

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: Natalia Panagiotakopoulos et al. Confirmation No.:

Serial No.: 17/948,180 Group No.:

Filing or 371(c) Date: September 19, 2022 Examiner:

Entitled: PSILOCYBIN DERIVED COMPOSITIONS AND METHODS USING SAME

**THIRD-PARTY PRE-ISSUANCE SUBMISSION**

Examiner:

The following documents, which are also identified in the Form PTO/SB/429 filed herewith, are submitted for your consideration as being of potential relevance to the examination of the present application:

1. MILNE (2020) “Metabolic engineering of *Saccharomyces cerevisiae* for the de novo production of psilocybin and related tryptamine derivatives” *Metabolic Engineering*. 60: 25-36.
2. W.I.P.O. Pat. App. No. 2018/135943 “PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES” (Published July 26, 2018)
3. U.S. Pat. App. Pub. No. 2021/0251976 “TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH” (Published August 19, 2021)
4. U.S. Pat. App. Pub. No. 2021/0268046 “CANNABINOID & PROBIOTIC SUPPOSITORIES & METHODS OF USE” (Published September 02, 2021)
5. U.S. Pat. App. Pub. No. 2022/0280482 “FORMULATIONS OF PSILOCIN THAT HAVE ENHANCED STABILITY” (Published September 08, 2022)
6. U.S. Pat. App. Pub. No. 2022/0313713 “VAPORIZABLE PSYCHOACTIVE ALKALOID COMPOSITION AND PREPARATION THEREOF” (Published October 06, 2022)
7. LIN (2020) “Case Report: Resolution of Rheumatoid Arthritis in a Patient Consuming Psilocybin Mushrooms” *Journal of Healthcare*. 3(1): 25-32
8. U.S. Pat. App. Pub. No. 20220331344 “ORAL FORMULATIONS OF PSYCHOTROPIC MACROFUNGUS BOTANICAL EXTRACTS WITH MOUTHFEEL EXPERIENCE ENHANCERS” (Published October 20, 2022)
9. NATOF9, “Psilocybin helped heal my Irritable Bowel Disease” Published on March 05, 2017; <https://www.shroomery.org/forums/showflat.php/Number/24137933>, retrieved April 26, 2023
10. W.I.P.O. Pat. App. No. 2021/101926 “TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH” (Published May 27, 2021)

Attached hereto is a claim chart providing a concise description of the relevance of each reference in the document list to the elements of the presently pending claims.

U.S.S.N. 17/948,180 Pending Claims	References
<p>1. An alkaloid composition comprising an alkaloid compound selected from the group consisting of psilocybin, psilocin, baeocystin, norpsilocin, and any combination thereof.</p>	<p>1. MILNE (2020) “Metabolic engineering of <i>Saccharomyces cerevisiae</i> for the de novo production of psilocybin and related tryptamine derivatives” <i>Metabolic Engineering</i>. 60: 25-36.</p> <p>From page 25: “<b>Psilocybin is a tryptamine-derived psychoactive alkaloid</b> found mainly in the fungal genus <i>Psilocybe</i>, among others, and is the active ingredient in so-called “magic mushrooms”.... In this work, we demonstrate the <b>de novo biosynthetic production of psilocybin</b> and related tryptamine derivatives in <i>Saccharomyces cerevisiae</i> by expression of a heterologous biosynthesis pathway sourced from <i>Psilocybe cubensis</i>... Further rational engineering resulted in a final production strain producing <math>627 \pm 140</math> mg/L of <b>psilocybin</b> and <math>580 \pm 276</math> mg/L of the dephosphorylated degradation product <b>psilocin</b> in triplicate controlled fed-batch fermentations in minimal synthetic media. Pathway intermediates <b>baeocystin</b>, nor norbaeocystin as well the dephosphorylated <b>baeocystin degradation product norpsilocin</b> were also detected in strains engineered for <b>psilocybin production.</b>”</p> <p>10. W.I.P.O. Pat. App. No. 2021/101926 “TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH” (Published May 27, 2021)</p> <p>From claim 28: "28. A method of treating or preventing serotonin (5-hydroxytryptamine, 5-HT) receptor disorders, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement, physical or motor neuron enhancement, or general improvement of mental health in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of <b>a composition comprising norpsilocin, norbaeocystin, baeocystin, or psilocybin</b>, combined with one or more erinacines or hericenones in pure form or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomer thereof, or combinations thereof, extracts or isolates from <i>Hericium</i> mushroom species, combinations thereof and one or more pharmaceutically acceptable excipients."</p>
<p>2. The alkaloid composition of claim 1, wherein the alkaloid compound is psilocybin.</p>	<p>1. MILNE (2020) “Metabolic engineering of <i>Saccharomyces cerevisiae</i> for the de novo production of psilocybin and related tryptamine derivatives” <i>Metabolic Engineering</i>. 60: 25-36.</p> <p>From page 25: “<b>Psilocybin is a tryptamine-derived psychoactive alkaloid</b> found mainly in the fungal genus <i>Psilocybe</i>, among others, and is the active ingredient in so-called “magic mushrooms”.... In this work, we demonstrate the <b>de novo biosynthetic production of</b></p>

	<p><b>psilocybin</b> and related tryptamine derivatives in <i>Saccharomyces cerevisiae</i> by expression of a heterologous biosynthesis pathway sourced from <i>Psilocybe cubensis</i>... Further rational engineering resulted in a final production strain producing <math>627 \pm 140</math> mg/L of psilocybin and <math>580 \pm 276</math> mg/L of the dephosphorylated degradation product psilocin in triplicate controlled fed-batch fermentations in minimal synthetic media. Pathway intermediates baecocystin, nor norbaecocystin as well the dephosphorylated baecocystin degradation product norpsilocin were also detected in strains engineered for psilocybin production.”</p> <p>10. W.I.P.O. Pat. App. No. 2021/101926 “TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH” (Published May 27, 2021)</p> <p>From claim 28: "28. A method of treating or preventing serotonin (5-hydroxytryptamine, 5-HT) receptor disorders, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement, physical or motor neuron enhancement, or general improvement of mental health in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of <b>a composition comprising norpsilocin, norbaecocystin, baecocystin, or psilocybin</b>, combined with one or more erinacines or hericenones in pure form or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomer thereof, or combinations thereof, extracts or isolates from <i>Hericium</i> mushroom species, combinations thereof and one or more pharmaceutically acceptable excipients."</p>
<p><b>3.</b> The alkaloid composition of claim 2, wherein the alkaloid composition further comprising baecocystin.</p>	<p>1. MILNE (2020) “Metabolic engineering of <i>Saccharomyces cerevisiae</i> for the de novo production of psilocybin and related tryptamine derivatives” <i>Metabolic Engineering</i>. 60: 25-36.</p> <p>From page 25: “Psilocybin is a tryptamine-derived psychoactive alkaloid found mainly in the fungal genus <i>Psilocybe</i>, among others, and is the active ingredient in so-called “magic mushrooms”.... In this work, we demonstrate the de novo biosynthetic production of psilocybin and related tryptamine derivatives in <i>Saccharomyces cerevisiae</i> by expression of a heterologous biosynthesis pathway sourced from <i>Psilocybe cubensis</i>... Further rational engineering resulted in a final production strain producing <math>627 \pm 140</math> mg/L of psilocybin and <math>580 \pm 276</math> mg/L of the dephosphorylated degradation product psilocin in triplicate controlled fed-batch fermentations in minimal synthetic media. Pathway intermediates <b>baecocystin</b>, nor norbaecocystin as well the dephosphorylated <b>baecocystin</b> degradation</p>

	<p>product norpsilocin were also detected in strains engineered for psilocybin production.”</p> <p>10. W.I.P.O. Pat. App. No. 2021/101926 “TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH” (Published May 27, 2021)</p> <p>From claim 28: "28. A method of treating or preventing serotonin (5-hydroxytryptamine, 5-HT) receptor disorders, neuronal injuries, neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement, physical or motor neuron enhancement, or general improvement of mental health in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of <b>a composition comprising norpsilocin, norbaeocystin, baeocystin, or psilocybin</b>, combined with one or more erinacines or hericenones in pure form or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomer thereof, or combinations thereof, extracts or isolates from <i>Herichium</i> mushroom species, combinations thereof and one or more pharmaceutically acceptable excipients."</p>
<p>4. The alkaloid composition of claim 2, wherein the alkaloid composition further comprising norpsilocin.</p>	<p>1. MILNE (2020) “Metabolic engineering of <i>Saccharomyces cerevisiae</i> for the de novo production of psilocybin and related tryptamine derivatives” <i>Metabolic Engineering</i>. 60: 25-36.</p> <p>From page 25: “Psilocybin is a tryptamine-derived psychoactive alkaloid found mainly in the fungal genus <i>Psilocybe</i>, among others, and is the active ingredient in so-called “magic mushrooms”.... In this work, we demonstrate the de novo biosynthetic production of psilocybin and related tryptamine derivatives in <i>Saccharomyces cerevisiae</i> by expression of a heterologous biosynthesis pathway sourced from <i>Psilocybe cubensis</i>... Further rational engineering resulted in a final production strain producing <math>627 \pm 140</math> mg/L of psilocybin and <math>580 \pm 276</math> mg/L of the dephosphorylated degradation product psilocin in triplicate controlled fed-batch fermentations in minimal synthetic media. Pathway intermediates baeocystin, nor norbaeocystin as well the dephosphorylated baeocystin degradation product <b>norpsilocin</b> were also detected in strains engineered for psilocybin production.”</p> <p>10. W.I.P.O. Pat. App. No. 2021/101926 “TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH” (Published May 27, 2021)</p> <p>From claim 28: "28. A method of treating or preventing serotonin (5-hydroxytryptamine, 5-HT) receptor disorders, neuronal injuries,</p>

	<p>neurodegeneration, neurological diseases, congenital or organic cognitive impairment, learning disabilities, autism spectrum disorder, psychiatric and mood disorders, cognitive enhancement, physical or motor neuron enhancement, or general improvement of mental health in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of <b>a composition comprising norpsilocin, norbaeocystin, baeocystin, or psilocybin</b>, combined with one or more erinacines or hericenones in pure form or pharmaceutically acceptable salts, hydrates, solvates, prodrugs, stereoisomers, or tautomer thereof, or combinations thereof, extracts or isolates from <i>Herichium</i> mushroom species, combinations thereof and one or more pharmaceutically acceptable excipients."</p>
<p>5. The alkaloid composition of claim 1, further comprising cannabidiol.</p>	<p>2. WO2018135943 PSILOCYBIN AND/OR PSILOCIN IN COMBINATION WITH CANNABINOIDS AND/OR TERPENES (wipo.int) (priority date 01/18/2017)</p> <p>From claim 5: "5. <b>Psilocybin and/or psilocin in combination with at least one cannabinoid</b> and/or at least one terpene for use according to any of the preceding claims, wherein the at least one cannabinoid is at least one, two or three chosen from the group consisting of <b>cannabidiol (CBD)</b>; cannabidiolic acid (CBDA); tetrahydrocannbidivarin (THCV)"</p>
<p>6. The alkaloid composition of claim 1, wherein the alkaloid composition further consists of one selected from the group consisting of an erinacines, hericenones, cyanthane terpenes, extracts from <i>Herichium</i> mushroom, and any combination thereof.</p>	<p>3. U.S. Pat. App. Pub. No. 2021/0251976 "TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH" (Published August 19, 2021)</p> <p>From claims 1: "1. A method of treating or improving a mental health disorder in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of a composition comprising from about 1 mg to about 10 mg of one or more of <b>psilocybin, psilocin</b>, esters, or salts thereof; or an equivalent amount of a psilocybin containing mushroom; and one or more pharmaceutically acceptable excipients."</p> <p>From [0007]: "One embodiment described herein is a composition comprising <b>norpsilocin</b> or a salt or hydrate thereof or combinations thereof combined with one or more erinacines or hericenones in pure form, <b>extracts or isolates from Herichium mushroom</b> species, or combinations thereof. In one aspect, the <b>erinacines or hericenones</b> comprise...In another aspect, the composition comprises an extract of extracts or isolates from <b>Herichium erinaceus</b>. In another aspect, the composition further comprises <b>baeocystin</b> or a salt or hydrate thereof."</p> <p>From [0005]: "Lion's Mane (<b>Herichium erinaceus</b>), Bear's Head (<i>H. coralloides</i>), or Comb Tooth (<i>H. ramosum</i>) mushrooms and mycelium are reported to influence myelin regeneration myelin on the axons of</p>

	<p>nerves. Two <b>cyanthane terpenes the erinacines and hericenones</b> are thought to promote NGF (nerve growth factor) synthesis.”</p>
<p>7. The alkaloid composition of claim 1, further comprising a psychobiotic.</p>	<p>4. U.S. Pat. App. Pub. No. 2021/0268046 “CANNABINOID &amp; PROBIOTIC SUPPOSITORIES &amp; METHODS OF USE” (Published September 02, 2021)</p> <p>From abstract: “Cannabinoids and probiotics formulated into a suppository and used to treat urogenital, gastrointestinal or aural infections and/or inflammation by local use of the suppository for a period of time are described.”</p> <p>From [0021]: “Preferred probiotics for vaginal use include, <b>Lactobacilli</b>: acidophilus, brevis, bulgaricus, plantarum, <b>rhamnosus</b>, gasseri, casei, salivarius, paracasei, fermentum, salivarius, reuteri, helveticus, lactis, cremoris, kefir, parakefir, faecium, crispatus, delbrueckii, and Lactococcus: lactus.”</p> <p>From [0049]: “<b>Other active ingredients that may advantageously be combined with cannabinoids</b> and probiotics include those in Table 3:</p> <p>TABLE-US-00004 TABLE 3 Additional ingredients <b>Mushrooms Psilocybin</b> (P. azurescens, P. semilanceata, P. cyanescens, P. subaeruginosa, P. bohemica, P. cubensis, P. cyanofibrillosa) 5-10 mg 10-25 mg, 30-45+ mg &amp; root network Cordyceps militaris &amp; sinensis (mycelium) &amp; adaptogens Organic reishi (ganoderma lucidum) Organic <b>lions mane (hericiumerinaceus)</b> ...”</p> <p>From [0006]: “However, millennia before the HMP initiative, women around the world appreciated the value of vaginal flora in maintaining a healthy and comfortable vaginal environment. Thus, women have long treated, e.g., yeast infections, by supplementing with <b>Lactobacillus cultures, both orally</b> and locally.”</p>
<p>8. The alkaloid composition of claim 7, wherein the psychobiotic is <i>Lactobacillus rhamnosus</i>.</p>	<p>4. U.S. Pat. App. Pub. No. 2021/0268046 “CANNABINOID &amp; PROBIOTIC SUPPOSITORIES &amp; METHODS OF USE” (Published September 02, 2021)</p> <p>From abstract: “Cannabinoids and probiotics formulated into a suppository and used to treat urogenital, gastrointestinal or aural infections and/or inflammation by local use of the suppository for a period of time are described.”</p> <p>From [0021]: “Preferred probiotics for vaginal use include, <b>Lactobacilli</b>: acidophilus, brevis, bulgaricus, plantarum, <b>rhamnosus</b>, gasseri, casei, salivarius, paracasei, fermentum, salivarius, reuteri, helveticus, lactis, cremoris, kefir, parakefir, faecium, crispatus, delbrueckii, and Lactococcus: lactus.”</p>

	<p>From [0049]: “<b>Other active ingredients that may advantageously be combined with cannabinoids</b> and probiotics include those in Table 3:</p> <p>TABLE-US-00004 TABLE 3 Additional ingredients <b>Mushrooms Psilocybin</b> (P. azurescens, P. semilanceata, P. cyanescens, P. subaeruginosa, P. bohemica, P. cubensis, P. cyanofibrillosa) 5-10 mg 10-25 mg, 30-45+ mg &amp; root network Cordyceps militaris &amp; sinensis (mycelium) &amp; adaptogens Organic reishi (ganoderma lucidum) Organic <b>lions mane (hericiumerinaceus)</b> ...”</p> <p>From [0006]: “However, millennia before the HMP initiative, women around the world appreciated the value of vaginal flora in maintaining a healthy and comfortable vaginal environment. Thus, women have long treated, e.g., yeast infections, by supplementing with <b>Lactobacillus cultures, both orally</b> and locally.”</p>
<p>9. The alkaloid composition of claim 1, further comprising a prebiotic.</p>	<p>5. U.S. Pat. App. Pub. No. 2022/0280482 “FORMULATIONS OF PSILOCIIN THAT HAVE ENHANCED STABILITY” (Published September 08, 2022)</p> <p>From claim 1 “A composition of <b>psilocin that is stable including at least one agent that provides enhanced stability</b> in combination with psilocin.”</p> <p>From [0056]: “Any of the photostabilizing or antioxidant agents can also work synergistically with the <b>psilocin or provide additional beneficial effects</b>. For example, <b>prebiotics</b> such as lactulose provide antioxidant effects as well as other advantageous effects in pain treatment.”</p>
<p>10. The alkaloid composition of claim 1, further comprising one or more medicinal mushrooms or extracts thereof.</p>	<p>10. W.I.P.O. Pat. App. No. 2021/101926 “TRYPTAMINE COMPOSITIONS FOR ENHANCING NEURITE OUTGROWTH” (Published May 27, 2021)</p> <p>From page 4 line 24-34: “In another aspect, the composition further comprises one or more extracts or pure chemicals from other fungi comprising one or more of, <b>Antrodia, Beauveria, Copelandia, Cordyceps, Fomitopsis, Ganoderma, Grifola, Hericium, Hypsizygus, Inonotus, Isaria, Panaeolus, Phellinus, Piptoporus, Pleurotus, Polyporus or Trametes species or combinations thereof; a mycelium extract of Antrodia, Beauveria, Copelandia, Cordyceps, Fomitopsis, Ganoderma, Grifola, Hericium, Hypsizygus, Inonotus, Isaria, Panaeolus, Phellinus, Piptoporus, Pleurotus, Polyporus or Trametes species or combinations thereof; or a fruiting body extract of Antrodia, Beauveria, Copelandia, Cordyceps, Fomitopsis, Ganoderma, Grifola, Hericium, Hypsizygus, Inonotus, Isaria, Panaeolus, Phellinus, Piptoporus, Pleurotus, Polyporus or Trametes species or combinations thereof, or combinations thereof.</b>”</p>

<p>11. The alkaloid composition of claim 1, further comprising docosahexaenoic acid.</p>	<p>6. U.S. Pat. App. Pub. No. 2022/0313713 “VAPORIZABLE PSYCHOACTIVE ALKALOID COMPOSITION AND PREPARATION THEREOF” (Published October 06, 2022)</p> <p>From claim 1 “A liquid, vaporizable <b>psychoactive alkaloid composition</b> made by mixing, by weight: 0.1-15% of a psychoactive alkaloid component; 5-71.9% of alcohol, polyol, or an alcohol and polyol mixture; 2-78.1% of fatty acid; 5-40% of fatty alcohol; 0-10% of antioxidant; and 0-10% of flavorant.”</p> <p>From claim 3 “The composition of claim 2, wherein: the <b>phosphorylated psychoactive alkaloid is psilocybin, baeocystin, norbaeocystin, aeruginascin, or any combination selected therefrom;</b> and the dephosphorylated psychoactive alkaloid is <b>psilocin, bufotenine, bufotenidine, norpsilocin, 4-hydroxytryptamine, N,N,N-trimethyl-4-hydroxytryptamine, or any combination selected therefrom.</b>”</p> <p>From: “13. The composition of claim 1, wherein the fatty acid is palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidonic acid, eicosapentaenoic acid, <b>docosahexaenoic acid</b>, ascorbyl palmitate, cetyl palmitate, colfosceril palmitate, ehtylhexyl palmitate, isopropyl palmitate, palmitoyl-CoA, retinyl palmitate, sucrose monopalmitate or any combination selected therefrom.”</p> <p>From [0006] “<b>Oral administration of phosphorylated psychoactive alkaloid compositions</b> via the human gastrointestinal tract allows the conversion of the phosphorylated form to the corresponding biological effective dephosphorylated form...”</p>
<p>12. The alkaloid composition of claim 1, wherein the alkaloid composition is formulated as an oral formulation.</p>	<p>6. U.S. Pat. App. Pub. No. 2022/0313713 “VAPORIZABLE PSYCHOACTIVE ALKALOID COMPOSITION AND PREPARATION THEREOF” (Published October 06, 2022)</p> <p>From claim 1 “A liquid, vaporizable <b>psychoactive alkaloid composition</b> made by mixing, by weight: 0.1-15% of a psychoactive alkaloid component; 5-71.9% of alcohol, polyol, or an alcohol and polyol mixture; 2-78.1% of fatty acid; 5-40% of fatty alcohol; 0-10% of antioxidant; and 0-10% of flavorant.”</p> <p>From claim 3 “The composition of claim 2, wherein: the <b>phosphorylated psychoactive alkaloid is psilocybin, baeocystin, norbaeocystin, aeruginascin, or any combination selected therefrom;</b> and the dephosphorylated psychoactive alkaloid is <b>psilocin, bufotenine, bufotenidine, norpsilocin, 4-hydroxytryptamine, N,N,N-trimethyl-4-hydroxytryptamine, or any combination selected therefrom.</b>”</p>



	<p>From [0006] “<b>Oral administration of phosphorylated psychoactive alkaloid compositions</b> via the human gastrointestinal tract allows the conversion of the phosphorylated form to the corresponding biological effective dephosphorylated form...”</p>
<p><b>13.</b> A method of treating rheumatoid arthritis, comprising administering an alkaloid composition, wherein the alkaloid composition comprising an alkaloid compound selected from the group consisting of psilocybin, psilocin, baeocystin, norpsilocin, and any combination thereof.</p>	<p>7. LIN (2020) “Case Report: Resolution of Rheumatoid Arthritis in a Patient Consuming Psilocybin Mushrooms” Journal of Healthcare. 3(1): 25-32</p> <p>From page 25: “Shortly after that he <b>consumed some psilocybin mushrooms</b> and was surprised to observe that <b>his joint pain and swelling completely resolved for about 24 hours</b>. In addition, his seasonal allergy symptoms also completely resolved. <b>When he had another flare of joint pain several years later, he took four doses of psilocybin mushrooms of 2 grams each over a two-week period and again had complete resolution of his symptoms</b>. That was one year prior to the writing of this paper. Subsequently he has been using psilocybin mushrooms periodically and he has not experienced any signs or symptoms of <b>rheumatoid arthritis</b> since then.”</p> <p>From page 26: “<b>Psilocybin and its active metabolite psilocin</b> are tryptamines [28] found in more than a hundred species of mushroom, many of which belong to the Psilocybe genus.”</p>
<p><b>14.</b> The method of claim 13, wherein the administering comprises a micro-dosing regimen.</p>	<p><i>From the application of interest, 17/948,180, paragraph [0012]: “In some embodiments, an alkaloid composition comprising an amount of at least one alkaloid compound may be formulated such that the amount of the at least one alkaloid compound is a micro-dose. The term “micro-dose” refers to an amount of the at least one alkaloid compound being <b>less than 5 mg</b>. In some embodiments a micro-dose may constitute about <b>10 µg to about 1 mg</b>...”</i></p> <p>8. U.S. Pat. App. Pub. No. 20220331344 “ORAL FORMULATIONS OF PSYCHOTROPIC MACROFUNGUS BOTANICAL EXTRACTS WITH MOUTHFEEL EXPERIENCE ENHANCERS” (Published October 20, 2022)</p> <p>From [0056]: “The oral formulations of the present disclosure can be configured to deliver a heroic dose of psychoactive compound(s) in one or more unit dosage forms, or a <b>microdose of psychoactive compound(s)</b>. For example, a heroic dose can be the quantity of psychoactive compounds in 5 grams of whole, <b>dry Psilocybe Cubensis mushrooms</b>, whereas a microdose is a sub-hallucinogenic quantity associated with enhanced creativity and meta-creative processes, such as perspective-shifting/divergent thinking and openness/curiosity. The concentration of botanical extract in the formulation can be based upon the amount needed to provide about 1-25 mg psilocybin per 70 kg body weight. For example, a single dosage</p>

	<p>unit can include about 0.5 mg-40 mg, such as <b>0.75 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 22 mg, 25 mg, 27 mg, 30 mg, 35 mg, or 40 mg</b>, depending on the desired psychophysiological effect.”</p> <p>From claim 1: “An <b>oral formulation</b> comprising at least one botanical extract of a <b>psychotropic macrofungus</b> and at least one mouthfeel experience enhancer.”</p> <p>From claim 3: “The <b>oral formulation</b> of claim 1, wherein the at least one botanical extract comprises at least one psychoactive compound selected from the group consisting of <b>psilocybin, psilocin, norpsilocin, baeocystin</b>, norbaeocystin, aeruginascin, serotonin, bufotenin, <math>\beta</math>-carboline alkaloids, muscarine, muscimol, muscazone, and ibotenic acid, or a combination thereof.</p> <p>From [0060]: “Formulations further comprising one or more cannabinoids can be used to address a variety of diseases and/or medical conditions. In some embodiments, the diseases include, but are not limited to, Acquired Hypothyroidism, Acute Gastritis, Acute Pain, Adrenal Disease, Agoraphobia, AIDS Related Illness, Alcohol Abuse, Alcoholism, Alopecia Areata, Alzheimer's Disease, Amphetamine Dependency, Amyloidosis, Amyotrophic Lateral Sclerosis (ALS), Angina Pectoris, Ankylosis, Anorexia, Anorexia Nervosa, Anxiety Disorders, any Chronic Medical Symptom that Limits Major Life Activities, Arteriosclerotic Heart Disease, <b>Arthritis, Arthritis (Rheumatoid)</b>...”</p>
<p>15. The method of claim 13, wherein the administering comprises a macro-dosing regimen.</p>	<p><i>From the application of interest, 17/948,180 paragraph [0013]: “In some embodiments, an alkaloid composition comprising an amount of at least one alkaloid compound may be formulated such that the amount of the at least one alkaloid compound is a macro-dose. The term “macro-dose” refers to an amount of the at least one alkaloid compound being about 5 mg to about 50 mg...”</i></p> <p>8. U.S. Pat. App. Pub. No. 20220331344 “ORAL FORMULATIONS OF PSYCHOTROPIC MACROFUNGUS BOTANICAL EXTRACTS WITH MOUTHFEEL EXPERIENCE ENHANCERS” (Published October 20, 2022)</p> <p>From [0056]: “The oral formulations of the present disclosure can be configured to deliver a heroic dose of psychoactive compound(s) in one or more unit dosage forms, or a microdose of psychoactive compound(s). For example, a heroic dose can be the quantity of psychoactive compounds in 5 grams of whole, <b>dry Psilocybe Cubensis mushrooms</b>, whereas a microdose is a sub-hallucinogenic quantity associated with enhanced creativity and meta-creative processes, such as perspective-shifting/divergent thinking and</p>

	<p>openness/curiosity. The concentration of botanical extract in the formulation can be based upon the amount needed to provide about <b>1-25 mg psilocybin per 70 kg body weight</b>. For example, a <b>single dosage unit can include about 0.5 mg-40 mg, such as 0.75 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 22 mg, 25 mg, 27 mg, 30 mg, 35 mg, or 40 mg</b>, depending on the desired psychophysiological effect. The amount of <b>psilocin, norpsilocin, baeocystin, norbaeocystin, aeruginascin, serotonin, bufotenin, <math>\beta</math>-carboline alkaloids, muscarine, muscimol, muscazone, and/or ibotenic acid</b> in the formulation can be based on the dosage of psilocybin and approximate a whole mushroom ratio as described above.”</p> <p>From claim 1: “An <b>oral formulation</b> comprising at least one botanical extract of a <b>psychotropic macrofungus</b> and at least one mouthfeel experience enhancer.”</p> <p>From [0060]: “Formulations further comprising one or more cannabinoids can be used to address a variety of diseases and/or medical conditions. In some embodiments, the diseases include, but are not limited to, Acquired Hypothyroidism, Acute Gastritis, Acute Pain, Adrenal Disease, Agoraphobia, AIDS Related Illness, Alcohol Abuse, Alcoholism, Alopecia Areata, Alzheimer's Disease, Amphetamine Dependency, Amyloidosis, Amyotrophic Lateral Sclerosis (ALS), Angina Pectoris, Ankylosis, Anorexia, Anorexia Nervosa, Anxiety Disorders, any Chronic Medical Symptom that Limits Major Life Activities, Arteriosclerotic Heart Disease, <b>Arthritis, Arthritis (Rheumatoid)...</b>”</p>
<p><b>16.</b> The method of claim 13, wherein the alkaloid composition is formulated as an oral formulation.</p>	<p>8. U.S. Pat. App. Pub. No. 20220331344 “ORAL FORMULATIONS OF PSYCHOTROPIC MACROFUNGUS BOTANICAL EXTRACTS WITH MOUTHFEEL EXPERIENCE ENHANCERS” (Published October 20, 2022)</p> <p>From [0056]: “The oral formulations of the present disclosure can be configured to deliver a heroic dose of psychoactive compound(s) in one or more unit dosage forms, or a microdose of psychoactive compound(s). For example, a heroic dose can be the quantity of psychoactive compounds in 5 grams of whole, <b>dry Psilocybe Cubensis mushrooms</b>, whereas a microdose is a sub-hallucinogenic quantity associated with enhanced creativity and meta-creative processes, such as perspective-shifting/divergent thinking and openness/curiosity. The concentration of botanical extract in the formulation can be based upon the amount needed to provide about <b>1-25 mg psilocybin per 70 kg body weight</b>. For example, a <b>single dosage unit can include about 0.5 mg-40 mg, such as 0.75 mg, 1 mg, 5 mg, 10 mg, 15 mg, 20 mg, 22 mg, 25 mg, 27 mg, 30 mg, 35 mg, or 40 mg</b>, depending on the desired psychophysiological effect. The</p>

	<p>amount of <b>psilocin, norpsilocin, baeocystin, norbaeocystin, aeruginascin, serotonin, bufotenin, β-carboline alkaloids, muscarine, muscimol, muscazone, and/or ibotenic acid</b> in the formulation can be based on the dosage of psilocybin and approximate a whole mushroom ratio as described above.”</p> <p>From claim 1: “An <b>oral formulation</b> comprising at least one botanical extract of a <b>psychotropic macrofungus</b> and at least one mouthfeel experience enhancer.”</p> <p>From [0060]: “Formulations further comprising one or more cannabinoids can be used to address a variety of diseases and/or medical conditions. In some embodiments, the diseases include, but are not limited to, Acquired Hypothyroidism, Acute Gastritis, Acute Pain, Adrenal Disease, Agoraphobia, AIDS Related Illness, Alcohol Abuse, Alcoholism, Alopecia Areata, Alzheimer's Disease, Amphetamine Dependency, Amyloidosis, Amyotrophic Lateral Sclerosis (ALS), Angina Pectoris, Ankylosis, Anorexia, Anorexia Nervosa, Anxiety Disorders, any Chronic Medical Symptom that Limits Major Life Activities, Arteriosclerotic Heart Disease, <b>Arthritis, Arthritis (Rheumatoid)...</b>”</p>
<p><b>17.</b> A method of treating irritable bowel syndrome, comprising administering an alkaloid composition, wherein the alkaloid composition comprising an alkaloid compound selected from the group consisting of psilocybin, psilocin, baeocystin, norpsilocin, and any combination thereof.</p>	<p>9. NATOF9, “Psilocybin helped heal my Irritable Bowel Disease” Published on March 05, 2017; <a href="https://www.shroomery.org/forums/showflat.php/Number/24137933">https://www.shroomery.org/forums/showflat.php/Number/24137933</a>, retrieved April 26, 2023</p> <p>From website #24137933 - 03/05/17 06:44 AM (6 years, 1 month ago): “While also in a flare up, I decided to go on a liquid diet prior to consuming <b>2-3g of psilocybin</b> in the form of ginger tea. It was the most pleasant trip I've had since being dx'd with <b>IBD</b>. I was also taking horrible medication(prednisone) with crazy side effects, but during the trip I felt "normal". My adrenal glands were not their usual agony. The next morning I awoke with energy and great digestion.</p> <p><b>Thus began my first real remission of the "disease".</b></p> <p>As this forum is likely aware of, there's an unfortunate amount of scientific literature on psilocybin, but we know there is <b>psilocin that targets proteins typically responsible for IBD inflammation</b>. It is suppressed by activating hormonal receptors. Some claim it can work better than pharmaceuticals.</p> <p>I also experimented with <b>micro-dosing for a month and found the results to be beneficial with both digestion, energy and motivation.</b>”</p>

	<p>4. U.S. Pat. App. Pub. No. 2021/0268046 “CANNABINOID &amp; PROBIOTIC SUPPOSITORIES &amp; METHODS OF USE” (Published September 02, 2021)</p> <p>From [0006] “...In addition, probiotics have been applied rectally to the GI tract to aid in immunological function, digestion, protect against pathogenic bacteria such as Salmonella typhimurium, Helicobacter pylori, and Escherichia coli, improve lactose intolerance, decrease cholesterol levels, treat Crohn's disease, ulcerative colitis, <b>irritable bowel syndrome (“IBS”)</b>, and replenish intestinal flora after antibiotic therapy to prevent antibiotic-induced diarrhea. Indeed, the global market for probiotics reached a value of about 49.4 billion U.S. dollars in 2018.”</p> <p>From [0049]: “Other active ingredients that may advantageously be combined with cannabinoids and probiotics include those in Table 3:</p> <p>TABLE-US-00004 TABLE 3 <b>Additional ingredients Mushrooms Psilocybin (P. azurescens, P. semilanceata, P. cyanescens, P. subaeruginosa, P. bohemica, P. cubensis, P. cyanofibrillosa) 5-10 mg 10-25 mg, 30-45+ mg &amp; root network Cordyceps militaris &amp; sinensis (mycelium) &amp; adaptogens Organic reishi (ganoderma lucidum) Organic lions mane (hericium erinaceus) Organic shitake (lentinus edodes/mycelium) Organic Poria Organic Maitake Organic Himematsutake (Royal Sun Agaricus) Oyster Mushrooms Porcini White Button Mushrooms Shimeji Chanterelle Black truffle Organic Turkey Tail Ashwagandha Rhodiola Tulsi Chaga (Inonotus obliquus)...</b>”</p> <p>From [0031]: “As used herein, “supplement” is a product <b>taken orally</b> that contains one or more ingredients (such as vitamins or amino acids) that are intended to supplement one's diet and are not considered food or drugs under the US regulatory scheme.”</p>
<p><b>18.</b> The method of claim 17, wherein the administering comprises a micro-dosing regimen.</p>	<p><i>From the application of interest, 17/948,180 paragraph [0012]: “In some embodiments, an alkaloid composition comprising an amount of at least one alkaloid compound may be formulated such that the amount of the at least one alkaloid compound is a micro-dose. The term “micro-dose” refers to an amount of the at least one alkaloid compound being <b>less than 5 mg</b>. In some embodiments a micro-dose may constitute about 10 µg to about 1 mg...”</i></p> <p>4. U.S. Pat. App. Pub. No. 2021/0268046 “CANNABINOID &amp; PROBIOTIC SUPPOSITORIES &amp; METHODS OF USE” (Published September 02, 2021)</p> <p>From [0006] “...In addition, probiotics have been applied rectally to the GI tract to aid in immunological function, digestion, protect against pathogenic bacteria such as Salmonella typhimurium, Helicobacter pylori, and Escherichia coli, improve lactose intolerance, decrease</p>

cholesterol levels, treat Crohn's disease, ulcerative colitis, **irritable bowel syndrome (“IBS”)**, and replenish intestinal flora after antibiotic therapy to prevent antibiotic-induced diarrhea. Indeed, the global market for probiotics reached a value of about 49.4 billion U.S. dollars in 2018.”

From Table 8:

**TABLE 8**

Formations 1-4 for aural/nasal use

Ingredient	Function	Amount F1	Amount F2	Amount F3	Amount F4
CBGA/CBG, CBD	Anti- inflammatory, analgesic, immune support	<50	50-100	100-400	400+
THCA/THC	anti- inflammatory, analgesic	Trace- <50 mg	50-100	100-400	400+
L- Acidophilus, L- Plantarum, L- Rueten, S. Salvarius	Microbiome support.	<6 billion CFUs, 6 billion- 90 billion CFUs, 90 billion + CFUs.	<6 billion CFUs, 6 billion- 90 billion CFUs, 90 billion + CFUs.	<6 billion CFUs, 6 billion- 90 billion CFUs, 90 billion + CFUs.	<6 billion CFUs, 6 billion- 90 billion CFUs, 90 billion + CFUs.
Psilocybin, MDMA	“bliss molecule” Antifungals/ antibacterials	Trace to <5 mg	Trace to 45 mg	Trace to 45 mg	Trace to 45 mg
Theobroma oil, and or Coconut oil, and or cocobutter, and or palm oil	Binder	<1 to 5 grams	<1 to 5 grams	<1 to 5 grams	<1 to 5 grams
Dimensions		Nasal, < or = 1.2 grams, and <9 mm- 10 mm long	Nasal, < or = 1.2 grams, and <9 mm- 10 mm long	Nasal, < or = 1.2 grams, and <9 mm- 10 mm long	Nasal, < or = 1.2 grams, and <9 mm- 10 mm long

From [0031]: “As used herein, “supplement” is a product **taken orally** that contains one or more ingredients (such as vitamins or amino acids) that are intended to supplement one's diet and are not considered food or drugs under the US regulatory scheme.”

9. NATOF9, “Psilocybin helped heal my Irritable Bowel Disease”  
 Published on March 05, 2017;  
<https://www.shroomery.org/forums/showflat.php/Number/24137933>,  
 retrieved April 26, 2023

From website #24137933 - 03/05/17 06:44 AM (6 years, 1 month ago): “While also in a flare up, I decided to go on a liquid diet prior to consuming **2-3g of psilocybin** in the form of ginger tea. It was the most pleasant trip I've had since being dx'd with **IBD**. I was also taking horrible medication(prednisone) with crazy side effects, but during the trip I felt "normal". My adrenal glands were not their usual agony. The next morning I awoke with energy and great digestion.

**Thus began my first real remission of the "disease".**

	<p>As this forum is likely aware of, there's an unfortunate amount of scientific literature on psilocybin, but we know there is <b>psilocin that targets proteins typically responsible for IBD inflammation</b>. It is suppressed by activating hormonal receptors. Some claim it can work better than pharmaceuticals.</p> <p>I also experimented with <b>micro-dosing for a month and found the results to be beneficial with both digestion</b>, energy and motivation.”</p>						
<p><b>19.</b> The method of claim 17, wherein the administering comprises a macro-dosing regimen.</p>	<p><i>From the application of interest, 17/948,180 paragraph [0013]: “In some embodiments, an alkaloid composition comprising an amount of at least one alkaloid compound may be formulated such that the amount of the at least one alkaloid compound is a macro-dose. The term “macro-dose” refers to an amount of the at least one alkaloid compound being about 5 mg to about 50 mg...”</i></p> <p>4. U.S. Pat. App. Pub. No. 2021/0268046 “CANNABINOID &amp; PROBIOTIC SUPPOSITORIES &amp; METHODS OF USE” (Published September 02, 2021)</p> <p>From [0006] “...In addition, probiotics have been applied rectally to the GI tract to aid in immunological function, digestion, protect against pathogenic bacteria such as Salmonella typhimurium, Helicobacter pylori, and Escherichia coli, improve lactose intolerance, decrease cholesterol levels, treat Crohn's disease, ulcerative colitis, <b>irritable bowel syndrome (“IBS”)</b>, and replenish intestinal flora after antibiotic therapy to prevent antibiotic-induced diarrhea. Indeed, the global market for probiotics reached a value of about 49.4 billion U.S. dollars in 2018.”</p> <p>From [0049]: “Other active ingredients that may advantageously be combined with cannabinoids and probiotics include those in Table 3:  <b>[0049]</b> Other active ingredients that may advantageously be combined with cannabinoids and probiotics include those in Table 3:</p> <table border="1" data-bbox="581 1430 1317 1648"> <thead> <tr> <th colspan="2" style="text-align: center;">TABLE 3</th> </tr> <tr> <th colspan="2" style="text-align: center;">Additional ingredients</th> </tr> </thead> <tbody> <tr> <td style="vertical-align: top;">Mushrooms</td> <td>Psilocybin (P. azurescens, P. semilanceata, P. cyanescens, P. subaeruginosa, P. bohemica, P. cubensis, P. cyanofibrillosa) 5-10 mg 10-25 mg, 30-45+ mg</td> </tr> </tbody> </table> <p>From [0031]: “As used herein, “supplement” is a product <b>taken orally</b> that contains one or more ingredients (such as vitamins or amino acids) that are intended to supplement one's diet and are not considered food or drugs under the US regulatory scheme.”</p>	TABLE 3		Additional ingredients		Mushrooms	Psilocybin (P. azurescens, P. semilanceata, P. cyanescens, P. subaeruginosa, P. bohemica, P. cubensis, P. cyanofibrillosa) 5-10 mg 10-25 mg, 30-45+ mg
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<p><b>20.</b> The method of claim 17, wherein the alkaloid composition is formulated as an oral formulation.</p>	<p>9. NATOF9, “Psilocybin helped heal my Irritable Bowel Disease”  Published on March 05, 2017;  <a href="https://www.shroomery.org/forums/showflat.php/Number/24137933">https://www.shroomery.org/forums/showflat.php/Number/24137933</a>,  retrieved April 26, 2023</p> <p>From website #24137933 - 03/05/17 06:44 AM (6 years, 1 month ago): “While also in a flare up, I decided to go on a liquid diet prior to consuming <b>2-3g of psilocybin in the form of ginger tea</b>. It was the most pleasant trip I've had since being dx'd with <b>IBD</b>.  I was also taking horrible medication(prednisone) with crazy side effects, but during the trip I felt "normal". My adrenal glands were not their usual agony. The next morning I awoke with energy and great digestion.</p> <p><b>Thus began my first real remission of the "disease".</b></p> <p>As this forum is likely aware of, there's an unfortunate amount of scientific literature on psilocybin, but we know there is <b>psilocin that targets proteins typically responsible for IBD inflammation</b>. It is suppressed by activating hormonal receptors. Some claim it can work better than pharmaceuticals.”</p>
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## Electronic Acknowledgement Receipt

<b>EFS ID:</b>	47906695
<b>Application Number:</b>	17948180
<b>International Application Number:</b>	
<b>Confirmation Number:</b>	9403
<b>Title of Invention:</b>	PSILOCYBIN DERIVED COMPOSITIONS AND METHODS USING SAME
<b>First Named Inventor/Applicant Name:</b>	Natalia Panagiotakopoulos
<b>Customer Number:</b>	165931
<b>Filer:</b>	Sisi Li
<b>Filer Authorized By:</b>	
<b>Attorney Docket Number:</b>	37427.0122PTUS (119)
<b>Receipt Date:</b>	26-APR-2023
<b>Filing Date:</b>	19-SEP-2022
<b>Time Stamp:</b>	14:17:45
<b>Application Type:</b>	

### Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$72
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**File Listing:**

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Concise Description of Relevance	Concise-description-generated.pdf	44460 8502ec3ff04c18bf0aaffb81e1b311572c6048c4	no	6

**Warnings:**

**Information:**

2	Third-Party Submission Under 37 CFR 1.290	Third-party-preissuance-submission.pdf	69464 78422a12efe96256c1e0427cda91e6db2ed1f7a8	no	3
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**Warnings:**

**Information:**

3	Request for Notification of Non-compliant Third-Party Submission	Third-party-notification-request.pdf	23614 d862044f186cfc218cc6b8e55a4c340953886b53	no	1
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**Warnings:**

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4	Evidence of Publication	LIN.pdf	776433 d09f630fd3dca9f9f020326e06326256682540e81	no	8
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**Warnings:**

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5	Evidence of Publication	MILNE.pdf	6412595 98074a739718d63709d4709ef4fa9e99d0da3081	no	12
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**Warnings:**

**Information:**

6	Evidence of Publication	NATOF9.pdf	592902 0ccca9288d64281a26b565b4d385a140936d00b	no	2
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**Warnings:**

**Information:**

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7	Concise Description of Relevance	Claims_Chart.pdf	448572	no	16
			f3a0523f22836df4e3eacac3a5014dbb54e4109c		

**Warnings:**

**Information:**

8	Fee Worksheet (SB06)	fee-info.pdf	37537	no	2
			e96171bc6d599997f9fd7927baf38b300f8bf68f		

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<b>Total Files Size (in bytes):</b>	8405577
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