Thus, as can be seen in Table 1, street cannabis contains relatively low amounts of THC (mean = 1.45%) but large amounts of the non-psychoactive phytocannabinoid THCA (mean = 12.95%). Heating cannabis plant material above 160°C causes the rapid conversion (decarboxylation) of THCA into THC. This is generally why cannabis plant material is smoked, vaporized or baked by recreational users in order to achieve psychoactive effects. If cannabis plant material is ingested without heating (e.g. “juicing”) then very different cannabinoid levels and physiological effects are achieved.

Similarly, heat causes the conversion of CBDA into CBD, and CBGA into CBG. Thus, it is important to consider not only the cannabinoid content of a given preparation, but the potential transformational effects of heating on phytocannabinoid profile.

Caveat 3: Extrapolation from preclinical concentrations/doses to therapeutic levels in humans

As noted above, for many of the phytocannabinoids considered in this review there are no published human studies involving their administration, and so therapeutic plasma levels in humans are undefined. For most of these phytocannabinoids, however, there are published studies involving *in vitro* cellular or *in vivo* rodent preclinical studies and some qualified inferences can be made from such data regarding possible therapeutic levels in humans. For *in vitro* (cellular) experiments, molar doses of phytocannabinoids are usually presented where some therapeutic effect is observed, while with *in vivo* studies in laboratory animals doses are usually

presented in terms of mg/kg.

So for example, it might be the case that a phytocannabinoid prevents the proliferation of cancer cells when applied to these cells at a 10 micromolar concentration, or it may cause analgesic effects in a mouse when injected intraperitoneally (IP) at a dose of 80 mg/kg. As outlined below, such information provides some clues regarding effective therapeutic doses in humans, but extrapolation from these preclinical *in vitro* concentrations and *in vivo* rodent doses to humans should only be made with caution.

Interpreting molar concentrations from *in vitro* studies

When interpreting concentrations from *in vitro* cellular studies, the lower the concentration at which a given effect occurs, the more likely that it will be clinically relevant in humans. In general, nanomolar (nM) to low micromolar (µM) concentrations are those that would be attained from the administration of a pure substance to a human. When a cellular effect requires much higher micromolar or millimolar concentrations of a cannabinoid, it is unlikely to be therapeutically relevant.

Accounting for differences between systemic and oral dosing in animal studies

Most preclinical studies involving laboratory animals administer phytocannabinoids intraperitoneally (IP), while the primary route of administration for hemp-derived products involves oral administration. It thus becomes important to consider how therapeutic effects obtained with IP dosing in rodents can be related to these same effects when a phytocannabinoid is given via oral dosing to humans. Oral administration of phytocannabinoids leads to “first-pass metabolism” whereby the drugs are substantially metabolised by the liver prior to reaching the brain or other tissues. Oral administration of phytocannabinoids also leads to more variable and generally poorer absorption into the blood stream than IP injection. As a result, the oral route usually requires much higher doses to achieve equivalent tissue concentrations than IP injection.

A recent study directly compared the tissue concentrations achieved for the phytocannabinoids CBD, CBG, THCV and CBDV following oral and IP dosing in mice [3]. On average, IP dosing achieved 7 fold higher phytocannabinoid tissue concentrations than oral dosing. Therefore, in the current review, when considering possible therapeutic concentrations of uncharacterized phytocannabinoids, we have generally estimated the effective oral dose from animal studies by multiplying the effective IP dose by 7, except in a few cases in which more specific and detailed information was available.

Extrapolating from rodent doses to a human therapeutic dose

An additional correction is necessary when extrapolating from doses in laboratory animal species (such as rats and mice) into humans. This “interspecies scaling” factor primarily relates to differences in body surface area between species. The USA Food and Drug Administration (FDA) provides information on how to calculate the approximate human equivalent dose (HED) for doses given to different laboratory animals. This involves dividing the dose by 12.3 (mice), 6.2 (rat), 4.6 (guinea pig) or 3.1 (rabbit) to yield the human mg/kg dose.

So, for example, a 100 mg/kg dose in a rat would represent approximately $(100/6.2)$ 16 mg/kg dose in a human. To then calculate the total human dose in mg, we would multiply this mg/kg dose by 60 (since the average weight of an adult is 60 kg).

So in the case above, the human equivalent dose (HED) for a 100 mg/kg dose in a rat would equal $16 \text{ mg/kg} \times 60 =$ approximately 1 gram. However, if the drug had been given to a rat using an IP route of administration then a multiplication factor would be applied ($\times 7$) to account for oral administration, meaning that the human equivalent oral dose would become 7 grams.

3 Methodology: search strategy

To conduct the current review, the specified phytocannabinoids listed in Table 1 (above) were systematically reviewed according to their pharmacological and possible therapeutic effects with regard to the following therapeutic indication terms: Anti-inflammatory; Antibiotic; Anticonvulsant; Antifungal; Analgesic; Anxiolytic; Antipsychotic; Antioxidant; Antispasmodic; Antiemetic; Anti-ischemic; Anticancer; Antidiarrhoeal; Antibacterial; Antidepressant; Anti-Psoriasis/skin disorders; Anti-tussive, Anti-glaucoma; Antileishmanial; Euphoriant; Metabolic; Sedative.

Inclusion Criteria

All included evidence sources had to be available in English language.

Literature Search

1. The review included peer reviewed publications in academic databases including: Cochrane, PubMed and Google Scholar.
2. Grey literature was included in the search (e.g. Government reports, policy statements and issue papers, conference proceedings, theses and dissertations, research reports, newsletters and bulletins, fact sheets). Grey literature searches used: Google, Google Scholar.

Search Terms

Searches were conducted for the terms listed in the table below in publication titles, abstracts, keywords, and database subject headings. The search was conducted for the period up to December 2015. Terms within columns were combined using the Boolean operator 'OR', and the resulting strings will be combined using the Boolean operator 'AND'.

The titles and abstracts of all records obtained from database searches were examined, and full texts of all potentially relevant publications retrieved and examined to determine whether they hold relevant information. Additional relevant studies were identified from the reference lists of those studies meeting the inclusion criteria.

Quality Assessment

Preclinical animal and cellular studies were labelled as such. The methodological quality of studies involving human cannabinoid administration meeting the inclusion criteria was assessed using the NHMRC criteria for levels of evidence as outlined below:

- **Level I:** Evidence obtained from a systematic review of all relevant randomised controlled trials
- **Level II:** Evidence obtained from at least one properly designed randomised controlled trial
- **Level III-1:** Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method)
- **Level III-2:** Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group

- **Level III-3:** Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group
- **Level IV:** Evidence obtained from case series, either post-test or pre-test and post-test.

Data Extraction

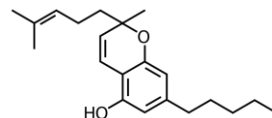
Where available, the following information was extracted from publications and tabulated prior to descriptive review:

1. Pharmacological characteristic (i.e. anti-inflammatory, anti-cancer etc.)
2. Therapeutic levels per pharmacological characteristic (dose of specified cannabinoid delivered in study)
3. Best level of evidence per pharmacological characteristic (i.e. *in vitro* assay, animal, human)
4. Relevance of source of evidence (i.e. detailed brief description of the major study design elements)
5. References (all papers reviewed are cited in the relevant table in the appendix for each cannabinoid reviewed)
6. Key research question addressed (primary aim or hypothesis of study).

Format of Results

A descriptive review is given for each cannabinoid and relevant therapeutic action in the main section of the report, and the tabulated version of data extracted are provided in the Tables presented in the Appendix.

4 Individual cannabinoid summaries



CANNABICHROMENE (CBC)

Introduction

Cannabichromene (CBC) is a relatively common phytocannabinoid found in both street cannabis and industrial hemp. It was first isolated from hashish and described by Gaoni and Mechoulam in 1966.

CBC is produced in the cannabis plant from the precursor cannabigerol (CBG) via the action of the enzyme CBC synthase. The original report of Gaoni and Mechoulam (1966) said that “when administered to a dog, CBC caused sedation and ataxia”. However, a subsequent study failed to replicate this effect [37]. Subsequent research has suggested that CBC is generally non-intoxicating and non-psychoactive.

Levels of CBC in Australian street cannabis were reported to be very low (0.06%) by Swift et al (2013) while USA and UK studies have shown slightly higher levels of around 0.2-0.35% [38, 39]. In hashish and hash oil, levels of CBC are generally higher, at around 0.7% and 0.9%, respectively [39].

Relevant pharmacological actions

CB1 and CB2 receptor affinity

CBC has relatively low affinity for the human CB1R ($K_i = 713 \mu\text{M}$) and CB2R ($K_i = 256 \mu\text{M}$) [40]. Very low affinity for mouse CB1Rs was confirmed by Booker et al (2009) [41]. This implies a low likelihood of CBC producing intoxicating THC-like effects in humans.

Effects on the endocannabinoid system

CBC does not appear to affect either FAAH or MAGL, suggesting an absence of modulatory effects on endocannabinoid levels. However, CBC inhibits the cellular uptake of anandamide [42].

Effects on TRP channels

CBC is a very potent agonist at TRPA1 channels ($\text{EC}_{50} = 0.06 \mu\text{M}$) [42, 43] and this has been linked to analgesic actions [44]. CBC has only weak actions at TRPM8 and TRPV1 channels.

Effects on other targets

There appear to be no relevant studies of CBC actions at other receptors.

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans and non-human primates

An early review by Turner et al (1980) [45] refers to a publication by Isbell et al (1967) where consumption of CBC was found to have no intoxicating effects (the original paper could not be sourced at this time). CBC did not have intoxicating effects in the Rhesus monkey when given at a low dose intravenously with CBG, CBN and cannabicyclol (CBL) [15].

Tetrad effects in rodents

Davis and Hatoum [46] showed that CBC (up to 75 mg/kg) caused a modest decrease in locomotor activity while Hatoum et al [47] demonstrated hypothermic effects. More recently, El-Alfy et al [48] found that CBC caused significant decreases in locomotor activity and body temperature at 80 mg/kg but did not cause any catalepsy. CBC was recently found to exert antinociceptive effects in the tail flick test via TRPA1 receptors [44]. In a comprehensive assessment, DeLong et al [49] found that the highest dose of CBC tested (100 mg/kg, IV) produced all four tetrad effects in mice (catalepsy, hypothermia, reduced locomotor activity and analgesia). However, these effects were not reversed by a CB1R antagonist suggesting that CBC was working to produce such effects through a different receptor.

Therapeutic potential

Appendix Table 3 presents details of therapeutic potential for CBC.

Anti-inflammatory effects

CBC (1 mg/kg) displayed strong anti-inflammatory effects in a murine model of colitis. This was associated with a TRPA1 mediated reduction in nitric oxide production in peritoneal macrophages [2]. CBC also reduced inflammation following injection of lipopolysaccharide or carrageenan into the paws of mice [49, 50] or croton oil topically onto the ears of mice [51]. In this latter study the anti-inflammatory effects of CBC were less than indomethacin, a standard anti-inflammatory medication.

Analgesic effects

CBC (up to 75 mg/kg) had mild analgesic effects in mice and also potentiated the analgesic effects of THC [46]. Only a trend towards analgesic effects with CBC were seen in the tail flick test in one study with mice [48] but more convincing effects were obtained in another study when a higher intravenous dose of 100 mg/kg was used [49]. No antinociceptive effects of CBC were evident however in an acetic acid model of visceral pain in rats [41].

Anticonvulsant effects

CBC (up to 75 mg/kg) had modest anticonvulsant effects in mice in the electroshock model [46].

Antidepressant-like effects

CBC (20-80 mg/kg) had antidepressant-like effects in the mouse forced swim and tail suspension tests [48].

Sedative effects

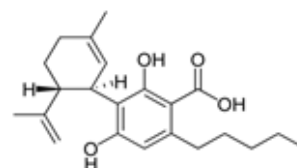
CBC was able to prolong the sleep time induced by the barbiturate hexobarbital in mice [47], while (as noted above) several groups have shown reduction in locomotor activity in rodents with CBC, consistent with a sedative like effect.

Conclusions

There is little evidence for THC-like effects of CBC at CB1Rs, although there is evidence of sedation and catalepsy in laboratory animals at very high intravenous doses. CBC has a range of intriguing in vitro and in vivo actions in preclinical models that imply therapeutic efficacy as an anti-inflammatory agent and also perhaps as a mild sedative, analgesic and antibiotic. However, further confirmation in human studies is required.

The doses required for pharmacological effects are generally quite high with the exception of the effect on colitis in mice which required only 1 mg/kg IP [2]. As IP phytocannabinoid doses achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels might be as high as 7 mg/kg in humans. Applying the FDA calculation to this dose, the estimated

therapeutic oral dose in a 60 kg human for CBC to produce anti-inflammatory effects would be 35 mg.³ To produce sedative, hypothermic or analgesic effects 20-80 fold higher doses are required, namely 0.7 - 3.0 grams. It is very implausible that such dose would be achieved with even excessive consumption of any current hemp seed or hemp oil preparations.



CANNABIDIOLIC ACID (CBDA)

Introduction

CBDA is the chemical precursor to CBD in the cannabis plant. CBDA is formed from cannabigerolic acid (CBGA) by the enzyme *CBDA synthase*. It is then decarboxylated to CBD by a non-enzymatic reaction catalysed by heating. CBDA is found in Australian street cannabis at very low levels with only an average of 0.14% of the weight of cannabis. However industrial hemp may have much higher levels of CBDA (> 10%) as shown in Table 1 above [52, 53]. Very little research has been conducted on the pharmacological properties of CBDA, and it has not been administered to humans under controlled conditions, which limits the strength of our conclusions when evaluating its pharmacological activity and therapeutic actions.

Relevant pharmacological actions

CB1 and CB2 receptor affinity

CBDA binds to murine CB1Rs with low affinity (e.g. THC binds at low nM whereas CBDA bind at low μ M) [54]. CBDA does not activate the CB1R and thus appears to be a weak CB1R antagonist [54]. To the best of our knowledge effects of CBDA on CB2Rs have not been studied.

Effects on the endocannabinoid system

CBDA may reduce levels of endocannabinoids by inhibiting the 2-AG synthesizing enzyme DAGL α at concentrations around 20 μ M [42]. CBDA also inhibits N-acyl ethanolamine acid amide hydrolase (NAAA) at 20 μ M [42], an enzyme that degrades *N*-palmitoylethanolamine (PEA). PEA is a lipid mediator that activates the PPAR- α receptor which plays an important role in energy balance and is vital for ketogenesis. CBDA does not inhibit the function of the anandamide degradative enzyme FAAH, the 2-AG degradative enzyme MAGL, and does not affect anandamide reuptake [42].

Effects on TRP channels

CBDA also modulates various TRP channels at low to medium μ M concentrations (1-20 μ M) (TRPA1 agonist, TRPM8 antagonist, and weak TRPV1 and TRPV4 agonist) [42]. It was ineffective in modulating TRPV2 and TRPV3 channels.

³ Please refer back to Introduction to the Review section above under “*Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans*” for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in in vitro and in vivo animal models may not translate. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

Effects on neurotransmitter receptors

CBDA influences other receptor targets as shown in various in vitro studies. However the functional and therapeutic significance of all these interactions remains to be demonstrated. CBDA potently potentiates the activity of the 5-HT_{1A} receptor (0.1 – 100 nM) which is a relevant target for emesis, depression, anxiety and pain [54]. CBDA blocks the GPR55 receptor at 1-10 µM. GPR55 is often viewed of as the third cannabinoid receptor [55].

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

CBDA to the best of our knowledge has never been administered to humans as a pure compound. A proper controlled psychopharmacological study is required to specifically confirm whether CBDA possesses or lacks psychoactive effects.

Tetrad effects in rodents

CBDA did not suppress locomotor activity in rats at doses up to 1 mg/kg [4], although higher doses should be tested to further confirm an absence of cannabimimetic effects. Overall, it would seem unlikely that CBDA is psychoactive.

Therapeutic potential

Several preclinical studies have evaluated the therapeutic potential of CBDA (see Appendix Table 4) but there are no relevant human studies.

Anti-inflammatory effects

CBDA inhibits cyclooxygenase enzymes [56], the targets of NSAIDs and aspirin. However there are conflicting findings pertaining to its potency and likely clinical relevance in this regard [56, 57].

Antiemetic effects

Preclinical research shows CBDA has potent antiemetic actions. In shrews (*Suncus murinus*) CBDA potently inhibited vomiting induced by lithium chloride, the chemotherapeutic agent cisplatin and by motion at 0.1-0.5 mg/kg [54]. These effects appeared to be mediated by 5-HT_{1A} receptors rather than CB1Rs. In rats CBDA reduced lithium-induced conditioned gaping (a model of anticipatory nausea) at doses as low as 0.001 mg/kg [4]. Moreover, subthreshold doses of both CBDA and THCA interacted to significantly reduce lithium-induced conditioned gaping. A subthreshold dose of CBDA was also shown to potentiate the actions of the established antiemetics metoclopramide and ondansetron in this model [58, 59].

Anticancer effects

CBDA inhibits human breast cancer cell migration in vitro and reduces the expression of genes involved in metastasis at doses as low as 5µM [60, 61]. Interestingly, CBDA did not inhibit the proliferation of breast cancer cells, unlike the structurally similar phytocannabinoid CBD. However, the opposite was observed for migration whereby CBDA was effective and CBD was not. CBDA also inhibited human glioma cells and rat thyroid cancer cells in vitro at around 10-20 µM [62].

Antibacterial effects

Drug resistance is a major issue in the treatment of bacterial infections and various phytocannabinoids are effective in inhibiting the growth of drug-resistant bacterial strains. CBDA has potent antibacterial activity at low µM concentrations against various drug-resistant strains of *Staphylococcus aureus* [63].

Antidiarrhoeal effects

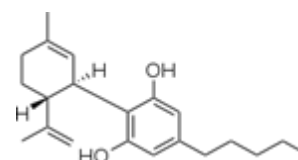
CBDA may have potential as an antidiarrhoeal agent: it inhibited contraction of shrew intestine at 1-30 µM concentrations [64]. These effects were not mediated by CB1 or CB2 receptors.

Conclusions

CBDA has never been administered to a human as a pure substance. However, the preclinical evidence described above suggests that CBDA is unlikely to have intoxicating effects in humans. CBDA only binds to CB1Rs at relatively high concentrations and does not activate the receptor. It does not appear to produce THC-like cannabimimetic effects in laboratory animals.

CBDA has various pharmacological actions that might be clinically relevant based on the effective concentrations and doses used in cell systems and animal studies respectively. Some effects have been shown at very low concentrations, including antiemetic effects and the potentiation of 5-HT_{1A} receptor activity.

The lowest CBDA dose we identified in the literature to be effective in an animal model of disease was 0.001 mg/kg (IP). This dose inhibited lithium-induced conditioned gaping (an animal model of anticipatory nausea) in rats [4]. As IP phytocannabinoid doses achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels might be 0.007 mg/kg. Applying the FDA calculation to this dose, the estimated therapeutic oral dose of CBDA for this anticipatory nausea therapeutic effect in a 60 kg human is approximately 0.07 mg.⁴



CANNABIDIOL (CBD)

Introduction

Cannabidiol (CBD) is a phytocannabinoid that is present at a wide variety of concentrations across different cannabis strains [38]. In Australian street cannabis, levels of CBD were low to non-existent [52]. As noted in Table 1 above, CBD is more prevalent in industrial hemp cultivars (which have very low THC) and in hashish (which tends to have similar CBD and THC levels [39]). CBD is produced in the cannabis plant from the carboxylic acid precursor (CBDA) through a decarboxylation process involving heating. As with THCA, CBDA is produced from the common precursor CBGA by the enzyme *cannabidiolic acid synthase*.

CBD is one of the best-studied cannabinoids in humans, a result of it exhibiting broad-spectrum therapeutic potential [65-67].

Relevant pharmacological actions

CB1 and CB2 Receptor Affinity

CBD has low micromolar affinity for the CB1R and CB2R. Despite this low affinity, CBD has displayed a capacity in some studies to antagonise effects of CB1R and CB2R agonists at nanomolar concentrations [68, 69]. This may reflect negative allosteric modulation by CBD at the CB1R and CB2R.

⁴ Please refer back to Introduction to the Review section above under “*Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans*” for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in in vitro and in vivo animal models may not translate. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

Effects on the endocannabinoid system

CBD can increase levels of endocannabinoids via inhibition of the anandamide degradative enzyme FAAH [8]. CBD can also inhibit the enzymes which break down PEA and 2-AG [42]. CBD also has been shown to inhibit AEA cellular uptake (with an IC₅₀ around 25uM) [42, 70]. CBD does not appear to have any effect on MAGL and DAGL [42].

Effects on TRP channels

CBD activates and desensitises TRPV1 channels in vitro, which may be relevant to its effects on epileptiform activity [71]. CBD also activates TRPA1, TRPV1–3, TRPV4 and blocks TRPM8 channels [69, 72]. The functional significance of these actions for pharmacological activity requires further investigation [42].

Effects on other receptor systems

CBD is a neurochemically promiscuous compound and affects numerous other targets including enhancing 5-HT_{1A} receptor activation and PPAR-gamma receptors [72, 73]. There is some suggestive evidence of CBD being an allosteric modulator at mu and delta opioid receptors, D2 dopamine receptors and GABA-A receptors [74]. CBD also exerts a bidirectional effect on intracellular calcium levels, depending on the excitability of cells, by targeting mitochondria [75]. CBD also antagonizes 5-HT₃ARs, enhances alpha-3GlyR, and inhibits the Cav3 ion channel as well as adenosine reuptake [72, 76].

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

CBD is well tolerated across a wide range of doses in humans [77-79]. Acute CBD administration in humans by oral, inhalation, or intravenous routes does not induce any significant intoxicating and/or toxic effects [80]. CBD has been administered to humans in doses as high as 1500 mg (orally) [81] or 30 mg (intravenously) with no reported adverse events. CBD is reported to have been safe and well tolerated with both acute and chronic administration to healthy subjects [82, 83]. Chronic administration of CBD for 30 days to healthy volunteers, at daily oral doses ranging from 10 to 400 mg, did not induce any significant alteration in neurological, psychiatric or clinical measures [84].

Limited safety data exist for long-term administration of pure CBD in humans, although there have been many patient-years of exposure to Nabiximols (*Sativex*) (which contains both CBD and THC) which is an approved medication in more than 25 different countries. CBD is currently in Phase 3 clinical trials in the USA (*Epidiolex*) for the treatment of intractable pediatric epilepsy, and a variety of other CBD-rich plant extracts are being used worldwide for the same indication.

Tetrad Effects in Rodents

CBD does not induce classic tetrad effects of hypolocomotion, analgesia, catalepsy and hypothermia in mice, although it did produce mild hypothermia at higher doses [48, 85].

Other considerations

The main area of caution with the use of CBD in humans relates to its inhibitory effects on several cytochrome P450 isoenzymes, including CYP1A2, CYP2B6, CYP2C9, CYP2D6, and CYP3A4. This is especially important in the management of chronic pain and epilepsy, since conventionally used analgesics (opioids and non-opioids) and anticonvulsants are sometimes metabolised via these pathways (e.g. CYP2D6 and CYP3A4) [86]. There is also a theoretical risk of immunosuppression from CBD as it suppresses interleukin 8 and 10 production and induces lymphocyte apoptosis in vitro, but this has not been demonstrated clinically [87, 88].

Therapeutic potential

CBD is a major focus of current medicinal cannabinoid research. There are at least 59 currently active clinical trials of CBD listed on *clinicaltrials.gov* for indications including schizophrenia, inflammatory bowel disease,

pediatric epilepsy, addiction, chronic pain, cancer, Huntington's Disease, Multiple Sclerosis, diabetes, nausea and vomiting, bipolar disorder and ADHD. Of all the cannabinoids reviewed here CBD has the largest number of level II RCTs in clinical and healthy populations and a robust preclinical literature (Appendix Table 5).

Anxiolytic effects

CBD exhibits anxiolytic effects in humans. A double blind RCT involving 24 social anxiety patients demonstrated reductions in anxiety with 600 mg CBD (orally) administered prior to delivering an anxiety-provoking public speech [89]. A smaller study with 10 social anxiety patients undergoing SPECT imaging showed that CBD reduced anxiety-related brain activity [90].

Antipsychotic effects

A phase II double blind RCT administered 800 mg CBD/day *versus* an amisulpride (standard antipsychotic medication) active control to 42 hospitalised schizophrenic patients and found therapeutically relevant improvement in PANSS scores in both groups indicating therapeutic equivalence of CBD. CBD exhibited far fewer side effects (e.g extrapyramidal symptoms) than amisulpride [8].

Sedative effects

Of the 20 papers identified where CBD had been given to humans, 8 showed no signs of sedation, and 5 studies reported some form of sedation, somnolence or extended sleep duration. Sedation was either not measured or not discussed in the remaining 7 human studies.

Looking in more detail at the 5 papers reporting some form of sedation, one administered pure CBD at a range of doses between 10 and 600 mg to a small number of healthy volunteers across a number of poorly designed phase I experiments [91], with a minority of subjects self reporting somnolence (in 3 of 5 experiments). The same paper also reports a clinical trial of CBD (40, 80 or 160 mg) as a hypnotic medication compared to nitrazepam (5 mg) or placebo using a within-subjects design over 5 weeks, in 15 participants (family members of the investigator) self-reporting poor sleep. The study found that 160 mg CBD resulted in several (but not all) measures on a self-made sleep quality questionnaire being significantly improved, including longer sleep duration than placebo or 5 mg nitrazepam [91]. However sleep duration might not equate with sedation *per se*.

Another recent paper, this time with no control group, reported somnolence in 25% of treatment resistant epileptic children [92] although the lack of control group and the use of concomitant anti-epileptic drugs, including clobazam which is sleep-inducing, renders this finding unusable in drawing firm conclusions on the sedation issue.

An experimental model of impaired perception during psychotic states was tested with 200 mg CBD in 9 healthy male volunteers and reported sedative effects in the text but with no details of how sedation was measured, and no data [7].

A small study of the effects of 300 (n=7) and 600 (n=4) mg CBD on plasma prolactin in healthy human volunteers recorded a sedative effect on a self evaluation scale [6].

Finally 400 mg oral CBD was given to 10 healthy male volunteers in a SPECT imaging study of the effects of CBD on cerebral blood flow, reporting increases in mental sedation measured using the Visual Analogue Mood scale [5].

Anticonvulsant effects

CBD displays anticonvulsant effects across different preclinical epilepsy models [93-96]. In the maximal electroshock model of epilepsy in mice CBD (120 mg/kg IP) exhibited therapeutically relevant anticonvulsant effects [97, 98]. Similarly, seizures were suppressed at 100 mg/kg (IP) CBD in a rat PTZ epilepsy model [96] and

at 1, 10, and 100 mg/kg (IP) in a rat pilocarpine induced seizure model [95]. In that same study a rat penicillin seizure model demonstrated improvements in mortality due to seizures, and fewer tonic-clonic seizures with ≥ 10 mg/kg (IP) CBD [96]. In mice PTZ and MES models of epileptic activity seizures were suppressed at 200 ng CBD (intracerebroventricular; ICV) and at 20-200 ng CBD (ICV) respectively [94]. CBD at 50 mg/kg (IP) also suppressed seizures in a chronic administration model of PTZ induced seizures where rats were administered PTZ daily for 28 days [93].

In humans, a 2014 Cochrane review on CBD for epilepsy identified four RCTs (with a total of 48 patients) being administered 200-300 mg CBD per day for 1 - 3 months [99]. The effects on seizure frequency were mixed and the review deemed the studies were of insufficient quality to draw conclusions about the efficacy of CBD for epilepsy at this time. A proprietary oral formulation of CBD (*Epidiolex*) is currently in testing in the USA for the treatment of pediatric epilepsy with ongoing blinded placebo controlled trials in progress. One report from an open label uncontrolled dose ranging study did find that daily doses of CBD titrated up to an average of 22.9 mg/kg resulted in a median reduction in the weekly rate of convulsive seizures of 34.6% across multiple drug-resistant epilepsy syndromes and seizure types in treatment resistant epileptic children [92].

Analgesic effects

Daily oral treatment with CBD (2.5-20 mg/kg) reduced hyperalgesia to thermal and mechanical stimuli in rat models of neuropathic pain (sciatic nerve constriction) and a rat inflammatory pain model (complete Freund's adjuvant intraplantar injections) [100]. CBD (3 nmol) reduced the ongoing activity of ON and OFF neurons and induced antinociceptive responses in the tail flick-test measured by extracellular electrical activity of ON and OFF neurons of the rostral ventromedial medulla in anaesthetized rats [44]. CBD (2.5 - 10 mg/kg IP) also prevented chemotherapy induced mechanical sensitivity in mice, an effect that was reversed by a 5-HT_{1A} antagonist, but not by CB1R or CB2R antagonists [101]. In humans, a double blind RCT in 24 patients with a neurological pain condition demonstrated therapeutically relevant pain relief at an average of 24 mg CBD per day delivered as a sublingual spray [102]. However the study is confounded by the use of a "CBD rich plant extract" leaving room for uncertainty as to the presence of other cannabinoids beside CBD.

Anti-inflammatory effects

There is preclinical evidence for anti-inflammatory effects of CBD in the 1-30 mg/kg range. Preclinical studies also suggest efficacy of CBD in inflammatory bowel disease [103-105].

Antioxidant

CBD in the 2-4 μ M range was an effective antioxidant in rat cortical neuron cultures exposed to toxic levels of glutamate [106]. CBD in the 5-10 mg/kg range decreased cellular markers of oxidative stress in several mouse models including a chemically-induced oxidative stress [107] and an alcohol-induced stenosis model [108].

Anti-ischemic effects

There is substantial and convincing preclinical work showing anti-ischemic effects of CBD, particularly with neonatal animals and the hypoxic ischemia encephalopathy (HIE) models where CBD is effective in the 0.1-5 mg/kg range. This work has progressed with considerable success in neonatal piglets [109, 110]. Human clinical trials in this area are imminent.

Anticancer effects

There is abundant preclinical in vitro work examining the antiproliferative properties of CBD in a range of cancers, including Kaposi sarcoma [111], breast cancer [112], lung cancer [113], bladder cancer [114], glioblastoma [115-117], leukemia [118], and colon cancer [119]. In cellular models, CBD induces cell death in the low micromolar range (0.25 - 2 μ M), although higher doses are required for some cancers.

Antispasmodic

CBD has been extensively trialed in humans in combination with THC (in the form of Nabiximols) for spasticity in Multiple Sclerosis (MS). However, only a single study has trialed CBD alone (700 mg/day oral for 6 weeks) as an antispasmodic, but no reductions in chorea severity were observed. Mouse models of MS have demonstrated significant efficacy of CBD as an antispasmodic in the 5 mg/kg range with CBD ameliorating signs of autoimmune encephalomyelitis [120] and motor deficits in the chronic phase of the disease.

Antiemetic

CBD at 20 mg/kg suppressed nicotine-, Lithium Chloride (LiCl)- and Cisplatin-induced vomiting in the asian house shrew *S. murinus*, as well as Lithium Chloride-induced conditioned gaping in rats. However CBD was ineffective at a higher dose (40 mg/kg) [121]. Similar dose response profiles have been observed previously in the house musk shrew [122], with 5 mg/kg inhibiting vomiting but 40 mg/kg CBD inducing vomiting [123].

Antidepressant

CBD had significant antidepressant-like effects at 30 mg/kg (IP) in the forced swim and tail suspension tests in mice (standard preclinical models of antidepressant effects). CBD was ineffective at doses of 3, 10 and 100 mg/kg [124]. Significant antidepressant-like effects were obtained in other study with CBD at 200 mg/kg IP [48].

Anti-psoriasis/skin disorders

In vitro assays have started to explore the effects of CBD on skin cell growth and proliferation, with therapeutically relevant effects found in the 0.5 – 10 μ M range. CBD inhibited the growth of cultured human sebocytes and human skin organ culture in the 1-10 μ M range, suggesting a possible acne treatment [125].

Conclusions

CBD has numerous pharmacological actions and is already showing strong clinical promise in the treatment of epilepsy, anxiety and psychosis. Complications may arise with pharmacokinetic interactions when CBD is combined with other medications such as opioids or anticonvulsants.

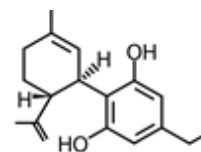
CBD appears to lack significant intoxicating effects in animals or humans. While some studies suggest mild sedative effects at doses ranging from 200 – 800 mg [5-7, 92], the majority of studies do not, and a lack of sedative effects has been reported even at doses as high as 1280 mg. Further studies are required to verify the nature, reliability and severity of the putative sedative effects obtained with CBD.

Across all of the human studies performed with CBD, the lowest dose at which a therapeutically relevant effect was observed in a double blind RCT with an adequate control group (amisulpride) in a clinical population was 800 mg/day (oral) in the control of symptoms of schizophrenia [8]. Please note though that this study is a Phase 2 RCT and thus cannot provide sufficient evidence for CBD to be formally approved as a therapeutic agent. Larger scale Phase 3 RCT trials are necessary for this, some of which are being conducted now with results forthcoming in 2016. We therefore conclude that a human oral dose of 800 mg of CBD constitutes a threshold therapeutic dose based on the best available evidence. This dose estimation might be subject to change when results of Phase 3 trials become available. The therapeutic dose of 800 mg would be reached easily with oral dosing of a high CBD concentration product such as Elixinol, which contains 180 mg/ml CBD.

While there are other reports of CBD administration to humans achieving a therapeutic response at lower doses in clinical populations, all of those studies had methodological flaws leading to ambiguity in interpretation and a chance of bias (i.e. no control group and variable dose uncertainty [92], uncertain timing of outcome measurement [84], use of “CBD rich” plant extract of unknown purity [102], or a very small sample size and subjective outcomes [90]). Additionally it should be noted that it is our opinion that across the full range of human studies administering CBD (including healthy human subjects) there has been inadequate

assessment of dose response for any particular indication, and that it is imperative that this work be carried out.

CANNABIDIVARIN (CBDV)



Introduction

Cannabidivarin (CBDV) is the propyl homologue of cannabidiol (CBD), differing only in the length of its alkyl side chain (CBD has a pentyl side chain while CBDV has a shorter propyl side chain). CBDV was first discovered in hashish by Vollner and colleagues in 1969 [126].

CBDV is generally present in quite low levels in cannabis plant material. However, CBDV was not examined in the analysis of Australian street cannabis by Swift *et al* [52], the analysis of UK cannabis by Potter *et al* [38] or the analysis of USA cannabis/hashish by Mehmedic *et al* [39].

Recent therapeutic interest in CBDV has centred around its anticonvulsant effects that have been widely established in animal models. GW Pharmaceuticals currently have a Phase 2A clinical trial of CBDV (known as GWP42006) underway in the USA examining its safety and efficacy for the treatment of focal seizures in adult humans as well as its pharmacokinetic profile. GW Pharmaceuticals have also developed a CBDV enriched botanical extract known as CBDV-BDS (botanical drug substance). Despite this, there are no available published studies of CBDV effects in humans.

Relevant pharmacological actions

CB1 and CB2 receptor affinity

CBDV has very low affinity for human CB1R ($K_i=14,711 \mu\text{M}$) and CB2R ($K_i=574 \mu\text{M}$) [40]. Similarly, Hill *et al* (2013) showed very low affinity for CBDV at human CB1Rs [127]. This indicates a very low likelihood of CBDV producing THC-like intoxicating effects in humans.

Effects on the endocannabinoid system

CBDV strongly inhibits DAGL α , which may cause reduced synthesis of the endocannabinoid 2-AG. CBDV does not appear to affect either FAAH or MAGL, suggesting no likely effect on endocannabinoid enzymatic breakdown. CBDV inhibits the cellular uptake of anandamide [42].

Effects on TRP channels

CBDV is an agonist at TRPA1 channels ($\text{EC}_{50} = 0.42 \mu\text{M}$), TRPV1 channels ($\text{EC}_{50} = 3.6 \mu\text{M}$) [42] and TRPV4 channels ($\text{EC}_{50} = 0.9 \mu\text{M}$) [128]. It also has antagonist effects at TRPM8 channels ($\text{IC}_{50} = 0.9 \mu\text{M}$). Following initial stimulation, CBDV elicits rapid desensitization of TRPV1, TRPV2 and TRPA1 channels [71].

Effects on other targets

There appear to be no relevant studies of CBDV actions at other receptors.

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

To our knowledge there are no published studies of CBDV effects in humans, although the ongoing Phase 2 clinical trials involving CBDV implies that the compound lacks obvious intoxicating effects.

Tetrad effects in rodents

To our knowledge there are no reports of CBDV effects on the rodent tetrad battery. CBDV (50-200 mg/kg) had no effects in the beam test of motor co-ordination and the grip strength test of muscle relaxation in rodents [9].

Therapeutic potential

Appendix Table 6 presents details of therapeutic effects relevant to CBDV.

Anti-inflammatory effects

CBDV reduced the inflammation caused by topical administration of croton oil onto the ears of mice, albeit to a lesser extent than indomethacin [51].

Anticonvulsant effects

CBDV (50-200 mg/kg) had significant anticonvulsant effects on the electroshock (100 mg/kg), audiogenic (50 mg/kg) and pentylenetetrazole-induced seizure models in rodents (100 mg/kg) [9]. CBDV also reduced the duration of epileptiform-like burst firing in hippocampal neurons [71]. The cannabis extract that is enriched in CBDV (CBDV-BDS) also had powerful anticonvulsant effects in rodents [127].

Antiemetic effects

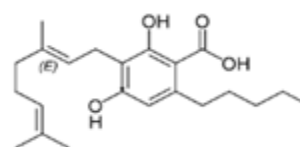
CBDV at a dose of 200 mg/kg reduced gaping in rats to a saccharin solution that had been paired with the emetic agent Lithium Chloride [129]. This implies an anti-nausea effect of CBDV.

Conclusions

CBDV is clearly of major therapeutic interest as an anticonvulsant, given its current investigation in human clinical trials. Although there has been comparatively little work done with CBDV, there is nothing in its profile to suggest CB1 affinity or intoxicating effects. Evidence for inflammatory and antiemetic actions are preliminary and reflect single preclinical studies. Anticonvulsant effects may reflect actions of CBDV at TRPV1 channels.

The lowest CBDV dose we identified in the literature to be effective in an animal model of disease was 50 mg/kg IP which inhibited tonic convulsions induced by audiogenic seizures in rats [9]. As IP doses of CBDV achieve 1.6 times higher brain concentrations (the site of anticonvulsant drug action) than oral doses in rats [3], the oral dose needed to achieve equivalent plasma levels might be as high as 80 mg/kg. Applying the FDA calculation to this dose, the estimated human oral therapeutic dose in a 60 kg human is 774 mg.⁵

CANNABIGEROLIC ACID (CBGA)



⁵ Please refer back to Introduction to the Review section above under “Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans” for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in in vitro and in vivo animal models may not translate. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

Introduction

Cannabigerolic acid (CBGA) is the precursor to both THCA and CBDA in the cannabis plant. It is found in street cannabis at very low levels: on average 0.28% of the total weight of cannabis [52]. CBGA comes in A and B forms however most scientific papers do not specify which they are using. Very little research has been conducted on the pharmacological properties of CBGA which seriously limits the strength of the conclusions that can be reached regarding its pharmacological activity and therapeutic potential.

Relevant pharmacological actions

CB1 and CB2 receptor affinity

CBGA does not appear to have affinity at CB1Rs: however the actual data supporting this conclusion were not provided [130]. To the best of our knowledge CBGA actions on CB2Rs have not been studied.

Effects on the endocannabinoid system

CBGA may reduce levels of the endocannabinoid 2-AG by inhibiting the 2-AG synthesizing enzyme DAGL α , but this occurs at relatively high concentrations of CBGA (30 μ M) [42]. CBGA did not inhibit the function of the anandamide degradative enzyme FAAH, the 2-AG degradative enzyme MAGL, or affect anandamide reuptake [42].

Effects on TRP channels

CBGA affects various protein targets in vitro: however the functional and therapeutic significance of these effects remains to be demonstrated. CBGA modulates various TRP channels at low to medium μ M concentrations (1-10 μ M) (TRPA1 agonist, TRPM8 antagonist) [42]. It also blocks TRPV1 (20 μ M), TRPV3 (13 μ M) and TRPV4 (30 μ M) at higher concentrations that may not be clinically relevant [42, 128].

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

CBGA to the best of our knowledge has never been administered to humans as a pure compound. A proper controlled psychopharmacological study is required to specifically confirm whether CBGA has psychoactive effects.

Tetrad effects in rodents

CBGA has not been tested in the cannabinoid tetrad in rodents.

Therapeutic potential

Several preclinical studies that have evaluated the therapeutic potential of CBGA (see Appendix Table 7).

Anti-inflammatory effects

CBGA inhibits cyclooxygenase enzymes in vitro [56], but only at relatively high concentrations that are unlikely to be clinically relevant.

Anticancer effects

CBGA inhibited human leukaemia cell proliferation, albeit at relatively high concentrations [32].

Antibacterial effects

CBGA has potent antibacterial activity at low μ M concentrations against various drug-resistant strains of *Staphylococcus aureus* [63].

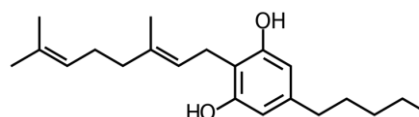
Anti-leishmanial effects

CBGA has antileishmanial properties, killing this parasitic protozoan at μ M concentrations [131].

Conclusions

CBGA has never been administered to humans as a pure substance. It is unlikely to have intoxicating effects in humans given its lack of affinity at CB1Rs. However studies testing in the rodent tetrad and in humans are needed to rule this out definitively. It has various pharmacological actions that may or may not be clinically relevant given the relatively high effective concentrations and doses needed to affect cell systems. In the absence of clinical evidence it is difficult to determine what constitutes a therapeutic dose of CBGA. Extrapolation from animals to humans is also not possible, as CBGA has never been tested in an *in vivo* animal study.

CANNABIGEROL (CBG)



Introduction

Cannabigerol (CBG) is formed by non-enzymatic decarboxylation from CBGA. It is found in Australian street cannabis at low levels with on average 0.93% of the weight of cannabis, although some plants had up to 15% CBG [41]

Relevant pharmacological actions

CB1 and CB2 Receptor Affinity

CBG binds to human CB1Rs with relatively low affinity (e.g. THC binds at low nM whereas CBG bind at high nM; it also binds CB2Rs) [40]. CBG does not appear to be effective in mobilizing G-protein that is necessary to activate CB1Rs, and thus behaves as a CB1R and CB2R antagonist in the submicromolar range [132].

Effects on the endocannabinoid system

CBG does not inhibit the function of the anandamide degradative enzyme FAAH but inhibited anandamide uptake at 11 μ M [42, 128]. CBG inhibits the 2-AG degradative enzyme MAGL at high μ M concentrations that are unlikely to be clinically relevant [42].

Effects on TRP channels

CBG modulates various TRP channels at the submicromolar range. It activates TRPA1 at 700 nM and antagonises TRPM8 at 160 nM [42]. It also activates TRPV1-4 in the 1-10 μ M range.

Effects on neurotransmitter receptors

CBG is a highly potent α_2 -adrenoceptor agonist, in mouse brain and mouse vas deferens, activating this receptor at 0.2 nM and 73 nM respectively [132]. It also antagonizes 5-HT_{1A} receptors at 1 μ M [132]. CBG also inhibits the synaptic uptake of noradrenaline, 5-HT and GABA at 50 – 67 μ M, however these concentrations are very high and unlikely to be clinically relevant [133].

Eicosanoid enzymes

CBG stimulated phospholipase A2 at 10 μ M [134], an enzyme that converts phospholipids or diacylglycerol into arachidonic acid, a precursor to the production of endocannabinoids and also eicosanoids such as prostaglandin, leukotrienes and thromboxanes. It also inhibited lipoxygenase in the 1-10 μ M range, an enzyme involved in the production of leukotrienes from arachidonic acid [135].

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

CBG to the best of our knowledge has never been administered to humans as a pure compound. A proper controlled psychopharmacological study is required to specifically confirm whether CBG lacks psychoactive effects.

Tetrad effects in rodents

CBG did not exhibit THC-like activity in mice, rats, gerbils and non-human primates, consistent with it lacking psychoactivity [15, 136]. Moreover, CBG was without effect up to 80 mg/kg in the mouse tetrad test of cannabimimetic activity (locomotor suppression, catalepsy, hypothermia and analgesia) [48]. Another classic effect of THC is promoting conjunctival erythema, an effect that was not observed with CBG administration in cats [137]. Taken together it would seem highly unlikely that CBG has pronounced intoxicating or psychoactive effects.

Therapeutic potential

Several preclinical studies have evaluated the therapeutic potential of CBG (see Appendix Table 8) but there are no relevant studies in humans.

Anti-inflammatory effects

There is preclinical evidence for anti-inflammatory properties of CBG. CBG has beneficial actions in a mouse model of colitis, where it reduced the concentrations of various inflammatory markers such as cytokines and interleukin-1 β (IL-1 β) [138]. The anti-inflammatory effects of CBG were also observed in peritoneal macrophages at low μ M concentrations. CBG inhibited cyclooxygenase 2, however at a concentration that is not likely to be clinically relevant [56].

Antioxidant effects

There is in vitro evidence that CBG is an antioxidant in colon cancer cells [138]. CBG had a subtle, low efficacy, prooxidant effect as evidenced by a reduction in the levels of glutathione, an antioxidant, in mouse primary cultured dopamine brain cells. However, this did not translate into any loss of viability in the cells, questioning the overall physiological significance of this observation [40].

Antibacterial effects

CBG inhibited the growth of bacterial strains that are resistant to drug treatment, with potent antibacterial activity at low μ M concentrations against various drug-resistant strains of *Staphylococcus aureus* [63] and also *Mycobacterium intracellulare* in vitro [131].

Anti-Psoriasis/skin disorders

The endocannabinoid system regulates skin physiology and all major components of the endocannabinoid system are found in human epidermis, the outmost layer of the skin [139, 140]. CBG potently inhibited the proliferation and differentiation of keratinocytes in vitro, a major cellular component of the epidermis. Keratinocytes contain keratin, a fibrous structural protein that provides strength and flexibility to the skin [139, 140]. These results suggest that topical applications of cannabinoid products for skin disorders such as psoriasis might be justified, but this would require further preclinical and clinical examination.

Anticancer effects

CBG reduces the proliferation of various cancer cells in vitro including human leukaemia, breast, prostate, glioma and neuroblastoma cells at μ M concentrations [10, 32, 40, 62, 141]. One of the more promising applications is colorectal cancer, where CBG reduced the proliferation of cancer cells in vitro, but also reduced

the size of human colorectal cancer tumours grafted onto mice *in vivo* [10]. These studies have yet to be translated into the clinic.

Huntington's Disease

Repeated exposure to CBG reduced the motor dysfunction and neuronal cell loss observed in toxin-induced and genetic mouse models of Huntington's disease. These beneficial neuroprotective effects were associated with reductions in markers of neuroinflammation and oxidative stress [142].

Bladder dysfunction

CBG potently inhibited chemical-induced contractions of the mouse and human bladder in organ bath preparations at 10 nM [143]. The therapeutic significance of this finding remains to be determined.

Antiglaucoma

CBG potently inhibited intraocular pressure in cats, suggesting utility as an antiglaucoma agent [137].

Conclusions

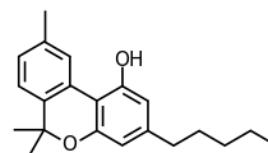
CBG has never been administered to a human as a pure substance. It binds to the CB1Rs only at relatively high concentrations and does not activate the receptor. It does not produce THC-like cannabimimetic effects in animals. It is therefore unlikely to have intoxicating effects in humans based on preclinical evidence.

CBG has various pharmacological actions that might be clinically relevant based on the effective concentrations and doses used in cell systems and animal studies respectively. Some effects have been shown at nanomolar concentrations such as α_2 -adrenoceptor agonism and CB1R antagonism.

The lowest CBG dose we identified in the literature to be effective in an animal model of disease was 3 mg/kg IP which inhibited the size of colon tumors in a mouse xenograft model [10]. As IP phytocannabinoid doses achieve 60.9 times higher plasma concentrations than oral doses in mice [3], the oral dose needed to achieve equivalent plasma levels might be as high as 183 mg. Applying the FDA calculation to this dose, the estimated therapeutic oral dose in a 60 kg human would be 892 mg.⁶

⁶ Please refer back to Introduction to the Review section above under "*Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans*" for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in *in vitro* and *in vivo* animal models may not translate. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

CANNABINOL (CBN)



Introduction

Cannabinol (CBN) was the first cannabinoid isolated from the cannabis plant in 1895, and as a result of this long history there are many studies that have examined its pharmacological activity [144]. CBN is mostly formed through the oxidation of THC, and is found in trace amounts in street cannabis in Australia constituting on average 0.09% of the plant [52]. If cannabis plant material is stored longer without being consumed, particularly at room temperature, so CBN levels increase.

Relevant pharmacological actions

CB1 and CB2 receptor affinity

CBN binds CB1 and CB2 receptors at high nanomolar concentrations, significantly higher than THC which binds at the low nanomolar range [145]. Like THC, CBN is a partial agonist at the CB1 receptor [146].

Effects on the endocannabinoid system

CBN does not appear to modulate endocannabinoid enzymes such as DAGL α , MAGL and FAAH. Nor does it influence anandamide uptake [42].

Effects on TRP channels

CBN is a TRPA1 agonist and a TRPM8 antagonist at nanomolar concentrations [42]. It also activates TRPV1, TRPV2, TRPV3 and TRPV4 at between 6-20 μ M, but with low efficacy [42, 128].

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

At least four studies have administered CBN to humans. One study found that 600 mg CBN given orally every day for 20 days induced no chromosomal abnormalities in 27 healthy subjects [147]. In another study [148] infrequent cannabis users were given access to intravenous CBN. They were told to self-administer the drug until they felt they had reached a sufficient level of "high". The amount of THC delivered to achieve intoxication was much less than for CBN. However CBN was still self-administered and to a greater extent than the non-psychoactive CBD which produced no noticeable effect. The participants reported that they felt CBN effects (at high doses) were mild but enjoyable, but much less intense than smoking cannabis. In another human study, 25 mg oral THC increased heart rate, decreased estimates of the passage of time, and increased feelings of being drugged, drunk, dizzy and drowsy. No such effects were observed with 50 mg oral CBN [149]. In a final study, oral CBN was administered at a maximum of 1200 mg to human cannabis smokers and failed to induce dose-related physiological effects, such as bronchodilation [150].

Tetrad effects in rodents

CBN promotes modest locomotor suppression in mice at high doses (40-80 mg/kg) [48]. However, no effects were observed on catalepsy, body temperature or antinociception. CBN produced conjunctival erythema (red eyes) in cats, a common effect of THC administration [137]. CBN substituted for THC in the drug discrimination paradigm in rats and monkeys, suggesting CBN and THC have similar subjective qualities in laboratory animals [151].

Therapeutic potential

Appendix Table 9 presents details of therapeutic effects relevant to CBN.

Immunosuppressant effects

Immunosuppression may be beneficial in autoimmune conditions, where an overactive immune system causes pathology. In immortalized astroglial cells, CBN inhibited the levels of nitrites released in response to the immune challenges lipopolysaccharide (LPS) and interferon- γ (IFN γ) when administered in nanomolar concentrations [152]. This effect was mediated by CB1Rs. Similar CBN inhibition of IFN γ -induced nitrite concentrations were seen in macrophages, albeit at lower potency (10 μ M) [153].

Analgesic effects

CBN had antinociceptive effects at 50 mg/kg in the acetic acid model of visceral pain in mice. This was mediated by CB1 receptors [41]. THC was far more potent with equivalent effects at a 1 mg/kg dose. CBN had similar antinociceptive potency in the hot-plate test in mice [154].

Anticonvulsant effects

CBN at a very high dose of 250 mg/kg showed anticonvulsant activity in the maximum electroshock test in mice [155].

Antidiarrhoeal effects

CBN inhibited the enhanced gastrointestinal motility caused by the administration of the intestinal inflammatory agent croton oil in mice, albeit with much less potency than the synthetic CB1R agonist WIN 55,212-2. This was mediated by CB1 receptors and croton oil increased CB1 receptor expression in the intestine [156]. CBN at 11-20 mg/kg also decreased small intestine and colonic propulsion [157, 158].

Anti-Psoriasis/skin disorders

CBN potentially inhibited the proliferation and differentiation of keratinocytes in vitro, a major cellular component of the epidermis [140]. These results suggest that topical applications of cannabinoid products for skin disorders such as psoriasis might be justified, but would require further preclinical and clinical examination.

Anticancer effects

CBN reduces the proliferation of human leukaemia and neuroblastoma cells at μ M concentrations [40].

Appetite stimulant effects

CBN stimulated feeding behavior in rats at 26 mg/kg and this effect was mediated by CB1 receptors [159].

Antibacterial effects

CBN has potent antibacterial activity at low μ M concentrations against drug-resistant strains of *Staphylococcus aureus* [63].

Amyotrophic lateral sclerosis (ALS)

CBN at 5 mg/kg daily for 12 days delayed the onset of symptoms in a mouse model of ALS which involves mutations in the superoxide dismutase 1 gene (SOD1) [11]. SOD1 is an enzyme that detoxifies reactive oxygen species.

Neuroprotective effects

CBN at 4 μ M inhibited apoptosis and NF- κ B induced by the anticancer drug camptothecin and TNF α in primary mice cortical cells cultures [160].

Antioxidant effects

CBN's chemical structure resembles the antioxidant vitamin E. Submicromolar concentrations of CBN inhibited cell death promoted by serum starvation via an antioxidant mechanism of action [161]. CBN also showed an antioxidant profile like CBD and THC using cyclic voltammetry with a electron donating profile similar to that of the known antioxidant, butylhydroxy-toluene (BHT) [106].

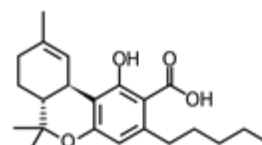
Conclusions

CBN may have mild psychoactivity when large quantities of the drug are administered intravenously to humans. This presumably reflects lower efficacy of CBN at CB1Rs than THC, despite its higher affinity. In the absence of adequate clinical evidence it is difficult to determine a therapeutic dose of CBN.

In a recent analysis of cannabiol in hempseed oils CBN was present at a maximum concentration approaching 10 mg/kg [1]. This would mean that consuming 5 kg (5.5 L) of hemp seed oil would be required to reach a non-psychoactive CBN dose of 50 mg.

The lowest CBN dose we identified in the literature to be effective in an animal model of disease was 5 mg/kg administered subcutaneously which delayed the onset of symptoms in a mouse model of ALS [11]. As systemic phytocannabinoid doses achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels might be as high as 35 mg/kg. Applying the FDA calculation to this dose, the estimated therapeutic oral dose in a 60 kg human for this indication would be 171 mg.⁷

TETRAHYDROCANNABINOLIC ACID (THCA)



Introduction

THCA is the chemical precursor of THC in the cannabis plant. THCA is formed from cannabigerolic acid (CBGA) by the enzyme THCA synthase. Heating cannabis plant material to around 160°C causes the decarboxylation of THCA to THC by a non-enzymatic reaction.

THCA is the most abundant cannabinoid found in police seized Australian street cannabis, representing on average almost 13% of the weight of cannabis flowering heads (up to 40% in some samples)[52].

THCA is generally considered to be non-psychoactive. However, very little research has been conducted on the pharmacological properties of THCA and this limits the strength of our conclusions when evaluating its pharmacological activity and toxicity.

⁷ Please refer back to Introduction to the Review section above under “*Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans*” for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in in vitro and in vivo animal models may not translate. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

Relevant pharmacological actions

CB1 and CB2 receptor affinity

A single study suggests that THCA binds to human CB1 receptors with similar affinity to THC [40]. However, this requires further verification and, in any case, there is no evidence that it activates the receptor (low efficacy) in a way that would be necessary to achieve intoxication. The same report suggests that THCA also binds the human CB2 receptor at low nM concentrations [40], but this requires further independent verification.

Effects on the endocannabinoid system

THCA inhibits the 2-AG synthesizing enzyme DAGL α and the degradative enzyme MAGL [42] at > 10 μ M. THCA does not inhibit the function of the anandamide degradative enzyme FAAH [42].

Effects on TRP channels

THCA blocks TRPM8 channels and activates TRPA1 at submicromolar concentrations [42]. The functional significance of these actions for pharmacological activity is unclear at present.

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

Anecdotal reports suggest that "juicing" cannabis, that is, the oral consumption of liquefied raw cannabis plant material, which is very rich in THCA, does not produce intoxication. This is despite probable gram quantities of THCA being administered in juiced products due to the high concentration of THCA in plant material [162]. A proper controlled psychopharmacological study is required to specifically confirm whether THCA lacks psychoactive effects.

Other human studies

Only one study could be located that administered THCA to humans (10 mg oral and 5 mg intravenous). While the study has been cited by others as evidence of no psychoactive effects of THCA, the subjective effects of THCA were not explicitly assessed [163]. The primary focus of the study was to determine THCA pharmacokinetics. The highest serum level achieved following an oral dose of 10 mg THCA was 600 ng/ml (1.6 μ M concentration) and with the intravenous 5 mg dose the level was 1100 ng/ml (3 μ M concentration) [164]. It is worth noting that THCA is not converted into THC in humans or rats *in vivo* [12, 13].

Tetrad effects in rodents

THCA did not suppress locomotor activity or produce hypothermia in rats, two typical actions of the psychoactive cannabinoid THC [12]. However, studies assessing higher doses may be required to completely rule out cannabimimetic actions.

Therapeutic potential

Several preclinical studies that have evaluated the therapeutic potential of THCA (see Appendix Table 10), but there are no relevant studies in humans.

Antiemetic effects

The most impressive potential therapeutic effect of THCA emerging from preclinical studies is an antiemetic action. In shrews (*Suncus murinus*) THCA potently inhibited vomiting induced by lithium chloride at 0.05 mg/kg [12]. In rats THCA also reduced lithium-induced conditioned gaping (a model of anticipatory nausea) at plasma levels of around 16 ng/ml or 0.043 μ M [12]. This suggests that the effective plasma level could be attained from consuming medium μ g to low mg quantities in humans when reflecting upon the data of Wohlfarth et al. (2012) where low μ M levels were attained in the plasma following a small oral dose of 10 mg.

The antiemetic effects of THCA appear mediated by cannabinoid CB1 receptors, as a cannabinoid CB1 receptor antagonist reversed the ability of THCA to reduce emesis in rodents [12]. Thus THCA might activate the receptor directly or increase levels of endocannabinoids like anandamide and 2-AG.

Anti-inflammatory effects

There is also preclinical evidence for anti-inflammatory properties of THCA, perhaps via inhibition of cyclooxygenase enzymes [56]. These enzymes are the drug targets of various non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin. However THCA has relatively low potency at this target and this mechanism is unlikely to be clinically relevant. THCA also inhibits the release of inflammatory cytokines such as TNF- α from macrophages [162].

Antioxidant effects

There is in vitro evidence that THCA may also be a weak antioxidant [165].

Conclusions

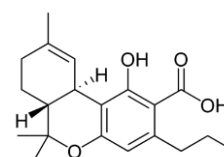
Overall the weight of evidence suggests that THCA is unlikely to have intoxicating effects in humans.

However, it is problematic that THCA is readily converted to THC by heating plant material e.g. at 100 degrees or more 80% of THCA is converted to THC [13]. THCA is quite stable in the short term (24 h) even at high temperatures such as 50°C, although there is a relatively small but significant conversion to THC at room temperature across a year of observation (e.g. a 2% THC content can increase to 5.6% THC [13]).

Thus THCA content should be measured in hemp food products and maintained at low levels given that it could be readily converted to THC *via* heating by knowledgeable consumers. Similar concentrations of THCA in seed, oil, and beverages might be adopted to that proposed for THC in FSANZ Application A1039.

The lowest THCA dose we identified in the literature to be effective in an animal model of disease was 0.05 mg/kg IP which had anti-nausea effects in rats [12]. As IP phytocannabinoid doses achieve on average 7 times higher tissue concentrations than oral doses in rodents [3], the oral dose needed to achieve equivalent plasma levels might be as high as 0.35 mg/kg. Applying the FDA calculation to this dose, the estimated therapeutic oral dose in a 60 kg human for this indication would be 3.5 mg.⁸

TETRAHYDROCANNABIVARINIC ACID (THCVA)



Introduction

THCVA is formed in the cannabis plant from cannabigerovaric acid (CBGVA). Very little research has been conducted on the pharmacological properties of THCVA and this limits the strength of our conclusions when evaluating its pharmacological activity and toxicity.

⁸ Please refer back to Introduction to the Review section above under “*Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans*” for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in in vitro and in vivo animal models may not translate. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

Relevant pharmacological actions

CB1 and CB2 receptor affinity

To the best of our knowledge no study has examined the binding of THCVA to cannabinoid receptors.

Effects on the endocannabinoid system

THCVA does not appear to modulate endocannabinoid enzymes such as DAGL α , MAGL and FAAH, and does not affect anandamide uptake [42].

Effects on TRP channels

THCVA modulates various TRP channels at low to medium micromolar concentrations. It antagonises TRPM8 channels at 1 μ M and activates TRPA1 at 16 μ M [42]. It also activates TRPV1, TRPV3 and TRPV4 at relatively high micromolar concentrations and with low efficacy (26 μ M, 48 μ M and 4 μ M respectively) [42, 128].

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

THCVA has never been administered to humans as a pure compound.

Tetrad effects in rodents

THCVA has not been examined in the tetrad test battery.

Therapeutic potential

Note that there is no summary table in the Appendix for this phytocannabinoid owing to an overall lack of research activity.

Anticancer effects

One GW Pharmaceuticals patent (*Phytocannabinoids in the treatment of cancer* US 20130059018 A1) reported that THCVA induces apoptosis in hormone-sensitive and hormone-insensitive prostate cancer cells in culture at 25 μ M.

Conclusions

There is extremely limited evidence available to form an opinion about the psychopharmacological, therapeutic and intoxicating actions of THCVA. THCVA has cytotoxic effects in prostate cancer cells at medium micromolar concentrations. Without more evidence it is impossible to estimate a human therapeutic dose.

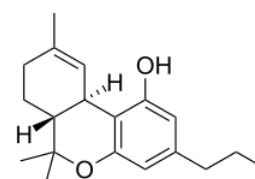
TETRAHYDROCANNABIVARIN (THCV)

Introduction

THCV is the propyl homologue of THC differing only in its slightly shortened alkyl side chain. It was discovered in the 1960s [166].

THCV occurs naturally at low levels in the cannabis plant with variation across different strains. THCV was detectable in 36% of 206 illicit cannabis seizures analysed in NSW [52], while cannabis “cigarettes” supplied for human research by the US National Institute of Drug Abuse (NIDA) contained an average of 0.12% (0.96 mg) THCV [167]. Furthermore, GW Pharmaceuticals flagship product Nabiximols (*Sativex*) also contains THCV (~1% of the total cannabinoid content).

THCV appears to be the only phytocannabinoid discovered to date that acts as an antagonist at CB1Rs. It is a *neutral* antagonist making it a potentially safer alternative to the *inverse* CB $_1$ agonist SR141716 (*Rimonabant*)



[168], which was marketed in Europe as a treatment for metabolic disorders and obesity until serious neuropsychiatric side effects became apparent [169, 170].

Relevant pharmacological actions

CB1 and CB2 receptor affinity

THCV binds to the CB1R with similar affinity to THC [41], but unlike THC it has low efficacy and therefore acts as an antagonist [171]. THCV displaces the highly potent synthetic cannabinoid compound CP55940 from human CB1 and CB2 receptors [69]. While, THCV exhibits neutral antagonist properties in mice at doses less than 3 mg/kg, it may act as a partial agonist of the CB1Rs and CB2Rs when doses exceed 10 mg/kg [69].

Other in vitro evidence come from experiments with murine cerebellar slices indicates that THCV can block activation of neuronal CB1 receptors [172]. In this study THCV prevented the inhibition of GABA release caused by the CB1R agonist WIN 55212 and mimicked the effects of the CB1 receptor antagonist/inverse agonist AM251 in increasing GABA release.

THCV (68.4 nM) also activated CB2 receptors in vitro [173], exhibiting high affinity for the CB2 receptor, signaling as a partial agonist [30].

Effects on the endocannabinoid system

THCV can block CB1-mediated effects of endogenously released endocannabinoids when administered *in vivo*. THCV did not appreciably inhibit DAGL, MAGL, FAAH or NAAA [42, 128].

Effects on TRP channels

THCV stimulates TRPV3 channels with high efficacy (50-70% of the effect of ionomycin) and potency ($EC_{50} \sim 3.7 \mu\text{M}$) [128]. THCV stimulated TRPV4 channels with moderate to high efficacy (30-60% of the effect of ionomycin) and potency [42, 128]. TRPV1 was also stimulated and desensitised by THCV, and THCV-BDS was the most potent cannabinoid trialed at TRPA1 and at TRPM8 and was a potent activator of TRPV2 [42, 128].

Evidence for intoxicating and other behavioural effects

Evidence for intoxicating effects in humans

Two human studies have reported administration of THCV. Pure THCV was first administered to 6 humans in 1974 at a dose of 7 mg intravenously, and was generally well tolerated. One subject experienced no subjective effect while the remaining subjects experienced mild to moderate effects similar to THC but at approximately 25% the potency [174]. In a later study 10 mg THCV was administered to 20 healthy humans [175] and reportedly enhanced activation of key reward and aversion related areas of the brain, a profile that was distinct from the prototypical CB1R antagonist rimonabant [176]. No euphoria, sedation, or any changes in mood or affect were found in this study [175].

Tetrad effects in rodents

Early pharmacological experiments with THCV indicated that it induced signs of catalepsy in the mouse ring test [166] but with a potency in mouse and human four or five times weaker than THC. THCV also produces antinociception in the tail flick test [177]. This is consistent with the notion that THCV activates CB1Rs weakly at higher doses.

Therapeutic potential

Refer to Appendix Table 11.

Metabolic

Owing to its *neutral* antagonist properties at CB₁ receptors there is interest in the possibility that THCV might

modify food and appetite-related phenomena. THCV, like the CB1R antagonist AM251, reduced the food intake and body weight of non-fasted and fasted mice when administered singly [178] and reduced the food intake and body weight of mice rendered obese with a junk food diet when administered repeatedly over 30-45 days [179].

Anxiolytic effects

THCV did not have anxiogenic properties, but nor was it demonstrated to be anxiolytic at 2.5mg/kg (IV) in a rat model of anxiety [180].

Antipsychotic effects

THCV had antipsychotic-like effects in a rat phencyclidine model of psychosis [181].

Anticonvulsant effects

THCV (20 μ M) significantly reduced seizure-like activity in rat brain slices *in vitro*. THCV (0.25 mg/kg) significantly reduced seizure incidence in the PTZ model in rats when tested *in vivo* [14].

Analgesic effects

THCV administered alone (50 mg/kg) did not have antinociceptive effects, but prevented the antinociceptive effects of THC in an acetic acid stretching model of rodent visceral pain [41]. However THCV (5 mg/kg) exhibited analgesic effects when tested in an inflammatory pain model, most likely due to CB2R activation [182].

Anti-inflammatory effects

THCV (0.3 or 1 mg/kg IP) decreased signs of inflammation in a rat paw inflammatory pain model using intraplantar injection of carrageenan or formalin, and these effects were blocked with the use of CB1 and CB2 receptor antagonists [183].

Antioxidant

THCV provided signs of neuroprotection in the form of an attenuation of the loss of tyrosine hydroxylase-positive neurons in rats lesioned with 6-hydroxydopamine and in mice lesioned with lipopolysaccharide (LPS) [182].

Anti-ischemic effects

THCV activated CB2 receptors *in vitro*, and decreased tissue injury and inflammation *in vivo*, associated with ischaemia-reperfusion injury, partly via CB2 receptor activation [173].

Conclusions

The literature on THCV, particularly in humans, is clearly very limited. However, THCV shows some exciting promise as a treatment for metabolic disorders. In the absence of sound clinical evidence it is impossible to determine a therapeutic dose of THCV.

The lowest THCV dose we identified in the literature to be effective in an animal model of disease was 0.25 mg/kg IP which reduced seizure severity in a rat model of epilepsy [14]. As IP doses of THCV achieve 5.4 times higher brain concentrations (the site of anticonvulsant drug action) than oral doses in rats [3], the oral dose required could be as high 1.35 mg/kg. Applying the FDA calculation to this dose, the estimated therapeutic oral dose in a 60 kg human is 13 mg.⁹

⁹ Please refer back to Introduction to the Review section above under “*Caveat 3: Difficulties in extrapolation from preclinical concentrations/doses to therapeutic levels in humans*” for an explanation of the FDA-recommended animal to human dose calculation and its significant limitations in being able to predict a human therapeutic dose. There is high likelihood that potential therapeutic effects in in vitro and in vivo animal models may not translate. If they do translate, there is no certainty that the human oral doses will reflect animal doses. **We do not endorse setting limits for cannabinoids in hemp food products based on therapeutic doses that were estimated from animal studies.**

5 General conclusions and summary of therapeutic levels

Table 2 (see below) summarises the information from the preceding sections to give our estimate of the lowest effective oral human therapeutic dose for each of the phytocannabinoids of interest, as well as the potential of each phytocannabinoid to produce THC-like intoxicating effects. Note that most of the therapeutic effects listed are potentially beneficial to human consumers, so these limits should not be necessarily seen as providing a level at which hemp-derived products should become restricted or scheduled. Note, also, the previously described caveats involved in extrapolating from studies with laboratory animals into the human situation, and in inferring oral human doses from rat or mouse systemic doses.

Obviously, proposed limits of phytocannabinoid levels will become better contextualised once more information on actual concentrations of the phytocannabinoids in hemp seed, hemp seed oil and hemp food products can be provided. The data being collected by our colleagues at Southern Cross University may be important to allow us to determine the potential hazards or therapeutic benefits accruing from consumption of specific hemp-derived products produced in, or imported into, Australia. In the absence of such data it is difficult at present to formulate an opinion on the feasibility of setting a total cannabinoid limit in such products.

There is reasonably good evidence of the therapeutic effects of CBD in humans at 800 mg (absolute dose). There is the possibility of mild sedation at such doses of CBD, although the current literature is ambiguous on this point with the balance of studies suggesting no sedative effects. There is no evidence of THC-like intoxication with CBD.

Evidence relating to potential therapeutic effects of the remaining phytocannabinoids mostly comes from preclinical studies involving cellular models and laboratory animals. Some evidence is available relating to effects arising from the consumption of THCA, THCV, CBDV, CBC and CBN in humans. In general there is little evidence of intoxication with these phytocannabinoids using an oral route of administration. However, CBN and THCV may be mildly intoxicating at relatively high intravenous doses. Only limited preclinical evidence is available for CBDA, THCVA, CBG and CBGA. On the basis of such evidence, none of these phytocannabinoids appear to have intoxicating properties.

The specific conclusions for setting limits in hemp-derived products are (also see Table 2 below):

1. **A limit could be set for CBD** given that it has therapeutic effects in humans (lowest human therapeutic absolute dose is 800 mg).
2. **The same limit might also be set for CBDA** (ie. 800 mg) given it is almost completely converted to CBD upon heating.
3. **A limit could be set for THCA** identical to that already set by FSANZ for THC. THCA is almost completely converted to THC when it is heated and so might be heated by some consumers seeking intoxication
4. **At this stage limits may not be required for the remaining phytocannabinoids CBC, CBDV, CBN, CBGA, CBG, THCV and THCVA.** No strong evidence supports these compounds having intoxicating effects following oral administration. The evidence for therapeutic potential comes only from animal studies and so the estimated human doses calculated from animal studies may not be relevant to human consumption.

Table 2: Lowest human therapeutic doses of the phytocannabinoids and potential intoxicating effects

Note: Except for CBD, all phytocannabinoid "therapeutic doses" have been estimated from animal studies. We do not endorse setting limits of cannabinoids in hemp food products based on therapeutic doses that are estimated from animal studies.

	Phyto-canna binoid	Set limit? (dose)	Estimated lowest therapeutic oral dose in 60 kg human*	Species from which therapeutic dose was calculated	Indication for therapeutic dose	Ref	Potential to induce intoxication
1	CBC	No, insufficient data	35 mg	Mice	Colitis	[2]	No
2	CBDA	Possibly** (800 mg)	0.07 mg	Rat	Anti-Nausea	[4]	No
3	CBD	Possibly (800 mg)	800 mg (absolute dose)	Human	Schizophrenia	[8]	No#
4	CBDV	No, insufficient data	774 mg	Rat	Seizures	[9]	No
5	CBGA	No, insufficient data	No data		-	-	Unknown
6	CBG	No, insufficient data	892 mg	Mice	Colon cancer	[10]	No
7	CBN	No, insufficient data	171 mg	Mice	Amyotrophic Lateral Sclerosis	[11]	Possible at high i.v. dose
8	THCA	Yes### Use FSANZ THC limit	3.5 mg	Rat	Nausea	[12]	No
9	THCVA	No, insufficient data	No data	-	-	-	Unknown
10	THCV	No, insufficient data	13 mg	Rat	Seizures	[14]	Possible at high i.v. dose

*Calculated using FDA method <http://www.fda.gov/downloads/Drugs/.../Guidances/UCM078932.pdf>

** CBDA is converted to CBD with heating

Weak evidence for sedative effects in humans – most likely not present but requires further testing;

###Note issues of THCA conversion to THC

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7 Appendices: Cannabinoid evidence tables

Table 3: Summary Table for CBC

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Anti-inflammatory	10-100 mg/kg (IV)	Preclinical	Mouse: LPS-induced paw edema	[49]	<i>CBC reduces paw edema</i>
	120-480 mg/kg (IP)	Preclinical	Rat: carrageenan-induced paw edema	[50]	<i>CBC reduces paw edema</i>
	1 mg/kg	Preclinical	Mouse: model of colitis	[2]	<i>CBC prevents inflammation of the colon</i>
	0.3-1.0 $\mu\text{mol}/\text{cm}^2$	Preclinical	Mouse: Topical croton oil induced ear edema	[51]	<i>CBC prevents inflammation</i>
Antifungal	0.39-25 $\mu\text{g}/\text{ml}$	Preclinical	In vitro: Agar well diffusion assay	[50]	<i>Antifungal effects of CBC</i>
Anticonvulsant	25-75 mg/kg (IP)	Preclinical	Mouse: Maximal Electroshock method	[46]	<i>Anticonvulsant effects of CBC</i>
Antibiotic	0.39-25 $\mu\text{g}/\text{ml}$	Preclinical	In vitro: Agar well diffusion assay	[50]	<i>Antibacterial effects of CBC</i>
Analgesic	30-100 mg/kg (IV)	Preclinical	Mouse: Tail-flick assay	[49]	<i>Analgesic effects of CBC in mice</i>
	3-6 nmol to PAG	Preclinical	Rat: Tail-flick assay	[44]	<i>Actions of CBC in PAG in analgesia</i>
Sedative	100 mg/kg (IV)	Preclinical	Mouse: Tetrad	[49]	<i>CBC produces tetrad effects</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	75 mg/kg (IP)	Preclinical	Mouse: Locomotor activity test	[46]	<i>CBC reduces spontaneous activity</i>
	50 mg/kg (IP)	Preclinical	Mouse: body temperature	[47]	<i>CBC causes hypothermia</i>

Table 4: Summary Table for CBDA

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Anti-inflammatory	470 μM (IC_{50})	Preclinical	In vitro: COX assay	[56]	<i>CBDA inhibits COX</i>
	20 μM COX1, 2.2 μM COX2 (IC_{50}).	Preclinical	In vitro: COX assay	[57]	<i>CBDA inhibits COX</i>
Antibiotic	5.6 μM (MIC)	Preclinical	In vitro: antibacterial assays	[63]	<i>CBD inhibits drug-resistant bacteria</i>
Antiemetic	Effective as low as 0.001 mg/kg (IP)	Preclinical	Rat and shrew: gaping toward LiCl-paired taste and vomiting	[4] [58] [59] [54]	<i>CBDA has antiemetic effects in rodents</i>
Anticancer	5-25 μM	Preclinical	In vitro: Human breast cancer cells	[61] [60]	<i>CBDA inhibits breast cancer migration</i>
	20-30 μM	Preclinical	In vitro: Human leukaemia cells (ALL and AML)	[32]	<i>CBDA inhibits leukaemia cell proliferation</i>
	13->25 μM	Preclinical	In vitro: Human and rat cancer cells	[62]	<i>CBDA inhibits tumour growth</i>
Antidiarrhoeal	1-30 μM	Preclinical	In vitro: shrew intestine organ bath	[64]	<i>CBDA inhibits intestinal contraction</i>
Anxiolytic	Up to 1 mg/kg	Preclinical	Rat: fear conditioning	[4]	<i>CBDA doesn't affect conditioned fear</i>
Antitussive	Tested up to 20 mM	Preclinical	Guinea pig: Citric acid-induced coughs	[184]	<i>CBDA doesn't inhibit cough</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Sedative	Up to 1 mg/kg	Preclinical	Mice: Locomotor activity	[4]	<i>CBDA doesn't affect locomotor activity</i>

Table 5: Summary Table for CBD

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Anti-inflammatory	Oral: 5–40 mg/kg	Preclinical	Rats: Carrageenan-induced inflammation in the rat paw	[185]	<i>CBD reduced edema and hyperalgesia</i>
	1 mg/kg, IP	Preclinical	Mice: lipopolysaccharide-induced inflammation	[186]	<i>CBD suppressed serum TNF production induced by lipopolysaccharide</i>
	20mg/kg IP	Preclinical	Mice: Inflammatory acute lung injury model	[187]	<i>CBD decreases biological markers of inflammation</i>
	30 mg kg(-1) either oral & IP	Preclinical	Mice & cells: production of interleukin (IL)-12 and IL-10	[188]	<i>CBD increased IL-12 and IL-10 with anti-inflammatory effects.</i>
	1–10 mg/kg i.v	Preclinical	Mice & Cells: Colitis induced in mice.	[103]	<i>CBD reduced colon injury in mice & reactive oxygen species production & lipid peroxidation</i>
	10 mg/kg IP & 20 mg/kg Intra-rectal & 20 mg/kg oral	Preclinical	Mice: Application of CBD for colonic inflammation in mice	[104]	<i>CBD improved colonic inflammation. Oral CBD did not.</i>
	10mg/kg IP	Preclinical	Mouse & Human cellular: Ulcerative colitis intestinal biopsies	[105]	<i>CBD downregulated biomarkers of enteric glia-mediated neuroinflammation</i>
Antifungal	Petroleum ether extract chromatograph	Preclinical	Fungus: germination in petri dish	[189]	<i>CBD inhibited P. ganjae conidia germination and hyphal growth</i>
Antibiotic	0.5–2 µg/mL	Preclinical	Bacterial cultures: Staphylococcus aureus	[63]	<i>CBD inhibited Staphylococcus aureus growth</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	1-5 µg/mL	Preclinical	Bacterial cultures: Staphylococci and streptococci	[190]	<i>CBD inhibited growth in broth cultures.</i>
Analgesic	24 mg /day sublingual spray	NHMRC LII	Human clinical: RCT in 24 adult patients with neurological symptoms (eg. MS, Spinal cord injury, brachius plexus damage)	[102]	<i>CBD reduced pain significantly</i> <i>No sedation</i>
	Oral 2.5-20 mg/kg (neuropathic) & 20 mg/kg (inflammatory)	Preclinical	Rats: neuropathic (sciatic nerve constriction) and inflammatory pain (adjuvant intraplantar injection)	[100]	<i>CBD reduced hyperalgesia to thermal and mechanical stimuli.</i>
	3 nmol intra-vl-PAG microinjection	Preclinical	Rats & cellular: Extracellular electrical activity of ON/OFF neurons of the rostral ventromedial medulla & tail flick	[44]	<i>CBD reduced the ongoing activity of ON and OFF neurons and induced antinociception in the tail flick-test</i>
	2.5 - 10 mg/kg IP	Preclinical	Mice: Chemotherapy-induced neuropathic pain	[101]	<i>CBD prevented chemotherapy induced mechanical sensitivity</i>
Anxiolytic	Oral 1 mg/kg	NHMRC LII Note: healthy humans	Human: RCT in 8 healthy human adults	[79]	<i>CBD caused a reduction in THC induced anxiety;</i> <i>No sedation</i>
	Oral 300 mg	NHMRC LII	Human: public speaking task in 10 healthy humans adults	[191]	<i>CBD reduced anxiety after the test</i> <i>No sedation</i>
	Oral 400 mg	NHMRC LII	Human: SPECT imaging RCT of 10 healthy male adult volunteers	[5]	<i>CBD decreased subjective anxiety and increased mental sedation</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	Oral 400 mg	NHMRC LII	Human: SPECT RCT in 10 adult patients with Social Anxiety Disorder	[90]	<i>CBD reduced subjective anxiety – reductions of brain activity in the limbic regions observed.</i> <i>No sedation</i>
	Oral 600 mg	NHMRC LII	Human: RCT simulated public speaking test of anxiety using adult healthy controls and treatment naive Social Anxiety Disorder patients	[89]	<i>CBD reduced anxiety, cognitive impairment and discomfort in giving speech</i> <i>No sedation</i>
Antipsychotic	Oral 1500 mg	NHMRC LIV	Human: <i>Single person case study in an adult psychotic patient</i>	[192]	<i>CBD reduced psychotic symptoms</i> <i>Unknown effect on sedation</i>
	Oral 1280 mg	NHMRC LIV	Human: case study (n=3 schizophrenic adults) over 30 days	[193]	<i>CBD reduced Brief Psychiatric Rating Scale scores</i> <i>No sedation</i>
	Oral 300mg & 600 mg	NHMRC LII	Human: RCT with Schizophrenic adult patients	[194]	<i>Low dose CBD) improved stroop colour word test but not high dose</i> <i>Unknown effect on sedation</i>
	Oral 800 mg/day	NHMRC LII	Human: RCT CBD vs amisulpride in 42 schizophrenic adult patients	[8]	<i>CBD improved PANSS scores (as did amisulpride) but with fewer side effects</i> <i>Unknown effect on sedation</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Antioxidant	10 mg/kg IP	Preclinical	Mice: DOX induced oxidative stress	[107]	<i>CBD improved DOX-induced oxidative/nitrative stress and cell death</i>
	5 mg/kg IP	Preclinical	Mice: ethanol gavage model of oxidative stress in liver	[108]	<i>CBD protects liver from alcohol-generated oxidative stress-induced steatosis</i>
	2–4 µM	Preclinical	In vitro: Rat cortical neuron cultures exposed to glutamate	[106]	<i>CBD prevented hydroperoxide-induced oxidative damage</i>
Antispasmodic	Oral CBD 700 mg/day for 6 weeks	NHMRC LII	Human: 15 neuroleptic-free adult patients with Huntington's Disease	[195]	<i>No improvement in chorea severity</i> <i>No sedation</i>
	5mg/kg IP	Preclinical	Mice: Microglial activation in a mouse model (autoimmune encephalomyelitis) of MS	[120]	<i>CBD ameliorates signs of autoimmune encephalomyelitis</i>
	5mg/kg IP	Preclinical	Mice: Murine encephalomyelitis virus-induced demyelinating disease	[196]	<i>CBD ameliorates motor deficits with reduced microglial activation and pro-inflammatory cytokine production</i>
Antiemetic	20 mg/kg SC	Preclinical	Shrew/Rats: antiemesis (shrews) and antinausea (rats) In vitro: 5-HT1A receptors	[121]	<i>CBD suppressed nicotine, LiCl and cisplatin induced vomiting and conditioned gaping in rats</i>
	2.5 mg/kg IP	Preclinical	Shrew: Lithium chloride (LiCl) induced vomiting model	[122]	<i>CBD lower doses produced suppression and higher doses producing enhancement of Li-induced vomiting</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	5 mg/kg IP	Preclinical	Shrew: Cisplatin induced vomiting test with CBD vs ondansetron	[123]	<i>CBD suppressed vomiting at 5 mg/kg but potentiated it at 40 mg/kg</i>
Antiischemic	100 μ M	Preclinical	In vitro: Experimentally induced Hypoxic Ischemia in brain slices of mice	[197]	<i>CBD reduced acute and apoptotic HI brain damage</i>
	1 mg/kg IV	Preclinical	Rats: Experimentally induced Hypoxic Ischemia	[198]	<i>CBD reduced brain excitotoxicity, oxidative stress and inflammation seven days after HI</i>
	1mg/kg IV	Preclinical	Pigs: Experimentally induced Hypoxic Ischemia	[110]	<i>CBD reduced viable neuron damage, improved EEG, reduced excitotoxicity, oxidative stress and inflammation (brain IL-1 levels)</i>
	0.1mg/kg -PV	Preclinical	Pigs: Experimentally induced Hypoxic Ischemia	[109]	<i>CBD improved brain tissue oxygenation during the first 3H after Hypoxic Ischemia, and partial EEG recovery</i>
	5 mg/kg, IV	Preclinical	Rats: Induced ischemia	[199]	<i>CBD ameliorated ischemia/reperfusion-induced kidney damage</i>
Anticonvulsant	Oral or gastric tube 22.9 mg/kg (patient body weights not reported)	NHMRC LIV	Human open label single arm (no control) in 162 treatment resistant epileptics aged between 1 and 30 yrs old (mean age 10 yrs)	[92]	<i>CBD reduced seizure frequency by 34.6% across all epilepsy and seizure types.</i> <i>Somnolence was reported in 25% of cases but effects of CBD confounded by concomittant AEDs</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	Oral 200-300mg/day	NHMRC LII	Human RCT: Chronic administration of CBD for 3-18 weeks to adult patients with temporal lobe epilepsy	[84]	<i>CBD improved seizure control</i> <i>Unknown effect on sedation</i>
	Oral 200mg/day	NHMRC LII	Human RCT: non blinded with a placebo arm administered CBD for 3 months (age of participants not reported)	[200]	<i>2 of 4 receiving CBD were seizure free, 1 had partial improvement, 1 no change</i> <i>Unknown effect on sedation</i>
	-	NHMRC LII	Human RCT in treatment resistant epilepsy (letter to editor only, does not state age of participants)	[201]	<i>No difference in seizure frequency (Oral CBD 200-300 mg/day for 4 weeks)</i> <i>Unknown effect on sedation</i>
	-	NHMRC LII	Human RCT in adults with treatment resistant epilepsy	[202]	<i>No change in seizure frequency (Oral CBD 300 mg/day for 6 months with cross over)</i> <i>Unknown effect on sedation</i>
	120 mg/kg	Preclinical	Mice: Maximal electroshock model of epilepsy	[97]	<i>Significant anticonvulsant effects of CBD</i>
	-	Preclinical	Rats: Cobalt induced focal seizures	[203]	<i>Not therapeutically relevant at 60mg/kg on cobalt induced focal seizure</i>
	94.9 – 481.7 mg/kg IP	Preclinical	Mice: Transcorneal (electroshock) current or convulsant drugs in mice	[98]	<i>CBD significantly reduced seizures resulting from: MES, PIC, INH, PTZ and BIC.</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
					<i>Strychnine convulsions not reduced.</i>
	0.3-3 mg/kg CBD IP	Preclinical	Rats: Electrically kindled seizures	[204]	<i>Significant antiepileptiform activity</i>
	30 mg/kg IP	Preclinical	Mice: Forced swimming test	[124]	<i>CBD reduced immobility; 5-HT(1A) receptor blockade removed antidepressant effects.</i> <i>CBD (3, 10, 100 mg/kg) did not reduce immobility.</i>
Antidepressant	200mg/kg IP	Preclinical	Mice: Automated mouse forced swim (FST) and tail suspension (TST) tests	[48]	<i>Significant antidepressant effect</i>
	0.25 to 1.0 μ M	Preclinical	In vitro: kaposi sarcoma	[111]	<i>CBD inhibits growth and induces programmed cell death</i>
Anticancer	1.0– 1.9 μ mol/L	Preclinical	In vitro: breast cancer	[112]	<i>CBD was able to inhibit Id-1 expression at the mRNA and protein level inhibiting metastatic breast cancer spread</i>
	0.01 μ M or 0.1 μ M	Preclinical	In vitro: Human lung cancer cell lines	[113]	<i>CBD caused 29% and 63% inhibition of A549 cell invasion</i>
	3 μ mol & 30 μ mol	Preclinical	In vitro: Urothelial carcinoma cells –viability assays	[114]	<i>The viability of T24 cells decreased with increasing concentrations of CBD</i>
	7.5 mg/kg/day	Preclinical	In vitro: Glioblastoma multiforme cell culture and xenografts into mice	[115]	<i>CBD reduces cell growth in TMZ resistant cells</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	0.4 - 1.4 μ M	Preclinical	In vitro: Glioblastoma multiforme cell culture	[116]	<i>CBD enhanced the inhibitory properties of Δ9-THC on growth and survival</i>
	12.5 or 25 mg/kg	Preclinical	In vitro: leukemia cell line viability	[118]	<i>CBD induced apoptosis</i>
	1 and 5 mg/kg in mice 0.01-10 μ M In cell lines	Preclinical	Animal & In vitro: Chemopreventive effect of CBD on colon cancer in mice	[119]	<i>CBD reduced ACF, polyps and tumours in mice. In cell lines, CBD protected DNA from oxidative damage.</i>
	1–12 μ M	Preclinical	In vitro: Glioma cell line proliferation studies	[117]	<i>CBD inhibited U87-MG and T98G cell proliferation and invasiveness</i>
Sedative	Oral 160mg	NHMRC LII	Human: blinded RCT in 15 adult Insomniac volunteers	[91]	<i>CBD increased sleep duration at 160 mg but not at 40 or 80 mg.</i>
	Oral or gastric tube 22.9 mg/kg (patient body weights not reported)	NHMRC LIV	Human open label single arm (no control) in 162 treatment resistant epileptics aged between 1 and 30 yrs old (mean age 10 yrs)	[92]	<i>Somnolence was reported in 25% of cases but effects of CBD confounded by concomittant AEDs and lack of control group</i>
	Oral 300 and 600 mg	NHMRC LII	Human: RCT in Healthy adult humans	[6]	<i>Self report sedation at 300 and 600 mg CBD</i>
	Oral 200mg	NHMRC LII	Human: RCT schizophrenia model in healthy adult male volunteers	[7]	<i>CBD caused sedation</i>
	Oral 400 mg	NHMRC LII	Human: SPECT imaging RCT of 10 healthy male adult volunteers	[5]	<i>CBD decreased subjective anxiety and increased mental sedation on a VAS</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	-	NHMRC LII	Human: fMRI study of CBD and THC effects on emotion in adults.	[205]	<i>600 mg oral CBD DID NOT cause sedation</i>
	-	NHMRC LII	Human: RCT of 8 healthy human adults, double blind CBD vs to diazepam and placebo	[79]	<i>NOT sedating at 1 mg/kg oral</i>
Anti-psoriasis/skin disorders	1–10 µM	Preclinical	In vitro: Acne model cultured human sebocytes and human skin organ culture	[125, 139]	<i>Suppressed the proliferation of acne vulgaris.</i>
	0.5 µM	Preclinical	In vitro: Skin cell growth and maturation	[139, 205]	<i>Repressed cell differentiation</i>

Table 6: Summary Table for CBDV

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Anti-inflammatory	0.3-1.0 $\mu\text{mol}/\text{cm}^2$	Preclinical	Mouse: Topical croton oil induced ear edema	[51]	<i>CBDV prevents inflammation</i>
Antiemetic	200 mg/kg (IP)	Preclinical	Rat: gaping towards a LiCL-paired taste	[129]	<i>CBDV has anti-nausea effects</i>
Anticonvulsant	50-200 mg/kg (IP)	Preclinical	Rat: variety of seizure models	[127]	<i>CBDV has anticonvulsant effects</i>
	87-422 mg/kg (CBDV-BDS, IP)	Preclinical	Rat: variety of seizure models	[9]	<i>CBDV-BDS has anticonvulsant effects</i>
	10 μM	Preclinical	In vitro: burst firing in hippocampal slices	[71]	<i>CBDV prevents epileptiform activity</i>

Table 7: Summary Table for CBGA

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Anti-inflammatory	460 μ M COX1 and 200 μ M COX2	Preclinical	In vitro: COX assay	[56]	<i>CBGA weakly inhibits COX1 and COX2</i>
Anti-leishmanial	33 μ M IC ₅₀	Preclinical	In vitro: <i>Leishmania Donovanii</i>	[131]	<i>CBGA kills parasitic protozoa</i>
Antibiotic	5.5-11 μ M MIC	Preclinical	In vitro: antibacterial assay	[63]	<i>CBGA inhibits drug-resistant bacteria</i>
Anticancer	30-40 μ M	Preclinical	In vitro: leukaemia cells (ALL and AML)	[32]	<i>CBGA inhibits proliferation of leukaemia cells</i>

Table 8: Summary Table for CBG

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Anti-inflammatory	270 μ M	Preclinical	In vitro: COX assay	[56]	<i>CBG weakly inhibits COX</i>
	1-10 μ M 1, 5 and 30 mg/kg	Preclinical	In vitro: peritoneal macrophages Mice: chemical-induced colitis	[138]	<i>CBG reduces colitis</i>
Antioxidant	1-10 μ M	Preclinical	In vitro: Reactive oxygen species in colon cells	[138]	<i>CBG has antioxidant effects</i>
	0.1 – 1 μ M	Preclinical	In vitro: Mouse cultured dopamine neurons	[40]	<i>CBG doesn't affect neuronal cell viability, but has low efficacy prooxidant effects</i>
Antibiotic	47 μ M IC ₅₀	Preclinical	In vitro: mycobacteria assay	[131]	<i>CBG kills mycobacterium intracellular</i>
	3 - 6 μ M MIC	Preclinical	In vitro: antibacterial assay	[63]	<i>CBG has antibacterial properties</i>
Antipsoriasis/skin disorders	0.5 μ M	Preclinical	In vitro: skin cells	[139]	<i>CBG inhibits skin cell growth and maturation</i>
	2.3 μ M	Preclinical	In vitro: skin cells	[140]	<i>CBG inhibits skin cell growth and maturation</i>
Anticancer	10-30 μ M 3-10 mg/kg	Preclinical	In vitro: human colorectal cancer cells; Mouse: xenograft model	[10]	<i>CBG kills colorectal cancer cells</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
	10-15 µM	Preclinical	In vitro: Human leukaemia cells (ALL and AML)	[32]	<i>CBG inhibits proliferation of leukaemia cells</i>
	8-20 µM	Preclinical	In vitro Human and at cancer cells	[62]	<i>CBG inhibits tumour growth</i>
	0.1-1 µM	Preclinical	In vitro: neuroblastoma cells	[40]	<i>CBG modestly inhibits cell proliferation</i>
	45 µM	Preclinical	In vitro: KB cells	[141]	<i>CBG inhibits proliferation of oral carcinoma cells</i>
Huntington's disease (HD)	10 mg/kg	Preclinical	Mouse model of HD	[142]	<i>CBG displays neuroprotective, anti-inflammatory and antioxidant effects</i>
Bladder function	10 nM	Preclinical	In vitro: mouse and human bladder organ bath	[143]	<i>CBG inhibits mouse and human bladder contractility</i>
Antiglaucoma	0.48 mg/day	Preclinical	Cat: IOP measurement	[137]	<i>CBG lowers intraocular pressure</i>
Anticonvulsant	Up to 200 mg/kg	Preclinical	Rat: PTZ-chemical –induced seizures	[206]	<i>CBG was not an anticonvulsant</i>
Antitussive	Tested up to 20 mM	Preclinical	Guinea pig: Citric acid-induced coughs	[184]	<i>CBG was ineffective in treating cough</i>
Appetite stimulant	No effect up to 17.6 mg/kg	Preclinical	Rat: Feeding behaviour	[207]	<i>CBG did not stimulate feeding</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Sedative	Up to 80 mg/kg	Preclinical	Mice: Tetrad	[48]	<i>CBG did not have tetrad effects</i>

Table 9: Summary Table for CBN

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Respiratory/bronchial dilator	-	NHMRC LII	Human: RCT compared to THC and CBD with a diazepam control.	[150]	<i>CBN 1200 mg oral was not a bronchodilator</i>
Safety – cytogenetic abnormalities	-	NHMRC LII	Human trial: cytogenetic effects in a prospective double blind RCT study	[147]	<i>600 mg CBN oral daily for 20 days led to no chromosomal abnormalities.</i>
Immunosuppressant	700 nM	Preclinical	In vitro: Rat C6 glioma cells	[152]	<i>CBN inhibits LPS and IFNγ-induced nitrite release</i>
	10 μ M	Preclinical	In vitro: mice macrophages	[153]	<i>CBN inhibits IFNγ-induced nitrite release</i>
Neuroprotective	4 μ M	Preclinical	In vitro: Mouse cortical neurons	[160]	<i>CBN inhibits anticancer drug and TNFα-induced apoptosis</i>
Anticonvulsant	250 mg/kg IP	Preclinical	Mice: maximum electroshock test	[155]	<i>CBN has anticonvulsant effects</i>
Antibiotic	1 μ g/ml (MIC)	Preclinical	In vitro: antibacterial assay	[63]	<i>CBN inhibits bacterial growth</i>
Analgesic	50 mg/kg	Preclinical	Mice: Acetic acid-induced abdominal stretching	[41]	<i>CBN inhibits nociception</i>
	32 mg/kg	Preclinical	Mice: Hot-plate test	[154]	<i>CBN inhibits nociception</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Amyotrophic lateral sclerosis	5 mg/kg/day s.c. for 12 days	Preclinical	Mice: SOD transgenics	[11]	<i>CBN delays symptom onset in mouse model of ALS</i>
Antioxidant	nM concentrations	Preclinical	In vitro: Leukaemia and 3T3 cells	[161]	<i>CBN inhibits serum starved cell death</i>
	Not defined	Preclinical	Cyclic voltammetry	[106]	<i>CBN has antioxidant properties</i>
Anticancer	36 μ M	Preclinical	In vitro: Human leukaemia cells (ALL)	[10, 208]	<i>CBN reverses multidrug resistance</i>
	0.1-10 μ M	Preclinical	In vitro: neuroblastoma cells	[40]	<i>CBN modestly reduced cell viability</i>
Antipsoriasis/skin disorders	2.1 μ M	Preclinical	In vitro: skin cells	[140]	<i>CBN inhibits proliferation of skin cells</i>
Appetite stimulant	26 mg/kg p.o.	Preclinical	Rat: feeding behaviour	[207]	<i>CBN stimulated feeding</i>
Antidiarrhoeal	1.36 μ mol/mouse	Preclinical	Mice: Croton oil inflammatory model	[156]	<i>CBN inhibits intestinal motility</i>
	11.2 mg/kg IC ₅₀	Preclinical	Mice: colonic propulsion	[157]	<i>CBN inhibits colonic propulsion?</i>
	12-20 mg/kg	Preclinical	Rat: GIT motility	[158]	<i>CBN inhibits gastric emptying and small intestine motility</i>
Antiglaucoma	0.48 mg/day	Preclinical	Cat: IOP	[137]	<i>CBN lowers Intraocular pressure</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Euphoriant	CBN (200 µg/kg) IV	NHMRC LII	Human trial	[148]	<i>CBN was capable of producing a THC like high at high doses</i>
	Oral CBN 50 mg	NHMRC LII	Human trial	[149]	<i>CBN had no effect on any physiological or subjective measures of intoxication</i>

Table 10: Summary Table for THCA

Pharmacological characteristic	Effective Concentration/Dose	Level of evidence	Source of evidence	References	Key findings
Anti-inflammatory	630 – 1700 µM	Preclinical	In vitro: COX assay	[56]	<i>THCA weakly inhibits COX</i>
	40 – 160 µM	Preclinical	In vitro: macrophages	[162]	<i>THCA inhibits LPS-induced TNFα release</i>
Antioxidant	10 µM	Preclinical	In vitro: MPP toxicity in rat dopamine neurons	[165]	<i>CBN is a free radical scavenger and modestly reverses damage in in vitro model of PD</i>
Antiemetic	0.05 mg/kg IP at 0.043 µM in plasma	Preclinical	Rat and shrew: LiCl-induced gaping and vomiting	[12]	<i>THCA has antiemetic actions</i>

Table 11: Summary Table for THCV

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Metabolic	-	NHMRCLII	Human: fMRI RCT	[175]	<i>10 mg THCV increases neural responding to rewarding and aversive stimuli but not subjective response</i>
	3 mg/kg	Preclinical	Mice: Assessment of feeding behavior	[178]	<i>3 mg/kg reduced the food intake and body weight</i>
	0.1, 0.5, 2.5 and 12.5mg/kg	Preclinical	Mice: insulin sensitivity in dietary induced (DIO) and genetically obese mice	[179]	<i>THCV dose-dependently reduced glucose intolerance</i>
	5 µM in zebrafish 12.5 mg/kg in obese mice	Preclinical	Animal and In vitro: models of non alcoholic fatty liver disease	[209]	<i>THCV increased yolk lipid mobilization (zebrafish) and inhibited the development of hepatosteatosis (obese mice) respectively</i>
Anti-inflammatory	0.3 or 1 mg/kg-1 IP (Inflammation) 5 mg/kg IP (Pain)	Preclinical	Rat: injection of carrageenan or formalin in a rat paw pain/analgesia model	[183]	<i>THCV can activate CB2 receptors in vitro and decrease signs of inflammation and inflammatory Pain.</i>
Analgesic	-	Preclinical	Mice: Acetic acid stretching test, a visceral pain model	[41]	<i>THCV (50 mg/kg) IP did not produce antinociceptive effects but blocked the antinociceptive effects of THC.</i>
Anxiolytic (Anxiogenic)	-	Preclinical	Rat: Light/Dark immersion model of anxiety	[180]	<i>THCV (2.5 mg/kg IV) was not anxiolytic (or anxiogenic)</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
Antipsychotic	100 nM – 5-HT _{1A} receptor activation 2 mg/kg – rat psychosis	Preclinical	Rat & in vitro: Rat brainstem and human 5-HT _{1A} binding assays & rat phencyclidine model of psychosis	[181]	<i>THCV enhanced 5-HT_{1A} receptor activation.</i> <i>THCV exhibited significant antipsychotic effects</i>
Antioxidant	2 mg/kg IP	Preclinical	Mice & Rats: Neuroprotection in lesioned mice and rats	[182]	<i>THCV attenuated lesion related neuronal loss by antioxidant activity (or CB₂ activation)</i>
Antiischemic	68.4 nM (in vitro) 3 or 10 mg/kg IP (in mice)	Preclinical	Mice & In vitro: experimental ischemia & In vitro CB ₂ binding assays	[173]	<i>D8-THCV activated CB₂ receptors, and decreased tissue injury and inflammation in vivo</i>
Anticonvulsant	10 - 20 µM (in vitro). 0.25 mg/kg IP (in rats).	Preclinical	Rats and In vitro: Brain slices of epileptiform activity & a generalized PTZ seizure model.	[14]	<i>THCV significantly reduced seizure activity in rat brain slice.</i> <i>THCV significantly reduced seizure incidence in PTZ model in rats.</i>
	1 & 5 µM	Preclinical	In vitro: Testing inhibitory effects on neurotransmission in mouse membranes	[210]	<i>1 & 5 µM THCV caused a non CB receptor depression in basal [35S]GTPγS binding</i>
	5–58 µM	Preclinical	In vitro: Inhibitory neurotransmission at interneurone-Purkinje cells (PC)	[172]	<i>THCV induced decreases in spike firing suggest a mechanism of PC inhibition.</i>
Euphoriant	7 mg IV	NHMRC LII	Human: Exploratory administration to healthy humans to compare to THC	[174]	<i>THCV produced mild to moderate effects similar to THC but at ~25% strength</i>

Pharmacological characteristic	Effective concentration/dose	Level of evidence	Source of evidence	Reference	Key findings
			effects		