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(54) Title: METHOD AND COMPOSITION FOR TREATING CNS DISORDERS

(57) Abstract: Compositions and methods for treating a range of Central Nervous System (CNS) disorders and diseases such as amyloidosis, protein folding diseases, tauopathy, and specifically Alzheimer's Disease and Parkinson's Disease, among others, in humans and in veterinary animals, by administering to a subject in need thereof a formulation comprising of melatonin, curcumin and cannabis, specifically THC alone or with CBD.

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METHOD AND COMPOSITION FOR TREATING CNS DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] The present application claims priority on prior U.S. Provisional Application S.N. 62/650,942, filed March 30, 2018, which is hereby incorporated herein in its entirety by reference.

[0002] This invention relates to compositions and methods for treating a range of Central Nervous System (CNS) disorders and diseases such as amyloidosis, protein folding diseases, tauopathy, and specifically for example Alzheimer's Disease (AD) and Parkinson's Disease (PD), among others, in humans and animals using a formulation comprising of a combination of a cannabis compound, or compounds, melatonin, and turmeric.

BACKGROUND
ALZHEIMER'S DISEASE (AD)

[0003] About 45 million suffer from Alzheimer's Disease ("AD") worldwide. The estimated economic burden in 2017 was over $200 billion for AD related services. By 2050, an estimated 11 to 16 million Americans will be living with the disease. Several clinical trials had indicated that combination therapy has greater efficacy over monotherapy. (Alzheimer's, Assn, 2012 Alzheimer's disease facts and figures. Alzheimer's Dement. 2012; 8: 131-168; Brookmeyer, et al, Forecasting the global burden of Alzheimer's disease. Alzheimer's Dement. 2007; 3: 186-191; Schitt et al, CNS Drugs 2004;18:827- 844).

[0004] AD poses an enormous burden on caregivers, as well as the health care system. About 30 percent of the cost of treating AD is the cost of care givers. Currently, there is no cure for AD. (Saxena, Bioenergetics breakdown in Alzheimer's disease: Targets for new therapies. Int J Physiol Pathophysiol Pharmacol. 2011; 3: 133-139; Götz , et al., Modes of Aβ toxicity in Alzheimer's disease. Cell Mol Life Sci. 2011; 68: 3359-3375).

[0005] AD pathology can be grouped into two forms, familial inherited AD, and sporadic AD. The pathologies of early onset familial AD and late onset sporadic AD are indistinguishable. The two forms of AD are characterized by extracellular amyloid-β (Aβ) peptide plaque deposits, and by tau-containing neurofibrillary tangles (Götz, et al., Modes of Aβ toxicity in Alzheimer's disease. Cell Mol Life Sci. 2011; 68: 3359-3375).

[0006] The misfolded structure of the Aβ peptides, alongside with neurofibrillary tangles, makes a characteristic tendency for their aggregation around damaged or dead neurons and within cerebral vasculature in the brain. It establishes by memory loss followed by advanced AD. (Chiti & Dobson, Protein misfolding, functional amyloid, and human disease. Annu Rev Biochem. 2006; 75: 333-366).

[0007] It has long been agreed that Aβ1–40 (Aβ40) and Aβ1–42 (Aβ42) aggregates are the constituents of the insoluble plaques that are characteristic of AD. This disease is also accompanied with neuro-inflammation, excitotoxicity, and oxidative stress. (Campbell & Gowran, Alzheimer's disease; taking the edge off with cannabinoids? Br J Pharmacol. 2007; 152: 655-662; Rich, et al., Nonsteroidal anti-inflammatory drugs in Alzheimer's disease. Neurology. 1995; 45: 51-55). However, the continuous aggregation of Aβ peptides along with hyper-phosphorylation of tau protein inside the cell, producing neurofibrillary tangle formation, are generally recognized as the major etiological factors of the neuronal cell death associated with the evolution of AD (Octave, The amyloid peptide and its precursor in Alzheimer's disease. Rev Neurosci. 1995; 6: 287-316; Reitz, et al., Epidemiology of Alzheimer disease. Nat Rev Neurol. 2011; 7: 137-152; Pillay, et al., Molecular mechanisms, emerging etiological insights and models to test potential therapeutic interventions in Alzheimer's disease. Curr Alzheimer Res. 2004; 1: 295-306).

[0008] The studies show that Aß peptides are neurotoxic, as they are reported intermediaries of apoptosis, inflammation, and oxidative stress. For this purpose, some of the initial proposed therapeutic strategies involve the prevention or elimination of these Aß peptides and following formation of toxic oligomers. Aβ peptides are produced via the amyloidogenic pathway of amyloid precursor protein (APP) proteolysis, which involves the combined effort of ß- and γ-secretases. Initially, ß-secretase (BACE) cleaves APP, creating an Aß-containing carboxyl-

terminal fragment known as ß-C-terminal fragment (β-CTF), or C99 and an amino-terminal, soluble APP-ß (sAPP-ß) fragment, which is released extracellularly. Intracellularly, the ß-CTF fragment is then cleaved by a multiprotein γ-secretase complex, resulting in production of the Aß peptide and a smaller γ-CTF, also known as C57. Aß is known to surge: cellular Ca^{2+}, mitochondrial progression of the disease condition.

[0009] Prior studies have also suggested that glycogen synthase kinase 3 (GSK-3) has a key role in the pathogenesis of both sporadic and familial AD (Hooper, et al., The GSK3 hypothesis of Alzheimer's disease. J Neurochem. 2008; 104: 1433-1439; Proctor & Gray, GSK3 and p53 - is there a link in Alzheimer's disease? Mol Neurodegener. 2010; 5: 7).

[0010] It has been demonstrated that GSK-3β induces hyperphosphorylation of tau. (Lovestone, et al., Alzheimer's disease-like phosphorylation of the microtubule- associated protein tau by glycogen synthase kinase-3 in transfected mammalian cells. Curr Biol. 1994; 4: 1077- 1086;

[0011] Ishiguro, et al., Phosphorylation sites on tau by tau protein kinase I, a bovine derived kinase generating an epitope of paired helical filaments. Neurosci Lett. 1992; 148: 202- 206;

[0012] Hanger, et al., Glycogen synthase kinase-3 induces Alzheimer's disease-like phosphorylation of tau: Generation of paired helical filament epitopes and neuronal localization of the kinase. Neurosci Lett. 1992; 147: 58-62;

[0013] Cho & Johnson, Glycogen synthase kinase 3beta phosphorylates tau at both primed and unprimed sites. Differential impact on microtubule binding. J Biol Chem. 2003; 278: 187-193;

[0014] Asuni, et al., GSK3alpha exhibits beta-catenin and tau directed kinase activities that are modulated by Wnt In. Eur J Neurosci. 2006; 24: 3387-3392).

[0015] Furthermore, over expression of GSK-3 in Tet/GSK-3β mice exhibit pathological symptoms that parallel AD pathology with respect to spatial learning deficits, reactive astrocytosis, increased Aβ production, and plaque associated inflammation, as well as tau hyperphosphorylation resulting in Aβ-mediated neuronal death (Hernandez, et al., GSK3 and tau: Two convergence points in Alzheimer's disease. J Alzheimers Dis. 2013; 33(Suppl 1): S141-S144).

[0016] Moreover, chronic lithium (GSK-3 inhibitor) usage in transgenic mice over expressing GSK-3β and tau has shown to check tau hyperphosphorylation and neurofibrillary tangle formation (Engel, et al., Chronic lithium administration to FTDP-17 tau and GSK- 3beta over expressing mice checks tau hyperphosphorylation and neurofibrillary tangle formation, but pre-formed neurofibrillary tangles do not revert. J Neurochem. 2006; 99: 1445-1455). Some reports have also demonstrated that GSK-3α plays a role in regulating amyloid-β protein precursor (AβPPP) cleavage, resulting in increased Aβ production (Phiel, et al., (2003) GSK-3alpha controls production of Alzheimer's disease amyloid-beta peptides. Nature. 2003; 423: 435-439; Sun, et al., Lithium inhibits amyloid secretion in COS7 cells transfected with amyloid precursor protein C100. Neurosci Lett. 2002; 321: 61-64).

[0017] It has also been discovered that the Aβ load in mouse brain can be strongly decreased by the inhibition of GSK-3β (DaRocha-Souto, et al., Activation of glycogen synthase kinase-3 beta mediates beta-amyloid induced neuritic damage in Alzheimer's disease. Neurobiol Dis. 2012; 45: 425-437).

[0018] Along with prior research suggesting an involvement of GSK-3 in the pathogenesis of AD, there has also been recent studies indicating the intricate participation of the cannabinoid system in AD. It was reported that the cannabinoid system can limit the neurodegenerative processes that drive the progression of the disease, and may provide a new possibility for disease control (Jackson, et al., Cannabinoids and neuroprotection in CNS inflammatory disease. J Neurol Sci. 2005; 233: 21-25).

[0019] Currently, the complete pathway and mechanism of action of the cannabinoid system are not clear, however, studies have been performed to determine the involvement of the cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors in AD brain (Campbell & Gowran, Alzheimer's disease; taking the edge off with cannabinoids? Br J Pharmacol. 2007; 152: 655-662). The CB1 receptor is rich in the brain and contributes to learning, memory, and cognitive processes which are interrupted early in the onset of AD. (Riedel & Davies, Cannabinoid function in learning, memory and plasticity. Handb Exp Pharmacol. 2005; 445-477). While, CB2 receptor expression is more limited and has been anatomically found in neurons within the brainstem (Van Sickle, et al., Identification and functional characterization

of brainstem cannabinoid CB2 receptors. Science. 2005; 310: 329-332), cerebellum (Ashton, et al., Expression of the cannabinoid CB2 receptor in the rat cerebellum: An immunohistochemical study. Neurosci Lett. 2006; 396: 113-116), and microglia (Nunez, et al., Cannabinoid CB2 receptors are expressed by perivascular microglial cells in the human brain: An immunohistochemical study. Synapse. 2004; 53: 208-213).

[0020] Recent research has also examined the propensity of endocannabinoid receptor sub- types 1 (CB1) and 2 (CB2) to elicit a neuroprotective and anti-inflammatory effects on the brain when stimulated by endocannabinoids (Marchalant, et al., Cannabinoids attenuate the effects of aging upon neuroinflammation and neurogenesis. Neurobiol Dis. 2009; 34: 300-307). An increased expression of CB1 and CB2 receptors on microglia within the plaque, while CB1 expression is reduced in neurons more remote from the plaque in the postmortem brains of AD patients (Ramírez, et al., Prevention of Alzheimer's disease pathology by cannabinoids: Neuroprotection mediated by blockade of microglial activation. J Neurosci. 2005; 25: 1904-1913).

[0021] The endocannabinoid metabolizing enzyme, fatty acid amide hydrolase, is upregulated in the plaque in AD brains (Benito, et al., Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. J Neurosci. 2003; 23: 11136-11141). There is also an increase in levels of anandamide metabolites, such as arachidonic acid, in the vicinity of the plaque (Benito, et al., Cannabinoid CB2 receptors and fatty acid amide hydrolase are selectively overexpressed in neuritic plaque-associated glia in Alzheimer's disease brains. J Neurosci. 2003; 23: 11136-11141). These findings may indirectly suggest that the increase in CB1 and CB2 receptors may be to counterbalance the lack of activity with their ligands due to increased metabolic activity of fatty acid amide hydrolase.

[0022] These changes in the cannabinoid system suggest an involvement of endogenous cannabinoids in the pathogenesis of AD or that this system may be altered by the pathophysiology of the disease (Campbell & Gowran, Alzheimer's disease; taking the edge off with cannabinoids? Br J Pharmacol. 2007; 152: 655-662). Understanding that microglial activation is unaffected in all cases of AD, it is

important to identify that endogenous cannabinoids stop Aβ- induced microglial activation both in vitro and in vivo models (Martín-Moreno, et al., Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: Relevance to Alzheimer's disease. Mol Pharmacol. 2011; 79: 964-973). These receptors are known to experience time-dependent and brain region specific changes during neurodegenerative and neuroinflammatory disorders to try to respond excitotoxicity and inflammation (Bisogno & Di Marzo, Cannabinoid receptors and endocannabinoids: Role in neuroinflammatory and neurodegenerative disorders. CNS Neurol Disord Drug Targets. 2010; 9: 564-573).

BACKGROUND: EFFECT OF THC ON AD BIOMARKERS AND SYMPTOMS

[0023] Endocannabinoid receptors, CB1 and CB2, have been confirmed to interact with the endocannabinoid molecules: 2-arachidonoyl glycerol and anandamide. However, it has also been stated that CB1 and CB2 also react interact with Δ^9-tetrahydrocannabinol (THC) an ingredient from the Cannabis sativa plant (Piomelli, The molecular logic of endocannabinoid signaling. Nat Rev Neurosci. 2003; 4: 873-884). Furthermore, early reports show that Dronabinol, an oil-based solution of Δ^9-THC, improves the disturbed behavior and stimulates appetite in AD patients (Volicer, et al., Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. Int J Geriatr Psychiatry. 1997; 12: 913-919). THC possesses antioxidant, anti-inflammatory and neuroprotective properties (Jackson, et al., Cannabinoids and neuroprotection in CNS inflammatory disease. J Neurol Sci. 2005; 233: 21-25).

[0024] In the year 2006, Eubanks and et al, demonstrated that THC competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE induced amyloid beta- peptide (Abeta) aggregation. The concentration of THC used was 50 micromolar at the cellular level (Eubanks Lm, Rogers CJ, Beuscher AE 4^{th}, Koob GF, Olson AJ, Dickerson TJ, Janda KD. A molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharm. 2006 Nov-Dec 3(6): 773-7).

[0025] Several studies have shown that cannabis ingestion, specifically THC, causes acute psychotic reactions, anxiety, impaired neuropsychological performance, impaired memory, executive functioning disorder, mitochondrial dysfunction, neuron apoptosis, and severe side effects such as feeling high, anxiety, depression, among others. (Morrison PD1, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, Kapur S, Murray RM. Morrison PD1, Zois V, McKeown DA, Lee TD, Holt DW, Powell JF, Kapur S, Murray RM. Epub 2009 Apr 1). The acute effects of synthetic intravenous Delta9- tetrahydrocannabinol on psychosis, mood and cognitive functioning.

BACKGROUND: EFFECT OF MELATONIN ON AD BIOMARKERS AND SYMPTOMS

[0026] Melatonin (N-acetyl-5-methoxytryptamine), a tryptophan metabolite and synthesized mainly in the pineal gland and plays an important role in regulation of many physiological functions. This include regulating circadian rhythms, clearing free radicals, improving immunity and generally inhibiting the oxidation of biomolecules. Studies have shown decreased levels of melatonin in serum and cerebrospinal fluid (CSF) of AD patients. (The human pineal gland and melatonin in aging and Alzheimer's disease. J. Pineal Res. 2005;38:145–152; Wu Y.H., Feenstra M.G., Zhou J.N., Liu R.Y., Torano J.S., van Kan H.J., Fischer D.F., Ravid R., Swaab D.F. Molecular changes underlying reduced pineal melatonin levels in Alzheimer's disease: Alterations in preclinical and clinical stages. J. Clin. Endocr. Metab. 2003;88:5898–5906.).

[0027] Clinical studies have indicated that melatonin supplementation has been shown to improve circadian rhythmicity, for example, decreasing agitated behavior, confusion and "sundowning", and to produce beneficial effects on memory in AD patients (Cohen- Mansfield J., Garfinkel D., Lipson S. Melatonin for treatment of sundowning in elderly persons with dementia—A preliminary study. Arch. Gerontol. Geriatr. 2000;31:65–76; Cardinali D.P., Brusco L.I., Perez Lloret S., Furio A.M. Melatonin in sleep disorders and jet-lag. Neuro Endocrinol. Lett. 2002;23:9–13.

[0028] Melatonin supplementation poses low toxicity and may be one of the possible strategies for symptomatic treatment. (Karasek M., Reiter R.J., Cardinali D.P., Pawlikowski M. Future of melatonin as a therapeutic agent. Neuro Endocrinol. Lett. 2002;23:118–121.; 23. Singer C., Tractenberg R.E., Kaye J., Schafer K., Gamst

A., Grundman M., Thomas R., Thal L.J. Alzheimer's disease cooperative, SA multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. Sleep. 2003; 26:893–901.

[0029] Several studies have reported that ingestion of Melatonin has side effects such as causes headache, dizziness, nausea, drowsiness depression, anxiety, tremor, camps, irritability, confusion, hypotension, among others. (Nordlund JJ, Lerner AB. The effects of oral melatonin on skin color and on the release of pituitary hormones. J Clin Endocrinol Metab. 1977; 45: 768-774; 140. Papvasiliou PS, Cotzias GC, Duby SE, Steck AJ, Bell M, Lawrence WH. Melatonin and parkinsonism [letter]. JAMA. 1972; 221: 88).

BACKGROUND: EFFECT OF CURCUMIN ON AD BIOMARKERS AND SYMPTOMS

[0030] Curcumin is a polyphenolic natural compound derived from the root Curcuma longa or turmeric. Several studies have demonstrated that curcumin possess a properties of anti-carcinogenic, anti-inflammatory and anti-oxidative properties (Goel A, Kunnumakkara AB, Aggarwal BB. Curcumin as "Curecumin": from kitchen to clinic. Biochem Pharmacol. 2008 Feb 15; 75(4):787-809). Curcumin has been reported to binds to Aβ protein and prevents the aggregation of Aβ in-vitro studies (Maiti P and Dunbar GL. Use of Curcumin, a Natural Polyphenol for Targeting Molecular Pathways in Treating Age-Related Neurodegenerative Diseases Int J Mol Sci. 2018 May 31; 19(6)). Several pre-clinical studies have reported that curcumin has possess an anti-amyloidogenic property by inhibiting formation of amyloid beta oligomers and fibrils, binds plaques in animal models of AD (Koronyo-Hamaoui M, Koronyo Y, Ljubimov AV, Miller CA, Ko MK, Black KL, Schwartz M, Farkas DL. Identification of amyloid plaques in retinas from Alzheimer's patients and noninvasive in vivo optical imaging of retinal plaques in a mouse model. Neuroimage. 2011 Jan; 54 Suppl 1():S204-17; Maiti P, Hall TC, Paladugu L, Kolli N, Learman C, Rossignol J, Dunbar GL. A comparative study of dietary curcumin, nanocurcumin, and other classical amyloid-binding dyes for labeling and imaging of amyloid plaques in brain tissue of 5×-familial Alzheimer's disease mice. Histochem Cell Biol. 2016 Nov; 146(5):609-625; Maiti P, Paladugu L, Dunbar GL . Solid lipid curcumin particles provide greater anti-amyloid, anti-inflammatory and neuroprotective effects than curcumin in the 5xFAD mouse model of Alzheimer's

disease.BMC Neurosci. 2018 Feb 23; 19(1):7). Curcumin has been shown to binds to neurofibrillary tangles in AD brain tissue (Mohorko N, Repovs G, Popović M, Kovacs GG, Bresjanac M. Curcumin labeling of neuronal fibrillar tau inclusions in human brain samples. J Neuropathol Exp Neurol. 2010 Apr; 69(4):405-14; Mutsuga M, Chambers JK, Uchida K, Tei M, Makibuchi T, Mizorogi T, Takashima A, Nakayama H. of curcumin to senile plaques and cerebral amyloid angiopathy in the aged brain of various animals and to neurofibrillary tangles in Alzheimer's brain. J Vet Med Sci. 2012 Jan; 74(1):51-7)

[0031] Studies have reported that curcumin can decrease the level of Aβ-induced increases in reactive oxygen species, curcumin can also enhance decreases in mitochondrial membrane potential, and activates or inhibits caspase, a protein that is intimately involved in the regulation of apoptosis activation, as well as defend human neurons from oligomeric Aβ induced toxicity (Mishra, et al.,2011) It is also reported that cannabinoids are active against inflammation (Mishra S, Mishra M, Seth P, Sharma SK. Tetrahydrocurcumin confers protection against amyloid β-induced toxicity. Neuroreport. 2011 Jan 5;22(1):23-7).

[0032] A small double-blind, placebo-controlled 18-Month trial reported that daily oral theracurmin (90 mg) treatment lead to improved memory and attention and a reduction in brain amyloid and tau levels in nondemented adults (Small et al., Memory and Brain Amyloid and Tau Effects of a Bioavailable Form of Curcumin in Non-Demented Adults: A Double-Blind, Placebo-Controlled 18-Month Trial, Am J Geriatr Psychiatry. 2018 Mar;26(3):266-277).

[0033] It is well established that AD is complex chronic disease arising from alterations in various signaling pathways. Several hypotheses have been put forward and investigated in AD pathology including beta amyloid pathology, inflammation, neurodegeneration and oxidative stress, hyperphosphorylation of tau, mitochondrial cascade, prion, and so on. Targeting one hypothesis has failed to provide protection against AD. Several studies have demonstrated that monotherapy has limited efficacy ass compared to polytherapy. Polytherapy involves two or more active ingredients which target key signaling pathways.

[0034] Several studies have reported that ingestion of curcumin has side effects such as rash, yellow stool, among others. (Lao C.D., Ruffin M.T., Normolle

D., Heath D.D., Murray S.I., Bailey J.M., Boggs M.E., Crowell J., Rock C.L., Brenner D.E. Dose escalation of a curcuminoid formulation. BMC Complement. Altern. Med. 2006;6: 10 doi: 10.1186/1472- 6882-6-10).

SUMMARY

[0035] The invention provides methods and compositions for treating central nervous system (CNS) disorders in humans and animals which involves treating a patient with a CNS disorder such as Alzheimer's disease or Parkinson's disease with a composition including (i) tetrahydrocannabinol (THC) in a dose amount per 70kg patient of from about 14µg to about 10.0mg, preferably in an ultra-low dose per 70kg patient of from about 14µg to about 2.0mg; (ii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg; and (iii) curcumin in a dose amount per 70kg patient of about 0.35mg to about 500mg.

[0036] In a preferred embodiment, cannabidiol (CBD) in a dose amount per 70kg patient of from about 14µg to about 200mg is administered to a patient along with THC, melatonin and curcumin in the dose amounts specified herein or with THC and melatonin without curcumin. These formulations are preferred for treating Parkinson's disease. In a further embodiment, a composition for treating central nervous system (CNS) disorders in humans and animals includes: (i) tetrahydrocannabinol (THC) in an ultra-low dose amount per 70kg patient of from about 14µg to about 2.0mg; and (ii) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14˜g mg to about 200mg. Another composition for treating central nervous system (CNS) disorders in humans and animals includes: (i) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14˜g mg to about 200mg; and (ii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg. Additional compositions comprise THC or CBD each with curcumin in the dose amounts disclosed herein without melatonin. The compositions and methods for treating central nervous system (CNS) disorders and diseases such as amyloidosis, protein folding diseases, tauopathy, and specifically for example Alzheimer's Disease and Parkinson's Disease among others, in humans and in veterinary animals are effective to reduce Aß expression; reduce Aß aggregation; maintain APP expression; enhance mitochondrial functioning; decrease phosphorylation of GSK3ß protein; decrease the expression of GSK3ß protein; decrease phosphorylation of tau protein;

reduce anxiety; reduce agitation; reduce sleep disorder, and/or reduce care giver distress, without severe side effects associated with high doses of THC, CBD melatonin and /or high doses of curcumin.

[0037] In another preferred embodiment the compositions of the invention are administered orally in a liquid carrier which includes a non-ionic emulsifier in an amount sufficient to maintain stability and solubility of the formulation. Suitable non-ionic emulsifiers include lecithin from soy or sunflower, polysorbate 80) and vitamin E TPGS (d-α-tocopheryl polyethylene glycol 1000 succinate). Natural anti-fungal agents such as rutin are also preferred to maintain stability.

DESCRIPTION

[0038] The invention provides a method and compositions for treating central nervous system (CNS) disorders in humans and animals which involves treating a patient with a CNS disorder such as Alzheimer's or Parkinson's with a composition including (i) tetrahydrocannabinol (THC) in an ultra-low dose amount per 70kg patient of from about 14μg to about 2.0mg without severe psychological impairments and side effects associated with higher doses of THC; (ii) melatonin in a dose amount per 70kg patient of from about 14μg to about 77.0mg; and (iii) curcumin in a dose amount per 70kg patient of about 7mg to about 100mg.

[0039] In a preferred embodiment, cannabidiol (CBD) in a dose amount per 70kg patient of from about 14μg to about 100mg is administered to a patient along with THC, melatonin and curcumin.

[0040] In another preferred embodiment the composition of the invention is administered orally in a liquid carrier which includes a non-ionic emulsifier in an amount sufficient to maintain stability and solubility of the composition components. Suitable non-ionic emulsifiers include lecithin from soy or sunflower, Tween 80 (polysorbate 80), and vitamin E TPGS (d-α-tocopheryl polyethylene glycol 1000 succinate).

[0041] This invention provides a method for treating certain CNS disorders and symptoms, and diseases classified broadly as amyloidosis, protein folding diseases, tauopathy, and specifically for example Alzheimer's Disease (AD), among others, in humans and veterinary animals which includes administering to a subject in need thereof a composition including (i) an effective amount of melatonin, (ii) an

effective amount of curcumin and (iii) a cannabis compound containing THC in a micro dosage amount that is sufficient to provide efficacy while not inducing side effects commonly associated with cannabis, melatonin or curcumin.

[0042] Compositions of the invention for treating Alzheimer's and related CNS diseases in humans and veterinary animals include: (i) an effective amount of melatonin, (ii) an effective amount of curcumin and (iii) a cannabis compound containing THC in an amount that is sufficient to provide efficacy while not inducing side effects commonly associated with cannabis, melatonin or curcumin. The composition is administered orally in a suitable carrier.

[0043] Compositions of the invention for treating Alzheimer's and related CNS diseases in humans and veterinary animals include: (i) an effective amount of melatonin, (ii) an effective amount of curcumin (iii) a cannabis compound containing THC, and (iv) a cannabis compound containing CBD, in an amount that is sufficient to provide efficacy while not inducing side effects commonly associated with cannabis, melatonin or curcumin. The composition is administered orally in a suitable carrier.

[0044] Compositions of the invention for treating Alzheimer's and related CNS diseases in humans and veterinary animals include: (i) an effective amount of melatonin, (ii) an effective amount of curcumin and (iii) a cannabis compound containing CBD, in an amount that is sufficient to provide efficacy while not inducing side effects commonly associated with cannabis, melatonin or curcumin. The composition is administered orally in a suitable carrier.

[0045] Compositions of the invention for treating Alzheimer's and related CNS diseases in humans and veterinary animals include: (i) an effective amount of melatonin, and (ii) an effective amount of curcumin in an amount that is sufficient to provide efficacy while not inducing side effects commonly associated with higher doses of melatonin and curcumin. The composition is administered orally in a suitable carrier.

[0046] Cannabis compounds can be synthetic (chemically synthesized) or extracted from cannabis plants such as sativa, indica, hemp or hybrid strains of sativa and indica. A preferred source of tetrahydrocannabinol (THC) is so-called organic THC, which is extracted from cannabis and contains minor amounts of other

cannabinoids such as CBD. Full spectrum cannabis oil, full spectrum hemp oil and full spectrum marijuana are extracted from hemp

[0047] This invention provides a method for treating certain disorders, symptoms, and diseases classified broadly as amyloidosis, protein folding diseases, tauopathy, and specifically for example Alzheimer's Disease (AD), among others, in mammals by administering to a subject in need thereof a composition including: (i) an effective amount of melatonin, (ii) an effective amount of curcumin and (iii) a cannabis compound in an amount that is sufficient to provide efficacy while not inducing side effects commonly associated with cannabis.

[0048] A preferred 1ml oral suspension for a 70-kg human is administered once a day, twice a day, thrice a day or four times a day depending on the severity of the symptoms and comprises up to 2.5mg of THC, up to 1.5 mg of melatonin, and up to 0.5 mg curcumin.

[0049] A preferred 1ml oral suspension for a 70-kg human is administered once a day, twice a day, thrice a day or four times a day depending on the severity of the symptoms and comprises up to 2.5mg of THC, up to 1.5 mg of melatonin and up to 200mg CBD.

[0050] Dose ranges for the components of the inventive composition follow.

[0051] THC is administered with the other inventive components in dose amounts as follows:

Per kg of patient weight: from about 0.2μg to about 0.14mg

Per 70kg patient: from about 14μg to about 10mg

Preferred per kg of patient weight: from about 0.2μg to about 0.03mg.

Preferred per 70kg patient: from about 14μg to about 2.0mg.

[0052] Melatonin is administered with the other inventive components in dose amounts as follows:

Per kg of patient weight: from about 0.02 mg to about 0.3mg.

Per 70kg patient: from about 1.4mg to about 20mg.

Preferred per kg of patient weight: from about 0.01mg to about 0.15mg.

Preferred per 70kg patient: from about 0.7mg to about 10mg.

[0053] CBD is administered with the other inventive components in dose amounts as follows:

Per kg of patient weight: from about 0.2μg to about 3.0mg.

Per 70kg patient: from about 14μg to about 200mg.

Preferred per kg of patient weight: from about 0.03mg to about 3.0mg.

Preferred per 70kg patient: from about 2.0mg to about 200mg.

Also preferred per kg of patient weight: from about 0.02μg to about 0.036mg.

Also preferred per 70kg patient: from about 14μg to about 2.5mg.

[0054] Curcumin is administered with the other inventive components in dose amounts as follows:

Per kg of patient weight: from about 0.005mg to about 7.0mg.

Per 70kg patient: from about 0.35mg to about 500mg.

Preferred per kg of patient weight: from about 0.01mg to about 3.5mg.

Preferred per 70kg patient: from about 0.7mg to about 250mg.

[0055] The preferred oral dose is in the range of 1 ml of an oral suspension, for a 70-Kg human, once a day, twice a day, thrice a day or four times a day depending on the severity of the symptoms comprising of a cannabis compound with up to 2.5mg of THC, but less than the amount which causes psychological impairments and side effects associated with higher doses of THC, up to 1.5 mg of melatonin, and up to 0.5 mg curcumin.

[0056] A preferred 1ml oral suspension, for a 70-Kg human, once a day, twice a day, thrice a day or four times a day depending on the severity of the symptoms comprises THC in the range from about 14μg to about 10mg, melatonin in the range from about 0.02 mg to about 0.3mg, curcumin in the range from about 0.35mg to about 500mg and CBD in the range from about 14μg to about 200mg, but with THC, less than the amount which causes psychological impairments and side effects associated with higher doses of THC, melatonin, curcumin and CBD.

[0057] The preferred oral dose is in the range of 1 ml of an oral suspension, for a 70-Kg human, once a day, twice a day, thrice a day or four times a day depending on the severity of the symptoms comprising of THC in the range shown in Table 1, CBD in the range shown in Table 1 but with THC, less than the amount which causes psychological impairments and side effects associated with higher doses of THC, and CBD.

[0058] The combination of melatonin, curcumin, and cannabis is believed to work along several pathways in controlling various end points and the hallmarks of Alzheimer's Disease as well as diseases classified broadly as amyloidosis, protein folding diseases, and /or tauopathy. It is believed that the dosing in the formulation does not cause any of the side effects commonly associated with cannabis, melatonin or turmeric. The dosing of cannabis prescribed in the formulation herein is below the 5mg levels prescribed by the FDA for Dronabinol and well below the 50 micromolar level used in the Eubanks 2006 study (Eubanks Lm, Rogers CJ, Beuscher AE 4th, Koob GF, Olson AJ, Dickerson TJ, Janda KD. A molecular link between the active component of marijuana and Alzheimer's disease pathology. Mol Pharm. 2006 Nov-Dec 3(6): 773-7). Using time- release formulations for any of the components, can further enhance bioavailability.

[0059] The combination of lower dose of melatonin, curcumin, cannabis compounds unexpectedly leads to (i) a reduction of side effects, such as transient, acute psychotic reactions, anxiety, impaired neuropsychological performance, memory impairments, executive functioning disorder, mitochondrial dysfunction, and (ii) other side effects like headache, dizziness, nausea, drowsiness, depression, anxiety, tremor, camps, irritability, confusion, hypotension, rash, yellow stool, among others, otherwise present with higher doses of melatonin, curcumin and cannabis compounds, or when each of melatonin, curcumin and or cannabis is used alone.

[0060] Suitable pharmaceutically acceptable cannabis compounds include cannabis extract, which includes phytocannabinoids such as tetrahydrocannabinol "THC" (9- Tetrahydrocannabinol (delta-9 THC), 8-tetrahydrocannabinol (Delta -8 THC) and 9-THC Acid), cannabidiol (CBD), other phytocannabinoids such as cannabinol (CBN), cannabichromene (CBC), cannabigerol (CBG) among others, terpenoids and flavonoids. Standardized cannabis extract (SCE) consists of mostly THC, CBD and CBN. Organic THC consists of solvent extracted THC from cannabis with lesser or trace amounts of other cannabinoids and terpenoids. Synthetic or pure THC is free of CBD and other compounds is a preferred cannabis compound.

[0061] THC and CBD can be extracted from a cannabis indica dominant strain using, for example, high pressure and carbon dioxide or ethanol as a solvent in a

1500-20L subcritical/supercritical CO2 system made by Apeks Super Critical Systems, 14381 Blamer Rd., Johnstown, Ohio, 43031.

[0062] The cannabis plant in its natural form contains THCA. The resin called shatter is extracted from the cannabis flower using any of a variety of methods including CO2 extraction as described herein. Shatter is produced using a three-step process: kief separation, extraction, and winterization. Cannabis flower is introduced into a steel tumbler over a mesh sieve with dry ice. Flower is frozen and broken while tumbled with dry ice chunks allowing fine THCA bearing particles (kief) to fall through the sieve. THCA is then extracted from kief using supercritical extraction. A solvent such as CO2 and kief are introduced into a chamber. That sealed chamber is pressurized to approximately 2800psi and heated to 53 degrees C. Supercritical CO2 is then allowed to flow out of the pressurized chamber into a vile at room temperature and pressure (while more CO2 is introduced to maintain pressure in the chamber). As the CO2 vaporizes in the collector vile, it deposits shatter. In the third, optional step, called winterization, the CO2 oil is dissolved in ethanol (3/4ounce shatter dissolved in 400ml ethanol). This mixture is then poured through a filter (such as a coffee filter) frozen for 48 hours, then warmed, filtered again, and then spun with heat to evaporate off the ethanol. The remaining resin contains a combination of THCA, THC and other cannabis compounds. The resin is heated for 60 minutes at 240^0 F. An HPLC test is run to determine the amount of THC and THCA present in the resin. 45 mg of the resin containing 99% THC (as determined by HPLC) is dissolved in 1 ml of ethyl alcohol. The dissolved resin is transferred and mixed with the solution of curcumin-honey-ascorbic acid-melatonin solution. The solution is filtered and sterilized using a 0.2-micron PES Nalgene filtration unit under constant pressure in a sterilized environment. The filtered 30 ml solution is transferred to and stored in an amber glass bottle that is autoclaved in an aseptic condition.

[0063] Animals, especially dogs and cats, can be treated according to the invention. Dosage amounts, and serum levels of drug are the same as disclosed above for human patients.

[0064] The term "about" as used herein is intended to allow for variations in formulations of plus or minus 1μg or 1 mg.

[0065] The transitional term "comprising" is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, un-recited elements or method steps. The transitional phrase "consisting essentially of" is intended to embrace only specified components or ingredients or steps and those that do not materially affect the basic and novel characteristics of the claimed invention. In other words, elements or ingredients which materially affect the essence of the invention are excluded by the phrase consisting essentially of.

Example 1: General Method of Preparation:

[0066] The following example sets out a method for the preparing the formulation. One dose of the liquid formulation is measured at 1 ml, comprising of 70% of water, 20 % honey and 10% ethyl alcohol, 1.5 mg THC, 1.5 mg melatonin, 1mg turmeric, 1mg ascorbic acid as an anti-oxidative agent and 0.1% sodium benzoate as an anti- fungal agent. Food grade, solvents and carriers include among others DMSO and polyethylene glycol. Food grade anti-oxidative agents include among others carotenoids and tocopherols. Food grade agents with anti-fungal properties include flavonoids among others.

[0067] The following is a list of ingredients for making 30ml of the formulation:

Melatonin procured from Bulk Inc: 45 mg.

Curcumin procured from Bulk Inc: 30m.

Ascorbic acid: 30 mg

Ethyl alcohol 200 proof: 3 ml.

Water (USP grade RMBI): 21 ml

Honey (Kirkland – Costco): 6 ml

THC procured as "shatter": 45 mg

Sodium benzoate USP, 33mg

[0068] Weigh 30 mg of curcumin in a digital weighing machine and place it in a glass beaker containing 1 ml ethyl alcohol (200 proof). Add 21 ml of water to the curcumin alcohol mixture. Boil the water and curcumin mixture for 10 minutes on the hot plate and stir the mixture using a magnetic stirrer. After the mixture cools to room temperature, add 6 ml of honey to the curcumin mixture slowly with stirring. Weigh 30 mg of ascorbic acid and add to the curcumin–honey mixture.

Weigh 45 mg of melatonin and dissolve it in a 1 ml of ethyl alcohol. Once melatonin is completely dissolved in alcohol, transfer the melatonin mixture to curcumin-honey-ascorbic solution.

[0069] A further embodiments of Example 1 comprises of replacing turmeric with any of, or a combination of curcumin, nano-curcumin, and turmeric.

Example 2:

[0070] An Alzheimer's patient exhibiting slight anxiety and/or agitation is given 1ml of the formulation set out in Example 1, in the morning on an empty stomach, prior to breakfast, and 1 ml prior to dinner in the evening. The patient exhibits reduced anxiety and agitation.

Example 3:

[0071] An advanced stage Alzheimer's patient exhibiting moderate to severe anxiety, sleep disorder and/or agitation is given 1ml of the formulation three to four times a day, morning afternoon and evening, prior to meals. The patient exhibits reduced anxiety and agitation vastly improving the distress caused to the caregivers.

Example 4:

[0072] The formulation in Example 1, is supplemented with 50 mg of Cannabidiol (CBD) dissolved in 1 ml of ethyl alcohol and added to the overall solution of Example 1. A moderate stage Parkinson's patient exhibiting levodopa induced dyskinesia, stammering, anxiety, gait, sleep disorder and/or agitation is given 1ml of the formulation of Example 4, three to four times a day, morning afternoon and evening, prior to meals. The patient exhibits reduced symptoms.

Example 5:

[0073] The formulation of Example 4, without the THC component, is administered three times a day prior to meals to a moderate stage Parkinson's patient exhibiting levodopa induced dyskinesia, stammering, anxiety, gait, sleep disorder and/or agitation. The patient exhibits reduced symptoms.

Example 6:

[0074] The formulation and dosing in Example 4, is administered to a patient with moderate incontinence, two times a day, morning and evening, prior to meals. The patient exhibits reduced symptoms.

Example 7:

[0075] The formulation and dosing in Example 1, is administered, once a day, twice a day, to an individual exhibiting early signs of Alzheimer's disease, including plaques and tangles, as determined by a PET scan, as a prophylactic. The patient exhibits a slowdown in the buildup of plaques and tangles.

Example 8:

[0076] The formulation and dosing in Example 1, without the THC component is administered to a patient with mild symptoms of Alzheimer's disease two times a day, morning and evening, prior to meals as a prophylactic. The patient exhibits reduced symptoms.

Example 9

[0077] To address the solubility and stability of THC in an alcohol/water mixture, the following active ingredients were combined in 30 ml solution:

Turmeric: 30 mg
Melatonin: 45 mg
THC: 45 mg
Honey: 6ml
Water: 21 ml
Ascorbic acid (THC antioxidant): 30 mg
Rutin (antifungal agent): 33 mg
Ethyl alcohol: 3 ml
Polysorbate-80

[0078] An nonionic emulsifier is preferably added to increase the solubility of THC and other active ingredients in the solution. Nonionic emulsifiers include lecithin from soy and sunflower, polysorbate 80 and vitamin E TPGS (d-α-tocopheryl polyethylene glycol 1000 succinate). Polysorbate 80 is a nonionic surfactant and emulsifier derived from polyethoxylated sorbitan and oleic acid.

[0079] Preferred emulsifiers are from 1-3% poltsorbate-80, 2-5% vitamin E TPGS and a combination of 1% poltsorbate-80 and 1-2.5% Vitamin TPGS.

[0080] Sodium benzoate in Example 1 serves as an antifungal agent and natural antifungal agents such as Rutin are also suitable. Natural antifungal agents

with broad spectrum antifungal properties are more potent and less toxic compared to sodium benzoate.

[0081] Rutin, also called rutoside, quercetin-3-O-rutinoside and sophorin, is a glycoside combining the flavonol quercetin and the disaccharide rutinose. It is a citrus flavonoid found in a wide variety of plants including citrus fruit.

Example 10

[0082] A preferred formulation in a 30 ml solution which maintains THC and the other components in a stable solution is as follows:

Curcumin: 0.05 %

Melatonin: 0.15 %

THC: 0.25 %

Honey: 20 %

Water: 65 to 55%

Ascorbic acid: 1 %

Rutin: 0.05%

Ethyl alcohol: 12%

Polysorbate -80 (1%) and Vitamin E -TPGS (1 to 2.5%).

CBD: 0.25% to 5%

[0083] It is preferred to use 20-30% honey and/or 12% alcohol to increase the solubility of THC. The use of 1% of an antioxidant such as ascorbic acid is also preferred to counter degradation of THC when exposed to atmospheric oxygen.

[0084] While this invention has been described as having preferred sequences, ranges, ratios, steps, order of steps, materials, structures, symbols, indica, sativa, hemp, graphics, color scheme(s), shapes, configurations, features, components, or designs, it is understood that it is capable of further modifications, uses and/or adaptations of the invention following in general the principle of the invention, and including such departures from the present disclosure as those come within the known or customary practice in the art to which the invention pertains, and as may be applied to the central features hereinbefore set forth, and fall within the scope of the invention and of the limits of the claims appended hereto or presented later. The invention, therefore, is not limited to the preferred embodiment(s) shown/described herein.

CLAIMS:

1. Composition for treating central nervous system (CNS) disorders in humans and animals comprising: (i) tetrahydrocannabinol (THC) in a dose amount per 70kg patient of from about 14μg to about 10.0mg; (ii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg; and (iii) curcumin in a dose amount per 70kg patient of about 0.35mg to about 500mg.

2. Composition of claim 1 wherein the dose amount of THC per 70kg patient is of from about 14μg to about 2.0mg.

3. Composition of claim 1 wherein THC is selected from the group of organic THC, synthetic THC, Dronabinol, Δ9-THC, and THC-A.

4. Composition of claim 1 wherein the dose amount of melatonin per 70kg patient is of from about 0.7mg to about 10mg.

5. Composition of claim 1 wherein the dose amount of melatonin per 70kg patient is of from about 14μg to about 1.4mg.

6. Composition of claim 1 which includes cannabidiol (CBD) in a dose amount per 70kg patient of from about 14μg to about 200mg.

7. Composition for treating central nervous system (CNS) disorders in humans and animals comprising: (i) tetrahydrocannabinol (THC) in a dose amount per 70kg patient of from about 14μg to about 10.0mg; (ii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg and (iii) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14~g mg to about 200mg;

8. Composition of claim 1 wherein the curcumin is selected from the group of turmeric, organic turmeric, synthetic curcumin, synthetic turmeric, organic curcumin

and/or curcumin enhanced for better absorption, taste, and/or bioavailability, and mixtures thereof.

9. Composition of claim 1 in liquid carrier including a non-ionic emulsifier in an amount sufficient to maintain stability and solubility of the composition.

10. Composition of claim 9 wherein the non-ionic emulsifier is selected from the group of lecithin from soy or sunflower, polysorbate 80, and vitamin E TPGS (d-α-tocopheryl polyethylene glycol 1000 succinate).

11. Composition for treating central nervous system (CNS) disorders in humans and animals comprising: (i) tetrahydrocannabinol (THC) in an ultra-low dose amount per 70kg patient of from about 14μg to about 2.0mg; and (ii) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14~g mg to about 200mg;

12. Composition for treating central nervous system (CNS) disorders in humans and animals comprising: (i) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14~g mg to about 200mg; and (ii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg and;

13. Composition of claim 1 including an anti-fungal agent.

14. Composition of claim 1 wherein the anti-fungal agent is a natural anti-fungal agent.

15. Method for treating central nervous system (CNS) disorders in humans and animals comprising administering to a patient suffering from a CNS disorder (i) tetrahydrocannabinol (THC) in a dose amount per 70kg patient of from about 14μg to about 10.0mg; (ii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg; and (iii) curcumin in a dose amount per 70kg patient of about 0.35mg to about 500mg.

16. Method of claim 15 wherein cannabidiol (CBD) in a dose amount per 70kg patient of from about 14μg to about 200mg is administered to a patient along with THC, melatonin and curcumin.

17. Method for treating central nervous system (CNS) disorders in humans and animals comprising administering to a patient suffering from a CNS disorder (i) tetrahydrocannabinol (THC) in an ultra-low dose amount per 70kg patient of from about 14μg to about 2.0mg; (ii) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14μg to about 200mg; and (iii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg.

18. Method for treating central nervous system (CNS) disorders in humans and animals comprising administering to a patient suffering from a CNS disorder (i) tetrahydrocannabinol (THC) in an ultra-low dose amount per 70kg patient of from about 14μg to about 2.0mg; and (ii) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14μg to about 200mg.

19. Method for treating central nervous system (CNS) disorders in humans and animals comprising administering to a patient suffering from a CNS disorder (i) cannabidiol (CBD) in a dose amount per 70kg patient of from about 14μg to about 200mg; and (ii) melatonin in a dose amount per 70kg patient of from about 1.4mg to about 20.0mg.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/00014

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/05; A61K 31/137; A61K 31/4045 (2019.01)
CPC - A61K 31/05; A61K 31/137; A61K 31/4045; A61K 31/433; A61K3 1/4409

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)
See Search History Document

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	US 2007/0049576 A1 (BARLOW et al.) 01 March 2007 (01.03.2007); para [0009]-[0010], [0060], [0062], [0104], [0116], [0148], [0151]-[0152], [0217], [0284], [0290], [0297]-[0299]	1-8, 11-12, 15-19 ---------- 9-10, 13-14
Y	US 2016/0081927 A1 (VIRUN INC.) 24 March 2016 (24.03.2016); para [0022], [0077], [0305], [0310], [0319], [0383]	9-10, 13-14
A	US 2011/0257256 A1 (FUCHS et al.) 20 October 2011 (20.10.2011); see entire document	1-19
A	US 2008/0033027 A1 (BASCOMB et al.) 07 February 2008 (07.02.2008); see entire document	1-19

☐ 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
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2019	'14 JUN 2019

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

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