

Composition and method for treating pain

Field

[0001] The invention relates to pharmaceutical compositions comprising cannabidiol (CBD) and Δ^9 -tetrahydrocannabinol (THC), and their use in the treatment of pain. The invention also relates to methods for treating pain as a replacement for opioid therapy.

Background

[0002] The biological activity of *Cannabis* is well known and has led it to become a "recreational" drug. However, with the discovery of a class of cannabinoid (CB) receptors, and the relaxation of laws regulating *Cannabis* use - in some jurisdictions decriminalisation - there now exists the opportunity to explore the potential of *Cannabis* as a source of new therapeutics.

[0003] One of the early drivers for the medicinal use of *Cannabis* is its analgesic or antinociceptive efficacy, with medicinal *Cannabis* typically being prescribed to cancer patients to assist in pain management.

[0004] There is a continuing need to develop new treatments for pain management. In particular, in light of the current opioid epidemic that sees existing prescription opioid analgesics leading to dependence in patients, and abuse by other elements of society.

[0005] Opioid based analgesia is commonly prescribed for both acute post-surgical pain and for chronic pain. In Australia, evidence-based guidelines support the use of opioids in the acute post-surgical setting but not for chronic non-cancer pain. There are numerous adverse effects of opioids including: over-sedation, which can lead to accidents and increased risk of falls, respiratory depression, sleep apnoea, nausea, vomiting, constipation, opioid-induced androgen deficiency and peripheral oedema. Other negative consequences of opioid use include unintentional overdose, the development of opioid dependence and diversion of opioids to individuals for non-medical purposes. Nevertheless, many patients with chronic pain (e.g. pain experienced daily for more than 3 months) are on long term treatment with high dose (OMEDD >60mg) opioid analgesia.

[0006] Dose reduction is indicated where there is a pattern of escalating opioid use due to ineffective pain relief, where adverse effects are limiting quality of life, and where opioids are being misused. Generally, a fairly rapid dose reduction of between 10-25% per week is recommended. However, in cases where the patient has been on opioids for many years the

dose reduction may be between 10-25% per month. Drop-out rates from dose taper regimens are high, some studies reporting drop-out rates between 75-100%.

[0007] There is some evidence that cannabinoids may enable patients to reduce their opioid medication whilst maintaining adequate analgesia - known as opioid sparing. If so, cannabinoids could prove effective in reducing drop-out rates in opioid dose taper regimen, assisting patients with poorly managed pain.

[0008] Lynch and Clark (Journal Pain Symptom Management. 2003; 25:496-498) reported the results of a clinical case series in which 3 patients with non-cancer pain reported regular use of smoked marijuana and were able to reduce their opioid dose by 60-100%.

[0009] Other studies have reported more mixed results. For example, Johnson *et al.* (Journal Pain Symptom Management. 2010; 39:167-179) reported that the efficacy of a cannabinoids in the oro-mucosal spray formulations (A: 2.7mg THC:2.5mg CBD; B: THC only 2.7mg, and C: placebo) in moderate to severe cancer-related pain. In this two week double blind, randomized, placebo controlled, parallel group trial (n=177), patients could self-titrate their dose up to a maximum of 48 sprays per 24 hour period. Use of opioid medication was a secondary endpoint. No change in the median amount of opioid breakthrough medication was observed in any group.

[0010] Seeling *et al.* (Anaesthetist. 2006;55:391-400) examined the use of dronabinol (5mg THC) versus placebo in acute post-surgical pain. Median dose of micro-opioid agonist piritramide in the two days post surgery was 54mg in the treatment group versus 74mg in the control group; however, this difference was not statistically significant (n=105).

[0011] Despite the mixed results from previous studies, interest in the opioid sparing effects of cannabinoids remains high especially in the US where dependence on prescribed opioids for chronic non-cancer pain conditions has been declared an epidemic. Very recently the NIH has provided \$3.8 million to fund what is being described as the first long-term study to investigate whether treatment with medicinal cannabinoids can lead to a reduction in opioid use in adults with chronic pain (1R01DA044171-01A1). Over 18 months, 250 HIV-positive and HIV-negative adults with chronic pain who use opioids and who have received certification from their physicians to use medicinal cannabinoids, will complete fortnightly web-based questionnaires which will focus on pain levels and the medical and illicit use of marijuana and opioids. Urine and blood samples will be collected every three months and in-depth interviews will explore their perceptions of how medical marijuana use affects the use of opioids.

[0012] This US study will provide important information on how chronic pain sufferers are self-medicating with medical and illicit cannabinoids. However, this is not a clinical trial and will not provide quality data to inform guidelines needed now by clinicians to assist patients with chronic pain and problematic opioid use and/or dependence.

[0013] The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".

[0014] This definition recognizes pain as a subjective experience with both psychologic and sensory components. It also recognizes that tissue damage does not need to be present for pain to be experienced. Pain can be categorized along a variety of dimensions, including one of the most important divisions, nociceptive versus neuropathic pain. Nociceptive pain results from activity in neural pathways secondary to actual tissue damage or potentially tissue-damaging stimuli. Neuropathic pain is chronic pain that is initiated by nervous system lesions or dysfunction and can be maintained by a number of different mechanisms. It is thought that cannabinoids may benefit those people with neuropathic pain.

[0015] Chronic non-cancer pain is usually defined as pain persistent beyond 3 months, deemed the duration of tissue healing. Chronic non-cancer pain may be time-unlimited, although an annual recovery rate of 9.4% was reported in a Danish study. Rather than treating the original acute cause, which may no longer exist, therapy serves to suppress the perceived pain. The manner in which sensory stimuli become transformed into perception is complex and highly variable and involve genetic, environmental, cognitive and emotional processes.

[0016] Of the 28 completed interventional clinical trials on clinicaltrials.gov the majority (n=17; 61%) were conducted by GW Pharma in the development and approval of Sativex for the treatment of pain. An additional two studies investigated the effect of Sativex to treat neuropathic pain following chemotherapy or to provide relief for diabetic neuropathy.

[0017] Of the 8 remaining completed interventional clinical trials, 6 evaluated the effectiveness of vaporised cannabis for treating neuropathic pain associated with conditions such as sickle cell disease (SCD), spinal cord injury, HIV, and diabetes.

[0018] However, few trials have used whole plant extracts delivered orally, nor is there a clear consensus on the optimal ratio of THC:CBD for treatment of pain.

[0019] It would therefore be advantageous to provide alternative cannabinoid-based pharmaceutical compositions that may be useful in the treatment of pain.

Summary

[0020] The inventors believe that treatment of patients suffering from non-cancer chronic pain with a pharmaceutical composition comprising Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) and a synergistic terpene fraction may provide sufficient analgesia or antinociception to assist in pain management strategies. Further, as the pharmaceuticals of the invention may be provided as whole extracts of a *Cannabis* plant production costs may be minimised and the number of processing steps may be reduced.

[0021] In one aspect, there is provided an analgesic or antinociceptive agent comprising THC, CBD and a terpene fraction obtained by extraction of a *Cannabis* plant. The pharmaceutical composition may optionally comprise one or more pharmaceutically acceptable excipient(s).

[0022] In another aspect, there is provided a method of treating pain, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition of the invention.

[0023] In some embodiments, the pharmaceutical composition is administered according to the following dosage regimen:

- (1) administering an effective amount of a *Cannabis* extract comprising THC as primary cannabinoid and a terpene fraction preceding a period of sleep of the subject, and
- (2) administering an effective amount of a *Cannabis* extract comprising CBD as primary cannabinoid and a terpene fraction following a period of sleep of the subject; and optionally
- (3) administering an effective amount of an analgesic or antinociceptive agent of the invention comprising THC and CBD in a ratio of THC:CBD of 2:1 or more to manage breakthrough pain.

[0024] In still a further aspect, there is provided use of one or more of (a) a *Cannabis* extract; (b) THC and (c) CBD in the manufacture of a medicament for treating pain, wherein the medicament comprises THC, CBD and a terpene fraction obtained by extraction of a *Cannabis* plant.

[0025] In yet a further aspect, there is provided a kit comprising in separate parts:

- (a) an effective amount of the pharmaceutical composition of the invention comprising THC as primary cannabinoid; and
- (b) an effective amount of the pharmaceutical composition of the invention comprising CBD as primary cannabinoid.

Definitions

[0026] The term “cannabinoid” as used herein relates to any compound that has been isolated from a *Cannabis* plant or synthetically created that has activity involving the endocannabinoid system. The term is used to describe the relevant compound itself irrespective of its source.

[0027] The term “cannabinoid fraction” is used to describe the combination of cannabinoid compounds present in the Cannabis extract.

[0028] The term “terpenes” or “terpenoids” as used herein refers to a class of hydrocarbon molecules, which often provide a unique smell. Terpenes are derived from units of isoprene, which has the molecular formula C_5H_8 . The basic molecular formula of terpenes are multiples of the isoprene unit, i.e. $(C_5H_8)_n$, where n is the number of linked isoprene units. Terpenoids are terpene compounds that have been further metabolised in the plant, typically through an oxidative process, and therefore usually contain at least one oxygen atom.

[0029] The term “terpene fraction” is used to describe the combination of terpene and terpenoid compounds present in the Cannabis extract.

[0030] As used herein, the terms “treating”, “treatment”, “treat” and the like mean affecting a subject, patient, tissue or cell to obtain a desired pharmacological and/or physiological effect. The effect may be prophylactic in terms of completely or partially preventing, or reducing the severity of the experienced pain and/or may be therapeutic in terms of a partial or complete cure of the underlying cause of the pain.

[0031] The term “administering” refers to providing the pharmaceutical composition to a patient suffering from or at risk of the disease(s) or condition(s) to be treated or prevented.

[0032] By “effective amount” it is meant an amount sufficient that, when administered to the patient, an amount of the drug is provided to achieve an effect. In the case of a therapeutic method, this effect may be the treatment of the specified disease and/or

condition or a symptom thereof. Therefore, the “effective amount” may be a “therapeutically effective amount”. By “therapeutically effective amount” it is meant an amount sufficient that when administered to the patient an amount of active ingredient is provided to treat the disease or a symptom of the disease.

[0033] As used herein and in the appended claims, the singular forms “a,” “an,” and “the” include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to “an excipient” may include a plurality of excipients, and a reference to “a subject” may be a reference to one or more subjects, and so forth.

[0034] The term “(s)” following a noun contemplates the singular or plural form, or both.

[0035] The term “and/or” can mean “and” or “or”.

[0036] Unless the context requires otherwise, all percentages referred to herein are percentages by weight of the composition.

[0037] Various features of the invention are described and/or claimed with reference to a certain value, or range of values. These values are intended to relate to the results of the various appropriate measurement techniques, and therefore should be interpreted as including a margin of error inherent in any particular measurement technique. Some of the values referred to herein are denoted by the term “about” to at least in part account for this variability. The term “about”, when used to describe a value, preferably means an amount within $\pm 25\%$, $\pm 10\%$, $\pm 5\%$, $\pm 1\%$ or $\pm 0.1\%$ of that value.

[0038] The term “comprising” as used in this specification means “consisting at least in part of”. When interpreting statements in this specification that include that term, the features, prefaced by that term in each statement, all need to be present but other features can also be present. Related terms such as “comprise” and “comprised” are to be interpreted in the same manner.

[0039] Before describing the present invention in detail, it is to be understood that this invention is not limited to particularly exemplified pharmaceutical compositions, methods of production or treatment, which may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments of the invention only, and is not intended to be limiting.

[0040] The inventions described and claimed herein have many attributes and embodiments including, but not limited to, those set forth or described or referenced in this summary section, which is not intended to be all-inclusive. The inventions described and claimed herein are not limited to or by the features or embodiments identified in this summary section, which is included for purposes of overview illustration only and not limitation.

[0041] All publications, patents and patent applications cited herein, whether *supra* or *infra*, are hereby incorporated by reference in their entirety. However, publications mentioned herein are cited for the purpose of describing and disclosing the protocols and reagents which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

[0042] In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

[0043] Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any materials and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred materials and methods are now described.

Description of Embodiment(s)

[0044] The present invention provides a pharmaceutical composition comprising THC and CBD and a terpene fraction obtained from extraction of a *Cannabis* plant.

[0045] CBD is the main non-psychotropic phytocannabinoid present in the *Cannabis sativa* plant, in some cases constituting up to 40 per cent of its extract depending on extraction technique. Both animal and human studies suggest that the pharmacokinetics and pharmacodynamics of CBD are very complex. CBD appears to operate at both CB1 and CB2 endocannabinoid receptors within the endocannabinoid system (ECS) indirectly stimulating endogenous cannabinoid signaling (anandamine) by suppressing fatty acid amide hydrolase

(FAAH), the enzyme that breaks down anandamide. Importantly, this enables more anandamide to remain at the receptors, which elicits anxiolytic and antidepressant like effects. This indirect agonist property at the cannabinoid receptors may also explain its promising safety profile. Furthermore, CBD has been shown to also act on the vanilloid, adenosine and serotonin receptors explaining its broad spectrum of potential therapeutic properties in animal models and humans, including anxiolytic, antidepressant, neuroprotective, anti-inflammatory and immunomodulatory actions.

[0046] THC is the main psychotropic constituent of *Cannabis*, its main pharmacological effects including analgesia, muscle relaxation, antiemesis, appetite stimulation and psychoactivity. THC mimics the action of the endogenous cannabinoid receptor ligands. THC is a partial agonist of CB1 receptors, which are primarily expressed in the central nervous system, especially in areas associated with pain. It is believed that THC induces analgesia by binding presynaptic CB1 receptors, inhibiting neurons activated by pain in these areas.

[0047] There is evidence that THC and CBD used in combination, act synergistically to maximize analgesic response. CBD has been demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties.

[0048] The pharmaceutical composition may comprise THC and CBD in ratio of THC:CBD from about 10:1 to about 1:10. In some embodiments, the ratio of THC:CBD will be balanced, for example from about 2:1 to about 1:2, such as about 0.8:1 to about 1.2:1 or about 1:1.

[0049] It is intended that reference to a range of numbers disclosed herein (for example, 1 to 10) also incorporates reference to all rational numbers within that range (for example, 1, 1.1, 2, 3, 3.9, 4, 5, 6, 6.5, 7, 8, 9 and 10) and also any range of rational numbers within that range (for example, 2 to 8, 1.5 to 5.5 and 3.1 to 4.7) and, therefore, all sub-ranges of all ranges expressly disclosed herein are hereby expressly disclosed. These are only examples of what is specifically intended and all possible combinations of numerical values between the lowest value and the highest value enumerated are to be considered to be expressly stated in this application in a similar manner.

[0050] The ratio of THC to CBD may be readily determined by methods known in the art, including High-Performance Liquid Chromatography (HPLC) and Ultra Performance Liquid Chromatography (UPLC).

[0051] In some embodiments, pharmaceutical compositions comprising THC may comprise THC in a minimum amount of at least about 15wt%, for example, at least about 25wt%, about 35wt% or about 40wt%. In some embodiments, the pharmaceutical composition comprises THC in a maximum amount of up to about 85wt%, about 80wt%, about 75wt%, about 70wt%, about 65wt%, about 60wt%, about 55wt%, about 50wt%, about 45wt%, about 40wt%, about 35wt%, about 30wt%, about 25wt% or about 20wt%. It will be appreciated that the amount of THC may be within the range from any of these minimum amounts to any of these maximum amounts. All combinations of these minimum and maximum amounts are contemplated. For example, in some embodiments, the pharmaceutical composition comprises THC in an amount of from about 15wt% to about 85wt%, about 15wt% to about 75wt%, about 15wt% to about 40wt% or about 40wt% to about 60wt%.

[0052] In some embodiments, pharmaceutical compositions comprising CBD may comprise CBD in a minimum amount of at least about 15wt%, for example, at least about 25wt%, about 35wt% or about 40wt%. In some embodiments, the pharmaceutical composition comprises CBD in a maximum amount of up to about 60wt%, about 55wt%, about 50wt%, about 45wt%, about 40wt%, about 35wt%, about 30wt%, about 25wt% or about 20wt%. It will be appreciated that the amount of CBD may be within the range from any of these minimum amounts to any of these maximum amounts. All combinations of these minimum and maximum amounts are contemplated. For example, in some embodiments, the pharmaceutical composition comprises CBD in an amount of from about 15wt% to about 60wt%, about 15wt% to about 55wt%, about 15wt% to about 40wt% or about 40wt% to about 55wt%.

[0053] In some embodiments, the pharmaceutical composition comprises THC and CBD in a minimum total amount of at least about 30wt%, for example, at least about 35wt%, about 40wt%, about 45wt%, about 50wt%, about 55wt%, about 60wt%, about 65wt%, about 70wt%, about 75wt%, about 80wt%, about 85wt%, about 90wt%, about 95wt% or about 99wt%. In some embodiments, the pharmaceutical composition comprises THC and CBD in a total maximum amount of up to about 99wt%, for example, up to about 95wt%, about 90wt%, about 85wt%, about 80wt%, about 70wt%, about 60wt%, about 50wt%, about 40wt%, about 30wt%, about 20wt% or about 15wt%. It will be appreciated that the total amount of CBD and THC may be within the range from any of these minimum amounts to any of these maximum amounts. All combinations of these minimum and maximum amounts

are contemplated. For example, in some embodiments, the pharmaceutical composition comprises CBD and THC in an amount of from about 30wt% to about 99wt%.

[0054] References to THC and CBD (and any other natural product, including cannabinoid(s), terpene(s) and terpenoid(s)) used herein include the relevant compound and pharmaceutically acceptable salts and/or solvates (including hydrates) thereof.

[0055] The THC and CBD may be combined from purified forms of the compounds, which may be purified after extraction from a natural source, or produced synthetically or semi-synthetically. Any means known in the art for producing CBD and/or THC is contemplated. Alternatively, the pharmaceutical composition may comprise a *Cannabis* extract comprising THC, CBD and a terpene fraction.

[0056] *Cannabis* plants produce a diverse array of secondary metabolites, including cannabinoids, terpenes, terpenoids, sterols, triglycerides, alkanes, squalenes, tocopherols, carotenoids and alkaloids. The mix of these secondary metabolites varies depending on several factors, including *Cannabis* variety, part of the *Cannabis* plant extracted, method of extraction, processing of the extract and season.

[0057] There are several varieties of *Cannabis* plant, which have been described under two distinct naming conventions. One of these conventions identifies three distinct species of *Cannabis* plant, namely *Cannabis sativa* Linnaeus, *Cannabis indica* LAM., and *Cannabis ruderalis*. Another convention identifies all *Cannabis* plants as belonging to the *Cannabis sativa* L. species, with the various varieties divided amongst several subspecies, including: *Cannabis sativa* ssp. *sativa* and ssp. *indica*. As used herein, the term "*Cannabis*" refers to any and all of these plant varieties.

[0058] Extracts of *Cannabis* may be prepared by any means known in the art. The extracts may be formed from any part of the *Cannabis* plant containing cannabinoid and terpene and/or terpenoid compounds. Extracts may be formed from a leaf, seed, trichome, flower, keif, shake, bud, stem or a combination thereof. The part of the *Cannabis* plant may be used fresh or dried prior to extraction. All known means of drying the plant material are contemplated. In some embodiments, the extract is formed by contacting any part of the *Cannabis* plant with an extractant. Any suitable extractant known in the art may be used, including, for example, alcohols (e.g. methanol, ethanol, propanol, butanol, propylene glycol etc.), water, hydrocarbons (e.g. butane, hexane, etc.), oils (e.g. olive oil, vegetable oil, essential oil, etc.), a polar organic solvent (e.g. ethyl acetate, polyethylene glycol, etc.) or a

supercritical fluid (e.g. liquid CO₂). The extractant may be completely or partially removed prior to incorporation of the *Cannabis* extract into the pharmaceutical composition, or it may be included in the pharmaceutical composition as a carrier. The extractant may be removed by heating the extract optionally under reduced pressure (e.g. under vacuum). It will be appreciated that some of the more volatile plant metabolites (such as terpenes) may also be removed with the extractant. Accordingly, in some embodiments, removing the extractant may enrich the cannabinoid fraction of the extract. In some embodiments, the extract is filtered to remove particulate material, for example, by passing the extract through filter paper or a fine sieve (e.g. a sieve with pore sizes of 5 µm).

[0059] In some embodiments, the *Cannabis* extract is formed by applying heat and/or pressure to the plant material. Typically, in these embodiments, no extractant is required.

[0060] In some embodiments, one or more additional compounds (e.g. cannabinoid, terpene or terpenoid compounds) may be added to the *Cannabis* extract. The addition of compounds may be to compensate for natural variations in the relative amounts of certain compounds being expressed in the *Cannabis* plant or may be to enhance the activity of one or more cannabinoid, terpene or terpenoid compounds present in the extract or to provide the desired amount of the compound that is added. The added compounds may be synthetic versions of the desired compounds, they may be purified compounds obtained from other *Cannabis* extracts, or they may be added by blending two or more *Cannabis* extracts.

[0061] The cannabinoid fraction typically accounts for the majority of the compounds present in the *Cannabis* extract.

[0062] In some embodiments, the *Cannabis* extract may comprise about 35% to about 95% by weight cannabinoids, for example, about 40% to about 90%, about 45% to about 70% or about 45% to about 55% by weight of the *Cannabis* extract. In some embodiments, the *Cannabis* extract comprises about 5% to about 65% by weight of non-cannabinoids, for example, about 5% to about 50%, about 10% to about 40% by weight or about 15% to about 30% by weight non-cannabinoids.

[0063] The cannabinoid fraction of a *Cannabis* extract may comprise a primary (or main) cannabinoid. As used herein, the term "primary cannabinoid" relates to the cannabinoid present in a *Cannabis* extract is the highest concentration. Typically, the primary cannabinoid may be Δ⁹-Tetrahydrocannabinol (THC) or cannabidiol (CBD). The primary cannabinoid may be present in the *Cannabis* extract in an amount of at least about 0.1%, about 0.5%, about

1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 10%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50% or about 55% by weight of the *Cannabis* extract. Accordingly, when THC is the primary cannabinoid, the *Cannabis* extract may comprise at least about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 4.5%, about 10%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50% or about 55% by weight Δ^9 -tetrahydrocannabinol (THC), for example, about 0.1% to about 97%, about 0.1% to about 20%, or about 50 to about 90% by weight of Δ^9 -tetrahydrocannabinol (THC). When CBD is the primary cannabinoid, the *Cannabis* extract may comprise at least about 0.1%, about 0.5%, about 1%, about 1.5%, about 2%, about 2.5%, about 3%, about 3.5%, about 4%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55% or about 60% by weight CBD, for example, about 0.1% to about 97%, about 0.1% to about 10% or about 50 to about 90% by weight CBD.

[0064] In addition to the primary cannabinoid, the *Cannabis* extract may further comprise a secondary cannabinoid. As used herein, the term “secondary cannabinoid” relates to the cannabinoid present in a *Cannabis* extract is the second highest concentration. The secondary cannabinoid is therefore present in the *Cannabis* extract in an amount less than the primary cannabinoid. In some embodiments where the primary cannabinoid is THC, the secondary cannabinoid may be CBD. In some embodiments where the primary cannabinoid is CBD, the secondary cannabinoid may be THC. The secondary cannabinoid may be present in the *Cannabis* extract in an amount of at least about 0.001% by weight, for example, at least about 0.005%, 0.01%, 0.05%, 0.1%, 0.5%, 1%, 1.5% or 2% by weight of the extract. The secondary cannabinoid may be present in a maximum amount of less than the amount of the primary cannabinoid, such as up to about 10%, for example, up to about 9%, 8%, 7%, 6%, 5% by weight of the extract. It will be appreciated that the amount of secondary cannabinoid may be within the range from any of these minimum amounts to any of these maximum amounts.

[0065] In some embodiments, the *Cannabis* extract is enriched in one and/or the other of CBD or THC. It has been shown that cannabinoids, including CBD and THC, interact with a class of G protein-coupled receptors (GPCRs) named the “cannabinoid receptors”, e.g. the CB1 or CB2 receptors. However, structurally related cannabinoid compounds may have vastly different activity. Despite these differences in activity, the present invention relies on the activity of the combination of THC, CBD and the terpene fraction.

[0066] In some embodiments, the *Cannabis* extract may comprise at least about 0.001% by weight THC and/or CBD, for example, from about 0.001% to about 99.999% by weight THC and/or CBD, at least about 0.001% to about 20% by weight THC and/or CBD, about 0.01% to about 20% by weight THC and/or CBD, about 0.01% to about 15% by weight THC and/or CBD.

[0067] In some embodiments, the *Cannabis* extract may comprise THC and CBD in a combined weight of at least about 1% by weight, for example, at least about 5% by weight. In some embodiments, the combined amount of CBD and THC may be 1-20%, 1-15%, 6-11% or 50-90% by weight of the pharmaceutical composition. The ratio of THC to CBD may be from about 100:0 to about 0:100, about 100:1 to about 1:100, about 80:1 to about 1:80, about 60:1 to about 1:60, about 40:1 to about 1:40 or about 20:1 to about 1:20. In some embodiments, the ratio of THC to CBD may be balanced, for example in a ratio of THC:CBD of about 2:1 to about 1:2 or about 1:1. The ratio of THC:CBD may be expressed as a single number by dividing the amount of THC by the amount of CBD present. Accordingly, the ratio of THC:CBD in the pharmaceutical compositions may be 0.001, 0.1, 0.2, 0.3, 0.4, 0.45, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2, 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 3, or higher. In some embodiments, the ratio of THC:CBD in a *Cannabis* extract may be between any of these values, for example, from 0.001 to 3, 0.2 to 3 or 0.4 to 2.6.

[0068] Embodiments of the pharmaceutical composition comprising a balanced amount of THC and CBD may be obtained by, for example, adding CBD to a *Cannabis* extract that comprises THC as primary cannabinoid, adding THC to a *Cannabis* extract that comprises CBD as primary cannabinoid, or combining a *Cannabis* extract comprising THC as primary cannabinoid with a *Cannabis* extract comprising CBD as primary cannabinoid.

[0069] Embodiments of the pharmaceutical composition enriched in one or the other of THC or CBD may be obtained by, for example, adding purified or synthetic THC or CBD to a *Cannabis* extract, to obtain the desired amount of THC or CBD or the desired ratio of THC to CBD.

[0070] Typically, the *Cannabis* extract may also comprise other cannabinoids in addition to THC and/or CBD, such as any of the cannabinoids previously identified in *Cannabis* extracts. To date, over 100 cannabinoids have been identified in *Cannabis* plants. A comprehensive list of these cannabinoids may be found in Mahmoud A. El Sohly and Waseem Gul, "Constituents of *Cannabis Sativa*." *In Handbook of Cannabis* Roger Pertwee (Ed.) Oxford University Press (2014) (ISBN: 9780199662685). Cannabinoids that have been

identified in *Cannabis* plants include: Cannabigerol (E)-CBG-C5, Cannabigerol monomethyl ether (E)-CBGM-C5 A, Cannabigerolic acid A (Z)-CBGA-C5 A, Cannabigerovarin (E)-CBGV-C3, Cannabigerolic acid A (E)-CBGA-C5 A, Cannabigerolic acid A monomethyl ether (E)CBGAM-C5 A and Cannabigerovarinic acid A (E)-CBGVAC3A; (±)-Cannabichromene CBC-C5, (±)-Cannabichromenic acid A CBCA-C5 A, (±)-Cannabivarichromene, (±)-Cannabichromevarin CBCV-C3, (±)-Cannabichromevarinic acid A CBCVA-C3 A; (-)-Cannabidiol CBD-C5, Cannabidiol momomethyl ether CBDMC5, Cannabidiol-C4 CBD-C4, (-)-Cannabidivarin CBDVC3, Cannabidiorcol CBD-CI, Cannabidiolic acid CBDA-C5, Cannabidivarinic acid CBDVA-C3; Cannabinodiol CBND-C5, Cannabinodivarin CBND-C3; Δ^9 -Tetrahydrocannabinol Δ^9 -THC-C5, Δ^9 -Tetrahydrocannabinol-C4 Δ^9 -THCC4, Δ^9 -Tetrahydrocannabivarin Δ^9 -THCV-C3, Δ^9 -Tetrahydrocannabiorcol Δ^9 -THCO-CI, Δ^9 -Tetrahydrocannabinolic acid A Δ^9 -THCA-C5 A, Δ^9 -Tetrahydrocannabinolic acid B Δ^9 -THCA-C5 B, Δ^9 -Tetrahydrocannabinolic acid-C4 A and/or B Δ^9 -THCA-C4 A and/or B, Δ^9 -Tetrahydro-cannabivarinic acid A Δ^9 -THCVA-C3 A, Δ^9 -Tetrahydrocannabiorcolic acid A and/or B Δ^9 -THCOA-CI A and/or B), (-)- Δ^8 -trans-(6aR,10aR)- Δ^8 -Tetrahydrocannabinol Δ^8 -THC-C5, (-)- Δ^8 -trans-(6aR,10aR)-Tetrahydrocannabinolic acid A Δ^8 -THCA-C5 A, (-)-(6aS,10aR)- Δ^9 -Tetrahydrocannabinol (-)-cis- Δ^9 -THC-C5; Cannabinol CBN-C5, Cannabinol-C4 CBN-C4, Cannabivarin CBN-C3, Cannabinol C2 CBN-C2, Cannabiorcol CBN-CI, Cannabinolic acid A CBNA-C5 A, Cannabinol methyl ether CBNM-C5, (-)-(9R,10R)-trans-Cannabitriol (-)-trans-CBT-C5, (+)-(9S,10S)-Cannabitriol (+)-trans-CBT-C5, (±)-(9R,10S/9S,10R)—); Cannabitriol (±)-cis-CBT-C5, (-)-(9R,10R)-trans-10-O-Ethylcannabitriol (-)-trans-CBT-OEt-C5, (±)-(9R,10R/9S,10S)-Cannabitriol-C3 (±)-trans-CBT-C3, 8,9-Dihydroxy- Δ^6 a(10a)-tetrahydrocannabinol 8,9-Di-OH-CBT-C5, Cannabidiolic acid A cannabitriol ester CBDA-C5 9-OH-CBT-C5 ester, (-)-(6aR,9S,10S,10aR)-9,10-Dihydroxyhexahydrocannabinol, Cannabiripsol, Cannabiripsol-C5, (-)-6a,7,10a-Trihydroxy- Δ^9 -tetrahydrocannabinol (-)-Cannabitetrol, 10-Oxo- Δ^6 a(10a)tetrahydrocannabinol OTHC); (5aS,6S,9R,9aR)-Cannabielsoin CBE-C5, (5aS,6S,9R,9aR)-C3-Cannabielsoin CBE-C3, (5aS,6S,9R,9aR)-Cannabielsoic acid A CBEA-C5 A, (5aS,6S,9R,9aR)-Cannabielsoic acid B CBEA-C5 B; (5aS,6S,9R,9aR)-C3-Cannabielsoic acid B CBEA-C3 B, Cannabiglendol-C3 OH-iso-HHCV-C3, Dehydrocannabifuran DCBF-C5, Cannabifuran CBF-C5), (-)- Δ^7 -trans-(1R,3R,6R)-Isotetrahydrocannabinol, (±)- Δ^7 -1,2-cis-(1R,3R,6S/1S,3S,6R)-Isotetrahydrocannabivarin, (-)- Δ^7 -trans-(1R,3R,6R)-Isotetrahydrocannabivarin; (±)-(1aS,3aR,8bR,8cR)-Cannabicyclol CBL-C5, (±)-(1aS,3aR,8bR,8cR)-Cannabicyclic acid A CBLA-C5 A,

(±)-(1aS,3aR,8bR,8cR)-Cannabicyclovarin CBLV-C3; Cannabicitran CBTC5; Cannabichromanone CBCN-C5, CannabichromanoneC3 CBCN-C3, and Cannabicumaronone CBCON-C5.

[0071] In some embodiments, the *Cannabis* extract further comprises one or more of Δ^9 -Tetrahydrocannabinolic acid (THCA), Δ^9 -Tetrahydrocannabivarin (THCV), (-)-Cannabidivarin (CBDV), Cannabinodiol (CBN), Cannabichromene (CBC) and Cannabigerol (CBG). Each of these cannabinoids may be present in an amount from about 0.001% to about 40% by weight of the *Cannabis* extract. Typically, the other cannabinoids are present in amounts lower than the primary cannabinoid or, if present, the secondary cannabinoid(s).

[0072] In some embodiments, certain cannabinoids may be absent, or present in non-detectable amounts (e.g. less than about 0.001% by weight of the analyte). In some embodiments, the *Cannabis* extract may exclude one or more of the following cannabinoids: Δ^9 -Tetrahydrocannabinolic acid (THCA), Δ^9 -Tetrahydrocannabivarin (THCV), Cannabidiolic acid (CBDA), Cannabinodiol (CBN), (-)-Cannabidivarin (CBDV), Cannabigerol (CBG) and Cannabichromene (CBC).

[0073] *Cannabis* extracts may further comprise a non-cannabinoid fraction. The non-cannabinoid fraction may include a terpene fraction. In some embodiments, the *Cannabis* extract comprises a terpene fraction in an amount of less than about 50% by weight, for example, less than about 45%, about 40%, about 35%, about 30%, about 25%, about 20%, about 15%, about 10%, about 9%, about 8%, about 7%, about 6%, about 5%, about 4%, about 3%, about 2% or about 1% by weight of the extract. In some embodiments, the *Cannabis* extract may comprise terpene and terpenoid compounds in an amount of at least about 0.001% by weight of the extract, for example, at least about 0.005%, about 0.01%, about 0.05%, about 0.1%, about 0.2%, about 0.25%, about 0.3%, about 0.35%, about 0.4%, about 0.45%, about 0.5%, about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 10%, about 15% or more of the total weight of the extract. In some embodiments, the pharmaceutical composition comprises about 0.001% to about 50% by weight of terpene and terpenoid compounds, for example, about 0.01% to about 50% by weight, about 0.01% to about 10% by weight, about 0.01% to about 6% by weight or about 0.01 to about 5% by weight of the pharmaceutical composition.

[0074] Typically, the terpene fraction in the plant material used to form the extract may have a different terpene/terpenoid profile than the terpene profile of the final extract, both in terms of the amounts of specific compounds in the terpene fraction and the weight of the

terpene fraction relative to the other components. For example, a *Cannabis* flower may comprise about 20% by weight cannabinoids and about 3% by weight terpenes. Following extraction and concentration (i.e. removal of the extractant), the cannabinoid fraction may amount to about 50-90% by weight and the terpene fraction may amount to about 0.1-6% by weight of the *Cannabis* extract. This typical scenario shows that the cannabinoids are concentrated when the extractant is removed, the relative amount of the terpene fraction is reduced, likely due to the volatility of many of the terpenes/terpenoids present in the terpene fraction. Therefore, the profile of the terpene fraction present in the *Cannabis* extract is significantly different from the profile of the terpene fraction that exists in Nature.

[0075] The efficacy of a composition may be enhanced when the terpene fraction has a certain profile, i.e. a certain proportion of particular terpenes/terpenoids are present in the extract. It is believed that the increase in efficacy may be synergistic (i.e. non-additive). It is also believed that the presence of specific components in the terpene fraction may enhance the patient's tolerance to cannabinoid therapy.

[0076] A variety of terpenes and terpenoids have also been identified in *Cannabis* extracts, including monoterpenes, monoterpenoids, sesquiterpenes and sesquiterpenoids. For example, the following terpenes and terpenoids have been identified in *Cannabis* extracts: Alloaromadendrene, allyl hexanoate, benzaldehyde, (Z)- α -cis-bergamotene, (Z)- α -trans-bergamotene, β -bisabolol, epi- α -bisabolol, β -bisabolene, borneol (camphol), cis- γ -bisabolene, bomeol acetate (bomyl acetate), α -cadinene, camphene, camphor, cis-carveol, caryophyllene (β -caryophyllene), α -humulene (α -caryophyllene), γ -cadinene, Δ -3-carene, caryophyllene oxide, 1,8-cineole, citral A, citral B, cinnamaldehyde, α -copaene (aglaiene), γ -curcumene, β -cymene, p-cymene, β -elemene, γ -elemene, ethyl decadienoate, ethyl maltol, ethyl propionate, ethylvanillin, eucalyptol, α -eudesmol, β -eudesmol, γ -eudesmol, eugenol, cis- β -farnesene ((Z)- β -farnesene), trans- α -farnesene, trans- β -farnesene, trans- γ -bisabolene, fenchone, fenchol (norbomanol, β -fenchol), geraniol, α -guaiene, guaiol, gurjunene, methyl anthranilate, methyl salicylate, 2-methyl-4-heptanone, 3-methyl-4-heptanone, hexyl acetate, ipsdienol, isoamyl acetate, lemenol, limonene, d-limonene (limonene), linolool (linalyl alcohol, β -linolool), α -longipinene, menthol, γ -muurolene, myrcene (β -myrcene), nerolidol, trans-nerolidol, nerol, β -ocimene (cis-ocimene), octyl acetate, α -phellandrene, phytol, α -pinene (2-pinene), β -pinene, pulegone, sabinene, cis-sabinene hydrate (cis-thujanol), β -selinene, α -selinene, γ -terpinene, terpinolene (isoterpine), terpineol (α -terpineol), terpineol-4-ol, α -terpinene (terpilene), α -thujene (organene), vanillin, viridiflorene (ledene), and α -ylange. In

some embodiments, the pharmaceutical composition comprises one or more of these terpenes and/or terpenoids, for example, the terpene fraction may comprise 2, 3, 4, 5, 6, 7, 8, 9, 10 or more of these compounds. In some embodiments, the terpene fraction comprises all of the above terpene and terpenoid compounds.

[0077] In some embodiments, the *Cannabis* extract may comprise one or more of β -myrcene, α -terpinene, linalool, α -phellandrene, camphene, terpinolene, p-cymene, 1,8-cineole, β -caryophyllene, d-limonene, γ -terpinene, α -pinene, guaial, gurjunene, β -ocimene, β -pinene, γ -cadinene, caryophyllene oxide, nerolidol and β -farnesene. For example, the *Cannabis* extract may comprise one, two, three, four, five or more of these terpenes/terpenoids. Each of these terpenoids may be absent or may be present in an amount in the range of 0.001 % to 50 % by weight of the terpene fraction.

[0078] In some embodiments, the terpene fraction comprises at least one of β -myrcene, α -terpinene, linalool, α -phellandrene, camphene, terpinolene, p-cymene, 1,8-cineole, β -caryophyllene, d-limonene, γ -terpinene, α -pinene and guaial, especially at least two, at least three or at least four of these terpene/terpenoids.

[0079] In some embodiments, the terpene fraction comprises at least one of β -myrcene, α -terpinene, linalool, α -phellandrene, camphene, terpinolene, p-cymene, 1,8-cineole and β -caryophyllene, especially at least two, at least three or at least four of these terpene/terpenoids.

[0080] In some embodiments, the terpene fraction comprises at least one of β -myrcene, α -terpinene, linalool and α -phellandrene, especially two, three or four of these terpenes. In some embodiments the terpene fraction comprises all of β -myrcene, α -terpinene, linalool and α -phellandrene.

[0081] In some embodiments, the terpene fraction comprises at least one of the combinations β -myrcene and α -terpinene; β -myrcene and linalool; β -myrcene and α -phellandrene; α -terpinene and linalool; α -terpinene and α -phellandrene; linalool and α -phellandrene; β -myrcene, α -terpinene and linalool; β -myrcene, α -terpinene and α -phellandrene; β -myrcene, linalool and α -phellandrene; α -terpinene, linalool and α -phellandrene; and β -myrcene, α -terpinene, linalool and α -phellandrene or any of the above combinations with one or more terpene/terpenoids selected from camphene, terpinolene, p-cymene, 1,8-cineole and β -caryophyllene.

[0082] In some embodiments, specific terpenes or terpenoids may be absent, or present in non-detectable amounts (e.g. less than about 0.001% by weight of the analyte).

[0083] The identity and amounts of terpenes and/or terpenoids obtained by extraction of a *Cannabis* plant may be determined by methods known in the art, including gas chromatography (GC). Typically, the profile of a cannabinoid fraction and a terpene fraction of a *Cannabis* extract are determined separately using different analytical techniques.

[0084] The pharmaceutical composition comprises THC, CBD and a terpene fraction. In some embodiments, the pharmaceutical composition consists of a *Cannabis* extract and optionally one or more pharmaceutically acceptable excipients, such as a carrier. In some embodiments, the pharmaceutical composition comprises a *Cannabis* extract to which has been added one or more of THC, CBD, terpenes and/or terpenoids. The addition of compounds may be to compensate for natural variations in the relative amounts of certain compounds being expressed in the *Cannabis* plant or may be to enhance the activity of one or more cannabinoid, terpene or terpenoid compounds present in the extract or to provide the desired amount of the compound that is added. Terpenes and/or terpenoids may be added to adjust their content in the pharmaceutical composition to compensate for loss during an extraction process or to provide a desired non-natural terpene/terpenoid content in the pharmaceutical composition. The added compounds may be synthetic versions of the desired compounds, they may be purified compounds obtained from other *Cannabis* extracts or from other plant extracts, or they may be added by blending two or more *Cannabis* extracts.

[0085] In some embodiments, the pharmaceutical composition optionally comprises one or more pharmaceutically acceptable excipient(s). The excipient may be a carrier, diluent, adjuvant, or other excipient, or any combination thereof, and "pharmaceutically acceptable" meaning that they are compatible with the other ingredients of the pharmaceutical composition and are not deleterious to a patient upon or following administration. The pharmaceutical compositions may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilisers, flavours, etc.) according to techniques such as those well known in the art of pharmaceutical formulation (See, for example, Remington: The Science and Practice of Pharmacy, 21st Ed., 2005, Lippincott Williams & Wilkins). The pharmaceutically acceptable carrier may be any carrier included in the United States Pharmacopeia/National Formulary

(USP/NF), the British Pharmacopoeia (BP), the European Pharmacopoeia (EP), or the Japanese Pharmacopoeia (JP). In some embodiments, the excipient may be non-natural (e.g. synthetically produced).

[0086] The pharmaceutical composition includes those suitable for oral, rectal, nasal, topical (including oro-mucosal such as buccal and sublingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

[0087] The ingredients of the pharmaceutical composition may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules or syringes, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use.

[0088] Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active ingredient(s), and such unit dosage forms may contain any suitable effective amount of the active ingredients commensurate with the intended daily dosage range to be employed.

[0089] For preparing pharmaceutical compositions described herein, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispensable granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

[0090] Suitable carriers include magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

[0091] Liquid form preparations include solutions, dispersions, suspensions, and emulsions, for example, water or water-propylene glycol solutions or in oils such as vegetable oils. For example, parenteral injection liquid preparations can be formulated as

solutions in aqueous polyethylene glycol solution. Liquid preparations are preferred for embodiments involving sublingual administration.

[0092] In some embodiments, the pharmaceutical composition is formulated for sublingual or buccal administration. Typically, a sublingual or buccal pharmaceutical composition is a liquid; however, any other suitable dosage form known in the art may be employed including aerosols, lozenges, troches, films, foams, pastes and dissolvable tablets.

[0093] Sterile liquid form pharmaceutical compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient(s) may be suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both.

[0094] Other liquid form preparations include those prepared by combining the *Cannabis* extract with one or more naturally derived oils (e.g. an essential oil) or waxes. An "essential oil" is an oil derived by extraction (e.g. steam extraction, or contacting the plant material with an extractant) or pressing, which contains primarily hydrophobic, and generally fragrant, components of the plant material. Suitable naturally derived oils and waxes include Sesame oil, Olive oil, Arnica essential oil, Lavender essential oil, Lavender Spike essential oil, Frankincense essential oil, Lemongrass essential oil, Cinnamon Leaf essential oil, Rosemary Cineole essential oil, Rosemary essential oil, Bergamot essential oil, Myrrh essential oil, Sage essential oil, Coconut oil, Bees wax and Hemp oil.

[0095] The pharmaceutical compositions may be formulated for parenteral administration (e. g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers optionally with an added preservative. The pharmaceutical compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

[0096] Pharmaceutical forms suitable for injectable use include sterile injectable solutions or dispersions, and sterile powders for the extemporaneous preparation of sterile injectable solutions. They should be stable under the conditions of manufacture and storage

and may be preserved against oxidation and the contaminating action of microorganisms such as bacteria or fungi.

[0097] The solvent or dispersion medium for the injectable solution or dispersion may contain any of the conventional solvent or carrier systems, and may contain, for example, water, ethanol, polyol (for example, glycerol, propylene glycol and liquid polyethylene glycol, and the like), suitable mixtures thereof, and vegetable oils.

[0098] Pharmaceutical forms suitable for injectable use may be delivered by any appropriate route including intravenous, intramuscular, intracerebral, intrathecal, epidural injection or infusion.

[0099] Sterile injectable solutions are prepared by incorporating the active ingredients in the required amount in the appropriate carrier with various other ingredients such as those enumerated above, as required, followed by sterilisation. Generally, dispersions are prepared by incorporating the various sterilised active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, preferred methods of preparation are vacuum drying or freeze-drying of a previously sterile suspension of the active ingredient plus any additional desired ingredients.

[0100] For oral administration, the active ingredient(s) may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like.

[0101] The amount of active ingredient(s) in a therapeutically useful pharmaceutical composition should be sufficient that a suitable dosage will be obtained. Accordingly, the active ingredient(s) are preferably provided in an effective amount.

[0102] The tablets, troches, pills, capsules and the like may also contain the components as listed hereafter: a binder such as gum, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, lactose or saccharin may be added or a flavouring agent such as

peppermint, oil of wintergreen, or cherry flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier.

[0103] Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance, tablets, pills, or capsules may be coated with shellac, sugar or both. A syrup or elixir may contain the active ingredient(s), sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavouring such as cherry or orange flavour. Of course, any material used in preparing any dosage unit form should be pharmaceutically pure and substantially non-toxic in the amounts employed. In addition, the active ingredient(s) may be incorporated into sustained-release preparations and formulations, including those that allow specific delivery of the active peptide to specific regions of the gut.

[0104] Aqueous solutions can be prepared by dissolving the active ingredient(s) in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired. Aqueous suspensions can be made by dispersing the finely divided active ingredient(s) in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well-known suspending agents.

[0105] Pharmaceutically acceptable carriers and/or diluents include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like.

[0106] Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral and/or sublingual administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active ingredient(s), colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents, and the like.

[0107] For topical administration to the epidermis the active ingredient(s) may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

[0108] Formulations suitable for topical administration in the mouth (oro-mucosal e.g. sublingual or buccal administration) include any liquid formulation described herein, preferably liquid formulations with a viscosity suitable for administration by dropper or syringe; lozenges comprising active ingredient(s) in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient(s) in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient(s) in a suitable liquid carrier.

[0109] For administration to the nasal cavity, solutions or suspensions may be applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension.

[0110] In the case of a spray, this may be achieved for example by means of a metering atomising spray pump. For such sprays, active ingredient(s) may be encapsulated with cyclodextrins, or formulated with other agents expected to enhance delivery and retention in the nasal mucosa.

[0111] Administration to the respiratory tract may be achieved by means of an aerosol formulation in which the active ingredient(s) are provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas.

[0112] The aerosol may conveniently also contain a surfactant. The dose of drug may be controlled by provision of a metered valve.

[0113] Alternatively, the active ingredient(s) may be provided in the form of a dry powder, for example a powder mix of the active ingredient(s) in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). The pharmaceutical composition as a powder may be presented in unit dose form for example in capsules or cartridges of, e.g. gelatin, or blister packs from which the powder may be administered by means of an inhaler.

[0114] In formulations intended for administration to the respiratory tract, including intranasal formulations, the pharmaceutical composition may have a small particle size for example of the order of 5 to 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

[0115] When desired, formulations adapted to give sustained release of the active ingredient(s) may be employed.

[0116] The pharmaceutical composition may be prepared in unit dosage form. In such form, the composition is subdivided into unit doses containing appropriate quantities of the active ingredient(s). The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

[0117] Pharmaceutical compositions for parenteral administration may also be provided in unit dosage form for ease of administration and uniformity of dosage. Unit dosage form as used herein refers to physically discrete units suited as unitary dosages for the patients to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical excipient. The specification for the unit dosage forms are dictated by and directly dependent on (a) the unique characteristics of the active ingredient(s) and the particular therapeutic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active ingredient(s) for the treatment of living patients having a diseased condition in which bodily health is impaired.

[0118] In some embodiments, the pharmaceutical composition comprises a further active ingredient. In some embodiments, the pharmaceutical composition comprises a further active ingredient other than a cannabinoid and/or terpene. Any suitable further active ingredient may be used provided that the activity of the active ingredient, THC, CBD and the terpene fraction is not diminished when combined. In some embodiments, the further active ingredient is an analgesic or antinoiceptive drug or an opioid antagonist. In some embodiments, the analgesic or antinoiceptive drug is a non-opioid analgesic or antinoiceptive drug. Suitable non-opioid analgesic or antinoiceptive drugs include FAAH inhibitors (such as paracetamol), non-steroidal antiinflammatory drugs (NSAIDs) (such as

ibuprofen, aspirin and naproxen), COX-2 inhibitors (such as refecoxib, celecoxib and etoricoxib), anti-depressants (such as amitriptyline, duloxetine, hydroxyzine, promethazine, carisoprodol, tripeleennamine, clomipramine, amitriptyline), adjuvant analgesics (such as nefopam, orphenadrine, pregabalin, cyclobenzaprine, hycosine), anticonvulsants (such as carbamazepine, gabapentin), non-opioid NMDA antagonists (such as piritamide and flupirtine), stimulants (such as methylphenidate, caffeine, ephedrine, dextroamphetamine, methamphetamine, pseudoephedrine, phenylephrine and cocaine), and combinations thereof. Opioid antagonists include naloxone, naltrexone, nalmeferone, nalorphine, nalorphine dinicotinate, levallorphan, samidorphan, cyprodime, naltrindole, norbinaltorphimine, J-113,397, AT-076 and combinations thereof.

[0119] In some embodiments, the further active ingredient is an opioid. These embodiments may be useful during the early phases of treatment, or during the tapering phase of the therapy. Suitable opioids include morphinan opioids and non-morphinan opioids, for example, oxycodone, hydrocodone, oxymorphone, morphine, codeine, fentanyl, buprenorphine, tramadol, pethidine, and combinations thereof. The pharmaceutical composition may comprise an opioid in an effective amount, or in a sub-clinical amount.

[0120] The practice of the present invention employs, unless otherwise indicated, conventional pharmaceutical, veterinary and medical techniques within the skill of the art. Such techniques are well known to the skilled worker, and are explained fully in the literature.

Methods of treatment

[0121] The present invention provides a method for treating pain, comprising administering to a subject in need thereof an effective amount of a pharmaceutical composition of the invention.

[0122] Any pharmaceutical composition described herein may be used in this method.

[0123] In some embodiments, the method is for treating chronic pain. Chronic pain includes any pain requiring treatment for a period of greater than 1 month, for example, 6 months, 8 months, 10 months, 1 year or longer.

[0124] In some embodiments, the method is for treating pain that is not associated with cancer or cancer therapy (sometimes referred to as non-cancer pain).

[0125] In some embodiments, the method is for treating chronic non-cancer pain.

[0126] The methods will be understood as treating pain associated with the activity of the endocannabinoid system or the activity of any of the cannabinoid receptors, including CB1 and/or CB2.

[0127] The pain treated in the present methods may be noiceptive pain, psychogenic pain and/or neuropathic pain. Noiceptive pain is associated with stimulation of sensory nerve endings (or noiceptors). Psychogenic pain is associated with psychological factors resulting in a pain disorder (often diagnosed when other physical causes for pain are ruled out). Neuropathic pain is associated with damage or malfunction of the peripheral nervous system (PNS) or central nervous system (CNS). The *Cannabis* extracts of the invention contain compounds that act on different endocannabinoid receptors, and it is therefore believed that various embodiments of the pharmaceutical composition of the invention may be used in the treatment of all forms of pain.

[0128] In some embodiments, the dosage of THC administered to the subject may be from about 5mg to about 100mg per day, for example, from about 10mg to about 90mg, about 30mg to about 60mg or about 50mg per day.

[0129] In some embodiments, the dosage of CBD administered to the subject may be from about 5mg to about 100mg per day, for example, from about 10mg to about 90mg, about 30mg to about 60mg or about 50mg per day.

[0130] The dosage of the terpene fraction will typically be about 0.01wt% to about 20wt% or about 0.1wt% to about 6wt% based on the amount of THC or CBD, whichever is greater.

[0131] The effective amount of the pharmaceutical composition of the invention may be held constant throughout the dosage regimen, or it may be altered depending on the symptoms of the subject. In some embodiments, the method further comprises a step of titrating the dose of the pharmaceutical composition for an individual subject.

[0132] In some embodiments, the pharmaceutical composition may be administered 1, 2, 3, 4 or more times per day.

[0133] The method may comprise administering more than one pharmaceutical composition of the present invention to the patient in need thereof. For example, in some circumstances, it is preferred to administer a pharmaceutical composition high in THC (or THC-rich) and a pharmaceutical composition high in CBD (or CBD-rich) to the patient. These pharmaceutical compositions may be administered in an alternating order and separated by

a period of time. For example, the administration of THC-rich and CBD-rich formulations may be on alternating days, alternating sequences of days, or alternating from a THC-rich formulation before a period of sleep (e.g. at night) to a CBD-rich formulation after a period of sleep (e.g. in the morning).

[0134] THC-rich formulations include those being substantially free of CBD (e.g. less than about 0.001wt%) and those where the ratio of THC:CBD is greater than 2:1, for example, at least 2.5:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 or 10:1. In some embodiments, the THC-rich formulation comprises a *Cannabis* extract comprising THC as primary cannabinoid and a terpene fraction.

[0135] CBD-rich formulations include those being substantially free of THC (e.g. less than about 0.001wt%) and those where the ratio of CBD:THC is greater than 2:1, for example, at least 2.5:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1 or 10:1. In some embodiments, the THC-rich formulation comprises a *Cannabis* extract comprising CBD as primary cannabinoid and a terpene fraction.

[0136] The methods of the invention may involve the following dosage regimen:

- (1) administering an effective amount of a THC-rich formulation preceding a period of sleep of the subject, followed by
- (2) administering an effective amount of a CBD-rich formulation following a period of sleep of the subject; and optionally
- (3) administering an effective amount of a further THC-rich formulation for the management of breakthrough pain.

[0137] The method may also comprise administering any of the further active ingredient(s) described above including any of the opioid and non-opioid analgesic and/or antinociceptive drugs described above. This further active ingredient may be administered simultaneously, separately or consecutively with pharmaceutical compositions of the invention. By simultaneously it is meant that each of pharmaceutical composition and the other active ingredient are administered at the same time either in the same pharmaceutical composition. By separately it is mean that each of pharmaceutical composition and the other active ingredient are administered at the same time in different pharmaceutical compositions and optionally by different routes of administration. By consecutively it is meant that each of pharmaceutical composition and the other active ingredient are administered separately and may be at different times. Typically, when the pharmaceutical composition and the other active ingredient are administered consecutively they are administered within 24 hours, or within 12, 8, 6, 5, 4, 3, 2, or 1 hour(s) of each other. The pharmaceutical composition may be

administered before or after the other active ingredient. Further, the route of administration for the pharmaceutical composition and the other active ingredient may be the same or different.

[0138] The pharmaceutical composition may be administered by any suitable route of administration.

[0139] The present invention also provides use of one or more of (a) THC, (b) CBD and (c) a *Cannabis* extract in the manufacture of a medicament for treating chronic non-cancer pain, wherein the medicament comprises THC, CBD and a terpene fraction. The *Cannabis* extract comprises at least the terpene fraction obtained by extraction of a *Cannabis* plant. In some embodiments, the *Cannabis* extract also comprises THC and CBD; however, where one or both of these cannabinoids are absent from the *Cannabis* extract used in the manufacture of the medicament, they may be added from another source, for example, from a synthetic source or from one or more further *Cannabis* extracts. The *Cannabis* extract may be obtained by any of the methods described above.

[0140] Also provided is a pharmaceutical composition comprising THC, CBD and a terpene fraction obtained by extraction of a *Cannabis* plant for treating chronic non-cancer pain.

[0141] Accordingly, also described here is an analgesic and/or antinociceptive agent comprising a pharmaceutical composition of the invention. The analgesic and/or antinociceptive agent may comprise any pharmaceutical composition described herein in an effective amount for treating pain. The analgesic and/or antinociceptive agent may therefore comprise a therapeutically effective amount of THC, CBD and the terpene fraction.

[0142] The present invention further provides a kit comprising in separate parts: (A) THC and (B) CBD, wherein at least one of the parts (a) and/or (b) further comprise a terpene fraction obtained from extraction of a *Cannabis* plant.

[0143] The present invention further provides a kit comprising in separate parts: (a) an effective amount of a THC-rich pharmaceutical composition of the invention, and (b) an effective amount of a CBD-rich pharmaceutical composition of the invention.

Example(s)

[0144] The invention will be further described by way of non-limiting example(s). It will be understood to persons skilled in the art of the invention that many modifications may be made without departing from the spirit and scope of the invention.

Example 1 – Preparation of oral formulation

[0145] Oral capsules were prepared from *Cannabis* extracts obtained by extraction of a *Cannabis* plant with ethanol, followed by removal of extractant by heating *in vacuo*. This resulted in a solid granule, which was divided into capsules having the constitution described in Table 1.

Table 1. Orally bioavailable capsules

Ingredient	Amount per capsule
THC ¹	50mg
CBD ¹	50mg
Excipient(s)	qs 150mg

Notes: (1) The THC and CBD are obtained from extraction of a *Cannabis* plant and each cannabinoid comprises up to about 6wt% of a terpene fraction from the extraction process.

Example 2 – The effectiveness of medicinal *Cannabis* in a rapid opioid dose taper regimen for patients with chronic non-cancer pain

[0146] Twenty (20) patients with chronic non-cancer pain on a stable opioid medication regimen of daily morphine equivalent dose of >60mg for more than 12 months are enrolled into a double blind, randomized, placebo-controlled Phase II study.

[0147] These patients are administered the capsule of Example 1 once daily, in addition to their opioid therapy. The opioid dosage is reduced over a period of 10 weeks by 10wt% per week. This treatment period is followed by a period of 6 weeks follow-up where patients are administered neither cannabinoid or opioid therapy.

[0148] Amongst other endpoints, this study provides data supporting the use of cannabinoid-therapy for treating non-cancer chronic pain. This is assessed during reviews prior to commencement of the trial and in Weeks 5, 10 and 16 of the study. These reviews include:

- Time Line Follow Back – alcohol and tobacco use in preceding 30 days,
- Self-reported psycho-social functioning using:
 - Pain Self-efficacy questionnaire (PSEQ),
 - Pain Catastrophizing Scale (PCS),
 - K10 (Kessler Psychological Distress Scale),
 - DASS21 (Depression, Anxiety and Stress Rating Scale, 21 questions), and/or
 - ATOP Version 7.

[0149] The data collected during these scheduled reviews assess the following endpoints:

- a. Change in opioid analgesia (OMEDD) from baseline at 5 weeks, 10 weeks, and 16 weeks (%).
- b. Number of weeks until stepped dose taper is halted.
- c. Retention in dose taper regimen at 5 weeks and 10 weeks.
- d. Self-reported pain scores (Brief Pain Inventory) – daily.
- e. Patient characteristics at baseline, 5, 10, and 16 weeks:
- f. Pain Self-efficacy questionnaire (PSEQ)
- g. Pain Catastrophizing Scale (PCS)
- h. K10 (Kessler Psychological Distress Scale),
- i. DASS21 (Depression, Anxiety and Stress Rating Scale, 21 questions),
- j. ATOP (Australian Treatment Outcome Profile, version 7),
- k. Urine profiles of cannabinoid metabolites (THC and its primary metabolite (THC-COOH) and CBD and its primary metabolite (CBD-7-oic acid)) (taken weekly).
- l. Adverse events during the treatment period. This is assessed by a self-report Adverse Events Checklist administered by a clinician during assessment.

[0150] Each of endpoints a.-j. assesses the efficacy of analgesia/antinociception of the formulation.

Example 3 – Mouse models for treatment of neuropathic pain

[0151] The pharmaceutical compositions of the invention are tested in an established mouse model for pain treatment, for example, see WO2012/160358, the contents of which is entirely incorporated herein by reference. Other suitable animal models for various pain types are reviewed in the book: National Research Council (US) Committee on Recognition and Alleviation of Pain in Laboratory Animals. Recognition and Alleviation of Pain in Laboratory Animals. Washington (DC): National Academies Press (US); 2009. A, Models of Pain, the contents of which are entirely incorporated herein by reference.

[0152] Cannabidiol (CBD) is used as positive control as previous studies have demonstrated positive results in the animal models of pain used in this example.

[0153] The formulations are administered orally or by intraperitoneal (i.p.) gavage.

[0154] Male CD-1 mice (35-40 g) are housed under controlled illumination (12:12 h light: dark cycle; light on 06.00 h) and environmental conditions (room temperature 20-22° C,

humidity 55-60%) for at least 1 week before the commencement of experiments. Mouse chow and tap water are available *ad libitum*. All efforts are made to minimize animal suffering and to reduce the number of animals used.

[0155] Behavioural testing is performed before surgery to establish a baseline for comparison with post-surgical values.

[0156] Mice are anaesthetized with sodium pentobarbital (60 mg/kg i.p.). The right hind limb is immobilized in a lateral position and slightly elevated. Incision is made at mid-thigh level using the femur as a landmark. The sciatic nerve is exposed at mid-thigh level distal to the trifurcation and freed of connective tissue; the three peripheral branches (sural, common peroneal, and tibial nerves) of the sciatic nerve are exposed without stretching nerve structures.

[0157] Both tibial and common peroneal nerves are ligated and transacted together. A micro-surgical forceps with curved tips is delicately placed below the tibial and common peroneal nerves to slide a thread (e.g. 5.0 silk, Ethicon, Johnson, and Johnson Intl, Brussels, Belgium or similar) around the nerves. A tight ligation of both nerves is performed. The sural nerve is carefully preserved by avoiding any nerve stretch or nerve contact with surgical tools. Muscle and skin are closed in two distinct layers with sutures (e.g. silk 5.0, or similar).

[0158] Sham-operated mice underwent the operation but the manipulations of the nerves were omitted.

[0159] Intense, reproducible and long-lasting thermal hyperalgesia and mechanical allodynia-like behaviours are measurable in the non-injured sural nerve skin territory.

[0160] A group of mice are subjected to a sham procedure to serve as a control group. The sham procedure consisted of the same surgery without ligation and transection of the nerves.

[0161] The groups of mice (n=1-16) are divided as follows, each formulation is tested with a separate group of mice:

- i) Naive control mice;
- ii) Sham-operated mice treated with vehicle;
- iii) Sham-operated mice treated with cannabinoid;
- iv) SNI mice treated with vehicle;

v) SNI mice treated with formulation of the invention. The formulations were dosed daily.

[0162] Mechanical allodynia is measured by using Dynamic Plantar Anesthesiometer (Ugo Basile, Varese, Italy). Mice are allowed to move freely in one of the two compartments of the enclosure positioned on the metal mesh surface. Mice are adapted to the testing environment before any measurements were taken. After that, the mechanical stimulus is delivered to the plantar surface of the hindpaw of the mouse from below the floor of the test chamber by an automated testing device. A steel rod (2 mm) is pushed with electronic ascending force (0-30g in 10 sec). When the animal withdrew its hindpaw, the mechanical stimulus was automatically withdrawn and the force recorded to the nearest 0.1 g.

[0163] Thermal hyperalgesia is evaluated by using a Plantar Test Apparatus (Ugo Basile, Varese, Italy). On the day of the experiment, each animal is placed in a plastic cage (22cm x 17cm x 14cm; length x width x height) with a glass floor. After a 60 min habituation period, the plantar surface of the hind paw is exposed to a beam of radiant heat (such as from an infrared bulb) through the glass floor. A photoelectric cell detects light reflected from the paw and turns off the heat source when paw movement interrupts the reflected light. The paw withdrawal latency is automatically displayed to the nearest 0.1 sec; the cut-off time is 20 sec in order to prevent tissue damage.

[0164] Responses for thermal and mechanical sensitivity are expressed as thermal paw withdrawal latency (PWL) in seconds and mechanical paw withdrawal threshold (PWT) in grams.

[0165] Each mouse serves as its own control, the responses being measured both before and after surgical procedures. PWL and PWT are quantified by an observer blinded to the treatment.

[0166] Behavioural and molecular data are calculated as means $\pm$ S.E.M. ANOVA, followed by Student-Neuman-Keuls *post hoc* test. These data are used to determine the statistical significance among groups. $P < 0.01$ is considered statistically significant.

Example 4 – Preparation of oro-mucosal formulation

[0167] The liquid composition comprising 10mg/mL THC and 10mg/mL CBD was prepared from *Cannabis* extracts obtained by extraction of a *Cannabis* plant with ethanol, followed by removal of extractant by heating *in vacuo*. The extract was solubilized in olive

oil. If required, THC and/or CBD or one or more terpenes/terpenoids may be added to the composition to provide the desired dosage.

[0168] The composition was packaged into pre-filled syringes containing the desired dosages.

Example 5 – Effectiveness of oro-mucosal delivery of Cannabinoid composition

[0169] Nine (9) patients with chronic non-cancer pain on a stable opioid medication regimen of daily morphine equivalent dose of >60mg for more than 12 months are enrolled into the study.

[0170] These patients are administered the liquid formulation of Example 4 diluted as necessary, in addition to their opioid therapy in accordance with the dosage regimen below. All doses are split and administered morning and evening. The patients are to monitor their opioid usage over the study period.

[0171] Dosage Regimen

Stage 1: Participants receive a single dose of composition containing 2.5 mg THC and 2.5 mg CBD followed by a 7 day wash out period.

Stage 2: Participants receive a single dose of composition containing 2.5 mg THC and 2.5 mg CBD followed by a high fat meal. Participants receive a total daily dose of a composition comprising 5 mg THC and 5 mg CBD for administration over the following week.

Stage 3: Participants receive a total daily dose of a composition comprising 10 mg THC and 10 mg CBD for administration over the following week.

Stage 4: Participants receive a total daily dose of a composition comprising 15 mg THC and 15 mg CBD for administration over the following 7 days.

Stage 5: Participants receive a single dose of composition containing 25 mg THC and 25 mg CBD followed by a 7 day wash out period.

[0172] The duration of the study is 36 days.

[0173] In addition to exploring the effects of medicinal cannabinoids and retention rates, this study also investigates the therapy's efficacy on improving patient mental health outcomes, well-being and cognition and the effects of a high fat diet.

[0174] In addition to the pharmacokinetic and safety parameters monitored, the effect parameters monitored include:

- Brief Pain Inventory (BPI)
- Depression, Anxiety and Stress Scale – 21 questions (DASS-21)
- Insomnia Severity Index (ISI) modified
- Actigraphy - Sleep Onset Latency (SOL), Wake After Sleep Onset (WASO), Total Sleep Time (TST) and Sleep Efficiency (SE)
- Sleep diary – total sleep time (sTST), time to fall asleep (sSOL), number of awakenings (sWASO), quality of sleep (sQual 5-point scale), refreshed feeling on waking (sFRESH 5-point scale, rating of daytime energy/mood/functioning)
- Self-reported opioid medication use

[0175] Each of the above endpoints assesses the efficacy of the pharmaceutical composition of the invention and the last point will assess the reduction in use of opioids over the study period.

Claims

1. An analgesic or antinociceptive agent comprising Δ^9 -tetrahydrocannabinol (THC), cannabidiol (CBD) and a terpene fraction obtained by extraction of a *Cannabis* plant.
2. The analgesic or antinociceptive agent according to claim 1 wherein the ratio of THC:CBD is about 10:1 to about 1:10.
3. The analgesic or antinociceptive agent according to claim 2 wherein the ratio of THC:CBD is about 0.8:1 to about 1:1.2.
4. The analgesic or antinociceptive agent according to claim 2 wherein the ratio of THC:CBD is 2:1 or more.
5. The analgesic or antinociceptive agent according to claim 2 wherein the ratio of THC:CBD is 1:2 or more.
6. The analgesic or antinociceptive agent according to any one of claims 1 to 4 wherein the THC is present in an amount of about 15wt% to about 85wt%.
7. The analgesic or antinociceptive agent according to claim 6 wherein the THC is present in an amount of about 15wt% to about 40wt%.
8. The analgesic or antinociceptive agent according to any one of claims 1 to 3 and 5 wherein the CBD is present in an amount of about 15wt% to about 60wt%.
9. The analgesic or antinociceptive agent according to claim 8 wherein the CBD is present in an amount of about 15wt% to about 40wt%.
10. The analgesic or antinociceptive agent according to any one of claims 1 to 9 wherein the total amount of THC and CBD is present is in the range of about 30wt% to about 99wt%.
11. The analgesic or antinociceptive agent according to any one of claims 1 to 10 wherein the agent is enriched in one or the other of THC and CBD.
12. The analgesic or antinociceptive agent according to any one of claims 1 to 11 further comprising one or both of Cannabichromene (CBC) and Cannabigerol (CBG).

13. The analgesic or antinociceptive agent according to any one of claims 1 to 12 wherein the terpene fraction is present in an amount of about 0.1wt% to about 10wt% of the agent.
14. The analgesic or antinociceptive agent according to claim 13 wherein the terpene fraction comprises one or more of β -myrcene, α -terpinene, linalool, α -phellandrene, camphene, terpinolene, p-cymene, 1,8-cineole, β -caryophyllene, d-limonene, γ -terpinene, α -pinene, guaiol, gurjunene, β -ocimene, β -pinene, γ -cadinene, caryophyllene oxide, nerolidol and β -farnesene.
15. The analgesic or antinociceptive agent according to claim 14 wherein the terpene fraction comprises one or more of β -myrcene, α -terpinene, linalool, α -phellandrene, camphene, terpinolene, p-cymene, 1,8-cineole and β -caryophyllene.
16. The analgesic or antinociceptive agent according to claim 15 wherein the terpene fraction comprises one or more of β -myrcene, α -terpinene, linalool and α -phellandrene.
17. A method of treating pain, comprising administering to a subject in need thereof an effective amount of the pharmaceutical composition of any one of claims 1 to 16.
18. The method according to claim 17 wherein the pain is nociceptive pain, psychogenic pain or neuropathic pain.
19. The method of either one of claim 17 or claim 18, wherein the pharmaceutical composition is administered according to the following dosage regimen:
 - (1) administering an effective amount of a *Cannabis* extract comprising THC as primary cannabinoid and a terpene fraction preceding a period of sleep of the subject, followed by
 - (2) administering an effective amount of a *Cannabis* extract comprising CBD as primary cannabinoid and a terpene fraction following a period of sleep of the subject.
20. The method according to claim 19 wherein in step 1, the ratio of THC:CBD is greater than 2:1.

21. The method according to claim 20 wherein the ratio of THC:CBD is 2.5:1 to 10:1.
22. The method according to claim 19 wherein in step 2, the ratio of CBD:THC is greater than 2:1.
23. The method according to claim 22 wherein the ratio of CBD:THC is 2.5:1 to 10:1.
24. The method according to any one of claims 19 to 23 further comprising administering an effective amount of an analgesic or antinociceptive agent according to claim 1 comprising THC and CBD in a ratio of THC:CBD of 2:1 or more to manage breakthrough pain.
25. Use of one or more of (a) a Cannabis extract; (b) THC and (c) CBD in the manufacture of a medicament for treating pain, wherein the medicament comprises THC, CBD and a terpene fraction obtained by extraction of a *Cannabis* plant.
25. A kit comprising in separate parts:
 - (a) an effective amount of the pharmaceutical composition of claim 1 comprising THC as primary cannabinoid; and
 - (b) an effective amount of the pharmaceutical composition of claim 1 comprising CBD as primary cannabinoid.