(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 September 2021 (23.09.2021)

WIPO | PCT

(10) International Publication Number
WO 2021/185890 A1

(51) International Patent Classification:

A61K 36/258 (2006.01)	*A61P 25/24* (2006.01)
A61K 31/704 (2006.01)	*A61P 25/28* (2006.01)
A61P 1/00 (2006.01)	*A23L 33/105* (2016.01)
A61P 3/04 (2006.01)	*A61P 11/00* (2006.01)
A61P 9/00 (2006.01)	*A61P 31/00* (2006.01)
A61P 25/16 (2006.01)	*A61P 35/00* (2006.01)
A61P 25/20 (2006.01)	*A61P 37/00* (2006.01)

(21) International Application Number: PCT/EP2021/056788

(22) International Filing Date: 17 March 2021 (17.03.2021)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

2004121.6	20 March 2020 (20.03.2020)	GB
2005288.2	09 April 2020 (09.04.2020)	GB

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK,

(54) Title: GINSENOSIDE COMPOSITIONS

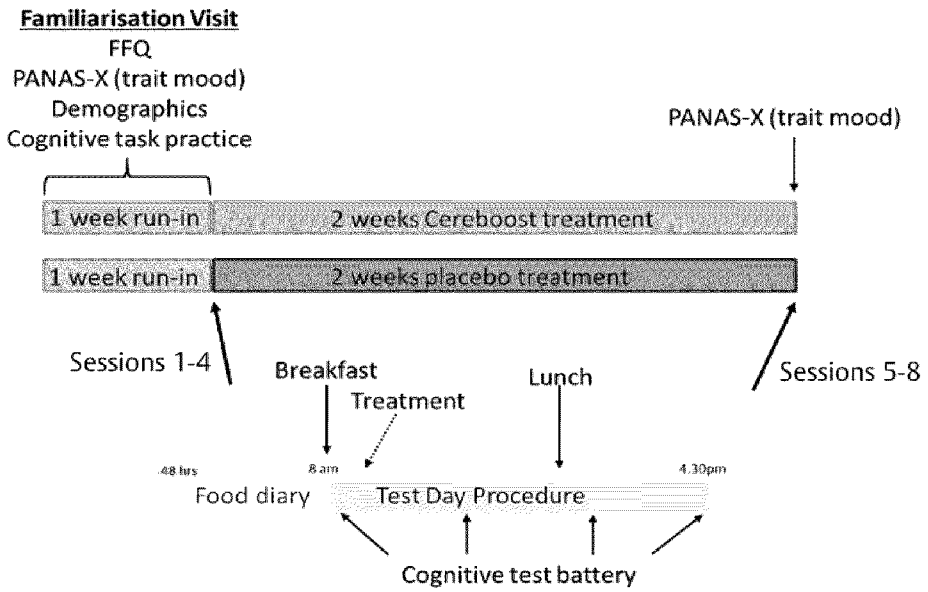

Figure 1

(57) Abstract: The present invention relates to the use of American Ginseng (Panax quinquefolius) to preventing and/or reducing fatigue in a subject. The invention also relates to the use of composition comprising ginsenosides and an extract of American Ginseng (Panax quinquefolius) to increase attention/alertness in a subject. The invention also relates to the use of American Ginseng (Panax quinquefolius) to increase self-assurance in a subject.

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EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

GINSENOSIDE COMPOSITIONS

Field of the Invention

The present invention relates to the use of American Ginseng (*Panax quinquefolius*) to preventing and/or reducing fatigue in a subject. The invention also relates to the use of American Ginseng (*Panax quinquefolius*) to increase attention/alertness in a subject. The invention also relates to the use of American Ginseng (*Panax quinquefolius*) to increase self-assurance in a subject.

Background of the invention

The listing or discussion of an apparently prior-published document in this specification should not necessarily be taken as an acknowledgement that the document is part of the state of the art or is common general knowledge.

The term “Ginseng” is generally used to refer to the species of the genus Panax of the family of Atraliaceae. Extracts of Asian Ginseng (*Panax ginseng*) have been used for millennia in Traditional Chinese Medicine.
American ginseng (*Panax quinquefolius*) has a distinct ginsenoside profile form Panax ginseng and has recognized cognitive enhancing properties.

A study assessed the potential learning and memory benefits of HT1001, a standardized proprietary North American ginseng (*Panax quinquefolius*) extract containing Rb1, Rb2, Rc, Rd, Re, and Rg1 (total ginsenoside of 13-20%) in healthy volunteers. Neuropsychological assessments were conducted using the Clinical Memory Scale (CMS), which has two parallel forms for baseline and post-treatment assessments. A young adult sample (YAS, n = 10) and a middle aged sample (MAS, n = 10) completed the CMS at baseline and again after 14 days’ exposure to 200mg HT1001 daily. The CMS Memory Quotient (MQ) showed significant main effects of time, with higher CMS-MQ on the second assessment compared to the first, and of age group, with the YAS performing better than the MAS. There was no interaction between time and age group. Secondary analyses indicated benefits for both groups on free

recall of word lists, cued recall of word pairs, and recognition of figures, and benefits in the YAS but not the MAS on free recall of pictures. Taken together, the results suggest that memory, as measured with the CMS-MQ, was significantly improved with open-label HT1001. A limit to this study was the lack of placebo control and therefore the effects of this extract lack demonstration.

Summary of the Invention

The applicant has now found in a surprising manner that the extract of American ginseng (*Panax quinquefolius*) has an unexpected effect in the reduction of a fatigue condition.

Until now, the beneficial effects of American Ginseng on fatigue, alertness and self-assurance have not been known. The present invention provides extracts and methods of using American Ginseng to reduce the fatigue in a subject, including the reduction of the feeling of being tired, sleepy, etc The inventors have also discovered that administering American Ginseng improves an improvement in mood and alertness.

In a first aspect, the invention provides a composition comprising ginsenosides (or composition of the invention) for use in treating, reducing, preventing and/or ameliorating fatigue, improving or increasing attention/alertness and/or improving or increasing self-assurance.

Accordingly, in a second aspect, the invention provides a Panax quinquefolius extract for use in

(a) treating, reducing, preventing and/or ameliorating fatigue;

(b) improving or increasing attention/alertness

and/or

(c) improving or increasing self-assurance in a subject.

In a second aspect, the invention provides the use of a composition of the invention or an extract of the invention (Panax quinquefolius extract) for (a) treating, reducing, preventing and/or ameliorating fatigue; (b) improving or increasing attention/alertness and/or (c) improving or increasing self-assurance in a subject.

In a third aspect, the invention provides a method of

(a) treating, reducing, preventing and/or ameliorating fatigue;

(b) improving or increasing attention/alertness

and/or

(c) improving or increasing self-assurance

comprising the administration of an effective amount of a composition comprising ginsenosides or a *Panax quinquefolius* extract to a subject in need thereof.

The details, examples and preferences provided in relation to any one or more of the stated aspects of the present invention will be further described herein and apply equally to all aspects of the present invention. Any combination of the embodiments, examples and preferences described herein below in all possible variations thereof is encompassed by the present invention unless otherwise indicated herein, or otherwise clearly contradicted by context.

Detailed Description of the Invention

It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the embodiments, as claimed. Herein, the use of the singular includes the plural unless specifically stated otherwise. As used herein, the use of "or" means "and/or" unless stated otherwise. Furthermore, the use of the term "including" as well as other forms, such as "includes" and "included", is not limiting.

The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including, but not limited to, patents, patent applications, articles, books, etc are hereby expressly incorporated by reference for the portions of the document discussed herein, as well as in their entirety.

The present invention is based on the surprising discovery that chronic consumption of *Panax quinquefolius* (American Ginseng) can reverse fatigue and can improve self-assurance, attention and alertness.

Composition comprising ginsenosides

According to the present invention, there is provided a composition comprising ginsenosides, which may be referred to hereinafter as the "first composition of the invention".

Ginsenosides are saponins, which are the major pharmacologically active components of the Panax plant genus.

More than 40 structurally divergent ginsenosides have been isolated and identified from the root of Panax genus and are described, for example, in the publication of Razgonova et al. and included here by reference. (Razgonova, M. P.,et al. . (2019). Molecular medicine reports, 19(4), 2975-2998.). Ginsenosides are divided into three groups based on their chemical structures: protopanaxadiols (PD) including Rb1, Rb2, Rb3, Rc etc, protopanaxatriols (PT) including Re, Rf, Rg1, Rg2, Rhl; and oleanolic acid group (e.g. Ro) (Qi, L. W., Wang, C. Z., & Yuan, C. S. (2011). Isolation and analysis of ginseng: advances and challenges. Natural product reports, 28(3), 467-495).

As used herein, the term "ginsenosides" or “ginsenoside(s) may refer to any one of the more than 40 ginsenosides isolated and purified from the root of the Panax genus (Panax ginseng, Panax notoginseng and/or Panax quinquefolius) that has being described widely on the literature, such as Rb1, Rb2, Rb3, Rc, Re, Rf, Rg1, Rg2, Rhl, Ro, etc. It can be only one specific ginsenoside (i.e more than 99,9% of for example Rb1) or a mixture of two or more of said ginsenosides (Rb1 and Rb2, etc).

Typically, the ginsenoside(s) may be obtained from any natural source containing ginsenosides like for example the Panax genus, specifically the Panax ginseng (or Korean ginseng or KG) , Panax notoginseng (or south China ginseng or CHG) and/or

Panax quinquefolius (American Ginseng or AG) using processes as described herein. In a preferred embodiment, the ginsenosides are extracted from Panax quinquefolius.

The composition comprising ginsenosides (or first composition of the invention) may be obtained directly from a milled root of Panax ginseng, Panax notoginseng and/or Panax quinquefolius.

Methods for preparing the composition comprising ginsenosides (or first composition of the invention) may be extraction methods using different suitable solvents for extracting said ginsenosides from the natural sources containing ginsenosides such as Panax ginseng, Panax notoginseng and/or Panax quinquefolius.

In a preferred embodiment, ginsenosides of the first composition of the invention may be isolated from a ginsenoiside containing natural source (such as American ginseng, in particular, AG roots) using separation techniques that can be select for the required extract, which may be determined by those skilled in the art.

Typically, the ginsenoisides of the first composition of the invention may be obtained by the extraction and isolation processes as generally described herein, or routine modifications thereof.

For example, processes for extraction and isolation of the ginsenosides comprised in the composition of the invention may comprise (or consist essentially/consist of) the following steps:

(i) extraction of a natural source containing ginsenosides, such as Panax ginseng, Panax notoginseng and/or Panax quinquefolius roots (which may be ground) by a suitable solvent;
(ii) evaporation of the solvent; and, if required
(iii) purification of the ginsenosides (e.g. by chromatography).

Typically, Panax ginseng, Panax notoginseng or Panax quinquefolius roots are ground into granules with a particle size in a range from about 0.1 mm to about 30 mm, to increase the surface area for the solvent to contact and to increase extraction efficiency.

Particular solvents that may be used in the extraction process include alcohols (such as methanol), and alcohol/water mixtures (such as mixtures of methanol and water). For example, the extraction solvents can be water, a water-alcohol mixture (from about 1 % to about 99% alcohol in water. For example, from about 30% to about 75% alcohol in water, or from about 30% to about 50% alcohol in water, such as from about 35% or from about 40% alcohol in water), or alcohol. Particular alcohols that may be mentioned include ethanol (EtOH) and methanol (MeOH).

In particular embodiments, the extraction solvent may be an ethanol-water mix, such as from about 30% to about 90% ethanol in water, or from about 30% to about 50% ethanol in water. For example, from about 35% or from about 40% ethanol in water. In a preferred embodiment the extraction solvent is ethanol-water mix with about 80% ethanol and about 20% water.

In one embodiment, the temperature of extraction is in a range of from about 20 °C to about 100 °C. In a particular embodiment, the temperature for extraction is in a range of from about 50 °C to about 70 °C. Typically, the ratio of plant material to solvent mixture used in the extraction process varies from about 1 : 1 to about 1 :10 on a gram to milliliter basis, such as from about 1 :3 to about 1 :8. The incubation period (i.e. the period during which the plant material is in contact with the solvent) is typically from about 2 hours to about 24 hours.

After the plant materials and solvent have been incubated, the solvent is separated from residual plant material and the extraction composition is concentrated (i.e. the solvent is removed) until the extraction composition has a solid component.

Typically, the solid component may comprise (or consist essentially/consist of) from about 1 % to about 35% of ginsenosides and other components can be also presented such as terpenes, phenolic compounds, amino acids, flavonoids, volatile oils, vitamins,

and minerals. This natural extracts containing ginsenosides and other natural components can be used for the formulation of the composition of the invention.

However, after completion of the extraction process, the ginsenoside(s) can themselves be isolated from the extract (i.e. purified) using suitable purification processes such as a chromatographic process.

For example, purified ginsenosides may be obtained using the following process:

- the natural source containing ginsenosides such as Panax ginseng, Panax notoginseng and/or Panax quinquefolius powder (i.e. obtained by preparing ground roots) is dissolved in an alcohol and the ginsenoside (s) are extracted by alcohol from the powder.

The alcohol is then evaporated and the remaining residue including ginsenoside(s) is loaded into a chromatography column filled with reverse-phase C-18 resin;

- several fractions containing different compounds are eluted with a series of water and 10% MeOH/90% water, and MeOH system. The fractions are compared by high performance liquid chromatography (HPLC) analysis and those elutes having similar HPLC patterns are combined;

- the combined fractions are separated on normal phase silica gel column chromatography and eluted with chloroform (CHCI3), CHC

- methanol mixture starting from 90%, 80% CHCI3 to 100% MeOH to give several sub-fractions. The sub-fractions are compared by HPLC and the fractions which contain ginsenoside(s) are combined, respectively. The combined fractions are further purified by a combination of column chromatography over C-18, MCI GEL CHP-20P and/or Sephadex LH-20 resins to provide pure ginsenoside(s). The terms "isolated" and "purified" as used herein refer to the extract or ginsenoside(s) being separated from at least one other component (e.g. a polypeptide or cellulose derivative) present with the extract or ginsenoside(s) in its natural source. In one embodiment, the extract or ginsenoside(s) are provided in pure form or in the presence of a solvent, buffer, ion, or other component normally present in a solution of the same. In a preferred embodiment, the purification ginsenosides is more that 60%, 70%, 80% more than 99%.

Additionally, a fermentation process can be used as described in Kazuyoshi Kitaoka, et al. (Sleep. 2009 Mar 1; 32(3): 413–421). A culture medium including AG mixture and a fermenting organism is prepared. In a preferred embodiment, the fermenting organism is a safety recognized probiotics. In a preferred embodiment, the fermenting organism is L. paracasei A221, a homo-fermentative lactic acid bacterium isolated from a traditional fermented food. Its 16S rRNA sequence was deposited in the GenBank database under accession number AB126872. The genus Lactobacillus bacteria are used as starters for fermented foods, including yogurt and cheese. Their safety as probiotics has been traditionally established. L. paracasei A221 hydrolyzed plant glycosides including ginsenoside, glycyrrhizin (Glycyrrhizae Radix), and soy isoflavone glycoside (Glycine max). As for ginsenoside, L. paracasei A221 hydrolyzed ginsenosides Rb1, Rb2, Rc, and Rd (protopanaxadiol-type), and also ginsenosides Rg1 and Re (protopanaxatriol-type).

The culture medium will typically contain the natural source of ginsenosides (such as Panax ginseng, Panax notoginseng and/or Panax quinquefolius, preferable ground roots) and other components needed by the fermenting organism for the fermentation process (i.e 15% AG, 84%; yeast extract [Asahi Food – Healthcare Co., Ltd, Japan] 6.5%; soybean peptide [Fuji Oil Co., Ltd, Japan] 3% and calcium carbonate 6.5%). The fermentation process conditions (such as the temperature, time of fermentation etc.) will be determined by a person skilled in the art to as to obtain a concentration of more than 3%, more than 5%, 6%, 7%, 8%, 9%, 10%, 13%, 15%, 18%, 20%, 30%, 40%, 60%, 70%, 80%, 99% of ginsenosides. For example, the temperatures used can be from 20°C to about 80°C, from 20 °C to about 50°C, preferably as about 28°C. The time of fermentation can be determined by the person skilled in the art so as to obtain a concentration of ginsenosides of more than 3%. The time of fermentation can be from about 2 h to about 10 h, from about 4 h to about 20 h, from about 1 day to about 10 days. Following fermentation the cultured medium can be sterilized using methods well known in the art (i.e at 121°C for 10 min) and spray-dried. The rest of yeast cells and other cellular components (such as plant cellulose etc.) can be removed before or after the sterilization process using separation techniques well known in the art (i.e. filtration). The fermented culture medium before or after sterilization can be processes using the extraction, isolation and purification methods described herein as to obtain an extract of

AG with a ginsenosides concentration of more than 3%, more than 4%, 5%, 6%, 7%, 8%, 9%, 10%, 13%, 15%, 18%, 20%, 30%, 40%, 60%, 70%, 80% more than 99%.

The ginsenoside(s) can be of synthetic origin. Also bioengineering can be used for biosynthesis of ginsenosides as it was reported in Wang, P. et al (Wang, P. Wei, W., Ye, W. et al. Synthesizing ginsenoside Rh2 in Saccharomyces cerevisiae cell factory at high-efficiency. Cell Discov 5, 5 (2019). The purification of the resulting ginsenosides can be done using purification techniques already described herein.

The composition comprising ginsenosides (or first composition of the invention) may have a purity (based on total ginsenosides) of from about 3% to about 100% by weight, such as from, 3%, 4%, 5%, 6%, 7 %, 8%, 9%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80%, 90% or 100% to about 95%, 85%, 75%, 70%, 65%, 60%, 55%, 50%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% of total ginsenosides in the composition. In a preferred embodiment the total ginsenosides in from about 9% to about 15% weight, in a more preferred embodiment, total ginsenosides is from about 10% to about 13% weight.

In certain embodiments, the composition comprising ginsenosides (or first composition of the invention) may comprise (or consist essentially/consist of) the following compounds (ginsenosides):

a) Rg1: from about 0.5% to about 8% by weigh of total ginsenosides, such as from about 1% to about 4% by weigh of total ginsenosides, preferably such as from about 2% to about 4%, by weigh of total ginsenosides

b) Re : from about 4% to about 50% by weigh of total ginsenosides, such as from about 4 % to about 35% by weigh of total ginsenosides, preferably such as from about 10% to about 20%, by weigh of total ginsenosides

c) Rb1: from about 10% to about 100% by weigh of total ginsenosides, such as from about 30% to about 80% by weigh of total ginsenosides, preferably such as from about 40% to about 70%, by weigh of total ginsenosides

d) Rc from about 0.5 % to about 40% by weigh of total ginsenosides, such as from about 5% to about 35% by weigh of total ginsenosides, preferably such as from about 10% to about 20%, by weigh of total ginsenosides

e) Rb2 : from about 0.5% to about 20% by weigh of total ginsenosides, such as from about 2 to about 15% by weigh of total ginsenosides, preferably such as from about 2% to about 8%, by weigh of total ginsenosides, and / or

f) Rd from about 5% to about 50% by weigh of total ginsenosides, such as from about 9% to about 30% by weigh of total ginsenosides, preferably such as from about 10% to about 20%, by weigh of total ginsenosides.

In a preferred embodiment, the composition comprising ginsenosides (or first composition of the invention) comprises: Rg1 from about 3% to 4% by weigh of total ginsenosides, preferably 3,6 % by weigh of total ginsenosides, Re from 12 % to 17 % by weigh of total ginsenosides, preferably 16% by weigh of total ginsenosides, Rb1 from 40% to 50% by weigh of total ginsenosides, preferably 48% by weigh of total ginsenosides, Rc from 12 % to 17% by weigh of total ginsenosides, preferably 16% by weigh of total ginsenosides, Rb2 from 2% to 5% by weigh of total ginsenosides , preferably 4% by weigh of total ginsenosides, and / or Rd from 12% to 15% by weigh of total ginsenosides, preferably 14% by weight of total ginsenosides.

As mentioned before, the ginsenosides can be of natural origin as well as chemically synthetized ginsenosides. In a preferred embodiment the origin of the ginsenosides is a natural origin, in a more preferred embodiment, the ginsenosides are extracted from a Panax genus member such as Panax ginseng, Panax notoginseng and/or Panax quinquefolius, preferably the roots. For the avoidance of doubt, the ginsenosides can be obtained from Panax quinquefolius, from Panax ginseng or from Panax notoginseng but also can be obtained from two of them in any proportion (i.e Panax ginseng and Panax notoginseng, Panax notoginseng and Panax quinquefolius) or from the three of them: Panax ginseng, Panax notoginseng and Panax quinquefolius. For the avoidance of doubt, the ginsenosides can be only one type of ginsenoside or a mixture of two or more of the different ginsenosides reported in the literature, such as Rb1, Rb2, Rb3, Rc, Re, Rf, Rg1, Rg2, Rhl, Ro, etc.

<u>Extracts and processes for obtaining extracts</u>

According to the present invention, there is provided a *Panax quinquefolius* (American Ginseng) (AG) extract (in particular, a *Panax quinquefolius* leaf-stem or roots extract), which may be referred to hereinafter as the "extract of the invention".

Typically, the extract of the invention may be an extract obtained from American Ginseng (in particular, the roots of AG) using processes as described herein. For the avoidance of doubt, all references herein to a *Panax quinquefolius* (AG) extract will refer in particular to extracts obtained from AG leaf-stem or roots (more particularly, roots) extract.

The extract of the invention may be a milled root of American Ginseng, which contains between about 3 and 15 % of ginsenosides.

Other methods for preparing the extract of the invention may be an aqueous extract, an alcoholic extract or a hydro- alcoholic extract. Preferably, the extract of the invention is a hydro-alcoholic extract, such as a hydro-methanolic or hydro-ethanolic extract. For example, the extract of the invention may be a hydro-ethanolic extract obtained using an extraction solvent comprising from about 1 to about 99% ethanol in water, such as from about 30% to about 75% ethanol in water, or from about 30% to about 50% ethanol in water, such as from about 35% or from about 40% ethanol in water.

The term "aqueous extract" as used herein, refers to the extract obtained from *Panax quinquefolius* (AG) when the extraction from the plant (particularly, roots) has been performed using water as the only solvent.

The term "alcohol extract" as used herein, refers to the extract obtained from *Panax quinquefolius* (AG) when the extraction from the plant (particularly, root) has been performed using alcohol as the only solvent. For example, 100% methanol or 100% ethanol. The term "hydro-alcoholic extract' as used herein, refers to the extract obtained from *Panax quinquefolius* (AG) when the extraction from the plant has been performed using a mixture of water and alcohol. For example, from about 1 % to about 99% alcohol (e.g. ethanol) in water, such an extract would be termed a hydro-ethanolic extract.

The extract of the invention may be isolated from American ginseng (in particular, AG roots) using separation techniques that select for the required extract, which may be determined by those skilled in the art.

Typically, the extract of the invention may be obtained by the extraction and isolation processes as generally described herein, or routine modifications thereof.

For example, processes for extraction and isolation of extracts of the invention may comprise (or consist essentially/consist of) the following steps:

(i) extraction of AG roots (which may be ground) by a suitable solvent;
(ii) evaporation of the solvent; and, if required
(iii) purification of the extract (e.g. by chromatography).

Typically, AG roots are ground into granules with a particle size in a range from about 0.1 mm to about 30 mm, to increase the surface area for the solvent to contact and to increase extraction efficiency.

Particular solvents that may be used in the extraction process include alcohols (such as methanol), and alcohol/water mixtures (such as mixtures of methanol and water). For example, the extraction solvents can be water, a water-alcohol mixture (from about 1 % to about 99% alcohol in water. For example, from about 30% to about 75% alcohol in water, or from about 30% to about 50% alcohol in water, such as from about 35% or from about 40% alcohol in water), or alcohol. Particular alcohols that may be mentioned include ethanol (EtOH) and methanol (MeOH).

In particular embodiments, the extraction solvent may be an ethanol-water mix, such as from about 30% to about 75% ethanol in water, or from about 30% to about 50% ethanol in water. For example, from about 35% or from about 40% ethanol in water.

In one embodiment, the temperature of extraction is in a range of from about 20 °C to about 100 °C. In a particular embodiment, the temperature for extraction is in a range of from about 50 °C to about 70 °C. Typically, the ratio of plant material to solvent mixture

used in the extraction process varies from about 1 : 1 to about 1 :10 on a gram to milliliter basis, such as from about 1 :3 to about 1 :8. The incubation period (i.e. the period during which the plant material is in contact with the solvent) is typically from about 2 hours to about 24 hours.

After the plant materials and solvent have been incubated, the solvent is separated from residual plant material and the extraction composition is concentrated (i.e. the solvent is removed) until the extraction composition has a solid component. Typically, the solid component may comprise (or consist essentially/consist of) from about 1 % to about 35% of AG ginsenosides. Other components include terpenes, phenolic compounds, amino acids, flavonoids, volatile oils, vitamins, and minerals. After completion of the extraction process, the ginsenoside(s) can themselves be isolated from the AG extract (i.e. purified) used a chromatographic process, if required.

Typically, the extract of the invention may be obtained using the following process:
- the AG extract powder (i.e. obtained by preparing ground roots) is dissolved in an alcohol and the ginsenoside (s) are extracted by alcohol from the powder.
The alcohol is then evaporated and the remaining residue including ginsenoside(s) is loaded into a chromatography column filled with reverse-phase C-18 resin;
- several fractions containing different compounds are eluted with a series of water and 10% MeOH/90% water, and MeOH system. The fractions are compared by high performance liquid chromatography (HPLC) analysis and those elutes having similar HPLC patterns are combined;
- the combined fractions are separated on normal phase silica gel column chromatography and eluted with chloroform (CHCl3), CHC
-methanol mixture starting from 90%, 80% CHCl3 to 100% MeOH to give several sub-fractions. The sub-fractions are compared by HPLC and the fractions which contain ginsenoside(s) are combined, respectively. The combined fractions are further purified by a combination of column chromatography over C-18, MCI GEL CHP-20P and/or Sephadex LH-20 resins to provide pure ginsenoside(s). The terms "isolated" and "purified" as used herein refer to the extract or ginsenoside(s) being separated from at least one other component (e.g. a polypeptide or cellulose derivative) present with the extract or ginsenoside(s) in its natural source. In one embodiment, the extract or

ginsenoside(s) are provided in pure form or in the presence of a solvent, buffer, ion, or other component normally present in a solution of the same.

Additionally, a fermentation process can be used as described in Kazuyoshi Kitaoka, et al. (Sleep. 2009 Mar 1; 32(3): 413–421). A culture medium including AG mixture and a fermenting organism is prepared. In a preferred embodiment, the fermenting organism is a safety recognized probiotics. In a preferred embodiment, the fermenting organism is *L. paracasei* A221, a homo-fermentative lactic acid bacterium isolated from a traditional fermented food. Its 16S rRNA sequence was deposited in the GenBank database under accession number AB126872. The genus Lactobacillus bacteria are used as starters for fermented foods, including yogurt and cheese. Their safety as probiotics has been traditionally established. L. paracasei A221 hydrolyzed plant glycosides including ginsenoside, glycyrrhizin (Glycyrrhizae Radix), and soy isoflavone glycoside (Glycine max). As for ginsenoside, L. paracasei A221 hydrolyzed ginsenosides Rb1, Rb2, Rc, and Rd (protopanaxadiol-type), and also ginsenosides Rg1 and Re (protopanaxatriol-type).

The culture medium will typically contain the AG (preferable in ground AG) and other components needed by the fermenting organism for the fermentation process (i.e 15% AG, 84%; yeast extract [Asahi Food – Healthcare Co., Ltd, Japan] 6.5%; soybean peptide [Fuji Oil Co., Ltd, Japan] 3% and calcium carbonate 6.5%). The fermentation process conditions (such as the temperature, time of fermentation etc.) will be determined by a person skilled in the art to as to obtain a concentration of more than 3%, more than 5%, 6%, 7%, 8%, 9%, 10%, 13%, 15%, 18%, 20%, 30%, 40%, 60%, 70%, 80%, 99% of ginsenosides. For example, the temperatures used can be from 20°C to about 80°C, from 20 °C to about 50°C, preferably as about 28°C. The time of fermentation can be determined by the person skilled in the art so as to obtain a concentration of ginsenosides of more than 3%. The time of fermentation can be from about 2 h to about 10 h, from about 4 h to about 20 h, from about 1 day to about 10 days. Following fermentation the cultured medium can be sterilized using methods well known in the art (i.e at 121°C for 10 min) and spray-dried. The rest of yeast cells and other cellular components (such as plant cellulose etc.) can be removed before or after the sterilization process using separation techniques well known in the art (i.e. filtration).

The fermented culture medium before or after sterilization can be processes using the extraction, isolation and purification methods described herein as to obtain an extract of AG with a ginsenosides concentration of more than 3%, more than 4%, 5%, 6%, 7%, 8%, 9%, 10%, 13%, 15%, 18%, 20%, 30%, 40%, 60%, 70%, 80% more than 99%.
Thus, the terms "isolated" and "purified" do not refer to the extract or ginsenoside(s) present in their natural source. Similarly, the term extract refers to components of the natural material having been obtained through a process of extraction, rather than those components as present in their natural source (e.g. as AG roots).

In particular embodiments, the extract of the invention as obtained from such methods may be:
substantially free of other plant material (e.g. free of plant cellulose);
substantially free of plant cells; and/or
substantially free of plant cellular matter,
substantially free of toxic components like quintozene, aflatoxins, ochratoxin A, cadmium, arsenic or mercury.

As used herein, references to a material being "substantially free" of another material may refer to the material consisting of less than 1 % by weight (e.g. less than 0.1 %, such as less than 0.01 % or less than 0.001 %, by weight) of that other material.

In alternative embodiments, the method of extracting and isolating a AG extract from a AG roots may be described as comprising (or consisting essentially/consisting of) the steps of:
(a) grinding a AG roots into particles; (optionally performing a fermentation process as described before)
(b) containing the particles with a solvent mixture;
(c) separating the ground particles from the solvent mixture; and
(d) evaporating the solvent mixture.

In further such embodiments, the process may also comprise (or consist essentially/consist of) the steps of:

(e) dissolving the product of (d) in alcohol; and
(f) evaporating the alcohol.

Typically, in the extraction of the AG extract from an AG roots (i.e. steps (a) to (d) as described herein above): the ground particles have a diameter from about 0.1 mm to 30mm; and/or the temperature is from about 20°C to about 100°C; and/or the ratio of ground particles to solvent mixture is from about 1 g to 1 ml to about 1g to 8ml; and/or the ground particles are in contact with the solvent mixture from about 2 hours to about 24 hours; and/or the solvent mixture is water, a water-alcohol mixture or alcohol.

In particular embodiments, the extract of the invention as described herein may be an extracted obtained from (or obtainable by) a process as described herein.

The person ordinary skilled in the art would understand how to make the American gingeng extracts using different extraction technics (other powders, extracts, and modified products) for obtaining an American Ginseng containing ginsenosides.

Ginsenosides can be classified into three groups on the basis of their chemical structure; the Panaxadiol group (Rb1 , Rb2, Rb3, Rc etc.), Panaxatriol group (Re, Rf, Rg1, Rg2, RhI), and the oleanolic acid group (e.g. Ro). American Ginseng (Panax quinquefolius), has its own characteristic profile exhibiting a high expression of the Ginsenoside Rb1.

The Panax quinquefolius extract of the invention may have a purity (based on total ginsenosides) of from about 3% to about 100% by weight, such as from, 3%, 4%, 5%, 6%, 7 %, 8%, 9%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80% or 90% to about 95%, 85%, 75%, 70%, 65%, 60%, 55%, 50%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% of total ginsenosides in the extract. In a preferred embodiment the total ginsenosides in from about 9% to about 15% weight, in a more preferred embodiment, total ginsenosides is from about 10% to about 13% weight.

In certain embodiments, the extract of the invention may comprise (or consist essentially/consist of) the following compounds (ginsenosides):

a) from about 0.05% to about 0.8% by weight of Rg1, such as from about 0.1% to about 0.4% by weight, preferably such as from about 0.3% to about 0.5%, by weight
b) from about 0.3% to about 5% by weight of Re, such as from about 1 % to about 3.5% by weight, preferably such as from about 0.4 % to about 3.5%, by weight
c) from about 1% to about 10% by weight of Rb1, such as from about 3% to about 8% by weight, preferably such as from about 4% to about 7%, by weight
d) from about 0.1 to about 5% by weight of Rc, such as from about 0.3 to about 4% by weight, preferably such as from about 0.5% to about 3.5%, by weight
e) from about 0.1 to about 3% by weight of Rb2, such as from about 0.5 to about 2% by weight, preferably such as from about 0.2% to about 1.5%, by weight, and / or
f) from about 0.5 to about 5% by weight of Rd, such as from about 0.7 to about 4% by weight, preferably such as from about 0.9% to about 3%, by weight

In a preferred embodiment, the AG extract contains from about 10% to 13%, preferably about 10% of ginsenosides and the specific ginsenosides concentration is: Rg1 from about 0.1% to 0.4% , preferably 0.36 %, Re from 0.4 % to 3.5 %, preferably 1.6%, Rb1 from 4% to 7%, preferably 4.8%, Rc from 0.5% to 3.5%, preferably 1.6%, Rb2 from 0.2% to 1.5% , preferably 0.4%, and / or Rd from 0.9% to 3% , preferably 1.4% by weight.

Unless otherwise stated herein, the weight percentages listed are based on the total weight of (dry) extract obtained.

In certain embodiments, the extract of the invention may comprise (or consist essentially/consist of) the following compounds (ginsenosides):

a) Rg1: from about 0.5% to about 8% by weigh of total ginsenosides, such as from about 1% to about 4% by weigh of total ginsenosides, preferably such as from about 3% to about 4%, by weigh of total ginsenosides
b) Re : from about 4% to about 50% by weigh of total ginsenosides, such as from about 4 % to about 35% by weigh of total ginsenosides, preferably such as from about 10 % to about 20%, by weigh of total ginsenosides

c) Rb1: from about 10% to about 100% by weigh of total ginsenosides, such as from about 30% to about 80% by weigh of total ginsenosides, preferably such as from about 40% to about 70%, by weigh of total ginsenosides
d) Rc from about 1 % to about 40% by weigh of total ginsenosides, such as from about 5 to about 35% by weigh of total ginsenosides, preferably such as from about 10% to about 20%, by weigh of total ginsenosides
e) Rb2 : from about 1% to about 20% by weigh of total ginsenosides, such as from about 2 to about 15% by weigh of total ginsenosides, preferably such as from about 2% to about 8%, by weigh of total ginsenosides, and / or
f) Rd from about 5% to about 50% by weigh of total ginsenosides, such as from about 7% to about 30% by weigh of total ginsenosides, preferably such as from about 10% to about 20%, by weigh of total ginsenosides.

In a preferred embodiment, the AG extract contains: Rg1 from about 3% to 4% by weigh of total ginsenosides ,preferably 3,6 % by weigh of total ginsenosides, Re from 12 % to 17 % by weigh of total ginsenosides, preferably 16% by weigh of total ginsenosides, Rb1 from 40% to 50% by weigh of total ginsenosides, preferably 48% by weigh of total ginsenosides, Rc from 12 % to 17% by weigh of total ginsenosides, preferably 16% by weigh of total ginsenosides, Rb2 from 2% to 5% by weigh of total ginsenosides , preferably 4% by weigh of total ginsenosides, and / or Rd from 12% to 15% by weigh of total ginsenosides, preferably 14% by weight of total ginsenosides.

For the avoidance of doubt, preferences, options, particular features and the like indicated for a given aspect, 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 preferences, options particular features and the like as indicated for the same or other aspects, features and parameters of the invention.

When we use the term "comprising" or "comprises" we mean that the extract or composition being described must contain the listed ingredient(s) but may optionally contain additional ingredients. When we use the term "consisting essentially of" or "consists essentially of" we mean that the extract or composition being described must

contain the listed ingredient(s) and may also contain small (for example up to 5% by weight, or up to 1 % or 0.1 % by weight) of other ingredients provided that any additional ingredients do not affect the essential properties of the extract or composition. When we use the term "consisting of" or "consists of we mean that the extract or composition being described must contain the listed ingredient(s) only. The term "about" as used herein, e.g. when referring to a measurable value (such as an amount or weight of a particular component in the reaction mixture), refers to variations of ±20%, ±10%, ±5%, ±1 %, ±0.5%, or, particularly, ±0.1 % of the specified amount.

Further, other compounds may also be present in the extract of the invention. In certain embodiments, other compounds that may be present include, but are not limited to terpenes, phenolic compounds, amino acids, flavonoids, volatile oils, vitamins, and minerals.

The skilled person will understand that the extract of the invention may be provided in solid form. By solid form, it is included that the compound may be provided as an amorphous solid, or as a crystalline or part-crystalline solid.

Compositions and administration

According to the present invention, the composition comprising ginsenosides of the invention or the extract of the invention may be provided in the form of a (suitable) composition, such as a pharmaceutical, nutraceutical composition or a food composition (which may be referred to as a functional food composition or a dietary composition).

In particular embodiments, the composition comprising ginsenosides of the invention or the extract of the invention may be provided in the form of a pharmaceutical composition (which may also be referred to as a pharmaceutical formulation), a nutraceutical composition or functional food composition comprising the extract of the invention and optionally a pharmaceutically acceptable excipient or (functional) food acceptable ingredient, as appropriate.

As used herein, references to pharmaceutically acceptable excipients may refer to pharmaceutically acceptable adjuvants, diluents and/or carriers as known to those skilled in the art.

Food acceptable ingredients include those known in the art (including those also referred to herein as pharmaceutically acceptable excipients) and that can be natural or non- natural, i.e. their structure may occur in nature or not. In certain instances, they can originate from natural compounds and be later modified (e.g. maltodextrin).

In particular embodiments, the composition comprising ginsenosides of the invention or the extract of the invention may be provided in the form of a pharmaceutical composition, a nutraceutical composition or a functional food composition, further comprising a non- natural carrier or a modified natural carrier, such as maltodextrin or arabic gum. In a preferred embodiment the extract of the invention is formulated with maltrodextrin, in another preferred embodiment, the extract of the invention is formulated with arabic gum.

By "pharmaceutically acceptable" we mean that the additional components of the composition are sterile and pyrogen free. Such components must be "acceptable" in the sense of being compatible with the extract of the invention and not deleterious to the recipients thereof. Thus, "pharmaceutically acceptable" includes any compound(s) used in forming a part of the formulation that is intended to act merely as an excipient, i.e. not intended to have biological activity itself. Thus, the pharmaceutically acceptable excipient is generally safe, non-toxic, and neither biologically nor otherwise undesirable. The skilled person will understand that extracts of the invention (e.g. in the form of compositions, such as pharmaceutical compositions, as known to those skilled in the art, such as those as described herein) may be administered to a patient or subject (e.g. a human or animal patient or subject) by any suitable route, such as by the oral, rectal, nasal, pulmonary, buccal, sublingual, transdermal, intracisternal, intraperitoneal, and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route. In particular, extracts of the invention may be administered orally. In such instances, pharmaceutical or nutraceutical compositions according to the present invention may be specifically formulated for administration by the oral route.

Pharmaceutical and nutraceutical compositions for oral administration include solid dosage forms such as hard or soft capsules, tablets, troches, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings, or they can be formulated so as to provide controlled release of the active ingredient, such as sustained or prolonged release, according to methods well known in the art. Liquid dosage forms for oral administration include solutions, emulsions, aqueous or oily suspensions, syrups and elixirs.

Compositions (e.g. pharmaceutical, nutraceutical or food compositions) described herein, such as those intended for oral administration, may be prepared according to methods known to those skilled in the art, such as by bringing the components of the composition into admixture.

Such compositions as described herein may contain one or more additional components selected from the group consisting of food ingredients, such as sweetening agents, flavouring agents, colouring agents and preserving agents. Tablets may contain the active ingredient(s) in admixture with non-toxic pharmaceutically acceptable excipients (or ingredients) which are suitable for the manufacture of tablets. These excipients (or ingredients) may, for example, be: inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, maltodextrin or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solutions and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, maltodextrin, talc, gelatin, silica, agar, pectin, acacia, magnesium stearate, stearic acid, arabic gum, modified starch and lower alkyl ethers of

cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethyiene and water. Moreover, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

Depending on the disorder, and the patient, to be treated, as well as the route of administration, extracts of the invention may be administered at varying doses (i.e. therapeutically effective doses, as administered to a patient in need thereof). In this regard, the skilled person will appreciate that the dose administered to a mammal, particularly a human, in the context of the present invention should be sufficient to affect a therapeutic response in the mammal over a reasonable timeframe. One skilled in the art will recognize that the selection of the exact dose and composition and the most appropriate delivery regimen will also be influenced by inter alia the pharmacological properties of the formulation, the nature and severity of the condition being treated, and the physical condition and mental acuity of the recipient, as well as the potency of the specific compound, the age, condition, body weight, sex and response of the patient to be treated, and the stage/severity of the disease.

Typically, in the use or method of the invention described herein the extract or composition comprising the extract of the invention or the composition comprising ginsenosides of the invention is administered in an amount of from about 100mg/day to about 2000mg/day, or from about 500mg/day to about 1500mg/day, or about 1000mg/day. In a preferred embodiment, the amount is from about 100 mg/day to about 400 mg/day, more preferred from about 150mg/day to about 250mg/day, more preferred 200mg/day. In any event, the medical practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual patient. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

When included within a composition (e.g. a pharmaceutical or nutraceutical composition) as described herein, the composition comprising ginsenosides of the invention or the extract of the invention is typically present in an amount from about 1%

by weight to about 100% by weight, for example, from about 10% by weight to about 90% by weight or about 20% by weight to about 80% or from about 30% by weight to about 70% or from about 40% by weight to about 60% by weight.

Functional food composition can be presented as beverages, dairy products, bakery products, etc.

Uses and methods of the invention

The composition comprising ginsenosides of the invention or the extract of the invention (and the pharmaceutical, nutraceutical or food compositions of the invention) may also have an effect in reducing fatigue (as shown in figure 9).

The composition comprising ginsenosides of the invention or the extract of the invention may also have an effect in improving the mood of a subject. Typically, the extract of the invention may reduce of reduce negative affect and increase self-assurance (as shown in figure 10). Also, the composition comprising ginsenosides of the invention or the extract of the invention increases the attention and alertness after chronic treatment (as shown in figures 2, 3, 4, 5, 6, 7, and 8).

As used herein, the term "fatigue" may refer an overall feeling of tiredness or lack of energy in a healthy subject but also related to some medical condition. Fatigue is a common symptom of many medical conditions that range in severity from mild to serious. Many medical conditions can also cause fatigue. Examples include: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic obstructive pulmonary disease (COPD) aging , neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer's disease, Parkinson's disease or emphysema. Fatigue can be also described as a situation where the subject has, among others, the feeling of being sleepy, the feeling of being tired, the feeling of being sluggish and /or the feeling

of being drowsy. The fatigue (overall lack of energy) can be measured using standard methods known by the person skilled in the art. Examples of methods that can be used are, among others and without limiting to the following examples, the PANAS-X (Watson, D., & Clark, L. A. (1994). The PANAS-X: Manual for the positive and negative affect schedule-expanded form) and the mental fatigue visual analogue scale (Scholey, A. B., French, S. J., Morris, P. J., Kennedy, D. O., Milne, A. L., & Haskell, C. F. (2010). Journal of Psychopharmacology, 24(10), 1505-1514).

The PANAS-X scale consists of a number of words and phrases that describe different feelings and emotions including self-assurance (sleepy, tired, sluggish, drowsy). Participants Read each item and then mark the appropriate answer (giving a score from 1 to 5) in the space next to that word. Indicate to what extent you have felt this way during the past week. A higher rating means a higher fatigue state.

Fatigue can also be measured via a mental fatigue visual analogue scale: Participants rated their current subjective mental fatigue state by making a mark on a 9-point Likert scale with the end points labelled ‘not at all’(left hand end) and ‘very much so’(right hand end) (Scholey, A. B., French, S. J., Morris, P. J., Kennedy, D. O., Milne, A. L., & Haskell, C. F. (2010) Journal of Psychopharmacology, 24(10), 1505-1514.

As used herein, the term "attention” and “alertness" are interchangeable and may refer to an overall state of higher awareness or higher focus and concentration or determination in a healthy subject but also related to some medical condition. The lack of attention/alertness is a common symptom of many medical conditions that range in severity from mild to serious. Many medical conditions can also cause attention/alertness deficiency. Examples include: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison’s disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic obstructive pulmonary disease (COPD), aging, neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer’s disease, Parkinson’s disease or emphysema. Attention and alertness can be also described as a capacity to

process high cognitive demanding task such as, and not limited as, reaction time to process complex information or correct answers to complex tasks requiring to synthetize multiple information. The state of attention/alertness can be measured using standard methods known by the person skilled in the art. Examples of methods that can be used are, among others and without limitation to the following measurement methods, are the accuracy and reaction time in the Modified attention network task described in the examples of the present application. Attention and alertness can be also described as a capacity to process high cognitive demanding task such as Rapid Visual Information Processing task. In this sustained attention task, a series of digits are presented on screen in quick succession. The participant is required to monitor the digits for sequences of three consecutive even or three consecutive odd digits. Participants indicate the end of a target sequence by pressing the space bar as quickly as possible. The dependent variables are reaction time, accuracy, and commission errors. (Watson, A. W., Haskell-Ramsay, C. F., Kennedy, D. O., Cooney, J. M., Trower, T., & Scheepens, A. (2015). Acute supplementation with blackcurrant extracts modulates cognitive functioning and inhibits monoamine oxidase-B in healthy young adults. *Journal of functional foods*, *17*, 524-539.

As used herein, the term "self-assurance" may refer to an overall feeling of being confident, proud, strong, bold, fearless, daring in a healthy subject but also related to some medical condition. The lack of self-assurance is a common symptom of many medical conditions that range in severity from mild to serious. Many medical conditions can also cause self-assurance decline. Examples include: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic obstructive pulmonary disease (COPD), aging, neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer's disease, Parkinson's disease or emphysema. Self-assurance can be also described as a capacity to overcome difficulties by surpassing oneself. The state of self-assurance can be measured using standard methods known by the person skilled in the art. Examples of methods that can be used are, among others and without limitation to the

following measurement methods, the PANAS-X (Watson, D., & Clark, L. A. (1994). The PANAS-X: Manual for the positive and negative affect schedule-expanded form) described in the examples of the present application. This scale consists of a number of words and phrases that describe different feelings and emotions including self-assurance (proud, strong, confident, bold, fearless, daring). Participants Read each item and then mark the appropriate answer (giving a score from 1 to 5) in the space next to that word. Indicate to what extent you have felt this way during the past week. A higher rating means a higher self-assurance state.

Thus, in an aspect of the invention there is provided a composition comprising ginsenosides of the invention or a *Panax quinquefolius* extract (i.e. an extract of the invention) for use in: (a) treating, reducing, preventing and/or ameliorating fatigue; (b) improving or increasing attention/alertness and/or (c) improving or increasing self-assurance in a subject. Certain embodiments disclosed herein provide compounds or compositions comprising a composition comprising ginsenosides of the invention *or a Panax quinquefolius* extract. Such compounds or compositions (e.g. pharmaceutical, nutraceutical or food compositions) are useful to treat, reduce, prevent and/or ameliorate fatigue. In further aspects of the invention there is provided a composition comprising ginsenosides of the invention *or* a *Panax quinquefolius* extract, or a compound or composition comprising a composition comprising ginsenosides of the invention *or Panax quinquefolius* extract (e.g. pharmaceutical, nutraceutical or food compositions) for use in: (a) treating, reducing, preventing and/or ameliorating fatigue in a subject, (b) improving or increasing attention/alertness in a subject and/or (c) improving or increasing self-assurance in a subject. In certain embodiments, the subject is human. In a further preferred embodiment, the subject is a healthy subject, in a more preferred embodiment; the subject is a healthy human.

In further aspects of the invention there is provided a composition comprising ginsenosides of the invention *or* a *Panax quinquefolius* extract or a compound or composition comprising a composition comprising ginsenosides of the invention *or a Panax quinquefolius* extract (e.g. pharmaceutical, nutraceutical or food compositions) for use in (a) treating, reducing, preventing and/or ameliorating fatigue; (b) improving or increasing attention/alertness and/or (c) improving or increasing self-assurance. In

certain embodiments, the subject is human. In a further preferred embodiment, the subject is a healthy subject, in a more preferred embodiment; the subject is a healthy human.

In certain embodiments, it is provided the use of a composition comprising ginsenosides of the invention *or a Panax quinquefolius* extract, or a compound or composition comprising a composition comprising ginsenosides of the invention *or a Panax quinquefolius* extract, for (a) treating, reducing, preventing and/or ameliorating fatigue in a subject, (b) improving or increasing attention/alertness in a subject and/or (c) improving or increasing self-assurance in a subject. In certain embodiments, the subject is human.

Certain embodiments provide methods, compounds, and compositions (e.g. pharmaceutical, nutraceutical or food compositions) for (a) treating, reducing, preventing and/or ameliorating fatigue, (b) improving or increasing attention/alertness and/or (c) improving or increasing self-assurance, or a symptom thereof, in a subject by administering the compound or composition to the subject, wherein the compound or composition (e.g. pharmaceutical, nutraceutical or food compositions) comprises a composition comprising ginsenosides of the invention *or a Panax quinquefolius* extract. In further alternative aspect of the invention, there is provided a method of: (a) treating, reducing, preventing and/or ameliorating fatigue; (b) improving or increasing attention/alertness, and/or (c) improving or increasing self-assurance comprising the administration of an effective amount of a composition comprising ginsenosides of the invention *or* a *Panax quinquefolius* extract, or a compound or composition (e.g. pharmaceutical, nutraceutical or food compositions) comprising a composition comprising ginsenosides of the invention *or a Panax quinquefolius* extract, to a subject in need thereof. In certain embodiments, the subject is human. In a further preferred embodiment, the subject is a healthy subject, in a more preferred embodiment; the subject is a healthy human.

In an alternative aspect of the invention, there is provided the use of a composition comprising ginsenosides of the invention *or* a *Panax quinquefolius* extract or a compound or composition comprising a composition comprising ginsenosides of the

invention *or a* Panax quinquefolius extract, in the manufacture or preparation of a medicament or a nutraceutical composition for: (a) treating, reducing, preventing and/or ameliorating fatigue; (b) improving attention/alertness, and/or (c) improving or increasing self-assurance in a subject. In certain embodiments, the subject is human. In a further preferred embodiment, the subject is a healthy subject, in a more preferred embodiment; the subject is a healthy human.

In a further embodiment, it is provided a method of treating, preventing, delaying, or ameliorating fatigue in a subject having, or at risk of having, fatigue comprising administering a composition comprising ginsenosides of the invention *or* a *Panax quinquefolius* extract or a composition comprising AG extract, (e.g. pharmaceutical, nutraceutical or food compositions) to the subject, thereby preventing, delaying or ameliorating the fatigue in the subject. In certain embodiments, the subject is human. In a further preferred embodiment, the subject is a healthy subject, in a more preferred embodiment; the subject is a healthy human. In another embodiment, the subject is not healthy and the fatigue is related to a medical condition.

In a further embodiment of the uses and methods described before, the subject suffers from one or more of the following medical conditions: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic obstructive pulmonary disease (COPD) aging , neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer's disease, Parkinson's disease or emphysema.

In a further embodiment of the uses and methods described before, the fatigue is related to a one or more of the following medical conditions: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic

obstructive pulmonary disease (COPD) aging , neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer's disease, Parkinson's disease or emphysema.

In certain embodiments, the treatment, reduction, prevention and/or amelioration of fatigue is due of the treatment, reduction, prevention and/or amelioration of the feeling of being sleepy, of being tired, of being sluggish and / or the feeling of being drowsy.

Typically, the extract of the invention may decrease the feelings of being sleepy or tired (as shown in Figure 9) Thus, in an aspect of the invention there is provided a composition comprising ginsenosides of the invention *or* a *Panax quinquefolius* extract or a compound or composition comprising a composition comprising ginsenosides of the invention *or Panax quinquefolius* extract for use in:

a) decreasing the feeling of being sleepy,
b) decreasing the feeling of being tired,
c) decreasing the feeling of being sluggish, and /or
d) decreasing the feeling of being drowsy

In a further embodiment of the uses and methods described before, the problem in attention and /or alertness is related to a one or more of the following medical conditions: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic obstructive pulmonary disease (COPD) aging , neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer's disease, Parkinson's disease or emphysema.

The extract of the invention may also improve the self-assurance of a subject. Typically, the extract of the invention may increase the feeling of being confident or fearless (as shown in Figure 10).

In a further embodiment of the uses and methods described before, the problems or decrease in self-assurance is related to a one or more of the following medical

conditions: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic obstructive pulmonary disease (COPD), aging, neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer's disease, Parkinson's disease or emphysema.

In certain embodiments, the improve the self-assurance is due of the increase in the feeling of being proud, increase on the feeling of being strong, increase on the feeling of being confident, increase on the feeling of being fearless and /or increase on the feeling of being daring.

Thus, in an aspect of the invention there is provided a composition comprising ginsenosides of the invention *or* a *Panax quinquefolius* extract or a compound or composition comprising *Panax quinquefolius* extract for use in:

a) increasing the feeling of being proud,
b) increasing the feeling of being strong,
c) increasing the feeling of being confident,
d) increasing the feeling of being bold,
e) increasing the feeling of being fearless and / or
f) increasing the feeling of being daring

For the avoidance of doubt, in particular embodiments of the uses and methods described herein, the composition comprising ginsenosides of the invention *or* the *Panax quinquefolius* extract may comprise (or consist essentially/consist of) the following compounds (ginsenosides): about 3% to about 100% by weight, such as from, 3%, 4%, 5%, 6%, 7 %, 8%, 9%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80% or 90% to about 95%, 85%, 75%, 70%, 65%, 60%, 55%, 50%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% of total ginsenosides in the extract.

In a preferred embodiment the total ginsenosides in the composition comprising ginsenosides of the invention *or the Panax quinquefolius* extract is from about 9% to

about 15% weight, in a more preferred embodiment, total ginsenosides is from about 10% to about 13% weight.

For the avoidance of doubt, in particular embodiments of the uses and methods described herein, the composition comprising ginsenosides of the invention *or* the extract of the invention may comprise (or consist essentially/consist of) the following compounds (ginsenosides):

a) from about 0.01% to about 0.8% by weight of Rg1, such as from about 0.05% to about 0.4% by weight, preferably such as from about 0.1% to about 0.4%, by weightb)from about 0..1% to about 5% by weight of Re, such as from about 0.4 % to about 4% by weight, preferably such as from about 0.8 % to about 3.5%, by weight
b) from about 1% to about 10% by weight of Rb1, such as from about 3% to about 8% by weight, preferably such as from about 4% to about 7%, by weight
c) from about 0.05 to about 5% by weight of Rc, such as from about 0.1 to about 4% by weight, preferably such as from about 0.5% to about3.52%, by weight
d) from about 0.05 to about 3% by weight of Rb2, such as from about 0.1 to about 2% by weight, preferably such as from about 0.2% to about 1.5%, by weight, and / or
e) from about 0.5 to about 5% by weight of Rd, such as from about 0.7 to about 4% by weight, preferably such as from about 0.9% to about 3%, by weight

In a preferred embodiment of the uses and methods described herein, the composition comprising ginsenosides of the invention *or the* AG extract contains from about 10% to 13%, preferably about 10% of ginsenosides and the specific ginsenoisdes concentration is : Rg1 from about 0.1% to 0.4% , preferably 0.36 %, Re from 0.8 % to 3.5 %, preferably 1.6%, Rb1 from 4% to 7%, preferably 4.8%, Rc from 0.5 % to 3.5%, preferably 1.6%, Rb2 from 0.2% to 1.5% , preferably 0.4%, and / or Rd from 0.9% to 3% , preferably 1.4% by weight.

Unless otherwise stated herein, the weight percentages listed are based on the total weight of (dry) extract obtained.

For the avoidance of doubt, in particular embodiments of the uses and methods described herein, the composition comprising ginsenosides of the invention *or* the AG extract of the invention may comprise (or consist essentially/consist of) the following compounds (ginsenosides) :

a) Rg1: from about 0.5% to about 8% by weigh of total ginsenosides, such as from about 1% to about 4% by weigh of total ginsenosides, preferably such as from about 3% to about 4%, by weigh of total ginsenosides
b) Re : from about 5% to about 50% by weigh of total ginsenosides, such as from about 10 % to about 35% by weigh of total ginsenosides, preferably such as from about 12 % to about 20%, by weigh of total ginsenosides
c) Rb1: from about 10% to about 100% by weigh of total ginsenosides, such as from about 30% to about 80% by weigh of total ginsenosides, preferably such as from about 40% to about 60%, by weigh of total ginsenosides
d) Rc from about 1 % to about 40% by weigh of total ginsenosides, such as from about 5 to about 35% by weigh of total ginsenosides, preferably such as from about 10% to about 20%, by weigh of total ginsenosides
e) Rb2 : from about 1% to about 20% by weigh of total ginsenosides, such as from about 2 to about 10% by weigh of total ginsenosides, preferably such as from about 2% to about 5%, by weigh of total ginsenosides, and / or
f) Rd from about 5% to about 50% by weigh of total ginsenosides, such as from about 7% to about 30% by weigh of total ginsenosides, preferably such as from about 10% to about 20%, by weigh of total ginsenosides.

In a preferred embodiment of the methods and uses described herein, the AG extract contains: Rg1 from about 3% to 4% by weigh of total ginsenosides , preferably 3,6 % by weigh of total ginsenosides, Re from 12 % to 17 % by weigh of total ginsenosides, preferably 16% by weigh of total ginsenosides, Rb1 from 40% to 50% by weigh of total ginsenosides, preferably 48% by weigh of total ginsenosides, Rc from 12 % to 17% by weigh of total ginsenosides, preferably 16% by weigh of total ginsenosides, Rb2 from 2% to 5% by weigh of total ginsenosides , preferably 4% by weigh of total ginsenosides,

and / or Rd from 12% to 15% by weigh of total ginsenosides, preferably 14% by weight of total ginsenosides.

Moreover, for the avoidance of doubt, the *Panax quinquefolius* (AG) extract may be in the form of a composition (e.g. a pharmaceutical, nutraceutical or food compositions) as described herein.

In particular embodiments of the uses or methods of the invention described herein, the composition comprising ginsenosides of the invention *or* extract or composition comprising the composition comprising ginsenosides of the invention *or AG* extract is administered in an amount of from about 100mg/day to about 2000mg/day, or from about 500mg/day to about 1500mg/day, or from about 200 to about 1000mg/day. In a preferred embodiment, the amount is from about 100 mg/day to 600 mg/day, from about 100mg to about 400mg, such as 200mg/day. In any event, the medical practitioner, or other skilled person, will be able to determine routinely the actual dosage, which will be most suitable for an individual patient. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

The composition comprising ginsenosides of the invention *or the Panax quinquefolius* extract or composition comprising said composition comprising ginsenosides of the invention or the AGextract may provide ginsenosides in an amount of from about 0.11 to about 10mg/kg of body weight, such as from 2,5 to about 6 mg/kg of body weight or about 3mg/kg.

In a preferred embodiment, the composition comprising ginsenosides of the invention *or the Panax quinquefolius* extract or composition (e.g. a pharmaceutical, nutraceutical or food compositions) is administrated chronically. Typically the period of administration of the composition comprising ginsenosides of the invention *or the* AG extract or composition comprising the composition comprising ginsenosides of the invention or the AG extract in the uses of methods of the invention described herein, is of more than 2 days, more than 3 days more than 4 days, more than 5 days, more than 6 days, more than 7 days; more than 1 week, more than 2 weeks, more than 3 weeks, more than 4

weeks, more than 5 weeks, more than 6 weeks, more than 7 weeks, more than 8 weeks, more than 9 weeks, more than 10 weeks, more than 1 month, more than 1 months, more than 2 months, more than 3 months, more than 4 months, more than 5 months, more than 6 months, more than 7 months, more than 8 months, more than 9 months, more than 10 months, more than 11 months, more than 12 months.

As used herein, the terms "subject" and "patient" may be used interchangeably and include mammalian species (particularly humans).

"Mammals" refers to a human or non-human animal, including, but not limited to, mice, rats, rabbits, dogs, cats, pigs, and non-human primates, including, but not limited to, monkeys and chimpanzees.

As used herein, the term "therapeutically effective amount" may refers to an amount of the extract of the invention, or composition comprising the *Panax quinquefolius* extract of the invention, which confers a therapeutic effect on the treated patient (e.g. an amount sufficient to treat or prevent fatigue). The effect may be objective (i.e. measurable by some test or marker) or subjective (i.e. the subject gives an indication of or feels an effect).

As used herein, the term "treatment" (and, similarly, "treating") takes its normal meaning in the field of medicine. In particular, the term may refer to achieving a reduction in the severity of one or more clinical symptom associated with the disease or disorder (e.g. the fatigue), as may be determined using techniques known to those skilled in the art (for example, by a medical physician) and/or to slowing the progression of the disease or disorder (i.e. increasing the amount of time taken for the disease or disorder to progress to a more severe state, e.g. when compared to the time expected to be taken in a patent not so treated). As used herein, the term "prevention" (and, similarly, "preventing") includes references to the prophylaxis of the disease or disorder (and vice-versa). In particular, the term may refer to achieving a reduction in the likelihood of the patient (or healthy subject) developing the condition (for example, at least a 10% reduction, such as at least a 20%, 30% or 40% reduction, e.g. at least a 50% reduction).

For the avoidance of doubt, in the context of the present invention, the terms "treating" and "preventing" include the therapeutic, or palliative, treatment of subjects/patients in need of, as well as the prophylactic treatment and/or diagnosis of patients which are susceptible to, the relevant disease states.

As used herein in relation to medical conditions, the term "reducing" may refer to making the observed quantity smaller or decrease in size (i. e. decreasing the fatigue in a subject).

"Administration" or "administering" refers to routes of introducing a compound or composition provided herein to an individual to perform its intended function. An example of a route of administration that can be used includes, but is not limited to oral, parenteral administration, such as subcutaneous, intravenous, or intramuscular injection or infusion, etc.

"Amelioration" or “ameliorating” refers to an improvement or lessening of at least one indicator, sign, or symptom of an associated disease, disorder, or condition. In certain embodiments, amelioration includes a delay or slowing in the progression or severity of one or more indicators of a condition or disease. The progression or severity of indicators may be determined by subjective or objective measures, which are known to those skilled in the art.

"Healthy subject” refers to an individual who is not known to suffer of any significant illness and corresponds to the general population

Brief description of the figures

Figure 1: study design of the Cereboost chronic study.

Figure 2a: After 4 and 6 h, Cereboost improves proportion of correct responses compared to placebo.

Figure 2b: After 2 h, Cereboost improves reaction time compared to placebo

Figure 3a: After 2, 4 and 6 h, Cereboost improves proportion of correct responses compared to placebo

Figure 3b: After 2, 4 and 6 h, Cereboost improves reaction time compared to placebo

Figure 4: After 4h, Cereboost improves proportion of correct responses compared to placebo

Figure 5: After 4h, Cereboost improves reaction time compared to placebo

Figure 6. 6A. After 6h in acute 2 Cereboost improves proportion of correct responses compared to placebo and compared to acute 1. 6B: After 4h in acute 2 Cereboost improves reaction time compared to placebo and compared to acute 1.

Figure 7: Chronic Cereboost intake improves proportion of correct responses compared to placebo

Figure 8: Chronic Cereboost intake limits numbers of errors compared to placebo

Figure 9a, b and c: Chronic Cereboost intake reduces fatigue before, during and after a cognitively demanding series of tasks

Figure 10: Chronic Cereboost intake increase self-assurance.

Figure 11: Chronic Cereboost intake increase joviality

Examples

Study design

The objective of the experiment was to assess the impact of the intake of 200 mg of an American ginseng extract named Cereboost on healthy adults (n=60) on attention/alertness and mood. Mood is defined as a way participants feel at a particular time: energized, self-assured, sad, hostile, shy.

The American ginseng extract (cereboost) used in the present study has a total ginsenosides content from about 10% to 12% (HPLC). The concentration of the specific ginsenosides is: Rg1 from 0.1 to 0.4%, R2 from 0.4 to 3,5%, Rf non detectable, Rb1 from 4 to 7%, Rc from 0.5 to 3.5 %, Rb2 from 0.2 to 1.5 % and Rd from 0.9 to 3 % by weight of the extract. The extract has no quintozene and has a particle size of <250 micrometres.

The study design is represented into the figure 1.

Following recruitment to the study, participants (N=60) started a one-week 'run-in' phase where they completed a food frequency questionnaire to give a measure of their

habitual diet and attended the laboratory for an initial 'practice' session of the cognitive task battery. Thereafter, they attended the laboratory for two further test days over a 2 weeks period. On the first test day (acute 1, baseline), participants arrived at the laboratory in a fasted state where they received a standard breakfast, followed by a battery of cognitive and mood tasks. Subjects were then administered their allocated intervention and were re-tested on the task battery at two-hourly intervals over a 6 hours period (acute 1, results versus baseline). Before leaving the laboratory, participants were given sufficient capsules to consume 1 capsule/day of their allocated intervention every morning with their breakfast for the next 13 days. After 2 weeks of treatment, subjects returned to the lab and the procedure for test day 1 was repeated- a baseline test session to assess effects of 14 days of treatment on cognition (Chronic results versus baseline acute 1 and baseline score for acute 2), followed by administration of a final dose of their allocated intervention and test sessions at 2, 4 and 6 hours post-dosing to assess the effects of tolerance (acute 2, results versus baseline 2). For all test sessions a computerised test battery was employed to assess effects on cognitive function and mood. The tasks comprised of:

1) Positive and Negative Affect schedule Now (PANAS-NOW):
   The Positive and Negative Affect Scale (PANAS - N) will be used to examine mood states at the start and end of the cognitive task battery. It is regarded as a reliable measure for non-clinical populations (Crawford, J. R., & Henry, J. D. (2004). The Positive and Negative Affect Schedule (PANAS): Construct validity, measurement properties and normative data in a large non-clinical sample. British journal of clinical psychology, 43(3), 245-265.). Participants are asked to rate the extent to which they experienced each out of 20 emotions on a 5-point Likert scale ranging from "very slightly" to "very much". Half of the presented emotion words concern negative affect (distressed, upset, guilty, ashamed, hostile, irritable, nervous, jittery, scared, afraid), the other half positive affect (interested, alert, attentive, excited, enthusiastic, inspired, proud, determined, strong, active). The PANAS - X will be used to measure trait mood. Additionally, Fatigue 1 and 2 will be assessed before and after the cognitive session using a Visual Analogue Scale from 1 to 9,
2) Immediate and delayed word recall,
   Using the methodology outlined in Scholey et al., (2010) (Scholey, A., Ossoukhova, A., Owen, L., Ibarra, A., Pipingas, A., He, K., ... & Stough, C. (2010). Effects of

American ginseng (Panax quinquefolius) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study. *Psychopharmacology*, *212*(3), 345-356.), participants will be presented with a sequential list of 15 words, at a rate of 1 word per second. The participant will then have 60s to type as many of these words as possible, with the resulting score recorded as a percentage of accuracy. Approximately 35 minutes after the immediate word recall task, participants will be allowed 60seconds to write down as many items they can remember from the immediate word recall test.

3) Corsi blocks task,

This task examines visuospatial memory. Nine identical squares are fixed in a random arrangement on a screen. Participants observe spatial sequences of between two and nine blocks. Four versions of each sequence length presented during the task. The task is to reproduce the sequence, immediately after each presentation by pressing the relevant squares on the screen. The dependent variable is the number of blocks pointed out in the correct order. A novel sequence will be presented on each occasion, the order of which will be counterbalanced across participants.

4) Rapid Visual Information Processing task (RVIP),

This task will assess attention processes. In this task a series of digits are presented one at a time on the screen, in quick succession at a rate of 100/min. The participant must examine the continuous series for a sequence of three consecutive even or three consecutive odd digits. The participant must respond once they have detected a sequence string by pressing the space bar as quickly as possible. Up to 8 correct target strings will be presented in each minute, and the task will last approximately 6 minutes. The task will be scored for accuracy.

5) Modified attention network task (MANT),

This task examines execution function, attention and inhibition. In this task, participants have to respond to a centrally presented arrow, pointing to the left or the right by pressing the corresponding key on the keyboard. The central arrow is flanked by arrows that point in the same (congruent) or opposite (incongruent) direction. In order to perform the task effectively, participants have to ignore the flanking arrows. Previous studies have found that participants show larger latencies and more errors on incongruent trials when compared with congruent trials due to

the conflicting interference of the incongruently facing arrows. The response latencies to congruent trials reflect processing speed, while the amount of interference during incongruent trials indicates susceptibility to interference.

6) Task Switch task (TST).

This task measures executive function and attention. Participants view a circle with 8 equally spaced radii 2 of which form a bold bisecting line. Numbers are chosen randomly from a set of 1-4 & 6-9 and displayed sequentially in a clockwise direction. A response of higher or lower than 5 is made for trials below the bold line, and even or odd for numbers above the line. General measures of accuracy and response time along with specific measures of switching cost for the first trial after each task change are acquired.

Data has been analysed using Linear Mixed Modelling for each outcome variable, with post-hoc analysis to further investigate any main or interaction effects between variables. Using the design outlined above, three comparisons are available to be made:

1) Assessment of acute effect of Cereboost treatment comparing performance at baseline on Test Day 1 with performance two, four and six hours post-treatment (Session 1 Vs session 2, 3, and 4);

2) Assessment of acute effect of Cereboost treatment after chronic treatment by comparing performance at baseline on Test Day 14 with performance two, four and six hours post-treatment (Session 5 Vs session 6, 7, and 8)

3) Assessment of improvement between the acute 1 versus acute 2 by comparing acute performances at the same time during the day without or after chronic treatment (Session 2 Vs session 6; Session 3 Vs session 7; Session 4 Vs session 8)

4) Assessment of the effect of repeated Cereboost treatment by comparing performance at baseline on Test Day 1 with performance at baseline on Test Day 14 (i.e after 2 weeks of daily treatment: (Session 1 Vs session 5)

Results

1- Acute 1 results:

MANT task: Cereboost has been shown an increase of proportion of correct response and an improvement of reaction time in the MANT (Figure 2a and 2b). Overall, participants who took Cereboost responded faster as well as more accurately compared to placebo, demonstrating higher attention and alertness.

2-Acute 2 results:

MANT task: Cereboost has been shown an increase of proportion of correct response and an improvement of reaction time in the MANT (Figure 3a and 3b)
Overall, participants who took Cereboost responded faster as well as more accurately compared to placebo, demonstrating higher attention and alertness.

CORSI task:
Cereboost has been shown an increase of proportion of correct response in the CORSI task (Figure 4) Overall, participants who took Cereboost responded more accurately compared to placebo, demonstrating higher attention and alertness. Interestingling, 4h correspond to postprandial dips which appears in the placebo group but not after Cereboost intake.

Switch task:
Cereboost has been shown an increase of Reaction time in the Switch task (Figure 5)
Overall, participants who took Cereboost responded faster compared to placebo, demonstrating higher attention and alertness.

3- Acute 1 Vs Acute 2 results:

MANT task:
From Acute 1 to acute 2 Cereboost has been shown an increase of proportion of correct response and an improvement of reaction time in the MANT (Figure 6a and 6b)
Overall, participants who took Cereboost responded faster as well as more accurately compared to placebo, demonstrating higher attention and alertness. These

improvements were increased by 14 days of Cereboost pre-treatment which helped to outperformed the cognitive task.

4- Chronic results:

MANT task: Chronic Cereboost intake has been shown an increase of proportion of correct response in the MANT (Figure 7)

Overall, participants who took Cereboost chronically responded more accurately compared to placebo, demonstrating higher attention and alertness.

RVIP task: Chronic Cereboost intake has been shown to limit the numbers of error in the RVIP task (Figure 8).

Overall, participants who took Cereboost chronically responded more accurately compared to placebo, demonstrating higher attention and alertness.

Fatigue 1 and 2/ PANAS X Fatigue tasks : Chronic Cereboost intake has been shown to limit Fatigue before the serie of tasks (Fatigue 1: Figure 9a), during the task (PANAS-X Fatigue, measuring feelings and emotions such as: sleepy, tired, sluggish, drowsy, Figure 9b) and after the tasks (Fatigue 2: Figure 9C).

Overall, participants who took Cereboost chronically feel more energized compared to placebo.

PANAS X Self-assurance task: Chronic Cereboost intake has been shown to increase self-assurance, regrouping within the PANAX-X feelings and emotions such as: proud, strong, confident, bold, fearless, daring (Figure 10)

Overall, due to an increase of self-assurance, participants who took Cereboost chronically feel more confident and determinate.

PANAS X Joviality task: Chronic Cereboost intake has been shown to increase Joviality, regrouping within the PANAX-X feelings and emotions such as: cheerful, happy, joyful, delighted, enthusiastic, excited, lively, energetic (Figure 11)

Overall, participants who took Cereboost chronically feel more joyful.

Claims

1. A Panax quinquefolius extract for use in
(a) treating, reducing, preventing and/or ameliorating fatigue;
(b) improving or increasing attention/alertness
and/or
(c) improving or increasing self-assurance in a subject.

2. Use of a Panax quinquefolius extract for (a) treating, reducing, preventing and/or ameliorating fatigue; (b) improving or increasing attention/alertness and/or (c) improving or increasing self-assurance in a subject.

3. A method of
(a) treating, reducing, preventing and/or ameliorating fatigue;
(b) improving or increasing attention/alertness
and/or
(c) improving or increasing self-assurance
comprising the administration of an effective amount of a Panax quinquefolius extract to a subject in need thereof.

4. A composition comprising ginsenosides for use in
(a) treating, reducing, preventing and/or ameliorating fatigue;
(b) improving or increasing attention/alertness
and/or
(c) improving or increasing self-assurance in a subject.

5. Use of a composition comprising ginsenosides for (a) treating, reducing, preventing and/or ameliorating fatigue; (b) improving or increasing attention/alertness and/or (c) improving or increasing self-assurance in a subject.

6. A method of
(a) treating, reducing, preventing and/or ameliorating fatigue;
(b) improving or increasing attention/alertness

and/or

(c) improving or increasing self-assurance

comprising the administration of an effective amount of a composition comprising ginsenosides to a subject in need thereof.

7. The extract, composition, use or method according to any one of proceeding claims, wherein the extract or the composition is administered chronically.

8. The extract, composition, use or method according to any of the preceding claims, wherein the subject is healthy.

9. The extract, composition use or method according to any of claims 1 to 7, wherein the subject suffers from one or more of the following medical conditions: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, or underactive thyroid, hyperthyroidism, or overactive thyroid, sleep disorders, such as insomnia, eating disorders, such as anorexia, autoimmune disorders, congestive heart, cancer, diabetes, kidney disease, liver disease, chronic obstructive pulmonary disease (COPD) aging , neuropsychiatric disorders such as depression and anxiety, neurodegenerative disease such as schizophrenia, Alzheimer's disease, Parkinson's disease or emphysema.

10. The extract, composition use or method according to any of the preceding claims, wherein the treatment, reduction, prevention and/or amelioration of fatigue is due of the treatment, reduction, prevention and/or amelioration of the feeling of being sleepy, of being tired, of being sluggish and / or the feeling of being drowsy.

11. The extract, use or method according to any of claims 1 to 8, wherein the improving or increasing in self-assurance is the improving or increasing of the feeling of being proud, of being strong, of being confident, of being bold, of being fearless and / or the feeling of being daring.

12. The extract, use or method according to any one of preceding claims, wherein the composition comprising ginsenosides or the *Panax quinquefolius* extract comprises

ginsenosides from about 3% to about 100% by weight, such as from, 3%, 4%, 5%, 6%, 7 %, 8%, 9%, 10%, 20%, 30%, 40%, 50 %, 60%, 70%, 80% or 90% to about 95%, 85%, 75%, 70%, 65%, 60%, 55%, 50%, 40%, 35%, 30%, 25%, 20%, 15%, or 10% by weight, more preferably the total ginsenosides in from about 9% to about 15% by weight, more preferably, total ginsenosides is from about 10% to about 13% by weight.

13. The extract, use or method according to any one of preceding claims, wherein the composition comprising ginsenosides or the *Panax quinquefolius* extract comprises the ginsenosides: Rg1 from about 1% to 4% by weigh of total ginsenosides, from about 3% to 4% by weigh of total ginsenosides , preferably about 3,6 % by weigh of total ginsenosides, Re from about 4% to 35% by weigh of total ginsenosides , from about 12 % to 17 % by weigh of total ginsenosides, preferably about 16% by weigh of total ginsenosides, Rb1 from about 40% to 70% by weigh of total ginsenosides, from about 40% to 50% by weigh of total ginsenosides, preferably about 48% by weigh of total ginsenosides, Rc from about 5% to 35% by weigh of total ginsenosides, from about 12 % to 17% by weigh of total ginsenosides, preferably about 16% by weigh of total ginsenosides, Rb2 from about 2% to 15% by weigh of total ginsenosides, from about 2% to 5% by weigh of total ginsenosides , preferably about 4% by weigh of total ginsenosides, and / or Rd from about 9% to 30% by weigh of total ginsenosides, from about 12% to 15% by weigh of total ginsenosides, preferably about 14% by weight of total ginsenosides.

14. The extract or composition for use, use or method according to any one of the preceding claims, wherein the composition comprising ginsenosides or the *Panax quinquefolius* extract is administered in the form of: (a) a pharmaceutical or nutraceutical composition comprising a composition comprising ginsenosides or a *Panax quinquefolius* extract as defined in any one or more of the preceding claims and optionally a pharmaceutically/nutraceutical acceptable excipient; or (b) a food composition comprising a composition comprising ginsenosides or a *Panax quinquefolius* extract as defined in any one or more of the preceding claims and optionally a food acceptable ingredient.

15. The extract or composition for use, use or method according to Claim 14, wherein the composition is for oral administration.

16. The extract or composition for use, use or method according to any of the preceding claims, wherein the extract or the composition is administered in an amount of from about 100mg/day to about 2000mg/day, or from about 500mg/day to about 1500mg/day, preferably from about 100 mg/day to 400 mg/day, more preferably 200mg/day.

17. The extract, the use or method according to claim any of the preceding claims, wherein the administration of the extract or the composition is for a period of : more than 2 days, more than 3 days more than 4 days, more than 5 days, more than 6 days, more than 7 days; more than 1 week, more than 2 weeks, more than 3 weeks, more than 4 weeks, more than 5 weeks, more than 6 weeks, more than 7 weeks, more than 8 weeks, more than 9 weeks, more than 10 weeks, more than 1 month, more than 2 months, more than 3 months, more than 4 months, more than 5 months, more than 6 months, more than 7 months, more than 8 months, more than 9 months, more than 10 months, more than 11 months or more than 12 months.

18. The extract, use or method according to any one of proceeding claims, wherein the subject is a human.

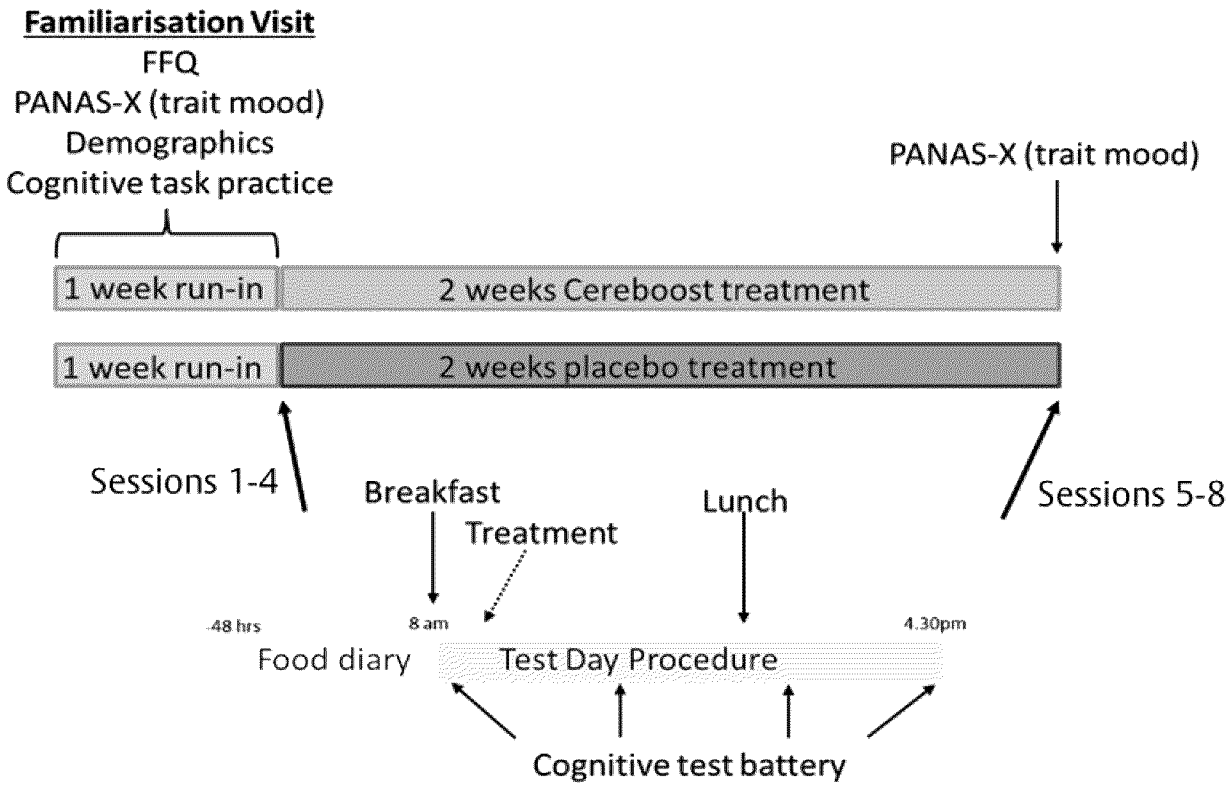
Familiarisation Visit
FFQ
PANAS-X (trait mood)
Demographics
Cognitive task practice
PANAS-X (trait mood)
1 week run-in
2 weeks Cereboost treatment
1 week run-in
2 weeks placebo treatment
Sessions 1-4
Breakfast
Treatment
Lunch
Sessions 5-8
-48 hrs
8 am
4.30pm
Food diary
Test Day Procedure
Cognitive test battery

Figure 1

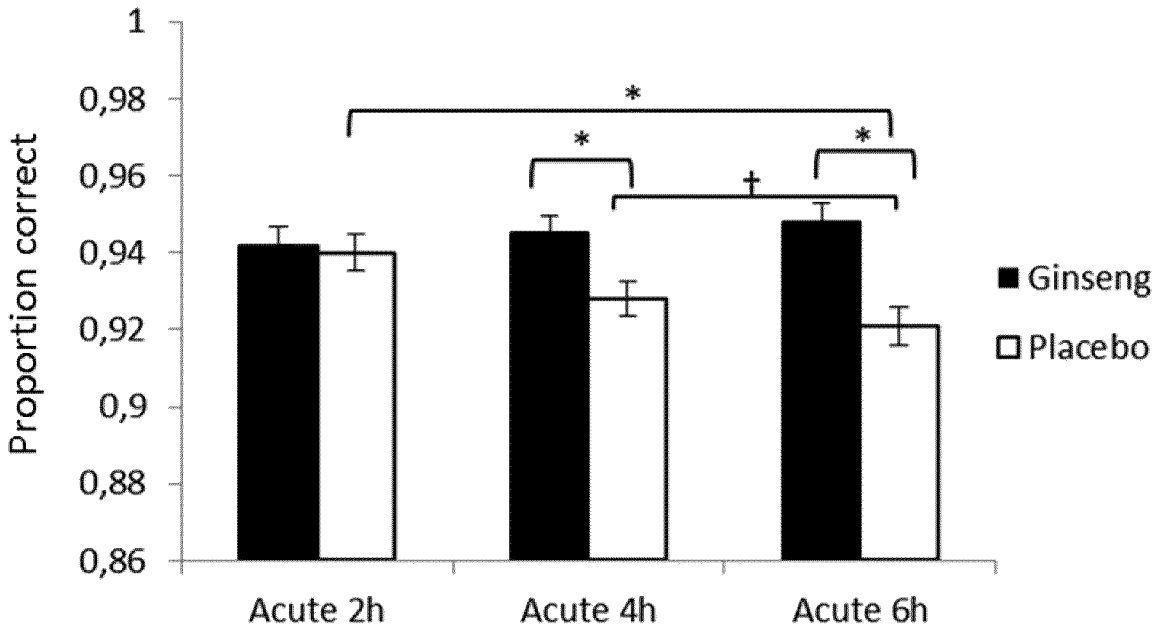

Figure 2A

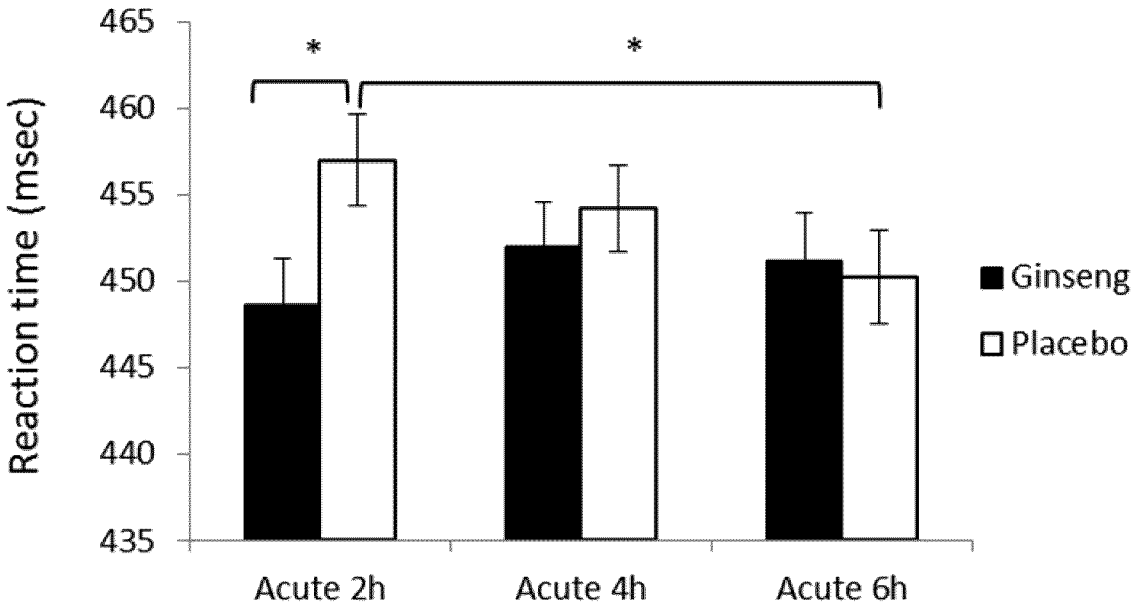

Figure 2B

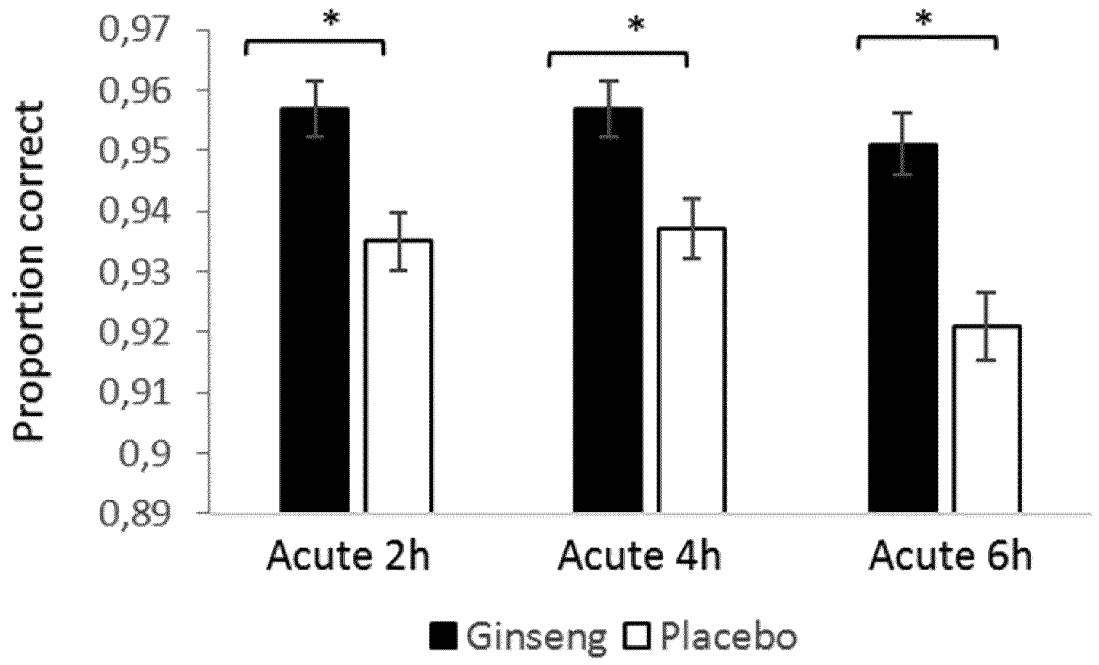

Figure 3A

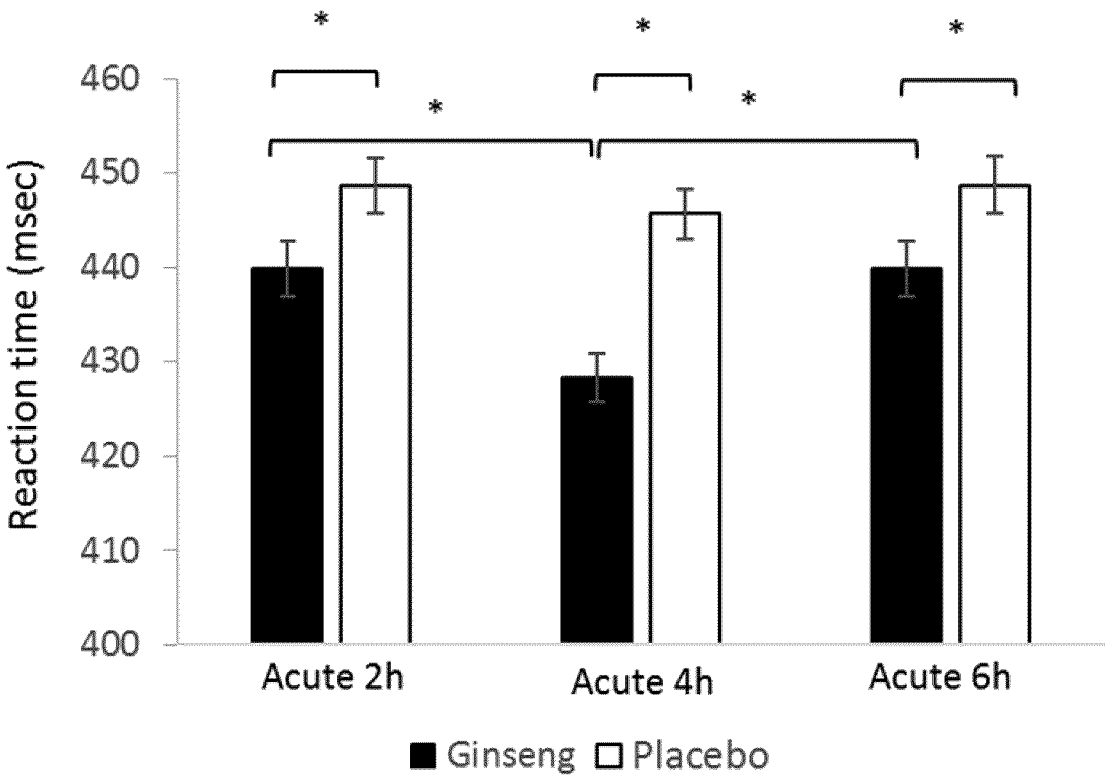

Figure 3B

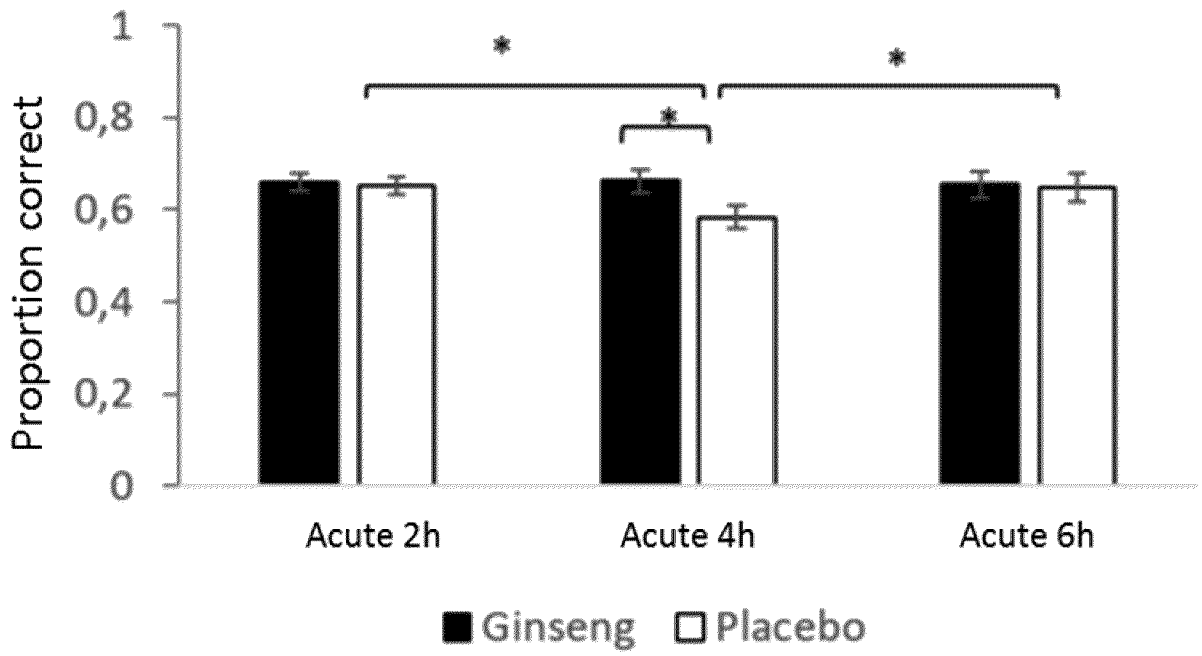

Figure 4

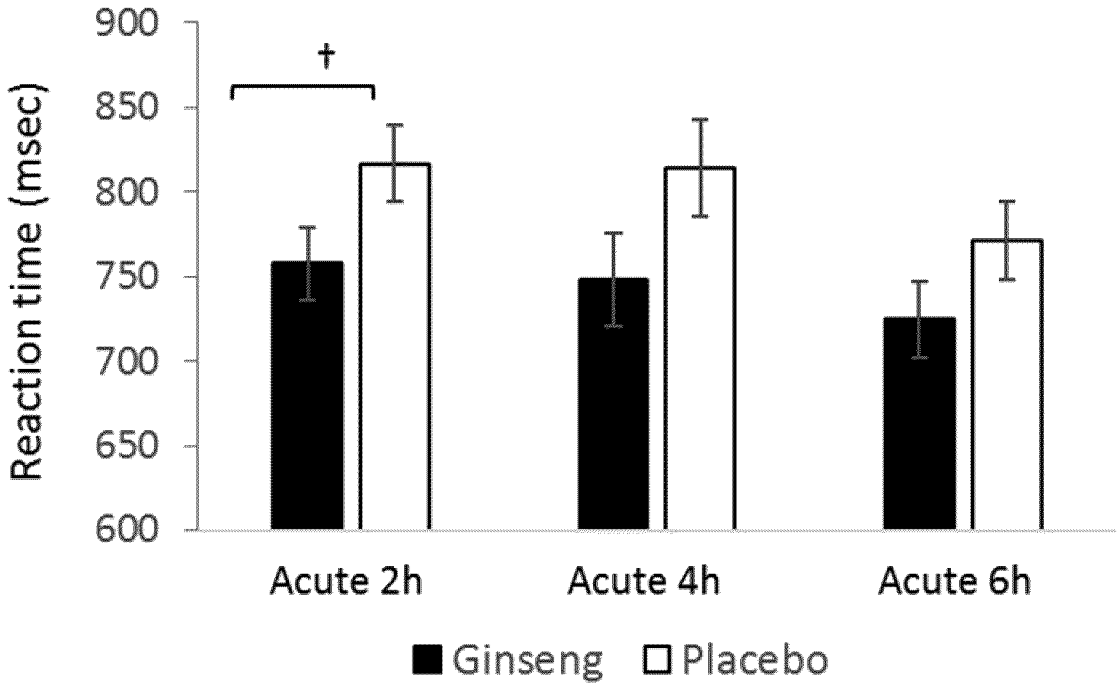

Figure 5

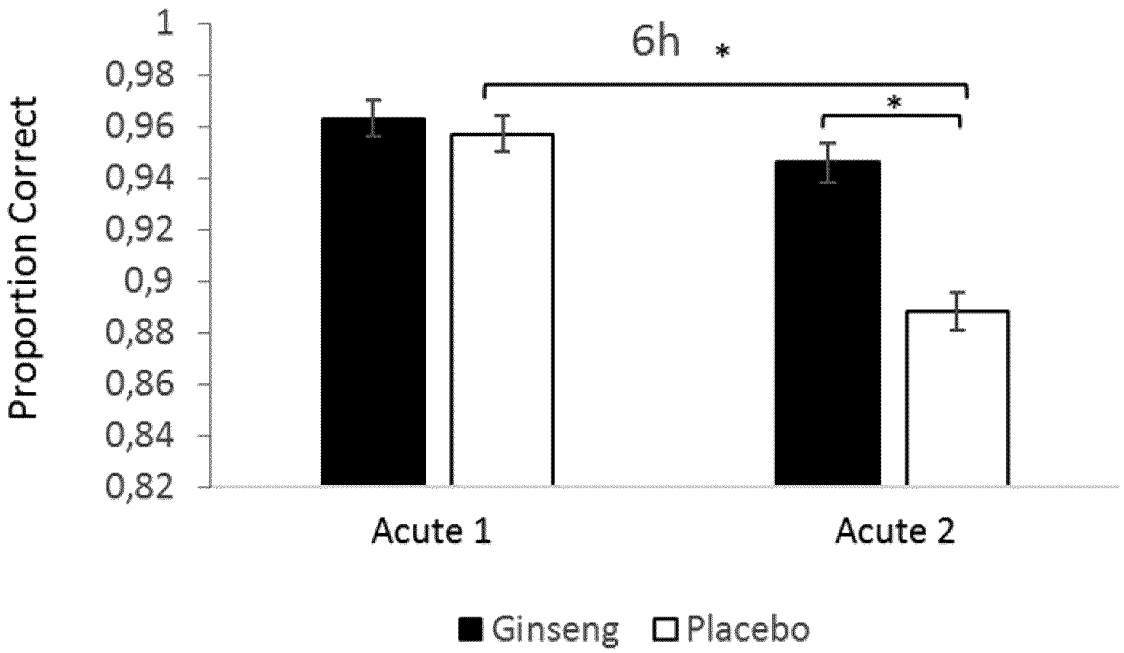

Figure 6A

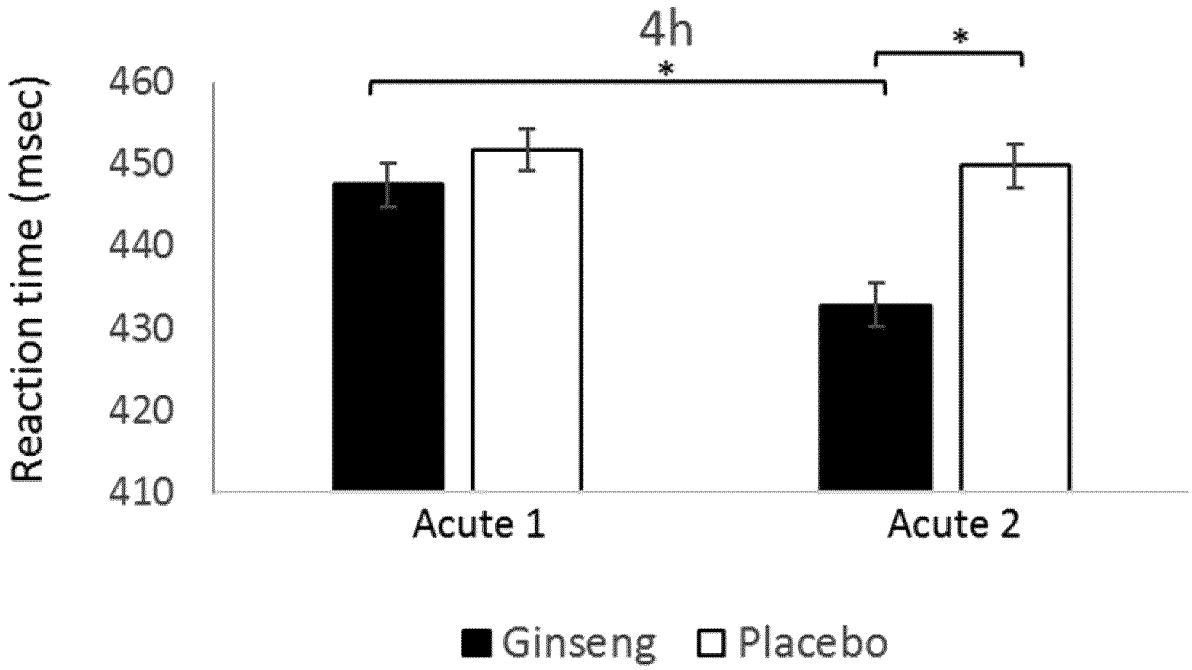

Figure 6B

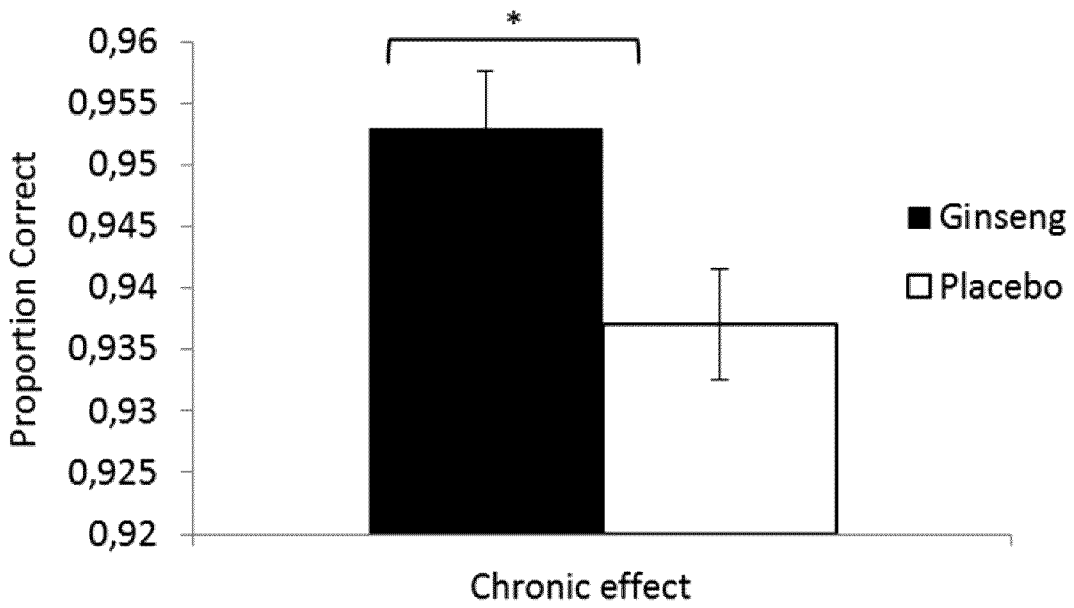

Figure 7

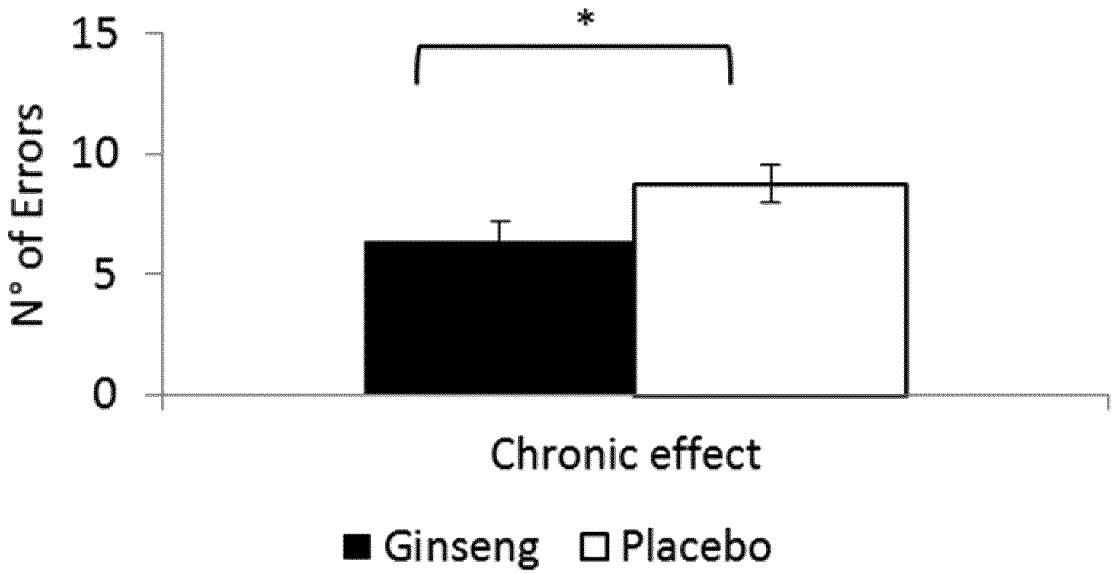

Figure 8

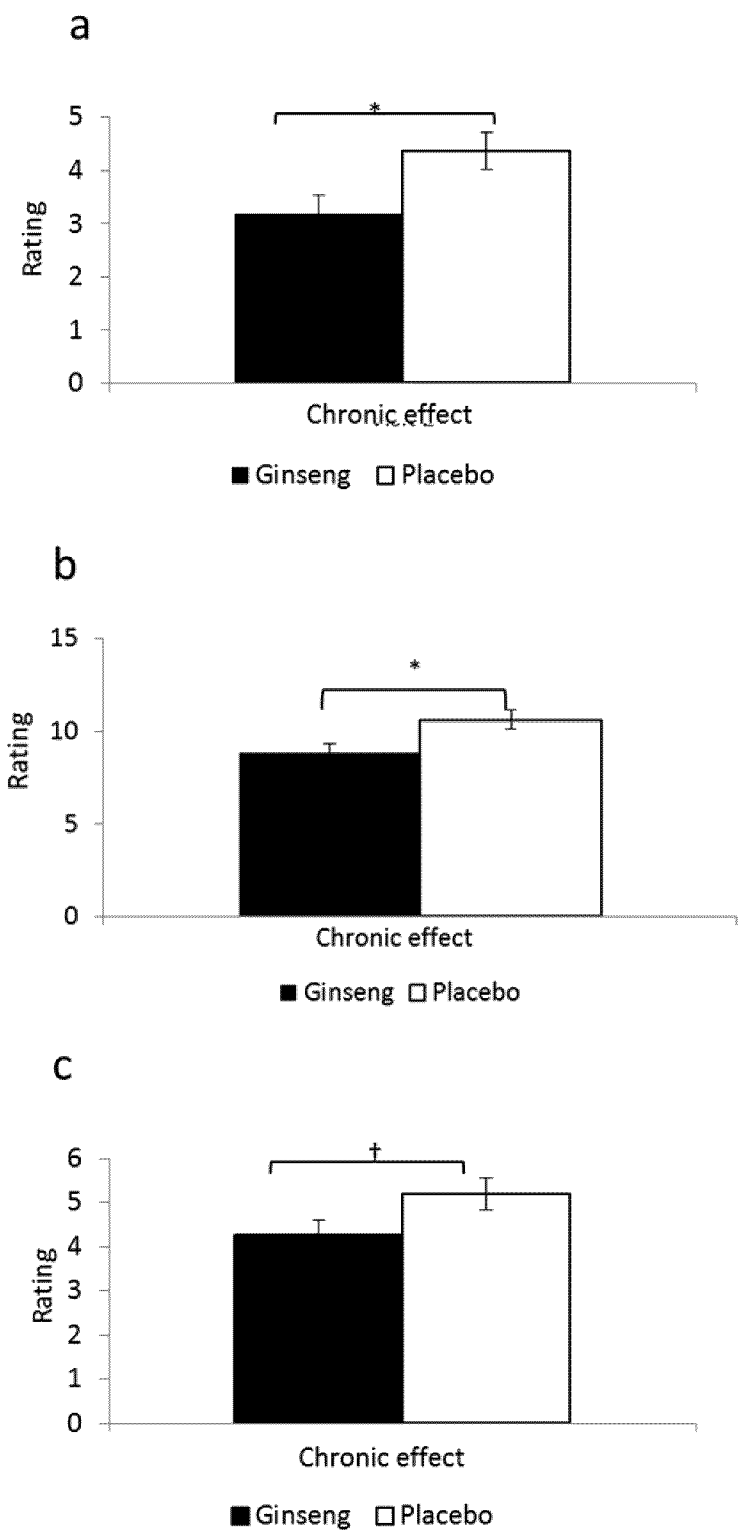

Figure 9a, 9b and 9c

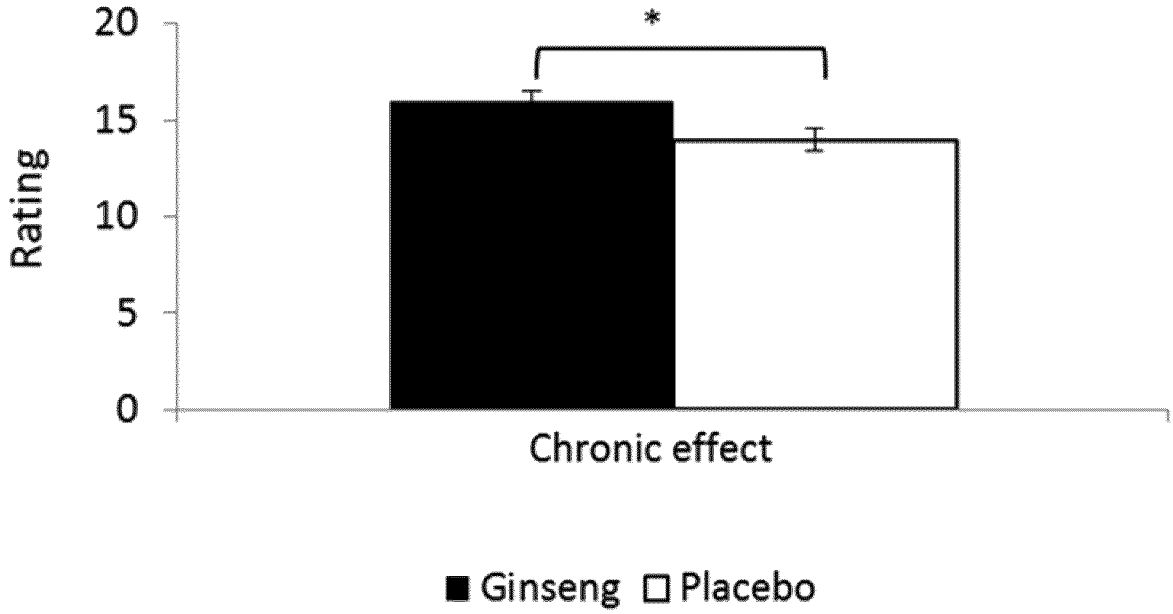

Figure 10

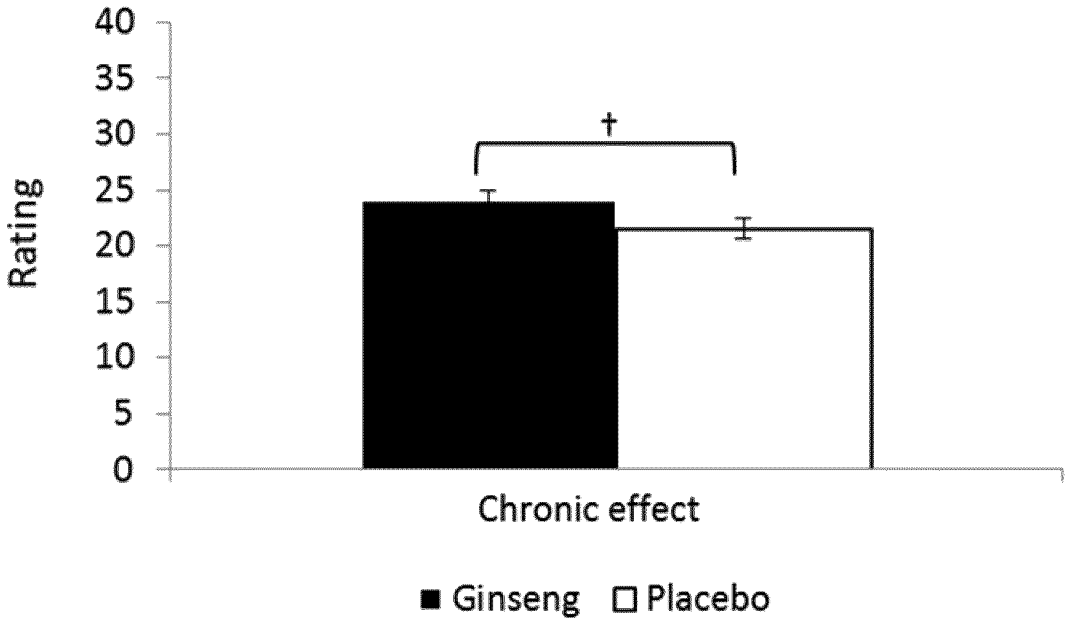

Figure 11

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/056788

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K36/258 A61K31/704 A61P1/00 A61P3/04 A61P9/00
A61P25/16 A61P25/20 A61P25/24 A61P25/28 A23L33/105
A61P11/00 A61P31/00 A61P35/00 A61P37/00

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)

A61K A61P A23L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MANCUSO CESARE ET AL: "Panax ginseng and Panax quinquefolius : From pharmacology to toxicology", FOOD AND CHEMICAL TOXICOLOGY, vol. 107, 1 September 2017 (2017-09-01), pages 362-372, XP055815138, GB ISSN: 0278-6915, DOI: 10.1016/j.fct.2017.07.019 Pharmacodynamics of ginseng- Clinical studies; page 365 - page 368 -----	1-18
X	CN 110 613 802 A (ZHUHAI QIWEI BIOTECHNOLOGY CO LTD) 27 December 2019 (2019-12-27) claims 1-11; examples 1-4 -----	1-18

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 June 2021	28/06/2021

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Markopoulos, Eytyxia

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SHIN KYUNGHA ET AL: "Cereboost(TM), an American ginseng extract, improves cognitive function via up-regulation of choline acetyltransferase expression and neuroprotection", REGULATORY TOXICOLOGY AND PHARMACOLOGY, ACADEMIC PRESS,NEW YORK, NY, US, vol. 78, 22 April 2016 (2016-04-22), pages 53-58, XP029548693, ISSN: 0273-2300, DOI: 10.1016/J.YRTPH.2016.04.006 Results, Discussion	1-18
X	US 2015/306119 A1 (SCHOLEY ANDREW [AU] ET AL) 29 October 2015 (2015-10-29) paragraph [0036]; claims 1-13; examples 1-6	1-18
X	ANDREW SCHOLEY ET AL: "Effects of American ginseng (Panax quinquefolius) on neurocognitive function: an acute, randomised, double-blind, placebo-controlled, crossover study", PSYCHOPHARMACOLOGY, SPRINGER, BERLIN, DE, vol. 212, no. 3, 31 July 2010 (2010-07-31) , pages 345-356, XP019839039, ISSN: 1432-2072 Results, Discussion	1-18
X	BARTON D. L. ET AL: "Wisconsin Ginseng (Panax quinquefolius) to Improve Cancer-Related Fatigue: A Randomized, Double-Blind Trial, N07C2", JOURNAL OF THE NATIONAL CANCER INSTITUTE , vol. 105, no. 16 13 July 2013 (2013-07-13), pages 1230-1238, XP055792551, GB ISSN: 0027-8874, DOI: 10.1093/jnci/djt181 Retrieved from the Internet: URL:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3888141/pdf/djt181.pdf Results, Discussion	1-18
X	CN 109 432 304 A (HANGZHOU HUQINGYUTANG CO LTD) 8 March 2019 (2019-03-08) examples 1,2	1-18

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2021/056788

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	IQBAL HAMID ET AL: "Ginseng alleviates microbial infections of the respiratory tract: a review", JOURNAL OF GINSENG RESEARCH, vol. 44, no. 2, 1 March 2020 (2020-03-01), pages 194-204, XP055815016, KR ISSN: 1226-8453, DOI: 10.1016/j.jgr.2019.12.001 introduction, item 4; table 3 -----	1-18

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2021/056788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 110613802 A	27-12-2019	NONE	
US 2015306119 A1	29-10-2015	NONE	
CN 109432304 A	08-03-2019	NONE	