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(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF PSYCHOSES AND PSYCHOTIC DISORDERS

(57) Abstract: Compositions and methods are provided for the treatment of psychological disorders that include psychosis or psychotic events, or abnormal anxiety or depression. The compositions generally comprise at least one serotonergic psychedelic, at least one cannabinoid, at least one terpene, and at least one edible or medicinal mushroom or extract thereof. Methods for optimizing compositions using artificial intelligence algorithms are also provided.



WO 2022/018709 A1

COMPOSITIONS AND METHODS FOR TREATMENT OF PSYCHOSES AND PSYCHOTIC DISORDERS

CROSS-REFERENCE TO RELATED APPLICATIONS

- [1] This claims the benefit of United States Provisional Patent Application No. 63/054,345, filed July 21, 2020, the entirety of which is incorporated herein by reference.

BACKGROUND

Field of the Invention

- [2] This relates generally to compositions and methods useful in the treatment of psychotic disorders, depression, anxiety, and related psychological conditions, and for patients afflicted therewith. More particularly this relates to nutraceutical and/or pharmaceutical compositions comprising serotonergic psychedelics, cannabinoids, terpenes, flavonoids, and/or other botanical extracts useful for treating such conditions.

Description of Related Art

- [3] The serotonergic psychedelic, psilocybin, and its active metabolite, psilocin, have been shown to have strong anti-psychotic effects. Conditions including PTSD, anxiety, addictions / substance abuse disorders, and major depressive disorders. Specific types of depression, such as end of life depression, have also responded favorably to treatment with psychedelics. Some uses of serotonergic psychedelics have been reviewed by Howland. *J. Psychosoc Nurs. Ment. Health. Serv.* (2016) Jul 1;54(7):21-4. [Copy available online at <https://pubmed.ncbi.nlm.nih.gov/27362381/>]. Baat also reviewed therapeutic effects of classic psychedelic drugs. *Ugeskr Laeger* (2017) Sep 11;179(37):V01170005. De Gregorio *et al.* reviewed the pharmacology of psychedelic drugs and their therapeutic potential including their antidepressant and anxiolytic effects in humans. *Prog. Brain Res.* (2018);242:69-96.
- [4] Other serotonergic psychedelic compounds, such as those found in various plants and mushrooms/fungi, have long been used in various religious or sacred practices for producing altered states. These compounds have been studied pharmacologically and there is a general consensus that these compounds

generally interact with serotonin pathways in the nervous system, particularly with the class of 5-HT receptors that recognize serotonin compounds.

- [5] In addition, improper functioning of the endocannabinoid system may serve as a biomarker for psychosis or other undesirable psychological conditions. It is known that the endocannabinoid system (ECS) can be affected by exogenous cannabinoids, including plant-based cannabinoids. A number of researchers have been testing the hypothesis that the activation of the ECS in the periphery is clinically relevant for psychotic illnesses. Cannabinoids such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are major cannabinoids from *Cannabis* spp. *Cannabis* spp. have also been used medicinally for centuries. Their therapeutic value is the subject of many current studies. As more and more minor cannabinoids are discovered, we are continuing to learn more about the range of cannabinoids in plants, and the regulation of the endocannabinoid system in humans. Our understanding of the role and potential therapeutic value of such compounds is ongoing. Thus, the use of exogenous cannabinoids and their ability to regulate (particularly upregulate) the endocannabinoid system as a therapeutic approach is being studied.
- [6] Other compounds such as terpenes, flavonoids and various botanicals are known to provide certain beneficial functions when consumed or administered.
- [7] Psychological disorders including those featuring psychoses or psychotic events as symptoms or underlying cause continue to plague the modern world. Afflicted individuals may have poor cognitive functioning and thus not become, or may cease being, truly productive members of society. Current treatments are not always effective, and patients may resist taking needed medications, or may not strictly adhere to a required dosage regimen, and thus experience relapse. Such resistance may be because of perceived or actual (and well-known) side effects. First- and second-generation treatments for psychosis have known toxicities and /or serious side effects such as drug-induced extrapyramidal effects (e.g. tremors, and similar involuntary / uncontrollable movements, akathisia), weight gain, obesity, cardiovascular and metabolic abnormalities, and the like. Thus, the available treatment cannot be consumed by or administered to all people needing treatment, and /or may not address a particular patient's problems. Moreover, the underlying illness is often refractory.

- [8] Similar concerns about available treatments, side effects, toxicity, and effectiveness exist for psychological conditions that involve abnormal anxiety or depression. The economic impact of these conditions is huge on both the personal level for those directly impacted and on the societal level.
- [9] There is an ongoing need for new treatment compositions and protocols that are useful for a variety of psychological conditions and which provide significant new features and benefits.

SUMMARY

- [10] In a first of the several aspects of this disclosure, the inventor has discovered that certain pharmaceutical and/or nutraceutical compositions generally comprising combinations of serotonergic psychedelics, certain cannabinoids, terpenes, and at least one edible or medicinal mushrooms or an extract or component derived therefrom are particularly useful or effective for treating a range of psychological disorders, particularly those in which psychoses or psychotic events are involved.
- [11] The serotonergic psychedelics generally comprise tryptamine psychedelics or phenylethylamine psychedelics. The cannabinoids can be derived from any *Cannabis* spp. The mushroom or mushroom extract present in the compositions is from any edible or medicinal mushroom species (other than a mushroom species known to contain psychedelics (e.g. 'magic mushrooms')). The compositions optionally include other nutraceutical or botanical compounds to provide additional functionality or support.
- [12] The inventor has surprisingly discovered that a composition comprising one or more serotonergic psychedelics, one or more cannabinoids, one or more terpenes, and at least one edible or medicinal mushroom has many benefits, and the compositions provide certain useful properties, such as effectiveness including over a long period of time, low toxicity, no serious side effects, and good tolerance on the part of a wide range of subjects.
- [13] In another of its several aspects, provided are methods of treating a subject suffering from a psychological disorder. The methods generally comprise a step of administering a therapeutic composition to the subject. The compositions generally comprise one or more serotonergic psychedelics, one or more

cannabinoids, one or more terpenes, and one or more edible or medical mushrooms or and extract, fraction, or isolate thereof. The composition further comprises one or more optional ingredients comprising at least one flavonoid, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or vitamin D or a compound providing a biologically-available form thereof. As above, the psychological disorder comprises a psychosis or psychotic events, or abnormal anxiety or depression.

[14] The disclosure also provides a plurality of dosing regimens that utilize the compositions, with and without serotonergic psychedelics included, on various schedules as dictated by the physiological or psychological health of the subject.

[15] In yet another aspect, methods are provided for optimizing a composition for use in treatment of a subject suffering from a psychological disorder. The methods employ the use of artificial intelligence algorithms, such as classification algorithms, regression algorithms, clustering algorithms, or a combination thereof.

[16] The methods generally comprise:

[17] a) providing data on the therapeutic effect on the psychological disorder of each of:

[18] i) a plurality of serotonergic psychedelics or combinations thereof;

[19] ii) a plurality of cannabinoids or combinations thereof on the psychological disorder;

[20] iii) a plurality of terpenes or combinations thereof;

[21] iv) a plurality of mushroom extracts of components; and optionally,

[22] v) a plurality of combination compositions comprising one or more of serotonergic psychedelics, cannabinoids, terpenes, and mushrooms; and

[23] vi) a plurality of optional ingredients comprising flavonoids, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or vitamin D or a compound providing a biologically-available form thereof, or combinations thereof;

[24] b) using an artificial intelligence algorithm to analyze the data for the serotonergic psychedelics, cannabinoids, terpenes, and mushroom extracts; and

- [25] c) generating one or more base profiles of compositions optimized for therapeutic treatment of the psychological disorder;
- [26] d) optionally, using the artificial intelligence algorithm to analyze the data for the combination compositions and the optional ingredients, and
- [27] e) generating one or more complete profiles of compositions with and without the optional ingredients;
- [28] wherein the psychological disorder comprises a psychosis or psychotic events, or abnormal anxiety or depression; and
- [29] wherein the data are obtained from original experiments or literature review.
- [30] In a final aspect, this disclosure provides methods for treating a psychological disorder in a patient in need thereof. The methods generally comprise the step of administering a composition comprising at least one serotonergic psychedelic in combination with at least one cannabinoid and at least one terpene, and at least one edible or medicinal mushroom or extract thereof. The at least one cannabinoid and at least one terpene can be administered separately from, sequentially to, or simultaneously with the serotonergic psychedelic and edible or medicinal mushroom. And the at least one edible or medicinal mushroom or extract thereof can also be administered separately from, sequentially to, or simultaneously with the serotonergic psychedelic and cannabinoid.
- [31] These and/or further aspects, features, and advantages of the present invention will become apparent to those skilled in the art in view of this disclosure.

BRIEF DESCRIPTION OF THE DRAWINGS

DETAILED DESCRIPTION

- [32] Provided herein are compositions and methods for treating psychological disorders that include psychoses, psychotic events, abnormal anxiety, or abnormal depression.
- [33] The compositions provide the benefits of certain compounds, serotonergic psychedelics, used for centuries by indigenous peoples and religious practitioners for their ability to produce altered states of consciousness, with the

positive benefits of another natural substance, cannabis, also used for centuries. The compositions further utilize certain beneficial edible or medicinal mushrooms, and other nutraceutical or pharmaceutical compounds. Used properly, these compositions have little risk, few side effects, and are effective for producing measurable and lasting results in patients suffering from such psychological disorders.

Definitions & Abbreviations

- [34] Unless expressly defined otherwise, all technical and scientific terms, terms of art, and acronyms used herein have the meanings commonly understood by one of ordinary skill in the art in the field(s) of the invention, or in the field(s) where the term is used. In accordance with this description, the following abbreviations and definitions apply.
- [35] The terms “anxiety” and “stress” as used herein are related terms. Stress is an unavoidable part of life and includes internal and/or external stimuli (stressors) which can impact individuals positively or negatively. Positive stress generally requires that a positive stressor manifests moderately and for a limited period of time. Negative stress can become anxiety for example when high levels of stress, which are perceived to have negative consequences are experienced over a prolonged periods of time. Statistics suggest that 10 – 30% of primary care patients suffer from anxiety disorders. Women, particularly those between 40-55 years, are more likely to experience problematic anxiety. A degree of anxiety is always present in everyday life and for most people most of the time, it does not interfere with the enjoyment or quality of life of the person or subject, and does not result in seeking or requiring medical or psychological help. Such anxiety is considered normal and may be associated with feelings of depression, frustration, anger, fear, or sadness. As used herein “abnormal anxiety” is anxiety that is present in a subject to an extent where the subject seeks or requires medical or psychological help, is unable to perform the tasks of everyday life, or whose enjoyment of or quality of life is diminished because of the anxiety they are experiencing. Abnormal anxiety can be determined by any qualified medical or psychological professional, by self-reporting, or by use of standardized

assessments instruments, inventories, or scales. "Abnormal anxiety" is not absolute, but rather, an amount that is 'abnormal' for a specific individual.

[36] "Depression", like 'anxiety' can be normal wherein it does not rise to the level of interfering with one's enjoyment or quality of life, and does not result in and "abnormal depression. Types of disorders the compositions and methods disclosed here are useful for include, in addition to psychotic disorders, disorders that entail abnormal anxiety or depression such as major depressive disorders, post-traumatic stress disorder, addictions and substance abuse disorders (including alcoholism, opiate and other drug additions, behavioral addictions), end-of-life depression, and the like.

[37] "Serotonergic psychedelics" as used herein mean any of the family of compounds that interact with serotonin pathways in the nervous system, particularly with the class of 5-HT receptors that recognize serotonin compounds, and which produce hallucinogenic effects in a subject. Serotonergic psychedelics useful herein include both tryptamine derivative and analogues and phenylethylamine derivatives and analogues, with affinity or avidity for any of the 5-HT receptors. Serotonergic psychedelics can be naturally occurring or synthetically produced.

[38] "*Cannabis*" or "*Cannabis spp.*" as used herein refers to any plant of the genus *Cannabis*, including plants that may be classified as *Cannabis sativa*, *Cannabis indica*, or *Cannabis ruderalis*. It is well-known that despite the foregoing list, some experts believe that there are only 2 species, and still others consider that there is only a single species (generally, *C. sativa*). Whatever nomenclature is used, for purposes of this disclosure, "*Cannabis*" includes all possible members of the genus, without regard to the species to which they are assigned.

[39] As used herein 'cannabinoids' means any of a class of compounds that generally can interact with one or more cannabinoid receptors, including the receptors of the endocannabinoid system, in particular, CB1 and CB2. Cannabinoids include e.g., phytocannabinoids and synthetic cannabinoids. Phytocannabinoids are found in several plant species, especially *Cannabis spp.* Among the most prevalent and most studied cannabinoids are tetrahydrocannabinol (THC), and cannabidiol (CBD). However, there are at least ~120 known cannabinoids that have been identified in *Cannabis* within certain

classes including the tetrahydrocannabinols, cannabidiols, cannabigerols, cannabinols, cannabichromenes, and cannabinodiol. Other cannabinoids, such as cannabicyclol, cannabielsoin, cannabitrinol are currently classed as 'miscellaneous' by some researchers. THC is not only a major cannabinoid in *Cannabis* spp., it is generally the compound responsible for the psychoactive effects of consuming *Cannabis*. However, other cannabinoids, such as cannabinol may also be at least mildly psychoactive. Certain other cannabinoids such as CBD may help regulate or attenuate the psychoactive effects of other cannabinoids. For purposes herein, compositions may be created with various ratios of cannabinoids, such as the ratio of CBD to THC or other ratios depending the specific person or the specific condition being treated.

- [40] As used herein, "terpenes" means any of the organic compounds commonly known as terpenes or terpenoids. Terpenes are generally aromatic compounds classified as isoprene derivatives. Terpenes suitable for use herein include hemiterpenes, monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, sesquaterpenes, tetraterpenes, polyterpenes, and norisoprenoids. Exemplary terpenes that are particularly useful herein include alpha bisabolol, alpha pinene, beta caryophyllene, beta pinene, borneol, camphor, camphene, caryophyllene oxide, cineole, delta-3 carene, eucalyptol, farnesenes, farnesol, fenchol, fenchone, geraniol, guaial, humulene, isopulegol, limonene, linalool, menthol, myrcene, nerol, nerolidol, ocimene, pinene, phytol, pulegone, terpinene, terpineol, terpinolene, and valencene.
- [41] As the skilled artisan will appreciate, as used herein the term "edible" does not mean merely capable of being eaten. In that overly broad sense, even poisonous or toxic mushrooms are 'edible' however lethal or sickening or the like. In contrast "edible mushrooms" is used herein in the sense of mushrooms that are used traditionally or in modern times as sources of food, nutrients, nutraceuticals, flavors, and the like. Edible mushrooms are not toxic or poisonous as consumed.
- [42] "Medicinal mushrooms" as used herein means any mushroom species that has been used traditionally or in modern times as a source of medicinal or therapeutic benefits, healing properties, or the like.

- [43] Generally, mushrooms are grouped together as 'edible or medicinal' as there may be many crossovers and it may be difficult to clearly distinguish between the two groups. Examples of edible and/or medicinal mushrooms useful herein include Reishi mushroom (*Ganoderma lucidum*), Lion's Mane (*Hericium erinaceus*), and Cordyceps. More generally edible and/or medicinal mushrooms of the genera *Ganoderma*, *Hericium*, or *Cordyceps* are all suitable for use herein.
- [44] Reishi mushrooms have been reported to calm the central nervous system and/or have neuroprotective effect, and stimulate the immune system. Reishi has been reported to have a beneficial effect on the adrenals, and to be anxiolytic, reducing anxiety and promoting sleep. Reishi has also been associated with improved memory, and sharpened concentration and focus. Lion's Mane reportedly calms mental activity and modulates certain neurotransmitters. Cordyceps has been reported to have adaptogenic properties and stimulate the adrenals glands and modulates the nervous system.
- [45] As used herein, "flavonoids" includes any of the class of polyphenolic molecules containing 15 carbon atoms that are naturally produced in plants and are soluble in water. Also included herein as "flavonoids" are natural or synthetic derivative or analogs thereof that have biological activity. Flavonoids of use herein can generally be divided in to 6 groups of structurally-related compounds: chalcones, flavones, isoflavonoids, flavanones, anthoxanthins and anthocyanins. Also useful are flavanols and catechins, as well as glucosides or other derivatives or analogs of any of the foregoing. The flavonoids are found in most fruits and vegetables, particular colorful ones. They are also prevalent in legumes (including soybeans), grains, green and black teas, as well as red wine.
- [46] Flavonoids have numerous functions in plants, and act as important cell messengers. Various flavonoids are believed to provide healthful benefits and functions to humans such as anti-viral, anti-cancer, anti-inflammatory, anti-allergic, and anti-oxidant properties. They may also be cardio-protective, cholesterol-lowering, and anti-atherosclerotic. Flavonoids from any source may be used herein. Flavonoids isolated from *Cannabis*, such as cannaflavins A, B, and or C, are of interest in certain applications, as are vitexin, isovitexin, apigenin, kaempferol, quercetin, orientin, and luteolin, as well as the catechins found in *Cannabis*.

- [47] As used herein, the singular form of a word includes the plural, and vice versa, unless the context clearly dictates otherwise. Thus, the references “a”, “an”, and “the” are generally inclusive of the plurals of the respective terms. For example, reference to “a composition” or “a serotonergic psychedelic” includes a plurality of such “compositions” or “serotonergic psychedelic.”
- [48] The words “comprise”, “comprises”, and “comprising” are to be interpreted inclusively rather than exclusively. Likewise, the terms “include”, “including” and “or” should all be construed to be inclusive, unless such a construction is clearly prohibited from the context. Further, forms of the terms “comprising” or “including” are intended to include embodiments encompassed by the phrases “consisting essentially of” and “consisting of”. Similarly, the phrase “consisting essentially of” is intended to include embodiments encompassed by the phrase “consisting of”.
- [49] Where used herein, ranges are provided in shorthand, so as to avoid having to list and describe each and every value within the range. Any appropriate value within the range can be selected, where appropriate, as the upper value, lower value, or the terminus of the range.
- [50] The methods and devices and/or other advances disclosed here are not limited to particular methodology, protocols, and/or structures described herein because, as the skilled artisan will appreciate, they may vary. Further, the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to, and does not, limit the scope of that which is disclosed or claimed.
- [51] Although any devices, methods, articles of manufacture, or other means or materials similar or equivalent to those described herein can be used in the practice of the present invention, the preferred compositions, methods, articles of manufacture, or other means or materials are described herein.
- [52] All patents, patent applications, publications, technical and/or scholarly articles, and other references cited or referred to herein are in their entirety incorporated herein by reference to the extent permitted under applicable law. Any discussion of those references is intended merely to summarize the assertions made therein. No admission is made that any such patents, patent applications, publications or references are prior art, or that any portion thereof is

either relevant or material to the patentability of what is claimed herein. Applicant specifically reserves the right to challenge the accuracy and pertinence of any assertion that such patents, patent applications, publications, and other references are prior art, or are relevant, and /or material.

Abbreviations

[53] The following abbreviations apply unless indicated otherwise:

APM:	“Apollon Medical” strain of <i>C. sativa</i>
CBD:	cannabidiol;
CBG:	cannabigerol;
CBN:	cannabinol;
DMT:	N,N-Dimethyltryptamine;
DOI:	1-(2,5-dimethoxy-4-iodophenyl-2-aminopropane;
ECS:	endocannabinoid system;
5-HT:	5-hydroxytryptamine;
KNN:	K Nearest Neighbor;
LSD:	lysergic acid diethylamide;
OCD:	obsessive compulsive disorder;
SVM:	Support Vector Machines;
THC:	tetrahydrocannabinol;

Detailed Description of Illustrative Embodiments

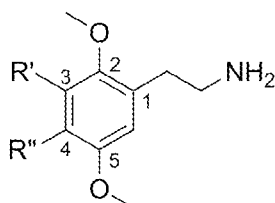
[54] In a first of its several aspects, compositions comprising one or more serotonergic psychedelics are provided. The compositions further comprise one or more cannabinoids, one or more terpenes, and one or more edible or medicinal mushrooms or an extract, fraction, or isolate thereof.

[55] The serotonergic psychedelics useful herein include but are not limited to tryptamine psychedelics, phenylethylamine psychedelics, or any combination thereof. Tryptamine psychedelics such as N,N-dimethyltryptamine (DMT) and psilocybin as both suitable for use, as are any serotonergic metabolites, derivatives, or analogs thereof. Phenylethylamine psychedelics suitable for use

herein include but are not limited to LSD, mescaline, 2c psychedelics, or DOI, or any serotonergic metabolites, derivatives, or analogs thereof.

[56] The class of 2c psychedelics useful herein generally have the structure:

[57]



[58] wherein:

[59] R' is hydrogen, chlorine, methyl, or not present;

[60] and R'' is bromine, benzyl, butyl, chlorine, cyano, cyclopropane, methyl, ethyl, fluoroethyl, fluorine, iodine, propyl, nitro, pyrrolidine, piperidine, methoxy, alkoxy, methoxy propyl, phenyl, SeCH_3 , SCH_3 , SCH_2CH_3 , $\text{SCH}(\text{CH}_3)_2$, $\text{S}(\text{CH}_2)_2\text{CH}_3$, $\text{SCH}_2\text{CH}(\text{CH}_2)_2$, $\text{S}(\text{CH}_2)_2\text{OCH}_3$, $\text{SCH}(\text{CH}_2)_2$, $\text{SCH}_2\text{CH}=\text{CH}_2$, $\text{SCH}(\text{CH}_3)\text{CH}_2\text{CH}_3$, $\text{SCH}_2\text{CH}_2\text{CH}_2\text{CH}_3$, $\text{S}(\text{CH}_2)_2\text{F}$, CHF_2 , CF_3 , CH_2CF_3 , $\text{C}\equiv\text{CH}$, $\text{CH}=\text{CH}_2$, $\text{CH}=\text{CH}_2$, or not present;

[61] or wherein R' and R'' share CH_2 , $(\text{CH}_2)_3$, $(\text{CH}_2)_4$, $(\text{CH}_2)_5$, or $(\text{CH}_2)_6$.

[62] In various embodiments, the serotonergic psychedelics used in the compositions are agonists of one or more 5-HT receptors, such as 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C} receptors.

[63] It is generally believed that hallucinogens activate 5-HT_{2A} receptor-regulated signaling pathways on cortical pyramidal neurons. Without limiting the invention to any particular theory of operation, the behavioral response of diverse 5-HT_{2A} agonists is believed to be highly relevant to the development of more specific therapeutic treatments and neuropharmacological drugs, such as those provided herein.

[64] Hallucinogens may serve as therapeutic treatments severe psychiatric disorders such as psychoses, anxiety, addictions (e.g. alcoholism), OCD, and cluster headache. However, the inventor has discovered that by providing serotonergic psychedelics with additional compounds such as cannabinoids,

terpenes, mushroom extracts, and such, more benefits can be derived from the treatments with better outcomes and fewer side effects.

- [65] Thus, in various embodiments, the compositions comprise one or more serotonergic psychedelics and cannabinoids comprising one or more of cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), or tetrahydrocannabinol (THC).
- [66] In certain embodiments, the cannabinoids are derived from hemp, or the THC content is removed from the cannabinoids such that THC is present in the composition at less than about 0.3 percent. In various embodiments, the THC content may be less than 0.2, or even less than 0.1% of the composition.
- [67] In other embodiments, the ratio of cannabinoids is set in the compositions. For example, in certain embodiments, the ratio of CBD to THC ranges from about 1:5 to about 30:1 or more. In other embodiments the ratio may range from about 1:2 to about 10:1. In still other embodiments, the ratio of CBD to THC may be about 1:1 to 5:1. In other cases, the ratio of e.g. CBD to CBG or CBN may be set based on any of a variety of factors, including the health status of the subject being treated, the symptoms of the subject, the condition(s) being treated, and or one or more physiological or genetic criteria.
- [68] In certain embodiments the compositions may be provided in completely customized or personalized formulations for each person being treated – i.e. as personalized medicines. In such cases, the compositions may be adjusted based on initial or subsequent blood work, enzyme test results, bioinformatic data (including measurements of e.g. the genome, transcriptome, proteome, metabolome, or any portion thereof, for a subject), specific symptomology, or the like. The formulation of the compositions may also be changed based on the results from an initial treatment, subsequent treatment, or based on subsequent tests.
- [69] In various presently preferred embodiments, the cannabinoids are derived from *Cannabis* spp. or an extract thereof. *Cannabis* can generally be concentrated or extracted (e.g. via mechanical or chemical means) to obtain cannabinoids. Mechanical means of extracting oils from plants, such as pressing, have been used for centuries, and may be suitable for use herein. Extraction via chemical means includes extraction with various volatile solvents that range from

hydrocarbon solvents such as butane, hexanes or propane, to supercritical fluids, alcohol, steam, or even water. Two very common methods are extraction with supercritical carbon dioxide, or ethanol, both of which are particularly useful herein.

- [70] In various embodiments, cannabinoids present in an ethanolic extract or supercritical CO₂ extract of *Cannabis sativa* are preferred for use herein. The extract comprises one or more of Ringo's Gift, Harle Tsu, ACDC, Charlotte's Web, The Gift, or Pineberry strains of *Cannabis sativa*. "Apollon Medical" ("APM"), a proprietary strain commercially available from Apollon Formularies, is also useful herein.
- [71] The composition in various embodiments include terpenes comprising one or more monoterpenes, one or more sesquiterpenes, or a combination thereof. The terpenes comprise one or more of alpha bisabolol, alpha pinene, beta caryophyllene, beta pinene, borneol, camphor, camphene, caryophyllene oxide, cineole, delta-3 carene, eucalyptol, farnesenes, farnesol, fenchol, fenchone, geraniol, guaialol, humulene, isopulegol, limonene, linalool, menthol, myrcene, nerol, nerolidol, ocimene, pinene, phytol, pulegone, terpinene, terpineol, terpinolene, or valencene.
- [72] In one embodiment, the terpenes preferably comprise one or more of limonene, myrcene, beta-caryophyllene, linalool, alpha pinene, or a combination thereof.
- [73] In presently preferred embodiments, the terpenes are derived from *Cannabis* spp. or an extract thereof. The terpenes can be derived from any source and in certain embodiments, they can be present in steam distillate or an ethanolic extract of *Cannabis sativa*.
- [74] The compositions in certain embodiments include extracts of *Cannabis* spp, such as *C. sativa* as a source of cannabinoids and/or terpenes. In various embodiments, the *C. sativa* comprises one or more of Ringo's Gift, Harle Tsu, ACDC, Charlotte's Web, The Gift, or Pineberry strains. In other embodiments, the *C. sativa* comprises the proprietary strain, APM, commercially-available from Apollon Formularies.
- [75] In various embodiments, the edible or medicinal mushroom comprises a species from the genus *Ganoderma*, the genus *Hericium*, or the genus *Cordyceps*.

- [76] These mushrooms are well-known edible and/or medicinal mushrooms with a long history of use. Without limiting the invention to any particular theory of operation, mushrooms, such as Reishi mushrooms, Lion's Mane, or Cordyceps contain hundreds of beneficial polysaccharide compounds (e.g. the long-chain sugars in mushroom cell-walls) and terpenes that are believed to have multiple beneficial neuropharmacological effects including on anxiety, mood, certain psychological disorders, and even seizures.
- [77] Examples of the beneficial effects are many. Certain mushroom polysaccharides have been proposed to improve cognitive dysfunction *in vivo*. These mushroom polysaccharides have shown a protective effect on neurons – protecting them from apoptosis (cell death), and oxidative stress. The polysaccharides and triterpene compounds, for example, in Reishi mushroom both exhibit significant neuroprotective effects against stress. The polysaccharide content in Reishi mushroom, particularly the beta-1,3 D-glucan, has been shown to up-regulate the production of certain lymphocytes, T-helper cells, T-killer cells, and macrophages. The same glycan has also been shown to be involved with suppressing tumor necrosis factor (TNF- α).
- [78] The active triterpenes found in certain medicinal mushrooms stimulate the production of nerve growth factor (NGF). NGF is required by the brain and important sensory neurons to keep the entire nervous system strong and healthy. The active constituents of various mushrooms also have potent effects on the induction of NGF in primary astrocytes. enhanced mitochondrial biogenesis in the brain.
- [79] Regardless of the mechanism(s) responsible, the compositions preferably comprise the benefits of such edible or medicinal mushroom(s) as *Ganoderma lucidum*, *Hericium erinaceus*, *Cordyceps sinensis*, *C. militaris*, *C. liangshanensis*, *C. gunnii*, or *C. cicadicola*.
- [80] The mushrooms can be present in the compositions as fresh mushrooms, as whole or partial mushrooms in lyophilized or dehydrated form, or as an extract or concentrate thereof, including as a hot or cold water extract of the mushroom, a dried powder, a partially purified fraction thereof, or a fully purified compound derived therefrom, or in any other convenient or useful form.

- [81] In various other embodiments, the compositions further comprise one or more additional or optional ingredients comprising at least one flavonoid, S-adenosylmethionine, methylfolate, omega-3 fatty acids, a B vitamin or a compound providing (directly or indirectly) a biologically-available form thereof, or vitamin D or a compound providing (directly or indirectly) a biologically-available form thereof.
- [82] In terms of compounding the compositions, the skilled artisan will appreciate that methods of maximizing the efficacy of the composition such as by enhancing the bioavailability of one or more components, or by providing the components in optimized ratios, for example one component to another with which it interacts, or each component to the others in ratio(s) that optimize the absorption into the gut or bloodstream, or enhance the therapeutic effect of the composition. The skilled artisan will also understand that some information useful in improving the compounding may be obtained empirically.
- [83] In various embodiments, the compositions, or one or more components thereof, may be solubilized, micronized, provided as, for example. extracts, powders, lyophilized powders, concentrates, tinctures, essential oils, aqueous or lipid suspensions, emulsions, microemulsions, or nano-emulsions, or in whole or part as liposomal, vesicular, or other delivery systems. As described below, the compounding or formulation of any of the compositions provided herein may be optimized for the intended delivery route.
- [84] The compositions may be administered and delivered as pharmaceuticals, however, it is also contemplated that one or more of the compositions may be formulated for administration and delivery by oral routes that include as food and beverages, including solid, semisolid, and liquid foods, such as smoothies, shakes, pudding, broths, teas, and soups. The food and or beverage compositions can also include hot, cold, or even frozen foods (such as frozen desserts).
- [85] In another aspect of the disclosure, provided are methods of treating a subject suffering from a psychological disorder. The methods comprise administering to the subject at least one therapeutically effective dose of a composition comprising one or more serotonergic psychedelics, one or more cannabinoids, one or more terpenes, and one or more edible or medical mushrooms or and extract, fraction,

or isolate thereof. Preferably the psychological disorder comprises a psychosis or psychotic events, or abnormal anxiety or depression.

[86] The composition for use in the methods is generally as described above for the first aspect. The description of the compositions above is incorporated by reference herein for purposes of the present methods.

[87] In various embodiments, the compositions for use in the methods further comprise one or more optional ingredients comprising at least one flavonoid, S-adenosylmethionine, methylfolate, omega-3 fatty acids, a B vitamin or a compound providing (directly or indirectly) a biologically-available form thereof, or vitamin D or a compound providing (directly or indirectly) a biologically-available form thereof.

[88] In certain embodiments, the methods further comprise one or more steps of administering an additional therapeutically effective dose of the composition.

[89] Preferably the additional administering steps are performed on a periodic basis of any frequency or schedule. For example, the administration or dosing can conveniently be on e.g. a daily, thrice weekly, twice weekly, weekly, biweekly, monthly, bimonthly, quarterly, semi-annual, or annual basis. The administration need not be the same over every period of time. By way of nonlimiting example, administration could be daily for a week, then weekly for a month. Or the administration could be every 4 months for a year, then every 6 months thereafter. Similarly, the actual amount of the composition or dosage administration can vary. For example, a monthly dosage schedule could feature a dose of x for the first dosage each quarter, and a dose of $0.1x$ for the remaining months in each quarter.

[90] Just as the composition can be 'personalized', so can the administration or dosing schedule. Thus, in various embodiments, the methods further comprise the step of periodically assessing one or more of the subject's medication levels, enzyme levels, psychological status, or other indicators of physiological or psychological health, in order to determine the periodic basis for administration.

[91] The inventor has also surprisingly discovered that the compositions disclosed herein in the first aspect of this disclosure can be formulated without any serotonergic psychedelics to create "modified compositions". These modified compositions are particularly useful in administering to subjects in between

doses of the compositions including the psychedelics. Because some subjects may require very infrequent dosing with the composition including a psychedelic, and because the modified compositions provide numerous benefits to subjects for the disorders, methods for doing so are therefore provided. In certain embodiments, the methods comprise an additional treatment step in between each administering or dosing step using the compositions with a psychedelic. The additional treatment step comprises providing to the subject a composition comprising one or more cannabinoids, one or more terpenes, one or more edible or medical mushrooms or and extract, fraction, or isolate thereof, and optionally, one or more of at least one flavonoid, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or a B vitamin or vitamin D or a compound providing a biologically-available form thereof.

- [92] The methods provide for administration of the compositions via any useful route, including parenteral (intravenous, intra-arterial, intramuscular, intraperitoneal, or subcutaneous), oral, nasal, ocular, transmucosal (buccal, vaginal, or rectal), transdermal, or via inhalation. As discussed above, the compositions may be formulated and optimized for delivery by any means.
- [93] It should be noted that the route of dosing or administration of compositions can vary. For example, administration via one route may be useful when administering a larger dose and a different route may be useful for smaller doses. Or, administration via a particular route may be appropriate initially, with subsequent doses conveniently administered through another route.
- [94] The skilled artisan will appreciate that the methods are flexible as set forth herein, an aspect which is particularly useful given the varied and nature of the psychological disorders which they are intended to treat.
- [95] In yet another aspect of the disclosure, methods of optimizing a composition for use in treatment of a subject suffering from a psychological disorder using artificial intelligence are provided herein. The methods generally comprise, for a psychological disorder of interest, or for a subject in need of therapeutic compositions for such disorder:
- [96] a) providing data on the therapeutic effect on the psychological disorder of each of:
- [97] i) a plurality of serotonergic psychedelics or combinations thereof;

- [98] ii) a plurality of cannabinoids or combinations thereof on the psychological disorder;
- [99] iii) a plurality of terpenes or combinations thereof;
- [100] iv) a plurality of mushroom extracts of components; and optionally,
- [101] v) a plurality of combination compositions comprising one or more of serotonergic psychedelics, cannabinoids, terpenes, and mushrooms; and
- [102] vi) a plurality of optional ingredients comprising flavonoids, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or a B vitamin or vitamin D or a compound providing a biologically-available form thereof, or combinations thereof;
- [103] b) using an artificial intelligence algorithm to analyze the data for the serotonergic psychedelics, cannabinoids, terpenes, and mushroom extracts; and
- [104] c) generating one or more base profiles of compositions optimized for therapeutic treatment of the psychological disorder;
- [105] d) optionally, using the artificial intelligence algorithm to analyze the data for the combination compositions and the optional ingredients, and
- [106] e) generating one or more complete profiles of compositions with and without the optional ingredients.
- [107] In certain embodiments, the psychological disorder comprises a psychosis or psychotic events, or abnormal anxiety or depression. Generally, the data for the method are obtained from original experiments and/or reviews of the relevant scientific literature.
- [108] The artificial intelligence algorithm can comprise any useful software or algorithm approach capable of making the distinctions required. In various embodiments, the algorithm comprises a classification algorithm, a regression algorithm, a clustering algorithm, or a combination thereof.
- [109] In one embodiment, the methods comprise a classification algorithm that is a naïve Bayes algorithm, decision tree, random forest algorithm, Support Vector Machines, or K Nearest Neighbor algorithm.
- [110] In another embodiment, the methods comprise a regression algorithm that is a liner regression, lasso regression, logistic regression, or multivariate regression.

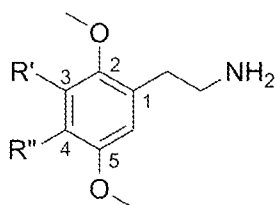
- [111] In yet another embodiment, the methods comprise a clustering algorithm that is a K-means clustering, fuzzy C-means algorithm, expectation-maximization algorithm, or hierarchical clustering algorithm.
- [112] The skilled artisan will appreciate that the methods are designed to optimize the compositions, and that such optimization as set forth above can be with respect to each particular disorder. However, the compositions can also be optimized for, and a profile of relevant compositions generated for each particular subject, e.g. for a 'personalized medicine' approach.
- [113] Thus, also provided herein are the methods comprising the additional step of providing subject-specific data comprising, e.g. initial or subsequent blood work, enzyme test results, bioinformatic data (including measurements of e.g. the genome, transcriptome, proteome, metabolome, or any portion thereof, for a subject), specific symptomology, or the like. The artificial intelligence algorithm is then used to further optimize the composition based on those data in addition to the disorder-specific data. The optimized formulation of the compositions may also be changed based on data from the results from an initial treatment, subsequent treatment, or based on subsequent tests of the subject.
- [114] A further aspect of the invention provides methods for the treatment of a psychological disorder comprising the step of administering to a patient in need thereof a composition comprising at least one serotonergic psychedelic in combination with at least one cannabinoid and at least one terpene, and at least one edible or medicinal mushroom or extract thereof. wherein the at least one cannabinoid and at least one terpene is administered separately from, sequentially to, or simultaneously with the serotonergic psychedelic and edible or medicinal mushroom; and wherein the at least one edible or medicinal mushroom or extract thereof is also administered separately from, sequentially to, or simultaneously with the serotonergic psychedelic and cannabinoid.
- [115] In various embodiments of the methods in connection with this aspect of the disclosure:
- [116] i) the at least one serotonergic psychedelic comprises psilocybin or psilocin, or serotonergic metabolites, derivatives, or analogs thereof;
- [117] ii) the at least one cannabinoid comprises CBD, CBG, CBN, and THC extracted from *Cannabis sativa* Ringo's Gift strain;

- [118] iii) the at least one terpene comprises limonene, myrcene, beta-caryophyllene, linalool, alpha pinene, or a combination thereof; and
- [119] iv) the at least one edible or medicinal mushroom or extract thereof comprises an extract of *Ganoderma lucidum*, *Hericium erinaceus*, *Cordyceps sinensis*, *C. militaris*, *C. liangshanensis*, *C. gunnii*, or *C. cicadicola*.

[120] The scope of the invention is set forth in the claims appended hereto, subject, for example, to the limits of language. Although specific terms are employed to describe the invention, those terms are used in a generic and descriptive sense and not for purposes of limitation. Moreover, while certain presently preferred embodiments of the claimed invention have been described herein, those skilled in the art will appreciate that such embodiments are provided by way of example only. In view of the teachings provided herein, certain variations, modifications, and substitutions will occur to those skilled in the art. It is therefore to be understood that the invention may be practiced otherwise than as specifically described, and such ways of practicing the invention are either within the scope of the claims, or equivalent to that which is claimed, and do not depart from the scope and spirit of the invention as claimed.

WHAT IS CLAIMED IS:

1. A composition comprising one or more serotonergic psychedelics, one or more cannabinoids, one or more terpenes, and one or more edible or medicinal mushrooms or an extract, fraction, or isolate thereof.
2. The composition of claim 1 wherein the serotonergic psychedelics comprise tryptamine psychedelics, phenylethylamine psychedelics, or a combination thereof.
3. The composition of claim 2 wherein the tryptamine psychedelics comprise N,N-dimethyltryptamine (DMT), psilocybin, or serotonergic metabolites, derivatives, or analogs thereof.
4. The composition of claim 2 wherein the phenylethylamine psychedelics comprise LSD, mescaline, 2c psychedelics, DOI, or serotonergic metabolites, derivatives, or analogs thereof.
5. The compositions of claim 4 wherein the 2c psychedelics have the structure:



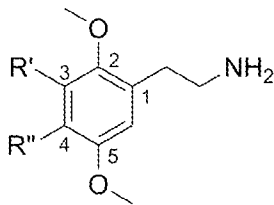
wherein:

R' is hydrogen, chlorine, methyl, or not present;
 and R'' is bromine, benzyl, butyl, chlorine, cyano, cyclopropane, methyl, ethyl, fluoroethyl, fluorine, iodine, propyl, nitro, pyrrolidine, piperidine, methoxy, alkoxy, methoxy propyl, phenyl, SeCH₃, SCH₃, SCH₂CH₃, SCH(CH₃)₂, S(CH₂)₂CH₃, SCH₂CH(CH₂)₂, S(CH₂)₂OCH₃, SCH(CH₂)₂, SCH₂CH=CH₂, SCH(CH₃)CH₂CH₃, SCH₂CH₂CH₂CH₃, S(CH₂)₂F, CHF₂, CF₃, CH₂CF₃, C≡CH, CH=CH₂, CH=CH₂, or not present;
 or wherein R' and R'' share CH₂, (CH₂)₃, (CH₂)₄, (CH₂)₅, or (CH₂)₆.

6. The composition of claim 1 wherein the serotonergic psychedelics are agonists of one or more 5-HT receptors.
7. The composition of claim 6 wherein the 5-HT receptors are 5-HT_{1A}, 5-HT_{2A}, or 5-HT_{2C} receptors.
8. The composition of claim 1 wherein the cannabinoids comprise one or more of cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), or tetrahydrocannabinol (THC).
9. The composition of claim 8 wherein the THC is present at less than about 0.3 percent.
10. The composition of claim 8 wherein the ratio of CBD to THC is about 1:5 to about 30:1 or more.
11. The composition of claim 1 wherein the cannabinoids are derived from *Cannabis* spp. or an extract thereof.
12. The composition of claim 11 wherein the cannabinoids are present in an ethanolic extract of *Cannabis sativa*.
13. The composition of claim 11 wherein the extract comprises one or more of Ringo's Gift, Harle Tsu, ACDC, Charlotte's Web, The Gift, or Pineberry strains of *Cannabis sativa*.
14. The composition of claim 1 wherein the terpenes comprise one or more monoterpenes, one or more sesquiterpenes, or a combination thereof.
15. The composition of claim 14 wherein the terpenes comprise one or more of alpha bisabolol, alpha pinene, beta caryophyllene, beta pinene, borneol, camphor, camphene, caryophyllene oxide, cineole, delta-3 carene, eucalyptol, farnesenes, farnesol, fenchol, fenchone, geraniol, guaial, humulene, isopulegol, limonene, linalool, menthol, myrcene, nerol, nerolidol, ocimene, pinene, phytol, pulegone, terpinene, terpineol, terpinolene, or valencene.
16. The composition of claim 14 wherein the terpenes are derived from *Cannabis* spp. or an extract thereof.
17. The composition of claim 16 wherein the terpenes are present in steam distillate or an ethanolic extract of *Cannabis sativa*.

18. The composition of claim 16 wherein the *Cannabis sativa* comprises one or more of Ringo's Gift, Harle Tsu, ACDC, Charlotte's Web, The Gift, or Pineberry strains.
19. The composition of claim 16 wherein the terpenes comprise limonene, myrcene, beta-caryophyllene, linalool, alpha pinene, or a combination thereof.
20. The composition of claim 1 wherein the edible or medicinal mushroom comprises a species from the genus *Ganoderma*, the genus *Hericium*, or the genus *Cordyceps*.
21. The composition of claim 20 wherein the edible or medicinal mushroom comprises *Ganoderma lucidum*, *Hericium erinaceus*, *Cordyceps sinensis*, *C. militaris*, *C. liangshanensis*, *C. gunnii*, or *C. cicadicola*.
22. The composition of claim 1 further comprising one or more optional ingredients comprising at least one flavonoid, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or vitamin D or a compound providing a biologically-available form thereof.
23. A method of treating a subject suffering from a psychological disorder which comprises administering to the subject a therapeutically effective dose of a composition comprising one or more serotonergic psychedelics, one or more cannabinoids, one or more terpenes, and one or more edible or medical mushrooms or and extract, fraction, or isolate thereof;
- wherein the psychological disorder comprises a psychosis or psychotic events, or abnormal anxiety or depression.
24. The method of claim 23 wherein the composition further comprises one or more optional ingredients comprising at least one flavonoid, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or vitamin D or a compound providing a biologically-available form thereof.
25. The method of claim 23 wherein the serotonergic psychedelics comprise tryptamine psychedelics, phenylethylamine psychedelics, or a combination thereof.

26. The method of claim 25 wherein the tryptamine psychedelics comprise N,N-dimethyltryptamine (DMT), psilocybin, or serotonergic metabolites, derivatives, or analogs thereof.
27. The method of claim 25 wherein the phenylethylamine psychedelics comprise LSD, mescaline, 2c psychedelics, DOI, or serotonergic metabolites, derivatives, or analogs thereof.
28. The method of claim 27 wherein the 2c psychedelics have the structure:



wherein:

R' is hydrogen, chlorine, methyl, or not present;
 and R'' is bromine, benzyl, butyl, chlorine, cyano, cyclopropane, methyl, ethyl, fluoroethyl, fluorine, iodine, propyl, nitro, pyrrolidine, piperidine, methoxy, alkoxy, methoxy propyl, phenyl, SeCH₃, SCH₃, SCH₂CH₃, SCH(CH₃)₂, S(CH₂)₂CH₃, SCH₂CH(CH₂)₂, S(CH₂)₂OCH₃, SCH(CH₂)₂, SCH₂CH=CH₂, SCH(CH₃)CH₂CH₃, SCH₂CH₂CH₂CH₃, S(CH₂)₂F, CHF₂, CF₃, CH₂CF₃, C≡CH, CH=CH₂, CH=CH₂, or not present;
 or wherein R' and R'' share CH₂, (CH₂)₃, (CH₂)₄, (CH₂)₅, or (CH₂)₆.

29. The method of claim 25 wherein the serotonergic psychedelics are agonists of one or more 5-HT receptors.
30. The method of claim 29 wherein the 5-HT receptors are 5-HT_{1A/2A/2C} or 5-HT_{2C} receptors.
31. The method of claim 23 wherein the cannabinoids comprise one or more of cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), or tetrahydrocannabinol (THC).
32. The method of claim 31 wherein the THC is present at less than about 0.3 percent.

33. The method of claim 31 wherein the ratio of CBD to THC is about 1:5 to about 30:1 or more.
34. The method of claim 23 wherein the cannabinoids are derived from *Cannabis* spp. or an extract thereof.
35. The method of claim 34 wherein the cannabinoids are present in an ethanolic extract of *Cannabis sativa*.
36. The method of claim 35 wherein the extract comprises one or more of Ringo's Gift, Harle Tsu, ACDC, Charlotte's Web, The Gift, or Pineberry strains of *Cannabis sativa*.
37. The method of claim 23 wherein the terpenes comprise one or more monoterpenes, one or more sesquiterpenes, or a combination thereof.
38. The method of claim 37 wherein the terpenes comprise one or more of alpha bisabolol, alpha pinene, beta caryophyllene, beta pinene, borneol, camphor, camphene, caryophyllene oxide, cineole, delta-3 carene, eucalyptol, farnesenes, farnesol, fenchol, fenchone, geraniol, guaialol, humulene, isopulegol, limonene, linalool, menthol, myrcene, nerol, nerolidol, ocimene, pinene, phytol, pulegone, terpinene, terpineol, terpinolene, or valencene.
39. The method of claim 23 wherein the terpenes are derived from *Cannabis* spp. or an extract thereof.
40. The method of claim 39 wherein the terpenes are present in steam distillate or an ethanolic extract of *Cannabis sativa*.
41. The method of claim 40 wherein the *Cannabis sativa* comprises one or more of Ringo's Gift, Harle Tsu, ACDC, Charlotte's Web, The Gift, or Pineberry strains.
42. The method of claim 23 wherein the terpenes comprise limonene, myrcene, beta-caryophyllene, linalool, alpha pinene, or a combination thereof.
43. The method of claim 23 wherein the edible or medical mushroom comprises a species from the genus *Ganoderma*, the genus *Hericium*, or the genus *Cordyceps*.

44. The method of claim 43 wherein the edible or medical mushroom comprises *Ganoderma lucidum*, *Hericium erinaceus*, *Cordyceps sinensis*, *C. militaris*, *C. liangshanensis*, *C. gunnii*, or *C. cicadicola*.
45. The method of claim 23 further comprising one or more steps of administering an additional therapeutically effective dose of the composition.
46. The method of claim 45 wherein the one or more steps of administering an additional therapeutically effective dose of the composition are performed on a periodic basis.
47. The method of claim 46 wherein the periodic basis comprises a daily, thrice weekly, twice weekly, weekly, biweekly, monthly, bimonthly, quarterly, semi-annual, or annual basis for administration.
48. The method of claim 46 further comprising the step of periodically assessing one or more of the subject's medication levels, enzyme levels, psychological status, or other indicators of physiological or psychological health, in order to determine the periodic basis for administration.
49. The method of claim 47 further comprising a step of providing to the subject, in between each administering step, a composition comprising one or more cannabinoids, one or more terpenes, one or more edible or medical mushrooms or and extract, fraction, or isolate thereof, and optionally, one or more of at least one flavonoid, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or vitamin D or a compound providing a biologically-available form thereof.
50. The method of claim 23 wherein the dose is administered via a route that is parenteral (intravenous, intra-arterial, intramuscular, intraperitoneal, or subcutaneous), oral, nasal, ocular, transmucosal (buccal, vaginal, or rectal), transdermal, or via inhalation.
51. A method of optimizing a composition for use in treatment of a subject suffering from a psychological disorder using artificial intelligence comprising, for each psychological disorder:
- a) providing data on the therapeutic effect on the psychological disorder of each of:

- i) a plurality of serotonergic psychedelics or combinations thereof;
- ii) a plurality of cannabinoids or combinations thereof on the psychological disorder;
- iii) a plurality of terpenes or combinations thereof;
- iv) a plurality of mushroom extracts of components; and optionally,
- v) a plurality of combination compositions comprising one or more of serotonergic psychedelics, cannabinoids, terpenes, and mushrooms; and
- vi) a plurality of optional ingredients comprising flavonoids, S-adenosylmethionine, methylfolate, omega-3 fatty acids, or vitamin D or a compound providing a biologically-available form thereof, or combinations thereof;
- b) using an artificial intelligence algorithm to analyze the data for the serotonergic psychedelics, cannabinoids, terpenes, and mushroom extracts; and
- c) generating one or more base profiles of compositions optimized for therapeutic treatment of the psychological disorder;
- d) optionally, using the artificial intelligence algorithm to analyze the data for the combination compositions and the optional ingredients, and
- e) generating one or more complete profiles of compositions with and without the optional ingredients;

wherein the psychological disorder comprises a psychosis or psychotic events, or abnormal anxiety or depression; and

wherein the data are obtained from original experiments or literature review.

52. The method of claim 51 wherein the artificial intelligence algorithm comprises a classification algorithm, regression algorithm, clustering algorithm, or a combination thereof.

53. The method of claim 52 wherein the classification algorithm comprises a naïve Bayes algorithm, decision tree, random forest algorithm, Support Vector Machines, or K Nearest Neighbor algorithm.

54. The method of claim 52 wherein the regression algorithm comprises liner regression, lasso regression, logistic regression, or multivariate regression.

55. The method of claim 52 wherein the clustering algorithm comprises K-means clustering, fuzzy C-means algorithm, expectation-maximization algorithm, or hierarchical clustering algorithm.

56. The method of claim 23 wherein the serotonergic psychedelic comprises psilocybin or psilocin, or serotonergic metabolites, derivatives, or analogs thereof.

57. A method for the treatment of a psychological disorder comprising the step of administering to a patient in need thereof a composition comprising at least one serotonergic psychedelic in combination with at least one cannabinoid and at least one terpene, and at least one edible or medicinal mushroom or extract thereof; wherein the at least one cannabinoid and at least one terpene is administered separately from, sequentially to, or simultaneously with the serotonergic psychedelic and edible or medicinal mushroom; and wherein the at least one edible or medicinal mushroom or extract thereof is also administered separately from, sequentially to, or simultaneously with the serotonergic psychedelic and cannabinoid.

58. The method of claim 57 wherein

i) the at least one serotonergic psychedelic comprises psilocybin or psilocin, or serotonergic metabolites, derivatives, or analogs thereof;

ii) the at least one cannabinoid comprises CBD, CBG, CBN, and THC extracted from *Cannabis sativa* Ringo's Gift strain;

iii) the at least one terpene comprises limonene, myrcene, beta-caryophyllene, linalool, alpha pinene, or a combination thereof; and

iv) the at least one edible or medicinal mushroom or extract thereof comprises an extract of *Ganoderma lucidum*, *Hericium erinaceus*, *Cordyceps sinensis*, *C. militaris*, *C. liangshanensis*, *C. gunnii*, or *C. cicadicola*.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2021/057019

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/05; A61K 31/4045; A61K 36/074; A61K 36/185; A61P 25/18; A61P 25/22 (2021.01)

CPC - A61K 31/05; A61K 31/4045; A61K 36/074; A61K 36/185; A61P 25/18; A61P 25/22; A61P 25/24 (2021.08)

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.
Y	US 2020/0054701 A1 (CONSTANCE THERAPEUTICS INC) 20 February 2020 (20.02.2020) entire document	1-3, 8, 11-18, 20-22
Y	US 2009/0110674 A1 (LOIZOU) 30 April 2009 (30.04.2009) entire document	1-3, 8, 11-18, 20-22
A	US 2019/0350949 A1 (PROCARE BEHEER B V) 21 November 2019 (21.11.2019) entire document	1-3, 8, 11-18, 20-22
A	US 2018/0221333 A1 (RISE RESEARCH INC) 09 August 2018 (09.08.2018) entire document	1-3, 8, 11-18, 20-22

☐ 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

16 November 2021

Date of mailing of the international search report

DEC 13 2021

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Harry Kim

Telephone No. PCT Helpdesk: 571-272-4300

Form PCT/ISA/210 (second sheet) (July 2019)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2021/057019

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See extra sheet(s).

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 8, 11-18, 20-22

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continued from Box No. III Observations where unity of invention is lacking

Claims 1-3, 8, 11-18, and 20-22 have been analyzed subject to the restriction that the claims read on a composition comprising one serotonergic psychedelic, one cannabinoid, one terpene, and an edible or medicinal mushroom or an extract, fraction, or isolate thereof, wherein the serotonergic psychedelic is N,N-dimethyltryptamine (DMT), wherein the cannabinoid is cannabidiol (CBD), wherein the terpene is alpha bisabolol, and wherein the edible or medicinal mushroom comprises *Ganoderma lucidum*.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees need to be paid.

Group I+: claims 1-22 are drawn to a composition comprising one or more serotonergic psychedelics, one or more cannabinoids, one or more terpenes, and one or more edible or medicinal mushrooms or an extract, fraction, or isolate thereof.

Group II: claims 23-50, 57, and 58 are drawn to a method of treating a subject suffering from a psychological disorder.

Group III: claims 51-56 are drawn to a method of optimizing a composition for use in treatment of a subject suffering from a psychological disorder using artificial intelligence.

The first invention of Group I+ is restricted to a composition comprising one serotonergic psychedelic, one cannabinoid, one terpene, and an edible or medicinal mushroom or an extract, fraction, or isolate thereof, wherein the serotonergic psychedelic is N,N-dimethyltryptamine (DMT), wherein the cannabinoid is cannabidiol (CBD), wherein the terpene is alpha bisabolol, and wherein the edible or medicinal mushroom comprises *Ganoderma lucidum*. It is believed that claims 1-3, 8, 11-18, and 20-22 read on this first named invention and thus these claims will be searched without fee to the extent that they read on the above embodiment.

Applicant is invited to elect additional serotonergic psychedelic, cannabinoid, terpene, and edible or medicinal mushroom for each composition to be searched in a specific combination by paying an additional fee for each set of election. An exemplary election would be a composition comprising one serotonergic psychedelic, one cannabinoid, one terpene, and an edible or medicinal mushroom or an extract, fraction, or isolate thereof, wherein the serotonergic psychedelic is psilocybin, wherein the cannabinoid is cannabidiol (CBD), wherein the terpene is alpha bisabolol, and wherein the edible or medicinal mushroom comprises *Ganoderma lucidum*. Additional serotonergic psychedelics, cannabinoids, terpenes, and edible or medicinal mushrooms will be searched upon the payment of additional fees. Applicants must specify the claims that read on any additional elected inventions. Applicants must further indicate, if applicable, the claims which read on the first named invention if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the "+" group(s) will result in only the first claimed invention to be searched/examined.

The inventions listed in Groups I+, II, and III do not relate to a single general inventive concept under PCT Rule 13.1, because under PCT Rule 13.2 they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I+, a composition comprising one or more serotonergic psychedelics, one or more cannabinoids, one or more terpenes, and one or more edible or medicinal mushrooms or an extract, fraction, or isolate thereof, are not present in Groups II and III; the special technical features of Group II, a method of treating a subject suffering from a psychological disorder, are not present in Groups I+ and III; and the special technical features of Group III, a method of optimizing a composition for use in treatment of a subject suffering from a psychological disorder using artificial intelligence, are not present in Groups I+ and II.

Groups I+, II, and III serotonergic psychedelics, cannabinoids, terpenes, and edible or medicinal mushrooms do not share a significant structural element, requiring the selection of alternatives for the serotonergic psychedelics, cannabinoids, terpenes, and edible or medicinal mushrooms, where "serotonergic psychedelics comprise tryptamine psychedelics, phenylethylamine psychedelics, or a combination thereof", "cannabinoids comprise one or more of cannabidiol (CBD), cannabinol (CBN), cannabigerol (CBG), or tetrahydrocannabinol (THC)", "the terpenes comprise one or more monoterpenes, one or more sesquiterpenes, or a combination thereof", and "the edible or medicinal mushroom comprises a species from the genus *Ganoderma*, the genus *Hericium*, or the genus *Cordyceps*" and accordingly these groups lack unity a priori.

Additionally, even if Groups I+, II, and III were considered to share the technical features of a composition comprising one or more serotonergic psychedelics, one or more cannabinoids, one or more terpenes, and one or more edible or medicinal mushrooms or an extract, fraction, or isolate thereof, these shared technical features do not represent a contribution over the prior art as disclosed by US 2019/0350949 A1 to Procure Beheer B.V. (hereinafter, "Procure") and US 2018/0221333 A1 to Rise Research Inc (hereinafter, "Rise").

Procure teaches a composition (Para. [0086]; see also Claim 16, pharmaceutical compositions) comprising one or more serotonergic psychedelics (Para. [0086]; see also Claim 16, compositions comprising the at least one cannabinoid and/or the at least one terpene, in combination with psilocybin and/or psilocin; Para. [0039], where psilocybin is a serotonergic psychedelic), one or more cannabinoids (Para. [0086]; see also Claim 16, compositions comprising at least one cannabinoid), and one or more terpenes (Para. [0086]; see also Claim 16, compositions comprising at least one terpene).

Rise teaches a composition comprising and one or more edible or medicinal mushrooms or an extract, fraction, or isolate thereof (Claim 10, formulated cannabis product for oral delivery (edible) comprising... *cordyceps sinensis* mushroom).

The inventions listed in Groups I+, II, and III therefore lack unity under Rule 13 because they do not share a same or corresponding special technical feature.