

PLACENTAL COMPOSITION

FIELD OF THE INVENTION

The present invention relates to the use of placental extract and compositions comprising placenta extract to treat or prevent inflammation of a disease or condition associated with TNF α , IL-1 β , IL-6 and other pro-inflammatory cytokines, such as asthma, infections, acute respiratory distress syndrome (ARDS), or COVID-19. The invention also relates to methods of treatment by administering placental extract and compositions comprising placenta extract, and the use of placenta extract in the manufacture of a medicament or composition for treating such diseases or conditions.

BACKGROUND TO THE INVENTION

Although the production of pro-inflammatory cytokines by cells of the innate immune system plays an important role in mediating the initial host defense against invading pathogens (O'Neill, L. A. et al., *Immunol. Today*, (2000), 21 (5):206-9), an inability to regulate the nature or duration of the host's inflammatory response can often mediate detrimental host effects as observed in chronic inflammatory diseases. Additionally, in the early stages of sepsis, the host's inflammatory response is believed to be in a hyperactive state with a predominant increase in the production of pro-inflammatory cytokines that mediate host tissue injury and lethal shock (Cohen, J., *Nature*, (2002), 420 (6917):885-91). In this regard, the ability to suppress pro-inflammatory cytokines and/or enhance anti-inflammatory cytokines, has been shown to severely reduce the toxic effects of endotoxin (Berg, D. J. et al., *J. Clin. Invest.*, (1995), 96 (5):2339-47; and Howard, M. et al., *J. Exp. Med.*, (1993), 177 (4):1205-8).

COVID-19, caused by SARS-CoV-2, is also characterised by an immune dysfunction rather than a viral load, which leads to abnormal production of pro-inflammatory cytokines (Ma W-T, et al. The protective and pathogenic roles of IL-17 in viral infections: friend or foe? *Open Biol.* 2019;9(7):190109). In particular, COVID-19 can trigger a cytokine storm in pulmonary tissues through hyperactivation of the immune system and the uncontrolled release of cytokines (Ye Q, Wang B, Mao J. Cytokine storm in COVID-19 and treatment. *J Infect.* 2020;80:607-13). Pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and tumor necrosis factor- α (TNF- α) play a very significant role in lung damage in COVID patients with acute respiratory distress syndrome (ARDS), through the impairments of the

respiratory epithelium Montazersaheb, S., Hosseiniyan Khatibi, S.M., Hejazi, M.S. et al. COVID-19 infection: an overview on cytokine storm and related interventions. Virol J 19, 92 (2022).

5 Other conditions associated with abnormal or undesirable inflammation such as skin conditions can also be difficult to manage. Treatments mainly consist of pharmacotherapy such as steroids, antihistamines and antibiotics. Steroids have anti-inflammatory and immunosuppressive effects and have good effects, but they are harmful to the intestines, kidneys, liver, bones and brain, and the conditions often recur when treatment is discontinued.

10 The availability of improved or alternative formulations suitable for cosmetic, pharmaceutical, nutraceutical, supplements and beverage products are important for subjects suffering conditions associated with abnormal or undesirable inflammation associated with TNF α , IL-1 β , IL-6 and other pro-inflammatory cytokines.

15 It is an object of the present invention to provide an improved or alternative composition, and/or to at least provide the public with an useful choice.

In this specification, where reference has been made to external sources of information, including patent specifications and other documents, this is generally for the purpose of providing a context for discussing the features of the present invention. Unless stated otherwise, reference to such sources of information is not to
20 be construed, in any jurisdiction, as an admission that such sources of information are prior art or form part of the common general knowledge in the art.

SUMMARY OF THE INVENTION

Accordingly, in one aspect the invention relates to a method of treating, preventing or ameliorating a disease, disorder or condition associated with inflammation or
25 immune-modulation, comprising administration to a subject in need thereof of an effective amount of a placental extract or an effective amount of a composition comprising a placental extract.

In another aspect the invention relates to a composition for use in treating, preventing or ameliorating a disease, disorder or condition associated with
30 inflammation or immune-modulation, wherein the composition comprises a placental extract.

In another aspect the invention relates to use of a placental extract, in the manufacture of a medicament or composition for treating, preventing or ameliorating a disease, disorder or condition associated with inflammation or immune-modulation.

5 Preferably, the composition or medicament is a food, drink, food additive, drink additive, food component, drink component, dietary supplement, nutritional product, medical food, nutraceutical, medicament or pharmaceutical.

In one embodiment the placenta extract is administered at a concentration sufficient to inhibit one or more pro-inflammatory cytokines, including cytokine IL-1 α , β , IL-2, IL-3, IL-6, IL-7, IL-9, IL-12, IL-17, IL-18, TNF- α , LT, LIF, Oncostatin, or IFN γ 1 α , β , γ .

10 In one embodiment the placenta extract is administered at a concentration sufficient to stimulate expression of one of more anti-inflammatory cytokine, including IL-4, IL-10, IL-11, W-13 or TGF β .

The following embodiments may relate to any of the above aspects.

15 In one embodiment the placental extract is derived from a deer, sheep, goat, horse, donkey, rabbit or bovine placenta. Preferably, the placental extract is derived from deer placenta. In one embodiment the placental extract is CerviCenta®.

20 Preferred methods of extraction from placenta material include solvent extraction, supercritical solvent extraction including supercritical CO₂ extraction, distillation, counter current extraction, decoction, percolation, maturation, molecular distillation, microwave extraction, ultrasound extraction, and chromatographic separation.

The method of extraction may include the steps of contacting the placenta material with a solvent, separating the placenta material from the solvent, and at least partially removing the solvent to yield the extract.

25 In one embodiment, placenta material is freeze dried and powdered prior to contact with the solvent. In one embodiment of the invention, the solvent is water. In another embodiment of the invention, any suitable organic solvent may be used. The solvent may be ethanol or a mixture of any such solvents. In one embodiment the extract is prepared by solvent extraction, such as ethanol extraction, followed by distillation or supercritical extraction.

30 Preferably, water extraction is used to prepare the extract.

In one embodiment the placental extract is or comprises dried or powdered placenta material. In one embodiment, the method of extraction comprises pulverising placenta material by wet grinding, and then powdering or granulating by freeze-, vacuum- or spray-drying, or fluid bed drying or the like. In an alternative
 5 embodiment, the placenta material is first dried, for example by freeze- or vacuum-drying, and then optionally ground into powder.

In preferred embodiments, the composition or medicament is provided in a delivery formulation selected from the group consisting of tablets, capsules, liquids, oils, suspensions, emulsions, pastes, jellies, puddings, solutions, and powders.

10 In one embodiment, the composition or medicament comprises, consists essentially of or consists of the placenta extract.

In one embodiment, the placenta extract comprises, consists essentially of, or consists of placenta material prepared by solvent extraction, dried or powdered placenta material, and/or combinations thereof.

15 In one embodiment the composition comprises or the medicament comprises at least about 0.1, 0.2, 0.5, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 99, 99.5, 99.8 or 99.9% by weight of the placental extract and useful ranges may be selected between any of these foregoing values (for example, from
 20 about 0.1 to about 50%, from about 0.2 to about 50%, from about 0.5 to about 50%, from about 1 to about 50%, from about 5 to about 50%, from about 10 to about 50%, from about 15 to about 50%, from about 20 to about 50%, from about 25 to about 50%, from about 30 to about 50%, from about 35 to about 50%, from about 40 to about 50%, from about 45 to about 50%, from about 0.1 to about 60%, from about 0.2 to about 60%, from about 0.5 to about 60%, from about 1 to about
 25 60%, from about 5 to about 60%, from about 10 to about 60%, from about 15 to about 60%, from about 20 to about 60%, from about 25 to about 60%, from about 30 to about 60%, from about 35 to about 60%, from about 40 to about 60%, from about 45 to about 60%, from about 0.1 to about 70%, from about 0.2 to about 70%, from about 0.5 to about 70%, from about 1 to about 70%, from about 5 to about
 30 70%, from about 10 to about 70%, from about 15 to about 70%, from about 20 to about 70%, from about 25 to about 70%, from about 30 to about 70%, from about 35 to about 70%, from about 40 to about 70%, from about 45 to about 70%, from about 0.1 to about 80%, from about 0.2 to about 80%, from about 0.5 to about 80%, from about 1 to about 80%, from about 5 to about 80%, from about 10 to
 35 about 80%, from about 15 to about 80%, from about 20 to about 80%, from about

25 to about 80%, from about 30 to about 80%, from about 35 to about 80%, from about 40 to about 80%, from about 45 to about 80%, from about 0.1 to about 90%, from about 0.2 to about 90%, from about 0.5 to about 90%, from about 1 to about 90%, from about 5 to about 90%, from about 10 to about 90%, from about 15 to about 90%, from about 20 to about 90%, from about 25 to about 90%, from about 30 to about 90%, from about 35 to about 90%, from about 40 to about 90%, from about 45 to about 90%, from about 0.1 to about 99%, from about 0.2 to about 99%, from about 0.5 to about 99%, from about 1 to about 99%, from about 5 to about 99%, from about 10 to about 99%, from about 15 to about 99%, from about 20 to about 99%, from about 25 to about 99%, from about 30 to about 99%, from about 35 to about 99%, from about 40 to about 99%, and from about 45 to about 99%).

In one embodiment the composition comprises or the medicament comprises, at least about 0.001, 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 grams or more of the placenta extract and useful ranges may be selected between any of these foregoing values (for example, from about 0.01 to about 1 grams, about 0.01 to about 10 grams, about 0.01 to about 19 grams, from about 0.1 to about 1 grams, about 0.1 to about 10 grams, about 0.1 to about 19 grams, from about 1 to about 5 grams, about 1 to about 10 grams, about 1 to about 19 grams, about 5 to about 10 grams, and about 5 to about 19 grams).

Preferably, the composition comprises or the medicament comprises, at least about 1, 10, 50, 100, 125, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900 or 1000mg or more of the placenta extract and useful ranges may be selected between any of these foregoing values (for example, from about 10 to about 1000mg, from about 50 to 1000 mg, from about 75 to about 800mg, from about 75 to about 500mg, from about 75 to about 350mg, from about 75 to about 300mg, from about 75 to about 250mg, from about 100 to about 350mg, from about 100 to about 300mg, from about 100 to about 250mg, from about 100 to about 200mg, from about 100 to about 150mg, more preferably from about 100 to about 125mg).

In one embodiment the composition comprises, the medicament comprises, or the method comprises administration of placenta extract in an amount of about 125mg, suitable for administration twice daily, or 250mg, suitable for administration once per day.

In one embodiment the composition comprises, the medicament comprises, or the method comprises administration of placenta extract in an amount of about 100mg

or 125mg, suitable for administration twice daily, or 200mg or 250mg, suitable for administration once per day.

5 In one embodiment the composition comprises, the medicament comprises, or the method comprises administration of about 40% to 90% by weight of placenta extract, for example about 50% to 80% by weight, or about 60% to 75% by weight placenta extract.

10 In one embodiment the composition or medicament further comprises about 0.1, 0.5, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50% by weight another anti-inflammatory agent and useful ranges may be selected between any of these foregoing values (for example, from about 0.1 to about 50%, from about 0.2 to about 50%, from about 0.5 to about 50%, from about 1 to about 50%, from about 5 to about 50%, from about 10 to about 50%, from about 15 to about 50%, from about 20 to about 50%, from about 25 to about 50%, from about 30 to about 50%, from about 35 to about 50%, from about 40 to about 50%, and from about 45 to about 50%).

15 In one embodiment the composition or medicament further comprises a carrier, for example a pharmaceutically acceptable carrier.

20 In one embodiment the composition or medicament is in the form of a tablet, a caplet, a pill, a hard or soft capsule or a lozenge. In one embodiment the composition or medicament is in the form of a cachet, a dispensable powder, granules, a suspension, an elixir, a liquid, or any other form that can be added to food or drink, including for example water or fruit juice. In one embodiment the composition or medicament further comprises one or more constituents (such as antioxidants) which prevent or reduce degradation of the composition during storage or after administration.

25 In one embodiment the composition or medicament is or is formulated as a food, drink, food additive, drink additive, dietary supplement, nutritional product, medical food, nutraceutical, medicament or pharmaceutical. Preferably, the composition or medicament is formulated as a powder, liquid, food bar, spread, sauce, paste, jelly, pudding, soup base, ointment, tablet or capsule.

30 In one embodiment the composition or medicament is formulated for oral, nasal, or parenteral (including topical, subcutaneous, intramuscular, and intravenous) administration. In one embodiment the composition or medicament is formulated for ingestion, inhalation, or topical application. Where the composition or medicament is formulated for inhalation, preferably it is formulated as an inhalable powder, solution,

or aerosol. Where the composition or medicament is formulated for topical application, preferably it is formulated as an ointment, cream, or lotion.

As will be appreciated, the dose of the composition or medicament administered, the period of administration, and the general administration regime may differ between
5 subjects depending on such variables as the severity of symptoms of a subject, the type of disorder to be treated, the mode of administration chosen, and the age, sex and/or general health of a subject. However, by way of general example, the inventors contemplate administration of from about 1 mg to about 1000 mg per kg
10 body weight of a composition or medicament of the invention is administered per day, preferably about 50 to about 500 mg per kg per day. In one embodiment, the inventors contemplate administration of from about 0.05 mg to about 250 mg per kg body weight of a pharmaceutical composition or medicament according to the invention. It should be appreciated that administration may include a single daily dose or administration of a number of discrete divided doses as may be appropriate.

15 In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction,
20 are prior art, or form part of the common general knowledge in the art.

It is intended that reference to a range of numbers disclosed herein (for example, 1 to 10) also incorporates reference to all rational numbers within that range (for example, 1, 1.1, 2, 3, 3.9, 4, 5, 6, 6.5, 7, 8, 9 and 10) and also any range of rational numbers within that range (for example, 2 to 8, 1.5 to 5.5 and 3.1 to 4.7) and,
25 therefore, all sub-ranges of all ranges expressly disclosed herein are hereby expressly disclosed. These are only examples of what is specifically intended and all possible combinations of numerical values between the lowest value and the highest value enumerated are to be considered expressly stated in this application in a similar manner.

30 The invention may also be said broadly to consist in the parts, elements and features referred to or indicated in the specification of the application, individually or collectively, in any or all combinations of two or more of said parts, elements or features, and where specific integers are mentioned herein which have known equivalents in the art to which the invention relates, such known equivalents are
35 deemed to be incorporated herein as if individually set forth.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described by way of example only and with reference to the drawings in which:

Figure 1 provides a determination of protein integrity of placenta extracts: protein extracts were resolved on a 4-20% BioRad gradient gel and subsequently stained with Coomassie Brilliant Blue as indicated. The following order can be observed. Lanes 1 to 10 from left to right: BioRad Precision Plus Protein Standard: Mw (kDa) from top to the bottom: 250 / 150 / 100 / 75 / 50 / 37 / 25 / 20 / 15. Lane 2: culture medium, lane 3: 0.9% NaCl, lane 4: PBS/1% Triton X100, lane 5: PBS/1% SDS, lane 6: overspill from lane 7, lane 7: distilled water, lanes 8/9: PBS.

Figure 2 provides an assessment of IL-1 β . PBMCs were treated with DPE and stimulating agents as described. Supernatants were isolated and transferred to the MSD U-Plex multiplexing platform in various dilutions (1/5, 1/20 and 1/50) to define an optimal range of reactivity. Best reactivities were achieved in a 1/5 dilution of the test extract. These data are depicted here. Zymosan 2 (1 μ g/mL), Endotoxin 1 (0.05 EU/mL). HSKA (10⁸ cells). DPE 1/5 (12.33 mg/mL), DPE 1/20 (3.08 mg/mL and DPE 1/50 (1.23 mg/mL). X-axis: reactivity (EC units), Y-Axis: stimulus

Figure 3 provides an assessment of IL-6. PBMCs were treated with DPE and stimulating agents as described. Supernatants were isolated and transferred to the MSD U-Plex multiplexing platform in various dilutions (1/5, 1/20 and 1/50) to define an optimal range of reactivity. Best reactivities were achieved in a 1/5 dilution of the test extract. These data are depicted here. Zymosan 3 (0.2 μ g/mL), Endotoxin 1 (0.05 EU/mL). HSKA (10⁸ cells). DPE 1/5 (12.33 mg/mL), DPE 1/20 (3.08 mg/mL and DPE 1/50 (1.23 mg/mL). X-axis: reactivity (EC units), Y-Axis: stimulus.

Figure 4 provides DPE Interference in the induction of IL-1 β . Human PBMCs were pre-treated with DPE as described. Subsequently established stimuli were added at the following concentrations: Zymosan (1 μ g/mL), HKSA (1 x10⁸), Endotoxin (0.05 EU/mL). Supernatants were collected and analyse on the Mesoscale U-PLEX platform. Data presented here resemble a 1/10 dilution on the Mesoscale platform.

Figure 5 provides dose finding of DPE in BEAS-2B cells after 24 hours supplementation. PC = positive control (ZDBC Polyurethane film (SPU-ZDBC); Lot No: B-172K; Hatano Research Institute, Japan). Values given as mean $\pm$ SD, n=6.

Figure 6 provides IL-10 release in BEAS-2B cells after 24 hours supplementation with DPE in three concentrations and subsequent stimulation with activated lymphocytes ($0,5 \times 10^6$ cells/mL, 24h). Values given as mean $\pm$ SD, n=3.

DETAILED DESCRIPTION OF THE INVENTION

- 5 The present invention is based on the discovery that a placenta extract has useful properties, including anti-inflammatory activity.

Definitions

- 10 The term "comprising" as used in this specification means "consisting at least in part of". When interpreting statements in this specification which include that term, the features, prefaced by that term in each statement or claim, all need to be present but other features can also be present. The related terms "comprises" and "comprised" are to be interpreted similarly.

As used herein the term "and/or" means "and" or "or", or both.

- 15 An "effective amount" is the amount required to confer therapeutic effect. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich, et al. (1966). Body surface area can be approximately determined from height and weight of the subject. See, e.g., Scientific Tables, Geigy Pharmaceuticals, Ardley, New York, 1970, 537. Effective doses also vary, as recognized by those skilled in the art, dependent on route of administration, carrier usage, and the like.

- 20 The term "extract" as used herein, refers to a preparation derived from source material, that is in a different form than the original material from which it is derived. An extract can be as simple as mechanically ground cellular material, in which case the preparation can be dehydrated to remove water, or it can be a preparation
25 derived by contacting the source material with one or more solvents. The term "extract" also encompasses preparations that undergo one or more separation and/or purification steps to enrich the content of active agent(s), as well as preparations comprising partially or substantially purified fractions derived from the placenta material.

- 30 The term "pharmaceutically acceptable carrier" is intended to refer to a carrier including but not limited to an excipient, diluent or auxiliary that can be administered to a subject as a component of a composition of the invention that does not reduce

the activity of the composition and is not toxic when administered in doses sufficient to deliver an effective amount of one or more active agents. The formulations can be administered orally, nasally, or parenterally (including topically, intramuscularly, intraperitoneally, subcutaneously, and intravenously).

5 The term "cosmetic composition" as used herein refers to a composition including the compound, having any type of formulation. Non-limiting examples of formulations of cosmetics prepared using the composition include creams such as skin creams, nutrition creams, eye creams, massage creams, and cleansing creams; packs; lotions
10 such as nutrition lotion; essences; serums, poultices, ointments; tonics such as skin softeners and nutrition tonics; powders; foundations, and makeup bases. To achieve the technical goal of the present disclosure, the cosmetic composition may be prepared in any formulation selected from the above-listed formulations to be commercialized, and the present disclosure is not limited to the above examples. In
15 addition, the cosmetic composition according to the present disclosure may be formulated using a general cosmetic preparation method.

The term "health functional food" as used herein refers to foods prepared and processed in the form of tablets, capsules, paste, jelly, pudding, soft gel, powder, granules, a liquid, pills, or the like by using raw materials or ingredients having
20 useful functionality in the human body. The term "functionality" as used herein refers to controlling nutrients for the structure of functions of the human body or providing useful effects of hygienic purposes, such as psychological effects, and the like. The health function food of the present disclosure may be prepared using a method commonly used in the art, and may be prepared by adding raw materials and ingredients commonly added in the art. In addition, the formulation of the health
25 function food is not particularly limited so long as it is recognised as a health functional food. The health functional food composition of the present disclosure uses a food as a raw material unlike generic drugs, and thus has no side effects that may occur during long-term administration thereof, is highly portable, and may be administered as an adjuvant for enhancing skin moisturizing, exfoliating skin,
30 improving skin elasticity, enhancing skin healing, inhibiting erythema, improving skin wrinkles, and/or alleviating skin photoaging.

The term "steroid sparing" is intended to mean that the dose of steroidal medication administered to a subject is able to be reduced to a level below that administered
35 before the subject began taking a composition of the present invention or began using a method of the present invention. Preferably the daily or weekly or monthly

dose of steroids is able to be reduced by at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 99%.

A "subject" in accordance with the invention is an animal, preferably a mammal, more preferably a mammalian companion animal or human. Preferred companion animals include cats, dogs and horses.

The term "synergy" as used in this specification means the effects of compositions useful herein are superior, as measured by, for example, the extent of the effect *in vitro* or *in vivo* or both, compared to use of individual agents alone. For example, the effect of the combination of placenta extract and another agent, such as another anti-inflammatory extract, is synergistic if the effect is superior to the effect achievable with the placenta extract alone or the other agent or extract alone. Further, the effect of the combination is synergistic if a beneficial effect is obtained in a group of subjects that does not respond (or responds poorly) to a placenta extract or the other agent or extract alone. In addition, the effect of the combination is synergistic if one of the components is used at its conventional dose and the other component is used at a reduced dose and the effect, as measured by, for example, the extent of the effect *in vitro* or *in vivo* or both, is equivalent to or better than that achievable with conventional amounts of either one of the components of the combination treatment alone. Related terms such as "synergistic" are to be interpreted similarly.

The term "treat" and its derivatives should be interpreted in their broadest possible context. The term should not be taken to imply that a subject is treated until total recovery. Accordingly, "treat" broadly includes amelioration and/or prevention of the onset of the symptoms or severity of a particular condition.

Methods of treatment or prevention

The data in the examples herein has demonstrated that placenta extract and compositions comprising placenta extract as described herein are useful in methods for treating or preventing a variety of conditions, including a disease, disorder or condition associated with inflammation or immune-modulation.

In one embodiment, the extract and compositions herein provide an immunomodulatory effect, useful for example in the treatment or prevention of conditions associated with inflammation.

In a preferred embodiment, the placenta extract is administered in an amount sufficient to treat the inflammatory-related disease by inhibiting pro-inflammatory cytokine expression and/or by stimulating anti-inflammatory cytokines.

5 It should be understood that the present uses include, but are not limited to, treating the inflammatory-related disease by preventing inflammation associated with the disease by regulating cytokines involved in the pathological progress, thus preventing the onset the inflammatory-related disease.

10 In one embodiment, the inflammatory-related disease is selected from the group consisting of diabetes type I; Sjogren's syndrome; uveitis; celiac disease; allergic conjunctivitis; and non-specific colitis.

Other inflammatory-related diseases disclosed herein but not claimed include: arthritis, rheumatoid arthritis, an inflammatory bowel disease; psoriasis; multiple sclerosis; a neurodegenerative disorder; congestive heart failure; stroke; aortic valve stenosis; kidney failure; lupus; pancreatitis; allergy; fibrosis; anemia;
15 atherosclerosis; a metabolic disease; a bone disease; a cardiovascular disease, a chemotherapy/radiation related complication; diabetes type II; a liver disease; a gastrointestinal disorder; an ophthalmological disease; diabetic retinopathy; a pulmonary disorder, a renal disease; dermatitis; HIV-related cachexia; cerebral malaria; ankylosing spondylitis; leprosy; anemia; and fibromyalgia.

20 Neurodegenerative disorders disclosed herein include: Alzheimer's disease and Parkinson disease, geroscience, osteoporosis, macular degeneration, healthspan extension; the inflammatory bowel disease is selected from the group consisting of: Crohn's disease or ulcerative colitis; the gastrointestinal complication is diarrhea; the liver disease is selected from the group consisting of: an autoimmune hepatitis,
25 hepatitis C, primary biliary cirrhosis, primary sclerosing cholangitis, or fulminant liver failure; the bone disease is osteoporosis; the pulmonary disorder is selected from the group consisting of: allergic rhinitis, asthma, chronic obstructive pulmonary disease, chronic granulomatous inflammation, cystic fibrosis, and sarcoidosis; the cardiovascular disease is selected from the group consisting of: atherosclerotic
30 cardiac disease, congestive heart failure and restenosis, thrombosis (Atrial fibrillation, AF), Hemodynamic Stress, Metabolic Syndrome (MetS), heart rate variability (HRV), vagal anti-inflammatory, arterial stiffness, heart failure, congenital heart disease, vascular disease; and the renal disease is selected from the group consisting of: glomerulonephritis and vasculitis.

Pro-inflammatory cytokines are also associated with a wide number of other diseases, disorders or conditions, all of which are amenable to treatment, amelioration or prevention by the extracts, compositions and methods of the invention, including:

- 5 AUTOIMMUNE – autoimmune and inflammatory disease (hypertension, fatigue, autism spectrum disorders, bipolar disorder, cancers, kidney transplant, Kawasaki disease;

- BRAIN HEALTH – cognitive impairment, vascular and neurodegenerative disorders, Alzheimer’s disease, brain morphology, tumour necrosis;

- 10 LUNG / RESPIRATORY HEALTH – macrophages, chronic respiratory disease, pulmonary fibrosis, autophagy, exuberant, dysregulated inflammation, interferon (Type I IFNs) response, cystic fibrosis (CF) lung disease, acute respiratory distress Syndrome, Chronic Bronchitis, chronic obstructive pulmonary disease (COPD), respiratory syncytial virus infection (RSV), mucus obstruction and neutrophilic
- 15 inflammation;

- CARDIOVASCULAR HEALTH – coronary artery disease (HIV+ individuals), cardiovascular disease (CVD), Atherosclerosis, Thrombosis (Atrial fibrillation, AF) , Hemodynamic Stress, Metabolic Syndrome (MetS), heart rate variability (HRV) – vagal anti-inflammatory, arterial stiffness, heart failure, congenital heart disease,
- 20 vascular disease;

- SKIN HEALTH – characterizing erythematotelangiectatic Rosacea (ETR) , psoriasiform skin inflammation, autoimmune skin disease (Psoriasis), cutaneous diseases (skin cancer), skin aging/ oxidative stress, chronological skin aging, photoaging, skin barrier dysfunction, extracellular matrix dysfunction, dendritic cells (DCs), skin
- 25 pigmentation, wrinkles;

- DEPRESSION – central nervous system disorders, chronic stress, depression, dementia, major depressive disorder (MDD);

- OBESITY – high fat diet (HFD), type 2 diabetes mellitues (T2DM), low grade inflammation;

- 30 ORGANS – Asthma-chronic obstructive pulmonary disease (ACOS), kidney disease, inflammatory bowel disease, organ disease (heart, pancreas, liver, kidney, lung, brain, intestinal tract, reproductive system, tissue damage);

CANCERS – liver cancers, breast cancer, gastric cancer, intestinal cancer, lung cancer, artery disease;

OTHERS – stroke , myocardial infarction, diabetes, psychomotor alterations.

5 The compound is in an amount to inhibit pro-inflammatory cytokine expression and/or to stimulate anti-inflammatory cytokine expression. In one embodiment, the compound is preferably in an amount to inhibit at least 30% expression of one or more of the pro-inflammatory cytokines selected from the group consisting of: IL-1 α , β , IL-2, IL-3, IL-6, IL-7, IL-9, IL-12, IL-17, IL-18, TNF- α , LT, LIF, Oncostatin, and IFN γ 1 α , β , γ : More preferably at least 40% expression of the cytokine is inhibited and
10 most preferably 50% or more is inhibited. In another embodiment, the compound is preferably in an amount to stimulate anti-inflammatory cytokine expression. In this embodiment, the compound is preferably in an amount to increase the anti-inflammatory cytokine selected from the group consisting of: cytokine IL-4, IL-10, IL-11, W-13 or TGF β by at least 25%, more preferably at least 50%, and most
15 preferably at least 75%.

In one embodiment the condition is joint inflammation, muscle inflammation, tendon inflammation, ligament inflammation, joint damage, joint sprain or strain, muscle sprain, muscle strain, cartilage damage, osteoarthritis, rheumatoid arthritis, an atopic condition, an allergy, arteriosclerosis, atherosclerosis, heart disease, high
20 blood pressure, blood clots, hypotension, vasoconstriction, cancer, or depression. In one embodiment the condition is joint inflammation. In one embodiment the condition is muscle inflammation, tendon inflammation, ligament inflammation, joint damage, joint sprain or strain, muscle sprain or strain, or cartilage damage. In another embodiment the conditions is osteoarthritis or rheumatoid arthritis. In
25 another embodiment the condition is an atopic condition. In another embodiment the condition is an allergy. In another embodiment the condition is arteriosclerosis, atherosclerosis, heart disease, high blood pressure, blood clots, hypotension, vasoconstriction, cancer, or depression. In various embodiments, the treatment is with steroid sparing effect.

30 In another embodiment, the combinations described herein are useful for reducing inflammation caused by skin/tissue injury, and are useful in atopic dermatitis, psoriasis, actinic keratosis, rosacea, skin tissue healing and other chronic skin disorders.

In another embodiment, the combinations described herein are useful for a disease, disorder or condition of the lung. In certain embodiments said disease, disorder or condition is (a) associated with or caused by an immune response; (b) an interstitial lung disease; (c) an obstructive lung disease; (d) an acute lung injury; or (e) a lung injury caused by a neoplastic or paraneoplastic disease, pneumonia, or cystic fibrosis.

In certain embodiments, said disease, disorder or condition associated with or caused by an immune response is an autoimmune disease, or a graft-versus-host disease. In yet another embodiment, said autoimmune disease is rheumatoid arthritis, scleroderma, inflammatory bowel disease, or systemic lupus erythematosus. In another embodiment, said interstitial lung disease is interstitial pulmonary fibrosis. In another embodiment, said obstructive lung disease is asthma, bronchitis, acute respiratory distress syndrome or chronic obstructive pulmonary disease.

In a specific embodiment, said lung disease, disorder, or condition is an acute lung injury. In more specific embodiments, said acute lung injury is one or more of physical trauma, a chemical injury, e.g., a chemical burn, smoke inhalation, or exposure to a toxic substance. In another specific embodiment, said lung disease, disorder, or condition is an injury caused by a neoplastic or paraneoplastic disease.

In certain embodiments, the disease, disorder or condition is one or more of a fibrotic disease of the lung, acute respiratory distress syndrome (ARDS), COVID-19, chronic obstructive pulmonary disease (COPD), emphysema, asthma, a viral or bacterial infection of the lung, pneumonia (including chemically-induced pneumonia), or cystic fibrosis. In a specific embodiment, the fibrotic disease of the lung is interstitial lung disease (diffuse parenchymal lung disease). In more specific embodiments, the interstitial lung disease is silicosis, asbestosis, berylliosis, systemic sclerosis, polymyositis, or dermatomyositis. In other more specific embodiments, the interstitial lung disease is caused by an antibiotic, a chemotherapeutic drug, an antiarrhythmic drug, or an infection.

In certain embodiments, the disease, disorder or condition of the lung is associated with or caused by a harmful, deleterious, inappropriate or unwanted immune response, e.g., inflammation, wherein said disease, disorder or condition affects, or manifests symptoms in, the lungs. In specific embodiments, said disease, disorder or condition is one or more of lupus, e.g., lupus erythematosus, scleroderma, or a rheumatological disease (e.g., rheumatoid arthritis).

- In another specific embodiment, said disease, disorder or condition is rheumatoid lung disease (RLD), e.g., rheumatoid lung disease associated with rheumatoid arthritis. In another specific embodiment, the administration is sufficient to cause a detectable improvement in one or more symptoms of RLD, or sufficient to detectably
- 5 reduce or slow the progression of one or more symptoms of RLD, e.g., in a lung of the individual. In a more specific embodiment, said symptom of RLD is a condition adjunct to RLD. In a more specific embodiment, said condition adjunct to RLD is an infection, e.g., a viral infection of the lungs, or fibrosis of the lungs (e.g., as a consequence of methotrexate therapy).
- 10 In another specific embodiment, the disease, disorder or condition is lupus erythematosus, e.g., systemic lupus erythematosus (SLE). In a more specific embodiment, said symptom of lupus erythematosus is one or more of lung and/or pleural inflammation, pleurisy, pleuritis, pleural effusion, lupus pneumonitis, or chronic diffuse interstitial lung disease.
- 15 In another embodiment, the combinations described herein are useful for the prevention or treatment of viral diseases and/or for inhibiting virus activation, in which said virus is selected from the group consisting of herpes virus, such as cytomegalovirus (CMV); influenza virus, such as H1N1, H3N2, H5N1 or H5N7 virus; paramixovirus, such as measles; respiratory syncytial virus; coronaviruses, such as
- 20 SARS or SARS-CoV-2 (Covid-19); HIV Virus; hepatitis virus; or rotavirus.

Compositions, medicaments and methods of treatment or prevention described and useful herein may employ compositions as described below.

Cosmetic uses

- Placenta extract and compositions comprising placenta extract as described herein
- 25 are useful in methods to treat, including prevent, reduce, ameliorate, and/or eliminate, signs and results of dermatological aging of skin, especially wrinkles and fine lines, blotches, red skin, dark spots and/or to improve the aesthetic appearance of skin, stimulate collagen production, increase elasticity and/or skin tone and hydration. The combinations provide treatment for wrinkles, fine lines and other
- 30 signs of dermatological aging (i.e., intrinsic aging) or sunlight exposure of the skin (i.e., extrinsic aging).

It is to be understood that, as used herein, the terms treating and treatment include and encompass preventing, reducing, ameliorating, improving, alleviating, and/or eliminating the dermatological effects of aging and sun exposure, with particular

regard to wrinkles, fine lines, folds, furrows, creases of the skin, and the like. The present invention further encompasses the treatment, as defined above, of "marionette" lines that run on either side of the mouth, as well as lines on the forehead, and the perpendicular lines between the brows. The present compositions and methods are also suitable for use in treating, as defined above, dermatological conditions of the skin in numerous areas of the body, including, without limitation, the face, forehead, neck, arms, hands, legs, knees, feet, chest, back, groin, buttocks, and the like.

It is another aspect of the present invention to provide compositions, formulations and methods containing materials newly determined to be useful in the treatment of dermatological aging of skin, especially wrinkles, fine lines, folds, furrows and other signs of aging skin, blotches, red skin, dark spots and/or to improve the aesthetic appearance of skin, stimulate collagen production, increase elasticity and/or skin tone and hydration.

In addition, because it is understood that the contraction or hypercontraction of certain muscles, particularly facial muscles, is related to the appearance of wrinkles, fine lines, etc., the relaxation of such muscles, and/or the control or modulation of the contraction of such muscles, by the newly-determined action of the placental extracts of the present invention can serve a pivotal function in the treatment, prevention, reduction, amelioration, or elimination of wrinkles, fine lines, folds, furrows and the like.

In accordance with this invention the disclosed combinations comprise compositions which include, without limitation, topically applied sunscreens, anti-oxidants, anti-inflammatories, cosmetics, including makeups, anti-aging formulations, e.g, creams for fine lines and/or wrinkles, topicals, skin permeants antiperspirants, deodorants and the like. Also in accordance with this invention, ingredients, components, or compounds that are formulated in such compositions in a variety of product forms, e.g., transdermals, such as patches, and the like, are encompassed, particularly for topical administration.

Another aspect of the present invention provides the compositions comprising the disclosed combinations preferably for topical administration without inducing significant irritation. Further, such compositions are preferably delivered by, but not limited to, the use of targeted delivery systems, for example, liposomes, microspheres, transdermal patches, and the like, so that the actives can more readily reach and affect the muscle layer of the area of application, e.g., face or neck, or the

dermal layer of the skin. Compositions comprising the disclosed combinations, including liposome formulations, can be administered by direct injection subcutaneously, intradermally, or through iontophoresis, to deposit the active agents at the sites requiring muscle relaxation or decontraction.

- 5 In another of its aspects, the present invention provides the disclosed combinations and methods thereof which can improve the aesthetic appearance of the skin by treating, including preventing, ameliorating and/or reducing at least one of the following: dermatological aging, especially chronological, actinic or hormonal aging. The improvement preferably results following topical application of a product or
10 formulation containing one or more of the disclosed combinations as described herein.

Compositions

- A composition described herein may be formulated as a food, drink, food additive, drink additive, dietary supplement, nutritional product, medical food, nutraceutical,
15 medicament or pharmaceutical. Preferably, a composition of the invention is formulated as a powder, liquid, food bar, spread, sauce, ointment, tablet or capsule. Appropriate formulations may be prepared by an art skilled worker with regard to that skill and the teaching of this specification.

- The compositions described herein may be formulated to allow for administration to a
20 subject by any chosen route, including but not limited to oral, nasal or parenteral (including topical, subcutaneous, intramuscular and intravenous) administration.

- Thus, a pharmaceutical composition useful in the invention may be formulated with an appropriate pharmaceutically acceptable carrier (including excipients and diluents) selected with regard to the intended route of administration and standard
25 pharmaceutical practice. For example, a composition of the invention can be administered orally as a powder, liquid, tablet or capsule, or topically as an ointment, cream or lotion. Suitable formulations may contain additional agents as required, including emulsifying, antioxidant, flavouring or colouring agents, and may be adapted for immediate-, delayed-, modified-, sustained-, pulsed- or controlled-
30 release.

The compositions useful herein may be used alone or in combination with one or more other therapeutic agents. The therapeutic agent may be a food, drink, food additive, drink additive, food component, drink component, dietary supplement, nutritional product, medical food, nutraceutical, medicament or pharmaceutical.

- When used in combination with another therapeutic agent the administration of a composition of the invention and other therapeutic agent may be simultaneous or sequential. Simultaneous administration includes the administration of a single dosage form that comprises all components and the administration of a composition of the invention and other therapeutic agent in separate dosage forms at substantially the same time. Sequential administration includes the administration of a composition of the invention and other therapeutic agent according to different schedules, preferably so that there is an overlap in the periods during which the composition of the invention and other therapeutic agent are provided.
- Suitable agents with which the compositions may find use in the invention can be co-administered include antihistamines, anti-inflammatories, anti-rheumatics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase-2 selective inhibitors, muscle relaxants, including combinations of any two or more thereof, and other suitable agents known in the art.
- As will be appreciated, the dose of the composition administered, the period of administration, and the general administration regime may differ between subjects depending on such variables as the severity of symptoms of a subject, the type of disorder to be treated, the mode of administration chosen, and the age, sex and/or general health of a subject. However, by way of general example, the inventors contemplate administration of from about 1 mg to about 1000 mg per kg body weight or more of a composition of the invention is administered per day, preferably about 50 to about 500 mg per kg per day. In one embodiment, the inventors contemplate administration of from about 0.05 mg to about 250 mg per kg body weight of a pharmaceutical composition according to the invention. It should be appreciated that administration may include a single daily dose or administration of a number of discrete divided doses as may be appropriate.
- Compositions described herein also include a cosmetic composition having an effect of enhancing skin moisturising, exfoliating skin, enhancing skin elasticity, enhancing skin healing, inhibiting erythema, improving skin wrinkles, and/or alleviating skin photoaging.
- In another exemplary embodiment, the cosmetic composition is prepared in any one formulation selected from the group consisting of a skin lotion, a skin softener, a skin toner, an astringent, a lotion, a milk lotion, a moisturizing lotion, a nutrition lotion, a massage cream, a nutrition cream, a moisturizing cream, a hand cream, an essence, a pack, a mask pack, a mask sheet, an exfoliating agent, a soap, a shampoo, a

cleansing foam, a cleansing lotion, a cleansing cream, a body lotion, a body cleanser, an emulsion, a press powder, a loose powder, and an eye shadow.

In one exemplary embodiment, an amount of the placenta extract ranges from about 0.05 to about 1% weight with respect to a total weight of the cosmetic composition.

5 Preferably, an amount of the placenta extract ranges from about 0.05 to about 0.5% weight, from about 0.05 to about 0.4% weight, from about 0.05 to about 0.35% weight, from about 0.1 to about 0.5% weight, from about 0.1 to about 0.4% weight, from about 0.135 to about 0.35% weight, or from about 0.15 to about 0.2% weight.

10 In one embodiment the composition is for application to skin, for example a face mask and comprises 0.13% weight placenta extract. In one embodiment the composition is a cream, gel or lotion for anti-aging uses, and comprises 0.135% to 0.35% weight placenta extract. In one embodiment the composition is a cream, gel or lotion for whitening, and comprises 0.15 to 0.2% weight placenta extract.

15 The cosmetic composition of the present disclosure may further include, in addition to the placenta extract, other additives such as an excipient, a carrier, and the like, and general ingredients added to general skin cosmetics may be applied to the cosmetic composition and mixed therewith in a needed amount.

20 In particular, the cosmetic composition of the present disclosure may further include a transdermal penetration enhancer. The term "transdermal penetration enhancer" as used herein refers to a composition that allows a desired component to permeate vascular cells of the skin at a high absorption rate. Non-limiting examples of the transdermal penetration enhancer may include other phospholipid components, liposomal components, and the like used in lecithin cosmetics.

25 In addition, oil that may be mainly used as an oil component may be at least one selected from vegetable oil, mineral oil, silicone oil, and synthetic oil. More particularly, mineral oil, cyclomethicone, squalane, octyldodecyl myristate, olive oil, Vitis vinifera seed oil, macadamia nut oil, glyceryl octanoate, castor oil, ethylhexyl isononanoate, dimethicone, cyclopentasiloxane, sunflower seed oil, and the like may be used.

30 In addition, to reinforce the emulsifying ability, about 0.1 wt % to about 5 wt % of a surfactant, a higher alcohol, or the like may be added. The surfactant may be a general surfactant such as a nonionic surfactant, an anionic surfactant, a cationic surfactant, an amphoteric surfactant, a phospholipid, or the like, and may be, for example, sorbitan sesquinoate, polysorbate 60, glyceryl stearate, lipophilic glyceryl

stearate, sorbitan oleate, sorbitan stearate, diacetyl phosphate, sorbitan stearate/sucrose cocoate, glyceryl stearate/polyethylene glycol-100 stearate, ceteareth-6 olivate, arachidyl alcohol/behenyl alcohol/arachidyl gluco side, polypropylene glycol-26-butes-26/polyethylene glycol-40 hydrogenated castor oil, or
5 the like. The higher alcohol may be a C12 to C20 alcohol, for example, cetyl alcohol, stearyl alcohol, octyldodecanol, isostearyl alcohol, or the like, and these higher alcohols may be used alone or at least two thereof may be used in combination.

To adjust the viscosity or hardness of a water-phase component, about 0.001 wt % to about 5 wt % of at least one thickening agent selected from carbomer, xanthan
10 gum, bentonite, magnesium aluminium silicate, cellulose gum, dextrin palmitate, and the like may further be added.

In addition, the cosmetic composition according to the present disclosure may further include, according to need, components, for example, a medicinal ingredient such as higher fatty acids, vitamins, or the like; a UV screening agent; an antioxidant
15 (butylhydroxyanisole, gallic acid propyl, erythorbic acid, tocopheryl acetate, butylated hydroxytoluene, or the like); a preservative (methylparaben, butylparaben, propylparaben, phenoxyethanol, imidazolidinyl urea, chlorphenethine, or the like); a colorant, a pH adjusting agent (triethanolamine, citric acid, sodium citrate, malic acid, sodium malate, fumaric acid, sodium fumarate, succinic acid, sodium succinate,
20 sodium hydroxide, sodium monohydrogen phosphate, or the like); a moisturizing agent (glycerin, sorbitol, propylene glycol, butylene glycol, hexylene glycol, diglycerin, betaine, glycereth-26, methyl gluceth-20, or the like); a lubricant; and the like.

In addition, the cosmetic composition of the present disclosure may further include
25 an adjuvant for supplying an essential nutrient to the skin, for example, an adjuvant with natural flavor or cosmetic flavor, or medicinal herbs, but may include any adjuvant without being limited to these examples.

Compositions described herein also include a health functional food composition having an effect of enhancing skin moisturizing, exfoliating skin, enhancing skin elasticity, inhibiting erythema, improving skin wrinkles, and/or alleviating skin
30 photoaging.

In an exemplary embodiment, the health functional food composition is prepared in any one formulation selected from the group consisting of tablets, granules, powder,

soft gel, paste, jelly, pudding, capsules, a liquid solution (such as a beverage), and pills.

5 In one exemplary embodiment, an amount of the placenta extract ranges from about 50 to about 500mg when present in a health functional food composition in the form of a beverage. Preferably, an amount of the placenta extract ranges from about 50 to about 350mg, from about 55 to about 350mg, from about 60 to about 300mg, from about 65 to about 250mg, from about 65 to about 200mg, from about 65 to about 180mg, from about 65 to about 160mg, or from about 65 to about 155mg. In one
10 embodiment the health functional food composition in the form of a shot and comprises from about 10 to about 100mg placenta extract, from about 10 to about 80mg, from about 20 to about 70mg, or from about 25 to about 50mg.

In another exemplary embodiment, the cosmetic composition or the health functional food composition may further include a skin wrinkle improving ingredient.

15 In another exemplary embodiment, the skin wrinkle improving ingredient includes one or more selected from the group consisting of vitamin C, retinoic acid, a transforming growth factor (TGF), an animal placenta-derived protein, betulinic acid, and a chlorella extract.

Various aspects of the invention will now be illustrated in non-limiting ways by reference to the following examples.

20 **EXAMPLES**

EXAMPLE 1

Evaluation of immune modulatory effects of deer Placenta

Materials & Methods

1. Generation of placenta extracts (DPE)

25 Freeze-dried Deer Placenta powder was dissolved in various solvents to create a final test extract solubilising major parts of the basic material and being compliant with physiological testing. The protein concentration of the extract (DPE) was determined by absorption at 280nm. Protein integrity was checked by SDS-PAGE / Coomassie Brilliant Blue staining.

30 2. Determination of cytotoxicity

Cytotoxicity was determined according to the demands of the ISO 10993-5, 2009.
Test performance will be described below.

3. Determination of acute systemic oral toxicity

Determination of acute oral toxicity was performed by an accredited animal testing
5 facility under GLP according to the OECD 423.

4. Determination of immune modulatory effects

Humane immune cells (PBMCs: peripheral blood mononuclear cells) have been
confronted with various concentrations of and additional immunological stimuli as
controls for a defined time span (16 h, 37°C). After this period the supernatant was
10 divided from the cells and the cytokine expression patterns were analysed on a
multiplexing platform (Mesoscale Discoveries U-Plex).

Experimental setup:

Table 1: Reagents and Media

Test Cell line	L929 (mouse fibroblasts), DSMZ (ACC2), according to ISO 10993-5, 2009
Cell culture medium	RPMI 1640 w/o phenole red, Cell line services (CLS) #820706a Lot: MG70a-1238B14 supplemented with FBS (10% f.c.), Gentamycine: 50µg/ml Gentamicin f.c.
Foetal bovine serum (FBS)	PAN Biotech, # P30 - 8100 Lot:
Antibiotics	Gentamycine sulfate, PAN Biotech, # P06-03050; Lot: 38220000
SDS	Sodium Lauryl Sulfate, Merck Chemicals Ltd #428029-1EA; Lot: 2638219
Vital dye	XTT sodium salt; Applichem GmbH #A2240,00100; Lot: 9F014774
Multiplexing device	Mesoscale U-PLEX Biomarker Group 1 (Human) Calibrator 3 Cat-Nr.. C0062-2; Lot: A00U0154

Table 2: Generation of placenta extracts / Determination of protein concentration and integrity

Solvent / Extractant	Distilled water Phosphate buffered Saline (PBS) PBS + 1% Sodium Lauryl Sulfate (SDS) PBS + 1% Triton X100 0.9% NaCl in distilled water Cell culture Medium: RPMI 1640 w/o phenole red (Cell Line Services: Lot: MG70a-1238B14)
Extraction conditions	1 g in 10 mL solvent (100 mg /mL); 24 ± 2h; 37 ± 1°C;
Determination of protein concentration	Pharmacia Ultrospec 2000 Photometer at 280nm (internal ID: G61)
SDS-PAGE	1BioRad Mini Protean: 4-20% ready to use gradient gels. SDS-PAGE at 25mA / 200V. Coomassie staining / Gel documentation: BioRad ChemiDoc XRS+ (internal ID: G1017)

Table 3: Determination of cytotoxicity

Solvent / Extractant	Cell culture medium: RPMI 1640 w/o Phenol red (CLS) Lot: MG70a-1238B14 (supplemented with 10% FCS, 50µg/ml Gentamicin after the extraction)
Extraction conditions	1 g-in 10 mL solvent (100 mg / mL); 24 ± 2h; 37 ± 1°C;
Test incubation conditions	24 ± 1h; 37 ± 1°C; 5% CO2
Sample application	Test extract: undiluted /diluted 1:2 / 1:5 / 1:10 / 1:20 / 1:40 / 1:100 / 1:1000 in complete cell culture medium (RPMI w/o Phenol red (CLS) Lot: MG70a-1238B14supplemented with 10% FBS, 50µg/ml Gentamicin after extraction

Positive Control	Sodium lauryl sulfate (SDS) 1%
Negative Control	Cell Culture Medium complete ((RPMI 1640 w/o phenol red supplemented with 10% FBS, 50µg/ml Gentamicin after extraction
Solvent / Extraction Control	Same extraction conditions without test item

Table 4: Determination of acute oral toxicity:

Regulation	Good Laboratory Praxis
Guideline / method	Study was conducted to comply with OECD Principles of Good Laboratory Practice (OECD Document C (81) 30 (Final), Paris, France, 1981, as revised by OECD Council in 1997 ([C(97)186/Final]); Gesetz zum Schutz vor gefährlichen Stoffen (Chemikaliengesetz. - ChemG) § 19b Abs.1 Chemikaliengesetz Ausfertigungsdatum: 16.09.1980, Neugefasst durch Bek. v. 28.8.2013 I 3498, 3991

Table 5: Determination of immune modulatory effects

Solvent / Extract	in culture medium (RPMI w/o phenole red). Protein concentration 61.6 mg / mL
DEER extract dilutions	1:5 (12.32 mg/mL), 1:20 (3.08 mg/mL, 1:50 (1.23 mg/mL)
Test cells	Human leucocytes / peripheral blood mononuclear cells (PBMCs); 1x 10 ⁵ cells / well in a 96 well plate
Controls	Endotoxin (0.1 / 0.05 / 0.01 EU/mL f.c.); Zymosan (5 / 1 / 0.2 mg/mL f.c.); Heat inactivated Staph. Aureus (HKSA: 1 x 10 ⁸ / 1x 10 ⁷ cells f.c.)
Test incubation conditions	24 ± 1h; 37 ± 1°C; 5% CO ₂

Method	PBMCs directly treated with the indicated extracts and stimuli (16h, 37°C, 5%CO ₂) or after 3h pre-incubation (1.23 mg/mL) for the same time period. Subsequently the supernatant from the individual test cultures was isolated and analysed on a Mesoscale U-PLEX
Read out	Mesoscale U-PLEX Biomarker Group 1 (Human) Calibrator 3 Cat-Nr. C0062-2; Lot: A00U0154. The test plate was analysed on a Mesoscale QuickPlex SQ 120 (S-Nr. 13001802141084)

Results

Generation of placenta extracts:

Freeze dried deer placenta powder was dissolved in various solvents to assure creating a final test extract solubilising major parts of the basic material and being compliant with physiological testing. The protein concentration of the extract was determined by absorption at 280nm. Protein integrity was checked by SDS-PAGE / Coomassie Brilliant Blue staining (Figure 1).

Table 6: Protein concentrations

Extraction conditions	1 g in 10 mL solvent (100 mg / mL); 24 ± 2h; 37 ± 1°C;
Extractant	Protein concentration
Distilled water	34, 8 mg/mL
0.9 % NaCl	22,8 mg/mL
Culture Medium	34,0 mg/mL
PBS	34,7 mg/mL
PBI/1% Triton X100	8,8 mg/mL
PBS /1% SDS	37,3 mg/mL

Conclusion:

Regarding the generation of protein extracts from it could be observed that a soluble protein fraction with a maximum of about 1/3 of the initially applied material was obtained after extraction for 24h at 37°C. In this context no relevant difference between distilled water, PBS and cell culture medium (RPMI 1640 w/o phenole red) giving us the option to stay in cell culture medium for the following physiological testing. Regarding the protein integrity similar banding patterns can be observed within the various extracts also not excluding extracts without detergents. The high molecular weight bands migrating at an apparent molecular weight > 150 kDa are typical for cytokeratins. Regarding these results the following settings were performed in cell culture medium (RPMI1640 w/o phenol red supplemented with FBS (10% f.c.) and gentamycin (50 µg /mL) prior to the physiological testing)

Determination of cytotoxicity

Cytotoxicity was determined according to the demands of the ISO 10993-5, 2009. In this special context various dilutions ranging from a 1/2 dilution to a 1/1000 dilution of the test extract were subjected for evaluation of a cytotoxic potential on the test cell line L929. The read out was generated by conversion of the vital dye XTT (ISO 10993-5, Annex D) in combination with a visual inspection of the cultures.

Controls:

Negative Control (NC): Test cells in complete culture medium (ccm)
 Positive Control (PC) : Test cells in complete culture medium plus 1% SDS
 Solvent Control (SC): Extraction medium w/o test substance

Table 7. Evaluation criteria

Regulation	Criterion	Evaluation
ISO 10993-5, 2009	Viability $\geq$ 70%	non cytotoxic
	Viability < 70%	cytotoxic

Table 8. Evaluation of cytotoxicity in vitro

Starting concentration of (DPE): 34.9 mg / mL				
Parameter	Concentration (mg / mL)	Optical Evaluation	Viability % (XTT-Test)	Classification
NC	-	0	100	Non cytotoxic
PC	-	4	-3.8	Cytotoxic
SC	-	-	95.2	Non cytotoxic

DPE diluted ½ in ccm	17.45	3	48.7	Cytotoxic
DPE 1:5 in ccm	6.98	3	82,3	Non cytotoxic
DPE 1:10 in ccm	3.49	1-2	105,8	Non cytotoxic
DPE 1:20 in ccm	1.745	1	106,6	Non cytotoxic
DPE 1:40 in ccm	0.875	1-0	110,6	Non cytotoxic
DPE 1:100 in ccm	0.349	0	106,0	Non cytotoxic
DPE 1:1000 in ccm	0.0349	0	141	Non cytotoxic

Optical evaluation (grading): 0: cells in optimal shape, 1: cells in good shape, some detached cells might be visible, 2-3: cells partly to critically detached showing signs of apoptosis, 4: culture completely damaged, no living cells

5 Conclusion:

Regarding the determination of cytotoxicity in vitro we observe that upon a dilution of 1:10 and a protein concentration below 3.49 mg / mL no cytotoxic effects can be observed.

Determination of acute oral toxicity

10 The determination of acute oral toxicity was performed as described above.

Table 9. Determination of acute oral toxicity

Assessment	The LD50 of the test material is higher than 2000 mg/kg body weight by oral route in rat. At this dose level, no mortality occurred and there were no adverse effects on clinical signs and body weight gain or abnormal necropsy finding that could be attributed to treatment with the test material.
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	Therefore, the test material is "not classified" according to the Globally Harmonized System of Classification and Labelling of (GHS)
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Determination of immune modulatory effects

For the determination of immune modulatory effects human PBMCs were directly treated with the indicated extracts and stimuli (16h, 37°C, 5%CO₂) or after 3h pre-incubation with (1.23 mg/mL) for the same time period. For determination of immune modulatory effects 3 different concentrations of were chosen. Beginning from a starting extract (61. 6 mg / mL) the following dilutions were tested

- 1/5 dilution: 12.32 mg / mL → extract in the cytotoxic range
- 1/20 dilution: 3.08 mg / mL → extract slightly below the border to cytotoxicity
- 1/50 dilution: 1.23 mg / mL → extract in the non-cytotoxic range. This dilution was also used for pre-treatment of the PBMCs before adding known immunological active stimuli (Endotoxin, Zymosan, Heat Inactivated Staph. aureus)

Subsequently upon treatment the supernatant from the individual test cultures was isolated and analysed on a multiplexing platform (Mesoscale U-Plex). The following parameters / cytokines were analysed: IL-1beta, IL-6, IL-10, TNF-alpha

Immune modulatory stimuli: Endotoxin (0.1 / 0.05 / 0.01 EU/mL f.c.); Zymosan (5 / 1 / 0.2 mg/mL f.c.); Heat inactivated Staph. Aureus (1 x 10⁸ / 1x 10⁷ cells f.c.)

Every parameter was analysed in at least 2 individual settings. The mean values of the signal intensities are being presented in the following graphs and tables

Table 10: Reactivity of DPE on cytokine induction and interference in cytokine induction upon pre-treatment

Parameter	DPE-reactivity	DPE-Interference
IL-1beta	XXX	Interference / repression of inflammatory cytokine induction

		with HKSA and Endotoxin
IL-6	XXX	Enhancement of the HSKA-signal. Minor effects on Endotoxin. Repression of Zymosan
IL-10	X	No interference observed
TNF-alpha	Background in all dilutions	Interference / repression of inflammatory cytokine induction with HSKA and Endotoxin

Conclusions:

IL-1 β

Regarding the induction of IL-1 β upon stimulation of human PBMCs it could be observed that DPE in a concentration inducing cytotoxicity (12.33 mg/mL) leads to an induction / release of IL-1 β from PBMCs in the range of the positive control HKSA, even higher than the stimuli Zymosan and Endotoxin. Regarding DPE concentrations below the cytotoxic border (1:20: 3.08 mg/mL; 1:50: 1.23 mg/mL) it can be observed that the induction of IL-1 β is strongly reduced (Fig. 2).

IL-6

Regarding the induction of IL-6 upon stimulation of human PBMCs it could be observed that DPE in a concentration inducing cytotoxicity (12.33 mg/mL) leads to an induction / release of IL-6 from PBMCs in the range of the positive control Endotoxin but clearly lower than stimulation with Zymosan (0.2 μ g/mL) and HKSA (10⁸ cells). Regarding DPE concentrations below the cytotoxic border (1:20: 3.08 mg/mL; 1:50: 1.23 mg/mL) it can be observed that the induction of IL-6 is clearly reduced (Fig. 3).

Interference of cytokine induction

In order to determine a potential interference of DPE with the induction of inflammatory cytokines upon stimulation human PBMCs were pre-treated with DPE at a concentration being clearly below the cytotoxic boarder (1/50 dilution of the initial extract: 1.23 mg/mL) for 3h. Subsequently the established PBMC stimulators Endotoxin, Zymosan and Heat killed Staph. Aureus (HKSA) are added to the cultures for further 16h. In the last step supernatants were removed and analysed on the Mesoscale U-Plex platform.

Table 11: Interference in the induction of IL-1 beta

Parameter	Reactivity (EC-units)	% Reactivity
Endotoxin	19058,5	100,0
DPE + Endotoxin	14533,5	76,3
HKSA	49626,5	100,0
DPE + HKSA	31160	62,8
Zymosan	36849	100,0
DPE + Zymosan	18603	50,5

10 **Conclusion:**

Interleukin 1 beta (IL-1 β) is regarded as a pro-inflammatory cytokine and is an important mediator of the inflammatory response,

Regarding the interference of a DPE treatment of human PBMCs at a concentration of 1.23 mg/mL prior to the addition of the indicated stimuli it can be observed that the IL-1beta expression by Endotoxin was reduced to 23.7%, by HSKA to 37.2% and the induction by Zymosan at 49.5% (Fig. 4).

Table 12: Interference in the induction of IL-6

Parameter	Reactivity	% Reactivity
Endotoxin 1	112246	100,0
DPE + Endotoxin 1	121599,5	108,3
HKSA 1	295415	100,0

DPE + HKSA 1	467737,5	158,3
Zymosan 2	465373,5	100,0
DPE + Zymosan 2	354093,5	76,1

Interleukin 6 (IL-6) is an interleukin that acts as a pro-inflammatory cytokine, and there is some evidence that IL-6 can be used as an inflammatory marker for severe COVID-19 infection with poor prognosis.

- 5 Regarding the interference of a DPE treatment of human PBMCs at a concentration of 1.23 mg/mL prior to the addition of the indicated stimuli it can be observed that the IL-6 expression by Zymosan at a DPE dependent repression (-24.9%).

Table 13: Induction of IL-10

Parameter	Reactivity (EC Units)	Reactivity (%)
Endotoxin 1	815,5	100,0
DPE + Endotoxin 1	643,5	78,9
HKSA 1	5138	100,0
DPE + HKSA 1	6131,5	119,3
Zymosan 2	5803,5	100,0
DPE + Zymosan 2	3017,5	52,0

10

Conclusion:

Interleukin 10 (IL-10) is regarded as anti-inflammatory cytokine with numerous functions in the regulation of the immune system.

15

Regarding the interference of DPE treatment of human PBMCs at a concentration of 1.23 mg/mL prior to the addition of the indicated stimuli it can be observed that the IL-10 expression by HKSA was induced (19.3%) by DPE.

Table 14: Interference in the induction of TNF-alpha

Parameter	Reactivity (EC Units)	Reactivity (%)
Endotoxin 1	228	100,0
DPE + Endotoxin 1	201	88,2
HKSA 1	26583,5	100,0
DPE + HKSA 1	24201,5	91,0
Zymosan 2	15699,5	100,0
DPE + Zymosan 2	6240,5	39,7

Human PBMCs were pretreated with DPE as described. Subsequently established stimuli were added at the following concentrations: Zymosan 2 (1µg/mL), HKSA 1 (1 x10⁸), Endotoxin 1 (0.05 EU/mL). Supernatants were collected and analyzed on the Mesoscale U-PLEX platform. Data presented here resemble a 1/10 dilution on the Mesoscale platform.

Conclusion:

In general, DPE treatment itself did not induce the expression of TNF-alpha. The reactivity of the stimulator Endotoxin was also in the background and was neither repressed nor induced by DPE pre-treatment of human PBMCs.

Regarding the interference of a DPE treatment of human PBMCs at a concentration of 1.23 mg/mL prior to the addition of the indicated stimuli it can be observed that the TNF-alpha expression by HKSA was slightly repressed by (9%) by Endotoxin repressed by (11.8%) DPE. IL-10 expression by Zymosan was clearly repressed by DPE pre-treatment (60.3%).

Final statement:

Determination of cytotoxicity:

Cytotoxic effects of DPE were observed at high concentrations > 3.5 mg/ mL. Dilutions below 3.5 mg / mL show no cytotoxic effects,

Determination of acute systemic oral toxicity:

Acute systemic oral toxicity was not observed

Determination of immune modulatory effects:

Regarding a direct effect on human PBMCs at concentrations in the cytotoxic range (12.33 mg/mL) an induction of inflammatory cytokines IL-1beta, and IL-6 were observed. At concentrations below 3.08 mg/mL these effects were reduced.

- 5 Regarding an immune modulatory effect of DPE it could be observed that pre-treatment of human PBMC in a non cytotoxic concentration of DPE (1.23 mg/mL) prior to stimulation with strong activators such as Endotoxin, Zymosan and Heat killed *Staph. aureus* it could be observed that DPE reduced the Zymosan dependent induction of IL-1beta, IL-6, and TNF-alpha. A general effect on the expression of IL-10
10 1beta could be observed. DPE was also shown to induce expression of the anti-inflammatory cytokine IL-10 in response to Heat killed *Staph. Aureus*.

- As discussed above, COVID-19, caused by SARS-CoV-2, is characterised by an immune dysfunction rather than a viral load, which leads to abnormal production of pro-inflammatory cytokines. In particular, COVID-19 can trigger a cytokine storm in
15 pulmonary tissues through hyperactivation of the immune system and the uncontrolled release of cytokines. Pro-inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and tumor necrosis factor-alpha (TNF- α) play a very significant role in lung damage in COVID patients with acute respiratory distress syndrome (ARDS), through the impairments of the respiratory epithelium.

- 20 The finding that DPE is able to repress the induction of each of IL-6, IL-1 β and TNF- α , as well as induce the expression of the anti-inflammatory cytokine IL-10, shows potential for DPE as a potential therapy for suppressing the inflammatory response associated with COVID-19.

25 **EXAMPLE 2**

METHODS**DPE generation**

Test product: DPE (Deer Placenta Powder, Lot no. NPR00/65 #2/2R008). Stored refrigerated at 4°C.

- 30 Deer Placenta powder (100mg/mL) was dissolved in cell culture medium (KGM2, Promocell) without additives and incubated for 24 $\pm$ 2 hours at 37 $\pm$ 1 °C. The extract (DPE) was centrifugated (2 min, 14000 rpm, RT) and filtered (0.4 μ m). The

protein concentration of the extract was determined by absorption measurement at 280nm.

Dose finding

5 The working concentrations of the DPE was assessed on the basis of their effect on cell viability. A neutral red uptake assay was performed.

For the following experiments, extracts were generated in 1 concentration (non-toxic) or 3 concentrations (non-toxic / borderline / toxic) according the results of this viability test.

Lymphocyte stimulation

10 As *in vitro* test system the BEAS-2B immortalized Human Bronchial Epithelial Cell Line was used. The BEAS-2B cell line is used as an in-vitro model for a variety of diseases based on inflammatory processes, such as asthma, infections, ARDS or COVID-19.

15 BEAS-2B cells were supplemented for 24 hours with three different concentrations of the DPE or left unsupplemented (control). End concentrations of DPE were: 3.6 mg/mL; 1.8 mg/mL; 0.9 mg/mL.

T-lymphocytes were isolated from freshly withdrawn human blood samples using Pan T Cell Isolation Kit (Miltenyi Biotec) and activated using T Cell TransAct (Miltenyi Biotec).

20 Subsequently, as a trigger for an inflammatory process, activated T-lymphocytes were added to the pre-supplemented cells for 1 h. After further 24 hours supernatant samples were withdrawn for cytokine analysis.

Cells were collected and total cellular protein was determined as the reference value.

Cytokine analysis

25 Human Interleukin 10 (IL-10) concentration in the supernatant was determined by ELISA techniques (Manufacturer: RnD Systems D1000B; Lot / Exp: P322071 18.10.2022).

RESULTS

Extract preparation

Protein content was determined photometrically by 280 nm method using a NanoQuant Plate and Infitite 200Pro Plate Reader (Tecan).

Protein content in deer placenta powder extract: 25.33 mg/mL

Dose finding

- 5 The working concentrations of the DPE was assessed on the basis of their effect on cell viability. Figure 5 depicts the result of the dose finding.

Based on the results of the viability assay, the concentrations of the DPE set out in Table 15 were used for the further investigations:

Table 15: Protein concentration of deer placenta powder extract in the assay

	Concentration (mg/mL)	Classified as
C1	3.6 mg/mL	borderline
C2	1.8 mg/mL	non-toxic optimal concentration
C3	0.9 mg/mL	non-toxic low concentration

10

Interleukin 10 after stimulation with activated lymphocytes

- For the assessment of the effect of DPE on IL-10 release in BEAS-2B cells, the cells were pre-supplemented for 24 hours with three different concentrations of the deer placenta extracts (C1: 3.6 mg/mL; C2: 1.8 mg/mL; C3: 0.9 mg/mL) or left
 15 unsupplemented (control). Subsequently as trigger for an inflammatory process, the cells were co-cultured with freshly isolated and activated lymphocytes or co-cultured with not activated lymphocytes. After 24 hours supernatant samples were withdrawn for cytokine analysis. Activated lymphocytes were chosen as representative for COVID-19 as trigger for the inflammatory processes in the in vitro test system.

- 20 Cells were collected and total cellular protein was determined as reference value. The results are shown in Figure 6.

IL-10 was not detectable in supernatants of BEAS-2B cultures with not activated lymphocytes. Upon stress induced by activated lymphocytes, IL-10 was detectable in all groups.

IL-10 release was enhanced by 1.0 mg/mL DPE compared to control.

The above methods should be considered in no way limiting and suitable variations or alternatives will be apparent to those skilled in the art.

INDUSTRIAL APPLICATION

- 5 The present invention has utility in treating or preventing inflammatory conditions. The described compositions and methods of the invention may be employed to treat or prevent one or more of the conditions discussed above.

Those persons skilled in the art will understand that the above description is provided by way of illustration only and that the invention is not limited thereto.

CLAIMS

1. A method of treating, preventing or ameliorating a disease, disorder or condition associated with inflammation or immune-modulation, comprising administration to a subject in need thereof of an effective amount of a placental extract or an effective amount of a composition comprising a placental extract.
2. A composition for use in treating, preventing or ameliorating a disease, disorder or condition associated with inflammation or immune-modulation, wherein the composition comprises a placental extract.
3. Use of a placental extract, in the manufacture of a medicament or composition for treating, preventing or ameliorating a disease, disorder or condition associated with inflammation or immune-modulation.
4. The method, composition or use according to any one of the preceding claims wherein, the composition or medicament is a food, drink, food additive, drink additive, food component, drink component, dietary supplement, nutritional product, medical food, nutraceutical, medicament or pharmaceutical.
5. The method, composition or use according to any one of the preceding claims wherein, the placenta extract is administered at a concentration sufficient to inhibit one or more pro-inflammatory cytokines, including cytokine IL-1 α , β , IL-2, IL-3, IL-6, IL-7, IL-9, IL-12, IL-17, IL-18, TNF- α , LT, LIF, Oncostatin, or IFN γ , β , γ .
6. The method, composition or use according to any one of the preceding claims wherein, the placenta extract is administered at a concentration sufficient to stimulate expression of one of more anti-inflammatory cytokine, including IL-4, IL-10, IL-11, W-13 or TGF β .
7. The method, composition or use according to any one of the preceding claims wherein, the placental extract is derived from a deer, sheep, goat, horse, donkey, rabbit or bovine placenta, preferably the placental extract is derived from deer placenta.
8. The method, composition or use according to any one of the preceding claims wherein, the placental extract is extracted from placenta material by a method of extraction selected from the group consisting of: solvent

extraction, supercritical solvent extraction including supercritical CO₂ extraction, distillation, counter current extraction, decoction, percolation, maturation, molecular distillation, microwave extraction, ultrasound extraction, and chromatographic separation.

- 5 9. The method, composition or use according to any one of the preceding claims wherein, the placental extract is extracted from placenta material by solvent extraction.
- 10 10. The method, composition or use according to claim 8 or 9 wherein, the method of extraction includes steps of contacting the placenta material with a solvent, separating the placenta material from the solvent, and at least partially removing the solvent to yield the extract.
11. The method, composition or use according to any one of claims 8 to 10 wherein, the placenta material is freeze dried and powdered prior to contact with the solvent.
- 15 12. The method, composition or use according to any one of claims 8 to 11 wherein the solvent is water.
13. The method, composition or use according to any one of claims 8 to 11 wherein, the solvent is an organic solvent.
- 20 14. The method, composition or use according to claim 13 wherein, the solvent is ethanol.
15. The method, composition or use according to any one of claims 1 to 11 or 13 to 14 wherein the extract is prepared by solvent extraction, such as ethanol extraction, followed by distillation or supercritical extraction.
- 25 16. The method, composition or use according to any one of claims 1 to 12 wherein water extraction is used to prepare the extract.
17. The method, composition or use according to any one of the preceding claims wherein the placental extract is or comprises dried or powdered placenta material.
- 30 18. The method, composition or use according to claim 17 wherein, the placenta material is pulverised by wet grinding, and then powdered or granulated by freeze-, vacuum- or spray-drying, or fluid bed drying or the like.

19. The method, composition or use according to claim 17 wherein, the placenta material is first dried, optionally by freeze- or vacuum-drying, and then optionally ground into powder.
- 5 20. The method, composition or use according to any one of the preceding claims wherein the composition or medicament is provided in a delivery formulation selected from the group consisting of tablets, capsules, liquids, oils, suspensions, emulsions, pastes, jellies, puddings, solutions, and powders.
21. The method, composition or use according to any one of the preceding claims wherein the composition comprises or the medicament comprises:
- 10 a. at least about 0.1, 0.2, 0.5, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 99, 99.5, 99.8 or 99.9% by weight of the placental extract;
- 15 b. at least about 0.001, 0.01, 0.05, 0.1, 0.15, 0.2, 0.3, 0.4, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18 or 19 grams or more of the placenta extract; or
- c. at least about 1, 10, 50, 100, 125, 150, 200, 250, 300, 350, 400, 450, 500, 600, 700, 800, 900 or 1000mg or more of the placenta extract.
22. The method, composition or use according to any one of the preceding claims wherein the composition comprises, the medicament comprises, or the method comprises
- 20 a. administration of placenta extract in an amount of about 125mg, suitable for administration twice daily, or 250mg, suitable for administration once per day;
- 25 b. administration of placenta extract in an amount of about 100mg or 125mg, suitable for administration twice daily, or 200mg or 250mg, suitable for administration once per day; or
- c. administration of about 40% to 90% by weight of placenta extract.
23. The method, composition or use according to any one of the preceding claims wherein the composition or the medicament further comprises about 0.1, 0.5, 1, 5, 10, 15, 20, 25, 30, 35, 40, 45 or 50% by weight another anti-inflammatory agent.
- 30

24. The method, composition or use according to any one of the preceding claims wherein the composition or medicament further comprises a carrier, optionally a pharmaceutically acceptable carrier.
- 5 25. The method, composition or use according to any one of the preceding claims wherein the composition or medicament is in the form of a tablet, a caplet, a pill, a hard or soft capsule, a lozenge, a cachet, a dispensable powder, granules, a suspension, an elixir, a liquid, or any other form that can be added to food or drink, including for example water or fruit juice.
- 10 26. The method, composition or use according to any one of the preceding claims wherein the composition or medicament further comprises one or more constituents, optionally antioxidants, which prevent or reduce degradation of the composition during storage or after administration.
- 15 27. The method, composition or use according to any one of the preceding claims wherein the composition or medicament is or is formulated as a food, drink, food additive, drink additive, dietary supplement, nutritional product, medical food, nutraceutical, medicament or pharmaceutical, optionally, the composition or medicament is formulated as a powder, liquid, food bar, spread, sauce, paste, jelly, pudding, soup base, ointment, tablet or capsule.
- 20 28. The method, composition or use according to any one of the preceding claims wherein the composition or medicament is formulated for:
- a. oral, nasal or parenteral administration, optionally topical, subcutaneous, intramuscular and intravenous administration; or
 - b. ingestion,
 - 25 c. inhalation, optionally formulated for administration as an inhalable powder, solution or aerosol; or
 - d. topical application, optionally formulated for topical application, preferably it is formulated as an ointment, cream or lotion.
- 30 29. The method, composition or use according to any one of the preceding claims wherein the placenta extract or composition is administered, or is formulated for administration, in an amount sufficient to treat the inflammatory-related disease by inhibiting pro-inflammatory cytokine expression and/or by stimulating anti-inflammatory cytokines.

30. The method, composition or use according to any one of claims 1 to 29 wherein the disease, disorder or condition is an inflammatory-related disease selected from the group consisting of: diabetes type I; Sjogren's syndrome; uveitis; celiac disease; allergic conjunctivitis; and non-specific colitis, arthritis, rheumatoid arthritis, an inflammatory bowel disease; psoriasis; multiple sclerosis; a neurodegenerative disorder; congestive heart failure; stroke; aortic valve stenosis; kidney failure; lupus; pancreatitis; allergy; fibrosis; anemia; atherosclerosis; a metabolic disease; a bone disease; a cardiovascular disease, a chemotherapy/radiation related complication; diabetes type II; a liver disease; a gastrointestinal disorder; an ophthalmological disease; diabetic retinopathy; a pulmonary disorder, a renal disease; dermatitis; HIV-related cachexia; cerebral malaria; ankylosing spondylitis; leprosy; anemia; and fibromyalgia.
31. The method, composition or use according to any one of claims 1 to 29 wherein the disease, disorder or condition is a disease, disorder or condition of the lung, for example a disease, disorder or condition that is (a) associated with or caused by an immune response; (b) an interstitial lung disease; (c) an obstructive lung disease; (d) an acute lung injury; or (e) a lung injury caused by a neoplastic or paraneoplastic disease, pneumonia, or cystic fibrosis.
32. The method, composition or use according to any one of claims 1 to 29 wherein the disease, disorder or condition is:
- a) a disease, disorder or condition associated with or caused by an immune response is an autoimmune disease, or a graft-versus-host disease;
 - b) an autoimmune disease selected from rheumatoid arthritis, scleroderma, inflammatory bowel disease, or systemic lupus erythematosus;
 - c) an interstitial lung disease such as interstitial pulmonary fibrosis;
 - d) an obstructive lung disease selected from asthma, bronchitis, acute respiratory distress syndrome or chronic obstructive pulmonary disease;
 - e) an acute lung injury selected from one or more of physical trauma, a chemical injury such as a chemical burn, smoke inhalation, or exposure to a toxic substance.

33. The method, composition or use according to any one of claims 1 to 29
wherein the disease, disorder or condition is one or more of a fibrotic disease
of the lung, acute respiratory distress syndrome (ARDS), COVID-19, chronic
obstructive pulmonary disease (COPD), emphysema, asthma, a viral or
5 bacterial infection of the lung, pneumonia (including chemically-induced
pneumonia), or cystic fibrosis.

34. The method, composition or use according to any one of claims 1 to 29 for
treating, preventing or ameliorating a viral disease and/or for inhibiting virus
activation, in which said virus is selected from the group consisting of herpes
10 virus, such as cytomegalovirus (CMV); influenza virus, such as H1N1, H3N2,
H5N1 or H5N7 virus; paramixovirus, such as measles; respiratory syncytial
virus; coronaviruses, such as SARS or SARS-CoV-2 (Covid-19); HIV Virus;
hepatitis virus; or rotavirus.

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