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(54) Title: COMPOSITIONS FOR REDUCING INFLAMMATION TO IMPROVE OR MAINTAIN MENTAL OR PHYSICAL HEALTH

(57) Abstract: The present disclosure provides compositions and methods for reducing inflammation to improve or maintain mental health or physical health in an individual. In some aspects, the compositions include at least one 5HT2A agonist and at least one TRP agonist, wherein the therapeutically effective amount of the 5HT2A agonist is between about 1 μg and about 300 mg and the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.01 mg and about 300 mg. The compositions may be formulated for any suitable ingestion mode, including gastrointestinal, transmucosal and parenteral.

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COMPOSITIONS FOR REDUCING INFLAMMATION TO IMPROVE OR MAINTAIN MENTAL OR PHYSICAL HEALTH

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

[0001] The present disclosure relates to compositions for reducing inflammation to improve or maintain mental or physical health.

BACKGROUND

[0002] Depression has become an epidemic in the United States and is only projected to get worse. The NIMH lists clinical depression is diagnosed in 7% of U.S. adults and there are growing numbers of children and teenagers in recent years. Depression and mental illness are the leading cause of disability in the world, costing the economy trillions a year in lost productivity, missed days of work and care for the many physical and mental illnesses related to depression, like anxiety, posttraumatic stress disorder, migraines and sleep disorders. Depressive episodes are periods of two weeks or longer experiencing low mood, coupled with other symptoms such as poor self-image, sleep difficulty, loss of appetite, poor concentration, and low energy. Among U.S. adolescents, a disturbingly high rate has reported having experienced either major depression or low-grade depression. According to the World Health Organization, about five percent of the world's population is depressed. Though psychotherapy is available to some individuals, a common strategy for dealing with depression increasingly includes pharmaceuticals and often more than one is prescribed in combination. Pharmaceutical antidepressants work by indirect methods through alter the signaling of stress hormones such as norepinephrine and neurotransmitters serotonin and dopamine that influence mood, energy, focus, and motivation. These drugs were designed based on the assumption that depression is due to biochemical imbalance in the brain. The most common antidepressants are serotonin re-uptake inhibitors ("**SSRIs**") which act to prevent re-uptake and subsequent breakdown of 5-hydroxy-tryptamine ("**5-HT**"), commonly referred to as serotonin, an important neurotransmitter. Increasing the pool of serotonin in the brain through breakdown

inhibition improves mood in many individuals after three to four weeks of regularly taking an SSRI medication.

[0003] There has been little innovation in the antidepressant field since SSRIs were first introduced. Current medications have limited efficacy in controlling the symptoms of major depressive disorder ("**MDD**"). SSRIs often take four to eight weeks to show efficacy and are associated with adverse events on long-term use. Side effects of antidepressants are common and include nausea, vomiting or diarrhea, headache, drowsiness, dry mouth, insomnia, nervousness, agitation or restlessness, dizziness, blurred vision, sexual problems, such as reduced sexual desire, difficulty reaching orgasm or inability to maintain an erection (erectile dysfunction), impact on appetite, leading to weight loss or weight gain and increased risk if suicide. With suicides in the U.S. at their highest number in thirty years, there is need for rapid solutions and for more effective solutions.

[0004] In addition to diagnosed chronic and clinical depressions, some depression arises for no apparent reason and persists chronically. Such depression sometimes goes undiagnosed. Similarly, situational depression may follow a significant loss or life event, such as the death of a loved one, chronic illness, separation or divorce. To an extent, depression is a normal and necessary adaptive response to the inevitable changes and phases of life. Current medications do little to deal with the chronic depression and the acute depression described in this paragraph in the general population. With depression diagnosis going up and increased prescriptions given for long periods of time, there is need for alternative solutions for dealing with both acute and chronic depression. Furthermore, there is no solution for those who have not been medically diagnosed as "depressed" and/or those who are not depressed (medically diagnosed or not), but are looking to enhance aspects of creativity, mindfulness/awareness, sexual desire and other natural feelings that may enhance the human experience.

SUMMARY

[0005] Compositions disclosed may be used to reduce inflammation for improving or maintaining mental or physical health, including to mitigate, eliminate or otherwise correct depression, anxiety, PTSD, mood disorders, pain and digestive problems, and to also reduce the use of other substances including pharmaceutical and illicit drugs. The

compositions include at least one 5HT2A serotonin receptor agonist and one TRP receptor agonist, and may include at least one TRP receptor antagonist. The compositions may be applied to multimodal treatment of inflammation and of conditions associated with inflammation, including depression. The interaction of the compositions with the 5HT2A and TRP receptors results in altered activity of nociceptor cells and may also influence the endocannabinoid signaling system.

[0006] A 5HT2A agonist in combination with a TRP agonist provides a multimodal effect and shows improved efficacy over a 5HT2A agonist alone at an equivalent dose. Some examples of 5HT2A agonists used in the compositions provided herein include 4AcO-DMT (psilacetin), psilocybin, serotonin, lysergic acid amide, lysergic acid α-hydroxyethylamide, myristicin and elemicin. These compounds may be found in psilocybin-containing fungi, morning glory seeds, Hawaiian baby woodrose seeds and nutmeg. Some examples of TRP agonists used in the compositions provided herein include capsaicin, carvacrol, cinnamaldehyde, curcumin, eugenol, and piperine, and myristicin. These compounds may be sourced from materials that are generally regarded as safe ("**GRAS**"), such as cayenne peppers, turmeric, oregano, cloves, cinnamon and nutmeg. Other examples of TRP receptor agonists used in the compositions provided herein include β-caryophyllene, α-terpineol, cannabidiol ("**CBD**"), cannabidivarin ("**CBDV**"), cannabigerol ("**CBG**"), cannabigerolic acid ("**CBGA**"), delta-9-tetrahydrocannabinol ("**THC**"), delta-9-tetrahydrocannabivarin ("**THCV**"), delta-9-tetrahydrocannabivarinic acid ("**THCVA**"), cannabigevarin ("**CBGV**"), myrcene, eriodictyol, carvacrol, myrcene, thymol, carvacrol, menthol, 1-8 cineole, piperine, gingerol, allicin, myrhhanol, boswellic acid and derivatives. These compounds may be sourced from materials that are GRAS, such as cannabis, coffee, chocolate, peppermint, thyme, ginger, garlic, onion, myrrh, frankincense and cardamom.

[0007] Each of these 5HT2A receptor agonists and TRP receptor agonists may be prepared synthetically, or extracted, purified or otherwise obtained from biomass of plants, fungi or microorganisms, including the GRAS materials described above. In contrast with standard pharmaceutical approaches of increased activity and activation potential at a single receptor target, the compositions provided herein provide therapeutic effects through a multi-modal action at 5HT2A and at least one TRP receptor, which supports dosing at lower concentrations of the 5HT2A agonist than would be observed

using only the 5HT2A agonist, and similarly dosing at lower concentrations of TRP receptor agonist that would be observed using only the TRP receptor agonist.

[0008] Through targeting the 5HT2A and TRP receptors together, inflammation markers and reactive oxygen species ("**ROS**") may be reduced; as such, glutamate metabolism may be regulated to reduce the severity or prevalence of mental health conditions that may be associated with or result from improper sugar signaling in the gut. The compositions may be formulated for use by individuals suffering from conditions including pain, mood disorders (anger/bipolar), inflammation, depression, anxiety, bowel inflammation, peripheral pain, neuropathic pain, traumatic brain injury ("**TBI**"), headaches, Alzheimer's disease, dementia, concussion, diabetes, arthritis, heart disease and cancer. The compositions may be formulated for use by individuals seeking to maintain or improve mental health, maintain or improve physical health, facilitate relaxation, facilitate focus, facilitate creativity, facilitate digestion, improve euphoria, improve libido and sex drive, and facilitate sleep, including for individuals suffering from pain and inflammation related conditions. Different TRPs influence different genes downstream, allowing the compositions to be adjusted for specific metabolic conditions or benefits.

[0009] Through agonism at both the 5HT2A receptor and one or more TRP receptors together, the amount of 5HT2A agonist used may be lowered relative to the amount that would be required to elicit a comparable response without the TRP receptor agonist. This may be advantageous where the 5HT2A receptor is psychoactive or otherwise produces effects that may be uncomfortable and/or inconvenient for an individual taking the 5HT2A agonist. For example, psilocybin is strongly psychoactive. Benefits of psilocybin can be obtained at lower doses of psilocybin when a TRP receptor agonist is taken along with, preceding or shortly after the psilocybin.

[0010] Combining multiple 5HT2A agonists with multiple TRP agonists may further enhance the activity or alter the effects of the formulation. Psilocybin mushrooms themselves may have multiple 5HT2A agonists present. The seeds of Hawaiian Baby woodrose and Morning glory also contain multiple 5HT2As. Spices or essential oils from medical plants often contain multiple TRP agonists. Furthermore, the addition of various ingredients from different sources allowed for a reduced dose of each individual ingredient while still achieving medically relevant results.

[0011] Some TRP receptor agonists, such as myristicin present in nutmeg, may themselves be 5HT2A agonists and may enhance the effects of another 5HT2A agonist. Compositions including psilocybin and nutmeg show greater psychoactive effects resulting from psilocybin than would be expected at the doses being applied, because myristicin may influence both 5HT2A and GABA receptors, and is thought to be processing into MMDA. As a result, including nutmeg in the compositions may allow for a reduced dose of psilocybin or other 5HT2A agonist. For example, about 0.5 grams of nutmeg taken with 0.5 grams of psilocybin produced a more extensive level of euphoria and other psychoactive effects than psilocybin alone, indicating synergy between psilocybin and nutmeg. Bergamot, which includes myrcene, eriodictyol, carvacrol, linalool and other compounds, also intensifies the psychoactive effects of psilocybin, especially in compositions that also include nutmeg.

[0012] Combining cayenne with psilocybin improved painkilling and anti-inflammatory effects of psilocybin, providing pain relief with about 0.2 g of dried fruiting bodies that include psilocybin and 0.2 g of crushed cayenne peppers. Cayenne may decrease the onset time of psilocybin, but may also result in greater anxiety being experienced that with psilocybin alone.

[0013] Combining turmeric with psilocybin may prolong the effects of psilocybin and increase antidepressant qualities by improving mood without appreciable negative side effects at the doses assessed. Turmeric may also increase analgesic effects from psilocybin, and may calm the anxiety that may result from consuming psilocybin, or from a combination of cayenne and psilocybin. Turmeric allowed for reduced amounts of both cayenne and psilocybin in the compositions while maintaining efficacy. Reduction of the amount of psilocybin and cayenne in the compositions may facilitated mitigation of stomach cramps, intestinal indigestion and anxiety that may result from consumption of psilocybin and cayenne.

[0014] Combining clove with psilocybin may reduce inflammation, as well as improve mood and digestion, and may mitigate anxiety associated with psilocybin use (including in combination with cayenne). Black Pepper had a similar effect, particularly the mental effects around mood and anxiety, but an equivalent amount of clove may be more palatable and may mix better with other ingredients of the composition.

[0015] Combining cinnamon with psilocybin may result in improved positive impacts on mood from the psilocybin and may also help with diet, reducing sugar cravings. The

calm that results from consuming cinnamon may reduce impulses such as fidgeting and may support increased focus.

[0016] Combining bergamot with psilocybin may enhance the effects of psilocybin and in some cases resulted in what was described as a "glow" or "light" feeling. Pure limonene or extract of orange flower did not result in the same effects as bergamot, indicating specific molecules in bergamot were essential to achieve this effect.

[0017] Combining chocolate or cocoa with psilocybin provides a TRP agonist that is synergistic with psilocybin the TRP3 receptor agonist (-)-epicatechin, a flavonol present in cocoa. Cacao may also provide stimulating effects through theophylline and other molecules present in chocolate. Chocolate may help mask strong flavours of other ingredients when the composition is formulated as a chew or other edible product.

[0018] Green tea also contains (−)-epicatechin and may be used as a means of administration of the formulations. (Uchida, 2018) Caffeine in green tea also does enhances the stimulant properties of psilocybin, mitigating side effects of psilocybin including yawning and drowsiness.

[0019] Combining coffee with psilocybin did not appear to be synergistic in terms of TRP receptor agonism or reduced dosage of psilocybin. Caffeine in coffee enhances the stimulant properties of psilocybin, mitigating side effects of psilocybin including yawning and drowsiness.

[0020] Combining peppermint or other plants high in menthol with psilocybin may improve mood enhancement and uplifting effects of psilocybin, increasing motivation and activity. Enhanced energy and concentration may also be reported. Peppermint also helped with stomach pain and digestion issues, particularly those resulting from psilocybin, and particularly stomach pain that may result from capsaicin.

[0021] Combining ginger which has gingerol, as well as garlic or onion which contain allicin with psilocybin may support correction of digestion issues and though there did not appear to be any effect with respect to mental health related issues such as mood, there does appear to be a synergistic effect with psilocybin with respect to inflammation which facilitates benefits at a lower dose of psilocybin.

[0022] Combining myrrh with psilocybin may result in stronger psychoactive effects from the psilocybin, and also enhance benefits in terms of neuroplasticity and neuroregeneration (Premkumar, 2014). Myrrh is a resin from the species of the genus

commiphora. The active ingredient in myrrh and similar resins is incensole, which has psychoactive properties and is a potent activator of TRPV3 (Moussaieff, 2008).

[0023] Combining frankincense with psilocybin may result in stronger psychoactive effects from the psilocybin, and also enhance benefits in terms of neuroplasticity and neuroregeneration. Frankincense is a resin obtained from the frankincense tree (*Boswellia thurifera*), which belongs to the family Buseraceae. The active ingredient is boswellic acid (Premkumar, 2014). Formulations including myrrh or frankincense may provide benefits to individuals suffering from post-traumatic stress disorder ("**PTSD**") and traumatic brain injury ("**TBI**"), and may help with libido.

[0024] Combining cardamom with psilocybin may amplify anti-inflammatory properties especially with respect to the digestive tracts. Cardamom may be phototoxic and may also carry contraindications for some medications.

[0025] Combining oregano with psilocybin may amplify anti-inflammatory properties especially with respect to the digestive tract issues.

[0026] Cannabis may also be included in the compositions, and may have effects on both the body and the mind depending on the dose and variety consumed. The variety of phytocannabinoids, terpenoids, flavonoids, phenylpropanoids and other secondary metabolites in *Cannabis sativa* complicate work with cannabis as an active ingredient. In addition, the consumption of two strongly psychoactive substances – psilocybin and delta-9-tetrahydrocannabinol ("**THC**") – may result in much stronger psychoactive effects. Other phytocannabinoids, such as cannabigerol ("**CBG"**), cannabidiol ("**CBD**"), and degradation products such as cannabinol ("**CBN**") may enhance specific compositions, including those directed to neuroprotection for CBD and sleep for CBN. In addition to broad-spectrum cannabis extracts or other preparations, individual phytocannabinoids may modulate the effect of specific formulations.

[0027] Combining psilocybin with TRP receptor agonists from preparations of cayenne pepper, turmeric, clove, cinnamon and nutmeg, and optionally chocolate, may provide effective enhancement of the 5HT2A activity resulting from psilocybin. In addition, optional additives such as bergamot, oregano, myrrh and frankincense further extend the duration of perceived effects resulting from the TRP receptor agonists. Addition of bergamot to compositions that also include cayenne pepper, turmeric, clove, cinnamon and nutmeg may improve focus of the individual taking a formulation of the composition, but may also result in some psychoactive effects remaining between 12 and 24 hours after

the dose was taken. As a result, bergamot may be avoided in compositions that are being formulated for use cases where a long return to baseline is unacceptable, and where there is a strong potential for overconsumption.

[0028] In a first aspect, herein disclosed is a composition for reducing inflammation to improve or maintain mental health or physical health in an individual. The composition includes at least on 5HT2A agonist and at least one TRP agonist. The 5HT2A agonist may include a tryptamine, ergoline, phenethylamine, phenylpropanoid or other 5HT2A agonist. The TRP agonist may include an agonist for one or more of the TRPV1, TRPA1, TRPM3, TRPM8, TRPV3 and TRPV4 receptors. The TRP agonist may include capsaicin, eugenol, curcumin, β-caryophyllene, myristicin or other TRP agonists. The 5HT2A agonist may include extracts from psilocybin-containing fungi, morning glory seeds, Hawaiian baby woodrose seeds or other fungi and plants. In some aspects, the 5HT2A agonist has a purity of at least about 99%. The TRP agonist may include extracts from cayenne pepper, clove, turmeric, nutmeg and other plants. In some aspects, the TRP agonist has a purity of at least about 99%. The compositions may be formulated for any suitable ingestion mode, including gastrointestinal, transmucosal and parenteral.

[0029] In a further aspect, herein disclosed is a composition for reducing inflammation to improve or maintain mental health or physical health in an individual comprising an effective amount of a 5HT2A agonist compound and an effective amount of a TRP agonist compound, wherein the therapeutically effective amount of the 5HT2A agonist is between about 1 µg and about 300 mg; and the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.01 mg and about 300 mg. In some aspects, the therapeutically effective amount is per dose. In some aspects, the dose is administered 1 to 10 times per day.

[0030] In some aspects and embodiments, the therapeutically effective amount of the 5HT2A agonist is between about 10 µg and about 195 mg, about 50 µg and about 190 mg, about 100 µg and about 185 mg, about 200 µg and about 180 mg, about 300 µg and about 175 mg, about 400 µg and about 170 mg, about 500 µg and about 165 mg, about 600 µg and about 160 mg, about 700 µg and about 155 mg, about 800 µg and about 150 mg, about 900 µg and about 145 mg, about 1 mg and about 140 mg, about 5 mg and about 135 mg, about 10 mg and about 130 mg, about 15 mg and about 125 mg, about 20 mg and about 120 mg, about 25 mg and about 115 mg, about 30 mg and about 110 mg, about 35 mg and about 105 mg, about 40 mg and about 100 mg, about 45 mg and about

95 mg, about 50 mg and about 90 mg, about 55 mg and about 85 mg, about 60 mg and about 80 mg, or about 65 mg and about 75 mg. In some aspects, the therapeutically effective amount is per dose. In some aspects, the dose is administered 1 to 10 times per day.

[0031] In some aspects and embodiments, the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.1 mg and about 24 mg, about 0.5 mg and about 23 mg, about 1 mg and about 22 mg, about 2 mg and about 21 mg, about 3 mg and about 20 mg, about 4 mg and about 19 mg, about 5 mg and about 18 mg, about 6 mg and about 17 mg, about 7 mg and about 16 mg, about 8 mg and about 15 mg, about 9 mg and about 14 mg, about 10 mg and about 13 mg, or about 11 mg and about 12 mg. In some aspects, the therapeutically effective amount is per dose. In some aspects, the dose is administered 1 to 10 times per day.

[0032] In some aspects and embodiments, the therapeutically effective amount of the 5HT2A agonist is between about 10 μg and about 195 mg, about 50 μg and about 190 mg, about 100 μg and about 185 mg, about 200 μg and about 180 mg, about 300 μg and about 175 mg, about 400 μg and about 170 mg, about 500 μg and about 165 mg, about 600 μg and about 160 mg, about 700 μg and about 155 mg, about 800 μg and about 150 mg, about 900 μg and about 145 mg, about 1 mg and about 140 mg, about 5 mg and about 135 mg, about 10 mg and about 130 mg, about 15 mg and about 125 mg, about 20 mg and about 120 mg, about 25 mg and about 115 mg, about 30 mg and about 110 mg, about 35 mg and about 105 mg, about 40 mg and about 100 mg, about 45 mg and about 95 mg, about 50 mg and about 90 mg, about 55 mg and about 85 mg, about 60 mg and about 80 mg, or about 65 mg and about 75 mg, and wherein the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.1 mg and about 24 mg, about 0.5 mg and about 23 mg, about 1 mg and about 22 mg, about 2 mg and about 21 mg, about 3 mg and about 20 mg, about 4 mg and about 19 mg, about 5 mg and about 18 mg, about 6 mg and about 17 mg, about 7 mg and about 16 mg, about 8 mg and about 15 mg, about 9 mg and about 14 mg, about 10 mg and about 13 mg, or about 11 mg and about 12 mg. In some aspects, the therapeutically effective amount is per dose. In some aspects, the dose is administered 1 to 10 times per day.

[0033] In some aspects and embodiments, the 5HT2A agonist comprises a tryptamine. In some aspects and embodiments, the tryptamine comprises a 4-substituted tryptamine. In some aspects and embodiments, the 4-substituted tryptamine comprises a 4-substituted

DMT compound. In some aspects and embodiments, the 4-substituted DMT compound comprises a compound selected from the group consisting of 3-[2-(dimethylamino)ethyl]-4-phosphoryloxyindole (psilocybin), 3-[2-(dimethylamino)ethyl]-4-hydroxyindole (psilocin), 3-[2-(dimethylamino)ethyl]-4-acetoxyindole (4-acetyl-DMT; also known as 4-ACO-DMT)) and any suitable salt of any of the foregoing. In some aspects and embodiments, the effective amount of the 4-substituted DMT compound comprises between 0.001 mg/kg and 0.30 mg/kg, with reference to the body weight of the individual. Average adult body weight is about 70 kg. In some aspects and embodiments, the 4-substituted tryptamine comprises a compound selected from the group consisting of 3-[2-(trimethylamino)ethyl]-4-phosphoryloxyindole (aeruginascin), 3-[2-(methylamino)ethyl]-4-phosphoryloxyindole (baeocystin), 3-[2-(methylamino)ethyl]-4-hydroxyindole, 3-[2-(amino)ethyl]-4-hydroxyindole (norpsilocin), 3-[2-(amino)ethyl]-4-phosphoryloxyindole (called norbaeocystin) and any suitable salt of any of the foregoing. In some aspects and embodiments, the 4-substituted tryptamine comprises a 4-substituted tryptamine sourced from fungi that biosynthesize the 4-substituted tryptamine. In some aspects and embodiments, the fungi includes a species selected from the group consisting of *Conocybe* species including *C. cyanopus*, *C. siligineoides* and *C. kuehneriana*; *Copelandia* species including *C. affinis*, *C. anomala*, *C. bispora*, *C. cambodginiensis*, *C. chlorocystis*, *C. cyanescens*, *C. lentisporus*, *C. tirunelveliensis*, *C. tropica*, *C. tropicalis* and *C. westii*; *Galerina species* including *G. steglichii*; *Gymnopilus* species including *G. thiersii*, *G. aeruginosus*, *G. braendlei*, *G. cyanopalmicola*, *G. intermedius*, *G. junonius*, *G. lateritius*, *G. liquiritiae*, *G. luteofolius*, *G. luteoviridis*, *G. luteus*, *G. purpuratus*, *G. subpurpuratus*, *G. validipes* and *G. viridans*; *Inocybe* species including *I. aeruginascens*, *I. aeruginascens*, *I. coelestium*, *I. corydalina*, *I. corydalina var. corydalina*, *I. corydalina var. erinaceomorpha*, *I. haemacta* and *I. tricolor*; *Panaeolus* species including *P. cinctulus*, *P. affinis*, *P. africanus*, *P. bisporus*, *P. cambodginiensis*, *P. castaneifolius*, *P. chlorocystis*, *P. cinctulus*, *P. cyanescens*, *P. fimicola*, *P. lentisporus*, *P. microsporus*, *P. moellerianus*, *P. olivaceus*, *P. rubricaulis*, *P. tirunelveliensis*, *P. tropicalis* and *P. venezolanus*; *Pholiotina* species including *P. cyanopus* and *P. smithii*; *Pluteus* species including *P. americanus*, *P. albostipitatus*, *P. americanus*, *P. cyanopus*, *P. glaucus*, *P. glaucotinctus*, *P. nigroviridis*, *P. phaeocyanopus*, *P. salicinus*, *P. saupei* and *P. villosus*; and *Psilocybe* species including *P. tampanensis*, *P. acutipilea*, *P. allenii*, *P. angustipleurocystidiata*, *P. antioquiensis*, *P. atlantis*, *P. aquamarina*, *P. armandii*, *P.*

aucklandii, *P. atlantis*, *P. aztecorum*, *P. aztecorum var. aztecorum*, *P. aztecorum var. bonetii*, *P. azurescens*, *P. baeocystis*, *P. banderillensis*, *P. bispora*, *P. brasiliensis*, *P. brunneocystidiata*, *P. cubensis*, *P. caeruleoannulata*, *P. caerulescens*, *P. caerulescens var. caerulescens*, *P. caerulescens var. ombrophila*, *P. caerulipes*, *P. callosa*, *P. carbonaria*, *P. caribaea*, *P. chuxiongensis*, *P. collybioides*, *P. columbiana*, *P. cordispora*, *P. cubensis*, *P. cyanescens*, *P. cyanofibrillosa*, *P. dumontii*, *P. egonii*, *P. fagicola*, *P. fagicola var. fagicola*, *P. fagicola var. mesocystidiata*, *P. farinacea*, *P. fimetaria*, *P. fuliginosa*, *P. furtadoana*, *P. tampanensis*, *P. galindoi*, *P. gallaeciae*, *P. graveolens*, *P. guatapensis*, *P. guilartensis*, *P. heimii Guzmán*, *P. herrerae Guzmán*, *P. hispanica Guzmán*, *P. hoogshagenii*, *P. hoogshagenii var. hoogshagenii*, *P. hoogshagenii var. convexa*, *P. inconspicua*, *P. indica*, *P. isabelae*, *P. jacobsii*, *P. jaliscana*, *P. kumaenorum*, *P. laurae*, *P. lazoi*, *P. liniformans*, *P. liniformans var. liniformans*, *P. liniformans var. americana*, *P. mexicana*, *P. mairei*, *P. makarorae*, *P. mammillata*, *P. medullosa*, *P. meridensis*, *P. meridionalis*, *P. mescaleroensis*, *P. mexicana*, *P. moseri*, *P. muliercula*, *P. naematoliformis*, *P. natalensis*, *P. natarajanii*, *P. neorhombispora*, *P. neoxalapensis*, *P. ovoideocystidiata*, *P. ovoideocystidiata*, *P. papuana*, *P. paulensis*, *P. pelliculosa*, *P. pintonii*, *P. pleurocystidiosa*, *P. plutonia*, *P. portoricensis*, *P. pseudoaztecorum*, *P. puberula*, *P. quebecensis*, *P. ricki*, *P. rostrata*, *P. rzedowskii*, *P. samuiensis*, *P. schultesii*, *P. semilanceata*, *P. septentrionalis*, *P. serbica*, *P. sierrae* , *P. silvatica*, *P. singeri*, *P. squamosa*, *P. strictipes*, *P. stuntzii*, *P. subacutipilea*, *P. subaeruginascens*, *P. subaeruginosa*, *P. subbrunneocystidiata*, *P. subcaerulipes*, *P. subcubensis*, *P. subpsilocybioides*, *P. subtropicalis*, *P. tampanensis*, *P. tampanensis*, *P. thaicordispora*, *P. thaiaerugineomaculans*, *P. thaiduplicatocystidiata*, *P. uruguayensis*, *P. uxpanapensis*, *P. venenata* , *P. villarrealiae*, *P. weraroa*, *P. wassoniorum*, *P. weilii*, *P. weldenii*, *P. weraroa*, *P. wrightii*, *P. xalapensis*, *P. yungensis*, *P. zapotecorum*, *P. zapotecoantillarum*, *P. zapotecocaribaea* and *P. zapotecorum*. In some aspects and embodiments, the composition includes dried fungal matter selected from the group consisting of fruiting bodies, mycelia, sclerotia and hyphae. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises capsaicin, and wherein the composition includes between 0.1 and 20 mg of the 4-substituted DMT compound and between 0.1 mg and 1 mg of capsaicin in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist

compound comprises capsaicin, and wherein the composition includes a ratio (w/w) of between 22:1 and 270,000:1 of the 4-substituted DMT compound:capsaicin in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises eugenol, and wherein the composition includes between 0.1 and 20 mg of the 4-substituted DMT compound and between 1 mg and 300 mg of eugenol in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises eugenol, and wherein the composition includes a ratio (w/w) of between 0.6:1 and 270,000:1 of the 4-substituted DMT compound:eugenol in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises curcumin, and the composition includes between 0.5 and 20 mg of the 4-substituted DMT compound and between 1.00 mg and 15 mg of curcumin in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises curcumin, and wherein the composition includes a ratio (w/w) of between 0.04:1 and 10:1 of the 4-substituted DMT compound:curcumin in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises β-caryophyllene, and the composition includes between 0.5 and 20 mg of the 4-substituted DMT compound and between 0.25 and 1.50 mg of β-caryophyllene in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises β-caryophyllene, and wherein the composition includes a ratio (w/w) of between 0.33:1 and 36:1 of the 4-substituted DMT compound:β-caryophyllene in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises cinnamaldehyde, and the composition includes between 0.5 and 20 mg of the 4-substituted DMT compound and between 0.25 and 1.0 mg of cinnamaldehyde in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises cinnamaldehyde, and wherein the composition includes a ratio (w/w) of between 0.5:1 and 36:1 of the 4-substituted DMT compound:cinnamaldehyde in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral

ingestion wherein the TRP agonist compound comprises myristicin, and the composition includes between 0.5 and 20 mg of the 4-substituted DMT compound and between 0.50 and 3.0 mg of myristicin in the dosage form. In some aspects and embodiments, the composition is formulated into a dosage form for oral ingestion wherein the TRP agonist compound comprises myristicin, and wherein the composition includes a ratio (w/w) of 0.2:1 and 20:1 of the 4-substituted DMT compound: myristicin in the dosage form. In some aspects and embodiments, the tryptamine comprises a 5-substituted tryptamine. In some aspects and embodiments, the 5-substituted tryptamine comprises a compound selected from the group consisting of 5-methoxy-DMT (bufotenin), N-acetyl-5-methoxy tryptamine (melatonin), 5-hydroxy tryptamine (serotonin), 5-hydroxy-tryptophan (5-HTP) and any suitable salt of any of the foregoing. In some aspects and embodiments, the 5HT2A agonist compound comprises an ergoline. In some aspects and embodiments, the ergoline comprises a compound selected from the group consisting of D-lysergic acid ethylamide ("**LAE**"), D-lysergic acid beta-propanolamide, also called ergometrine or ergonovine, D-lysergic acid 2-butyl amide ("**LSB**"), D-lysergic acid 1-butanolamide, also called methylergometrine or methylergonovine, 1-methyl-D-lysergic acid butanolamide, also called methysergide, D-lysergic acid 3-pentyl amide ("**LSP**"), D-N-morpholinyllysergamide ("**LSM-775**"), D-N-pyrrolidyllysergamide ("**LPD-824**"), (8β)-6-methyl-8-(piperidin-1-ylcarbonyl)-9,10-didehydroergoline ("**LSD-Pip**"), N,N-dimethyllysergamide ("**DAM**"), D-lysergic acid methylisopropyl amide ("**LAMIDE**") also called methylisopropyllysergamide ("**MIPLA**"), D-lysergic acid 2,4-dimethylazetidide ("**LSZ**"), LSD, D-1-acetyl-lysergic acid diethylamide ("**ALD-52**"), D-1-propionyl-lysergic acid diethylamide ("**1P-LSD**"), D-N1-butyryl-lysergic acid diethylamide ("**1B-LSD**"), D-N1-(cyclopropylmethanoyl)-lysergic acid diethylamide ("**1cP-LSD**"), D-N1-methyl-lysergic acid diethylamide ("**MLD**"), D-6-ethyl-6-nor-lysergic acid diethylamide ("**ETH-LAD**"), D-1-propionyl-6-ethyl-6-nor-lysergic acid diethyamide ("**1P-ETH-LAD**"), D-6-allyl-6-nor-lysergic acid diethylamide ("**AL-LAD**"), D-6-propyl-6-nor-lysergic acid diethylamide ("**PRO-LAD**"), D-6-isopropyl-6-nor-lysergic acid diethylamide ("**IP-LAD**"), D-6-propynyl-6-nor-lysergic acid diethylamide ("**PARGY-LAD**"), D-6-butyl-6-nor-lysergic acid diethylamide ("**BU-LAD**"), N,N-diallyllysergamide ("**DAL**") and D-N-ethyl-N-cyclopropyllysergamide ("**ECPLA**"). In some aspects and embodiments, the ergoline comprises an ergoline sourced from a fungus or plant that biosynthesizes the ergoline. In some aspects and

embodiments, the fungi or plant includes a species selected from the group consisting of *Claviceps purpurea*, other species of *Claviceps*, *Rivea corymbosa*, *Ipomoea violacea*, *I. tricolor*, *I. purpurae*, *I. alba*, *Periglandula spp.* other species of morning glory, *Argeyreia nervosa* or other species of Hawaiian baby woodrose. In some aspects and embodiments, the 5HT2A agonist compound comprises a phenethylamine. In some aspects and embodiments, the phenethylamine comprises a compound selected from the group consisting of 3,4,5-trimethoxyphenethylamine (mescaline), trimethoxyamphetamine ("**TMA**"), 4-bromo-2,5-dimethoxybenzeneethanamine ("**2C-B**"), 4-bromo-2,5-dimethoxyamphetamine ("**DOB**"), 4-methyl-2,5-dimethoxyamphetamine ("**DOM**"), 4-methyl-2,5-dimethoxybenzeneethanamine ("**2C-D**"), 3,4-methylenedioxyamphetamine ("**MDA**"), N-methyl-3,4-methylenedioxyamphetamine ("**MDMA**"). In some aspects and embodiments, the phenethylamine comprises a phenethylamine sourced from a plant that biosynthesizes the phenethylamine. In some aspects and embodiments, the plant includes a species selected from the group consisting of *Lophophora williamsii*, other *Lophophora* species, *Trichocereus pachanoi*, and other *Trichocereus* species. In some aspects and embodiments, the 5HT2A agonist compound comprises a phenylpropanoid. In some aspects and embodiments, the phenylpropanoid comprises a compound selected from the group consisting of 5-methoxy-3,4-methylenedioxy-allylbenzene (myristicin) and 1,2,3-timethoxy-5-(prop-2-en-1-yl)benzene (elemicin). In some aspects and embodiments, the phenylpropanoid comprises a phenylpropanoid sourced from a plant that biosynthesizes the phenylpropanoid. In some aspects and embodiments, the plant includes a species selected from the group consisting of *Myristica fragrans* or other species in the *Myristicaceae* family. In some aspects and embodiments, the TRP agonist compound comprises a TRPV1 agonist compound. In some aspects and embodiments, the TRPV1 agonist compound comprises a capsiate. In some aspects and embodiments, the TRPV1 agonist compound comprises eugenol. In some aspects and embodiments, the TRPV1 agonist compound comprises a compound selected from the group consisting of capsaicin, eugenol, myristicin, elemicin, CBD, CBDA, CBDV, CBG, CBGA, CBGV, THCV, THCVA, myrcene, piperine and gingerol. In some aspects and embodiments, the TRPV1 agonist compound is sourced from biomass of a plant that biosynthesizes the TRPV1 agonist compound. In some aspects and embodiments, the plant includes one or more species selected from the group consisting of cayenne pepper, turmeric, clove, cinnamon, nutmeg, pepper, cannabis, bergamot and ginger. In some aspects and

embodiments, the TRP agonist compound comprises a TRPA1 agonist compound. In some aspects and embodiments, the TRP agonist compound comprises a curcuminoid. In some aspects and embodiments, the curcuminoid comprises curcumin. In some aspects and embodiments, the TRPA1 agonist compound comprises a compound selected from the group consisting of curcumin, cinnamaldehyde, alpha terpineol, CBD, CBDA, CBDV, CBG, CBGA, CBGV, THCV, THCVA, thymol, piperine and allicin. In some aspects and embodiments, the TRPA1 agonist compound is sourced from biomass of a plant that biosynthesizes the TRPA1 agonist compound. In some aspects and embodiments, the plant includes one or more species selected from the group consisting of curcumin, cinnamon, turmeric, nutmeg, cannabis, thyme, pepper, garlic and onion. In some aspects and embodiments, the TRP agonist compound comprises a TRPM8 agonist compound. In some aspects and embodimentsects, the TRPM8 agonist compound comprises a compound selected from the group consisting of eugenol, cinnamaldehyde, CBD, CBDA, CBDV, CBG, CBGA, CBGV, THC, THCA, THCV, THCVA, carvacrol, thymol, menthol and 1-8 cineole. In some aspects and embodiments, the TRPM8 agonist compound is sourced from biomass of a plant that biosynthesizes the TRPM8 agonist compound. In some aspects and embodiments, the plant includes one or more species selected from the group consisting of turmeric, clove, cinnamon, pepper, nutmeg, cannabis, bergamot, oregano, thyme, cardamom, peppermint and eucalyptus. In some aspects and embodiments, the TRP agonist compound comprises a TRPV3 agonist compound. In some aspects and embodiments, the TRPV3 agonist compound comprises β-caryophyllene. In some aspects and embodiments, the TRPV3 compound comprises a compound selected from the group consisting of eugenol, β-caryophyllene, (-)-epicatechin, CBD, CBDA, CBGA, CBGV, THCV, THCVA, eriodictyol, cinnamaldehyde, incensole, boswellic acid, thymol. In some aspects and embodiments, the TRPM8 agonist compound is sourced from biomass of a plant that biosynthesizes the TRPM8 agonist compound. In some aspects and embodiments, the plant includes one or more species selected from the group consisting of turmeric, clove, cinnamon, pepper, nutmeg, cannabis, bergamot, oregano, thyme, cardamom, peppermint and eucalyptus. In some aspects and embodiments, the composition is formulated into an oral formulation for ingestion. In some aspects and embodiments, the composition comprises a pharmaceutically acceptable excipient, diluent or filler material.

[0034] In a further aspect, herein disclosed is a method of treating a health condition comprising administering a composition as described herein to an individual suffering from the condition. In some aspects and embodiments, the condition comprises a condition selected from the group consisting of cancer, neurological disorders, diabetic complications, mental health disorders, bone, muscular and skeletal disease, metabolic disorders, chronic or acute inflammatory disorders and cardiovascular disease. In some aspects and embodiments, the 5HT2A agonist compound comprises a 4-substituted DMT compound, and the effective amount of the 4-substituted DMT compound comprises between 0.015 mg/kg and 0.30 mg/kg, with reference to the body weight of the individual. In some aspects and embodiments, the TRP agonist compound comprises capsaicin, and the effective amount of capsaicin comprises between 0.0005 μg/kg and 1.0 μg/kg per day, with reference to the body weight of the individual. In some aspects and embodiments, the TRP agonist compound comprises eugenol, and the effective amount of eugenol comprises between 0.005 μg/kg and 400 μg/kg per day, with reference to the body weight of the individual. In some aspects and embodiments, the TRP agonist compound comprises curcumin, and the effective amount of curcumin comprises between 0.014 mg/kg and 0.55 mg/kg per day, with reference to the body weight of the individual. In some aspects and embodiments, the TRP agonist compound comprises β-caryophyllene, and the effective amount of β-caryophyllene comprises between 0.004 mg/kg and 0.064 mg/kg per day, with reference to the body weight of the individual. In some aspects and embodiments, the TRP agonist compound comprises myristicin, and the effective amount of myristicin comprises between 0.007 mg/kg and 0.130 mg/kg per day, with reference to the body weight of the individual.

[0035] In a further aspect, herein disclosed is use of a composition as described herein in the treatment of an individual suffering from a mental illness condition or physically debilitating condition. In some aspects and embodiments, the condition comprises a condition selected from the group consisting of cancer, neurological disorders, diabetic complications, mental health disorders, bone, muscular and skeletal disease, metabolic disorders, chronic inflammatory disorders and cardiovascular disease, and post-traumatic stress disorder.

[0036] In further aspects and embodiments, herein disclosed is a composition for reducing inflammation to improve or maintain mental health or physical health in an individual comprising an effective amount of a 5HT2A agonist compound, an effective

amount of a capsaicinoid, an effective amount of a curcuminoid and an effective amount of eugenol. In some aspects and embodiments, the 5HT2A agonist compound comprises a compound as described herein. In some aspects and embodiments, the capsaicinoid comprises capsaicin. In some aspects and embodiments, the curcuminoid comprises curcumin.

[0037] In one aspect and embodiment, a composition comprises a therapeutic combination of a 5HT2A agonist compound and at least one TRP agonist compound, wherein the therapeutically effective amount of the 5HT2A agonist is between about 1 μg and about 200 mg; and the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.1 mg and about 25 mg.

[0038] In some aspects and embodiments, the 5HT2A agonist compound is selected from the group consisting of a tryptamine, an ergoline, a phenethylamine, and a phenylpropanoid.

[0039] In some aspects and embodiments, the tryptamine is a 4-substituted tryptamine.

[0040] In some aspects and embodiments, the 4-substituted tryptamine is a 4-substituted DMT compound.

[0041] In some aspects and embodiments, the 4-substituted DMT compound is selected from the group consisting of 3-[2-(dimethylamino)ethyl]-4-phosphoryloxyindole (psilocybin), 3-[2-(dimethylamino)ethyl]- 4-hydroxyindole (psilocin), 3-[2-(dimethylamino)ethyl]-4-acetoxyindole (psilacetin), and any suitable salt of any of the foregoing.

[0042] In some aspects and embodiments, the 4-substituted tryptamine is selected from the group consisting of 3-[2(trimethylamino)ethyl]-4-phosphoryloxyindole (aeruginascin), 3-[2-(methylamino)ethyl]-4-phosphoryloxyindole (baeocystin), 3-[2-(methylamino)ethyl]-4-hydroxyindole, 3-[2-(amino)ethyl]-4-hydroxyindole (norpsilocin), 3-[2-(amino)ethyl]-4-phosphoryloxyindole (norbaeocystin), and any suitable salt of any of the foregoing.

[0043] In some aspects and embodiments, the 4-substituted tryptamine is derived from fungi.

[0044] In some aspects and embodiments, the fungi is a species of a genus selected from the group consisting of *Gymnopilus*, *Inocybe*, *Panaeolus*, *Pholiotina*, *Pluteus*, and *Psilocybe*.

[0045] In some aspects and embodiments, the fungi is a species of a genus selected from the group consisting of *Gymnopilus*, *Inocybe*, *Panaeolus*, *Pholiotina*, *Pluteus*, and *Psilocybe*.

[0046] In some aspects and embodiments, the fungi is selected from the group consisting of *C. cyanopus*, *C. siligineoides* and *C. kuehneriana*; *Copelandia* species including *C. affinis*, *C. anomala*, *C. bispora*, *C. cambodginiensis*, *C. chlorocystis*, *C. cyanescens*, *C. lentisporus*, *C. tirunelveliensis*, *C. tropica*, *C. tropicalis* and *C. westii*; *G. steglichii*; *G. thiersii*, *G. aeruginosus*, *G. braendlei*, *G. cyanopalmicola*, *G. intermedius*, *G. junonius*, *G. lateritius*, *G. liquiritiae*, *G. luteofolius*, *G. luteoviridis*, *G. luteus*, *G. purpuratus*, *G. subpurpuratus*, *G. validipes* and *G. viridans*; *I. aeruginascens*, *I. aeruginascens*, *I. coelestium*, *I. corydalina*, *I. corydalina var. corydalina*, *I. corydalina var. erinaceomorpha*, *I. haemacta* and *I. tricolor*; *P. cinctulus*, *P. affinis*, *P. africanus*, *P. bisporus*, *P. cambodginiensis*, *P. castaneifolius*, *P. chlorocystis*, *P. cinctulus*, *P. cyanescens*, *P. fimicola*, *P. lentisporus*, *P. microsporus*, *P. moellerianus*, *P. olivaceus*, *P. rubricaulis*, *P. tirunelveliensis*, *P. tropicalis* and *P. venezolanus*; *P. cyanopus* and *P. smithii*; *P. americanus*, *P. albostipitatus*, *P. americanus*, *P. cyanopus*, *P. glaucus*, *P. glaucotinctus*, *P. nigroviridis*, *P. phaeocyanopus*, *P. salicinus*, *P. saupei* and *P. villosus*; *P. tampanensis*, *P. acutipilea*, *P. allenii*, *P. angustipleurocystidiata*, *P. antioquiensis*, *P. atlantis*, *P. aquamarina*, *P. armandii*, *P. aucklandii*, *P. atlantis*, *P. aztecorum*, *P. aztecorum var. aztecorum*, *P. aztecorum var. bonetii*, *P. azurescens*, *P. baeocystis*, *P. banderillensis*, *P. bispora*, *P. brasiliensis*, *P. brunneocystidiata*, *P. cubensis*, *P. caeruleoannulata*, *P. caerulescens*, *P. caerulescens var. caerulescens*, *P. caerulescens var. ombrophila*, *P. caerulipes*, *P. callosa*, *P. carbonaria*, *P. caribaea*, *P. chuxiongensis*, *P. collybioides*, *P. columbiana*, *P. cordispora*, *P. cubensis*, *P. cyanescens*, *P. cyanofibrillosa*, *P. dumontii*, *P. egonii*, *P. fagicola*, *P. fagicola var. fagicola*, *P. fagicola var. mesocystidiata*, *P. farinacea*, *P. fimetaria*, *P. fuliginosa*, *P. furtadoana*, *P. tampanensis*, *P. galindoi*, *P. gallaeciae*, *P. graveolens*, *P. guatapensis*, *P. guilartensis*, *P. heimii Guzmán*, *P. herrerae Guzmán*, *P. hispanica Guzmán*, *P. hoogshagenii*, *P. hoogshagenii var. hoogshagenii*, *P. hoogshagenii var. convexa*, *P. inconspicua*, *P. indica*, *P. isabelae*, *P. jacobsii*, *P. jaliscana*, *P. kumaenorum*, *P. laurae*, *P. lazoi*, *P. liniformans*, *P. liniformans var. liniformans*, *P. liniformans var. americana*, *P. mexicana*, *P. mairei*, *P. makarorae*, *P. mammillata*, *P. medullosa*, *P. meridensis*, *P. meridionalis*, *P. mescaleroensis*, *P. mexicana*, *P. moseri*, *P. muliercula*, *P. naematoliformis*, *P. natalensis*,

P. natarajanii, P. neorhombispora, P. neoxalapensis, P. ovoideocystidiata, P. ovoideocystidiata, P. papuana, P. paulensis, P. pelliculosa, P. pintonii, P. pleurocystidiosa, P. plutonia, P. portoricensis, P. pseudoaztecorum, P. puberula, P. quebecensis, P. ricki, P. rostrata, P. rzedowskii, P. samuiensis, P. schultesii, P. semilanceata, P. septentrionalis, P. serbica, P. sierrae , P. silvatica, P. singeri, P. squamosa, P. strictipes, P. stuntzii, P. subacutipilea, P. subaeruginascens, P. subaeruginosa, P. subbrunneocystidiata, P. subcaerulipes, P. subcubensis, P. subpsilocybioides, P. subtropicalis, P. tampanensis, P. tampanensis, P. thaicordispora, P. thaiaerugineomaculans, P. thaiduplicatocystidiata, P. uruguayensis, P. uxpanapensis, P. venenata , P. villarrealiae, P. weraroa, P. wassoniorum, P. weilii, P. weldenii, P. weraroa, P. wrightii, P. xalapensis, P. yungensis, P. zapotecorum, P. zapotecoantillarum, P. zapotecocaribaea, and P. zapotecorum.

[0047] In some aspects and embodiments, the composition further comprises dried matter of the fungi, wherein the dried matter is selected from the group consisting of fruiting bodies, mycelia, sclerotia, and hyphae, or combinations thereof.

[0048] In some aspects and embodiments, the tryptamine is a 5-substituted tryptamine.

[0049] In some aspects and embodiments, the 5-substituted tryptamine is selected from the group consisting of 5-methoxy-DMT (bufotenin), N-acetyl-5-methoxy tryptamine (melatonin), 5-hydroxy tryptamine (serotonin), 5-hydroxy-tryptophan (5-HTP), and any suitable salt of any of the foregoing.

[0050] In some aspects and embodiments, the 5HT2A agonist compound is an ergoline.

[0051] In some aspects and embodiments, the ergoline is selected from the group consisting of D-lysergic acid ethylamide ("LAE"),D-lysergic acid beta-propanolamide, D-lysergic acid 2-butyl amide ("LSB"), D-lysergic acid 1-butanolamide, 1-methyl-D-lysergic acid butanolamide, D-lysergic acid 3-pentyl amide ("LSP"), D-N-morpholinyllysergamide ("LSM-775"), D-N-pyrrolidyllysergamide ("LPD-824"), (8β)-6-methyl-8-(piperidin-1-ylcarbonyl)-9,10-didehydroergoline ("LSD-Pip"), N,N-dimethyllysergamide ("DAM"), D-lysergic acid methylisopropyl amide ("LAMIDE"), D-lysergic acid 2,4-dimethylazetidide ("LSZ"), LSD, D-1-acetyl-lysergic acid diethylamide ("ALD-52"), D-1-propionyl-lysergic acid diethylamide ("1P-LSD"), D-N1-butyryl-lysergic acid diethylamide ("1B-LSD"), D-N1-(cyclopropylmethanoyl)-lysergic acid diethylamide ("1cP-LSD"), D-N1-methyl-lysergic acid diethylamide ("MLD"), D-6-ethyl-6-nor-lysergic acid diethylamide ("ETH-LAD"), D-1-propionyl-6-ethyl-6-nor-

lysergic acid diethyamide ("1P-ETH-LAD"), D-6-allyl-6-nor-lysergic acid diethylamide ("AL-LAD"), D-6-propyl-6-nor-lysergic acid diethylamide ("PRO-LAD"), D-6-isopropyl-6-nor-lysergic acid diethylamide ("IP-LAD"), D-6-propynyl-6-nor-lysergic acid diethylamide ("PARGY-LAD"), D-6-butyl-6-norlysergic acid diethylamide ("BU-LAD"), N,N-diallyllysergamide ("DAL") and D-N-ethyl-N-cyclopropyllysergamide ("ECPLA").

[0052] In some aspects and embodiments, the ergoline is derived from fungi or a plant.

[0053] In some aspects and embodiments, the fungi or plant is a species selected from the group consisting of Claviceps purpurea, Rivea corymbosa, Ipomoea violacea, I. tricolor, I. purpurae, I. alba, Argeyreia nervosa, and a Periglandula species.

[0054] In some aspects and embodiments, the 5HT2A agonist compound is a phenethylamine.

[0055] In some aspects and embodiments, the phenethylamine is selected from the group consisting of 3,4,5-trimethoxyphenethylamine (mescaline), trimethoxyamphetamine ("TMA"), 4-bromo-2,5-dimethoxybenzeneethanamine ("2C-B"), 4-bromo-2,5-dimethoxyamphetamine ("DOB"), 4-methyl-2,5-dimethoxyamphetamine ("DOM"), 4-methyl-2,5-dimethoxybenzeneethanamine ("2C-D"), 3,4-methylenedioxyamphetamine ("MDA"), N-methyl-3,4-methylenedioxyamphetamine ("MDMA").

[0056] In some aspects and embodiments, the phenethylamine is plant-derived.

[0057] In some aspects and embodiments, the plant includes a species selected from the group consisting of *Lophophora williamsii*, *Trichocereus pachanoi, Echinopsis pachanoi, Trichocereus peruvianus, Echinopsis peruviana, Trichocereus bridgesii, Echinopsis lageniformis*, and *Trichocereus/Echinopsis scopulicola*.

[0058] In some aspects and embodiments, the 5HT2A agonist compound is a phenylpropanoid.

[0059] In some aspects and embodiments, the phenylpropanoid is 1,2,3-timethoxy-5-(prop-2-en-1-yl)benzene (elemicin).

[0060] In some aspects and embodiments, the phenylpropanoid is plant-derived.

[0061] In some aspects and embodiments, the plant is a species in the *Myristicaceae* family.

[0062] In some aspects and embodiments, the TRP agonist compound is selected from the group consisting of a capsiate, eugenol, elemicin, myrcene, piperine and gingerol.

[0063] In some aspects and embodiments, the capsiate is capsaicin.

[0064] In some aspects and embodiments, the TRP agonist compound is plant-derived.

[0065] In some aspects and embodiments, the plant includes one or more species selected from the group consisting of cayenne pepper, turmeric, clove, cinnamon, nutmeg, pepper, cannabis, bergamot and ginger.

[0066] In some aspects and embodiments, the TRP agonist compound is selected from the group consisting of a curcuminoid, cinnamaldehyde, alpha terpineol, thymol, piperine and allicin.

[0067] In some aspects and embodiments, the curcuminoid is curcumin.

[0068] In some aspects and embodiments, the plant includes one or more species selected from the group consisting of curcumin, cinnamon, turmeric, nutmeg, cannabis, thyme, pepper, garlic, and onion.

[0069] In some aspects and embodiments, the TRP agonist compound is selected from the group consisting of eugenol, cinnamaldehyde, carvacrol, thymol, menthol, and 1-8 cineole.

[0070] In some aspects and embodiments, the plant includes one or more species selected from the group consisting of turmeric, clove, cinnamon, pepper, nutmeg, cannabis, bergamot, oregano, thyme, cardamom, peppermint, and eucalyptus.

[0071] In some aspects and embodiments, the TRP agonist compound is selected from the group consisting of eugenol, β-caryophyllene, (-)-epicatechin, CBD, CBDA, CBGA, CBGV, THCV, THCVA, eriodictyol, cinnamaldehyde, incensole, eucalyptol, and thymol.

[0072] Iaspects and embodiments, the plant includes one or more species selected from the group consisting of turmeric, clove, cinnamon, pepper, nutmeg, cannabis, bergamot, oregano, thyme, cardamom, peppermint, and eucalyptus.

[0073] In some aspects and embodiments, the 5HT2A agonist compound is psilocybin, and wherein the therapeutically effective amount of psilocybin is between about 100 mg and about 300 mg, or between about 0.5 mg and about 20 mg.

[0074] In some aspects and embodiments, the 5HT2A agonist is psilocybin, in an amount of between about 110 mg and about 290 mg, about 120 mg and about 280 mg, about 130 mg and about 270 mg, about 140 mg and about 260 mg, about 150 mg and about 250 mg, about 160 mg and about 240 mg, about 170 mg and about 230 mg, about 180 mg and about 220 mg, about 190 mg and about 210 mg, or about 195 mg and about 205 mg.

[0075] In some aspects and embodiments, the at least one TRP agonist compound is capsaicin in an amount of about 0.1 mg and about 1 mg, about 0.2 mg and about 0.9 mg,

about 0.3 mg and about 0.8 mg, about 0.4 and about 0.7 mg, or about 0.5 mg and about 0.6 mg

[0076] In some aspects and embodiments, the at least one TRP agonist compound is capsaicin, and wherein the composition comprises a ratio (w/w) of between about 22:1 and about 270,000:1 of the 5HT2A agonist to capsaicin, about 50:1 and about 200,000:1 of the 5HT2A agonist to capsaicin, about 100:1 and about 150,000:1 of the 5HT2A agonist to capsaicin, about 500:1 and about 100,000:1 of the 5HT2A agonist to capsaicin, about 1,000:1 and about 50,000:1 of the 5HT2A agonist to capsaicin, about 5,000:1 and about 40,000:1 of the 5HT2A agonist to capsaicin, about 10,000:1 and about 30,000:1 of the 5HT2A agonist to capsaicin, or about 15,000:1 and about 25,000:1 of the 5HT2A agonist to capsaicin.

[0077] In some aspects and embodiments, the at least one TRP agonist compound is eugenol in an amount of about 1 mg and about 300 mg, about 5 mg and about 290 mg, about 10 mg and about 280 mg, about 15 mg and about 270 mg, about 20 mg and about 260 mg, about 25 mg and about 250 mg, about 30 mg and about 240 mg, about 35 mg and about 230 mg, about 40 mg and about 220 mg, about 40 mg and about 210 mg, about 50 mg and about 210 mg, about 55 mg and about 200 mg, about 60 mg and about 190 mg, about 65 mg and about 180 mg, about 70 mg and about 170 mg, about 75 mg and about 160 mg, about 80 mg and about 150 mg, about 85 mg and about 140 mg, about 90 mg and about 130 mg, about 95 mg and about 120 mg, or about 100 mg and about 110 mg.

[0078] In some aspects and embodiments, the at least one TRP agonist compound is eugenol, and wherein the composition comprises a ratio (w/w) of between about 0.6:1 and about 270,000:1 of the 5HT2A agonist to eugenol, about 1:1 and about 250,000:1 of the 5HT2A agonist to eugenol, about 5:1 and about 225,000:1 of the 5HT2A agonist to eugenol, about 10:1 and about 200,000:1 of the 5HT2A agonist to eugenol, about 50:1 and about 175,000:1 of the 5HT2A agonist to eugenol, about 100:1 and about 150,000:1 of the 5HT2A agonist to eugenol, about 150:1 and about 125,000:1 of the 5HT2A agonist to eugenol, about 300:1 and about 100,000:1 of the 5HT2A agonist to eugenol, about 500:1 and about 75,000:1 of the 5HT2A agonist to eugenol, about 1,000:1 and about 50,000:1 of the 5HT2A agonist to eugenol, about 5,000:1 and about 45,000:1 of the 5HT2A agonist to eugenol, about 10,000:1 and about 40,000:1 of the 5HT2A agonist to

eugenol, about 15,000:1 and about 35,000:1 of the 5HT2A agonist to eugenol, or about 20,000:1 and about 30,000:1 of the 5HT2A agonist to eugenol.

[0079] In some aspects and embodiments, the at least one TRP agonist compound is curcumin in an amount of about 0.1 mg to about 10 mg, about 0.5 mg to about 9 mg, about 1 mg to about 8 mg, about 2 mg to about 7 mg, about 3 mg to about 6 mg, or about 4 mg to about 5 mg.

[0080] In some aspects and embodiments, the at least one TRP agonist compound is curcumin, and wherein the composition comprises a ratio (w/w) of between about 0.04:1 and about 10:1 of the 5HT2A agonist to curcumin, about 0.1:1 and about 9.5:1 of the 5HT2A agonist to curcumin, about 0.5:1 and about 9:1 of the 5HT2A agonist to curcumin, about 1:1 and about 8.5:1 of the 5HT2A agonist to curcumin, about 1.5:1 and about 8:1 of the 5HT2A agonist to curcumin, about 2:1 and about 7.5:1 of the 5HT2A agonist to curcumin, about 2.5:1 and about 7:1 of the 5HT2A agonist to curcumin, about 3:1 and about 6.5:1 of the 5HT2A agonist to curcumin, about 3.5:1 and about 6:1 of the 5HT2A agonist to curcumin, about 4:1 and about 5.5:1 of the 5HT2A agonist to curcumin, or about 4.5:1 and about 5:1 of the 5HT2A agonist to curcumin.

[0081] In some aspects and embodiments, the at least one TRP agonist compound is β-caryophyllene, and wherein the composition comprises a ratio (w/w) of between about 0.33:1 and about 36:1 of the 5HT2A agonist to β-caryophyllene, about 1:1 and about 33:1 of the 5HT2A agonist to β-caryophyllene, about 3:1 and about 30:1 of the 5HT2A agonist to β-caryophyllene, about 5:1 and about 27:1 of the 5HT2A agonist to β-caryophyllene, about 7:1 and about 25:1 of the 5HT2A agonist to β-caryophyllene, about 10:1 and about 22:1 of the 5HT2A agonist to β-caryophyllene, about 15:1 and about 20:1 of the 5HT2A agonist to β-caryophyllene, or about 17:1 and about 18:1 of the 5HT2A agonist to β-caryophyllene.

[0082] In some apsects and embodiments, the at least one TRP agonist compound is cinnamaldehyde in an amount of between about 0.1 mg and about 10 mg, about 0.5 mg and about 9.5 mg, about 1 mg and about 9 mg, about 1.5 mg and about 8.5 mg, about 2 mg and about 8 mg, about 2.5 mg and about 7.5 mg, about 3 mg and about 7 mg, about 3.5 mg and about 6.5 mg, about 4 mg and about 6 mg, or about 4.5 mg and about 5.5 mg.

[0083] In some aspects and embodiments, the at least one TRP agonist compound is cinnamaldehyde, and wherein the composition comprises a ratio (w/w) of between about 0.5:1 and about 36:1 of the 5HT2A agonist to cinnamaldehyde, about 1:1 and about 33:1

of the 5HT2A agonist to cinnamaldehyde, about 3:1 and about 30:1 of the 5HT2A agonist to cinnamaldehyde, about 5:1 and about 27:1 of the 5HT2A agonist to cinnamaldehyde, about 7:1 and about 25:1 of the 5HT2A agonist to cinnamaldehyde, about 10:1 and about 22:1 of the 5HT2A agonist to cinnamaldehyde, about 15:1 and about 20:1 of the 5HT2A agonist to cinnamaldehyde, or about 17:1 and about 18:1 of the 5HT2A agonist to cinnamaldehyde.

[0084] In some aspects and embodiments, the composition is formulated for oral administration.

[0085] In some aspects and embodiments, the composition further comprises at least one pharmaceutically acceptable excipient, diluent, or filler.

[0086] In some aspects and embodiments, the composition is selected from the group consisting of a tablet, capsule, sachets, granules, sublingual film, buccal film, and a suspension.

[0087] In another aspect and embodiments, a method for reducing inflammation in a subject, comprising administering any of the compositions described herein to the subject.

[0088] In some aspects and embodiments, the inflammation is acute or chronic.

[0089] In some aspects and embodiments, the method comprises administering the composition from 1-10 times per day.

[0090] In some aspects and embodiments, the reduction in inflammation is measured by a 40-60% or a 50% reduction of at least one biomarker selected from the group consisting of COX-2, interferon-γ, interleukin 1, interleukin-2, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor (TNF), and reactive oxygen species (ROS) when measured via densitometry.

[0091] In some aspects and embodiments, the ROS is inducible nitric oxide synthase (iNOS).

[0092] In some aspects and embodiments, the subject is suffering from a condition selected from the group consisting of cancer, neurological disorder, diabetic complications, mental health disorder (MHD), bone, muscular and skeletal disease, metabolic disorder, chronic inflammatory disorder and cardiovascular disease.

[0093] In some aspects and embodiments, the MHD is selected from depression, anxiety, post-traumatic stress disorder, schizophrenia, bipolar disorder, ADD, ADHD, borderline personality disorder, seasonal affective disorder, and premenstrual dysphoric disorder.

[0094] In some aspects and embodiments, the MHD is depression, and the reduction in inflammation is accompanied by a reduction in at least one symptom of depression.

[0095] In some apsects and embodiments, the MHD is anxiety, and the reduction in inflammation is accompanied by a reduction in at least one symptom of anxiety.

[0096] In another aspect and embodiment, a method for reducing at least one biomarker in a mammalian cell, wherein the biomarker is selected from the group consisting of COX-2, interferon-γ, interleukin 1, interleukin-2, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor (TNF), and reactive oxygen species (ROS), comprises administering the composition of any one of claims X to X to a subject, wherein administering the composition reduces the biomarker in the mammalian cell between about X% and about Y%.

[0097] In some aspects and embodiments, the 5HT2A agonist is psilocybin in an amount of about 100 mg to about 300 mg, and wherein the TRP agonist is eugenol in an amount of about 100 mg to about 300 mg. In some aspects, the amount of psilocybin and eugenol is per dose. In some aspects, the dose is administered 1 to 10 times per day.

[0098] In some aspect and embodiments, the 5HT2A agonist is psilocybin in an amount of about 100 mg to about 300 mg, about 110 mg to about 290 mg, about 120 mg to about 280 mg, about 130 mg to about 270 mg, about 140 mg to about 260 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, or about 195 mg to about 205 mg, and wherein TRP agonist is eugenol in an amount of about 100 mg to about 300 mg, about 110 mg to about 290 mg, about 120 mg to about 280 mg, about 130 mg to about 270 mg, about 140 mg to about 260 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, or about 195 mg to about 205 mg. In some aspects, the amount of psilocybin is per dose. In some aspects, the dose is administered 1 to 10 times per day.

[0099] In some aspects and embodiments, administering the composition reduces IL-6 in the mammalian cell by about an additional 20% relative to administering the therapeutically effective amount of psilocybin alone.

[0100] In some aspects and embodiments, administering the composition reduces IL-6 in the mammalian cell by about an additional 25% relative to administering the therapeutically effective amount of psilocybin alone.

[0101] Other aspects and features of the present disclosure will become apparent to those ordinarily skilled in the art upon review of the following description of specific aspects and embodiments in conjunction with the accompanying figures.

BRIEF DESCRIPTION OF THE DRAWINGS

[0102] Embodiments of the present disclosure will now be described, by way of example only, with reference to the attached figures.

[0103] Fig. 1 shows a schematic of a generalized single-molecule approach, as is used in most traditional pharmaceutical therapeutics.

[0104] Fig. 2 shows a schematic of a generalized multi-modal approach, providing a therapeutic that accounts for multiple portions of a metabolic pathway.

[0105] Fig. 3 shows a schematic illustrating the relationship between energy, sugar metabolism, homeostasis and depression.

[0106] Fig. 4 shows interactions between the gut and the brain related to sugar signaling.

[0107] Fig. 5 shows a schematic for the mechanism of action and effects of the compositions on 5HT2A receptors and TRP receptors together for reducing inflammation and improving mood.

[0108] Fig. 6 shows data used to establish MED50 with psilocybin alone and with a formulation of the 07 Base. A complete composition is described in Table 8 with psilocybin.

[0109] Fig. 7 shows data used to establish MED50 with morning glory seeds alone and with a formulation of the 07 Base. A complete composition is described in Table 8 with morning glory seeds.

[0110] Fig. 8 shows data used to establish MED50 with Hawaiian baby woodrose seeds alone and with a formulation of the 07 Base. A complete composition is described in Table 8 with Hawaiian baby woodrose seeds.

[0111] Fig. 9 shows data used to establish a timepoint post-TNF-α/IFN-γ treatment to evaluate the anti-inflammatory effects of the compositions described herein on human primary small intestinal epithelial cells (HSIEC).

[0112] Fig. 10 shows the structures of TRP agonists eugenol, capsaicin, and curcumin.

[0113] Fig. 11 shows the effects of escalating doses of eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0114] Fig. 12 shows the effects of escalating doses of capsaicin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0115] Fig. 13 shows the effects of escalating doses of curcumin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0116] Fig. 14 shows the structures of 5HT2A agonists psilocybin, 4-ACO-DMT, psilocin, and serotonin and 5HT2A antagonist ketanserin.

[0117] Fig. 15 shows the effects of escalating doses of psilocybin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0118] Fig. 16 shows the effects of escalating doses of 4-ACO-DMT on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0119] Fig. 17 shows the effects of escalating doses of ketanserin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0120] Fig. 18 shows the separate and combined effects of psilocybin and eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0121] Fig. 19 shows the separate and combined effects of psilocybin and eugenol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0122] Fig. 20 shows the separate and combined effects of psilocybin and eugenol on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ.

[0123] Fig. 21 shows the separate and combined effects of psilocybin and eugenol on TNF receptor 2 (TNF-R2) in the HSIEC cells treated with TNF-α/IFN-γ.

[0124] Fig. 22 shows the separate and combined effects of 4-ACO-DMT and eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0125] Fig. 23 shows the separate and combined effects of 4-ACO-DMT and eugenol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0126] Fig. 24 shows the separate and combined effects of ketanserin and eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0127] Fig. 25 shows the separate and combined effects of psilocybin and capsaicin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0128] Fig. 26 shows the separate and combined effects of psilocybin and capsaicin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0129] Fig. 27 shows the separate and combined effects of 4-ACO-DMT and capsaicin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0130] Fig. 28 shows the separate and combined effects of 4-ACO-DMT and capsaicin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0131] Figs. 29A and 29B show the separate and combined effects of ketanserin and capsaicin on COX-2 and IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0132] Fig. 30 shows the separate and combined effects of psilocybin and curcumin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0133] Fig. 31 shows the separate and combined effects of psilocybin and curcumin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0134] Fig. 32 shows the separate and combined effects of 4-ACO-DMT and curcumin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0135] Figs. 33A and 33B show the separate and combined effects of ketanserin and curcumin on COX-2 and IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0136] Fig. 34 shows the effects of psilocybin on iNOS in the HSIEC cells treated with TNF-α/IFN-γ.

[0137] Fig. 35 shows the separate and combined effects of psilocybin and eugenol on iNOS in the HSIEC cells treated with TNF-α/IFN-γ.

[0138] Fig. 36 shows the effects of 4-ACO-DMT on iNOS in the HSIEC cells treated with TNF-α/IFN-γ.

[0139] Fig. 37 shows the separate and combined effects of 4-ACO-DMT and eugenol on iNOS in the HSIEC cells treated with TNF-α/IFN-γ.

[0140] Fig. 38 shows the separate and combined effects of ketanserin and eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0141] Fig. 39 shows the structures of TRP agonists carvacrol, piperine, and cinnemaldehyde.

[0142] Fig. 40 shows the effects of carvacrol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0143] Fig. 41 shows the separate and combined effects of psilocybin and carvacrol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0144] Figs. 42A and 42B respectively show the effects of psilocybin on IL-6 and IL-8 in the HSIEC cells treated with TNF-α/IFN-γ.

[0145] Figs. 43A and 43B respectively show the effects of carvacrol on IL-6 and IL-8 in the HSIEC cells treated with TNF-α/IFN-γ.

[0146] Fig. 44 shows the separate and combined effects of psilocybin and carvacrol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0147] Fig. 45 shows the separate and combined effects of psilocybin and carvacrol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0148] Fig. 46 shows the effects of piperine on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0149] Fig. 47 shows the separate and combined effects of psilocybin and piperine on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ.

[0150] Figs. 48A and 48B respectively show the effects of piperine on IL-6 and IL-8 in the HSIEC cells treated with TNF-α/IFN-γ.

[0151] Fig. 49 shows the separate and combined effects of psilocybin and piperine on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0152] Fig. 50 shows the separate and combined effects of psilocybin and piperine on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ.

[0153] Fig. 51 shows the effects of cinnemaldehyde on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0154] Fig. 52 shows the separate and combined effects of psilocybin and cinnemaldehyde on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ.

[0155] Fig. 53 shows data used to establish a timepoint post-TNF-α/IFN-γ treatment to evaluate the anti-inflammatory effects of the compositions described herein on *in vitro* 3D tissue models.

[0156] Fig. 54 shows the separate and combined effects of psilocybin and capsaicin on COX-2 in the 3D tissue models treated with TNF-α/IFN-γ.

[0157] Fig. 55 shows the separate and combined effects of psilocybin and capsaicin on IL-6 in the 3D tissue models treated with TNF-α/IFN-γ.

[0158] Figs. 56A and 56B show the separate effects of psilocybin and eugenol on GABA in A-172 cells.

[0159] Figs. 57A and 57B show the separate effects of psilocybin and eugenol on BDNF in the A-172 cells.

[0160] Fig. 58A shows the separate and combined effects of psilocybin and eugenol on COX-2 in the A-172 cells.

[0161] Fig. 58B shows the separate and combined effects of psilocybin and eugenol on GABA in the A-172 cells.

[0162] Fig. 58C shows the separate and combined effects of psilocybin and eugenol on IL-6 in the A-172 cells.

[0163] Fig. 58D shows the separate and combined effects of psilocybin and eugenol on BDNF in the A-172 cells.

DETAILED DESCRIPTION

[0164] Generally, the present disclosure provides compositions useful for reducing inflammation through agonism of both 5HT2A signalling receptors and transient receptor potential ("**TRP**") nociceptors, thereby promoting and/or maintaining health and wellness in an individual. The compositions disclosed herein include at least two active compounds. A first compound is a serotonin 5HT2A receptor agonist. A second compound is an agonist for one or more TRP receptors. The second compound or additional compounds may also be an antagonist for one or more TRP receptors. The combination of molecules in the compositions shows enhanced effects over 5HT2A agonists alone for combined multimodal action providing benefits at lower doses of both the 5HT2A agonist and the TRP agonist. The interaction of the compositions with the 5HT2A and TRP receptors results in altered activity of nociceptors and may also influence the endocannabinoid signaling system (the "**ECS**") and/or glucose metabolism. The compositions may be prepared from medicinal plant and fungi, pure compounds or combinations of both.

[0165] The compositions disclosed herein may promote mental health and wellness in healthy individuals, and have applications as a therapeutic for promoting mental health and wellness in individuals suffering from addiction, depression or other mental health conditions. The compositions may reduce the need for other drugs, including pharmaceuticals taken at the direction of a health care practitioner ("**HCP**"), substances take under self-directed care and abused substances. The compositions may have application in broad harm reduction programs. The compositions may also mitigate inflammation issues unrelated to mental health, including inflammation of gut, inflammation of the bowels and pain associated with inflammation. The composition may also promote the enhancement of cognition, creativity, focus, concentration, sex drive and/or other functions in those considered to be part of the 'healthy normal' population.

Serotonin Receptors

[0166] 5-hydroxy-tryptamine ("**5-HT**"), commonly referred to as serotonin and its biosynthetic precursor tryptophan, play an important role in regulating many biological processes. Tryptophan is converted to serotonin in both the intestine and the brain. Serotonin is released by the cell to trigger receptors and cause signaling cascades. Serotonin is typically reabsorbed and broken down by monoamine oxygenase ("**MAO**") enzyme. Serotonin affects sleep, appetite, temperature, sexual behavior, and pain sensation. While serotonin an important neurotransmitter, the majority of serotonin is produced the intestine. Brain-gut abnormalities in serotonin signaling have recently been implicated to play a role in several disease processes. Serotonin is primarily synthesized in the intestinal epithelium by enterochromaffin ("**EC**") cells from tryptophan. This production then regulates aspects of gut-brain communication. Lower levels of serotonin in the brain elicit sugar craving, while ingestion of sugar rich diet generally improves mood and alleviates anxiety in the short term. However, high sugar diets also disrupt glucose metabolism and feed microbial populations that may produce toxic byproducts, resulting in inflammation. Neuromodulators that influence nociceptor activity are released in the periphery during the inflammation (Loyd, 2012). Serotonin is one such proinflammatory mediator that has been shown to acts as an inflammatory mediator that contributes to inflammatory pain. The presence of multiple 5-HT subtype receptors on peripheral and central nociceptors is relevant to the role of 5-HT in sugar metabolism, mood, pain and inflammation.

[0167] The 5HT2A Receptor is is a G protein-coupled receptor ("**GPCR**"). 5HT2A is the main excitatory serotonin GPCR subtype. Stimulation of 5HT serotonin receptors, and specifically the 5HT2A receptor, by molecules has been shown to be primarily responsible for the psychedelic response in humans including illusions, hallucinations, delusions and altered states of perception, often at relatively low concentrations of micrograms to milligrams. 5HT2A receptor agonists may include tryptamines, ergolines, phenethylamines, amphetamines, phenylpropanoids or other families of compounds.

TRP Receptors

[0168] The TRP receptor superfamily is divided into seven subfamilies, including the five group 1 TRPs (TRPC, TRPV, TRPM, TRPN and TRPA) and two group 2 subfamilies

(TRPP and TRPML). Many TRP receptors are activated by a variety of stimuli, providing the function of a signal integrator. TRP receptors are ion channel receptors and are a family of non-selective cation channels that play important roles in cellular signaling. TRP receptors have six transmembrane segments, varying degrees of sequence homology and permeability to various cations.

[0169] Transient receptor potential subfamily V member 1 ("**TRPV1**") has six members divided into two groups. A first group includes TRPV1, TRPV2, TRPV3, and TRPV4. TRPV1, TRPV2, TRPV3 and TRPV4 include thermo-TRPs that are activated by heat. TRPV1 is a non-selective cation channel involved primarily in in pain sensation. TRPV1 may affect mood and neuroplasticity in the brain, and there is a clear molecular link between TRPV1 activity and stress responses. TRPV3 mediates a weakly Ca^{2+}-selective cationic conductance in response to non-noxious heat, camphor and other molecules. TRPV3 is widely expressed in humans, with an important role in thermosensation. TRPV4 is a constitutively active Ca^{2+}-permeable cation channel displaying a response to moderate heating, hypotonic challenge, or the phorbol ester 4α-PDD. TRPV4 is involved in pressure and osmotic sensitivity, thermal selection and hearing. A second group of TRPV receptors includes TRPV5 and TRPV6, which are selective Ca^{2+} transporters but do not respond to heat.

[0170] Transient receptor potential canonical ("**TRPC**") channels represent a group of receptor-operated calcium-permeable nonselective cation channels of the TRP superfamily. Seven mammalian TRPC members can be divided into four subgroups (TRPC1, TRPC2, TRPC4/5, and TRPC3/6/7) are involved in a range of cellular and physiological functions. TRPC channels have been implicated in calcium release activated channels in many cell types and have been suspected to be involved in Alzheimer's disease and various cardiomyopathies.

[0171] Transient receptor potential subfamily 'A' ion channels ("**TRPA**") is a family of receptors made up of 7 subfamilies: TRPA1, TRPA- or TRPA1-like, TRPA5, painless, pyrexia, waterwitch, and HsTRPA. These channels have been identified as mechanical stress, temperature, and chemical sensors. TRPA1 was initially described as a cold sensitive nonselective cation channel, there is evidence that it functions as a ligand-gated channel in expression systems and sensory neurons. TRPA1 appears to be regulated by PLC-coupled receptors, exhibiting many functional characteristics of other TRP channels. TRPA1 also has been tentatively identified as a hearing transduction channel, while the

multiple ankyrin repeats in TRPA1 have been suggested to function as a mechanical spring, linking TRPA1 to cytoskeletal proteins.

[0172] Transient receptor potential subfamily M (M is shorthand for melastatin) subfamily comprises eight members divided into three groups. A first group includes TRPM1, TRPM2 and TRPM3. A second group includes TRPM4, TRPM5 and TRPM8. A third group includes TPRM6 and TRPM7. TRPM receptors have been implicated in various processes including regulation of calcium, modulation of insulin secretion and cold and heat sensation, inflammatory pain, magnesium reabsorption and regulation of cell adhesion.

[0173] TRPM3 has alternate functional splice variants. Mouse TRPM3α1 is monovalent-selective, while TRPM3α2 is divalent selective, suggesting that *in vivo* TRPM3 function may depend on the relative abundance of these variants. TRPM3α1 and TRPM3α2 both display constitutively active rectifying currents which are blocked by intracellular Mg^{2+}. TRPM3 has been implicated in microglial and choroid plexus functions.

[0174] TRPM8 has been mostly described as a cold- and menthol-activated nonselective cation channel displaying voltage dependent gating properties. TRPM8 is expressed in sensory neurons, potentially acting as a cold thermosensor. Channel agonists such as cold or menthol may shift the voltage dependence of TRPM8 to more negative potentials.

[0175] TRPN is a member of the transient receptor potential channel family of ion channels. The TRPN gene was named no mechanoreceptor potential C (*nomp*C) when first discovered in a *Drosophila* species. TRPN receptors are mechanoreceptors. Studies of TRPN indicate that null mutants in fruit flies have difficulty moving, suggesting a role in proprioception. Studies in worms have shown null mutants to have various locomotion defects while electrophysiological studies of single channels in worms have shown that TRPN responds to mechanical stimuli and has a preference for sodium ions.

[0176] TRPP (transient receptor potential polycystic) is a family of transient receptor potential ion channels named for mutations that can cause polycystic kidney disease.

[0177] TRPML (transient receptor potential cation channel, mucolipin subfamily) represent a group of three related proteins. The three proteins TRPML1, TRPML2 and TRPML3 are encoded by the mucolipin-1 (MCOLN1), mucolipin-2 (MCOLN2) and mucolipin-3 (MCOLN3) genes. The three members of the TRPML sub-family are not well characterized, while TRPML1 is known to be localized in late endosomes. This subunit also contains a lipase domain between its S1 and S2 segments, with the domain

hypothesized to be involved in channel regulation. Studies have described TRPML1 channels as proton leak channels in lysosomes responsible for preventing these organelles from becoming too acidic, with deficiencies leading to enlarged vesicles.

Multi-modal Treatment of Health Conditions

[0178] Fig. 1 shows a schematic of a generalized single-molecule approach, as is used in most traditional pharmaceutical therapeutics. Traditional pharmaceuticals target a single receptor with a single molecule to produce a predicted result of complete or partial activation or deactivation. Most commonly a receptor agonist or antagonist may be applied at a specific concentration to reduce the symptoms of a disease for a period of time. The single-molecule approach, particularly with strong agonists and strong antagonists, rarely restores balance to a system or cures a disease. This linear approach does not account for or otherwise leverage the complicated feedback mechanisms that may upregulate or downregulate the process itself. Furthermore, single molecule approaches have often focused on molecules with increased potency or pharmacodynamic properties under the assumption that increased activation is more efficacious in treating disease. As a result, these approaches often result in imbalanced biological systems rather than restoration of balance to cellular processes and other biological systems. The imbalances that often result from single-molecule pharmaceutical medications often lead to side effects that are commonly dealt with by a second medication, which may result in further imbalance.

[0179] Fig. 2 shows a schematic of a generalized multi-modal approach, providing a therapeutic that accounts for multiple portions of a metabolic pathway, accounting for stimulation and feedback loops that may result in imbalance or toxicity. A drug may have a single target or multiple receptor targets, and interaction with the targets of the drug will be affected by other features of the system. Endogenous molecules may interact with the same receptor and compete for receptor sites. Introduction of strong agonists or strong antagonists may amplify, reduce, prevent or otherwise perturb signaling within endogenous pathways. The extent and distribution of expression of receptors in the body may be heterogeneous. Interaction with any given receptor may have downstream changes in gene expression and signaling to other parts of the body. Multiple signaling pathways may converge within a cell to regulate one another and maintain homeostasis between many processes. Interaction of a drug with a given receptor may influence

homeostasis through downstream effects, in some cases drastically. Degradation of the drug may have result in byproducts that have further signaling consequences and potential side effects, including by modulating metabolites or other byproducts of endogenous processes. Natural molecules often have clear metabolic breakdown pathways and may a lack some of toxic bi-products resulting from synthetic drugs. As seen through traditional medicine approaches (Chinese medicine, Aruvedic formulas, etc), combinations of multiple natural molecules shows potential for treating disease with little to no side effects.

[0180] Restoring homeostasis to metabolic pathways requires attention to the production, reception, signaling and breakdown of each neurotransmitter or other signaling molecule entering the system, present in the system and exiting the system. Biological and molecular pathways are cycles with multiple inputs, convergence points and branch points resulting in different products or effects. Multiple enzymes are involved in most biological processes, including those that signal events in the nucleus and trigger gene expression. Such signals may result in positive or negative feedback at different parts of a metabolic pathway. If a metabolic system has been downregulated, stimulation at multiple points may facilitate restoration of homeostasis. If a metabolic system has been upregulated, attenuation at multiple points may facilitate restoration of homeostasis. Molecular pathways may be downregulated in one part and upregulated in another through interaction with one or multiple chemicals. Blocking or overstimulating any one part of the cycle may create imbalances resulting in side effects. For example, while serotonin does not cause intoxication, psilocin and other 5HT2A agonists may overstimulate the 5HT2A receptor causing hallucinations and other psychoactive effects. The compositions include ingredients in addition to a 5HT2A agonist that provide a multimodal molecular approach, combining both agonists and antagonists for other receptors that converge with 5HT2A signaling to provide benefits while mitigating psychoactive effects of 5HT2A agonists.

Mental Health and Gut Health

[0181] Many components found in food show antidepressant effects. Many of these same ingredients have also been associated with a reduction in inflammation and play a role in sugar metabolism. Relatively low doses of certain natural molecules including a 5HT2A agonist and a TRP receptor agonist may facilitate balance to inflammatory

mediators and use of compositions including a 5HT2A agonist and a TRP receptor agonist may present an option for treatment and prevention of inflammatory disease, mental illness and sugar metabolism issues.

[0182] Fig. 3 shows a schematic illustrating the relationship between energy, sugar metabolism, homeostasis and depression. Inflammation may result from an energetic imbalance. Where energy enters a cell or other system and is not converted by the system to something useful, and subsequently removed from the system, inflammation ensues. Inflammation, if left unchecked, will lead to a multitude of negative consequences that can be additive and exacerbate one another, compounding into much larger events. Correlative links between consumption of excess sugar and inflammation have long been suspected (Corte, 2018).

[0183] In humans, energy is primarily provided to the body as sugars (e.g. glucose, fructose, sucrose, etc.). Glucose is converted into energy in cells. Excess sugars, particularly those from high-fructose corn syrup or other processed sources, have been shown to influence inflammatory markers and result in inflammation. Inflammation associated with excess sugar intake may partially be a result of microbial metabolites from flora feeding on sugars in the intestine. Inflammation associated with excess sugar intake may also be due to excess energy that the body has no means to deal with and therefore results in the energy being stored as fats, subsequently altering glucose metabolism and leading to conditions including diabetes.

[0184] MDD has not been specifically defined or characterized as an inflammatory disease. However, there is evidence is to show crosstalk between depression and inflammation (Patel, 2013; Krishnadas, 2012; Lee, 2019; Slavich, 2014). Many metabolic pathways in the body may be influenced simultaneously in disease conditions and may also be influenced simultaneously by therapies. Individuals with inflammatory diseases are more likely to show increased rates of depression and individuals with depression are more likely to show increased rates of inflammatory diseases. Over 30% of people with MDD show elevated peripheral inflammatory biomarkers even in the absence of a diagnosed illness associated with inflammation (Slavich, 2014). Inflammation plays a role in the pathogenesis of a number of immune system, neurological and behavioral disorders, including depression, cognitive impairment, metabolic and autoimmune diseases. With respect to depression and inflammation, neither appears to be absolutely necessary or sufficient for the other. Each may occur in

the absence of the other, but depression and inflammation are often comorbid. In a significant subset of individuals, inflammation may precipitate or prolong depression or may significantly contribute to the inflammatory response, the course and the outcome of a comorbid disease. Biofeedback mechanisms between these inflammation and depression may exacerbate each condition.

[0185] Metabolism of sugar is vitally important for the body the primary source of energy. Glucose is normally broken down to pyruvate in the cytosol of cells. Pyruvate enters mitochondria to create adenosine triphosphate and other energy useful to the body. Pyruvate is also a direct metabolic precursor to alanine, to aspartate and asparagine through oxaloacetate, and to glutamate and glutamine through α-ketoglutarate. Glucose that is not used in this manner may enter other biosynthetic process or can be stored.

[0186] Glutamine is the most abundant amino acid in the human body and is involved in many metabolic processes, including glucose metabolism and biosynthesis of other amino acids. Some cells can directly transform glutamine into glucose through a series of chemical reactions. When glucose is then released into the blood, blood sugar level rises causing a cascade of changes throughout the body.

[0187] In addition to regulation of primary metabolism, glutamine and glutamate signaling appear to be intrinsically linked to brain activity and inflammation. Inflammatory mediators have been found to alter glutamate and monoamine neurotransmission, glucocorticoid receptor resistance and hippocampal neurogenesis. Inflammation can alter brain signaling patterns, altering cognition and contributing to the production of a pattern of symptoms, closely related to depression. Inflammation may exacerbate the complexity and severity of many illnesses, and influence treatment response. As such, inflammatory responses may lead to depression and depression may lead to inflammation in a way that each exacerbate each other.

[0188] The connection between consumption of processed sugar and diabetes is well known. There appears to also be direct correlations between excess consumption of processed sugar in a population and prevalence of mental health issues in the population. Specifically, high fructose corn syrup and artificial sweeteners can interfere with intestinal sugar signaling and brain signaling functions (de Sousa, 2017). A significant number of depression and mood disorder diagnoses may be a result of intestinal inflammation, which may be correlated to high sugar diets. Correction or mitigation of the intestinal inflammation may correct or mitigate the depression connected with the

intestinal inflammation. Compositions that include both a 5HT2A receptor agonist and a TRP receptor agonist may mitigate or correct the intestinal inflammation.

[0189] As individuals consume and process food, communication between the enteric nervous system (the "**ENS**") and the central nervous systems (the "**CNS**") is vital for maintaining homeostasis, particularly around sugars. The ENS is a portion of the peripheral nervous system (the "**PNS**"). The pathway between the ENS and the CNS is known as the gut-brain axis.

[0190] Fig. 4 shows interactions between the gut and the brain and sugar signaling progressing from the gut to the brain. Glutamate is key in sugar and energy signaling, but is also an important excitatory neurotransmitter in the nervous system. Glutamate plays an important role in nociception by transmission of signals from the PNR to the CNS following stimulation of specialized sensory TRP nociceptors. As such, glutamate is directly involved in the sensitization of inflammation pain and neuropathic pain.

[0191] Glutamate levels elevate and expression of ionotropic glutamate receptors ("**iGluRs**") is upregulated during cutaneous inflammation and during deep tissue inflammation. Peripheral inflammation increases the proportions of both unmyelinated and myelinated nerves expressing iGluRs. Nociceptor cells are found in any area of the body that can sense stimuli and are prevalent in the digestive tract. The peripheral terminal of a mature nociceptor is where the stimuli are detected and transduced into electrical energy. When the electrical energy reaches a threshold value, an action potential is induced and driven towards the CNS, where specific changes in metabolic activity result in production of neurotransmitters. Glutamate signaling in the brain and TRP signaling from the gut alters brain chemistry in at least the manner described in this paragraph, and shown in Figs. 4 and 5.

[0192] Nociceptor neuron sensitivity is modulated by a large variety of mediators in the extracellular space (Woolf, 2007). Peripheral sensitization represents a form of functional plasticity of the nociceptor. The nociceptor can change from being simply a noxious stimulus detector to a detector of non-noxious stimuli. The result is that low intensity stimuli from regular activity, initiates a painful sensation. Inflammation results in the sensitization of nociceptors. Normally problems cease when inflammation goes down; however, sometimes genetic defect or repeated injury, including from chronic exposure to excess energy from processed sugars, can result in aberrant issues and lead to chronic issues in this pathway.

[0193] Glutamate plays an important role in transmitting the nociceptive signals from the PNS to the spinal cord. Glutamate injections provoked nociceptive responses mediated by neuropeptides (substance P) released from C fibers by activation of glutamate receptors that stimulate the production of a variety of intracellular secondary messengers. These include nitric oxide, pro-inflammatory cytokines, such as tumor necrosis factor alpha ("**TNF-α**") and interleukins such as interleukin-1β ("**IL-1β**"), which act synergistically in the excitation of the neurons (Goldstein, 2009).

[0194] Several studies have pointed to the presence of increased inflammatory cytokines in individuals with MDD. Inflammatory cytokines are cell-signaling protein molecules that are released during inflammation and launch signaling cascades able to activate the immune system. Type 1 cytokines include TNF-α, interferon-γ, interleukin-1β. Type 1 cytokines enhance cellular immune responses. Pro-inflammatory cytokines may be produced in the brain itself or reach the brain from the PNS through active transport or "leaky" regions across the blood-brain barrier. Cytokines may signal the brain through the afferent vagal pathway or via the entry of activated monocytes into the brain from periphery. The compositions with both 5HT2A and TRP agonists reduce gut inflammation markers, which results in improved mental health.

[0195] Meta-analyses have compared individuals suffering from MDD to a control group, and shown differences in proinflammatory cytokines such as TNF-α (Liu, 2012, Ma, 2016). The meta-analyses showed that individuals with MDD had significantly higher concentrations of TNF-α compared with controls. Interleukin 6 ("**IL-6**") has also been linked to depression especially when comorbid with physical disorders. Both animal and clinical studies demonstrate increased peripheral or central cytokine interleukin-6 levels play an important role in stress reactions and depressive disorders. Ting, E. *et al.*, "Role of Interleukin-6 in Depressive Disorder," Int. J. Mol. Sci. 21(6):2194 (March 2020). The majority of researches indicate that individuals suffering from depression have shown elevations in the proinflammatory cytokines.

[0196] Cyclooxygenase ("**COX**"), officially known as prostaglandin-endoperoxide synthase ("**PTGS**") is a protein that is responsible for the synthesis of prostaglandins. Prostaglandins are bioactive lipids that have potent actions in inflammation, fever and pain as well as provide protection of gastric mucosa and platelet aggregation. COX2 specifically is another proinflammatory regulator of inflammation and has been linked depression. COX-2 inhibition directly effects the CNS and some components of the

inflammatory system, kynurenine-metabolism and glutamatergic neurotransmission. COX-2 inhibitors have been tested in animal models of depression and in preliminary clinical trials, the latter showing favorable effects compared to placebo, both, in schizophrenia and in MDD. The compositions are effective at reducing COX2.

[0197] Subsets of vagal afferent nerves have activation properties indicative of specialization to detect potentially harmful stimuli. A cascade of events occurs in the brain including regulation of inflammation markers and the perception of pain. When a high threshold is reached by either chemical, thermal, or mechanical environments, the nociceptors are triggered under normal conditions. TRP receptors are responsible for whether and how specific nerve endings respond to stimuli, providing for a variety of potential responses. Inclusion of different TRP agonists that may interact with different TRP receptors can differentially influence downstream gene expression as well as the over-perception of the effects of combined 5HT2A formulation.

[0198] Studies investigating the gut-brain axis demonstrate that the gut microbiota is an important regulator of interactions relevant to brain development, behavior and the immune system. Microbes influence the activation of peripheral immune cells, which regulates responses to neuroinflammation, brain injury, autoimmunity and neurogenesis. Both the gut microbiota and immune system are implicated in the etiopathogenesis or manifestation of neurodevelopmental, psychiatric and neurodegenerative diseases. Compositions with both 5HT2A and TRP agonists may influence gut microbiota in various ways.

[0199] Stress causes changes in neurotransmission in the brain and influences stress-induced behaviors. However, it is unclear how neurotransmission systems orchestrate stress responses at the molecular and cellular levels. Although the extent to which inflammation contributes to depression onset and relapse is unknown, studies have shown that elevated serum cytokine levels of inflammatory markers often precede, and therefore potentially cause depressive symptoms (Karlović, 2012; Krishnadas 2012) Many illnesses show difference in inflammation markers including diabetes, metabolic syndrome, rheumatoid arthritis, asthma, multiple sclerosis, cardiovascular disease, chronic pain, and psoriasis, which are also characterized by increased risk for depression (Gan, 2004; Stenvinkel 2002). For instance, nearly 20% of individuals with cardiovascular disease experience MDD (O'Neil, 2013), individuals suffering from diabetes are twice as likely to develop depression (Mezuk, 2008) and up to 70% of individuals suffering from

autoimmune diseases, such as systemic lupus erythematosus (Palagini, 2013) or rheumatoid arthritis (Dickens, 2002) all experience higher rates of depression. Compositions with both 5HT2A and TRP agonists may also help with disease states found to be comorbid with depression due to treatment of the underlying inflammation.

[0200] Conditions associated with chronic inflammation are listed in Table 1.

Table 1: Conditions Associated with Chronic Inflammation

Disease	Type	Signs and Symptoms
Arthritis	Bone, Muscular, Skeletal	Joint pain, tenderness, stiffness, inflammation in and around the joints, restricted movements of the joints, warm red skin over the affected joint, weakness and muscle wasting.
Osteoporosis	Bone, Muscular, Skeletal	Back pain (caused by a fractured or collapsed vertebra), loss of height over time, stooped posture, a bone that breaks much more easily than expected.
Osteoarthritis	Bone, Muscular, Skeletal	Pain and stiffness in joints, joint tenderness, increased pain and stiffness when immobile for long periods, joints swelling, grating/crackling sound or sensation in joints, limited range of movement in joints, weakness and muscle wasting (loss of muscle bulk).
Degenerative Disc Disease (DDD)	Bone, Muscular, Skeletal	Range from mild to severe pain, neck and lower back pain, pain extending to the arms and hands, pain extends through buttocks and thighs, pain amplifies when sitting/bending/lifting/twisting, weakness in leg muscles or foot drop
Muscular Dystrophy	Bone, Muscular, Skeletal	MD can include the following types; duchenne MD, myotonic dystrophy, facioscapulohumeral MD, becker MD, limb-girdle MD, oculopharyngeal MD and emery-dreifuss MD. All types of MD cause muscle weakness, but the areas affected and the severity of the symptoms differ by type.
Breast Cancer	Cancer	A change in the size or shape of one or both breasts, discharge from either of your nipples, which may be streaked with blood, a lump or swelling in either of your armpits, dimpling on the skin of your breasts, a rash on or around your nipple and a change in the appearance of your nipple (such as becoming sunken into your breast).
Colon Cancer	Cancer	Persistent change in bowel habit – pooing more often, with looser, runnier poos and sometimes tummy (abdominal) pain, blood in the poo without other symptoms of piles (haemorrhoids) – this makes it unlikely the cause is haemorrhoids, abdominal pain,

		discomfort or bloating always brought on by eating – sometimes resulting in a reduction in the amount of food eaten and weight loss.
Lung Cancer	Cancer	A cough that doesn't go away after 2 or 3 weeks, a long-standing cough that gets worse, chest infections that keep coming back, coughing up blood, an ache or pain when breathing or coughing, persistent breathlessness, persistent tiredness or lack of energy, loss of appetite or unexplained weight loss.
Kidney Cancer	Cancer	blood in your pee – you may notice your pee is darker than usual or reddish in colour, a persistent pain in your lower back or side, just below your ribs, a lump or swelling in your side (although kidney cancer is often too small to feel), extreme tiredness, loss of appetite and unintentional weight loss, persistent high blood pressure (hypertension), a high temperature, night sweats, swelling of the veins in the testicles (for men), swollen glands in your neck, bone pain and coughing up blood.
Gastric Cancer	Cancer	heartburn or acid reflux, having problems swallowing (dysphagia), feeling or being sick, symptoms of indigestion, such as burping a lot feeling full very quickly when eating, loss of appetite or losing weight without trying to, a lump at the top of your tummy, pain at the top of your tummy and feeling tired or having no energy.
Pancreatic Cancer	Cancer	The whites of your eyes or your skin turn yellow (jaundice), you may also have itchy skin, darker pee and paler poo than usual, loss of appetite or losing weight without trying to, feeling tired or having no energy, a high temperature, or feeling hot or shivery.
Lymphoma	Cancer	The two most common types of lymphoma are Hodgkin and non-Hodgkin lymphoma. The most common symptom of Hodgkin lymphoma is a swelling in the neck, armpit or groin. The swelling is usually painless, although some people find that it aches. The most common symptom of non-Hodgkin lymphoma is a painless swelling in a lymph node, usually in the neck, armpit or groin. Lymph nodes, also known as lymph glands, are pea-sized lumps of tissue found throughout the body.
Atherosclerosis	Cardiovascular + Diabetic	Chest pain, numbness, weakness in arms/legs, difficulty speaking, slurred speech, temporary loss of vision in one eye, drooping facial muscles, claudication, high blood pressure and kidney failure.

Cardiomyopathy	Cardiovascular + Diabetic	Shortness of breath, on exertion or at rest, recurrent chest infections, coughing up sputum or blood, palpitations, and an awareness of your heart beating faster or in an irregular way, chest pains, and/or angina pain, abnormal heart rhythms - called arrhythmias, fainting or near fainting, dizziness, swelling to the face, abdomen or extremities, undue tiredness and reduced exercise tolerance.
Cerebrovascular disorder	Cardiovascular Disease	There are a number of different types of cerebrovascular disease. The four most common types are; Stroke – a serious medical condition where one part of the brain is damaged by a lack of blood supply or bleeding into the brain from a burst blood vessel, Transient Ischaemic Attack (TIA) – a temporary fall in the blood supply to one part of the brain, resulting in brief symptoms similar to stroke, Subarachnoid Haemorrhage – a type of stroke where blood leaks out of the brain's blood vessels on to the surface of the brain, Vascular Dementia – persistent impairment in mental ability resulting from stroke or other problems with blood circulation to the brain.
Heart Failure	Cardiovascular Disease	Breathlessness – this may occur after activity or at rest; it may be worse when you're lying down, and you may wake up at night needing to catch your breath, Fatigue – you may feel tired most of the time and find exercise exhausting, Swollen ankles and legs – this is caused by a build-up of fluid (oedema); it may be better in the morning and get worse later in the day.
Stroke	Cardiovascular Disease	The main stroke symptoms can be remembered with the word FAST; **Face** – the face may have dropped on 1 side, the person may not be able to smile, or their mouth or eye may have drooped. **Arms** – the person may not be able to lift both arms and keep them there because of weakness or numbness in 1 arm. **Speech** – their speech may be slurred or garbled, or the person may not be able to talk at all despite appearing to be awake; they may also have problems understanding what you're saying to them. **Time** – it's time to dial 999 immediately if you notice any of these signs or symptoms.
Leaky Gut	Chronic Inflammatory Disorder	Proponents of "leaky gut syndrome" claim that many symptoms and conditions are caused by the immune system reacting to germs, toxins or other substances that have been absorbed into the bloodstream via a porous ("leaky") bowel.

Ulcerative Colitis	Chronic Inflammatory Disorder	The main symptoms of UC are: recurring diarrhoea, which may contain blood, mucus or pus, tummy pain, needing to empty your bowels frequently. You may also experience extreme fatigue, loss of appetite and weight loss.
Irritable Bowel Syndrome (IBD)	Chronic Inflammatory Disorder	The main symptoms of IBS are: stomach pain or cramps – usually worse after eating and better after doing a poo bloating – your tummy may feel uncomfortably full and swollen diarrhoea – you may have watery poo and sometimes need to poo suddenly constipation – you may strain when pooing and feel like you cannot empty your bowels fully
Chronic Obstructive Pulmonary Disease (COPD)	Chronic Inflammatory Disorder	ongoing cough (wet/dry), shortness of breath, wheezing, whistling/squeaky sound when breathing, chest tightness, hard time catching your breath, lips/fingernails turn blue or gray, lack of mental alertness, very fast heartbeat.
Rheumatoid Arthritis (RA)	Chronic Inflammatory Disorder	Pain or aching in more than one joint, stiffness in more than one joint, tenderness and swelling in more than one joint, the same symptoms on both sides of the body (such as in both hands or both knees), weight loss, fever, fatigue, tiredness, weakness.
Psoriasis	Chronic Inflammatory Disorder	Symptoms are dry red skin lesions, known as plaques, covered in silver scales. They normally appear on your elbows, knees, scalp and lower back, but can appear anywhere on your body. The plaques can be itchy or sore, or both. In severe cases, the skin around your joints may crack and bleed.
Chronic Pancreatitis	Chronic Inflammatory Disorder	Chronic pancreatitis is a condition where the pancreas has become permanently damaged from inflammation and stops working properly. The most common symptom of chronic pancreatitis is repeated episodes of severe pain in your tummy (abdomen). The pain usually develops in the middle or left side of your tummy and can move along your back. It's been described as a burning or shooting pain that comes and goes, but may last for several hours or days. Although the pain sometimes comes on after eating a meal, there's often no trigger. Some people might feel sick and vomit.
Chronic Inflammatory Demyelinating	Chronic Inflammatory Disorder	Tingling in arms and legs, gradual weakening of arms and legs, loss of reflexes, loss of balance and your ability to walk, loss of feeling in your arms and legs, which often starts with your inability to feel a pin prick.

Polyradiculoneuropathy (CIDP)		
Chronic Inflammatory Connective Tissue Diseases (CICTD)	Chronic Inflammatory Disorder	More than 200 different types of connective tissue diseases including rheumatoid arthritis (RA), scleroderma, granulomatosis with polyangiitis (GPA), churf-strauss syndrome, systemic lupus erythematosus (SLE), microscopic polyangiitis (MPA), polymyositis/dermatomyositis, mixed connective tissue disease (MCTD) and undifferentiated connective tissue diseases.
Gingivitis	Dental	Swollen gums, dark red gums, gums that bleed easily, bad breath, receding gum line, tender/sensitive gums.
Retinopathy	Diabetic Complications	Symptoms include gradually worsening vision, sudden vision loss, shapes floating in your field of vision (floaters), blurred or patchy vision and eye pain or redness.
Sepsis	Diabetic Complications	Sepsis can be hard to spot. There are lots of possible symptoms. Symptoms can be vague. They can be like symptoms of other conditions, including flu or a chest infection.
Neuropathy	Diabetic Complications	The main symptoms of peripheral neuropathy can include; numbness and tingling in the feet or hands, burning, stabbing or shooting pain in affected areas, loss of balance and co-ordination and muscle weakness, especially in the feet.
Chronic Kidney Disease (CKD)	Metabolic Disorder	Symptoms include tiredness, swollen ankles, feet or hands (due to water retention), shortness of breath, nausea and blood in the urine.
Fatty Liver Disease	Metabolic Disorder	There aren't usually any prevalent symptoms in the early stages. Some symptoms in more serious cases may include; a dull or aching pain in the top right of the tummy (over the lower right side of the ribs), fatigue (extreme tiredness), unexplained weight loss and weakness.
Heart Disease	Metabolic Disorder	Symptoms of a heart attack can include; - pain in other parts of the body – it can feel as if the pain is travelling from your chest to your arms, jaw, neck, back or stomach - light-headedness - sweating - nausea - breathlessness
Sleep Apnea	Metabolic Disorder	Symptoms of sleep apnea during sleep: breathing stopping and starting, making gasping, snorting or

		choking noises, waking up frequently, loud snoring. Symptoms of sleep apnea during the day: feel very tired, find it hard to concentrate, have mood swings, have a headache when you wake up.
Type 2 Diabetes	Metabolic Disorder	Typical symptoms include: - feeling very thirsty - passing urine more often than usual, particularly at night - feeling very tired - weight loss and loss of muscle bulk - slow to heal cuts or ulcers - frequent vaginal or penile thrush - blurred vision
Metabolic Syndrome	Metabolic Disorders	High blood sugar, hypertension, high triglycerides, low HDL-cholesterol, Visceral Obesity
Autoimmune Diseases	Metabolic Disorders	Despite the varying types of autoimmune disease, many of them share similar symptoms. Common symptoms of autoimmune disease include: - Fatigue - Joint pain and swelling - Skin problems - Abdominal pain or digestive issues - Recurring fever - Swollen glands
Amyotrophic Lateral Sclerosis (ALS)	Neurological	Early symptoms can include: - weakness in your ankle or leg – you might trip, or find it harder to climb stairs - slurred speech, which may develop into difficulty swallowing some foods - a weak grip – you might drop things, or find it hard to open jars or do up buttons - muscle cramps and twitches - weight loss – your arms or leg muscles may have become thinner over time - difficulty stopping yourself from crying or laughing in inappropriate situations
Alzheimer's	Neurological	The symptoms of Alzheimer's disease progress slowly over several years. Sometimes these symptoms are confused with other conditions and may initially be put down to old age. The rate at which the symptoms progress is different for

		each individual. In some cases, other conditions can be responsible for symptoms getting worse. These conditions include: - infections - stroke - delirium
Anxiety	Neurological	Symptoms can include: - restlessness - a sense of dread - feeling constantly "on edge" - difficulty concentrating - irritability
Dementia	Neurological	Some common early symptoms that may appear some time before a diagnosis of dementia. These include: - memory loss - difficulty concentrating - finding it hard to carry out familiar daily tasks, such as getting confused over the correct change when shopping - struggling to follow a conversation or find the right word - being confused about time and place - mood changes
Depression	Neurological	The symptoms of depression can be complex and vary widely between people. If you're depressed, you may feel sad, hopeless and lose interest in things you used to enjoy.
Stress	Neurological	Physical symptoms: headaches or dizziness muscle tension or pain stomach problems chest pain or a faster heartbeat sexual problems Mental symptoms: difficulty concentrating struggling to make decisions feeling overwhelmed constantly worrying being forgetful

Asthma Allergies	Respiratory	The most common symptoms of asthma are: - wheezing (a whistling sound when breathing) - breathlessness - a tight chest – it may feel like a band is tightening around it - coughing

Improving Mental Health by Mitigating Gut Inflammation

[0201] Mental health issues may be treated in many individuals by reducing inflammation in the intestines, specifically nociception of the enterochromaffin cells where the majority of serotonin is produced in the gut. Natural sources from plant and fungal medicines may be utilized to reduce gut inflammation through targeting specific receptors that regulate pain sensitization and inflammation thereby transmitting signals to the brain.

[0202] While serotonin is well known for its central nervous system regulation of mood, appetite, and vasoconstriction, it is becoming increasingly clear that 5-HT also plays a modulatory role in various acute and persistent pain states (Stiedl, 2015; (Loyd 2013; Sommer, 2004). The vast majority of 5-HT in the mammalian body is located in peripheral tissues with significant production in the intestinal enterochromaffin cells where 5-HT is actively taken up by the gut and released with other chemical messengers to interact with the PNS at other parts of the body. For example, serotonin acts as a neuromodulator of nociception by altering TRPV1 activity during inflammation (Loyd 2013). In sensory neurons 5-HT increases excitability to thermal stimuli and enhances capsaicin and heat evoked currents (Sugiuar, 2004; Ohta 2006). Depleting 5-HT attenuates visceral pain and reduces TRPV1 activation. 5-HT receptors regulate the stimulus threshold for sensory neurons by changing the properties of TRP receptor channels (Loyd, 2013).

[0203] Fig. 5 illustrates the mechanism of action of the compositions on 5HT2A receptors and TRP receptors together for reducing inflammation and improving mental health. Crossover with cannabinoid signaling is also illustrated. Simultaneous activation of these signaling pathways result in communication between the nociceptor cells of the gut (lower) and neurons in the brain (upper). The arrows demonstrate where the 5HT2A receptor agonists, the TRP agonists and CB receptor agonists included in the compositions bind with the 5HT2A, TPR and CB receptors. The arrows also show

convergence of signaling pathways including sugars and on microbiomes that flourish in the presence of sugars, and that result in inflammation and ROS.

[0204] Coactivation of 5HT2A and TRP receptors reduces the intensity of negative signals resulting from sugars and from microbiome changes resulting from altered sugar signaling. One approach to treating depression is to increase serotonin signaling while also allowing serotonin breakdown in turn balances output signaling molecules such as diacylglycerol ("**DAG**"). DAG acts as a secondary messenger that is a physiological activator of protein kinase C ("**PKC**"). DAG facilitates translocation of PKC from the cytosol to the plasma membrane and is linked to many processes such as sugar metabolism. Phosphorylation of TRP channels, involving Protein Kinase C (PKC) appears to be the predominant mechanism for channel sensitization. For example, Ca^{2+} influx through TRPV1 activates PKC and diacylglycerol kinase ("**DAGK**") enzymes. DAGK limits formation of DAG, providing a feedback mechanism to maintain homeostasis by inhibiting Ca^{2+} influx. Convergence of 5HT2A and TRP signaling pathways and the involvement of DAG and PKC results in an enhanced effect on the expression of inflammatory mediators and ROS.

[0205] The change in brain signaling may be affected through both altered signals from the gut and direct activity of the 5HT2A and TRP agonists in the brain. 5HT2A and TRP agonist activity in the brain, including glutamate signaling resulting from 5HT2A agonist activity, activates cAMP-response element binding protein ("**CREB**"). CREB increases expression of brain derived neurotrophic factor ("**BDNF**") expression, which in turn increases GABA production and signaling. Taken together, this results in increased neuroplasticity and improved mood.

[0206] Endocannabinoid receptor signaling also converges on this pathway involving PKC through arachidonic acid ("**AA**") metabolism and may further enhance the anti-inflammatory effects. While some cannabinoids may have direct psychoactive effects in the brain, some are thought to directly interact with TRP receptors as well. The corresponding reduction in inflammatory markers and ROS in the gut due to simultaneous signaling from 5HT2A and TRP in turn alters signaling cascades from the gut and subsequently improves brain chemistry.

[0207] Stimulation of the 5HT2A receptor with stimulation of one or more TRP receptors modulate key molecular signaling pathways that converge to reduce inflammation signaling from the gut to the brain and the developed compositions for regulating these

signals show enhanced activity. Nociceptor cells have TRP channels that respond to a wide variety of spices due to the presence of specific agonist molecules they contain. The compositions include combinations of substances, including natural substances from plants and fungi or extracted from plants and fungi, in ratios that show synergistic effects, which may be due to multimodal activity at numerous receptor sites, specifically 5HT2A and at least one TRP receptor. Synergy between the 5HT2A agonist and the TRP receptor agonist allows a reduced effective amount of each compound when the composition is used, while still achieving a medicinal, therapeutic or other positive effect. The lowered amount of the 5HT2A agonist and of the TRP receptor agonist mitigates side effects of either agonist. A multimodal approach of mixed TRP agonists and TRP antagonists allow for modulation of these pathways to treat a variety of medicinal diagnosis resulting from inflammation. Inflammation associated medical conditions that the compositions may be used to treat include cancer, neurological disorders (e.g. Alzheimer's, Huntington's chorea, dementia, Parkinson's, neurodevelopmental disorders, ALS, multiple sclerosis, etc.), diabetic complications (e.g. cardiovascular disease, neuropathy, nephropathy, sepsis, hypertension, retinopathy, atherosclerosis, etc.), mental health disorders (clinical depression, post-traumatic stress disorder, bipolar disorder, schizophrenia ,etc.), bone, muscular and skeletal disease (e.g. osteoporosis, osteoarthritis, muscular dystrophy, rheumatoid arthritis, osteopenia, etc.), metabolic disorders (e.g. fatty liver disease, heart disease, diabetes, metabolic syndrome, chronic fatigue syndrome, renal failure, etc.), chronic inflammatory disorders (e.g. irritable bowel disease, chronic obstructive pulmonary disease, pancreatitis, psoriasis, rheumatoid arthritis, colitis, lupus, etc.), cardiovascular disease (e.g. stroke, heart failure, congenital heart disease, atherosclerosis, cardiomyopathy, etc.).

[0208] TNF-α and COX2 are common markers for inflammatory disease and have been the targets of many drugs. TNF-α mediated inflammation was utilized in tissue cultures treated with ingredients from many of the compositions to assess anti-inflammatory potential. Many of the ingredients of the compositions reduce the prevalence of COX2 and interleukins, and may also reduce ROS, restoring homeostasis in terms of these biological signaling messengers. For each composition, there is a reduction in inflammation markers, with synergy demonstrated between the 5HT2A receptor agonist and the TRP receptor agonists.

[0209] Inflammatory cytokines COX2 and TNF-α, and ROS (e.g., inducible nitric oxide synthase ("iNOS") are increased within the cell in response to inflammation. The inflammatory state alters sensitization of the TRP channels and results in a lower threshold signal. Inflammatory markers are key in the process also play a role in cancer development. Intracellular Ca^{2+} buffering capacity by extracellular Ca^{2+} entering through TRP receptor channels and being released from intracellular stores, along with subsequent activation of calcium-dependent proteases is vital to maintenance of homeostasis. Dysregulation of this process results in disease progression.

[0210] TRPV1 and other TRP proteins regulate cell-environment crosstalk, thereby influencing cell behavior. Importantly, inflammatory sensitization leads to dramatically reduced activation thresholds of TRP channels (TRPV1, TRP ankyrin type 1 (TRPA1), and TRP melastatin type 8 (TRPM8). Reduced activation thresholds in turn contribute to establishing a systemic response of energy expenditure, energy allocation, and water retention which directly modulates the immune system in chronic inflammatory diseases (Straub, 2014).

[0211] 5HT2A and TRPV1 are expressed in nociceptors cells of both the ENS and the CNS. Cell bodies of sensory neurons for peripheral nociceptors are located in dorsal root ganglia alongside the spinal cord and in the trigeminal (V) ganglion for cranial nociceptors. These sensory neurons show a high expression of 5-HT receptors, including 5HT2A. Many of these same neurons co-express TRPV1. As such, compositions were developed to specifically activate the 5HT2A and TRP signaling pathways to reduce inflammation signaling. Reducing inflammation signaling may improve mental health and other conditions.

[0212] Inflammation and sugar signaling can lead to activation of TRP receptors at reduced threshold potential, leading to an influx of Ca^{2+} and upregulation of proinflammatory cytokines. High glutamate signaling suppresses serotonin signaling. 5HT2A receptor agonists including psilocin bind to 5HT2A receptors present in deep cortical layers, increasing extracellular glutamate levels in the prefrontal cortex.

[0213] The glutamate release activates AMPA and N-methyl-D-aspartate acid ("**NMDA**") receptors, leading to increased expression BDNF. BDNF acts on neurons of the CNS and helps to support the survival of existing neurons and to stimulate growth and differentiation of new neurons and synapses. CREB is one of the major regulators of neurotrophin responses since phosphorylated CREB binds to a specific sequence in the

promoter of BDNF and regulates its transcription. Coactivation of 5HT2A and TRP receptor channels leads to a synergistic effect from increased expression of BDNF and reactivation of pathways modulated by BDNF including an increase in GABA signaling. As a result, some balance is restored to this system, inflammation markers are downregulated, and significant mental health effects are observed.

[0214] Inflammatory cytokines can change brain function and structure through mechanisms including effects on neurotransmission. Proinflammatory cytokines increase the activity of serotonin transporter ("**SERT**") proteins, resulting in an increase of serotonin reuptake and a reduction of extracellular serotonin. Moreover, proinflammatory cytokines are able to up-regulate enzymes such as tryptophan 2,3-dioxygenase ("**TDO**") and indoleamine 2,3-dioxygenase ("**IDO**"), with a resulting decrease in tryptophan availability for serotonin synthesis, an increase in glutamate induced neurotoxicity and effects on the hypothalamic-pituitary-adrenal axis (the "**HPA**") or on hippocampal neurogenesis have been observed (Lu, 2018). The HPA is an interactive neuroendocrine unit comprising of the hypothalamus, the pituitary gland, and the adrenal glands. The HPA plays a key roles in basal homeostasis and in the body's response to stress. This overall reduction in serotonin signaling also has downstream effects on gamma-aminobutyric acid, ("**GABA**") signaling, which is the chief inhibitory neurotransmitter in the developmentally mature mammalian CNS. Co-Activation of TRP and 5HT2A regulates inflammation signaling pathways, leading to manipulation of these process and reduced symptoms of many diseases based on the ingredients included and which TRP channels are being influenced.

[0215] The combination of a 5HT2A agonist with a TRP agonist provides a multi-modal composition for reducing inflammation in the digestive tracts and simultaneously stimulate positive brain signalling processes. The reduced inflammation achieved through this mechanism may be useful for improving or maintaining mental health. Improving or maintaining mental health maybe useful for healthy individuals and for individuals suffering from a mental health condition or other conditions that result from inflammation. The combination a 5HT2A agonist with a TRP agonist is effective for reducing inflammation markers, which may provide benefits including a positive impact on certain mental health conditions, at lower doses (i.e. lower relative concentrations) of the 5HT2A agonist compound than would be expected through administration of the 5HT2A agonist without the TRP agonist.

[0216] Serotonin breakdown has also been a focus of treatment for depression. Monoamine oxidases ("**MAO**") play an important role in the central and peripheral nervous system (CNS and PNS) by modulating the levels of monoamine neurotransmitters MAOs exist as two isoforms, MAOA and MAOB where MAOA predominantly oxidizes norepinephrine and serotonin and MAOB predominantly oxidizes dopamine. MAO inhibitors mitigate symptoms of depression through blocking breakdown of serotonin. Some ingredients have been shown to have effects on MAO, though these could be indirect though TRP signaling. MAO inhibitors are known to increase psychedelic effects. Inclusion of ingredients that may influence the activity of MAO is likely to further alter the effects of the formulations.

Minimal Effective Dose

[0217] A therapeutically effective amount of the 5HT2A agonist may be lower in the presence of the TRP receptor agonist. By co-administering separate formulations or simultaneously administering the 5HT2A receptor agonist with the TRP receptor agonist in a single formulation, the therapeutically effective amount of the 5HT2A agonist required to achieve a therapeutic result may be lowered. Similarly, in the absence of a specific therapeutic indication but to maintain or improve wellness, co-administering the 5HT2A receptor agonist with the TRP receptor agonist, the amount of the 5HT2A receptor agonist needed to achieve the result is lowered. In the case of either a therapeutic indication or maintenance of wellness, a "minimum effective dose" or "**MED**" of the 5HT2A receptor agonist may be used when the 5HT2A receptor agonist is co-administered with a TRP receptor agonist. MED is defined as the least amount of a substance required to produce a given result, which in this case is perceptible effects and/or benefits from consumption of the 5HT2A agonist. With strongly psychoactive 5HT2A receptor agonists, such as some 4-substituted tryptamines, some ergolines and some phenethylamines, a therapeutic effect may be observed without inducing profound psychoactive effects in the user.

[0218] Use of a 5HT2A receptor agonist in combination with a TRP receptor agonist facilitates use of a lowered dose of the 5HT2A agonist for a defined benefit or other effect than would be necessary using the 5HT2A agonist alone. Many 5HT2A receptor agonists may be used in the compositions described here, including as detailed below. A low-cost, safe and simple 5HT2A agonist is psilocybin, which is found in fungi that biosynthesize

psilocybin. Fresh sclerotia including psilocybin are available in a regulated specialty foods market in the Netherlands. Dried fruiting bodies of fungi including psilocybin are readily available in unregulated and illicit markets worldwide. Psilocybin is listed in Schedule I of the *Convention on Psychotropic Substances*, 21 February 1971, 1019 UNTS 14956 (entered into force 8 August 1975). As a result, possession of psilocybin is prohibited in many jurisdictions. However, in Jamaica and a few other jurisdictions, psilocybin is simply not scheduled in domestic controlled substance legislation and as a consequence is unregulated.

[0219] With access to Jamaica and to dried fruiting bodies that contain psilocybin, experiments with dried fruiting bodies combined with TRP receptor agonists were undertaken to qualitatively measure any change in the effects of psilocybin observed from relatively low doses of the fruiting bodies. A standardized batch of a single genetic isolate of *P.cubensis* was selected. Because psilocybin is psychoactive and ingestion of larger amounts of the mushroom resulted in psychoactivity, the effects were discernable in a qualitative way that supported initial experiments to identify promising TRP receptor agonists.

[0220] Microdosing psilocybin by eating dried fruiting bodies is typically done with approximately 0.3 g of dried fruiting bodies, with a general range of between 0.1 and 1.0 g, 0.2 and 0.9 g, 0.3 and 0.8g, 0.4 and 0.7g, 0.5 and 0.5 g of dried fruiting bodies depending on the individual and the active metabolite profile of mushroom being consumed. The effects that were observed using the selected dried psilocybin mushroom combined with one or more of the TRP receptor agonists used in the compositions. At least one published study suggests subjective effects that are less pronounced at about 0.3 g of dried fruiting bodies than through using 0.3 g of dried fruiting bodies along with at least one TRP receptor agonist (Polito, 2019).

[0221] A baseline amount of psilocybin for a MED was selected as being 0.3 g of dried fruiting bodies of the fungal species used in the formulations. This dose was consumed regularly to establish and familiarize individuals with baseline psilocybin effects resulting from consuming 0.3 g of dried fruiting bodies. For each of the initial experiments using one or more additional herbal medicinal ingredients, the same batch of ground fruiting bodies was used as a source of psilocybin.

[0222] Additional herbal medicinal ingredient were added at a 1:1 ratio of dried fruiting bodies to herbal ingredient to assess the potential for any enhancement of the medical

effect of the psilocybin. Each ingredient was selected due to its reported medicinal benefits and agonist activity at least one TRP receptor. When a potential synergy was observed at 0.3 grams, the dose of both psilocybin and the additional herbal medicinal ingredient was reduced incrementally by 0.1 g, to 0.05 g from 0.1 g, of each ingredient. Incremental reductions of both ingredients were made to a point at which the effects were no longer felt. When no synergy was observed, the TRP agonist was increased incrementally in amounts of 0.3, 0.6, 0.9, 1.2 and 1.5, up to 5x the amount of psilocybin to determine whether the synergy at higher doses of TRP agonist or at different ratios of 5HT2A agonist to TRP agonist.

[0223] Combination of the 5HT2A receptor agonist (psilocybin) with additional herbal medicinal ingredients, including those with only mild effects, enhanced and altered the effects of psilocybin. The TRP agonists assessed produced synergistic effects with the psilocybin, resulting in a noticeable change in the effect of the psilocybin. In each case, the MED of psilocybin was reduced by inclusion of a TRP agonist, and the particular effects observed of a given formulation were variable depending on which TRP agonists were included with the psilocybin. The TRP agonists with the greatest effect, and particularly those resulting in a prolonged effect or in reduced side effects were considered for further compositions. The side effects that were reduced by lowering the MED were psychoactive effects from psilocybin and stomach issues from psilocybin.

[0224] An equivalent dose of amount of dried fruiting bodies and the additional herbal medicinal ingredient was taken to determine the medicinal effect or synergistic effect. A formulation including a composition of 0.3 gram of fruiting bodies and 0.3 gram of the additional herbal medicinal ingredient was consumed typically in gel capsules to reduce the difficulty of ingesting hundreds of milligrams of the additional herbal medicinal ingredients. For example, directly consuming cayenne pepper is difficult and painful. Alternatively, for oil extracts such as bergamot, peppermint and oregano, the recommended internal dose recommended on the package was consumed, which ranged from a few drops to about 1 ml depending on the liquid's concentration and the formulation.

[0225] The MED was defined as the dose required for 100% of individuals to report feeling a psychoactive effect of psilocybin, as defined subjectively by the individual. MED50 was set at the dosage where 50% of individuals report feeling the effects. Formulations of the composition were prepared based on the lowest MED50 value

observed and not the average. A microdose is considered a subperceptual dose, and since MED was pegged at the lowest perceptual dose, MED50 was selected for medical benefits. For psilocybin, or for a combination of psilocybin and other 4-substituted tryptamines, between 0.1 g and 1.0 g of dried fruiting bodies is between about 1 mg and 10 mg of psilocybin, or of psilocybin and other 4-substituted tryptamines.

[0226] Psilocybin was taken at doses of 0.0 to 1.0 g dried fruiting body, estimated to be equivalent to between 1 and 10 mg of psilocybin, suggesting a dose of 1 to 10 mg of psilocybin as 5HT2A agonist, with some of those doses being well above the microdosing range and well above the MED. For psilocybin alone, the MED was generally found to be over 0.3 g of dried fruiting bodies. For the compositions including the additional herbal medicinal ingredient, the MED was generally found to be between 0.90 and 0.12 g of dried fruiting bodies for a 70 kg individual.

[0227] Fig. 6 shows results of MED50 determination in individuals consuming a capsule including psilocybin formulated in the 07 Base – Complete Composition (diagonal lines in bar graphs and dashed regression line) compared with capsules including psilocybin alone (white bar graphs and solid regression line). MED50 is the Dose at which 50% of participants report feeling the effect of psilocybin. Data from microdosing different amounts of psilocybin compared to the complete recipe demonstrates a reduced amount of psilocybin required to achieve an effective perceptual dose in 50% of individuals. The MED50 was about 0.240 g of dried fruiting bodies alone but about 0.125 g of dried fruiting bodies with the 07 Base – Complete Composition. Most compositions used about 0.12 g of dried fruiting bodies, representing approximately 1 mg of psilocybin.

[0228] Fig. 7 shows results of MED50 determination in individuals consuming a capsule including morning glory seeds formulated in the 07 Base – Complete Composition (diagonal lines in bar graphs and dashed regression line) compared with capsules including morning glory seeds alone (white bar graphs and solid regression line). MED50 is the Dose at which 50% of participants report feeling the effect of the LSA, LSH and other ergolines present in morning glory. Data from microdosing different amounts of morning glory seeds compared to the complete recipe demonstrates a reduced amount of morning glory seeds required to achieve an effective perceptual dose in 50% of individuals. The MED50 was about 1.1 g of morning glory seeds alone but about 0.5 g of dried fruiting bodies with the 07 Base – Complete Composition. Most compositions used

about 0.4 g of dried morning glory seeds, representing between approximately 260 µg and 300 µg LSA per dosage unit and between 130 µg and 525 µg LSH.

[0229] Fig. 8 shows results of MED50 determination in individuals consuming a capsule including Hawaiian baby woodrose seeds formulated in the 07 Base – Complete Composition (diagonal lines in bar graphs and dashed regression line) compared with capsules including Hawaiian baby woodrose seeds alone (white bar graphs and solid regression line). MED50 is the Dose at which 50% of participants report feeling the effect of the LSA, LSH and other ergolines present in Hawaiian baby woodrose. Data from microdosing different amounts of Hawaiian baby woodrose seeds compared to the complete recipe demonstrates a reduced amount of Hawaiian baby woodrose seeds required to achieve an effective perceptual dose in 50% of individuals. The MED50 was about 0.280 g of Hawaiian baby woodrose seeds alone but about 0.125 g of Hawaiian baby woodrose seeds with the 07 Base – Complete Composition. Most compositions used about 0.15 g of dried Hawaiian baby woodrose seeds, representing approximately 220 µg LSA, 290 µg iso-LSA, 60 µg LSH and 40 µg iso-LSH.

[0230] As detailed below in the Examples, a positive effect on mental health observed rapidly after taking the compositions. Adjustment of inflammation signalling alters signals to the brain to reduce depressive effects. Reduction in TNF-α pro-inflammatory cytokine signalling, COX2 pro-inflammatory cytokine signalling, and reduction in ROS as well as increased BDNF may all result in this positive effect on mental health.

5HT2A Receptor Agonist

Tryptamines

[0231] The at least one 5HT2A agonist may include a tryptamine that binds the 5HT2A receptor. N,N-dimethyltryptamine or (3–[(2–dimethylamino) ethyl]indole) ("**DMT**") is a hallucinogenic tryptamine drug that occurs naturally in many plants and animals. DMT is produced in the pineal gland of rats (Dean, 2019). When used orally in the absence of a monoamine oxidase inhibitor, DMT is rapidly metabolized and inactivated in the blood of most individuals. 4-substituted DMT compounds are not metabolized and inactivated in the blood to the same extent as DMT. Orally-active 4-substituted DMT compounds display psychoactive effects associated with binding at 5HT2A receptors in the human brain.

[0232] A large number of 4-substituted DMT compounds show 5HT2A agonist activity. 4-substituted DMT compounds are potent 5HT2A agonists. Many 4-substituted DMT compounds show strong psychoactive effects at doses ranging between 20 mg and above. Microdoses of 4-substituted DMT compounds may be in the range of between 5 and 50% of a flood dose of the 4-substituted DMT compounds. Using 3-[2-(dimethylamino)ethyl]-4-phosphoryloxyindole, also called psilocybin, the best known 4-substituted DMT compounds, as a reference point, a typical flood dose may be between 20 mg and 50 mg. A typical microdose of psilocybin may be between 1 and 10 mg.

[0233] The at least one 5HT2A agonist may include a 4-substituted DMT compound or where applicable, suitable salt thereof. Examples of orally-active 4-substituted DMT compounds include 3-[2-(dimethylamino)ethyl]-4-hydroxyindole, also called psilocin, any suitable salt of psilocin, psilocybin, 3-[2-(dimethylamino)ethyl]-4-acetoxyindole, also called 4-acetyl-DMT and any suitable salt of 4-acteyl-DMT.

[0234] The at least one 5HT2A agonist may include 4-substituted tryptamines that are not dimethyltryptamines. Examples of orally active 4-substituted tryptamines that are not dimethylated include the trimethyltryptamine 3-[2-(trimethylamino)ethyl]-4-phosphoryloxyindole, also called aeruginascin, the monomethyltryptamine 3-[2-(methylamino)ethyl]-4-phosphoryloxyindole, also called baeocystin, 3-[2-(methylamino)ethyl]-4-hydroxyindole, and the unmethylated tryptamines 3-[2-(amino)ethyl]-4-hydroxyindole, also called norpsilocin, and 3-[2-(amino)ethyl]-4-phosphoryloxyindole, also called norbaeocystin. Tri-methylated, monomethylated, or unmethylated tryptamines alone shows each show some 5HT2A agonism and may be preferable to psilocybin, psilocin or 4-substituted DMT compounds for use minors, those with mental health contraindications (e.g. schizophrenia, etc.) or those averse to strongly psychoactive effects.

[0235] The compositions may be formulated from fungal biomass, extracts from fungal biomass, plant biomass, plant extracts from biomass, extracts from yeast or bacterial culture systems, synthetic compounds or combinations thereof. For example, any of the 5HT2A agonists (e.g. any of the 4-substituted tryptamines) or TRP agonists described herein may be synthesized in bacterial culture systems such as E. coli. Such biomass may be sourced from fruiting bodies, mycelia, sclerotia or other biomass of fungi. Psilocin and psilocybin are 4-substituted DMT compounds found in nature. Psilocybin is more chemically stable than psilocin and is a prodrug of psilocin.

[0236] Species of fungi containing psilocybin and psilocin have been studied extensively. Psilocybin is a name based on the use of "psilocybienne" as described by the French mycologist, Roger Heim (Heim, 1958). Psilocybin shows promise for treating mental health disorder, and high dose therapies using flood doses of psilocybin have been granted breakthrough status by the FDA. Despite being regulated in many countries, consumption of psilocybin is generally considered safe in that there is little if any evidence long term negative physical consequences from ingestion of large amounts of this substance. Some studies have shown psilocybin to be one of the least damaging psychoactive substances in terms of harm to society, far behind tobacco and alcohol (Nutt, 2007). Psilocin and psilocybin are found in many genera and species of fungi, as listed below.

[0237] Psilocin and psilocybin may be found in *Conocybe* species including *C. cyanopus*, *C. siligineoides* and *C. kuehneriana*.

[0238] Psilocin and psilocybin may be found in *Copelandia* species including *C. affinis*, *C. anomala*, *C. bispora*, *C. cambodginiensis*, *C. chlorocystis*, *C. cyanescens*, *C. lentisporus*, *C. tirunelveliensis*, *C. tropica*, *C. tropicalis* and *C. westii*.

[0239] Psilocin and psilocybin may be found in *Galerina species* including *G. steglichii*.

[0240] Psilocin and psilocybin may be found in *Gymnopilus* species including *G. thiersii*, *G. aeruginosus*, *G. braendlei*, *G. cyanopalmicola*, *G. intermedius*, *G. junonius*, *G. lateritius*, *G. liquiritiae*, *G. luteofolius*, *G. luteoviridis*, *G. luteus*, *G. purpuratus*, *G. subpurpuratus*, *G. validipes* and *G. viridans*.

[0241] Psilocin and psilocybin may be found in *Inocybe* species including *I. aeruginascens, I. aeruginascens, I. coelestium, I. corydalina, I. corydalina var. corydalina, I. corydalina var. erinaceomorpha, I. haemacta* and *I. tricolor*.

[0242] Psilocin and psilocybin may be found in *Panaeolus* species including *P. cinctulus, P. affinis, P. africanus, P. bisporus, P. cambodginiensis, P. castaneifolius, P. chlorocystis, P. cinctulus, P. cyanescens, P. fimicola, P. lentisporus, P. microsporus, P. moellerianus, P. olivaceus, P. rubricaulis, P. tirunelveliensis, P. tropicalis* and *P. venezolanus.*

[0243] Psilocin and psilocybin may be found in *Pholiotina* species including *P. cyanopus* and *P. smithii*.

[0244] Psilocin and psilocybin may be found in *Pluteus* species including *P. americanus*, *P. albostipitatus*, *P. americanus*, *P. cyanopus*, *P. glaucus*, *P. glaucotinctus*, *P. nigroviridis*, *P. phaeocyanopus*, *P. salicinus*, *P. saupei* and *P. villosus*.

[0245] Psilocin and psilocybin may be found in *Psilocybe* species including *P. tampanensis*, *P. acutipilea*, *P. allenii*, *P. angustipleurocystidiata*, *P. antioquiensis*, *P. atlantis*, *P. aquamarina*, *P. armandii*, *P. aucklandii*, *P. atlantis*, *P. aztecorum*, *P. aztecorum var. aztecorum*, *P. aztecorum var. bonetii*, *P. azurescens*, *P. baeocystis*, *P. banderillensis*, *P. bispora*, *P. brasiliensis*, *P. brunneocystidiata*, *P. cubensis*, *P. caeruleoannulata*, *P. caerulescens*, *P. caerulescens var. caerulescens*, *P. caerulescens var. ombrophila*, *P. caerulipes*, *P. callosa*, *P. carbonaria*, *P. caribaea*, *P. chuxiongensis*, *P. collybioides*, *P. columbiana*, *P. cordispora*, *P. cubensis*, *P. cyanescens*, *P. cyanofibrillosa*, *P. dumontii*, *P. egonii*, *P. fagicola*, *P. fagicola var. fagicola*, *P. fagicola var. mesocystidiata*, *P. farinacea*, *P. fimetaria*, *P. fuliginosa*, *P. furtadoana*, *P. tampanensis*, *P. galindoi*, *P. gallaeciae*, *P. graveolens*, *P. guatapensis*, *P. guilartensis*, *P. heimii Guzmán*, *P. herrerae Guzmán*, *P. hispanica Guzmán*, *P. hoogshagenii*, *P. hoogshagenii var. hoogshagenii*, *P. hoogshagenii var. convexa*, *P. inconspicua*, *P. indica*, *P. isabelae*, *P. jacobsii*, *P. jaliscana*, *P. kumaenorum*, *P. laurae*, *P. lazoi*, *P. liniformans*, *P. liniformans var. liniformans*, *P. liniformans var. americana*, *P. mexicana*, *P. mairei*, *P. makarorae*, *P. mammillata*, *P. medullosa*, *P. meridensis*, *P. meridionalis*, *P. mescaleroensis*, *P. mexicana*, *P. moseri*, *P. muliercula*, *P. naematoliformis*, *P. natalensis*, *P. natarajanii*, *P. neorhombispora*, *P. neoxalapensis*, *P. ovoideocystidiata*, *P. ovoideocystidiata*, *P. papuana*, *P. paulensis*, *P. pelliculosa*, *P. pintonii*, *P. pleurocystidiosa*, *P. plutonia*, *P. portoricensis*, *P. pseudoaztecorum*, *P. puberula*, *P. quebecensis*, *P. ricki*, *P. rostrata*, *P. rzedowskii*, *P. samuiensis*, *P. schultesii*, *P. semilanceata*, *P. septentrionalis*, *P. serbica*, *P. sierrae* , *P. silvatica*, *P. singeri*, *P. squamosa*, *P. strictipes*, *P. stuntzii*, *P. subacutipilea*, *P. subaeruginascens*, *P. subaeruginosa*, *P. subbrunneocystidiata*, *P. subcaerulipes*, *P. subcubensis*, *P. subpsilocybioides*, *P. subtropicalis*, *P. tampanensis*, *P. tampanensis*, *P. thaicordispora*, *P. thaiaerugineomaculans*, *P. thaiduplicatocystidiata*, *P. uruguayensis*, *P. uxpanapensis*, *P. venenata* , *P. villarrealiae*, *P. weraroa*, *P. wassoniorum*, *P. weilii*, *P. weldenii*, *P. weraroa*, *P. wrightii*, *P. xalapensis*, *P. yungensis*, *P. zapotecorum*, *P. zapotecoantillarum*, *P. zapotecocaribaea* and *P. zapotecorum*.

[0246] The at least one 5HT2A agonist may include 5-substituted tryptamines. Examples of 5-substituted tryptamines include 5-methoxy-DMT, also called bufotenin, N-acetyl-5-methoxy tryptamine, also called melatonin, 5-hydroxy tryptamine, also called serotonin, 5-hydroxy-tryptophan, also called 5-HTP, 5-hydroxyl-DMT, 3-[2-(dimethylamino)ethyl]-5-phosphoryloxyindole, 3-[2-(dimethylamino)ethyl]-5-hydroxyindole, 3-[2-(dimethylamino)ethyl]-5-acetoxyindole, also called 5-acetyl-DMT, 3-[2-(trimethylamino)ethyl]-5-phosphoryloxyindole, 3-[2-(methylamino)ethyl]-5-phosphoryloxyindole, 3-[2-(methylamino)ethyl]-5-hydroxyindole, 3-[2-(amino)ethyl]-5-hydroxyindole and 3-[2-(amino)ethyl]-5-phosphoryloxyindole. Serotonin, melatonin and 5-HTP alone each some efficacy and may be preferable to bufotenine, other 5-substituted tryptamines, psilocybin, psilocin, 4-substituted-DMT compounds or other 4-substituted tryptamine compounds for use minors, those with mental health contraindications (e.g. schizophrenia, etc.) or those averse to strongly psychoactive effects.

Ergolines

[0247] The at least one 5HT2A agonist may include ergolines. Examples of ergolines that are 5HT2A receptor agonists include lysergamides.

[0248] D-lysergic acid amide ("**LSA**"), also called d-lysergamide or ergine and its epimer isoergine ("**iso-LSA**"), is a 5HT2A agonist. A large number of lysergamides and other analogs of LSA show potent 5HT2A agonist activity. Many lysergamides show strong psychoactive effects at doses ranging between 50 µg and 5 mg, 100 µg and 4.5 mg, 200 µg and 4 mg, 300 µg and 3.5 mg, 400 µg and 3 mg, 500 µg and 2.5 mg, 600 µg and 2 mg, 700 µg and 1.5 mg, and 800 µg and 1 mg. Microdoses of lysergamides may be in the range of between 5 and 25%, 7.5 and 22.5%, 10 and 20%, and 12.5 and 17.5% of a flood dose of the lysergamide. Using D-lysergic acid diethylamide ("**LSD**"), the best known lysergamide, as a reference point, a typical flood dose may be between 100 µg and 350 µg, 150 µg and 300 µg, and 200 µg and 250 µg. A typical microdose of LSD may be between 10 and 25 µg, 12.5 and 22.5 µg, and 15 and 20 µg.

[0249] Lysergamides that are 5TH2A agonists with single substitutions at the amide group include D-lysergic acid ethylamide ("**LAE**"), lysergic acid α-hydroxyethylamide ("**LSH**") and its epimer iso lysergic acid α-hydroxyethylamide ("**iso-LSH**"), D-lysergic acid beta-propanolamide, also called ergometrine or ergonovine, D-lysergic acid 2-butyl amide ("**LSB**"), D-lysergic acid 1-butanolamide, also called methylergometrine or

methylergonovine, 1-methyl-D-lysergic acid butanolamide, also called methysergide, D-lysergic acid 3-pentyl amide ("**LSP**"), D-N-morpholinyllysergamide ("**LSM-775**"), D-N-pyrrolidyllysergamide ("**LPD-824**"), (8β)-6-methyl-8-(piperidin-1-ylcarbonyl)-9,10-didehydroergoline ("**LSD-Pip**"). Lysergamides that are 5TH2A agonists with single substitutions at the amide group include N,N-dimethyllysergamide ("**DAM**").

[0250] Lysergamides that are 5TH2A agonists with double substitutions at the amide group include D-lysergic acid methylisopropyl amide ("**LAMIDE**"), also called methylisopropyllysergamide ("**MIPLA**"), D-lysergic acid 2,4-dimethylazetidide ("**LSZ**"), LSD, D-1-acetyl-lysergic acid diethylamide ("**ALD-52**"), D-1-propionyl-lysergic acid diethylamide ("**1P-LSD**"), D-N1-butyryl-lysergic acid diethylamide ("**1B-LSD**"), D-N1-(cyclopropylmethanoyl)-lysergic acid diethylamide ("**1cP-LSD**"), D-N1-methyl-lysergic acid diethylamide ("**MLD**"), D-6-ethyl-6-nor-lysergic acid diethylamide ("**ETH-LAD**"), D-1-propionyl-6-ethyl-6-nor-lysergic acid diethyamide ("**1P-ETH-LAD**"), D-6-allyl-6-nor-lysergic acid diethylamide ("**AL-LAD**"), D-6-propyl-6-nor-lysergic acid diethylamide ("**PRO-LAD**"), D-6-isopropyl-6-nor-lysergic acid diethylamide ("**IP-LAD**"), D-6-propynyl-6-nor-lysergic acid diethylamide ("**PARGY-LAD**"), D-6-butyl-6-nor-lysergic acid diethylamide ("**BU-LAD**"), N,N-diallyllysergamide ("**DAL**") and D-N-ethyl-N-cyclopropyllysergamide ("**ECPLA**").

[0251] The compositions may be formulated from fungal biomass, extracts from fungal biomass, plant biomass, microorganism biomass, extracts from biomass, synthetic compounds or combinations thereof. Such biomass may be sourced from organisms including Lysergamides or other ergolines, such as *Claviceps purpurea*, other species of *Claviceps*, some species of morning glory, including *Rivea corymbosa*, *Ipomoea violacea*, *I. tricolor*, *I. purpurae*, *I. alba*,Hawaiian baby woodrose species (also called elephant creeper), including *Argeyreia nervosa*, and *Periglandula* species.

Phenethylamines

[0252] The at least one 5HT2A agonist may include phenethylamines, including amphetamines. Examples of phenethylamines that are 5HT2A receptor agonists include 3,4,5-trimethoxyphenethylamine, also known as mescaline, trimethoxyamphetamine ("**TMA**"), 4-bromo-2,5-dimethoxybenzeneethanamine ("**2C-B**"), 4-bromo-2,5-dimethoxyamphetamine ("**DOB**"), 4-methyl-2,5-dimethoxyamphetamine ("**DOM**"), 4-

methyl-2,5-dimethoxybenzeneethanamine ("**2C-D**"), 3,4-methylenedioxyamphetamine ("**MDA**"), N-methyl-3,4-methylenedioxyamphetamine ("**MDMA**").`

[0253] The compositions may be formulated from fungal biomass, extracts from fungal biomass, plant biomass, microorganism biomass, extracts from biomass, synthetic compounds or combinations thereof. Such biomass may be sourced from organisms including mescaline and other phenethylamines, such as *Lophophora williamsii*, other *Lophophora* species, *Trichocereus pachanoi*, *Trichocereus peruvianus*, *Trichocereus bridgesii*, and other *Trichocereus* species, *Echinopsis pachanoi*, *Echinopsis peruviana*, and *Trichocereus/Echinopsis scopulicola*.

Phenylpropanoids

[0254] The at least one 5HT2A agonist may include phenylpropanoids. Examples of phenylpropenes and other phenylpropanoids that are 5HT2A agonists include 5-methoxy-3,4-methylenedioxy-allylbenzene, also called myristicin, 1,2,3-timethoxy-5-(prop-2-en-1-yl)benzene, also called elemicin.

[0255] The compositions may be formulated from fungal biomass, extracts from fungal biomass, plant biomass, microorganism biomass, extracts from biomass, synthetic compounds or combinations thereof. Such biomass may be sourced from organisms including myristicin, elemicin or other phenylpropanoids, including *Myristica fragrans* or other species in the *Myristicaceae* family.

TRP Receptor Agonist

[0256] The at least one TRP agonist compound is an agonist for a TRP receptor, and may also be an antagonist for a TRP receptor. Agonists for various TRP receptors may be applied in the compositions. TRP receptor expression is variable in different neurons as well, and the effects of 5HT2A agonists in the presence of TRP receptor agonists, including at different dosage ranges and in different ratios, allows the compositions to be targeted to various specific indications that are caused by inflammation. The at least one TRP agonist compound may include a compound that is generally regarded as safe ("**GRAS**"). The at least one TRP agonist compound may be sourced from cayenne, turmeric, clove, cinnamon or nutmeg. The at least one TRP agonist compound may include capsaicin or other capsiates, curcumin or other curcuminoids, eugenol, β-caryophyllene, cinnamaldehyde, myristicin, elemicin, α-terpineol or 8-O-4'-neolignans.

[0257] The at least one TRP agonist compound may include a compound that is GRAS. The at least one TRP agonist compound may be sourced from cannabis, bergamot, oregano, thyme, cardamom, peppermint, eucalyptus, pepper, ginger, garlic or onion. The at least one TRP agonist compound may include β-caryophyllene, α-terpineol, cannabidiol ("**CBD**"), cannabidivarin ("**CBDV**"), cannabigerol ("**CBG**"), cannabigerolic acid ("**CBGA**"), delta-9-tetrahydrocannabivarin ("**THCV**"), delta-9-tetrahydrocannabivarinic acid ("**THCVA**"), cannabigevarin ("**CBGV**"), myrcene, eriodictyol, carvacrol, myrcene, thymol, carvacrol, menthol, 1-8 cineole, piperine, gingerol, allicin, thymol and combinations thereof. Cacao also seemed to show some effect both with onset and duration though not as pronounced.

[0258] The specific compounds sourced from cayenne, turmeric, clove, cinnamon, nutmeg, cannabis, bergamot, oregano, thyme, cardamom, peppermint, eucalyptus, pepper, ginger, garlic and onion listed above have activity at the TRPV1, TRPA1, TRPM8 and TRPV3 receptors as illustrated in Table 2.

Table 2: Agonism and antagonism of TRPV1, TRPA1, TRPM8 and TRPV3

Active	GRAS Substance	TRPV1	TRPA1	TRPM8	TRPV3
capsaicin	Cayenne Pepper	+++	n/a	n/a	n/a
curcumin	Turmeric	(-)	++	n/a	n/a
eugenol	Turmeric Clove Cinnamon Pepper	+	n/a	++	++
β-caryophyllene	Turmeric Clove Cinnamon Cannabis Pepper	n/a	n/a	n/a	+
cinnamaldehyde	Cinnamon	n/a	++	+	n/a
myristicin	Nutmeg	+	n/a	n/a	n/a
elemicin	Nutmeg	+	n/a	n/a	n/a
alpha terpineol	Turmeric Nutmeg Cannabis	n/a	+	n/a	n/a
8-O-4'-neolignans	Nutmeg	n/a	n/a	+	n/a

(-)-epicatechin	Cacao Green Tea	n/a	n/a	n/a	+
CBD	Cannabis	+	+	+	+
CBDA	Cannabis	+	+	+	+
CBDV	Cannabis	+	+	+	n/a
CBG	Cannabis	+	+	+	n/a
CBGA	Cannabis	+	+	+	+
CBGV	Cannabis	+	+	+	+
THC	Cannabis	n/a	n/a	+	n/a
THCA	Cannabis	n/a	n/a	+	n/a
THCV	Cannabis	+	+	+	+
THCVA	Cannabis	+	+	+	+
myrcene	Cannabis Bergamot Others	+	n/a	n/a	n/a
eriodictyol	Bergamot	n/a	n/a	n/a	+
carvacrol	Bergamot Oregano	n/a	n/a	+	n/a
thymol	Oregano Thyme	n/a	+	+	+
linalool	Bergamot Cardamom Cannabis	n/a	n/a	+	n/a
menthol	Peppermint	n/a	n/a	+++	n/a
1-8 cineole	Peppermint Eucalyptus Cardamom	n/a	(-)	+	n/a
piperine	Pepper	+	+	n/a	n/a
gingerol	Ginger	+	n/a	n/a	n/a
allicin	Garlic Onion	n/a	+	n/a	n/a
incensole	Myrrh	n/a	n/a	n/a	+++
incensole acetate	Frankincense	n/a	n/a	n/a	+

[0259] As shown in Table 2, the at least one TRP agonist compound may include a TRPV1 receptor agonist. TRPV1 agonists may include capsaicin, eugenol, myristicin, elemicin, CBD, CBDA, CBDV, CBG, CBGA, CBGV, THCV, THCVA, myrcene, piperine and gingerol. TRPV1 agonists reduce inflammation by competing for the TRP receptor site and sending altered signals that reduce expression of inflammation markers and generation of ROS. Inclusion of a TRPV1 agonist lowers the amount of 5HT2A agonist required for a given effect, including the MED of 5HT2A agonist. Inclusion of a TRPV1 agonist alters the effects of the formulation by reducing inflammation, improving digestion and improving symptoms of depression.

[0260] As shown in Table 2, the at least one TRP agonist compound may include a TRPA1 receptor agonist. TRPA1 agonists may include curcumin, cinnamaldehyde, alpha terpineol, CBD, CBDA, CBDV, CBG, CBGA, CBGV, THCV, THCVA, thymol, piperine, allicin. Some of these molecules may also act as antagonists for other TRP receptors by reducing signalling associated with other endogenous compounds associated with inflammation. For example, curcumin has shown to antagonize the effects of capsaicin at TRPV1 (Zhi, 2013). Inclusion of these molecules allowed for a reduced dose of the 5HT2A agonist and may alter the effects of the formulation reducing inflammation, improving digestion and improving mental health.

[0261] As shown in Table 2, the at least one TRP agonist compound may include a TRPM8 receptor agonist. TRPM8 agonists may include eugenol, cinnamaldehyde, CBD, CBDA, CBDV, CBG, CBGA, CBGV, THC, THCA, THCV, THCVA, carvacrol, thymol, menthol and 1-8 cineole. Activation of TRPM8 typically results from sensitization from cold and inclusion of molecules with activity at this receptor may alter the effects of the formulations, in some cases improving alertness, ability, and enhancing sexual experiences, including by increased libido.

[0262] As shown in Table 2, the at least one TRP agonist compound may include a TRPV3 receptor agonist. TRPV3 agonists may include eugenol, β-caryophyllene, (-)-epicatechin, eriodictyol, cinnamaldehyde, incensole, thymol and cannabinoids. Activation of TRPV3 typically results from sensitization to warm temperature and inclusion of molecules with activity at this receptor alters the effects of the formulations mood.

Capsaicin

[0263] Capsaicin is a well-known and potent potentiator of the TRPV1 receptor. Capsaicin has been shown to have healing properties as a topical for inflammation and pain. A product including capsaicin as an active pharmaceutical ingredient has been approved by the United States Food and Drug Administration (the "**FDA**") for topical pain relief.

[0264] A combination of capsaicin and a 5HT2A agonist improves the anti-inflammatory properties and the psychological benefits of both compounds. A combination of capsaicin and psilocybin decreased the onset time of the psilocybin, with perceived effects occurring within 15 to 30 minutes after ingestion. The peak effects of the psilocybin had a longer duration but the overall duration of the effects appeared unchanged. Capsaicin with psilocybin improved pain and inflammation in individuals with acute symptoms and improved mood often within one dose. Some individuals reported lasting positive benefits on pain levels and mental health for days following a single dose, and long after psychoactive effects of psilocybin had ended. The combination of capsaicin with psilocybin allowed a reduction in the dose of psilocybin required for perceived effects to reduce inflammation and peripheral pain, resulting in a lower amount of psilocybin at MED50. Increased alertness was also reported relative to psilocybin alone or relative to baseline.

[0265] The dose of capsaicinoids in dosage forms of the composition was calculated at between 0 and 2.5 mg based on inclusion of between 0 and 1 g of dried cayenne pepper. However, the dose of capsaicinoids in dosage forms of the composition can also be between 0.5 and 2 mg, and 1 and 1.5 mg. Cayenne pepper, or red chili pepper, typically includes about 300 μg capsaicinoids of gram dry weight reported in ground cayenne pepper (Al Othman, 2011) but has a reported range up to 2.5% w/w.

[0266] The spicy flavor of capsaicin may upset stomach and result in pain in some individuals. Capsaicin also caused intestinal issues at large doses. Various peppers were utilized as a source of capsaicin, with cayenne pepper being the most effective without side effects. While a similar amount of capsaicin per gram would be expected from many species, though there may be variations in minor capsiates. Many species caused serious stomach pains or gastrointestinal pains in some people, particularly people who do not typically consume spicy food. Heartburn was also occasionally reported. However, no

negative effects were reported from the cayenne pepper utilized at the doses listed. While the spicy flavor is still notable in chocolate formulations that include the compositions, it was often masked to some extent by the other ingredients in the composition and was tolerable to most people at the ratio included. For some, capsules were preferred over chocolates due to the spicy flavor of cayenne.

[0267] Species from the *Solanaceae* family that contain capsaicin are summarized in the below Table 3.

Table 3: Capsaicinoids in commonly used peppers

Species	Common Names	Part	Capsaicinoids (ppm)
Capsicum annuum	Cherry Pepper, Sweet Pepper, Bell Pepper, Paprika, Green Pepper, Cone Pepper	Resin, exudate, sap	634,000
		Fruit	4,000
		Tissue culture	590
Capsicum frutescens	Hot Pepper, Tabasco, Cayenne, Chili, Red Chili, Spur Pepper	Fruit	17,900
		Seed	5

Curcumin

[0268] Curcuminoids, are found in the spice turmeric from the ginger family *Zingiberacea*. (1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione, also called curcumin, is a linear diarylheptanoid and curcuminoid. Curcumin is a phytopolylphenol pigment isolated from *Curcuma longa*. Curcumin is used in a variety of products including herbal supplements, food coloring, food flavoring, and cosmetics. Curcumin belongs to a group of compounds known as curcuminoids. Curcumin is a tautomeric compound, stable in both enolic form in an organic solvent and in a keto form when in water. Curcumin is a TRPA1 receptor agonist and antagonize the effects of TRPV1 receptor agonists when combined (Yeon et al, 2010).

[0269] In addition to curcumin, species of turmeric also contain various amounts of antioxidant molecules sybisabolone-9-one, 4-methyllene-5-hydroxybisabola-2,10-diene-9-one, turmeronol B, 5-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-1-hepten-3-one, 3-hydroxy-1,7-bis(4-hydroxyphenyl)-6-hepten-1,5-dione, cyclobisdemethoxycurcumin, bisdemethoxycurcumin and demethoxycurcumin (Akter, 2019). Anti-inflammatory and antidepressant activity of turmeric and extracts from turmeric may be due to biologically

active molecule other than curcumin, such as these antioxidants or other molecules present in the turmeric, in addition to curcumin.

[0270] Curcumin has been investigated in numerous clinical and laboratory trials. Curcumin has been challenging to develop as an API in a drug because it is unstable, reactive and has limited bioavailability (Nelson, 2017). Nonetheless, curcumin has shown promise as a therapeutic agent for its activity as an antioxidant (Sreejayan, 1994), anti-inflammatory (Brouet, 1995), anticarcinogenic (Rao, 1995), antimicrobial (Limtrakul, 1997) hypoglycemic (Arun, 2002) and anti-depressive effects (Kulkarni, 2009). Curcumin has antidepressant effects in animal models. Chronic, but not acute, administration of 150 mg/kg curcumin significantly raised anandamide levels in a variety of brain regions (Smalheiser, 2019).

[0271] Curcumin shows agonist activity at TRPA1 and antagonist activity at TRPV1. Curcumin is also listed as an MAO inhibitor (Kulkarni, 2008) and while it does not appear to cross the blood-brain barrier and the active form is not detected to a significant extent in the blood, yet curcumin has been shown to increase levels of BDNF and reduce depression. Studies suggest that curcumin can normalize depressive-like behaviors, which may be independent of concurrent analgesic action. Correction of depressive behavior could potentially be mediated by the supraspinal serotonergic system and downstream GABA receptor (Zhao, 2014).

[0272] Curcumin has been extensively studied as a medicine, with nearly 6,000 published citations, most of which have appeared within the past 20 years. Wikipedia indicates that "*Curcumin, which shows positive results in most drug discovery assays, is regarded as a false lead that medicinal chemists include among "pan-assay interference compounds". This attracts undue experimental attention while failing to advance as viable therapeutic or drug leads.[3][11][12]. Factors that limit the bioactivity of curcumin or its analogs include chemical instability, water insolubility, absence of potent and selective target activity, low bioavailability, limited tissue distribution, and extensive metabolism.[3] Very little curcumin escapes the GI tract and most is excreted in feces unchanged.*" This interpretation shows a failure to understand that gut biology was also important for brain health, and that signals could be sent to the brain without the molecule itself ever leaving the digestive tract or entering the blood stream. The lack of attention on curcumin specifically demonstrates how a traditional pharmaceutical approach to depression that targets the brain has neglected and ignored useful compounds in favor of compounds that

cross the blood brain barrier and target a specific receptor with high affinity. Put otherwise, due to the complexity of the system and lack of molecular evidence for a mechanism of action on these compounds in the brain, they were ignored in favor of compounds with measurable activity at a neurotransmitter receptor in the brain.

[0273] A combination of curcumin and a 5HT2A agonist improves the anti-inflammatory properties and the psychological benefits of both compounds. Curcumins presence in the compositions increased the length of the subjective effects of psilocybin reported by the user and also improved mental health benefits. A combination of curcumin and psilocybin decreased the dosage of psilocybin at MED and prolonged the effects of the psilocybin at the dosage. Doses of curcumin were based on curcumin accounting for about 6% of the dry weight of turmeric. Turmeric was provided in approximately a 1:1 ratio of weight compared with dried fruiting bodies.

[0274] A combination of psilocybin and curcumin may antagonize or provide competition for binding at the TRPV receptor when present with capsaicin or other TRPV agonists, resulting in a longer duration of effects and a greater impact on mental health. Rather than a quick onset and rapid drop off with effects stopping within two hours, this combination resulted in a sustained effect for 4 to 6 hours. Combining curcumin with capsaicin and psilocybin also lead to greater anti-inflammatory activity than capsaicin and psilocybin alone. Combining curcumin with capsaicin and psilocybin also allowed the MED of capsaicin to be reduced by 50% while still achieving a similar effect. For example, a 2:2:1 ratio of dried psilocybin fruiting bodies:turmeric:cayenne pepper provided an effective MED at 160 mg:160 mg:80 mg. A combination of psilocybin with turmeric synergistically improved inflammation and depression without increasing anxiety, in contrast with a combination of capsaicin and psilocybin, or psilocybin alone.

[0275] Species from the *Curcuma* genus that may be applied to the compositions disclosed herein include *C. aeruginosa* (pink and blue ginger), *C. albicoma*, *C. albi ora*, *C. alismatifolia* (summer tulip), *C. amada* (mango ginger), *C. amarissima*, *C. Americana*, *C. angustifolia* (tall hidden ginger), *C. aromatica*, *C. attenuata*, *C. aurantiaca* (rainbow curcuma), *C. aurantiflora*, *C. australasica* (Cape York turmeric), *C. bakeriana*, *C. bicolor* (candy corn), *C. brog*, *C. burttii*, *C. caesia*, *C. cannanorensis*, *C. cannanorensis var. Lutea*, *C. caulina*, *C. careyana*, *C. certothecca*, *C. chuanezhe*, *C. chuanhuangjiang*, *C. chuanyujin*, *C. cochinchinensis*, *C. codonantha*, *C. coerulea*, *C. colorata*, *C. comosa*, *C. cordata* (jewel of Thailand), *C. cordifolia*, *C. coriacea*, *C. decipiens*, *C. domestica*

(Emperor variegated), *C. ecalcarata*, *C. ecomata*, *C. elata* (giant plume), *C. erubescens*, *C. euchroma*, *C. euclroma*, *C. exigua*, *C. ferruginea*, *C. flaviflora* (red fireball ginger), *C. glans*, *C. glaucophylla*, *C. gracillima* (chocolate zebra), *C. grahamiana*, *C. grandiflora*, *C. haritha*, *C. harmandii* (emerald pagoda ginger), *C. heyneana*, *C. inodora* (pink ginger), *C. karnatakensis*, *C. kudagensis*, *C. kwangsiensis*, *C. kwangsiensis var.affinis*, *C. kwangsiensis var. puberula*, *C. lanceolata*, *C. latiflora*, *C. latifolia*, *C. leopoldi*, *C. leucorhiza*, *C. loerzingii*, *C. lillicina* (pink cloud), *C. longa* (turmeric), *C. longiflora*, *C. longi spica*, *C. lutea*, *C. malabarica*, *C. mangga*, *C. meraukensis*, *C. montana*, *C. musacea*, *C. mutabilis*, *C. neilgherrensis*, *C. nilamburensis*, *C. ochrorhiza*, *C. of cinalis*, *C. olena*, *C. oligantha* (white turmeric), *C. oligantha var. lutea*, *C. ornate* (ornate plume ginger), *C. pallida*, *C. parviflora* (white angel), *C. parvula*, *C. peethapushpa*, *C. petiolata* (Temu Puteri in Java), *C. phaeocaulis*, *C. pierreana* (sleeping princess), *C. plicata*, *C. porphyrotaenia*, *C. prakasha*, *C. pseudomontana*, *C. purpurascens*, *C. purpurea*, *C. raktakanta*, *C. ranadei*, *C. reclinata*, *C. rhabdota*, *C. rhomba*, *C. roscoeana* (pride of Burma), *C. rotunda*, *C. rubescens* (wine red plume), *C. rubricaulis*, *C. rubrobracteata* (fire plug), *C. sessilis*, *C. siamensis*, *C. sichuanensis*, *C. singularis* (Easan white), *C. soloensis*, *C. sparganifolia*, *C. speciosa*, *C. spicata*, *C. stenochila*, *C. strobilifera*, *C. sulcata*, *C. sumatrana* (Sumatra ginger), *C. sylvatica*, *C. sylvestris*, *C. thalakaveriensis*, *C. thorelii* (Chiang Mai Snow), *C. trichosantha*, *C. vamana*, *C. vellanikkarensis*, *C. viridi ora*, *C. wenchowensis*, *C. wenyujin*, *C. xanthorrhiza*, *C. yunnanensis* (Yunnan plume ginger), *C. zanthorrhiza* (temulawak), *C. zedoaria* (zedoary white turmeric) and *C. zerumbet*.

Eugenol

[0276] In addition to curcumin, turmeric also contains eugenol. Eugenol can act as a local analgesic and is an agonist for TRPV1 and a strong agonist for TRPV3 (Xu, 2006). Turmeric may include about 0.3% essential oil, of which about 8% may be eugenol (Stanojević, 2015), supporting an estimate of about 240 µg eugenol per gram of turmeric.

[0277] In addition to turmeric, eugenol is also found in clove from the *Caryophyllus aromaticus* tree. Eugenol is used in dentistry as a topical analgesic (Chung, 2013). Eugenol is found in concentrations of ranging from 9,400 mg to 14,600 mg per 100 g of fresh plant material (Cortés-Rojas, 2014). Clove represents one of the major vegetal sources of phenolic compounds as flavonoids, hydroxybenzoic acids, hydroxycinnamic

acids and hydroxyphenyl propenes. Clove has historic use for toothache, joint pain and antispasmodic. The voltage dependent effects of eugenol in sodium and calcium channels and in receptors expressed in the trigeminal ganglion may be primarily responsible for the analgesic effect of clove (Wang, 2015).

[0278] Eugenol was selected for its potential to bind TRP receptors and its potential to interfere with several other cell-signaling pathways, specifically the nuclear factor kappa B ("**NF-κB**"). This factor is activated by free radicals and results in the expression of genes that suppress apoptosis and induce cellular transformation, proliferation, invasion, metastasis and other phenomena associated with cancer progression (Hoesel, 2013). Inclusion of the eugenol reduces inflammatory markers and ROS signaling from the gut to the brain.

[0279] Inclusion of ingredients including significant amounts of eugenol resulted in reports of a calming effect compared with psilocybin alone, with capsaicin and psilocybin or with capsaicin, curcumin and psilocybin. Eugenol is included in the compositions disclosed herein primarily through clove, turmeric and black pepper. The dose of eugenol was calculated at between 0.1 and 1.6 g based on 17-20% maximum amount in the the ingredients, with between 0.1 and 5 grams of turmeric and clove daily, and in some cases also the addition of black pepper. In some aspects, other doses of eugenol could be between 0.2 and 1.5 g, 0.3 and 1.4 g, 0.4 and 1.3 g, 0.5 and 1.2 g, 0.6 and 1.1 g, 0.7 and 1.0 g, and 0.8 and 0.9 g. Peripheral antinociceptive activity of eugenol has been reported as showing significant activity at doses of 50, 75 and 100 mg/kg (Daniel, 2009).

[0280] Other herbal sources of eugenol are summarized in Table 4. The concentrations for some of the herbal ingredients listed in Table 4 are cited from (Khalil, 2017). In addition to the sources of eugenol listed in Table 4, ginger, oregano, basil, mace, pepper and marjoram also include eugenol.

Table 4: Eugenol in commonly used herbal ingredients

Common Names	Part	Eugenol (mg/g)
Clove	Flowers and buds	180
Clover	Fruit	36
Betel Pepper	Leaves	18
Cinnamon	Bark	3.5
Tulsi	Leaves	4 to 5

Bay	Leaves	1.3
Turmeric	Leaves and Essential Oil	2.1
Nutmeg	Seeds	0.3
Thyme	Shoots	0.02

β-caryophyllene

[0281] Clove and turmeric contains significant amounts of β-caryophyllene ("**BCP**"), which is thought to be an agonist of the CB1 receptor and also a TRPV1 receptor agonist (Sharma, 2015). Clove may include about 2% BCP. Turmeric may also include BCP. Agonism at both CB1 and TRP receptors highlights the indirect linkage and cross talk between the TRP and ECS pathways. Numerous molecules are agonists on both sets of receptors. As shown in Fig. 5, arachidonic acid signaling interacts with TRP receptor signaling pathways. ECS stimulation results in arachidonic acid metabolism.

[0282] BCP was approved by the FDA and the European Food Safety Authority (EFSA) for human consumption. BCP is also used as flavor enhancer and in cosmetics (Sköld, 2016). Neuroinflammation or inflammation of the brain a process leading to nervous system degeneration, characterized by the activation of monocytes, macrophages, mast cells, lymphocytes, and the production of inflammation mediators, such as nitric oxide ("**NO**"), various cytokines (IL-1β, interleukin-6 ("IL-6"), interleukin-8 ("IL-8") and TNF-α), NF-κB and prostaglandins. While curcuminoids do not pass the blood-brain barrier, BCP does pass the blood-brain barrier and has anti-inflammatory effects directly on the brain.

[0283] Even at the low doses being administered, BCP being included in the compositions in addition to psilocybin alone improved mood in those with both depression and anxiety issues. Recipes including clove or clove oil contain both significant eugenol and some BCP. The isolated molecules have been tested in vitro and found to both possess anti-inflammatory properties.

[0284] Herbal sources of BCP are summarized in Table 5.

Table 5: Herbal Sources of BCP

Species	**Family**	**Common Names**	**Part**	**BCP (mg/g)**
Cannabis sativa	*Cannabaceae*	Marijuana	flower	3.8-37.5*

Carum nigrum	*Ranunculacea*	Black caraway	seeds	7.8*
Syzygium aromaticum	*Myrtaceae*	Clove	fruit, stems, buds	1.7-19.5*
Humulus lupulus	*Cannabaceae*	Hops	fruits	5.1-14.5*
Ocimum gratissimum	*Lamiaceae*	Clove basil	leaves	5.3-10.5*
Ocimum micranthum	*Lamiaceae*	Wild basil	leaves	4-19.8*
Origanum vulgare	*Lamiaceae*	Oregano	leaves	4.9-15.7*
Piper nigrum	*Piperaceae*	Black pepper	fruit	7.29*
Piper aleyreanum	*Piperaceae*	Black pepper	fruit	15.9
Lavandula angustifolia	*Lamiaceae*	Lavendar	Flowers , leaves	4.62-7.55*
Rosmarinus officinalis	*Lamiaceae*	Rosemary	Flowers , leaves	0.1-8.3*
Cinnamomum zeylanicum	*Lauraceae*	True cinnamon	Seeds, bark, leaves	6.9-11.1*
Cinnamomum tamala	*Lauraceae*	Tamala	Leaves	25*
Cananga odorata	*Annonaceae*	Cananga	Leaves, flowers	3.1 – 10.7*
Copaifera langsdorffii	*Fabaceae*	Diesel tree	Fruit	
Orthosiphon stamineus	*Lamiaceae*			24-35*
Knema kunstleri	*Myristicaceae*			23*
Croton glandulosus	*Euphorbiaceae*			53.2*
Pterodon emarginatus	*Fabaceae*	Sucupira	fruits	20.3
Cymbopogon olivieri				14.4
Pachira aquatica	*Malvaceae*	Money tree		11.5
Staudtia gabonensis	*Myristicaceae*		Seeds and bark	12.2
Gnetum africanum	*Gnetaceae*		leaves	18.1
Lallemantia peltata	*Lamiaceae*		flowers	20
Piper cyrtopodon	*Piperaceae*		Aerial parts	34.6
Mentha aquatica	*lamiaceae*		Aerial parts	12.8

Renealmia alpinia	*Zingiberacea*	Honey bract	Leaves	22.9
Persea americana	*Lauraceae*	Avocado	leaves	43.9
Vitex negundo	*lamiaceae*	Chinese chaste tree	fruits	36
Oyedaea verbesinoides	*Asteraceae*			27.1
Vitex doniana	*Verbenaceae*	Sweet	leaves	12.6
Salvia leucantha	*lamiaceae*		leaves	10.7
Phlomis cancellata	*Labiatae*		Aerial parts	17
Chromolaena odorata	*Asteraceae*	Christmas bush	leaves	25.2
Cnidium silaifolium	*Apiaceae*		Aerial parts	8.2
Zosimia absinthifolia	*Umbelliferae*			22.2
Lantana canescens	*Verbenaceae*			16.3
Pimpinella kotschyana	*Apiaceae*		Full plant	40
Acalypha fruticosa	*Euphorbiaceae*		leaves	42
Petitia domingensis	*lamiaceae*		flowers	35.7
Scutellaria havanensis	*lamiaceae*		leaves	75.6
Garcinia mangostana	*Clusiaceae*	Mangosteen	Leaves bark	17-21
Clerodendrum polycephalum	*lamiaceae*	Bagflower	leaf	28.9
Centaurea imperialis	*Asteraceae*	Centaury		14.1
Lantana camara	*Verbenaceae*			10.1

* percentage BCP in essential oil from that part

[0285] Other sources of BCP include thyme (*Thymus vulgaris*), sage (*Salvia officinalis*), mint (*Mentha piperita*) and ginger (*Zingiber officinale*),

Cinnamaldehyde

[0286] *Cinnamon zeylanicum* (cinnamon) is widely used in traditional system of medicine to treat diabetes in India. Cinnamon contains both eugenol and BCP. In addition, Cinnamon has a significant amount of the biologically active molecule (2E)-3-phenylprop-2-enal, also known as cinnamaldehyde, which is a phenylpropanoid that gives

cinnamon its flavor and odor. Cinnamaldehyde is found in the bark of cinnamon trees and other species of the genus *Cinnamomum*. Cinnamaldehyde has a range of uses including as a flavoring, an agrichemical and as a corrosion inhibitor. Cinnamaldehyde has also been shown to possess antibacterial (Doyle, 2019), antiviral (Feng, 2020), antifungal, anticancer (Tian, 2017), antipyretic (Sui, 2010), and anti-obesity (Jiang, 2017) properties. Though some of these may be attributed to the activity of BCP and eugenol, cinnamaldehyde has been shown to activate TRPA1, which may provide an additional synergistic effect (Bandell, 2004).

[0287] Cinnamaldehyde was found to cause nociceptive behavior in mice when administered via intraplantar injections (Bandell, 2004). Iwasaki et al. (2008) demonstrated that cinnamaldehyde was capable of increasing adrenaline secretions in rats (Iwasaki, 2008; Anderson 2013).

[0288] The dose of cinnamaldehyde was based on a content of 0.5% to 3.0% in cinnamon species and the inclusion of between 0 and 5 grams of ingredients containing cinnamaldehyde per dose. In some aspects, doses of cinnamaldehyde could be between 0.6% to 2.9%, 0.7% to 2.8%, 0.8% to 2.7%, 0.9% to 2.6%, 1.0% to 2.5%, 1.1% to 2.4%, 1.2% to 2.3%, 1.3% to 2.2%, 1.4% to 2.1%, 1.5% to 2.0%, 1.6% to 1.9%, and 1.7% to 1.8%. The dosing of cinnamaldehyde was estimated based on up to 3.0% cinnamaldehyde in cinnamon.

[0289] Addition of cinnamon allowed a reduction in the amount of clove in the recipe. Reducing clove and adding cinnamon may also improve flavor in formulations of the composition. Addition of cinnamon also appeared to reduce sugar cravings. Addition of cinnamon also may provide appetite suppression, weight loss and mitigation of uric acid crystals, which may be associated with gout. Cinnamon also helped mitigate aggression in men, potentially due to testosterone reduction in cases with elevated testosterone.

Endocannabinoids and Phytocannabinoid Agonists

[0290] Endocannabinoids ("**ECs**") and phytocannabinoids both at least partially modulate biological process via cannabinoid receptor types 1 ("**CB1**") and cannabinoid receptor type 2 ("**CB2**"). ECs and phytocannabinoids have also been shown to interact with the TRP receptors. The TRP receptors and the CB receptors are linked through the activity of endogenous ECs, such as AA and arachidonyl ethanolamide/anandamide ("**AEA**"). AA

has been shown to be an agonist at TRPA1, TRPM5, TRPV3 and TRPM2. AA is also an antagonist at TRPM8. AEA is an agonist of TRPV1 and TRPA1.

[0291] The differencing activity of ECs at the various TRP receptors indicated that phytocannabinoids also influence TRP channels and modulated the effects of the composition. Indeed, TRPA1 is also activated by THC and cannabinol ("**CBN**"). THC is the major psychoactive cannabinoid in *Cannabis sativa*. THC and cannabinol activate TRPA1 in TRPA1 overexpressing CHO cells and in trigeminal neurons. When consumed by humans, THC produces a wide range of biological effects, such as an increase in pulse rate, decreased blood-pressure, muscle weakening, increased appetite, and euphoria, followed by drowsiness (Ciardo, 2017). CBD, CBG, CBN and other cannabinoids in contract may produce markedly different effects without significant psychoactive effects.

[0292] Extracts or inclusion of either clove or cannabis were each found to have synergistic effects with low doses of psilocybin. Each such composition includes molecules active at TRP receptors and molecules active at CB receptors.

[0293] Similar metabolic pathways in individuals suffering from either post-traumatic stress disorder ("**PTSD**") and traumatic brain injury ("**TBI**"). Specifically, lower endocannabinoid signaling coupled with blocked calcium signaling downstream of TRP receptors CBD and other brain stimulation and neuroprotective molecules were included in compositions directed to improvement of mental health or treatment of the effects of brain injury.

[0294] A demographic of regular psilocybin users are often regular cannabis consumers as well. Cannabis is typically consumed as an unknown varietal and smoked in most instances where the actual amount has not been measured. However, low doses of cannabis in combination with psilocybin have not been reported or studied. In addition to the inclusion of a TRP agonist, the compositions may optionally include cannabis or ingredients from cannabis at doses below those required to cause significant psychoactive effects. Cannabis contains many phytocannabinoids that interact with the CB1 and CB2 receptors. THC and CBD are the most common phytocannabinoids. The precursor to each of THC and CBD is CBG. Cannabinol is a degradation product of THC that may be present in cannabis. THC converts to CBN under heat or catalysis. Additional rare phytocannabinoids such as CBDV have also shown to bind with TRP receptors.

[0295] Inclusion of phytocannabinoids extracted from select varieties of cannabis administered at low doses in the compositions facilitated reduced anxiety and increased

relaxation, and also showed increased libido in some individuals. Cannabis also includes many terpenoids, some of which have been shown to influence the TRP receptors. A dominant terpene in many cannabis varieties is myrcene. The compositions may also be prepared with an isolate of a phytocannabinoids to mitigate potential synergy, antagonism or contra-indications that may have occurred form the addition of unknown phytocannabinoids or terpenoids. In some cases CBD isolate was used to avoid the psychoactive properties that may result from the presence of other cannabinoids.

[0296] In many jurisdictions, cannabis is prohibited, and while an adult use market for cannabis is regulated in Canada, psilocybin remains prohibited in 2020 and Canadian regulations do not allow for 5HT2A agonists to be added to cannabis products in significant quantities. Clove was chosen as the preferred ingredient to include in most compositions to stimulate both a TRP receptor and potentially the CB receptors. Including cannabis or clove provided a more relaxing effect and promoted deeper sleep after the dose and again further reduced inflammation.

Myristicin

[0297] Nutmeg contains myristicin, which is also found in carrot, basil, cinnamon, and parsley. Myristicin, or methoxysafrole, is a benzodioxole that is active at the 5HT2A receptors in the brain with slight MAO inhibiting properties. Myristicin has hypotensive, sedative, anti-depressant, anesthetic, hallucinogenic, and serotonergic properties. Elemicin is another molecule has similar structure and shows similar effects. Both myristicin and elemicin appear to act as a significant potentiator of GABA. Large doses may cause hyper-excitability and may cause CNS depression among other negative effects. Nutmeg may include between 20 and 30 mg per gram, and the amount of myristicin in the compositions formulated with nutmeg was estimated to be up to 3% w/w.

[0298] Nutmeg also contains alpha terpineol and 8-O-4′-neolignans, which activate the TRPA1 and TRPM8 receptors respectively. Agonism at TRPA1 and TRPM8 may amplify antidepressant effects of the compositions and potentially support cessation of SSRIs. Many individuals who were taking SSRIs required a higher dose of the compositions in order to feel the effects of the compositions. With psilocybin and nutmeg, in some cases individuals were able to ween from (through sequentially reducing the dose) and/or replace their SSRIs within a matter of weeks without significant issues.

[0299] Nutmeg appeared to help with the and improve the overall antidepressant qualities and allow for a reduction in the amount of psilocybin (to about 0.1 g of dried fruiting bodies) while still achieving an improvement in mood, reduced anxiety, reduced depression or other therapeutic effects. This translated to improved happiness and elevation of positive thoughts associated with the compositions. Including nutmeg and reducing the amount of psilocybin also improved the therapeutic effects and allow for a better sleep. However, including nutmeg with psilocybin amplified the psychoactive effects of the psilocybin, which increase in psychoactivity may be offset by the reduced amount of psilocybin used when nutmeg is included in the composition.

[0300] Formulations that included nutmeg produced a more uplifting and euphoric effect and were often included stronger aphrodisiac properties, especially when combined with frankincense and myrrh.

[0301] Nutmeg was included in compositions for depression but not for stimulant compositions designed to treat ADD/ADHD. Individuals using stimulant medication often have difficulties sleeping. Nutmeg helped many individuals stop using stimulants and have an easier time falling asleep, as well as a more restful sleep, particularly when combined with phytocannabinoids.

1-8 Cineole

[0302] Bergamot citrus fruit flavonoids, including 1-8 cineole, are potent and selective blockers of TRPM3. Eucalyptus also includes 1-8 cineole, in addition to pinene and eucalyptol. The dose of 1-8 cineole vas variable based on inclusion of ingredients with or without it. Bergamot resulted in uplifting and extended effects but also amplified the psychoactive effects of the psilocybin, allowing a lowered dose of psilocybin relative to formulations that lacked bergamot.

[0303] Bergamot was found to support increased focus and concentration, and prolong the effects of the compositions. Some reported feeling a lasting benefit 12 to 24 hours after ingestion of a single dose. TRPM3 is expressed in nociceptive sensory neurons in dorsal root and trigeminal ganglia, similar to TRPV1. Similarly to TRPV1, activation of TRPM3 has been linked to thermal pain as well.

[0304] The physiological functions of TRPM3 and the antagonists known to interact with TRPM3 are different than TRVP1, although they both respond to thermal nociceptive stimuli, an effect that is maintained after induction of inflammatory hyperalgesia. The

ability of molecules in bergamot such as eriodictyol to block the capsaicin-induced activation of rat TRPV1 but still show activity on TRPM3 indicate a different mode of action, and it has been shown to be involved in signaling from the eyes (Janda, 2016).

[0305] Some individuals described the psychoactive effects of formulations including bergamot in some cases as "a light was turned on inside the brain" or "a glow". This may be connected to TRP receptors having been implicated in light sensitivity for both mammals and insects. Bergamot essential oil has phototoxic effects in humans when consumed in high doses, and transduction by TRP channels is associated with better information transfer in bright light (Katz, 2018). A relatively low amount of bergamot oil was sufficient to result in this effect and was notably different than formulations which lacked the bergamot. A dose of about was 0.012% (w/w) of the composition. Enhanced focus, concentration and energy were observed and reported from the compositions including citrus terpenoids in the bergamot.

TRPM8 Agonists

[0306] Menthol, commonly known for its cooling sensation when eaten, inhaled or applied to the skin through agonism of TRPM8. Menthol is a natural monoterpenoid synthesized in plants from the *Mentha* genus (Salehi, 2018). Peppermint menthol, a compound obtained from the oil of peppermint (*Mentha piperita*), popularly known for its cooling effect, activates heat-activated TRPV3 (Oz, 2017). At warm temperatures menthol might be interpreted as warm based on its sensitizing effect on TRPV3, while at cooler temperatures, its activation of TRPM8 dominates its sensory quality (Oz, 2017). Eugenol also shows activity at TRPM8.

[0307] Other monoterpenes that activate TRPM8 include eucalyptol or 1-8 cineole (present in essential oils from *Eucalyptus polybractea*), menthone (the precursor of menthol in monoterpene biosynthesis), geraniol (found in lemon-grass and aromatic herb oils), linalool (found in floral scents of *Onagraceae* species), menthyl lactate (from peppermint oil), trans- and cis-p-menthane-3,8-diol (from *E. citriodora*), L-carvone (from spearmint or Kuromoji oil), isopulegol (from *M. pulegium* or *Lilium ledebourri*) and hydroxyl-citronellal (from citronella oils, volatile oils such as lemon, lemongrass or melissa oils) (Bharate, 2012).

TRPA1 Agonists

[0308] TRPA1 is activated by pungent chemicals as allyl isothiocyanate (mustard oil), allicin (from garlic), cinnamaldehyde (from cinnamon), methylsalicylate (winter-green), eugenol (cloves) and gingerol (ginger).

[0309] Garlic and onion also contain allium. Including garlic and onion in the compositions may be practical in capsule formulation but was not typically included in food-based formulations as the combination with other spices may be off-putting. People with gastrointestinal issues often took garlic and ginger tablets, pills or capsules separately to mitigate bowel symptoms. The dose of allium was included for compositions directed to facilitating digestion. Garlic and onion may also improve weight loss, and may improve gastrointestinal issues along.

Other TRP Agonists

[0310] Black pepper is high in BCP and contains myristicin. In addition, black pepper, includes another potent TRPV1 agonist – piperine (McNamara, 2005). Black pepper also includes guineensine, an anandamide reuptake inhibitor (Nicolussi, 2014) which further improve the effects, especially with cannabis present in the composition.

[0311] Ginger contains gingerol, a bioactive compound with demonstrated anti-inflammatory and antioxidant effects. (Wang, 2014.)

[0312] Carvacrol, the major ingredient of oregano (*Origanum majorana*/ *O. vulgare*), and thymol, a lesser component of oregano but an important constituent of thyme (*Thymus vulgaris*) are both known to evoke a sense of warmth and sensitize skin (Can, 2008). Enhanced digestion through oregano oil and thyme may be due to carvacrol agonist binding at TRPV3.

Additional Ingredients

[0313] Additional molecules and carriers may influence the effects. These were consciously chosen so as to either prevent any additional effect or to enhance the effect and flavor, making the medication more enjoyable.

[0314] Chocolate cacao and its derivatives cocoa and chocolate contain N-linoleoylethanolamide and N-oleoylethanolamide, compounds which inhibit anandamide breakdown, as well as variable amounts of anandamide. Inclusion of at least 70% dark

cacao not only was used for flavor, but also increased the positive and euphoric affects associated with the formula (Smalheiser, 2019).

[0315] Vegan recipes were used to reduce any symptoms associated with cacao, which has been associated with an increase blood pressure and therefore removed from anxiety medications or for those with dietary issues. Vegan Carib chips maybe used to replace cacao and milk substitutes such as almond, soy or oat milk may be used to replace dairy milk as the liquid matrix.

[0316] Coffee was added to some compositions for stimulation where stimulation is consistent with the intended effect of the composition. It was also common for individuals to decide to take the edible chew formulation dissolved in coffee.

[0317] The compositions may include ingredients to suppress appetite as well and reduce sugar craving, which ultimately helps reduce inflammation in the body. Significant weight loss has been reported in many case studies, though theses cannot be attributed to the drug alone. Reduced sugar cravings and better adjusted appetite may have been a result of the experience during the psychoactive effects of the psilocybin and not due to neurochemical effects per se of the drug. In some cases, individuals using the compositions simply make decision to exercise more often and eat differently. Due to improved cognitive function and reduced depression, most individuals show drastic lifestyle changes that can also attribute to this. This includes an increased connection with nature, an increased connection with the environment and often drastic alterations in diet. Specific recipes were made to deal with dietary issues such as bowel inflammation.

Formulations

[0318] The compositions may be formulated in dry form, as extracts or solubilized. The compositions may be formulated with acceptable carrier, excipient or diluent for oral administration and absorption through the gut or oral mucosa (e.g. sublingual, gingival, etc.), for dermal application or suppository. The compositions may be prepared from purified or synthesized compounds, from extracts with broad spectrum ingredients from source biomass, from raw biomass or from other preparations of raw biomass (e.g. dried, ground, sifted or otherwise processed without extraction, etc.). In any such examples, the 5HT2A agonist(s) and/or the TRP agonist(s) in the compositions may be at least about 99% pure. Pharmaceutically acceptable forms of the compounds in the compositions include salts, solvates, esters, carbamates, and phosphate esters.

[0319] Formulations including the compositions may be used for promotion and maintenance of mental health in health individuals. The formulations could be prepared as edible chews, capsules such as gel caps or soft gels, tinctures, tablets, dissolvable strips (e.g., sublingual films or buccal films), sachets, granules, suspensions, beverages, as foods or any other suitable formulation. In some aspects, the formulations may be administered according to any suitable dosing regimen, such as from 1-10 times per day. In other aspects, the formulations may be administered from 1-9 times per day, 1-8 times per day, 1-7 times per day, 1-6 times per day, 1-5 times per day, 1-4 times per day, 1-3 times per day, 1-2 times per day, or once per day. In some aspects, the formulations may be administered 10, 9, 8, 7, 6, 5, 4, 3, 2, or 1 times per day.

[0320] The formulations may be used in a therapeutic product (e.g. a drug product, a natural health product, a nutraceutical, etc.) for the treatment of inflammation related to bowel conditions including IBS, Crohn's disease, colitis, leaky gut syndrome, as well a mental illness conditions including ADD, ADHD, situational depression, MDD, minor depression, bipolar disorder, borderline personality disorder, seasonal affective disorder, postpartum depression, premenstrual dysphoric disorder, any treatment resistant depressions, post-traumatic stress disorder ("**PTSD**"), any of which may be co-morbid with other conditions listed above, with other psychological conditions, or with physical conditions such as peripheral pain, neurological pain or other forms of pain.

[0321] A "therapeutically effective amount" of a drug is an amount effective to demonstrate a selected activity of the drug in an individual receiving the drug. A "therapeutically effective amount" may also be referred to as an "effective dose range." Preferred doses, effective dose ranges, recommended maximum doses, and/or recommended daily intake amounts for TRP agonists and 5HT2A agonists are listed below in Tables 6 and 7.

Table 6: Preferred, and Total Daily Intake Amounts for Selected TRP Agonists

Substance	**Molecule**	**Preferred Doses**	**Total Daily Amount**
Cayenne pepper	Capsiacin/ Capsiates	**0.1-1 mg, 0.2-0.9 mg, 0.3-0.8 mg, 0.4-0.7 mg, or 0.5-0.6 mg**	**0.1-50 mg**
Tumeric	Curciminoids	**0.1-10 mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-500mg**

Clove	Eugenol BetaCaryophyllene	**0.1-25mg, 1-24 mg, 2-23mg, 3-22mg, 4-21mg, 5-20mg, 6-19mg, 7-18mg, 8-17mg, 9-16mg, 10-15mg, 11-14mg, or 12-13mg** **0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1- 500mg** **1-200mg**
Cinnamon	Cinnamaldehye	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-100mg**
Nutmeg***	Elemicin Myristicin	**0.1-5mg, 0.5-4.5 mg, 1-4 mg, 1.5-3.5 mg, or 2-3mg** **0.1-5mg, 0.5-4.5 mg, 1-4 mg, 1.5-3.5 mg, or 2-3mg**	**1-200mg** **1-200mg**
*** also a 5HT2A			
Oregano	Carvacrol	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-100mg**
Thyme	Thymol	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-200mg**
Pepper	Piperine	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-150mg**
Peppermint	Menthol	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**0.5-150mg**
Eucalyptus/ Cardamom	Eucalyptol (1-8 cineole)	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-150mg**
Onion / Garlic	Allicin	**0.5-10mg, 1-9mg, 2-8mg, 3-7mg, or 4-6mg**	**0.1-100mg**
Bergamot	Eriodictyol Myrcene	**0.01-1mg, 0.05-0.9mg, 0.1-0.8mg, 0.2-0.7mg, 0.3-0.6mg, or 0.4-0.5mg** **0.01-1mg, 0.05-0.9mg, 0.1-0.8mg, 0.2-0.7mg, 0.3-0.6mg, or 0.4-0.5mg**	**0.1-20mg** **0.1-20mg**

Cannabis	THC	**0.01-0.5mg, 0.05-0.45mg, 0.1-0.4 mg, 0.15-3.5mg, or 0.2-0.3mg**	**0.1-10mg**
	CBD	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-100mg**
	CBG	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-100mg**
	CBN	**0.1-10mg, 1-9 mg, 2-8 mg, 3-7 mg, or 4-6 mg**	**1-100mg**
	THCV	**0.01-0.5mg, 0.05-0.45mg, 0.1-0.4 mg, 0.15-3.5mg, or 0.2-0.3mg**	**0.1-10mg**
	CBDV	**0.01-0.5mg, 0.05-0.45mg, 0.1-0.4 mg, 0.15-3.5mg, or 0.2-0.3mg**	**0.1-10mg**
	Minor Cannabinoids	**0.01-0.5mg, 0.05-0.45mg, 0.1-0.4 mg, 0.15-3.5mg, or 0.2-0.3mg**	**0.1-10mg**

Table 7: Preferred, Average, and Recommended Maximum Intake Amounts for Selected 5HT2A Agonists

Molecule	**Chemical Name**	**Preferred Doses**	**Average Dose**	**Recommended Maximum Dose**
Tryptamines		**0.1-20mg, 1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**		
Psilocybin	3-[2-(dimethylamino)ethyl]-4-phosphoryloxyindole	0.1-20mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	15-25 mg	40 mg
Psilocin	3-[2-(dimethylamino)ethyl]-4-hydroxyindole	0.1-20mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	15-25 mg	40 mg
Psilacetin (4AcO-DMT)	3-[2-(dimethylamino)ethyl]-4-acetoxyindole	0.1-20mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	15-30mg	60mg

Molecule	Chemical Name	Preferred Doses	Average Dose	Recommended Maximum Dose
Aeruginascin	3-[2(trimethylamino)ethyl]-4-phosphoryloxyindole	0.1-20mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	No tox studies found	
Baeocystin	3-[2-(methylamino)ethyl]-4-phosphoryloxyindole	0.1-20mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	No tox studies found	
Norpsilocin	3-[2-(methylamino)ethyl]-4-hydroxyindole, 3-[2-(amino)ethyl]-4-hydroxyindole	0.1-20mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	No tox studies found	
Norbaeocystin	3-[2-(amino)ethyl]-4-phosphoryloxyindole	0.1-20mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	No tox studies found	
Bufotenin	5-methoxy-DMT	1 - 20 mg, **1-19mg, 2-18mg, 3-17mg, 4-16mg, 5-15mg, 6-14mg, 7-13mg, 8-12mg, or 9-11mg**	20 - 40 mg	60 mg
DMT	**N,N-Dimethyltryptamine**	1-10mg, 2-9mg, 3-8mg, 4-7mg, or 5-6mg	20-40	40-60
Endogenous molecules		**0.1-400mg, 1-375mg, 10-350mg, 50-325mg, 75-300mg, 100-275mg, 125-250mg, 150-225mg, or 175-200mg**		
Melatonin	N-acetyl-5-methoxy tryptamine	0.25 - 1 mg, 0.3-0.9mg, 0.4-0.8mg, or 0.5-0.7mg	1 - 3 mg	6 mg

Molecule	Chemical Name	Preferred Doses	Average Dose	Recommended Maximum Dose
Serotonin	5-hydroxy tryptamine	1-400mg, 25-375mg, 50-350mg, 75-325mg, 100-300mg, 125-275mg, 150-250mg, or 175-225mg		
5-HTP	5-hydroxy-tryptophan	50 - 200 mg, 60-190mg, 70-180mg, 80-170mg, 90-160mg, 100-150mg, 110-140mg, or 120-130mg	100 - 300 mg	300 - 400 mg
Ergolines		**10-500 µg, 50-450 µg, 100-400 µg, 150-350 µg, or 200-300 µg**		
LAE	D-lysergic acid ethylamide	0.1 - 0.5 mg, 0.15-0.45mg, 0.2-4mg, or 0.25-0.35mg	0.5 - 1.5 mg	
D-lysergic acid beta-propanolamide			0.2 - 0.4 mg	
LSA (ergine)	Lysergic acid amide	1-500µg**, 50-450 µg, 100-400 µg, 150-350 µg, or 200-300 µg**		
LSB	D-lysergic acid 2-butyl amide	0.03 - 0.06 mg	0.07 - 0.12 mg	0.24 mg
D-lysergic acid 1-butanolamide		0.1 - 0.2 mg	0.2 mg	0.8 mg
1-methyl-D-lysergic acid butanolamide		1 - 2 mg, 1.1-1.9mg, 1.2-1.8mg, 1.3-1.7mg, or 1.4-1.6mg	2 mg	8 mg
LSP	D-lysergic acid 3-pentyl amide		75% potency of LSD?	
LSM-775	D-N-morpholinyllysergamide	500 - 750 µg, 525-725 µg, 550 - 700 µg, 575 – 675µg, or 600 - 650 µg	750 - 1250 µg	1.5 mg
LPD-824	D-N-pyrrolidyllysergamide		800 µg	

Molecule	Chemical Name	Preferred Doses	Average Dose	Recommended Maximum Dose
LSD-Pip	(8β)-6-methyl-8-(piperidin-1-ylcarbonyl)-9,10-didehydroergoline	More potent than LPD-824 and LSM-775, but still several times less potent than LSD as a 5HT2A agonist		
DAM	N,N-dimethyllysergamide		1 mg	
LAMIDE	D-lysergic acid methylisopropyl amide	50 - 200 µg, 60 - 190 µg, 70 - 180 µg, 80 - 170 µg, 90 - 160 µg, 100 - 150 µg, 110 - 140 µg, or 120 - 130 µg	180 - 300 µg	
LSZ	D-lysergic acid 2,4-dimethylazetidide	10 - 150 µg, 20 - 140 µg, 30 - 130 µg, 40 - 120 µg, 50 - 110 µg, 60 - 100 µg, or 70 - 90 µg	100 - 300 µg	200 µg
LSD	Lysergic acid diethylamimde	10 - 75 µg, 20 - 65 µg, 30 - 55 µg, or 40 - 55 µg	50 - 150 µg	400 µg
ALD-52	D-1-acetyl-lysergic acid diethylamide	30 - 125 µg, 40 - 115 µg, 50 - 105 µg, 60 - 95 µg, or 70 - 85 µg	100 - 175 µg	325 µg
1P-LSD	D-1-propionyl-lysergic acid diethylamide	10 - 50 µg, 15 - 45 µg, 20 - 40 µg, or 25 - 35 µg	50 - 150 µg	200 - 300 µg
1B-LSD	D-N1-butyryl-lysergic acid diethylamide	15 - 75 µg, 20 - 70 µg, 25 - 65 µg, 30 - 60 µg, 35 - 55 µg, or 40 - 50 µg	75 - 150 µg	150 - 300 µg
1cP-LSD	D-N1-(cyclopropylmethanoyl)-lysergic acid diethylamide	15 - 75 µg, 20 - 70 µg, 25 - 65 µg, 30 - 60 µg, 35 - 55 µg, or 40 - 50 µg	75 - 150 µg	150 - 300 µg
LSH	D-Lysergic acid α-hydroxyethylamide	1-500µg, 25-475µg, 50-450µg, 75-425µg, 100-400µg, 125-375µg, 150-350µg, 175-325µg, 200-300µg, or 225-275µg		

Molecule	Chemical Name	Preferred Doses	Average Dose	Recommended Maximum Dose
MLD	D-N1-methyl-lysergic acid diethylamide		100 - 300 µg	
ETH-LAD	D-6-ethyl-6-nor-lysergic acid diethylamide	15 - 60 µg, 20 - 55 µg, 25 - 50 µg, 30 - 45 µg, or 35 - 40 µg	60 - 150 µg	225 µg
1P-ETH-LAD	D-1-propionyl-6-ethyl-6-nor-lysergic acid diethyamide	25 - 60 µg, 30 - 55 µg, 35 - 50 µg, or 40 - 45 µg	60 - 100 µg	100 - 200 µg
AL-LAD	D-6-allyl-6-nor-lysergic acid diethylamide	50 - 100 µg, 55 - 95 µg, 60 - 90 µg, 65 - 85 µg, or 70 - 80 µg	100 - 200 µg	200 - 300 µg
PRO-LAD	D-6-propyl-6-nor-lysergic acid diethylamide	10 - 75 µg, 15 - 70 µg, 20 - 65 µg, 25 - 60 µg, 30 - 55 µg, 35 - 50 µg, or 40 - 45 µg	100 - 200 µg	200 - 300 µg
IP-LAD	D-6-isopropyl-6-nor-lysergic acid diethylamide	10 - 75 µg, 15 - 70 µg, 20 - 65 µg, 25 - 60 µg, 30 - 55 µg, 35 - 50 µg, or 40 - 45 µg	100 - 200 µg	200 - 300 µg
PARGY-LAD	D-6-propynyl-6-nor-lysergic acid diethylamide	50 - 275 µg, 75 - 250 µg, 100 - 225 µg, 125 - 200 µg, or 150 - 175 µg	275 - 650 µg	700 µg
BU-LAD	D-6-butyl-6-norlysergic acid diethylamide	100 - 500 µg, 125 - 475 µg, 150 - 450 µg, 175 - 425 µg, 200 - 400 µg, 225 - 375 µg, 250 - 350 µg, or 275 - 325µg		
DAL	N,N-diallyllysergamide		No tox studies found	
ECPLA	D-N-ethyl-N-cyclopropyllysergamide		40% potency of LSD?	
Phenethylamines		**0.1-200mg, 1-190mg, 10-180mg, 20-170mg, 30-160mg, 40-150mg, 50-140mg, 60-130mg, 70-**		

Molecule	Chemical Name	Preferred Doses	Average Dose	Recommended Maximum Dose
		120mg, 80-110mg, or 90-100mg		
Mescaline	3,4,5-trimethoxyphenethylamine	10 - 200 mg, 20-190mg, 30-180mg, 40-170mg, 50-160mg, 60-150mg, 70-140mg, 80-130mg, 90-120mg, or 100-110mg	200 - 300 mg	700 mg
TMA	trimethoxyamphetamine	20-100mg, 25-95mg, 30-90mg, 35-85mg, 40-80mg, 45-75mg, 50-70mg, or 55-65mg	100 - 250mg	Shulgin Research
2C-B	4-bromo-2,5-dimethoxybenzeneethanamine	2 - 15 mg, 3-14 mg, 4-13 mg, 5-12 mg, 6-11 mg, 7-10 mg, or 8-9 mg	15 - 25 mg	50 mg
DOB	4-bromo-2,5-dimethoxyamphetamine	0.2 - 0.75 mg, 0.25-0.7 mg, 0.3-0.65 mg, 0.35-0.6 mg, 0.4-0.55 mg, or 0.45-0.5 mg	0.75 - 1.75 mg	3.5 mg
DOM	4-methyl-2,5-dimethoxyamphetamine	0.5 - 2mg, 0.6-1.9mg, 0.7-1.8mg, 0.8-1.7mg, 0.9-1.6mg, 1-1.5mg, 1.1-1.4mg, or 1.2-1.3mg	2 - 6mg	12 mg
2C-D	4-methyl-2,5-dimethoxybenzeneethanamine	3 - 15 mg, 4-14 mg, 5-13 mg, 6-12 mg, 7-11 mg, or 8-10 mg	20 - 50 mg	100 mg
MDA	3,4-methylenedioxyamphetamine	1-100mg, 5-95mg, 10-90mg, 15-85mg, 20-80mg, 25-75mg, 30-70mg, 35-65mg, 40-60mg, or 45-55mg	60 - 150 mg	200 mg
MDMA	N-methyl-3,4-methylenedioxyamphetamine	1-100mg, 5-95mg, 10-90mg, 15-85mg, 20-80mg,	60 - 150 mg	200 mg

Molecule	Chemical Name	Preferred Doses	Average Dose	Recommended Maximum Dose
		25-75mg, 30-70mg, 35-65mg, 40-60mg, or 45-55mg		
Isoroscaline	4-isopropoxy-3,5-dimethoxyphenethylamine	1-50mg, 5-45mg, 10-40mg, 15-35mg, or 20-30mg	50-200mg	
Proscaline	4-propoxy-3,5-DMPEA	1-50mg, 5-45mg, 10-40mg, 15-35mg, or 20-30mg	20-40mg	60mg
allylescaline		1-50mg, 5-45mg, 10-40mg, 15-35mg, or 20-30mg		
Escaline		1-50mg, 5-45mg, 10-40mg, 15-35mg, or 20-30mg		
Phenylpropanoids/ Aromatic Ethers		**0.1-200mg, 1-190mg, 10-180mg, 20-170mg, 30-160mg, 40-150mg, 50-140mg, 60-130mg, 70-120mg, 80-110mg, or 90-100mg**		
Elemicin	1,2,3-timethoxy-5-(prop-2-en-1-yl)benzene	50 - 200 mg, 55-195 mg, 60-190mg, 65-185mg, 70-180mg, 75-175mg, 80-170mg, 85-165mg, 90-160mg, 95-155mg, 100-150mg, 105-145mg, 110-140mg, 115-135mg, or 120-130mg	200 - 500 mg	500 - 800 mg
Myristicin		50 - 200 mg, 55-195 mg, 60-190mg, 65-185mg, 70-180mg, 75-175mg, 80-170mg, 85-165mg, 90-160mg, 95-155mg,		

Molecule	Chemical Name	Preferred Doses	Average Dose	Recommended Maximum Dose
		100-150mg, 105-145mg, 110-140mg, 115-135mg, or 120-130mg		

[0322] A "combination therapy" is a treatment with a certain substance or composition in which an individual is treated with, or given, one or more other compositions or drugs for the disorder or condition in conjunction with the first therapy or in conjunction with one or more other therapies. A combination therapy may be sequential therapy wherein an individual is treated first with one treatment modality (e.g. drug, psychotherapy, etc.) and then the other (e.g. drug, psychotherapy, etc.) or one more drugs, one or more therapies, or one or more drugs and one or more therapies, can be administered simultaneously. In either case, these drugs or therapies are said to be "coadministered". It is to be understood that "coadministered" does not necessarily mean that the drugs or therapies are administered in a combined form. The drugs or therapies may be administered separately or together to the same or different sites at the same or different times.

EXAMPLES

EXAMPLE 1

[0323] Eighteen initial experimental compositions including combinations of TRP receptor agonists were prepared are named based on their intended use. Each of these compositions could be formulated, for example into edible chews or gel caps as described in specific examples provided herein.

[0324] Each of the initial eighteen compositions utilized may be prepared including any suitable 5HT2A agonist obtained from a natural source with no special chemistry or extractions required. Each of these compositions was prepared using food ingredients or simple extracts from these food ingredients, as sources of the TRP receptor agonists described herein, including at Table 1 and Table 2. Any suitable source of the active ingredients present in these food ingredients as described in Table 1 and in Table 2 could be used to prepare the compositions described herein.

[0325] Seven base compositions were prepared, as shown in Table 8.

Table 8: Base Compositions

Composition	Cayenne	Clove	Turmeric	Cinnamon	Nutmeg
Base 1 – Analgesia	Yes	Yes	**No**	**No**	**No**
Base 2 – Mood Support	**No**	Yes	Yes	**No**	**No**
Base 3 – Anti-Inflammatory	Yes	**No**	Yes	**No**	**No**
Base 4 – General	Yes	Yes	Yes	**No**	**No**
Base 5 – Anti-Depression	Yes	Yes	Yes	**No**	Yes
Base 6 – Anti-Anxiety	Yes	Yes	Yes	Yes	**No**
Base 7 – Complete	Yes	Yes	Yes	Yes	Yes

[0326] From the above seven base compositions listed in Table 8, eleven additional example compositions were prepared and named based on their intended use, as shown in Table 9.

Table 9: Specific Compositions

No / Base	Composition	Additional ingredients	Optional Ingredients
8; 2	Sleep	cinnamon, nutmeg, serotonin, melatonin	cannabis, passion flower
9; 5	Anti-depression	(none), cacao	cinnamon, cannabis, kratom, frankincense, myrrh, kava, pepper
10; 6	Anti-anxiety	(none)	cannabis, kratom
11; 7	Relaxation	coffee, cannabis, bergamot	peppercorns, cacao
12; 7	Focus	gingko biloba	cannabis, cacao, peppermint, peppercorns
13; 7	Creativity	coffee, pepper, peppermint	cannabis, cacao, gingko biloba, bergamot, myrrh
14; 6	Anti-inflammatory for bowel	garlic, ginger, cardamom, onion, thyme	cannabis, frankincense, oregano, cacao, pepper
15; 2	Digestion	cinnamon, garlic, ginger, peppermint, cardamom	cannabis, frankincense, oregano, cacao, pepper
16; 6	Analgesia	pepper, peppermint, thyme, oregano	cannabis, kratom, cacao, pepper
17; 7	TBI Treatment	cacao, gingko biloba, myrrh, frankincense	Cannabis, pepper

No / Base	Composition	Additional ingredients	Optional Ingredients
18; 7	Aphrodisiac	peppermint, gingko biloba, cardamom, myrrh, frankincense, kava,	peppercorns, ginseng, cannabis, kratom

EXAMPLE 2

[0327] Thirty experimental formulations were prepared including many of the example compositions described herein. The formulations were prepared as capsules and as cocoa-based chews. Fourteen of the above compositions were prepared for each of these two formulations. Specifically, example formulations are provided for the compositions Base 1 – Analgesia, Base 2 – Mood Support, Base 3 – Anti-Inflammatory, Base 6 – Anti-Anxiety, Sleep, Anti-depression, Relaxation, Focus, Creativity, Anti-inflammatory for bowel, Digestion, Analgesia, TBI Treatment and Aphrodisiac.

[0328] Each of these formulations included psilocybin as a 5HT2A agonist, but could be prepared with any suitable 5HT2A agonist. The psilocybin used in each of these formulations was sourced from dried fruiting bodies of *P. cubensis*, but the compositions could be prepared with fruiting bodies, sclerotia, mycelia, cell culture or any suitable species of psilocybin containing fungi or other source of psilocybin. Since dried fruiting bodies were used as a source of psilocybin, it is likely that some amounts of psilocin, baeocystin, aeruginascin, norpsilocybin, norpsilocin, norbaeocystin or other tryptamines that are 5HT2A agonists were also present in the formulations.

[0329] The 5HT2A agonist used in each of these formulations included psilocybin from dried fruiting bodies. In sleep, the 5HT2A agonist also included serotonin and melatonin. In all formulations other than Base 1 – Analgesia, Base 2 – Mood Support, Base 3 – Anti-Inflammatory, Base 6 – Anti-Anxiety, Sleep, Anti-inflammatory for bowel, Digestion and Analgesia, the 5HT2A agonist also included myristicin and elemicin.

[0330] All ingredients in the capsule formulation were dried and ground other than as indicated in the below Tables with even numbers from among Tables 10 to 37.

[0331] The "liquid matrix" in the edible chew formulation may be any suitable and palatable liquid for mixing with the cacao (e.g. dairy milk, almond milk, hemp milk, soy milk, oat milk, etc.). All ingredients in the edible chew formulation were dried and ground other than ingredients that were not dried and ground in the corresponding capsule formulation, the dark chocolate and the liquid matrix.

[0332] When formulated as an edible chew, the dark chocolate is heated with sufficient liquid matrix to melt the dark chocolate without burning. The liquid matrix is further added as additional dried powdered ingredients are added. Finely ground dried fruiting bodies were added last without heating and stirred thoroughly to homogenize. Once the material had mixed sufficiently and begun to cool below flow temperature, then the material was put into moulds and cooled to allow solidifying into individual dosage units.

[0333] In formulations that included the ingredients, capsaicin was present at between 0.05 and 2.5 mg per dosage unit, curcumin was present at between 1.00 and 15 mg per dosage unit, eugenol was included at between 0.5 and 15 mg per dosage unit, BCP was included at between 0.25 and 5 mg per dosage unit, cinnamaldehyde was included at between 0.25 and 3 mg per dosage unit and myristicin and elemicin was present at between 0.50 and 3 mg per dosage unit.

Example Formulation 01 – Base Analgesia

[0334] Table 10 shows the ingredients for Base Analgesia formulated as material to be included in a capsule dosage form.

Table 10: Ingredients for Base Analgesia formulated for capsules

Ingredient	Weight (g)	Ratio
P. cubensis dried fruiting bodies	20	0.50
Cayenne pepper fruit and seeds	10	0.25
Clove fruit, stems and buds	10	0.25

[0335] The ingredients in Table 10 provide a total mass of 40 g. The weight per dosage unit is 0.3 g, including about 0.15 g of dried fruiting bodies of the *P. cubensis*. This provides approximately 133 dosage units from the ingredients in Table 10. Through a Controlled Substance Dealers license obtained through the Office of Controlled Substances with Health Canada, we were able to legally propagate and analyze the exact strain of mushrooms being utilized in the formulations referred to as *P.cubensis*. HPLC analysis on Psilocybin/psilocin content in the fungal biomass was determined using methanol mushroom extracts (100 mg of dry homogenized mushroom biomass + 5 mL of 100% methanol incubated at 60 °C for 1 h with vortexing and then filtered through a 0.2 um filter) were separated on an Agilent 1200 Series HPLC system using the following parameters:

Column: iHILIC-Fusion, PEEK, P/N: 100.152.0310.

Column temperature: 40 °C.

Mobile Phase: 80:20 (v/v) acetonitrile - ammonium formate (10mM, pH 3.5).

Flow Rate: 0.3 mL/min.

Results indicate a range between approximately 0.5-2.25% active metabolites by weight at various stages of growth with an average of around 1% in the freshly harvested and dried fruiting bodies. As such, we calculate the amount of psilocybin to be approximately 1-1.5 mg in most of the recipes and formulations tested depending on the amount of dried fruiting bodies included. As the dried fruiting bodies are about 1.0% psilocybin in this formulation, this provides about 1.5 mg psilocybin per dosage unit.

[0336] Table 11. HPLC results from cultivated Psilocybin cubensis mushrooms including many results from various harvests of the mushroom as well as some more common strains for comparison. This specific strain of mushroom also has a relative psilocybin to psilocin content of 10:1 compared to other varieties found to be closer to 1:1 or 2:1 ratios.

Table 11: HPLC results from cultivated Psilocybin cubensis mushrooms including results from various harvests of the mushroom and more common strains for comparison.

HPLC of isolated *P.cubensis* variety					
Experiment	**Sample Description**	**Psilocin (% w/w)**	**Psilocybin (% w/w)**	**Combined Total (% w/w)**	**Ratio Psilocybin /Psilocin**
Anatomical analysis					
P.cubensis Batch 16	Primordial stage	0.05	0.65	0.70	13.13
P.cubensis Batch 16	Small Immature mushroom	0.21	2.01	2.23	9.55
P.cubensis Batch 16	Medium Immature mushroom	0.19	1.22	1.41	6.54
P.cubensis Batch 16	Mature Stem (interior)	0.08	0.53	0.60	6.85
P.cubensis Batch 16	Mature Stem (exterior)	0.09	0.94	1.02	10.89
P.cubensis Batch 16	Mature Blended stems	0.07	1.00	1.07	14.29
P.cubensis Batch 16	Mature Gills	0.09	1.50	1.59	17.60
P.cubensis Batch 16	Mature Cap	0.10	0.74	0.85	7.11
P.cubensis Batch 16	Blended Harvests	0.08	0.84	0.92	10.04
P.cubensis Batch 16	Spores	ND	ND	NA	NA
	Average	**0.11**	**1.05**	**1.15**	**10.67**
Sequential Harvests					

P.cubensis Batch 42	First Harvest (Flush)	0.16	0.87	1.03	5.44
P.cubensis Batch 42	Second Harvest	0.11	0.96	1.07	9.16
P.cubensis Batch 42	Third Harvest	0.08	0.84	0.92	10.54
P.cubensis Batch 42	Forth Harvest	0.06	0.87	0.93	13.85
	Average	**0.10**	**0.89**	**0.99**	**9.75**
Degradation analysis					
P.cubensis Batch 2	~6 months post harvest	0.06	0.51	0.57	8.00
P.cubensis Batch 9	~5 months post harvest	0.06	0.55	0.61	9.50
P.cubensis Batch 23	~3 months post harvest	0.06	0.51	0.57	8.09
P.cubensis Batch 25	~3 months post harvest	0.07	0.57	0.64	8.34
P.cubensis Batch 26	~3 months post harvest	0.05	0.47	0.52	8.68
P.cubensis Batch 42	~2 months post harvest	0.06	0.74	0.79	12.81
	Average	**0.06**	**0.56**	**0.62**	**9.24**
Strain Comparison					
P.cubensis strain 'Alacabenzi'		0.25	0.48	0.73	1.89
P.cubensis strain 'Avery's Albino'		0.25	0.45	0.70	1.82
P.cubensis strain 'B+'		1.64	1.86	3.50	1.13

[0337] Table 12 shows the ingredients for Base Analgesia formulated as an edible chew dosage form.

Table 12: Ingredients for Base Analgesia formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	550	0.821
Liquid matrix	80 ml	80	0.119
Dried fruiting bodies	n/a	20	0.030
Clove fruit, stems and buds	2 tbsp	10	0.015
Cayenne pepper fruit and seeds	2 tbsp	10	0.015

[0338] The ingredients in Table 12 provide a total mass of 670. The weight per dosage unit is 5 g, including about 0.15 g of dried fruiting bodies. This provides 133 dosage units from the ingredients in Table 12. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.5 mg psilocybin per dosage unit.

Example Formulation 02 – Base Mood Support

[0339] Table 13 shows the ingredients for Base Mood Support formulated as material to be included in a capsule dosage form.

Table 13: Ingredients for Base Mood Support formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	20	0.40
Turmeric root	20	0.40
Clove fruit, stems and buds	10	0.20

[0340] The ingredients in Table 13 provide a total mass of 50 g. The weight per dosage unit is 0.3 g, including about 0.12 g of dried fruiting bodies. This provides 133 dosage units from the ingredients in Table 13. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.2 mg psilocybin per dosage unit.

[0341] Table 14 shows the ingredients for Base Mood Support formulated as an edible chew dosage form.

Table 14: Ingredients for Base Mood Support formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	550	0.821
Liquid matrix	80 ml	80	0.119
Turmeric root	2 tbsp	20	0.030
Dried fruiting bodies	n/a	15	0.022
Clove fruit, stems and buds	2 tsp	5	0.007

[0342] The ingredients in Table 14 provide a total mass of 670 g. The weight per dosage unit is 5 g, including about 0.15 g of dried fruiting bodies. This provides 133 dosage units from the ingredients in Table 14. The dried fruiting bodies are about 1.0% psilocybin, providing about 0.11 mg psilocybin per dosage unit.

Example Formulation 03 – Base Anti-Inflammatory

[0343] Table 15 shows the ingredients for Base Anti-Inflammatory formulated as material to be included in a capsule dosage form.

Table 15: Ingredients for Base Anti-Inflammatory formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	25	0.50
Turmeric root	20	0.40
Cayenne pepper fruit and seeds	5	0.10

[0344] The ingredients in Table 15 provide a total mass of 50 g. The weight per dosage unit is 0.3 g, including about 0.15 g of dried fruiting bodies. This provides 166 dosage units from the ingredients in Table 15. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.5 mg psilocybin per dosage unit.

[0345] Table 16 shows the ingredients for Base Anti-Inflammatory formulated as an edible chew dosage form.

Table 16: Ingredients for Base Anti-Inflammatory formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	600	0.828
Liquid matrix	80 ml	80	0.110
Dried fruiting bodies	n/a	20	0.028
Turmeric root	2 tbsp	20	0.028
Cayenne pepper fruit and seeds	1 tbsp	5	0.007

[0346] The ingredients in Table 16 provide a total mass of 725 g. The weight per dosage unit is 5 g, including about 0.14 g of dried fruiting bodies. This provides 145 dosage units from the ingredients in Table 16. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.4 mg psilocybin per dosage unit.

Example Formulation 06 – Base Anti-Anxiety

[0347] Table 17 shows the ingredients for Base Anti-Anxiety formulated as material to be included in a capsule dosage form.

Table 17: Ingredients for Base Anti-Anxiety formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	25	0.42
Turmeric root	20	0.33

Ingredient	Weight (g)	Ratio
Cayenne pepper fruit and seeds	5	0.08
Cinnamon stalk	5	0.08
Clove fruit, stems and buds	5	0.08

[0348] The ingredients in Table 17 provide a total mass of 70 g. The weight per dosage unit is 0.3 g, including about 0.11 g of dried fruiting bodies. This provides 233 dosage units from the ingredients in Table 17. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.1 mg psilocybin per dosage unit.

[0349] Table 18 shows the ingredients for Base Anti-Anxiety formulated as an edible chew dosage form.

Table 18: Ingredients for Base Anti-Anxiety formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Vegan carob chips	n/a	600	0.821
Liquid matrix	80 ml	80	0.110
Turmeric root	2 tbsp	20	0.027
Dried fruiting bodies	n/a	15	0.021
Cayenne pepper fruit and seeds	1 tbsp	5	0.007
Cinnamon stalk	2 tsp	5	0.007
Clove fruit, stems and buds	2 tsp	5	0.007

[0350] The ingredients in Table 18 provide a total mass of 730 g. The weight per dosage unit is 5 g, including about 0.10 g of dried fruiting bodies. This provides 146 dosage units from the ingredients in Table 18. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.0 mg psilocybin per dosage unit.

Example Formulation 08 – Sleep

[0351] Table 19 shows the ingredients for Sleep formulated as material to be included in a capsule dosage form.

Table 19: Ingredients for Sleep formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	15	0.23
Turmeric root	10	0.15

Ingredient	Weight (g)	Ratio
Nutmeg seed	10	0.15
Cinnamon stalk	5	0.08
Clove fruit, stems and buds	5	0.08
70% cacao dark chocolate	5	0.08
Cannabis flower with about 10% CBD and about 0.5% CBN	5	0.08
Serotonin formulated into 400 mg capsules including 50 mg serotonin	5	0.08
Melatonin formulated into 250 mg capsules including 5 mg melatonin	5	0.08

[0352] The ingredients in Table 19 provide a total mass of 65 g. The weight per dosage unit is 0.3 g, including about 0.07 g of dried fruiting bodies. This provides 217 dosage units from the ingredients in Table 19. The dried fruiting bodies are about 1.0% psilocybin, providing about 0.7 mg psilocybin per dosage unit.

[0353] Table 20 shows the ingredients for Sleep formulated as an edible chew dosage form.

Table 20: Ingredients for Sleep formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	600	0.816
Liquid matrix	80 ml	80	0.110
Dried fruiting bodies	n/a	10	0.013
Turmeric root	1 tbsp	10	0.013
Nutmeg seed	1 ½ tbsp	10	0.013
Cinnamon stalk	2 tsp	5	0.07
Clove fruit, stems and buds	2 tsp	5	0.07
cannabis extract with over 50% CBD and over 2% CBN content	1 tsp	5	0.07
Serotonin formulated into 400 mg capsules including 50 mg serotonin	n/a	5	0.07
Melatonin formulated into 250 mg capsules including 5 mg melatonin	n/a	5	0.07

[0354] The ingredients in Table 20 provide a total mass of 735 g. The weight per dosage unit is 5 g, including about 0.07 g of dried fruiting bodies. This provides 147 dosage units from the ingredients in Table 20. The dried fruiting bodies are about 1.0% psilocybin, providing about 0.7 mg psilocybin per dosage unit.

Example Formulation 09 – Anti-Depression

[0355] Table 21 shows the ingredients for Anti-Depression formulated as material to be included in a capsule dosage form.

Table 21: Ingredients for Anti-Depression formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	25	0.33
Turmeric root	20	0.27
70% cacao dark chocolate	10	0.13
Nutmeg seed	5	0.07
Cayenne pepper fruit and seeds	5	0.07
Cinnamon stalk	5	0.07
Clove fruit, stems and buds	5	0.07

[0356] The ingredients in Table 21 provide a total mass of 75 g. The weight per dosage unit is 0.3 g, including about 0.10 g of dried fruiting bodies. This provides 250 dosage units from the ingredients in Table 21. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.0 mg psilocybin per dosage unit.

[0357] Table 22 shows the ingredients for Anti-Depression formulated as an edible chew dosage form.

Table 22: Ingredients for Anti-Depression formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	550	0.797
Liquid matrix	80 ml	80	0.116
Turmeric root	2 tbsp	20	0.029
Dried fruiting bodies	n/a	15	0.022
Nutmeg seed	1 ½ tbsp	10	0.014
Cayenne pepper fruit and seeds	1 tbsp	5	0.007

Ingredient	Volume	Weight (g)	Ratio
Cinnamon stalk	2 tsp	5	0.007
Clove fruit, stems and buds	2 tsp	5	0.007

[0358] The ingredients in Table 22 provide a total mass of 690 g. The weight per dosage unit is 5 g, including about 0.11 g of dried fruiting bodies. This provides 138 dosage units from the ingredients in Table 22. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.1 mg psilocybin per dosage unit.

Example Formulation 11 – Relax

[0359] Table 23 shows the ingredients for Relax formulated as material to be included in a capsule dosage form.

Table 23: Ingredients for Relax formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	30	0.33
Turmeric root	20	0.22
Nutmeg seed	10	0.11
Cayenne pepper fruit and seeds	5	0.05
Cinnamon stalk	5	0.05
Clove fruit, stems and buds	5	0.05
70% cacao dark chocolate	5	0.05
Ground coffee beans	5	0.05
Bergamot flower	3	0.03
Peppercorns	3	0.03

[0360] The ingredients in Table 23 provide a total mass of 88 g. The weight per dosage unit is 0.3 g, including about 0.09 g of dried fruiting bodies. This provides 293 dosage units from the ingredients in Table 23. The dried fruiting bodies are about 1.0% psilocybin, providing about 0.9 mg psilocybin per dosage unit.

[0361] Table 24 shows the ingredients for Relax formulated as an edible chew dosage form.

Table 24: Ingredients for Relax formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	600	0.801
Liquid matrix	80 ml	80	0.107
Turmeric root	2 tbsp	20	0.027
Dried fruiting bodies	n/a	15	0.020
Nutmeg seed	1 ½ tbsp	10	0.013
Cayenne pepper fruit and seeds	1 tbsp	5	0.007
Cinnamon stalk	2 tsp	5	0.007
Clove fruit, stems and buds	2 tsp	5	0.007
Coffee beans	1 tbsp	5	0.007
Peppercorns	1 ¼ tsp	3	0.004
Cannabis extract with 60% w/w THC (not present in capsule formulation)	n/a	1	0.001
Bergamot 100% essential oil	0.15 ml	0.15	<0.001

[0362] The ingredients in Table 24 provide a total mass of 748 g. The weight per dosage unit is 5 g, including about 0.10 g of dried fruiting bodies. This provides 149 dosage units from the ingredients in Table 24. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.0 mg psilocybin per dosage unit.

Example Formulation 12 – Focus

[0363] Table 25 shows the ingredients for Focus formulated as material to be included in a capsule dosage form.

Table 25: Ingredients for Focus formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	25	0.27
Turmeric root	20	0.22
Nutmeg seed	10	0.11
Cayenne pepper fruit and seeds	5	0.05
Cinnamon stalk	5	0.05
Clove fruit, stems and buds	5	0.05
Coffee beans	5	0.05

Ingredient	Weight (g)	Ratio
70% cacao dark chocolate	5	0.05
Peppermint leaves	5	0.05
Ginkgo biloba leaves	3	0.03
Peppercorns	3	0.03

[0364] The ingredients in Table 25 provide a total mass of 91 g. The weight per dosage unit is 0.3 g, including about 0.08 g of dried fruiting bodies. This provides 303 dosage units from the ingredients in Table 25. The dried fruiting bodies are about 1.0% psilocybin, providing about 0.8 mg psilocybin per dosage unit.

[0365] Table 26 shows the ingredients for Focus formulated as an edible chew dosage form.

Table 26: Ingredients for Focus formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	500	0.772
Liquid matrix	80 ml	80	0.123
Turmeric root	2 tbsp	20	0.031
Dried fruiting bodies	n/a	15	0.023
Nutmeg seed	3/4 tbsp	5	0.008
Cayenne pepper fruit and seeds	1 tbsp	5	0.008
Cinnamon stalk	2 tsp	5	0.008
Clove fruit, stems and buds	2 tsp	5	0.008
Coffee beans	1 tbsp	5	0.008
Peppercorns	2 tsp	5	0.008
Ginkgo biloba leaves	n/a	2	0.003
Peppermint extract	1 ml	1	0.002

[0366] The ingredients in Table 26 provide a total mass of 648 g. The weight per dosage unit is 5 g, including about 0.12 g of dried fruiting bodies. This provides 129 dosage units from the ingredients in Table 26. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.2 mg psilocybin per dosage unit.

Example Formulation 13 – Creative

[0367] Table 27 shows the ingredients for Creative formulated as material to be included in a capsule dosage form.

Table 27: Ingredients for Creative formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	30	0.31
Turmeric root	20	0.21
Nutmeg seed	10	0.10
Cayenne pepper fruit and seeds	5	0.05
Cinnamon stalk	5	0.05
Clove fruit, stems and buds	5	0.05
70% cacao dark chocolate	5	0.05
Coffee beans	5	0.05
Peppermint leaves	5	0.05
Peppercorns	3	0.03
Bergamot flower	3	0.03

[0368] The ingredients in Table 27 provide a total mass of 96 g. The weight per dosage unit is 0.3 g, including about 0.09 g of dried fruiting bodies. This provides 320 dosage units from the ingredients in Table 27. The dried fruiting bodies are about 1.0% psilocybin, providing about 0.9 mg psilocybin per dosage unit.

[0369] Table 28 shows the ingredients for Creative formulated as an edible chew dosage form.

Table 28: Ingredients for Creative formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	500	0.768
Liquid matrix	80 ml	80	0.123
Dried fruiting bodies	n/a	20	0.031
Turmeric root	2 tbsp	20	0.031
Nutmeg seed	1 ½ tbsp	10	0.015
Cayenne pepper fruit and seeds	1 tbsp	5	0.008
Cinnamon stalk	2 tsp	5	0.008

Ingredient	Volume	Weight (g)	Ratio
Clove fruit, stems and buds	2 tsp	5	0.008
Coffee beans	1 tbsp	5	0.008
Peppermint extract	1 ml	1	0.002
Bergamot extract	0.15 ml	0.15	<0.001

[0370] The ingredients in Table 28 provide a total mass of 665 g. The weight per dosage unit is 5 g, including about 0.15 g of dried fruiting bodies. This provides 133 dosage units from the ingredients in Table 28. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.5 mg psilocybin per dosage unit.

Example Formulation 14 – Anti-Inflammatory for Bowel

[0371] Table 29 shows the ingredients for Anti-Inflammatory for Bowel formulated as material to be included in a capsule dosage form.

Table 29: Ingredients for Anti-Inflammatory for Bowel formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	30	0.385
Turmeric root	10	0.128
Cayenne pepper fruit and seeds	5	0.064
Cinnamon stalk	5	0.064
Clove fruit, stems and buds	5	0.064
Cannabis flower (not present in edible chew formulation) with between 10 and 20 % combined THC and CBD	5	0.064
70% cacao dark chocolate	5	0.064
Ginger	3	0.038
Garlic	2.5	0.032
Onion	2.5	0.032
Thyme	2	0.026
Oregano	2	0.026
Cardamom	1	0.013

[0372] The ingredients in Table 29 provide a total mass of 78 g. The weight per dosage unit is 0.3 g, including about 0.12 g of dried fruiting bodies. This provides 260 dosage

units from the ingredients in Table 29. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.2 mg psilocybin per dosage unit.

[0373] Table 30 shows the ingredients for Anti-Inflammatory for Bowel formulated as an edible chew dosage form.

Table 30: Ingredients for Anti-Inflammatory for Bowel formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	550	0.797
Liquid matrix	80 ml	80	0.116
Turmeric root	2 tbsp	20	0.029
Dried fruiting bodies	n/a	15	0.022
Cayenne pepper fruit and seeds	1 tbsp	5	0.007
Cinnamon stalk	2 tsp	5	0.007
Clove fruit, stems and buds	2 tsp	5	0.007
Ginger	1 2/3 tsp	3	0.004
Garlic	1 tsp	2.5	0.004
Onion	1 tsp	2.5	0.004
Cardamom	1 tsp	2	0.003
Oregano oil	10 drops	0.5	0.001
Thyme oil	2 drops	1	<0.001

[0374] The ingredients in Table 30 provide a total mass of 691 g. The weight per dosage unit is 5 g, including about 0.11 g of dried fruiting bodies. This provides 138 dosage units from the ingredients in Table 30. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.1 mg psilocybin per dosage unit.

Example Formulation 15 – Digestion

[0375] Table 31 shows the ingredients for Digestion formulated as material to be included in a capsule dosage form.

Table 31: Ingredients for Digestion formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	25	0.37
Turmeric root	10	0.15

Ingredient	Weight (g)	Ratio
Cinnamon stalk	5	0.07
Clove fruit, stems and buds	5	0.07
70% cacao dark chocolate	5	0.07
Decarboxylated cannabis flower with 1:1 ratio of THC:CBD and 20% w/w total phytocannabinoids	5	0.07
Peppermint leaves	5	0.07
Ginger	2.5	0.04
Garlic	2.5	0.04
Cardamom	2	0.03

[0376] The ingredients in Table 31 provide a total mass of 67 g. The weight per dosage unit is 0.3 g, including about 0.11 g of dried fruiting bodies. This provides 223 dosage units from the ingredients in Table 31. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.1 mg psilocybin per dosage unit.

[0377] Table 32 shows the ingredients for Digestion formulated as an edible chew dosage form.

Table 32: Ingredients for Digestion formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	500	0.790
Liquid matrix	80 ml	80	0.126
Turmeric root	2 tbsp	20	0.032
Dried fruiting bodies	n/a	15	0.024
Cinnamon stalk	2 tsp	5	0.008
Clove fruit, stems and buds	2 tsp	5	0.008
Garlic	1 tsp	2.5	0.004
Ginger	1 tsp	2.5	0.004
Cardamom	¾ tsp	2	0.003
Peppermint extract	1 ml	1 g	0.002

[0378] The ingredients in Table 32 provide a total mass of 633 g. The weight per dosage unit is 5 g, including about 0.11 g of dried fruiting bodies. This provides 126 dosage

units from the ingredients in Table 32. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.1 mg psilocybin per dosage unit.

Example Formulation 16 – Analgesia

[0379] Table 33 shows the ingredients for Analgesia formulated as material to be included in a capsule dosage form.

Table 33: Ingredients for Analgesia formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	25	0.34
Turmeric root	10	0.14
Cayenne pepper fruit and seeds	5	0.07
Cinnamon stalk	5	0.07
Clove fruit, stems and buds	5	0.07
Decarboxylated cannabis flower with 1:4 ratio or lower of THC:CBD and about 20% w/w total phytocannabinoids	5	0.07
70% cacao dark chocolate	5	0.07
Peppermint leaves	5	0.07
Peppercorns	3	0.04
Thyme	2.5	0.03
Oregano	2.5	0.03

[0380] The ingredients in Table 33 provide a total mass of 73 g. The weight per dosage unit is 0.3 g, including about 0.10 g of dried fruiting bodies. This provides 243 dosage units from the ingredients in Table 33. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.0 mg psilocybin per dosage unit.

[0381] Table 34 shows the ingredients for Analgesia formulated as an edible chew dosage form.

Table 34: Ingredients for Analgesia formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	550	0.797
Liquid matrix	80 ml	80	0.116
Turmeric root	2 tbsp	20	0.029

Ingredient	Volume	Weight (g)	Ratio
Dried fruiting bodies	n/a	15	0.022
Cayenne pepper fruit and seeds	1 tbsp	5	0.007
Cinnamon stalk	2 tsp	5	0.007
Clove fruit, stems and buds	2 tsp	5	0.007
Decarboxylated cannabis extract with 1:4 ratio or lower of THC:CBD and about 60% to 80% w/w total phytocannabinoids	n/a	5	0.007
Peppercorns	n/a	3	0.004
Oregano oil	10 drops	0.5	0.001
Peppermint oil	10 drops	0.5	0.001
Thyme oil	2 drops	0.1	<0.001

[0382] The ingredients in Table 34 provide a total mass of 689 g. The weight per dosage unit is 5 g, including about 0.11 g of dried fruiting bodies. This provides 137 dosage units from the ingredients in Table 34. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.1 mg psilocybin per dosage unit.

Example Formulation 17 – TBI Treatment

[0383] Table 35 shows the ingredients for TBI Treatment formulated as material to be included in a capsule dosage form.

Table 35: Ingredients for TBI Treatment formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	40	0.37
Turmeric root	20	0.19
Nutmeg seed	10	0.09
Decarboxylated cannabis flower with 2:1 ratio or greater of THC:CBD and about 20% w/w total phytocannabinoids	10	0.09
Cayenne pepper fruit and seeds	5	0.05
Cinnamon stalk	5	0.05
Clove fruit, stems and buds	5	0.05
70% cacao dark chocolate	5	0.05
Ginkgo biloba	3	0.03

Ingredient	Weight (g)	Ratio
Myrrh	2.5	0.02
Frankincense	2.5	0.02

[0384] The ingredients in Table 35 provide a total mass of 108 g. The weight per dosage unit is 0.3 g, including about 0.11 g of dried fruiting bodies. This provides 360 dosage units from the ingredients in Table 35. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.1 mg psilocybin per dosage unit.

[0385] Table 36 shows the ingredients for TBI Treatment formulated as an edible chew dosage form.

Table 36: Ingredients for TBI Treatment formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	650	0.812
Liquid matrix	80 ml	80	0.100
Dried fruiting bodies	n/a	20	0.025
Turmeric root	2 tbsp	20	0.025
Nutmeg seed	1 ½ tbsp	10	0.012
Cayenne pepper fruit and seeds	1 tbsp	5	0.006
Cinnamon stalk	2 tsp	5	0.006
Clove fruit, stems and buds	2 tsp	5	0.006
Ginkgo biloba leaves	2 tsp	5	0.006
Myrrh extract	10 drops	0.5	0.001
Frankincense extract	2 drops	0.1	<0.001

[0386] The ingredients in Table 36 provide a total mass of 801 g. The weight per dosage unit is 5 g, including about 0.12 g of dried fruiting bodies. This provides 160 dosage units from the ingredients in Table 36. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.2 mg psilocybin per dosage unit.

Example Formulation 18 – Aphrodisiac

[0387] Table 37 shows the ingredients for Aphrodisiac formulated as material to be included in a capsule dosage form.

Table 37: Ingredients for Aphrodisiac formulated for capsules

Ingredient	Weight (g)	Ratio
Dried fruiting bodies	30	0.28
Turmeric root	20	0.19
Nutmeg seed	10	0.09
Cayenne pepper fruit and seeds	5	0.05
Cinnamon stalk	5	0.05
Clove fruit, stems and buds	5	0.05
Coffee beans	5	0.05
70% cacao dark chocolate	5	0.05
Peppermint leaves	5	0.05
Kava kava root	5	0.05
Peppercorns	3	0.03
Ginkgo biloba	3	0.03
Frankincense	2.5	0.02
Myrrh	2.5	0.02
Cardamom	1	0.01

[0388] The ingredients in Table 37 provide a total mass of 107 g. The weight per dosage unit is 0.3 g, including about 0.14 g of dried fruiting bodies. This provides 356 dosage units from the ingredients in Table 37. The dried fruiting bodies are about 1.0% psilocybin, providing about 0.14 mg psilocybin per dosage unit.

[0389] Table 38 shows the ingredients for Aphrodisiac formulated as an edible chew dosage form.

Table 38: Ingredients for Aphrodisiac formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	500	0.748
Liquid matrix	80 ml	80	0.120
Dried fruiting bodies	n/a	25	0.037
Turmeric root	2 tbsp	20	0.030
Nutmeg seed	1 ½ tbsp	10	0.015
Kava kava root	2 tsp	5	0.007
Cayenne pepper fruit and seeds	1 tbsp	5	0.007

Ingredient	Volume	Weight (g)	Ratio
Cinnamon stalk	2 tsp	5	0.007
Clove fruit, stems and buds	2 tsp	5	0.007
Coffee beans	1 tbsp	5	0.007
Peppercorns	1 ½ tsp	3	0.004
Ginkgo biloba leaves	¾ tsp	2	0.003
Cardamom seeds	n/a	2	0.003
Peppermint extract	1 ml	1	0.001
Myrrh	10 drops	0.5 g	0.001
Frankincense	2 drops	0.1 g	<0.001

[0390] The ingredients in Table 38 provide a total mass of 668 g. The weight per dosage unit is 5 g, including about 0.18 g of dried fruiting bodies. This provides 133 dosage units from the ingredients in Table 38. The dried fruiting bodies are about 1.0% psilocybin, providing about 1.8 mg psilocybin per dosage unit.

EXAMPLE 3

[0391] Three example formulations were prepared including some of the examples compositions described in Tables 8 and 9. The Base Complete and Focus formulations were prepared as capsules. The Focus formulation was also prepared as an edible chew. These formulations were prepared with serotonin as the primary 5HT2A agonist, but could be prepared with any suitable 5HT2A agonist. The serotonin was provided as purified and formulated serotonin with 50 mg serotonin in each 400 mg capsule.

[0392] Unlike psilocybin, many other tryptamines, many ergolines and many phenethylamines, serotonin is not strongly psychoactive and in many jurisdictions is not a controlled substance. The safety and daily consumption limit have been well studied allowing these formulations to be administered to a broader range of individuals including minors.

Example Formulation 07 – Complete

[0393] Table 39 shows the ingredients for Base Complete formulated as material to be included in a capsule dosage form.

Table 39: Ingredients for Base Complete formulated for capsules

Ingredient	Weight (g)	Ratio
Turmeric root	20	0.26
Compounded serotonin powder	10	0.13
Nutmeg seed	10	0.13
Coffee beans	10	0.13
70% cacao dark chocolate	10	0.13
Cayenne pepper fruit and seeds	7	0.09
Cinnamon stalk	5	0.06
Clove fruit, stems and buds	5	0.06

[0394] The ingredients in Table 39 provide a total mass of 77 g. The weight per dosage unit is 0.5 g, including about 0.06 g of compounded serotonin powder. This provides 154 dosage units from the ingredients in Table 39. The compounded serotonin powder is about 12.5% serotonin, providing about 7.5 mg serotonin per dosage unit.

Example Formulation 12 – Focus

[0395] Table 40 shows the ingredients for Focus formulated as material to be included in a capsule dosage form.

Table 40: Ingredients for Focus formulated for capsules

Ingredient	Weight (g)	Ratio
Compounded serotonin powder	20	0.23
Turmeric root	20	0.23
Nutmeg seed	10	0.12
Cayenne pepper fruit and seeds	5	0.06
Cinnamon stalk	5	0.06
Clove fruit, stems and buds	5	0.06
Coffee beans	5	0.06
70% cacao dark chocolate	5	0.06
Peppermint leaves	5	0.06
Ginkgo biloba leaves	3	0.03
Peppercorns	3	0.03

[0396] The ingredients in Table 40 provide a total mass of 86 g. The weight per dosage unit is 0.3 g, including about 0.07 g of compounded serotonin powder. This provides 286 dosage units from the ingredients in Table 40. The compounded serotonin powder is about 12.5 % serotonin, providing about 8.75 mg serotonin per dosage unit.

[0397] Table 41 shows the ingredients for Focus formulated as an edible chew dosage form.

Table 41: Ingredients for Focus formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	500	0.778
Liquid matrix	80 ml	80	0.124
Turmeric root	2 tbsp	20	0.031
Compounded serotonin powder	n/a	15	0.016
Nutmeg seed	3/4 tbsp	5	0.008
Cayenne pepper fruit and seeds	1 tbsp	5	0.008
Cinnamon stalk	2 tsp	5	0.008
Clove fruit, stems and buds	2 tsp	5	0.008
Coffee beans	1 tbsp	5	0.008
Peppercorns	2 tsp	5	0.008
Ginkgo biloba leaves	n/a	2	0.003
Peppermint extract	1 ml	1	0.002

[0398] The ingredients in Table 41 provide a total mass of 643 g. The weight per dosage unit is 5 g, including about 0.08 g of compounded serotonin powder. This provides 128 dosage units from the ingredients in Table 41. The compounded serotonin powder is about 12.5 % serotonin, providing about 1.0 mg serotonin per dosage unit.

EXAMPLE 4

[0399] Three example formulations were prepared including some of the examples compositions described in Tables 8 and 9. The Base Complete, formulations were prepared as capsules. These formulations were prepared with ergolines as the 5HT2A agonist, but could be prepared with any suitable 5HT2A agonist. The ergolines were

provided either morning glory seeds or Hawaiian baby woodrose seeds that have been crushed and pulverized into a fine powder.

Example Formulation 07 – Base Complete

[0400] Table 42 shows the ingredients for Base Complete formulated as material to be included in a capsule dosage form.

Table 42: Ingredients for Base Complete formulated for capsules

Ingredient	Weight (g)	Ratio
Morning glory seed	40	0.42
Turmeric root	20	0.21
Nutmeg seed	10	0.11
Cayenne pepper fruit and seeds	5	0.05
Cinnamon stalk	5	0.05
Clove fruit, stems and buds	5	0.05
Coffee beans	5	0.05
70% cacao dark chocolate	5	0.05

[0401] The ingredients in Table 42 provide a total mass of 95 g. The weight per dosage unit is 0.5 g, including about 0.21 g of morning glory seeds. This provides 253 dosage units from the ingredients in Table 42.

[0402] According to one study, morning glory seeds are between 260 µg/g and 300 µg/g LSA and about 0.5 to 1.75 relative abundance of LSH to LSA and ergometrine, providing between 130 µg/g and 525 µg/g LSH in morning glory seeds (Nowak, J., Woźniakiewicz, M., Klepacki, P., Sowa, A., & Kościelniak, P. (2016). Identification and determination of ergot alkaloids in Morning Glory cultivars. *Analytical and bioanalytical chemistry*, *408*(12), 3093–3102, which is incorporated herein by reference in its entirety). At these concentrations of ergolines, each dosage unit includes between 54 to 63 µg LSA per dosage unit and between 27 and 95 µg LSH per dosage unit.

Example Formulation 07 – Base Complete

[0403] Table 43 shows the ingredients for Base Complete formulated as material used in in a tea format. Peppermint tea may be used to mitigate potential stomach cramping,

through the addition to menthol providing a 5HT3 antagonist. The tea may also be combined with bergamot, garlic or ginger.

Table 43: Ingredients for Base Complete formulated for use in tea

Ingredient	Weight (g)	Ratio
Morning glory seed	42	0.42
Turmeric root	21	0.21
Nutmeg seed	12	0.12
Cayenne pepper fruit and seeds	5	0.05
Cinnamon stalk	5	0.05
Clove fruit, stems and buds	5	0.05
Coffee beans	5	0.05
70% cacao dark chocolate	5	0.05

[0404] The ingredients in Table 43 provide a total mass of 99 g. One gram of the formulation is used in a cup of tea, which includes including about 0.42 g of morning glory seeds.

[0405] According to one study, morning glory seeds are between 260 µg/g and 300 µg/g LSA and about 0.5 to 1.75 relative abundance of LSH to LSA and ergometrine, providing between 130 µg/g and 525 µg/g LSH in morning glory seeds (Nowak, 2016). At these concentrations of ergolines, each dosage unit includes between 260 µg and 300 µg LSA per dosage unit and between 130 µg and 525 µg LSH per dosage unit.

Example Formulation 07 – Base Complete

[0406] Table 44 shows the ingredients for Base Complete formulated as an edible chew dosage form. This formulation may also include peppercorns or CBD.

Table 44: Ingredients for Focus formulated as edible chews

Ingredient	Volume	Weight (g)	Ratio
Dark chocolate (70% cacao)	n/a	600	0.780
Liquid matrix	80 ml	80	0.104
Morning glory seeds	n/a	42	0.055
Turmeric root	2 tbsp	20	0.027
Nutmeg seed	2 tbsp	12	0.016

Ingredient	Volume	Weight (g)	Ratio
Cinnamon stalk	2 tsp	5	0.006
Clove fruit, stems and buds	2 tsp	5	0.006
Cayenne pepper fruit and seeds	¾ tbsp	4	0.005
Peppermint oil extract	0.5 ml	0.5	0.001

[0407] The ingredients in Table 44 provide a total mass of 769.5 g. Each dosage unit is 9 g, which includes including about 0.49 g of morning glory seeds. This provides 86 dosage units from the ingredients in Table 44.

[0408] According to one study, morning glory seeds are between 260 µg/g and 300 µg/g LSA and about 0.5 to 1.75 relative abundance of LSH to LSA and ergometrine, providing between 130 µg/g and 525 µg/g LSH in morning glory seeds (Nowak, 2016). At these concentrations of ergolines, each dosage unit includes between 130 and 150 µg LSA and between 65 and 260 µg LSH.

Example Formulation 07 – Base Complete

[0409] Table 45 shows the ingredients for Base Complete formulated as material to be included in a capsule dosage form with Hawaiian Baby woodrose seeds.

Table 45: Ingredients for Base Complete formulated for capsules

Ingredient	Weight (g)	Ratio
Turmeric root	20	0.35
Nutmeg seed	10	0.18
70% cacao dark chocolate	10	0.18
Cayenne pepper fruit and seeds	7	0.12
Cinnamon stalk	5	0.09
Clove fruit, stems and buds	5	0.09

[0410] The ingredients in Table 45 provide a total mass of 57 g. The weight per dosage unit is 0.3 g. This provides 190 dosage units from the ingredients in Table 45. The capsules may be taken with a separate capsule including between 50 and 300 mg Hawaiian baby woodrose seeds. Due to the number of doses required to achieve efficacy with Morning glory seeds, Hawaiian baby woodrose seeds were pulverized and

distributed as a separate pill as a preferred method of consumption. This allows the user to increase either the 5HT2A agonists or the TRP agonists separately.

[0411] According to one study, Hawaiian baby woodrose seeds are about 1,400 µg/g LSA, 1,800 µg/g iso-LSA, 350 µg/g LSH and 240 µg/g iso-LSH (Chao, 1973). At these concentrations of ergolines, each 50 mg to 300 mg dosage unit of Hawaiian baby woodrose seeds includes between 70 µg and 420 µg LSA, between 90 µg and 540 µg iso-LSA, between 20 µg and 120 µg LSH and between 10 µg and 70 µg iso-LSH.

Example Formulation 07 – Base Complete with Garlic and Onion

[0412] Table 46 shows the ingredients for Base Complete with garlic and onion formulated as material to be included in a capsule dosage form.

Table 46: Ingredients for Base Complete formulated for capsules

Ingredient	Weight (g)	Ratio
Turmeric root	20	0.33
Nutmeg seed	10	0.17
Cayenne pepper fruit and seeds	5	0.08
70% cacao dark chocolate	5	0.08
Cinnamon stalk	5	0.08
Clove fruit, stems and buds	5	0.08
Ginger	5	0.08
Garlic	5	0.08

[0413] The ingredients in Table 46 provide a total mass of 60 g. The weight per dosage unit is 0.3 g, This provides 200 dosage units from the ingredients in Table 46. The capsules may be taken with a separate capsule including between 50 and 300 mg Hawaiian baby woodrose seeds.

[0414] According to one study, Hawaiian baby woodrose seeds are about 1,400 µg/g LSA, 1,800 µg/g iso-LSA, 350 µg/g LSH and 240 µg/g iso-LSH (Chao, 1973). At these concentrations of ergolines, each 50 mg to 300 mg dosage unit of Hawaiian baby woodrose seeds includes between 70 µg and 420 µg LSA, between 90 µg and 540 µg iso-LSA, between 20 µg and 120 µg LSH and between 10 µg and 70 µg iso-LSH.

Example Formulation 07 – Base Complete

[0415] Table 47 shows the ingredients for Base Complete formulated as material to be included in a capsule dosage form.

Table 47: Ingredients for Base Complete formulated for capsules

Ingredient	Weight (g)	Ratio
Turmeric root	20	0.31
Hawaiian baby woodrose seeds	10	0.16
Nutmeg seed	10	0.16
Cinnamon stalk	5	0.08
Clove fruit, stems and buds	5	0.08
Coffee beans	5	0.08
70% cacao dark chocolate	5	0.08
Cayenne pepper fruit and seeds	4	0.06

[0416] The ingredients in Table 47 provide a total mass of 64 g. The weight per dosage unit is 0.5 g, including about 0.16 g of Hawaiian baby woodrose seeds. This provides 128 dosage units from the ingredients in Table 47.

[0417] According to one study, Hawaiian baby woodrose seeds are about 1,400 µg/g LSA, 1,800 µg/g iso-LSA, 350 µg/g LSH and 240 µg/g iso-LSH (Chao, 1973). At these concentrations of ergolines, each dosage unit includes 220 µg LSA, 290 µg iso-LSA, 60 µg LSH and 40 µg iso-LSH.

Example Formulation 19 – Enhanced Focus

[0418] Table 48 shows the ingredients for an Enhanced Focus LSA/LSH recipe that can be made with either morning glory or Hawaiian baby woodrose.

Table 48: Ingredients for Enhanced Focus formulated for capsules

Ingredient	Weight (g)	Ratio
Morning Glory citrate powder	42	0.66
Nutmeg seed	21	0.33
Peppermint oil	0.5	0.01
Frankincense oil	0.25	3.92E-05

[0419] The ingredients in Table 48 provide a total mass of 63.75g. Each dosage unit is 0.3 g, which includes including about 0. 198g of morning glory seeds in citrate powder form. This provides 212 dosage units from the ingredients in Table 44.

[0420] Reformulation and extraction of LSA and LSH with citric juices or citric acid was found to make the recipe significantly more tolerable and palatable. Seeds were pulverized and soaked in juices of lemon, lime or orange, followed by dehydration in a standard food dehydrator. An alcohol may be added to aid in the process or even extract the active metabolites if desired. The seed mash is soaked in the liquid overnight (12 hours minimum), dried and then reground and used in formulations. The process was also repeated with Citric Acid at pH 3.5 with a similar result being achieved. Conversion of LSA/LSH to a citrate form of the molecule can be confirmed with a UV 'black' light as the seed mash fluoresces after this treatment. Though the complete conversions of the molecules cannot be confirmed, it is presumed that at least some of the metabolites are converted. It is suspected this allows them to pass the stomach more easily and bypass some of the interaction with 5HT3 receptors that may cause nausea. According to one study, morning glory seeds are between 260 µg/g and 300 µg/g LSA and about 0.5 to 1.75 relative abundance of LSH to LSA and ergometrine, providing between 130 µg/g and 525 µg/g LSH in morning glory seeds (Nowak, 2016). At these concentrations of ergolines, each dosage unit includes between 130 and 150 µg LSA and between 65 and 260 µg LSH, though at least some of this is suspected to be in a citrate form through chemical reaction processes.

EXAMPLE 5

[0421] Product development studies were directed to defining MED formulations that would reduce or eliminate any potential negative side effects and also mitigate the psychoactive effects of psilocybin. The specific objectives were fivefold. **First**, to develop a multimodal a broad spectrum treatment for multi-symptomatic individuals and those who present with more than one persistent medical condition including those related to inflammation, pain and a mental health condition or mood disorder. **Second**, to prevent any tolerance or resistance to the 5HT2A agonist activity being established with prolonged or consecutive use. Some issues have been reported with taking microdose formulations everyday resulting in a reduction in efficacy, requiring a higher dose to be

taken subsequently or a period of abstinence time between doses, for example taken once every three days. Ramping doses of the 5HT2A agonist may complicate stabilization of a condition or of general health. **Third**, to eliminate any intoxicating effects associated with 5HT2A agonism, facilitating use of formulations during everyday activities without compromising, impairing, perturbing or otherwise altering mental ability as a result of strongly psychoactive effects of the 5HT2A agonist. To mitigate intoxicating effects, potentiator compounds were assessed that would allow for a reduced dose of the 5HT2A agonist while still retaining efficacy of the 5HT2A agonist. **Fourth**, to achieve a prolonged and sustained effect. Often psilocybin shows a relatively rapid onset with maximum effects at 45min to 1 hour and then notable reduced effects tapering off from this point. In contrast, some other 5HT2A agonists show sustained activity for sometimes 8 to 12 hours or more. Inclusion of specific ingredients were meant to prolong the effect of the psilocybin or other ingredients to reduce the need for regular dosing and to allow for individuals to gauge the duration of the effects of the compositions. **Fifth**, to achieve little to no side physical side-effects, including mitigating psychoactive effects, and to mitigate stomach and bowel discomfort, each of which are often reported with use of psilocybin. Some ingredients was specifically to reduce unpleasant physical effects from any of the active ingredients in the formulation.

Methods

[0422] Edible chew and capsule formulations including the Base 07 – Complete with coffee beans, the 5HT2A agonist alone with corn starch (positive control) or sugar and placebo formulations including corn starch (negative control) or sugar alone (double negative control) were prepared and provided to small groups of individuals for assessment of the effects of the compositions.

[0423] All participants were informed that each dosage unit of active composition or psilocybin control that included, depending on the study, between 0.05 and 0.30 g of dried *P. cubensis* fruiting bodies, between 0.05 and 0.50 g of morning glory seeds or between 0.05 and 0.50 g of Hawaiian baby woodrose seeds. The formulations also included additional GRAS material. Participants were informed that the data would be used for research and for protection of intellectual property rights. All participants were informed that a survey would follow and that participation in the survey was voluntary. No potential benefits were communicated to participants. All studies with psilocybin

were conducted in Jamaica where psilocybin is not scheduled as a controlled substance. All studies with morning glory seeds or Hawaiian baby woodrose seeds were in a jurisdiction where possession and person use of morning glory seeds or Hawaiian baby woodrose seeds is compliant with controlled substances law. Some studies were undertaken in the context of a music festival. Other studies were undertaken at psilocybin retreat events. Numerous individuals also self-administered the formulations in their personal space and observed their daily routines over an extended number of days of using the formulations. Exclusion criteria were applied in a questionnaire to exclude individuals with a schizophrenia diagnosis, individuals with a family history of schizophrenia, pregnant individuals, minors and other high-risk categories for using psilocybin.

[0424] Typically, between 1 and 9 dosage units were provided to each participant per day. The studies varied in duration from one day to four weeks. Heavier individuals (<75kg) were typically given larger dosages. This conservative approach to dosing participants is consistent with the MED approach and with mitigating potential negative results from the study.

Results from Music Festival Surveys

[0425] On multiple occasions a standard dose of the chocolate format of the complete recipe was distributed prior to a music festival event in Jamaica. Participants signed waivers and knowingly were consuming a "psilocybin microdose formulation" and a minimal education and safety session was given regarding the dose prior to being distributed. The GRAS material in the formulation was not identified. Some participants completed optional surveys following the experience, and data was gathered from the surveys. Participants were allowed to consume up to 3 chocolates throughout an evening though only one is distributed to start. A minimum delay of one hour was applied for all participants before a second dose or third dose.

[0426] Overall, there was an astoundingly positive response. Individuals were happily surprised that they consumed less alcohol or other drugs after taking the formulation. Individuals reported feeling alert and good overall the following day. No hangover of strong intoxication effects was reported. Out of one hundred participants at a music festival, only one participant reported feeling overwhelmed by anxiety related to the effects to the extent of choosing to leave the music festival. A few individuals reported

not feeling anything at all. Most reported having an excellent experience with elevation in mood and enhancement of feelings of well-being and energy, as well as lasting positive changes post-experience. Some individuals experienced profound and lasting changes in perspective on life. One individual reported that previous intrusive suicidal thoughts were completely eliminated following one dose of the formulation. All individuals who chose to also consume alcohol reported reduced consumption.

Results from Wellness Retreat Surveys

[0427] Participants attended a five-day all inclusive retreat in Jamaica with a complete integrative wellness package. While no health benefits were attributed to psilocybin, participants were aware of optional microdose chocolates or capsules offered up to three times a day. The formulations were of the 07 – Base Complete composition. In some cases, the composition was adjusted for guests who may have had specific conditions they were looking to address and formulations of other compositions were provided to these guests. Formulations including Base 2 – Mood Support, 11 – Relaxation, 12 – Focus, 13 – Creativity and 18 – Aphrodisiac.

[0428] Many participants reported a life altering experience with lasting and meaningful change in their lives. Some participants reported that the experience felt like the first vacation they feel truly rested from. Many felt renewed and able to return to their lives and struggles with new skills and tools around health and well being. Both single individuals and couples showed benefits in their lives and relationships.

[0429] More specifically, participants reported reduction in negative symptoms, such as, depression, anxiety, suicidal ideation, PTSD symptoms, and negative self-talk. Participants also reported improvements of personal and work relationship communication, sleep health, inspiration to perform self-care tasks, increased creativity and more. No negative side effects or other negative consequences by individuals attending the retreat have been reported.

[0430] Formulations of the 07 Base – Complete were provided to multiple individuals who subsequently reported that they had been on the verge of attempting suicide or had recently attempted to commit suicide. In some cases, a single MED drastically improved the individual's mental state. In all cases, the desire to commit suicide was drastically reduced or completely eliminated, facilitating other therapeutic interventions. Most continued daily activities after taking a MED of a formulation of the 07 Base – Complete

composition with only intermittent breaks. These individuals have often reported feeling like "themselves again" or "not having felt as good in years".

[0431] Often these individuals were using or addicted to other drugs, whether prescription pharmaceuticals or illicit substances – and have replaced these substances with the formulation, and in some cases reported maintaining societal functions such as working, driving, and other regular activities. Many reported increased interest in daily life activities, a shift in perspective, a presence of positive emotions, increased energy and an increased desire and ability to interact, communicate or feel connected with others.

Results from Unsupervised Regular Home Use.

[0432] Many individuals consumed the 07 Base – Complete composition in a capsule or chocolate formulation. In some cases, other recipes were formulated based on the specific condition the individual might have been facing such as comorbidities with depression. Many saw profound changes within a short period of time (hours to days). These changes were often associated with both mental and physical health. Improved mood and increased energy are reported by most individuals consuming the formulation daily. Little to no tolerance was reported with daily use. Some individuals increased dosage as weeks progressed, though most found a single dose effective and were able to perform regular tasks at this dose. Most individuals who used pharmaceutical drugs such as painkillers and antidepressants reported decreased use of these substances, but often required a higher dose (such as 2x) to obtain efficacy. Most individuals who used alcohol reported reduced consumption of alcohol and regular use of other potentially impairing substances after using the formulations.

Overall Summary of Results

[0433] After over three thousand doses distributed in Jamaica, including hundreds of individuals who consumed the compositions for at least three days in a row, there have had almost no reports of negative side effects and zero serious adverse events reported.

[0434] In all cases of placebo, no statistical significant improvement was noted and no effects reported. For psilocybin alone, at the point which the individual reported feeling the effects of the psilocybin, they also reported some psychoactive effects and sometimes physical side-effects. With the inclusion of TRP agonists with psilocybin, the amount of psilocybin needed to achieve a notable effect was reduced, resulting in a reduction in

psychoactive effects and other side effects. In some cases, TRP agonists alone helped with pain or inflammation issues, but again the addition of both TRP and 5HT2A increases efficacy and reduced the amount of either class of substance required to achieve the effect. In order to achieve a similar effect with Psilocybin, a higher amount (almost triple) was required than when combined with TRP receptor agonists. Formulations of the Base 07 – Complete composition produced what many individuals referred to as a "lightness" or "glow" for 4 to 6 hours and a sustained good mood for days or weeks afterwards in some cases. Alterations of the ingredients and amounts of certain ingredients altered the effect of the formulation and allows adjustment to treat specific conditions more effectively, as shown above in Tables 8 and 9. There are many agonists for both the 5HT2A receptor and TRP family receptors. Various molecules and combinations of molecules alter the effects in a subjectively noticeable way

[0435] Lack of effect from a single dose was the most common complaint and most these were able to feel the effects of the formulation within three doses. Many individuals who complained of not feeling one dose were over 200 lbs in weight, well above the 150 lb average that was used in calculating the MED. Conversely, some smaller individuals, often female, would half the MED dose, suggesting that even 50% of a MED is enough for some people. In individuals who used the formulation for several days, a double dose was common for regular users over 70 kg, but not for those under 70 kg. No significant tolerance effects or buildup have been reported beyond situationally increasing dosage based on increased stress to the system, whether mental or physical.

[0436] Many individuals reported minimal to no psychoactive effects from a single MED, but nearly all individuals felt psychoactive effects from three MEDs. There is some contraindication of psilocybin with SSRI based on both literature and observation. Blocking serotonin reuptake at the brain may limit the effect of the incoming signal from the gut. Individuals taking SSRIs do not appear to feel the effects of a MED and require an increased dose in order to feel anything at all in most cases. Individuals on low levels of citalopram appeared to show significant results but those on higher doses of fluoxetine or other stronger SSRIs do not often feel the effect from a MED that affects healthy individuals who are not using SSRIs. This trend result was not as pronounced with Wellbutrin, which is a dopamine uptake inhibitor, but still there appeared to be a cross-tolerance or lack of effect to the formulations when SSRIs were present in the system.

Some individuals who weened off SSRI medications saw similar results to those not using SSRIs after a few months.

[0437] The most commonly noted side effects were digestive issues or stomach cramping. In many cases, stomach cramping was minor and subsided quickly. Two individuals reported severe intestinal pain. One awoke the morning after with sharp pains that were not accompanied by irregular bowel activity. Cramps were sharp and painful but went away within an hour of waking. The second individual develop the symptoms after using the formulation for a significant period of time (over three weeks). Severe cramping would occur not often occur during the dosage, but hours after when the effects had worn off. The second individual then tried psilocybin mushrooms alone with no other additives and the cramping returned, indicating it was not specific to the formulation, but rather psilocybin. The second individual responded well to a formulation lacking psilocybin but containing serotonin as a 5HT2A substitute, demonstrating that psilocybin is not required for efficacy and that serotonin or other 5HT2A agonists may effectively combine with TRP molecules. These cases indicate that a small subset of the population may have some sensitivity to psilocybin or the mushrooms themselves, perhaps as a result of abnormal pain receptor signaling following 5HT2A receptor agonism. It is possible that improper signaling between 5HT2A and TRP Receptors may occur as a result of this stimulated signaling, resulting in the painful sensation. Alternatively, TRP agonists may be flooding the system in large concentrations once metabolized and cause this pain. Regardless, this appears to be sensitization of TRP channels to signal heat and pain.

[0438] At the amount of Psilocybin consumed in one MED (>150mg dried fruiting bodies), there were no reports of intoxication or other psychoactive effects to a degree that influenced motor skills or coordination. The vast majority of individuals reported normal ability to perform simple motor tasks. Some report enhanced positive feelings and none report enhanced negative feelings. Some report this positive effect lasted for weeks after a single MED.

[0439] Effects observed in individuals included increased ability to relax, increased ability to concentrate, enhanced cognitive effects, increased energy levels, lower appetite levels, increased disposition to avoid sugar and lowered requirement for prescription medications.

[0440] Some individuals reported difficulty sleeping before taking the formulations. Some individuals who reported difficulty sleeping after an active dose were provided with formulations excluding coffee beans or cacao, and thereafter reported less difficulty sleeping.

[0441] Most individuals reported persistent effects of the medication six hours after consumption of a MED. In contrast most individuals who took equivalent or higher doses of psilocybin alone do not report feeling effects at 6 hours after consumption.

[0442] Some individuals reported an absence of suicidal ideation after taking even a single MED, and reported generally higher to feeling amazing and having no desire to kill themselves within a single dose. Amazing results in most individuals following one day of treatment. This is contrary to all available antidepressants on the market.

[0443] The compositions may be applied to reduce addiction and pleasure seeking behaviors, finding application in harm reduction approaches. Drug addicts often show reduced 5HT2A expression and lower abundance of 5HT2A receptors. Formulations of the compositions provided herein improved the ability of people to cease use of addictive drugs including alcohol, tobacco (or other nicotine), cocaine and opiates, even when the formulations were consumed at music festivals. Individuals have also reported mitigated addictive behaviors such as gambling.

EXAMPLE 6

[0444] Variation in the activity of different 5HT2A agonists was confirmed through analysis of compounds known to interact with serotonin receptors, and specifically ergoline class molecules. The *Convolvulaceae* family, commonly referred to as the bindweed or morning glory family, comprises approximately sixty genera and more than 1,650 species of mostly herbaceous vines. Morning glory seeds have been used to produce psychedelic experiences through ingestion due to the presence of LSA or LSH. A number of species in this family are known to produce hallucinogenic effects when consumed. (Grzegorz, 2013)

[0445] Experiments were performed with seeds from three different species, Heavenly Blue morning glory (*Ipomoea tricolor*), Mexican Morning glory (*Ipomoea hederacea*), traditionally known as Ololiuqui, and Hawaiian Baby Woodrose (*Argyreia nervosa*) also known as Elephant creeper. The Heavenly Blue morning glory seemed to be slightly more

potent than the Mexican variety at an equivalent weighted dose. The Hawaiian baby woodrose was at least three times as strong as the Heavenly Blue variety of morning glory when considered by mass. This was reflected in the MED50, which was under >300 mg of seeds for Hawaiian baby woodrose and over 1000 mg for Heavenly Blue morning glory. This correlates with literature regarding the amounts of LSA or LSH in the seeds with Hawaiian baby woodrose containing approximately triple the ergoline content compared with the morning glory.

[0446] Ingestion of Hawaiian baby woodrose or morning glory seeds alone resulted in significant psychoactive effects at higher doses. For Hawaiian baby woodrose 300 mg of ground seed was required to achieve MED50 and over 500 mg typically resulted in intoxicating effects including visual distortions and mild hallucinations. Similar to psilocybin, the MED for Hawaiian baby woodrose seeds is lowered by the inclusion of TRP agonists and these potentiator compounds influence the effects of the LSA, the LSH and potentially other 5HT2A agonist molecules present in the seeds. With TRP agonists included, even 250 mg was too much for most people to tolerate comfortably and was well above the established MED50 of around 140 mg. The TRP agonists potentiate the combination of LSA, LSH significantly to the point of making it uncomfortable for most individuals even at moderate doses (<200 mg seed with TRPs).

[0447] As seen with Psilocybin, the addition of the TRP agonists to species containing LSA, LSH and other ergolines also significantly reduced the MED50, by a similar margin of 2/3. There was a reduction in the MED50 with TRP agonists added to psilocybin by nearly 60% and similar reductions were achieved for both morning glory and Hawaiian baby woodrose seeds (see Figs. 6 to 8). As such, the TRP agonists make the effects of the 5HT2A agonists about three times more noticeable as when taken alone.

[0448] The active ergoline molecules present in *Convolvulaceae* species are more similar in subjective to LSD than to psilocybin and when consumed on their own, which is consistent with the presence of LSA, LSH and other ergolines. Without the inclusion of the TRP receptor agonists, the effects were significantly different than psilocybin. Even at lower doses, the effects were notably different than previously described formulations with psilocybin. While still producing an improved mood and slight euphoric feeling, there were subjective differences in many areas. The duration was significantly longer with most still feeling the effects 9 hours after a single dose, and in some cases 12 hours after dosing. Unlike psilocybin, the effects do not result in a feeling of connection to

others or the environment. While psilocybin often improves openness and promotes communication, LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds almost seem to do the opposite. Instead, these appear to be quite introspective. Definitely a desire to be away from groups of people or unknown situations and remain in a comfortable setting. Subjects report a desire to avoid being alone due to the anxiety, and also a desire to avoid strangers or to participate in situations wherein the individual lacks control. Comfort is key to a stress-free or low-stress environment due to the anxiety that may be caused by LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds.

[0449] While subjects generally appear activities outdoor such as gardening, or in nature such as hiking, the LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds appears to be more useful for individual tasks not involving groups or other people. Some individuals described feeling "energized" and compelled to do things after taking formulations including LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds. Unfortunately there also appears to be negative effects on the hippocampus, including difficulties with spatial memory. Multiple subjects report forgetting what they were doing or where they had put things down. Participants report it being easy to get lost in thought and also difficult to sit still.

[0450] Without the TRP agonists, the effects appeared to overlap somewhat with attention deficit disorder inducing and most individuals did not enjoy the experience. With the presence of TRPs and a reduced dose of LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds, therapeutic effects to the formulations may be more accessible, particularly with respect to creativity. Despite a lack of mental focus, there was also an underlying clarity of being, an enhancement of visual and auditory senses, but overpowering or hallucinogenic effects were uncommon. Tunnel-like vision was reported by a few individuals, yet most were still able to perform regular tasks such as riding a bicycle, mowing the lawn, washing dishes, etc. Manty individuals were able to concentrate on specific tasks, but tasks with math, numbers or spreadsheets seemed almost impossible to some individuals. In contrast, music and art are most enjoyable, as either a spectator or creator. Individuals note seeing things they have never seen before and noticing small details they had overlooked. Music appeared to some individuals to have more depth and color.

[0451] As indicated by the predicted amounts of LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds, the Hawaiian baby woodrose was very strong and felt somewhat "heavy" compared to the morning glory seeds. In some individuals, breathing felt heavy or slowed with Hawaiian baby woodrose and adds to the anxiety effects. This was not as pronounced with morning glory where about 0.5 grams of seeds seems to be an effective and comfortable dose for most people when TRP receptor agonists are present.

[0452] Anxiety was reported in almost all users, particularly within the first two hours following ingestion. This is likely due to interaction with 5HT3 serotonin receptor. The 5HT3 serotonin receptor is activated by LSA and LSH. The activation of 5HT3 along with differential activity at the 5HT2A receptor likely accounts for some of the differences between psilocybin and the seeds containing LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds. Psilocybin is less likely to activate 5HT3 than are LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds. Menthol is an antagonist of 5HT3 (Ashoor, 2013), and inclusion of peppermint in the formulations helped alleviate symptoms of nausea and anxiety. Mixing the ingredients directly into green tea with peppermint was an effective method of administration which likely improved the speed at which the materials exited the stomach and entered the digestive tract.

[0453] The 5HT3 receptor is expressed throughout the central and peripheral nervous systems, and mediates a variety of physiological functions. On a cellular level, postsynaptic 5-HT3 receptors mediate fast excitatory synaptic transmission in neocortical interneurons, amygdala, and hippocampus, and in visual cortex. 5HT3 agonism is known to induce nausea through influencing the vomiting center in brain stem. 5HT3 agonism has also been linked to anxiety, seizure propensity, pro-nociception. This may account for some of the unpleasant side effects of morning glory and Hawaiian baby woodrose seed consumption which was mitigated by the inclusion of citric acid as described previously. The conversion of these molecules to a citrate form at lower ph along reduced feelings of uneasiness and anxiety as well as the associated stomach pain or cramping.

[0454] While LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds resulted in different effects from psilocybin alone or in combination with TRPs, there still appeared to be therapeutic value. The ergolines seemed to result in a greater tendency to lose focus or want to wander. Nature was reported to be the best

scenario for consumption of these products. Visual acuity seems enhanced, but with some degree of tunnel vision. Focus and concentration as well as creativity appear to be restored somewhat by the inclusion of Frankincense with LSA/LSH, especially in the citrate form.

[0455] One effect of formulations including LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds with the TRP agonists that may have therapeutic value is intense polyphagia that may occur within a few hours of consuming the dose. Some participants report hunger that cannot seem to be satiated when using formulations including the TRP agonists and LSA, LSH and other ergolines present in morning glory or Hawaiian baby woodrose seeds as 5HT2A agonists. Polyphagia was unexpected as most 5HT2A agonists are reported to curb appetite. This effect may provide therapeutic benefits for individuals suffering from anorexia and bulimia. Once over the queasiness in the first few hours, appetite stimulation became intense for many individuals and eating is very pleasurable, to the extent that these formulations may have efficacy for reducing nausea. Eating before using the formulations is recommended to mitigate polyphagia. However, eating before using the formulations also appeared to lengthen the onset of the dosage and therefore increase the period of anxiety sometimes reported. Some reported yawning and feeling tired at lower doses. Numerous subjects took a nap while on the dose and reported vivid dreams. This is also contrary to most reported psychoactive 5HT2A agonists, which often prevent sleep while active in the body.

In Vitro Examples 7-49 Showing Effects of 5HT2A Agonists and/or TRP Agonists on Inflammatory Markers on Human Primary Small Intestinal Epithelial Cells (HSIECs)

Overview of Methods

[0456] Cell Culture: Human primary small intestinal epithelial cells (HSIEC), purchased from Cell Biologics were cultured in Epithelial Cell Medium /w Kit. HSIEC cells were incubated at 37°C in a humidified atmosphere of 5% CO2. HSIEC cells were treated with mycoplasma removal reagent BM-Cyclin (Roche) to ensure mycoplasma negative before treatment.

[0457] MTT Cell Viability Assay: The MTT assay is used to measure cellular metabolic activity as an indicator of cell viability, proliferation and cytotoxicity. Cytotoxicity of psilocybin (Psygen), 4-AcO-DMT (ChemLogix), ketanserin (TCI America), capsaicin

(Sigma), curcumin (Sigma), and eugenol (Sigma) was measured using MTT assay. Once HSIEC cells grown to 80% confluency, 3×10^3 cells/well were replated in 96-well plates. At 24 h after incubation, cells were treated with the indicated concentration of psilocybin, 4-AcO-DMT, ketanserin, capsaicin, curcumin, carvacrol, piperine, cinnemaldehyde, or eugenol, individually or in combination(s), DMSO and/or ethanol served as a control. Assays were performed with 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) using the Cell Proliferation Kit I (Roche Diagnostics GmbH) in triplicate, as described by the manufacturer. The spectrophotometric absorbance of samples was measured at 595 nm using a microtiter plate reader (FLUOstar Omega, BMG LABTECH). Psilocybin and Eugenol were also analyzed on A172 glioblastoma cell line using a similar methodology as described below. As shown in Table 49 below, most of the compounds tested did not have a significant negative effect on cellular metabolic activity at most of the concentrations tested. Further studies are generally only performed at doses which do no show aberrant cell growth, meaning significantly increased or decreased from the control. High doses of psilocybin and 4AcO-DMT increase growth of cells whereas doses of 40 um and less did not. Most other substances showed some toxicity, reducing cellular growth in a dose dependent fashion. Ketanserin showed an inhibitory effect above 20 μM. All initial doses of capsaicin were found to be inhibitory with very low doses (<10 μM) showing no effect. Cinnamaldehyde also demonstrated significant toxicity over 10 μM concentration. This was similar for piperine, and carvacrol which could only be studied at very low dose (2.5 μM). Eugenol only had a slight inhibitory effect on cell growth but only became toxic at very high concentrations. Combinations of low doses of each 5HT2A agonist with TRP agonists were performed at doses where the individual ingredients did not show significant cellular aberrations. Most substances when combined with either psilocybin or 4AcO-DMT did not significantly reduced growth withing the first 72 hours at concentrations that did not influence cell growth for each individual compound. The dose of Curcumin and Capsaicin specifically had to be reduced farther to combine these ingredients with the 5HT2A agonists and antagonist without causing toxicity.

Table 49: Cellular Metabolic Activity in HSIEC Cells Treated with Compounds of Interest

Single Molecules

Psilocybin		0	24 h	48 h	72 h	96 h
Control	Ethanol	0.040	0.097	0.196	0.463	0.660
	5μM	0.047	0.098	0.186	0.380	0.621
	10μM	0.038	0.107	0.198	0.388	0.624
	20μM	0.038	0.150	0.238	0.415	0.635
	40μM	0.041	0.182	0.259	0.467	0.685
	80μM	0.042	0.345	0.371	0.579	0.805
	160μM	0.042	0.523	0.604	0.808	1.099
Curcumin		0	24 h	48 h	72 h	96 h
Control	Ethanol	0.040	0.097	0.196	0.463	0.660
	1μM	0.040	0.086	0.184	0.375	0.611
	5μM	0.036	0.079	0.148	0.299	0.595
	10μM	0.036	0.070	0.115	0.215	0.466
	20μM	0.040	0.059	0.057	0.060	0.038
	40μM	0.039	0.038	0.026	0.014	0.00
	80μM	0.041	0.042	0.019	0.018	0.005
Eugenol		0	24 h	48 h	72 h	96 h
Control	Ethanol	0.040	0.099	0.190	0.384	0.837
	10μM	0.047	0.064	0.168	0.346	0.632
	50μM	0.038	0.079	0.145	0.337	0.647
	100μM	0.038	0.075	0.136	0.346	0.662
	200μM	0.041	0.064	0.111	0.296	0.652
	400μM	0.042	0.059	0.128	0.242	0.549
	800μM	0.042	0.053	0.091	0.146	0.268
Capsaicin		0	24 h	48 h	72 h	96 h
Control	Ethanol	0.040	0.099	0.190	0.384	0.837
	10μM	0.040	0.075	0.174	0.331	0.708
	50μM	0.036	0.062	0.155	0.292	0.681
	100μM	0.036	0.063	0.150	0.272	0.623
	200μM	0.040	0.044	0.082	0.144	0.231
	400μM	0.039	0.016	0.031	0.016	0.018
	800μM	0.041	0	0	0	0
Capsaicin (Low Dose repeat)		0	24 h	48 h	72 h	96 h
Control	Ethanol	0.065	0.102	0.159	0.348	0.571
	0.5uM	0.068	0.088	0.154	0.288	0.469
	1uM	0.066	0.084	0.150	0.326	0.502
	2.5uM	0.066	0.078	0.137	0.279	0.422
	5uM	0.068	0.080	0.148	0.296	0.477
4-AcO-DMT		0	24 h	48 h	72 h	96 h

Control	DMSO	0.016	0.073	0.116	0.230	0.441
	5uM	0.022	0.084	0.137	0.305	0.580
	10uM	0.020	0.194	0.233	0.370	0.647
	20uM	0.019	0.127	0.176	0.319	0.599
	40uM	0.020	0.194	0.233	0.370	0.647
	80uM	0.017	0.338	0.377	0.518	0.755
	160uM	0.018	0.595	0.621	0.780	0.912
Ketanserin		0	24 h	48 h	72 h	96 h
Control	DMSO	0.016	0.073	0.116	0.230	0.441
	1uM	0.015	0.084	0.128	0.251	0.529
	5uM	0.014	0.072	0.122	0.258	0.509
	10uM	0.016	0.066	0.123	0.252	0.510
	20uM	0.015	0.075	0.114	0.253	0.466
	40uM	0.013	0.063	0.113	0.121	0.229
	80uM	0.014	0.054	0.078	0.113	0.226
Piperine		0	24 h	48 h	72 h	96 h
Control	EtOH	0.026	0.068	0.163	0.261	0.559
	2.5µM	0.033	0.073	0.175	0.276	0.460
	5µM	0.035	0.077	0.170	0.278	0.517
	10µM	0.026	0.073	0.183	0.271	0.438
	20µM	0.022	0.075	0.166	0.268	0.445
	40µM	0.025	0.069	0.169	0.226	0.423
	80µM	0.026	0.068	0.171	0.224	0.391
	100µM	0.030	0.071	0.175	0.248	0.410
	200µM	0.027	0.071	0.171	0.243	0.426
	400µM	0.031	0.068	0.191	0.187	0.255
Carvacrol		0	24 h	48 h	72 h	96 h
Control	EtOH	0.026	0.068	0.163	0.261	0.559
	2.5µM	0.021	0.071	0.176	0.245	0.515
	5µM	0.022	0.072	0.175	0.261	0.501
	10µM	0.021	0.070	0.164	0.267	0.487
	20µM	0.022	0.071	0.171	0.266	0.461
	40µM	0.022	0.070	0.159	0.272	0.544
	80µM	0.025	0.076	0.120	0.221	0.423
	100µM	0.026	0.069	0.106	0.259	0.397
	200µM	0.027	0.061	0.088	0.179	0.238
	400µM	0.027	0.062	0.079	0.139	0.137
Cinnamaldehyde		0	24 h	48 h	72 h	96 h
Control	EtOH	0.033	0.175	0.158	0.255	0.587

	2.5μM	0.035	0.170	0.159	0.249	0.417
	5μM	0.026	0.183	0.148	0.236	0.423
	10μM	0.022	0.166	0.119	0.160	0.321
	20μM	0.025	0.169	0.095	0.105	0.152
	40μM	0.026	0.171	0.049	0.018	0.015
	80μM	0.030	0.175	0.021	0	
	100μM	0.027	0.171	0.016		
	200μM	0.031	0.191	0.009		
Molecules in Combination						
Psilocybin + Eugenol		0	24 h	48 h	72 h	96 h
Control	EtOH	0.046	0.049	0.110	0.192	0.358
	10μM PSI+25μM EUG	0.045	0.069	0.108	0.197	0.307
	20μM PSI+25μM EUG	0.046	0.079	0.136	0.221	0.311
	40μM PSI+25μM EUG	0.046	0.141	0.170	0.284	0.377
Psilocybin + Curcumin		0	24 h	48 h	72 h	96 h
Control	EtOH	0.046	0.049	0.110	0.192	0.358
	10μM PSI+25μM CUR	0.045	0.075	0.114	0.141	0.150
	20μM PSI+25μM CUR	0.044	0.089	0.122	0.141	0.137
	40μM PSI+25μM CUR	0.042	0.157	0.163	0.195	0.189
Psilocybin + Curcumin (0.5μM CUR)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.094	0.116	0.185	0.494	0.759
0.5μM Curcumin	10μM PSI+0.5μM CUR	0.083	0.106	0.166	0.485	0.611
	20μM PSI+0.5μM CUR	0.090	0.135	0.169	0.421	0.595
	40μM PSI+0.5μM CUR	0.089	0.251	0.247	0.579	0.761
Psilocybin + Curcumin (1μM CUR)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.094	0.116	0.185	0.494	0.759
1μM Curcumin	10μM PSI+1μM CUR	0.090	0.116	0.157	0.439	0.640
	20μM PSI+1μM CUR	0.097	0.138	0.176	0.422	0.578
	40μM PSI+1μM CUR	0.091	0.299	0.264	0.677	0.855
Psilocybin + Curcumin (2.5μM CUR)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.094	0.116	0.185	0.494	0.759
2.5μM Curcumin	10μM PSI+2.5μM CUR	0.093	0.089	0.148	0.422	0.637
	20μM PSI+2.5μM CUR	0.092	0.131	0.171	0.480	0.661
	40μM PSI+2.5μM CUR	0.098	0.182	0.199	0.467	0.778
Psilocybin + Capsaicin (0.5μM CAP)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.065	0.102	0.159	0.348	0.571
0.5μM Capsaicin	10μM PSI+0.5μM CAP	0.067	0.101	0.174	0.328	0.487

	20μM PSI+0.5μM CAP	0.066	0.201	0.264	0.432	0.550
	40μM PSI+0.5μM CAP	0.061	0.185	0.208	0.390	0.599
Psilocybin + Capsaicin (1μM CAP)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.065	0.102	0.159	0.348	0.571
1μM Capsaicin	10μM PSI+1μM CAP	0.070	0.113	0.147	0.318	0.460
	20μM PSI+1μM CAP	0.062	0.155	0.205	0.355	0.553
	40μM PSI+1μM CAP	0.070	0.247	0.265	0.469	0.599
Psilocybin + Piperine (2.5μM)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.080	0.140	0.340	0.490	0.495
	10μM PSI+2.5μM PIP	0.076	0.177	0.355	0.506	0.328
	20μM PSI+2.5μM PIP	0.074	0.238	0.395	0.554	0.391
	40μM PSI+2.5μM PIP	0.072	0.345	0.430	0.599	0.292
Psilocybin + Carvacrol (2.5μM CAR)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.080	0.140	0.340	0.490	0.495
	10μM PSI+2.5μM CAR	0.075	0.181	0.376	0.529	0.378
	20μM PSI+2.5μM CAR	0.080	0.231	0.429	0.586	0.438
	40μM PSI+2.5μM CAR	0.073	0.335	0.474	0.637	0.484
Psilocybin + Cinnamaldehyde (0.5μM CINN)		0	24 h	48 h	72 h	96 h
Control	EtOH	0.080	0.140	0.340	0.490	0.495
	10μM PSI+0.5μM CINN	0.079	0.179	0.378	0.516	0.353
	20μM PSI+0.5μM CINN	0.078	0.250	0.410	0.563	0.348
	40μM PSI+0.5μM CINN	0.062	0.372	0.504	0.704	0.547
4-AcO-DMT + Eugenol (25μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.047	0.046	0.103	0.191	0.342
	10μM 4-AcO+25μM EUG	0.048	0.069	0.133	0.194	0.313
	20μM 4-AcO+25μM EUG	0.044	0.084	0.148	0.229	0.343
	40μM 4-AcO+25μM EUG	0.042	0.136	0.164	0.281	0.345
4-AcO-DMT + Curcumin (25μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.047	0.046	0.103	0.191	0.342
	10μM 4-AcO+25μM CUR	0.044	0.068	0.095	0.120	0.127
	20μM 4-AcO+25μM CUR	0.045	0.080	0.114	0.140	0.148
	40μM 4-AcO+25μM CUR	0.049	0.125	0.154	0.193	0.196
4-AcO-DMT + Curcumin (0.5μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.089	0.091	0.162	0.458	0.753
0.5μM Curcumin	10μM 4-AcO+0.5μM CUR	0.084	0.116	0.161	0.470	0.625
	20μM 4-AcO+0.5μM CUR	0.086	0.130	0.173	0.484	0.676
	40μM 4-AcO+0.5μM CUR	0.088	0.190	0.197	0.481	0.684
4-AcO-DMT + Curcumin (1μM)		0	24 h	48 h	72 h	96 h

Control	DMSO	0.089	0.091	0.162	0.458	0.753
1μM Curcumin	10μM 4-AcO+1μM CUR	0.090	0.107	0.155	0.400	0.595
	20μM 4-AcO+1μM CUR	0.090	0.140	0.165	0.411	0.639
	40μM 4-AcO+1μM CUR	0.084	0.203	0.209	0.458	0.674
4-AcO-DMT + Curcumin (2.5μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.089	0.091	0.162	0.458	0.753
2.5μM Curcumin	10μM 4-AcO+2.5μM CUR	0.094	0.116	0.138	0.340	0.512
	20μM 4-AcO+2.5μM CUR	0.086	0.137	0.153	0.399	0.661
	40μM 4-AcO+2.5μM CUR	0.096	0.181	0.191	0.368	0.580
4-AcO-DMT + Capsaicin (0.5μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.066	0.067	0.154	0.262	0.491
0.5μM Capsaicin	10μM 4-AcO+0.5μM CAP	0.065	0.102	0.174	0.312	0.569
	20μM 4-AcO+0.5μM CAP	0.062	0.127	0.205	0.402	0.620
	40μM 4-AcO+0.5μM CAP	0.063	0.197	0.242	0.456	0.647
4-AcO-DMT + Capsaicin (1μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.066	0.067	0.154	0.262	0.491
1μM Capsaicin	10μM 4-AcO+1μM CAP	0.064	0.097	0.174	0.306	0.517
	20μM 4-AcO+1μM CAP	0.069	0.143	0.225	0.357	0.531
	40μM 4-AcO+1μM CAP	0.065	0.209	0.259	0.452	0.601
Ketanserin + Eugenol (25μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.046	0.114	0.208	0.503	0.844
	1μM KET+25μM EUG	0.045	0.118	0.217	0.471	0.713
	5μM KET+25μM EUG	0.046	0.114	0.217	0.516	0.740
	10μM KET+25μM EUG	0.046	0.116	0.216	0.469	0.720
Ketanserin + Curcumin (5μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.046	0.114	0.208	0.503	0.844
	1μM KET+5μM CUR	0.046	0.118	0.164	0.394	0.565
	5μM KET+5μM CUR	0.045	0.096	0.157	0.340	0.585
	10μM KET+5μM CUR	0.044	0.104	0.151	0.328	0.557
Ketanserin + Curcumin (0.5μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.064	0.048	0.108	0.256	0.476
0.5μM Curcumin	10M KET+0.5μM CUR	0.065	0.052	0.103	0.239	0.522
	5μM KET+0.5μM CUR	0.068	0.058	0.101	0.233	0.540
	10μM KET+0.5μM CUR	0.066	0.045	0.099	0.223	0.472
Ketanserin + Curcumin (1μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.064	0.048	0.108	0.256	0.476
1μM Curcumin	1μM KET+1μM CUR	0.066	0.057	0.097	0.217	0.442
	5μM KET+1μM CUR	0.068	0.054	0.101	0.226	0.494

	10μM KET+1μM CUR	0.067	0.047	0.101	0.215	0.468
Ketanserin + Curcumin (2.5μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.064	0.048	0.108	0.256	0.476
2.5μM Curcumin	1μM KET+2.5μM CUR	0.066	0.045	0.084	0.186	0.354
	5μM KET+2.5μM CUR	0.061	0.045	0.098	0.209	0.399
	10μM KET+2.5μM CUR	0.070	0.044	0.086	0.158	0.298
Ketanserin + Capsaicin (0.5μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.064	0.048	0.108	0.256	0.476
0.5μM Capsaicin	10M KET+0.5μM CAP	0.066	0.049	0.109	0.252	0.507
	5μM KET+0.5μM CAP	0.065	0.046	0.113	0.263	0.521
	10μM KET+0.5μM CAP	0.062	0.044	0.109	0.251	0.520
Ketanserin + Capsaicin (1μM)		0	24 h	48 h	72 h	96 h
Control	DMSO	0.064	0.048	0.108	0.256	0.476
1μM Capsaicin	1μM KET+1μM CAP	0.063	0.054	0.103	0.240	0.464
	5μM KET+1μM CAP	0.064	0.051	0.103	0.258	0.525
	10μM KET+1μM CAP	0.069	0.043	0.094	0.234	0.454

[0458] Induction of Inflammation in HSIECs and Treatment with Molecules of Interest: HSIEC cells grown to 80% confluence were treated with 10 ng/ml TNF-α/IFN-γ (Sigma) (Yang et al., 2015), for the time points indicated in FIG. 9, to assess the best time point for determination of anti-inflammatory potential of the molecules and formulations of interest. To do so, COX-2, an enzyme which mediates the bioconversion of arachidonic acid to inflammatory prostaglandins (PGs), was measured via densitometry. GAPDH was used as a reference housekeeping marker for relative densitometry measures. As shown in FIG. 9, the greatest inflammatory effect was observed at 12 hours after treatment with TNF-α/IFN-γ. The anti-inflammatory potential of the molecules and formulations of interest were evaluated at 48 hours post-TNF-α/IFN-γ treatment in the HSIEC assays described below due to reduced variability and ability to assess differences between treatments. Ethanol or DMSO was used, as indicated in the figures, as a vehicle for dilution and as a negative control showing the amount of the inflammatory marker present when inflammation was not induced.

[0459] Increasing doses of each molecule of interest, or each combination of molecules of interest, were then distributed to the HSIEC cells treated to induce inflammatory response. Inflammatory markers COX-2 and/or IL-6 were assessed at specific timepoints after induction of inflammation for protein content marker measured via western blot.

GAPDH was used as a reference housekeeping marker for relative densitometry measures of protein content.

EXAMPLES 7–9

Effects of 5HT2A Agonists Psilocybin, and 4-ACO-DMT on COX-2 in *In Vitro* HSIEC Cell Assays

[0460] The anti-inflammatory effects of 5HT2A agonists psilocybin and 4-ACO-DMT, as evaluated based on their effects on COX-2, are described below and shown in FIGs. 14-17. FIG. 14 illustrates the structures of 5HT2A agonists psilocybin, 4-ACO-DMT, psilocin, and serotonin. 5HT2A antagonist ketanserin, used as a control in assays 2A-2C, also is shown. Psilocybin is a potent 5HT2A agonist. 4-ACO-DMT (psilacetin) is a synthetic 5HT2A agonist that is similar in structure to psilocybin and psilocin. Ketanserin is a synthetic, high-affinity non-selective antagonist of 5-HT_2 receptors in rodents. Based on the mechanism of action of the 5HT2A agonists psilocybin and 4-ACO-DMT, it was hypothesized that both would have anti-inflammatory activity while ketanserin would not.

EXAMPLE 7

[0461] *In vitro* HSIEC Cell Assay Example 7 is illustrated in FIG. 15, which shows the effects of escalating doses of 5 μM, 10 μM, 20 μM, and 40 μM psilocybin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 15, all doses of psilocybin resulted in the reduction of inflammatory marker COX-2, with 10 μM and 40 μM psilocybin reducing COX-2 to the greatest extent.

EXAMPLE 8

[0462] *In vitro* HSIEC Cell Assay Example 8 is illustrated in FIG. 16, which shows the effects of escalating doses of 5 μM, 10 μM, 20 μM, and 40 μM 4-ACO-DMT on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 16, 20 μM, and 40 μM doses resulted in significant reduction of inflammatory marker COX-2, with 40 μM 4-ACO-DMT reducing COX-2 to the greatest extent.

EXAMPLE 9

[0463] *In vitro* HSIEC Cell Assay Example 9 is illustrated in FIG. 17, which shows the effects of escalating doses of 1 μM, 5 μM, 10 μM, and 20 μM ketanserin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As expected, none of the doses of ketanserin resulted in a significant reduction in COX-2, while 20 μM ketanserin significantly increased COX-2.

EXAMPLES 10–12

Effects of TRP Agonists Eugenol, Capsaicin, and Curcumin on COX-2 in *In Vitro* HSIEC Cell Assays

[0464] The anti-inflammatory effects of TRP agonists eugenol, capsaicin, and curcumin, as evaluated based on their effects on COX-2, are described below and shown in FIGs. 11-13. FIG. 10 illustrates the structures of TRP agonists eugenol, capsaicin, and curcumin. Eugenol is a TRPA1, TRPV1, TRPV3 and TRPM8 agonist. Capsaicin is a potent TRPV1 agonist and may have some activity on others TRP receptors such as V3. Curcumin is a TRPV1 antagonist and also predicted to be a TRPA1 agonist. Based on the mechanism of action of these TRP agonists, it was hypothesized that all three would demonstrate some anti-inflammatory activity on their own.

EXAMPLE 10

[0465] *In vitro* HSIEC Cell Assay Example 10 is illustrated in FIG. 11, which shows the effects of escalating doses of 10 μM, 50 μM, 100 μM, 200 μM, and 400 μM eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 11, lower doses of 10 μM–100 μM eugenol resulted in the greatest reduction in inflammatory marker COX-2, while higher doses of 200 μM and 400 μM eugenol reduced COX-2 to a lesser extent.

EXAMPLE 11

[0466] *In vitro* HSIEC Cell Assay Example 11 is illustrated in FIG. 12, which shows the effects of escalating doses of 0.5 μM, 1 μM, 2.5 μM, and 5 μM capsaicin on COX-2 in

the HSIEC cells treated with TNF-α/IFN-γ as described above. As with eugenol, lower doses of 0.5 μM and 1 μM capsaicin resulted in the greatest reduction in inflammatory marker COX-2, while higher doses of 2.5 μM and 5 μM capsaicin reduced COX-2 to a lesser extent.

EXAMPLE 12

[0467] *In vitro* HSIEC Cell Assay Example 12 is illustrated in FIG. 13, which shows the effects of escalating doses of 0.5 μM, 1 μM, 2.5 μM, and 5 μM curcumin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As with eugenol and capsaicin, lower doses of 0.5 μM and 1 μM curcumin resulted in the greatest reduction in inflammatory marker COX-2, while higher doses of 2.5 μM and 5 μM curcumin reduced COX-2 to a lesser extent.

[0468] In each of HSIEC Cell Assay Examples 10–12, low doses of the TRP agonist are anti-inflammatory but decrease in efficacy as the concentration increases. This indicates that lower doses may be optimal for reducing inflammatory response. These lower doses were assessed in combination with 5HT2A agonists, as described below with respect to the assays illustrated in FIGs. 18-24 to assess potential synergistic reduction in inflammation of combinations of the 5HT2A with the TRP agonists of interest.

EXAMPLES 13–19

Effects of Combinations of 5HT2A Agonists Psilocybin and 4-ACO-DMT with Eugenol on COX-2, IL-6, IL-8, and iNOS in *In Vitro* HSIEC Cell Assays

[0469] The anti-inflammatory effects of combinations of 5HT2A agonists psilocybin and 4-ACO-DMT with eugenol, as evaluated based on their effects on COX-2, IL-6, IL-8, and TFN are described below and shown in FIGs. 18-24. Based on the mechanism of action of the 5HT2A agonists psilocybin and 4-ACO-DMT and eugenol, it was hypothesized that combinations of psilocybin and 4-ACO-DMT with eugenol would have synergistic effects on COX-2 and IL-6 while a combination of the 5HT2A antagonist ketanserin with eugenol would not.

EXAMPLE 13

[0470] *In vitro* HSIEC Cell Assay Example 13 is illustrated in FIG. 18, which shows the separate and combined effects of psilocybin and eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 18, combinations of psilocybin and eugenol resulted in the reduction of inflammatory marker COX-2, with the combination of 40 μM psilocybin and 25 μM eugenol reducing COX-2 to the greatest extent, thus indicating synergistic effects of psilocybin and eugenol on COX-2. A combination of 40 μM psilocybin and 25 μM eugenol reduced COX-2 by 83% more than 40 μM psilocybin alone.

EXAMPLE 14

[0471] *In vitro* HSIEC Cell Assay Example 14 is illustrated in FIG. 19, which shows the separate and combined effects of psilocybin and eugenol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 19, combinations of psilocybin and eugenol resulted in the reduction of inflammatory marker IL-6, with the combination of 40 μM psilocybin and 25 μM eugenol reducing IL-6 to the greatest extent, thus indicating synergistic effects of psilocybin and eugenol on IL-6. A combination of 40 μM psilocybin and 25 μM eugenol reduced IL-6 by 63% more than 40 μM psilocybin alone.

EXAMPLE 15

[0472] *In vitro* HSIEC Cell Assay Example 15 is illustrated in FIG. 20, which shows the separate and combined effects of psilocybin and eugenol on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 20, combinations of psilocybin and eugenol resulted in the reduction of inflammatory marker IL-8, with the combination of 40 μM psilocybin and 25 μM eugenol reducing IL-8 to the greatest extent, thus indicating synergistic effects of psilocybin and eugenol on IL-8. A combination of 40 μM psilocybin and 25 μM eugenol reduced IL-8 by 17% more than 40 μM psilocybin alone.

EXAMPLE 16

~~[0473]~~ *In vitro* HSIEC Cell Assay Example 16 is illustrated in FIG. 21, which shows the separate and combined effects of psilocybin and eugenol on TNF receptor 2 (TNF-R2) in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 21, combinations of psilocybin and eugenol resulted in the reduction of inflammatory marker TNF-R2, with the combination of 10 μM psilocybin and 25 μM eugenol reducing TNF-R2 to the greatest extent, thus indicating synergistic effects of psilocybin and eugenol on TNF-R2. A combination of 10 μM psilocybin and 25 μM eugenol reducing TNF by 52% more than 10 μM psilocybin alone.

EXAMPLE 17

[0474] *In vitro* Assay Example 17 is illustrated in FIG. 22, which shows the separate and combined effects of 4-ACO-DMT and eugenol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 22, combinations of 4-ACO-DMT and eugenol resulted in the reduction of inflammatory marker COX-2, with 40 μM 4-ACO-DMT and 25 μM eugenol reducing COX-2 to the greatest extent, thus indicating synergistic effects of 4-ACO-DMT and eugenol on COX-2. A 40 μM 4-ACO-DMT and 25 μM eugenol reduced COX-2 by 13% more than 40 μM 4-ACO-DMT alone.

EXAMPLE 18

[0475] *In vitro* Assay Example 18 is illustrated in FIG. 23, which shows the separate and combined effects of 4-ACO-DMT and eugenol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 23, combinations of 4-ACO-DMT and eugenol resulted in the reduction of inflammatory marker IL-6, with the combination of 20 μM 4-ACO-DMT and 25 μM eugenol reducing IL-6 to the greatest extent, thus indicating synergistic effects of 4-ACO-DMT and eugenol on IL-6. A combination of 20 μM 4-ACO-DMT and 25 μM eugenol reduced IL-6 by 63% more than 20 μM 4-ACO-DMT.

EXAMPLE 19

[0476] *In vitro* HSIEC Cell Assay Example 19 is illustrated in FIG. 24, which shows the effects of escalating doses of 1 μM, 5 μM, and 10 μM ketanserin, alone or in combination with 25 μM eugenol, on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As expected, none of the doses of ketanserin resulted in a significant reduction in COX-2 when combined with eugenol, while 1 μM ketanserin significantly increased COX-2.

EXAMPLE 20

[0477] In vitro HSIEC Cell Assay Example 20 is illustrated in FIG. 34, which shows the effects of escalating doses of 5 μM, 10 μM, 20 μM, and 40 μM psilocybin on iNOS in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 34, all doses of psilocybin resulted in the reduction of inflammatory marker iNOS, with 10 μM psilocybin reducing iNOS to the greatest extent.

EXAMPLE 21

[0478] *In vitro* HSIEC Cell Assay Example 21 is illustrated in FIG. 35, which shows the separate and combined effects of psilocybin and eugenol on iNOS in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 35, the combination of psilocybin with eugenol resulted in an attenuation in the reduction of inflammatory marker iNOS relative to psilocybin alone, with the combinations of 10 μM psilocybin with 25 μM eugenol resulting in the greatest attenuation in the reduction of inflammatory marker iNOS relative to psilocybin alone, thus indicating that eugenol attenuates the reduction in iNOS resulting from psilocybin. A combination of 10 μM psilocybin with 25 μM eugenol reduced iNOS by 77% more than10 μM psilocybin alone.

EXAMPLE 22

[0479] In vitro HSIEC Cell Assay Example 22 is illustrated in FIG. 36, which shows the effects of escalating doses of 5 μM, 10 μM, 20 μM, and 40 μM 4-ACO-DMT on iNOS in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG.

36, all doses of 4-ACO-DMT resulted in the reduction of inflammatory marker iNOS, with 10 μM 4-ACO-DMT reducing iNOS to the greatest extent.

EXAMPLE 23

[0480] *In vitro* HSIEC Cell Assay Example 23 is illustrated in FIG. 37, which shows the separate and combined effects of 4-ACO-DMT and eugenol on iNOS in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 37, the combination of 4-ACO-DMT with eugenol resulted in an attenuation in the reduction of inflammatory marker iNOS relative to 4-ACO-DMT alone, with the combinations of 20 μM 4-ACO-DMT with 25 μM eugenol and 40 μM 4-ACO-DMT with 25 μM eugenol resulting in the greatest attenuation in the reduction of inflammatory marker iNOS relative to 4-ACO-DMT alone, thus indicating that eugenol attenuates the reduction in iNOS resulting from 4-ACO-DMT. A combination of 20 μM 4-ACO-DMT with 25 μM eugenol reduced iNOS by 71% more than 20 μM 4-ACO-DMT alone.

EXAMPLE 24

[0481] *In vitro* HSIEC Cell Assay Example 24 is illustrated in FIG. 38, which shows the effects of doses of 1 μM, 5 μM, and 10 μM ketanserin, alone or in combination with 25 μM eugenol, on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As expected, none of the doses of ketanserin resulted in a significant reduction in COX-2 when combined with eugenol, while 1 μM and 5 μM ketanserin significantly increased COX-2.

EXAMPLES 25-29

Effects of Combinations of 5HT2A Agonists Psilocybin and 4-ACO-DMT with Capsaicin on COX-2 and IL-6 in *In Vitro* HSIEC Cell Assays

[0482] The anti-inflammatory effects of combinations of 5HT2A agonists psilocybin and 4-ACO-DMT with capsaicin, as evaluated based on their effects on COX-2 and IL-6, are described below and shown in FIGs. 25-29. Based on the mechanism of action of the 5HT2A agonists psilocybin and 4-ACO-DMT and capsaicin, it was hypothesized that combinations of psilocybin and 4-ACO-DMT with capsaicin would have synergistic

effects on COX-2 and IL-6 while a combination of the 5HT2A antagonist ketanserin with capsaicin would not.

EXAMPLE 25

[0483] *In vitro* HSIEC Cell Assay Example 25 is illustrated in FIG. 25, which shows the separate and combined effects of psilocybin and capsaicin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 25, combinations of psilocybin and capsaicin resulted in the reduction of inflammatory marker COX-2, with the combinations of 10 μM, 20 μM, and 40 μM psilocybin with 0.5 μM capsaicin reducing COX-2 to the greatest extent, thus indicating synergistic effects of psilocybin and capsaicin on COX-2. A combination of 40 μM psilocybin with 0.5 μM capsaicin reduced COX-2 by 33% more than 40 μM psilocybin alone.

EXAMPLE 26

[0484] *In vitro* HSIEC Cell Assay Example 26 is illustrated in FIG. 26, which shows the separate and combined effects of psilocybin and capsaicin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 26, combinations of psilocybin and capsaicin resulted in the reduction of inflammatory marker IL-6, with the combinations of 10 μM, 20 μM, and 40 μM psilocybin with 0.5 μM capsaicin reducing IL-6 to the greatest extent, thus indicating synergistic effects of psilocybin and capsaicin on IL-6. A combination of 40 μM psilocybin with 0.5 μM capsaicin reduced IL-6 by 8% more than 40 μM psilocybin alone.

EXAMPLE 27

[0485] *In vitro* HSIEC Cell Assay Example 27 is illustrated in FIG. 27, which shows the separate and combined effects of 4-ACO-DMT and capsaicin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 27, the combinations of 4-ACO-DMT and capsaicin resulted in the reduction of inflammatory marker IL-6, with the combination of 10 μM 4-ACO-DMT with 0.5 μM capsaicin reducing IL-6 to the greatest extent, thus indicating synergistic effects of 4-ACO-DMT

and capsaicin on IL-6. A combination of 10 μM 4-ACO-DMT with 0.5 μM capsaicin reduced IL-6 by 32% more than 10 μM 4-ACO-DMT alone.

EXAMPLE 28

[0486] *In vitro* HSIEC Cell Assay Example 28 is illustrated in FIG. 28, which shows the separate and combined effects of 4-ACO-DMT and capsaicin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 28, the combinations of psilocybin and capsaicin resulted in the reduction of inflammatory marker COX-2, with the combinations of 10 μM 4-ACO-DMT and 20 μM 4-ACO-DMT with 0.5 μM capsaicin reducing COX-2 to the greatest extent, thus indicating synergistic effects of 4-ACO-DMT and capsaicin on COX-2. A combination of 20 μM 4-ACO-DMT with 0.5 μM capsaicin reduced COX-2 by 23% more than 20 μM 4-ACO-DMT alone.

EXAMPLE 29

[0487] *In vitro* HSIEC Cell Assay Example 29 is illustrated in FIGS. 29A and 29B, which show the effects of doses of 1 μM and 5 μM ketanserin, alone or in combination with 0.5 μM capsaicin, on COX-2 and IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As expected, none of the doses of ketanserin resulted in a significant reduction in COX-2 or IL-6 when combined with capsaicin, while 1 μM ketanserin significantly increased COX-2.

EXAMPLES 30-33

Effects of Combinations of 5HT2A Agonists Psilocybin and 4-ACO-DMT with Curcumin on COX-2 and IL-6 in *In Vitro* HSIEC Cell Assays

EXAMPLE 30

[0488] *In vitro* HSIEC Cell Assay Example 30 is illustrated in FIG. 30, which shows the separate and combined effects of psilocybin and curcumin on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 30, combinations of psilocybin and curcumin resulted in the reduction of inflammatory marker COX-2, with the combinations of 10 μM and 40 μM psilocybin with 0.5 μM curcumin reducing

COX-2 to the greatest extent, thus indicating synergistic effects of psilocybin and curcumin on COX-2. A combination of 40 μM psilocybin with 0.5 μM curcumin reduced COX-2 by 20% more than 40 μM psilocybin alone.

EXAMPLE 31

[0489] *In vitro* HSIEC Cell Assay Example 31 is illustrated in FIG. 31, which shows the separate and combined effects of psilocybin and curcumin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 31, combinations of psilocybin and curcumin resulted in the reduction of inflammatory marker IL-6, with the combinations of 10 μM and 40 μM psilocybin with 0.5 μM curcumin reducing IL-6 to the greatest extent, thus indicating synergistic effects of psilocybin and curcumin on IL-6. A combination of 40 μM psilocybin with 0.5 μM curcumin reduced IL-6 by 28% more than 40 μM psilocybin alone.

EXAMPLE 32

[0490] *In vitro* HSIEC Cell Assay Example 32 is illustrated in FIG. 32, which shows the separate and combined effects of 4-ACO-DMT and curcumin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 32, the combinations of 4-ACO-DMT and curcumin resulted in the reduction of inflammatory marker IL-6, with the combinations of 10 μM, 20 μM, and 40 μM 4-ACO-DMT with 0.5 μM curcumin reducing IL-6 to the greatest extent, thus indicating synergistic effects of 4-ACO-DMT and curcumin on IL-6. A combination of 40 μM 4-ACO-DMT with 0.5 μM curcumin reduced IL-6 by 76% more than 40 μM 4-ACO-DMT alone.

EXAMPLE 33

[0491] *In vitro* HSIEC Cell Assay Example 33 is illustrated in FIGS. 33A and 33B, which show the effects of doses of 1 μM, 5 μM, and 10 μM ketanserin, alone or in combination with 0.5 μM curcumin, on COX-2 and IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As expected, none of the doses of ketanserin resulted in a significant reduction in COX-2 or IL-6 when combined with curcumin, while 1 μM, 5 μM, and 10 μM ketanserin significantly increased COX-2.

EXAMPLES 34–48

Effects of TRP Agonists Carvacrol, Piperine, and Cinnamaldehyde, Alone or in Combination with 5HT2A Agonist Psilocybin, on COX-2, IL-6, and IL-8 in *In Vitro* HSIEC Cell Assays

[0492] The anti-inflammatory effects of TRP agonists carvacrol, piperine, and cinnamaldehyde, as evaluated based on their effects on COX-2, IL-6, and IL-8 are described below and shown in FIGs. 39-53. FIG. 39 illustrates the structures of TRP agonists carvacrol, piperine, and cinnamaldehyde. Carvacrol is a TRPA1, TRPM7, and TRPV3 agonist. Piperine is a TRPA1 agonist and a TRPV3 agonist. Cinnamaldehyde is a TRPA1 agonist. Based on the mechanism of action of these TRP agonists, it was hypothesized that all three would have some anti-inflammatory activity.

EXAMPLE 34

[0493] In vitro HSIEC Cell Assay Example 34 is illustrated in FIG. 40, which shows the effects of escalating doses of 2.5 μM, 5 μM, 10 μM, 20 μM, and 40 μM carvacrol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 40, doses of carvacrol of 2.5 μM, 5 μM, and 10 μM resulted in the reduction of inflammatory marker COX-2, with 5 μM carvacrol reducing COX-2 to the greatest extent. Doses of carvacrol of 20 μM and 40 μM resulted in the increase of inflammatory marker COX-2.

EXAMPLE 35

[0494] *In vitro* HSIEC Cell Assay Example 35 is illustrated in FIG. 41, which shows the separate and combined effects of psilocybin and carvacrol on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 41, combinations of psilocybin and carvacrol resulted in the reduction of inflammatory marker COX-2, with the combinations of 20 μM psilocybin with 2.5 μM carvacrol reducing COX-2 to the greatest extent, thus indicating synergistic effects of psilocybin and carvacrol on COX-2. A combination of 20 μM psilocybin with 2.5 μM carvacrol reducing COX-2 by 77% more than 20 μM psilocybin alone.

EXAMPLE 36

[0495] *In vitro* HSIEC Cell Assay Example 36 is illustrated in FIG. 42A, which shows the effects of psilocybin on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 42A, psilocybin resulted in the reduction of inflammatory marker IL-6, with 20 μM and 40 μM psilocybin reducing IL-6 to the greatest extent.

EXAMPLE 37

[0496] *In vitro* HSIEC Cell Assay Example 37 is illustrated in FIG. 42B, which shows the separate and combined effects of psilocybin on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 42B, most dosages of psilocybin resulted in the reduction of inflammatory marker IL-8, with 10 μM and 40 μM psilocybin reducing IL-8 to the greatest extent.

EXAMPLE 38

[0497] In vitro HSIEC Cell Assay Example 38 is illustrated in FIG. 43A, which shows the effects of escalating doses of 2.5 μM, 5 μM, 10 μM, 20 μM, and 40 μM carvacrol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 43A, doses of carvacrol of 10 μM resulted in the reduction of inflammatory marker IL-6. Doses of 2.5 μM, 5 μM, 20 μM, and 40 μM carvacrol resulted in no substantial decrease or in the increase of inflammatory marker IL-6.

EXAMPLE 39

[0498] In vitro HSIEC Cell Assay Example 39 is illustrated in FIG. 43B, which shows the effects of escalating doses of 2.5 μM, 5 μM, 10 μM, 20 μM, and 40 μM carvacrol on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 43B, all doses of carvacrol resulted in the reduction of inflammatory marker IL-8. Doses of 20 μM, and 40 μM carvacrol resulted in the greatest decrease of inflammatory marker IL-8.

EXAMPLE 40

[0499] *In vitro* HSIEC Cell Assay Example 40 is illustrated in FIG. 44, which shows the separate and combined effects of psilocybin and carvacrol on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 44, combinations of psilocybin and carvacrol resulted in the reduction of inflammatory marker IL-6, with the combinations of 40 μM psilocybin with 2.5 μM carvacrol reducing IL-6 to the greatest extent, thus indicating synergistic effects of psilocybin and carvacrol on IL-6. A combination of 40 μM psilocybin with 2.5 μM carvacrol reduced IL-6 by 63% more than 40 μM psilocybin alone.

EXAMPLE 41

[0500] *In vitro* HSIEC Cell Assay Example 41 is illustrated in FIG. 45, which shows the separate and combined effects of psilocybin and carvacrol on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 45, combinations of psilocybin and carvacrol resulted in the reduction of inflammatory marker IL-8, with the combinations of 40 μM psilocybin with 2.5 μM carvacrol reducing IL-8 to the greatest extent, thus indicating synergistic effects of psilocybin and carvacrol on IL-8. A combination of 40 μM psilocybin with 2.5 μM carvacrol reducing IL-8 by 55% more than 40 μM psilocybin alone.

EXAMPLE 42

[0501] In vitro HSIEC Cell Assay Example 42 is illustrated in FIG. 46, which shows the effects of escalating doses of 2.5 μM, 5 μM, 10 μM, 20 μM, and 40 μM piperine on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 46, doses of piperine of 2.5 μM and 5 μM resulted in the reduction of inflammatory marker COX-2, with 2.5 μM piperine reducing COX-2 to the greatest extent. Doses of piperine of 10 μM, 20 μM, and 40 μM resulted in the increase of inflammatory marker COX-2.

EXAMPLE 43

[0502] *In vitro* HSIEC Cell Assay Example 43 is illustrated in FIG. 47, which shows the separate and combined effects of psilocybin and piperine on COX-2 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 47, combinations of psilocybin and piperine resulted in the reduction of inflammatory marker COX-2, with the combinations of 20 μM psilocybin with 2.5 μM piperine reducing COX-2 to the greatest extent, thus indicating synergistic effects of psilocybin and piperine on COX-2. A combination of 20 μM psilocybin with 2.5 μM piperine reducing COX-2 by 93% more than 20 μM psilocybin alone.

EXAMPLE 44

[0503] *In vitro* HSIEC Cell Assay Example 44 is illustrated in FIG. 48A, which shows the effects of piperine on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 48A, piperine resulted in the reduction of inflammatory marker IL-6, with 5 μM and 40 μM piperine reducing IL-6 to the greatest extent.

EXAMPLE 45

[0504] *In vitro* HSIEC Cell Assay Example 45 is illustrated in FIG. 48B, which shows the effects of piperine on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 48B, most dosages of piperine resulted in the reduction of inflammatory marker IL-8, with 10 μM, 20 μM, and 40 μM piperine reducing IL-8 to the greatest extent.

EXAMPLE 46

[0505] *In vitro* HSIEC Cell Assay Example 46 is illustrated in FIG. 49, which shows the separate and combined effects of psilocybin and piperine on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 49, combinations of psilocybin and piperine resulted in the reduction of inflammatory marker IL-6, with the combinations of 20 μM or 40 μM psilocybin with 2.5 μM piperine reducing IL-6 to the greatest extent, thus indicating synergistic effects of psilocybin and piperine on IL-6. A

combination of 20 μM psilocybin with 2.5 μM piperine reduced IL-6 by 92% more than 20 μM psilocybin, and 40 μM psilocybin with 2.5 μM piperine reduced IL-6 by 91% more than 40 μM psilocybin.

EXAMPLE 47

[0506] *In vitro* HSIEC Cell Assay Example 47 is illustrated in FIG. 50, which shows the separate and combined effects of psilocybin and piperine on IL-8 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 50, combinations of psilocybin and piperine resulted in the reduction of inflammatory marker IL-8, with the combinations of 20 μM or 40 μM psilocybin with 2.5 μM piperine reducing IL-8 to the greatest extent, thus indicating synergistic effects of psilocybin and piperine on IL-8. A combination of 20 μM psilocybin with 2.5 μM piperine reduced IL-8 by 44% more than 20 μM psilocybin, and 40 μM psilocybin with 2.5 μM piperine reduced IL-8 by 72% more than 40 μM psilocybin.

EXAMPLE 48

[0507] *In vitro* HSIEC Cell Assay Example 48 is illustrated in FIG. 51, which shows the effects of escalating doses of 0.5 μM, 1.25 μM, 2.5 μM, and 5 μM cinnemaldehyde on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 51, doses of cinnemaldehyde of 0.5 μM and 2.5 μM resulted in the reduction of inflammatory marker IL-6. Doses of 1.25 μM and 5 μM cinnemaldehyde resulted in no substantial decrease or in the increase of inflammatory marker IL-6.

EXAMPLE 49

[0508] *In vitro* HSIEC Cell Assay Example 49 is illustrated in FIG. 52, which shows the separate and combined effects of psilocybin and cinnemaldehyde on IL-6 in the HSIEC cells treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 52, combinations of psilocybin and cinnemaldehyde resulted in the reduction of inflammatory marker IL-6, with the combination of 10 μM psilocybin with 0.5 μM cinnemaldehyde showing synergistic effects of psilocybin and cinnemaldehyde on IL-6. A combination of

10 μM psilocybin with 0.5 μM cinnemaldehyde reduced IL-6 by 18% more than 10 μM psilocybin alone.

In Vitro Examples 50-51 Showing Effects of 5HT2A Agonists and/or TRP Agonists on Inflammatory Markers on 3-Dimensional Intestinal Tissue Model

Overview of Methods

[0509] Model: An EpiIntestinal tissue model (Mat Tek) was used as inflammation model that exhibits *in vivo*-like growth and morphological characteristics, in which cells sustain differentiation and metabolic status similar to those of human intestinal epithelium.

[0510] Induction of Inflammation in 3D Tissue Assays: One Mat Tek model was exposed to 10 ng/ml (i.e., the concentration was shown to effectively induce inflammation in the HSIEC assays described above) of TNF/IFN for periods of time ranging from 0-72 hours. GAPDH was used as a reference housekeeping marker for relative densitometry measures. As shown in FIG. 53, the greatest inflammatory effect was observed at 12 hours after treatment with TNF-α/IFN-γ. Thus, the anti-inflammatory potential of the molecules and formulations of interest were evaluated at 12 hours post-TNF-α/IFN-γ treatment in the Mat Tek 3D tissue assays described below. Ethanol was used as a vehicle for dilution and as a negative control showing the amount of the inflammatory marker present when inflammation was not induced.

EXAMPLES 50–51

Effects of Combinations of 5HT2A Agonist Psilocybin with Capsaicin on COX-2 and IL-6 in *In Vitro* 3D Tissue Assays

[0511] The anti-inflammatory effects of combinations of the 5HT2A agonist psilocybin with TRP agonist capsaicin, as evaluated based on their effects on COX-2 and IL-6, are described below and shown in FIGs. 54-55. Based on the mechanism of action of the 5HT2A agonist psilocybin and capsaicin, it was hypothesized that combinations of psilocybin and 4-ACO-DMT with capsaicin would have synergistic effects on COX-2 and IL-6 in 3D tissue assays.

EXAMPLE 50

[0512] *In vitro* 3D Tissue Assay Example 50 is illustrated in FIG. 54, which shows the separate and combined effects of psilocybin and capsaicin on COX-2 in the 3D Mat Tek tissue model treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 54, combinations of psilocybin and capsaicin resulted in the reduction of inflammatory marker COX-2, with the combinations of 10 μM, 20 μM, and 40 μM psilocybin with 0.5 μM capsaicin reducing COX-2 to the greatest extent, thus indicating synergistic effects of psilocybin and capsaicin on COX-2. A combination of 40 μM psilocybin with 0.5 μM capsaicin reduced COX-2 by 91% more than 40 μM psilocybin alone.

EXAMPLE 51

[0513] *In vitro* Assay Example 51 is illustrated in FIG. 55, which shows the separate and combined effects of psilocybin and capsaicin on IL-6 in the 3D Mat Tek tissue model treated with TNF-α/IFN-γ as described above. As can be seen in FIG. 55, combinations of psilocybin and capsaicin resulted in the reduction of inflammatory marker IL-6, with the combinations of 10 μM, 20 μM, and 40 μM psilocybin with 0.5 μM capsaicin reducing IL-6 to the greatest extent, thus indicating synergistic effects of psilocybin and capsaicin on IL-6. A combination of 10 μM psilocybin with 0.5 μM capsaicin reduced IL-6 by 31% more than 10 μM psilocybin.

In Vitro Examples 52-59 Showing Effects of 5HT2A Agonists and/or TRP Agonists on Markers of Depression and Inflammatory Markers in A-172 Glioblastoma Cells

Overview of Methods

[0514] This experiment was designed to explore the synergistic interaction of 5HT2A agonist and a TRP agonists on receptors in the brain that are associated with depression and/or inflammation. A-172 neuronal cells are glioblastoma (cancer) cells. The development of an inflammatory microenvironment is considered important to the initiation and progression of glioblastoma; however, therapeutic approaches to target inflammation have previously been limited. The abnormal function of IL-6 and IL-8 has been predicted to lead to glioblastoma. The effects of psilocybin and eugenol, alone or in combination, on GABA/BDNF (markers related to depression in which patients are often deficient) and IL-6 and IL-8 (markers of inflammation) were analyzed for potential to

reduce inflammatory markers and simultaneously increase brain markers associated with depression.

[0515] MTT Cell Viability Assay: An MTT assay evaluating the effects of psilocybin and eugenol on cellular metabolic activity was conducted on the A-172 cells in the manner described above with respect to the MTT assay conducted on the HSIEC cells. As shown in Table 50 below, the 80 μM dose of psilocybin resulted in a modest increase in cell growth, while eugenol was observed to have a slight inhibitory effect. Thus, as with the HSIEC cells, relatively low doses of the 5HT2A agonists and the TRP agonists were used with the A-172 cells as described in the Examples below.

Table 50: Cellular Metabolic Activity in A-172 Cells Treated with Compounds of Interest

MTT in A172 Cells						
Psilocybin		0	24 h	48 h	72 h	96 h
Control	EtOH	0.092	0.149	0.236	0.341	0.638
	5μM	0.090	0.155	0.253	0.374	0.530
	10μM	0.090	0.181	0.269	0.363	0.577
	20μM	0.082	0.201	0.303	0.370	0.636
	40μM	0.086	0.287	0.369	0.457	0.703
	80μM	0.084	0.469	0.528	0.586	0.871
Eugenol		0	24 h	48 h	72 h	96 h
Control	EtOH	0.092	0.149	0.236	0.341	0.638
	10μM	0.084	0.137	0.234	0.329	0.533
	25μM	0.083	0.153	0.266	0.318	0.557
	50μM	0.086	0.146	0.229	0.327	0.542
	100μM	0.082	0.170	0.230	0.322	0.516
	200μM	0.089	0.170	0.224	0.313	0.431
	400μM	0.088	0.173	0.208	0.272	0.422
Psilocybin + Eugenol		0	24 h	48 h	72 h	96 h
Control	EtOH	0.123	0.197	0.269	0.430	0.316
	25μM EUG	0.134	0.202	0.297	0.473	0.319
	5μM PSI	0.132	0.199	0.261	0.438	0.321
	5μM PSI+μm25 EUG	0.131	0.201	0.280	0.436	0.288
	10μM PSI	0.139	0.206	0.279	0.431	0.311
	10μM PSI+25μM EUG	0.138	0.195	0.293	0.332	0.251
	20μM PSI	0.143	0.204	0.282	0.451	0.270
	20μM PSI+25μM EUG	0.139	0.199	0.299	0.432	0.342

[0516] The A-172 cells already had elevated content of COX-2 and IL-6 compared to normal cells due to aberrant genetic regulation. Thus, unlike the experiments on HSIEC cells described above, no inflammatory treatment was applied to the A-172 cells. The A-172 cells were grown to ~60% confluence on T-25 flasks to allow a 96-hour duration of exposure of the cells to the compounds of interest

EXAMPLE 52

[0517] In vitro A-172 Cell Assay Example 52 is illustrated in FIG. 56A, which shows the effects of escalating doses of 2.5 μM, 5 μM, 10 μM, 20 μM, and 40 μM psilocybin on GABA in the A-172 cells described above. As can be seen in FIG. 56A, doses of psilocybin of 2.5 μM, 5 μM, and 20 μM resulted in the increase of depression-related marker GABA, with the 5 μM dose resulting in the greatest increase. Doses of psilocybin of 10 μM and 40 μM resulted in the decrease of GABA.

EXAMPLE 53

[0518] In vitro A-172 Cell Assay Example 53 is illustrated in FIG. 56B, which shows the effects of escalating doses of 10 μM, 25 μM, 50 μM, and 100 μM eugenol on depression-related marker GABA in the A-172 cells described above. As can be seen in FIG. 56B, doses of eugenol of 25 μM and 50 μM resulted in the increase of GABA. Doses of eugenol of 10 μM and 100 μM had little effect on GABA.

EXAMPLE 54

[0519] In vitro A-172 Cell Assay Example 54 is illustrated in FIG. 57A, which shows the effects of escalating doses of 2.5 μM, 5 μM, 10 μM, and 20 μM psilocybin on depression-related marker BDNF in the A-172 cells described above. As can be seen in FIG. 57A, doses of psilocybin of 2.5 μM, 5 μM, and 10 μM resulted in the increase of BDNF. Doses of psilocybin of 20 μM resulted in the decrease of BDNF.

EXAMPLE 55

[0520] In vitro A-172 Cell Assay Example 55 is illustrated in FIG. 57B, which shows the effects of escalating doses of 10 μM, 25 μM, 50 μM, and 100 μM eugenol on depression-related marker BDNF in the A-172 cells described above. As can be seen in FIG. 57B, doses of 10 μM, 25 μM, 50 μM, and 100 μM of eugenol all resulted in the increase of BDNF, with the 100 μM dose resulting in the greatest increase in BDNF.

EXAMPLE 56

[0521] *In vitro* A-172 Cell Assay Example 56 is illustrated in FIG. 58A, which shows the separate and combined effects of psilocybin and eugenol on COX-2 in the A-172 cells described above. As can be seen in FIG. 58A, the combination of 5 μM psilocybin with 25 μM eugenol resulted in a greater reduction of inflammatory marker COX-2 than 5 μM psilocybin alone, while 25 μM eugenol alone resulted in an increase in COX-2. This indicates the synergistic effects of psilocybin and eugenol on COX-2. A combination of 5 μM psilocybin with 25 μM eugenol reduced COX-2 by 51% more than 5 μM psilocybin alone and by 71% more than 25 μM eugenol alone.

EXAMPLE 57

[0522] *In vitro* A-172 Cell Assay Example 57 is illustrated in FIG. 58B, which shows the separate and combined effects of psilocybin and eugenol on GABA in the A-172 cells described above. As can be seen in FIG. 58B, the combination of 5 μM psilocybin with 25 μM eugenol resulted in a greater increase in depression-related marker GABA than 5 μM psilocybin or 25 μM eugenol alone, thus indicating the synergistic effects of psilocybin and eugenol on GABA. A combination of 5 μM psilocybin with 25 μM eugenol increased GABA by 64% more than 5 μM psilocybin alone and by 43% more than 25 μM eugenol alone.

EXAMPLE 58

[0523] *In vitro* A-172 Cell Assay Example 58 is illustrated in FIG. 58C, which shows the separate and combined effects of psilocybin and eugenol on IL-6 in the A-172 cells

described above. As can be seen in FIG. 58C, the combination of 5 μM psilocybin with 25 μM eugenol resulted in a greater reduction of inflammatory marker IL-6 than 5 μM psilocybin or 25 μM eugenol alone, thus indicating the synergistic effects of psilocybin and eugenol on IL-6. Indeed, psilocybin and eugenol together resulted in approximately 40% decrease in IL-6 compared to psilocybin alone. A combination of 5 μM psilocybin with 25 μM eugenol reduced IL-6 by 38% more than 5 μM psilocybin alone and by 14% more than 25 μM eugenol alone.

EXAMPLE 59

[0524] *In vitro* A-172 Cell Assay Example 59 is illustrated in FIG. 58D, which shows the separate and combined effects of psilocybin and eugenol on BDNF in the A-172 cells described above. As can be seen in FIG. 58D, the combination of 5 μM psilocybin with 25 μM eugenol resulted in a greater increase in depression-related marker BDNF than 5 μM psilocybin or 25 μM eugenol alone, thus indicating the synergistic effects of psilocybin and eugenol on BDNF. A combination of 5 μM psilocybin with 25 μM eugenol increased BDNF by 51% more than 5 μM psilocybin alone and by 133% more than 25 μM eugenol alone.

EXAMPLE 60

[0525] Psilocybin combined with Eugenol are selected for further study. Combinations of these two pure compounds demonstrate efficacy as an anti-inflammatory, with increases in brain markers GABA and BDNF. The combination also lacks toxic effects in the MTT assay. The safety and pharmacokinetics of both molecules is well established. Formulations combining these two active molecules are created. Eugenol is a liquid that can be applied directly to a powder as a concentrate or can be diluted in ethanol (or another alcohol) in order to achieve a more consistent mixture at higher volumes. Pure Psilocybin crystal can be added and this mixture can be consumed directly as a tincture to achieve the desired dose (mg) as seen in Table 51.

[0526] Alternatively, a eugenol/alcohol solution of desired concentration can be directly applied to the dried fruiting bodies of psilocybin fungi. The ethanol is then allowed to evaporate at low temperature (<35 °C) as it has a significantly lower vapor and boiling

point than eugenol, leaving the eugenol infused in the fungal biomass. This can then be homogenized for even distribution during production. Various ratios can be made as seen in Table 51.

[0527] Alternatively, both the pure compounds (~99%) Psilocybin and Eugenol can be formulated to achieve the desired concentrations of both ingredients. In this case, due to the small amounts required, binders, fillers or excipients are likely required to fill out the formulations. The liquid alcohol based solution again can be applied to the powder, dehydrated and homogenized before final productization into a pill or tablet format. Pure psilocybin and pure eugenol can also be applied directly to any number of carriers binders, fillers, excipients or flavoring agents included in the final formulation. Psilocybin may also be first added to the eugenol and/or eugenol ethanol blend and applied to a filler substrate. Formulations outlining the desired concentrations and ratios can be found in Table 51.

Table 51: Example Formulations of Psilocybin + Eugenol

Product	Psilocybin	Eugenol (99%+)	Ratio Range (between)	Carriers/Fillers/ Binders/Excipients/ Flavoring Agents	Final Mass or Volume
Mushroom-based pill	100 mg-300 mg @1%	1-3 µL (mg)	3:1 to 1:3	none	101-303 mg
	100 mg-300 mg @1%	10-30 µL (mg)	1:10 to 3:10	0-190 mg	300-330 mg
	100 mg @ 1%	100-300 µL (mg)	1:100 to 1:300	100mg-300 mg	500 mg
Pure Pressed Tablet	1 mg-3 mg	1-3 µL (mg)	3:1 to 1:3	294-298 mg	300 mg
	1 mg-3 mg	10-30 µL (mg)	1:10 to 3:10	267-289 mg	300 mg
	1 mg-3 mg	100 µL (mg)	1:33 to 1:100	197-199 mg	300 mg
Pure Solid Capsule	1 mg-3 mg	1-3 µL (mg)	3:1 to 1:3	294-298 mg	300 mg
	1 mg-3 mg	10-30 µL (mg)	1:10 to 3:10	267-289 mg	300 mg
	1 mg-3 mg	100 µL (mg)	1:100 to 1:300	197-199 mg	300 mg
Pure Tincture	1 mg-3 mg	1-3 µL (mg)	3:1 to 1:3	244-248 µL	0.25 mL
	1 mg-3 mg	10-30 µL (mg)	1:10 to 3:10	217-239 µL	0.25 mL
	1 mg-3 mg	100 µL (mg)	1:33 to 1:100	147-149 µL	0.25 mL

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Examples Only

[0609] In the preceding description, for purposes of explanation, numerous details are set forth in order to provide a thorough understanding of the embodiments. However, it will be apparent to one skilled in the art that these specific details are not required. The above-described embodiments are intended to be examples only. Alterations, modifications and variations can be effected to the particular embodiments by those of skill in the art. The scope of the claims should not be limited by the particular embodiments set forth herein, but should be construed in a manner consistent with the specification as a whole.

WHAT IS CLAIMED IS:

1. A composition comprising a therapeutic combination of a 5HT2A agonist compound and at least one TRP agonist compound,

wherein the therapeutically effective amount of the 5HT2A agonist is between about 1 μg and about 300 mg; and the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.01 mg and about 300 mg.

2. The composition of claim 1, wherein the 5HT2A agonist compound is selected from the group consisting of a tryptamine, an ergoline, a phenethylamine, and a phenylpropanoid.

3. The composition of claim 2, wherein the tryptamine is a 4-substituted tryptamine.

4. The composition of claim 3, wherein the 4-substituted tryptamine is a 4-substituted DMT compound.

5. The composition of claim 4, wherein the 4-substituted DMT compound is selected from the group consisting of 3-[2-(dimethylamino)ethyl]-4-phosphoryloxyindole (psilocybin), 3-[2-(dimethylamino)ethyl]- 4-hydroxyindole (psilocin), 3-[2-(dimethylamino)ethyl]-4-acetoxyindole (psilacetin), and any suitable salt of any of the foregoing.

6. 6. The composition of claim 3, wherein the 4-substituted tryptamine is selected from the group consisting of 3-[2(trimethylamino)ethyl]-4-phosphoryloxyindole (aeruginascin), 3-[2-(methylamino)ethyl]-4-phosphoryloxyindole (baeocystin), 3-[2-(methylamino)ethyl]-4-hydroxyindole, 3-[2-(amino)ethyl]-4-hydroxyindole (norpsilocin), 3-[2-(amino)ethyl]-4-phosphoryloxyindole (norbaeocystin), and any suitable salt of any of the foregoing.

7. The composition of any one of claims 3 to 6, wherein the 4-substituted tryptamine is derived from fungi.

8. The composition of claim 7, wherein the fungi is a species of a genus selected from the group consisting of *Gymnopilus*, *Inocybe*, *Panaeolus*, *Pholiotina*, *Pluteus*, and *Psilocybe*.

9. The composition of claim 7 or 8, wherein the fungi is selected from the group consisting of *C. cyanopus*, *C. siligineoides* and *C. kuehneriana*; *Copelandia* species including *C. affinis*, *C. anomala*, *C. bispora*, *C. cambodginiensis*, *C. chlorocystis*, *C. cyanescens*, *C. lentisporus*, *C. tirunelveliensis*, *C. tropica*, *C. tropicalis* and *C. westii*; *G. steglichii*; *G. thiersii*, *G. aeruginosus*, *G. braendlei*, *G. cyanopalmicola*, *G. intermedius*, *G. junonius*, *G. lateritius*, *G. liquiritiae*, *G. luteofolius*, *G. luteoviridis*, *G. luteus*, *G. purpuratus*, *G. subpurpuratus*, *G. validipes* and *G. viridans*; *I. aeruginascens*, *I. aeruginascens*, *I. coelestium*, *I. corydalina*, *I. corydalina var. corydalina*, *I. corydalina var. erinaceomorpha*, *I. haemacta* and *I. tricolor*; *P. cinctulus*, *P. affinis*, *P. africanus*, *P. bisporus*, *P. cambodginiensis*, *P. castaneifolius*, *P. chlorocystis*, *P. cinctulus*, *P. cyanescens*, *P. fimicola*, *P. lentisporus*, *P. microsporus*, *P. moellerianus*, *P. olivaceus*, *P. rubricaulis*, *P. tirunelveliensis*, *P. tropicalis* and *P. venezolanus*; *P. cyanopus* and *P. smithii*; *P. americanus*, *P. albostipitatus*, *P. americanus*, *P. cyanopus*, *P. glaucus*, *P. glaucotinctus*, *P. nigroviridis*, *P. phaeocyanopus*, *P. salicinus*, *P. saupei* and *P. villosus*; *P. tampanensis*, *P. acutipilea*, *P. allenii*, *P. angustipleurocystidiata*, *P. antioquiensis*, *P. atlantis*, *P. aquamarina*, *P. armandii*, *P. aucklandii*, *P. atlantis*, *P. aztecorum*, *P. aztecorum var. aztecorum*, *P. aztecorum var. bonetii*, *P. azurescens*, *P. baeocystis*, *P. banderillensis*, *P. bispora*, *P. brasiliensis*, *P. brunneocystidiata*, *P. cubensis*, *P. caeruleoannulata*, *P. caerulescens*, *P. caerulescens var. caerulescens*, *P. caerulescens var. ombrophila*, *P. caerulipes*, *P. callosa*, *P. carbonaria*, *P. caribaea*, *P. chuxiongensis*, *P. collybioides*, *P. columbiana*, *P. cordispora*, *P. cubensis*, *P. cyanescens*, *P. cyanofibrillosa*, *P. dumontii*, *P. egonii*, *P. fagicola*, *P. fagicola var. fagicola*, *P. fagicola var. mesocystidiata*, *P. farinacea*, *P. fimetaria*, *P. fuliginosa*, *P. furtadoana*, *P. tampanensis*, *P. galindoi*, *P. gallaeciae*, *P. graveolens*, *P. guatapensis*, *P. guilartensis*, *P. heimii Guzmán*, *P. herrerae Guzmán*, *P. hispanica Guzmán*, *P. hoogshagenii*, *P. hoogshagenii var. hoogshagenii*, *P. hoogshagenii var. convexa*, *P. inconspicua*, *P. indica*, *P. isabelae*, *P. jacobsii*, *P. jaliscana*, *P. kumaenorum*, *P. laurae*, *P. lazoi*, *P. liniformans*, *P. liniformans var. liniformans*, *P. liniformans var. americana*, *P. mexicana*, *P. mairei*, *P. makarorae*, *P. mammillata*, *P. medullosa*, *P. meridensis*, *P. meridionalis*, *P. mescaleroensis*, *P. mexicana*, *P. moseri*, *P. muliercula*, *P. naematoliformis*, *P. natalensis*, *P. natarajanii*, *P. neorhombispora*, *P. neoxalapensis*, *P. ovoideocystidiata*, *P. ovoideocystidiata*, *P. papuana*, *P. paulensis*, *P. pelliculosa*, *P. pintonii*, *P. pleurocystidiosa*, *P. plutonia*, *P. portoricensis*, *P. pseudoaztecorum*, *P. puberula*, *P.*

quebecensis, P. ricki, P. rostrata, P. rzedowskii, P. samuiensis, P. schultesii, P. semilanceata, P. septentrionalis, P. serbica, P. sierrae , P. silvatica, P. singeri, P. squamosa, P. strictipes, P. stuntzii, P. subacutipilea, P. subaeruginascens, P. subaeruginosa, P. subbrunneocystidiata, P. subcaerulipes, P. subcubensis, P. subpsilocybioides, P. subtropicalis, P. tampanensis, P. tampanensis, P. thaicordispora, P. thaiaerugineomaculans, P. thaiduplicatocystidiata, P. uruguayensis, P. uxpanapensis, P. venenata , P. villarrealiae, P. weraroa, P. wassoniorum, P. weilii, P. weldenii, P. weraroa, P. wrightii, P. xalapensis, P. yungensis, P. zapotecorum, P. zapotecoantillarum, P. zapotecocaribaea, and P. zapotecorum.

10. The composition of any one of claims 7 to 9, wherein the composition further comprises dried matter of the fungi, wherein the dried matter is selected from the group consisting of fruiting bodies, mycelia, sclerotia, and hyphae, or combinations thereof.

11. The composition of any one of claims 1 or 2, wherein the tryptamine is a 5-substituted tryptamine.

12. The composition of claim 11, wherein the 5-substituted tryptamine is selected from the group consisting of 5-methoxy-DMT (bufotenin), N-acetyl-5-methoxy tryptamine (melatonin), 5-hydroxy tryptamine (serotonin), 5-hydroxy-tryptophan (5-HTP), and any suitable salt of any of the foregoing.

13. The composition of any one of claims 1 or 2, wherein the 5HT2A agonist compound is an ergoline.

14. The composition of claim 13, wherein the ergoline is selected from the group consisting of D-lysergic acid ethylamide ("LAE"),D-lysergic acid beta-propanolamide, D-lysergic acid 2-butyl amide ("LSB"), D-lysergic acid 1-butanolamide, 1-methyl-D-lysergic acid butanolamide, D-lysergic acid 3-pentyl amide ("LSP"), D-N-morpholinyllysergamide ("LSM-775"), D-N-pyrrolidyllysergamide ("LPD-824"), (8β)-6-methyl-8-(piperidin-1-ylcarbonyl)-9,10-didehydroergoline ("LSD-Pip"), N,N-dimethyllysergamide ("DAM"), D-lysergic acid methylisopropyl amide ("LAMIDE"), D-lysergic acid 2,4-

dimethylazetidide ("LSZ"), LSD, D-1-acetyl-lysergic acid diethylamide ("ALD-52"), D-1-propionyl-lysergic acid diethylamide ("1P-LSD"), D-N1-butyryl-lysergic acid diethylamide ("1B-LSD"), D-N1-(cyclopropylmethanoyl)-lysergic acid diethylamide ("1cP-LSD"), D-N1-methyl-lysergic acid diethylamide ("MLD"), D-6-ethyl-6-nor-lysergic acid diethylamide ("ETH-LAD"), D-1-propionyl-6-ethyl-6-nor-lysergic acid diethyamide ("1P-ETH-LAD"), D-6-allyl-6-nor-lysergic acid diethylamide ("AL-LAD"), D-6-propyl-6-nor-lysergic acid diethylamide ("PRO-LAD"), D-6-isopropyl-6-nor-lysergic acid diethylamide ("IP-LAD"), D-6-propynyl-6-nor-lysergic acid diethylamide ("PARGY-LAD"), D-6-butyl-6-norlysergic acid diethylamide ("BU-LAD"), N,N-diallyllysergamide ("DAL") and D-N-ethyl-N-cyclopropyllysergamide ("ECPLA").

15. The composition of any one of claims 13 or 14, wherein the ergoline is derived from fungi or a plant.

16. The composition of claim 15, wherein the fungi or plant is a species selected from the group consisting of Claviceps purpurea, Rivea corymbosa, Ipomoea violacea, I. tricolor, I. purpurae, I. alba, Argeyreia nervosa, and a Periglandula species.

17. The composition of any one of claims 1 or 2, wherein the 5HT2A agonist compound is a phenethylamine.

18. The composition of claim 17, wherein the phenethylamine is selected from the group consisting of 3,4,5-trimethoxyphenethylamine (mescaline), trimethoxyamphetamine ("TMA"), 4-bromo-2,5-dimethoxybenzeneethanamine ("2C-B"), 4-bromo-2,5-dimethoxyamphetamine ("DOB"), 4-methyl-2,5-dimethoxyamphetamine ("DOM"), 4-methyl-2,5-dimethoxybenzeneethanamine ("2C-D"), 3,4-methylenedioxyamphetamine ("MDA"), N-methyl-3,4-methylenedioxyamphetamine ("MDMA").

19. The composition of any one of claims 17 or 18, wherein the phenethylamine is plant-derived.

20. The composition of claim 19, wherein the plant includes a species selected from the group consisting of *Lophophora williamsii*, *Trichocereus pachanoi, Echinopsis pachanoi, Trichocereus peruvianus, Echinopsis peruviana, Trichocereus bridgesii, Echinopsis lageniformis*, and *Trichocereus/Echinopsis scopulicola*.

21. The composition of any one of claims 1 or 2, wherein the 5HT2A agonist compound is a phenylpropanoid.

22. The composition of claim 21, wherein the phenylpropanoid is 1,2,3-timethoxy-5-(prop-2-en-1-yl)benzene (elemicin).

23. The composition of any one of claims 21 or 22, wherein the phenylpropanoid is plant-derived.

24. The composition of claim 23, wherein the plant is a species in the *Myristicaceae* family.

25. The composition of any one of claims 1 to 24, wherein the TRP agonist compound is selected from the group consisting of a capsiate, eugenol, elemicin, myrcene, piperine and gingerol.

26. The composition of claim 25, where the capsiate is capsaicin.

27. The composition of any one of claims 1 to 26, wherein the TRP agonist compound is plant-derived.

28. The composition of claim 27, wherein the plant includes one or more species selected from the group consisting of cayenne pepper, turmeric, clove, cinnamon, nutmeg, pepper, cannabis, bergamot and ginger.

29. The composition of any one of claims 1 to 28, wherein the TRP agonist compound is selected from the group consisting of a curcuminoid, cinnamaldehyde, alpha terpineol, thymol, piperine and allicin.

30. The composition of claim 29, wherein the curcuminoid is curcumin.

31. The composition of any one of claims 29 or 30, wherein the TRP agonist compound is plant-derived.

32. The composition of claim 31, wherein the plant includes one or more species selected from the group consisting of curcumin, cinnamon, turmeric, nutmeg, cannabis, thyme, pepper, garlic, and onion.

33. The composition of any one of claims 1 to 32, wherein the TRP agonist compound is selected from the group consisting of eugenol, cinnamaldehyde, carvacrol, thymol, menthol, and 1-8 cineole.

34. The composition of claim 33, wherein the TRP agonist compound is plant-derived.

35. The composition of claim 34, wherein the plant includes one or more species selected from the group consisting of turmeric, clove, cinnamon, pepper, nutmeg, cannabis, bergamot, oregano, thyme, cardamom, peppermint, and eucalyptus.

36. The composition of any one of claims 1 to 35, wherein the TRP agonist compound is selected from the group consisting of eugenol, β-caryophyllene, (-)-epicatechin, CBD, CBDA, CBGA, CBGV, THCV, THCVA, eriodictyol, cinnamaldehyde, incensole, boswellic acid, eucalyptol, and thymol.

37. The composition of claim 36, wherein the TRP agonist compound is plant-derived.

38. The composition of claim 37, wherein the plant includes one or more species selected from the group consisting of turmeric, clove, cinnamon, pepper, nutmeg, cannabis, bergamot, oregano, thyme, cardamom, peppermint, and eucalyptus.

39. The composition of any one of claims 1 to 5, 7 to 10, and 25 to 38, wherein the 5HT2A agonist compound is psilocybin, and wherein the therapeutically effective amount of psilocybin is between about 100 mg and about 300 mg.

40. The composition of any one of claims 1 to 5, 7 to 10, and 25 to 39, wherein the 5HT2A agonist is psilocybin, and wherein the therapeutically effective amount of psilocybin is between about 110 mg and about 290 mg, about 120 mg and about 280 mg, about 130 mg and about 270 mg, about 140 mg and about 260 mg, about 150 mg and about 250 mg, about 160 mg and about 240 mg, about 170 mg and about 230 mg, about 180 mg and about 220 mg, about 190 mg and about 210 mg, or about 195 mg and about 205 mg.

41. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is capsaicin in an amount of about 0.1 mg and about 1 mg, about 0.2 mg and bout 0.9 mg, about 0.3 mg and about 0.8 mg, about 0.4 and about 0.7 mg, or about 0.5mg and about 0.6 mg.

42. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is capsaicin, and wherein the composition comprises a ratio (w/w) of between about 22:1 and about 270,000:1 of the 5HT2A agonist to capsaicin, about 50:1 and about 200,000:1 of the 5HT2A agonist to capsaicin, about 100:1 and about 150,000:1 of the 5HT2A agonist to capsaicin, about 500:1 and about 100,000:1 of the 5HT2A agonist to capsaicin, about 1,000:1 and about 50,000:1 of the 5HT2A agonist to capsaicin, about 5,000:1 and about 40,000:1 of the 5HT2A agonist to capsaicin, about 10,000:1 and about 30,000:1 of the 5HT2A agonist to capsaicin, or about 15,000:1 and about 25,000:1 of the 5HT2A agonist to capsaicin.

43. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is eugenol in an amount of about 1 mg and about 300 mg, about 5 mg and

about 290 mg, about 10 mg and about 280 mg, about 15 mg and about 270 mg, about 20 mg and about 260 mg, about 25 mg and about 250 mg, about 30 mg and about 240 mg, about 35 mg and about 230 mg, about 40 mg and about 220 mg, about 40 mg and about 210 mg, about 50 mg and about 210 mg, about 55 mg and about 200 mg, about 60 mg and about 190 mg, about 65 mg and about 180 mg, about 70 mg and about 170 mg, about 75 mg and about 160 mg, about 80 mg and about 150 mg, about 85 mg and about 140 mg, about 90 mg and about 130 mg, about 95 mg and about 120 mg, or about 100 mg and about 110 mg.

44. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is eugenol, and wherein the composition comprises a ratio (w/w) of between about 0.6:1 and about 270,000:1 of the 5HT2A agonist to eugenol, about 1:1 and about 250,000:1 of the 5HT2A agonist to eugenol, about 5:1 and about 225,000:1 of the 5HT2A agonist to eugenol, about 10:1 and about 200,000:1 of the 5HT2A agonist to eugenol, about 50:1 and about 175,000:1 of the 5HT2A agonist to eugenol, about 100:1 and about 150,000:1 of the 5HT2A agonist to eugenol, about 150:1 and about 125,000:1 of the 5HT2A agonist to eugenol, about 300:1 and about 100,000:1 of the 5HT2A agonist to eugenol, about 500:1 and about 75,000:1 of the 5HT2A agonist to eugenol, about 1,000:1 and about 50,000:1 of the 5HT2A agonist to eugenol, about 5,000:1 and about 45,000:1 of the 5HT2A agonist to eugenol, about 10,000:1 and about 40,000:1 of the 5HT2A agonist to eugenol, about 15,000:1 and about 35,000:1 of the 5HT2A agonist to eugenol, or about 20,000:1 and about 30,000:1 of the 5HT2A agonist to eugenol.

45. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is curcumin in an amount of about 0.1 mg to about 10 mg, about 0.5 mg to about 9 mg, about 1 mg to about 8 mg, about 2 mg to about 7 mg, about 3 mg to about 6 mg, or about 4 mg to about 5 mg.

46. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is curcumin, and wherein the composition comprises a ratio (w/w) of between about 0.04:1 and about 10:1 of the 5HT2A agonist to curcumin, about 0.1:1 and about 9.5:1 of the 5HT2A agonist to curcumin, about 0.5:1 and about 9:1 of the 5HT2A agonist

to curcumin, about 1:1 and about 8.5:1 of the 5HT2A agonist to curcumin, about 1.5:1 and about 8:1 of the 5HT2A agonist to curcumin, about 2:1 and about 7.5:1 of the 5HT2A agonist to curcumin, about 2.5:1 and about 7:1 of the 5HT2A agonist to curcumin, about 3:1 and about 6.5:1 of the 5HT2A agonist to curcumin, about 3.5:1 and about 6:1 of the 5HT2A agonist to curcumin, about 4:1 and about 5.5:1 of the 5HT2A agonist to curcumin, or about 4.5:1 and about 5:1 of the 5HT2A agonist to curcumin.

47. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is β-caryophyllene, and wherein the composition comprises a ratio (w/w) of between about 0.33:1 and about 36:1 of the 5HT2A agonist to β-caryophyllene, about 1:1 and about 33:1 of the 5HT2A agonist to β-caryophyllene, about 3:1 and about 30:1 of the 5HT2A agonist to β-caryophyllene, about 5:1 and about 27:1 of the 5HT2A agonist to β-caryophyllene, about 7:1 and about 25:1 of the 5HT2A agonist to β-caryophyllene, about 10:1 and about 22:1 of the 5HT2A agonist to β-caryophyllene, about 15:1 and about 20:1 of the 5HT2A agonist to β-caryophyllene, or about 17:1 and about 18:1 of the 5HT2A agonist to β-caryophyllene.

48. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is cinnamaldehyde in an amount of between about 0.1 mg and about 10 mg, about 0.5 mg and about 9.5 mg, about 1 mg and about 9 mg, about 1.5 mg and about 8.5 mg, about 2 mg and about 8 mg, about 2.5 mg and about 7.5 mg, about 3 mg and about 7 mg, about 3.5 mg and about 6.5 mg, about 4 mg and about 6 mg, or about 4.5 mg and about 5.5 mg.

49. The composition of any one of claims 1 to 40, wherein the at least one TRP agonist compound is cinnamaldehyde, and wherein the composition comprises a ratio (w/w) of between about 0.5:1 and about 36:1 of the 5HT2A agonist to cinnamaldehyde, about 1:1 and about 33:1 of the 5HT2A agonist to cinnamaldehyde, about 3:1 and about 30:1 of the 5HT2A agonist to cinnamaldehyde, about 5:1 and about 27:1 of the 5HT2A agonist to cinnamaldehyde, about 7:1 and about 25:1 of the 5HT2A agonist to cinnamaldehyde, about 10:1 and about 22:1 of the 5HT2A agonist to cinnamaldehyde, about 15:1 and

about 20:1 of the 5HT2A agonist to cinnamaldehyde, or about 17:1 and about 18:1 of the 5HT2A agonist to cinnamaldehyde.

50. The composition of any one of claims 1 to 49, wherein the composition is formulated for oral administration.

51. The composition of claim 50, further comprising at least one pharmaceutically acceptable excipient, diluent, or filler.

52. The composition of any one of claims 50 or 51, wherein the composition is selected from the group consisting of a tablet, capsule, sachets, granules, sublingual film, buccal film, and a suspension.

53. A method for reducing inflammation in a subject, comprising administering the composition of any one of claims 1 to 52 to the subject.

54. The method of claim 53, wherein the inflammation is acute or chronic.

55. The method of any one of claims 53 or 54, comprising administering the composition 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 times per day.

56. The method of any one of claims 53 to 55, whereby the reduction in inflammation is measured by an 50% reduction of at least one biomarker selected from the group consisting of COX-2, interferon-γ, interleukin 1, interleukin-2, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor (TNF), and reactive oxygen species (ROS) when measured via densitometry.

57. The method of claim 56, wherein the ROS is inducible nitric oxide synthase (iNOS).

58. The method of any one of claims 53 to 57, wherein the subject is suffering from a condition selected from the group consisting of cancer, neurological disorder, diabetic

complications, mental health disorder (MHD), bone, muscular and skeletal disease, metabolic disorder, chronic inflammatory disorder and cardiovascular disease.

59. The method of claim 58, wherein the MHD is selected from depression, anxiety, post-traumatic stress disorder, schizophrenia, bipolar disorder, ADD, ADHD, borderline personality disorder, seasonal affective disorder, and premenstrual dysphoric disorder.

60. The method of claim 58, wherein the MHD is depression, and wherein the reduction in inflammation is accompanied by a reduction in at least one symptom of depression.

61. The method of claim 58, wherein the MHD is anxiety, and wherein the reduction in inflammation is accompanied by a reduction in at least one symptom of anxiety.

62. A method for reducing at least one biomarker in a mammalian cell, wherein the biomarker is selected from the group consisting of COX-2, interferon-γ, interleukin 1, interleukin-2, interleukin-6, interleukin-8, interleukin-10, tumor necrosis factor (TNF), and reactive oxygen species (ROS), comprising administering the composition of any one of claims 1 to 52 to a subject,

wherein administering the composition reduces the biomarker in the mammalian cell between about 10% and about 90%.

63. The method of claim 62, wherein the 5HT2A agonist is psilocybin in an amount of about 100 mg to about 300 mg, and wherein the TRP agonist is eugenol in an amount of about 100 mg to about 300 mg.

64. The method of claim 62 or 63, wherein the 5HT2A agonist is psilocybin in an amount of about 100 mg to about 300 mg, about 110 mg to about 290 mg, about 120 mg to about 280 mg, about 130 mg to about 270 mg, about 140 mg to about 260 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, or about 195 mg to about 205 mg, and wherein TRP agonist is eugenol in an amount of about 100 mg to about 300 mg, about 110 mg to about 290 mg, about 120 mg to about 280 mg, about 130 mg to about

270 mg, about 140 mg to about 260 mg, about 150 mg to about 250 mg, about 160 mg to about 240 mg, about 170 mg to about 230 mg, about 180 mg to about 220 mg, about 190 mg to about 210 mg, or about 195 mg to about 205 mg.

65. The method of any one of claims 62-64, wherein administering the composition reduces IL-6 in the mammalian cell by about an additional 20% relative to administering the therapeutically effective amount of psilocybin alone.

66. The method of claim 65, wherein administering the composition reduces IL-6 in the mammalian cell by about an additional 25% relative to administering the therapeutically effective amount of psilocybin alone.

67. The composition of any one of claims 1-38, wherein the therapeutically effective amount of the 5HT2A agonist is between about 10 µg and about 195 mg, about 50 µg and about 190 mg, about 100 µg and about 185 mg, about 200 µg and about 180 mg, about 300 µg and about 175 mg, about 400 µg and about 170 mg, about 500 µg and about 165 mg, about 600 µg and about 160 mg, about 700 µg and about 155 mg, about 800 µg and about 150 mg, about 900 µg and about 145 mg, about 1 mg and about 140 mg, about 5 mg and about 135 mg, about 10 mg and about 130 mg, about 15 mg and about 125 mg, about 20 mg and about 120 mg, about 25 mg and about 115 mg, about 30 mg and about 110 mg, about 35 mg and about 105 mg, about 40 mg and about 100 mg, about 45 mg and about 95 mg, about 50 mg and about 90 mg, about 55 mg and about 85 mg, about 60 mg and about 80 mg, or about 65 mg and about 75 mg.

68. The composition of any one of claims 1-38, wherein the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.1 mg and about 24 mg, about 0.5 mg and about 23 mg, about 1 mg and about 22 mg, about 2 mg and about 21 mg, about 3 mg and about 20 mg, about 4 mg and about 19 mg, about 5 mg and about 18 mg, about 6 mg and about 17 mg, about 7 mg and about 16 mg, about 8 mg and about 15 mg, about 9 mg and about 14 mg, about 10 mg and about 13 mg, or about 11 mg and about 12 mg.

69. The composition of any one of claims 1-38, wherein the therapeutically effective amount of the 5HT2A agonist is between about 10 μg and about 195 mg, about 50 μg and about 190 mg, about 100 μg and about 185 mg, about 200 μg and about 180 mg, about 300 μg and about 175 mg, about 400 μg and about 170 mg, about 500 μg and about 165 mg, about 600 μg and about 160 mg, about 700 μg and about 155 mg, about 800 μg and about 150 mg, about 900 μg and about 145 mg, about 1 mg and about 140 mg, about 5 mg and about 135 mg, about 10 mg and about 130 mg, about 15 mg and about 125 mg, about 20 mg and about 120 mg, about 25 mg and about 115 mg, about 30 mg and about 110 mg, about 35 mg and about 105 mg, about 40 mg and about 100 mg, about 45 mg and about 95 mg, about 50 mg and about 90 mg, about 55 mg and about 85 mg, about 60 mg and about 80 mg, or about 65 mg and about 75 mg, and wherein the therapeutically effective amount of the at least one TRP receptor agonist is between about 0.1 mg and about 24 mg, about 0.5 mg and about 23 mg, about 1 mg and about 22 mg, about 2 mg and about 21 mg, about 3 mg and about 20 mg, about 4 mg and about 19 mg, about 5 mg and about 18 mg, about 6 mg and about 17 mg, about 7 mg and about 16 mg, about 8 mg and about 15 mg, about 9 mg and about 14 mg, about 10 mg and about 13 mg, or about 11 mg and about 12 mg.

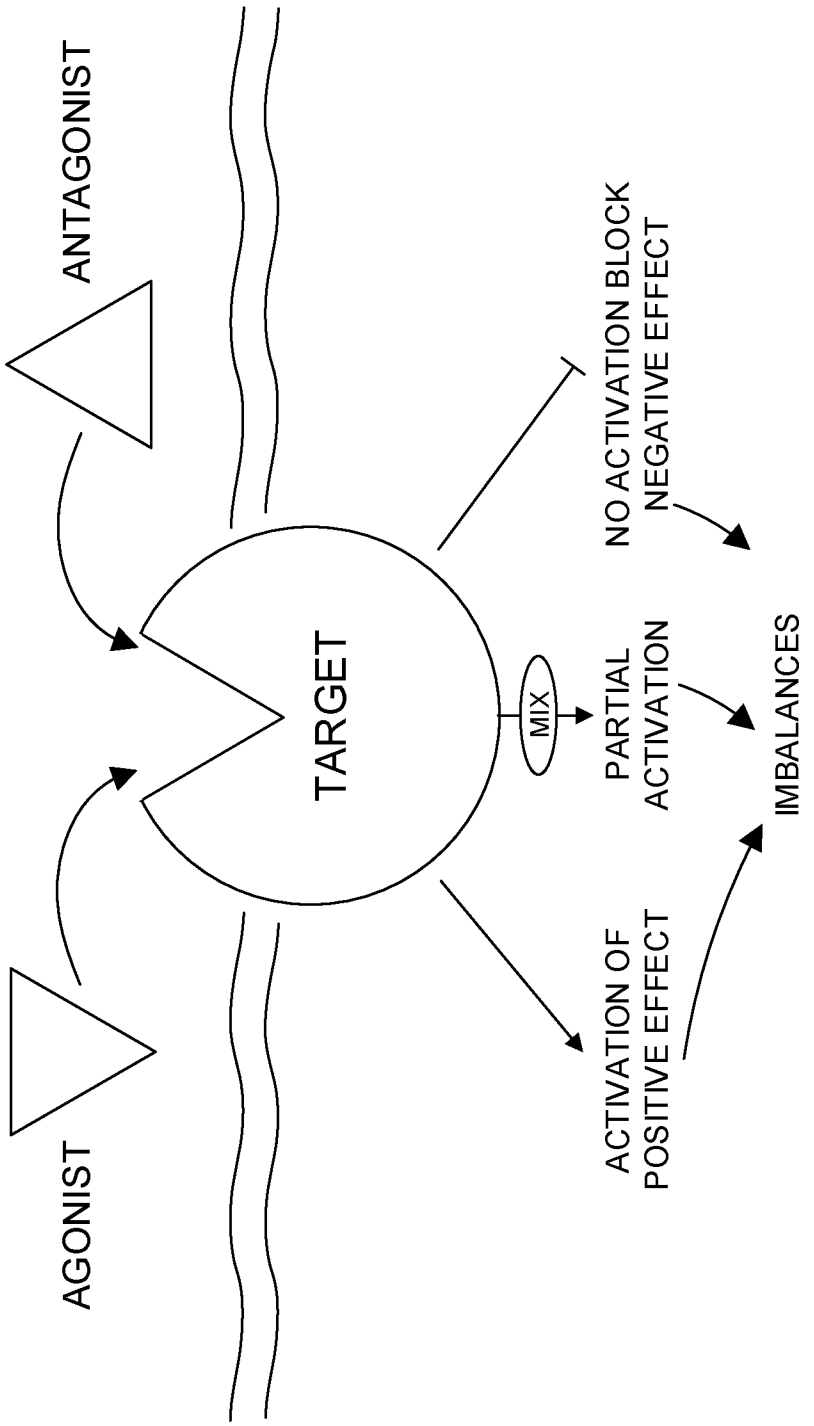
ANTAGONIST
AGONIST
TARGET
MIX
NO ACTIVATION BLOCK
NEGATIVE EFFECT
PARTIAL
ACTIVATION
ACTIVATION OF
POSITIVE EFFECT
IMBALANCES

FIG. 1

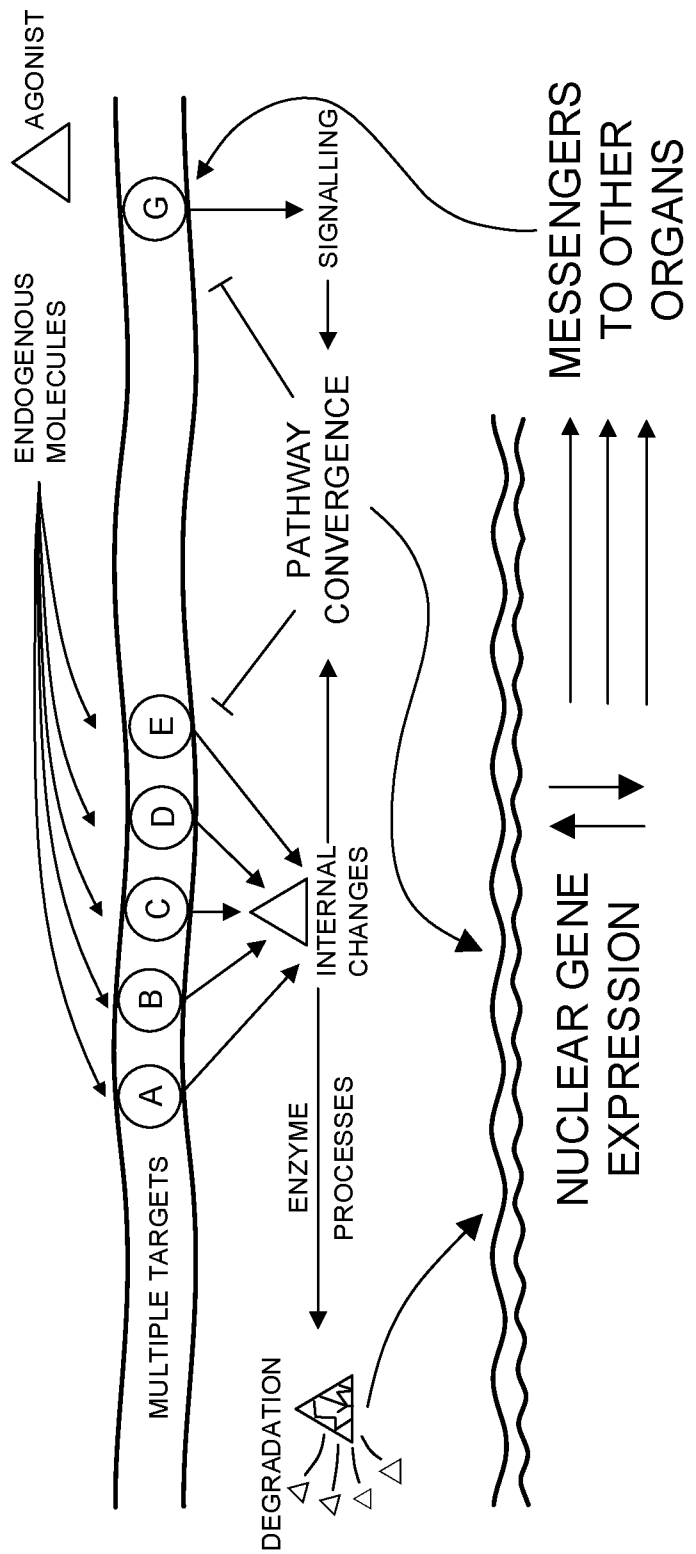
AGONIST
ENDOGENOUS MOLECULES
MULTIPLE TARGETS
A
B
C
D
E
G
SIGNALLING
PATHWAY CONVERGENCE
INTERNAL CHANGES
ENZYME
PROCESSES
DEGRADATION
MESSENGERS TO OTHER ORGANS
NUCLEAR GENE EXPRESSION

FIG. 2

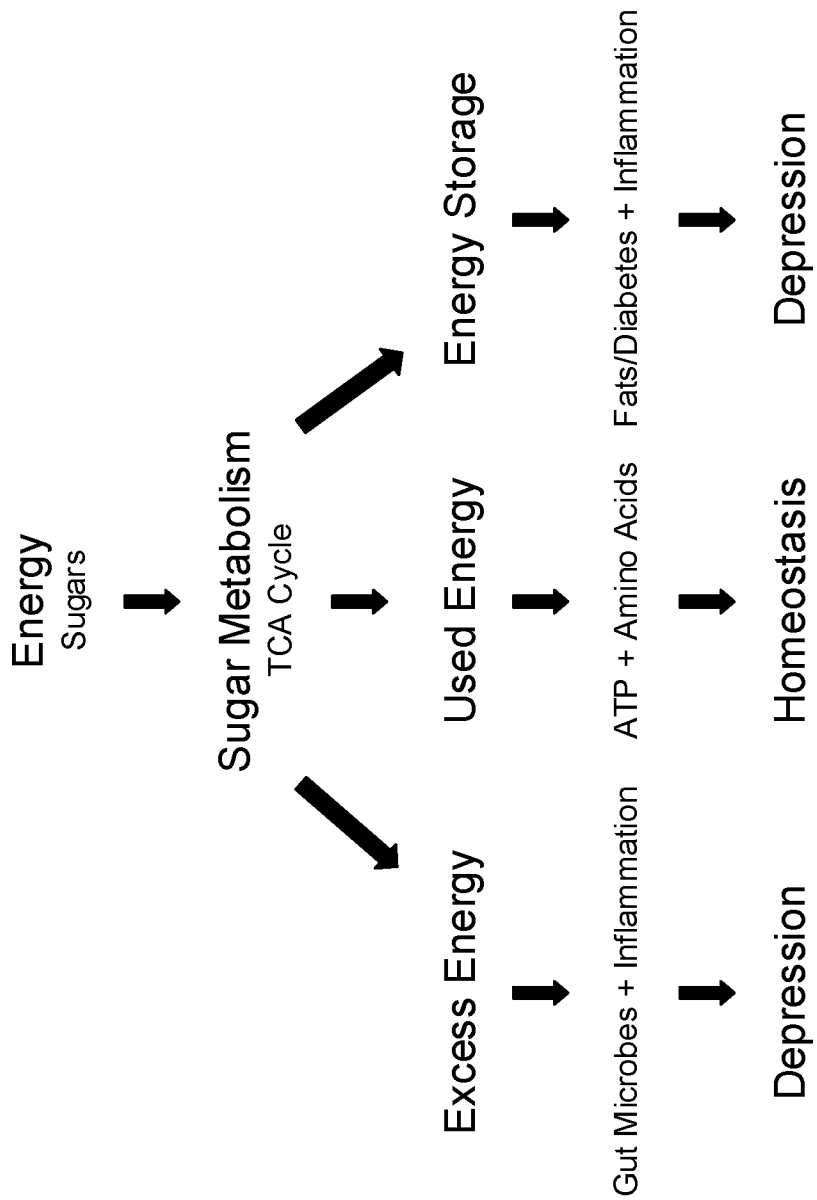
Energy
Sugars
Sugar Metabolism
TCA Cycle
Energy Storage
Used Energy
Excess Energy
Fats/Diabetes + Inflammation
ATP + Amino Acids
Gut Microbes + Inflammation
Depression
Homeostasis
Depression

FIG. 3

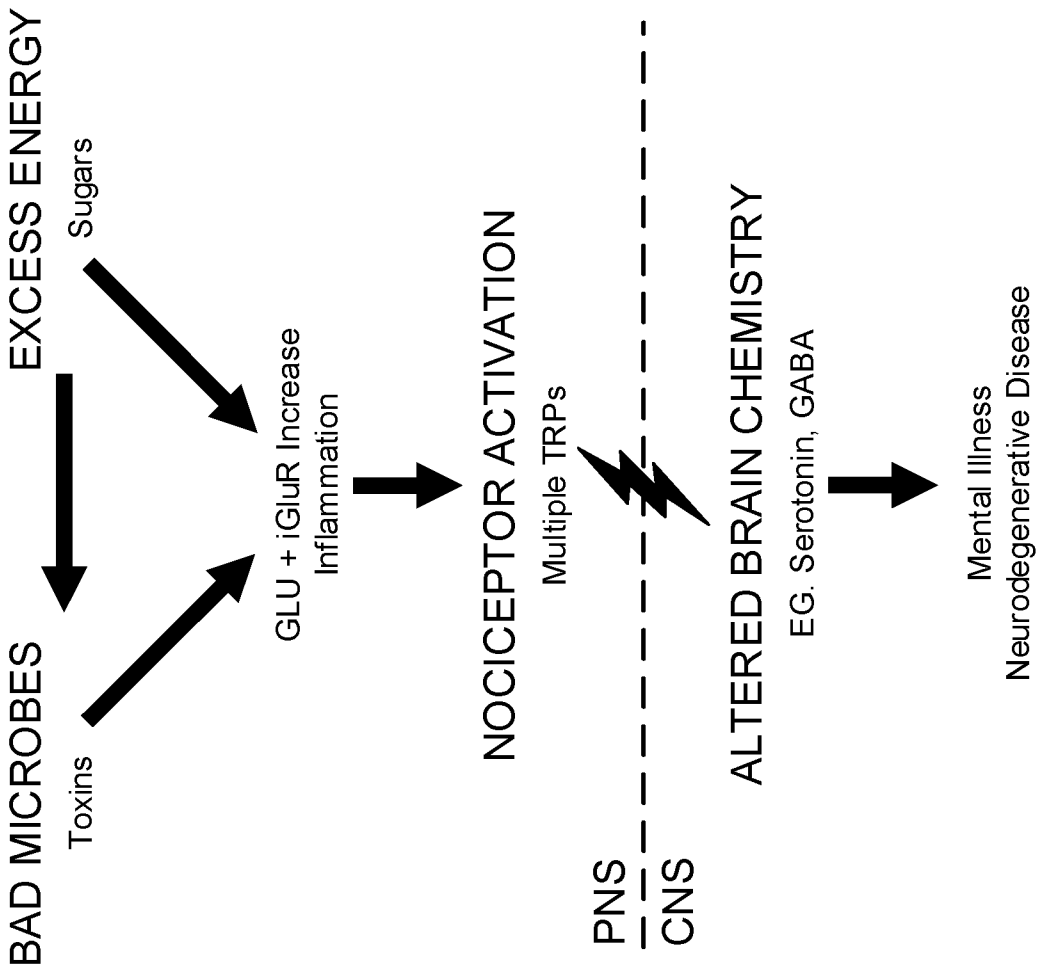
BAD MICROBES
Toxins
EXCESS ENERGY
Sugars
GLU + iGluR Increase
Inflammation
NOCICEPTOR ACTIVATION
Multiple TRPs
PNS
CNS
ALTERED BRAIN CHEMISTRY
EG. Serotonin, GABA
Mental Illness
Neurodegenerative Disease

FIG. 4

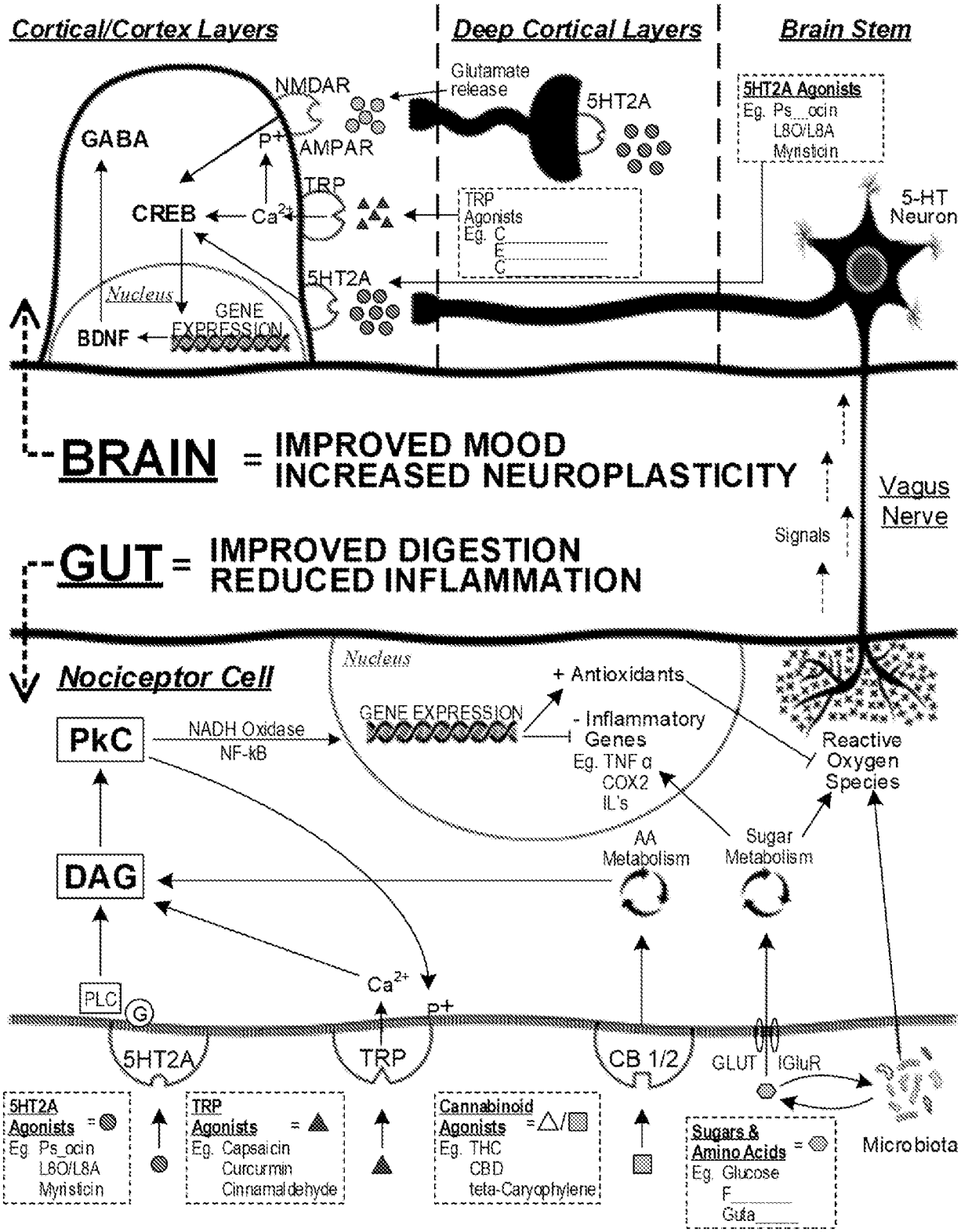
Cortical/Cortex Layers
Deep Cortical Layers
Brain Stem
NMDAR
AMPAR
Glutamate release
5HT2A
5HT2A Agonists
Eg. Ps_ocin
L8O/L8A
Myristicin
GABA
P+
TRP
CREB
Ca2+
TRP Agonists
Eg. C
E
C
5-HT Neuron
5HT2A
Nucleus
GENE EXPRESSION
BDNF
BRAIN = IMPROVED MOOD
INCREASED NEUROPLASTICITY
Vagus Nerve
Signals
GUT = IMPROVED DIGESTION
REDUCED INFLAMMATION
Nociceptor Cell
Nucleus
+ Antioxidants
GENE EXPRESSION
- Inflammatory Genes
Eg. TNF α
COX2
IL's
PkC
NADH Oxidase
NF-kB
Reactive Oxygen Species
AA Metabolism
Sugar Metabolism
DAG
Ca2+
P+
PLC
G
5HT2A
TRP
CB 1/2
GLUT
IGluR
Microbiota
5HT2A Agonists = ●
Eg. Ps_ocin
L8O/L8A
Myristicin
TRP Agonists = ▲
Eg. Capsaicin
Curcurmin
Cinnamaldehyde
Cannabinoid Agonists = △/▨
Eg. THC
CBD
teta-Caryophylene
Sugars & Amino Acids = ◎
Eg. Glucose
F
Guta

FIG. 5

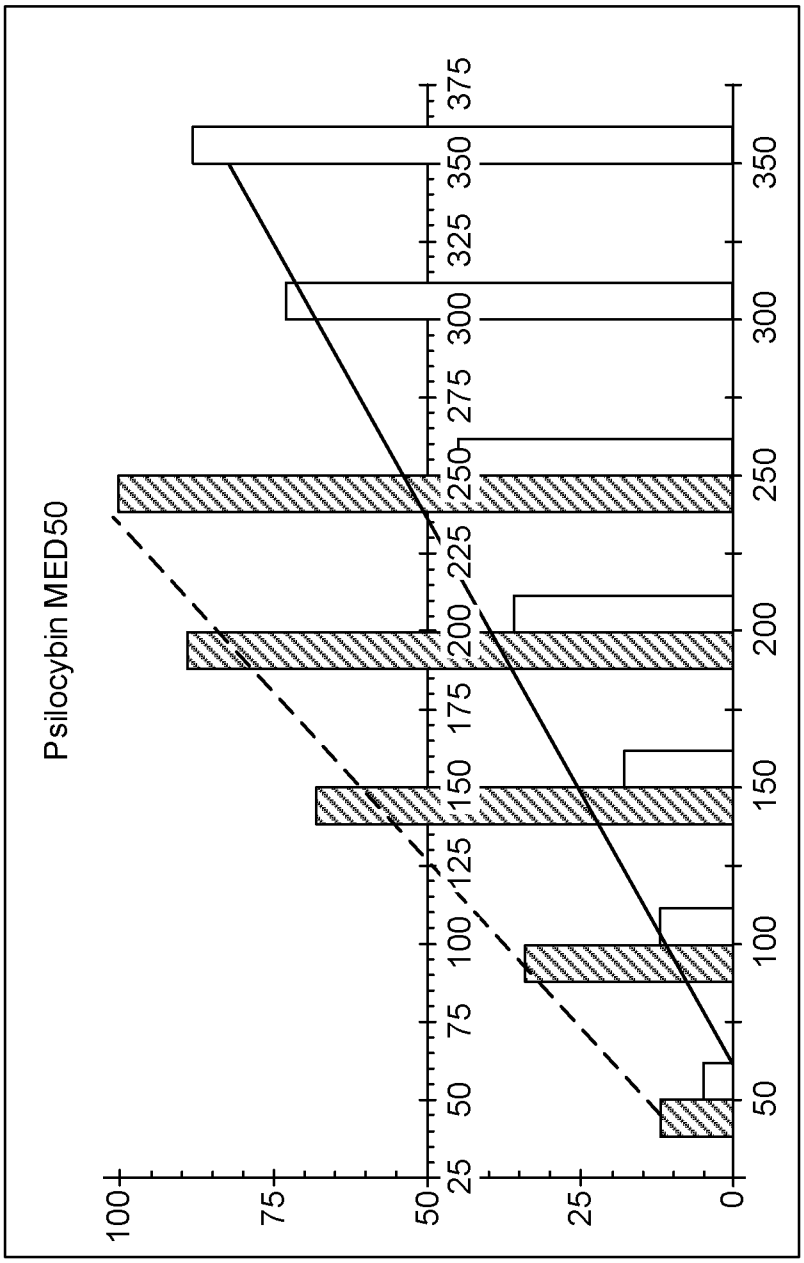
Psilocybin MED50
100
75
50
25
0
25
50
75
100
125
150
175
200
225
250
275
300
325
350
375
50
100
150
200
250
300
350

FIG. 6

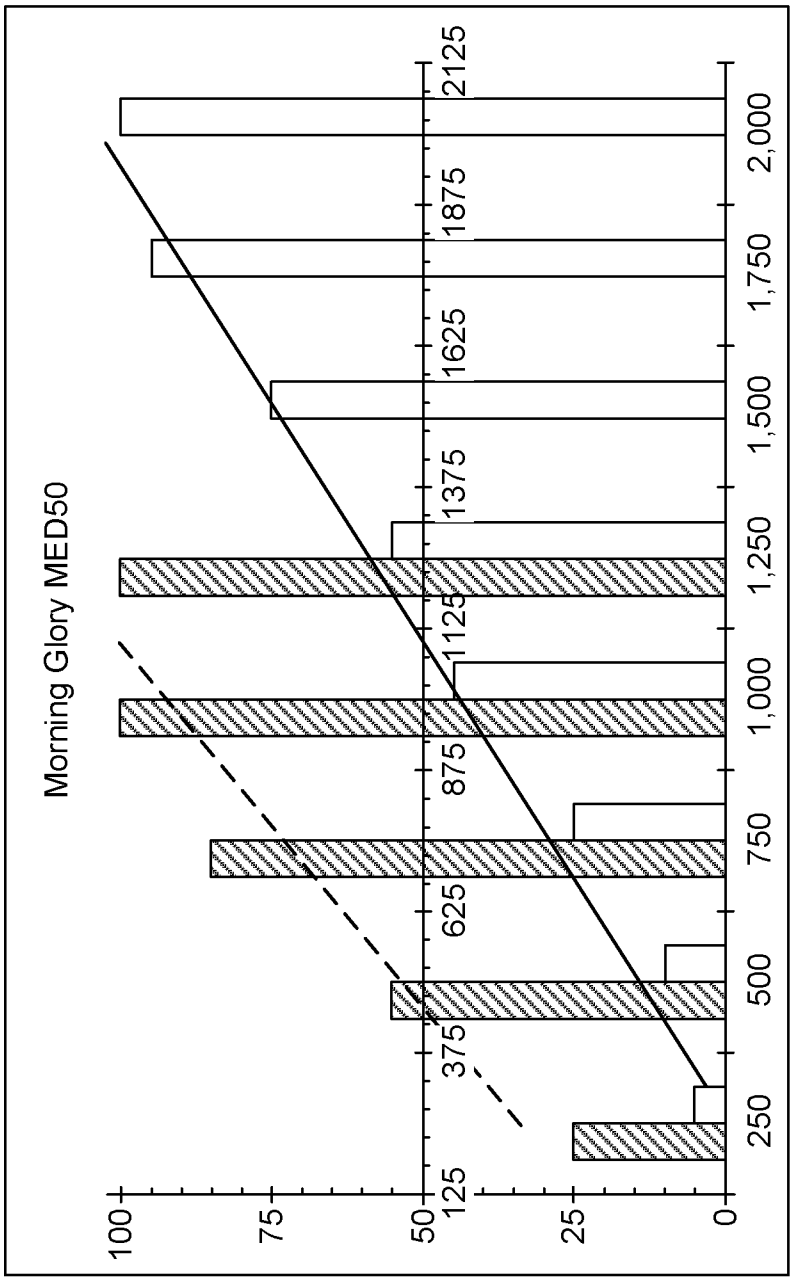
Morning Glory MED50
100
75
50
25
0
125
375
625
875
1125
1375
1625
1875
2125
250
500
750
1,000
1,250
1,500
1,750
2,000

FIG. 7

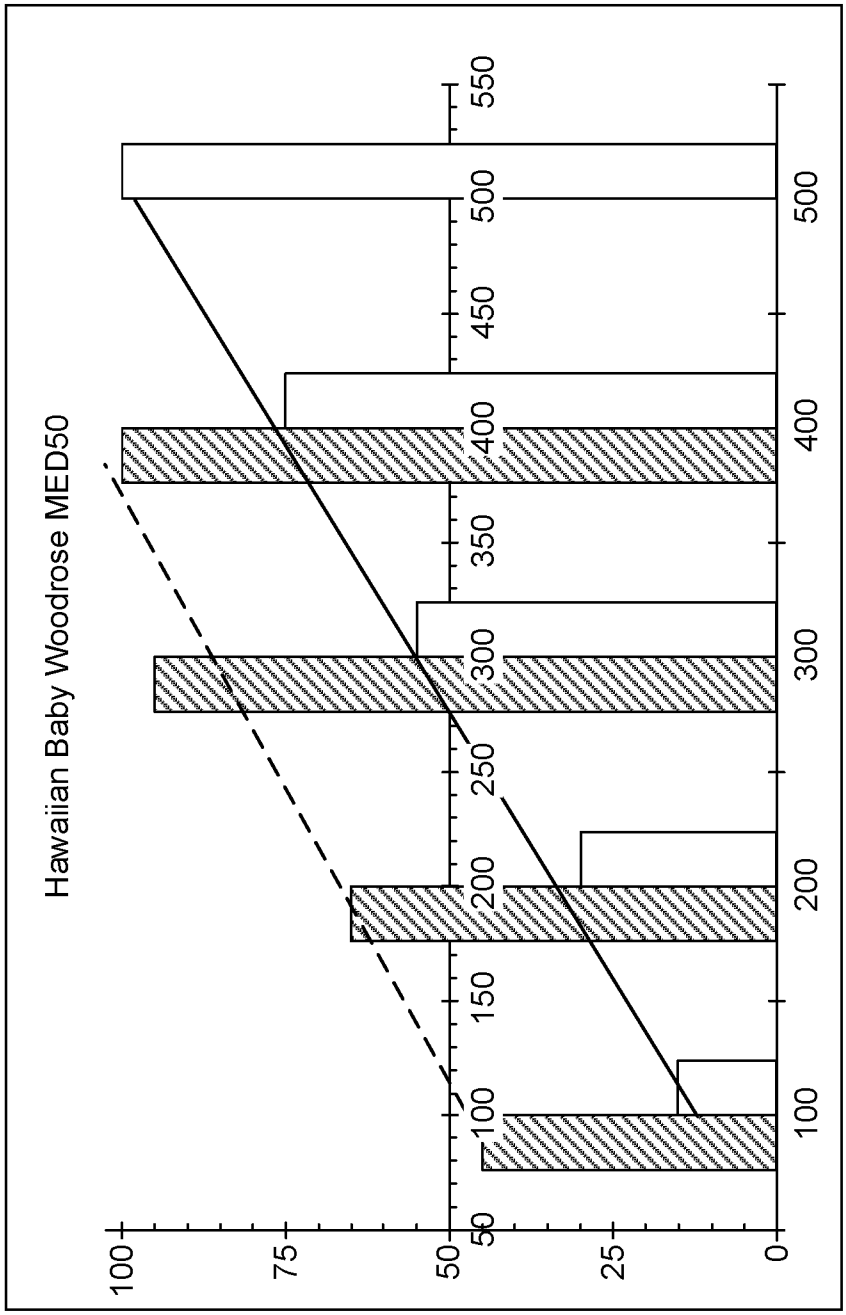
Hawaiian Baby Woodrose MED50
100
75
50
25
0
550
500
450
400
350
300
250
200
150
100
50
500
400
300
200
100

FIG. 8

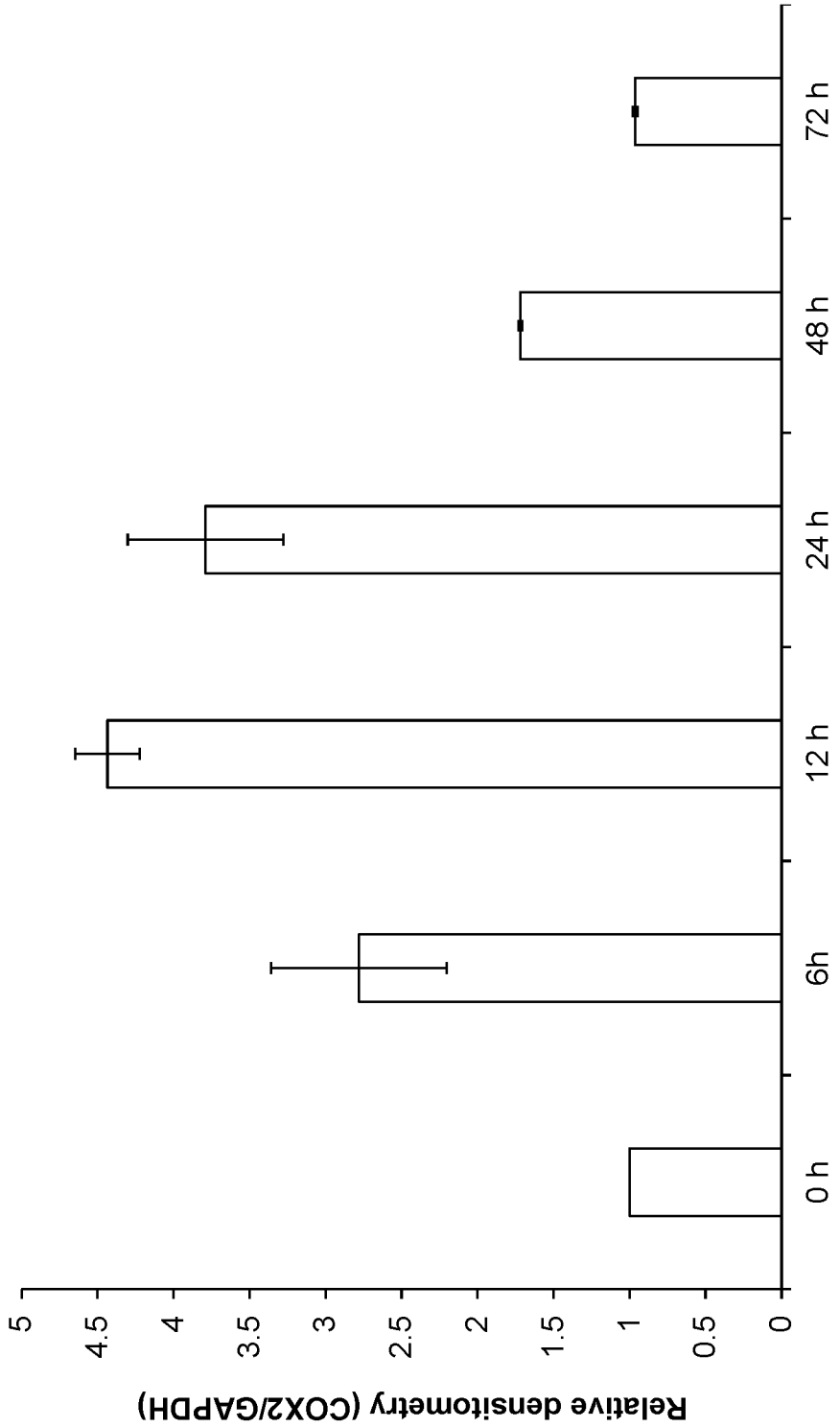
Relative densitometry (COX2/GAPDH)
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5
0 h
6h
12 h
24 h
48 h
72 h

FIG. 9

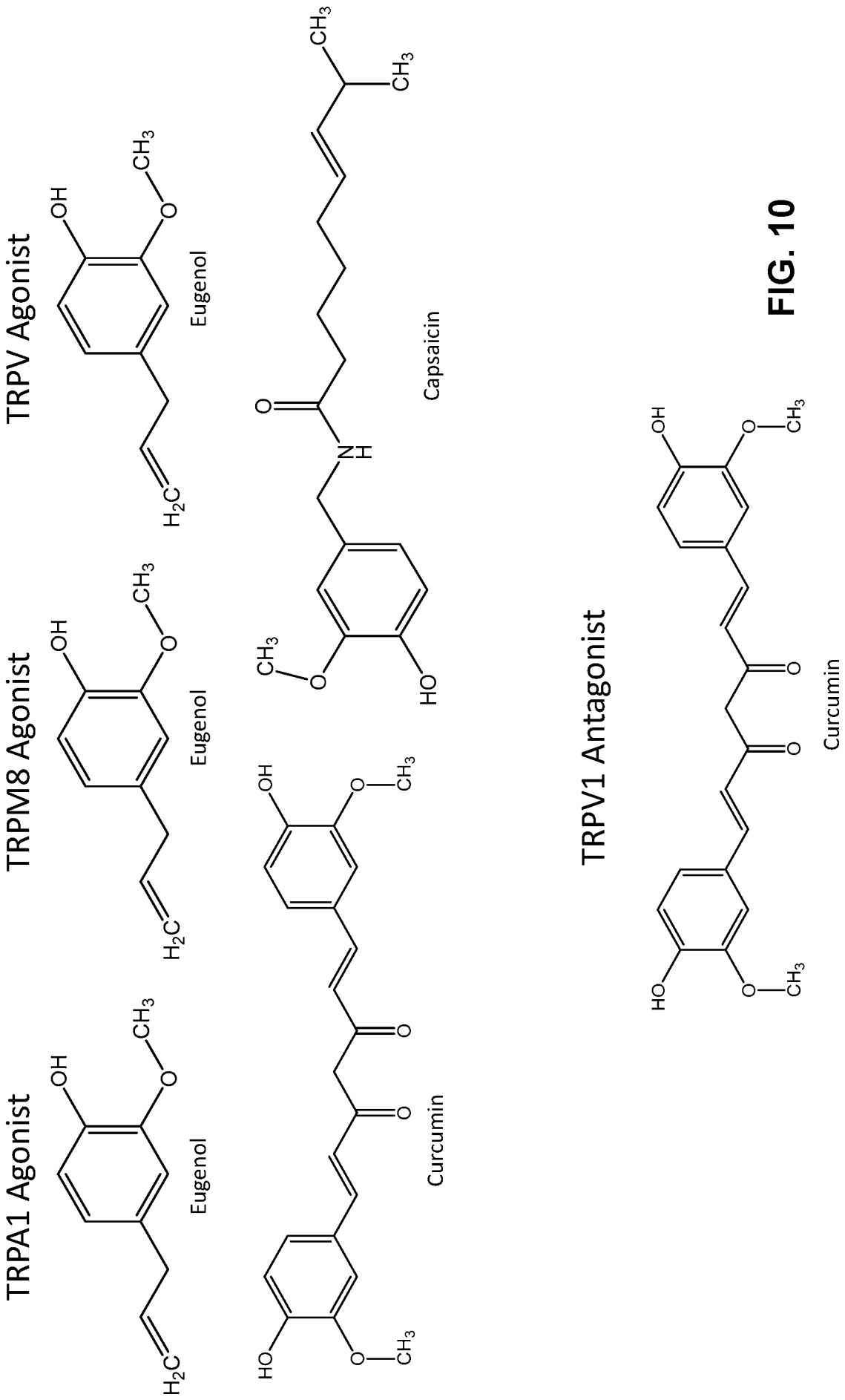
TRPA1 Agonist
Eugenol
TRPM8 Agonist
Eugenol
TRPV Agonist
Eugenol
Curcumin
Capsaicin
TRPV1 Antagonist
Curcumin

FIG. 10

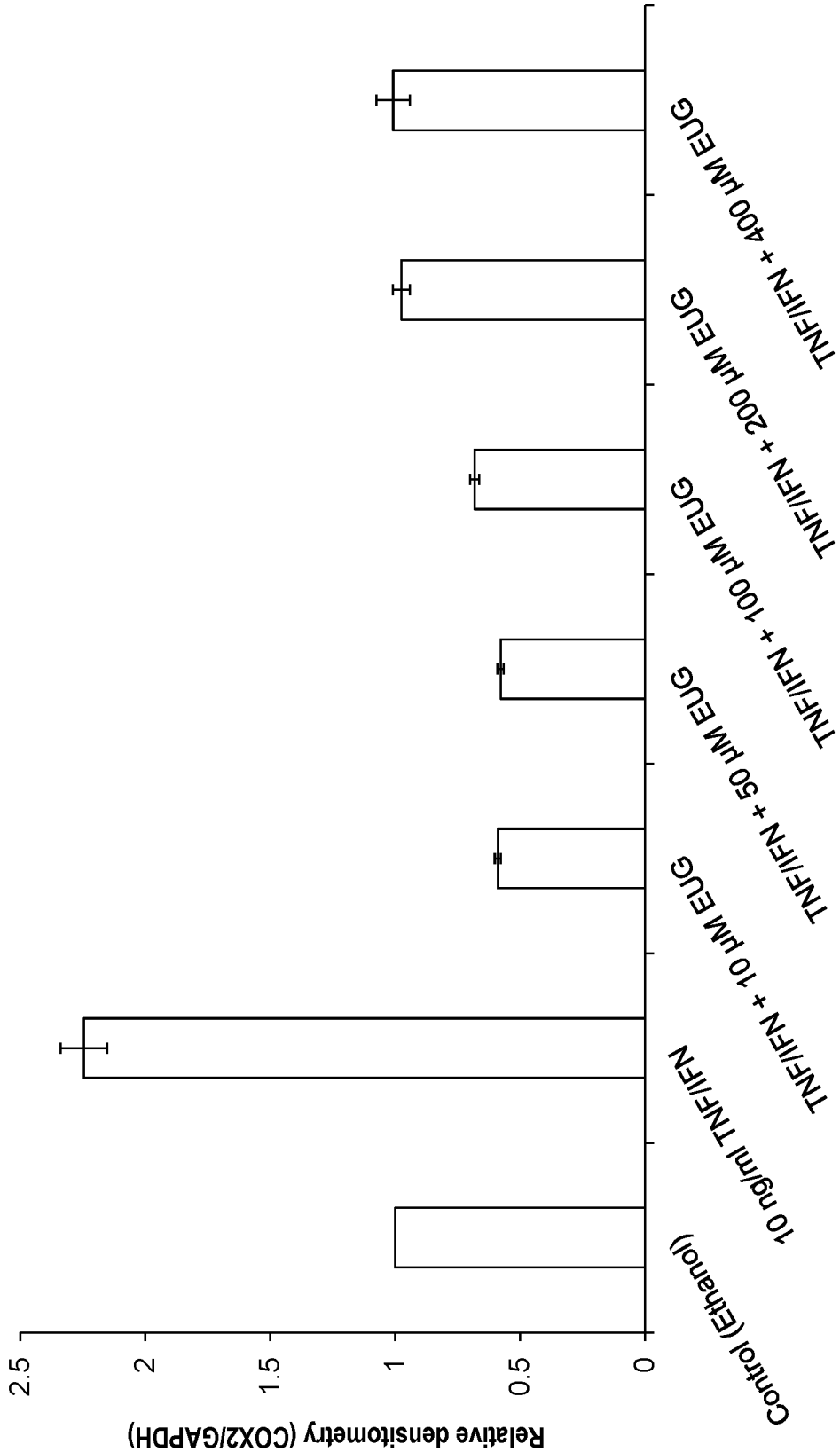
Relative densitometry (COX2/GAPDH)
2.5
2
1.5
1
0.5
0
Control (Ethanol)
10 ng/ml TNF/IFN
TNF/IFN + 10 µM EUG
TNF/IFN + 50 µM EUG
TNF/IFN + 100 µM EUG
TNF/IFN + 200 µM EUG
TNF/IFN + 400 µM EUG

FIG. 11

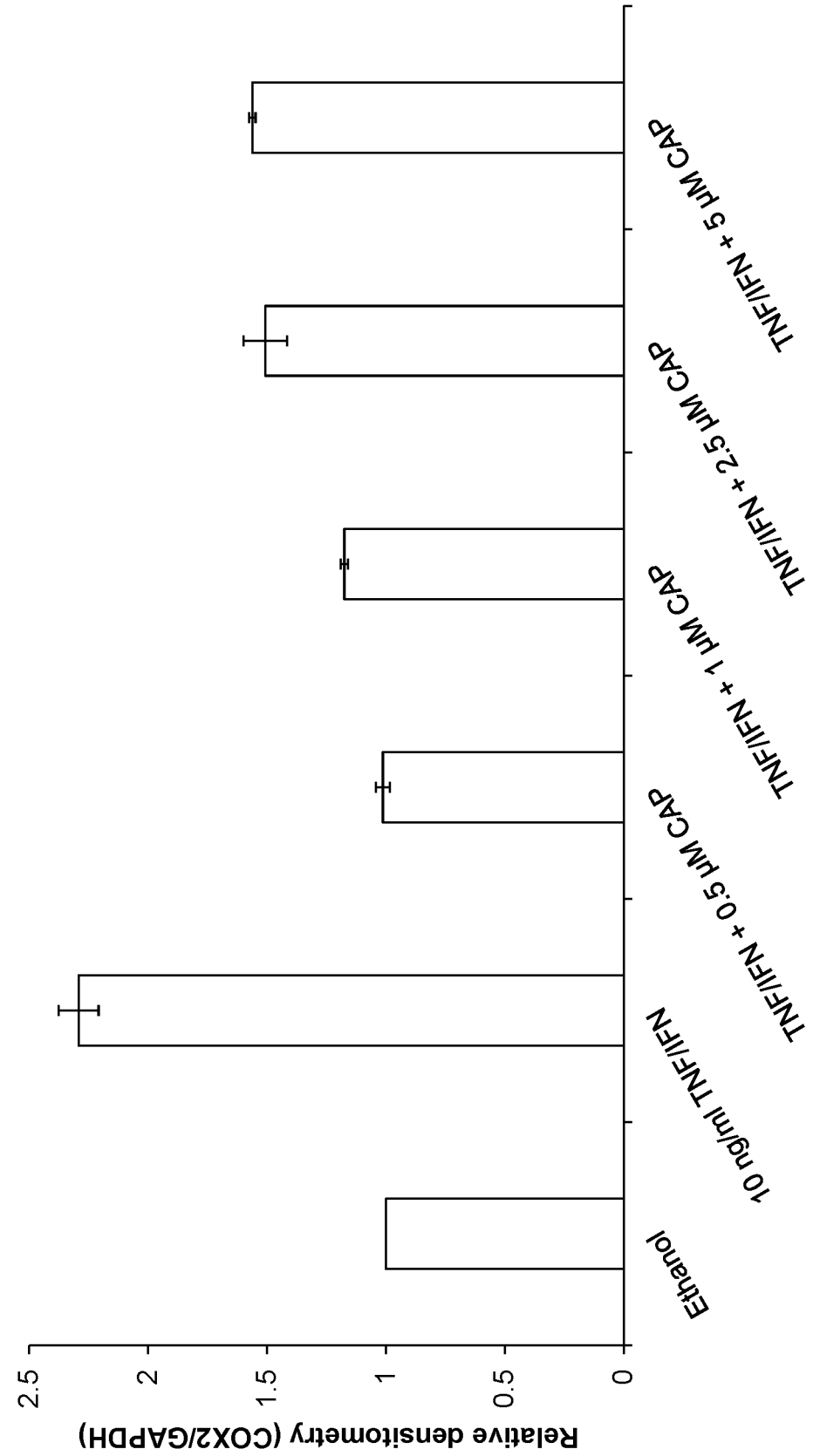
Relative densitometry (COX2/GAPDH)
2.5
2
1.5
1
0.5
0
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 0.5 µM CAP
TNF/IFN + 1 µM CAP
TNF/IFN + 2.5 µM CAP
TNF/IFN + 5 µM CAP

FIG. 12

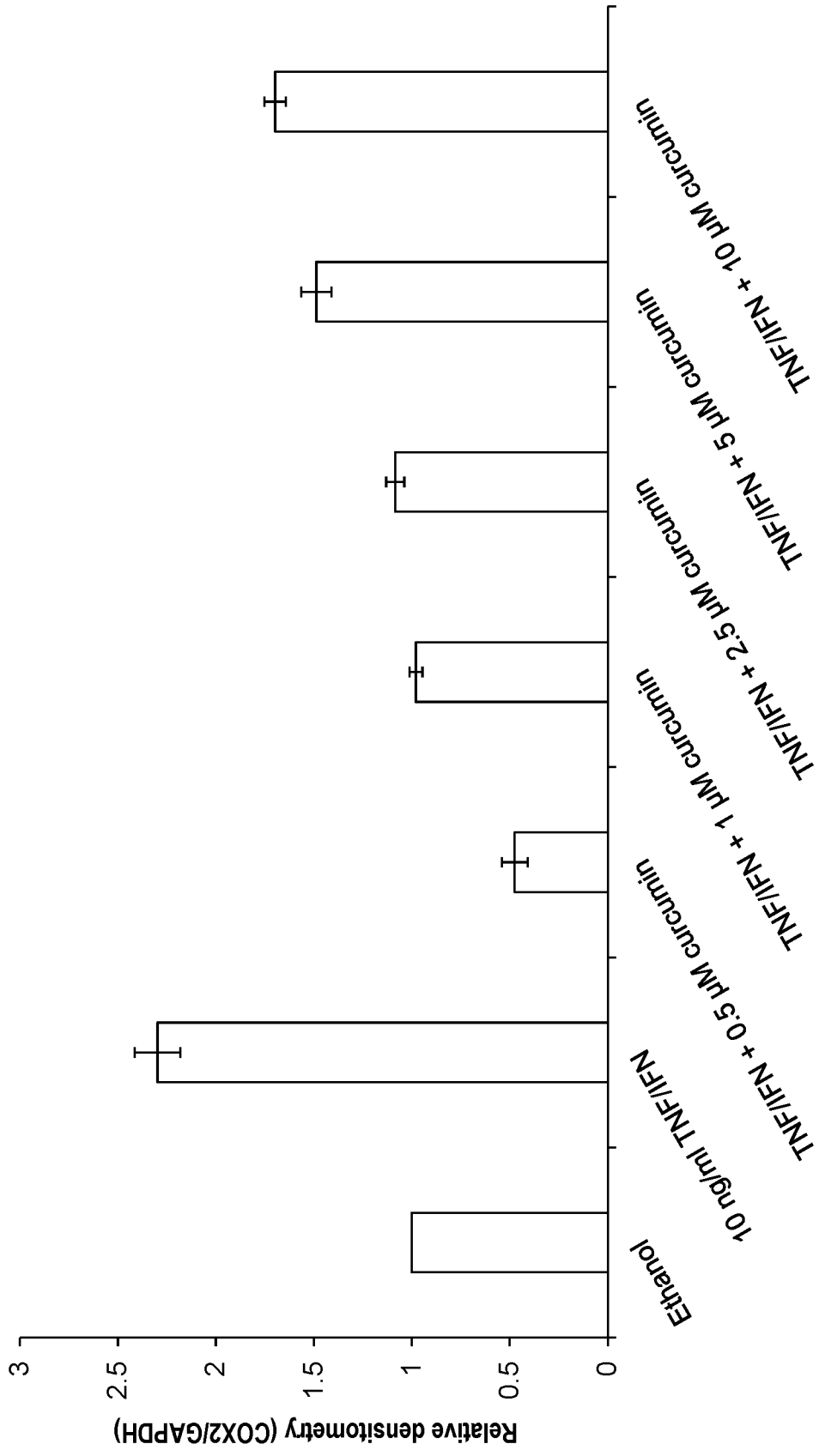
Relative densitometry (COX2/GAPDH)
0
0.5
1
1.5
2
2.5
3
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 0.5 µM curcumin
TNF/IFN + 1 µM curcumin
TNF/IFN + 2.5 µM curcumin
TNF/IFN + 5 µM curcumin
TNF/IFN + 10 µM curcumin

FIG. 13

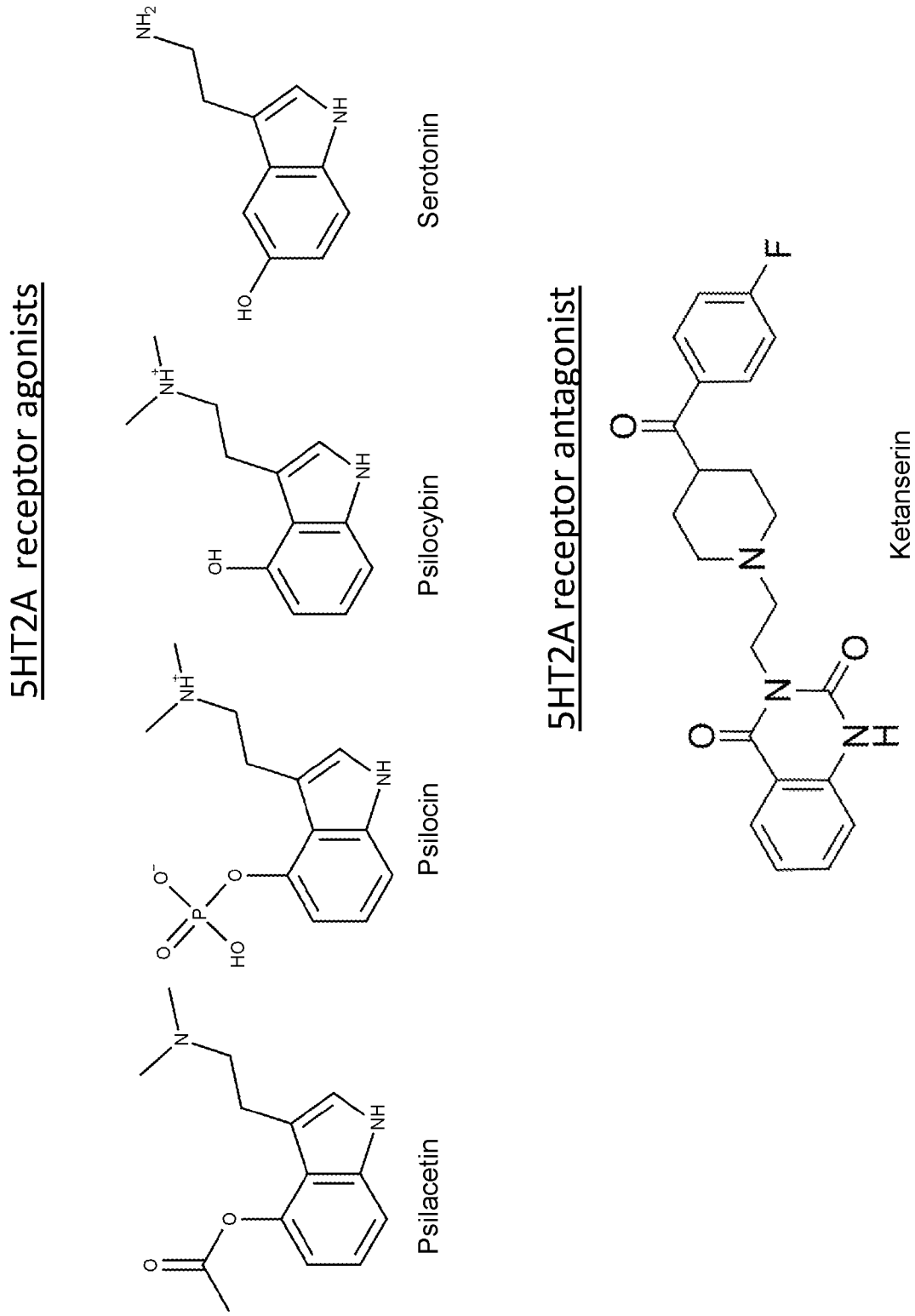
5HT2A receptor agonists
Psilacetin
Psilocin
Psilocybin
Serotonin
5HT2A receptor antagonist
Ketanserin

FIG. 14

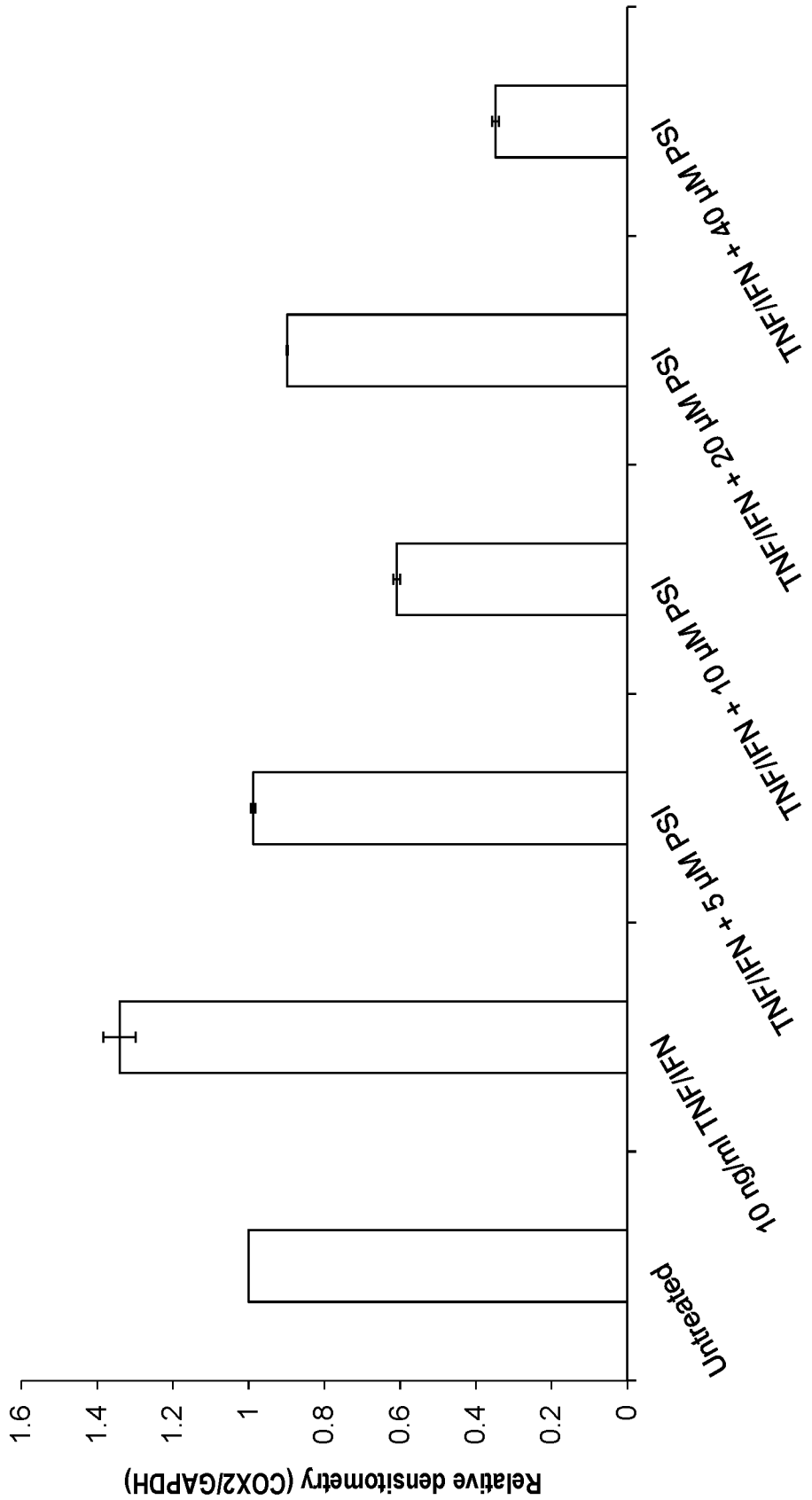
Relative densitometry (COX2/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
Untreated
10 ng/ml TNF/IFN
TNF/IFN + 5 µM PSI
TNF/IFN + 10 µM PSI
TNF/IFN + 20 µM PSI
TNF/IFN + 40 µM PSI

FIG. 15

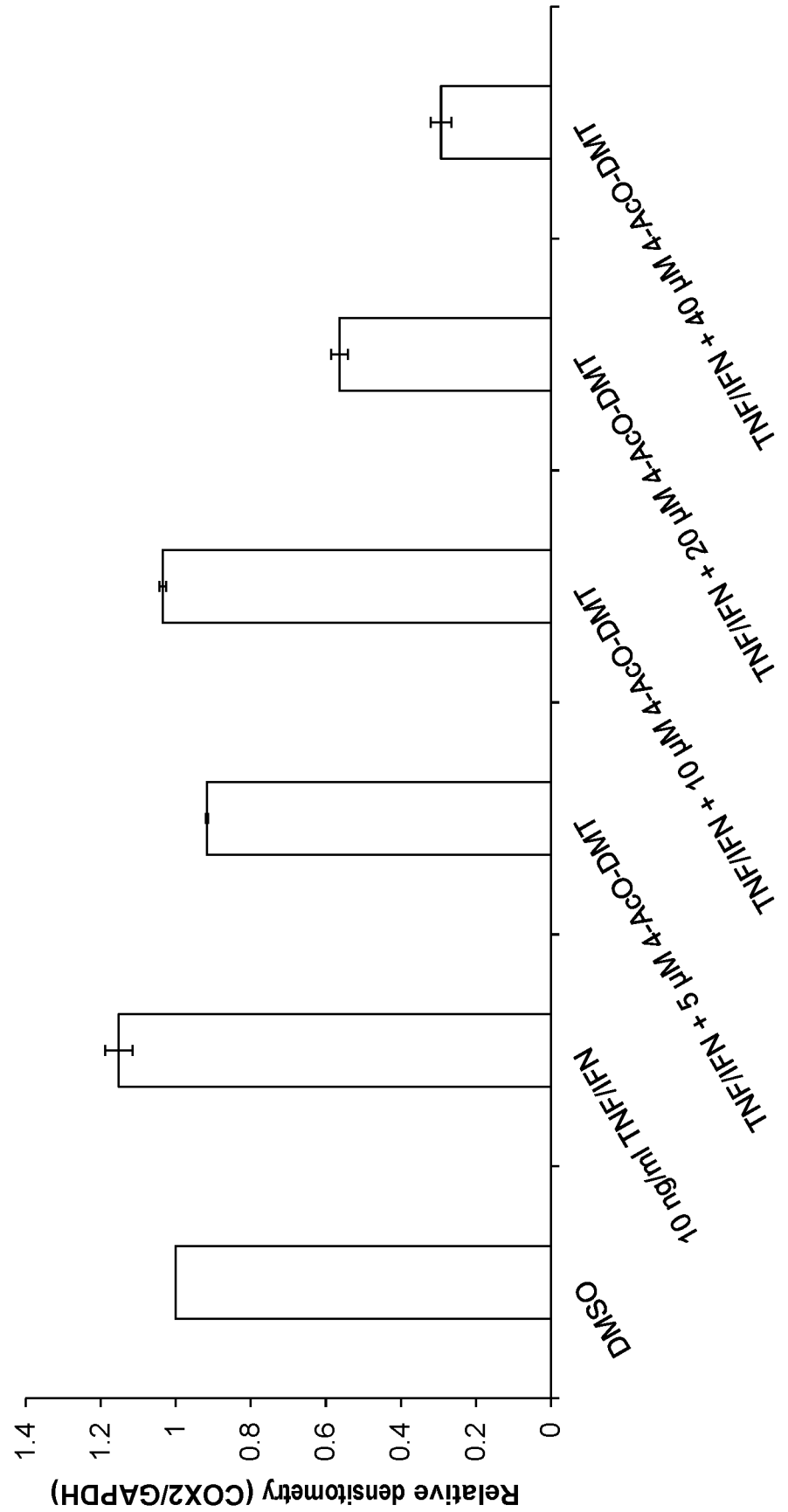
Relative densitometry (COX2/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 5 µM 4-AcO-DMT
TNF/IFN + 10 µM 4-AcO-DMT
TNF/IFN + 20 µM 4-AcO-DMT
TNF/IFN + 40 µM 4-AcO-DMT

FIG. 16

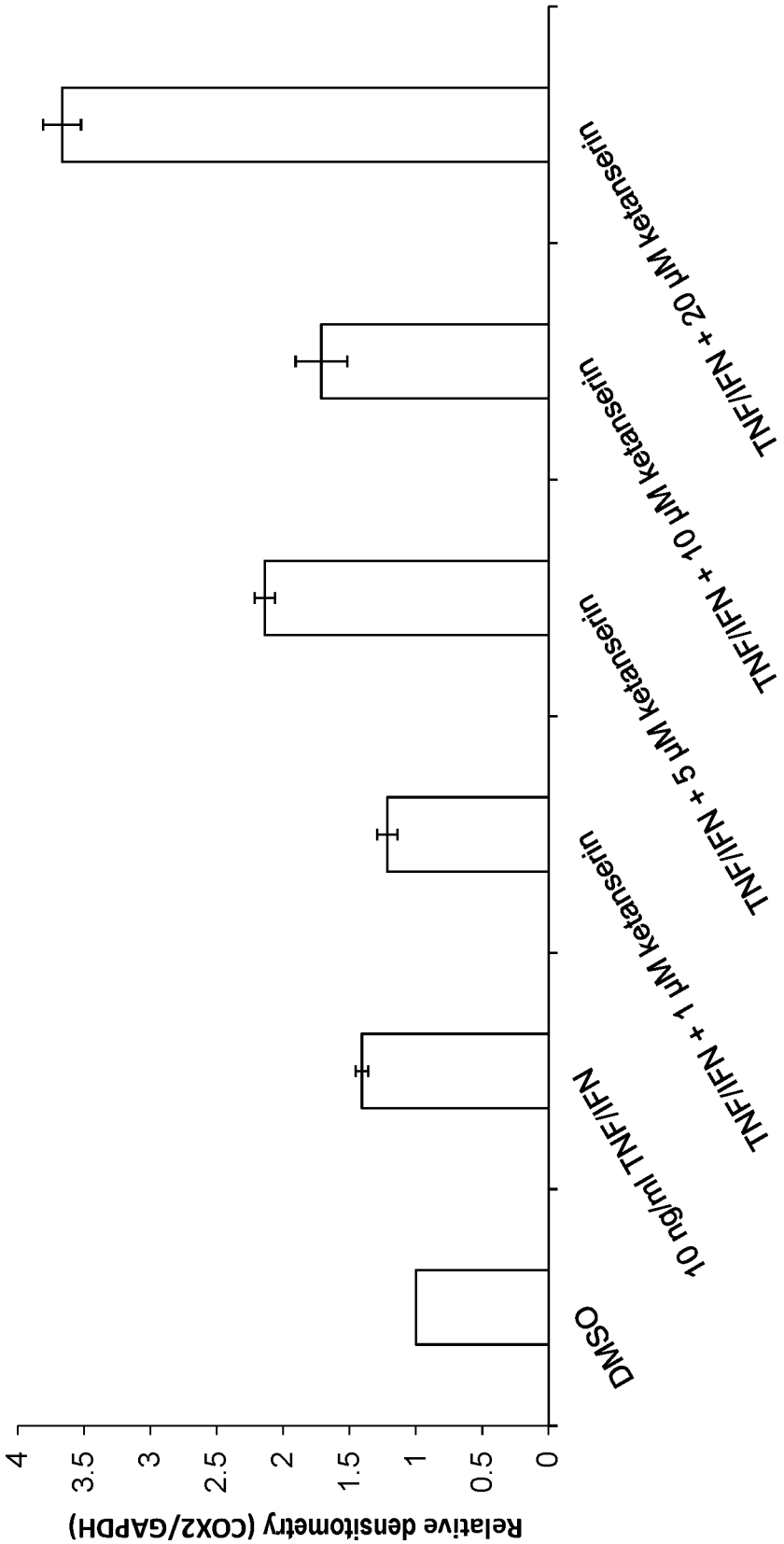
Relative densitometry (COX2/GAPDH)
0
0.5
1
1.5
2
2.5
3
3.5
4
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 1 µM ketanserin
TNF/IFN + 5 µM ketanserin
TNF/IFN + 10 µM ketanserin
TNF/IFN + 20 µM ketanserin

FIG. 17

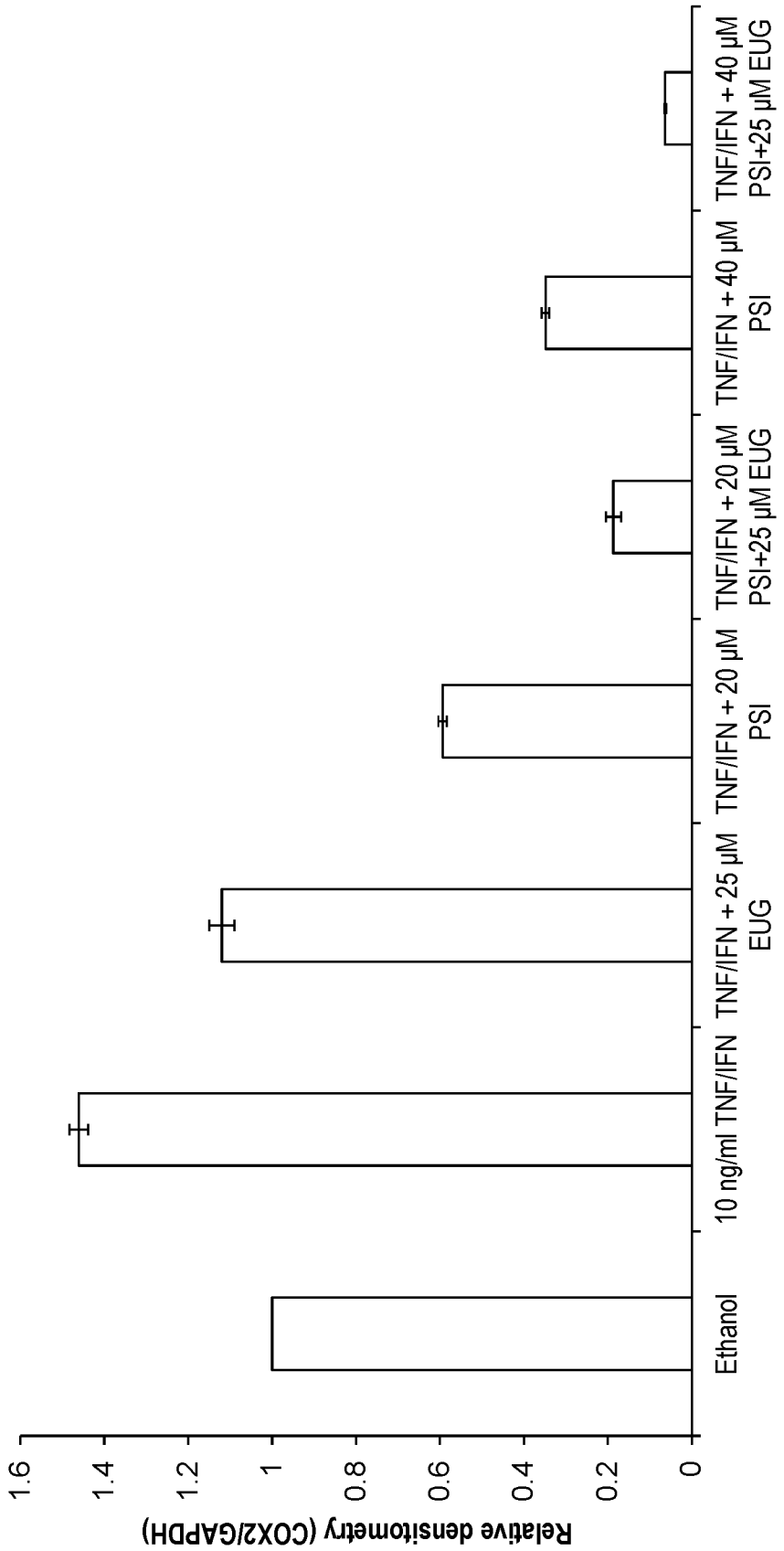
Relative densitometry (COX2/GAPDH)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 25 µM EUG
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+25 µM EUG
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+25 µM EUG

FIG. 18

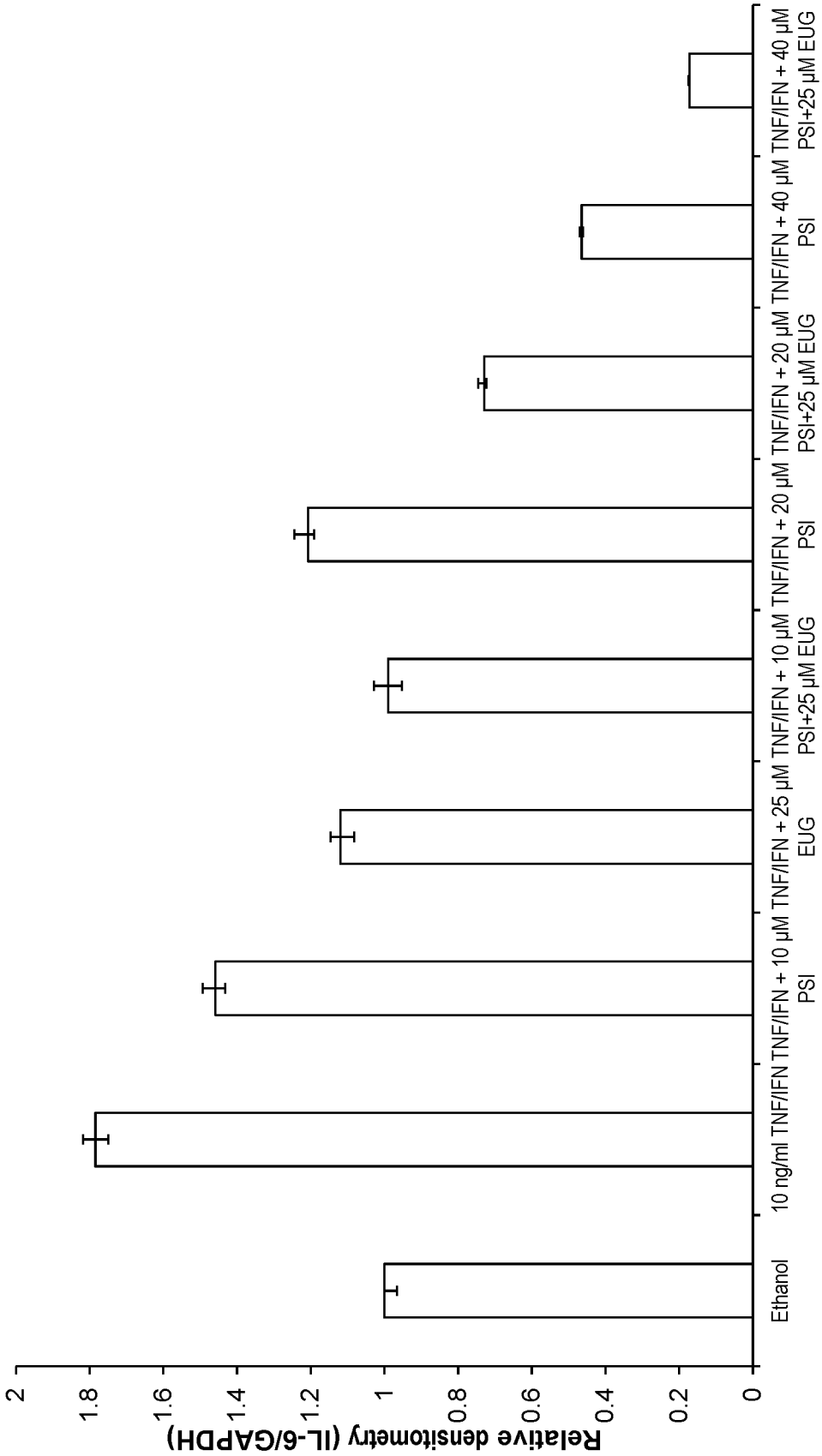
Relative densitometry (IL-6/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 25 µM EUG
TNF/IFN + 10 µM PSI+25 µM EUG
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+25 µM EUG
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+25 µM EUG

FIG. 19

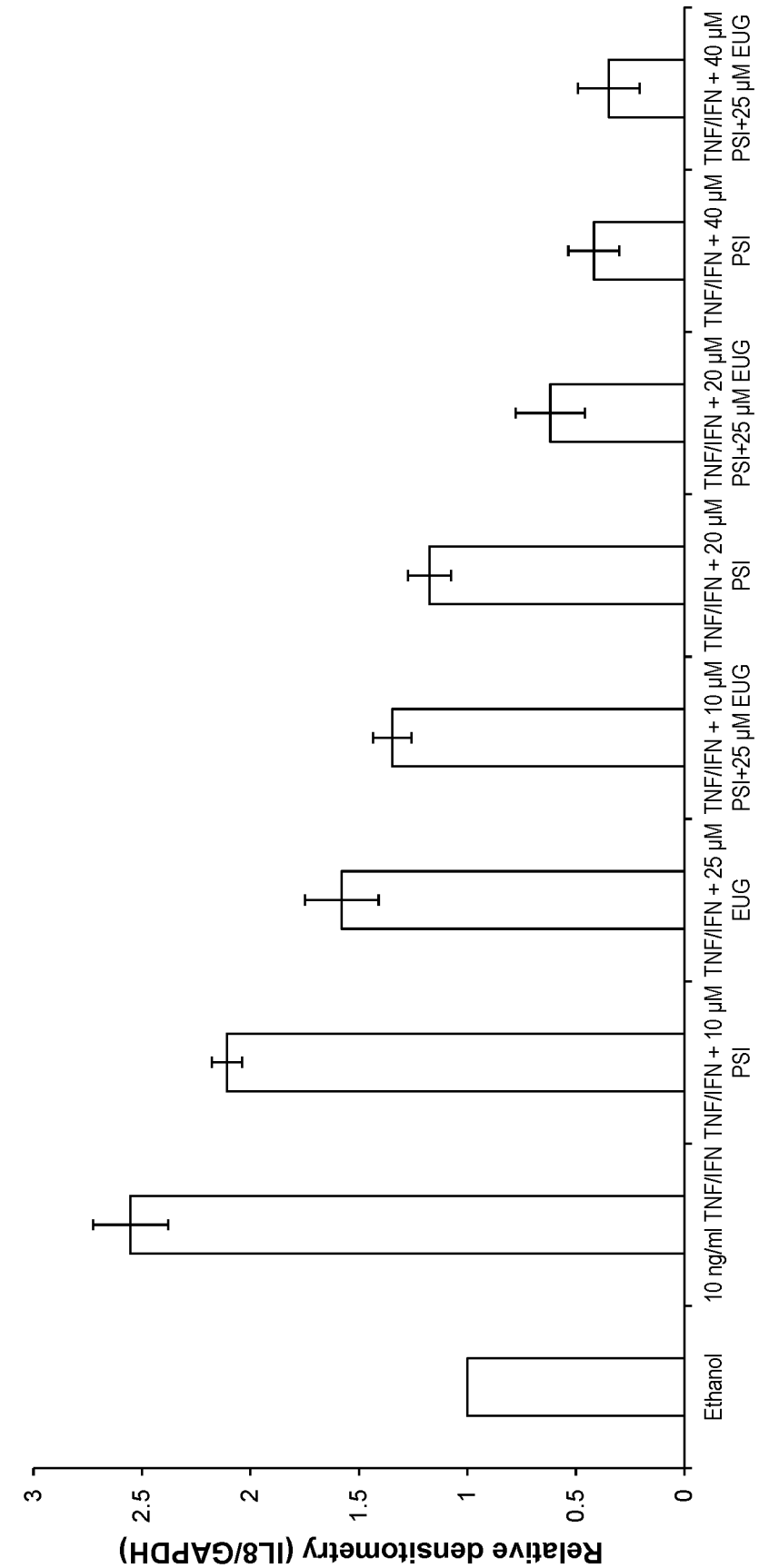
Relative densitometry (IL8/GAPDH)
0
0.5
1
1.5
2
2.5
3
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 25 µM EUG
TNF/IFN + 10 µM PSI+25 µM EUG
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+25 µM EUG
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+25 µM EUG

FIG. 20

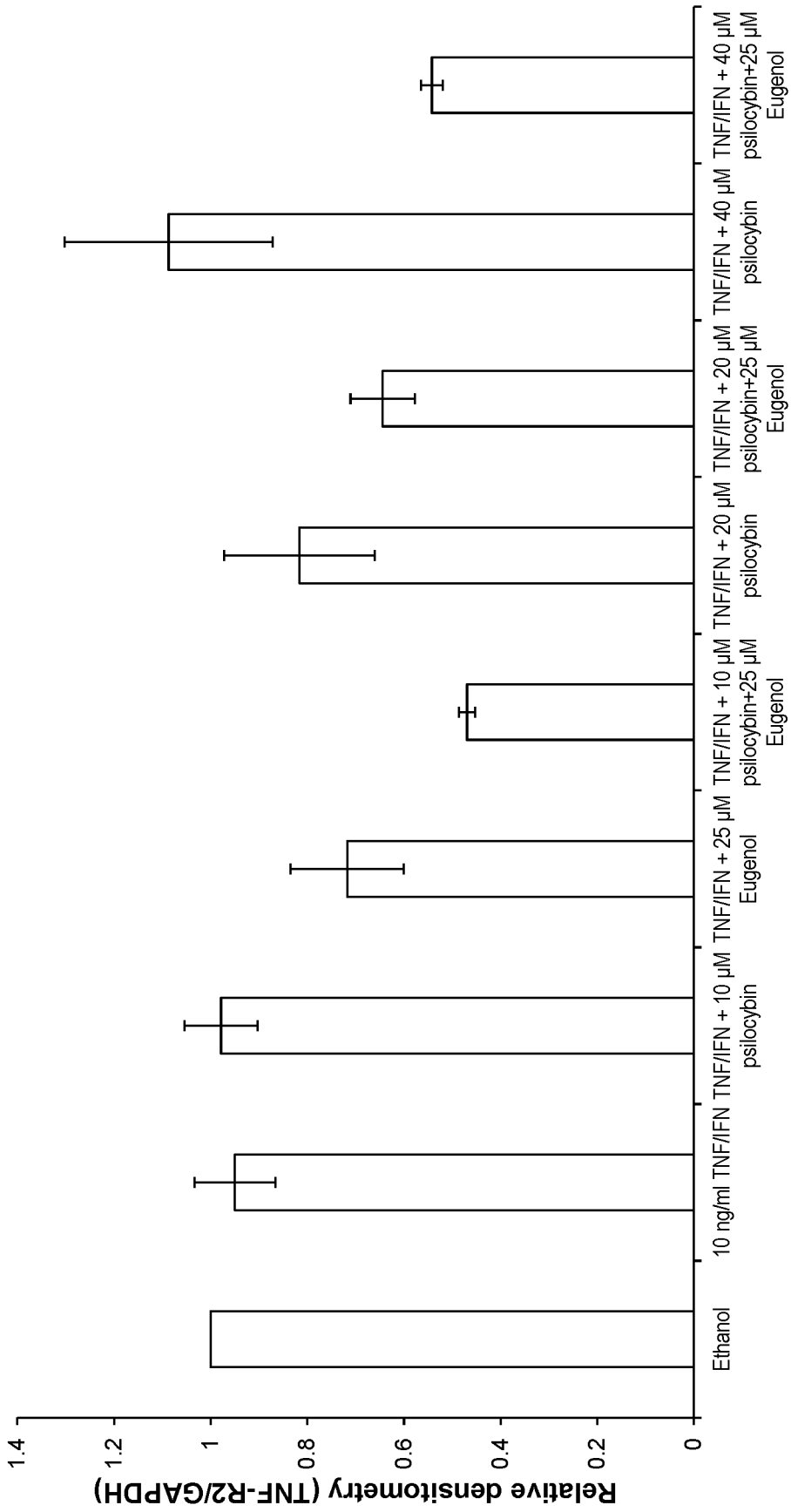
Relative densitometry (TNF-R2/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM psilocybin
TNF/IFN + 25 µM Eugenol
TNF/IFN + 10 µM psilocybin+25 µM Eugenol
TNF/IFN + 20 µM psilocybin
TNF/IFN + 20 µM psilocybin+25 µM Eugenol
TNF/IFN + 40 µM psilocybin
TNF/IFN + 40 µM psilocybin+25 µM Eugenol

FIG. 21

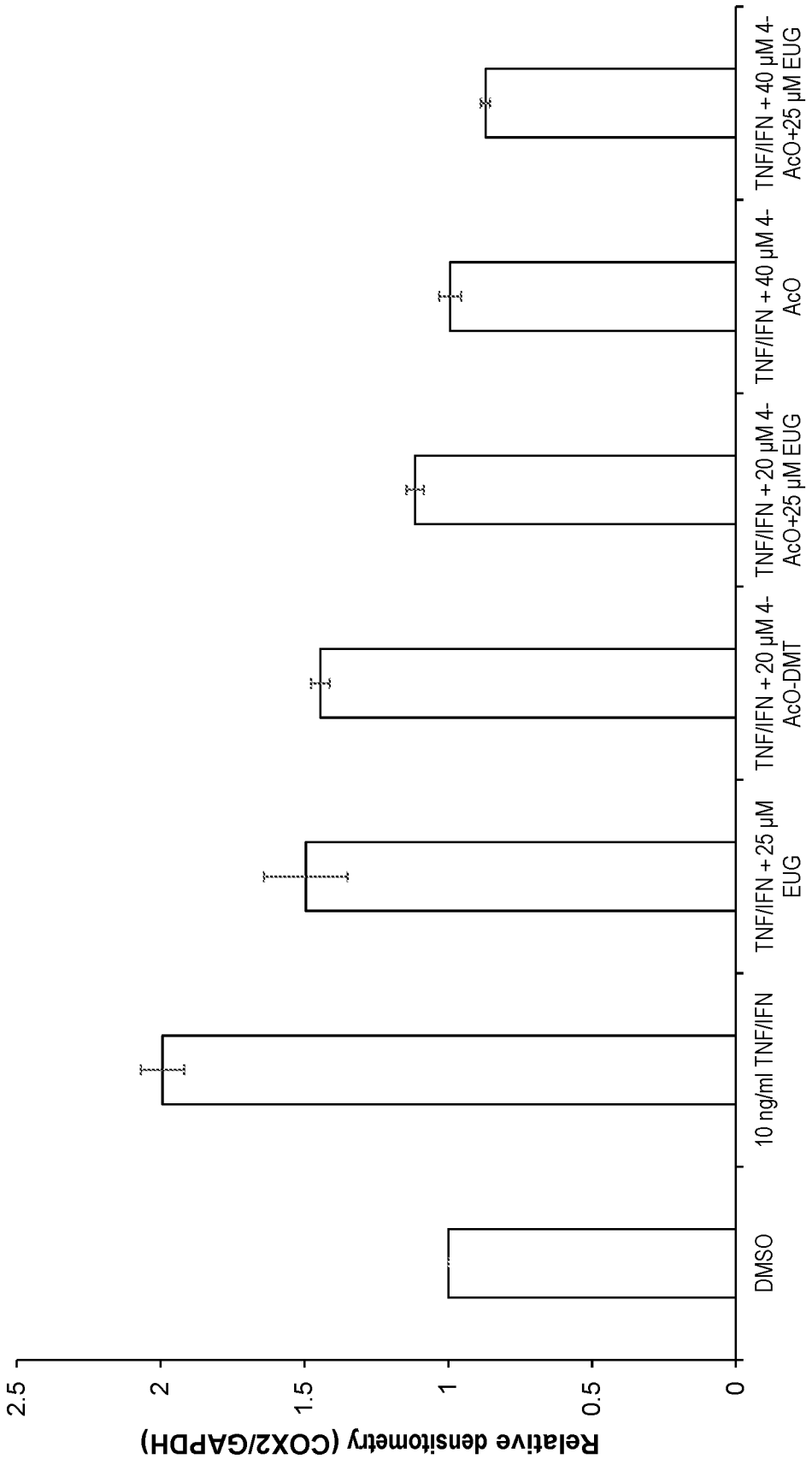
Relative densitometry (COX2/GAPDH)
2.5
2
1.5
1
0.5
0
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 25 µM EUG
TNF/IFN + 20 µM 4-AcO-DMT
TNF/IFN + 20 µM 4-AcO+25 µM EUG
TNF/IFN + 40 µM 4-AcO
TNF/IFN + 40 µM 4-AcO+25 µM EUG

FIG. 22

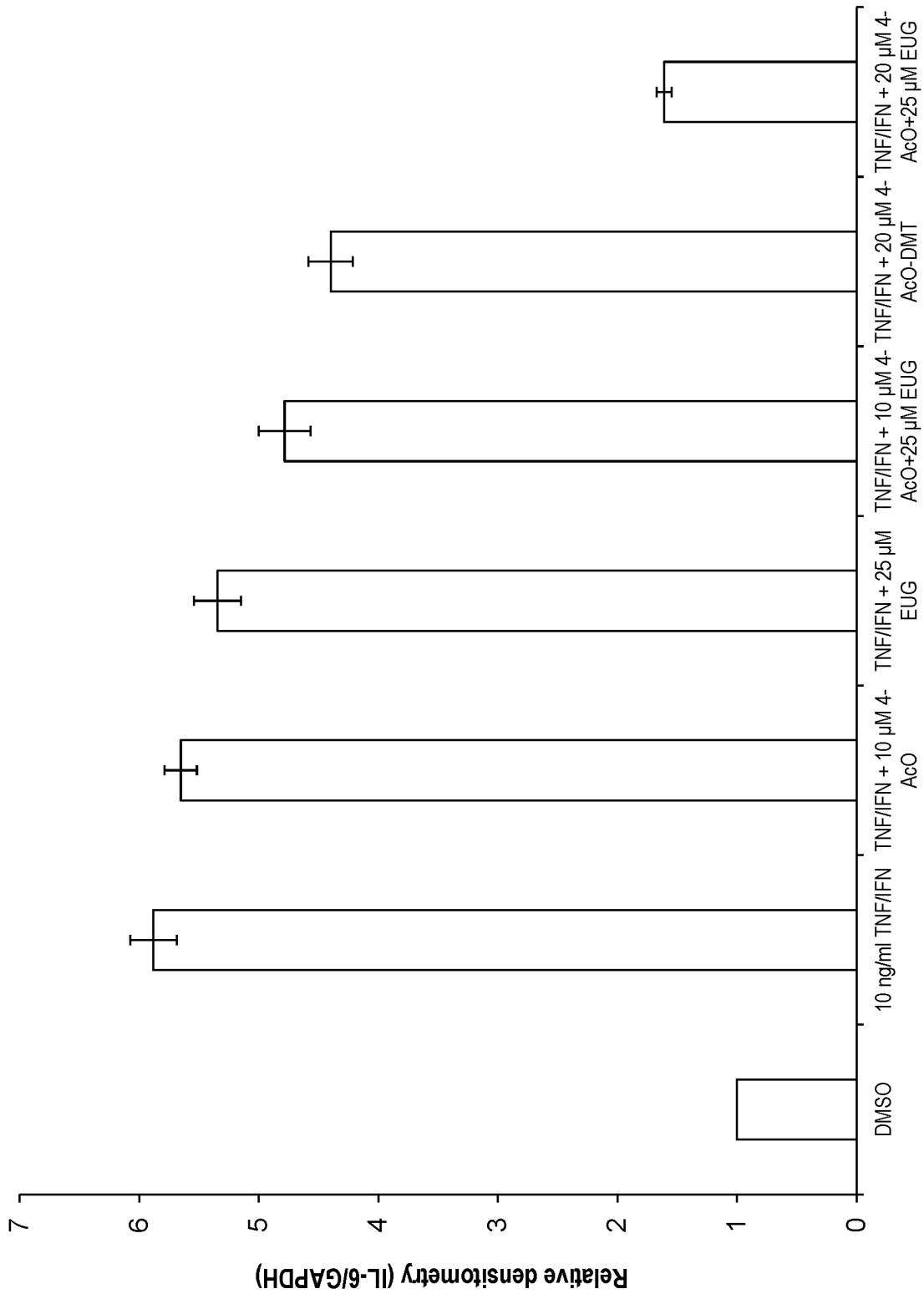
Relative densitometry (IL-6/GAPDH)
0
1
2
3
4
5
6
7
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 10 µM 4-AcO
TNF/IFN + 25 µM EUG
TNF/IFN + 10 µM 4-AcO+25 µM EUG
TNF/IFN + 20 µM 4-AcO-DMT
TNF/IFN + 20 µM 4-AcO+25 µM EUG

FIG. 23

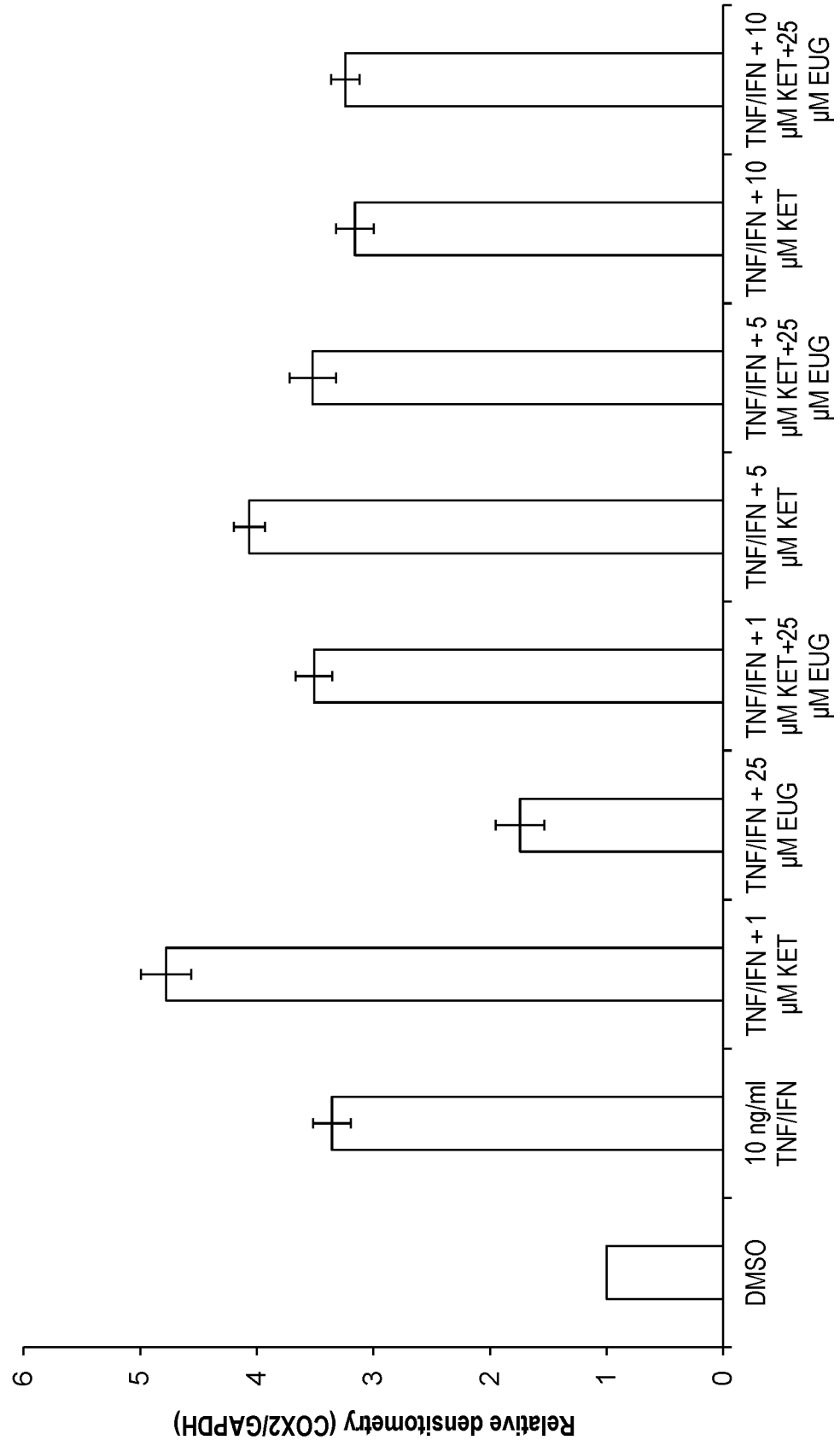
Relative densitometry (COX2/GAPDH)
0
1
2
3
4
5
6
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 1 µM KET
TNF/IFN + 25 µM EUG
TNF/IFN + 1 µM KET+25 µM EUG
TNF/IFN + 5 µM KET
TNF/IFN + 5 µM KET+25 µM EUG
TNF/IFN + 10 µM KET
TNF/IFN + 10 µM KET+25 µM EUG

FIG. 24

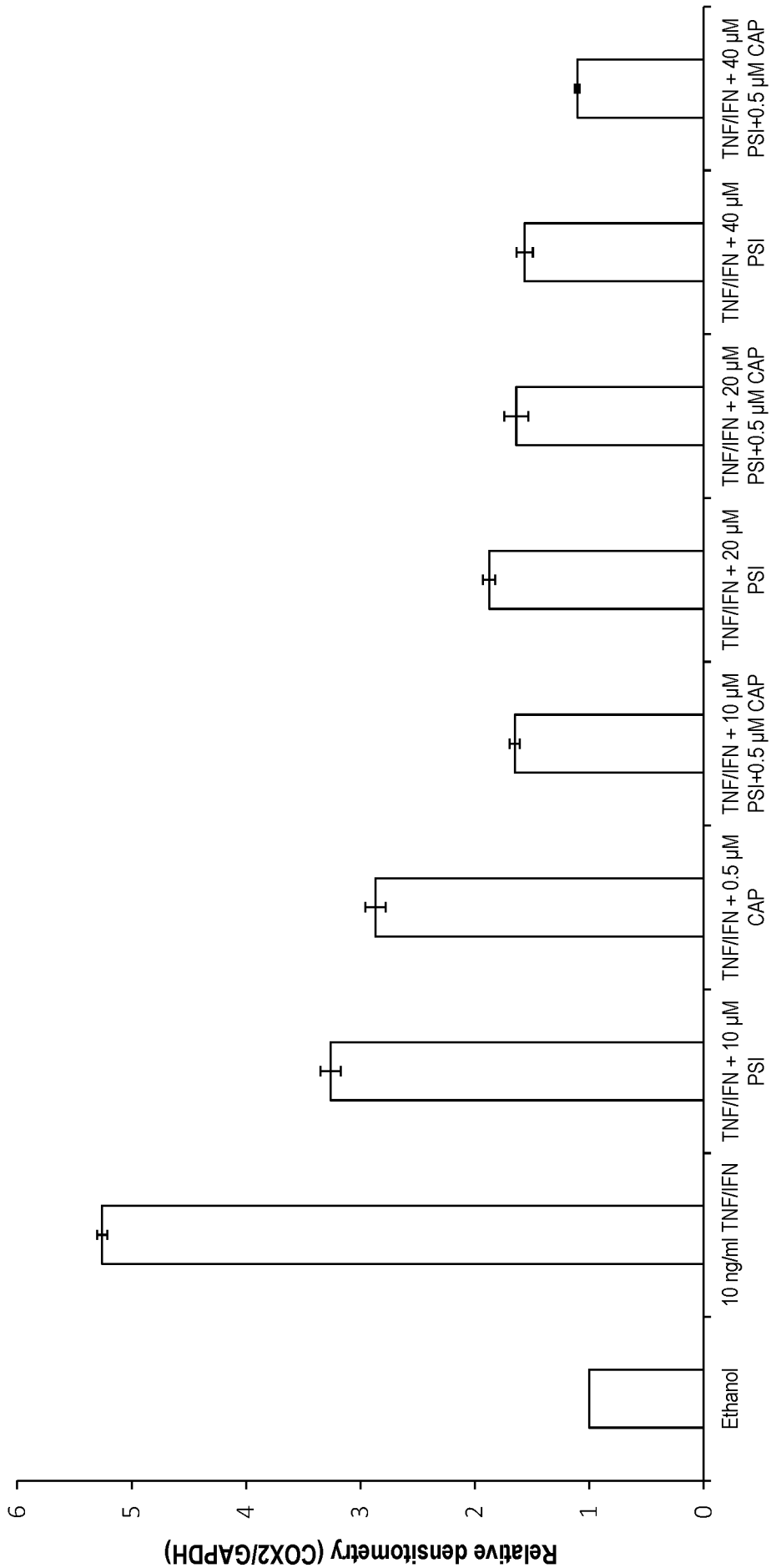
Relative densitometry (COX2/GAPDH)
0
1
2
3
4
5
6
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 0.5 µM CAP
TNF/IFN + 10 µM PSI+0.5 µM CAP
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+0.5 µM CAP
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+0.5 µM CAP

FIG. 25

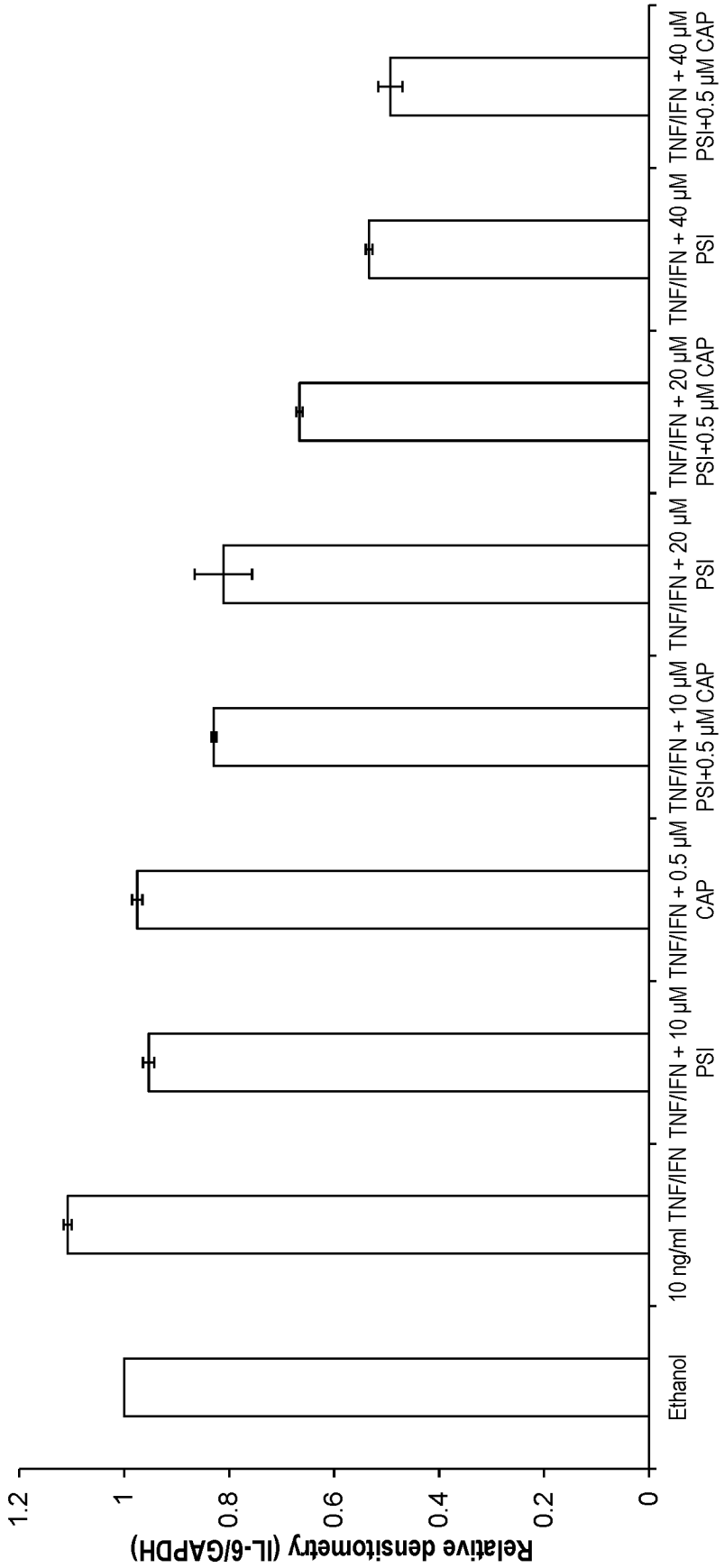
Relative densitometry (IL-6/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 0.5 µM CAP
TNF/IFN + 10 µM PSI+0.5 µM CAP
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+0.5 µM CAP
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+0.5 µM CAP

FIG. 26

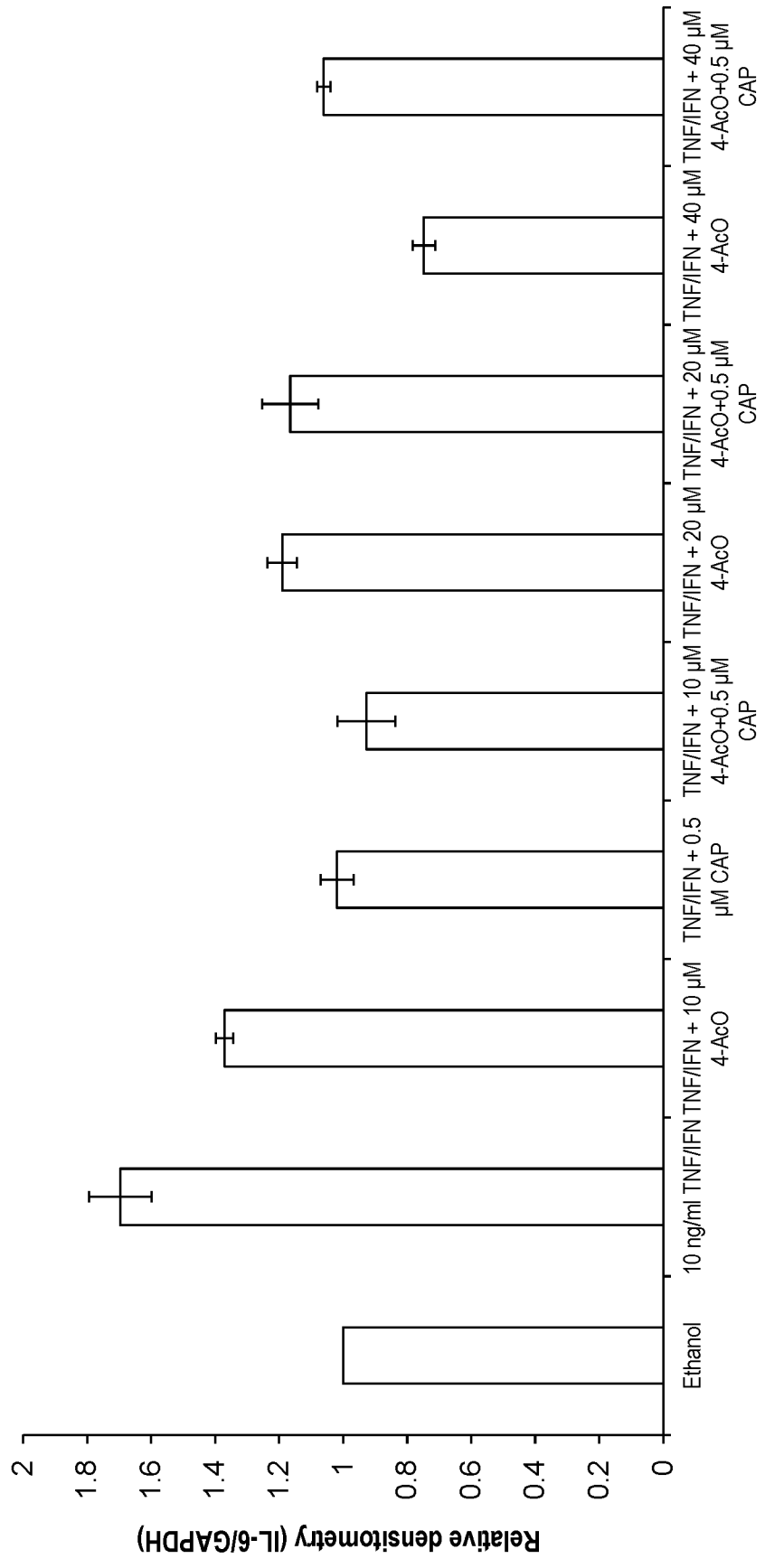
Relative densitometry (IL-6/GAPDH)
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM 4-AcO
TNF/IFN + 0.5 µM CAP
TNF/IFN + 10 µM 4-AcO+0.5 µM CAP
TNF/IFN + 20 µM 4-AcO
TNF/IFN + 20 µM 4-AcO+0.5 µM CAP
TNF/IFN + 40 µM 4-AcO
TNF/IFN + 40 µM 4-AcO+0.5 µM CAP

FIG. 27

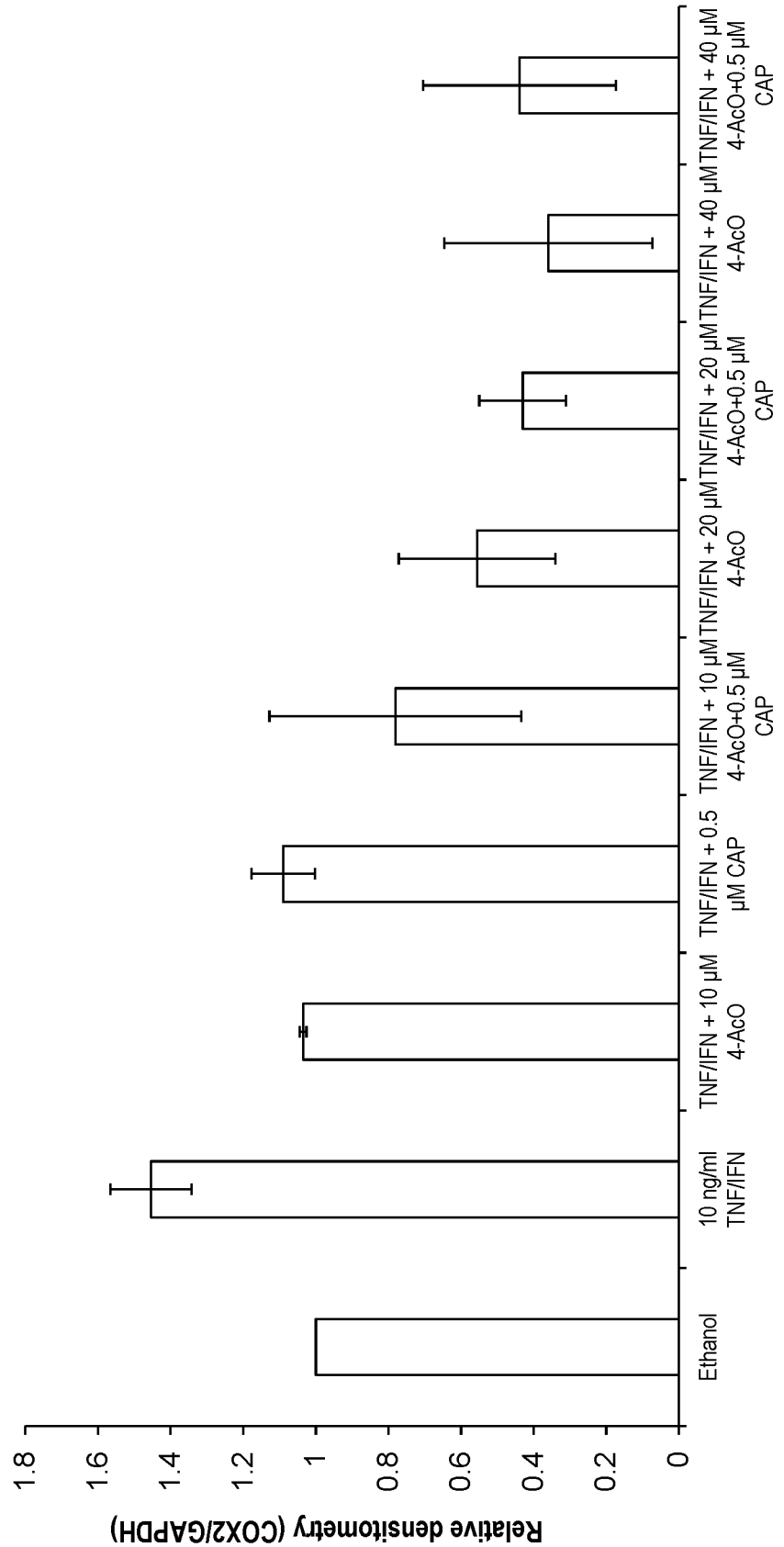
Relative densitometry (COX2/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM 4-AcO
TNF/IFN + 0.5 µM CAP
TNF/IFN + 10 µM 4-AcO+0.5 µM CAP
TNF/IFN + 20 µM 4-AcO
TNF/IFN + 20 µM 4-AcO+0.5 µM CAP
TNF/IFN + 40 µM 4-AcO
TNF/IFN + 40 µM 4-AcO+0.5 µM CAP

FIG. 28

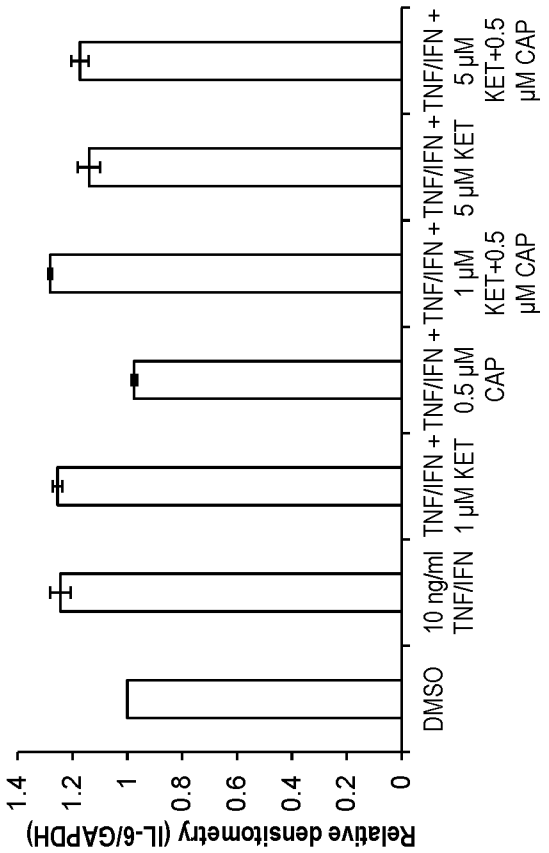

FIG. 29B

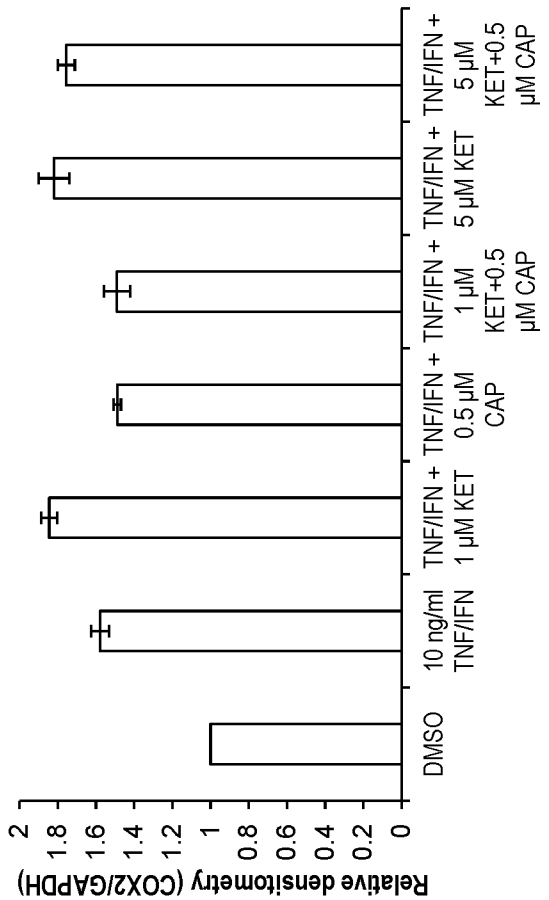

FIG. 29A

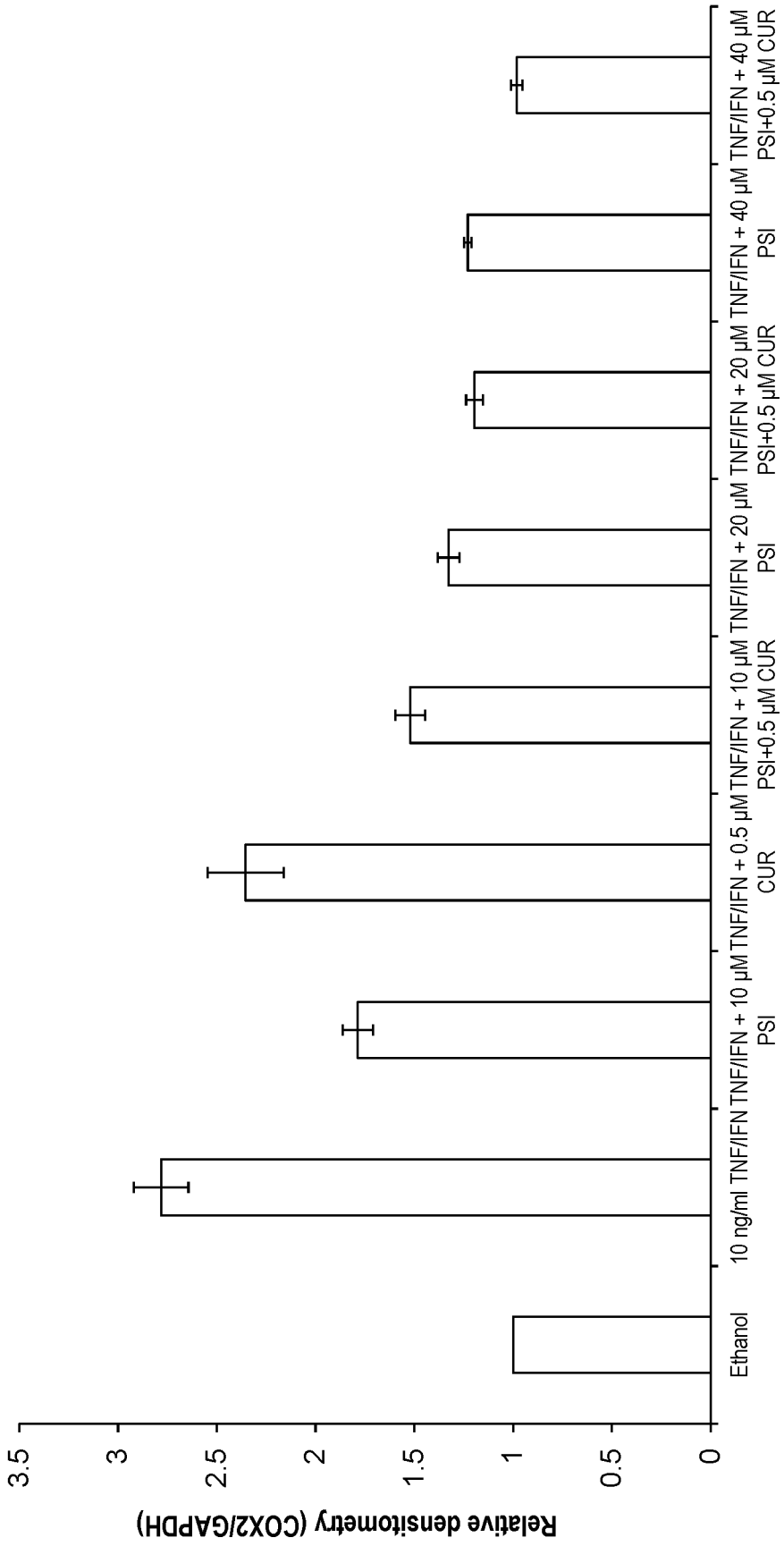
Relative densitometry (COX2/GAPDH)
0
0.5
1
1.5
2
2.5
3
3.5
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 0.5 µM CUR
TNF/IFN + 10 µM PSI+0.5 µM CUR
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+0.5 µM CUR
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+0.5 µM CUR

FIG. 30

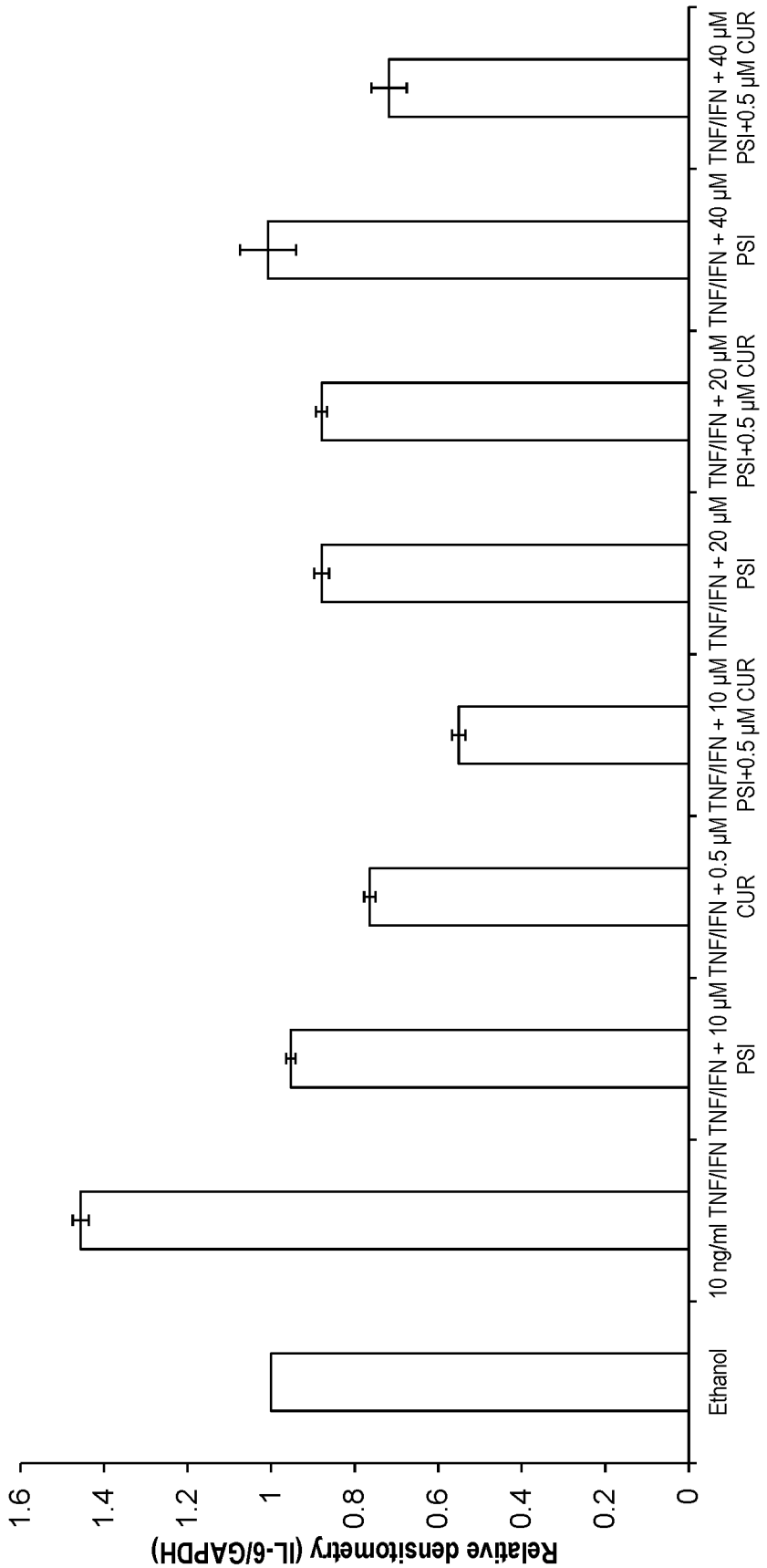
Relative densitometry (IL-6/GAPDH)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 0.5 µM CUR
TNF/IFN + 10 µM PSI+0.5 µM CUR
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+0.5 µM CUR
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+0.5 µM CUR

FIG. 31

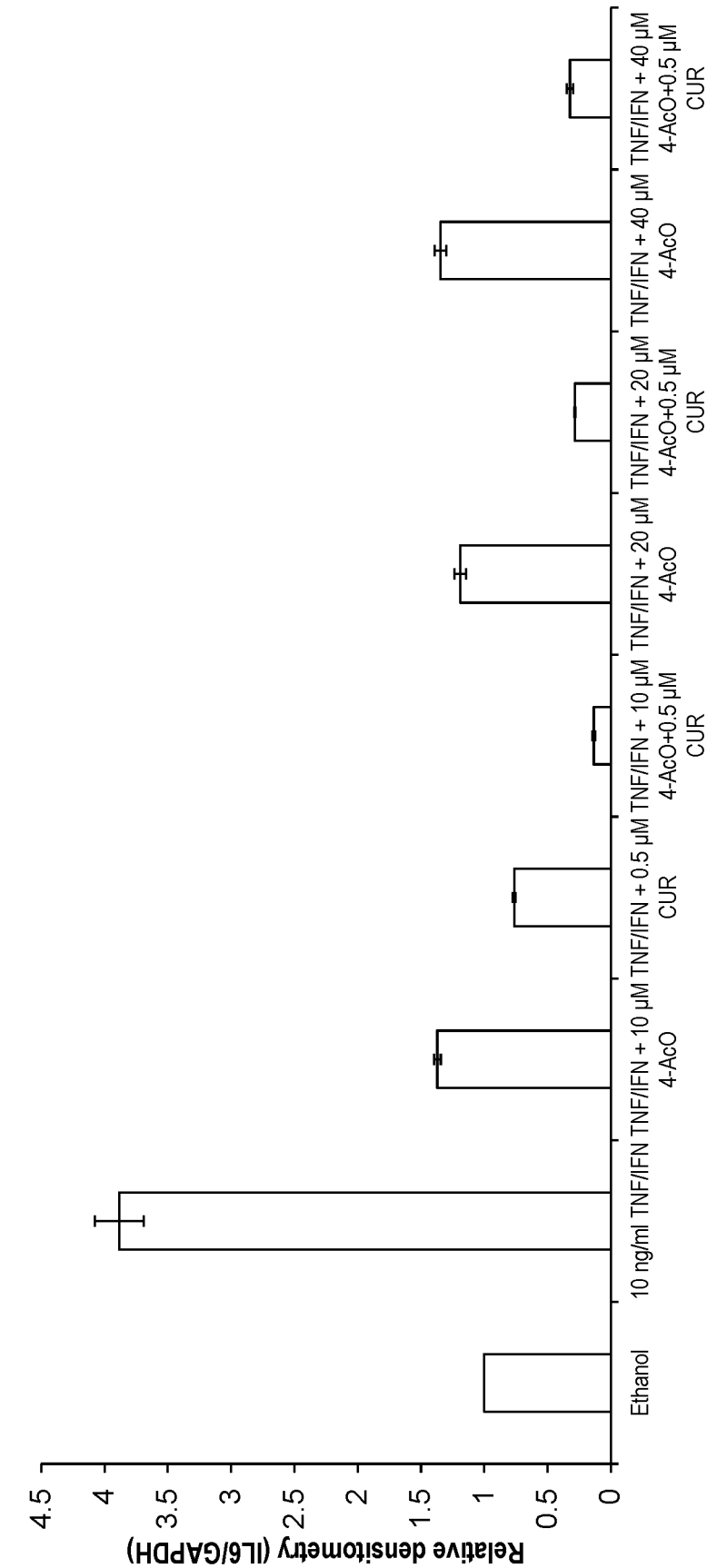
Relative densitometry (IL6/GAPDH)
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM 4-AcO
TNF/IFN + 0.5 µM CUR
TNF/IFN + 10 µM 4-AcO+0.5 µM CUR
TNF/IFN + 20 µM 4-AcO
TNF/IFN + 20 µM 4-AcO+0.5 µM CUR
TNF/IFN + 40 µM 4-AcO
TNF/IFN + 40 µM 4-AcO+0.5 µM CUR

FIG. 32

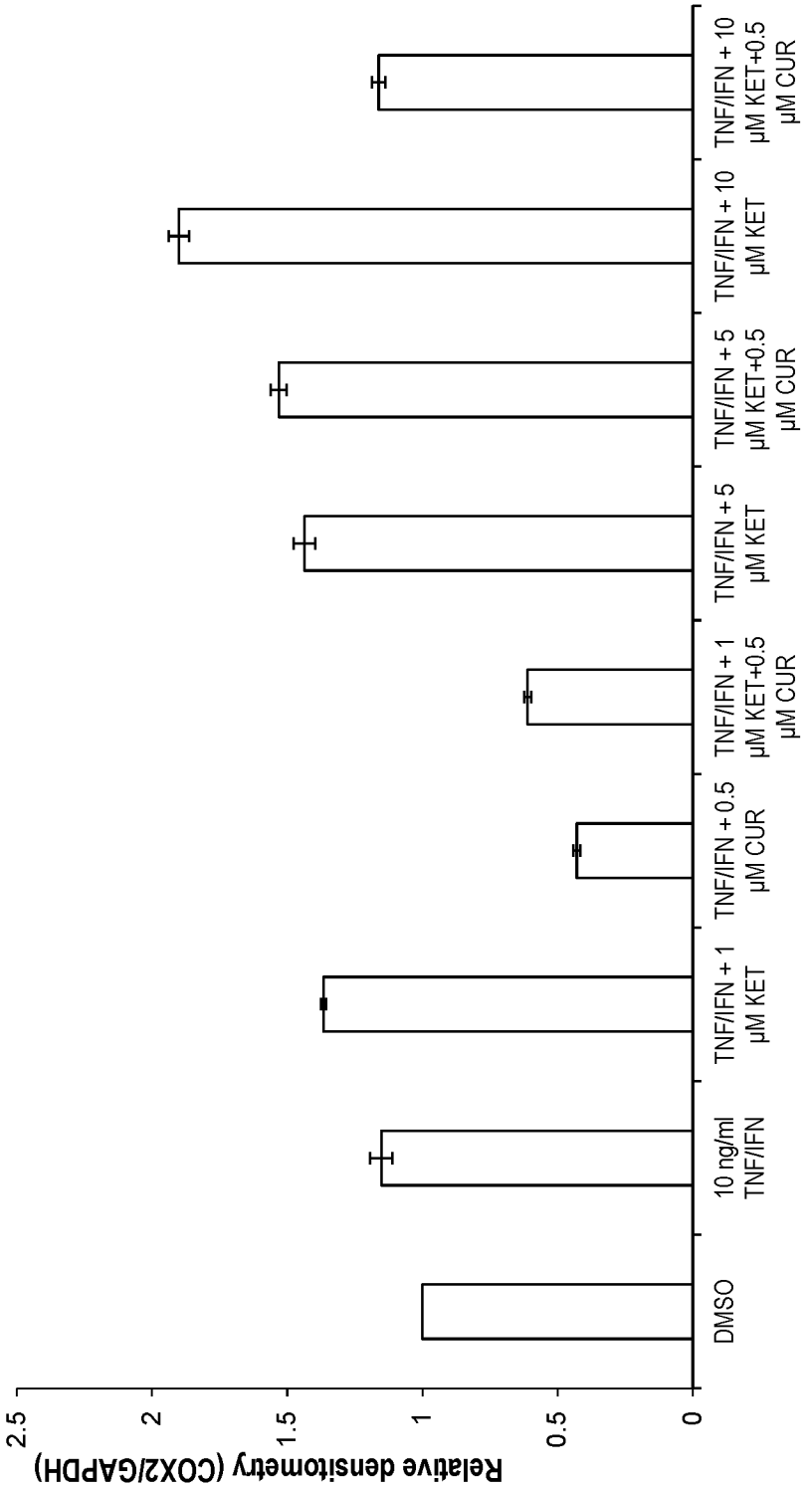
Relative densitometry (COX2/GAPDH)
2.5
2
1.5
1
0.5
0
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 1 µM KET
TNF/IFN + 0.5 µM CUR
TNF/IFN + 1 µM KET+0.5 µM CUR
TNF/IFN + 5 µM KET
TNF/IFN + 5 µM KET+0.5 µM CUR
TNF/IFN + 10 µM KET
TNF/IFN + 10 µM KET+0.5 µM CUR

FIG. 33A

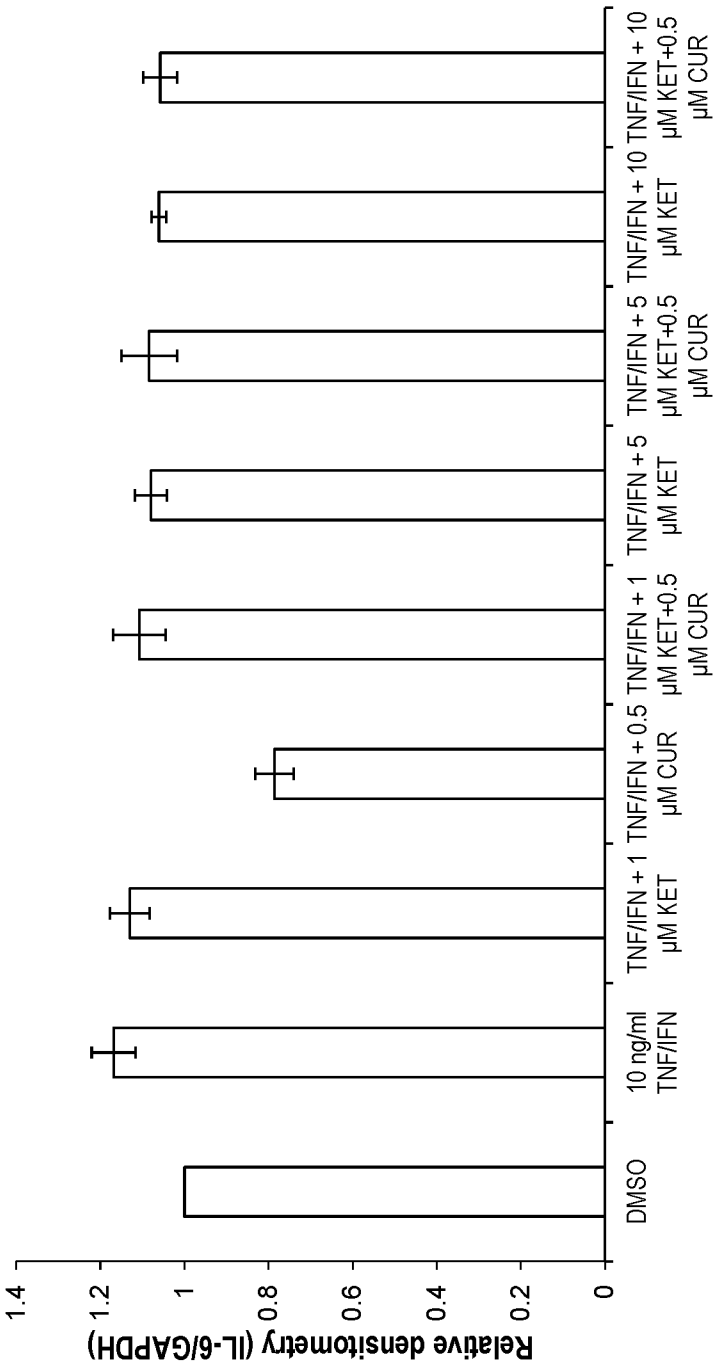
Relative densitometry (IL-6/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 1 µM KET
TNF/IFN + 0.5 µM CUR
TNF/IFN + 1 µM KET+0.5 µM CUR
TNF/IFN + 5 µM KET
TNF/IFN + 5 µM KET+0.5 µM CUR
TNF/IFN + 10 µM KET
TNF/IFN + 10 µM KET+0.5 µM CUR

FIG. 33B

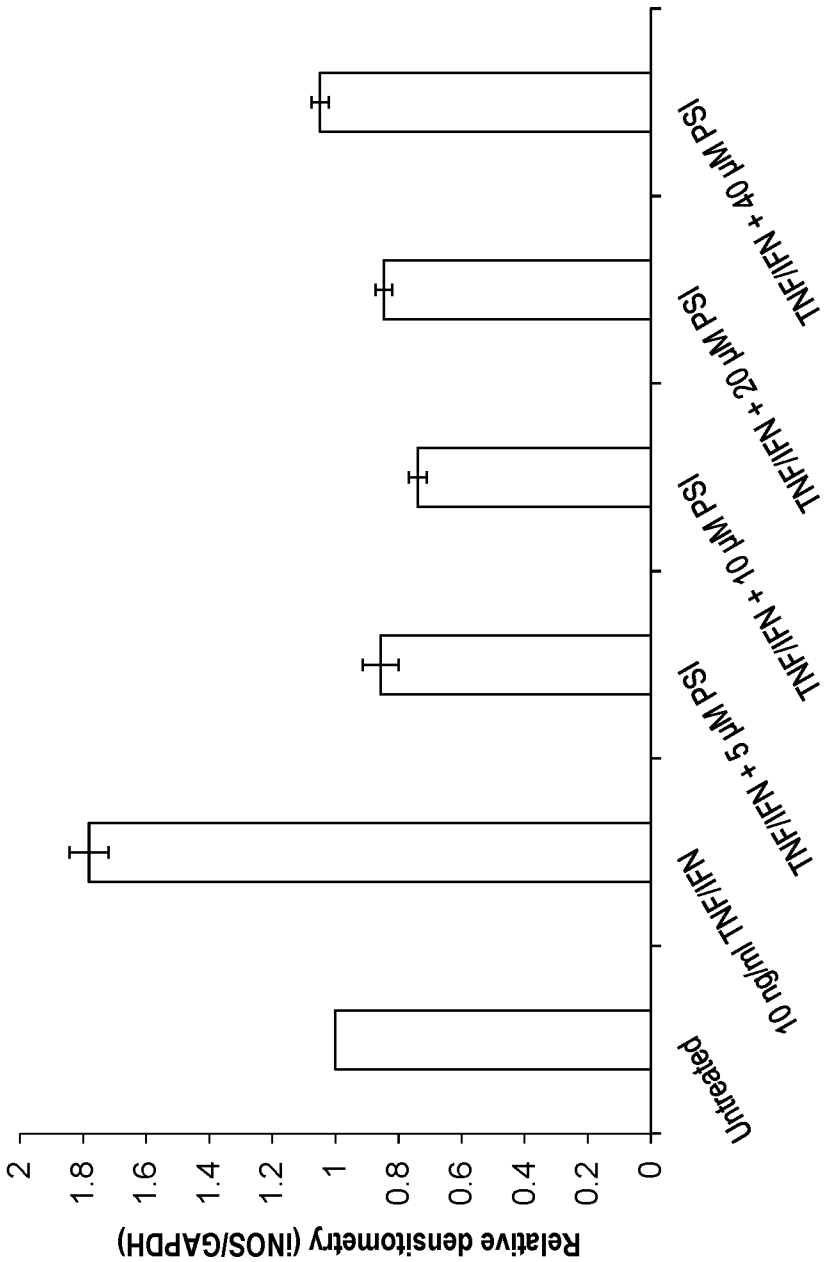
Relative densitometry (iNOS/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
Untreated
10 ng/ml TNF/IFN
TNF/IFN + 5 µM PSI
TNF/IFN + 10 µM PSI
TNF/IFN + 20 µM PSI
TNF/IFN + 40 µM PSI

FIG. 34

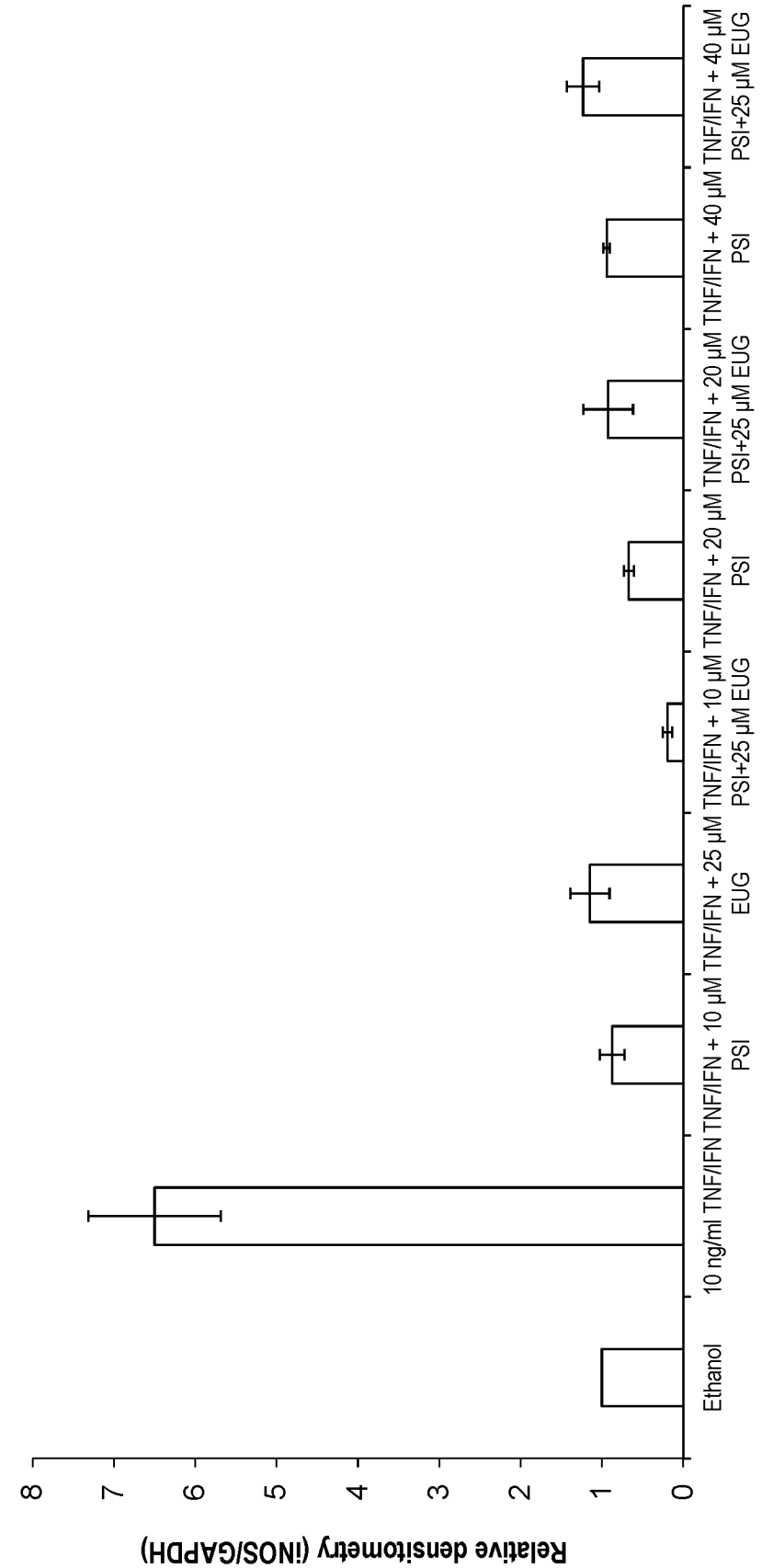
Relative densitometry (iNOS/GAPDH)
0
1
2
3
4
5
6
7
8
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 25 µM EUG
TNF/IFN + 10 µM PSI+25 µM EUG
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI+25 µM EUG
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI+25 µM EUG

FIG. 35

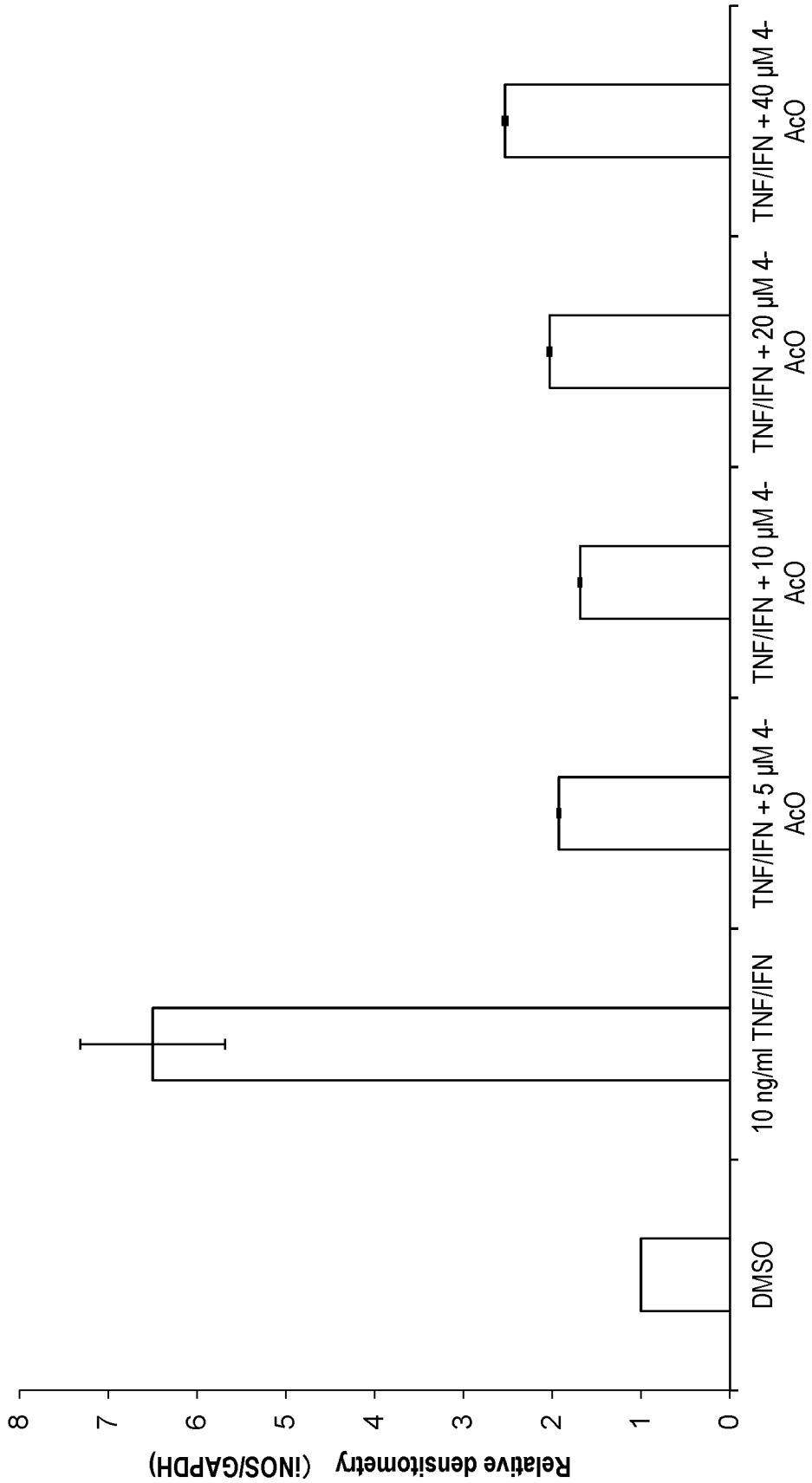
Relative densitometry (iNOS/GAPDH)
0
1
2
3
4
5
6
7
8
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 5 µM 4-AcO
TNF/IFN + 10 µM 4-AcO
TNF/IFN + 20 µM 4-AcO
TNF/IFN + 40 µM 4-AcO

FIG. 36

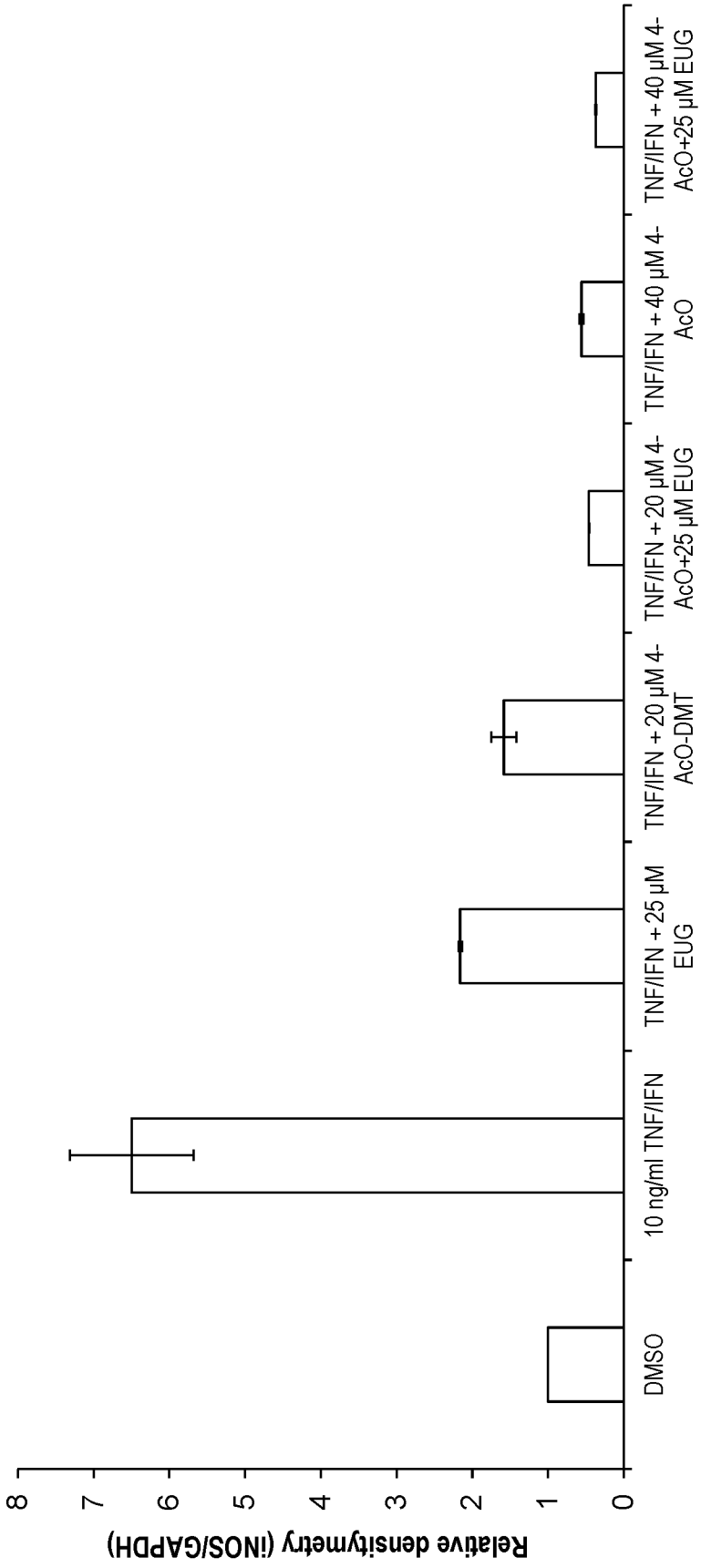
Relative densitymetry (iNOS/GAPDH)
0
1
2
3
4
5
6
7
8
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 25 µM EUG
TNF/IFN + 20 µM 4-AcO-DMT
TNF/IFN + 20 µM 4-AcO+25 µM EUG
TNF/IFN + 40 µM 4-AcO
TNF/IFN + 40 µM 4-AcO+25 µM EUG

FIG. 37

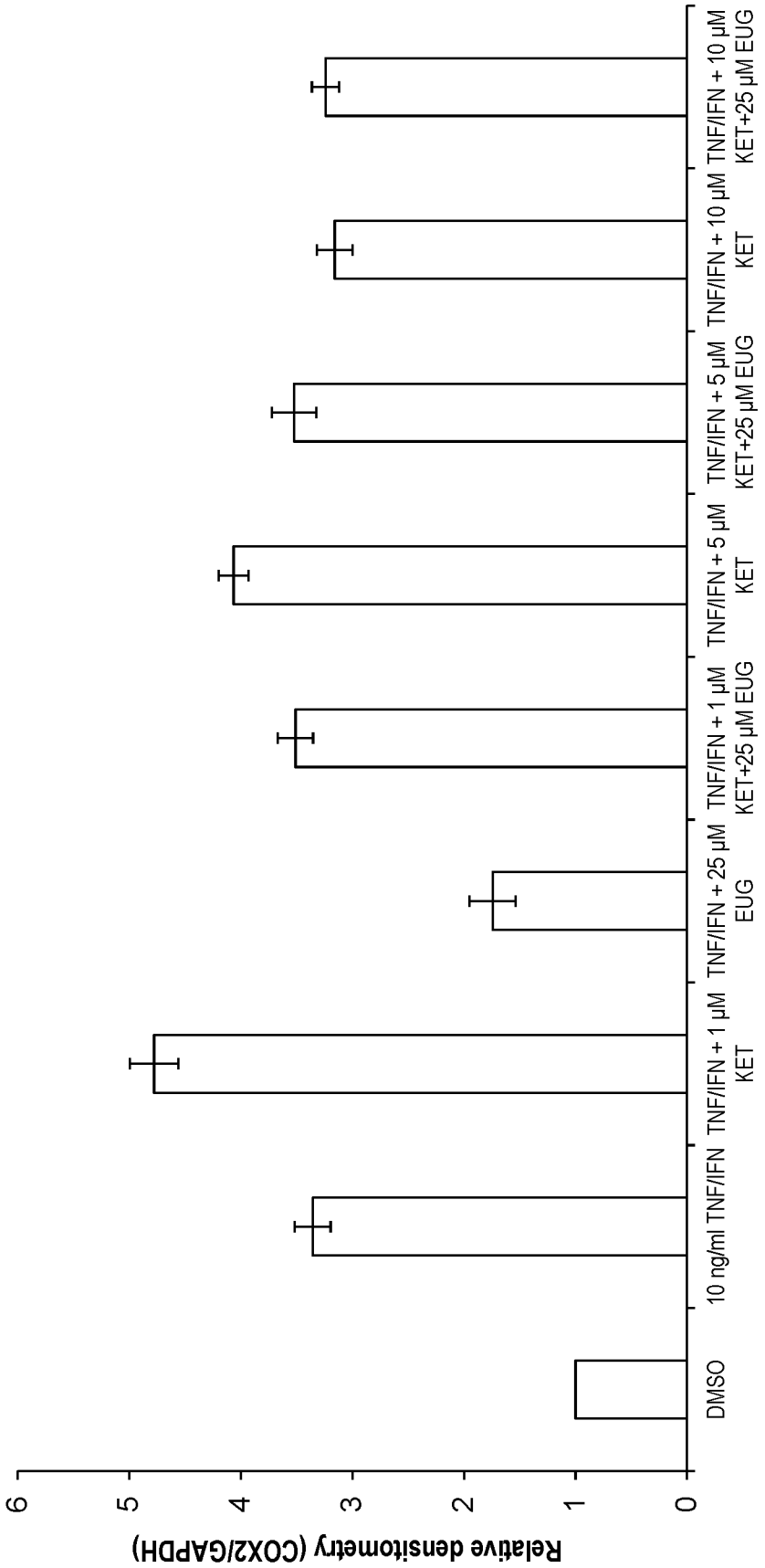
Relative densitometry (COX2/GAPDH)
0
1
2
3
4
5
6
DMSO
10 ng/ml TNF/IFN
TNF/IFN + 1 µM KET
TNF/IFN + 25 µM EUG
TNF/IFN + 1 µM KET+25 µM EUG
TNF/IFN + 5 µM KET
TNF/IFN + 5 µM KET+25 µM EUG
TNF/IFN + 10 µM KET
TNF/IFN + 10 µM KET+25 µM EUG

FIG. 38

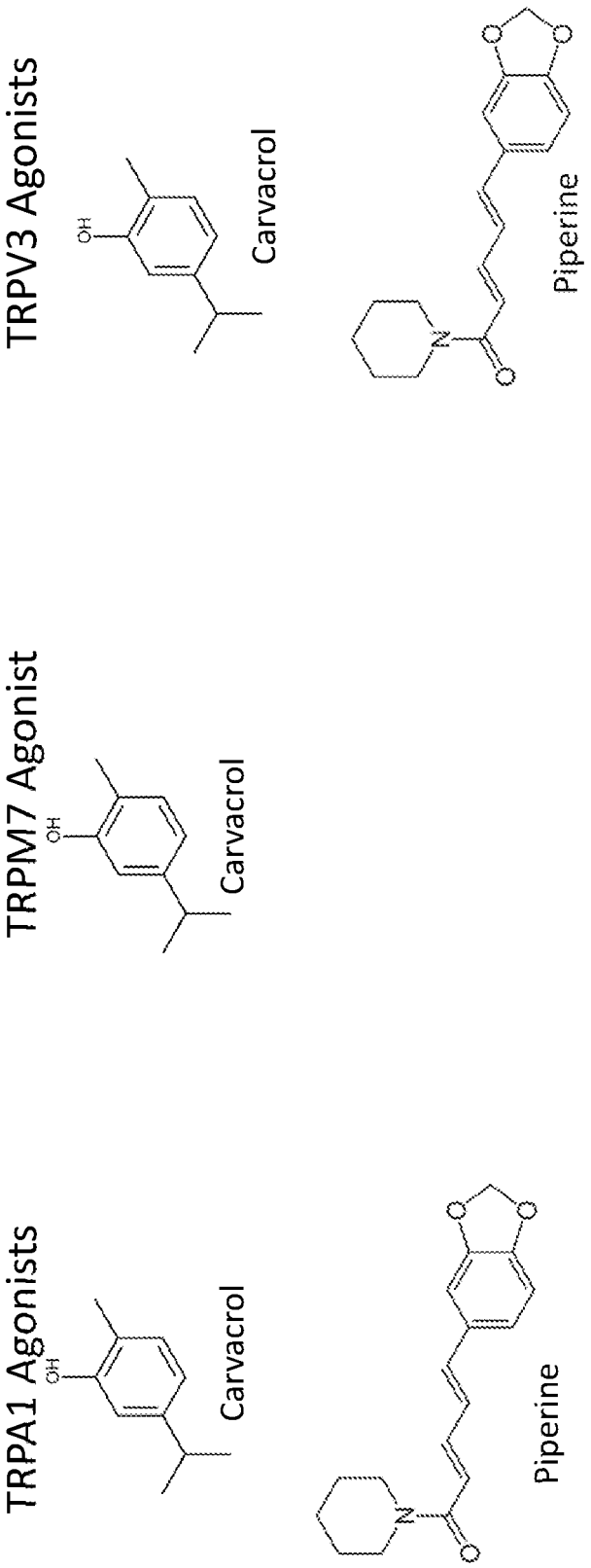
TRPV3 Agonists
Carvacrol
Piperine
TRPM7 Agonist
Carvacrol
TRPA1 Agonists
Carvacrol
Piperine
Cinnamaldehyde

FIG. 39

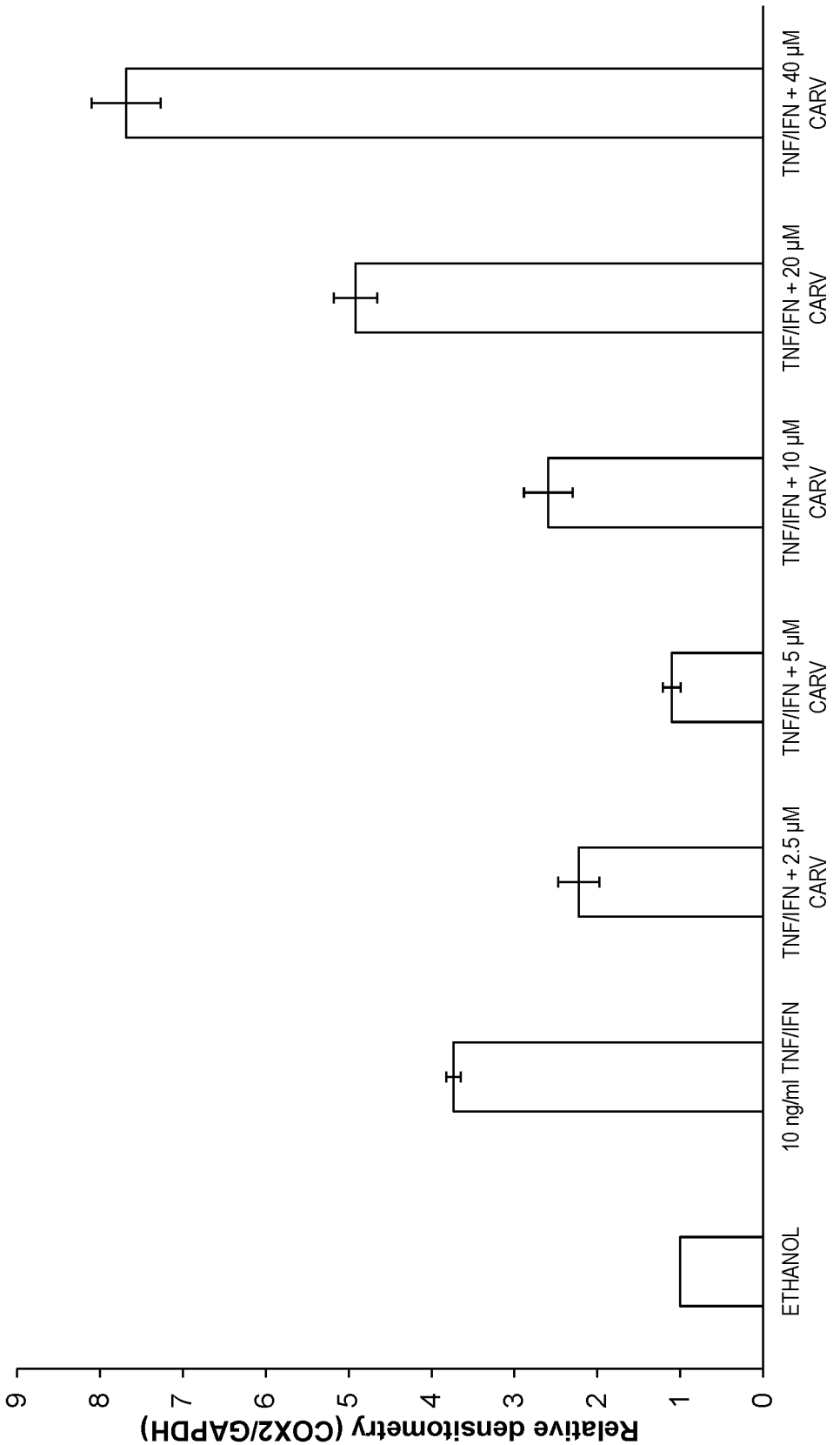
Relative densitometry (COX2/GAPDH)
0
1
2
3
4
5
6
7
8
9
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM CARV
TNF/IFN + 5 µM CARV
TNF/IFN + 10 µM CARV
TNF/IFN + 20 µM CARV
TNF/IFN + 40 µM CARV

FIG. 40

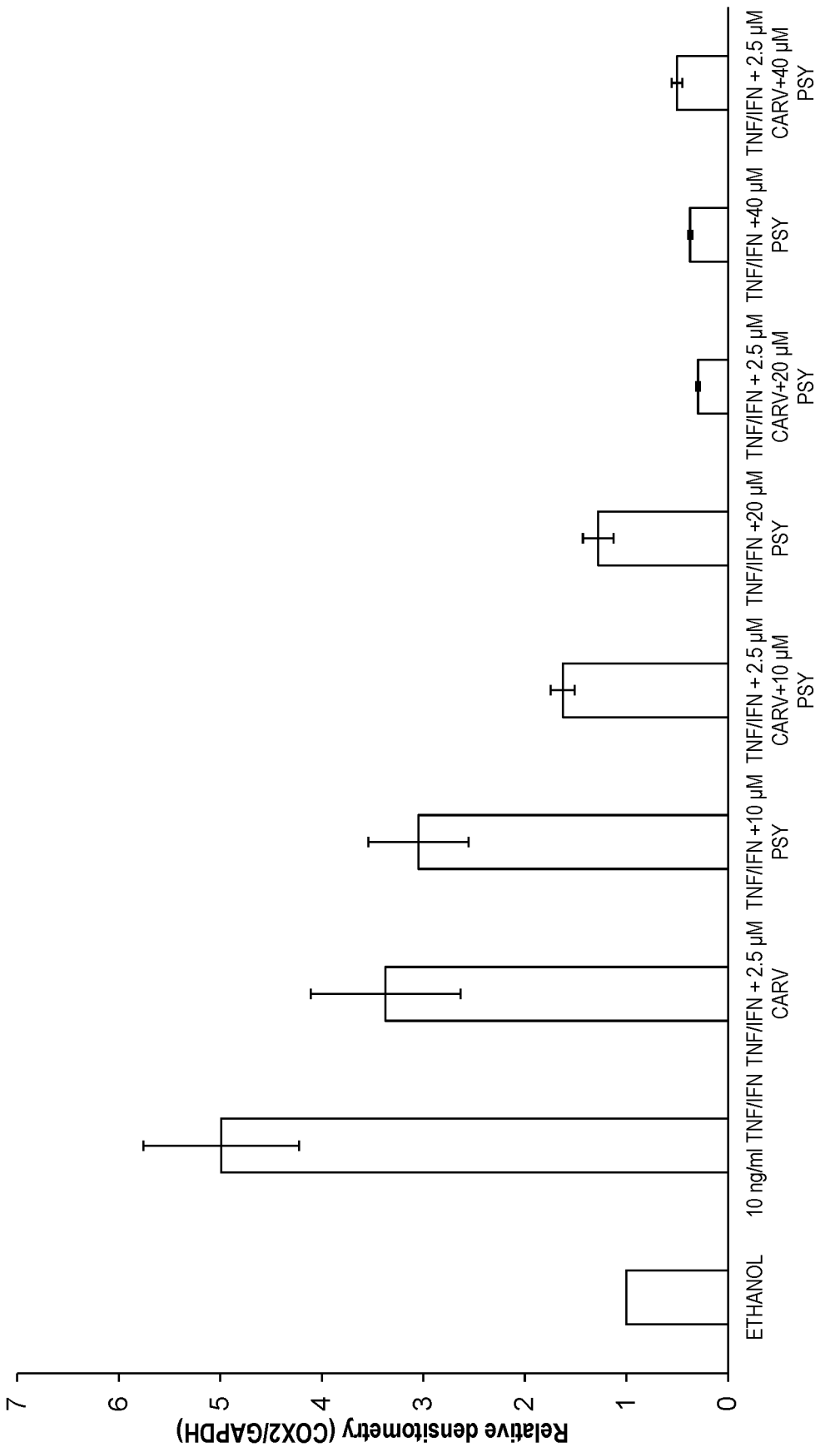
Relative densitometry (COX2/GAPDH)
0
1
2
3
4
5
6
7
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM CARV
TNF/IFN +10 µM PSY
TNF/IFN + 2.5 µM CARV+10 µM PSY
TNF/IFN +20 µM PSY
TNF/IFN + 2.5 µM CARV+20 µM PSY
TNF/IFN +40 µM PSY
TNF/IFN + 2.5 µM CARV+40 µM PSY

FIG. 41

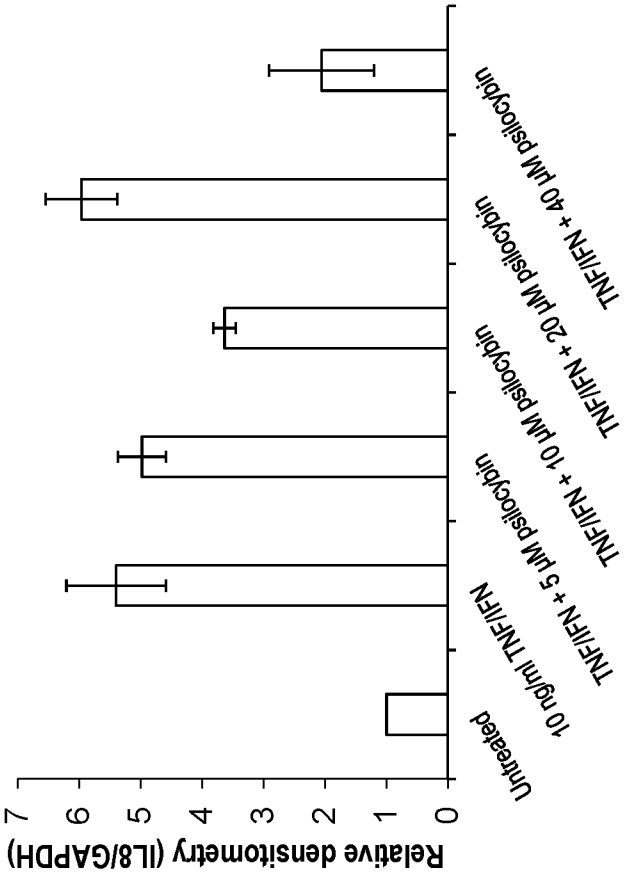

FIG. 42B

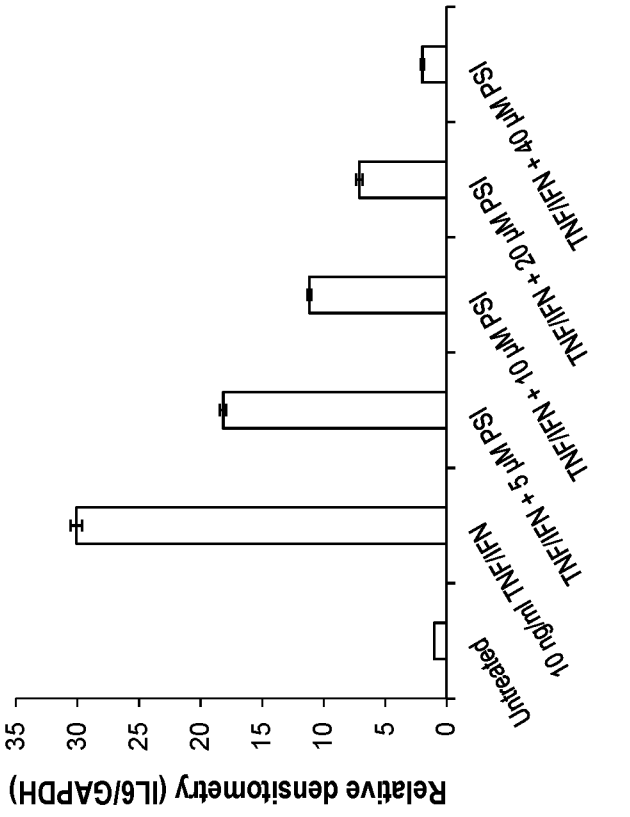

FIG. 42A

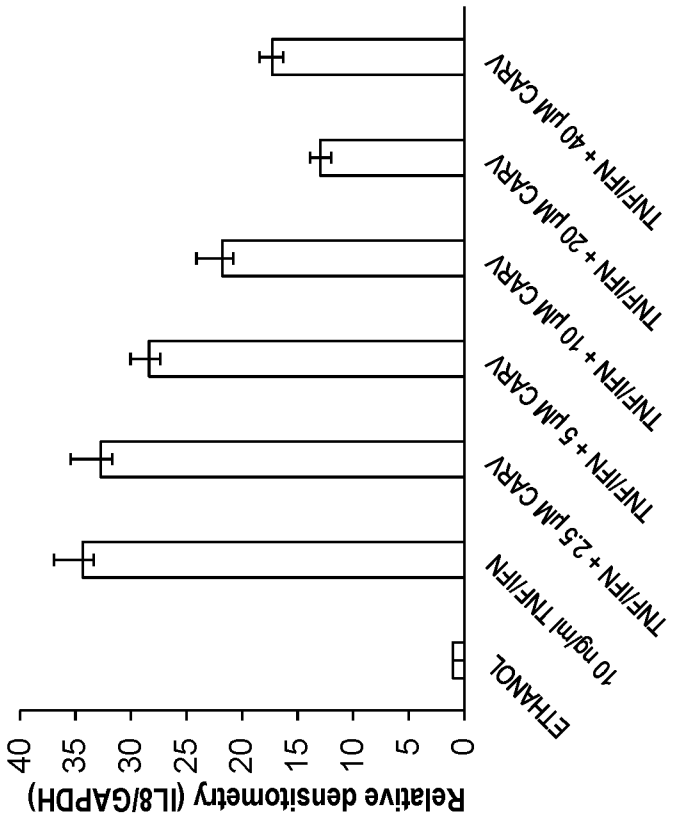

FIG. 43B

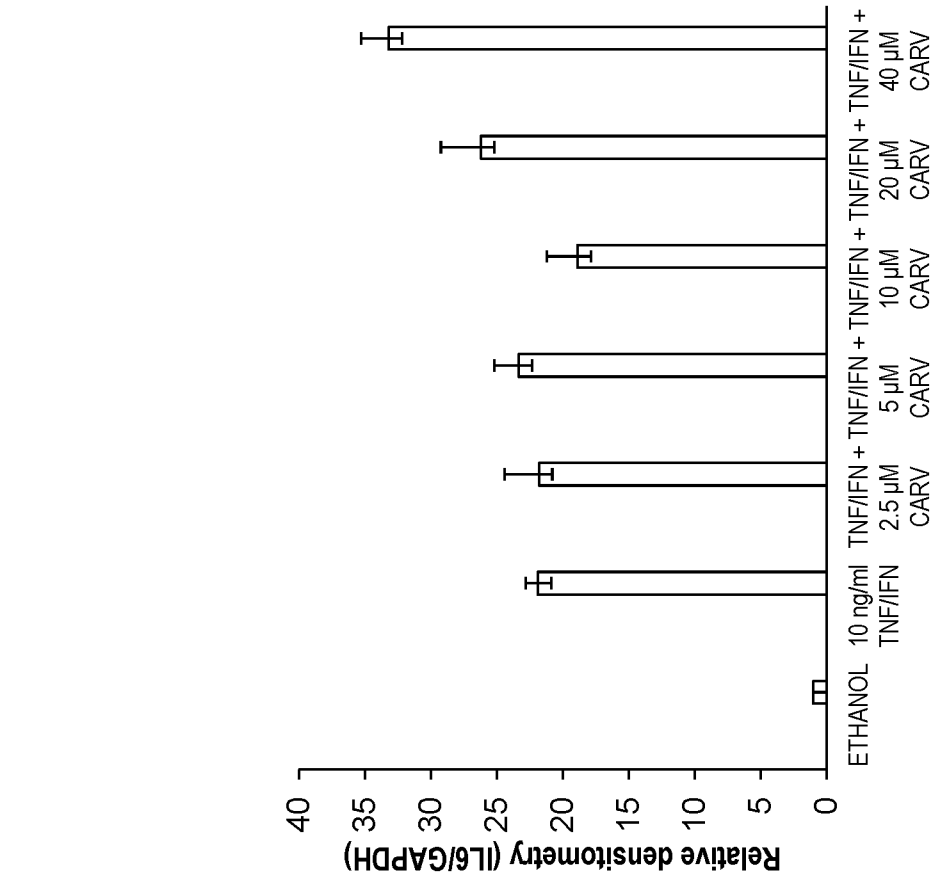

FIG. 43A

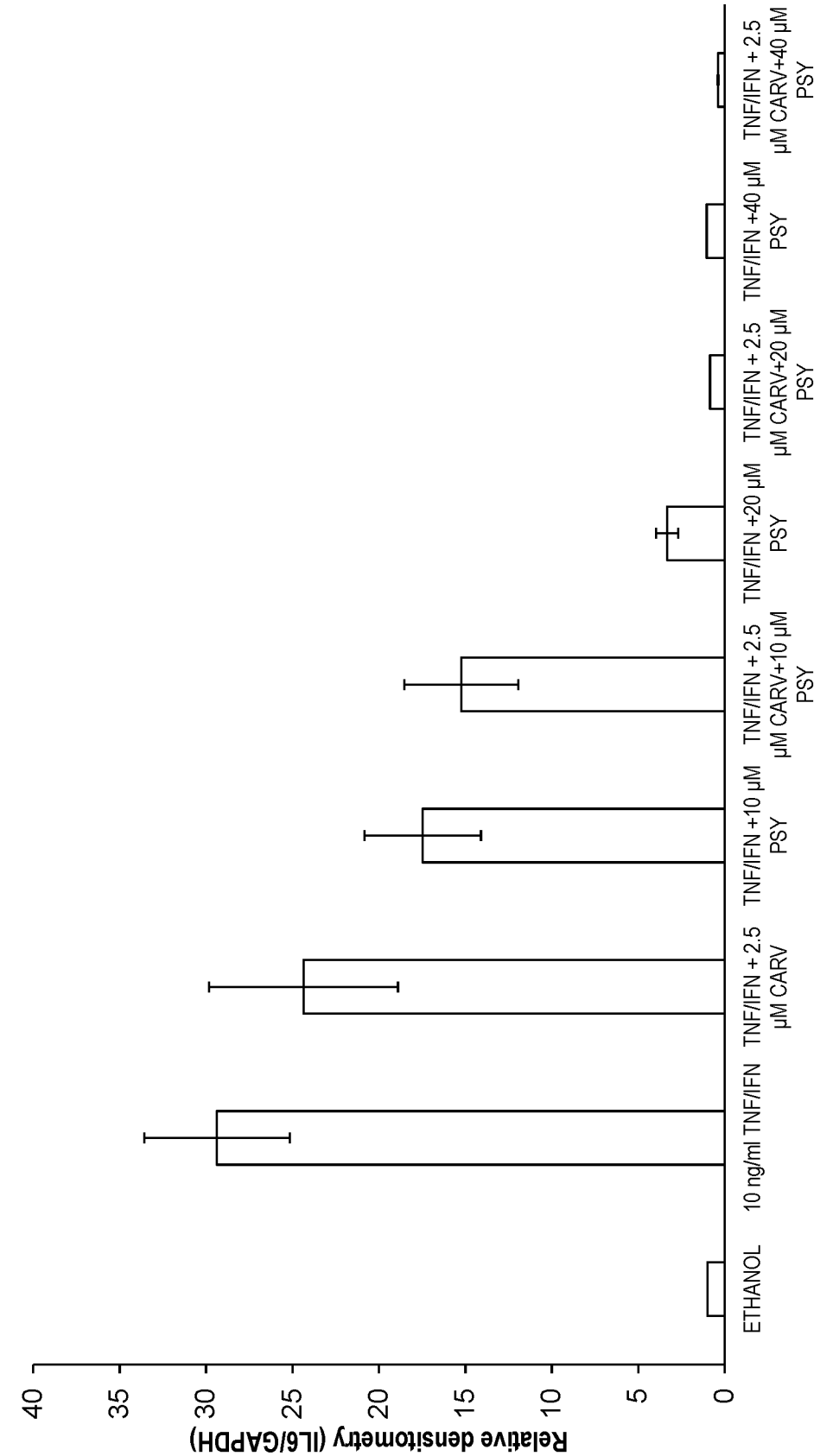
Relative densitometry (IL6/GAPDH)
0
5
10
15
20
25
30
35
40
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM CARV
TNF/IFN +10 µM PSY
TNF/IFN + 2.5 µM CARV+10 µM PSY
TNF/IFN +20 µM PSY
TNF/IFN + 2.5 µM CARV+20 µM PSY
TNF/IFN +40 µM PSY
TNF/IFN + 2.5 µM CARV+40 µM PSY

FIG. 44

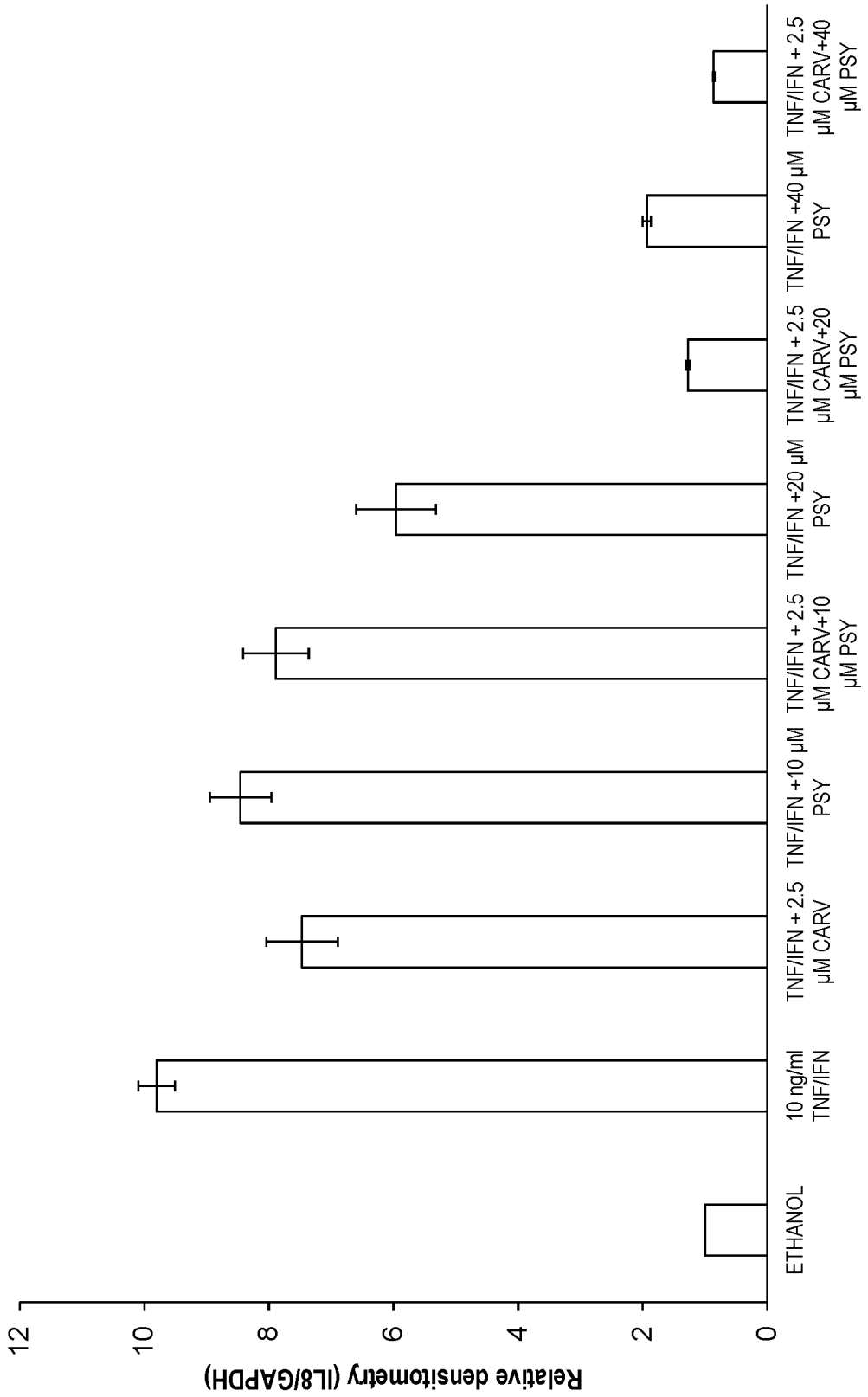
Relative densitometry (IL8/GAPDH)
0
2
4
6
8
10
12
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM CARV
TNF/IFN +10 µM PSY
TNF/IFN + 2.5 µM CARV+10 µM PSY
TNF/IFN +20 µM PSY
TNF/IFN + 2.5 µM CARV+20 µM PSY
TNF/IFN +40 µM PSY
TNF/IFN + 2.5 µM CARV+40 µM PSY

FIG. 45

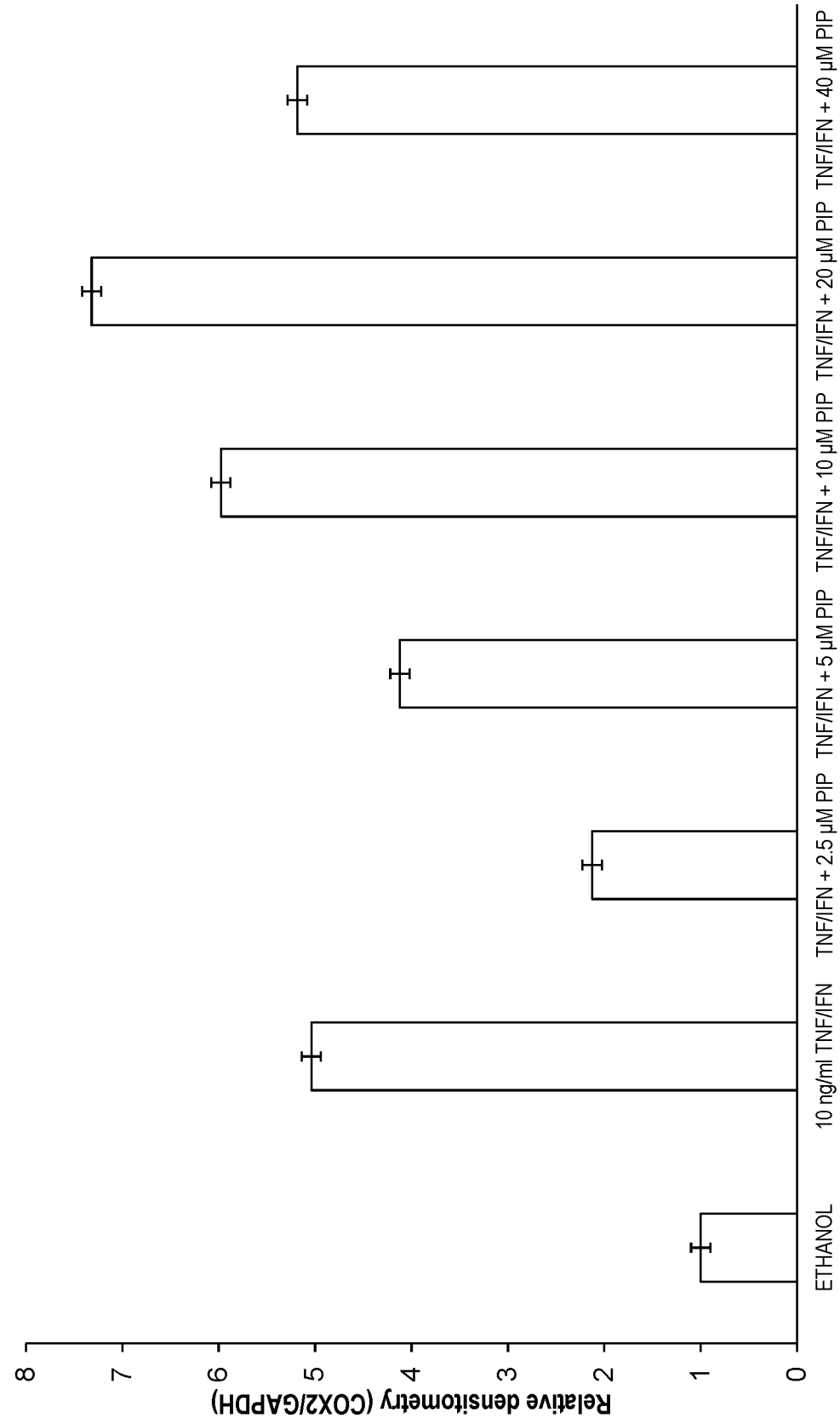
Relative densitometry (COX2/GAPDH)
0
1
2
3
4
5
6
7
8
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM PIP
TNF/IFN + 5 µM PIP
TNF/IFN + 10 µM PIP
TNF/IFN + 20 µM PIP
TNF/IFN + 40 µM PIP

FIG. 46

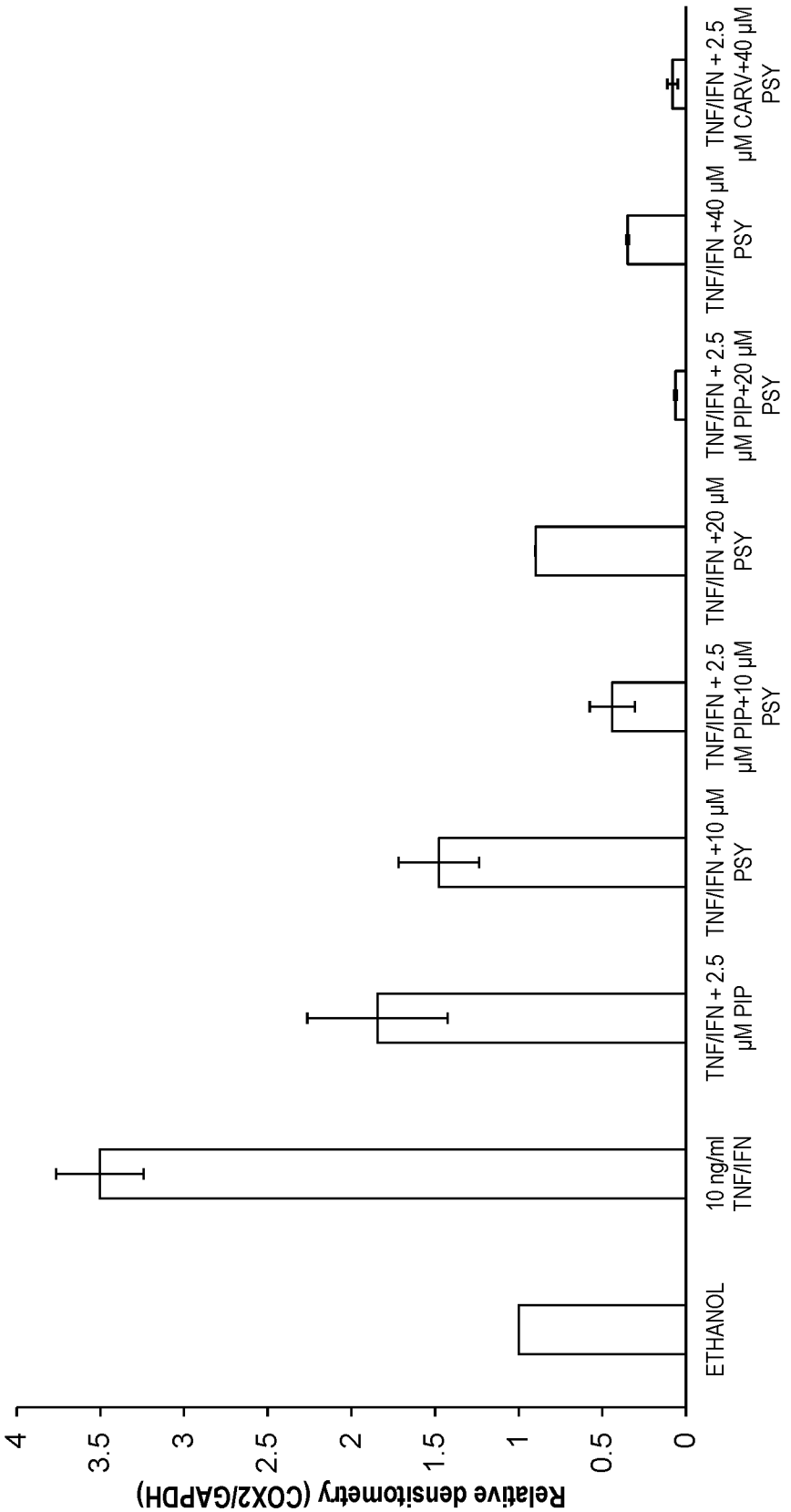
Relative densitometry (COX2/GAPDH)
0
0.5
1
1.5
2
2.5
3
3.5
4
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM PIP
TNF/IFN +10 µM PSY
TNF/IFN + 2.5 µM PIP+10 µM PSY
TNF/IFN +20 µM PSY
TNF/IFN + 2.5 µM PIP+20 µM PSY
TNF/IFN +40 µM PSY
TNF/IFN + 2.5 µM CARV+40 µM PSY

FIG. 47

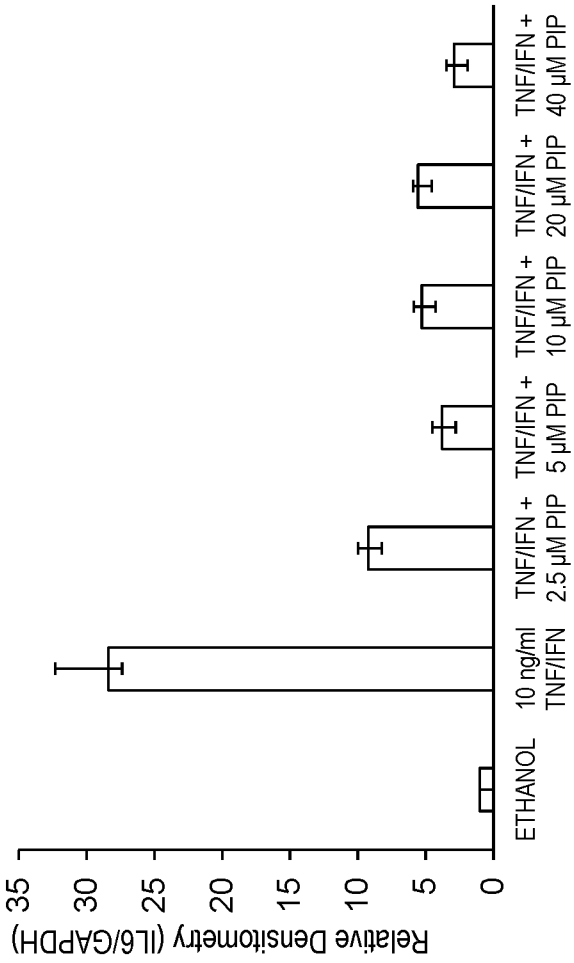

FIG. 48A

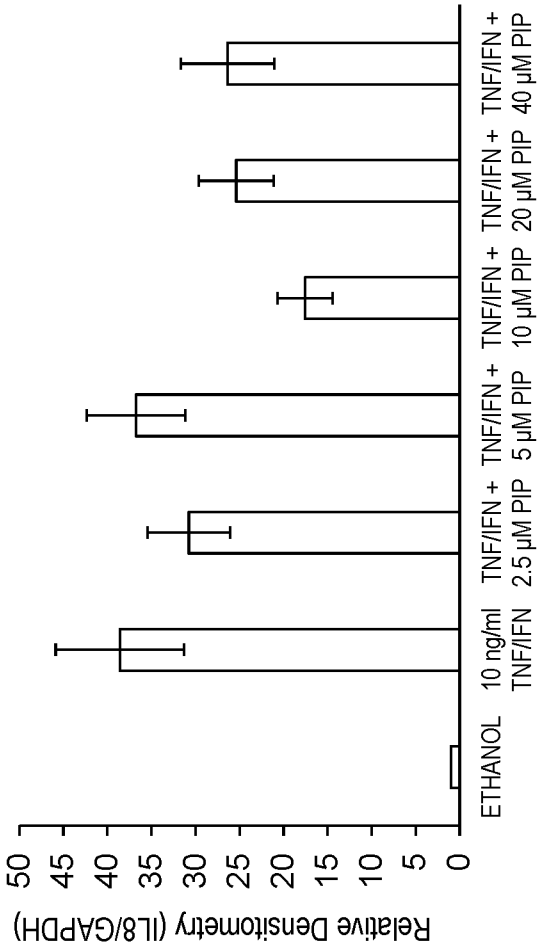

FIG. 48B

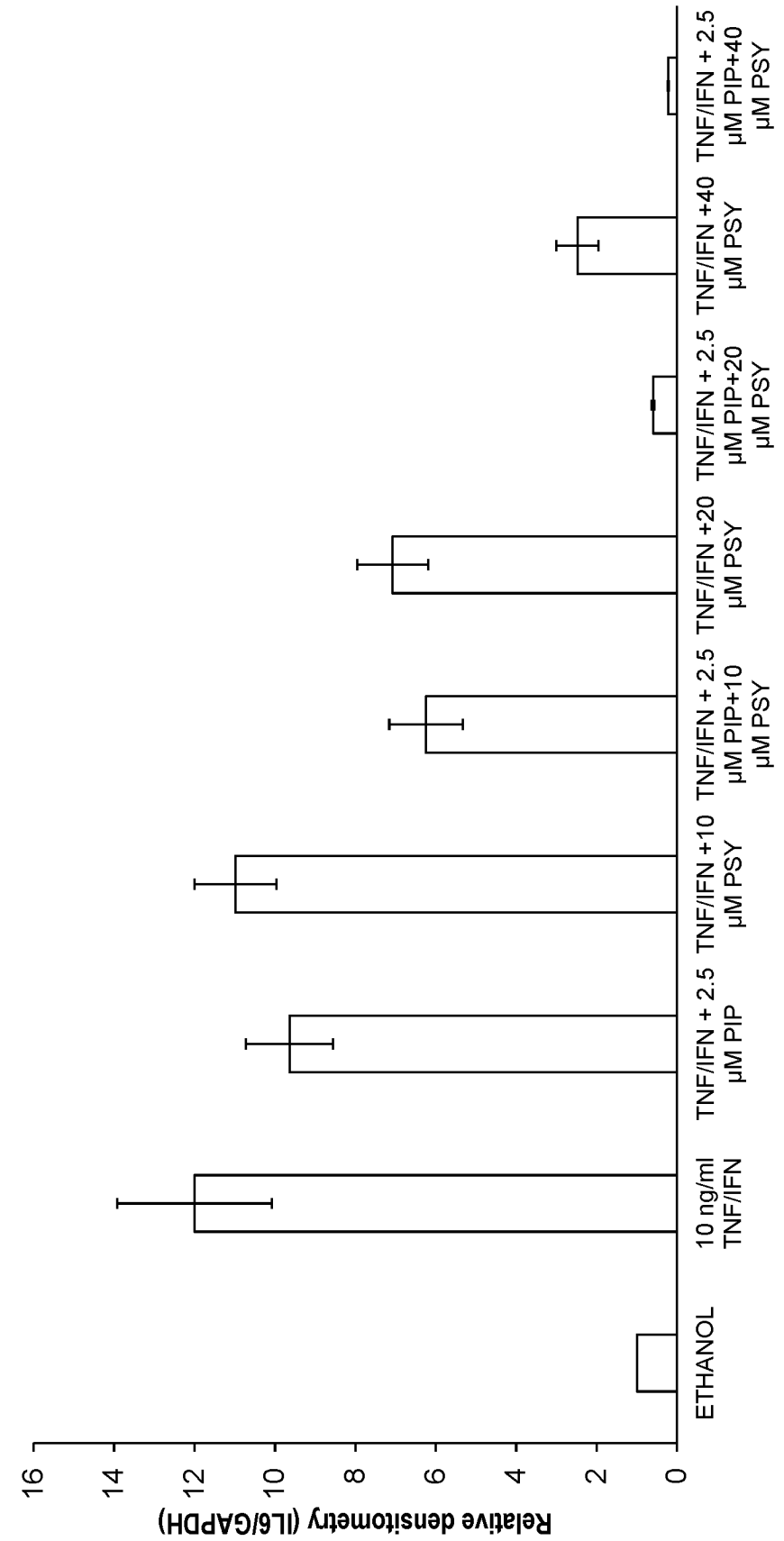
Relative densitometry (IL6/GAPDH)
0
2
4
6
8
10
12
14
16
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM PIP
TNF/IFN +10 µM PSY
TNF/IFN + 2.5 µM PIP+10 µM PSY
TNF/IFN +20 µM PSY
TNF/IFN + 2.5 µM PIP+20 µM PSY
TNF/IFN +40 µM PSY
TNF/IFN + 2.5 µM PIP+40 µM PSY

FIG. 49

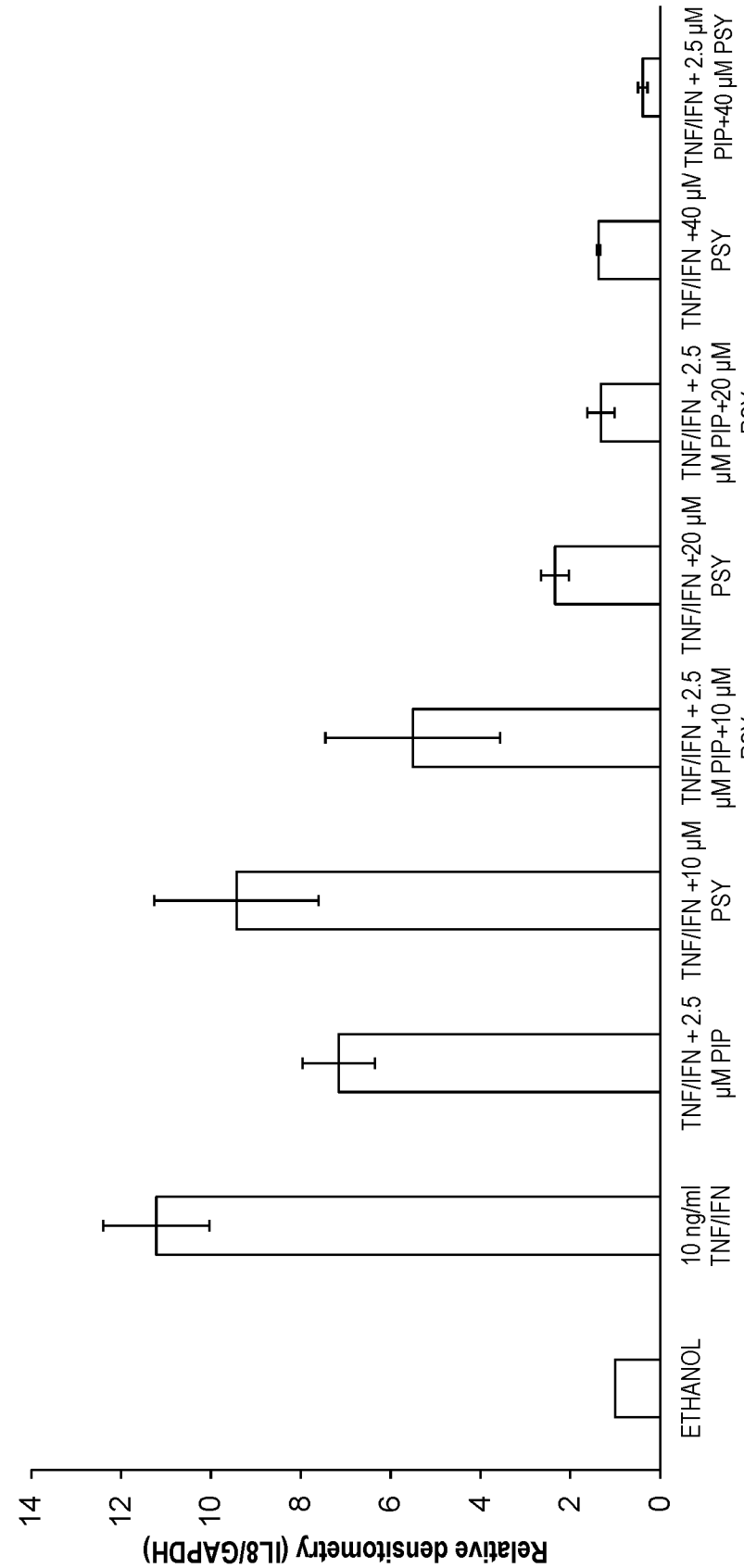
Relative densitometry (IL8/GAPDH)
0
2
4
6
8
10
12
14
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 2.5 µM PIP
TNF/IFN +10 µM PSY
TNF/IFN + 2.5 µM PIP+10 µM PSY
TNF/IFN +20 µM PSY
TNF/IFN + 2.5 µM PIP+20 µM PSY
TNF/IFN +40 µM PSY
TNF/IFN + 2.5 µM PIP+40 µM PSY

FIG. 50

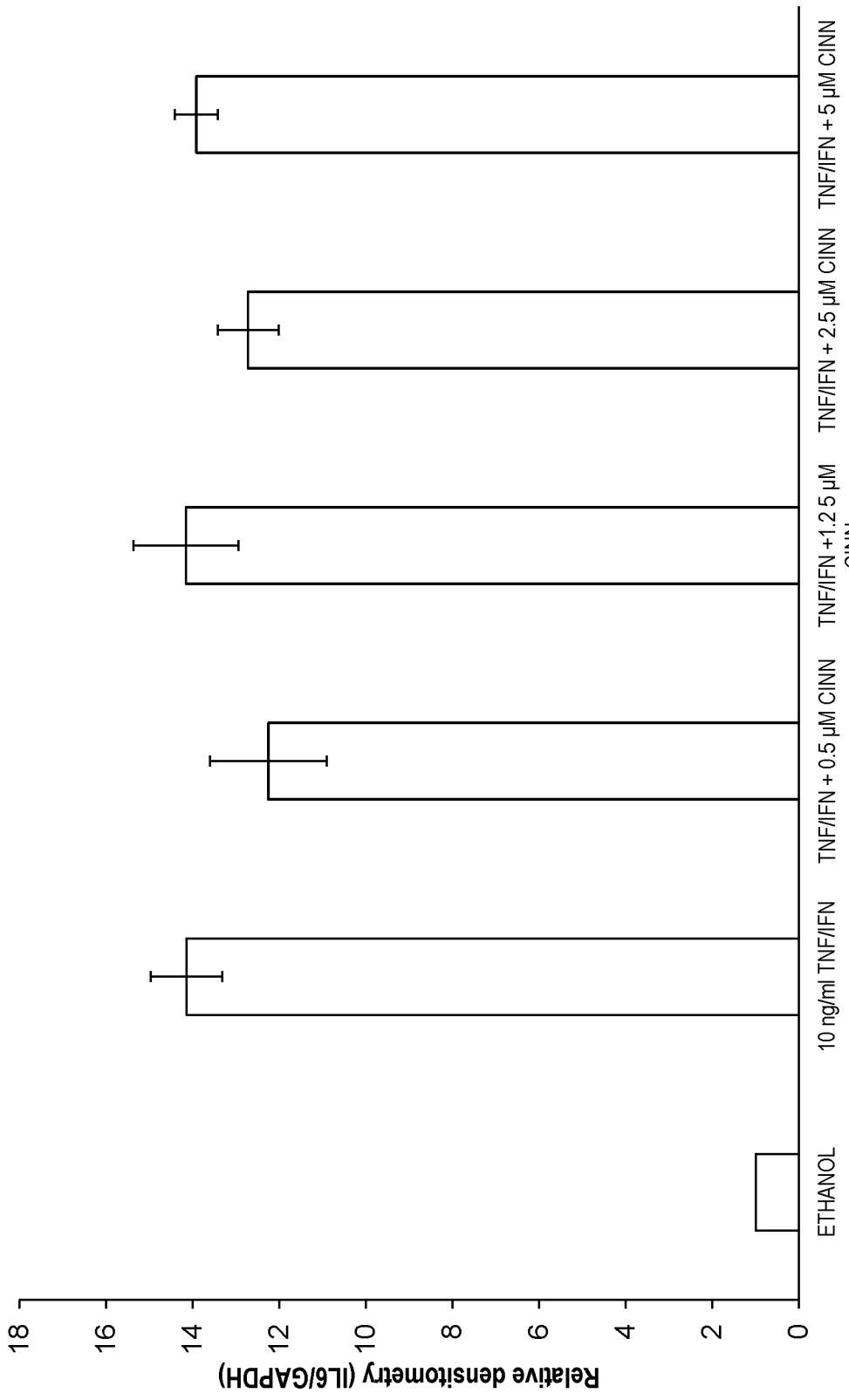
Relative densitometry (IL6/GAPDH)
0
2
4
6
8
10
12
14
16
18
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 0.5 µM CINN
TNF/IFN +1.2 5 µM CINN
TNF/IFN + 2.5 µM CINN
TNF/IFN + 5 µM CINN

FIG. 51

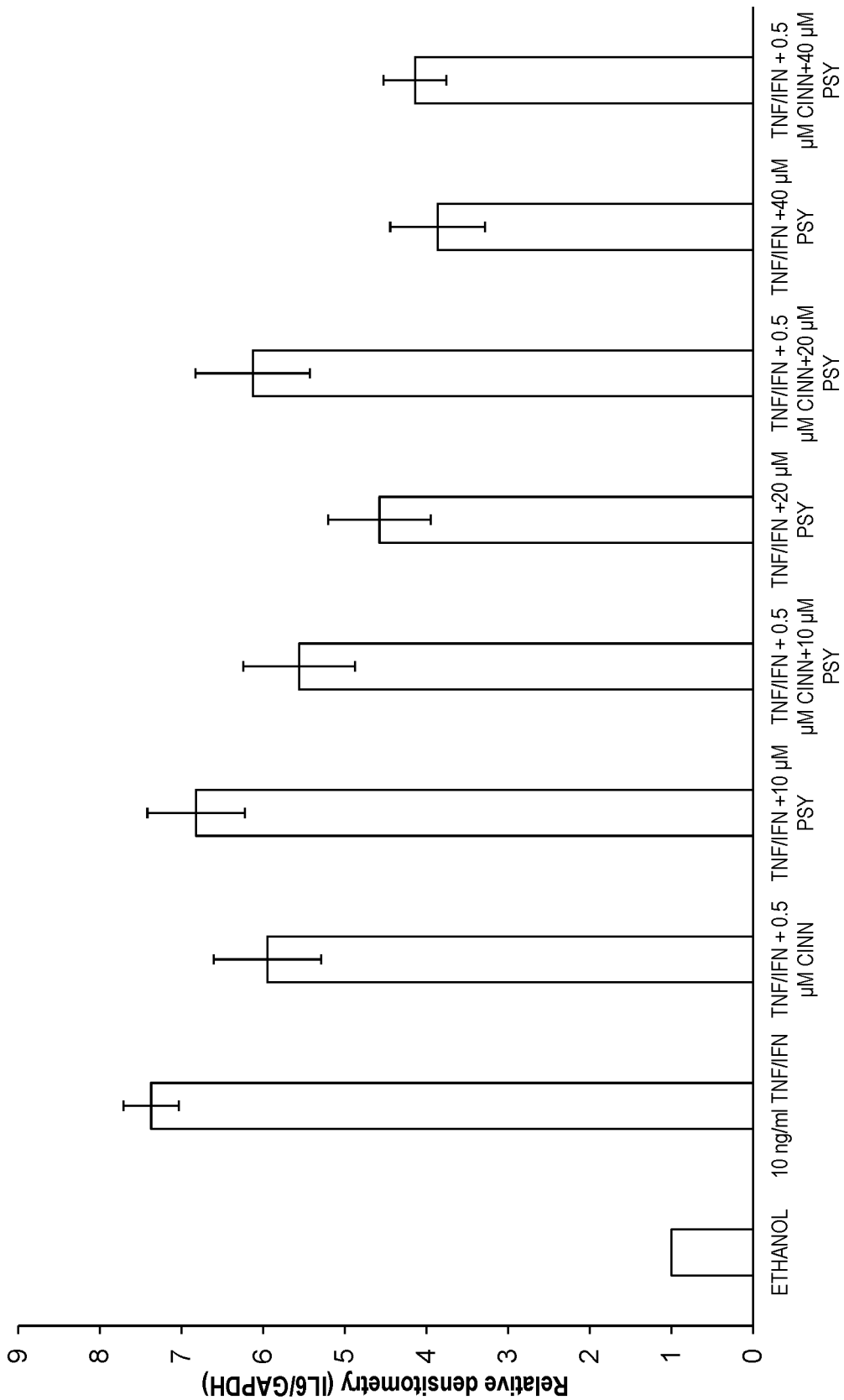
Relative densitometry (IL6/GAPDH)
0
1
2
3
4
5
6
7
8
9
ETHANOL
10 ng/ml TNF/IFN
TNF/IFN + 0.5 µM CINN
TNF/IFN +10 µM PSY
TNF/IFN + 0.5 µM CINN+10 µM PSY
TNF/IFN +20 µM PSY
TNF/IFN + 0.5 µM CINN+20 µM PSY
TNF/IFN +40 µM PSY
TNF/IFN + 0.5 µM CINN+40 µM PSY

FIG. 52

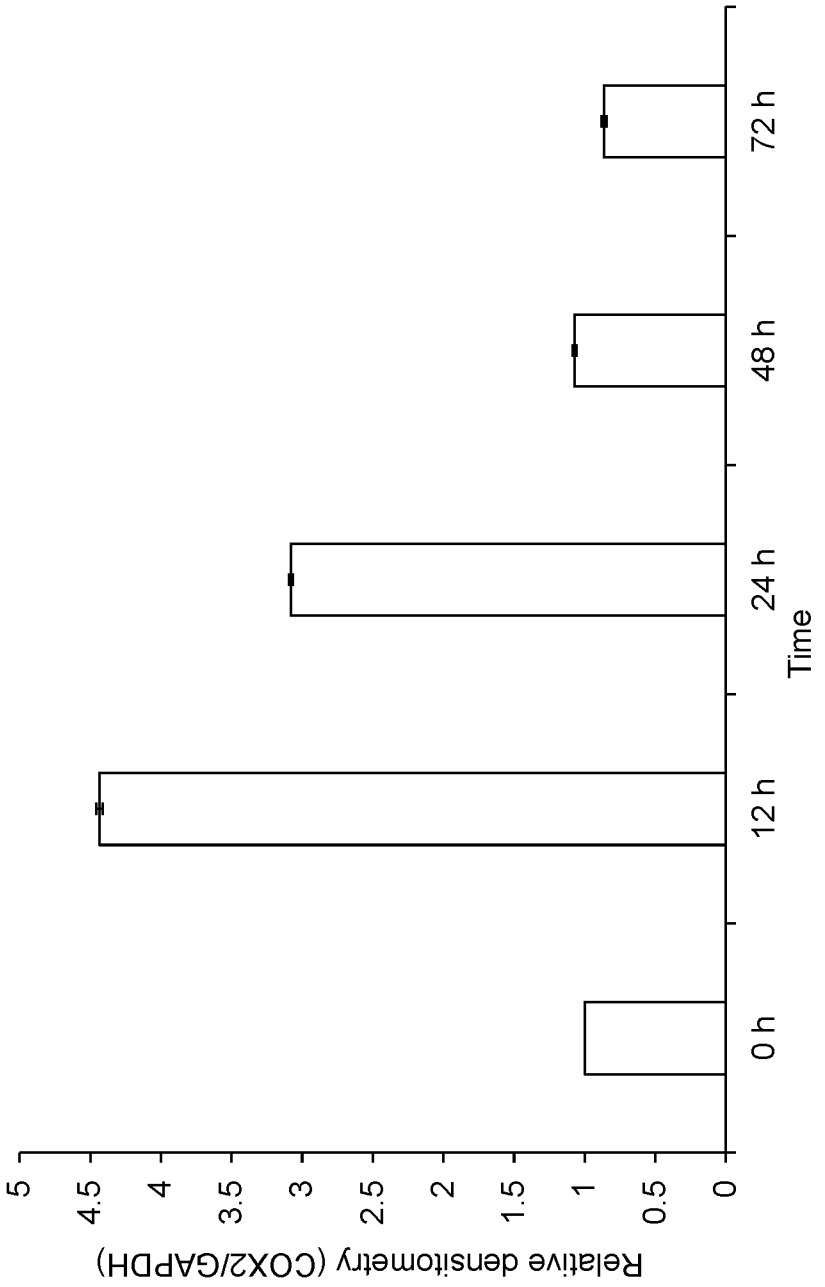
Relative densitometry (COX2/GAPDH)
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
0 h
12 h
24 h
48 h
72 h
Time

FIG. 53

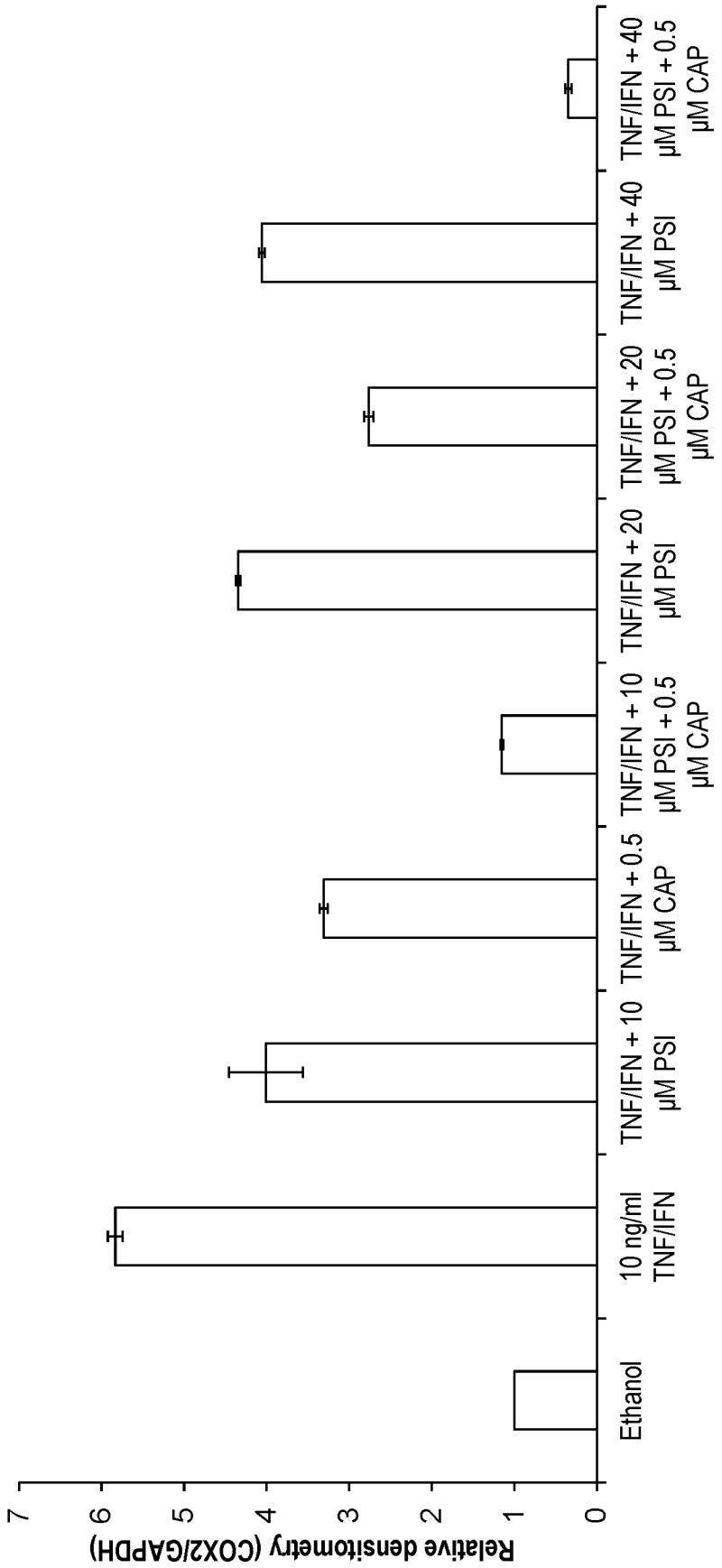
Relative densitometry (COX2/GAPDH)
0
1
2
3
4
5
6
7
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 0.5 µM CAP
TNF/IFN + 10 µM PSI + 0.5 µM CAP
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI + 0.5 µM CAP
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI + 0.5 µM CAP

FIG. 54

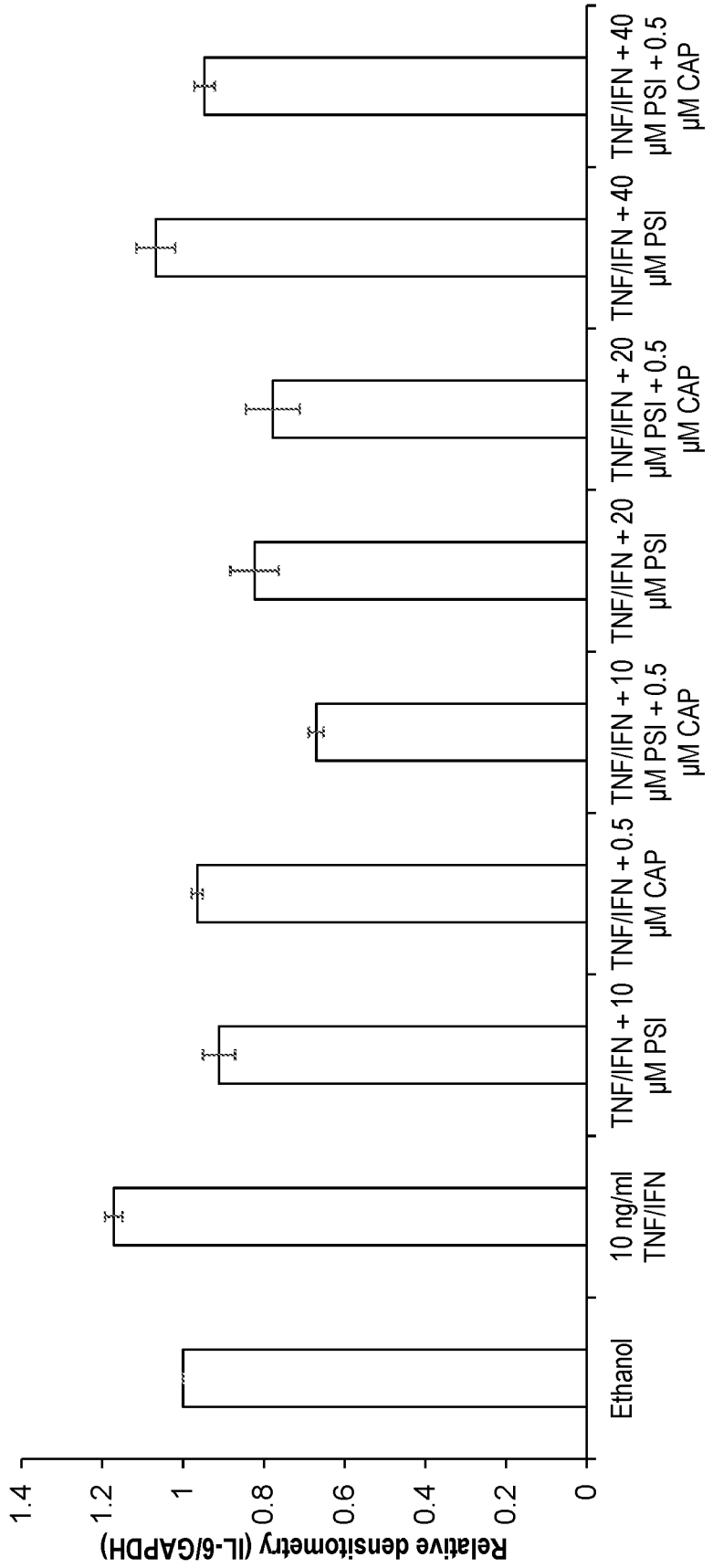
Relative densitometry (IL-6/GAPDH)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
Ethanol
10 ng/ml TNF/IFN
TNF/IFN + 10 µM PSI
TNF/IFN + 0.5 µM CAP
TNF/IFN + 10 µM PSI + 0.5 µM CAP
TNF/IFN + 20 µM PSI
TNF/IFN + 20 µM PSI + 0.5 µM CAP
TNF/IFN + 40 µM PSI
TNF/IFN + 40 µM PSI + 0.5 µM CAP

FIG. 55

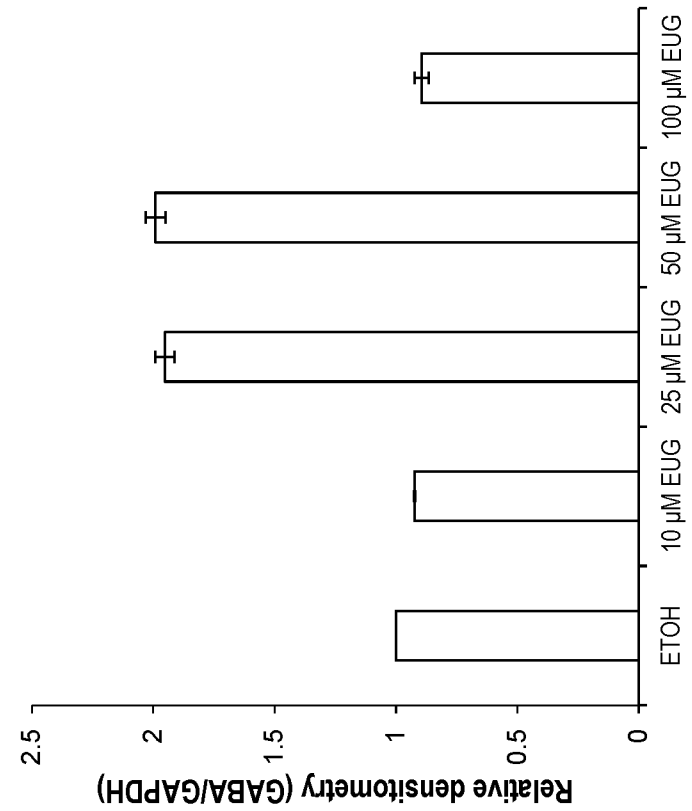

FIG. 56B

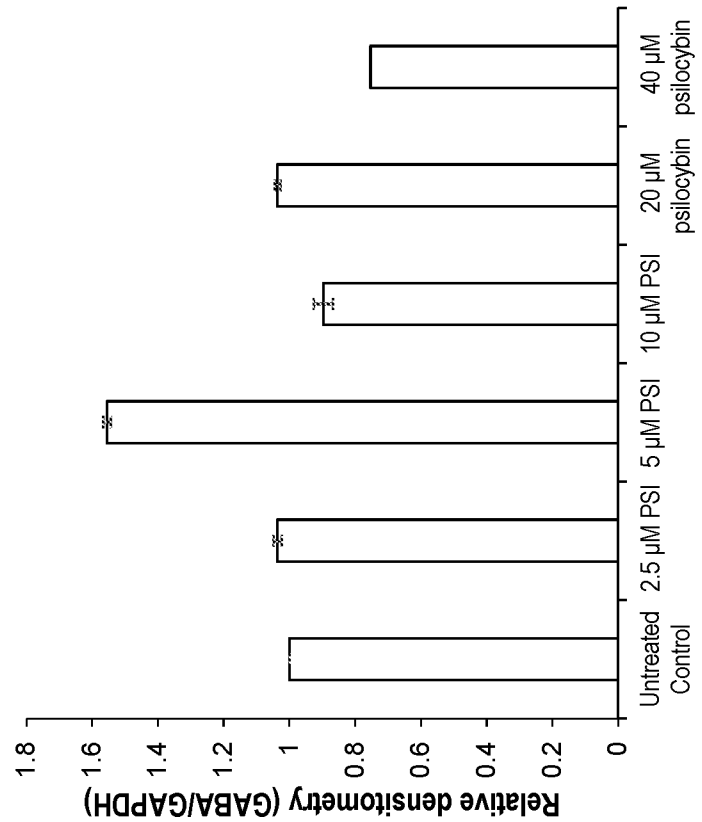

FIG. 56A

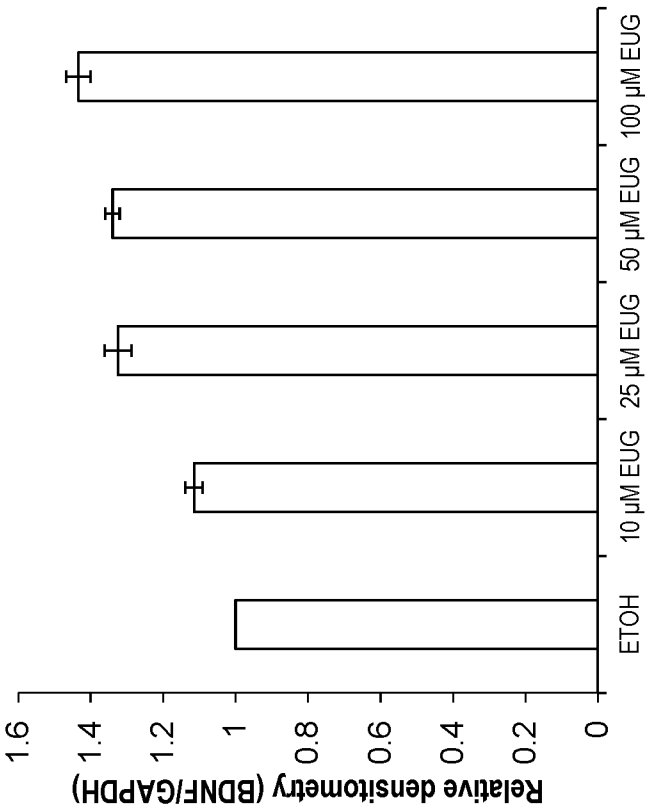

FIG. 57B

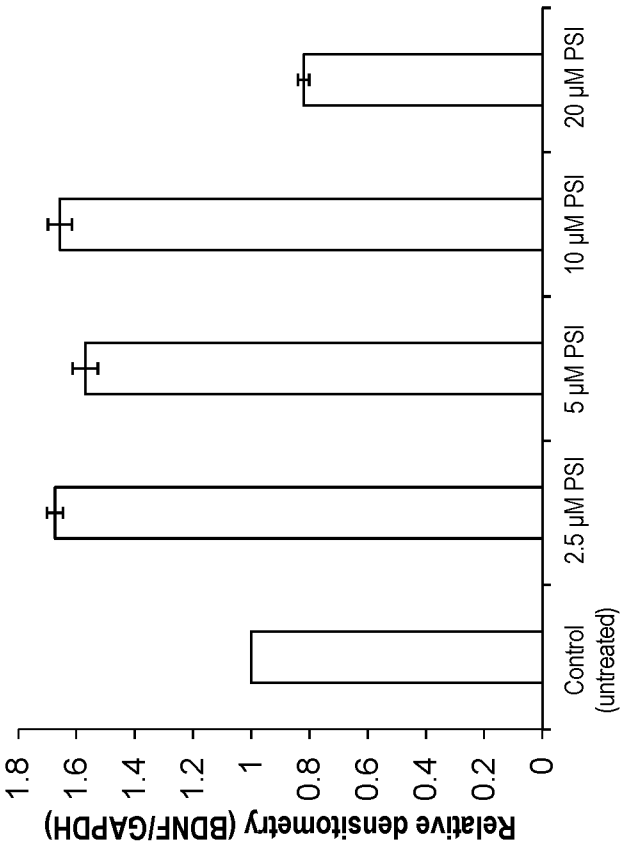

FIG. 57A

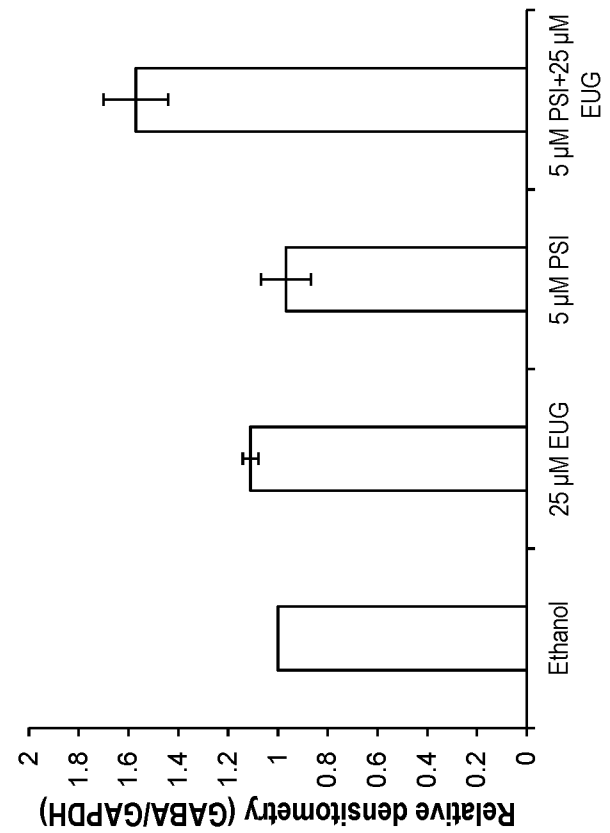

FIG. 58B

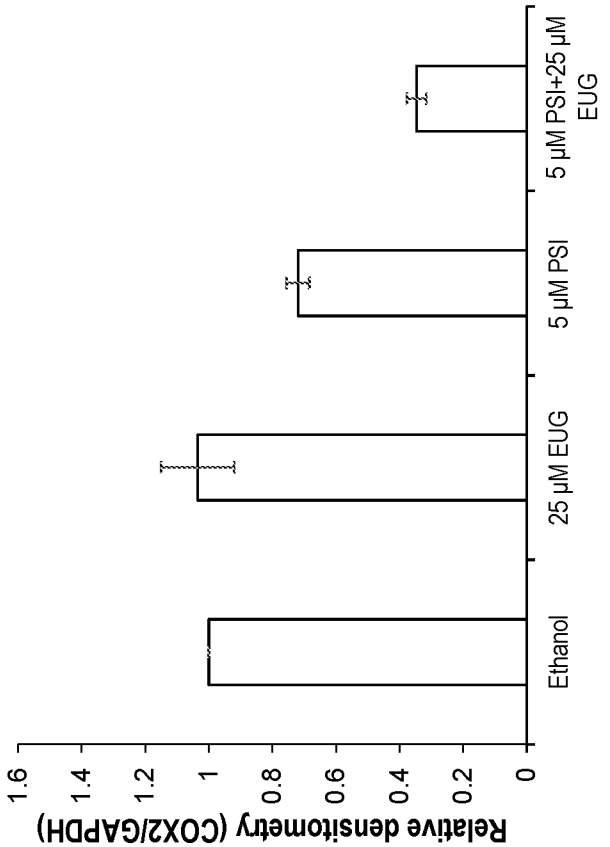

FIG. 58A

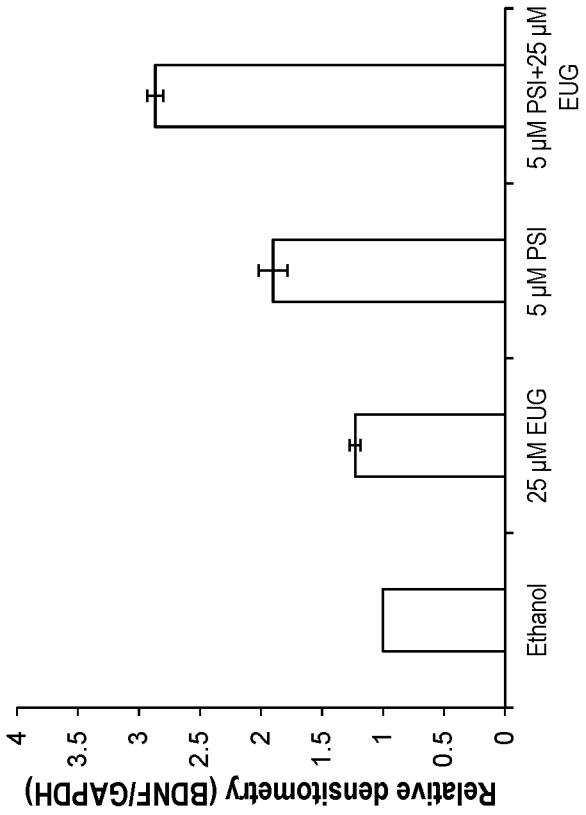

FIG. 58D

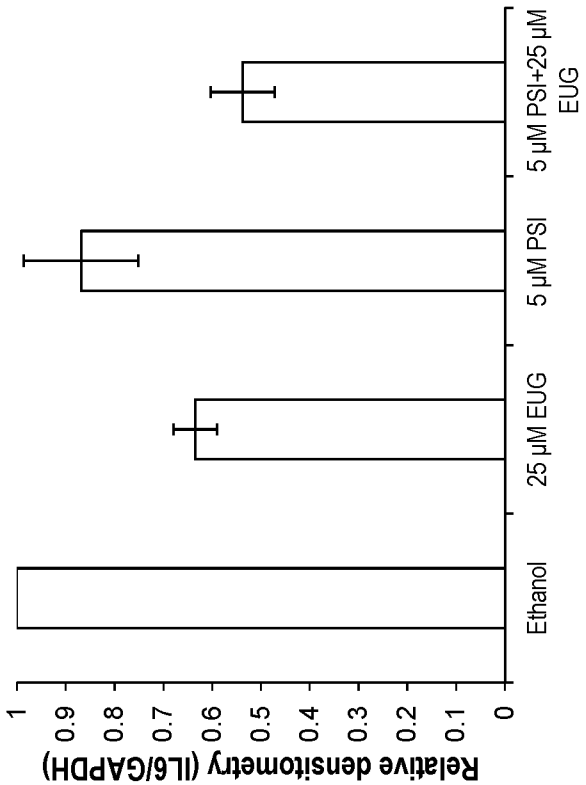

FIG. 58C

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/059301

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61K 31/675*** (2006.01) , ***A61K 31/09*** (2006.01) , ***A61K 31/12*** (2006.01) , ***A61K 31/137*** (2006.01) , ***A61K 31/165*** (2006.01) , ***A61K 31/4045*** (2006.01) (more IPCs on the last page)

CPC:

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: ***A61K 31/675*** (2006.01), ***A61K 31/09*** (2006.01), ***A61K 31/12*** (2006.01), ***A61K 31/137*** (2006.01), ***A61K 31/165*** (2006.01), ***A61K 31/4045*** (2006.01) (more IPCs on the last page)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)

Databases: SciFinder, PubMed, Google, Questel Orbit & Canadian Patent Database.
Keywords: 5HT2A, TRP, agonist, drug, tryptamine, ergoline, phenethylamine, phenylpropanoid, psilocybin, serotonin, elemicin, Hawian, morning glory, capsaicin, eugenol, curcumin, caryophyllene, piperine, turmeric, cinnamon, nutmeg, CBD, THC, inflammation, etc.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA2305190A1 (SEROTOEN INC.) 15 April 1999 (15-04-1999) *see entire document, especially claims 1, 12, 13, 15, 16 and 18*	1-61 and 67-69
X	CA3127854A1 (DIAMOND THERAPEUTICS INC.) 06 August 2020 (06-08-2020) *see entire document, especially claims 1-6, 12-14, 16, 18, 21, 29 and 36-49*	1-61 and 67-69
X	CA3052974A1 (CAAMTECH) 16 August 2018 (16-08-2018) *see entire document, especially claims 1, 14, 15, 24, 51-55, 59, 62, 65, 82, 96, 98, 100, 115, 117 and 121*	1-61 and 67-69

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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

Date of the actual completion of the international search 17 December 2021 (17-12-2021)	Date of mailing of the international search report 10 January 2022 (10-01-2022)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 819-953-2476	Authorized officer Ayub Reayi (819) 639-4406

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA3050679A1 (PROCARE BEHEER B.V.) 26 July 2018 (26-07-2018) *see entire document, especially claims 1, 2, 5, 6 and 10-15*	1-61 and 67-69
X	Sharma et al. Medicinal attributes of major phenylpropanoids present in cinnamon. *BMC Complementary and Alternative Medicine* 16(156), 2016, 1-11 *see entire document, especially page 5, right-hand column*	1, 21, 23, 24, 28, 29, 35, 36 and 38
A	Aggarwal, B.B. et al. Molecular Targets of Nutraceuticals Derived from Dietary Spices: Potential Role in Suppression of Inflammation and Tumorigenesis. *Exp Biol Med (Maywood)* 234(8), 2009, 825–849	1-61 and 67-69

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2021/059301

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

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

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claim Nos.: Claims 1-61 and 67-69
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

***See Page 7.

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

***See Page 7.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos.:

Claims 1-61 and 67-69.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

***Continued from Box No. II

The International Searching Authority has not carried out a comprehensive search for claims 1-61 and 67-69 under Article 17(2)(b) of the PCT. The description, claims, and/or drawings fail to comply with the prescribed requirements to such an extent that a meaningful search could not be carried out. At the present time, a search over the whole of the claimed scope would be exceedingly onerous and impossible as there are numerous possible combinations of a 5HT2A agonist compound and a TRP agonist compound. Moreover the present application not only claims compounds themselves, but also claims fungi and plants containing the 5HT2A agonist compounds and/or the TRP agonist compounds and a search of all fungi and plants claimed is not possible. Consequently, a very limited, basic search has been established for the parts of the application which appear to be clear and supported, namely to a few combinations of some 5HT2A agonist compounds as claimed in claim 2 and some TRP agonist compounds as generally claimed in the present application.

***Continued from Box No. III

The claims are directed to a plurality of inventive concepts as follows:

Group A - Claims 1-61 and 67-69 are directed to a composition comprising a therapeutic combination of a 5HT2A agonist compound and at least one TRP agonist compound, and method for reducing inflammation in a subject thereof; and

Group B - Claims 62-66 are directed to a method for reducing at least one biomarker in a mammalian cell comprising administering the composition of any one of claims 1 to 52 to a subject.

The claims in the present application are directed to a plurality of alleged inventions and an "*a priori*" lack of unity exists between Groups A and B.

The claims must be limited to one inventive concept as set out in PCT Rule 13.

*Note claims 53-66 relate to subject matter considered to be a method of medical treatment and some jurisdictions such as Canada, do not recognize the patentability of claims to methods of medical treatment.

IPC:
A61K 31/405 (2006.01) , ***A61K 31/48*** (2006.01) , ***A61K 36/06*** (2006.01) , ***A61K 36/185*** (2006.01) , ***C07C 217/60*** (2006.01) , ***C07C 233/20*** (2006.01) , ***C07C 43/285*** (2006.01) , ***C07C 43/295*** (2006.01) , ***C07D 209/16*** (2006.01) , ***C07D 209/20*** (2006.01) , ***C07F 9/572*** (2006.01)

CPC:

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2021/059301

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2305190A1	15 April 1999 (15-04-1999)	AU9780598A	27 April 1999 (27-04-1999)
		BR9813856A	19 September 2000 (19-09-2000)
		CN1279582A	10 January 2001 (10-01-2001)
		EP1021087A1	26 July 2000 (26-07-2000)
		EP1021087A4	22 August 2001 (22-08-2001)
		IL134958D0	20 May 2001 (20-05-2001)
		JP2001518481A	16 October 2001 (16-10-2001)
		KR20010024462A	26 March 2001 (26-03-2001)
		MXPA00003385A	20 November 2002 (20-11-2002)
		NO20001717D0	03 April 2000 (03-04-2000)
		NO20001717L	03 April 2000 (03-04-2000)
		US6017946A	25 January 2000 (25-01-2000)
		WO9917612A1	15 April 1999 (15-04-1999)
CA3127854A1	06 August 2020 (06-08-2020)	AU2020215150A1	09 September 2021 (09-09-2021)
		EP3917537A1	08 December 2021 (08-12-2021)
		IL285186D0	30 September 2021 (30-09-2021)
		KR20210134313A	09 November 2021 (09-11-2021)
		WO2020157569A1	06 August 2020 (06-08-2020)
CA3052974A1	16 August 2018 (16-08-2018)	AU2018217829A1	12 September 2019 (12-09-2019)
		BR112019016489A2	07 April 2020 (07-04-2020)
		CN110740728A	31 January 2020 (31-01-2020)
		EP3579832A1	18 December 2019 (18-12-2019)
		EP3579832A4	30 December 2020 (30-12-2020)
		JP2020506246A	27 February 2020 (27-02-2020)
		US2018221396A1	09 August 2018 (09-08-2018)
		US10933073B2	02 March 2021 (02-03-2021)
		US2019142851A1	16 May 2019 (16-05-2019)
		US2021085671A1	25 March 2021 (25-03-2021)
		US2021346346A1	11 November 2021 (11-11-2021)
		US2021353615A1	18 November 2021 (18-11-2021)
		US2021361679A1	25 November 2021 (25-11-2021)
		WO2018148605A1	16 August 2018 (16-08-2018)
		WO2019099745A1	23 May 2019 (23-05-2019)
CA3050679A1	26 July 2018 (26-07-2018)	DK3570830T3	12 July 2021 (12-07-2021)
		EP3570830A1	27 November 2019 (27-11-2019)
		EP3570830B1	21 April 2021 (21-04-2021)
		ES2884949T3	13 December 2021 (13-12-2021)
		HRP20211105T1	15 October 2021 (15-10-2021)
		NL2018190B1	26 July 2018 (26-07-2018)
		SI3570830T1	30 November 2021 (30-11-2021)
		US2019350949A1	21 November 2019 (21-11-2019)
		US10729706B2	04 August 2020 (04-08-2020)
		WO2018135943A1	26 July 2018 (26-07-2018)