COMPOSITION

This disclosure relates to a composition comprising rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A.

This disclosure also relates to a composition comprising at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A.

In certain embodiment, the composition further comprises at least 0,1 weight percent of caftaric acid.

In certain embodiments, the composition comprises at least about 17 weight percent of total hydroxycinnamic acids.

The present invention also relates to pharmaceutical formulations, nutraceutical formulations and food products comprising the composition.

Sleep disorders are conditions that affect the quality, amount and timing of sleep you are able to get at night. Sleep disorders can affect the mental health including cognitive performance and physical health including sports activities.

Stress is a state of mental or emotional strain or tension resulting from adverse or demanding circumstances which can affect the mental health including cognitive performance and physical health including sports activities.

There is an increasing public demand for natural alternatives in health/pharmaceutical/cosmetic products for stress management, ameliorating sleep and increase relaxation with improved effects.

SUMMARY

According to a first illustrative embodiment, disclosed is a composition comprising rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A.

According to a second illustrative embodiment, disclosed is a composition comprising at least about 7 weight percent of rosmarinic acid, at least about 0.3 weight percent of Schizotenuin A and optionally at least 0,1 weight percent of caftaric acid.

According to a third illustrative embodiment, provided is a consumer product comprising a composition comprising at least about 7 weight percent of rosmarinic acid, at least about 0.3 weight percent of Schizotenuin A and optionally at least 0,2 weight percent of caftaric acid

According to a further illustrative embodiment, provided is a consumable composition comprising a consumable base and a composition comprising at least about 7 weight percent of rosmarinic acid, at least about 0.3 weight percent of Schizotenuin A and optionally at least 0,1 weight percent of caftaric acid.

According to a further illustrative embodiment, provided is an extract of lemon balm comprising at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A.

According to a further illustrative embodiment, provided is a consumable composition comprising a consumable base and an extract of lemon balm comprising at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A.

According to a further illustrative embodiment, provided is a Composition according to the invention or a consumer product according to the invention for use in ameliorating or improving sleep and/or to reduce stress and increase relaxation in a subject.

According to a further illustrative embodiment, provided is a Composition according to the invention or a consumer product according to the invention for use in ameliorating or improving GABA transaminase inhibition.

According to a further illustrative embodiment, provided is a Composition according to the invention or a consumer product according to the invention for use in ameliorating or improving GABA receptor activity.

DETAILED DESCRIPTION

The following text sets forth a broad description of numerous different embodiments of the present disclosure. The description is to be construed as exemplary only and does not describe every possible embodiment since describing every possible embodiment would be impractical, if not impossible. It will be understood that any feature, characteristic, component, composition, ingredient, product, step or methodology described herein can be deleted, combined with or substituted for, in whole or part, any other feature, characteristic, component, composition, ingredient, product, step or methodology described herein. Numerous alternative embodiments could be implemented, using either current technology or technology developed after the filing date of this patent, which would still fall within the scope of the claims.

The terms "comprises," "comprising," "has," "having," "includes," "including," "contains," "containing," or any other variation are open-ended and are intended to cover a non-exclusive inclusion of elements, such that an article, apparatus, compound, composition, combination, method, or process that "comprises," "has," or "includes," or "contains" a recited list of elements does not include only those elements but may include other elements not expressly listed, recited or written in the specification or claims. An element or feature proceeded by the language "comprises . . .a," "contains . . . a," "has . . . a," or "includes . . .a" does not, without more constraints, preclude the existence or inclusion of additional elements or features in the article, apparatus, compound, composition, combination, method, or process that comprises, contains, has, or includes the element or feature.

The terms "a" and "an" are defined as one or more unless expressly stated otherwise or constrained by other language herein. An element or feature proceeded by "a" or "an" may be interpreted as one of the recited element or feature, or more than one of the element or feature.

The terms "about," "approximately," "essentially," "substantially," any other version thereof, or any other similar relative term, or similar term of approximation, are defined as being close to as understood by one having ordinary skill in the art. By way of non-limiting, illustrative embodiments, these terms are defined to be within 10% of recited value, or defined to be within 5% of a recited value, or defined to be within 4% of a recited value, or

defined to be within 3% of a recited value, or defined to be within 2% of a recited value, or defined to be within 1% of a recited value, or defined to be within 0.5% of a recited value, or defined to be within 0.25% of a recited value, or defined to be within 0.1% of a recited value.

It should be understood that when an amount in weight percent is described in the present disclosure, it is intended that any and every amount within the range, including the end points, is to be considered as having been expressly disclosed. For example, the disclosure of "a range of from about 1 to about 100" is to be read as indicating each and every possible number along the continuum between about 1 and about 100. It is to be understood that the inventors appreciate and understand that any and all data points within the range are to be considered to have been specified, and that the inventors have possession of the entire range and all points within the range.

When a concentration is expressed as “ppm”, the concentration is parts per million by weight based on the total weight of the composition or consumable. It should be understood that when a range of values is described in the present disclosure, it is intended that any and every value within the range, including the end points, is to be considered as having been disclosed. For example, “a range of from 1 ppm to 1000 ppm” of a component of the composition is to be read as indicating each and every possible number along the continuum between 1 and 1000. It is to be understood that the inventors appreciate and understand that any and all values within the range are to be considered to have been specified, and that the inventors have possession of the entire range and all the values within the range.

For the avoidance of doubt, alternative and optional features indicated for a given aspect, component, feature, or parameter of the invention should, unless the context indicates otherwise, be regarded as having been disclosed in combination with any and all other alternative or optional features and the like as indicated for the same or other aspects, features and parameters of the invention.

The inventors of the present invention have surprisingly found that a composition comprising rosmarinic acid, caftaric acid and Schizotenuin A provides a synergistic effect on GABA transaminase inhibition (see example 1 and 2). As demonstrated in the results (example 1 and 2) by increasing the presence of for schizotenuin A it is possible to reduce rosmarinic and caftaric acids concentration to reach similar benefits. Indeed, schizotenuin A will

potentiate the GABA transaminase inhibition of both compounds allowing a synergistically benefit of the association and an overall dose reduction to reach the GABA transaminase IC50.

As shown in example 3 there is a surprising benefit of the inventive composition to activate the GABA receptors compared to a classical water lemon balm extract. Indeed, at similar concentration the inventive composition activates the GABA receptors with an additional 16% at 3nM and an additional 24% at 10 nM compared to the classical extract (see figure 2).

This result shown the beneficial benefit of the defined active compounds within the inventive composition and the synergetic benefit of this composition comprising rosmarinic acid, schizotenuin A, caftaric acid and hydroxycinnamic to improve GABA release and or GABA transaminase inhibition.

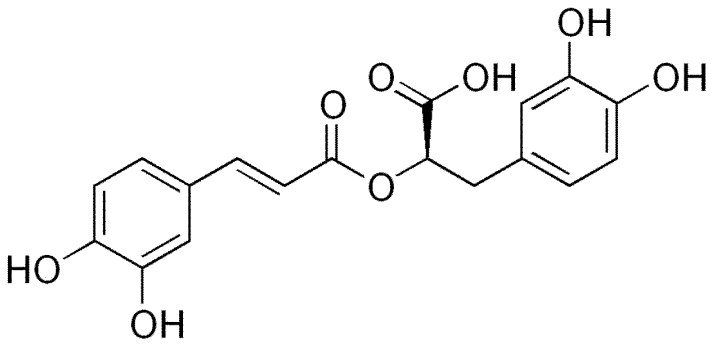
The inhibition of the GABA transaminase and/or the activation of the GABA receptors leads the inhibition of neural activities. As a result, various positive effects on the mind and body are observed, including improved sleep, reduced mental and physical stress, lowered anxiety, and enhanced mood (Hou et al., 2023; Liwinski et al., 2023).

Hou, D., Tang, J., Feng, Q., Niu, Z., Shen, Q., Wang, L., & Zhou, S. (2023). Gamma-aminobutyric acid (GABA): a comprehensive review of dietary sources, enrichment technologies, processing effects, health benefits, and its applications. Critical Reviews in Food Science and Nutrition, 1-23.

Liwinski, T., Lang, U. E., Brühl, A. B., & Schneider, E. (2023). Exploring the Therapeutic Potential of Gamma-Aminobutyric Acid in Stress and Depressive Disorders through the Gut–Brain Axis. Biomedicines, 11(12), 3128.

According to a first illustrative embodiment, disclosed is a composition comprising rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A.

Rosmarinic acid is an ester formed via the esterification of caffeic acid with 3,4-dihydroxyphenyl lactic acid. Rosmarinic acid is defined in the entry of the database CAS Registry with the number 20283 92 5 as well as structurally by formula (i)



(i)

In certain embodiments the composition of the invention comprises at least 4, at least 5, at least 6, at least about 7 weight percent of rosmarinic acid, such as at least 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or such as at least 35 weight percent of rosmarinic acid. In certain embodiments, the composition of the invention comprises from about 7 weight percent to about 15 weight percent of rosmarinic acid, such as from about 7 weight percent to about 10 weight percent of rosmarinic acid.

Disclosed is a composition comprising at least about 7 weight percent of rosmarinic acid, at least about 0.3 weight percent of Schizotenuin A and optionally at least about 0.1 weight percent of caftaric acid.

Schizotenuin A ((R)-3-(3,4-Dihydroxyphenyl)-2-[3-[7-hydroxy-2-(3,4-dihydroxyphenyl)-3-[[(R)-1-carboxy-2-(3,4-dihydroxyphenyl)ethyl]oxycarbonyl]benzofuran-5-yl]propenoyloxy]propionic acid). Schizotenuin A is defined in the entry of the database CAS Registry with the number 144608-09-3.

Schizotenuin A can be derived from a natural extract, or can be synthetic, or can be a combination of natural extract and synthetic. It may be extracted from a variety of natural sources such

In certain embodiments, the composition of the invention comprises at least 0.3 weight percent of Schizotenuin A, such as at least 0.4, 0.5, 0.6, 0.7. 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or such as at least 35 weight percent of Schizotenuin A.

In certain embodiments, the composition of the invention comprises from about 0.3 weight percent to about 15 weight percent of Schizotenuin A, such as from about 0.4 weight percent to about 1 weight percent of Schizotenuin A.

In certain embodiments, the composition of the invention further comprises caftaric acid. In certain embodiments, the composition comprises at least 0.1 weight percent of caftaric acid, such as at least 0.2, 0.3, 0.4, 0.5, 0.6, 0.7. 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30 or such as at least 35 weight percent of caftaric acid.

In certain embodiments, the composition of the invention comprises from about 0.1 weight percent to about 4 weight percent of caftaric acid, such as from about 0.2 weight percent to about 1 weight percent of caftaric acid.

In certain embodiments, the composition of the invention comprises at least about 17 weight percent of total hydroxycinnamic acids.

Hydroxycinnamic acids are phenolics structurally simple widely distributed in plants and includes but is not limited to rosmarinic acid, schizotenuin A, caftaric acid, caffeic acid, verboscoside isomer and lithospermic acid isomer. “Total hydroxycinnamic acids” in the present invention refers to the addition of the concentrations of different hydroxycinnamic acids including but not limited to rosmarinic acid, schizotenuin A, caftaric acid, caffeic acid, verboscoside isomer and lithospermic acid isomer. Total hydroxycinnamic acids is quantified against rosmarinic acid response factor using UV spectrum and MS/MS fragmentation similarity.

In certain embodiments, the composition of the invention comprises at least about 17 weight percent of total hydroxycinnamic acids, such as at least 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40 or such as at least 45 weight percent of total hydroxycinnamic acids. In certain embodiments, the composition of the invention comprises from about 17 weight percent to about 30 weight percent of total hydroxycinnamic acids, such as from about 18 weight percent to about 26 weight percent of total hydroxycinnamic acids.

Quantification of rosmarinic acid, hydroxycinnamic acids, schizotenuin A and caftaric acid compounds may be performed by Quantitative HPLC analysis on an HPLC Agilent 1260 system equipped with UV detection, using a C18 reverse phase column (Zorbax Eclipse Plus

C18 - 4.6 x250mm 5µm) and an external standard calibration as described in the present examples. The mobile phase consisted of 0.01% phosphoric acid in water (Solvent A) / Acetonitrile (Solvent B) with a flow rate 0.7 mL/min and a gradient elution as follows: 0-10min 95%A, 10-30min 70%A and 30-35min 0%A. Samples were dissolved in 50% methanol to 0.8mg/mL, subjected to sonication and filtered through 0.45µm prior to injection. UV monitoring was carried out at 330nm. Measurements may be done in triplicate.

In certain embodiments of the composition of the invention, the ratio between rosmarinic acid and Schizotenuin A is of from about 2: 1 to about 50:1, such as from 2:1 to about 22:1, such as from 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, 15:1,16:1, 17:1, 18:1, 19:1, 20:1, 21:1 or 22:1. In certain embodiments of the composition of the invention, the ratio between rosmarinic acid and Schizotenuin A is of from 4/1 to about 22/1.

In certain embodiments, the ratio between rosmarinic acid and total hydroxycinnamic acids is of from about 0.2: 1 to about 1:1, such as from about 0.3:1, 0.4:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1. In certain embodiments, the range is from 0.3/1 to about 0.8/1.

In certain embodiments, the ratio between rosmarinic acid and total caftaric acid is of from about 20: 1 to about 100:1, such as from about 20:1, 30:1, 40:1, 50:1, 60:1, 70:1, 80:1, 90:1 or 100:1. In certain embodiments, the range is 30/1 to about 80/1.

The concentration of the rosmarinic acid, total hydroxycinnamic acids, caftaric acid and Schizotenuin A are quantified by liquid chromatography with UV-Vis detection using an external calibration as described in the examples.

One or more of the components present in the composition of the invention (i.e c rosmarinic acid, the Schizotenuin A, caftaric acid or the hydroxycinnamic acids) may be extracted from one or more botanical sources and/or may be of synthetic origin.

One or more natural botanical sources may be used to extract rosmarinic acid, Schizotenuin A caftaric acid or total hydroxycinnamic acids. In certain embodiments, the rosmarinic acid, Schizotenuin A caftaric acid or total hydroxycinnamic acids may be extracted from one botanical source. For example, in certain preferred embodiments, the composition of the invention comprises rosmarinic acid and Schizotenuin A that are obtained from one or

more members of the Lamiacea family such as basil, mint, rosemary, sage, savory, marjoram, oregano, hyssop, thyme, lemon balm (Melissa officinalis), etc.

For example, in certain preferred embodiments, the composition of the invention comprises the rosmarinic acid, Schizotenuin A caftaric acid or total hydroxycinnamic acids that are obtained from one or more members of the Lamiacea family such as basil, mint, rosemary, sage, savory, marjoram, oregano, hyssop, thyme, lemon balm (Melissa officinalis), etc. In certain preferred embodiments, the rosmarinic acid, Schizotenuin A caftaric acid or total hydroxycinnamic acids from the composition of the invention are extracted from lemon balm (Melissa officinalis L.).

In certain preferred embodiments the composition of the invention is an extract of lemon balm (*Melissa officinalis)*.

In certain preferred embodiments the composition of the invention is an extract of lemon balm comprising at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A. In certain embodiments, the extract of lemon balm further comprises at least about 17 weight percent of total hydroxycinnamic acids. In certain preferred embodiments the composition of the invention is a water extract of lemon balm comprising at least about 7 weight percent of rosmarinic acid and at least about 0.4 weight percent of Schizotenuin A, and optionally wherein the total hydroxycinnamic acids concentration is of at least about 17 weight percent.

In certain embodiments, the composition of the invention further comprises one or more of Amino acid, phenylpropane, flavone, flavonoid, oleic acid, linoleic acid, linalool, fibers and sugars.

By way of example, and not by way of limitation, suitable starting material (such as aerial parts of lemon balm) may be extracted with constant agitation in solvents composed of water and polar organic solvents. The organic solvents that may be used include methanol, ethanol, n-propanol, 2-propanol, acetone and propylene glycol. The extraction may be carried out either with water alone or with water in combination with one or more solvents listed above. The composition of the solvents may range between 100/0 water/organic solvent (w/w) to 10/90 water/organic solvent (w/w). In a preferred embodiment, the solvent is 100% water. The extraction temperature may be between 30° C. to 90° C. and the extraction time

may be between 1 hours and 40 hours. Extraction may be carried out with equipment known to those skilled in the art, such as a counter current extractor or an extractor with constant solvent circulation. It will be well known to those skilled in the art that the extraction can be carried out in various types of equipment.

The extract may be collected either by decanting, centrifuging or filtering. The plant material optionally may then be extracted one or two more times under similar conditions, and the extracts combined and the solvents evaporated under vacuum to concentrate the extract.

The aqueous solution obtained after any of the above operations may be further concentrated under vacuum. It may be directly dried under vacuum to a powder. Alternatively, it may be concentrated and spray-dried to a powder. The spray-drying may be performed with or without carriers.

The composition may be prepared in the form of a liquid, a paste or a powder. For example, the composition may be in the form of a free-flowing powder.

In certain embodiments, the composition of the invention the composition is in form of a powder substantially free of carriers. In certain embodiments, the composition of the invention does not have unpleasant off notes. In certain embodiments, the composition of the invention is soluble in water. In certain embodiments, the composition of the invention is fully soluble in water.

In certain embodiments, the composition of the invention has a better palatability within beverage applications such as, but limited to, ready to drink or ready to mix and within food application such as, but not limited to gummies, bars, chocolate.

Further provided is a consumable composition comprising a consumable base and a composition of the invention of any of the illustrative embodiments disclosed herein. In certain embodiments, the composition comprises at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A, and optionally wherein the total hydroxycinnamic acids concentration is of at least about 17 weight percent. In certain preferred embodiments, the composition is an extract from *Melissa officinalis*.

The consumable composition may be selected from foods, beverages, nutraceutical product.

According to certain illustrative embodiments, the consumable includes but is not limited to nutraceuticals, food supplements, capsules, tablets, gummies, cereal bars, teas and herbal infusions, soft drinks, energy drinks, isotonic and sports drinks, flavoured/enhanced waters, non-alcoholic beers/spirits, hard candy, chocolate (bars/candies), coffee, meat and meat analogue products, dairy and dairy analogue products, bakery products, etc.

According to certain illustrative embodiments, the consumable composition comprises a beverage composition comprising a beverage base and a composition of the invention of any of the illustrative embodiments disclosed herein. In certain embodiments, the beverage comprises the beverage base and a composition comprising at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A of any of the illustrative embodiments disclosed herein.

According to certain embodiments, the beverage comprises a carbonated beverage, such as a carbonated soft drink, and the composition of any of the illustrative embodiments disclosed herein.

The “beverage base” as used herein means a combination of the normal ingredients used to prepare a beverage, apart from the disclosed composition. These are standard ingredients used in art-recognized quantities, and include water, carbonated water, sugars, artificial/synthetic sweeteners, natural sweeteners, artificial/synthetic flavors, natural flavors, surfactants, and suspending agents, thickeners, rheology modifiers, dyes, coloring agents, stabilizers, and preservatives. The beverage base may comprise carbonated water, flavor, sweetener, and all other ingredients desired or necessary for a complete carbonated beverage, apart from the composition.

According to certain illustrative embodiments, the consumable is an acidic beverage. According to certain illustrative embodiments, the consumable is a beverage having a pH of 4 or less, or 3.5 or less, or 3 or less, or in the range of about 2 to about 4.5, or in the range of about 2 to about 4, or in the range of about 2 to about 3.5, or in the range of about 2 to about 3, or in the range of about 2.2 to about 4.2, or in the range of about 2.5 to about 3.5. Any food grade acid can be used in order to reduce the pH of the beverage to the desired acidic

condition. Examples of acids include hydrochloric acid, lactic acid, phosphoric acid, acetic acid, citric acid, malic acid, tartaric acid, oxalic acid, tannic acid, caffeic acid, benzoic acid, butyric acid, and combinations thereof. In general, the amount of acid required depends on the type of acid.

The beverage composition may include at least one flavor. Without limitation, and only by way of illustration, suitable flavors include, a tea flavorant, a coffee flavorant, a peach flavorant, a citrus flavorant (e.g. a lemon flavorant, a lime flavorant, an orange flavorant, a grapefruit flavorant, a mandarin orange flavorant, a tangerine flavorant, or a combination of any of the foregoing), an herbal flavorant, a berry flavoring (e.g., a flavorant derived from one or more of Barbados cherry, bearberry, blackberry, blueberry, boysenberry, cherry, choke cherry, cloudberry, cranberry, current, date, dewberry, elderberry, grape, gooseberry, huckleberry, loganberry, olallieberry, mulberry, raisin, plains berry, prairie berry, raspberry, saskatoon berry, salmonberry, seabuckthorn berry, sloe berry, strawberry, thimbleberry, thornberry, wineberry, whortleberry, or a combination of any of the foregoing), a botanical flavorant (e.g. one or more flavors derived from a part of a plant other than the fruit, including flavors derived from essential oils and extracts of nuts, bark, roots and leaves along with synthetically prepared flavors made to simulate botanical flavors derived from natural sources), and mixtures thereof.

The beverages may comprise full sugar, reduced sugar, or zero sugar added carbonated beverages. The full sugar or reduced sugar beverages may include at least one nutritive sweetener. Without limitation, and only by way of illustration, suitable nutritive sweeteners include sucrose, fructose, glucose, high fructose corn syrup, corn syrup, xylose, arabinose, rhamnose, erythritol, xylitol, mannitol, sorbitol, isomaltulose, inositol, allulose, tagalose, trehalose, and combinations thereof.

Reduced sugar and zero sugar beverages of the present disclosure include at least one non-nutritive sweetener that either partially (reduced sugar beverages) or wholly (zero sugar beverages) replaces the nutritive sweetener in the carbonated beverage composition.

According to certain illustrative embodiments, the non-nutritive sweeteners that may be used in the reduced sugar and/or zero sugar beverages are selected from natural non-nutritive sweeteners, synthetic non-nutritive sweeteners, and combinations thereof.

Without limitation, and only by way of illustration, suitable synthetic non-nutritive sweeteners that may be included in the reduced sugar or zero sugar beverages maybe selected from acesulfame K, advantame, aspartame, cyclamate, neotame, neohesperidin dihydrochalcone, saccharin, sucrolose and combinations thereof.

Without limitation, and only by way of illustration, suitable natural non-nutritive sweeteners include steviol glycosides selected from stevioside, rebaudioside A, rebaudioside B, rebaudioside C, rebaudioside D, rebaudioside E, rebaudioside F, rebaudioside G, rebaudioside H, rebaudioside I, rebaudioside J, rebaudioside K, rebaudioside L, rebaudioside M, rebaudioside N, rebaudioside O, dulcoside A, dulcoside B, rubusoside, and combinations thereof, mogrol glycosides selected from mogroside I, mogroside II, mogroside III, mogroside IV, mogroside V, isomogroside V, 11-oxomogroside, siamenoside I and combinations thereof, naringin dihydrochalcone, Luo Han Guo Extract, Swingle Extract, brazzein, cellobiose, glycyrrhizic acid, monatin, psicose, stevioside, thaumatin, trilobatin, and combinations thereof.

In certain embodiments, the beverage is a carbonated beverage.

According to other embodiments, a beverage concentrate is provided. The beverage concentrate comprises a beverage concentrate base. The term “beverage concentrate base” as used herein means a combination of the normal ingredients used to prepare a carbonated beverage or non-carbonated beverage, apart from still water or carbonated water and the disclosed composition.

Further disclosed is a method of making a consumable composition comprising adding a composition of the invention of any of the illustrative embodiments disclosed herein to a consumable base. In certain embodiments the composition of the invention comprises at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A. In certain embodiments the total hydroxycinnamic acids concentration is of at least about 17 weight percent. In certain embodiments the composition of the invention further comprises at least 0.1 weight percent of caftaric acid.

The method of making the consumable, such as, for example, a beverage, gummies, bars, chocolate etc, comprises adding from about 50 ppm to about 700000 ppm, or from about 1000 ppm to about 650000 ppm or from about 150 ppm to about 600000 ppm , or from about

200 ppm to about 550000 ppm, or from about 250 ppm to about 500000 ppm, or from about 300 to about 450000 ppm, or from about 300 ppm to about 40000 ppm, and from about 300 ppm to about 350000 ppm, or any percentage ranges or specific percentages within these ranges, of the composition of any of the illustrative embodiments disclosed herein to a consumable base.

According to certain embodiments, provided is the use of a composition of the invention of any of the illustrative embodiments disclosed herein or a consumer product as disclosed herein for use in inhibit from about 5 mg/ml to about 12 mg/ml IC50 of GABA transaminase, such as 8,6 mg/ml of IC50 of GABA transaminase. In certain embodiments the composition of the invention comprises at least about 7 weight percent of rosmarinic acid, least about 0.3 weight percent of Schizotenuin A and optionally at least 0.1 weight percent of caftaric acid. Inhibition of GABA transaminase is measured as measured in the examples of the present disclosure.

According to certain embodiments, provided is the use of a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A as disclosed herein or a consumer product as disclosed herein for use in ameliorating or improving sleep and/or to reduce stress, anxiety, depression, chronic stress, insomnia, seasonal affective disorder and increase relaxation in a subject.

According to certain embodiments, provided is the use of a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) at least about 0.3 weight percent of Schizotenuin A, at least about 0.1 weight percent of caftaric acid, and at least about 17 weight percent of total hydroxycinnamic acids as disclosed herein or a consumer product as disclosed herein for use in ameliorating or improving sleep and/or to reduce stress, anxiety, depression, chronic stress, insomnia, seasonal affective disorder and increase relaxation in a subject.

The present invention provides a method for ameliorating or improving sleep and/or to reduce stress, anxiety, depression, chronic stress, insomnia, seasonal affective disorder and increase relaxation, wherein the method comprises administering a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least

about 0.3 weight percent of Schizotenuin A as disclosed herein or a consumer product comprising said composition as disclosed herein.

In certain embodiments, the present invention provides a method for ameliorating or improving sleep and/or to reduce stress, anxiety, depression, chronic stress, insomnia, seasonal affective disorder and increase relaxation, wherein the method comprises administering a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) at least about 0.3 weight percent of Schizotenuin A, at least about 0.1 weight percent of caftaric acid, and at least about 17 weight percent of total hydroxycinnamic acids as disclosed herein or a consumer product comprising said composition as disclosed herein.

Also provided is a method for ameliorating or improving sleep and/or to reduce stress, anxiety, depression, chronic stress, insomnia, seasonal affective disorder and increase relaxation, wherein the method comprises administering a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A and optionally at least about 0.1 weight percent of caftaric acid or a consumer product comprising said composition as disclosed herein to a patient in need thereof.

In certain embodiments, the present invention provides a method for ameliorating or improving sleep and/or to reduce stress, anxiety, depression, chronic stress, insomnia, seasonal affective disorder and increase relaxation, wherein the method comprises administering a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) at least about 0.3 weight percent of Schizotenuin A, at least about 0.1 weight percent of caftaric acid and at least about 17 weight percent of total hydroxycinnamic acids or a consumer product comprising said composition as disclosed herein to a patient in need thereof.

According to certain embodiments, provided is the use of a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A as disclosed herein or a consumer product as disclosed herein for use in ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or

more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder in a subject.

According to certain embodiments, provided is the use of a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) at least about 0.3 weight percent of Schizotenuin A, at least about 0.1 weight percent of caftaric acid, and at least about 17 weight percent of total hydroxycinnamic acids as disclosed herein or a consumer product as disclosed herein for use in ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder in a subject.

The present invention provides a method for ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder, wherein the method comprises administering a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A as disclosed herein or a consumer product comprising said composition as disclosed herein.

In certain embodiments, the present invention provides a method for ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder, wherein the method comprises administering a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) at least about 0.3 weight percent of Schizotenuin A, at least about 0.1 weight percent of caftaric acid, and at least about 17 weight percent of total hydroxycinnamic acids as disclosed herein or a consumer product comprising said composition as disclosed herein.

Also provided is a method for ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder, wherein the method comprises administering a composition

as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A and optionally at least about 0.1 weight percent of caftaric acid or a consumer product comprising said composition as disclosed herein to a patient in need thereof.

In certain embodiments, the present invention provides a method for ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder, wherein the method comprises administering a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) at least about 0.3 weight percent of Schizotenuin A, at least about 0.1 weight percent of caftaric acid and at least about 17 weight percent of total hydroxycinnamic acids or a consumer product comprising said composition as disclosed herein to a patient in need thereof.

According to certain embodiments, provided is a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid), at least about 0.3 weight percent of Schizotenuin A and optionally at least about 0.1 weight percent of caftaric acid or a consumer product comprising said composition as disclosed herein for use in ameliorating or improving GABA transaminase inhibition.

According to certain embodiments, provided is a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid), at least about 0.3 weight percent of Schizotenuin A, at least about 0.1 weight percent of caftaric acid and at least about 17 weight percent of total hydroxycinnamic acids or a consumer product comprising said composition as disclosed herein for use in for use in ameliorating or improving GABA transaminase inhibition.

According to certain embodiments, provided is a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid), at least about 0.3 weight percent of Schizotenuin A and optionally at least about 0.1 weight percent of caftaric acid as disclosed herein or a consumer product comprising said composition for preparing a medicament for ameliorating or improving GABA receptor activity.

According to certain embodiments, provided is a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid), at least about 0.3 weight percent of Schizotenuin A and at least about 17 weight percent of total hydroxycinnamic acids as disclosed herein or a consumer product comprising said composition for preparing a medicament for ameliorating or improving GABA receptor activity.

The present invention provides a method for ameliorating or improving GABA receptor activity, wherein the method comprises administering a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A, and optionally at least about 0.1 weight percent of caftaric acid or a consumer product comprising said composition as disclosed herein.

Also provided is a method for ameliorating or improving GABA receptor activity, wherein the method comprises administering a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid), at least about 0.3 weight percent of Schizotenuin A and at least about 17 weight percent of total hydroxycinnamic acids as disclosed herein or a consumer product comprising said composition to a patient in need thereof.

The present invention provides a method for ameliorating or improving GABA transaminase inhibition, wherein the method comprises administering a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid), at least about 0.3 weight percent of Schizotenuin A and optionally at least about 0.1 weight percent of caftaric acid or a consumer product comprising said composition as disclosed herein.

Also provided is a method for ameliorating or improving GABA transaminase inhibition, wherein the method comprises administering a composition comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid), at least about 0.3 weight percent of Schizotenuin A and at least about 17 weight percent of total hydroxycinnamic acids as disclosed herein or a consumer product comprising said composition as disclosed herein to a patient in need thereof.

The present invention provides a composition as described herein or a consumer product comprising said composition for use in ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder in a subject in a stressful environment.

The present invention provides a method ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder in a subject in a stressful environment, wherein the method comprises administering a composition as disclosed herein comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A, and optionally at least about 0.1 weight percent of caftaric acid or a consumer product comprising said composition as disclosed herein.

A stressful environment, as used herein includes without limitation, a cognitively demanding day, a cognitively demanding task, stressful & frustrating tasks, exhausting situations which requires a high level of attention, etc.

In certain preferred embodiments of the uses and methods described herein, at least one of the rosmarinic acid and Schizotenuin A is of natural origin. In certain more preferred embodiments, the composition comprising rosmarinic acid and Schizotenuin A is a lemon balm aqueous extract comprising rosmarinic acid (such as least about 7 weight percent of rosmarinic acid acid) and at least about 0.3 weight percent of Schizotenuin A.

In the uses and methods described herein, the composition is administered in an amount sufficient to provide from about 50mg/kg to about 120mg/kg of the composition and/or from about 150 mg per day to about mg per day to about 600 mg per day of the composition.

In the uses and methods described herein, the composition is administered in an amount sufficient to provide rosmarinic acid in an amount of from about 10 mg/kg to about 19000 mg/kg, such as from about 20 mg/kg to about 17000 mg/kg, such as about 30 mg/kg or about 15000 mg/kg;

In the uses and methods described herein, the composition is administered in an amount sufficient to provide total hydroxycinnamic acids in an amount of from about 20 mg/kg to about 40000 mg/kg, such as from about 30 mg/kg to about 35000 mg/kg, such as about 40 mg/kg or about 30000 mg/kg.

In the uses and methods described herein, the composition is administered in an amount sufficient to provide Schizotenuin A in an amount of from about 0.001 mg/day to about 750 mg/day, such as from about 0.01 mg/day to about 700 mg/day, such as about 0.1 mg/day or about 650 mg/day.

In the uses and methods described herein, the composition is administered in an amount sufficient to provide caftaric acid in an amount of from about 0.01 mg/day to about 450 mg/day, such as from about 0.01mg/day to about 400 mg/day, such as about 0.1 mg/day or about 350 mg/day.

In one embodiment of the uses and methods described herein the subject is a mammal such as dogs, cats, cows, pigs, etc. In a preferred embodiment the subject is a male or a female human.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1: GABA transaminase IC50 of the inventive composition compared to classical water lemon balm extract

Figure 2. shows the comparison of the activity on the GABA receptors between the inventive composition and a classical water lemon balm extract.

Figure 3. Bond Lader calmness after cognitive demanding tasks

Figure 4 shows a statistically significant difference of calmness between groups at the 5 hr time point.

Figure 5 shows that participants who received the placebo experienced a statistically significant reduction in their contentedness rating score over time

Figure 6 shows that participants who received the inventive solution, unlike those under placebo, were more alert after treatment

Figure 7 demonstrates a statistically significant treatment effect (p=0.047) between the groups.

Figure 8 shows a statistically significant difference between groups in the accuracy score at 5 hr after treatment ($p \leq 0.05$).

Figure 9 shows a statistically significant difference between groups in the accuracy score at 5 hr after treatment ($p \leq 0.05$).

EXAMPLES

The present invention will be further described by reference to the following, non-limiting examples.

Anxiety and related neurological disorders often result from low levels of the inhibitory neurotransmitter GABA. A mechanism to increase GABA levels in the brain and potentially control anxiety is to inhibit the enzyme GABA- Transaminase: GABA-T. Key element to modulate sleep, anxiety and stress is GABA content.

The goal of this study is to develop an in vitro assay to determine the inhibitory concentration IC50 (concentration to inhibit 50% of enzymatic activity) of active compounds present in lemon balm extract (Melissa officinalis L. Lamiaceae family) and to identified synergistically benefit of their uses.

Example 1: Effect of different compositions on GABA transaminase inhibition

The aim of this study was to evaluate the IC50 on the GABA transaminase of different compositions Blueness (lemon balm water extract) and the composition of the invention with improved conditions to increase the previously defined active compounds such as hydroxycinnamic acids such as, but not limited, schizotenuin A, rosmarinic acid as well as caftaric acid.

1.1. Materials and methods

Reagents and consumables

GABase is a mixture of γ-aminobutyrate glutamate aminotransferase (GABA-T, EC 2.6.1.19) and succinic semialdehyde dehydrogenase (SSDH, EC 1.2.1.16) from Pseudomonas fluorescens and was purchased from Merck KGaA, Darmstadt (Germany). One unit will convert 1.0 µmole of γ-aminobutyric acid (GABA) to succinic semialdehyde and then to succinate per min with a stoichiometric reduction of 1.0 µmole of NADP+ at pH 8.6 at 25 °C.

The chemicals sodium hydroxide, sodium sulfate, Trizma HCl, Dithio-1,4-thréitol (DTT), GABA, sodium salt of α-ketoglutaric acid, β-nicotinamide adenine dinucleotide phosphate (NADP-RO) disodium salt, vigabatrin were purchased from Merck KGaA, Darmstadt (Germany). Microplate UV-Star 96 wells with flat bottom UV-transparent Bio-One were obtained from Greiner.

Microtiter plate assay for GABA

The reaction mixture contained Tris–HCl buffer with 750 mM sodium sulfate, 10 mM DTT, 1.4 mM NADP+, 2.0 mM α-ketoglutaric acid and GABase was added to each well of microplate. The extract or standard solution at different concentrations were added to the reaction mixture and then the microplate was incubated for 15 min at 30°C before the addition of 100 mM GABA solution. Microplate was incubated at 30°C for 60 min. The conversion of NADP+ to NADPH was measured every minute in absorbance at 340 nm with a microplate reader Spark 10M from Tecan (Männedorf, Switzerland) and the change is proportional to GABA-T activity. Vigabatrin is a known inhibitor of GABA-T and was used as the positive control whereas water as the negative control.

Tested products

In this experiment, different compositions were tested: Blueness (lemon balm water extract) obtained from Fytexia uand the composition of the invention with increased hydroxycinnamic compounds (such as rosmarinic acid and schizotenuin A) and caftaric acid within the composition.

Extracts
Blueness (5.8 % w/w of rosmarinic acid, 0.2% w/w schizotenuin A, 0.2% w/w caftaric acid and 14.7% w/w total hydroxycinnamic acids)

Inventive composition with 8.8% w/w rosmarinic acid, 1.5% w/w schizotenuin A, 0.2% w/w caftaric acid and 21.8 w/w total hydroxycinnamic acids

Table 1: composition of the tested extracts

Analysis:

Quantitative HPLC analysis

Quantification of rosmarinic acid, hydroxycinnamic acids, schizotenuin A and caftaric acid compounds was performed on an HPLC Agilent 1260 system equipped with UV detection, using a C18 reverse phase column (Zorbax Eclipse Plus C18 - 4.6 x250mm 5µm) and an external standard calibration.

The mobile phase consisted of 0.01% phosphoric acid in water (Solvent A) / Acetonitrile (Solvent B) with a flow rate 0.7 mL/min and a gradient elution as follows: 0-10min 95%A, 10-30min 70%A and 30-35min 0%A.

Samples were dissolved in 50% methanol to 0.8mg/mL, subjected to sonication and filtered through 0.45µm prior to injection.

UV monitoring was carried out at 330nm.

1.2. Results summary:

All analyses were done using Excel IC50 formula and presented in Figure 1 to provide comparative data in one support.

The results presented in the figure 1 shows that the inventive composition has an IC50 on GABA transaminase improved by 1,84 fold compared with classical water lemon balm extract. Interestingly, the inventive composition has a relative improved composition of active compounds such as 7.5 more schizotenuin A, 1.5 more rosmarinic acid, 1.5 more hydroxycinnamic acids and an equivalent amount of caftaric acid compared to the classical water extract (Blueness). However, when considering the improvement in GABA transaminase inhibition (1.84 fold) achieved by the inventive composition, the concentrations of these active compounds within the inventive composition were further enhanced. Schizotenuin A

showed a 4.08fold improvement, while the required concentration of rosmarinic acid, hydroxycinnamic acids, and caftaric acid decreased by 0.83, 0.81 and 0.54 (Table 2).

All together these results highlight that the inventive composition contains more active compounds compared to the classical water extract. Interestingly while the GABA transaminase IC50 is reduced by 1.84 the needed concentration of the active compounds appears to be redistributed within the inventive composition suggesting a synergistic benefit of the schizotenuin A increases, linked with rosmarinic and caftaric acids reduction, for which one could benefits from the others. In other words, the active compounds can potentiate each other's to reduce their overall concentration to reach the targeted IC50. (Figure 1 and Table 2).

	Inventive composition		Classical water lemon balm extract	
Compounds	**%**	**mg/ml**	**%**	**mg/ml**
Caftaric acid	0.2	0.017	0.2	0.03
Rosmarinic acid	8.8	0.757	5.8	0.92
Schizotenuin A	1.5	0.129	0.2	0.03
Total hydroxycinnamic acids	21.8	1.875	14.7	2.32
IC50	100	8.6	100	15.80

Table 2. Percentages of the active compounds and their relative concentration based on their respective IC50 GABA transferase within the inventive composition and the classical lemon balm extract.

Example 2: Effect of active compounds on GABA transaminase inhibition

The aim of this study was to evaluate the IC50 on the GABA transaminase of different actives compounds such as Schizotenuin A, rosmarinic acid and caftaric acid.

2.1. Materials and methods

Reagents and consumables

GABase is a mixture of γ-aminobutyrate glutamate aminotransferase (GABA-T, EC 2.6.1.19) and succinic semialdehyde dehydrogenase (SSDH, EC 1.2.1.16) from Pseudomonas fluorescens and was purchased from Merck KGaA, Darmstadt (Germany). One unit will convert 1.0 µmole of γ-aminobutyric acid (GABA) to succinic semialdehyde and then to succinate per min with a stoichiometric reduction of 1.0 µmole of NADP+ at pH 8.6 at 25 °C.

The chemicals sodium hydroxide, sodium sulfate, Trizma HCl, Dithio-1,4-thréitol (DTT), GABA, sodium salt of α-ketoglutaric acid, β-nicotinamide adenine dinucleotide phosphate (NADP-RO) disodium salt, vigabatrin were purchased from Merck KGaA, Darmstadt (Germany). Microplate UV-Star 96 wells with flat bottom UV-transparent Bio-One were obtained from Greiner.

Microtiter plate assay for GABA

The reaction mixture contained Tris–HCl buffer with 750 mM sodium sulfate, 10 mM DTT, 1.4 mM NADP+, 2.0 mM α-ketoglutaric acid and GABase was added to each well of microplate. The extract or standard solution at different concentrations were added to the reaction mixture and then the microplate was incubated for 15 min at 30°C before the addition of 100 mM GABA solution. Microplate was incubated at 30°C for 60 min. The conversion of NADP+ to NADPH was measured every minute in absorbance at 340 nm with a microplate reader Spark 10M from Tecan (Männedorf, Switzerland) and the change is proportional to GABA-T activity. Vigabatrin is a known inhibitor of GABA-T and was used as the positive control whereas water as the negative control.

Tested products

In this experiment three compounds were tested: schizotenuin A, rosmarinic acid and caftaric acid. Each compounds were tested individually and also in a combination of two compounds to test synergistically activity.

Standards		MW
positive control = Vigabatrin		129.2
Schizotenuin A		716.6
Caftaric acid		312.2
Rosmarinic acid		360.3
Rosmarinic acid +	Caftaric acid	
Rosmarinic acid +	Schizotenuin A	
Schizotenuin A +	Caftaric acid	

Table 3: Composition of the individual active compounds and the different tested combinations

Analysis:

All analyses were done using Excel IC50 formula and presented in a table to provide comparative data in one support.

2.2. Results summary:

	mM	% of inhibition	IC50
Vigabatrin	74.4	50	X
Rosmarinic acid	6.9	50	X
Caftaric acid	12.3	50	X
Rosmarinic acid	1.4	4.6	
Caftaric acid	9.8	29.4	
Rosmarinic acid and Caftaric acid	1.4 9.8	50	X

Table 4: Correspondence of the respective concentration related to the % of inhibition of the GABA transaminase

The results in table 5 show that 1.1 mM of rosmarinic acid associated with 2.4 mM of schizotenuin A induces 50% of the GABA transaminase inhibition while, similar concentrations are inhibiting the enzyme at 0.1 % and 32.9 % and the needed concentration to reach 50% of inhibition on their own are 6.9 mM and 3.7 mM respectively. In conclusion, the needed combination is allowing to reduce each concentration by 6.3 and 1.5 of rosmarinic acid and schizotenuin A respectively. Therefore, both active compounds in specific concentrations will allow to reduced their individual concentration to reach a similar benefit which demonstrate a synergistic effect of the combination.

The results in table 5 show that 1.4 mM of rosmarinic acid associated with 9.8 mM of caftaric acid induces 50% of the GABA transaminase inhibition while, similar concentrations are inhibiting the enzyme at 4.6 % and 29.4% and the needed concentration to reach 50% of inhibition on their own are 6.9 mM and 12.3 mM respectively. In conclusion, the needed

combination is allowing to reduce each concentration by 4.9 and 1.2 of rosmarinic acid and caftaric acid respectively. Therefore, both active compounds in specific concentrations will allow to reduced their individual concentration to reach a similar benefit which demonstrate a synergistic effect of the combination.

Standards	mM		% of inhibition	IC50
Vigabatrin	74.4		50	X
Rosmarinic acid	6.9		50	X
Schizotenuin A	3.7		50	X
Rosmarinic acid	1.1		0.1	
Schizotenuin A	2.4		32.9	
Rosmarinic acid and Schizotenuin A	1.1	2.4	50	X

Table 5: Correspondence of the respective concentration related to the % of inhibition of the GABA transaminase

The results in table 6 show that 3.3 mM of caftaric acid associated with 1.1 mM of schizotenuin A induces 50% of the GABA transaminase inhibition while, similar concentrations are inhibiting the enzyme at 5.6 % and 23.6 % and the needed concentration to reach 50% of inhibition on their own are 12.3 mM and 3.7 mM respectively. In conclusion, the needed combination is allowing to reduce each concentration by 3.7 and 3.4 of caftaric acid and schizotenuin A respectively. Therefore, both active compounds in specific concentrations will allow to reduced their individual concentration to reach a similar benefit which demonstrate a synergistic effect of the combination.

Standards	mM		% of inhibition	IC50
Vigabatrin	74.4		50	X
Caftaric acid	12.3		50	X
Schizotenuin A	3.7		50	X
Caftaric acid	3.3		5.6	
Schizotenuin A	1.1		23.6	
Caftaric acid and Schizotenuin A	3.3	1.1	50	X

Table 6: Correspondence of the respective concentration related to the % of inhibition of the GABA transaminase

Overall it appears that there is a synergistic effect of the compounds association to reduce the needed quantities to reach GABA transaminase IC50. Taking together the results are showing that by increasing the presence of for schizotenuin A it is possible to reduce rosmarinic and caftaric acids concentration to reach similar benefits. Indeed, schizotenuin A will potentiate the GABA transaminase inhibition of both compounds allowing a synergistically benefit of the association and an overall dose reduction to reach the GABA transaminase IC50.

Example 3: Effect of different compositions on GABA receptor activation

The aim of this study was to evaluate the GABA receptor activation (agonist) of different compositions Blueness (lemon balm water extract) and the composition of the invention with improved conditions to increase the previously defined active compounds such as hydroxycinnamic acids such as, but not limited, schizotenuin A, rosmarinic acid as well as caftaric acid.

3.1. Materials and methods

Two compositions, described in table 1, were tested for agonist activity at the human GABA B1a/B2 (FAST-0102A & FAST-0102G) and GABA B1b/B2 (FAST-0122C) receptors, at three concentrations (10, 3 and 1 nM), in triplicate.

The Cell lines were established as follow:

Receptor	Accession Number	Assay	Cell line	Reference agonist
GABA B_{1a}/B_2	CAA09939.1	AEQ	CHO-K1	GABA
	CAA09942.1	GTP		SKF97541
GABA B_{1b}/B_2	CAA09940.1 CAA09942.1	cAMP	CHO-K1-mt aequorin	GABA

Table 7

On each day of experimentation, reference compounds were tested at several concentrations in duplicate (n=2) to obtain a dose-response curve and an estimated EC50/IC50 value. Reference values thus obtained for the test were compared to historical values obtained from the same receptor and used to validate the experimental session. For replicate determinations, the maximum variability tolerated in the test was of +/-20% around the average of the replicates Tested products

In this experiment different composition were tested: Blueness (classical lemon balm water extract) and the composition of the invention with increased rosmarinic acid, schizotenuin A and caftaric acid within the composition.Analysis:

Dose-response data from test compounds were analyzed with XLfit (IDBS) software using nonlinear regression applied to a sigmoidal dose-response model. Agonist activity of test compounds is expressed as a percentage of the activity of the reference agonist at its EC100 concentration

3.2. Results summary:

The figure 2 highlight a benefit of the inventive composition to activate the GABA receptors compared to a classical water lemon balm extract. Indeed, at similar concentration the inventive composition activates the GABA receptors with an additional 16% at 3nM and an additional 24% at 10 nM compared to the classical extract.

This result brings complementary data regarding the beneficial benefit of the defined active compounds within the inventive composition and the synergetic benefit of this composition comprising rosmarinic acid, schizotenuin A, caftaric acid and hydroxycinnamic to improve GABA release and or GABA transaminase inhibition.

Example 4. Clinical benefit of the Inventive composition

A randomized, placebo-controlled, double-blind, single-centre trial was done to determinate the benefit of the inventive solution to reduce stress related impairment (i.e. calmness, alertness, cognitive abilities such as memories and attention) of a healthy population in a stressful situation defined by a highly demanding cognitive tasks occurring 4 times during the days: baseline and then 1h, 3h and 5h after the intervention.

4.1. Materials and methods

Participants, healthy men and women aged 18-40 years, completed an online PSS to determine their perceived stress, participants with scores between 14 to 26 indicating moderate stress were invited to take part in the study. If eligible, participants came to an in-person site where they were provided written informed consent before completing a detailed in-person screening to assess medical and health history, habitual diet and lifestyle, and they

practiced the cognitive task battery. On the test day (acute) participants attended the laboratory in a fasted state (overnight fast of at least 8 hours) where they received a standard breakfast (2 croissants with butter and a glass of water), followed by a battery of cognitive and mood tasks. Subjects were then being given one capsule of 300 mg of innovative composition or 300 mg of placebo (maltodextrine) with water, and were re-tested on the task battery 1h, 3h and 5h later before being allowed to return home. Lunch (a ham or cheese sandwich with a small packet of crisps and a piece of fruit) was be provided after the 3h assessment.

Subject satisfaction using a 4-point Likert scale, calmness and fatigue ratings using a 9-point Likert scale was given after baseline cognitive overload and at the end of the day after 5h cognitive overload, while other mood assessments (Bond Ladder-VAS and Stress-VAS) were given before and after 1, 3 and 5h cognitive overload time points. Participants were free to consume water as they wished throughout the day, and were free to operate their time as they wished in between test sessions in the available waiting room at the nutrition laboratory.

A summary of visits including screening are presented in Table 8 below.

		Visit Number	Day
1 week		Email screening Review of inclusion/exclusion criteria (general non-identifiable questions	
Randomized, Placebo-Controlled, Double-Blinded, Intervention Period	Screening visit	1	7 days before acute
	Acute test day	2	Timepoints 0h, 1h, 3h and 5h

Table 8: Study Design and Number of Required Visits by Each Subject

Outcomes (Mood)

- Calmness rating will be measured using a 9-point Likert scale

- Various clusters of subjective transient mood will be measured to support the primary outcome of 9-point calmness anchor ratings (CAR).

- Stress changes will be assessed using a stress visual analogue scale (S-VAS) which measures transient changes in levels of stress, anxiety, calmness and relaxation between ratings 'not at all' to 'extremely.' These scores are then combined into two scores 'stress/anxiety' and 'calm/relaxed' where a higher score (average % along the line) represents more of the respective descriptor.

- Assessment of three mood factors alertness, calmness and contentedness will be captured using a 16 Bond-Lader Visual Analog Scale (BL-VAS) where 100mm scales anchored by various antonyms (e.g. Alert-Drowsy, Lethargic-Energetic) are then clustered into these respective mood factors.

- Changes in Fatigue will be measured via Fatigue Anchor Points (FAP) on a 9-point Likert Scale between '1. Not at all mentally fatigued' and '9. Extremely mentally fatigued'.

- To measure levels of tiredness, mental overload and relaxation scores a subject satisfaction 4-category rate questionnaire from not satisfied at all (score 1) to entirely satisfied (score 4) will capture these satisfaction domains.

Outcomes (Cognition)

- Several memory and executive function tasks will be presented at baseline, 1h, 3h and 5h to determine changes in cognitive ability.

- Attention Network Task (ANT) will be performed to measure executive function and attention. In this task participants respond to the direction of a centrally presented arrowhead by pressing the corresponding left and right arrow keys. Across multiple trials, the target stimulus was either flanked by arrows pointing in the same direction (congruent), or the opposite direction (incongruent). The number of flanking arrows also varies between trials (load). The task will be completed in two blocks. During the second block, participants will be distracted by noise through headphones. The dependent variables will be reaction time and accuracy by changes in congruency, load and noise. In addition, during two blocks of the ANT an oral serial 3 (S3) task will also be performed as a further measure to assess attention and working memory function. In this S3 task participants subtract backwards starting with the number 50 until they can go no further. The S3 performance will be in place as a distractor and the dependent variable will be ANT performance on congruency and load.

- Immediate word recall (IWR) will be undertaken to measure episodic memory. Participants are visually presented with a sequential list of fifteen words where they are then given 1 minute to type as many words as they can remember. At each sitting of the task, a different word list will be presented which will be matched for linguistic familiarity, concreteness and frequency. The dependent variable will be the number of correctly recalled words.

- A sustained attention task called the Rapid Visual Information Processing (RVIP) task involves presenting a series of digits on a screen in quick succession. The participant will then be required to monitor the digits for sequences of three consecutive even or three consecutive odd digits. To indicate the end of a target sequence, participants will press the space bar as quickly as possible. The dependent variables are reaction time, correct responses and commission errors.

- A Switching task (SWT) will be undertaken to assess executive function. In this task participants are presented with a computerised visual circle with 8 equally spaced radii that form 8 segments, 4 above and 4 below a bold line. A stimulus digit appears sequentially in each segment in a clockwise direction. If the digit was located above the bold line, participants then indicate whether the digit was odd or even using labelled arrow keys (left for odd, right for even). When the digit is below the bold line, participants again use the arrow keys to indicate whether the digit is higher or lower than 5 (left for higher, right for lower). The dependent variables are accuracy and reaction time.

- Delayed Word Recall (DWR) will be completed to assess the level of delayed episodic memory. Participants will be required to type as many words as they can remember from the immediate word recall presentation here the task takes place approximately 30 minutes after the initial presentation. The dependent variable will be the number of correctly recalled words.

Statistical analysis

Repeated measures data will be analysed in RStudio v4.0 using linear mixed-effects models (LMMs). This technique can be used to model variance relating to both fixed parameters such as experimental doses and random parameters such as individual differences between subjects, within multiple layers of the same model. The model was adjusted for severity of

baseline stress complaints (PSS score). Post-hoc Bonferroni corrected parametric tests such as independent t-tests will be performed to estimate differences between placebo and intervention groups where appropriate.

4.2. Results:

Mood assessment:

- Bond Lader calmness after cognitive demanding tasks:

The results presented in figure 3 shows that participants who received the placebo tend to reduce their calmness rating score over time (0 hr session /baseline vs 5 hr session: p=0.06) which is not the case for the participants who received the inventive composition.

Overall, the results highlight the benefits of the inventive composition in maintaining participants' calmness over time during a highly demanding cognitive and stressful journey, where participants need a high level of attention.

- Bond Lader change from baseline expressed as pre-assessment versus after cognitive demanding task:

The results from figure 4 show a statistically significant difference of calmness between groups at the 5 hr time point (p=0.04) and a statically non-significant trend at the 1 hr time point (p=0.09).

This result supports the previous outcome and confirms the benefit of the inventive composition in maintaining calmness over time during a highly demanding cognitive and stressful journey, where participants need a high level of attention. In other words, unlike participants who received the placebo, those who received the inventive composition did not demonstrate a decrease of their calmness level during the day.

- Responders assessment expressed as participants who improved their calmness during the day

Table 9 below represents the percentage of responders from Figure 4. Responders are defined as participants who improved their calmness rating score on the Bond Lader scale during the day compared to baseline (0 hr).

While in the placebo group there is a drop of around 10% of responders between the beginning of the tasks (after 1 hr) and the end of the task (after 5 hr), in the inventive composition group, the level of responders over time remains stable at around 60%, compared to around 50% in the placebo group.

These results highlight a difference in the percentage of responders between the two groups, reaching a maximum after 5 hr (end of the day), where the inventive composition group has 16% more calmer participants (responders) compared to the placebo group.

	1 hr	3 hr	5 hr
Responder			
Inventive composition	62%	59%	61%
Placebo	52%	54%	45%
No benefit			
Inventive composition	2%	2%	2%
Placebo	0%	3%	2%
Non responder			
Inventive composition	36%	39%	37%
Placebo	48%	43%	53%

Table 9: Percentage of responders defined as participants who improved their calmness level compared to baseline/ pre-assessment level by group and over time.

- Bond Lader contentedness after cognitive demanding tasks:

The results presented in Figure 5 show that participants who received the placebo experienced a statistically significant reduction in their contentedness rating score over time (0 hr session/baseline vs. 5 hr session: p=0.002), which is not the case for participants who received the inventive composition.

Overall, the results highlight the benefits of the inventive composition in maintaining participants' contentedness over time during a highly demanding cognitive and stressful journey, where participants need a high level of attention.

- Bond Lader alertness after cognitive demanding tasks

The results presented in Figure 6 show that participants who received the inventive solution, unlike those under placebo, were more alert after treatment. Indeed, there was a statistically significant increase in alertness at 1 hr (p=0.003) and 3 hr (p=0.0007) after treatment in the inventive composition group, but not in the placebo group.

Overall, the results highlight the benefits of the inventive composition in improving participants' alertness over time during a highly demanding cognitive and stressful journey, where participants need a high level of attention.

- Calmness recovery after a cognitive demanding tasks:

Calmness recovery is expressed as the participants' capability to improve their calmness level before starting a new cognitively demanding task. This is measured as the difference between calmness before a new session versus calmness score after the previous session. The results in Figure 7 demonstrate a statistically significant treatment effect (p=0.047) between the groups, with an overall higher calmness recovery score for participants under the inventive composition compared to those under placebo.

In summary, the inventive composition improves fast-acting calmness recovery (less than 2 hr between sessions) between two cognitively and stressful demanding sessions.

- Attention Networking Task performances:

In this particularly demanding task, participants must focus on the direction of arrows while counting backward by threes, all while being distracted by noise through headphones.

The results from Figure 8 show a statistically significant difference between groups in the accuracy score at 5 hr after treatment ($p \leq 0.05$).

In summary, during a stressful and cognitively demanding exercise, the inventive composition group demonstrates a higher level of attention compared to the placebo group.

- Responders assessment expressed as participants who improved their attention in the ANT during the day

Table 10 below represents the percentage of responders from Figure 8. Responders are defined as participants who improved their attention level compared to baseline (0 hr) during the ANT.

In the inventive composition group, there is an increase of 12% of responders over time, showing an improvement in attention, reaching a level of 60% of the participants, which is around twice the percentage of responders within the placebo group (33%, 5 hr after consumption).

	1 hr	3 hr	5 hr
Responder			
Inventive composition	48%	50%	60%
Placebo	37%	35%	33%
No benefit			
Inventive composition	23%	23%	17%
Placebo	24%	32%	32%
Non responder			
Inventive composition	29%	27%	23%
Placebo	39%	33%	35%

Table 10: Percentage of responders defined as participants who improved their attention compared to baseline by group and over time.

- Task Switching Task performances:

During the Task Switching Task, participants need to remember different rules that apply in different situations. This extremely demanding task requires a lot of attention and memory, which are key components of executive function.

The results from Figure 9 show a statistically significant difference between groups in the accuracy score at 5 hr after treatment ($p \leq 0.05$).

In summary, during a stressful and cognitively demanding exercise, the inventive composition group demonstrates a higher level of attention, memory, and executive function compared to the placebo group.

4.3. Summary:

The study found that in participants who received the inventive composition exhibited significant benefits in mood (calmness, attention, contentedness) and cognitive performance ('attention, memory, executive function) compared to those who received a placebo.

Specifically, the inventive composition helped maintain calmness and contentedness over time, while the placebo group experienced declines in these areas. Additionally, participants in the inventive group demonstrated improved alertness and calmness recovery between demanding tasks, as well as enhanced performance in attention, memory and executive function.

Overall, the inventive composition proved effective in supporting participants' emotional stability and cognitive function during stressful situations.

While the composition, method of making the composition, uses of the composition, consumables, and methods of making consumables have been described in connection with various embodiments, it is to be understood that other similar embodiments may be used or modifications and additions may be made to the described embodiments for performing the same function. Furthermore, the various illustrative embodiments may be combined to produce the desired results. Therefore, composition, consumables containing the composition and methods of making the composition and consumables should not be limited

to any single embodiment, but rather construed in breadth and scope in accordance with the recitation of the appended claims. It will be understood that the embodiments described herein are merely exemplary, and that one skilled in the art may make variations and modifications without departing from the spirit and scope of the invention. All such variations and modifications are intended to be included within the scope of the invention as described hereinabove.

CLAIMS:

1. A composition comprising at least about 7 weight percent of rosmarinic acid and at least about 0.3 weight percent of Schizotenuin A.

2. The composition according to claim 1, further comprising least about 0.1 weight percent of caftaric acid.

3. The composition according to claim 1 or 2, comprising at least about 17 weight percent of total hydroxycinnamic acids.

4. The composition according to any one of the preceding claims, comprising from about 7 weight percent to about 15 weight percent of rosmarinic acid.

5. The composition according to any one of the preceding claims, comprising from about 17 weight percent to about 30 weight percent of total hydroxycinnamic acids.

6. The composition according to any one of the preceding claims, comprising from about 17 weight percent to about 25 weight percent of total hydroxycinnamic acids.

7. The composition according to any one of the preceding claims, comprising from about 0.3 weight percent to about 5 weight percent of Schizotenuin A.

8. The composition according to any one of the preceding claims, comprising from about 0.4 weight percent to about 1% weight percent of Schizotenuin A.

9. The composition according to any one of the preceding claims, wherein the rosmarinic acid is extracted from one or more botanical sources or is of synthetic origin.

10. The composition according to any one of preceding claims, wherein the hydroxycinnamic acids are extracted from one or more botanical sources and/or are of synthetic origin.

11. The composition according to any one of preceding claims, wherein the Schizotenuin A is extracted from one or more botanical sources or is of synthetic origin.

12. The composition according to any one of preceding claims, wherein the rosmarinic acid, Schizotenuin A or hydroxycinnamic acids are extracted from a plant from the Lamiaceae family.

13. The composition according to claim 12, wherein the plant is *Melissa officinalis*.

14. The composition according to any one of claims 1 to 13, wherein the composition is an extract from *Melissa officinalis*.

15. The composition according to claims 12 or 13, wherein the extract is obtained from the aerial parts of *Melissa officinalis*.

16. The composition according to any one of preceding claims, wherein the composition is in form of a powder substantially free of carriers.

17. The composition according to any one of preceding claims, wherein the composition is soluble in water and/or the composition has a better palatability within beverage applications such as, but not limited to, ready to drink or ready to mix and within food application such as, but not limited to gummies, bars, chocolate.

18. Consumer product comprising a composition according to any of the preceding claims.

19. Consumer product according to claim 18 selected from capsules, tablets, gummies, cereal bars, teas and herbal infusions, soft drinks, energy drinks, isotonic and sports drinks, flavoured/enhanced waters, non-alcoholic beers/spirits, hard candy, chocolate (bars/candies), coffee.

20. Composition according to any one of claims 1 to 17 or a consumer product according to claims 18 and 19 for use in ameliorating or improving sleep and/or to reduce stress, anxiety, depression, chronic stress, insomnia, seasonal affective disorder and increase relaxation in a subject.

21. Composition according to any one of claims 1 to 17 or a consumer product according to claims 18 and 19 for use in ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder in a subject.

22. Composition according to any one of claims 1 to 17 or a consumer product according to claims 18 and 19 for use in ameliorating or improving GABA transaminase inhibition.

23. Composition according to any one of claims 1 to 17 or a consumer product according to claims 18 and 19 for use in ameliorating or improving GABA receptor activity.

24. Composition according to any one of claims 1 to 17 or a consumer product according to claims 18 and 19 for use in ameliorating or improving one or more of mood, sleep, relaxation, contentedness, calmness, alertness, attention, executive function and/or to reduce one or more of stress, mental overload, anxiety, depression, chronic stress, insomnia and seasonal affective disorder in a subject in a stressful environment.