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(71) Applicant: **EPM (IP), INC.** [US/US]: 1600 Webster Street #407, San Francisco, California 94115 (US).

(71) Applicant (for RW only): **WEBB, Cynthia** [IL/IL]: c/o WEBB+Co., P.O. Box 4177, 7414003 Ness Ziona (IL).

(72) Inventors: **IOSUB-AMIR, Anat**; 20 Carmon Street, 9630834 Jerusalem (IL). **WELBURN, Peter James**; 7 Eden Drive, Eatons Hill, Queensland QLD 4037 (AU).

(74) Agent: **WEBB, Cynthia** et al.; Webb & Co., P.O. BOX 4177, 7414003 Ness Ziona (IL).

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(54) Title: CANNABIDIOLIC ACID ESTERS FOR TREATING RESPIRATORY DISTRESS INCLUDING ACUTE RESPIRATORY DISTRESS SYNDROME AND CORONAVIRUS

(57) Abstract: The present invention provides compositions and methods for treating respiratory distress including coronavirus and acute respiratory distress syndrome. In particular, the present invention provides pharmaceutical compositions and formulations comprising a cannabidiolic acid (CBDA) ester alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating respiratory distress including coronavirus and acute respiratory distress syndrome.



WO 2021/224924 A1

**CANNABIDIOLIC ACID ESTERS FOR TREATING RESPIRATORY
DISTRESS INCLUDING ACUTE RESPIRATORY DISTRESS SYNDROME
AND CORONAVIRUS**

5 FIELD OF THE INVENTION

The present invention relates to compositions and methods for treating respiratory distress including acute respiratory distress syndrome and coronavirus. In particular, the present invention relates to pharmaceutical compositions and formulations comprising a cannabidiolic acid (CBDA) ester alone or in combination with one or
10 more additional cannabinoid compound(s), for use in treating respiratory inflammation including acute respiratory distress syndrome and coronavirus.

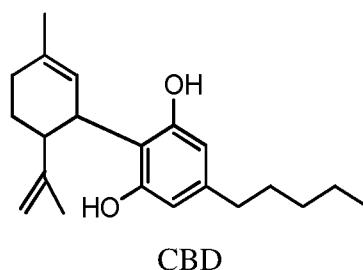
BACKGROUND OF THE INVENTION

Respiratory Inflammation or inflammation in the lung is usually caused by
15 pathogens, such as viruses and bacteria, or by exposure to toxins, pollutants, irritants, and allergens. The inflammation can also be a result of genetic disorders, e.g., Alpha-1 antitrypsin (AAT) deficiency that causes COPD (chronic obstructive pulmonary disease). The inflammation is initiated by stimuli at the epithelial surface, and cells already present in the tissue mediate acute inflammation. The stimuli activate the
20 resident leukocytes and structural cells to produce various cytokines, chemokines, and growth factors that cause inflammatory symptoms. Clinically, acute inflammation is seen in pneumonia and acute respiratory distress syndrome (ARDS), whereas chronic inflammation is represented by asthma and chronic obstructive pulmonary disease (COPD) (Moldoveanu et al. Journal of Inflammation Research 2009:2 1–11). Chronic
25 inflammation of the thin tissue lining each air sac causes scarring that is called pulmonary fibrosis. In severe cases, pulmonary fibrosis can cause respiratory failure, heart failure, and death.

Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes Coronaviridae, Arteriviridae, and Roniviridae
30 families. The Coronavirinae comprise one of two subfamilies in the Coronaviridae family, with the other being the Torovirinae. Coronaviruses are associated with illness from the common cold to more severe conditions such as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the positive-sense, single-

stranded RNA coronavirus that causes the coronavirus disease 2019 (COVID-19). Coronaviruses are zoonotic, meaning they are transmitted between animals and people. Common signs of coronavirus infection include respiratory symptoms, fever, coughing, shortness of breath and breathing difficulties. High concentrations of cytokines were recorded in plasma of critically ill patients infected with COVID-19. In more severe cases, infection can cause pneumonia, respiratory inflammation, severe acute respiratory syndrome, kidney failure and death.

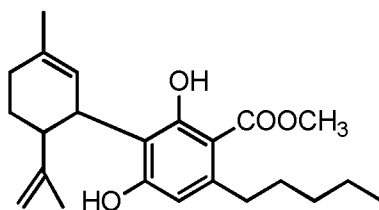
Cannabidiol (CBD) is the major non-psychotropic phytocannabinoid compound in the plant *Cannabis sativa*, making up to 40% of the cannabinoids in Cannabis extracts (Grlic, Bull. Narc., 1976, 14:37-46). CBD is considered a lead compound for treating and preventing inflammatory and oxidative damage, see for example WO1999/053917.



In contrast to the extensive knowledge on CBD, there is very limited literature on cannabidiolic acid (CBDA), also a major constituent of the *Cannabis sativa* plant, which may be due to its instability. It was first isolated in 1955 (Krejčí and Šantavý, 1955, Acta Univ Palacki Olomuc 6:59-66). Its structure was elucidated in 1965 by analysis of the physical properties of its methyl ester, cannabidiolic acid methyl ester (CBDA-ME) (Mechoulam and Gaoni, Tetrahedron, 1965, 21:1223-1229). Its synthesis from cannabidiol was subsequently reported (Mechoulam and Ben-Zvi, J. Chem. Soc. Commun., 1969, 7:343-344).

The decarboxylation of CBDA into CBD is enhanced by heat, indicating the relative instability of CBDA, thus lowering its potential to serve as a medication (Mechoulam, Academic Press, New York, 1973, 1-99; Citti et al., J. Pharm. Biomed. Anal., 2018, 16:532-540). Thus, CBDA-ME is a relatively unknown cannabinoid and remains understudied and its effects are only just starting to become clear.

3



CBDA-ME

CBDA-ME is a stable derivative of CBDA and can be pharmacological active in vivo. Pertwee et al. (Brit. J. Pharmacology, 2018, 175:100-112) reported that the methyl ester of CBDA, designated HU-580 (also denoted herein EPM301), displays a greater potency than CBDA in suppressing signs of both acute and anticipatory nausea, and of stress-induced anxiety in rats, and that it produces these effects in a 5-HT_{1A} receptor-dependent manner. Another recent study (Hen-Shoval et al., Behav. Brain Res., 2018, 351:1-3) provides support for a potent anti-depressant effect after oral ingestion of a low dose (1 mg/kg) of CBDA-ME in two rat models.

WO 2018/235079 discloses compositions comprising CBDA esters and uses thereof in the treatment of a condition, disease or symptom associated with 5-HT_{1A} receptors.

WO 2020/186010 discloses pharmaceutical compositions including a cannabinoid acid ester compound alone or in combination with one or more additional cannabinoid compounds. The PCT application discloses the uses of the pharmaceutical compositions in treating a variety of diseases including joint disease, skin disease, gastrointestinal disease, uterine-related disorder, Non-Alcoholic Fatty Liver Disease (NAFLD), chronic kidney disease (CDK), diabetes dyslipidemia, metabolic syndrome, hyperglycemia, obesity and reducing or maintaining cholesterol levels or lowering LDL/HDL ratio.

Ribeiro et al., disclose that CBD decreases inflammation in a murine model of acute lung injury (European Journal of Pharmacology 678 (2012) 78–85).

Vuolo et al. disclose that CBD reduces airway inflammation and fibrosis in experimental allergic asthma (European Journal of Pharmacology 843 (2019) 251–259).

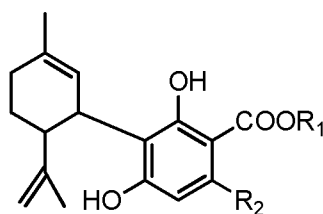
There still an unmet medical need for well-tolerated, and effective therapies for respiratory distress or inflammation including coronavirus and acute respiratory distress syndrome that can ameliorate their symptoms.

SUMMARY OF THE INVENTION

The present invention provides pharmaceutical compositions comprising a cannabinoid, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent, for treating respiratory distress including acute respiratory distress syndrome and coronavirus. According to some embodiments, the respiratory distress is caused by coronavirus. According to certain embodiments, the respiratory distress is acute respiratory distress syndrome (ARDS). According to additional embodiments the respiratory inflammation is asthma or chronic obstructive pulmonary disease (COPD). According to certain embodiments the cannabinoid component comprises CBDA ester in combination with one or more extract of a cannabis plant, and a pharmaceutically acceptable carrier, excipient or diluent.

In some embodiments, the CBDA esters are more active in treating coronavirus and respiratory inflammation than either CBDA or CBD. The compositions comprising CBDA esters exhibit a prolonged and significant therapeutic effect in respiratory inflammation. Without wishing to be bound by any particular theory or mechanism of action, the therapeutic effect of the composition may be due to the stability of the CBDA ester. In some embodiments, the significant anti-inflammatory effect of CBDA-ME reduces the coronavirus impact on lungs at the critical stage of infection and therefore, enables the body to recover and deal effectively with the respiratory distress.

According to one aspect, the present invention provides a pharmaceutical composition comprising a cannabinoid component, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating respiratory distress or inflammation,



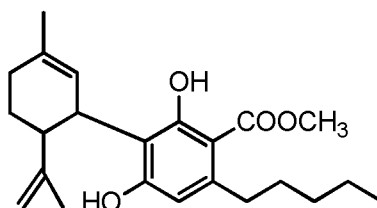
Formula I

R₁ and R₂ are each independently selected from the group consisting of a linear or branched, unsubstituted or substituted C₁-C₁₅ alkyl, a linear or branched, unsubstituted or substituted C₂-C₁₅ alkenyl, and a linear or branched, unsubstituted or substituted C₂-C₁₅ alkynyl;

and stereoisomers and salts thereof.

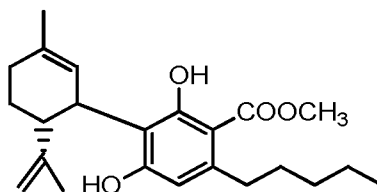
According to some embodiments, R₁ is methyl. According to some embodiments, the cannabidiolic acid ester is cannabidiolic acid methyl ester (CBDA-ME).

According to some embodiments, the CBDA ester in the compositions of the present invention is represented by the formula (Ia):



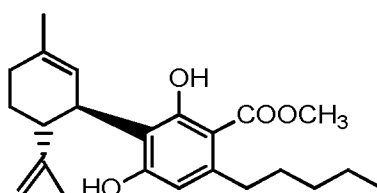
Formula Ia

According to some embodiments, the CBDA ester in the compositions of the present invention is represented by the formula (Ib):



Formula Ib

According to a particular embodiment, the CBDA ester is designated HU-580 (also denoted herein EPM301):



HU-580

According to some embodiments, the respiratory distress is caused by a virus. According to some embodiments, the respiratory distress is caused by coronavirus.

According to some embodiments, the coronavirus is selected from the group consisting

of Severe Acute Respiratory Syndrome (SARS-CoV), Middle East Respiratory Syndrome (MERS-CoV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). According to specific embodiments, the coronavirus is COVID-19.

According to some embodiments, the respiratory distress is acute respiratory distress syndrome (ARDS).

According to some embodiments, the additional cannabinoid compound is selected from the group consisting of cannabidiol (CBD), cannabigerol (CBG), Δ^8 -tetrahydrocannabinol (Δ^8 -THC), Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabinol (CBN), $\Delta^9(11)$ -tetrahydrocannabinol (exo-THC), cannabichromene (CBC), tetrahydrocannabinol-C3 (THC-C3), tetrahydrocannabinol-C4 (THC-C4), tetrahydrocannabinol-C7 (THC-C7), esters thereof and combination thereof.

According to some embodiments the one or more additional cannabinoid compound(s) are present in one or more extracts of a cannabis plant.

According to some embodiments, the cannabis plant extract is obtained from a strain selected from the group consisting of *Cannabis sativa*, *Cannabis indica*, *Cannabis ruderalis*, a hybrid strain, and combinations thereof. According to further embodiments, the cannabis plant extract is obtained from a strain selected from the group consisting of a high-CBD strain, a high-THC strain, and a combination thereof. According to some embodiments, the cannabis plant extract comprises at least one cannabinoid selected from the group consisting of cannabidiol (CBD), tetrahydrocannabinol (THC), cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), acids thereof and combinations thereof.

According to some embodiments, the cannabis plant extract comprises about 1% (w/w) of CBD. According to some embodiments, the cannabis plant extract comprises about 10% (w/w) of CBD. According to some embodiments, the cannabis plant extract comprises about 25% (w/w) of CBD.

According to some embodiments, the cannabis plant extract comprises about 1% (w/w) of THC. According to some embodiments, the cannabis plant extract comprises about 10% (w/w) of THC. According to some embodiments, the cannabis plant extract comprises about 25% (w/w) of THC.

According to some embodiments, the cannabis plant extract is formed through contact with a suitable solvent or a combination of solvents. According to some embodiments, the solvent is selected from the group consisting of a polar solvent, a hydrocarbon solvent, carbon dioxide, and combinations thereof.

According to some embodiments the cannabinoid component can be emulsified, dissolved, dispersed or encapsulated in formulations suitable for use in either aqueous based or oil-based carriers. Thus, according to some embodiments, the present pharmaceutical composition is in the form of an emulsion, solution or dispersion. Each possibility represents a separate embodiment. Also, according to some embodiments, the present pharmaceutical composition may include an aqueous based or an oil-based carrier. Each possibility represents a separate embodiment.

According to some embodiments, the pharmaceutical composition is formulated for inhalation. According to specific embodiments, the pharmaceutical composition is a dry powder formulation. According to some embodiments, the pharmaceutical composition is formulated for an administration via vaporization.

According to alternative embodiments, the pharmaceutical composition is formulated into a dosage form suitable for intranasal, oral, intravenous, intraarterial, or subcutaneous administration. Each embodiment represents a separate embodiment of the invention. According to additional embodiments, the pharmaceutical composition is formulated for an oral administration.

According to some embodiments, the pharmaceutical composition is a non-aqueous composition. According to some embodiments, the pharmaceutical composition is formulated in a form of a powder. According to some embodiments, the pharmaceutical composition is powder suitable for multi-dose reservoir dry powder inhaler (DPI).

According to other embodiments, the pharmaceutical composition is a liquid composition.

According to some embodiments, the pharmaceutical composition is formulated as a capsule, a tablet, a liquid, or a syrup. According to certain embodiments, the dosage form is granules or pellets delivered in a solution, a suspension or filled into a capsule or compressed into a tablet.

According to some embodiments, the pharmaceutical composition further comprises triglycerides, fats, lipids, oils, fatty acids, solvents or mixtures thereof. According to specific embodiments, the pharmaceutical composition comprises an edible oil selected from the group consisting of copaiba oil, coconut oil, cottonseed oil, soybean oil, safflower oil, sesame oil, sunflower oil, castor oil, corn oil, olive oil, palm oil, peanut oil, and poppy seed oil. Each possibility represents a separate embodiment of the invention.

According to some embodiments, the pharmaceutical composition comprises an alcohol and a second solvent. According to some embodiments, the alcohol is ethanol. According to certain embodiments, the second solvent is polyethylene glycol (PEG) or propylene glycol.

5 According to some embodiments, the pharmaceutical composition is formulated for slow release of the CBDA ester. In certain embodiments, the pharmaceutical composition further comprises a release retarding agent or a mixture of release retarding agents. According to some embodiments, the pharmaceutical composition is at least partly coated by an enteric-coating agent.

10 According to some embodiments, the CBDA ester is provided in microencapsulation particles. According to certain embodiments, the CBDA ester is provided in liposomal capsule particles.

 According to some embodiments, the pharmaceutical composition comprises phospholipid(s). According to certain embodiments, the pharmaceutical composition
15 comprises a phospholipid selected from the group consisting of naturally occurring phospholipids and synthetic phospholipids. According to specific embodiments, the naturally occurring phospholipid is selected from the group consisting of soy lecithin, egg lecithin, hydrogenated soy lecithin, hydrogenated egg lecithin, and a combination thereof. According to certain embodiments, the synthetic phospholipid is selected from
20 the group consisting of phosphocholines, phosphoethanolamines, phosphatidic acids, phosphoglycerols, phosphoserines, mixed chain phospholipids, lysophospholipids, pegylated phospholipids, and a combination thereof. Each possibility represents a separate embodiment of the invention.

 According to some embodiments, the phospholipid may form micelles, emulsions
25 or liposomes.

 According to some embodiments, the pharmaceutical composition comprises cyclodextrins. According to certain embodiments, the cyclodextrin is selected from the group consisting of hydroxypropyl β -cyclodextrin, sulfobutylether β -cyclodextrin, and methyl- β -cyclodextrin (M β CD) and a combination thereof.

30 According to some embodiments, the excipient is selected from the group consisting of emulsifiers, buffering agents, pH adjusting agents, preservatives, antioxidants, stabilizers, and a combination thereof. Each possibility represents a separate embodiment of the invention.

According to some embodiments, the pharmaceutical composition further comprises vitamins, anti-oxidants, minerals, and/or flavoring agents.

According to some embodiments, the composition comprises less than about 10% (w/w) of the cannabinoid component. According to additional embodiments, the composition comprising less than about 7% (w/w) of the cannabinoid component. According to further embodiments, the composition comprising less than about 5% (w/w) of the cannabinoid component. According to yet further embodiments, the composition comprising less than about 2% (w/w) of the cannabinoid component. According to some embodiments, the composition comprising less than about 1% (w/w) of the cannabinoid component. According to additional embodiments, the composition comprising less than about 0.5% (w/w) of the cannabinoid component.

According to some embodiments, the pharmaceutical composition comprises a unit dosage form of at least about 20 mg of CBDA ester or a mixture of cannabinoids comprising CBDA ester. In certain embodiments, the dosage form comprises about 20 mg to about 2,000 mg of CBDA ester or a mixture of cannabinoids comprising CBDA ester. In certain embodiments, the dosage form comprises about 20 mg to about 500 mg of CBDA ester. In certain embodiments, the dosage form comprises about 50 mg to about 1,000 mg of CBDA ester. In certain embodiments, the dosage form comprises about 200 mg to about 1,000 mg of CBDA ester. In certain embodiments, the dosage form comprises about 50 mg, 100 mg, about 200 mg, about 300 mg, about 400 mg, about 500 mg, about 600, about 700 mg, about 800 mg, about 900 mg, or about 1000 mg of CBDA ester or a mixture of cannabinoids comprising CBDA ester.

The pharmaceutical composition described herein can be administered with one or more other therapeutic agents.

According to some embodiments, the pharmaceutical composition further comprises an anti-inflammatory drug. According to certain embodiments, the pharmaceutical composition further comprises corticosteroid(s).

According to additional embodiments, the pharmaceutical composition further comprises an antibiotic drug.

According to some embodiments, the respiratory inflammation is acute respiratory inflammation.

According to some embodiments, the respiratory inflammation is chronic respiratory inflammation. According to certain embodiments, the respiratory inflammation is pneumonitis. According to certain embodiments, the respiratory

inflammation is asthma. According to certain embodiments, the respiratory inflammation is COPD.

According to some embodiments, the respiratory inflammation is caused by a condition selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), pneumonia and eosinophilic bronchitis, airways viral infection, airways bacterial infection, fungal infection, airways parasite infection, pulmonary vasculitis, pulmonary sarcoidosis, inflammation and/or infection associated with lung transplantation, acute lung graft rejection or bronchiolitis obliterans syndrome (BOS), pulmonary artery hypertension (PAH), bronchitis, chronic bronchitis, sinusitis, cystic fibrosis (CF), primary ciliary dyskinesia (PCD), alveolar proteinosis, idiopathic pulmonary fibrosis (IPF), eosinophilic acute respiratory distress syndrome (ARDS), mechanical ventilation-associated inflammation and/or infection, silicosis, chemical agent-related airway disease, and any combination thereof. Each possibility represents a separate embodiment of the invention.

According to some embodiments, the respiratory inflammation is caused by a pathogen. According to certain embodiments, the respiratory inflammation is caused by a pathogen selected from the group consisting of viruses, bacteria, parasites and fungi.

According to an additional aspect, the present invention provides a method for treating or preventing respiratory distress or inflammation comprising administering to a subject in need of such treatment a therapeutically effective amount of the pharmaceutical composition described herein.

According to some embodiments, the method is for treating coronavirus. According to additional embodiments, the method is for treating acute respiratory distress syndrome.

According to some embodiments, the pharmaceutical composition is administered through inhalation from a vaporizer or metered dose inhaler. According to other embodiments, the pharmaceutical composition is administered orally.

According to some embodiments, the pharmaceutical composition is administered once a day, once a week, once in two weeks, once in three weeks or once a month.

According to some embodiments, the subject is a mammal. According to certain embodiments, the subject is a human subject.

According to some embodiments, the pharmaceutical composition is used in combination with other therapeutic agents for treatment or prevention of respiratory inflammation.

5 According to some embodiments, the method further comprises administering an anti-inflammatory agent. According to certain embodiments, the method further comprises administering corticosteroids. According to certain embodiments, the method comprises administering an additional non-steroidal anti-inflammatory drug.

According to some embodiments, the method further comprises administering an antibiotic drug.

10 According to some embodiments, the treatment decreases respiratory inflammation in said patient compared to said patient prior to treatment with CBDA ester.

According to some embodiments, the pharmaceutical composition is administered through inhalation from a vaporizer or metered dose inhaler. According to other
15 embodiments, the pharmaceutical composition is administered orally.

According to some embodiments, the pharmaceutical composition is administered once a day, once a week, once in two weeks, once in three weeks or once a month.

According to some embodiments, the subject is a mammal. According to certain embodiments, the subject is a human subject.

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According to some embodiments, the method further comprises administering an antibiotic drug.

30 According to some embodiments, the treatment decreases respiratory inflammation in said patient compared to said patient prior to treatment with CBDA ester.

Further embodiments and the full scope of applicability of the present invention will become apparent from the detailed description given hereinafter. However, it

should be understood that the detailed description and specific examples, while indicating preferred embodiments of the invention, are given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art from this detailed description.

5

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides methods of treating respiratory inflammation including coronavirus and acute respiratory distress syndrome (ARDS), comprising administering to a subject in need thereof a therapeutic effective amount of a
10 cannabidiolic acid (CBDA) ester alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly known as the 2019 novel coronavirus (2019-nCoV), is a positive-sense single-stranded
15 RNA virus. It is contagious among humans and is the cause of coronavirus disease 2019 (COVID-19). There is no vaccine, but several antiviral drugs are already in clinical trials. SARS-CoV-2 has strong genetic similarity to known bat coronaviruses, making a zoonotic origin in bats likely, although an intermediate reservoir such as a pangolin is thought to be involved. From a taxonomic perspective SARS-CoV-2 is classified as
20 a strain of the species severe acute respiratory syndrome-related coronavirus. SARS-CoV-2 is the cause of the ongoing 2019–20 coronavirus outbreak.

Without wishing to be bound by theory or mechanism of action, the highly stable compounds of the present invention allow prolonged biological activities for treating respiratory inflammation.

25 The description below of several embodiments are made with the understanding that the present disclosure is to be considered as an exemplification of the claimed subject matter, and is not intended to limit the attached claims to the specific embodiments illustrated. The headings used throughout this disclosure are provided for convenience only and are not to be construed to limit the claims in any way.
30 Embodiments illustrated under any heading may be combined with embodiments illustrated under any other heading.

Cannabinoid component

The word "cannabinoid" used in this description, claims, and other conjugations is used to mean any compound that interacts with a cannabinoid receptor. Ligands for

these receptor proteins include the endocannabinoids (produced naturally in the body by humans and animals), the phytocannabinoids (found in cannabis and some other plants), and synthetic cannabinoids (manufactured artificially). The term "cannabinoid acid", refers to the acid form of the above-mentioned cannabinoids.

5 Suitable cannabinoids include but are not limited to certain tetrahydropyran analogs: Δ^8 -tetrahydrocannabinol, Δ^9 -tetrahydrocannabinol (THC), cannabinol (CBN), cannabidiol (CBD), cannabigerol (CBG), $\Delta^9(11)$ -tetrahydrocannabinol (exo-THC), cannabichromene (CBC), tetrahydrocannabinol-C3 (THC-C3), tetrahydrocannabinol-C4 (THC-C4), tetrahydrocannabinol-C7 (THC-C7), their salts, solvates, metabolites,
10 and metabolic precursors.

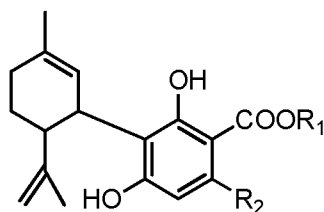
 The word "cannabidiol" refers to CBD. As used in this application, CBD is obtained from industrial hemp extract with a trace amount of THC or from cannabis extract using high CBD cannabis cultivars. According to some embodiments, cannabidiol may be obtained from plant extract, or may be prepared synthetically
15 (manufactured artificially).

 The abbreviation "CBDA" is used herein to refer to cannabidiolic acid, which is the acid form of CBD. The term "cannabidiolic acid ester" or "cannabidiolic ester" refers to various molecules, which are the alkyl, alkenyl, alkynyl or aryl ester form of CBDA. The abbreviation "CBDA-ME" is used herein to refer to cannabidiolic acid
20 methyl ester, which is the methyl ester form of CBDA.

 It is to be understood that the compounds provided herein may contain one or more chiral centers. Such chiral centers may each be of either of the (*R*) or (*S*) configuration. In case a compound of the invention contains more than one chiral center, each one of those chiral centers may be of the (*R*) or (*S*) configuration,
25 independently. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures.

 According to an aspect, the present invention provides a pharmaceutical composition comprising a cannabinoid, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or
30 in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating or preventing respiratory inflammation or distress,

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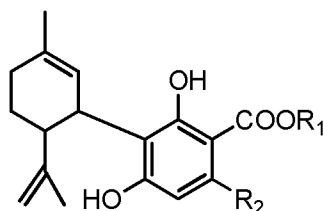
Formula (I)

wherein

R₁ and R₂ are each independently selected from the group consisting of a linear or branched, unsubstituted or substituted C₁-C₁₅ alkyl, a linear or branched, unsubstituted or substituted C₂-C₁₅ alkenyl, and a linear or branched, unsubstituted or substituted C₂-C₁₅ alkynyl;

and stereoisomers and salts thereof.

According to another aspect, the present invention provides a pharmaceutical composition comprising a cannabinoid, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating or preventing respiratory inflammation or distress,



Formula (I)

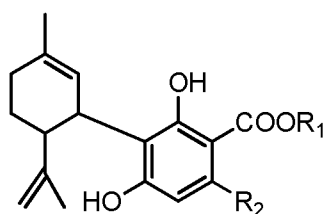
wherein

R₁ and R₂ are each independently selected from the group consisting of a linear or branched C₁-C₁₅ alkyl unsubstituted or substituted by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, and phosphate, a linear or branched C₂-C₁₅ alkenyl unsubstituted or substituted by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, and phosphate, and a linear or branched C₂-C₁₅ alkynyl unsubstituted or substituted by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, and phosphate;

and stereoisomers and salts thereof.

According to some embodiments, the respiratory distress is caused by coronavirus. According to some embodiments, the respiratory distress is acute respiratory distress syndrome (ARDS).

According to an aspect, the present invention provides a pharmaceutical composition comprising a cannabinoid, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating coronavirus,

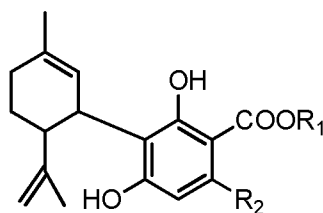


Formula I

wherein

R₁ and R₂ are each independently selected from the group consisting of a linear or branched, unsubstituted or substituted C₁-C₁₅ alkyl, a linear or branched, unsubstituted or substituted C₂-C₁₅ alkenyl, and a linear or branched, unsubstituted or substituted C₂-C₁₅ alkynyl; and stereoisomers and salts thereof.

According to another aspect, the present invention provides a pharmaceutical composition comprising a cannabinoid, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating or preventing coronavirus,



Formula I

wherein

R₁ and R₂ are each independently selected from the group consisting of a linear or branched C₁-C₁₅ alkyl unsubstituted or substituted by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, and phosphate, a linear or branched C₂-C₁₅ alkenyl unsubstituted or substituted by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, and phosphate, and a linear or branched C₂-C₁₅ alkynyl unsubstituted or substituted by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, and phosphate; and stereoisomers and salts thereof.

In certain embodiments the one or more additional cannabinoid compound(s) are present in one or more extracts of a cannabis plant.

According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₁-C₁₅ alkyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₁-C₁₀ alkyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₅-C₁₀ alkyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₅-C₁₅ alkyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₂-C₁₅ alkenyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₂-C₁₀ alkenyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₅-C₁₀ alkenyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₅-C₁₅ alkenyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₂-C₁₅ alkynyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₂-C₁₀ alkynyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₅-C₁₀ alkynyl. According to some embodiments, R₁ is a linear or branched, substituted or unsubstituted C₅-C₁₅ alkynyl.

According to some embodiments, R₁ is a linear substituted C₁-C₁₅ alkyl. According to some embodiments, R₁ is a linear unsubstituted C₁-C₁₅ alkyl. According to some embodiments, R₁ is a branched substituted C₃-C₁₅ alkyl. According to some embodiments, R₁ is a branched unsubstituted C₃-C₁₅ alkyl.

According to some embodiments, R₁ is a linear substituted C₂-C₁₅ alkenyl. According to some embodiments, R₁ is a linear unsubstituted C₂-C₁₅ alkenyl. According

to some embodiments, R₁ is a branched substituted C₃-C₁₅ alkenyl. According to some embodiments, R₁ is a branched unsubstituted C₃-C₁₅ alkenyl.

According to some embodiments, R₁ is a linear substituted C₂-C₁₅ alkynyl.

According to some embodiments, R₁ is a linear unsubstituted C₂-C₁₅ alkynyl.

5 According to some embodiments, R₁ is a branched substituted C₄-C₁₅ alkynyl.

According to some embodiments, R₁ is a branched unsubstituted C₄-C₁₅ alkynyl.

According to some embodiments, R₁ is unsubstituted. According to some

embodiments, R₁ is a linear unsubstituted C₁-C₁₀ alkyl. According to some

embodiments, R₁ is a linear unsubstituted C₁-C₆ alkyl. According to some

10 embodiments, R₁ is a linear unsubstituted C₁-C₄ alkyl. According to some

embodiments, R₁ is methyl or ethyl. According to some embodiments, R₁ is methyl.

According to some embodiments, R₂ is a linear or branched, substituted or unsubstituted C₁-C₁₅ alkyl. According to some embodiments, R₂ is a linear or branched,

substituted or unsubstituted C₁-C₁₀ alkyl. According to some embodiments, R₂ is a

15 linear or branched, substituted or unsubstituted C₅-C₁₀ alkyl. According to some

embodiments, R₂ is a linear or branched, substituted or unsubstituted C₅-C₁₅ alkyl.

According to some embodiments, R₂ is a linear or branched, substituted or

unsubstituted C₂-C₁₅ alkenyl. According to some embodiments, R₂ is a linear or

branched, substituted or unsubstituted C₂-C₁₀ alkenyl. According to some

20 embodiments, R₂ is a linear or branched, substituted or unsubstituted C₅-C₁₀ alkenyl.

According to some embodiments, R₂ is a linear or branched, substituted or

unsubstituted C₅-C₁₅ alkenyl. According to some embodiments, R₂ is a linear or

branched, substituted or unsubstituted C₂-C₁₅ alkynyl. According to some

embodiments, R₂ is a linear or branched, substituted or unsubstituted C₂-C₁₀ alkynyl.

25 According to some embodiments, R₂ is a linear or branched, substituted or

unsubstituted C₅-C₁₀ alkynyl. According to some embodiments, R₂ is a linear or

branched, substituted or unsubstituted C₅-C₁₅ alkynyl.

According to some embodiments, R₂ is a linear substituted C₁-C₁₅ alkyl.

According to some embodiments, R₂ is a linear unsubstituted C₁-C₁₅ alkyl. According

30 to some embodiments, R₂ is a branched substituted C₃-C₁₅ alkyl. According to some

embodiments, R₂ is a branched unsubstituted C₃-C₁₅ alkyl.

According to some embodiments, R₂ is a linear substituted C₂-C₁₅ alkenyl.

According to some embodiments, R₂ is a linear unsubstituted C₂-C₁₅ alkenyl. According

to some embodiments, R_2 is a branched substituted C_3 - C_{15} alkenyl. According to some embodiments, R_2 is a branched unsubstituted C_3 - C_{15} alkenyl.

According to some embodiments, R_2 is a linear substituted C_2 - C_{15} alkynyl.

According to some embodiments, R_2 is a linear unsubstituted C_2 - C_{15} alkynyl.

5 According to some embodiments, R_2 is a branched substituted C_4 - C_{15} alkynyl.

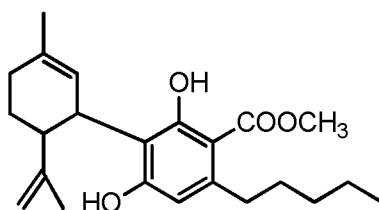
According to some embodiments, R_2 is a branched unsubstituted C_4 - C_{15} alkynyl.

According to some embodiments, R_2 is a linear unsubstituted C_1 - C_6 alkyl.

According to some embodiments, R_2 is a linear unsubstituted C_1 - C_4 alkyl. According

to some embodiments, R_2 is C_5H_{11} .

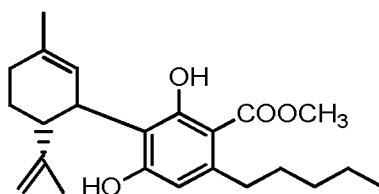
10 According to some embodiments, the CBDA ester in the compositions of the present invention is represented by the formula (Ia):



Formula (Ia)

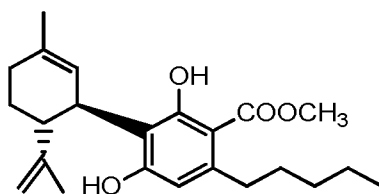
According to some embodiments, the CBDA ester in the compositions of the

15 present invention is represented by the formula (Ib):



Formula (Ib)

According to a particular embodiment, the CBDA ester is designated EPM301:



HU-580

20

An "alkyl" group refers to a saturated aliphatic hydrocarbon, including straight-chain or linear-chain, branched-chain and cyclic alkyl groups. In one embodiment, the alkyl group has 1-15 carbons designated here as C_1 - C_{15} alkyl. In another embodiment, the alkyl group has 2-6 carbons designated here as C_2 - C_6 -alkyl. In another embodiment,

25

the alkyl group has 2-4 carbons designated here as C₂-C₄-alkyl. Each possibility represents a separate embodiment of the invention. The alkyl group may be unsubstituted or substituted by one or more groups selected from the group consisting of hydroxyl, halogen, amino, thiol, phosphate, and combinations thereof.

5 The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo atoms. There can be one or more halogens, which are the same or different.

 An "alkenyl" group refers to an aliphatic hydrocarbon group containing at least one carbon-carbon double bond including straight-chain or linear-chain, branched-chain and cyclic alkenyl groups. In one embodiment, the alkenyl group has 2-15 carbon
10 atoms (a C₂₋₁₅ alkenyl). In another embodiment, the alkenyl group has 2-4 carbon atoms in the chain (a C₂₋₄ alkenyl). Exemplary alkenyl groups include, but are not limited to, ethenyl, propenyl, n-butenyl, i-butenyl, 3-methylbut-2-enyl, n-pentenyl, heptenyl, octenyl, cyclohexyl-butenyl and decenyl. An alkylalkenyl is an alkyl group as defined herein bonded to an alkenyl group as defined herein. The alkenyl group can be
15 unsubstituted or substituted through available carbon atoms with one or more groups defined hereinabove for alkyl.

 An "alkynyl" group refers to an aliphatic hydrocarbon group containing at least one carbon-carbon triple bond including straight-chain and branched-chain. In one embodiment, the alkynyl group has 2-15 carbon atoms in the chain (a C₂₋₁₅ alkynyl). In
20 another embodiment, the alkynyl group has 2-4 carbon atoms in the chain (a C₂₋₄ alkynyl). Exemplary alkynyl groups include, but are not limited to, ethynyl, propynyl, n-butyne, 2-butyne, 3-methylbutynyl, n-pentyne, heptyne, octyne and decyne. An alkylalkynyl is an alkyl group as defined herein bonded to an alkynyl group as defined herein. The alkynyl group can be unsubstituted or substituted through available carbon
25 atoms with one or more groups defined hereinabove for alkyl.

 According to some embodiments, the additional cannabinoid compound is selected from the group consisting of cannabidiol (CBD), cannabigerol (CBG), Δ^8 -tetrahydrocannabinol (Δ^8 -THC), Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabinol (CBN), $\Delta^9(11)$ -tetrahydrocannabinol (exo-THC), cannabichromene (CBC),
30 tetrahydrocannabinol-C3 (THC-C3), tetrahydrocannabinol-C4 (THC-C4), tetrahydrocannabinol-C7 (THC-C7), esters thereof and combination thereof.

 It is contemplated that the CBDA ester of Formula (I) or the cannabinoid compound includes any solvate thereof. The term "solvate" as used herein refers to a physical association of a compound disclosed herein with one or more solvent

molecules. This physical association involves varying degrees of ionic and covalent bonding, including hydrogen bonding. In certain instances, the solvate will be capable of isolation. "Solvate" encompasses both solution-phase and isolatable solvates. Non-limiting examples of suitable solvates include ethanolates, methanolates and the like.

5 A "hydrate" is a solvate in which the solvent molecule is water.

In embodiments in which the CBDA ester is incorporated into a composition in solid state form, the present disclosure also includes any polymorph thereof. The term "polymorph" refers to a particular crystalline or amorphous state of a substance, which can be characterized by particular physical properties such as X-ray diffraction, electron
10 diffraction, IR spectra, Raman spectra, melting point, and the like.

Any of the cannabinoids disclosed herein, specifically, the CBDA ester of Formula (I), can be prepared by any manner known to those skilled in the art. For example, it may be isolated or extracted from a natural source or prepared by synthetic or semi-synthetic means. For example, cannabinoids can be isolated by extraction from
15 cannabis plants. Plants in the cannabis genus include, but are not limited to, *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Each possibility represents a separate embodiment. These plants are the natural sources of cannabinoids. According to some embodiments, certain cannabinoids are isolated or extracted from cannabis plants and then derivatized to the CBDA ester of Formula (I). It is, however, to be understood by
20 the skilled in the art that some of the cannabinoid esters of Formula (I) do not occur in nature, and therefore chemical synthesis is required for their production.

The term "extract" as used herein refers a product prepared by extraction by physical means (e.g. by comminuting, pressing, heating, pulsed electric field assisted treatments, shear treatments and pressure wave treatments), by chemical means (e.g. by
25 treatment with an acid, a base and/or a solvent) and/or by biochemical means. The term refers to a liquid substance obtained through extraction from a given substance, or to a concentrate or essence which is free of, or substantially free of solvent. The term extract may be a single extract obtained from a particular extraction step or series of extraction steps. Extract also may be a combination of extracts obtained from separate extraction
30 steps or separate feedstocks. Such combined extracts are thus also encompassed by the term "extract". Any methods of extraction with suitable solvent are encompassed. Exemplary extraction methods can be found for example in US patent 6,403,126. The extract may be obtained from any part of the plant e.g. from leaves, flowers, stems, roots, fruits and seeds. The extract may be aqueous or oily.

According to some embodiments, the cannabis plant extract is formed with a suitable solvent or a combination of solvents. According to some embodiments, the solvent is selected from the group consisting of a polar solvent, a hydrocarbon solvent, carbon dioxide, and a combination thereof. According to some embodiments, the cannabis plant extract is produced by a process, which comprises contacting the cannabis plant material with a suitable solvent or a combination of solvents. According to some embodiments, the process further comprises isolating a fraction soluble in said solvent. According to some embodiments, the process further comprises removing the solvent from the soluble fraction, to acquire the extract.

Suitable solvents include but not limited to water, ethanol, ethyl acetate, CO₂, methanol, acetone, and acetic acid. Suitable polar solvents include polar organic solvent(s), including, but not limited to halogenated hydrocarbons (e.g. chloroform, dichloromethane), ethers (e.g. diethyl ether, tetrahydrofuran), alcohols (e.g. ethanol, methanol, isopropanol), esters (e.g. ethyl acetate), nitriles (e.g. acetonitrile), sulfones and sulfoxides (e.g. dimethyl sulfoxide, sulfolane), amides (e.g. dimethylformamide) and/or acids (e.g. acetic acid). Suitable non-polar solvents include hydrocarbons, including but not limited to aliphatic hydrocarbons (e.g. hexane, pentane, heptane, petroleum ether) and/or aromatic hydrocarbons (e.g. benzene, toluene). According to one embodiment, the solvent is ethanol. According to one embodiment, the solvent comprises ethanol, such as aqueous ethanol. According to another embodiment, the extraction is by CO₂. In particular, the term "extract" refers to a liquid or semi-solid or resinous substance obtained through extraction from plants defined in the present application, i.e. extracts obtained from cannabis plant e.g. *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. In some embodiments, the term refers to a mixture of liquid or semi-solid, resinous substances obtained through extraction from two or more different plants. In some embodiments, the term refers also to a compound purified from the extract. According to some embodiments, the term "extract" has the meaning of a mixture or combination of two or more extracts.

The term "cannabis extract" as used herein refers to one or more plant extracts from the cannabis plant. A cannabis extract 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. In some embodiments, the term refers to a mixture of liquid or semi-solid, resinous substances obtained through extraction from two or more different cannabis species. In some embodiments, the term refers also to a compound purified from the extract. The term "cannabis plant" as used herein, refers to plants of the genus *Cannabis*, including but not limited to *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. According to some embodiment, cannabis plant is a CBD-rich strain of cannabis plant or THC-rich strain of cannabis plant. Each possibility represents a separate embodiment.

According to some embodiments, the cannabis plant extract is obtained from a strain selected from the group consisting of *Cannabis sativa*, *Cannabis indica*, *Cannabis ruderalis*, a hybrid strain, a high-CBD strain, a high-THC strain, and a combination thereof. According to some embodiments, the cannabis plant extract comprises at least one cannabinoid selected from the group consisting of cannabidiol (CBD), tetrahydrocannabinol (THC), cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), acids thereof and combination thereof.

According to some embodiments, the cannabis plant extract comprises about 1% (w/w) of CBD. According to some embodiments, the cannabis plant extract comprises about 10% (w/w) of CBD. According to some embodiments, the cannabis plant extract comprises about 25% (w/w) of CBD. According to some embodiments, the cannabis plant extract comprises about 45% (w/w) of CBD.

According to some embodiments, the cannabis plant extract comprises about 1% (w/w) of THC. According to some embodiments, the cannabis plant extract comprises about 10% (w/w) of THC. According to some embodiments, the cannabis plant extract comprises about 25% (w/w) of THC. According to some embodiments, the cannabis plant extract comprises about 45% (w/w) of THC.

The term "hybrid strain" refers to different strains of *Cannabis* which include differing amounts and/or ratios of the various cannabinoid compounds. For example, *Cannabis sativa* typically has a relatively high THC/CBD ratio. Conversely, *Cannabis indica* has a relative low THC/CBD ratio compared to *Cannabis sativa* (although the absolute amount of THC can be higher in *Cannabis indica* than in *Cannabis sativa*).

As used herein the terms “high-CBD strain” and “CBD-rich strain” are directed to a strain of cannabis plant which comprises CBD and optionally one or more additional cannabinoids, such as, for example, but not limited to: THC, CBN, and the like. According to some embodiments, CBD is the main component in the high-CBD strain.

As used herein the terms “high-THC strain” and “THC-rich strain” are directed to a strain of cannabis plant which comprises THC and optionally one or more additional cannabinoids, such as, for example, but not limited to: CBD, CBN, and the like. According to some embodiments, THC is the main component in the high-THC strain.

The cannabinoid component combination of the present invention is generally prepared by conventional methods such as are known in the art of making a mixture with the ratio described above. Such methods typically involve mixing of the CBDA ester and one or more additional cannabinoid compound(s), or one or more extract of a cannabis plant in one or more steps to a relatively uniform state, with or without heating, cooling, application of vacuum, and the like.

Pharmaceutical compositions

The compositions disclosed herein may be administered locally or systemically.

According to some embodiments, the pharmaceutical composition is formulated for inhalation. According to some embodiments, the pharmaceutical composition is a non-aqueous composition. According to specific embodiments, the pharmaceutical composition is a dry powder formulation. According to some embodiments, the pharmaceutical composition is formulated for an administration via vaporization.

According to some embodiments, the pharmaceutical composition is powder suitable for multi-dose reservoir dry powder inhaler (DPI).

The term “dry powder” as used herein refers to a composition that contains respirable dry particles that are capable of being dispersed in an inhalation device and subsequently inhaled by a subject. Such a dry powder may contain no more than about 25%, no more than about 20%, or no more than about 15% water or other solvent, or be substantially free of water or other solvent, or be anhydrous.

The powders described herein may contain one or more metal cation salts, which can be monovalent metal cation salts, divalent metal cation salts, or combinations thereof. Salts suitable for use in the dry powders include, for example, a sodium salt, a potassium salt, a lithium salt and any combination thereof.

Preferably, the dry particles are highly dispersible, and can be delivered to the respiratory tract of a patient using a passive DPI solely relying on the patient's own breathing pattern. In certain embodiments, the delivery of the respirable dry particles to the respiratory tract is relatively independent of patient's inspiratory flowrate, meaning that the delivered dose is very similar for patients breathing in at a relatively high or low flow rates.

The respirable dry particles described herein can include a physiologically or pharmaceutically acceptable excipient. For example, a pharmaceutically-acceptable excipient includes any of the standard carbohydrates, sugar alcohols, and amino acids that are known in the art to be useful excipients for inhalation therapy, either alone or in any desired combination. These excipients are generally relatively free-flowing particulates, do not thicken or polymerize upon contact with water, are toxicologically innocuous when inhaled as a dispersed powder and do not significantly interact with the therapeutic agent in a manner that adversely affects the desired physiological action. Carbohydrate excipients that are useful in this regard include the mono- and polysaccharides. Representative monosaccharides include carbohydrate excipients such as dextrose (anhydrous and the monohydrate; also referred to as glucose and glucose monohydrate), galactose, mannitol, D-mannose, sorbose and the like. Representative disaccharides include lactose, maltose, sucrose, trehalose and the like. Representative trisaccharides include raffinose and the like. Other carbohydrate excipients include maltodextrin and cyclodextrins. Representative sugar alcohols include mannitol, sorbitol and the like.

The excipient may be present in an amount less than about 90%, in an amount less than about 80%, in an amount less than about 70%, in an amount less than about 60%, in an amount less than about 50%, in an amount less than about 40%, in an amount less than about 35%, in an amount less than about 30%, in an amount less than about 25%, in an amount less than about 20%, in an amount less than about 17%, in an amount less than about 15%, in an amount less than about 12%, in an amount less than about 10%, in an amount less than about 8%, in an amount less than about 6%, in an amount less than about 5%, in an amount less than about 4%, in an amount less than about 3%, in an amount less than about 2%, or in an amount less than about 1%, all percentages are by weight of the dry particles.

In some embodiments, the dry particles contain an excipient selected from leucine, maltodextrin, mannitol and any combination thereof. In certain embodiments, the excipient is leucine, maltodextrin, or mannitol.

According to some embodiments, the pharmaceutical composition is formulated for inhalation, comprising propellant. Pharmaceutically acceptable propellants include inhalation acceptable hydrofluoroalkanes (HFAs). These include, but are not limited to, HFA 134a (tetrafluoroethane) HFA 227 (heptafluoropropane) and mixtures thereof.

According to some embodiments, the pharmaceutical composition is formed into a dosage form suitable for intranasal, oral, intravenous, intraarterial, peritoneal, transmucosal, or subcutaneous administration.

According to additional embodiments, the pharmaceutical composition is formulated as a capsule, a tablet, a liquid, or a syrup. In certain embodiments, the dosage form is granules or pellets delivered in a sachet or filled into capsule or compressed into a tablet.

According to some embodiments, the pharmaceutical composition further comprises triglycerides, fats, lipids, oils, fatty acids, co-solvents or mixtures thereof. According to certain embodiments, the pharmaceutical composition comprises an edible oil or fat.

According to specific embodiments, the pharmaceutical composition comprises an edible oil selected from the group consisting of copaiba oil, coconut oil, cottonseed oil, soybean oil, safflower oil, sesame oil, sunflower oil, castor oil, corn oil, olive oil, palm oil, peanut oil, and poppy seed oil. According to specific embodiments, the pharmaceutical composition comprises copaiba oil.

According to some embodiments, the pharmaceutical composition comprises alcohol and a solvent. According to some embodiments, the alcohol is ethanol. According to certain embodiments, the solvent is polyethylene glycol (PEG) or propylene glycol.

According to some embodiments, the pharmaceutical further comprises vitamins, minerals, and/or flavoring agents.

According to some embodiments, the pharmaceutical composition is formulated for slow release of the cannabinoid component. According to some embodiments, the pharmaceutical composition is formulated for slow release of the CBDA ester. In certain embodiments, the pharmaceutical composition further comprises a release retarding agent or a mixture of release retarding agents. According to some

embodiments, the pharmaceutical composition is at least partly coated by an enteric-coating agent.

According to some embodiments, the composition is a gel, wherein the cannabinoid component or acceptable salt thereof is entrapped in a gel matrix. The gel compositions of the present invention may comprise an oil-in water (o/w) emulsion.

Solubilizing and emulsifiers are used to improve the bioavailability of the cannabinoid component. Bioavailability refers to the extent and rate at which the active moiety (drug or metabolite) enters systemic circulation, thereby accessing the site of action.

According to some aspects, within the compositions and methods of the present invention, the bioavailability enhancing agent is an edible oil or fat, a protective colloid, or both a protective colloid and an edible oil or fat. In another aspect, the bioavailability enhancing agent is also a lipophilic active agent taste masking agent. In other aspects, the bioavailability of the lipophilic active agent in a subject is at least about 2 times, 5 times, or 10 times greater than the bioavailability of the lipophilic active agent in the subject in the absence of the bioavailability enhancing agent.

According to some embodiments, the cannabinoid component provided in microencapsulation particles. According to some embodiments, the CBDA ester provided in microencapsulation particles. Encapsulation may result in cannabinoids and other materials present in cannabinoid materials in liposomal capsule particles or other types of particles.

Microencapsulation or nanoencapsulation may increase cannabinoid bioavailability, thereby increasing cannabinoid efficacy after absorption through the mucosal membrane. Microencapsulation or nanoencapsulation may result in particles of 20-40 nm in size. Microencapsulation or nanoencapsulation promotes dissolution of cannabinoid particles in an aqueous environment.

According to some embodiments, the pharmaceutical composition comprises at least one micelle-forming compound selected from the group consisting of a polyoxyethylene ether, ester or alcohol; an alkali metal alkyl sulfate; a bile acid; lecithin, hyaluronic acid, pharmaceutically acceptable salts of hyaluronic acid, octylphenoxypolyethoxyethanol, glycolic acid, lactic acid, chamomile extract, cucumber extract, oleic acid, linolenic acid, borage oil, evening of primrose oil, trihydroxy oxo-cholanylglycine, glycerin, poly glycerin, lysine, polylysine, triolein, salts thereof, and mixtures thereof. According to certain embodiments, the bile acids

or bile acid salts are selected from the group consisting of chenodesoxycholic acid (CDCA), desoxycholic acid (DCA), lithocholic acid (LCA), taurodesoxycholic acid (TDCA), hyodeoxycholic acid (HDCA), taurocholic acid (TCA), glycocholic acid (GCA), and combinations thereof.

5 According to some embodiments, the pharmaceutical composition comprises phospholipids. According to certain embodiments, the pharmaceutical composition comprises a phospholipid selected from the group consisting of naturally occurring phospholipids and synthetic phospholipids. According to specific embodiments, the naturally occurring phospholipid is selected from the group consisting of soy lecithin,
10 egg lecithin, hydrogenated soy lecithin, hydrogenated egg lecithin, and a combination thereof. According to certain embodiments, the synthetic phospholipid is selected from the group consisting of phosphocholines, phosphoethanolamines, phosphatidic acids, phosphoglycerols, phosphoserines, mixed chain phospholipids, lysophospholipids, pegylated phospholipids, and a combination thereof. Each possibility represents a
15 separate embodiment of the invention.

 According to some embodiments, the phospholipid may form micelles, emulsions or liposomes. Thus, according to some embodiments, the present pharmaceutical composition is in the form of an emulsion, which includes the phospholipid as an emulsifying agent. According to some embodiments, the present pharmaceutical
20 composition is in the form of a micelle, which includes the phospholipid as a micelle-forming agent. According to some embodiments, the present pharmaceutical composition is in the form of a liposomal composition, which includes the phospholipid as the liposome-forming agent.

 According to some embodiments, the pharmaceutical composition comprises
25 cyclodextrins. According to certain embodiments, the cyclodextrin is selected from the group consisting of hydroxypropyl β -cyclodextrin, sulfobutylether β -cyclodextrin, and methyl- β -cyclodextrin (M β CD) and a combination thereof.

 According to some embodiments, the pharmaceutical composition comprises a pharmaceutically acceptable solvent, i.e. a non-toxic solvent that is suitable for
30 administration to a mammal with no unacceptable adverse effects. The solvent may be an aqueous or non-aqueous solvent. Suitable solvents include alcohol solutions, especially ethanol.

 The pharmaceutical composition may optionally contain a stabilizer and/or a preservative. Phenolic compounds, i.e. compounds comprising one or more hydroxyl

groups on a benzyl ring, are particularly suited for this purpose as they not only stabilize the composition, but they also enhance absorption of the composition. Preferred phenolic compounds include phenol, methyl phenol and mixtures thereof.

The pharmaceutical composition may also comprise one or more of the following
5 additional additives: inorganic salts, antioxidants, protease inhibitors, colorants and flavoring agents. Non-limiting examples of inorganic salts include sodium, potassium, calcium and zinc salts, especially sodium chloride, potassium chloride, calcium chloride, zinc chloride and sodium bicarbonate.

Orally administered formulations such as tablets may optionally be coated and
10 may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein.

The term “sustained” as used herein refers to a composition which provides prolonged, long or extended release of the therapeutic agent. This term may further refer to a composition which provides prolonged, long or extended duration of action
15 (pharmacokinetics) of a pharmaceutical composition comprising a therapeutically effective amount of the pharmaceutical composition of the present invention.

The pharmaceutical composition can include additional ingredients including but not limited to the excipients described herein. According to certain embodiments, one or more therapeutic agents of the dosage unit may exist in an extended or control release
20 formulation and additional therapeutic agents may not exist in extended release formulation. For example, the cannabinoid component ester described herein may exist in a controlled release formulation or extended release formulation in the same dosage unit with another agent that may or may not be in either a controlled release or extended release formulation. Thus, in certain embodiments, it may be desirable to provide for
25 the immediate release of one or more of the agents described herein, and the controlled release of one or more other agents.

According to some embodiments, the composition further comprises at least one pharmaceutically acceptable excipient. According to additional embodiments, the excipient is selected from the group consisting of emulsifiers, buffering agents, pH
30 adjusting agents, tonicity modifiers, preservatives, antioxidants, stabilizers, and a combination thereof.

According to some embodiments, the pharmaceutically acceptable carrier is an aqueous carrier. In some embodiments the aqueous carrier is a physiologically acceptable buffer having physiological or near-physiological pH.

According to some embodiments, the composition further comprising at least one pharmaceutically acceptable excipient. According to further embodiments, the excipient is selected from, but not limited to, emulsifiers, buffering agents, pH adjusting agents, tonicity modifiers, preservatives, antioxidants, stabilizers, or any other pharmaceutically acceptable excipient known in the art.

The pharmaceutical composition may comprise at least one physiologically acceptable film forming agent such as pullulan, methyl cellulose, ethyl cellulose, sodium carboxymethyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, polyvinyl pyrrolidone, methacrylic acid polymers, methacrylic acid copolymers, acrylic acid polymers, acrylic acid copolymers, polyacrylamides, polyalkylene oxides, carrageenan, polyvinyl alcohol, sodium alginate, polyethylene glycol, polyacrylic acid, glycolide, polylactide, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, alginic acid, pea starch, dextrin, pectin, chitin, chitosan, levan, elsinan and mixtures thereof. Additional film forming agents may be added to optimize characteristics such as tensile strength, stability, flexibility and brittleness including agents such xanthan gum, tragacanth gum, guar gum, locust bean gum, acacia gum, arabic gum, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

According to some embodiment, the orally administrable formulation comprises a mixture of sodium carboxymethylcellulose and hydroxypropyl- cellulose or methyl cellulose as the film-forming agents. The ratio of sodium carboxymethylcellulose to hydroxypropyl cellulose (or methylcellulose) used to make the formulation is chosen to yield the desired dissolution time and to further impart acceptable product handling characteristics.

According to some embodiments, the composition comprises less than about 10% (w/w) of the cannabinoid component. According to additional embodiments, the composition comprises less than about 7% (w/w) of the cannabinoid component. According to further embodiments, the composition comprises less than about 5% (w/w) of the cannabinoid component. According to yet further embodiments, the composition comprises less than about 2% (w/w) of the cannabinoid component. According to some embodiments, the composition comprises less than about 1% (w/w) of the cannabinoid component. According to additional embodiments, the composition comprises less than about 0.5% (w/w) of the cannabinoid component. It is to be

understood that the w/w unit is intended to refer to the relative weight amount of the cannabinoid component within the composition. For example, if the total weight of the composition is 1 gram and the weight of the cannabinoid component therein is 50 milligrams, the composition is said to comprise 5% (w/w) of the cannabinoid component.

According to some embodiments, the pharmaceutical composition is in a solid or semisolid form. The term "semisolid" refers to a form which on one hand supports its own weight and holds its shape and on the other hand is capable of conforming in shape in response to external pressure.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the pharmaceutical compositions of the invention.

It shall be understood that the amount of any active agent that is administered to a patient to treat that patient, will be administered in a therapeutically effective amount, as determined by ordinarily skilled physicians, pharmacologists, and toxicologists, that take into account the weight and age of the patient. In any event, where the drug has been approved by a regulatory authority (e.g., the U.S. Food and Drug Administration), a therapeutically effective amount of the cannabinoid component is an amount approved by the regulatory authority.

According to some embodiments, the pharmaceutical composition further comprises an additional therapeutic agent.

According to some embodiments the additional therapeutic agent is corticosteroids. Suitable corticosteroids include budesonide, fluticasone, flunisolide, triamcinolone, beclomethasone, mometasone, ciclesonide, dexamethasone, and the like.

According to some embodiments, the pharmaceutical composition further comprises an anti-asthma molecule. Anti-asthma molecules include but not limited to AVE0547 (anti-inflammatory, Sanofi-Aventis), AVE0675 (TLR agonist, Pfizer, Sanofi-Aventis), AVE5883 (NK1/NK2 antagonist, Sanofi-Aventis), AVE8923 (tryptase beta inhibitor, Sanofi-Aventis), CGS21680 (adenosine A2A receptor agonist, Novartis AG), ATL844 (A2B receptor antagonist, Novartis AG), BAY443428 (tryptase inhibitor, Bayer AG), CHF5407 (M3 receptor inhibitor, Chiesi Farmaceutici S.p.A.), CPLA2 Inhibitor Wyeth, IMA-638 (Anrukizumab; IL-13 antagonist, Wyeth), LAS100977 (LABA, Laboratorios Almirall, S.A.), MABA (M3 and beta-2 receptor antagonist), CS003 (Neurokinin receptor antagonist, Daiichi Sankyo Company,

Limited), DPC168 (CCR antagonist, Bristol-Myers Squibb), E26 (anti-IgE, Genentech Inc), HAE1 (Genentech), AMG853 (CRTH2 and D2 receptor antagonist, Amgen), IPL576092 (LSAID, Sanofi-Aventis), SVT47060 (Laboratorios Salvat, S.A.), VML530 (leukotriene synthesis inhibitor, Abbott Laboratories), MCC847 (D4 receptor antagonist, Mitsubishi Tanabe Pharma Corporation), TBC4746 (VLA-4 antagonist, Schering-Plough Corp), VR694 (Vectura Group PLC), and AMG009 (Amgen Inc), AMG853 (D2 receptor antagonist, Amgen Inc). Each possibility represents a separate embodiment of the invention.

According to some embodiments, the pharmaceutical composition further comprises an antibiotic, such as a macrolide (e.g., azithromycin, clarithromycin and erythromycin), a tetracycline (e.g., doxycycline, tigecycline), a fluoroquinolone (e.g., gemifloxacin, levofloxacin, ciprofloxacin and moxifloxacin), a cephalosporin (e.g., ceftriaxone, cefotaxime, ceftazidime, cefepime), a penicillin (e.g., amoxicillin, amoxicillin with clavulanate, ampicillin, piperacillin, and ticarcillin) optionally with a β -lactamase inhibitor (e.g., sulbactam, tazobactam and clavulanic acid), such as ampicillin-sulbactam, piperacillin-tazobactam and ticarcillin with clavulanate, an aminoglycoside (e.g., amikacin, arbekacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, rhodostreptomycin, streptomycin, and tobramycin), a penem or carbapenem (e.g. doripenem, ertapenem, imipenem and meropenem), a monobactam (e.g., aztreonam), an oxazolidinone (e.g., linezolid), vancomycin, glycopeptide antibiotics (e.g. telavancin), tuberculosis-mycobacterium antibiotics, tobramycin, azithromycin, ciprofloxacin, colistin, and the like.

Methods of preparation

The compositions of the present invention may be formulated for an inhalation as known in the art. In such a formulation, CBDA-ME is prepared in some embodiments as an inhalable dry powder or as an aerosol solution. Dry powder formulations for inhalation therapy are described, e.g., in U.S. Pat. No. 10,588,870 to Lipp and Sung; U.S. Pat. No. 5,993,805 to Sutton et al.; U.S. Pat. No. 6,921,527 to Platz et al.; WO 1999016419 to Tarara et al.; and WO 2000000215 to Bot et al.

The compositions of the present invention may be formulated as single-phase aqueous, emulsion or multiple emulsions. According to some embodiments, the composition is formulated as emulsion. These emulsions may be oil-in-water (o/w) (including silicone in water) emulsions, water-in-oil (including water-in-silicone) (w/o)

emulsions, or multiple emulsions such as oil-in-water-in-oil (o/w/o) or water-in-oil-in-water (w/o/w). It is understood that the oil phase can comprise silicone oils, non-silicone organic oils, or mixtures thereof. The compositions can comprise two immiscible phases that are admixed at the time of use by shaking. Each possibility
5 represents a separate embodiment of the present invention.

According to some embodiments, the composition is made by preparing a dispersion of each component in a suitable solvent (dispersant), adjusting the dispersion pH with a pH adjusting agent, if necessary, and admixing the dispersions with shear to permit the formation of the desired matrix.

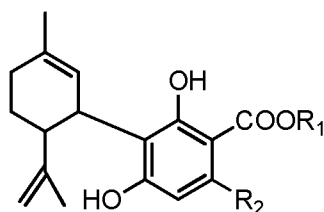
10 A common mode of administration of medical cannabis is by dissolving the cannabis extract or pure cannabinoid in triglyceride oils, such as vegetable oils, for oral delivery. The oil is either filled into capsules or used as-is in various volumes. In contrast to inhalation, the oral route of drug administration is most convenient to most people, and is perceived as an acceptable mode of self-medication, such as consuming
15 a pill. In such cases, an immediate release of the cannabinoids is obtained with fast absorption and an intermediate duration time of activity, but longer than smoking or vaporizing. A major drawback of dissolving cannabinoids in triglyceride oils is the inability to reach high concentrations of cannabinoids in a single unit dose, due to the limited solubility of cannabinoids and specifically cannabidiol in vegetable oils.
20 Therefore, many products are “cannabis oils” which are cannabinoids dissolved in a vegetable oil and administered in relatively large volumes. However, a limitation of this approach is the unfavorable taste and smell, characteristic of the vegetable oils and cannabinoids, which often result in poor patient compliance.

A person skilled in the art can select the appropriate presentation form, and the
25 method of preparing it on the basis of general knowledge, taking into account the nature of the constituents used and the intended use of the composition. Kits containing the above compositions are also contemplated. Compositions of the present invention can be packaged to contain, separately or in kit form together with a container, instructions or instruction brochure.

30 Methods of use

According to an aspect, the present invention provides a method for treating or preventing respiratory inflammation or distress including coronavirus and ARDS, comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a cannabinoid component, wherein the

cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent,

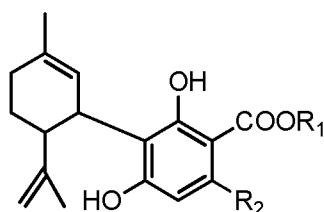


Formula (I)

wherein

R₁ and R₂ are each independently selected from the group consisting of a linear or branched, unsubstituted or substituted C₁-C₁₅ alkyl, a linear or branched, unsubstituted or substituted C₂-C₁₅ alkenyl, and a linear or branched, unsubstituted or substituted C₂-C₁₅ alkynyl; and stereoisomers and salts thereof.

According to an additional aspect, the present invention provides a method for treating or preventing coronavirus or ARDS, comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a cannabinoid component, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound(s), and a pharmaceutically acceptable carrier, excipient or diluent,



Formula (I)

wherein

R₁ and R₂ are each independently selected from the group consisting of a linear or branched, unsubstituted or substituted C₁-C₁₅ alkyl, a linear

or branched, unsubstituted or substituted C₂-C₁₅ alkenyl, and a linear or branched, unsubstituted or substituted C₂-C₁₅ alkynyl; and stereoisomers and salts thereof.

In certain embodiments the one or more additional cannabinoid compound(s) are present in one or more extracts of a cannabis plant.

The term "effective amount," as in "a therapeutically effective amount," of a therapeutic agent refers to the amount of the agent necessary to elicit the desired biological response. As will be appreciated by those of ordinary skill in this art, the effective amount of an agent may vary depending on such factors as the desired biological endpoint, the agent to be delivered, the composition of the pharmaceutical composition, the target tissue or cell, and the like. More particularly, the term "effective amount" refers to an amount sufficient to produce the desired effect, e.g., to reduce or ameliorate the severity, duration, progression, or onset of a disease, disorder, or condition, or one or more symptoms thereof; prevent the advancement of a disease, disorder, or condition, cause the regression of a disease, disorder, or condition; prevent the recurrence, development, onset or progression of a symptom associated with a disease, disorder, or condition, or enhance or improve the prophylactic or therapeutic effect(s) of another therapy. For example, a "therapeutically effective amount" of the CBDA ester refers to an amount that is effective for preventing, ameliorating, or treating the specified disease or disorder. Similarly, a "therapeutically effective amount" of a combination of the CBDA ester and a second compound refers to an amount of CBDA ester and an amount of the second compound that, in combination, is effective for preventing, ameliorating, or treating the specified disease or disorder.

The term "treatment" or any grammatical variation thereof (e.g., treat, treating, and treatment etc.), as used herein, includes but is not limited to, alleviating a symptom of a disease or condition; and/or reducing, suppressing, inhibiting, lessening, or affecting the progression, severity, and/or scope of a disease or condition.

As used herein, the term "subject" designates a mammal, preferably a human.

Coronaviruses treated with compositions described herein include veterinary and human coronaviruses. Human coronaviruses to be treated include Human coronavirus 229E (HCoV-229E), Human coronavirus OC43 (HCoV-OC43), Severe acute respiratory syndrome coronavirus (SARS-CoV), Human coronavirus NL63 (HCoV-NL63, New Haven coronavirus), Human coronavirus HKU1, Middle East respiratory syndrome-related coronavirus (MERS-CoV), previously known as novel coronavirus

2012 and HCoV-EMC, and COVID-19 or Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), previously known as 2019-nCoV or "novel coronavirus 2019".

In some embodiments, the method described herein is for used in treating the
5 respiratory inflammation caused by the coronavirus.

In some embodiments, the pharmaceutical composition described herein is for use in treating respiratory inflammation that caused by other infections or pathologies.

As used herein, the term "inflammation" refers to the biological response that occurs in airway conditions caused by either disease or environmental causes.
10 Inflammation is a localized physical condition in which part of the body becomes reddened, swollen, hot, and often painful, especially as a reaction to the airway condition.

The term "respiratory inflammation" refers to a disease or disorder that one of its symptoms is inflammation in the lungs. Further, the term "respiratory inflammation"
15 refers to any local response in the airway or lungs that is marked by capillary dilatation, leukocytic infiltration, and edema, and that serves as a mechanism initiating the elimination of noxious agents and of damaged tissue. The respiratory inflammation can be associated with a disease or disorder including, but not limited to, asthma, chronic obstructive airway disorder, pneumonia, respiratory syncytial viral infection,
20 bronchitis, bronchiolitis, idiopathic pulmonary fibrosis, cystic fibrosis, acute respiratory distress syndrome, bronchopulmonary dysplasia, occupational respiratory disease, particulate exposure, pleurisy, emphysema, and pulmonary edema.

According to some embodiments, the respiratory inflammation is acute respiratory inflammation.

25 According to some embodiments, the respiratory inflammation is chronic respiratory inflammation. According to certain embodiments, the respiratory inflammation is asthma. According to certain embodiments, the respiratory inflammation is COPD.

According to some embodiments, the inflammation is caused by a pathogen.
30 According to certain embodiments, the inflammation is caused by a pathogen selected from the group consisting of bacteria, viruses, or fungi.

According to some embodiments, the inflammation is caused by a virus. According to additional embodiments, the inflammation is caused by Severe acute

respiratory syndrome (SARS). According to additional embodiments, the inflammation is caused by COVID-19.

According to some embodiments, the method is for treating respiratory inflammation related disease or disorder.

5 According to some embodiments, the respiratory inflammation related disease is lung cancer.

According to some embodiments, the pharmaceutical composition is used in combination with other therapeutic agents for treatment or prevention of respiratory inflammation.

10 According to some embodiments, the method further comprises administering an anti-inflammatory drug. According to some embodiments, the drug is acetaminophen, acetylsalicylic acid (ASA), alclometacin, alminoprofen, azapropazone, benorylate, benoxaprofen, bucloxic acid, carprofen, choline magnesium trisalicylate, clidanac, dapsone, diclofenac, diflunisal, droxicam, etodolac, fenoprofen, fenbufen, fenclofenac, fentiazac, floctafenine, flufenisal, flurbiprofen, (r)-flurbiprofen, (s)-flurbiprofen, furofenac, flufenamic acid, fluprofen, ibufenac, ibuprofen, indometacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, mioprofen, piroxicam, meloxicam, mefenamic, mefenamic acid, meclofenamic acid, meclofen, nabumetone, naproxen, niflumic acid, oxaprozin, oxyphenbutazone, phenylbutazone, piroprofen, pranoprofen, sudoxicam, suprofen, sulindac, tenoxicam, tiaprofenic acid, tiopinac, tioxaprofen, 20 tolfenamic acid, tolmetin, zidometacin, or zomepirac. Each possibility represents a separate embodiment of the invention.

According to some embodiments, the treatment reduces inflammatory.

25 According to some embodiments, the treatment ameliorates the symptoms of the inflammation.

The beneficial effect can be evidenced, for example, by a delayed onset of clinical symptoms of the disease or condition in a susceptible subject, a reduction in severity of some or all clinical symptoms of the disease or condition, a slower progression of the disease or condition, a reduction in the number of relapses of the disease or condition, 30 an improvement in the overall health or well-being of the subject, by other parameters well known in the art that are specific to the particular disease or condition, and combinations of such factors.

The route of administration can be by any route and will be determined based on the physician and the patient. All other routes of administration of a therapeutically

effective amount of an agent to treat a patient having respiratory inflammation are contemplated herein and include, without limitation, enteral (e.g., orally), or parenteral (e.g., intravenous, subcutaneous or by inhalation), or other routes (e.g., intranasal, intradermal, subcutaneous, and transdermal).

5 According to some embodiments, the pharmaceutical composition is administered by inhalation. According to certain embodiments, the pharmaceutical composition is administered intranasally. According to other embodiments, the pharmaceutical composition is administered orally.

 According to some embodiments, the pharmaceutical composition is administered
10 once a day, twice a week, once a week, once in two weeks, once in three weeks or once a month. According to yet further embodiments, the composition is administered once in two months, once in three months, once in four months, once in five months or once in six months.

 According to some embodiments, the pharmaceutical composition is administered
15 for a period of greater than a week. According to some embodiments, the pharmaceutical composition is administered for a period of greater than four weeks. According to some embodiments, the pharmaceutical composition is administered for a period of greater than two months. According to some embodiments, the pharmaceutical composition is administered for a period of greater than 3, 4, 5, or 6
20 months.

 According to some embodiments, the effective dose of the cannabinoid component ranges from 0.1 to 500 mg/kg/day of body weight, from 1 to 250 mg/kg/day of body weight, from 2 to 100 mg/kg/day of body weight, or from 5 to 30 mg/kg/day, and may be in single dose or divided throughout the day. Each possibility represents a
25 separate embodiment of the invention.

 According to some embodiments, the effective dose of the CBDA ester ranges from 0.1 to 500 mg/kg/day of body weight, from 1 to 250 mg/kg/day of body weight, from 2 to 100 mg/kg/day of body weight, or from 5 to 30 mg/kg/day, and may be in single dose or divided throughout the day. Each possibility represents a separate
30 embodiment of the invention.

 According to some embodiments, the effective dose of CBDA-ME ranges from 0.1 to 500 mg/kg/day of body weight, from 1 to 250 mg/kg/day of body weight, from 2 to 100 mg/kg/day of body weight, or from 5 to 30 mg/kg/day, and may be in single dose

or divided throughout the day. Each possibility represents a separate embodiment of the invention.

According other embodiments, the pharmaceutical composition is administered at a unit dosage form of approximately 0.05 g/kg/day to approximately 0.5 g/kg/day.

5 The active agents of the present invention are effective over a wide dosage range. According to certain embodiments, the cannabinoid component dosage is 0.5 mg, 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25, mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 1000 mg per day orally. According to certain embodiments, the CBDA ester dosage is 0.5 mg, 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25, 10 mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 1000 mg per day orally. According to certain embodiments, CBDA-ME dosage is 0.5 mg, 1 mg, 2 mg, 3 mg, 5 mg, 10 mg, 15 mg, 20 mg, 25, mg, 50 mg, 75 mg, 100 mg, 200 mg, 300 mg, 400 mg, 500 mg, or 1000 mg per day orally.

 According to some embodiments, the unit dosage form is administered with food 15 at any time of the day, without food at any time of the day, with food after an overnight fast (e.g., with breakfast).

 It is conceived that in some embodiments the therapeutic methods according to the invention may involve combination therapies. In other words, that the compositions of the invention may be administered in combination with one or more additional 20 compounds or therapies, the latter using enteral or parenteral and include, but are not limited to, by inhalation, oral, intradermal, intramuscular, intravenous, subcutaneous, intranasal, and transdermal administration routes.

 The following examples describe specific aspects of the invention to illustrate the invention and provide a description of the present methods for those skilled in the art. 25 It should be noted that the term “and” or the term “or” is generally employed in its sense including “and/or” unless the content clearly dictates otherwise. As used herein, the term "about", when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 10\%$, more preferably $\pm 5\%$, even more preferably $\pm 1\%$, and still more preferably $\pm 0.1\%$ from the specified value, 30 as such variations are appropriate to perform the disclosed methods.

 The Examples should not be construed as limiting the invention as the examples merely provide specific methodology useful in the understanding and practice of the invention and its various aspects. While certain preferred and alternative embodiments

of the invention have been set forth for purposes of disclosing the invention, modification to the disclosed embodiments can occur to those who are skilled in the art.

5 **EXAMPLES**

Example 1. Synthesis of Cannabidiolic Acid (CBDA)

The preparation process described in the PCT application WO 2018/235079 was applied. A mixture of Cannabidiol (CBD, 314 mg, 1 mmol) and 2 molar solution of
10 Magnesium Methyl Carbonate (MMC/2M, 1.5 ml, 3 mmol) in dimethylformamide (DMF) was heated at 130°C for 3 hours. Then the reaction was cooled to 0°C, acidified with 10% hydrochloric acid and extracted with ether. The organic layer was washed with saline, dried over the drying agent magnesium sulfate (MgSO₄) and then evaporated. The crude compound was then cleaned by column chromatography (20%
15 ether-petroleum ether).

Example 2. Synthesis of Cannabidiolic Acid Methyl Ester

The preparation process described in the PCT application WO 2018/235079 was applied. To a solution of Cannabidiolic Acid (CBDA) (175 mg, 0.488 mmol) in 2.5 ml
20 dichloromethane (CH₂Cl₂), was added 0.02 ml of methanol (CH₃OH, 0.488 mmol) and 7.2 mg of 4-Pyrrolidinopyridine (0.048 mmol). The reaction was stirred for 5 minutes at room temperature followed by the addition of the coupling agent, N,N'-Dicyclohexylcarbodiimide (DCC) (121 mg, 0.585 mmol) and stirred overnight. Then the solvent was evaporated and the crude mixture acidified with 5% hydrochloric acid
25 and extracted with dichloromethane (CH₂Cl₂). The organic layer was washed with saturated aqueous sodium bicarbonate (NaHCO₃), dried over the drying agent magnesium sulfate (MgSO₄) and then evaporated. The crude compound is then cleaned by column chromatography (2% ether-petroleum ether).

¹H-NMR spectra were obtained using a Bruker AMX 300 MHz apparatus using
30 the deuterated DMSO. Thin-layer chromatography (TLC) was run on silica gel 60F254 plates (Merck). Column chromatography was performed on silica gel 60 Å (Merck). Compounds were located using a UV lamp at 254 nm.

¹H NMR (300 MHz, ((CD₃)₂SO)) δ 6.18 (1H, s, Ar), 5.07 (1H, s), 4.44 (1H, s), 4.41 (1H, s), 3.82 (3H, s), 3.35 (1H, m), 2.66 (1H, m), 2.49 (2H, t), 2.09 (1H, b), 1.95 (3H, s), 1.71-1.05 (12, ms), 0.86 (3H, t).

5 Example 3. Preparing CBDA-ME for inhalation

CBDA-ME is prepared for inhalation as known in the art, e.g., US patent Nos. 10,588,870 and 10,064,821. Briefly, CBDA-ME oil is weighed and transferred to a suitable container, and ethanol (1:2) is added till solution is observed. The solution is transferred to an appropriate aerosol container and a metered dose inhaler valve is
10 crimped on. The sample is then pressure filled with HFA 134a.

Example 4. Ovalbumin-induced respiratory inflammation model

A murine model of allergen-induced airway inflammation is used to examine the effects of CBDA-ME on airway inflammation and remodeling. Sensitized BALB/c
15 mice are intraperitoneal injected with ovalbumin (10 µg of OVA in 100 µl saline) every alternate day for two weeks. Then, 20 µg of OVA in 20 µl saline are instilled intratracheally. The mice are then intranasally or orally administered with 5 or 10 mg/kg CBDA-ME, CBD or saline as control. Following treatment, the mice are examined for airway responsiveness as well as lung mechanics with methacholine challenge. Then,
20 the mice are killed and analyzed for the number of mononuclear cells (MN), and eosinophils in the lung. Lung homogenates are used to measure cytokines in the lungs.

Example 5. Efficacy of CBDA-ME compositions in mice model of SARS-CoV

The therapeutic effect of CBDA-ME is examined in mouse models of SARS-
25 CoV, such as described in US2017/0027975. CBDA-ME, CBD, or control are administered to the mice as described in Example 4. The therapeutic effect is evaluated by measuring the inflammatory factors as described in Example 4, as well as the ability of the compounds to protect the mice from weight loss, clinical disease and reduce virus titer.

30

Example 6. Efficacy of CBDA-ME compositions in mice model of ARDS

The therapeutic effect of CBDA-ME is examined in mouse models of ARDS. ARDS was induced by LPS: LPS of *Escherichia coli* serotype O55:B5 is dissolved in

sterile PBS at 2 mg/ml. LPS is aliquoted into glass vials and kept frozen. On the day of the experiment the vials are thawed for 1 hr in 25°C and diluted in sterile PBS to a final concentration of 1 mg/ml. To generate aerosol the PulmoAide (DeVilbiss) vaporizer is used. Aerosol is administered at a pressure of 2.5 bar and a rate of 0.15 ml/min. While receiving the aerosol the mice are kept in a Polypropylene (PP) and Polycyclohexane 1, 4 Dimethylterephthalate (Tritan) closed lead (5L) cage (22X14X17cm). Aerosol is administered and then removed from the cage using plastic tubing. A liquid trap is connected to the exhaust tubing to capture residual LPS. Groups of 10 mice are placed in the breathing chamber and 8 ml of LPS (1 mg/ml) are added to the Nebulizer cup. After 50 min of nebulization the mice are removed. Before placing a new group of mice, the chamber is cleaned using disposable disinfectant wipes. Control groups received nebulization with 8 ml of sterile PBS only with a clean nebulization chamber and nebulizer.

Two formulations are used:

1. Aerosol based formulation - CBDA-ME (5, 10 and 20 mg/Kg); CBD (5, 10, and 20 mg/Kg), prednisolone (10, 20, 40mg/Kg) or PBS. The mice are treated once.

2. I.V. injection - CBDA-ME (5 and 20 mg/Kg); CBD (5 and 20 mg/Kg), prednisolone (10 and 40 mg/Kg) or PBS. The mice are treated once a day.

Lavage is performed using PBS with 100 µM EDTA. A 23 G needle inserted into transparent plastic polyethylene 21 G tubing (inner diameter: 0.58 mm, outer diameter: 0.965 mm, and length: 0.5 cm) is used as the catheter.

Before bronchoalveolar fluid (BALF) removal, animals are sacrificed using ketamine and xylazine lethal dose. The Animal is placed on its back on a surgical plate and fixed by pinning down the limbs. After spraying the animal with ethanol, an incision the skin in the neck is made, the muscle and salvia glands is set aside and the trachea is exposed. Once the trachea is exposed, a cotton surgical thread is placed around the trachea. The trachea is then carefully punctured at the middle using a 26 G needle. The catheter is inserted about 0.5 cm into the trachea. Stabilizing the catheter is ensured by tying the trachea around the catheter using the cotton thread placed earlier.

Aspiration with PBS-EDTA is performed three times, 700 µl each time. The first aspiration fluid is collected into an Eppendorf test tube. The other two aspiration are collected into a separate tube. The lavage fluid from the first tube is centrifuged for 7 min at 400 x g, 4 °C. The supernatant from this tube is collected for ELISA testing and frozen in -80. The cell pellet is suspended with the fluids collected in aspiration 2 and

3. From this tube 200 μ l is taken to FACS analysis. The remaining fluid is centrifuged 7 min at 400 x g and 4 °C and the cell pellet is taken to RNA extraction using EZ-RNA extraction kit.

The mice are examined for hematological parameters:

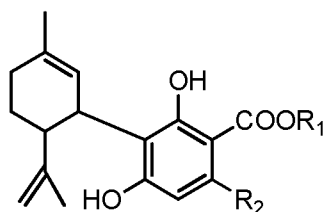
- 5 Number and differential of leukocytes subsets (macrophages, neutrophils, lymphocytes, monocytes) and cytokines level: TNFa, IL-6, IL-10, IL-12p40, IL1beta (either by ELISA or by mRNA levels via qPCR).

10

Although the present invention has been described herein above by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims.

CLAIMS

1. A pharmaceutical composition comprising a cannabinoid component, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional
5 cannabinoid compound, and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating respiratory distress or inflammation,



Formula (I)

wherein

- 10 R_1 and R_2 are each independently selected from the group consisting of a linear or branched, unsubstituted or substituted C_1 - C_{15} alkyl, a linear or branched, unsubstituted or substituted C_2 - C_{15} alkenyl, and a linear or branched, unsubstituted or substituted C_2 - C_{15} alkynyl; and stereoisomers and salts thereof.
- 15 2. The pharmaceutical composition for use according to claim 1, wherein R_1 is methyl.
3. The pharmaceutical composition for use according to any one of claim 1 or 2, wherein the cannabidiolic acid ester is cannabidiolic acid methyl ester (CBDA-ME).
- 20 4. The pharmaceutical composition for use according to any one of claims 1 to 3, wherein the respiratory distress is caused by coronavirus.
5. The pharmaceutical composition for use according to claim 4, wherein the coronavirus is SARS-CoV-2 (COVID-19).
6. The pharmaceutical composition for use according to any one of claims 1 to 3,
25 wherein the respiratory distress is acute respiratory distress syndrome (ARDS).
7. The pharmaceutical composition for use according to any one of claims 1 to 6, wherein the additional cannabinoid compound is selected from the group consisting of cannabidiol (CBD), cannabigerol (CBG), Δ^8 -tetrahydrocannabinol (Δ^8 -THC), Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabinol (CBN), $\Delta^9(11)$ -

tetrahydrocannabinol (exo-THC), cannabichromene (CBC), tetrahydrocannabinol-C3 (THC-C3), tetrahydrocannabinol-C4 (THC-C4), tetrahydrocannabinol-C7 (THC-C7), esters thereof and combination thereof.

8. The pharmaceutical composition for use according to any one of claims 1 to 7,
5 wherein the one or more additional cannabinoid compound is present in one or more extracts of a cannabis plant.
9. The pharmaceutical composition for use according to claim 8, wherein the cannabis plant extract is obtained from a strain selected from the group consisting of *Cannabis sativa*, *Cannabis indica*, *Cannabis ruderalis*, a hybrid strain, and
10 combinations thereof.
10. The pharmaceutical composition for use according to claim 8, wherein the cannabis plant extract is obtained from a strain selected from the group consisting of a high-CBD strain, a high-THC strain, and a combination thereof.
11. The pharmaceutical composition according to claim 8, wherein the cannabis plant
15 extract comprises at least one cannabinoid selected from the group consisting of cannabidiol (CBD), tetrahydrocannabinol (THC), cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), acids thereof and combination thereof.
12. The pharmaceutical composition for use according to claim 8, wherein cannabis plant extract comprises about 1% (w/w) of CBD.
- 20 13. The pharmaceutical composition for use according to claim 8, wherein cannabis plant extract comprises about 10% (w/w) of CBD.
14. The pharmaceutical composition for use according to claim 8, wherein cannabis plant extract comprises about 1% (w/w) of THC.
15. The pharmaceutical composition for use according to claim 8, wherein cannabis
25 plant extract comprises about 10% (w/w) of THC.
16. The pharmaceutical composition for use according to any one of claims 8 to 15, wherein the cannabis plant extract is produced by a process, which comprises contacting the cannabis plant material with a suitable solvent or a combination of solvents.
- 30 17. The pharmaceutical composition for use according to claim 16, wherein the solvent is selected from the group consisting of a polar solvent, a hydrocarbon solvent, carbon dioxide, and combinations thereof.
18. The pharmaceutical composition for use according to any one of claims 1 to 17, wherein the cannabinoid component is emulsified, dissolved, dispersed or

encapsulated in formulations suitable for use in either aqueous based or oil-based carriers.

19. The pharmaceutical composition for use according to any one of claims 1 to 18, wherein the pharmaceutical composition is formulated for inhalation.
- 5 20. The pharmaceutical composition for use according to claim 19, wherein the pharmaceutical composition is a dry powder formulation.
21. The pharmaceutical composition for use according to any one of claims 1 to 18, wherein the pharmaceutical composition is formulated into a dosage form suitable for intranasal, oral, intravenous, intraarterial, or subcutaneous administration.
- 10 22. The pharmaceutical composition for use according to any one of claims 1 to 21, further comprising an excipient selected from the group consisting of triglycerides, fats, lipids, oils, fatty acids, solvents or mixtures thereof.
23. The pharmaceutical composition for use according claim 22, wherein the solvent is polyethylene glycol or propylene glycol.
- 15 24. The pharmaceutical composition for use according to any one of claims 1 to 23, further comprising a phospholipid selected from the group consisting of naturally occurring phospholipids and synthetic phospholipids.
25. The pharmaceutical composition for use according to claim 24, wherein the naturally occurring phospholipid is selected from the group consisting of soy
20 lecithin, egg lecithin, hydrogenated soy lecithin, hydrogenated egg lecithin, and a combination thereof.
26. The pharmaceutical composition for use according to claim 24, wherein the synthetic phospholipid is selected from the group consisting of phosphocholines, phosphoethanolamines, phosphatidic acids, phosphoglycerols, phosphoserines,
25 mixed chain phospholipids, lysophospholipids, pegylated phospholipids, and a combination thereof.
27. The pharmaceutical composition for use according to any one of claims 24 to 26, wherein the phospholipid forms micelles, emulsions or liposomes.
28. The pharmaceutical composition for use according to any one of claims 1 to 27,
30 further comprising cyclodextrins.
29. The pharmaceutical composition for use according to claim 28, wherein the cyclodextrin is selected from the group consisting of hydroxypropyl β -cyclodextrin, sulfobutylether β -cyclodextrin, and methyl- β -cyclodextrin (M β CD).

30. The pharmaceutical composition for use according to any one of claims 1 to 29, wherein the pharmaceutically acceptable carrier is an aqueous carrier.
31. The pharmaceutical composition for use according to any one of claims 1 to 30, wherein the excipient is selected from the group consisting of emulsifiers,
5 buffering agents, pH adjusting agents, preservatives, antioxidants, stabilizers, and a combination thereof.
32. The pharmaceutical composition for use according to any one of claims 1 to 19 or 21 to 31, formulated in a form of liquid or gel.
33. The pharmaceutical composition for use according to any one of claims 1 to 32,
10 comprising less than about 10% (w/w) of the cannabinoid component.
34. The pharmaceutical composition for use according to any one of claims 1 to 32, comprising less than about 7% (w/w) of the cannabinoid component.
35. The pharmaceutical composition for use according to any one of claims 1 to 32, comprising less than about 5% (w/w) of the cannabinoid component.
- 15 36. The pharmaceutical composition according to any one of claims 1 to 32, comprising less than about 1% (w/w) of the cannabinoid component.
37. The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 36, wherein the respiratory inflammation is acute respiratory inflammation.
38. The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 37,
20 wherein the respiratory inflammation is caused by pneumonia.
39. The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 37, wherein the respiratory inflammation is caused by a pathogen selected from the group consisting of viruses, bacteria, parasites or fungi.
40. The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 36,
25 wherein the respiratory inflammation is chronic respiratory inflammation.
41. The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 36, wherein the respiratory inflammation is asthma.
42. The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 36, wherein the respiratory inflammation is chronic obstructive pulmonary disease
30 (COPD).
43. A method for treating respiratory distress or inflammation comprising administering to a subject in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a cannabinoid component, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester

represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound, and a pharmaceutically acceptable carrier, excipient or diluent, wherein Formula (I), R¹ and R² are as defined in claim 1.

5 44. The method according to claim 43, wherein the respiratory distress is caused by coronavirus.

45. The method according to claim 43, wherein the respiratory distress is ARDS.

46. The method according to claim 43, wherein the additional cannabinoid compound is present in one or more extracts of a cannabis plant.

10 47. The method of claim 43, comprising administering by inhalation.

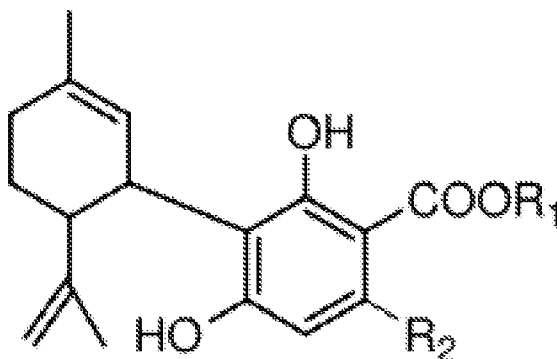
48. The method of claim 43, comprising administering orally, nasally, intravenously, or intramuscularly.

49. The method of claim 43, administered twice a day, once a day, a week, once in two weeks, once in three weeks or once a month.

AMENDED CLAIMS

received by the International Bureau on 20 July 2021 (20.07.2021)

- [Claim 1] A pharmaceutical composition comprising a cannabinoid component, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound, and a pharmaceutically acceptable carrier, excipient or diluent, for use in treating respiratory distress or respiratory inflammation,



Formula (I)

wherein

R_1 and R_2 are each independently selected from the group consisting of a linear or branched, unsubstituted or substituted C_1 - C_{15} alkyl, a linear or branched, unsubstituted or substituted C_2 - C_{15} alkenyl, and a linear or branched, unsubstituted or substituted C_2 - C_{15} alkynyl; and stereoisomers and salts thereof.

- [Claim 2] The pharmaceutical composition for use according to claim 1, wherein R_1 is methyl.
- [Claim 3] The pharmaceutical composition for use according to any one of claim 1 or 2, wherein the cannabidiolic acid ester is cannabidiolic acid methyl ester (CBDA-ME).
- [Claim 4] The pharmaceutical composition for use according to any one of claims 1 to 3, wherein the respiratory distress is caused by coronavirus.
- [Claim 5] The pharmaceutical composition for use according to claim 4, wherein the coronavirus is SARS-CoV-2 (COVID-19).
- [Claim 6] The pharmaceutical composition for use according to any one of claims 1 to 3, wherein the respiratory distress is acute respiratory distress syndrome (ARDS).
- [Claim 7] The pharmaceutical composition for use according to any one of claims 1 to 6, wherein the additional cannabinoid compound is selected from the group consisting of cannabidiol (CBD), cannabigerol (CBG), Δ^8 -

tetrahydrocannabinol (Δ^8 -THC), Δ^9 -tetrahydrocannabinol (Δ^9 -THC), cannabinol (CBN), $\Delta^9(11)$ - tetrahydrocannabinol (exo-THC), cannabichromene (CBC), tetrahydrocannabinol-C3 (THC-C3), tetrahydrocannabinol-C4 (THC-C4), tetrahydrocannabinol-C7 (THC-C7), esters thereof and combination thereof.

[Claim 8] The pharmaceutical composition for use according to any one of claims 1 to 7, wherein the one or more additional cannabinoid compound is present in one or more extracts of a cannabis plant.

[Claim 9] The pharmaceutical composition for use according to claim 8, wherein the cannabis plant extract is obtained from a strain selected from the group consisting of *Cannabis sativa*, *Cannabis indica*, *Cannabis ruderalis*, a hybrid strain, and combinations thereof.

[Claim 10] The pharmaceutical composition for use according to claim 8, wherein the cannabis plant extract is obtained from a strain selected from the group consisting of a high-CBD strain, a high-THC strain, and a combination thereof.

[Claim 11] The pharmaceutical composition according to claim 8, wherein the cannabis plant extract comprises at least one cannabinoid selected from the group consisting of cannabidiol (CBD), tetrahydrocannabinol (THC), cannabinol (CBN), cannabigerol (CBG), cannabichromene (CBC), acids thereof and combination thereof.

[Claim 12] The pharmaceutical composition for use according to claim 8, wherein cannabis plant extract comprises about 1% (w/w) of CBD.

[Claim 13] The pharmaceutical composition for use according to claim 8, wherein cannabis plant extract comprises about 10% (w/w) of CBD.

[Claim 14] The pharmaceutical composition for use according to claim 8, wherein cannabis plant extract comprises about 1% (w/w) of THC.

[Claim 15] The pharmaceutical composition for use according to claim 8, wherein cannabis plant extract comprises about 10% (w/w) of THC.

[Claim 16] The pharmaceutical composition for use according to any one of claims 8 to 15, wherein the cannabis plant extract is produced by a process, which comprises contacting the cannabis plant material with a suitable solvent or a combination of solvents.

[Claim 17] The pharmaceutical composition for use according to claim 16, wherein the solvent is selected from the group consisting of a polar solvent, a hydrocarbon solvent, carbon dioxide, and combinations thereof.

[Claim 18] The pharmaceutical composition for use according to any one of claims 1 to 17, wherein the cannabinoid component is emulsified, dissolved,

dispersed or encapsulated in formulations suitable for use in either aqueous based or oil-based carriers.

- [Claim 19] The pharmaceutical composition for use according to any one of claims 1 to 18, wherein the pharmaceutical composition is formulated for inhalation.
- [Claim 20] The pharmaceutical composition for use according to claim 19, wherein the pharmaceutical composition is a dry powder formulation.
- [Claim 21] The pharmaceutical composition for use according to any one of claims 1 to 18, wherein the pharmaceutical composition is formulated into a dosage form suitable for intranasal, oral, intravenous, intraarterial, or subcutaneous administration.
- [Claim 22] The pharmaceutical composition for use according to any one of claims 1 to 21, further comprising an excipient selected from the group consisting of triglycerides, fats, lipids, oils, fatty acids, solvents or mixtures thereof.
- [Claim 23] The pharmaceutical composition for use according claim 22, wherein the solvent is polyethylene glycol or propylene glycol.
- [Claim 24] The pharmaceutical composition for use according to any one of claims 1 to 23, further comprising a phospholipid selected from the group consisting of naturally occurring phospholipids and synthetic phospholipids.
- [Claim 25] The pharmaceutical composition for use according to claim 24, wherein the naturally occurring phospholipid is selected from the group consisting of soy lecithin, egg lecithin, hydrogenated soy lecithin, hydrogenated egg lecithin, and a combination thereof.
- [Claim 26] The pharmaceutical composition for use according to claim 24, wherein the synthetic phospholipid is selected from the group consisting of phosphocholines, phosphoethanolamines, phosphatidic acids, phosphoglycerols, phosphoserines, mixed chain phospholipids, lysophospholipids, pegylated phospholipids, and a combination thereof.
- [Claim 27] The pharmaceutical composition for use according to any one of claims 24 to 26, wherein the phospholipid forms micelles, emulsions or liposomes.
- [Claim 28] The pharmaceutical composition for use according to any one of claims 1 to 27, further comprising cyclodextrins.
- [Claim 29] The pharmaceutical composition for use according to claim 28, wherein the cyclodextrin is selected from the group consisting of hydroxypropyl β -cyclodextrin, sulfobutylether β -cyclodextrin, and methyl-

β -cyclodextrin (M β CD).

- [Claim 30] The pharmaceutical composition for use according to any one of claims 1 to 29, wherein the pharmaceutically acceptable carrier is an aqueous carrier.
- [Claim 31] The pharmaceutical composition for use according to any one of claims 1 to 30, wherein the excipient is selected from the group consisting of emulsifiers, buffering agents, pH adjusting agents, preservatives, antioxidants, stabilizers, and a combination thereof.
- [Claim 32] The pharmaceutical composition for use according to any one of claims 1 to 19 or 21 to 31, formulated in a form of liquid or gel.
- [Claim 33] The pharmaceutical composition for use according to any one of claims 1 to 32, comprising less than about 10% (w/w) of the cannabinoid component.
- [Claim 34] The pharmaceutical composition for use according to any one of claims 1 to 32, comprising less than about 7% (w/w) of the cannabinoid component.
- [Claim 35] The pharmaceutical composition for use according to any one of claims 1 to 32, comprising less than about 5% (w/w) of the cannabinoid component.
- [Claim 36] The pharmaceutical composition according to any one of claims 1 to 32, comprising less than about 1% (w/w) of the cannabinoid component.
- [Claim 37] The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 36, wherein the respiratory inflammation is acute respiratory inflammation.
- [Claim 38] The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 37, wherein the respiratory inflammation is caused by pneumonia.
- [Claim 39] The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 37, wherein the respiratory inflammation is caused by a pathogen selected from the group consisting of viruses, bacteria, parasites or fungi.
- [Claim 40] The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 36, wherein the respiratory inflammation is chronic respiratory inflammation.
- [Claim 41] The pharmaceutical composition according to any one of claims 1 to 3 or 7 to 36, wherein the respiratory inflammation is asthma.
- [Claim 42] The pharmaceutical composition according to any one of claims 1 to 3

or 7 to 36, wherein the respiratory inflammation is chronic obstructive pulmonary disease (COPD).

- [Claim 43] A method for treating respiratory distress or respiratory inflammation comprising administering to a subject in need of such treatment a therapeutically effective amount of a pharmaceutical composition comprising a cannabinoid component, wherein the cannabinoid component comprises a cannabidiolic acid (CBDA) ester represented by the structure of Formula (I) alone or in combination with one or more additional cannabinoid compound, and a pharmaceutically acceptable carrier, excipient or diluent, wherein Formula (I), R¹ and R² are as defined in claim 1.
- [Claim 44] The method according to claim 43, wherein the respiratory distress is caused by coronavirus.
- [Claim 45] The method according to claim 43, wherein the respiratory distress is ARDS.
- [Claim 46] The method according to claim 43, wherein the additional cannabinoid compound is present in one or more extracts of a cannabis plant.
- [Claim 47] The method of claim 43, comprising administering by inhalation.
- [Claim 48] The method of claim 43, comprising administering orally, nasally, intravenously, or intramuscularly.
- [Claim 49] The method of claim 43, administered twice a day, once a day, a week, once in two weeks, once in three weeks or once a month.

Statement under Article 19(1)

Claims of International Application No. PCT/IL2021/050518 were amended to better define certain embodiments of the claimed invention as described in the specification as filed. No new matter has been added.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2021/050518

A. CLASSIFICATION OF SUBJECT MATTER IPC (20210101) A61K 31/235, A61P 29/00, A61P 11/00, A61P 31/14 CPC (20130101) A61K 31/235, A61P 29/00, A61P 11/00, A61P 31/14 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) IPC (20210101) A61K 31/235, A61P 29/00, A61P 11/00, A61P 31/14 CPC (20130101) A61K 31/235, A61P 29/00, A61P 11/00, A61P 31/14 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) See extra sheet.		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Takeda S, et al. Cannabidiolic acid as a selective cyclooxygenase-2 inhibitory component in cannabis. Drug metabolism and disposition. 2008 Sep 1; 36(9):1917-21. Retrieved from the Google Scholar. 01 Sep 2008 (2008/09/01) The whole document.	1-49
Y		4-6,37-42,44,45
Y	Roh GS, et al. Anti-inflammatory effects of celecoxib in rat lungs with smoke-induced emphysema. American journal of physiology-lung cellular and molecular physiology. 2010 August 31; 299(2):L184-91. 31 Aug 2010 (2010/08/31) The whole document	1-49
A	Nichols JM, et al. Immune responses regulated by cannabidiol. Cannabis and cannabinoid research, vol. 5, no 1, 2020. Published Online: 27 Feb 2020. URL: < https://doi.org/10.1089/can.2018.0073 >. 27 Feb 2020 (2020/02/27) The whole document.	1-49
☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "D" document cited by the applicant in the international application "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 23 Jun 2021		Date of mailing of the international search report 23 Jun 2021
Name and mailing address of the ISA: Israel Patent Office Technology Park, Bldg.5, Malcha, Jerusalem, 9695101, Israel Email address: pctoffice@justice.gov.il		Authorized officer GARBER Nathan Telephone No. 972-73-3927258

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2021/050518

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Byrareddy SN, Mohan M. SARS-CoV2 induced respiratory distress: Can cannabinoids be added to anti-viral therapies to reduce lung inflammation? Brain, behavior, and immunity. 87 (2020):120-121. Published online 28 Apr 2020. 28 Apr 2020 (2020/04/28) The whole document.	1-49

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IL2021/050518

B. FIELDS SEARCHED:

* Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Databases consulted: PATENTSCOPE, Google Patents, CAPLUS, REGISTRY, Google Scholar

Search terms used: "Cannabidiolic acid", Cannabidiolic & ester, Cannabidiol, CBDA and ester, cannabinoid, "respiratory distress", inflammation, inflammation & cytokine*, Cannabidiolic & cytokine*, Cannabidiolic & cytokine* and pro*inflamm*, "Cannabidiolic & THC", "Cannabidiolic & Cannabidiol.