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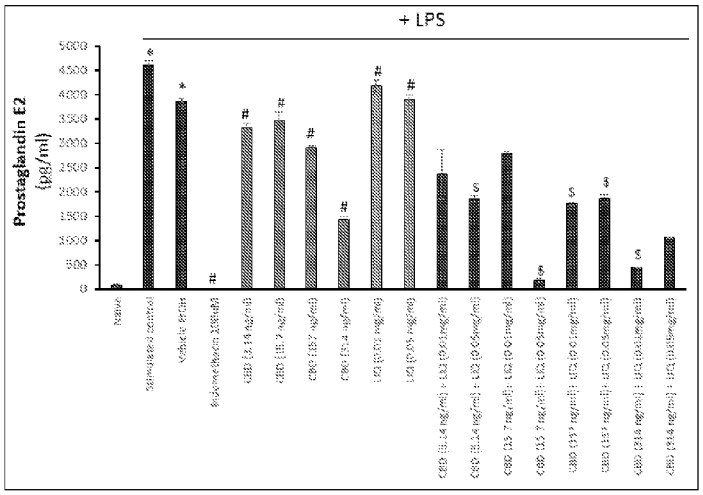
(54) Title: ANTI-INFLAMMATORY SYNERGISTIC COMPOSITIONS COMPRISING CANNABINOIDS AND LICORICE

Fig. 1



(57) Abstract: The present invention is directed to an anti-inflammatory composition comprising a combination of (a) at least one cannabis-related substance; and (b) at least one licorice-related substance, wherein the weight ratio of said cannabis-related substance(s) to said licorice-related substance(s) is in the range of from about 10:1 to about 1:100. Preferably, the concentration of the licorice-related substance(s) in the composition is at least 0.2% (w/w). The invention also includes a method for treating inflammatory and/or auto-immune disorders, wherein said method comprises the administration of a composition of the invention to a subject in need of said treatment.

[Continued on next page]

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ANTI-INFLAMMATORY SYNERGISTIC COMPOSITIONS COMPRISING CANNABINOIDS AND LICORICE

FIELD OF THE INVENTION

[0001] The present invention is generally related to anti-inflammatory compositions containing a synergistic combination of two or more substances. More specifically, the present invention relates to pharmaceutical, nutraceutical, cosmetic or veterinary compositions comprising a synergistic combination of a) at least one anti-inflammatory cannabinoid and b) Glycyrrhiza plant material or its extracts or isolates or bio active ingredients thereof, such as glycyrrhizic acid or its aglycon or salts or derivatives. The compositions of the present invention may be used for treating inflammatory, immune and auto-immune diseases.

BACKGROUND OF THE INVENTION

[0002] Cannabis, commonly known as marijuana, is a product of Cannabis species such as *Cannabis sativa*, *Cannabis Indica* and *Cannabis Hemp* plants. These plant species generally contain a very large number of active compounds, including those that are collectively referred to as **cannabinoids**. Cannabis or Marijuana has been found effective in alleviating symptoms of many auto-immune and inflammatory diseases such as multiple sclerosis, colitis, rrheumatoid arthritis, and cannabinoids were demonstrated to have anti-inflammatory activity in-vitro and in-vivo animal models and humans.

[0003] Potent anti-inflammatory actions of a crude marijuana extract and of the non-psychoactive *Cannabis* constituents, for example, cannabidiol (CBD), cannabidiolic acid (CBDA), tetrahydro cannabinolic acid (THCA), cannabinol, cannabigerol, cannabivarin, and cannabichromene has been demonstrated in many animal models such as in the carrageenan paw edema model of acute inflammation in rats. Tetra hydro cannabinol (THC) was also demonstrated to have anti-inflammatory activity in various in-vitro and animal models. Cannabinoids apparently act on inflammation through mechanisms different from those of agents such as nonsteroidal anti-inflammatory drugs (NSAIDs). As a class, the cannabinoids are generally free from the adverse effects associated with steroids

and NSAIDs. Their clinical development thus provides a new approach to treatment of various diseases, including, for example, those characterized by acute and chronic inflammation and fibrosis.

[0004] Volatile oil products of the plant also have biological activity. The geranylated flavone cannflavin A, is 30 times more potent than aspirin as an inhibitor of prostaglandin E_2. Some volatile Cannabis terpenes, for example humulene and caryophyllene, are potent anti-inflammatory agents. Liquorice or licorice which is an extract of Glycyrrhiza species such as glabra is one of the most used plants in food medicine and cosmetics, and belong to the Genus Glycyrrhiza, family Leguminosae; many species are used to obtain licorice, the chief commercial source being the cultivated *G. glabra*.

[0005] Licorice is a chewy, aromatic black substance made by evaporation from the juice of a root and used as a sweet and in medicine. The extract from the Glycyrrhiza glabra plant contains glycyrrhizic acid (GZA). GZA is made of one molecule of glycyrrhetic acid and two molecules of glucuronic acid. The extracts from the root of the plant can also be referred to as licorice, sweet root, and glycyrrhiza extract. When administered orally, the product of glycyrrhetic acid is found in human urine whereas GZA is not. This shows that glycyrrhetic acid is absorbed and metabolized in the intestines in humans. GZA is hydrolyzed to glycyrrhetic acid in the intestines by bacteria.

[0006] For thousands of years *G. glabra* has been used for medicinal purposes including the treatment of disorders of digestion and stomach inflammation. Some other medicinal uses include cough suppression, ulcer treatment, and use as a laxative. Also, salts of GZA can be used in many products as sweeteners and aromatizers. Licorice extract is often found in sweets and many candies, some drugs, and beverages like root beer. They can also be used in chewing gum, tobacco products and toothpaste.

[0007] Laboratory studies done in Japan (where an injectable glycyrrhizin compound is used in people with chronic hepatitis C who do not respond to conventional treatment) suggest that glycyrrhizin may have some effect against hepatitis C.

[0008] Topical licorice extract may improve skin rash symptoms, such as redness, swelling, and itching.

[0009] Some of the common medical benefits of licorice are: allergy relief, as demonstrated in various *in vitro* and *in vivo* studies which support the traditional use of Licorice (*Glycyrrhiza glabra*) for allergies. Glycyrrhizin is attributed with relieving IgE-induced allergies (e.g. asthma). Licorice has also been used for its anti-oxidant, anti-convulsant, anti-oxidant actions that also protected against neuron damage. It has also shown potential as a modulator of genotoxins and free radical scavenger; anti-inflammatory abilities, and in reducing nitric oxide synthase expression; treatment of oral mucositis post radiation and chemotherapy in cancer patients; inhibition of cancer cell proliferation; Conjunctivitis; protection against liver and kidney damage from acetaminophen in a dose dependent manner and neuroprotection.

[0010] Licorice is traditionally used in tobacco products in order to reduce airway injury and may be formulated into cigarettes. Licorice-derived or related compounds have been tested for reduced coughing and treating airways inflammation.

[0011] While many of the severe autoimmune and inflammatory diseases are well treated with steroids, these agents also possess many severe and dose-limiting unwanted side effects.

[0012] There is thus an unmet need for compositions and methods for the effective treatment of many autoimmune and inflammatory diseases and a need for an effective and safe non-steroidal anti-inflammatory medication.

[0013] Neuro-inflammation is considered as a factor or a cause of many neurological diseases and chronic pain disorders. There is a need to provide a better treatment for many neurological disorders and pain of neurological inflammatory origin that is currently not well treated and sometimes treated only by steroids, while acute and flair conditions are treated with mega doses of steroids that resulting in sever and irreversible and debilitating adverse effects.

[0014] Fibrosis is a result of injury and chronic inflammation, there is a need for an anti-inflammatory medication that will alleviate chronic inflammation and will prevent fibrosis and be anti-fibrotic.

[0015] It is widely accepted that cancer is associated with inflammation and alterations to cyclooxygenase-2 (COX-2) expression and the abundance of its enzymatic product prostaglandin E2 (PGE2) have key roles in influencing the development of colorectal cancer. Deregulation of the COX-2/PGE2 pathway appears to affect colorectal tumorigenesis via a number of distinct mechanisms: promoting tumor maintenance and progression, encouraging metastatic spread, and perhaps even participating in tumor initiation.

[0016] Within the context of cancer and inflammation, PGE_2 is generally considered to possess potent tumor-promoting activity. This inference is based on a substantial body of evidence obtained from rodent studies, as well as several decades of clinical research on the effects of NSAIDs on cancer risk.

[0017] Chronic inflammation contributes to cancer development via multiple mechanisms. One potential mechanism is that chronic inflammation can generate an immunosuppressive microenvironment that allows advantages for tumor formation and progression. The immunosuppressive environment in certain chronic inflammatory diseases and solid cancers is characterized by accumulation of proinflammatory mediators, infiltration of immune suppressor cells and activation of immune checkpoint pathways in effector T cells. Many inflammatory diseases, such as mucositis, gingivitis, conjunctivitis, otitis, skin ulcers and wounds, diabetic foot ulcers, are multifactorial, involving inflammation and infection that can be a mixture of bacterial, viral or fungal. Such conditions are difficult to treat and there is a great need for an anti-inflammation medication that will be on the same time anti-infective and analgesic.

SUMMARY OF THE INVENTION

[0018] The present inventor has now unexpectedly found that a combination of a cannabinoid with licorice extract (or with isolates of said extract) possesses a synergistic anti-inflammatory effect that has the potential to provide effective treatment for many inflammatory diseases and provide a safer, yet highly effective, alternative to medication with steroids. In addition, Cannabis extract and licorice extracts possess anti-infective and analgesic properties in addition to their anti-inflammatory activities.

[0019] The present invention relates to a synergistic or a potentiating anti-inflammatory composition comprising a combination of, firstly, at least one cannabis extract and/or its isolates and/or cannabinoids and, secondly, at least one of Glycyrrhiza plant material or licorice extract or its bioactive anti-inflammatory isolates, such as glycyrrhizic acid or its glycone.

[0020] Thus, the present invention is primarily directed to an anti-inflammatory composition comprising a combination of (a) at least one cannabis-related substance; and (b) at least one licorice-related substance. In one preferred embodiment, the weight ratio of said cannabis-related substance(s) to said licorice-related substance(s) is in the range of from about 10:1 to about 1:100.

[0021] It is to be noted that the term "cannabis-related substance" refers to one or more of the following entities (alone or in combination): intact cannabis plant material, an extract of cannabis plant material (either of the whole plant or of defined anatomical portions thereof, such as leaves, stems, roots etc.), fractions and/or subfractions of the plant material, purified or partially purified cannabinoids and other bioactive molecules obtained from the cannabis plant, and/or synthetic analogues, derivatives and equivalent obtained from non-cannabis plant sources.

[0022] The term 'licorice-related substance' is to be understood to refer to material obtained from Glycyrrhiza plant species (e.g. *G. glabra* and other species of the Glycyrrhiza genus), either from whole plants or from individual plant parts such as roots, leaves etc., extracts of said plants, fractions or sub-fractions of said extracts, and purified

and partially-purified bioactive compounds, such as glycyrrhizic acid and other compounds as are well known to the skilled artisan and as are described hereinbelow, and derivatives and analogues of said compounds.

[0023] Thus, in one preferred embodiment of the composition of the present invention, the cannabis-related substance is selected from the group consisting of cannabis plant whole material, extract, isolate and/or cannabinoid or other bioactive molecule contained therein. In another preferred embodiment, the cannabis-substance is selected from: cannabidiol (CBD), cannabidiolic acid (CBDA), tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCA), cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), cannabielsoin (CBE), iso-tetrahydrocannabinol (iso-THC), cannabicyclol (CBL), cannabicitran (CBT), cannabivarin (CBV), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), cannabigerol momomethyl ether (CBGM), salts thereof, derivative thereof and mixtures of cannabinoids.

[0024] In one preferred embodiment, the licorice-related substance is selected from the group consisting of Glycyrrhiza whole plant material, extract, isolate or bioactive molecule contained therein. In another preferred embodiment of the composition, the licorice-related substance is selected from: glycyrrhizin/glycyrrhetinic acid, glabridin, glabrene, licochalcone A, liquiritigenin, isoliquiritigenin, coumarins, including licopyranocoumarin, licoarylcoumarin and glycycoumarin, formononetin, glisoflavone, hispaglabridins A and B, rutin, isoangustone A, prunetin and dehydroglyasperin C, salts thereof, derivatives thereof and mixtures of glycyrrhzanoids.

[0025] In one preferred embodiment, the composition of the present invention comprises a combination of purified CBD and a dried licorice extract.

[0026] In another aspect, the present invention provides a dosage form comprising a composition as defined hereinabove, together with one or more pharmaceutical excipients. Examples of suitable dosage forms are described hereinbelow.

[0027] In another aspect, the present invention encompasses a method for treating an inflammatory condition or an auto-immune disease or disorder in a mammalian subject

(preferably, but not exclusively, a mammalian subject) in need of such treatment, wherein said method comprises the administration (systemically, topically or by a combination of routes) of a composition of the present invention.

[0028] The present invention further provides a composition for use as medicament or other therapeutic entity (such as 'herbal remedy', 'food supplement' and the like) in the treatment of an inflammatory condition or an autoimmune disease. In one embodiment of this aspect, said composition is provided for use as a medicament or other therapeutic entity in the treatment of a systemic or topical or mucosal inflammatory disorder.

[0029] The present invention further provides the use of a composition as disclosed herein for the preparation of a medicament. In some embodiments, this aspect of the invention relates to the use of a composition as disclosed herein in the preparation of a medicament for use in the treatment of an inflammatory condition or auto-immune disease or disorder.

[0030] The inventor has also unexpectedly found that macrophages that were excited with lipopolysaccharides (LPS) show dramatic and synergistic reduction of inflammation markers, using compositions comprising a combination of CBD and a glycyrrhiza standard extract. Surprisingly, the efficacy of this combination in inhibiting inflammatory mediators is comparable to the efficacy of dexamethasone, as will be shown in the experimental results presented hereinbelow.

[0031] In certain embodiments, the composition comprises about 0.01 % to about 60 % by weight of a cannabinoid or a mixture of cannabinoids. In certain embodiments, the composition comprises about 0.5 % to about 20 % by weight of a cannabinoid or a mixture of cannabinoids. In certain embodiments, the cannabinoid is selected from the group consisting of cannabidiol (CBD), cannabidiolic acid (CBDA), tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCA), cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), cannabielsoin (CBE), iso-tetrahydrocannabimol (iso-THC), cannabicyclol (CBL), cannabicitran (CBT), cannabivarin (CBV), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), cannabigerol monomethyl ether (CBGM), salts thereof, derivatives thereof and mixtures of cannabinoids.

[0032] In certain embodiments, the composition comprises about 0.01 to about 80% by weight of a licorice or a licorice extract or its isolates. In certain embodiments, the composition comprises about 0.5 % to about 40 % by weight of a licorice or licorice extract or isolate or derivatives. In certain embodiments, the licorice isolate is selected from the group of Glycyrrhizin/Glycyrrhetinic Acid, Glabridin, Glabrene, Licochalcone A, liquiritigenin, isoliquiritigenin, Coumarins, include licopyranocoumarin, licoarylcoumarin, and glycycoumarin, Formononetin, Glisoflavone, Hispaglabridins A and B, Rutin, Isoangustone A, Prunetin and Dehydroglyasperin C.

[0033] In certain embodiments, the ratio of the at least one cannabis-related substance to the at least one licorice-related substance is from about 0.0001 to about 10.0, or from about 0.001 to 2.0 or from 0.01 to 1.0 and more preferably from about 0.001 to about 0.5 and more preferably from about 0.01 to about 0.1.

[0034] In certain embodiments, the dosage form is formulated as granules, pellets, micro-particles, tablet, hard shell capsules, suspended in a liquid, suspended in a syrup or enema. In certain embodiments, the dosage form is formulated for oral or mucosal delivery. In certain embodiments, the dosage form is formulated as or in a lozenge, candy, toffee, chocolate or cookie. In certain embodiments, the tablet or pellets are an immediate release or slow or controlled release dosage forms. In certain embodiment the tablet is enteric coated or is a melt or dissolved in the mouth or is muco-adhesive dosage form.

[0035] In certain embodiments, the unit dosage form which is a unit particles, such as tablet, capsule, granules, pellets, micro-particles and film, are enteric coated or coated with a colonic coat that protect the unit dose from being decomposed at the acidic gastric pH and swells in time manner of pH controlled manner or both, to release the cannabinoids at the distal intestine and may also release part of the cannabinoids in the intestines for systemic absorption and part of the cannabinoids at the colon for local colonic pharmacological effect.

[0036] In certain embodiments, the composition is formulated in a semi solid or liquid dosage form such as cream, lotion, ointment, dispersion, suspension, gel, foam, spray,

syrup, liquid, eye drops, ear drops, enema or an oral dosage form or a topical dosage form or a local ophthalmic or otic or oral cavity or vaginal or rectal or uterine dosage form.

[0037] In certain embodiments, any one of the compositions described above, or any one of the dosage forms described above, is for use in a method of treating inflammation symptoms, ant immune and auto-immune diseases or disorders.

[0038] In certain embodiments, the composition or dosage form comprises CBD. In certain embodiments, the pharmaceutical composition or dosage form further comprises tetrahydrocannabinol (THC). In certain embodiments, the CBD:THC weight ratio is about 20:1. In certain embodiments, the mixture comprises CBD. In certain embodiments, the mixture comprises THC. In certain embodiments, the mixture comprises CBD and THC. In certain embodiments, the mixture comprises CBD and THC in a weight ratio of about 1:1. In certain embodiments, the mixture comprises CBD and THC in a weight ratio of about 10:1 to about 1:10.

[0039] In one preferred embodiment, the licorice-related substance is present in the above-defined composition at a concentration of at least 0.2% (w/w). In another preferred embodiment, the licorice concentration of said composition is at least 0.5% (w/w).

DEFINITIONS

[0040] The term "cannabinoid" as used herein generally refers to one of a class of diverse chemical compounds that act on a cannabinoid receptor in cells that repress neurotransmitter release in the brain. The term "cannabinoid" as used herein further refers a chemical compound that acts on cannabinoid receptors or has a structure similar the stature of a compound acting on cannabinoid receptor in cells. Ligands for these receptor proteins include the endocannabinoids (produced naturally in the body by humans and animals), the Phyto cannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured artificially).

[0041] The term "anti-inflammatory cannabinoid" is any cannabis plant material or synthetic equivalent, derivative or analogue (regardless of whether or not it interacts with cannabinoid receptors) that is derived from, or mimics the cannabinoids found in the

cannabis plants and that has an anti-inflammatory effect. Such an anti-inflammatory effect is demonstrated by inhibiting or reducing the release of cytokines in macrophage cells that are in contact with an allergen such as LPS (lipopolysaccharide) that cause release of cytokines as part of the inflammation and pro-inflammatory activity or by inhibiting the cyclo-oxygenase enzymes. Anti-inflammatory cannabinoids reduce the amount of pro-inflammatory cytokines release, for example; TNF alpha, IL-1, IL-6, NO, PGE2 and or any of the about eighty (80) cytokines and the inflammation mediators and immune mediators known in the art and more specifically, pro-inflammatory cytokines or mediators.

[0042] The term "cannabis extract" as used herein refers to one or more plant extracts from the cannabis plant. A cannabis extract usually contains, in addition to one or more cannabinoids, one or more non-cannabinoid components which are co-extracted with the cannabinoids from the plant material. Their respective ranges in weight will vary according to the starting plant material and the extraction methodology used. Cannabinoid-containing plant extracts may be obtained by various means of extraction of cannabis plant material. Such means include but are not limited to: supercritical or subcritical extraction with CO2, extraction with hot or cold gas and extraction with solvents.

[0043] The term licorice or liquorice extract as used herein refers to one or more Glycyrrhiza species plant extract from the Glycyrrhiza glabra plant and other species and to its extracts or its purified isolated molecules from the plant Glycyrrhiza glabra and its species and sub types and isolates and derivatives and combinations thereof.

[0044] The term “synergistic” as used herein is refers to the phenomenon wherein the cumulative pharmacological effect of two ingredients when used in combination is higher than the sum of the effect of each of them tested individually. The term “potentiating” as used herein refers to the phenomenon where the efficacy of an active ingredient is significantly enhanced when it is combined with a second ingredient, wherein said second ingredient itself does not demonstrate any efficacy in the same pharmacological test. In some cases of potentiation, not only is said second ingredient devoid of the pharmacological effect being measured, it may even cause an opposite effect, when assayed alone. An example of such a case would be as follows: ingredient A is anti-inflammatory;

ingredient B is pro-inflammatory; when A and B are combined, said combination produces an anti-inflammatory effect that is greater than seen with A alone. In the context of the present invention, potentiation is regarded as a special case of synergism. Thus, the term 'synergism' (or synergistic, or the like), when used to define the properties of a composition of the present invention, also includes within its range of meaning the potentiation effect described immediately hereinabove.

The term "glycyrrhizanoids" as used herein is refers to active ingredients or active constituents or active isolates obtained from the plant glycyrrhiza species.

[0045] The term "about" as used herein refers to any value which lies within a range of ± 5% of original value. For example, "about 100" refers to "95 to 105".

[0046] The term "pharmaceutical composition" as used herein has its conventional meaning and refers to a composition which is pharmaceutically acceptable. The term "pharmaceutically acceptable" as used herein has its conventional meaning and refers to compounds, material, compositions and/or dosage forms, which are, within the scope of sound medical judgment suitable for contact with the tissues of mammals, especially humans, without excessive toxicity, irritation, allergic response and other problem complications commensurate with a reasonable benefit/risk ratio. The term "excipient" as used herein has its conventional meaning and refers to a pharmaceutically acceptable ingredient, which is commonly used in the pharmaceutical technology for preparing a granulate, solid or liquid oral dosage formulation. The term "cosmetic composition" is intended to mean a substance or a preparation intended to be brought into contact with the various superficial parts of the body, in particular the epidermis, the body-hair and head-hair systems, the nails, the lips and the oral mucous membranes. The term "veterinary composition" encompasses the full range of compositions for internal administration and feeds and drinks which can be consumed by animals.

[0047] Unless otherwise stated, all ratios between different components of the compositions disclosed herein are weight ratios.

[0048] The methods, uses, materials, and examples that will now be described are illustrative only and are not intended to be limiting; materials, uses and methods similar or equivalent to those described herein can be used in practice or testing of the invention. Other features and advantages of the invention will be apparent from the following figures, detailed description, and from the claims.

[0049] BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. graphically depicts the synergistic interaction between CBD and licorice extract in inhibiting LPS-induced prostaglandin E_2 secretion.

Figure 2. graphically depicts the synergistic interaction between CBD and licorice extract in inhibiting LPS-induced NO secretion.

Figure 3. graphically depicts the synergistic interaction between CBD and Glabridin 40% (test item 7), in inhibiting LPS-induced NO secretion.

Figure 4. graphically depicts the synergistic interaction between CBD and dipotassium glycyrrhizinate, (test item 3), in inhibiting LPS-induced IL-6 secretion.

Figure 5. graphically depicts the synergistic interaction between CBD and 18 beta glycyrrhitinic acid, (test item 5), in inhibiting LPS-induced IL-6 secretion.

Figure 6. graphically depicts the synergistic interaction between CBD and Glabridin 40% (test item 7), in inhibiting LPS-induced IL-6 secretion.

Figure 7. graphically depicts the synergistic interaction between CBD and Glabridin 40% (test item 7), in inhibiting LPS-induced Granulocyte-macrophage colony-stimulating factor (*GM-CSF*) secretion.

Figure 8. graphically depicts the synergistic interaction between CBD and Glabridin 40% (test item 7), in inhibiting LPS-induced monocyte chemoattractant protein 1 (MCP1) secretion.

Figure 9. graphically depicts the potentiating interaction between CBD and licorice extract in inhibiting LPS-induced TNF-alfa secretion.

Figure 10. graphically depicts the synergistic interaction between CBD and pure Glycyrrhizic acid in inhibiting LPS-induced prostaglandin E_2 secretion.

Figure 11. graphically depicts the synergistic interaction between CBD and pure disodium glycyrrhizinate in inhibiting LPS-induced prostaglandin E_2 secretion.

DETAILED DESCRIPTION OF THE INVENTION

[0050] Provided by the present invention are compositions comprising a) anti-inflammatory cannabis extract or at least one of its isolates or cannabinoids and b) licorice extract or at least one of its components, fractions, isolates or derivatives or salts thereof, providing a potentiating or synergistic anti-inflammatory pharmacological activity.

[0051] The present invention is based on the surprising finding that there is a synergistic or potentiating interaction between a) at least one anti-inflammatory cannabinoid and b) at least one licorice isolates or licorice extracts, with respect to the reduction or inhibition of the of pro-inflammatory cytokines and mediators.

[0052] It has also been unexpectedly discovered that a composition comprising a combination of at a) least one anti-inflammatory cannabinoid and with b) at least one licorice isolate or extracts, reduces the secretion of pro-inflammatory cytokines in a macrophage cell line that was stimulated by means of pre-treated with lipopolysaccharides (LPS), in a synergistic or a potentiating manner, whereas the magnitude of inhibition of

cytokine secretion is higher for the composition than the sum of the inhibition of cytokines release by the individual ingredients. In many cases, the efficacy of this anti-inflammatory effect of the composition is comparable to the effect obtained by the use of a steroidal or non-steroidal anti-inflammatory (NSAID) agent. In a particularly preferred embodiment of the invention, the at least one cannabinoid is selected from: Cannabidiol (CBD), Cannabidiol acid (CBDA), tetra hydro cannabinol or tetrahydrocannabinolic acid (THC) or (THCA), compounds which has been found to possess a strong anti-inflammatory activity as well as a broad range of other biological activities.

[0053] In a particular preferred embodiment of the invention, the licorice extract or its isolates comprise: Glycyrrhizin/Glycyrrhetinic Acid, Glabridin, Glabrene, Licochalcone A, liquiritigenin, isoliquiritigenin, Coumarins, include licopyranocoumarin, licoarylcoumarin, and glycycoumarin, Formononetin, Glisoflavone, Hispaglabridins A and B, Rutin, Isoangustone A, Prunetin and Dehydroglyasperin C.

Inflammatory diseases and indications

[0054] For the purpose of this disclosure, inflammatory diseases and conditions include any disease that is associated with inflammation, such as for example eye diseases, including (but not limited to) dry eyes, conjunctivitis, uveitis, pink eyes, keratoconjunctivitis of any origin (including viral, bacterial and allergic); mucositis such as chemotherapy and radiation induced mucositis or gastro intestinal inflammation; inflammatory bowel diseases, ulcerative colitis and Crohn`s disease, inflammatory gastric and intestinal ulcers, skin inflammation and skin inflammation associated with dry skin, atopic dermatitis, psoriasis and similar skin diseases; ear, nose and throat infections and non-infective inflammatory conditions; vaginal infections and other vaginal inflammatory conditions; anal or rectal inflammation; inflammation of any tissue or organ that results from physical or chemical insult, from heat, irradiation, auto immune disease, oxidation stress or chemotherapy.

[0055] Many neurological and central nervous system (CNS) diseases such as multiple sclerosis and Alzheimer disease are related to chronic inflammatory condition.

[0056] Atherosclerosis is also considered to possess autoimmune and chronic inflammatory aspects in its pathogenesis.

[0057] Tumor microenvironment is an inflammatory state which is an immune suppressive condition, thus hindering the body immune response to attack the cancer.

The vehicle forms

[0058] Preferred dosage forms include, but are not limited to, any liquid or semi solid or solid dosage form. The composition may be formulated in a medicament by preparing a topical or mucosal or oral delivery system. The topical delivery system may be in form of eye drops, a suspension, ointment, cream, foam, spray, topical patch. The oral delivery system may be a tablet or capsule or soft capsule or sachet or granules or a syrup. The mucosal delivery system may be a gel, pessary, enema, douche, wash, foam, mucoadhesive gel or tablet for immediate or for slow or controlled release. The vehicle may comprise any acceptable solvent and inactive ingredients as well as preservatives anti-oxidants and coloring agents. The delivery form may be single dose or multiple dose as well as micro particle granulate nano particle microcapsule liposome micelle, and the like as known in the art of pharmaceutical, cosmetic, veterinary medicine and art of formulation. Further details of suitable dosage forms may be obtained from any standard reference work in this field, including, for example: Remington's Pharmaceutical Sciences, Mack Publishing Co, Easton, Pa, USA (1980).

[0059] Thus, in some embodiments of the present invention, the composition further comprises one or more excipients selected from the group consisting of solvents, stabilizers, suspending agents, emulsifiers, release modifying, targeting and viscosity agents and combinations thereof.

[0060] In some embodiments, the composition of the present invention is formulated as a dosage form selected from the group consisting of a liquid, a suspension, an emulsion, a foam, a spray, a liposome, a semi-solid, a cream, an ointment, a patch, a particulate formulation, a granulate, a micro-particulate formulation, a nano-particulate formulation, a

solid dosage form, a tablet, a capsule, an orally-disintegrable capsule, a mouth wash and an adhesive buccal tablet.

[0061] In some embodiments, the composition of the present invention is formulated such that the release profile of the composition is selected from the group consisting of immediate, delayed, controlled, sustained and prolonged.

The anti-inflammatory cannabinoid

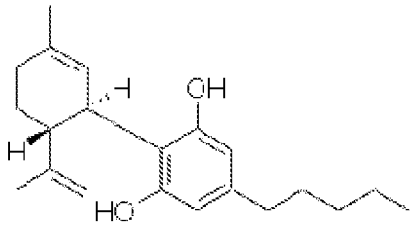
[0062] In certain embodiments, the cannabinoid is a natural cannabinoid. In certain embodiments, the cannabinoid is a natural cannabinoid found in a Cannabis plant. In certain embodiments, the cannabinoid is a synthetic cannabinoid. In certain embodiments, the cannabinoid is a mixture of natural cannabinoids. In certain embodiments, the cannabinoid is a mixture of synthetic cannabinoids. In certain embodiments, the cannabinoid is a mixture of natural and synthetic cannabinoids.

[0063] The term "natural cannabinoid" as used herein generally refers to a cannabinoid which can be found in, isolated from and/or extracted from a natural resource, such as plants. "Synthetic cannabinoids" are a class of chemicals that are different from the cannabinoids found e.g. in cannabis but which also bind to cannabinoid receptors.

[0064] In certain embodiments, the cannabinoid is selected from the group consisting of cannabidiol (CBD), cannabidiolic acid (CBDA), tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCA), cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), cannabielsoin (CBE), iso-tetrahydrocannabimol (iso-THC), cannabicyclol (CBL), cannabicitran (CBT), cannabivarin (CBV), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV) and cannabigerol monomethyl ether (CBGM), salts thereof, derivatives thereof and mixtures of cannabinoids. Each possibility represents a separate embodiment of the invention.

[0065] The terms "cannabidiol" and "CBD" are interchangeably used herein and refer to a non-psychotropic cannabinoid having structure as described in formula 1 below, salt or

derivatives thereof, such as Δ4-cannabidiol, Δ5-cannabidiol, Δ6-cannabidiol, Δ1,7-cannabidiol, Δ1-cannabidiol, Δ2-cannabidiol, Δ3-cannabidiol.

[0066] Formula 1 

[0067] In another embodiment, the pharmacologically active cannabinoid may be selected from the group consisting of tetrahydrocannabinol, Δ9-tetrahydrocannabinol (THC), Δ8-tetrahydrocannabinol, standardized marijuana extracts, Δ8-tetrahydrocannabinol-DMH, Δ9-tetrahydrocannabinol propyl analogue (THCV), 11-hydroxy-tetrahydrocannabinol, 11-nor-9-carboxy-tetrahydrocannabinol, 5'-azido-.Δ8-tetrahydrocannabinol, AMG-1 (CAS Number 205746-46-9), AMG-3 (CAS Number 205746-46-9), AM-411 (CAS Number 212835-02-4), (-)-11-hydroxy-7'-isothiocyanato-Δ8-THC (AM-708), (-)-11-hydroxy-7'-azido-Δ8-THC (AM-836), AM-855 (CAS Number 249888-50-4), AM-919 (CAS Number 164228-46-0), AM926, AM-938 (CAS Number 303113-08-8), cannabidiol (CBD), cannabidiol propyl analogue (CBDV), cannabinol (CBN), cannabichromene, cannabichromene propyl analogue, cannabigerol, CP 47,497 (CAS Number (1S,3R): 114753-51-4), CP 55,940 (CAS Number 83002-04-4), CP 55,244 (CAS Number 79678-32-3), CT-3 (ajulemic acid), dimethylheptyl HHC, HU-210 (1,1-Dimethylheptyl- 11-hydroxy-tetrahydrocannabinol), HU-211 (CAS Number 112924-45-5), HU-308 (CAS Number 1220887-84-2), WIN 55212-2 (CAS Number 131543-22-1), desacetyl-L-nantradol, dexanabinol, JWH-051 (Formula C25H38O2), levonantradol, L-759633 (Formula C26H40O2), nabilone, O-1184, and mixtures thereof.

[0068] In another embodiment, the pharmacologically active cannabinoid may further be selected from the group consisting of palmitoylethanolamide (PEA), alkylethanolamide, oleyl-serine, cannabinomimetic, caryophyllene, CB1 and/or CB2 agonist and/or antagonist, partial agonist, reversible or not, and any combination thereof.

[0069] The cannabinoid may be included in its free form, or in the form of a salt; an acid addition salt of an ester; an amide; an enantiomer; an isomer; a tautomer; a prodrug; a derivative of an active agent of the present invention; different isomeric forms (for example, enantiomers and diastereoisomers), both in pure form and in admixture, including racemic mixtures; and enol forms.

[0070] In some embodiments, the cannabinoid(s) utilized in the present invention are a lipophilic concentrate of cannabinoid(s). In some embodiments, the cannabinoid(s) utilized in the present invention are a lipophilic concentrate of cannabinoid(s) achieved via CO2, solvents or liquid gas extraction techniques or by oil maceration or oil pressure of partial or whole plant.

[0071] Extraction of active materials from various parts of the cannabis plant, may be performed by using techniques such as CO_2 extraction, solvent extraction or solvent-less compression to obtain an oily viscous material, waxy material or solid material. The types of plant material, plant parts and extraction methods to be used are all well known to the skilled artisan in this field. Extraction and processing may result in broad spectrum of cannabis molecules, cannabinoids, terpenes and other families of natural cannabis molecules or in a pure extract of cannabinoids or concentrated cannabinoid terpenes extract. Cannabis or marijuana extract may be further decarboxylated, winterized and/or purified, for example by distillation, as known in the art.

[0072] In certain embodiments, the composition comprises an essential oil or terpenes or combinations thereof. In certain embodiments, the terpene is a natural terpene found in a Cannabis plant. In certain embodiments, the terpene is a synthetic terpene. In certain embodiments, the terpene is a mixture of natural terpenes. In certain embodiments, the terpene is a mixture of synthetic terpenes. In certain embodiments, the terpene is a mixture of natural and synthetic terpenes. In certain embodiment the terpene is a cannabis anti-inflammatory agent.

[0073] In certain embodiments, the terpene is selected from the group consisting of bisabolol, borneol, caryophyllene, carene, camphene, cineol, citronella, eucalyptol, geraniol, guaiol, humulene, isopropyltoluene, isopulegol, linalool, limonene, methyl

salicylate, menthol, myrcene, nerolidol, ocimene, pinene, phytol, pulegone, terpinene, terpinolene, thymol, salts thereof, derivatives thereof and mixtures thereof. Each possibility represents a separate embodiment of the invention.

[0074] In certain embodiments the terpene is a cannabis plant terpene, or a terpene derived from a non-cannabis plant material or a synthetic terpene. In certain embodiment the terpene is a taste modifier or smell modifier agent, a food grade or pharmaceutical grade, a solubilizer or solvent and an excipient in the formulation.

[0075] About 120 distinct terpenes are produced by the genus Cannabis, with the relative concentrations of the individual terpenes varying greatly among the 700 distinct strains currently in cultivation. Aside from taste and smell differences between varieties, this helps contribute to the broad diversity of potential medical applications of Cannabis.

[0076] In certain embodiments of the pharmaceutical composition, the natural cannabinoid is derived or isolated from an extract of a Cannabis plant. In certain embodiments of the composition, the natural terpene is derived or isolated from an extract of a Cannabis plant.

[0077] In certain embodiments, a terpene or the mixture of terpenes solubilized with a cannabinoid or a mixture of cannabinoid. Each possibility represents a separate embodiment of the invention.

[0078] These optional components can be used either alone or in combination with other ingredients to improve the chemical and physical properties of the cannabinoid isolate or extract or the drug delivery systems and the cannabinoids or the terpenes chemical stability and shelf life.

[0079] The present invention further provides, in an aspect, a dosage form, comprising or consisting of any one of the compositions described above.

[0080] The term "dosage form" denotes any form of the solid formulation that contains an amount of a cannabinoid or of a mixture of cannabinoids sufficient to achieve at least a partial therapeutic effect with a single administration.

[0081] In certain embodiments, the dosage form is an oral dosage form. In certain embodiments, the dosage form is a rectal dosage form. In certain embodiments, the dosage form is a nasal dosage form. In certain embodiment, the dosage form is mucosal dosage form. In certain embodiments, the dosage form is a rectal or vaginal dosage form. In certain embodiments, the dosage form is a topical dosage form.

[0082] The dosage from as is in form of films, granules, pellets, micro particles or any shape or be used in the production of a specific dosage form such as tablet or capsule with functional additives that serves to form the specific dosage form.

[0083] In certain embodiments, the dosage form is formulated as a tablet, enteric coated tablet, enteric coated capsule, dissolve in mouth tablet, dissolve in mouth strip, or capsule, enteric coated granules, granules or pellets. Each possibility represents a separate embodiment of the invention. In certain embodiments, the dosage form is formulated for mucosal delivery. The term "mucosal delivery" refers to the delivery to a mucosal surface, including nasal, vaginal, rectal, urethral, sublingual and buccal delivery. In certain embodiments, the dosage form is formulated in a candy, toffee, dragee, chocolate, cookie or lozenge. In certain embodiments, the dosage form is formulated in a liquid or semi-solid delivery form such as cream, ointment, syrup, spray, foam, liquid, suspension, emulsion, paste, spray and the like, as known in the art.

[0084] In certain embodiments, the dosage form of the cannabinoid, or cannabinoids and licorice or its extract or derivative is targeted to be released at distal (lower) intestine or upon entering the colon. Such formulations are designed to release the cannabinoids essentially at the colon or at the end of jejunum and in the colon or partly in the jejunum and partly in the colon.

[0085] Preferred cannabinoids for colon delivery are anti-inflammatory cannabinoids such as CBDA and THCA, which are not psychotropic. Preferred polymers for producing solid solution of cannabinoids for IBD are pH responsive polymers are polyacrylates Eudragit™. Preferred polymer forming matrix for IBD targeting are polymers that do not degrade by stomach and jejunal enzymes such as dietary fibers, such as pectin and zein.

[0086] According to the principles of the present invention, the synergistic or the potentiating anti-inflammatory composition, comprises an "anti-inflammatory cannabinoid component" (i.e. Cannabis-extracted and purified cannabinoid or synthetic cannabinoid or cannabis extract), and optionally a terpene, and a licorice extract or its isolate or derivatives or salts thereof and a dosage form for convenient and efficient delivery of the composition. The advantages of the pharmaceutical composition of the present invention over known cannabis compositions are manifold and include: (a) higher anti-inflammatory pharmacological effect (b) pharmacological anti-inflammatory effect that may replace steroids use (c) analgesic effect and (d) a safe and highly acceptable analgesic and anti-inflammatory medication and (e) low adverse effect medication.

[0087] In some embodiments, a functional inactive ingredient maybe optionally added, such as colorant or antioxidants or chelating agent or microbial preservative or viscosity modifier, pH modifying agents, buffer, or melting point modifier or anti-microbial agent or suspending agent.

Licorice

[0088] Licorice is prepared from a Glycyrrhiza plant variety such as (but not limited to) Glycyrrhiza uralensis Fisch., G. inflata Bat. and G. glabra L. The licorice cuts from the dry roots and rhizomes of licorice are widely used in clinical and botanical medicine. Preparations of Glycyrrhiza may be prepared from dry ground plant or from various types of extract of fresh or dried herb and from isolates.

[0089] Anti-inflammatory preparations of licorice may include: Licorice extracts, triterpenes and flavonoids isolates having evident anti-inflammatory properties mainly by decreasing TNF, MMPs, PGE2 and free radicals. Currently, about five hundred and fifty-four drugs containing licorice have been approved by CFDA (china FDA).

Isolates of Glycyrrhiza plant species such as Glabra uralensis and others having anti-inflammatory activity include (but are not limited to): Alpha-glycyrrhizin Beta-glycyrrhizin glycyrrhetinic acids, licochalcone, Dehydroglyasperin, Isoangustone, Isoliquintigenin, Licoricidin, Glabridin, Echinatin and Licorisoflavan, also named "glycyrrhizanoids"

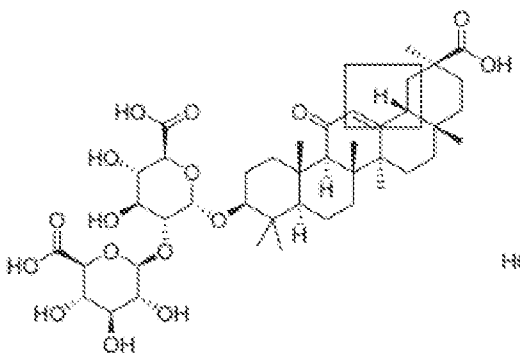
[0090] The bioactive components of *Glycyrrhiza* include: Glycyrrhetinic Acid and its diglycoside of Glycyrrhizin. The latter generally constitutes about 2-15% of the dry weight of the plant and up to 9.1% can be found in a hydroalcoholic extract thereof, and when identifying both the 18α and 18β isomers of Glycyrrhetinic Acid, their ranges in mg/g dry weight are 0.062-0.475 and 0.015-0.13 respectively. Glycyrrhizic Acid (inactive analogue of Glycyrrhetic Acids), Glabridin within the range of 0.08 to 0.35%, Liquiritigenin (flavonoid; 0.108-2.174mg/g) and when diprenylated, Glabrol (2.3mg/g dry weight). Also, Isoliquiritigenin (0.073-0.489mg/g), and Liquiritigenin's glycoside Liquirtin (0.451-30.7mg/g; up to 3% Licorice by dry weight). Liquiritigenin is unique to Licorice and Alfalfa. Coumarins (Licopyranocoumarin, Licoarylcoumarin, Glycycoumarin), Formononectin, Glisoflavone, Various prenylated flavonoids (Prenylicoflavone A, Glysasperin A, Licoricidin, Hispaglabridin A, Isoagnusone A, Kanzonol K, and Glycyrrhisoflavone), Various volatiles such as β-caryophyllene oxide, decadienol, 1α, 10α-epoxyamorpha-4-ene, β-dihydroionone, thymol, and carvacrol (mostly related to flavor and scent), Isoangustone A (*Glycyrrhiza Uralensis*), Licochalcone A-E (mostly from the *inflata* species) with at least A and C isolated form *Glycyrrhiza Glabra* and limited amounts in *Uralensis*

[0091] The main active component of Licorice is known to be Glycyrrhizin and its metabolite 18-β glycyrrhetinic acid, flavonoids - mainly Liquiritigenin and Isoliquirtigenin - and the subset of polyphenolics based on Glabridin.

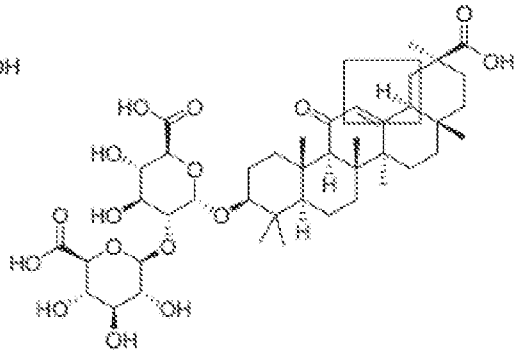
[0092] And polysaccharides found in Licorice (bioactive compounds that belong to the carbohydrate class; found in caloric vessels of Licorice but not isolated calorie-free extracts): Glycyrrhizin UC (69,000kDa; L-arabinose, D-galactose, D-glucose, and L-rhamnose at 10:30:27:1 in arabino-3, 6- galactoglucan-type structure) found in *Uralensis* Glycyrrhizin UA found in *Uralensis* A collection of lesser known *Uralensis* polysaccharides (n=10) Glycyrrhizin GA (85,000kDa; L-arabinose: D-galactose: L-rhamnose: D-galacturonic acid: D-glucuronic acid at 22:10:1:2:1) found in *Glabra* Unidentified pro-immunity polysaccharide

[0093] About 20% of the bioactives can be removed from the water extract, which consist of the sweetened fragment (mostly Glycyrrhizin up to 7-25% of the water extract) and flavanoids related to Liquiritigenin (1-1.5% total weight, 5-7.5% of the water extract).

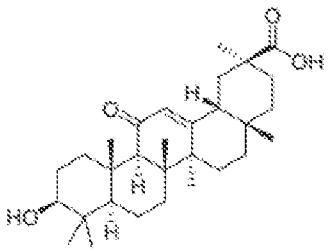
[0094] Some glycyrrhiza isolated bioactives;



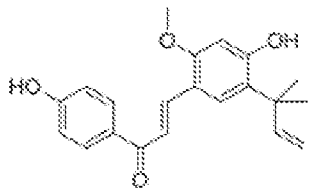
18Beta-glycyrrhizin (18β-GC)



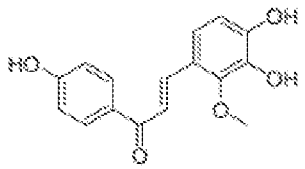
18Alpha-glycyrrhizin (18α-GC)



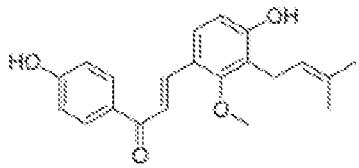
18Beta-Glycyrrhetinic acid (18β-GA)



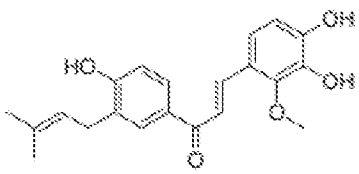
licochalcone A (LCA)



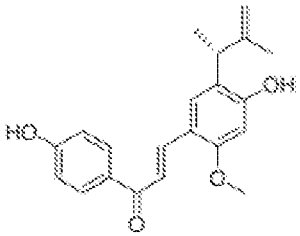
licochalcone B (LCB)



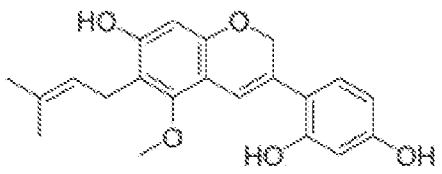
licochalcone C (LCC)



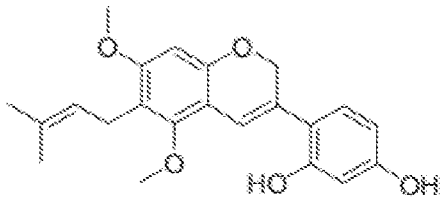
licochalcone D (LCD)



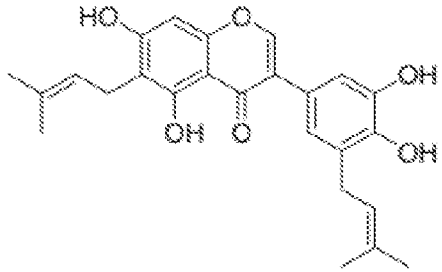
licochalcone E (LCE)



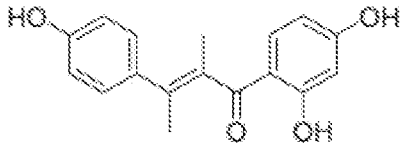
Dehydroglyasperin C (DGC)



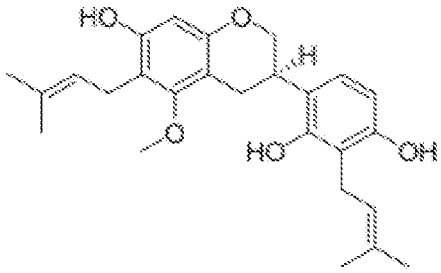
Dehydroglyasperin D (DGD)



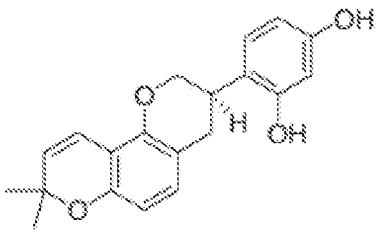
Isoangustone A (ISOA)



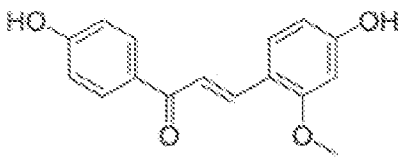
Isoliquiritigenin (ISL)



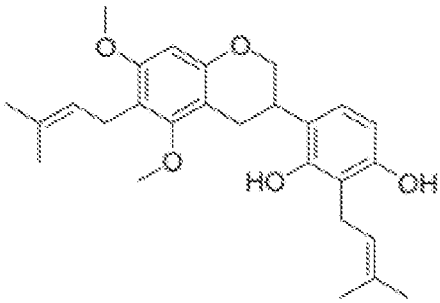
Licoricidin (LID)



Glabridin (GLD)



Echinatin (EC)



Licorisoflavan A (LIA)

Table I, below, provides the INCI names and corresponding CAS numbers for several licorice-derived substances and products.

Table I Common licorice INCI and CAS names for pure or isolated derivatives products (licorice-related substances)

INCI Name	CAS Number
Dipotassium Glycyrrhizate	68797-35-3
Ammonium Glycyrrhizate	53956-04-0
Stearyl Glycyrrhetinate	13832-70-7
Disodium Glycyrrhizate	71277-79-7
Trisodium Glycyrrhizate	71277-78-6
Glycyrrhetinic Acid	471-53-4
Glycyrrhizic Acid	1405-86-3
Glycyrrhiza glabra (Licorice) root extract (40% Glabridin)	97676-23-8
Glabridin	59870-68-7
Glycyrrhiza glabra root extract	84775-66-6
Glycyrrhiza uralensis root extract	94349-91-4
Glycyrrhiza inflata root extract	488-230-4

Benefits and uses of the present invention

[0095] The present invention further provides, in another aspect, a composition as described above, or a dosage form as described above, for use in a method of treating an inflammatory disease or disorder.

[0096] In certain embodiments, the inflammatory symptom, disease or disorder are selected from the group consisting of: pain associated with cancer, neuropathic pain and HIV-associated sensory neuropathy; side effects of chemotherapy including nausea; symptoms of neurology and neurodegenerative diseases such as Huntington's disease, Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, post-traumatic stress disorder (PTSD), alcohol abuse, bipolar disorder,

depression, anxiety, anorexia nervosa; cancer such as gliomas, leukemia, skin tumors, colorectal cancer; diseases including hepatitis C, methicillin-resistant Staphylococcus aureus (MRSA), pruritus, psoriasis, asthma, sickle-cell disease, insomnia, fatigue, sleep apnea, digestive diseases, inflammatory bowel diseases, collagen-induced arthritis, atherosclerosis and dystonia and geriatric syndromes.

[0097] The composition of the present invention may be beneficial to those with certain liver disorders. In the case of liver fibrosis (scarring), a cannabinoid found in marijuana, specifically, CBD may contribute to the cell death of hepatic stellate cells that contribute to liver scarring. This suggests that CBD may reduce the extent of scarring in the liver when it is damaged.

[0098] In certain embodiments, the cannabinoid responsive disease is selected from inflammatory bowel disease (IBD) such as Crohn`s disease, ulcerative colitis, irritable bowel syndrome and intestinal and colon cancers.

[0099] In certain embodiment the cannabinoid or cannabinoids are anti-inflammatory cannabinoids. In certain embodiments, the oral dosage form is resistant to low pH and disintegrates or decomposes and releases the cannabinoid only upon contact with neutral pH intestinal or colon fluids. In certain embodiments, the dosage form is acid resistant and does not release the cannabinoids in a low pH environment. Rather, in this embodiment, the cannabinoids are released at a pH of greater than 6.5 or greater than 7.0. In certain embodiments the solid solution releases the cannabinoids only in presence of pectinases. In certain embodiments the solid solution dosage form releases the cannabinoids only at neutral pH and presence of pectinases, a condition prevailing in the colon. In certain embodiment the solid solution is acid resistant and release the at least one cannabinoid upon crossing the stomach and entering a pH of greater than 6.5 and over at least four hours and more preferably over at least six hours.

[00100] The anti-inflammatory synergistic composition comprising cannabis and licorice, or isolates, fractions or components obtained therefrom, provides many benefits such as increased pharmacological efficacy, use of lower steroid or NSAID concentration, thus having the required therapeutic effect with reduced side effects, prolonged use with a

lower dose or period limits or contra indications due to adverse effects. Moreover, the accompanying anti-viral, anti-bacterial and anti-biofilm activity provides great usability in treating inflammation symptoms in conditions of infectious origin or in subjects prone to infection. The composition may be used to both treat and prevent inflammation of both infectious and non-infectious origin.

[00101] Generally, the two main active components of the synergistic combination (i.e. the anti-inflammatory cannabis and the licorice) will be administered together in a single composition. In some cases, however, these two components will be administered in separate compositions – either simultaneously (e.g. the patient will swallow two different oral dosage forms, each containing one of the two active components; or will apply two different topical preparations) or consecutively, in either order.

[00102] Licorice may be prepared in an extract form or in root form. The extract can be prepared in the form ofteas, capsules, tablets, dry powder, and in combination with other herbal remedies. Since the side effects of licorice root are mostly related to the substance glycyrrhizin, most of the clinical research done on the herb is made with modified licorice extract from which most of the glycyrrhizin has been removed. Deglycyrrhizinated licorice (DGL) is usually standardized to contain no more than three percent natural glycyrrhizin. The contents of glycyrrhizin in pure licorice root can be between one and 24 percent but usually is between six to 14 percent. The German Commission E accepts an intake of an average daily dose of 200 to 600 mg glycyrrhizin, which corresponds to five to 15 g of licorice. Licorice root may be used in daily doses from 2 to 15 g for ulcer and gastritis.

[00103] As a treatment for ulcers, a dose of 1.5 to 3g of licorice root daily has been recommended. The maximum dose of glycyrrhizin licorice when used as a flavor ingredient in food and beverages, should not exceed 100 mg per day. Licorice appears to increase cortisol at higher doses (500mg or more), with no significant influence at lower doses; this is related to the glycyrrhizin content and would not occur in deglycyrrhizinated supplements and appears to be a testosterone reduction associated with intake of licorice above 500mg, but the magnitude of this reduction is quite variable and there is no robust information on the topic.

[00104] Almost 50 years ago, a scientist by the name of Revers reported that licorice paste reduced abdominal symptoms and caused radiographic evidence of ulcer healing. However, about 20% of patients developed edema, headache and other symptoms due to overdose, leading to a loss of enthusiasm. This led to the development of DGL (deglycyrrhizinated licorice), a form of licorice that does not contain the agents responsible for the side effects such as electrolyte changes. The de-acidified DGL tablet or capsule form used in Europe and America is therefore devoid of any major side effects, and is effective for healing the intestinal membranes. Because it is chewable, it also is helpful to the esophagus.

[00105] In the case of oral administration, for systemic delivery, the amount of each of the active components to be administered each day is generally as follows:

a) Anti-inflammatory cannabinoid: about 1-1,500 mg/day, more preferably from about 20mg to about 600 mg/day

b) Glycyrrhiza extract: about 100 - 2000 mg/day, or about 1.0 to about 20.0 grams of licorice root

[00106] In the case of topical administration, the amount of each of the active components to be administered each day is generally as follows:

a) Anti-inflammatory cannabinoid or cannabis extract: 0.01-10 mg/day

b) Licorice extract or its isolates: 0.1-100 mg/day

[00107] In the case of topical administration to the skin (e.g. in a cream, ointment, gel, foam or lotion), the concentration of each of the active components within the topical dosage form is as follows:

a) Anti-inflammatory cannabinoid or cannabis extract: 0.01% - 2.0%

b) Licorice extract: 0.1% - 4% or its bioactive isolate from about 0.01% to 2.0%

[00108] In the case of topical administration to mucosal membranes such as the eyes (e.g. by way of eye drops) or oral cavity (e.g. as a rinse solution or suspension), the concentration of each of the active components within the topical dosage form is as follows:

a) Anti-inflammatory cannabinoid or cannabis extract: 0.01% to about 2.0%

b) Licorice extract or its isolates: 0.1% to about 2.0%

[00109] In the case of parenteral administration by injection (e.g. subcutaneous, intramuscular), the concentration of each of the active components within the injection dosage form is as follows:

a) Anti-inflammatory cannabinoid: 0.01% - 2.0%

b) Licorice bioactive isolate: 0.1% - 4%

[00110] In certain preferred embodiments the ratio on a weight per weight basis (W/W), of the at least one cannabinoid or cannabis extract to the at least one licorice isolate or extracts in the drug product is from about 1000:1 to about 1:1000, more preferably from about 100:1 to about 1:100, more preferably from about 10:1 to about 1:100, more preferably from about 5:1 to about 1:500, more preferably from about 1:1 to about 1:100, more preferably from about 1:2 to about 1:60, and more preferably from about 1:3 to about 1:50 and more preferably from about 1:4 to about 1:40 and more preferably from 1:5 to about 1:30 and more preferably from 1:6 to about 1:20.

[00111] In certain preferred embodiments the at least one cannabinoid or cannabis extract is present at a concentration of at least about 0.1% W/W in the composition. In certain preferred embodiments the amount of the cannabinoid or cannabis extract is at least about 0.5% W/W. . In certain preferred embodiments the amount of the cannabinoid or cannabis extract is at least about 1.0% W/W. In certain preferred embodiments the amount of the cannabinoid or cannabis extract is at least about 2.0% W/W. In certain preferred embodiments the amount of the cannabinoid or cannabis extract is at least about 5.0%

W/W. In certain preferred embodiments the amount of the cannabinoid or cannabis extract is at least about 10.0% W/W. In certain preferred embodiments the amount of the cannabinoid or cannabis extract is at least about 20.0% W/W. In certain preferred embodiments the amount of the cannabinoid or cannabis extract is at least about 30.0% W/W.

[00112] In certain preferred embodiments the at least one licorice-related substance is present at a concentration of at least about 0.1% W/W of the composition. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 0.2% W/W. In certain preferred embodiments the amount of the at least licorice-related substance is at least about 0.3% W/W. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 0.4% W/W. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 0.5% W/W. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 1.0% W/W . In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 2.0% W/W. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 3.0% W/W In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 4.0% W/W. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 5.0% W/. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 10.0% W/W. In certain preferred embodiments the amount of the at least one licorice-related substance is at least about 20.0% W/W.

[00113] In certain preferred embodiments the concentration of the at least one cannabinoid or cannabis extract is from about 0.1% W/W to about 1.0% W/W. In certain preferred embodiments the concentration of the at least one cannabinoid or cannabis extract is from about 1.0% W/W to about 5.0% W/W. In certain preferred embodiments the concentration of the at least one cannabinoid or cannabis extract is from about 2.0% W/W to about 10.0% W/W. In certain preferred embodiments the concentration of the at least one cannabinoid or cannabis extract is from about 10.0% W/W to about 50.0% W/W.

[00114] In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.1% W/W to about 1.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.2% W/W to about 2.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.3% W/W to about 3.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.4% W/W to about 4.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.5% W/W to about 5.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.6% W/W to about 6.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.7% W/W to about 7.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.8% W/W to about 8.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 0.9% W/W to about 9.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 1.0% W/W to about 10.0% W/W. In certain preferred embodiments the concentration of the at least one licorice-related substance is from about 2.0% W/W to about 2.0% W/W.

[00115] In a certain preferred embodiment, there is a method of mixing a gradient of concentrations of the at least one cannabinoid and at the at least one licorice related substance and measuring the ratio that provides the highest pharmacological benefit. Such testing methods in animal model or human tests should consider the route of administration and the pharmacokinetic of the ingredients.

[00116] The synergistic or potentiating anti-inflammatory composition of at least one cannabinoid or cannabis extract to at least one licorice isolate or extracts can be used for any disease or indication or condition or ailment or syndrome or health problem associated with inflammation, or its manifestations of pain, heat, redness and swelling and for administration to the oral cavity as wash gel spray balm, tooth paste, strip, for skin care,

face skin care scalp treatment, lip treatment, antiperspirants, acne products, eczema, dermatitis, psoriasis and after sun or sun protecting products.

[00117] The synergistic or potentiating anti-inflammatory composition of at least one cannabinoid or cannabis extract to at least one licorice isolate, or extracts can be used for any disease or indication or condition or ailment or syndrome or health problem associated with auto-immune diseases and CNS or liver or diseases associated with inflammation and fibrosis and inflammatory bowel diseases and cancer diseases associated with inflammation and inflammation of the tumor environment.

[00118] While the invention will now be described in connection with certain preferred embodiments in the following examples so that aspects thereof may be more fully understood and appreciated, it is not intended to limit the invention to these particular embodiments. On the contrary, it is intended to cover all alternatives, modifications and equivalents as may be included within the scope of the invention as defined by the appended claims. Thus, the following examples which include preferred embodiments will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purposes of illustrative discussion of preferred embodiments of the present invention only and are presented in the cause of providing what is believed to be the most useful and readily understood description of formulation procedures as well as of the principles and conceptual aspects of the invention.

EXAMPLES

IN VITRO WORKING EXAMPLES

[00119] The objective of the following *in vitro* experiments was to investigate the anti-inflammatory properties of various combinations of a cannabis-derived substance (CBD) and a licorice extract. The potential for synergistic interaction was tested by assaying inflammatory mediator secretion by a macrophage cell line (RAW 264.7), following stimulation with lipopolysaccharide (LPS). The inflammatory mediators assayed

were: prostaglandin E2 (PGE2), nitric oxide (NO), TNF-alpha, IL-6, GM-CSF and MCP-1.

[00120] The study was initiated by preliminary cell-viability dose-response analyses to ascertain the maximal concentrations of the compounds tolerated by the cells. Only non-toxic concentrations were used in the following tests.

[00121] *General methods:*

[00122] The CBD used in the studies described hereinbelow was 99% pure as tested by HPLC assay. In most cases, the CBD used in the follow study was obtained from IK Hemp S.p.A (Bari, Italy). The licorice extract used in the studies described hereinbelow was spray dried licorice extract flavor 9, obtained from Mafco Worldwide LLC (Camden, New Jersey, USA). This extract has the following composition (w/w percentages measured in the dried material):

Glycyrrhizic acid	8.1
Sucrose	2.0
Hot insoluble	1.2
Loss on drying	1.9

The pH of the composition was 5.0.

[00123] RAW 264.7 monocyte macrophage cells (approximately $4x10^5$/ml) were seeded in 24 well plates containing 800 microliters/well of complete growth medium (DMEM containing 2mM glutamine, 100U/ml penicillin and 100µg/ml streptomycin and 10% fetal bovine serum). The cells were then incubated at 37 degrees Celsius with 5% carbon dioxide for 24 h. At the end of this period, growth medium supplemented with 1µg/ml lipopolysaccharide (LPS) was added to the cells, together with the test substances (licorice extract, CBD, and their combinations) and various controls, and the cells were then incubated for a further 24 hr. period under the same conditions as before. Following

this incubation period, the conditioned medium was aspirated from the various test and control wells and centrifuged at 14,000 g for 5 minutes to remove particulate matter. The clear supernatants were then stored at -70 degrees Celsius prior to assaying the inflammatory mediatory content therein.

[00124] The cytokine/mediator content in the thawed supernatants was assayed using a standard ELISA kit for PGE_2 and a colorimetric kit for NO, the details of which are as follows:

ELISA kit for Prostaglandin E2 – Enzo. Cat number ADI-901-001.

Nitrate/Nitrite Colorimetric Assay Kit – Cayman Chemical. Cat number 780001.

TNFα, IL-6, GM-CSF and MCP-1 by Q Plex- mouse cytokine inflammation (14 plex). ref: 110449MS

Example 1

Synergistic interaction between CBD and Licorice extract in inhibiting Prostaglandin E_2 secretion

[00125] *Method:* The effect of CBD was investigated on Prostaglandin E_2 (PGE_2) secretion, as an independent inflammation marker derived from arachidonic acid metabolism. Raw 264.7 macrophage cells were incubated (as described above) in the absence or presence of LPS and treated without or with the CBD, Licorice or a combination thereof for 24 hr. Then, PGE_2 levels in the supernatant medium were quantified by ELISA, as explained above.

[00126] *Results:* As seen in Fig. 1, both the CBD and Licorice extract inhibited LPS-stimulated Prostaglandin E2 secretion to a certain degree, a synergistic effect was observed when tested in lower concentrations. As expected, the induction of inflammation by administration of LPS increased the secretion levels of this pro-inflammatory eicosanoid. The various treatments are indicated as follows: TI_1 (CBD at 3.14, 15.7, 157 and 314 ng/ml and 31.4); TI_2 (Licorice at 0.01 and 0.05 mg/ml). Unexpectedly, combination of CBD with Licorice dry extract shows a significant greater reduction of Prostaglandin E2 than the

cumulative effect of both of them separately. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *p<0.05 for difference from the naïve control. #for significant difference in comparison from the respective stimulated control; $for synergistic effect.

Example 2

Synergistic interaction between CBD and Licorice in inhibiting Nitric oxide secretion

[00127] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol), Licorice (dissolved in media) or a combination thereof for 24 hr. Then, Nitric oxide (NO) levels in the supernatant medium were quantified by colorimetry, as explained above.

[00128] *Results:* The results of this study are presented in Fig. 2, in which the various treatments are indicated as follows: TI_1 (CBD at 3.14, 15.7, 157 and 314 ng/ml and 31.4); TI_2 (Licorice at 0.01 and 0.05 mg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of NO. Moreover, CBD alone attenuated NO secretion in a biophysical manner, whereas Licorice did not cause any significant decrease in NO secretion. Unexpectedly , several combinations of these compounds, caused a much greater than additive inhibitory result, indicating a synergistic interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *p<0.05 for difference from the naïve control. #for significant difference in comparison from the respective stimulated control; $for synergistic effect.

Example 3

Synergistic interaction between CBD and Glabridin 40%, (Licorice extract) in inhibiting Nitric oxide secretion

[00129] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol),

Glabridin 40% (dissolved in media) or a combination thereof for 24 hr. Then, Nitric oxide (NO) levels in the supernatant medium were quantified by colorimetry, as explained above.

[00130] *Results:* The results of this study are presented in Fig. 3, in which the various treatments are indicated as follows: TI_1 (CBD 1.0µg/ml and 0.5 µg/ml); TI_2 (Licorice at 1.0 µg/ml and 0.1 µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of NO. Moreover, CBD alone attenuated NO secretion in a biophysical manner, whereas Glabridin 40% did not cause any significant decrease in NO secretion. Unexpectedly, several combinations of these compounds, caused a much greater than additive inhibitory result, indicating a synergistic interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *$p<0.05$ for difference from the naïve control. $^{\#}$for significant difference in comparison from the respective stimulated control; $^{\$}$for synergistic effect.

Example 4

Synergistic interaction between CBD and synergistic interaction between CBD and dipotassium glycyrrhizinate (DPG) isolate in inhibiting IL-6 secretion

[00131] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol), synergistic interaction between CBD and pure dipotassium glycyrrhizinate (dissolved in media) or a combination thereof for 24 hr. Then, IL-6 levels in the supernatant medium were quantified by ELISA, as explained above.

[00132] *Results:* The results of this study are presented in Fig. 4, in which the various treatments are indicated as follows: TI_1 (CBD 1.0µg/ml and 0.5 µg/ml); TI_2 (pure dipotassium glycyrrhizinate at 1.0 µg/ml and 0.1 µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of IL-6. Moreover, CBD alone attenuated IL-6 secretion in a biophysical manner, whereas DPG did not cause any significant decrease in IL-6 secretion. Importantly, several combinations of these

compounds, caused a much greater than additive inhibitory result, indicating a synergistic interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *p<0.05 for difference from the naïve control. #for significant difference in comparison from the respective stimulated control; $for synergistic effect.

Example 5

Synergistic interaction between CBD and synergistic interaction between CBD and 18 beta glycyrrhitinic acid in inhibiting IL-6 secretion

[00133] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol), synergistic interaction between CBD and 18 beta glycyrrhitinic acid (dissolved in media) or a combination thereof for 24 hr. Then, IL-6 levels in the supernatant medium were quantified by ELISA, as explained above.

[00134] *Results:* The results of this study are presented in Fig. 5, in which the various treatments are indicated as follows: TI_1 (CBD 1.0µg/ml and 0.5 µg/ml); TI_2 (18 beta glycyrrhitinic acid at 0.001 µg/ml and 0.0001 µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of IL-6. Moreover, CBD alone attenuated IL-6 secretion in a biophysical manner, whereas 18 beta glycyrrhitinic acid did not show significant decrease in IL-6 secretion. Unexpectedly, several combinations of these compounds, caused a much greater than additive inhibitory result, indicating a synergistic interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *p<0.05 for difference from the naïve control. #for significant difference in comparison from the respective stimulated control; $for synergistic effect.

Example 6

Synergistic interaction between CBD and synergistic interaction between CBD and Glabridin 40% in inhibiting IL-6 secretion

[00135] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol), synergistic interaction between CBD and Glabridin 40% (Mafco Corp, USA) (dissolved in media) or a combination thereof for 24 hr. Then, IL-6 levels in the supernatant medium were quantified by ELISA, as explained above.

[00136] *Results:* The results of this study are presented in Fig. 6, in which the various treatments are indicated as follows: TI_1 (CBD 1.0µg/ml and 0.5 µg/ml); TI_2 (Glabridin 40% at 1.0 µg/ml and 0.1 µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of IL-6. Moreover, CBD alone attenuated IL-6 secretion in a biophysical manner, whereas Glabridin 40% did not cause any significant decrease in IL-6 secretion. Unexpectedly, several combinations of these compounds, caused a much greater than additive inhibitory result, indicating a synergistic interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *$p<0.05$ for difference from the naïve control. $^{\#}$for significant difference in comparison from the respective stimulated control; $^{\$}$for synergistic effect.

Example 7

Synergistic interaction between CBD and synergistic interaction between CBD and Glabridin 40% in inhibiting Granulocyte-macrophage colony-stimulating factor (GM-CSF) secretion

[00137] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol), synergistic interaction between CBD and Glabridin 40% (dissolved in media) or a

combination thereof for 24 hr. Then, GM-CSF levels in the supernatant medium were quantified by ELISA, as explained above.

[00138] *Results:* The results of this study are presented in Fig. 7, in which the various treatments are indicated as follows: TI_1 (CBD 1.0µg/ml and 0.5 µg/ml); TI_2 (Glabridin 40% at 1.0 µg/ml and 0.1 µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of GM-CSF. Moreover, CBD alone or Glabridin 40% alone did not cause any significant decrease in GM-CSF secretion. Unexpectedly, several combinations of these compounds, caused a much greater than additive inhibitory result, indicating a synergistic interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *$p<0.05$ for difference from the naïve control. #for significant difference in comparison from the respective stimulated control; $for synergistic effect.

Example 8

Synergistic interaction between CBD and Glabridin 40% in inhibiting (MCP-1) secretion

[00139] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol), synergistic interaction between CBD and Glabridin 40% (dissolved in media) or a combination thereof for 24 hr. Then, MCP-1 levels in the supernatant medium were quantified by ELISA, as explained above.

[00140] *Results:* The results of this study are presented in Fig. 8, in which the various treatments are indicated as follows: TI_1 (CBD 1.0µg/ml and 0.5 µg/ml); TI_2 (Glabridin 40% at 1.0 µg/ml and 0.1 µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of IL-6. Moreover, CBD alone or Glabridin 40% alone did not cause any significant decrease in MCP-1 secretion. Importantly, several combinations of these compounds, caused a significant inhibitory

result of MCP-1 reduced secretion, indicating a synergistic or potentiating interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *p<0.05 for difference from the naïve control. #for significant difference in comparison from the respective stimulated control; $for synergistic effect.

Example 9

Synergistic interaction between CBD and Licorice dry extract (Glycyrrhizic acid 8.1%) in inhibiting TNFα secretion

[00141] *Method*: Raw 264.7 macrophage cells were incubated in the absence or presence of LPS and treated without or with Cannabidiol (CBD, dissolved in Ethanol), synergistic interaction between CBD and Licorice dry extract (dissolved in media) or a combination thereof for 24 hr. Then, TNFα levels in the supernatant medium were quantified by ELISA, as explained above.

[00142] *Results:* The results of this study are presented in Fig. 9, in which the various treatments are indicated as follows: TI_1 (CBD 1.0μM); TI_2 (Licorice dry extract 0.01 μg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of IL-6. Moreover, CBD alone attenuated TNFα secretion in a biophysical manner, whereas Licorice dry extract did not cause any significant decrease in TNFα secretion. Importantly, the combinations of these compounds, caused a significant inhibitory result of TNFα reduced secretion, indicating a potentiating interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *p<0.05 for difference from the naïve control. #for significant difference in comparison from the respective stimulated control; $for synergistic effect.

Example 10

Synergistic interaction between CBD and Licorice dry extract (Glycyrrhizic acid 8.1%) in inhibiting PGE_2 secretion

[00143] *Method:* The effect of CBD was also investigated on Prostaglandin E_2 (PGE_2) secretion, as an independent inflammation marker derived from arachidonic acid metabolism. Raw 264.7 macrophage cells were incubated (as described above) in the absence or presence of LPS and treated without or with the CBD, pure Glycyrrhizic acid (GA) or a combination thereof for 24 hr. Then, PGE_2 levels in the supernatant medium were quantified by ELISA, as explained above.

[00144] *Results:* The results of this study are presented in Fig. 10, in which the various treatments are indicated as follows: TI_1 (CBD at 0.01µg/ml); TI_2 (GA) at 0.001µg/ml and 0.001µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of PFE_2. However, CBD alone or GA alone at the specified concentrations did not inhibited the PGE_2 secretion in a biophysical manner. Unexpectedly, the combination of CBD with GA significantly inhibited PGE_2 secretion, indicating a potentiating interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *$p<0.05$ for difference from the naïve control. $^{\#}$for significant difference in comparison from the respective stimulated control; $^{\$}$for synergistic effect.

Example 11

Synergistic interaction between CBD and the licorice-related compound disodium glycyrrhizinate in inhibiting PGE_2 secretion

[00145] *Method:* The effect of CBD was also investigated on Prostaglandin E_2 (PGE_2) secretion, as an independent inflammation marker derived from arachidonic acid metabolism. Raw 264.7 macrophage cells were incubated (as described above) in the absence or presence of LPS and treated without or with the CBD, pure disodium glycyrrhizinate (DSG) or a combination thereof for 24 hr. Then, PGE_2 levels in the supernatant medium were quantified by ELISA, as explained above.

[00146] *Results:* The results of this study are presented in Fig. 11, in which the various treatments are indicated as follows: TI_1 (CBD at 0.01µg/ml); TI_2 (DSG) at 0.01 µg/ml, 0.001µg/ml and 0.001µg/ml). As expected, the induction of inflammation by administration of LPS increased the secretion levels of PFE_2. However, CBD alone or DSG alone at the specified concentrations did not inhibited the PGE_2 secretion in a biophysical manner. Unexpectedly, the combination of CBD with DSG significantly inhibited PGE_2 secretion, indicating a potentiating interaction between them. The results summarized in this figure are shown as the mean of triplicate samples +/- SEM. The statistical significance levels shown in the figure are as follows: *$p<0.05$ for difference from the naïve control. $^{\#}$for significant difference in comparison from the respective stimulated control; $^{\$}$for synergistic effect.

FORMULATION EXAMPLES

[00147] The following section provides details of several possible formulations containing the composition of the present invention. These formulations are brought for exemplary purposes only, and do not limit the scope of the present invention in any way.

Example 12

Anhydrous cream

Formula	A	B	C	D	E	F
Ingredients	W/W%	W/W%	W/W%	W/W%	W/W%	W/W%
Cannabis ethanol extract	0.5	1.0	0.5	1.0	0.5	1.0
Licorice dry extract	1.0	2.0	1.0	2.0	1.0	2.0
jojoba oil	6.0	6.0	6.0	6.0	6.0	6.0
coconut oil	6.0	6.0	6.0	6.0	6.0	6.0
cetearyl glucoside	3.0	3.0	3.0	--	--	--
Montanov 68	--	--	--	3.0	3.0	3.0
ceteth-2	2.0	2.0	2.0	--	--	--
polyglyceryl 3 stearate	--	==	--	2.0	2.0	2.0
PPG15 stearyl ether	--	==	--	2.0	2.0	2.0
cetostearyl alcohol	2.0	2.0	2.0	2.0	2.0	2.0
glyceryl monostearate	2.0	2.0	2.0	2.0	2.0	2.0
Polyethylene glycol 400	6.0	--	6.0	--	6.0	--
Propylene glycol	--	6.0	--	6.0	--	6.0
Glycerin	To 100	To 100	To 100	To 100	To 100	To 100

Example 13

Topical cream containing cannabidiol and freeze dried licorice extract

Formula	A	B	C	D	E	F	G	H
Ingredient	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W
Cannabidiol	1.0	--	1.0	--	0.1	--	0.1	--
Cannabis ACDC alcoholic extract	--	1.0	--	1.0	--	0.5	--	0.5

Licorice dry extract	1.0	2.0	3.0	4.0	1.0	2.0	3.0	4.0
benzyl alcohol	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Glycerin	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
glyceryl monostearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
isopropyl palmitate	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
lactic acid	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Paraffin	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
polyoxyl 40 stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
cetostearyl alcohol	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
potassium sorbate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
sorbitan monostearate	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Water	To 100	To 100	To 100	To 100	To 100	To 100	To 100	To 100

Example 14

Topical cream containing CBD or CBDA and glycyrrhizin or glycyrrhitin

Formula	A	B	C	D	E	F	G	H
Ingredient	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W
CBD	0.01	0.05	0.1	0.5	1.0	---	----	----
CBDA	---	---	---	---	---	0.1	0.5	1.0
glycyrrhyzin	0.1	0.5	1.0	---	---	1.0	0.5	---
Glycyrrhitin				0.5	1.0		---	1.0
aluminum starch octylsuccinate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

hexylene glycol	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
hydrogenated soybean lecithin	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
phosphoric acid	QS	QS	QS	QS	QS	QS	QS	QS
white soft paraffin	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
white wax	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Purified water	To 100	To 100	To 100	To 100	To 100	To 100	To 100	To 100

Example 15

Topical cream containing CBDA and Glycyrrhetinic acid

A topical cream containing cannabidiol and Glycyrrhetinic acid may be prepared using the following ingredients:

Cannabidiol 0.2% and Glycyrrhetinic acid 1.0% in aloe barbadensis leaf juice, avena sativa (oat) kernel extract, benzyl alcohol, butylated hydroxytoluene, cetostearyl alcohol, cetyl alcohol, chamomilla recutita (matricaria) flower extract, diazolidinyl urea, dimethicone, distearyldimonium chloride, edetate disodium, glycerin, glyceryl monostearate, hydrolyzed collagen, hydrolyzed elastin, hydrolyzed jojoba esters, jojoba esters, magnesium ascorbyl phosphate, menthyl lactate, methyl gluceth-20, methylparaben, petrolatum, polysorbate 60, potassium hydroxide, PPG-12/SMDI copolymer, propylparaben, purified water, retinyl palmitate, stearamidopropyl PG-dimonium chloride phosphate, steareth-2, steareth-21, stearyl alcohol, tocopheryl acetate

Example 16

Topical cream containing Cannabidiol and Glycyrrhetinic acid

A topical cream containing Cannabidiol and licorice dry extract may be prepared using the following ingredients:

1. Cannabidiol 0.5%, Glycyrrhetinic acid 2.0%, cetearyl octanoate 6.0%, jojoba oil 6.0%, Montanov-68™ 4.0%, cetostearyl alcohol 2.0%, glyceryl monostearate 2.0%, sorbitan oleate 1.0%, glycerin 20%, microbial preservative QS, and purified water to 100, or
2. Cannabis ethanol extract 1.0%, Glycyrrhetinic acid 2.0%, cetearyl octanoate 6.0%, jojoba oil 6.0%, Montanov-68™ 4.0%, cetostearyl alcohol 2.0%, glyceryl monostearate 2.0%, sorbitan oleate 1.0%, glycerin 20%, microbial preservative QS, and purified water to 100

Example 17

Topical ointment containing cannabis extract and licorice extract

Formula	A	B	C	D	E	F
Ingredient	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W
High CBD Cannabis extract (80% of total cannabinoids)	0.5	0.1	0.01	----	----	----
High THC Cannabis extract (80% of total	----	----	----	0.5	0.1	0.01

cannabinoids)						
Glabridin	0.5	1.0	0.5	1.0	0.5	1.0
Mineral oil	30.0	30.0	30.0	30.0	30.0	30.0
White petrolatum	To 100	To 100	To 100	To 100	To 100	To 100

Example 18

Eye drops containing Cannabidiol and Glycyrrhizin

Eye drops containing Cannabidiol and Glycyrrhizin may be prepared using the following ingredients:

Cannabidiol 0.1 mg/ml and Glycyrrhizin 0.5 mg/ml eye drops, solution, preservative-free, also containing sodium chloride, disodium edetate, disodium phosphate dodecahydrate and purified water.

Example 19

Controlled-release tablet or capsules containing CBDA and Licorice dry extract

Delayed- and extended-release dosage forms of cannabidiolic acid (CBDA) with deglycyrrhizinated licorice (DGL) in the form of colon-targeted granules for oral administration may be prepared from the following ingredients:

Capsules or compressed tablets containing or made of granules composed of 100 mg CBDA and 400 mg DGL in a polymer matrix with a matrix or an enteric-coating that dissolves at pH 6.5 and above.

The inactive ingredients of capsules are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, simethicone emulsion ethyl acrylate/methyl methacrylate copolymer nonoxynol 100 dispersion, Hypromellose, methacrylic acid copolymer, talc,

titanium dioxide, triethyl citrate, aspartame, anhydrous citric acid, povidone, vanilla flavor, and edible black ink.

Example 20

Rectal foam containing CBDA and Glycyrrhetinic acid

An aerosol foam for use in a pressurized canister with an applicator is prepared from the following ingredients:

CBDA 1.0% and Glycyrrhetinic acid 1.0% in cetyl alcohol, methyl hydroxybenzoate, propyl hydroxybenzoate, polyoxyethylene-10-stearyl ether, propylene glycol, triethanolamine, purified water, propellant HP 70 and emulsifying wax.

Example 21

Oral cavity wash containing Cannabis extract or Glycyrrhiza dry extract or its isolates

Sterile solutions for use as a mouthwash in the management of conditions such as oral mucositis may be prepared using the ingredients listed in the following table. Citric Acid and/or Sodium Hydroxide may be used to adjust the pH of the final solution to a value in the range of 7.0 to 8.5.

Formula	A	B	C	D	E	F
Ingredient	% W/W	% W/W	% W/W	% W/W	% W/W	% W/W
ACDC cannabis ethanolic extract	0.5	1.0	0.5	1.0	0.5	1.0
Glycyrrhiza dry extract	1.0	2.0	--	--	--	--
Glycyrrhizin			1.0	2.0	--	--

Glabridin	--	--	--	--	0.5	1.0
sodium hyaluronate	1.0	1.0	1.0	1.0	1.0	1.0
polyvinylpyrrolidone	2.0	2.0	2.0	2.0	2.0	2.0
Edetate Disodium	0.01	0.01	0.01	0.01	0.01	0.01
Sodium Citrate Anhydrous	1.0	1.0	1.0	1.0	1.0	1.0
Citric Acid and/or Sodium Hydroxide	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Purified water	To 100	To 100	To 100	To 100	To 100	To 100

Example 22

Licorice and cannabis toothpaste

Licorice dry extract 1.0%, cannabis extract 0.5% comprising not less than 5% terpenes, hydrated silica 20%, sodium lauryl sulfate 1.5%, Citric acid anhydrous 1.0%, peppermint oil 0/1%, Glycerol anhydrous to 100.

Example 23

Foaming face wash cleansing mousse

Water, Sodium Lauroyl Succosinate, Cocamidopropyl Betaine, Disodium Laureth Sulfosucccinate, Polysorbate 20 Sorbitan Monolaurate, Propylene Glycol, Sodium PCA, Citric Acid, Camellia Sinensis (Green Tea) Leaf Extract, Glycyrrhiza Glabra (Licorice) Extract, Aloe Barbadensis Leaf Extract, Ginkgo Biloba Extract, Carica Papaya Fruit Extract, Algae Extract and CBD or cannabis extract.

Example 24

Antiperspirants & Deodorants

Cannabis ethanolic extract 0.2%, Licorice dry extract 0.5%, Aluminium chlorohydrate 40.0%, propylene glycol 24.0%, Cetyl PEG/PPG-10/1 Dimethicone 2.0%, Cyclopentasiloxane 5.0%,

Dimethicone (and) Trisiloxane 5.0% and water to 100.

Example 25

After-Sun lotion

Ingredient	W/W%
CBD	0.20
Licorice dry extract	1.00
HEXYLDECANOL	2.00
CETEARYL ETHYLHEXANOATE	3.45
DIMETHICONE	0.50
ISOPROPYL MYRISTATE	0.55
ACRYLATES / C10-30 ALKYL ACRYLATE CROSSPOLYMER	0.30
PEG-90 STEARATE / GLYCERYL	2.00
Glycerin	2.00
Microbial preservative	0.30
Water	To 100

Example 26

Lip Care

Ingredient	W/W%
CBDA	0.20
Licorice dry extract	1.00
Myristyl Myristate	10.00
Cetyl Esters	5.00
Tribehenin	10.00
Pentaerythrityl Tetraisostearate	To 100
Polyglyceryl-3 Disostearate	5.00
Caprylic / Capric Triglyceride	37.00

Example 27

Scalp Treatment

INCI Name	w/w %
Cannabis extract	0.2
Licorice dry extract	1.0
Water	to 100
Propanediol	2.0
Gluconolactone, Sodium Benzoate	1.5
Xanthan Gum	0.1
Dicaprylyl Ether Cetiol OE	3.0
Oleyl Erucate	8.0
Hydrogenated Olive Oil, Olea Europaea (Olive) Fruit Oil, Olea Europaea Olive Oil Unsaponifiables	1.5
Behenyl Alcohol	0.5
Tocopherol, Helianthus Annuus	0.1
Cetearyl Olivate, Sorbitan Olivate	3.5
Cetearyl Alcohol	4.0
Linoleic Acid, Linolenic Acid Vitamin F forte	1.0

Water, Hydrolyzed Corn Starch, Beta Vulgaris (Beet) Root Extract	1.0
NaOH (10%)	QS

[00148] It will be evident to those skilled in the art that the invention is not limited to the details of the foregoing illustrative example and that the present invention may be embodied in other specific forms without departing from the essential attributes thereof, and it is therefore desired that the present embodiments and examples be considered in all respects as illustrative and not restrictive, reference being made to the appended claims, rather than to the foregoing description, and all changes which come within the meaning and range of equivalency of the claims are therefore intended to be embraced therein.

CLAIMS

1. An anti-inflammatory composition comprising a combination of (a) at least one cannabis-related substance; and (b) at least one licorice-related substance, wherein the weight ratio of said cannabis-related substance(s) to said licorice-related substance(s) is in the range of from about 10:1 to about 1:100.

2. The composition according to claim 1, wherein the at least one licorice-related substance is present in said composition at a concentration of at least about 0.2% (w/w).

3. The composition according to claim 1, wherein the at least one licorice-related substance is present in said composition at a concentration of at least about 0.5% (w/w).

4. The composition according to claim 1, wherein the cannabis-related substance is selected from the group consisting of cannabis plant whole material, extract, isolate and/or cannabinoid or other bioactive molecule contained therein.

5. The composition according to claim 1, wherein the cannabis-related substance is selected from: cannabidiol (CBD), cannabidiolic acid (CBDA), tetrahydrocannabinol (THC), tetrahydrocannabinolic acid (THCA), cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), cannabielsoin (CBE), iso-tetrahydrocannabinol (iso-THC), cannabicyclol (CBL), cannabicitran (CBT), cannabivarin (CBV), tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerovarin (CBGV), cannabigerol monomethyl ether (CBGM), salts thereof, derivatives thereof and mixtures of cannabinoids.

6. The composition according to claim 1, wherein the licorice-related substance is selected from the group consisting of Glycyrrhiza whole plant material, extract, isolate or bioactive molecule contained therein.

7. The composition according to claim 1, wherein the licorice-related substance is selected from: Glycyrrhizin/Glycyrrhetinic Acid, Glabridin, Glabrene, Licochalcone A, liquiritigenin, isoliquiritigenin, Coumarins, including licopyranocoumarin, licoarylcoumarin, and glycycoumarin, Formononetin, Glisoflavone, Hispaglabridins A and B, Rutin, Isoangustone A, Prunetin and Dehydroglyasperin C, salts thereof, derivatives thereof and mixtures of glycyrryhzanoids.

8. The composition according to claim 1, comprising a combination of purified CBD and a dried licorice extract.

9. A dosage form comprising a composition according to any one of claims 1 to 8 and one or more pharmaceutical excipients.

10. A method for treating an inflammatory condition or an auto-immune disease in a mammalian subject in need of such treatment, comprising the administration of a composition according to claim 1.

11. The method according to claim 10, wherein the mammalian subject is a human.

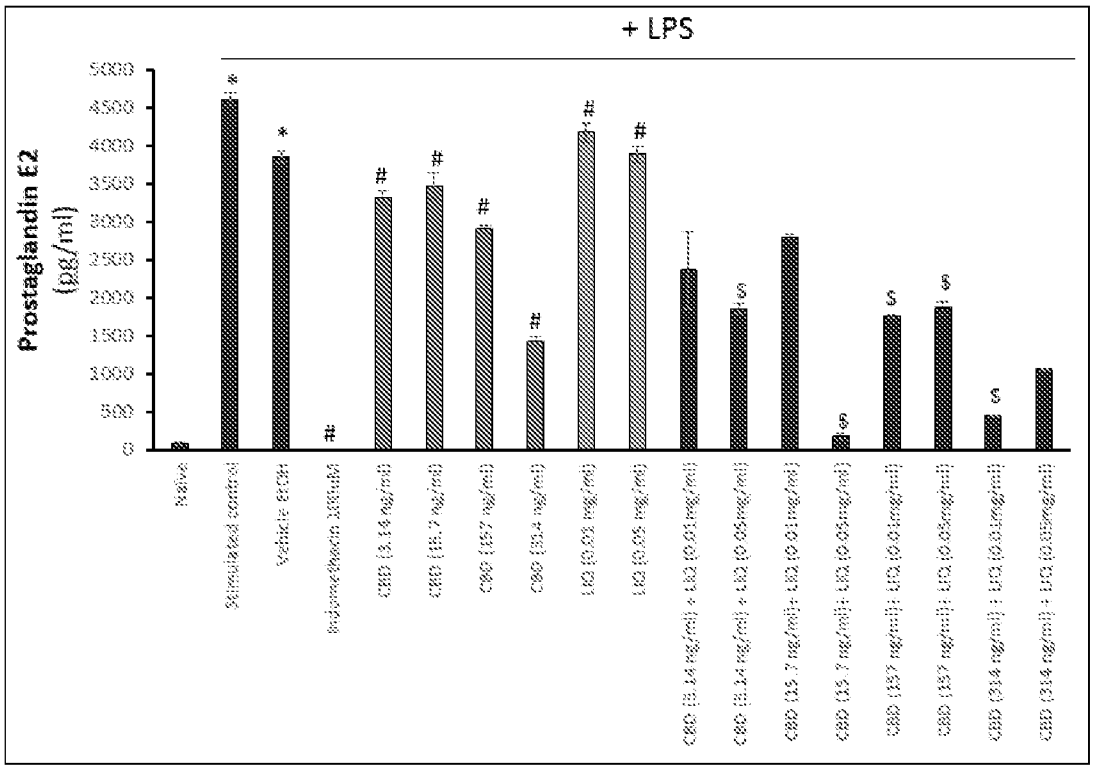
12. A composition according to claim 1, for use in the treatment of an inflammatory condition or an auto-immune disease.

13. The composition for use according to claim 12, wherein, said composition is used in the treatment of a systemic or topical or mucosal inflammatory disorders.

14. The use of a composition according to claim 1 for the preparation of a medicament.

15. The use of a composition according to claim 14, wherein the medicament is suitable for the treatment of an inflammatory condition or an auto-immune disease.

Fig. 1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4000
3500
3000
2500
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1000
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Stimulated control
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Indomethacin 1000nM
CBD (3.14 ng/ml)
CBD (15.7 ng/ml)
CBD (157 ng/ml)
CBD (314 ng/ml)
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LIQ (0.05 ng/ml)
CBD (3.14 ng/ml) + LIQ (0.01 ng/ml)
CBD (3.14 ng/ml) + LIQ (0.05 ng/ml)
CBD (15.7 ng/ml) + LIQ (0.01 ng/ml)
CBD (15.7 ng/ml) + LIQ (0.05 ng/ml)
CBD (157 ng/ml) + LIQ (0.01 ng/ml)
CBD (157 ng/ml) + LIQ (0.05 ng/ml)
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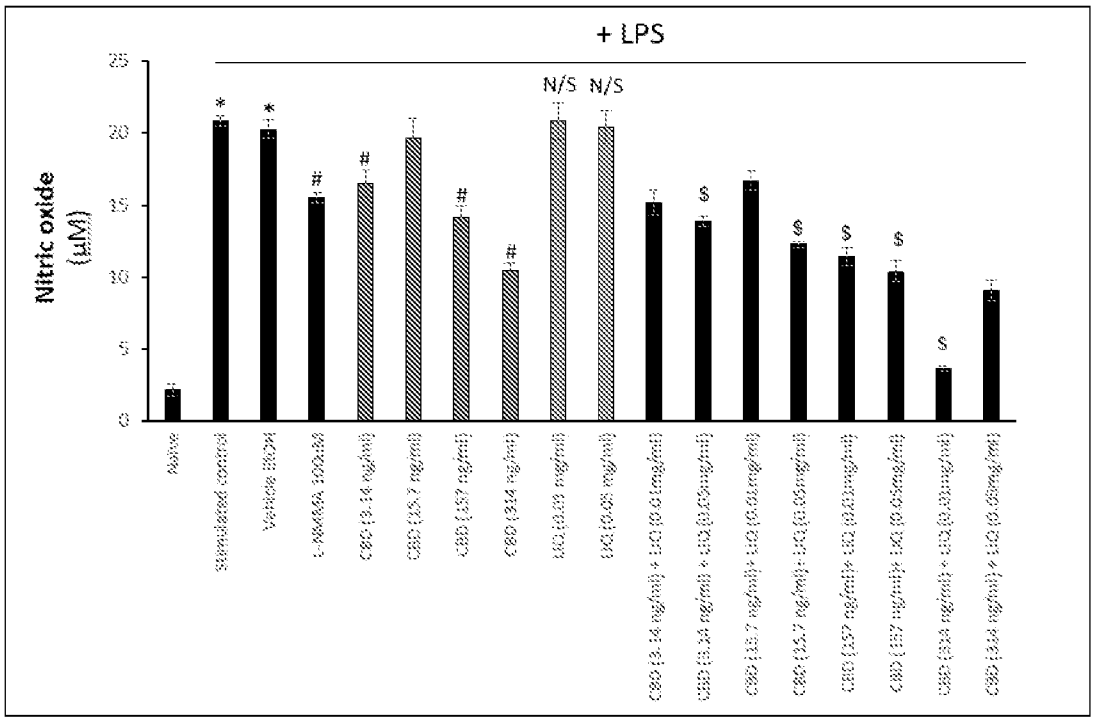
CBD (314 ng/ml) + LIQ (0.05 ng/ml)

Fig. 2



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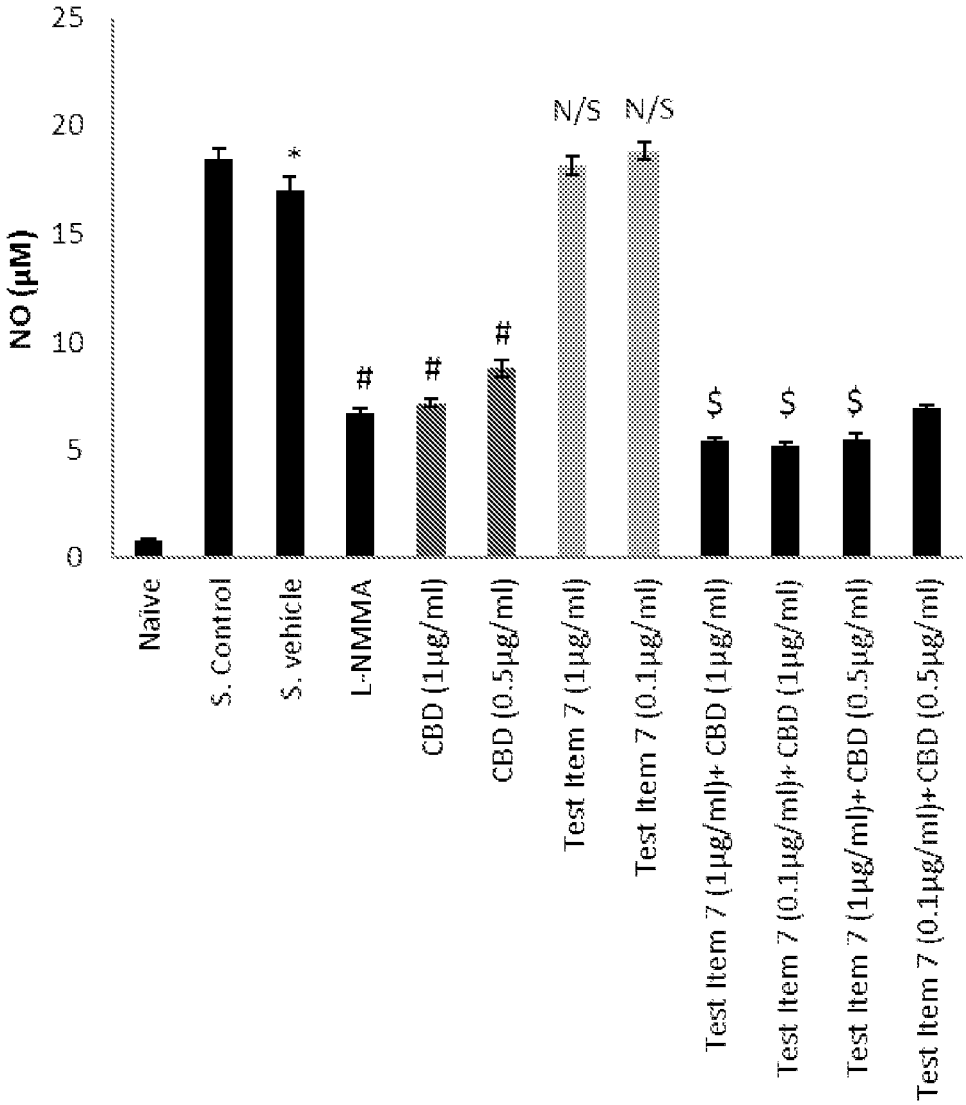
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15
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N/S
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#
#
#
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$
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S. vehicle
L-NMMA
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CBD (0.5µg/ml)
Test Item 7 (1µg/ml)
Test Item 7 (0.1µg/ml)
Test Item 7 (1µg/ml)+ CBD (1µg/ml)
Test Item 7 (0.1µg/ml)+ CBD (1µg/ml)
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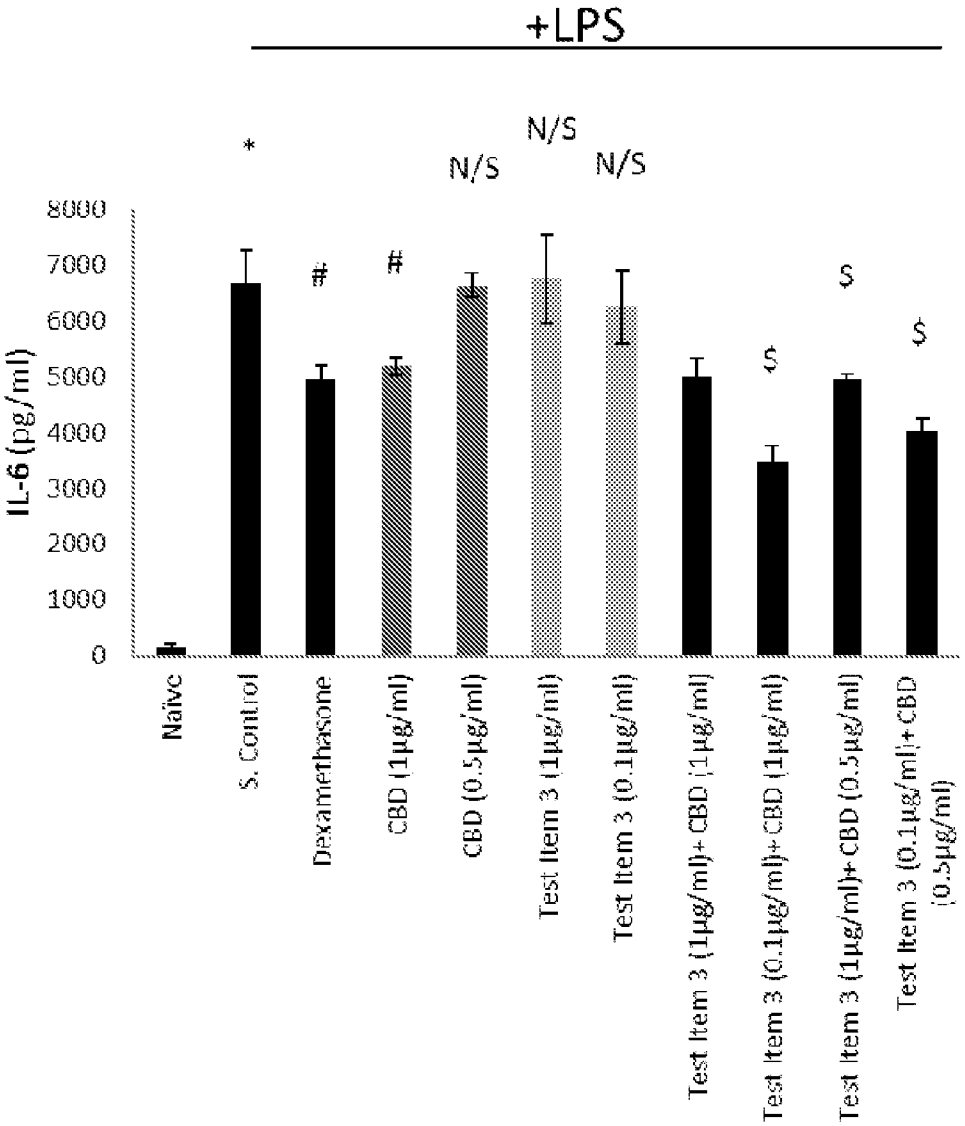
Test Item 7 (0.1µg/ml)+ CBD (0.5µg/ml)

Fig. 4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N/S
N/S
N/S
#
#
$
$
$
Naive
S. Control
Dexamethasone
CBD (1µg/ml)
CBD (0.5µg/ml)
Test Item 3 (1µg/ml)
Test Item 3 (0.1µg/ml)
Test Item 3 (1µg/ml)+ CBD (1µg/ml)
Test Item 3 (0.1µg/ml)+ CBD (1µg/ml)
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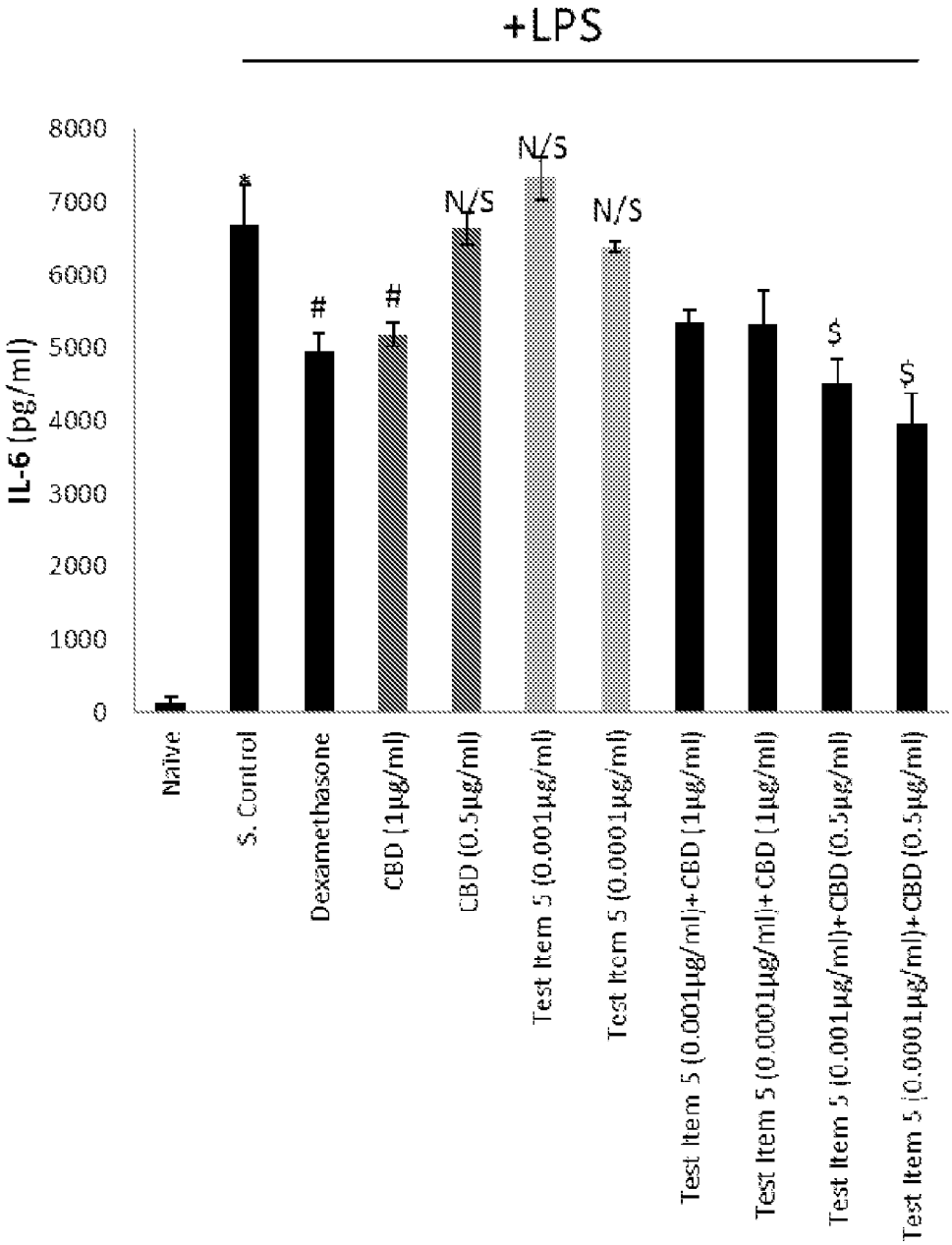
Fig. 5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#
#
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N/S
N/S
$
$
Naive
S. Control
Dexamethasone
CBD (1µg/ml)
CBD (0.5µg/ml)
Test Item 5 (0.001µg/ml)
Test Item 5 (0.0001µg/ml)
Test Item 5 (0.001µg/ml)+CBD (1µg/ml)
Test Item 5 (0.0001µg/ml)+CBD (1µg/ml)
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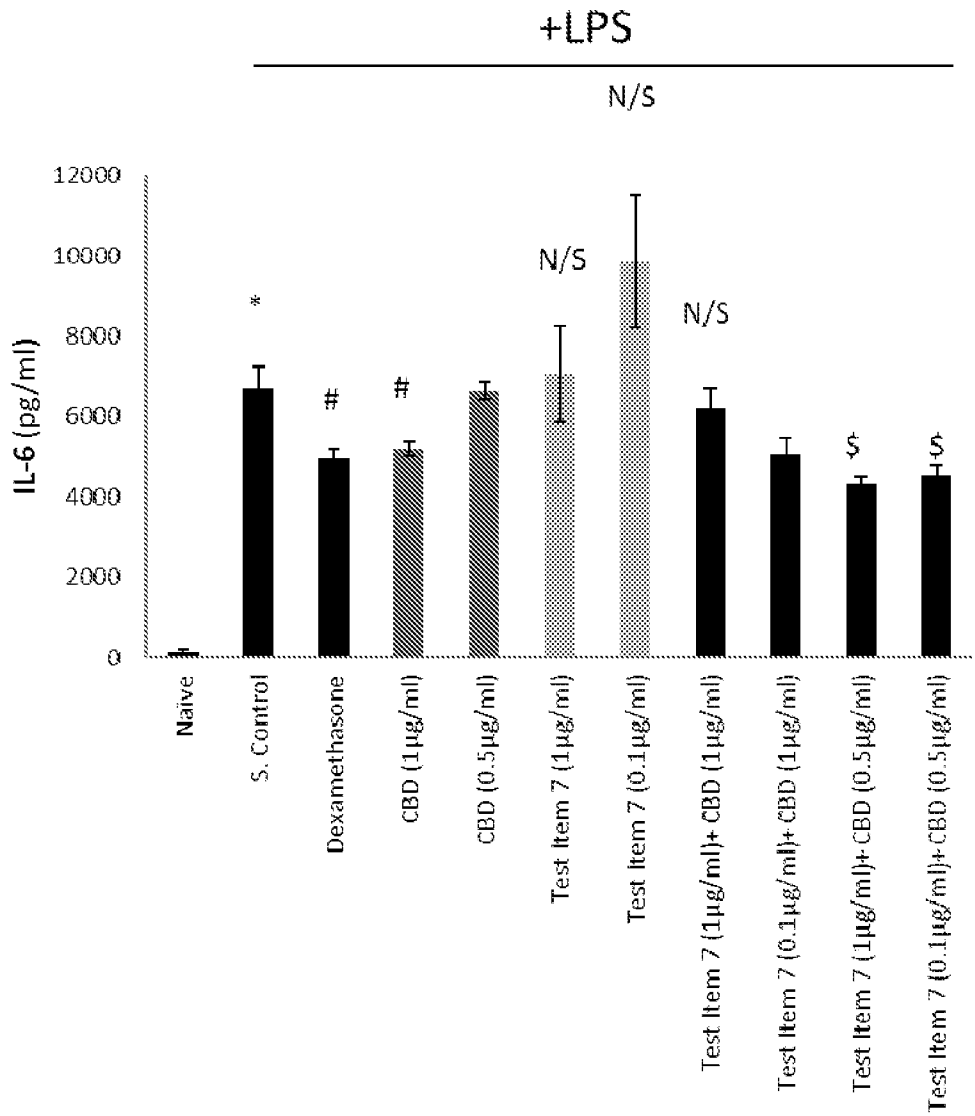
Fig. 6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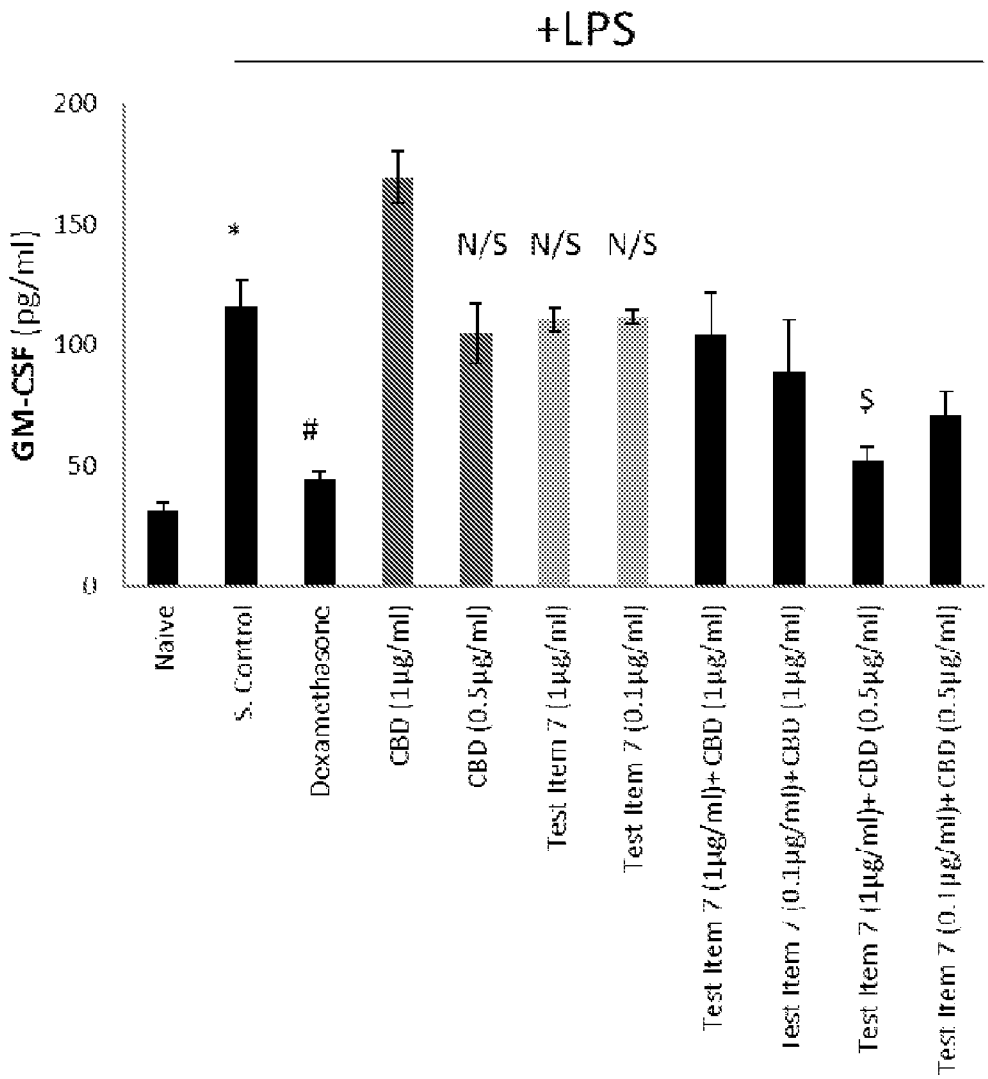
N/S
$
$
Naive
S. Control
Dexamethasone
CBD (1µg/ml)
CBD (0.5µg/ml)
Test Item 7 (1µg/ml)
Test Item 7 (0.1µg/ml)
Test Item 7 (1µg/ml)+ CBD (1µg/ml)
Test Item 7 (0.1µg/ml)+ CBD (1µg/ml)
Test Item 7 (1µg/ml)+ CBD (0.5µg/ml)
Test Item 7 (0.1µg/ml)+ CBD (0.5µg/ml)

Fig. 7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#
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N/S
N/S
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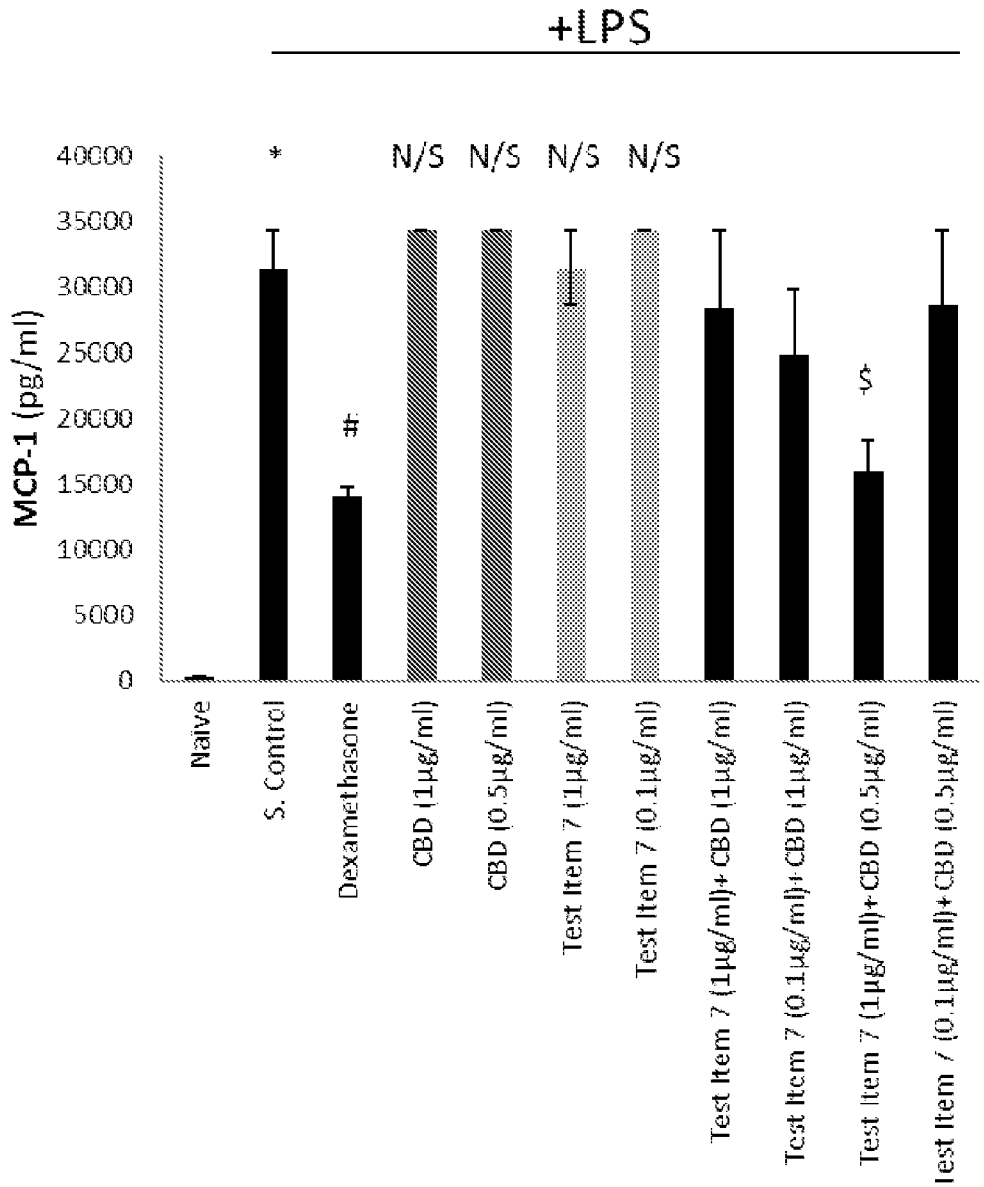
S. Control
Dexamethasone
CBD (1µg/ml)
CBD (0.5µg/ml)
Test Item 7 (1µg/ml)
Test Item 7 (0.1µg/ml)
Test Item 7 (1µg/ml)+ CBD (1µg/ml)
Test Item 7 (0.1µg/ml)+ CBD (1µg/ml)
Test Item 7 (1µg/ml)+ CBD (0.5µg/ml)
Test Item 7 (0.1µg/ml)+ CBD (0.5µg/ml)

Fig. 8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N/S
#
$
Naive
S. Control
Dexamethasone
CBD (1µg/ml)
CBD (0.5µg/ml)
Test Item 7 (1µg/ml)
Test Item 7 (0.1µg/ml)
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Test Item 7 (0.1µg/ml)+ CBD (1µg/ml)
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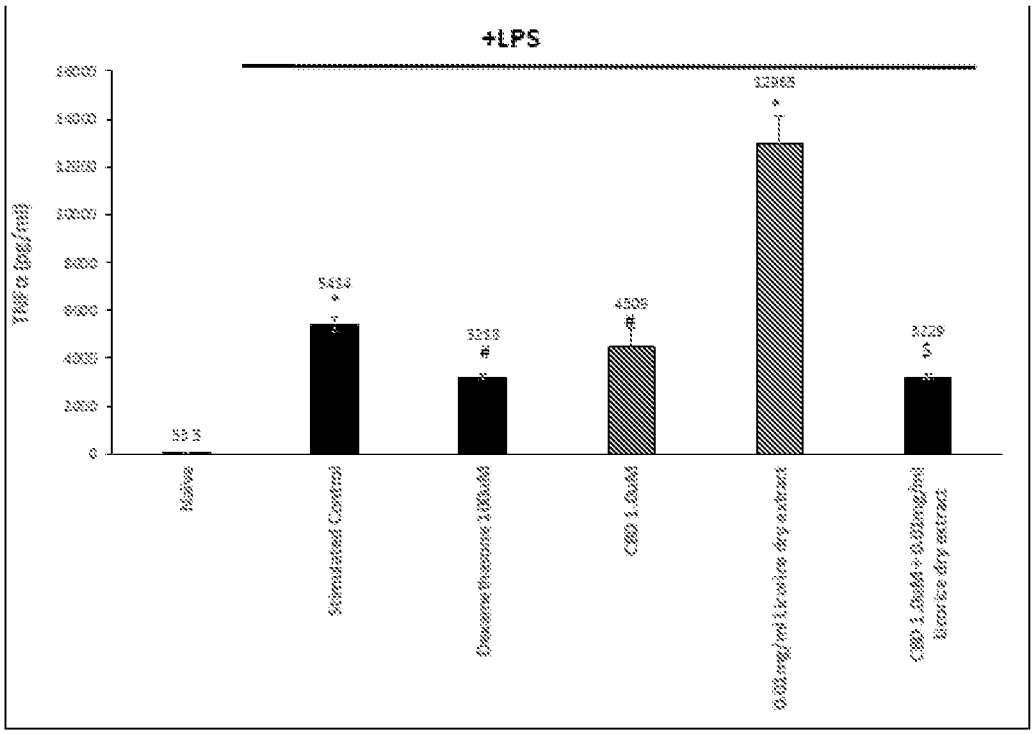
Fig. 9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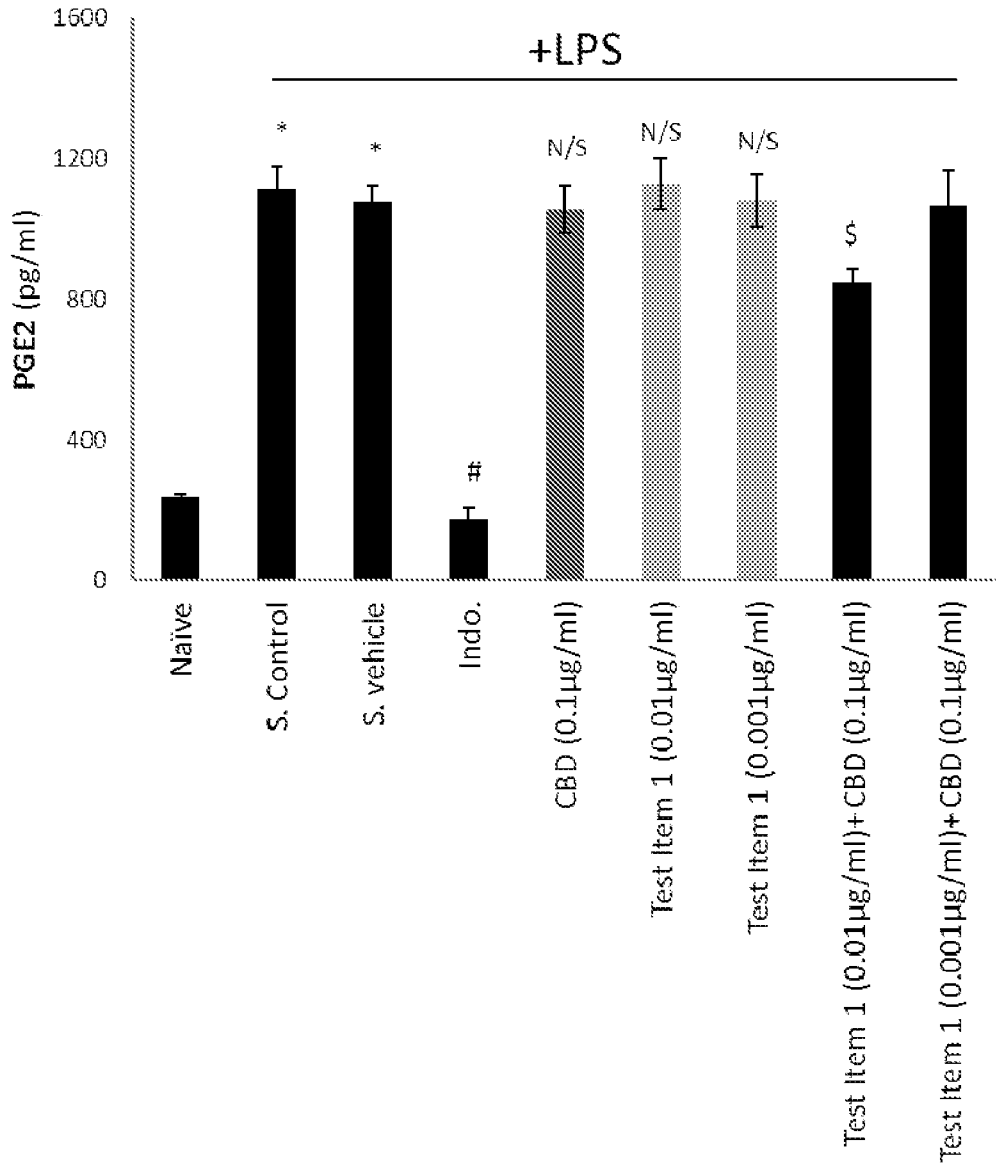
CBD 1.0uM + 0.01mg/ml licorice dry extract

Fig. 10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*
N/S
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N/S
#
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Naïve
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S. vehicle
Indo.
CBD (0.1µg/ml)
Test Item 1 (0.01µg/ml)
Test Item 1 (0.001µg/ml)
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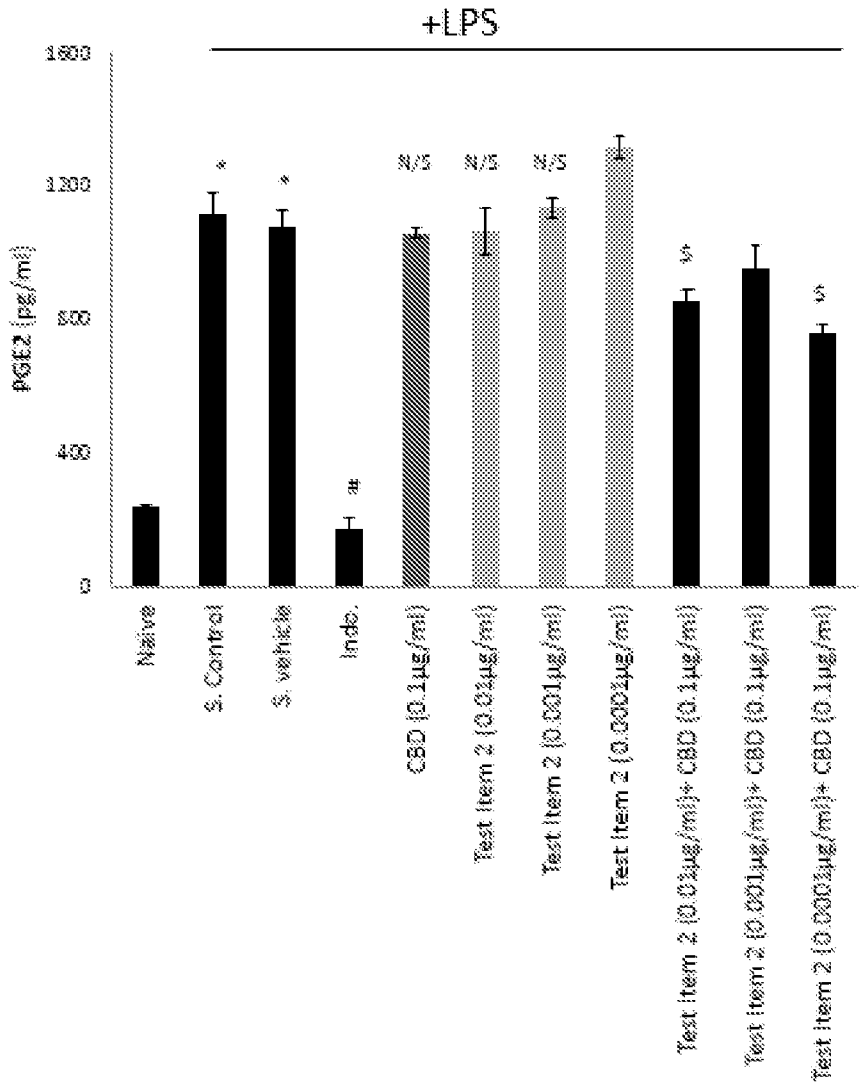
Test Item 1 (0.001µg/ml)+CBD (0.1µg/ml)

Fig. 11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#
#/$
#/$
#/$
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$
$
Naive
S. Control
S. vehicle
Indo.
CBD (0.1µg/ml)
Test item 2 (0.01µg/ml)
Test item 2 (0.001µg/ml)
Test item 2 (0.0001µg/ml)
Test item 2 (0.01µg/ml)+ CBD (0.1µg/ml)
Test item 2 (0.001µg/ml)+ CBD (0.1µg/ml)
Test item 2 (0.0001µg/ml)+ CBD (0.1µg/ml)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2019/050642

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K36/185 A61K36/484 A61P29/00 A61P37/00 A61K31/05
A61K31/192 A61K31/56
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/235661 A1 (CHANGOER LEKHRAM [NL] ET AL) 18 August 2016 (2016-08-18) example 4 paragraph [0021] claims 1-4	1,4-7, 9-15
X	US 2015/245991 A1 (NIHART TROY [US]) 3 September 2015 (2015-09-03) claims 1,11,12,16	1-4,6,9, 14,15
X	US 8 242 178 B2 (NAGARKATTI PRAKASH S [US]; NAGARKATTI MITZI [US] ET AL.) 14 August 2012 (2012-08-14) column 2, paragraph 3 - paragraph 5 claim 1	1-15

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

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Date of the actual completion of the international search	Date of mailing of the international search report
1 October 2019	09/10/2019

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

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2019/050642

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