(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
30 December 2015 (30.12.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/198078 A1

(51) International Patent Classification:
A61K 31/05 (2006.01) *A61P 25/08* (2006.01)

(21) International Application Number:
PCT/GB2015/051894

(22) International Filing Date:
29 June 2015 (29.06.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1411496.1 27 June 2014 (27.06.2014) GB

(71) Applicant: **GW PHARMA LIMITED** [GB/GB]; Sovereign House, Vision Park, Chivers Way, Histon, Cambridge Cambridgeshire CB24 9BZ (GB).

(72) Inventors: **STOTT, Colin**; GW Pharma Limited, Sovereign House, Vision Park, Chivers Way, Histon Cambridge Cambridgeshire CB24 9BZ (GB). **JONES, Nick**; c/o GW Pharm Limited, Sovereign House, Vision Park, Chivers Way, Histon Cambridge Cambridgeshire CB24 9BZ (GB). **WHALLEY, Benjamin**; c/o Professor of Neuropharmacology, Hopkins Life Sciences Building, University of Reading, Whiteknights, Reading Berkshire RG6 6AP (GB). **STEPHENS, Gary**; c/o Professor of Neuropharmacology, Hopkins Life Sciences Building, University of Reading, Whiteknights, Reading Berkshire RG6 6AP (GB). **WILLIAMS, Claire**; c/o School of Psychology Clinical, Language Sciences, University of Reading, Whiteknights, Reading Berkshire RG6 6AP (GB).

(74) Agent: **HGF LIMITED**; 4th Floor, Merchant Exchange, 17-19 Whitworth Street West, Manchester, Greater Manchester M1 5WG (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2015/198078 A1

(54) Title: 7-OH-CANNABIDIOL (7-OH-CBD) AND/OR 7-OH-CANNABIDIVARIN (7-OH-CBDV) FOR USE IN THE TREATMENT OF EPILEPSY

(57) Abstract: The present invention relates to the use of 7-hydroxy-cannabidol (7-OH-CBD) and / or 7-hydroxy-cannabidivarin (7-OH-CBDV) in the treatment of epilepsy. Preferably the cannabinoid metabolites are isolated from plants to produce a highly purified extract or can be reproduced synthetically.

7-OH-CANNABIDIOL (7-OH-CBD) AND/OR 7-OH-CANNABIDIVARIN (7-OH-CBDV) FOR USE IN THE TREATMENT OF EPILEPSY

[0001] The present invention relates to the use of 7-hydroxy-cannabidol (7-OH-CBD) and / or 7-hydroxy-cannabidivarin (7-OH-CBDV) in the treatment of epilepsy.

[0002] Preferably the cannabinoid metabolites are isolated from plants to produce a highly purified extract or can be reproduced synthetically.

BACKGROUND TO THE INVENTION

[0003] Epilepsy occurs in approximately 1% of the population worldwide, (Thurman *et al.*, 2011) of which 70% are able to adequately control their symptoms with the available existing anti-epileptic drugs (AED). However, 30% of this patient group, (Eadie *et al.*, 2012), are unable to obtain seizure freedom from the AED that are available and as such are termed as suffering from "treatment-resistant epilepsy" (TRE).

[0004] There are several different types of AED available to treat epilepsy, some of the most common AED defined by their mechanisms of action are described in the following tables:

[0005] **Examples of narrow spectrum AED**

Narrow-spectrum AED	**Mechanism**
Phenytoin	Sodium channel
Phenobarbital	GABA / Calcium channel
Carbamazepine	Sodium channel
Oxcarbazepine	Sodium channel
Gabapentin	Calcium channel
Pregabalin	Calcium channel
Lacosamide	Sodium channel
Vigabatrin	GABA

[0006] **Examples of broad spectrum AED**

Broad-spectrum AED	**Mechanism**

Valproic acid	GABA / Sodium channel
Lamotrigine	Sodium channel
Topiramate	GABA / Sodium channel
Zonisamide	GABA / Calcium /Sodium channel
Levetiracetam	Calcium channel
Clonazepam	GABA
Rufinamide	Sodium channel

[0007] Individuals who develop epilepsy during the first few years of life are often difficult to treat and as such are often termed treatment-resistant. Children who undergo frequent seizures in childhood are often left with neurological damage which can cause cognitive, behavioral and motor delays.

[0008] Childhood epilepsy is a relatively common neurological disorder in children and young adults with a prevalence of approximately 700 per 100,000. This is twice the number of epileptic adults per population.

[0009] When a child or young adult presents with a seizure, investigations are normally undertaken in order to investigate the cause. Childhood epilepsy can be caused by many different syndromes and genetic mutations and as such diagnosis for these children may take some time.

[0010] Childhood epilepsy refers to the many different syndromes and genetic mutations that can occur to cause epilepsy in childhood. Examples of some of these are as follows: Dravet Syndrome; Myoclonic-Absence Epilepsy; Lennox-Gastaut syndrome; Generalized Epilepsy of unknown origin; CDKL5 mutation; Aicardi syndrome; bilateral polymicrogyria; Dup15q; SNAP25; and febrile infection related epilepsy syndrome (FIRES); benign rolandic epilepsy; juvenile myoclonic epilepsy; infantile spasm (West syndrome); and Landau-Kleffner syndrome. The list above is non-exhaustive as many different childhood epilepsies exist.

[0011] **Examples of AED used specifically in childhood epilepsy**

AED	**Mechanism**
Clobazam	GABA

Stiripentol	GABA

[0012] The International League Against Epilepsy (ILAE) in 2011 have reclassified the old terms of "general" and "partial" seizures". The new term "generalized seizure" refers to seizures conceptualized as originating at some point within the brain and rapidly engaging bilaterally distributed networks.

[0013] The new term "focal seizure" now refers to seizures conceptualized as originating at some point within the brain and being limited to one hemisphere.

[0014] The etiology of epilepsy has also been reclassified by the ILAE as being of genetic origin; structural or metabolic origin; or of unknown origin.

[0015] There is also now no specific classification for focal seizure types, therefore the terms complex partial and simple partial seizure are no longer in use.

[0016] There are several different animal models that can be used to test the efficacy of compounds as anti-convulsants. These include the pentylenetetrazole-induced (PTZ) model of generalised seizures and the Maximal Electroshock (MES) model of generalised seizures.

[0017] Over the past forty years there have been a number of animal studies on the use of the non-psychoactive cannabinoid cannabidiol (CBD) to treat seizures. For example, Consroe *et al.*, (1982) determined that CBD was able to prevent seizures in mice after administration of pro-convulsant drugs or an electric current.

[0018] Studies in epileptic adults have also occurred in the past forty years with CBD. Cunha *et al.* reported that administration of CBD to eight adult patients with generalized epilepsy resulted in a marked reduction of seizures in 4 of the patients (Cunha *et al.*, 1980).

[0019] A study in 1978 provided 200 mg/day of pure CBD to four adult patients, two of the four patients became seizure free, whereas in the remainder seizure frequency was unchanged (Mechoulam and Carlini, 1978).

[0020] Carlini *et al.* in 1981 described a further study where CBD was provided to healthy volunteers, insomniacs and epileptic patients. Seven out of the eight epileptic patients described an improvement in their condition.

[0021] In contrast to the studies described above, an open label study reported that 200 mg / day of pure CBD was ineffective in controlling seizures in twelve institutionalized adult patients (Ames and Cridland, 1986).

[0022] In the past forty years of research there have been over thirty drugs approved for the treatment of epilepsy none of which are cannabinoids. Indeed, there appears to have been a prejudice against cannabinoids, possible due to the scheduled nature of these compounds and / or the fact that THC, which is a known psychoactive, has been ascribed as a pro-convulsant (Consroe *et al.*, 1977).

[0023] More recently the applicant has discovered that the cannabinoids CBD and CBDV are effective in animal models of epilepsy. For example EP 2,448,637 describes the use of CBD in the treatment of partial seizures and WO 2011/121351 describes the use of CBDV in the treatment of epilepsy. Hill *et al.* (2012) and Amada *et al.* (2013) both also describe the use of CBDV in the treatment of epilepsy. Jones *et al.* (2012) describes the anti-convulsant activity of CBD in animal models.

[0024] Furthermore GB 2495118 describes the use of a pharmaceutical composition comprising a combination of CBDV and CBD.

[0025] The synthetic production of the metabolite of CBD, 7-hydroxy-cannabidiol, (7-OH CBD) is disclosed in WO 01/95899 in addition to many other CBD derivatives. The compound was tested in a model of inflammation and found to be effective. The application goes on to suggest that the compound may be of use as an analgesic, anti-anxiety, anti-convulsant, neuroprotective, anti-psychotic and anti-inflammatory based on the mechanisms the compound displays in the model of inflammation. However no data is presented to support the use of 7-OH-CBD as an anti-convulsant.

[0026] To date there have been no studies into the anti-convulsant effect of metabolites of CBD and CBDV.

[0027] Surprisingly, it has now been found that a metabolite of CBD, 7-hydroxy-cannabidiol, (7-OH CBD) and a metabolite of CBD, 7-hydroxy-cannabidivarin, (7-OH CBDV) are effective in the treatment of epilepsy. The metabolites appear to be more effective than their parent compounds in certain aspects of seizure control.

BRIEF SUMMARY OF THE DISCLOSURE

[0028] In accordance with a first aspect of the present invention there is provided 7-hydroxy-cannabidivarin (7-OH-CBDV) in a pure, isolated or synthetic form for use as a medicament.

[0029] In accordance with a second aspect of the present invention there is provided 7-hydroxy-cannabidivarin (7-OH-CBDV) in a pure, isolated or synthetic form for use in the treatment of epilepsy.

[0030] In accordance with a third aspect of the present invention there is provided 7-hydroxy-cannabidol (7-OH-CBD) in a pure, isolated or synthetic form for use in the treatment of epilepsy.

[0031] In one embodiment the 7-hydroxy-cannabidivarin (7-OH-CBDV) in a pure, isolated or synthetic form is used in combination with 7-hydroxy-cannabidol (7-OH-CBD) in a pure, isolated or synthetic form.

[0032] In accordance with a fourth aspect of the present invention there is provided a pharmaceutical composition comprising 7-hydroxy-cannabidivarin (7-OH-CBDV) and / or 7-hydroxy-cannabidol (7-OH-CBD) with a pharmaceutically acceptable carrier.

[0033] In accordance with a fifth aspect of the present invention there is provided a pharmaceutical composition comprising 7-hydroxy-cannabidivarin (7-OH-CBDV) and / or 7-hydroxy-cannabidol (7-OH-CBD) with a pharmaceutically acceptable carrier for use in the treatment of epilepsy.

[0034] In one embodiment the 7-hydroxy-cannabidol (7-OH-CBD) and / or 7-hydroxy-cannabidivarin (7-OH-CBDV) are used in combination with one or more concomitant anti-epileptic drugs (AED).

[0035] Preferably the one or more AED is selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

[0036] Preferably the dose of 7-OH-CBD and / or the 7-OH-CBDV is between 1 and 2000 mg/kg.

[0037] Preferably the 7-OH-CBDV may be formulated for administration separately, sequentially or simultaneously with the 7-OH-CBD or the combination may be provided in a single dosage form.

[0038] It is envisaged that the composition be administered as an oral liquid solution. Other modes of administration including solids, semi-solids, gels, sprays, aerosols, inhalers, vaporisers, enemas and suppositories are alternative administration forms. Such medicaments could be administered via the oral, buccal, sublingual, respiratory, nasal and distal rectum route.

[0039] In accordance with a sixth aspect of the present invention there is provided a method of treating epilepsy comprising administering a therapeutically effective amount of 7-hydroxy-cannabidiol (7-OH-CBD) and / or 7-hydroxy-cannabidivarin (7-OH-CBDV) to a subject in need thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

[0040] Embodiments of the invention are further described hereinafter with reference to the accompanying drawings, in which:

[0041] Figure 1 shows CBDV and CBD, and their 7-OH metabolites in the PTZ model of acute seizure.

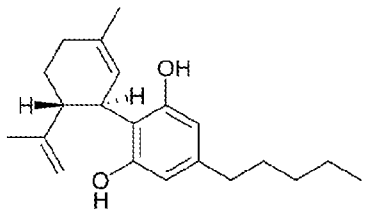
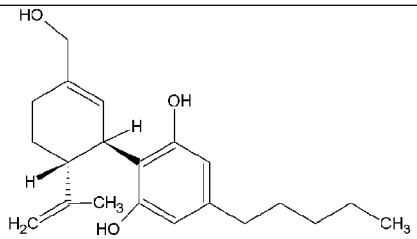
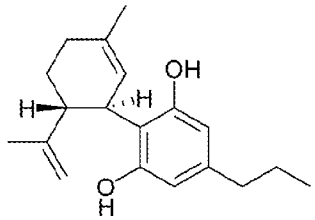
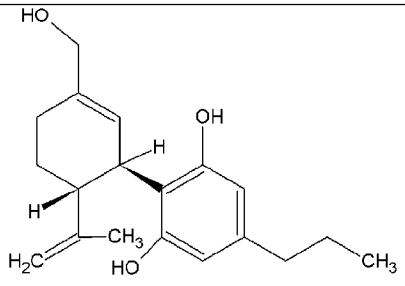
[0042] Legend to the figures:

[0043] Figure 1. CBDV and 7-OH CBDV were dosed at 200 mg/kg, and CBD and 7-OH CBD were dosed at 100 mg/kg (A) Maximum observed seizure severity (median severity in grey, box represents interquartile range, whiskers represent maxima and minima; Kruskal-Wallis test, with a post-hoc Mann-Whitney U) (B) Mortality (Chi-squared test, with a post-hoc Fisher exact) (C) Animals exhibiting tonic-clonic seizures (Chi-squared test, with a post-hoc Fisher exact) (D) Latency to seizure onset (median with interquartile range; Kruskal-Wallis test, with a post-hoc Mann-Whitney U). n=11 for each dose, * = p≤0.05, ** = p≤0.01.

DEFINITIONS

[0044] Definitions of some of the terms used to describe the invention are detailed below:

[0045] The cannabinoids described in the present application are listed below along with their standard abbreviations.

CBD	Cannabidiol	
7-OH-CBD	7-hydroxy-cannabidiol	
CBDV	Cannabidivarin	
7-OH-CBDV	7-hydroxy-cannabidivarin	

[0046] The table above is not exhaustive and merely details the cannabinoids which are identified in the present application for reference. So far over 60 different cannabinoids have been identified and these cannabinoids can be split into different groups as follows: Phytocannabinoids; Endocannabinoids and Synthetic cannabinoids (which may be novel cannabinoids or synthetically produced phytocannabinoids or endocannabinoids).

[0047] "Cannabinoid metabolites" are metabolites from cannabinoids that originate when the parent cannabinoid is metabolised or broken down. The cannabinoid metabolites can be isolated from plants to produce a highly purified extract or can be reproduced synthetically.

[0048] "Highly purified cannabinoid metabolites" are defined as cannabinoids that have been extracted from the cannabis plant and purified to the extent that other cannabinoids and non-cannabinoid components that are co-extracted with the cannabinoids have been removed, such that the highly purified cannabinoid is greater than 90%, more preferably greater than 95%, most preferably greater than 98% (w/w) pure.

[0049] The cannabinoid metabolites may be manufactured synthetically and / or produced from the parent cannabinoid by enzymatic means.

[0050] Phytocannabinoids can be obtained as either the neutral (decarboxylated form) or the carboxylic acid form depending on the method used to extract the cannabinoids. For example it is known that heating the carboxylic acid form will cause most of the carboxylic acid form to decarboxylate into the neutral form.

[0051] The human dose equivalent (HED) can be estimated using the following formula:

$$\text{HED} = \text{Animal dose (mg/kg)} \textit{ multiplied by } \frac{\text{Animal } K_m}{\text{Human } K_m}$$

The K_m for a rat is 6 and the K_m for a human is 37.

Thus, for a human of approximately 60Kg a 200mg/Kg dose in rat would equate to a human daily dose of about 2000mg.

[0052]

DETAILED DESCRIPTION

[0053] The following Examples describe for the first time the anti-convulsant activity of the metabolites of CBD, namely 7-OH-CBD and CBDV, namely, 7-OH-CBDV.

EXAMPLE 1: EFFICACY OF 7-HYDROXY CANNABIDIOL (7-OH-CBD) AND 7-HYDROXY CANNABIDIVARIN (7-OH-CBDV) IN THE PTZ MODEL OF SEIZURE

Materials and Methods

Compounds:

[0054] The compounds 7-OH CBD and 7-OH-CBDV have never been tested in a model of epilepsy and as such the effects were examined at one dose level in order to determine efficacy.

[0055] The hydroxy-metabolites of CBD and CBDV were also tested against their parent cannabinoids which were used as positive controls. The table below details the doses used in this study.

Compound	Dose (mg/kg)
Vehicle	-
CBDV	200
7-OH-CBDV	200
CBD	100
7-OH CBD	100

General methodology for PTZ model

Animals

[0056] Male Wistar rats (P24-29; 75-110g) were used to assess the effects of the cannabinoids listed above on the PTZ model of generalised seizures. Animals were habituated to the test environment, cages, injection protocol and handling prior to experimentation. Animals were housed in a room at 21ºC on a 12 hour light: dark cycle (lights on 0900) in 50% humidity, with free access to food and water.

Experimental setup

[0057] Five 6L Perspex (RTM) tanks with lids were placed on a single bench with dividers between them. Closed-circuit television (CCTV) cameras were mounted onto the dividers to observe rat behaviour. Sony Topica CCD cameras (Bluecherry, USA) were linked via BNC cables to a low-noise PC via Brooktree digital capture cards (Bluecherry, USA). Zoneminder

(http://www.zoneminder.com) software was used to monitor rats, start and end recordings and manage video files. In-house Linux (RTM) scripts were used to encode video files into a suitable format for further offline analysis

Experimental Protocols

[0058] On the day of testing, animals received an IP injection with either the cannabinoids (or a matched volume of the cannabinoids vehicle (1:1:18 ethanol:Cremophor: 0.9%w/v NaCl solution), which served as the negative control group. Animals were then observed for 30 mins, after which time they received an IP injection of 70 or 80mg/kg PTZ. Negative vehicle controls were performed in parallel with cannabinoid-dosed subjects. After receiving a dose of PTZ, animals were observed and videoed to determine the severity of seizure and latency to several seizure behaviour types (see *in vivo* analysis, below). Animals were filmed for half an hour after last sign of seizure, and then returned to their cage.

***In vivo* analysis**

[0059] Animals were observed during experimental procedures, but all analysis was performed offline on recorded video files using The Observer behavioural analysis software (Noldus, Netherlands). A seizure severity scoring system was used to determine the levels of seizure experienced by subjects (Table 1). All signs of seizure were detailed for all animals.

Table 1 Seizure severity scoring scale

Seizure score	Behavioural expression	Righting reflex
0	No changes to behaviour	Preserved
0.5	Abnormal behaviour (sniffing, excessive washing, orientation)	Preserved
1	Isolated myoclonic jerks	Preserved
2	Atypical clonic seizure	Preserved
3	Fully developed bilateral forelimb clonus	Preserved
3.5	Forelimb clonus with tonic component and body twist	Preserved
4	Tonic-clonic seizure with suppressed tonic phase	Lost
5	Fully developed tonic-clonic seizure	Lost
6	Death	

Latency from injection of PTZ to specific indicators of seizure development:

[0060] The latency (in seconds) from injection of PTZ to first myoclonic jerk (FMJ; score of 1), and to the animal attaining "forelimb clonus with tonic component and body twist" (score of 3.5)

were recorded. FMJ is an indicator of the onset of seizure activity, whilst >90% of animals developed scores of 3.5, and so is a good marker of the development of more severe seizures. Data are presented as the mean ± S.E.M. within an experimental group.

Maximum seizure severity:

[0061] This is given as the median value for each experimental group based on the scoring scale above.

Percentage mortality:

[0062] The percentage of animals within an experimental group that died as a result of PTZ-induced seizures. A score of 6 (death) automatically denotes that the animal also experienced tonic-clonic seizures.

Seizure duration:

[0063] The time (in seconds) from the first sign of seizure (typically FMJ) to either the last sign of seizure or, in the case of subjects that died, the time of death – separated into animals that survived and those that did not. This is given as the mean ± S.E.M. for each experimental group.

Statistics:

[0064] Differences in latencies and durations were assessed by one-way analysis of variance (ANOVA) with post-hoc Tukey's test. $P \leq 0.05$ was considered significant.

Results

[0065] Figure 1A shows that treatment with all of the compounds, both parents and metabolites resulted in a decrease the observed maximum seizure severity. CBDV significantly reduced seizure severity ($p \leq 0.01$).

[0066] Figure 1B shows that CBDV and 7-OH-CBDV had a significant effect on mortality of the animals. There was also a reduction in mortality observed for CBD and 7-OH-CBD.

[0067] Figure 1C demonstrates that the incidence of tonic clonic seizures was significantly reduced by CBDV and to a lesser extent 7-OH-CBDV.

[0068] Figure 1D demonstrates that the latency to the onset of seizures was also affected by the administration of cannabinoids. Indeed 7-OH CBD significantly reduced the latency to seizure onset ($p \leq 0.01$).

Conclusions

[0069] These results demonstrate that both 7-OH-CBD and 7-OH-CBDV show anti-convulsant action in the PTZ model of acute seizure.

[0070] Furthermore the ability 7-OH-CBD to significantly reduce the latency to onset of seizures and of 7-OH-CBDV to significantly reduce the median seizure severity, from 5 to 3 are remarkable as these data infer that the metabolites may be more effective than their parent compounds in certain aspects of seizure control.

[0071] The fact that the 7-OH-CBD and 7-OH-CBDV appear to be more potent than their parent cannabinoids, CBD and CBDV respectively, means that lower doses of the metabolites may be used in the treatment of epilepsy.

EXAMPLE 2: EFFICACY OF 7-HYDROXY CANNABIDIVARIN (7-OH-CBDV) IN THE MAXIMAL ELECTROSHOCK (MES) MODEL OF SEIZURE

Preparation of Test and Reference Compounds

[0072] The vehicle used in this study was 2:1:17 (ethanol:Cremophor:0.9% $^{w}/_{v}$ NaCl). The test compound used was 7-OH-CBDV. This was made to a solution at the highest concentration; then dissolved in ethanol before combination with Cremophor and 0.9% NaCl in the proportion described above. The 7-OH-CBDV was administered intraperitoneally at a volume of 10 ml/kg body weight.

Test System

[0073] Animal Species/Strain: Mouse/ICR, Microbiological grade: SPF, Inc. Sex: male, Age (at time of testing): 5-7 weeks old, Number of animals: about 5 animals per group. Temperature: 23 ± 2°C, Humidity: 60 ± 10%, Light conditions: 7 AM to 7 PM for the light period, 7 PM to 7 AM for the dark period. Chow and water: Free access to CRF-1 (Oriental Yeast Co, Ltd) and tap water.

Experimental Procedures

[0074] One day before each experiment, mice were weighed and randomized into several groups in each test. On the morning of the experiment day, body weight was measured in order to calculate the administration volume of each animal. Vehicle, 7-OH-CBDV or CBDV was interperitoneally administered 30 minutes before electric stimuli. Maximal electroshock seizures (MES) in mice was induced by a stimulator (UGO BASILE ECT UNIT 7801, Italia) using a current of 30 mA delivered with a pulse frequency of 100 Hz for 200 msec through earlap electrodes. The mice were observed for 10 seconds and the incidence of tonic hindlimb extension was noted.

Statistical Analysis

[0075] All statistical analyses were performed using SAS Software for Windows, Release 9.1. The difference of the number (hindlimb extension or deaths) in each group was assessed using two-tailed Fisher's exact test. The differences were considered statistically significant, when the p value was less than 0.05.

Results

[0076] Table 2 below demonstrates that the data obtained for the 7-OH-CBDV was statistically significant when compared to vehicle. Similarly to the parent compound, CBDV, 7-OH-CBDV at both doses produced a decrease in 90% of tonic clonic convulsions.

Table 2. Percentage decrease in tonic clonic convulsions

Compound (dose)	**Percentage decrease in tonic clonic convulsions compared with vehicle**
Vehicle	-
7-OH-CBDV (150mg/kg i.p.)	90%***
7-OH-CBDV (200mg/kg i.p.)	90% ***
CBDV (200mg/kg i.p.)	82% ***

*** - = $p < 0.001$

Conclusion

[0077] These data further demonstrate the surprising ability of the primary metabolite of CBDV, 7-OH-CBDV to produce anti-convulsant effects.

References:

Amada *et al.* (2013) PeerJ, 2013, pages 1-18 "Cannabidivarin (CBDV) suppresses pentylenetetrazole (PTZ)-induced increases in epilepsy-related gene expression."

Ames FR and Cridland S (1986). "Anticonvulsant effects of cannabidiol." S Afr Med J 69:14.

Carlini *et al.* (1981) Journal of Clinical Pharmacology, vol. 21, No. 8/9, 1981, pages 417S-427S "Hypnotic and antiepileptic effects of cannabidiol."

Consroe P, Martin P, Eisenstein D. (1977). "Anticonvulsant drug antagonism of delta-9-tetrahydrocannabinol induced seizures in rabbits." Res Commun Chem Pathol Pharmacol. 16:1-13

Consroe P, Benedicto MA, Leite JR, Carlini EA, Mechoulam R. (1982). "Effects of cannabidiol on behavioural seizures caused by convulsant drugs or current in mice." Eur J Pharmaco. 83: 293-8

Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimental C, Gagliardi R *et al.* (1980). "Chronic administration of cannabidiol to healthy volunteers and epileptic patient." Pharmacology. 21:175-85

Hill *et al.* (2012) British Journal of Pharmacology, vol. 167, No. 8, 2012, pages 1629-1642 "Cannabidivarin is anticonvulsant in mouse and rat."

Jones *et al.* (2012) Seizure, vol. 21, No. 5, 2012, pages 344-352 "Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures."

Mechoulam R and Carlini EA (1978). "Toward drugs derived from cannabis." Die naturwissenschaften 65:174-9.

CLAIMS

1. 7-hydroxy-cannabidivarin (7-OH-CBDV) in a pure, isolated or synthetic form for use as a medicament.

2. 7-hydroxy-cannabidivarin (7-OH-CBDV) in a pure, isolated or synthetic form for use in the treatment of epilepsy.

3. 7-hydroxy-cannabidol (7-OH-CBD) in a pure, isolated or synthetic form for use in the treatment of epilepsy.

4. 7-hydroxy-cannabidivarin (7-OH-CBDV) in a pure, isolated or synthetic form for use according to claim 2, in combination with 7-hydroxy-cannabidol (7-OH-CBD) in a pure, isolated or synthetic form.

5. A pharmaceutical composition comprising 7-hydroxy-cannabidol (7-OH-CBD) and / or 7-hydroxy-cannabidivarin (7-OH-CBDV) with a pharmaceutically acceptable carrier.

6. A pharmaceutical composition comprising 7-hydroxy-cannabidol (7-OH-CBD) and / or 7-hydroxy-cannabidivarin (7-OH-CBDV) with a pharmaceutically acceptable carrier for use in the treatment of epilepsy.

7. A pharmaceutical composition as claimed in claim 6, wherein the 7-OH-CBD and / or the 7-OH-CBDV are used in combination with one or more concomitant anti-epileptic drugs (AED).

8. A pharmaceutical composition as claimed in claim 7, wherein the one or more AED is selected from the group consisting of: clobazam; levetiracetam; topiramate; stiripentol; phenobarbital; lacsamide; valproic acid; zonisamide; perampanel; and fosphenytoin.

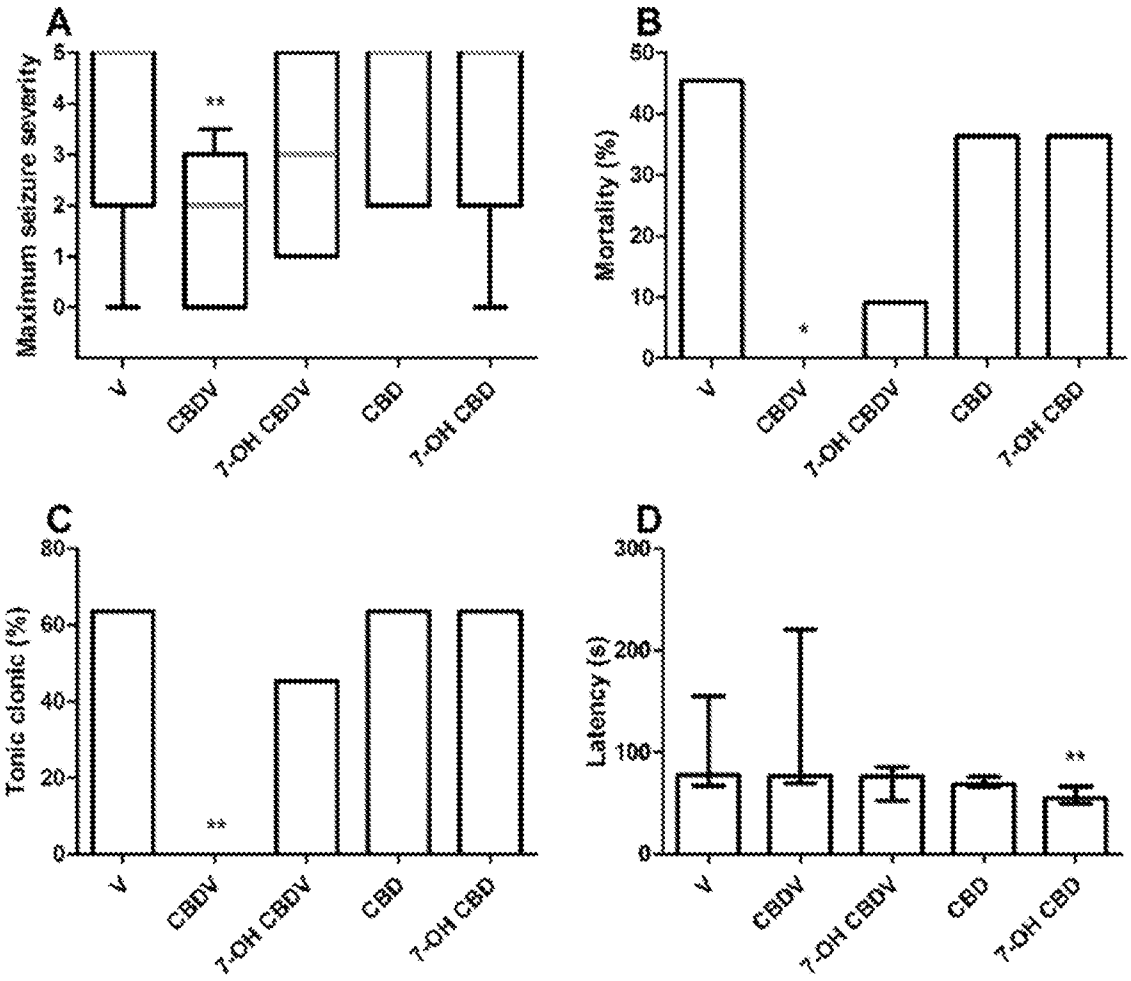
9. A pharmaceutical composition as claimed in claim 6, wherein the dose of 7-OH-CBD and / or the 7-OH-CBDV is between 1 and 2000 mg/kg.

10. A pharmaceutical composition as claimed in claim 6, wherein the 7-OH-CBD is used in combination with the 7-OH-CBDV, the 7-OH-CBD may be formulated for administration separately, sequentially or simultaneously with the 7-OH-CBDV or the combination may be provided in a single dosage form.

5

11. A method of treating epilepsy comprising administering a therapeutically effective amount of 7-hydroxy-cannabidiol (7-OH-CBD) and / or 7-hydroxy-cannabidivarin (7-OH-CBDV) to a subject in need thereof.

Figure 1. CBDV and CBD, and their 7-OH metabolites in the PTZ model of acute seizure



INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/051894

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/05 A61P25/08
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/95899 A2 (YISSUM RES DEV CO [IL]; MECHOULAM RAPHAEL [IL]; TCHILIBON SUSANA [IL];) 20 December 2001 (2001-12-20) cited in the application abstract page 1, line 1 - line 4 page 2, line 12 - page 3, line 21 example 15 page 24, line 8 - line 14 claims 1-9	3,5-7,9, 11
A	GB 2 487 183 A (GW PHARMA LTD [GB]; OTSUKA PHARMA CO LTD [JP]) 18 July 2012 (2012-07-18) abstract claims 1-19	1-11

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 August 2015	26/08/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Taylor, Mark

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2015/051894

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2011/121351 A1 (GW PHARMA LTD [GB]; OTSUKA PHARMA CO LTD [JP]; WHALLEY BENJAMIN [GB];) 6 October 2011 (2011-10-06) cited in the application abstract ----- GB 2 495 118 A (GW PHARMA LTD [GB]; OTSUKA PHARMA CO LTD [JP]) 3 April 2013 (2013-04-03) cited in the application abstract claims 1-22 ----- WO 2012/093255 A1 (GW PHARMA LTD [GB]; OTSUKA PHARMA CO LTD [JP]; WHALLEY BENJAMIN [GB];) 12 July 2012 (2012-07-12) abstract claims 1-12 -----	1-11 1-11 1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2015/051894

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0195899 A2	20-12-2001	AT 309798 T	15-12-2005
		AU 7445901 A	24-12-2001
		AU 2001274459 B2	07-07-2005
		CA 2411831 A1	20-12-2001
		DE 60115029 D1	22-12-2005
		DE 60115029 T2	03-08-2006
		DK 1289517 T3	03-04-2006
		EP 1289517 A2	12-03-2003
		ES 2254432 T3	16-06-2006
		IL 136839 A	10-12-2006
		JP 2004503498 A	05-02-2004
		US 2003166727 A1	04-09-2003
		WO 0195899 A2	20-12-2001
GB 2487183 A	18-07-2012	NONE	
WO 2011121351 A1	06-10-2011	AR 080730 A1	02-05-2012
		AU 2011234225 A1	08-11-2012
		CA 2794620 A1	06-10-2011
		CN 103025325 A	03-04-2013
		EA 201290975 A1	30-04-2013
		EP 2552430 A1	06-02-2013
		JP 2013523708 A	17-06-2013
		KR 20130065646 A	19-06-2013
		NZ 602925 A	28-11-2014
		SG 184236 A1	30-10-2012
		TW 201138759 A	16-11-2011
		US 2012004251 A1	05-01-2012
		WO 2011121351 A1	06-10-2011
GB 2495118 A	03-04-2013	AR 088047 A1	07-05-2014
		AU 2012314129 A1	20-03-2014
		CA 2845677 A1	04-04-2013
		CN 103826621 A	28-05-2014
		CO 6900149 A2	20-03-2014
		EA 201490711 A1	30-09-2014
		EP 2760440 A1	06-08-2014
		GB 2495118 A	03-04-2013
		GB 2514054 A	12-11-2014
		JP 2014528402 A	27-10-2014
		KR 20140069102 A	09-06-2014
		TW 201318620 A	16-05-2013
		US 2014243405 A1	28-08-2014
		WO 2013045891 A1	04-04-2013
WO 2012093255 A1	12-07-2012	AR 084559 A1	22-05-2013
		CA 2822907 A1	12-07-2012
		CN 103391775 A	13-11-2013
		CO 6731122 A2	15-08-2013
		EP 2661263 A1	13-11-2013
		GB 2487712 A	08-08-2012
		JP 2014501271 A	20-01-2014
		KR 20130132972 A	05-12-2013
		RU 2013136378 A	10-02-2015
		SG 191835 A1	30-08-2013
		TW 201306826 A	16-02-2013
		US 2013296398 A1	07-11-2013
		WO 2012093255 A1	12-07-2012

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2015/051894

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
----------			