

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: University of Zürich
Serial No.: 18/012,122
Filing or 371(c) Date: December 21, 2022

Confirmation No.: 5956
Group No.:
Examiner:

Entitled: Compositions and Kits of Parts Comprising N,N-Dimethyltryptamine and Harmine and Their Use in Therapy

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. Intl. Pat. Doc. No. WO2019081764A1 “Combination product for the treatment of neurological and/or psychiatric disorders” (Published May 2, 2019)
2. SOUZA (2019) “Validation of an analytical method for the determination of the main ayahuasca active compounds and application to real ayahuasca samples from Brazil” *Journal of Chromatography*. 1124: 197-203
3. INNEREXPLORER, “There Is Nothing To Be Afraid Of. Huasca Combo (B. caapi Extract & DMT Fumarate)” October 15, 2017; retrieved from Erowid Experience Vaults. <https://erowid.org/experiences/exp.php?ID=108203>, retrieved October 15, 2017
4. 1108, “Threshold Oral Experience Huasca Combo (Syrian Rue & M. tenuiflora)” December 31, 2009; retrieved from Erowid Experience Vaults. <https://erowid.org/experiences/exp.php?ID=76862>, retrieved December 31, 2009
5. OSORIO (2015) “Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report” *Revista Brasileira de Psiquiatria*. 37 (1): 13-20
6. NUNES (2016) “Effects of Ayahuasca and its Alkaloids on Drug Dependence: A Systematic Literature Review of Quantitative Studies in Animals and Humans” *Journal of Psychoactive Drugs*. 48(3): 195-205
7. INSERRA (2018) “Hypothesis: The Psychedelic Ayahuasca Heals Traumatic Memories via a Sigma 1 Receptor-Mediated Epigenetic-Mnemonic Process” *Frontier in Pharmacology*. 9: 330
8. RENELLI (2020) “An exploratory study of experiences with conventional eating disorder treatment and ceremonial ayahuasca for the healing of eating disorders” *Eating and Weight Disorders*. 25(2): 437-444
9. CAMERON (2018) “Dark Classics in Chemical Neuroscience: N,N-Dimethyltryptamine (DMT)” *ACS chemical neuroscience*. 9(10): 2344-2357
10. DMTNEXUS, “DMT Fumarate” February 22, 2013; retrieved from DMT-Nexus. https://wiki.dmt-nexus.me/DMT_Fumarate, retrieved February 22, 2013
11. STRASSMAN (1994) “Dose-Response Study of N,N-Dimethyltryptamine in Humans” *Archives of General Psychiatry*. 51(2): 85-97
12. EROWID, “DMT Dosage” February 21, 2015; retrieved from Erowid. https://erowid.org/chemicals/dmt/dmt_dose.shtml, retrieved February 21, 2015

13. U.S. Pat. App. Doc. No. US2020/0179349A1 “Methods Of Treating Food Allergy Conditions” (Published June 11, 2020)
14. GALLIMORE (2016) “A Model for the Application of Target-Controlled Intravenous Infusion for a Prolonged Immersive DMT Psychedelic Experience” *Frontiers in Pharmacology*. 7:1-11
15. EROWID, “Tihkal The Continuation Alexander & Ann Shulgin #14. HARMINE b-CARBOLINE, 7-METHOXY; 7-METHOXY-b-CARBOLINE; BANISTERINE; YAGEINE; TELEPATHINE; LEUCOHARMINE” February 21, 2015; retrieved from Erowid.
https://erowid.org/library/books_online/tihkal/tihkal14.shtml, retrieved February 21, 2015
16. SHROOMERY, “Re: Ayahuasca failure (Syrian Rue and MImosa) [Re: thoraxx]” March 19, 2016; retrieved from Shroomery. <https://www.shroomery.org/forums/showflat.php/Number/23022449>; retrieved March 19, 2016

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

U.S.S.N. 18/012,122 Pending Claims	References
<p>I. A kit of parts comprising: (a) N,N-dimethyltryptamine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier; and (b) harmine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.</p>	<p>1. Intl. Pat. Doc. No. WO2019081764A1 “Combination product for the treatment of neurological and/or psychiatric disorders” (Published May 2, 2019)</p> <p>From Page 18 lines 21-29 “Preferably, the compound described by formula (I) is N,N-dimethyltryptamine, N,N- diethyltryptamine, N,N-dipropyltryptamine, N,N-diisopropyltryptamine, 5-methoxy-N,N-dimethyltryptamine...”</p> <p>From page 27 lines 22-33 “In a preferred embodiment, any of the aforementioned combination products may further comprise a monoamine oxidase inhibitor which can boost the effectiveness of the compound described by formula (I). Preferably, the monoamine oxidase inhibitor is: a) a β-carboline such as harmine (CAS No. 442-51 -3), harmaline (CAS No. 304-21 -2), tetrahydroharmine (CAS No. 17019-01 -1), harmol (CAS No. 487-03-6), and/or harmalol (CAS No. 525-57-5), their salts and/or esters;...”</p> <p>From page 27 lines 35-37 to page 28 lines 1-5 “In a preferred embodiment, the combination product is a mixture of the compound described by formula (I) and the 5-HT2A receptor antagonist, i.e. the combination product is a composition. In an alternative embodiment, the compound described by formula (I) and the 5-HT2A receptor antagonist are physically separated. For example, the compound described by formula (I) could be contained in one blister pack while the 5-HT2A receptor antagonist is contained within a separate blister pack or the compound described by formula (I) and the 5- HT2A receptor antagonist could be contained in the same pill but be physically separated by a barrier, such as a gelatin barrier.”</p> <p>From page 18 lines 10-14 “Rather than a complex mixture of natural compounds derived from vegetation, the two active ingredients of the present invention may be substantially pure and may or may not be combined with pharmaceutically acceptable carrier and/or diluent as well as other controlled substances. In a preferred embodiment, the compound described by formula (I) is substantially pure.”</p> <p>2. SOUZA (2019) “Validation of an analytical method for the determination of the main ayahuasca active compounds and application to real ayahuasca samples from Brazil” Journal of Chromatography. 1124: 197-203</p> <p>From abstract “Ayahuasca is a brew prepared from the water decoction of two Amazonian plants, which is legally used for religious, cultural or therapeutic activities. The potential use of ayahuasca as a natural or phytotherapeutic drug is directly linked to</p>

the action of its active compounds and their connection with the **therapeutic efficacy** of the beverage. In this context, the aim of the present study was to establish a selective, sensitive and reproducible analytical method for the **quantification of the main active ayahuasca compounds**. **Thirty-eight** samples from the state of São Paulo, Brazil, were analyzed and the **simultaneous quantifications of N,N-dimethyltryptamine (DMT)**, tetrahydroharmine (THH), **harmine (HME)** and harmaline (HML) were performed. This study enabled the development of a fast validated analytical method with minimal matrix interference and high reproducibility for the tracing of active ayahuasca compound concentrations for the first time. This method is important as an auxiliary tool for the study of active compound effects in biological responses using different multi-omic platforms.”

From **page 199** “In order to calculate linearity, three analytical curves with seven points each were prepared, varying analyte concentrations according to the intervals described in the Suppl. Table 2. The equations of the lines, the correlation (r) and determination coefficients (R²) and the range of the values obtained for the statistical residuals were then determined from the analytical curves constructed for the four analytes (**Table 2**). **Based on the variance and linear regression, the linearity results were able to provide the concentration ranges for the determination of target analyte concentrations** [26,27].”

From **page 200**

Table 2
Regression data for each ayahuasca analyte.

Linearity (n = 21)	Concentration range			
	DMT	THH	HME	HML
	(1.5-15.0 mg/L)	(3.5-35.0 mg/L)	(6.0-60.0 mg/L)	(1.0-5.5 mg/L)
r	0.9956	0.9982	0.9966	0.9969
R ²	0.9912	0.9963	0.9933	0.9939
Linear equation	y = 0.2644x + 0.4749	y = 0.0925x + 0.1756	y = 0.1798x + 1.282	y = 0.1608x + 0.0766
Residual range	-0.16 to 0.23	-0.07 to 0.18	-0.33 to 0.50	-0.029 to 0.032

2. A composition comprising N,N-dimethyltryptamine fumarate and harmine hydrochloride.

16. SHROOMERY, “Re: Ayahuasca failure (Syrian Rue and MImosa) [Re: thoraxx]” March 19, 2016; retrieved from Shroomery. <https://www.shroomery.org/forums/showflat.php/Number/23022449>; retrieved March 19, 2016

From **webpage** “When using plain rue and root bark, you're throwing darts. If you wanna get serious, **order a gram of Harmine hcl + Harmaline hcl, and mix that with some DMT fumarate**. You can dial in your dose more easily and it has always been effective that way for me and others. **I use about 200mg harmalas + 150mg dmt.**”

From **webpage** “Aya is elusive. I struggled a lot to get a successful experience. **It came down to extracting the MAOI from caapi, and converting some DMT to the salt form, mixed together in 1 capsule down the hatch.**”

9. CAMERON (2018) “Dark Classics in Chemical Neuroscience: N,N-Dimethyltryptamine (DMT)” ACS chemical neuroscience. 9(10): 2344-2357

From **page 2346** “Typically, DMT is purified via sublimation of the free base under reduced pressure, crystallization/recrystallization of a DMT salt form, or a combination of the two. **The fumarate salt of DMT is perhaps one of the easiest forms to work with and store as other salts** (e.g., acetate, citrate, hydrochloride, etc.) tend to be hygroscopic. As with most indole-containing compounds, DMT should be stored in a dark freezer to avoid decomposition.”

11. STRASSMAN (1994) “Dose-Response Study of N,N-Dimethyltryptamine in Humans” Archives of General Psychiatry. 51(2): 85-97

From **page 86** “**Dimethyltryptamine fumarate** was prepared by David E. Nichols, PhD, Purdue University, West Lafayette, Ind. Purity, determined by gas chromatography-mass spectrometry and high-performance liquid chromatography, was greater than 99.9%. It was prepared for **clinical administration** by the Inpatient Pharmacy of the University of New Mexico Hospital in vials containing 40 mg/mL.”

10. DMTNEXUS, “DMT Fumarate” February 22, 2013; retrieved from DMT-Nexus. https://wiki.dmt-nexus.me/DMT_Fumarate, retrieved February 22, 2013

From **webpage** “

Advantages

DMT fumarate is more water soluble, more stable, has a longer shelf life, is much easier to crystallize, has a higher melting point, is less waxy, and easier to form into a powder than freebase DMT. Because of these characteristics DMT fumarate is much preferred over freebase DMT. Freebase DMT has no benefits other than the fact that it is easily vaporized.”

3. INNEREXPLORER, “There Is Nothing To Be Afraid Of. Huasca Combo (B. caapi Extract & DMT Fumarate)” October 15, 2017;

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From **webpage**

DOSE: T+ 0:00		oral	Banisteriopsis caapi	(extract)
T+ 0:20	50 mg	oral	DMT	

From **webpage** “I have had several experiences with **Caapi extract (180 mg harmine and 180 mg tetrahydroharmine)** as well as with vine-only brews, but I have taken a pretty long break from both and have lately felt that this is **the best medicine for me** to work with.”

From **webpage** “**After a few successful and very rewarding sessions with the Caapi extract, I thought it would be good to add in some DMT.** It just so happens that I had been planning on converting a gram of DMT freebase to **DMT Fumarate, which is the ideal form of DMT for oral** as well as IV/IM administration. At first, I was drawn to the idea of IM administration but I realized that I would need to spend a good deal of time preparing the proper safety precautions in order to minimize error or accidental injury. **As such, the best route seemed to be oral in combination with the Caapi extract.**”

Experiment #1:

I recently experienced Caapi extract with 21mg DMT Fumarate (.32mg/kg) which is a very very small dose, barely threshold. I did this purposely in order to ease my way into working with this powerful combination again. **The comeup on the Caapi extract was powerful as usual and I delayed taking the DMT an extra 20 minutes, taking it at t+0:40 instead of t+0:20.** I don't think that would have reduced the efficacy of the DMT at all, but rather it was the very low dose of DMT that led to very little effects. It was interesting that once I felt the DMT come on I felt very very tired and almost felt like I slept through the whole experience, though the two purges that I had were very emotionally based and were centered around purging negative thought patterns I have kept inside.

In my next experiment, **I plan on increasing the dose to 35mg DMT (.54mg/kg) in combination with the Caapi extract.** I think this will be a bit more of a trip and will give me a better sense of my flight navigation skills. I am deliberately taking my time with this to get to know these medicines I am deliberately taking my time with this to get

to know **these medicines as they work together** and how best to navigate the spaces they open up. This is how the shamans came to understand their work with the plants. Gradual increases in doses and getting to know the spirits of these medicines.

Experiment #2:

After careful research and reflection, I prepared to take my next journey with the **Caapi extract (which contains 180mg tetrahydroharmine and 180mg harmine) in combination with 50mg DMT Fumarate (.781mg/kg...**

... I poured the Caapi extract into a glass of grapefruit juice and allowed it to absorb into the juice, the process took about 3 minutes, and with the help of a stirring spoon, the powder was completely absorbed by the juice, forming citrate salts of the freebase alkaloids for more efficient absorption in the body. I read over my intentions again, reflected on them, asked the spirits of the four directions for protection on this journey, lit some incense, and drank the extract-containing juice. After drinking, **I set a timer for 20 minutes on my watch so I would know when to take the capsule containing the DMT Fumarate...**

... Eventually, the timer went off and **I promptly took the capsule containing 50mg DMT Fumarate.** Within 15 minutes, I was feeling the first alerts. A slight lethargy and softening of emotions. A slowing down..."

4. 1108, "Threshold Oral Experience Huasca Combo (Syrian Rue & M. tenuiflora)" December 31, 2009; retrieved from Erowid Experience Vaults. <https://erowid.org/experiences/exp.php?ID=76862>, retrieved December 31, 2009

From webpage

DOSE: T+ 0:00	160 mg	oral	Harmala Alkaloids	(powder / crystals)
T+ 0:35	580 mg	oral	Mimosa tenuiflora	(tea)
T+ 1:25	600 mg	oral	Mimosa tenuiflora	(tea)

From webpage "

1:00PM

I had previously **extracted the alkaloids from 2 ounces Syrian rue seeds yielding 1g of brownish crystals (which should be about 2/3 harmine HCl and 1/3 harmaline HCl).** I weighed out **600mg of**

	<p>extract and dissolved it in water. This was poured into 4 identical shot glasses, with the level on my glass slightly higher than my girlfriend's glass. I estimate that I took 160mg...</p> <p>1:35PM</p> <p>The combined cups of 'tea' were then split by volume into 4 portions. C and A both took 125ml, I took 138ml, and my girlfriend took 87ml. This works out to 0.58g of MHRB personally consumed, for an estimated 7mg of DMT, based on the results of an extraction on the rest of the root bark..."</p>
<p>3. A pharmaceutical composition comprising: (a) N,N-dimethyltryptamine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier; and (b) harmine or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.</p>	<p>1. Intl. Pat. Doc. No. WO2019081764A1 "Combination product for the treatment of neurological and/or psychiatric disorders" (Published May 2, 2019)</p> <p>From Page 18 lines 21-29 "Preferably, the compound described by formula (I) is N,N-dimethyltryptamine, N,N- diethyltryptamine, N,N-dipropyltryptamine, N,N-diisopropyltryptamine, 5-methoxy-N,N-dimethyltryptamine..."</p> <p>From page 27 lines 22-33 "In a preferred embodiment, any of the aforementioned combination products may further comprise a monoamine oxidase inhibitor which can boost the effectiveness of the compound described by formula (I). Preferably, the monoamine oxidase inhibitor is: a) a β-carboline such as harmine (CAS No. 442-51 -3), harmaline (CAS No. 304-21 -2), tetrahydroharmine (CAS No. 17019-01 -1), harmol (CAS No. 487-03-6), and/or harmalol (CAS No. 525-57-5), their salts and/or esters;...</p> <p>From page 27 lines 35-37 to page 28 lines 1-5 "In a preferred embodiment, the combination product is a mixture of the compound described by formula (I) and the 5-HT2A receptor antagonist, i.e. the combination product is a composition. In an alternative embodiment, the compound described by formula (I) and the 5-HT2A receptor antagonist are physically separated. For example, the compound described by formula (I) could be contained in one blister pack while the 5-HT2A receptor antagonist is contained within a separate blister pack or the compound described by formula (I) and the 5- HT2A receptor antagonist could be contained in the same pill but be physically separated by a barrier, such as a gelatin barrier."</p> <p>From page 18 lines 10-14 "Rather than a complex mixture of natural compounds derived from vegetation, the two active ingredients of the present invention may be substantially pure and may or may not be combined with pharmaceutically acceptable carrier and/or diluent as well as other controlled substances. In a preferred embodiment, the compound described by formula (I) is substantially pure."</p>

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From abstract “**Ayahuasca is a brew prepared from the water decoction of two Amazonian plants**, which is legally used for religious, cultural or therapeutic activities. The potential use of ayahuasca as a natural or phytotherapeutic drug is directly linked to the action of its active compounds and their connection with the **therapeutic efficacy** of the beverage. In this context, the aim of the present study was to establish a selective, sensitive and reproducible analytical method for the **quantification of the main active ayahuasca compounds**. **Thirty-eight** samples from the state of São Paulo, Brazil, were analyzed and the **simultaneous quantifications of N,N-dimethyltryptamine (DMT)**, tetrahydroharmine (THH), **harmine (HME)** and harmaline (HML) were performed. This study enabled the development of a fast **validated analytical method with minimal matrix interference and high reproducibility for the tracing of active ayahuasca compound concentrations for the first time**. This method is important as an auxiliary tool for the study of active compound effects in biological responses using different multi-omic platforms.”

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Residual range	-0.16 to 0.23	-0.07 to 0.18	-0.33 to 0.50	-0.029 to 0.032

4. The kit of parts according to claim 1 or the pharmaceutical composition of claim 3, wherein (a) is N,N-dimethyltryptamine fumarate and a pharmaceutically acceptable carrier.

16. SHROOMERY, “Re: Ayahuasca failure (Syrian Rue and MIMosa) [Re: thoraxx]” March 19, 2016; retrieved from Shroomery. <https://www.shroomery.org/forums/showflat.php/Number/23022449>; retrieved March 19, 2016

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The combined cups of 'tea' were then split by volume into 4 portions. C and A both took 125ml, I took 138ml, and my girlfriend took 87ml. This works out to 0.58g of MHRB personally consumed, for an **estimated 7mg of DMT**, based on the results of an extraction on the rest of the root bark...”

5. The kit of parts according to claim 1 or 4, or the pharmaceutical composition of claim 3 or 4, wherein (b) is harmine hydrochloride and a pharmaceutically acceptable carrier.

4. 1108, “Threshold Oral Experience Huasca Combo (Syrian Rue & M. tenuiflora)” December 31, 2009; retrieved from Erowid Experience Vaults. <https://erowid.org/experiences/exp.php?ID=76862>, retrieved December 31, 2009

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	<p>water. This was left to stand for a few minutes. We then began to filter out the powder and another cup of water was poured on the sludge that remained in the bottom of the cup. Filtering with coffee filters turned out to be a waste of time.</p> <p>1:35PM The combined cups of 'tea' were then split by volume into 4 portions. C and A both took 125ml, I took 138ml, and my girlfriend took 87ml. This works out to 0.58g of MHRB personally consumed, for an estimated 7mg of DMT, based on the results of an extraction on the rest of the root bark...”</p>										
<p>6. The kit of parts according to any one of claim 1, 4 or 5, or the kit of parts of any one of claim 3, 4 or 5, for use as a medicament.</p>	<p>3. INNEREXPLORER, “There Is Nothing To Be Afraid Of. Huasca Combo (B. caapi Extract & DMT Fumarate)” October 15, 2017; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=108203, retrieved October 15, 2017</p> <p>From webpage</p> <table border="1" data-bbox="586 919 1414 1014"> <tr> <td>DOSE: T+ 0:00</td> <td></td> <td>oral</td> <td>Banisteriopsis caapi</td> <td>(extract)</td> </tr> <tr> <td>T+ 0:20</td> <td>50 mg</td> <td>oral</td> <td>DMT</td> <td></td> </tr> </table> <p>From webpage “I have had several experiences with Caapi extract (180 mg harmine and 180 mg tetrahydroharmine) as well as with vine-only brews, but I have taken a pretty long break from both and have lately felt that this is the best medicine for me to work with.”</p> <p>From webpage “After a few successful and very rewarding sessions with the Caapi extract, I thought it would be good to add in some DMT. It just so happens that I had been planning on converting a gram of DMT freebase to DMT Fumarate, which is the ideal form of DMT for oral as well as IV/IM administration. At first, I was drawn to the idea of IM administration but I realized that I would need to spend a good deal of time preparing the proper safety precautions in order to minimize error or accidental injury. As such, the best route seemed to be oral in combination with the Caapi extract.</p> <p>Experiment #1:</p> <p>I recently experienced Caapi extract with 21mg DMT Fumarate (.32mg/kg) which is a very very small dose, barely threshold. I did this purposely in order to ease my way into working with this powerful combination again. The comeup on the Caapi extract was powerful</p>	DOSE: T+ 0:00		oral	Banisteriopsis caapi	(extract)	T+ 0:20	50 mg	oral	DMT	
DOSE: T+ 0:00		oral	Banisteriopsis caapi	(extract)							
T+ 0:20	50 mg	oral	DMT								

	<p>as usual and I delayed taking the DMT an extra 20 minutes, taking it at t+0:40 instead of t+0:20...</p> <p>In my next experiment, I plan on increasing the dose to 35mg DMT (.54mg/kg) in combination with the Caapi extract. I think this will be a bit more of a trip and will give me a better sense of my flight navigation skills. I am deliberately taking my time with this to get to know these medicines I am deliberately taking my time with this to get to know these medicines as they work together and how best to navigate the spaces they open up...</p> <p>Experiment #2:</p> <p>After careful research and reflection, I prepared to take my next journey with the Caapi extract (which contains 180mg tetrahydroharmine and 180mg harmine) in combination with 50mg DMT Fumarate (.781mg/kg)...</p> <p>... I poured the Caapi extract into a glass of grapefruit juice and allowed it to absorb into the juice, the process took about 3 minutes, and with the help of a stirring spoon, the powder was completely absorbed by the juice, forming citrate salts of the freebase alkaloids for more efficient absorption in the body. I read over my intentions again, reflected on them, asked the spirits of the four directions for protection on this journey, lit some incense, and drank the extract-containing juice. After drinking, I set a timer for 20 minutes on my watch so I would know when to take the capsule containing the DMT Fumarate...</p> <p>... Eventually, the timer went off and I promptly took the capsule containing 50mg DMT Fumarate..."</p>
<p>7. The kit of parts for use or the pharmaceutical composition for use according to claim 6, for use in treating a psychiatric, psychosomatic or somatic disorder.</p>	<p>5. OSORIO (2015) "Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report" <i>Revista Brasileira de Psiquiatria</i>. 37 (1): 13-20</p> <p>From abstract "Objectives: Ayahuasca (AYA), a natural psychedelic brew prepared from Amazonian plants and rich in dimethyltryptamine (DMT) and harmine, causes effects of subjective well-being and may therefore have antidepressant actions. This study sought to evaluate the effects of a single dose of AYA in six volunteers with a current depressive episode.</p> <p>Methods: Open-label trial conducted in an inpatient psychiatric unit.</p>

	<p>Results: Statistically significant reductions of up to 82% in depressive scores were observed between baseline and 1, 7, and 21 days after AYA administration, as measured on the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Anxious-Depression subscale of the Brief Psychiatric Rating Scale (BPRS)...</p> <p>Conclusions: These results suggest that AYA has fast-acting anxiolytic and antidepressant effects in patients with a depressive disorder.</p> <p>From page 19 “The findings of this preliminary study demonstrate the potential antidepressant and anxiolytic effects of AYA, effects that, importantly, have an earlier onset of action when compared to traditional antidepressants. These findings suggest that AYA may represent a powerful new substance for the treatment of depressive and anxiety symptoms. However, these results deserve careful analysis, given the inherent limitations of an uncontrolled, open-label study with a small sample size.”</p>
<p>8. The kit of parts for use or the pharmaceutical composition for use according to claim 6 or 7, wherein the psychiatric disorder is depression, stress-related affective disorder, major depressive disorder, dysthymia, treatment-resistant depression, burnout, anxiety, post-traumatic stress disorder, addiction, eating disorder, or obsessive-compulsive disorder.</p>	<p>1. Intl. Pat. Doc. No. WO2019081764A1 “Combination product for the treatment of neurological and/or psychiatric disorders” (Published May 2, 2019)</p> <p>From “The term "therapeutically effective amount refers to an amount of compound in a combination product which has a therapeutic effect and which is able to alleviate and/or cure a psychiatric and/or neurological disorder.”</p> <p>From “The term "psychiatric disorder" refers to a diagnosis by a mental health professional of a behavioral or mental pattern that may cause suffering or a poor ability to function in life. "Psychiatric disorders" may be persistent, relapsing and remitting, or occur as a single episode. In a preferred embodiment, the term "psychiatric disorder" refers to one or more disorders selected from the following: alcohol and substance use disorders, anxiety disorders, panic disorder, agoraphobia and other specific phobias, social anxiety disorder, post-traumatic stress disorder, obsessive compulsive disorder, generalized anxiety disorder, bipolar disorder, sleep and wake disorders, depression, anorexia nervosa, binge eating disorder, bulimia nervosa, psychosis, schizophrenia, autism spectrum disorders, developmental disorders, and personality disorders.”</p> <p>From Page 18 lines 21-29 “Preferably, the compound described by formula (I) is N,N-dimethyltryptamine, N,N- diethyltryptamine,</p>

N,N-dipropyltryptamine, N,N-diisopropyltryptamine, 5-methoxy-N,N-dimethyltryptamine...”

From **page 27 lines 22-33** “In a preferred embodiment, any of the aforementioned combination products may **further comprise a monoamine oxidase inhibitor which can boost the effectiveness of the compound** described by formula (I). **Preferably, the monoamine oxidase inhibitor is: a) a β -carboline such as harmine (CAS No. 442-51 -3), harmaline (CAS No. 304-21 -2), tetrahydroharmine (CAS No. 17019-01 -1), harmol (CAS No. 487-03-6), and/or harmalol (CAS No. 525-57-5), their salts and/or esters; ...**

From **page 27 lines 35-37 to page 28 lines 1-5** “**In a preferred embodiment, the combination product is a mixture of the compound described by formula (I) and the 5-HT_{2A} receptor antagonist, i.e. the combination product is a composition.** In an alternative embodiment, the compound described by formula (I) and the 5-HT_{2A} receptor antagonist are **physically separated**. For example, **the compound described by formula (I) could be contained in one blister pack while the 5-HT_{2A} receptor antagonist is contained within a separate blister pack or the compound described by formula (I) and the 5-HT_{2A} receptor antagonist could be contained in the same pill but be physically separated by a barrier, such as a gelatin barrier.**”

From **page 18 lines 10-14** “Rather than a complex mixture of natural compounds derived from vegetation, **the two active ingredients of the present invention may be substantially pure and may or may not be combined with pharmaceutically acceptable carrier and/or diluent** as well as other controlled substances. In a preferred embodiment, the compound described by formula (I) is substantially pure.”

11. STRASSMAN (1994) “Dose-Response Study of N,N-Dimethyltryptamine in Humans” Archives of General Psychiatry. 51(2): 85-97

From **page 86** “**Dimethyltryptamine fumarate** was prepared by David E. Nichols, PhD, Purdue University, West Lafayette, Ind. Purity, determined by gas chromatography-mass spectrometry and high-performance liquid chromatography, was greater than 99.9%. It was prepared for **clinical administration** by the Inpatient Pharmacy of the University of New Mexico Hospital in vials containing 40 mg/mL.”

From **page 88**

Demographic Characteristics of Subjects*

Subject No./ Age, y/ Sex	Occupation	Axis I Diagnoses	Marital Status	Family Psychiatric History	Times Used			
					Marijuana	Cocaine, Amphetamines	Hallucinogens	Methylene dioxymethamphetamine
1/45/M	Construction worker	None	Divorced ×2, married	None	10-20	0	10-20	10
2/39/F	Psychologist	None	Divorced ×2, married	Father, depression, chronic; eating disorder?; mother, "hysterical"	100s	50-100	>50	75-100
3/38/M	Physician	Major depression, resolved; cannabis dependence, partial remission	Divorced ×1	Father, depression (taking amitriptyline hydrochloride)	1000s	3	50	1
4/45/M	Psychologist	Adjustment disorder, depressed	Divorced ×3	Brother, adjustment disorder, mixed	>400	15	30	10-15
5/34/M	Graduate student	Alcohol dependence, in remission; cannabis abuse, in remission	Never married	Brother, major depression	1000s	20-25	20-30	1
6/37/M	Resident physician	Major depression, resolved	Never married	None	1000s	15-20	50-60	0
7/42/M	City administrator	None	Divorced ×1, married	None	100s	<10	>100	5-10
8/36/M	Drug dealer	Cannabis dependence, in remission; cocaine dependence, in remission; stimulant abuse, in remission	Divorced ×1, married	Father, alcohol abuse	1000s	100s	>200	5-10
9/46/M	Owner of large business	Adjustment disorder, depressed, resolved; alcohol abuse, in remission	Divorced ×1	Mother, alcohol abuse; father, alcohol abuse	100s	50-100	6	0
10/45/M	Restaurant manager, writer	Cocaine dependence, in remission; alcohol abuse, in remission; major depression, resolved; depressive disorder, NOS, resolved	Divorced ×3	Father, alcohol abuse	100s	100	>100	10-12
11/38/M	Physician	Prolonged (18-mo) grief reaction vs major depression, resolved	Divorced ×2	Mother, major depression; father, alcohol abuse	50	3	75-100	8
12/50/M	Counselor	None	Divorced ×2, married	Alcohol abuse	100s	15-20	10	2

*NOS indicates not otherwise specified. Subject 11 suffered a major depression during the study and was withdrawn before completing it. His data are included for illustrative purposes.

From page 86 “There was a high incidence of prior **major depression in the group**. Only one subject was suffering any current Axis I disorder; this was an **adjustment disorder** resulting from an impending divorce. There also was a high incidence of first-degree relatives suffering from **depression and/or alcohol abuse**. The number of exposures to hallucinogens ranged from six to "hundreds." Two subjects described a history of **cocaine dependence/abuse**, currently in remission; the remainder had little or no exposure to cocaine or amphetamines. Not all subjects had used marijuana equally, although all had some experience with it.”

5. OSORIO (2015) “Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report” Revista Brasileira de Psiquiatria. 37 (1): 13-20

From abstract “Objectives: **Ayahuasca (AYA), a natural psychedelic brew prepared from Amazonian plants and rich in dimethyltryptamine (DMT) and harmine, causes effects of subjective well-being and may therefore have antidepressant actions**. This study sought to evaluate the effects of a single dose of AYA in six volunteers with a current depressive episode.

Methods: Open-label trial conducted in an inpatient psychiatric unit.

Results: **Statistically significant reductions of up to 82% in depressive scores were observed between baseline and 1, 7, and 21 days after AYA administration**, as measured on the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Anxious-Depression subscale of the Brief Psychiatric Rating Scale (BPRS)...

Conclusions: **These results suggest that AYA has fast-acting anxiolytic and antidepressant effects in patients with a depressive disorder.**”

From **page 19** “The findings of this preliminary study demonstrate the **potential antidepressant and anxiolytic effects of AYA**, effects that, importantly, have an earlier onset of action when compared to traditional antidepressants. These findings suggest that **AYA may represent a powerful new substance for the treatment of depressive and anxiety symptoms**. However, these results deserve careful analysis, given the inherent limitations of an uncontrolled, open-label study with a small sample size.”

6. NUNES (2016) “Effects of Ayahuasca and its Alkaloids on Drug Dependence: A Systematic Literature Review of Quantitative Studies in Animals and Humans” *Journal of Psychoactive Drugs*. 48(3): 195-205

From **abstract** “Recently, **the anti-addictive potential of ayahuasca, a dimethyltryptamine(DMT)- and β-carboline-rich hallucinogenic beverage** traditionally used by indigenous groups of the Northwest Amazon and currently by syncretic churches worldwide, has received increased attention. To better evaluate this topic, we performed a systematic literature review using the PubMed database to find quantitative studies (using statistical analysis) that **assessed the effects of ayahuasca or its components in drug related symptoms or disorders**. We found five animal studies (using harmaline, **harmine**, or ayahuasca) and five observational studies of regular ayahuasca consumers. **All animal studies showed improvement of biochemical or behavioral parameters related to drug-induced disorders**. Of the five human studies, **four reported significant reductions of dependence symptoms or substance use, while one did not report significant results**. The mechanisms responsible for the anti-addictive

properties of ayahuasca and its alkaloids are not clarified, apparently involving both peripheral MAO-A inhibition by the **β-carbolines and central agonism of DMT** at 5-HT_{2A} receptors expressed in brain regions related to the **regulation of mood and emotions**. Although results are promising, controlled studies are needed to replicate these preliminary findings.”

7. INSERRA (2018) “Hypothesis: The Psychedelic Ayahuasca Heals Traumatic Memories via a Sigma 1 Receptor-Mediated Epigenetic-Mnemonic Process” *Frontier in Pharmacology*. 9: 330

From **page 1** “Ayahuasca ingestion modulates brain activity, neurotransmission, gene expression and epigenetic regulation. **N,N-Dimethyltryptamine (DMT, one of the alkaloids in Ayahuasca)** activates sigma 1 receptor (SIGMAR1) and others. SIGMAR1 is a multi-faceted stress responsive receptor which promotes cell survival, neuroprotection, neuroplasticity, and neuroimmunomodulation. **Simultaneously, monoamine oxidase inhibitors (MAOIs) also present in Ayahuasca prevent the degradation of DMT**. One peculiarity of SIGMAR1 activation and MAOI activity is the reversal of mnemonic deficits in preclinical models. **Since traumatic memories in post-traumatic stress disorder (PTSD) are often characterised by “repression” and PTSD patients ingesting Ayahuasca report the retrieval of such memories**, it cannot be excluded that DMT-mediated SIGMAR1 activation and the concomitant MAOIs effects during Ayahuasca ingestion might mediate such “anti-amnesic” process...”

8. RENELLI (2020) “An exploratory study of experiences with conventional eating disorder treatment and ceremonial ayahuasca for the healing of eating disorders” *Eating and Weight Disorders*. 25(2): 437-444

From **abstract** “Purpose Ayahuasca is a traditional Amazonian medicine that is currently being researched for its potential in treating a variety of mental disorders. This article reports on exploratory qualitative research relating to **participant experiences with ceremonial ayahuasca drinking and conventional treatment for eating disorders (EDs)**. It also explores the potential for ayahuasca as an adjunctive ED treatment.

	<p>Results Participant reports were organized with key themes including that ayahuasca: led to rapid reductions in ED thoughts and symptoms; allowed for the healing of the perceived root of the ED; helped to process painful feelings and memories; supported the internalization of greater self-love and self-acceptance; and catalyzed spiritual elements of healing.</p> <p>Conclusions The results suggest that ayahuasca may have potential as a valuable therapeutic tool, and further research—including carefully controlled clinical trials—is warranted.”</p>
<p>9. The kit of parts for use or the pharmaceutical composition for use according to any one of claims 6 to 8, wherein (a) and (b) are not to be administered perorally.</p>	<p>1. Intl. Pat. Doc. No. WO2019081764A1 “Combination product for the treatment of neurological and/or psychiatric disorders” (Published May 2, 2019)</p> <p>From page 33 lines 25-29 “In a preferred embodiment, the combination product is prepared for oral, sublingual, buccal, intranasal, intravenous, intramuscular, subcutaneous, rectal, transdermal, topical and/or inhalation-mediated administration routes, preferably oral, sublingual, inhalation-mediated and/or intranasal routes.”</p>
<p>10. The kit of parts for use or the pharmaceutical composition for use according to any one of claims 6 to 9, wherein (a) and (b) are to be administered simultaneously or sequentially.</p>	<p>1. Intl. Pat. Doc. No. WO2019081764A1 “Combination product for the treatment of neurological and/or psychiatric disorders” (Published May 2, 2019)</p> <p>From Page 18 lines 21-29 “Preferably, the compound described by formula (I) is N,N-dimethyltryptamine, N,N- diethyltryptamine, N,N-dipropyltryptamine, N,N-diisopropyltryptamine, 5-methoxy-N,N-dimethyltryptamine...”</p> <p>From page 27 lines 22-33 “In a preferred embodiment, any of the aforementioned combination products may further comprise a monoamine oxidase inhibitor which can boost the effectiveness of the compound described by formula (I). Preferably, the monoamine oxidase inhibitor is: a) a β-carboline such as harmine (CAS No. 442-51 -3), harmaline (CAS No. 304-21 -2), tetrahydroharmine (CAS No. 17019-01 -1), harmol (CAS No. 487-03-6), and/or harmalol (CAS No. 525-57-5), their salts and/or esters;...</p> <p>From page 27 lines 35-37 to page 28 lines 1-5 “In a preferred embodiment, the combination product is a mixture of the compound described by formula (I) and the 5-HT2A receptor antagonist, i.e. the combination product is a composition. In an alternative embodiment, the compound described by formula (I) and the 5-HT2A receptor antagonist are physically separated. For example, the compound described by formula (I) could be contained in one blister pack while the 5-HT2A receptor</p>

	<p>antagonist is contained within a separate blister pack or the compound described by formula (I) and the 5- HT2A receptor antagonist could be contained in the same pill but be physically separated by a barrier, such as a gelatin barrier.”</p> <p>3. INNEREXPLORER, “There Is Nothing To Be Afraid Of. Huasca Combo (B. caapi Extract & DMT Fumarate)” October 15, 2017; retrieved from Erowid Experience Vaults. https://erowid.org/experiences/exp.php?ID=108203, retrieved October 15, 2017</p> <p>From webpage</p> <table border="1" data-bbox="586 674 1416 764"> <tr> <td>DOSE: T+ 0:00</td> <td></td> <td>oral</td> <td>Banisteriopsis caapi</td> <td>(extract)</td> </tr> <tr> <td>T+ 0:20</td> <td>50 mg</td> <td>oral</td> <td>DMT</td> <td></td> </tr> </table> <p>From webpage “ Experiment #1: I recently experienced Caapi extract with 21mg DMT Fumarate (.32mg/kg) which is a very very small dose, barely threshold. I did this purposely in order to ease my way into working with this powerful combination again. The comeup on the Caapi extract was powerful as usual and I delayed taking the DMT an extra 20 minutes, taking it at t+0:40 instead of t+0:20. I don't think that would have reduced the efficacy of the DMT at all, but rather it was the very low dose of DMT that led to very little effects...”</p>	DOSE: T+ 0:00		oral	Banisteriopsis caapi	(extract)	T+ 0:20	50 mg	oral	DMT	
DOSE: T+ 0:00		oral	Banisteriopsis caapi	(extract)							
T+ 0:20	50 mg	oral	DMT								
<p>11. The kit of parts for use or the pharmaceutical composition for use according to any one of claims 6 to 10, wherein (a) is to be administered intranasally.</p>	<p>1. Intl. Pat. Doc. No. WO2019081764A1 “Combination product for the treatment of neurological and/or psychiatric disorders” (Published May 2, 2019)</p> <p>From page 33 lines 25-29 “In a preferred embodiment, the combination product is prepared for oral, sublingual, buccal, intranasal, intravenous, intramuscular, subcutaneous, rectal, transdermal, topical and/or inhalation-mediated administration routes, preferably oral, sublingual, inhalation-mediated and/or intranasal routes.”</p> <p>From Page 18 lines 21-29 “Preferably, the compound described by formula (I) is N,N-dimethyltryptamine, N,N- diethyltryptamine, N,N-dipropyltryptamine, N,N-diisopropyltryptamine, 5-methoxy-N,N-dimethyltryptamine...”</p> <p>From page 27 lines 22-33 “In a preferred embodiment, any of the aforementioned combination products may further comprise a</p>										

	<p>monoamine oxidase inhibitor which can boost the effectiveness of the compound described by formula (I). Preferably, the monoamine oxidase inhibitor is: a) a β-carboline such as harmine (CAS No. 442-51 -3), harmaline (CAS No. 304-21 -2), tetrahydroharmine (CAS No. 17019-01 -1), harmol (CAS No. 487-03-6), and/or harmalol (CAS No. 525-57-5), their salts and/or esters...</p>
<p>12. The kit of parts for use or the pharmaceutical composition for use according to any one of claims 6 to 11, wherein (a) is to be administered in a dose of between 10 mg to 100 mg of N,N-dimethyltryptamine per administration, preferably in an incremental manner over a period of time of between 60 to 180 minutes.</p>	<p>14. GALLIMORE (2016) “A Model for the Application of Target-Controlled Intravenous Infusion for a Prolonged Immersive DMT Psychedelic Experience” <i>Frontiers in Pharmacology</i>. 7:1-11</p> <p>From page 6 “To examine the possibility of effect site concentration overshoot, we performed simulations using the Gouzoulis-Mayfrank infusion protocol: 0.3 mg/kg bolus, followed by an infusion beginning at 1.5 min, at a rate of 0.02 mg/kg/min over 84 min. Figure 4 shows the expected effect site concentration over this infusion period for a 75 kg subject. The initial bolus produces an effect site concentration of 80 ng/ml; i.e., a breakthrough dose. Once the infusion begins, however, the concentration rises steadily, and reaches 150 ng/ml by the end of the session. This is a very high concentration and is certain to produce extremely intense effects in almost all individuals.</p> <p>Using our PK model, we developed an infusion protocol that maintains an effect site concentration of ~100 ng/ml in a 75 kg subject (Figure 5). An initial bolus of 25 mg infused over 30 s rapidly brings the effect site concentration to just over 100 ng/ml. Although the plasma concentration spikes at over 200 ng/ml, the desired effect site concentration is reached smoothly with very little overshoot. The infusion begins at 2 min at a rate of 4.2 mg/min. The infusion is updated every min, and decreases according to the peripheral transfer rate decay (the exponential term in the RT equation). Steady state does not occur until after 20 min of infusion, after which a constant maintenance infusion rate of 0.93 mg/min is employed.”</p>

From page 7 “

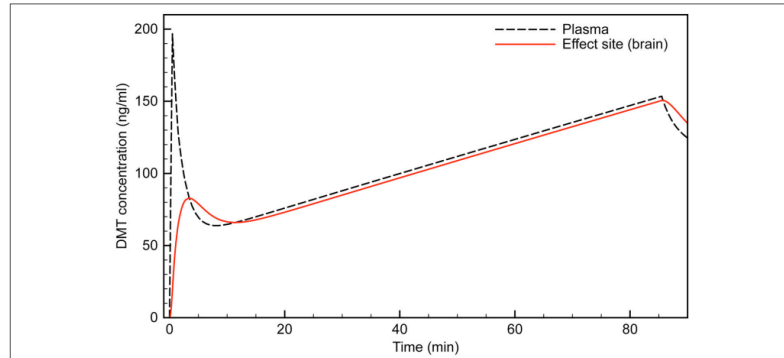


FIGURE 4 | Simulated time course of plasma and effect site DMT concentration using the (Gouzoulis-Mayfrank et al., 2005) protocol.

From page 8 “

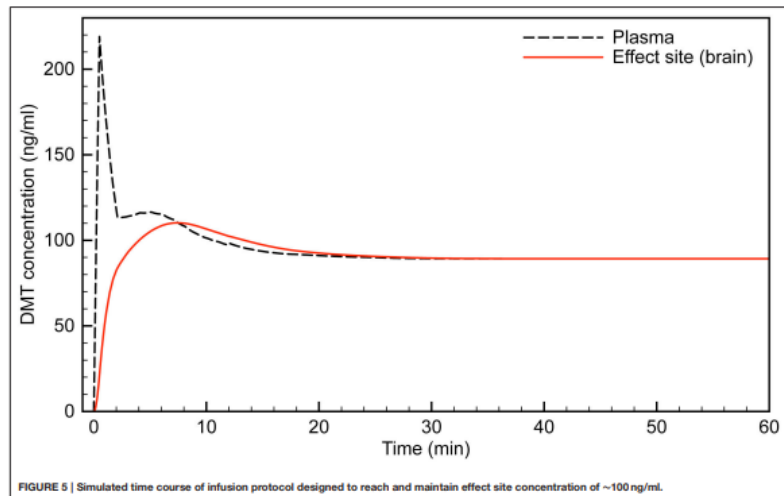


FIGURE 5 | Simulated time course of infusion protocol designed to reach and maintain effect site concentration of ~100 ng/ml.

11. STRASSMAN (1994) “Dose-Response Study of N,N-Dimethyltryptamine in Humans” Archives of General Psychiatry. 51(2): 85-97

From **abstract** “Methods: **Dimethyltryptamine**, an endogenous mammalian hallucinogen and drug of abuse, was administered **intravenously at 0.05, 0.1, 0.2, and 0.4 mg/kg** to 11 experienced hallucinogen users, in a double-blind, saline placebo controlled, randomized design. Treatments were separated by at least 1 week.”

13. U.S. Pat. App. Doc. No. US2020/0179349A1 “Methods Of Treating Food Allergy Conditions” (Published June 11, 2020)

From [0076] “In some embodiments, **DMT** may be administered at or above a threshold dose, including but not limited to e.g., a threshold dose at or above **10 milligrams (mg)**, including e.g., where smoked delivery is employed. In some instances, a threshold dose of DMT may range from **2 mg to 10 mg**, including e.g., by smoked delivery. In some embodiments, DMT may be administered as a light dose, including but not limited to e.g., a light dose ranging from **10 mg to 20 mg**, including e.g., by smoked delivery. In some embodiments, DMT may be administered as a common dose, including but not limited to e.g., a common dose ranging from **20 mg to 40 mg**, including e.g., by smoked delivery. In some embodiments, DMT may be administered as a strong dose, including but not limited to e.g., a strong dose ranging from **40 mg to 60 mg**, including e.g., by smoked delivery. In some embodiments, DMT may be administered as a heavy dose, including but not limited to e.g., where **DMT is administered at a dose above 60 mg**, e.g., by smoked delivery.”

From [0024] “In some instances, an amount of a **psychedelic agent administered** to a subject may be in the milligram range, including but not limited to e.g., from **1 mg to 1000 mg, from 2 mg to 1000 mg, from 3 mg to 1000 mg, from 4 mg to 1000 mg, from 5 mg to 1000 mg, from 10 mg to 1000 mg, from 15 mg to 1000 mg, from 20 mg to 1000 mg, from 30 mg to 1000 mg, from 40 mg to 1000 mg, from 50 mg to 1000 mg, from 75 mg to 1000 mg**, from 100 mg to 1000 mg, from 150 mg to 1000 mg, from 200 mg to 1000 mg, from 300 mg to 1000 mg, from 400 mg to 1000 mg, from 500 mg to 1000 mg, from 600 mg to 1000 mg, from 700 mg to 1000 mg, from 800 mg to 1000 mg, from 900 mg to 1000 mg, from 1 mg to 900 mg, from 1 mg to 800 mg, from 1 mg to 700 mg, from 1 mg to 600 mg, from 1 mg to 500 mg, from 1 mg to 450 mg, from 1 mg to 400 mg, from 1 mg to 350 mg, from 1 mg to 300 mg, from 1 mg to 250 mg, from 1 mg to 200 mg, from 1 mg to 175 mg, from 1 mg to 150 mg, from 1 mg to 125 mg, from **1 mg to 100 mg**, etc.”

From [0074] “Useful **tryptamine psychedelic agents** include but are not limited to e.g., diethyltryptamine (DET), N,N-**dimethyltryptamine (DMT)**...etc”

From [0161] “Any convenient and appropriate route of administration may be employed in **delivering a psychedelic agent** to a subject, including but not limited to e.g., **oral, inhalation** (e.g., smoked, vaporized, etc.), **intra-arteria injection/infusion, intravenous injection/infusion**, intramuscular injection, as well as topical routes, including e.g., transdermal, transmucosal (e.g., sublingual,

insufflation, and/or **buccal**), and the like. In some instances, a delivery device configured for delivering the one or more psychedelic agents according to any desired and appropriate route of delivery may be employed.”

3. INNEREXPLORER, “There Is Nothing To Be Afraid Of. Huasca Combo (B. caapi Extract & DMT Fumarate)” October 15, 2017; retrieved from Erowid Experience Vaults.
<https://erowid.org/experiences/exp.php?ID=108203>, retrieved October 15, 2017

From webpage

DOSE: T+ 0:00		oral	Banisteriopsis caapi	(extract)
T+ 0:20	50 mg	oral	DMT	

From **webpage** “I have had several experiences with **Caapi extract (180 mg harmine and 180 mg tetrahydroharmine)** as well as with vine-only brews, but I have taken a pretty long break from both and have lately felt that this is **the best medicine for me** to work with.”

From **webpage** “**After a few successful and very rewarding sessions with the Caapi extract, I thought it would be good to add in some DMT.** It just so happens that I had been planning on converting a gram of DMT freebase to **DMT Fumarate, which is the ideal form of DMT for oral** as well as IV/IM administration. At first, I was drawn to the idea of IM administration but I realized that I would need to spend a good deal of time preparing the proper safety precautions in order to minimize error or accidental injury. **As such, the best route seemed to be oral in combination with the Caapi extract.**

Experiment #1:

I recently experienced Caapi extract with 21mg DMT Fumarate (.32mg/kg) which is a very very small dose, barely threshold. I did this purposely in order to ease my way into working with this powerful combination again. **The comeup on the Caapi extract was powerful as usual and I delayed taking the DMT an extra 20 minutes, taking it at t+0:40 instead of t+0:20.** I don't think that would have reduced the efficacy of the DMT at all, but rather it was the very low dose of DMT that led to very little effects. It was interesting that once I felt the DMT come on I felt very very tired and almost felt like I slept through the whole experience, though the two purges that I had

were very emotionally based and were centered around purging negative thought patterns I have kept inside.

In my next experiment, **I plan on increasing the dose to 35mg DMT (.54mg/kg) in combination with the Caapi extract.** I think this will be a bit more of a trip and will give me a better sense of my flight navigation skills. I am deliberately taking my time with this to get to know these medicines I am deliberately taking my time with this to get to know **these medicines as they work together** and how best to navigate the spaces they open up. This is how the shamans came to understand their work with the plants. Gradual increases in doses and getting to know the spirits of these medicines.

Experiment #2:

After careful research and reflection, I prepared to take my next journey with the **Caapi extract (which contains 180mg tetrahydroharmine and 180mg harmine) in combination with 50mg DMT Fumarate (.781mg/kg)...**

... I poured the Caapi extract into a glass of grapefruit juice and allowed it to absorb into the juice, the process took about 3 minutes, and with the help of a stirring spoon, the powder was completely absorbed by the juice, forming citrate salts of the freebase alkaloids for more efficient absorption in the body. I read over my intentions again, reflected on them, asked the spirits of the four directions for protection on this journey, lit some incense, and drank the extract-containing juice. After drinking, **I set a timer for 20 minutes on my watch so I would know when to take the capsule containing the DMT Fumarate...**

... Eventually, the timer went off and **I promptly took the capsule containing 50mg DMT Fumarate.** Within 15 minutes, I was feeling the first alerts. A slight lethargy and softening of emotions..."

12. EROWID, "DMT Dosage" February 21, 2015; retrieved from Erowid. https://erowid.org/chemicals/dmt/dmt_dose.shtml, retrieved February 21, 2015

From webpage "

	<table border="1" style="background-color: black; color: yellow; text-align: center; width: 100%;"> <thead> <tr> <th colspan="2">Smoked/Vaporized DMT Dosages</th> </tr> </thead> <tbody> <tr> <td>Threshold</td> <td>2 - 5 mg</td> </tr> <tr> <td>Light</td> <td>10 - 20 mg</td> </tr> <tr> <td>Common</td> <td>20 - 40 mg</td> </tr> <tr> <td>Strong</td> <td>40 - 60 mg</td> </tr> </tbody> </table> <p style="background-color: black; color: yellow; padding: 5px;"> Onset : 15 - 60 seconds Duration : 5 - 20 minutes Normal After Effects : 15 - 60 minutes </p>	Smoked/Vaporized DMT Dosages		Threshold	2 - 5 mg	Light	10 - 20 mg	Common	20 - 40 mg	Strong	40 - 60 mg
Smoked/Vaporized DMT Dosages											
Threshold	2 - 5 mg										
Light	10 - 20 mg										
Common	20 - 40 mg										
Strong	40 - 60 mg										
<p>13. The kit of parts or the pharmaceutical composition for use according to any one of claims 6 to 12, wherein (b) is to be administered buccally and/or sublingually.</p>	<p>1. Intl. Pat. Doc. No. WO2019081764A1 “Combination product for the treatment of neurological and/or psychiatric disorders” (Published May 2, 2019)</p> <p>From page 33 lines 25-29 “In a preferred embodiment, the combination product is prepared for oral, sublingual, buccal, intranasal, intravenous, intramuscular, subcutaneous, rectal, transdermal, topical and/or inhalation-mediated administration routes, preferably oral, sublingual, inhalation-mediated and/or intranasal routes.”</p> <p>From Page 18 lines 21-29 “Preferably, the compound described by formula (I) is N,N-dimethyltryptamine, N,N- diethyltryptamine, N,N-dipropyltryptamine, N,N-diisopropyltryptamine, 5-methoxy-N,N-dimethyltryptamine...”</p> <p>From page 27 lines 22-33 “In a preferred embodiment, any of the aforementioned combination products may further comprise a monoamine oxidase inhibitor which can boost the effectiveness of the compound described by formula (I). Preferably, the monoamine oxidase inhibitor is: a) a β-carboline such as harmine (CAS No. 442-51 -3), harmaline (CAS No. 304-21 -2), tetrahydroharmine (CAS No. 17019-01 -1), harmol (CAS No. 487-03-6), and/or harmalol (CAS No. 525-57-5), their salts and/or esters...</p> <p>From page 27 lines 35-37 to page 28 lines 1-5 “In a preferred embodiment, the combination product is a mixture of the compound described by formula (I) and the 5-HT2A receptor antagonist, i.e. the combination product is a composition. In an alternative embodiment, the compound described by formula (I) and the 5-HT2A receptor antagonist are physically separated. For example, the compound described by formula (I) could be contained in one blister pack while the 5-HT2A receptor antagonist is contained within a separate blister pack or the compound described by formula (I) and the 5- HT2A receptor antagonist could be contained in the same pill but be physically separated by a barrier, such as a gelatin barrier.”</p>										

	<p>From page 18 lines 10-14 “Rather than a complex mixture of natural compounds derived from vegetation, the two active ingredients of the present invention may be substantially pure and may or may not be combined with pharmaceutically acceptable carrier and/or diluent as well as other controlled substances. In a preferred embodiment, the compound described by formula (I) is substantially pure.”</p>
<p>14. The kit of parts for use or the pharmaceutical composition for use according to any one of claims 6 to 13, wherein (b) is to be administered in a dose of between 75 mg to 300 mg of harmine per administration.</p>	<p>15. EROWID, “Tihkal The Continuation Alexander & Ann Shulgin #14. HARMINE b-CARBOLINE, 7-METHOXY; 7-METHOXY-b-CARBOLINE; BANISTERINE; YAGEINE; TELEPATHINE; LEUCOHARMINE” February 21, 2015; retrieved from Erowid. https://erowid.org/library/books_online/tihkal/tihkal14.shtml, retrieved February 21, 2015</p> <p>From webpage “... As with harmaline, a number of drug combinations have been studied using harmine as the potential deaminase inhibitor. This is, after all, much closer to the basic structure of ayahuasca, where the plant Banisteriopsis caapi is the native inhibitory component, and it contains much more harmine than harmaline. In measured experiments, the use of harmine in the 140 to 190 milligram range, administered with 35 to 40 milligrams DMT, produced unmistakable effects lasting from one to three hours. Trials with smaller amounts, with 120 to 140 milligrams of harmine and 30 milligrams of DMT produced no signs of central activity at all. Harmine apparently is an effective, although modest, promoter of oral activity of DMT. At least this occurs at levels where it itself is substantially without action, so here it may truly be a facilitator rather than a participant.”</p> <p>From webpage “(with 140 mg, orally) "There was no stimulation, no suggestion of entheogenic response, perhaps a little bit of sedation which was still evident several hours later. It was sufficiently mild as to make me forget I had ingested anything.”</p> <p>(with 150-200 mg, i.v. [clinical distillation of Pennes and Hoch]) "With this route, 5 of 11 subjects reported visual hallucinations of varying degrees of complexity and organization. Bradycardia and hypotension occurred with all doses of intravenous harmine despite a 20 to 30 minute injection time, thereby limiting maximum dosage to 300.0 mg. Recovery occurred in about 30 minutes. The drug was hallucinogenic by oral or subcutaneous routes.”</p>

(with 300 mg, sublingually) "I found myself pleasantly relaxed and withdrawn from my environment. There was a slightly diminished capacity to concentrate."...

3. INNEREXPLORER, "There Is Nothing To Be Afraid Of. Huasca Combo (B. caapi Extract & DMT Fumarate)" October 15, 2017; retrieved from Erowid Experience Vaults. <https://erowid.org/experiences/exp.php?ID=108203>, retrieved October 15, 2017

From webpage

DOSE: T+ 0:00		oral	Banisteriopsis caapi	(extract)
T+ 0:20	50 mg	oral	DMT	

From webpage "I have had several experiences with **Caapi extract (180 mg harmine and 180 mg tetrahydroharmine)** as well as with vine-only brews, but I have taken a pretty long break from both and have lately felt that this is **the best medicine for me** to work with."

From webpage "After a few successful and very rewarding sessions with the **Caapi extract, I thought it would be good to add in some DMT.** It just so happens that I had been planning on converting a gram of DMT freebase to **DMT Fumarate, which is the ideal form of DMT for oral** as well as IV/IM administration. At first, I was drawn to the idea of IM administration but I realized that I would need to spend a good deal of time preparing the proper safety precautions in order to minimize error or accidental injury. **As such, the best route seemed to be oral in combination with the Caapi extract.**

Experiment #1:

I recently experienced Caapi extract with 21mg DMT Fumarate (.32mg/kg) which is a very very small dose, barely threshold. I did this purposely in order to ease my way into working with this powerful combination again. **The comeup on the Caapi extract was powerful as usual and I delayed taking the DMT an extra 20 minutes, taking it at t+0:40 instead of t+0:20.** I don't think that would have reduced the efficacy of the DMT at all, but rather it was the very low dose of DMT that led to very little effects...

In my next experiment, **I plan on increasing the dose to 35mg DMT (.54mg/kg) in combination with the Caapi extract...** I am

deliberately taking my time with this to get to know these medicines I am deliberately taking my time with this to get to know **these medicines as they work together** and how best to navigate the spaces they open up...

Experiment #2:

After careful research and reflection, I prepared to take my next journey with the **Caapi extract (which contains 180mg tetrahydroharmine and 180mg harmine) in combination with 50mg DMT Fumarate (.781mg/kg)...**

... **I poured the Caapi extract into a glass of grapefruit juice** and allowed it to absorb into the juice, **the process took about 3 minutes, and with the help of a stirring spoon,** the powder was completely absorbed by the juice, **forming citrate salts of the freebase alkaloids for more efficient absorption in the body.** I read over my intentions again, reflected on them, asked the spirits of the four directions for protection on this journey, lit some incense, and drank the extract-containing juice. After drinking, **I set a timer for 20 minutes on my watch so I would know when to take the capsule containing the DMT Fumarate...**

... Eventually, the timer went off and **I promptly took the capsule containing 50mg DMT Fumarate...**”

15. The kit of parts for use or the pharmaceutical composition for use according to any one of claims 6 to 14, wherein the administration of (b) is to be followed by the administration of (a).

3. INNEREXPLORER, “There Is Nothing To Be Afraid Of. Huasca Combo (B. caapi Extract & DMT Fumarate)” October 15, 2017; retrieved from Erowid Experience Vaults. <https://erowid.org/experiences/exp.php?ID=108203>, retrieved October 15, 2017

From **webpage**

DOSE:				
T+ 0:00		oral	Banisteriopsis caapi	(extract)
T+ 0:20	50 mg	oral	DMT	

From **webpage** “I have had several experiences with **Caapi extract (180 mg harmine and 180 mg tetrahydroharmine)** as well as with vine-only brews, but I have taken a pretty long break from both and have lately felt that this is **the best medicine for me** to work with.”

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DMT. It just so happens that I had been planning on converting a gram of DMT freebase to **DMT Fumarate, which is the ideal form of DMT for oral** as well as IV/IM administration. At first, I was drawn to the idea of IM administration but I realized that I would need to spend a good deal of time preparing the proper safety precautions in order to minimize error or accidental injury. **As such, the best route seemed to be oral in combination with the Caapi extract.**

Experiment #1:

I recently experienced Caapi extract with 21mg DMT Fumarate (.32mg/kg) which is a very very small dose, barely threshold. I did this purposely in order to ease my way into working with this powerful combination again. **The comeup on the Caapi extract was powerful as usual and I delayed taking the DMT an extra 20 minutes, taking it at t+0:40 instead of t+0:20...**

In my next experiment, **I plan on increasing the dose to 35mg DMT (.54mg/kg) in combination with the Caapi extract.** I think this will be a bit more of a trip and will give me a better sense of my flight navigation skills. I am deliberately taking my time with this to get to know these medicines I am deliberately taking my time with this to get to know **these medicines as they work together** and how best to navigate the spaces they open up. This is how the shamans came to understand their work with the plants. Gradual increases in doses and getting to know the spirits of these medicines.

Experiment #2:

After careful research and reflection, I prepared to take my next journey with the **Caapi extract (which contains 180mg tetrahydroharmine and 180mg harmine) in combination with 50mg DMT Fumarate (.781mg/kg)...**

... I poured the Caapi extract into a glass of grapefruit juice and allowed it to absorb into the juice, **the process took about 3 minutes, and with the help of a stirring spoon,** the powder was completely absorbed by the juice, **forming citrate salts of the freebase alkaloids for more efficient absorption in the body.** I read over my intentions again, reflected on them, asked the spirits of the four directions for protection on this journey, lit some incense, and drank the extract-containing juice. After drinking, **I set a timer for 20 minutes on my watch so I would know when to take the capsule containing the DMT Fumarate...**

	<p>... Eventually, the timer went off and I promptly took the capsule containing 50mg DMT Fumarate..."</p>
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ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/012,122

RECEIPT DATE / TIME
11/20/2023 03:23:44 PM Z ET

ATTORNEY DOCKET #

Title of Invention

Application Information

APPLICATION TYPE	PATENT #
CONFIRMATION #	FILED BY Sisi Li
PATENT CENTER # 63323001	FILING DATE 12/21/2022
CUSTOMER # -	FIRST NAMED INVENTOR
INTL. APPLICATION # -	INTL. FILING DATE -
CORRESPONDENCE ADDRESS	AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 23

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
third-party-preissuance-submission.pdf	3	Third-Party Submission Under 37 CFR 1.290	79 KB
Concise-description-generated.pdf	2	Concise Description of Relevance	40 KB
Third-party-notification-request.pdf	1	Request for Notification of Non-compliant Third-Party Submission	14 KB
Claims_Chart.pdf	32	-	1034 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32) 32	Concise Description of Relevance	946 KB

Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
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Digest

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/012,122

RECEIPT DATE / TIME
11/20/2023 03:23:44 PM Z ET

ATTORNEY DOCKET #

Title of Invention

Application Information

APPLICATION TYPE	PATENT #
CONFIRMATION #	FILED BY Sisi Li
PATENT CENTER # 63323001	AUTHORIZED BY -
CUSTOMER # -	FILING DATE 12/21/2022
INTL. APPLICATION # -	INTL. FILING DATE -
CORRESPONDENCE ADDRESS -	FIRST NAMED INVENTOR

Payment Information

PAYMENT METHOD CARD / 0642	PAYMENT TRANSACTION ID E2023AJF25238803	PAYMENT AUTHORIZED BY Sisi Li
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1818	DOCUMENT FEE FOR THIRD-PARTY SUBMISSIONS (SEE 37 CFR 1.290(F))	180.00	1	180.00
			TOTAL AMOUNT:	\$180.00

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
18/012,122

RECEIPT DATE / TIME
11/20/2023 04:03:44 PM Z ET

ATTORNEY DOCKET #

Title of Invention

Application Information

APPLICATION TYPE	PATENT #
CONFIRMATION #	FILED BY Sisi Li
PATENT CENTER # 63324009	FILING DATE 12/21/2022
CUSTOMER # -	FIRST NAMED INVENTOR
INTL. APPLICATION # -	INTL. FILING DATE -
CORRESPONDENCE ADDRESS	AUTHORIZED BY -

Documents

TOTAL DOCUMENTS: 15

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
Third-party-notification-request.pdf	1	Request for Notification of Non-compliant Third-Party Submission	14 KB
third-party-preissuance-submission.pdf	2	Third-Party Submission Under 37 CFR 1.290	64 KB
Concise-description-generated.pdf	2	Concise Description of Relevance	33 KB
11_STRASSMAN.pdf	13	-	7892 KB
11_STRASSMAN-NPL.pdf (1-13)	13	Non Patent Literature	7880 KB

Claims_Chart.pdf		32	-	1034 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
Claims_Chart-3P.RELEVANCE.pdf	(1-32)	32	Concise Description of Relevance	946 KB
12_EROWID.pdf		1	-	226 KB
12_EROWID-NPL.pdf	(1-1)	1	Non Patent Literature	219 KB
14_GALLIMORE.pdf		11	-	1247 KB
14_GALLIMORE-NPL.pdf	(1-11)	11	Non Patent Literature	1052 KB
15_EROWID.pdf		2	-	426 KB
15_EROWID-NPL.pdf	(1-2)	2	Non Patent Literature	418 KB
16_SHROOMERY.pdf		3	-	806 KB
16_SHROOMERY-NPL.pdf	(1-3)	3	Non Patent Literature	798 KB
13_US20200179349A1.pdf		23	-	2877 KB
13_US20200179349A1-	(1-23)	23	Foreign Reference	2873 KB

FOR.pdf

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
Third-party-notification-request.pdf	5A028C936E387252DEC1AC9FF8CE1FE73C03DFE5C3463142E CB8A758BB179A5B745CB85989F1227ABB3C0FF8C41F184CA6 5D15087CA240705465AB91E8C864CA
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Claims_Chart- 3P.RELEVANCE.pdf	4863D11CBCDB716F063BDC145241BF624D006F82F0D7B2946 B4FB8A196B639E02570D687BF1AB23F9C1D26CA273F3E8FD1 0112829B1A53DD933C39330612CB70
Claims_Chart- 3P.RELEVANCE.pdf	BBE1391EA92CFE2629834136B1153636C87ACA73187BF6AD5 FF1CF0FCC1A1004546139B77A0FDED43952F34C22BAD1D9A C6935D0F1AC43C02E9105884C3CA1B0
Claims_Chart- 3P.RELEVANCE.pdf	DE4242E4DDC1B6C809C8F7AAFE20D4378D15A830E94C0ED8 299B8E94CF3B91D28E7D7601CF09A1C18BFDE7E357B4F4446 54E0EC48D04FFDA4A4C5BDF2BE71852
Claims_Chart- 3P.RELEVANCE.pdf	13DE24D9196F4AF111A49D3C11BA39F73191F49C8ED866097 F46A7A5679962556D8E3A17661ABC473701FE6F29FEB9AC375 C4BF2BBF693A3A833FC72F43EA3AA
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16_SHROOMERY.pdf	9E3FFC66A056924994CBD54372BF2AE7CE3F6FF23E56F8DEF 60A3695D185E5A70943A05F24C7FFF87361642D739EC48C967 104151292BBECF5149D03DFB47075
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13_US20200179349A1.pdf	0D1EC69A0ACEB84AD3A555FD6FF482A12E90532EC9D42529 FA8F9C6898BC85F0BD3C238D3A98B4E0ECF98BA2E30824064 8FD2534389EADE17F1B6F7D3265C34C
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ELECTRONIC PAYMENT RECEIPT

APPLICATION #
18/012,122

RECEIPT DATE / TIME
11/20/2023 04:03:44 PM Z ET

ATTORNEY DOCKET #

Title of Invention

Application Information

APPLICATION TYPE	PATENT #
CONFIRMATION #	FILED BY Sisi Li
PATENT CENTER # 63324009	AUTHORIZED BY -
CUSTOMER # -	FILING DATE 12/21/2022
INTL. APPLICATION # -	INTL. FILING DATE -
CORRESPONDENCE ADDRESS -	FIRST NAMED INVENTOR

Payment Information

PAYMENT METHOD CARD / 0642	PAYMENT TRANSACTION ID E2023AJG06196812	PAYMENT AUTHORIZED BY Sisi Li
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1818	DOCUMENT FEE FOR THIRD-PARTY SUBMISSIONS (SEE 37 CFR 1.290(F))	180.00	1	180.00
			TOTAL AMOUNT:	\$180.00

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