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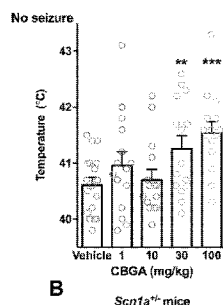
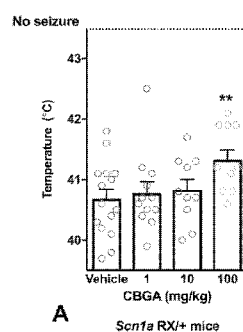
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(54) Title: METHODS AND COMPOSITIONS FOR TREATING OR PREVENTING SEIZURES

Figure 1



(57) Abstract: The present invention relates to cannabigerolic acid and compositions and kits thereof for use in the treatment and prevention of seizures, and to methods of preventing or treating seizures, treating epilepsy and controlling cell hyperexcitability using cannabigerolic acid alone or in combination with other cannabinoids or anticonvulsants such as clobazam.



Methods and compositions for treating or preventing seizures

Field of the invention

The present invention relates to novel methods and compositions for the treatment or prevention of seizures in an individual.

5 Related application

This application claims priority from Australian provisional application AU 2017904072, the entire contents of which are hereby incorporated by reference.

Background of the invention

Epilepsy is a chronic neurological disorder presenting a wide spectrum of
10 diseases that affects approximately 50 million people worldwide.

Epilepsy occurs in approximately 1% of the population worldwide, with around 3-3.5% of individuals experiencing some form or episode of epilepsy at some point in their lives. In around 70% of cases, epilepsy can be adequately managed with the use of various anticonvulsant drugs. However, there are significant side-effects associated with currently approved anticonvulsant agents, including motor effects and sedation, which severely limits their use.

Approximately 30% of epilepsy cases are so-called “intractable” epilepsies, where the patient does not respond to conventional pharmacological therapies. Childhood epilepsies, such as Lennox Gastaut syndrome, Dravet syndrome and infantile spasms, are particularly known for being resistant to currently available treatments.

Intractable or treatment-resistant epilepsy was defined in 2009 by the International League Against Epilepsy (ILAE) as “failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug (AED) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom” (Kwan et al., 2009).

Intractable epilepsies occur early in life and their large seizure burden is associated with increased mortality and developmental delays in cognition, speech and motor skills. 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
5 number of epileptic adults per population.

Current treatments for childhood epilepsy are grossly inadequate and many families, relying on anecdotal information relating to the anticonvulsant properties of cannabis, resort to the use of illegal cannabis extracts out of desperation.

There is a need for more effective anticonvulsant therapies, and in particular, for
10 therapies which are useful for treating or preventing intractable forms of epilepsy.

Reference to any prior art in the specification is not an acknowledgment or suggestion that this prior art forms part of the common general knowledge in any jurisdiction or that this prior art could reasonably be expected to be understood, regarded as relevant, and/or combined with other pieces of prior art by a skilled person
15 in the art.

Summary of the invention

The present invention provides a method for preventing or reducing the frequency of seizures in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of cannabigerolic acid (CBGA) thereby
20 preventing or reducing the frequency of seizures in the individual.

The present invention provides a method for reducing the severity of seizures in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of cannabigerolic acid (CBGA) thereby reducing the severity of seizures in the individual.

25 The present invention also provides a method of treating epilepsy in an individual, the method comprising administering to the individual, a therapeutically effective amount of CBGA, thereby treating epilepsy in the individual.

Further, the present invention provides a method of controlling cell hyperexcitability associated with or caused by a neurological disorder in an individual,

comprising administering to the individual, a therapeutically effective amount of CBGA, thereby controlling cell hyperexcitability associated with or caused by a neurological disorder in the individual.

5 The neurological disorder that is associated with cell hyperexcitability or causing cell hyperexcitability may be a disorder associated with epileptogenesis.

In any embodiment of the present invention, the seizures requiring treatment, prevention or reduced frequency are epileptic seizures.

10 The epileptic seizures may occur in an individual who has been diagnosed with epilepsy, or who is suspected of having epilepsy. Alternatively, the epileptic seizures may occur in an individual who does not have epilepsy but has previously experienced an epileptic seizure.

15 In any embodiment of the invention, the seizures may be associated with an epileptic syndrome selected from the group consisting of: idiopathic epilepsy, Dravet syndrome, Lennox-Gastaut syndrome, epilepsy characterised by infantile spasms, febrile seizures, childhood absence seizures and other forms of pharmacoresistant epilepsy.

In any embodiment of the present invention, the seizures are selected from the group consisting of: convulsive, focal, absence, tonic-clonic, tonic, clonic, myoclonic, atonic, and reflex.

20 In any embodiment of the invention, the seizures may be caused by, induced by, follow from, or be associated with one or more of the following environmental or physiological stimuli: heat, stress, alcohol abuse, lack of sleep, loud noises, flickering lights, trauma including head trauma, stroke, tumours, and infection of the central nervous system.

25 In alternative embodiments, the seizures may have no known cause and may be spontaneous. In any embodiment of the present invention, the seizures may be associated with one or more genetic mutations.

The seizures requiring prevention or treatment according to the present invention may occur in adult individuals or in infants or pre-adolescent individuals.

In any embodiment of the present invention, administration of CBGA may also comprise the administration of an additional anticonvulsant agent.

The additional anticonvulsant agent may be selected from known anti-epileptic drugs (AEDs) including acetazolamide, carbamazepine, clobazam, clonazepam, 5 eslicarbazepine acetate, ethosuxamide, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam, oxcarbazepine, perampanel, piracetam, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide. In a preferred embodiment, the additional anticonvulsant agent is clobazam. In an alternative preferred embodiment, the 10 additional anticonvulsant agent is sodium valproate.

In any embodiment of the present invention, the method comprises the administration of an additional cannabinoid. The additional cannabinoid may be selected from the group consisting of: cannabidivarin (CBDV), cannabidiolic acid (CBDA), cannabidiol (CBD) and THC.

15 The present invention also provides for the use of CBGA in the manufacture of a medicament for preventing or reducing the frequency of seizures in an individual.

Still further, the present invention contemplates compositions and kits comprising CBGA for preventing or reducing the frequency of seizures in an individual, and one or more pharmaceutically acceptable excipients. The compositions may also be for 20 reducing the severity of seizures in an individual.

In any embodiment of the present invention, the CBGA is in the form of a plant extract. The plant extract may contain CBGA in substantially purified form, for example, wherein the plant extract contains at least 90%, preferably more than 95% w/w of CBGA. Preferably the plant extract has little or no psychoactive substances present (for 25 example, less than 1% THC).

In alternative embodiments of the present invention, the CBGA may be synthetically produced.

In any method, use or composition of the present invention, a structural analog or functionally equivalent variant of CBGA may be used.

As used herein, except where the context requires otherwise, the term "comprise" and variations of the term, such as "comprising", "comprises" and "comprised", are not intended to exclude further additives, components, integers or steps.

5 Further aspects of the present invention and further embodiments of the aspects described in the preceding paragraphs will become apparent from the following description, given by way of example and with reference to the accompanying drawings.

Brief description of the drawings

Figure 1 CBGA displayed anticonvulsant properties in 2 genetic mouse models of drug-resistant epilepsy. Threshold temperature of individual mice for generalised tonic-clonic seizure (GTCS) induced by hyperthermia following acute treatment with varying doses of CBGA administered as a single i.p. injection. CBGA significantly increased the temperature threshold for thermally induced seizures in both (A) Scn1a^{RX/+} (at 100 mg/kg) and (B) Scn1a^{+/-} mice (at 30 mg/kg and 100 mg/kg). The average temperatures of seizure induction are represented by the bar graph and error bars show the SEM, with n=11-18 per group (**P < 0.01, ***P < 0.001; Mantel-Cox log-rank).

Figure 2 CBD displayed anticonvulsant properties in a genetic mouse model of drug-resistant epilepsy but only at 100 mg/kg. Threshold temperature of individual mice for GTCS induced by hyperthermia following acute treatment with varying doses of CBD administered as a single i.p. injection. Treatment with CBD was only effective at 100 mg/kg in increasing the body temperature of a GTCS in Scn1a^{+/-} mice. The average temperatures of seizure induction are represented by the bar graph and error bars show the SEM, with n=16-17 per group (vehicle versus 100 mg/kg ** P < 0.01; Mantel-Cox log-rank).

Figure 3 CBDA displayed anticonvulsant properties in only 1 of the 2 genetic mouse models of drug-resistant epilepsy. Threshold temperature of individual mice for GTCS induced by hyperthermia following acute treatment with varying doses of CBDA administered as a single i.p. injection. In the (A) Scn1a^{RX/+} mice CBDA at doses 10 and 30 mg/kg increased the temperature threshold for thermally induced seizures but had no effect in the (B) Scn1a^{+/-} mice. The average

temperatures of seizure induction are represented by the bar graph and error bars show the SEM, with n=11-16 per group (*P < 0.05; Mantel-Cox log-rank).

Figure 4 The combination of CBGA and clobazam significantly potentiated the anticonvulsant properties of either drug administered alone in a

5 **genetic mouse model of drug-resistant epilepsy.** Threshold temperature of individual mice for GTCS induced by hyperthermia following acute treatment with clobazam and CBGA administered individually or as a combination in an i.p. injection. Combination clobazam and CBGA treatment resulted in a significantly improved response to thermal seizure induction compared to treatment with CBGA or clobazam alone, with n = 15 - 34
10 per group (** P < 0.005, **** P < 0.0001, log-rank Mantel-Cox). All treatment groups have a significantly increased temperature threshold for thermally induced seizures compared to vehicle treatment (clobazam vs. vehicle, *** P < 0.0005; CBGA vs. vehicle, * P < 0.05; clobazam and CBGA combination vs. vehicle, **** P < 0.0001; log-rank Mantel-Cox).

15 Detailed description of the embodiments

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

20 Reference will now be made in detail to certain embodiments of the invention. While the invention will be described in conjunction with the embodiments, it will be understood that the intention is not to limit the invention to those embodiments. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined
25 by the claims.

One skilled in the art will recognize many methods and materials similar or equivalent to those described herein, which could be used in the practice of the present invention. The present invention is in no way limited to the methods and materials described. It will be understood that the invention disclosed and defined in this
30 specification extends to all alternative combinations of two or more of the individual

features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

For purposes of interpreting this specification, terms used in the singular will also include the plural and vice versa.

5 Advances in the understanding of the body's internal 'endocannabinoid' system has led to the suggestion that cannabis-based medicines may have the potential to treat this disorder of hyperexcitability in the central nervous system. Given the inadequacy of current treatments for childhood epilepsy, many families resort, out of desperation, to using illegal cannabis extracts to try to manage the frequency and severity of seizures in
10 infants. Anecdotal reports indicate that cannabis extracts show some anticonvulsant efficacy.

Cannabis extract is a complex mixture containing over 100 cannabinoid compounds and has been ascribed both proconvulsant and anticonvulsant effects. Therefore, the specific compounds responsible for anticonvulsant activity remain to be
15 fully elucidated.

The present inventors are the first to demonstrate that the cannabinoid compound cannabigerolic acid (CBGA), is a useful anticonvulsant and provides superior results to previously described anticonvulsant cannabinoids.

In particular, CBGA has been shown by the inventors to be effective for reducing
20 the frequency of seizures in models of intractable childhood epilepsy (specifically, by increasing tolerability to thermally-induced seizures in two genetically distinct mouse models of Dravet syndrome). Thus, the present invention provides for a novel and superior therapy for the treatment and management of epilepsy in cases of epilepsy which have previously not been possible to treat.

25 In addition, the inventors have shown that CBGA is useful as an anticonvulsant when combined with a conventional anticonvulsant (for example, clobazam), whereby the CBGA potentiates the efficacy of the conventional anticonvulsant. Thus, CBGA is expected to have utility both as an anticonvulsant when used on its own, but also when used as an adjunct therapy to conventional anticonvulsant medications. Moreover, the
30 potentiating effect of CBGA means that the dosage of conventional anticonvulsant

medication administered to the individual can be reduced, thereby mitigating any unwanted side effects (such as sedation, insomnia, gastrointestinal and others).

Further, the inventors have shown that CBGA is more efficacious than some known anticonvulsant drugs, such cannabidiol (CBD). While CBD has recently been
5 shown to reduce seizures in a phase III clinical trial in Dravet syndrome patients (Devinsky et al., 2017, N Eng J Med, 376: 2011-2020), the inventors have shown that CBD modulated thermally-induced seizures in an accepted model of intractable epilepsy, in circumstances where CBGA displayed anticonvulsant properties at a lower dose. In addition, the inventors have shown that another anticonvulsant, cannabidiolic
10 acid (CBDA) was only effective on one mouse line used to model intractable epilepsy, while CBGA was effective in the two mouse lines investigated.

The results obtained by inventors demonstrate that CBGA has superior anticonvulsant properties compared to some known anticonvulsant compounds. Further, the results underscore the reliability of CBGA as an anticonvulsant in models of
15 epilepsy representing traditionally difficult-to-treat, drug-resistant forms of the disease.

In addition to providing a superior outcome in reducing the severity and frequency of seizures in drug-resistant models of epilepsy, CBGA does not appear to have any overt toxicity or sedative effects. This provides a further advantage over currently existing treatments for epilepsy and indicates that CBGA may be preferable to
20 current treatments, even those which are not classified as intractable.

Treatment of seizures

The present invention relates to methods of treating seizures, including reducing the frequency and severity of a seizure in an individual.

The seizures may be epileptic seizures or non-epileptic seizures. An epileptic
25 seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

A non-epileptic seizure mimics an epileptic seizure but does not involve abnormal rhythmic discharges of neurons. Non-epileptic seizures may have physiological or psychological causes.

In a preferred embodiment of the present invention, the seizures are epileptic seizures. Epileptic seizures may occur in individuals who have an epilepsy syndrome, or may occur in individuals who do not have epilepsy syndrome, but have a seizure that is a result of a trauma such as a head injury, drug overdose, toxin, eclampsia or due to high fever (febrile convulsions). Epilepsy is a group of neurological disorders that are characterized by long-term risk of epileptic seizures. For example, while an epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain, "epilepsy" is a disease characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. In other words, a seizure is an event and epilepsy is the disease involving recurrent unprovoked seizures.

The skilled person will be familiar with the conventional definition of "epilepsy" in the context of the use of this term to define epilepsy syndrome. For example, the International League Against Epilepsy (ILAE) proposed that epilepsy be considered to be a disease of the brain defined by any of the following conditions:

- 1) at least two unprovoked (or reflex) seizures occurring >24 h apart;
- 2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years;
- 3) diagnosis of an epilepsy syndrome.

Epilepsy is considered to be resolved for individuals a) who had an age-dependent epilepsy syndrome but are now past the applicable age or b) who have remained seizure-free for the last 10 years, and have not required anti-seizure medication for the last 5 years.

The present invention finds particular application in methods for treating patients with epilepsy, particularly intractable epilepsy.

Medically intractable epilepsy has been defined as persistent seizure activity, which, despite maximal medical treatment, remains sufficiently debilitating to warrant

the risks of surgery. As described below, this definition has different meanings in pediatric and adult epilepsy populations.

Adults often have a low frequency of seizures, so it is not uncommon for adults to be diagnosed with intractable epilepsy, even at a frequency of only one seizure a month. As a result, the assessment process in these patients often involves a prolonged process wherein patient response to different medications and doses are evaluated in both mono- and polytherapy.

In contrast, certain pediatric seizure syndromes are uniquely defined by their seizure intractability, (e.g.) congenital malformations such as hemimeganencephaly, Sturge-Weber syndrome, or Rasmussen's encephalitis. It is not unusual for such pediatric patients to undergo 40-100 seizures a day, despite maximal medical therapy. Medical regimens for these conditions often fail, demonstrating poor responses to first- and second-line medications, as well as to polytherapy. Because of the high frequency of seizures, trials of therapeutic regimens can be tested in an expeditious manner, thereby facilitating an accurate assessment of the best mode for treatment.

Many factors may predispose a child to the development of seizures and epilepsy, including: genetic and congenital malformations, intrauterine and postnatal insults, anoxic injuries, infections (viral and bacterial), and vascular malformations and compromise due to, for example, ischemia, trauma, and tumors.

Intractable epilepsy is broadly characterized by:

1) a high incidence of partial seizure followed by a generalized seizure (particularly in temporal lobe epilepsy);

2) a high incidence of symptomatic epilepsy caused by an organic lesion in the brain;

3) a long duration time between onset of disease and diagnosis, and a high frequency of seizures; and

4) a high incidence of status epilepticus in the case history.

The features of intractable epilepsy suggest that the temporal lobe is of particular significance in the etiology of intractable epilepsy. Moreover, as epilepsy progresses in a patient, it can evolve to become intractable. Intractable epilepsy may also present clinically following trauma, brain surgery, or relapse following surgery for epilepsy.

- 5 Intractable epilepsy is categorized into three clinical types, including: localization-related epilepsies and syndromes, generalized epilepsies and syndromes, and indeterminate epilepsies and syndromes, whether focal or generalized.

Examples of localization-related epilepsies and syndromes include temporal lobe epilepsies, frontal lobe epilepsies, and multi-lobe epilepsies. Temporal lobe epilepsies
10 and frontal lobe epilepsies are typical examples of intractable epilepsy. Multi-lobe epilepsies are thought to involve two or more lobes. Examples of generalized epilepsies and syndromes include Lennox-Gastaut syndrome, West syndrome, and myoclonic epilepsy. An example of indeterminate epilepsies and syndromes, whether focal or
15 generalized, is severe myoclonic epilepsy in infancy, which exhibits a variety of seizure types. In particular, tonic-clonic seizures occur frequently, which often lead to status epilepticus. In view of the severity of such conditions, treatment at early age by a medical practitioner who specializes in epilepsy is essential to the well-being of the patient.

Seizures associated with intractable epilepsy have been classified into
20 categories, which include, but are not limited to, tonic seizures, tonic-clonic seizures, atypical absence seizures, atonic seizures, myoclonic seizures, clonic seizures, simple partial seizures, complex partial seizures, and secondary generalized seizures.

Temporal lobe epilepsy is a type of intractable epilepsy characterized by a seizure focus in the temporal lobe. It is categorized with symptomatic and localization-
25 related epilepsies, which also include frontal lobe epilepsies, parietal lobe epilepsies, and occipital lobe epilepsies, based on the international classification of epilepsy. The syndromes of temporal lobe epilepsy vary in accordance with the locale of the seizure focus and the type of seizure propagation. Of note in this regard, the temporal lobe has an anatomically complex structure including the neocortex, allocortex, and paleocortex.
30 Temporal lobe epilepsy generally causes complex partial seizures, but may also induce simple partial seizures, secondary generalized seizures, and combinations thereof.

Simple partial seizures include autonomic and mental symptoms, as well as sensory symptoms involving olfaction, audition, or vision. Complex partial seizures often exhibit motion stopping followed by eating-function automatism, and are divided into amygdala-hippocampus seizures and lateral temporal lobe seizures according to
5 localization. In the case of temporal lobe epilepsy, 70-80% of the seizures are localized to the hippocampus, in which aura, motion stopping, lip automatism, and clouding of consciousness are successively developed to result in amnesia. When the focus is in the amygdala, autonomic symptoms such as dysphoria in the epigastrium, phobia, and olfactory hallucination may result. Lateral temporal lobe seizures include auditory
10 illusion, hallucination, and speech disturbance when the focus is in the dominant hemisphere. Temporal lobe epilepsy exhibits a long-term psychosis-like state in addition to other symptoms and recognition-and-memory disorder more frequently than do other epilepsies. Treatment of temporal lobe epilepsy has routinely been directed to pharmacotherapy employing of a combination of drugs at maximum tolerated dose or
15 through surgical treatment.

Cortex epilepsy, another type of intractable epilepsy, is associated with a focus in the cerebral cortex, and is classified as a symptomatic epilepsy belonging to localization-related (focal) epilepsies and syndromes. In the international classification, seizures associated with cortex epilepsy are classified as simple partial seizures, in the
20 absence of a reduction in consciousness. Cortex epilepsies are usually caused by a cerebral tumor, an aftereffect of cephalotrauma or a perinatal insult. Based on the focus, cortex epilepsy is classified as temporal lobe epilepsy, parietal lobe epilepsy, or occipital lobe epilepsy.

Traumatic epilepsy is another type of intractable epilepsy. Traumatic epilepsy, in
25 a broad sense, is divided into two categories, "early epilepsy" and "late epilepsy". Early epilepsy is not considered a true epilepsy because it is caused by stimulation of the brain induced by convulsion within a week after suffering a trauma. In contrast, late epilepsy is considered a true epilepsy in that it presents one or more weeks after suffering a trauma.

30 Most of the traumatic epilepsies are associated with focus formation at the damaged portion of the cortex, and are viewed as typical examples of partial epilepsies.

Treatment of traumatic epilepsy is, therefore, directed to pharmacotherapy. Since the onset and progression of symptoms in different individuals are diverse, however, many cases become intractable through administration of an antiepileptic agent.

5 Secondary generalized seizure is one of the symptoms associated with intractable epilepsy. It is a type of partial seizure, which exhibits a clinical syndrome and an electrocephalogram feature detected as excitation of neurons with initiation of the seizure in a limited portion of one cerebral hemisphere. A secondary generalized seizure is initiated as a simple partial seizure (without impairment of consciousness) or a complex partial seizure (with impairment of consciousness), and develops to general
10 convulsion induced through secondary generalization. The main symptom thereof is a convulsion such as a tonic-clonic seizure, a tonic seizure, or a clonic seizure.

Intractable epilepsy also comprises the symptom of complex partial seizure, a term which refers to a partial seizure with impairment of consciousness. In the international classification draft (1981), the complex partial seizure is defined as a
15 seizure "with impairment of consciousness exhibiting an electrocephalogram during a seizure in which unilateral or bilateral electric discharge attributed to a focus in a diffuse or a temporal or front-temporal portion."

The neuromechanism responsible for complex partial seizure is thought to include the amygdala, hippocampus, hypothalamus, and parolfactory cortex, in addition
20 to the frontal and temporal lobes. The seizures typically last 1-2 minutes or slightly longer, and the onset and cessation of the seizures are not abrupt, but gradual. Examples of complex partial seizures include (1) seizures with reduction of consciousness (gradually evolving impairment of consciousness, arrest of motion, speech, and reaction, and amnesia); (2) cognitive seizures (deja-vu, jamais-vu, ideo-
25 seizures); (3) affective seizures (fear, anger, emptiness, strangeness, delight, joy); (4) psycho-sensory seizures (hallucinations; visual, auditory, gustatory, olfactory, cenesthesia); and (5) psycho-motor seizures (automatism, lip-licking, chewing, stereotypy).

In status epilepticus, another type of intractable epilepsy, consciousness is lost
30 and cannot be restored during the course of the seizure. Such seizures can last for 30 or more minutes and can become repetitive. Of note, any type of seizure may evolve to

status epilepticus. The most common example of which is a tonic-clonic seizure, and status epilepticus thereof is fatal and must be treated immediately. In many cases, cessation of an antiepileptic agent induces status epilepticus. Thus, an antiepileptic agent is administered intravenously while the central nervous system disorder and
5 whole-body conditions are monitored and controlled. In that status epilepticus convulsions are known to lead to intractable epilepsy, immediate and appropriate action is required for the diagnosis of and first aid for a status epilepticus convulsion. Suppression of a convulsive seizure at the early stage is an important key to aftercare.

The terms 'treatment' or 'treating' of an individual or subject patient includes the
10 application or administration of CBGA or composition comprising CBGA, as described herein, to an individual with the purpose of abating, delaying, slowing, stabilizing, curing, healing, alleviating, relieving, altering, remedying, lessening the rate of worsening, ameliorating, improving, improving an individual's physical or mental well-being, lessening the severity of a seizure, the frequency of seizures, or the risk of (or
15 susceptibility to) having a seizure.

The term "treating" refers to any indication of success in the treatment including any of the objective or subjective parameters outlined above. For example, success may be determined by a reducing in the severity or frequency of seizures, or a reduction in the threshold stimulus required to elicit a seizure.

20 As used herein, 'preventing' or 'prevention' is intended to refer to at least the reduction of likelihood or the risk of (or susceptibility to) suffering a seizure. As such, the present invention provides for prophylactic treatment of seizures. Biological and physiological parameters for identifying such patients are provided herein and are also well known by physicians. In the context of the present invention, preventing a seizure
25 may refer to reducing the likelihood that an individual will have a seizure in response to a known trigger, or the risk of an individual who is genetically predisposed to seizures having a spontaneous seizure.

As used herein, a "subject" or an "individual" is a human subject, including a patient, eligible for treatment for seizures, including epileptic seizures and non-epileptic
30 seizures.

The individual may have been diagnosed with epilepsy syndrome, or may have previously suffered one or more epileptic seizures indicative of epilepsy. The individual requiring treatment may be an adult or a child.

In any embodiment of the invention, the individual requiring treatment or
5 prevention is an individual who is determined to be at risk of epileptic seizures on the basis of a genetic marker which indicates predisposition. Examples of genetic markers which are indicative of a risk of seizures include: gene mutations in SCN1A (Dravet syndrome), PCDH19, SCN2A, SCN8A, SCN9A, SCN10A, SCN1B, KCNA2_[JA1], KCNB1, KCNH5, KCNQ2, KCNQ3, KCNT1, KCNC1, CACNA1A, CACNA1H, CACNB4, CLCN2,
10 CLCN4, CACNA2D2, CHRNA2, CHRNA4, CHRNA7, CHRNA2, GRIN1, GRIN2A, GRIN2B, GRIN2D, FRRS1L, GABRA1, GABRB1, GABRB2, GABRG2, GABRD, HCN1, ATPA3, SLC12A5, STXBP1, HCN1, CHD2, KCNJ10, KCNJ11, and KCNMA1.

The skilled person will also be familiar with methods for determining whether an individual has a relevant genetic mutation which is associated with or indicative of a risk
15 of seizures (such as for example, performing a genetic test on a DNA sample obtained from the individual).

In any embodiment of the invention, the seizures may be caused by, induced by, follow from, or be associated with one or more of the following environmental or physiological stimuli: heat, stress, alcohol abuse, lack of sleep, loud noises, flickering
20 lights, trauma including head trauma, stroke, tumours, and infection of the central nervous system.

Prophylaxis may include continuous therapy or may be commenced after the individual has suffered a recent seizure. Prophylaxis may also include administration of CBGA to an individual who is at risk of repeated seizures, after the individual is exposed
25 to an environmental or physiological stimuli that is known to result in seizures.

As used herein, reducing the frequency of seizures refers to reducing the likelihood that an individual will develop a seizure, whether spontaneous or in response to common environmental or physiological stimuli (such as stress, heat, noise, lack of sleep and the like). For example, the methods of the present invention may result in a
30 10%, 20%, 30%, 40%, 50%, 60%, 60%, 70%, 80%, 90% or 100% reduction in the

frequency of seizures in an individual, as compared with the frequency of seizures observed when the individual is not being treated according to the present invention.

As used herein, reducing the severity of seizures may refer to reducing the seizure frequency and duration. Reduction in seizure severity may also be any
5 quantitative or qualitative change in seizure semiology, EEG trace or other brain imaging result that indicates a reduction in disease burden in the individuals following treatment in accordance with the present invention. In addition, the skilled person will be familiar with methods for monitoring for a reduction in seizure burden and severity by: measuring the frequency of convulsive seizures, obtaining The Caregiver Global
10 Impression of Change, including in relation to seizure duration and severity, and/or measuring the number of hospitalisations due to epilepsy.

The Caregiver Global Impression of Change is a 7-point caregiver rated scale ranging from 1 (very much improved) to 7 (very much worse). Change is defined as a score of 1 (very much improved), 2 (much improved), 3 (a little improved), 4 (no
15 change), 5 (a little worse), 6 (much worse) or 7 (very much worse) on the scale.

The skilled person will be familiar with the methods used in the art for identifying an individual requiring treatment in accordance with the present invention. For example, the skilled person will be familiar with methods for diagnosing seizures, including epileptic and non-epileptic seizures and epilepsy syndrome. Examples of methods in
20 common use of diagnosis of epilepsy or for diagnosis of risk of seizure include electroencephalograms (EEG) to observe abnormal patterns of brain wave activity and neuroimaging (including CT scan and MRI) look for any defects or injuries in the brain (including bleeding and swelling). These tests may be performed after the individual experiences an initial seizure or after the individual has experienced more than two
25 seizures.

The skilled person will also be familiar with distinguishing between epileptic seizures and non-epileptic seizures which are unlikely to recur and may be idiopathic. For example, a number of conditions may present similar signs and symptoms to seizures, including syncope, hyperventilation, migraines, narcolepsy, panic attack and
30 psychogenic non-epileptic seizures.

Cannabinoids

Cannabis is a genus of flowering plants comprising three species: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis plants have long been used for hemp fiber, for seed and seed oils, for medicinal purposes, and as a recreational
5 drug.

Cannabis extract is composed of at least 480 known chemical compounds, which include cannabinoids, terpenoids, flavonoids, nitrogenous compounds, amino acids, proteins, glycoproteins, enzymes, sugars and related compounds, hydrocarbons, simple alcohols, aldehydes, ketones, simple acids, fatty acids, simple esters, lactones,
10 steroids, terpenes, non-cannabinoid phenols, vitamins, pigments, and elements. These compounds are secreted on the glandular trichomes. Cannabinoids are unique to the cannabis plant and there have been 100 cannabinoids that have been isolated as purified (single) molecules.

Cannabinoid receptors are present in mammalian systems and several classes of
15 G-Protein coupled receptors have been identified. The receptors that are present mainly in the central nervous system are known as CB1 receptors, whereas a different type of receptor, which are found substantially in the immune system, are known as the CB2 receptors.

Cannabinoid receptors are known to be constitutively active. This means that the
20 receptors undergo some degree of coupling to their signalling pathways even in the absence of an agonist. As such they exhibit a background tone.

A cannabinoid is one of a class of diverse chemical compounds that acts on cannabinoid receptors in cells that alter neurotransmitter release in the brain, although they may also act on a variety of other receptors. Ligands for these receptor proteins
25 include the endocannabinoids (produced naturally in the body by animals), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured artificially). The most notable cannabinoid is the phytocannabinoid tetrahydrocannabinol (THC), the primary psychoactive compound in cannabis. Cannabidiol (CBD) is another major constituent of the plant.

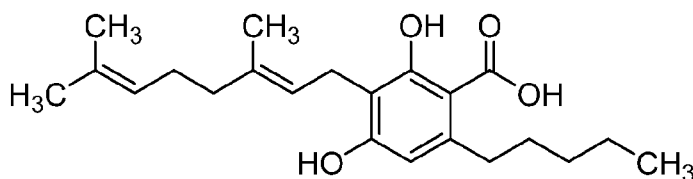
30 The cannabinoid can be a synthetic cannabinoid or a phytocannabinoid.

The principle cannabinoid components present in herbal cannabis are the cannabinoid acids Δ^9 -tetrahydrocannabinolic acid (Δ^9 THCA) and cannabidiolic acid (CBDA), with small amounts of the corresponding neutral cannabinoids, respectively Δ^9 tetrahydrocannabinol (Δ^9 THC) and cannabidiol (CBD).

5 In addition to these major cannabinoids, herbal cannabis is known to contain lower levels of other minor cannabinoids. These may be intermediates in the biosynthesis of the major cannabinoids and hence exist at only low levels in the plant as they are constantly undergoing further biotransformation once they are formed. An example of such a cannabinoid is cannabigerol (CBG) and its acidic form,
10 cannabigerolic acid (CBGA).

The present invention relates to the use of CBGA in the context of seizures.

Cannabigerolic acid (CBGA), also referred to as (E)-3-(3,7-Dimethyl-2,6-octadienyl)-2,4-dihydroxy-6-pentylbenzoic acid, or 3-[(2E)-3,7-dimethylocta-2,6-dien-1-yl]-2,4-dihydroxy-6-pentylbenzoic acid, is defined by the following structure:

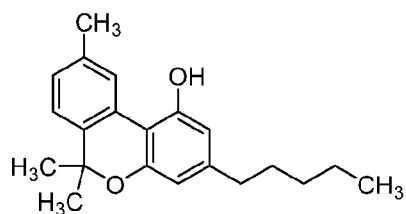


15

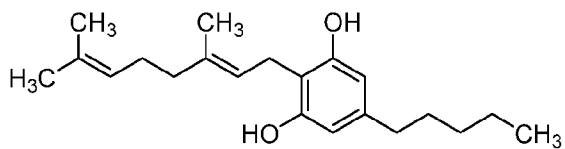
The biosynthesis of CBGA begins by loading hexanoyl-CoA onto a polyketide synthase assembly protein and subsequent condensation with three molecules of malonyl-CoA. This polyketide is cyclized to olivetolic acid via olivetolic acid cyclase, and then prenylated with a ten carbon isoprenoid precursor, geranyl pyrophosphate (GPP),
20 using an aromatic prenyltransferase enzyme, geranyl-pyrophosphate—olivetolic acid geranyltransferase, to biosynthesize cannabigerolic acid (CBGA).

Other cannabinoids include Tetrahydrocannabivarin (THCV), Cannabichromene(CBC), Cannabichromanon (CBCN), Cannabielsoin (CBE), Cannabidivarin (CBDV), Cannabifuran (CBF), Cannabicyclol (CBL), Cannabinol (CBN),
25 Cannabinodiol (CBND), Cannabitirol (CBT), Cannabivarin (CBV), and Isocannabinoids.

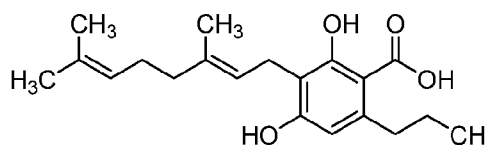
The following table provides some exemplary structures of known cannabinoids:



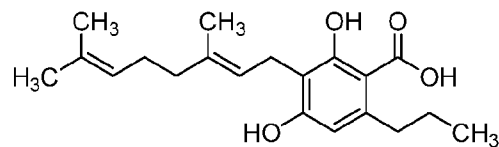
Cannabinol (CBN)



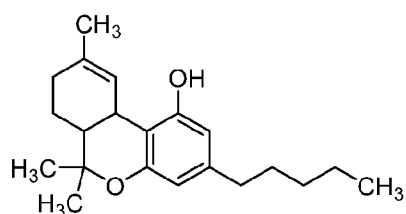
Cannabigerol (CBG)



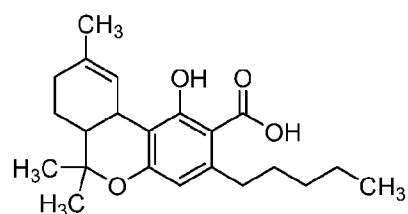
Cannabigerovarinic acid (CBGVA)



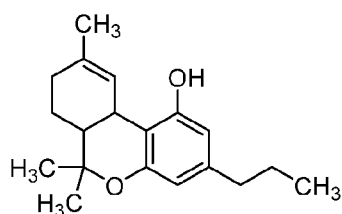
Cannabigerovarin (CBGV)



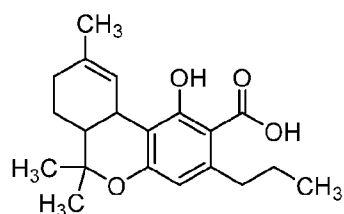
Tetrahydrocannabinol (THC)



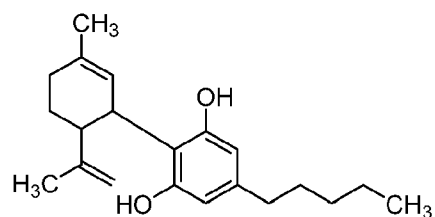
Tetrahydrocannabinolic acid (THCA)



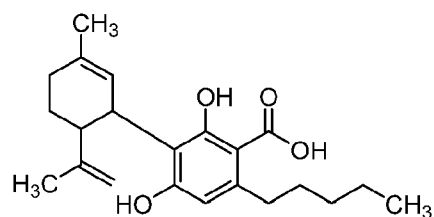
Tetrahydrocannabivarin (THCV)



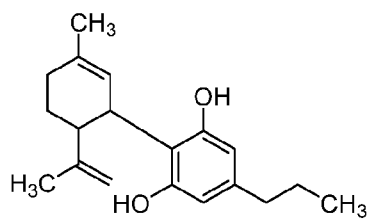
Tetrahydrocannabivarinic acid (THCVA)



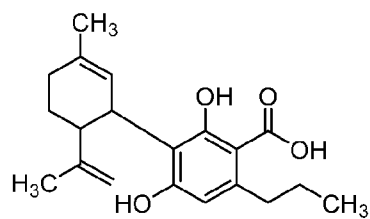
Cannabidiol (CBD)



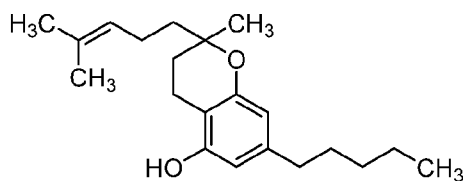
Cannabidiolic acid (CBDA)



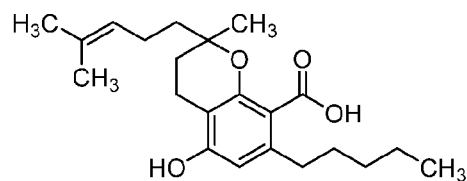
Cannabivarin (CBDV)



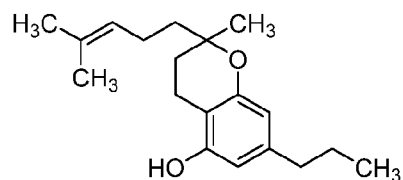
Cannabivarinic acid (CBDVA)



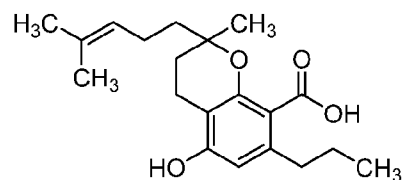
Cannabichromene



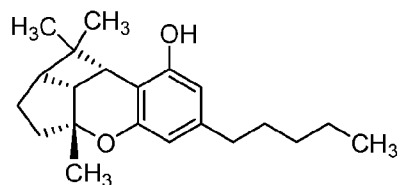
Cannabichromenic acid (CBCA)



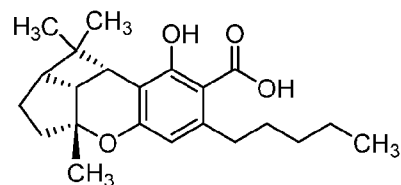
Cannabichromevarin (CBCV)



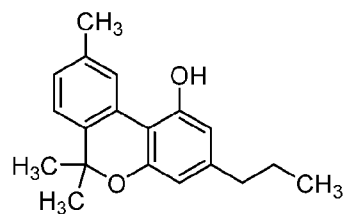
Cannabichromevarinic acid (CBCVA)



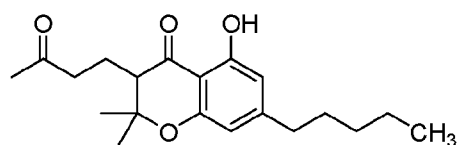
Cannabicyclol (CBN)



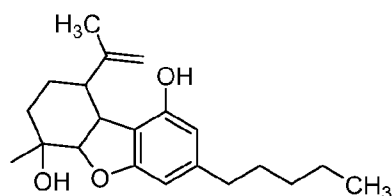
Cannabicyclic acid (CBNA)



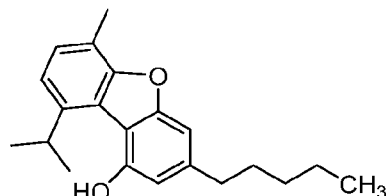
Cannabivarin (CBV)



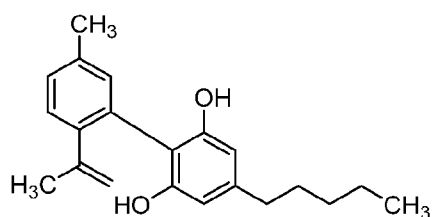
Cannabichromanone



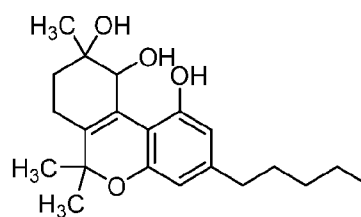
Cannabielsoin (CBE)



Cannabifuran (CBF)



Cannabinodiol (CBND)



Cannabitriol (CBT)

Formulations and compositions

The present invention provides pharmaceutical compositions and formulations comprising CBGA, optionally together with a pharmaceutically acceptable excipient.

- 5 In any embodiment of the invention, the CBGA may be derived from a purified extract of cannabis (i.e., an extract from a plant of the genus *Cannabis* including *Cannabis sativa*, *Cannabis indica*, or *Canabis ruderalis*).

Cannabinoids and other plant molecules may be extracted using various solvents and technologies including, but not limited to ethanol, butane, methane, carbon dioxide,
 10 ice, water, steam. Cannabinoids and other plant molecules may be extracted from plants bred to express desired cannabinoid and/or terpene and/or flavonoid profiles for purity.

Methods for obtaining purified or substantially purified solutions of cannabinoids, for example in the form of a cannabis extract, are known in the art, for example, in
 15 WO/2004/026857 and WO/2016/121351, the entire contents of which are incorporated herein in their entirety. WO/2004/026857 document describes general methods for obtaining cannabinoid and cannabinoid acids from plant material.

In a preferred embodiment an "extract containing CBGA" may be a solvent extract of a plant material. Preferred extraction solvents for use in the preparation of this extract include non-polar solvents, also alcohols such as ethanol or methanol and liquid carbon dioxide.

- 5 Non-polar solvents are particularly preferred for preparing an initial extract from the starting plant material. Any non-polar solvent capable of solubilising cannabinoids or cannabinoid acids may be used. Preferred non-polar solvents include liquid non-polar solvents comprising lower C5-C12, preferably C5 to C8, straight chain or branched chain alkanes. The most preferred non-polar solvent for the preparation of free
10 cannabinoids is hexane.

Preferably the extract is prepared by dissolving plant material in an extraction solvent, removing insoluble material from the resultant solution (preferably by filtration), and removing the extraction solvent from the solution (preferably by rotary evaporation) to form an extract containing a cannabinoid or cannabinoid acid.

- 15 In a preferred embodiment of the invention, the cannabis extract comprises at least 60% CBGA, and preferably is in the form of a highly purified botanical extract of cannabis, having greater than 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, of the total extract.

- 20 A "substantially pure" preparation of CBGA is defined herein as a preparation having a chromatographic purity (of CBGA) of greater than 95%, more preferably greater than 96%, more preferably greater than 97%, more preferably greater than 98%, more preferably greater than 99% and most preferably greater than 99.5%, as determined by area normalisation of an HPLC profile.

- 25 Within the context of this disclosure, where a compound comprises stereogenic centers, the term "purified" includes enantiomerically pure compositions and also mixtures of enantiomers or isomers.

- Preferably the cannabinoid extract has been treated to substantially remove the psychoactive cannabinoids tetrahydrocannabinol (THC) and/or tetrahydrocannabinol acid (THCA). Preferably, the extract comprises less than 5%, less than 4%, less than
30 3%, less than 2% or more preferably, less than 1% w/w THC and/or THCA.

US 6,403,126 discloses a process in which THC is removed from a cannabis extract using chromatography (the entire contents of this document are herein incorporated in their entirety).

5 In any embodiment of the present invention, the cannabinoid, including CBGA is synthetically produced. Methods for the biosynthetic production of cannabinoids, such as for example in yeast, are described in Zirpel et al., (2017) *Journal of Biotechnology*, 259: 204-212, and International Patent Application, WO2016010827, the entire contents of which are hereby incorporated in their entirety.

10 In any embodiment of the present invention, the CBGA may be pharmaceutical grade CBGA, obtained commercially, for example, from THCParm (Germany).

By the term "excipient" herein is meant a pharmaceutically acceptable material that is employed together with CBGA for the proper and successful administration of the CBGA to a patient. Suitable excipients are well known in the art, and are described, for example, in the *Physicians' Desk Reference*, the *Merck Index*, and
15 Remington's *Pharmaceutical Sciences*.

The formulation of the CBGA for use in accordance with the present invention, may be adapted for administration by a variety of routes. For example, the formulation may be adapted for parenteral administration, such as intravenous, intraarterial, intramuscular, intrathecal, subcutaneous or intraperitoneal injection. Alternatively, the
20 formulation may be adapted for intranasal, gastrointestinal, or other commonly used routes for administration of a pharmaceutical. Preferably, the formulation is adapted for oral administration.

The therapeutically effective amount of CBGA administered will depend for example, upon the severity of the symptoms of epilepsy in the individual to be treated,
25 the therapeutic objectives, route of administration and condition of the patients. For example the dose administered in an individual with a greater frequency of seizures may be greater than the amount of CBGA administered for an individual (for example, an older individual), who has experienced less frequent seizures. Accordingly, the therapist will be aware of methods for titrating the dosage and modifying the route of
30 administration as required to obtain the optimal therapeutic or prophylactic effect.

The dosage of any compositions of the present disclosure will vary depending on the symptoms, age, and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration, and the form of the subject composition. Any of the subject formulations can be administered in a single
5 dose or in divided doses.

In certain embodiments, the dosage of the subject compounds will generally be in the range of about 0.01 ng to about 10 g per kg body weight, specifically in the range of about 1 ng to about 0.1 g per kg, and more specifically in the range of about 100 ng to about 10 mg per kg.

10 The precise time of administration and amount of any particular subject composition that will yield the most effective treatment in a given patient will depend upon the activity, pharmacokinetics, and bioavailability of a subject composition, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage and type of medication),
15 route of administration, and the like.

The term 'administered' means administration of a therapeutically effective dose of the aforementioned cannabinoids, in particular CBGA, to an individual. By 'therapeutically effective amount' is meant a dose that produces the effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be
20 ascertainable by one skilled in the art using known techniques. As is known in the art and described above, adjustments for systemic versus localized delivery, age, body weight, general health, sex, diet, time of administration, drug interaction and the severity of the condition may be necessary, and will be ascertainable with routine experimentation by those skilled in the art.

25 The skilled person will be able to readily determine the appropriate dosage of CBGA to be administered in accordance with the present invention. Generally, the therapeutically effective amount of CBGA will be a dosage from about 0.5 mg/kg to about 50 mg/kg, from about 1 mg/kg to about 25 mg/kg, more preferably from about 2 mg/kg to about 10 mg/kg. However, the skilled person will appreciate that the precise
30 dosage required will depend on the route of administration and the severity of the condition being treated.

In an embodiment of the present invention, the therapeutically effective amount of CBGA may be administered to a subject once a day, twice a day, or three times a day to prevent or reduce the onset of seizures. Preferably, the CBGA is administered once daily.

5 In use, the CBGA may be used concomitantly with one or more other anticonvulsant drugs. Alternatively the CBGA may be formulated for administration separately, sequentially or simultaneously with one or more anticonvulsant drugs or the combination may be provided in a single dosage form. Where the CBGA is formulated for administration separately, sequentially or simultaneously it may be provided as a kit
10 or together with instructions to administer the one or more components in the manner indicated. It may also be used as the sole medication, i.e. as a monotherapy.

Examples of suitable anticonvulsant drugs (including standard anti-epileptic drugs) include: acetazolamide, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, ethosuxamide, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam,
15 oxcarbazepine, perampanel, piracetam, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide.

The skilled person will be familiar with the appropriate dosage, frequency and route of administration of standard anti-epileptic drugs.

20 Alternatively, CBGA may be administered in conjunction with another anticonvulsant drug in the form of another cannabinoid. Examples of suitable cannabinoids used on conjunction with CBGA include, Δ^9 -tetrahydrocannabinol (THC), cannabidiolic acid (CBDA), cannabidiol (CBD) and cannabidivarin (CBDV) or any other cannabinoid described herein.

25 Examples

Example 1

While conventional animal models of epilepsy have assisted in the development of anti-epileptic drugs, they have failed to find new agents that treat paediatric epilepsy. In the present studies, Dravet syndrome mice were used to provide a new platform to

discover novel therapeutic agents for childhood epilepsy. 80% of children with Dravet syndrome have heterozygous mutations in *SCN1A* that encodes the voltage-gated sodium channel Nav1.1.

Genetic mutations in *Scn1a* have been introduced to mice and these animals faithfully reproduce key features of the disorder, such as early-onset spontaneous seizures and hyperthermia-induced seizures. Further they have a reduced lifespan and exhibit developmental delays in cognitive, motor and social function.

Two different *Scn1a* mouse lines were used in these studies: 1) the *Scn1a*^{RX/+} mice which have been genetically engineered to contain the R1407X nonsense mutation in *Scn1a*; and 2) the *Scn1a*^{+/-} mice in which *Scn1a* has undergone heterozygous deletion. Both these strains are maintained on slightly different genetic backgrounds.

Materials and Methods

Hyperthermia-induced seizure experiments were examined in both *Scn1a*^{+/-} and *Scn1a*^{RX/+} mice at age postnatal day 14-16. All cannabinoids were administered as a single intraperitoneal (i.p.) injection in a volume of 10 mL/kg. Experimental time points used were 15 minutes (CBDA), 30 minutes (CBDV and THC), 45 minutes (CBGA) and 60 minutes (CBD). Fifteen minutes prior to the target experimental (post-dose) time point for each cannabinoid, a rectal temperature probe was inserted. Mice acclimated to the temperature probe for 5 minutes before the hyperthermia protocol was started. Mouse core body temperature was elevated 0.5 °C every two minutes until the onset of the first clonic convulsion with loss of posture or until 42.5 °C was reached. Mice that reached 42.5 °C were held at temperature for 3 minutes. If no seizure occurred during the hold period, the experiment was terminated and the mouse was considered seizure free. Statistical comparisons were made using Mantel-Cox log-rank test and $p < 0.05$ was considered statistically significant.

Results

The anticonvulsant potential of CBGA, CBD, CBDA, CBDV and THC for hyperthermia-induced seizures in the *Scn1a*^{+/-} and *Scn1a*^{RX/+} mouse models of Dravet syndrome was evaluated. Mice were treated acutely with a single cannabinoid and the

dose-effect was examined for each. CBGA (100 mg/kg, $p < 0.001$) significantly increased the temperature threshold for thermally induced seizures in Scn1a^{+/-} and Scn1aR^{X/+} mice. In Scn1a^{+/-} mice an additional dose (30 mg/kg, $p < 0.01$) of CBGA was examined and provided a significant dose-dependent effect for CBGA on thermal
5 seizures. Treatment with CBD had no effect on hyperthermia-induced seizures in the Scn1aR^{X/+} mouse model up to 25 mg/kg (a published study using a similar Scn1a^{+/-} Dravet mouse line showed CBD was only effective at greater and equal to 100 mg/kg on thermal-induced seizures – doses of 10 – 50 mg/kg were ineffective, Kaplan et al., (2017) PNAS 114(42): 11229-11234). In the Scn1a^{+/-} mice, unlike CBGA, CBD was
10 ineffective at 30 mg/kg and was only effective at 100 mg/kg. In Scn1a^{+/-} mice CBDA exhibited no anticonvulsant effects; however, 10 mg/kg and 30 mg/kg ($p < 0.05$) significantly increased threshold temperature in Scn1aR^{X/+} mice. Dose-effects of CBDV and THC were only examined in Scn1a^{+/-} mice. Both CBDV and THC (30 mg/kg and 0.1 mg/kg, respectively; $p < 0.05$) significantly increased the temperature threshold for
15 thermally induced seizures.

Discussion

CBGA was demonstrated to display anticonvulsant properties by increasing tolerability to hyperthermia-induced seizures in two genetically distinct mouse models of Dravet syndrome.

20 Further, CBGA was effective in modulating hyperthermia-induced seizures at a lower dose than CBD, a known anticonvulsant. This indicates that CBGA may be a superior anticonvulsant, particularly in the context of Dravet syndrome.

A previously characterised anticonvulsant CBDA was also effective however only in one of the mouse lines studied, underscoring that CBGA may be a more reliable
25 anticonvulsant across different genetic backgrounds.

The previously reported anticonvulsant drugs THC and CBDV displayed anticonvulsant properties in the present model. However, it is noteworthy that THCV, which has been characterised as anticonvulsant in the drug-sensitive PTZ model of epilepsy, displayed a *proconvulsant* profile in the drug-resistant model of epilepsy
30 described herein.

Example 2

The effects of CBGA on spontaneous seizures and mortality in Scn1a^{+/-} mice are examined. CBGA is administered to Scn1a^{+/-} mice in accordance with the protocol shown in Example 1 (except that the animals are not exposed to hyperthermia).

- 5 Administration of CBGA is expected to reduce the frequency of spontaneous seizures and improve the survival of Scn1a^{+/-} mice.

Example 3

The anti-convulsant efficacy of CBGA is examined in drug-sensitive animal models of epilepsy including: the pentylenetetrazol (PTZ) model and the maximal
10 electroshock seizure (MES) model. Methods describing testing for anticonvulsant efficacy in these models are described in the prior art, including for example in Kandratavicius, et al., (2014) Neuropsychiatr Dis Treat., 10:1693-1705, the entire contents of which are herein incorporated in their entirety.

- 15 CBGA, when administered alone, or when in combination with one or more additional cannabinoids, is expected to reduce seizure frequency, seizure severity and mortality in these animal models.

Example 4

The anticonvulsant effects of CBGA, when combined with another conventional anticonvulsant on hyperthermia-induced seizures in Scn1a^{+/-} mice was examined.

- 20 The threshold temperature of individual mice for generalised tonic-clonic seizure (GTCS) induced by hyperthermia was assessed following acute treatment with clobazam and CBGA administered individually or as a combination in an i.p. injection.

The combination of clobazam and CBGA treatment resulted in a significantly improved response to thermal seizure induction compared to treatment with CBGA or
25 clobazam alone, with n = 15 - 34 per group (** p < 0.005, **** p < 0.0001, log-rank Mantel-Cox). All treatment groups showed a significantly increased temperature threshold for thermally induced seizures compared to vehicle treatment (clobazam vs.

vehicle, *** $p < 0.0005$; CBGA vs. vehicle, * $p < 0.05$; clobazam and CBGA combination vs. vehicle, **** $p < 0.0001$; log-rank Mantel-Cox).

These results further highlight the anticonvulsant properties of CBGA. Moreover, the results indicate that when combined with a conventional anticonvulsant medication, CBGA can potentiate the anticonvulsant properties of that medication. Thus, CBGA has utility as an adjunct therapy for conventional anticonvulsants, and may also enable a reduction in the dosage of medication administered to an individual in order to control seizures.

It will be understood that the invention disclosed and defined in this specification extends to all alternative combinations of two or more of the individual features mentioned or evident from the text or drawings. All of these different combinations constitute various alternative aspects of the invention.

CLAIMS

1. A method of preventing or reducing the frequency of seizures, or of reducing the severity of seizures in an individual in need thereof, comprising administering to the individual a therapeutically effective amount of cannabigerolic acid, thereby preventing or reducing the frequency or the severity of seizures in the individual.
5
2. The method of claim 1, wherein the seizures are epileptic seizures.
3. The method of claim 2, wherein the epileptic seizures are associated with epileptic syndromes selected from the group consisting of: idiopathic epilepsy, Dravet syndrome, Lennox-Gastaut syndrome, epilepsy characterised by infantile spasms, febrile seizures, childhood absence seizures and other forms of pharmacoresistant epilepsy.
10
4. The method of any one of the preceding claims, wherein the seizures are selected from the group consisting of: convulsive, focal, absence, tonic-clonic, tonic, clonic, myoclonic, atonic, and reflex.
- 15 5. The method of any one of the preceding claims, wherein the seizures are caused by, induced by, follow from, or are associated with one or more of the following environmental or physiological stimuli: heat, stress, alcohol abuse, lack of sleep, loud noises, flickering lights, trauma including head trauma, stroke, tumours, and infection of the central nervous system.
- 20 6. The method of any one of the preceding claims, wherein the seizures are spontaneous and/or associated with a genetic marker indicative of risk of seizure.
7. The method of any one of the preceding claims, wherein the individual is an infant or pre-adolescent individual.
8. The method of any one of the preceding claims, wherein the method comprises the administration of an additional anticonvulsant agent.
25
9. The method of claim 8, wherein the additional anticonvulsant agent is selected from the group consisting of: acetazolamide, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, ethosuxamide, gabapentin, lacosamide,

lamotrigine, levetiracetam, nitrazepam, oxcarbazepine, perampanel, piracetam, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide, preferably wherein the additional anticonvulsant is clobazam and/or sodium valproate.

5 10. The method of any one of the preceding claims, wherein the method comprises the administration of an additional cannabinoid.

11. The method of claim 11, wherein the additional cannabinoid is selected from the group consisting of: cannabidivarin (CBDV), cannabidiolic acid (CBDA) and THC.

10 12. A method of treating epilepsy in an individual, the method comprising administering to the individual, a therapeutically effective amount of cannabigerolic acid, thereby treating epilepsy in the individual.

13. A method of controlling cell hyperexcitability associated with a neurological disorder in an individual, comprising administering to the individual, a therapeutically effective amount of cannabigerolic acid, thereby controlling cell hyperexcitability in the individual.

14. The method of claim 11, wherein the neurological disorder is a disorder associated with epileptogenesis.

15. Use of cannabigerolic acid in the manufacture of a medicament for preventing or reducing the frequency of seizures in an individual.

20 16. The use of claim 15, wherein the seizures are epileptic seizures.

17. The use of claim 15, wherein the epileptic seizures are associated with epileptic syndromes selected from the group consisting of: idiopathic epilepsy, Dravet syndrome, Lennox-Gastaut syndrome, epilepsy characterised by infantile spasms, febrile seizures, childhood absence seizures and other forms of pharmaco-resistant epilepsy.

25 18. Cannabigerolic acid, for use in the prevention or reduction of frequency of seizures in an individual.

19. Cannabigerolic acid, for the use of claim 18, wherein the seizures are epileptic seizures.

20. Cannabigerolic acid, for the use of claim 19, wherein the epileptic seizures are associated with epileptic syndromes selected from the group consisting of:
5 idiopathic epilepsy, Dravet syndrome, Lennox-Gastaut syndrome, epilepsy characterised by infantile spasms, febrile seizures, childhood absence seizures and other forms of pharmaco-resistant epilepsy.

21. A composition comprising cannabigerolic acid for preventing or reducing the frequency of seizures in an individual, and one or more pharmaceutically
10 acceptable excipients.

22. The composition of claim 21, wherein the composition is a plant extract.

23. The composition of claim 21, wherein the CBGA is synthetically produced.

24. A kit for use in preventing or reducing the frequency of seizures in an individual, the kit comprising:

- 15
- a containing cannabigerolic acid, or a pharmaceutical composition comprising cannabigerolic acid; and optionally,
 - a label or package insert with instructions for use of the kit.

25. The kit of claim 24, wherein the kit also comprises a further agent for preventing
20 or reducing the frequency of seizures in an individual, wherein the further agent is selected from a cannabinoid or an anticonvulsant agent.

26. The kit of claim 25 wherein the anticonvulsant agent is selected from
25 acetazolamide, carbamazepine, clobazam, clonazepam, eslicarbazepine acetate, ethosuxamide, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam, oxcarbazepine, perampanel, piracetam, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, sodium valproate, stiripentol, tiagabine, topiramate, vigabatrin and zonisamide, preferably wherein the agent is clobazam and/or sodium valproate.

Figure 1

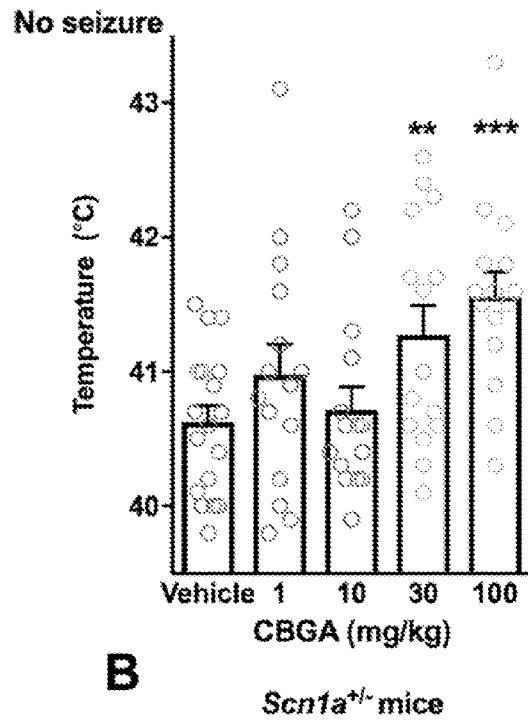
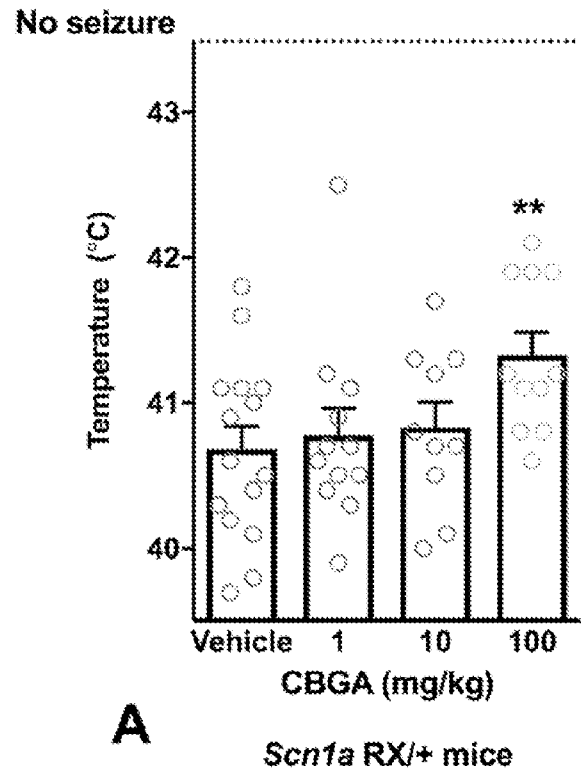


Figure 2

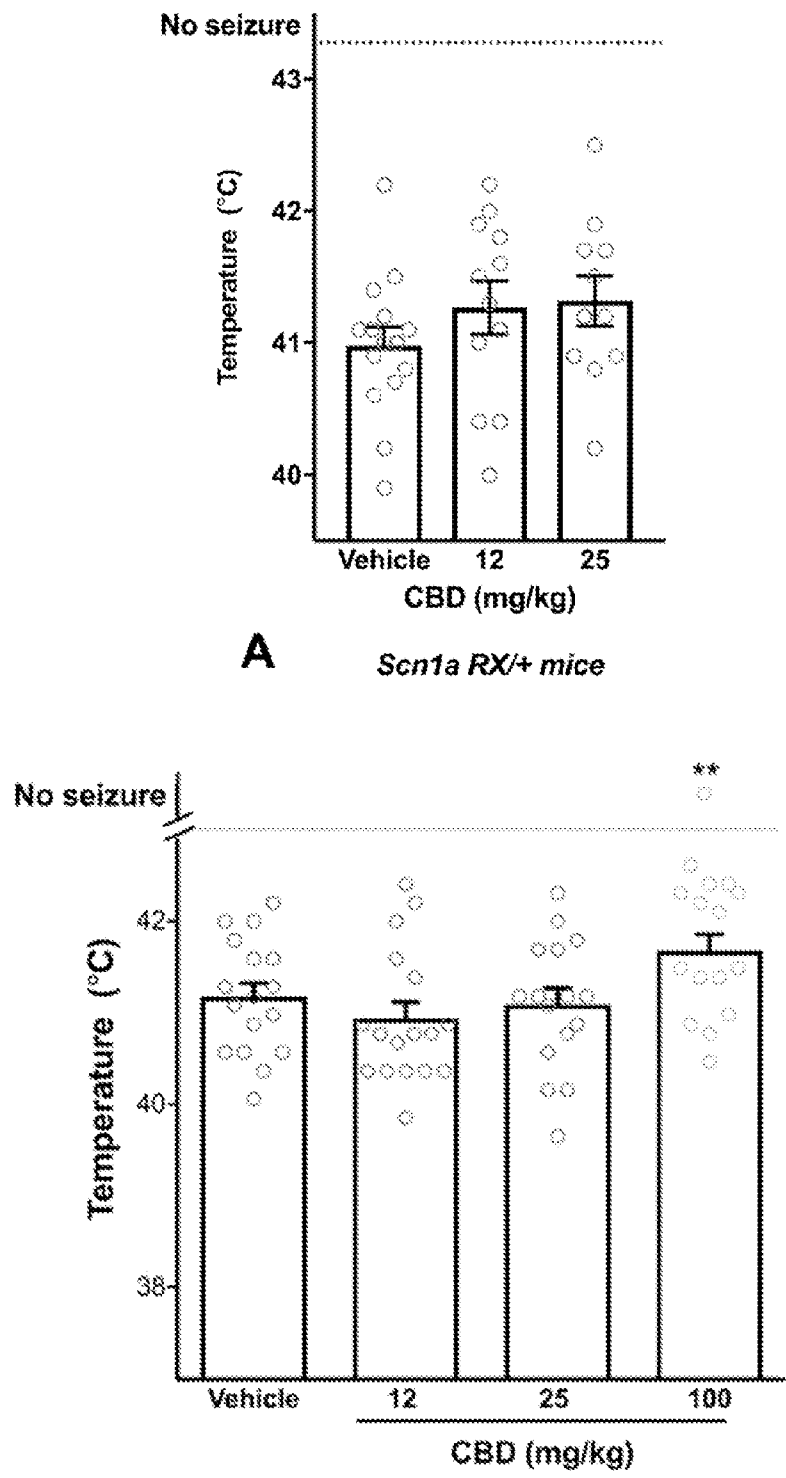
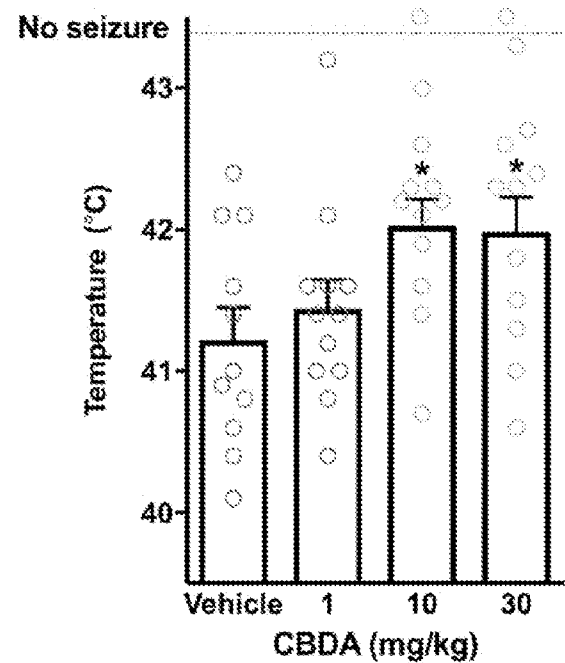
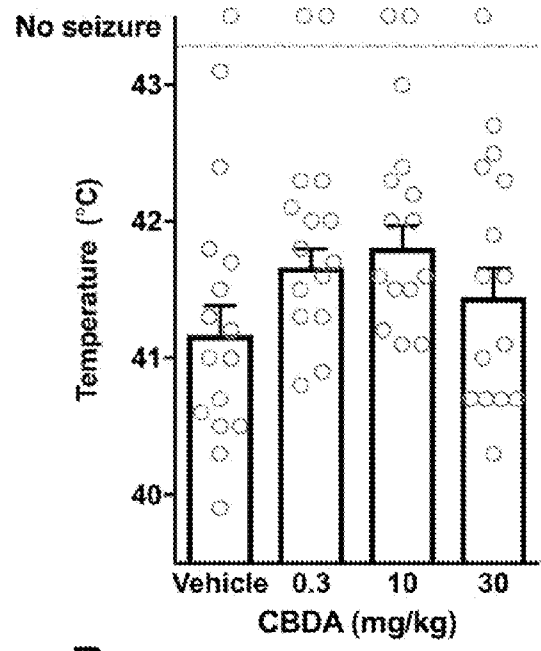


Figure 3

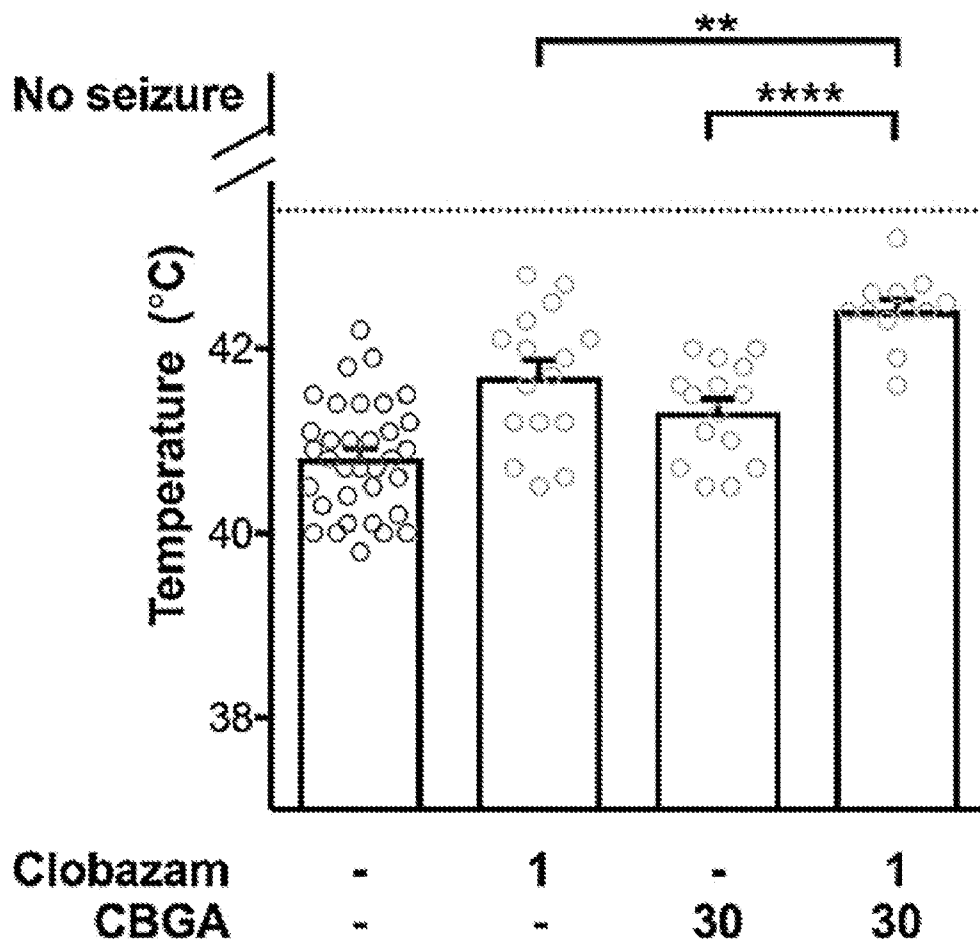


A
Scn1a RX/+ mice



B
Scn1a +/- mice

Figure 4



A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/192 (2006.01) A61P 25/08 (2006.01)

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)

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)

Applicant and Inventor Search: (Espacenet, Patentscope, Auspat, Google Patents and Internal Databases): keywords University of Sydney or ARNOLD, Jonathon or MCGREGOR, Iain or ANDERSON, Lyndsey and cannabigerolic acid or seizure or epilepsy

EPOQUE search of PATENW (EPODOC, WPIAP and TXP... databases) and STN search of CAPlus, Medline, Embase, and BIOSIS: keywords: Cannabigerolic, CBGA, Seizure, epilepsy, spasm, Dravet syndrome, Lennox gastaut syndrome, excitability, convulsant, cannabigerolic and similar terms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	



Further documents are listed in the continuation of Box C



See patent family annex

* "A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"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
"E"	earlier application or patent but published on or after the international filing date	"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
"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)	"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
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search
12 November 2018Date of mailing of the international search report
12 November 2018

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INTERNATIONAL SEARCH REPORT		International application No.
C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		PCT/AU2018/051089
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/109624 A1 (UNIVERSITY OF HOUSTON SYSTEM) 07 July 2016 Paras. 0019, 0030, 0055 and claims 16 and 19	1-26
X	WO 2016/116628 A1 (PHYTOPLANT RESEARCH S.L.) 28 July 2016 Paras. 0004, 0013, 0014, 0020, 0028, 0029, 0040, 0050, 0081, 0113, 0116 and 0117 (aspects 137, 146, 151 and 152) and Example 5	1-26

Form PCT/ISA/210 (fifth sheet) (January 2015)

INTERNATIONAL SEARCH REPORT		International application No.	
Information on patent family members		PCT/AU2018/051089	
This Annex lists known patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.			
Patent Document/s Cited in Search Report		Patent Family Member/s	
Publication Number	Publication Date	Publication Number	Publication Date
WO 2016/109624 A1	07 July 2016	WO 2016109624 A1	07 Jul 2016
WO 2016/116628 A1	28 July 2016	WO 2016116628 A1	28 Jul 2016
		AU 2016210070 A1	07 Sep 2017
		BR 112017015536 A2	17 Apr 2018
		CA 2977421 A1	28 Jul 2016
		CL 2017001873 A1	13 Apr 2018
		CN 107567435 A	09 Jan 2018
		CO 2017008437 A2	05 Jan 2018
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		US 9765000 B2	19 Sep 2017
		US 2018000879 A1	04 Jan 2018
		US 2018162828 A1	14 Jun 2018
		US 2018222879 A1	09 Aug 2018
	UY 36530 A	31 Aug 2016	
End of Annex			