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Methodology for testing the efficacy of functional botanical ingredients for support of stem cell surveillance and mitochondrial resilience. A preliminary randomized, double-blind, placebo-controlled, acute clinical proof-of-concept trial

Gitte S. Jensen [1]*, Krista Sanchez [1], Dina Cruickshank [2], and Christine Fields [3]

[1]NIS Labs, 1437 Esplanade, Klamath Falls, Oregon 97601, USA; [2]NIS Labs, 807 St. George St., Port Dover, ON N0A 1N0, Canada; [3]Applied Food Sciences, Inc., 675-B Town Creek Road, Kerrville, Texas 78028, USA

***Corresponding author:** Dr. Gitte S. Jensen, Natural Products Research Department, NIS Labs, 1437 Esplanade, Klamath Falls, Oregon 97601 USA

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ABSTRACT

Background: Natural compounds are increasingly recognized for their ability to support regenerative health and counteract age-related decline through modulation of stem cell activity and mitochondrial function.

Objective: This clinical proof-of-concept study evaluated the acute effects of four functional ingredients – Ginseng extract (from *Panax ginseng*), Olive extract (from *Olea europaea*), Chaga mushroom extract (from *Inonotus Obliquus*), and potassium hydrogen glucarate – using methods to document rapid changes in stem cells numbers and mitochondrial resilience in healthy adults.

Methods: Using a randomized, double-blind, placebo-controlled, cross-over design, four healthy participants were enrolled following IRB-approved informed consent and consumed each ingredient or placebo on five separate days at least one week apart. Each participant was scheduled at the same time of the morning for all visits to minimize circadian influences. Results from the visit where placebo was consumed allowed data collection on that person's normal circadian changes at that time, so this could be accounted for in the data analysis. Blood samples were collected at baseline, 1, 2, and 3 hours post-consumption. Stem cell numbers were quantified by flow cytometry. Mitochondrial volume and

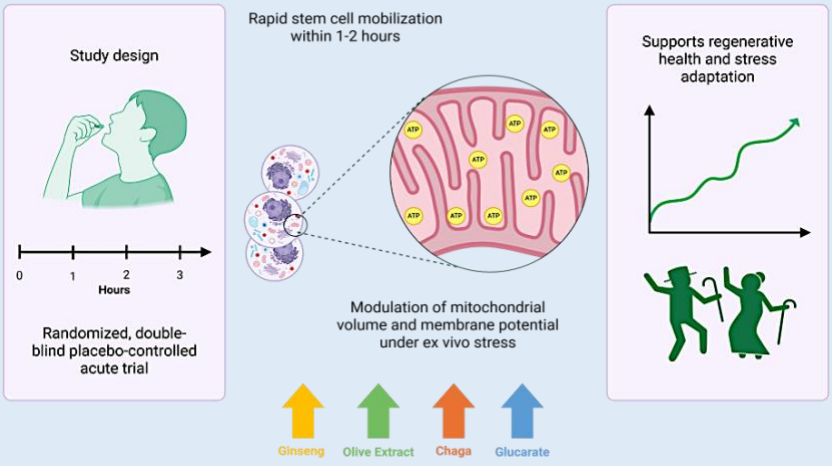
membrane potential were assessed ex vivo under oxidative and inflammatory stress using reporter dyes and flow cytometry.

Results: All ingredients induced rapid, ingredient-specific mobilization of distinct stem cell types, with Chaga extract and Olive extract demonstrated robust effects across multiple stem cell types. All functional ingredients increased circulating pluripotential stem cells at 1 hour by at least 10% above levels observed after placebo consumption. Chaga intake resulted in an average 36% increase in endothelial stem cells compared to placebo. All ingredients modulated stress-induced changes in mitochondrial volume and membrane potential, with Ginseng extract and Olive extract showing particularly pronounced effects on mitochondrial adaptability.

Novelty of the Study: This proof-of-concept clinical study presents novel evidence of acute biological effects following consumption of functional food extracts, with measureable changes in stem cell surveillance and mitochondrial stress responses observed as early as 1 hour after a single dose compared to placebo.

Conclusion: These preliminary findings demonstrate rapid bioactivity of the tested functional ingredients in modulating regenerative and stress-response pathways, supporting their potential as early-phase interventions for promoting cellular resilience. The results further support the use of assessing mitochondrial resilience ex vivo as part of clinical evaluation of acute effects of functional ingredients.

Keywords: Cellular resilience; Chaga mushroom; flow cytometry; mitochondrial volume; mito-chondrial membrane potential, olive extract; oxidative stress; Panax ginseng; polyphenols; pluripotential; potassium glucarate; progenitor; stem cell mobilization; stress response.



Graphical Abstract: Methodology for testing the efficacy of functional botanical ingredients for support of stem cell surveillance and mitochondrial resilience. A preliminary randomized, double-blind, placebo-controlled, acute clinical proof-of-concept trial

INTRODUCTION

The search for effective strategies to preserve cellular health and delay age-related decline has renewed scientific interest in the biological roles of stem cells and mitochondria. Stem cells function as the body's intrinsic repair system, capable of differentiating into multiple cell types and replenishing damaged tissues, while their ongoing trafficking through the body is essential for sustaining homeostasis [1]. Mitochondria, the central intracellular organelles responsible for energy production, are equally critical for cellular resilience and adaptation to physiological stress [2-3]. Impairments in stem cell function and mitochondrial integrity are closely associated with reduced regenerative capacity and increased susceptibility to disease with aging[3-6], making these processes important targets for interventions aimed at supporting longevity and vitality.

Stem cells are undifferentiated cells with the capacity to develop into specialized cell types. They serve as the body's internal repair system, replenishing tissues and maintaining homeostasis throughout life [7], and loss of this heterogeneity is linked to aging [4]. Stem cell reservoirs reside in bone marrow, adipose tissue, and other specialized niches, and undergo circadian cycles of mobilization into the circulation followed by homing into new tissue niches, a process referred to as stem cell surveillance. Circulating stem cells express chemokine receptors that allow them to respond to signals from tissues in need of repair [8,9]. This tightly regulated process is under circadian control, which becomes disrupted with aging [10-11]. In addition, hematopoietic stem cells continuously traffic to disseminate new stem cells to all anatomical areas of bone marrow to maintain healthy blood cell production in all bone marrow niches, a process under a tight circadian cycle [12-14]. The study of nutraceutical enhancement of this natural process necessitates a strictly controlled timing of blood draws when placebo versus active products is consumed.

Mitochondria are energy-producing intracellular organelles found in all eucaryotic species and are believed to have originated from an ancient endosymbiotic event involving an alpha-proteobacterium from the SAR11 clade—closely related to Rickettsiales—and a host cell, marking a pivotal moment in the evolution of eukaryotic life [15,16]. As a result of this evolutionary event, mitochondria retained key components of their original genome, which encodes essential parts of the electron transport chain, as well as the rNAs and tRNAs required for mitochondrial translation. However, most mitochondrial proteins are encoded by nuclear genes, and this necessitates a tightly coordinated expression between the nuclear and mitochondrial genomes during mitochondrial biogenesis [17-18].

The biology of stem cells and mitochondria–including stem cell surveillance and mitochondrial function–can be affected long-term by bioactive compounds, defined as non-nutrient compounds naturally present in foods and novel sources with health-promoting properties [19], as well as signals from prebiotics, probiotics, and the gut microbiome including prebiotics and synbiotics [20]. This study investigated the acute effects of four specific functional ingredients, well-known for their long-term health benefits: *Panax ginseng* extract, olive extract from *Olea europaea*, Chaga mushroom extract from *Inonotus obliquus*, and potassium hydrogen glucarate.

P. ginseng is widely associated with longevity in both traditional medicine and modern scientific research. It is known to boost immunity [21], regulate inflammation [22], and improve overall energy and vitality. Modern science also indicates that *P. ginseng's* benefits extend to broad anti-aging effects [23-25], including effects on stem cell biology [26-27], in part through the ability to support hematopoiesis, particularly under stress conditions [28]. These documented health benefits of *P. ginseng* are attributed to a diverse array of bioactive compounds, with the ginsenosides serving as the primary pharmacologically active components [29]. Specific ginsenosides have been shown to regulate the proliferation, migration, and anti-senescence of hematopoietic stem cells and their progenitors [26,27]. Also, ginsenosides help protect the stem cell microenvironment by mitigating oxidative stress and

inflammation, which are crucial for maintaining stem cell health and preventing their functional decline [30]. Ginseng-derived compounds showed support of stem cell migration into hearts during repair after infarction, associated with accelerated repair [31]. Extracts from *P. ginseng* were shown to support mitochondrial biogenesis [32,33], and promote mitochondrial transfer from healthy cells to damaged cells [34]. The product studied here, PurGinseng, is standardized to 8% ginsenosides to promote mitochondrial activity.

Extra-virgin olive oil is rich in polyphenols, including the secoiridoid polyphenols oleocanthal and oleacein, which exhibit strong antioxidant and anti-inflammatory properties [35]. These polyphenols can modulate cellular signaling, reduce oxidative stress, and directly influence cellular pathways of aging [36], and were found to activate cellular stress responses that favor longevity and anti-aging functions [37-39], including neuroprotective effects [40]. The olive extract studied here, Oligen, is standardized to 5% oleocanthal and oleacein.

The Chaga mushroom grows on birch trees in cold climates across Northern Eurasia and has been consumed for centuries in Eastern Europe, Russia, and Asia as a longevity tonic, traditionally prepared as a tea [41-42]. Its bioactive profile includes compounds absorbed from its host tree as well as metabolites produved through its own biology [43]. Chaga contains high levels of antioxidants, including melanin and triterpenoids, such as inotodiol and betulinic acids, is among the most potent known in medicinal mushrooms [44,45] and may be linked to the support of DNA repair and delay of cellular senescence [46]. The anti-inflammatory effects of Chaga's constituents translate to antiviral, anti-diabetic [47,48] neuroprotective [49,50] and hepatoprotective [51] effects, as well as a general support of energy and metabolic functions during physical activity [52]. The Chaga extract studied here, MycoThrive Chaga, is standardized to 1.7% inotodiol.

Glucarate compounds, including potassium hydrogen glucarate, are derivatives of D-glucaric acid known for their role in enhancing cellular detoxification via the glucuronidation pathway [53], a major Phase II detoxification process in the liver and other tissues. Emerging evidence suggests that these compounds exert beneficial effects on mitochondrial integrity and stem cell function, particularly through modulation of oxidative stress and inflammatory signaling [54,55]. These effects may be particularly relevant in regenerative medicine and aging-related tissue repair, where mitochondrial dysfunction and impaired stem cell renewal are common [3-6,56].

The objective of the clinical proof-of-concept trial reported here was to compare the immediate biological effects of consuming ingredients associated with long-term rejuvenating effects in healthy adults, using an established randomized, double-blinded placebo-controlled cross-over study design for evaluating acute effects of nutraceutical products, in which each participant served as their own control [57-61]. The timing of clinic visits aimed to control for each participant's circadian cycle [62 - Martirosyan and Stratton 2023], since this affects both stem cell surveillance [12] and mitochondrial status [63-65]. The study focused on rapid changes to stem cell numbers in the blood circulation and also explored a novel methodological approach for documenting rapid changes to mitochondrial function using ex vivo testing of mitochondrial resilience under oxidative versus inflamed stress, adapting methods from a previous long-term clinical study [66] into documentation of acute effects after consuming a single dose of each nutraceutical ingredient. To our knowledge, the results reported here are the first to document acute effects in humans, of consuming these four nutraceutical ingredients, on specific types of stem cells in the blood circulation as well as on a rapid support of the mitochondrial stress-response.

METHODS

Study design: A randomized, double-blind, placebo-controlled, cross-over study design was used for this clinical proof-of-concept study (clinical trial registration NCT07127705). The study was conducted in accordance with the Declaration of Helsinki and approved by

Elemental Independent Review Board, Las Vegas, NV, USA (study protocol 186-006). The study was carried out at NIS Labs, Klamath Falls, Oregon, USA. The study design and in/exclusion profile were similar to previously published trials [57-61]. Since this was an initial preliminary pilot study, no effect sizes were available on which to base power calculations, so the population size was set to four participants, with the goal of documenting similar directional effects in at least 3 participants (75%), allowing for generation of effect sizes for future power calculations. Accordingly, and consistent with a previous pilot study on immune surveillance [61], four participants were enrolled in the study (Table 1) after providing written informed consent and meeting eligibility requirements.

Subjects: Screening included an interview to document age, body mass index (BMI), medical/surgical history, diet and lifestyle, current health status, medication, and use of nutritional supplements. The following inclusion criteria were applied: healthy adult people of either gender, age 18-75 years (inclusive), body mass index (BMI) between 18.0 and 34.9 kg/m^2 (inclusive), veins easily accessible for the multiple blood draws, and willing to comply with the study requirements: maintaining a consistent diet and lifestyle routine throughout the study, bland breakfasts on mornings of clinic visits, abstaining from exercising and nutritional supplements on the morning of a study visit, abstaining from use of coffee, tea, soft drinks, and nicotine for at least one hour prior to a clinic visit, and refraining from music, candy, gum, computer/cell phone use with internet access (airplane mode allowed), during clinic visits.

The following exclusion criteria were used: Previous major gastrointestinal surgery; taking anti-inflammatory medications on a daily basis; currently experiencing intense stressful events/ life changes; currently in intensive athletic training; cancer during past 12 months; chemotherapy during past 12 months; currently treated with immune-suppressant medication; diagnosed with autoimmune disorder; donation of blood during the study or within the 4 weeks prior to study start; received a cortisone injection within the past 12 weeks; immunization during the past 4 weeks; currently taking anti-psychotic, hypnotic, or anti-depressant prescription medication; ongoing acute infections; participation in another clinical trial study during this trial; an unusual sleep routine; unwilling to maintain a constant intake of supplements over the duration of the study; anxiety about having blood drawn; pregnant, nursing, or trying to become pregnant; known allergies related to ingredients in the active test products or placebo. Following this set of in/exclusion criteria, specifically pertaining to good health, good sleep, and low stress has not revealed gender or age-related stratification regarding immune-related outcomes [57-60]. Twenty-one people were assessed for eligibility (Figure 1).

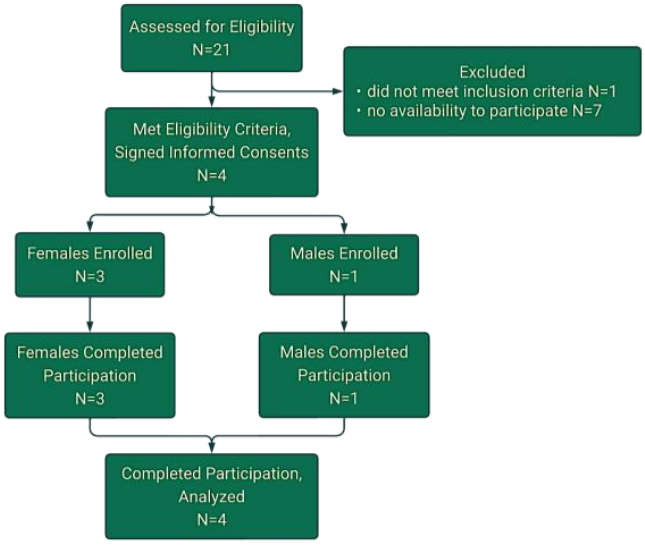


Figure 1. CONSORT flow chart showing the number of people screened, enrolled, and analyzed.

Table 1. Demographics of the study population.

Gender	Participant #	N	Age average[1]	Age range	BMI average[1]	BMI range
Females	1, 3, 4	3	59.7 ± 16.4	41.2 - 72.3	29 ± 4.6	23.7 - 31.7
Males	2	1	32	32	22	22

[1] The average ± standard deviation is shown when N is greater than 1.

The four people who met the inclusion and exclusion criteria were enrolled and scheduled for clinic visits where they consumed the active products and placebo on different clinic visits in randomized order, with at least one week wash-out period between visits (Figure 2).

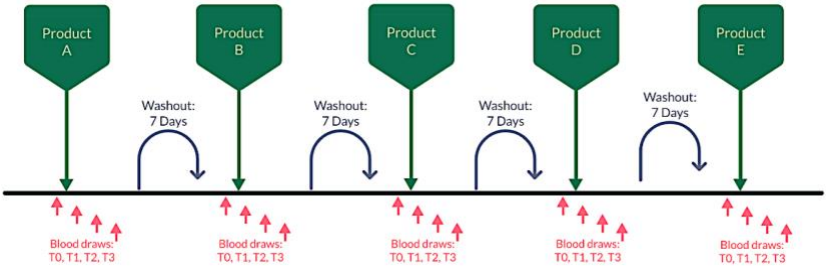


Figure 2. Diagram showing the timing and study procedures of the acute study reported here. The study involved five clinic visits, at least one week apart, where participants consumed one of the five products listed in Table 2, in blinded, randomized order.

Intervention: Visits were scheduled at the same time of the day during morning hours to minimize the effect of circadian fluctuations [10-14,63-,65,67-68]. Participants were asked to follow a similar routine in the morning of all clinic visits, including a bland breakfast if they normally have breakfast, to avoid stress due to fasting. Four clinic visits involved consuming an active test product and a fifth clinic visit involved consuming placebo. The placebo visit served as a within-subject control for circadian variation in stem cell surveillance and mitochondrial metabolic state at that time of day. Because exercise [69] and stress [70–72] can influence leukocyte release and homing, the study environment was managed to minimize physical and mental stress during each visit. Participants were instructed to remain calm and inactive for 4 hours, comfortably seated in a chair. After the first hour, the baseline blood sample was drawn. Immediately after the baseline blood draw, an encapsulated test product was provided with water and consumed in the presence of clinic staff. Blood samples were drawn at 1, 2, and 3 hours after consumption, where 6 mL of blood was drawn into heparinized vacutainer tubes. A portion of heparinized whole blood was used for subsequent immunostaining for stem cell enumeration, and the remaining blood was used for isolation of peripheral blood mononuclear and polymorphonuclear cells for the ex vivo testing of mitochondrial resilience.

Reagents: Heparin vacutainer tubes, serum separator tubes, butterfly needles, were obtained from Becton-Dickinson (Franklin Lakes, NJ, USA). The monoclonal antibodies CD31-Fluorescein isothiocyanate (FITC) (clone WM59), CD34-Peridinin-Chlorophyll-Protein (PerCP) (clone 8G12), CD45-Brilliant Violet 510 (BV510) (clone H130), CD90-SuperBright436 (SB436) (clone 5E10), CD309-Phycoerythrin (PE) (clone 89106), the two mitochondrial fluorescent dyes MitoTracker Green and the JC-1 Mito Probe; flow cytometer performance tracking beads, wash and shutdown solutions, de-bubble buffer, and Cal-Lyse™; Phosphate-Buffered Saline (PBS),

Roswell Park Memorial Institute (RPMI) 1640, Fetal Calf Serum and Penicillin Streptomycin were purchased from Thermo Fisher Scientific (Waltham, MA, USA).

Consumable Test Products: Four active test products were tested against placebo (Table 2), where the serving size was 2 capsules. The doses and percentages of bioactive compounds are listed in Table 2 below and were based on clinical dosage recommendations based on Good Clinical Practice (GCP) and established botanical safety guidelines (e.g., Botanical Safety Consortium). The placebo consisted of encapsulated white rice flour, matched in appearance to the active products. The choice of white rice flour for the placebo is due to its common use in foods, and low allergenicity. The dose of 1 gram white rice flour contains only trace amounts of rice-derived glucosylceramides known to modulate the innate immune system over 8 weeks' daily consumption [73].

Table 2. Nutraceutical ingredients compared in this clinical trial.

Name	Active(s)	Dose (mg)*
Panax ginseng extract (PurGinsengTM)	8% ginsenosides	150 mg
Olea europaea olive extract (Oligen®)	5% Oleocanthal/Oleacein	400 mg
Inonotus obliquus Chaga extract (MycoThriveTM Chaga)	1.7% Inotodiol	1000 mg
Potassium(K) hydrogen glucarate (CelluThriveTM PHG)	84% glucarate/15% K	500 mg
Placebo (white rice flour)		1000 mg

*The serving size of all active test products and placebo were provided in two capsules.

Stem Cell Evaluation by Flow Cytometry: Triplicate 100 µL samples of heparinized whole blood from each time point were stained using a five-color immunostaining panel consisting of CD31-FITC, CD34-PerCP, CD45-BV510, CD90-SB436, and CD309-PE. Staining followed the manufacturer's recommended protocol for whole blood (Thermo Fisher Scientific, Waltham, MA, USA), using a "no-wash" procedure. This involved fixation of white blood cells and lysis of red blood cells using Cal-Lyse® Lysing Solution. Samples of 100 µL whole blood were incubated with the antibody cocktail for at least 15 minutes at room temperature in the dark. Subsequently, 100 µL of Cal-Lyse® solution was added, and samples were incubated for 10 minutes at room temperature. Red blood cells were then lysed by adding 1 mL of deionized water, followed by a further 10-minute incubation in the dark. Samples were stored at 4°C in the dark overnight to allow white blood cells to settle. Prior to acquisition by flow cytometry, 1.1 mL supernatant was aspired from each sample to remove cellular debris, and 1 mL PBS was added. The total dilution factor of the whole blood sample was 11.355, and this factor was used to adjust the cell numbers per volume of sample from the Attune flow cytometry software to provide the actual number of stem cells per mL whole blood. Flow cytometric analysis was performed using an acoustic aligning Attune™ NxT flow cytometer (Thermo Fisher Scientific, Waltham, MA, USA) equipped with an autosampler. For each triplicate sample, 800 µL was analyzed, which provided analysis of 300,000 to 600,000 events per sample. Stem cell populations (Table 3) were identified within the CD45dimCD34$^+$ classical stem cell population and further subdivided into CD34$^+$CD309$^+$ pluripotential stem cells and CD34$^+$CD309$^-$ progenitor cells. Mesenchymal stem cells were CD45$^-$ CD90$^+$ lymphocytes. Endothelial stem cells were identified as CD45$^-$ CD34$^-$ lymphocytes, brightly positive for CD31. Data analysis was conducted using Attune software, which reports cell counts per microliter of sample. This was adjusted for the dilution factor introduced during staining, and results were expressed as stem cell counts per milliliter of whole blood.

Table 3. Types of stem cells included in analysis.

Phenotype	Indicative of
CD45dim $CD31^{-}CD34^{+}CD309^{+}$ lymphocytes	Pluripotential stem cells
CD45dim $CD31^{-}CD34^{+}CD309^{-}$ lymphocytes	Progenitor stem cells
CD45very dim $CD31^{++}CD34^{-}$ lymphocytes	Endothelial stem cells
$CD45^{-}CD90^{+}$ peripheral blood lymphocytes	Mesenchymal stem cells[1]

[1]The phenotype is suggestive of mesenchymal stem cells, especially in light of also being CD34-. The five-color panel used for this study did not include CD73 or CD105, other markers that help conclusively identify the mesenchymal stem cell type [74-75]. For that reason, in this paper we will refer to this cell type as $CD45^{-}CD90^{+}$ lymphocytes.

Testing for Mitochondrial Resilience Against Oxidative and Inflammatory Stress: To assess mitochondrial function and resilience, peripheral blood samples were collected from study participants at baseline and at 1, 2, and 3 hours post-consumption. The methodology was adapted from a previously published protocol on long-term effects in a fatigued population [66] to enable documentation of acute effects in healthy participants. White blood cells (leukocytes) were isolated from heparinized whole blood using Lympholyte-Poly density gradient centrifugation, after which the peripheral blood mononuclear cells (PBMC) and polymorphonuclear cells (PMN) were harvested and pooled. The cells were washed twice in PBS, counted and adjusted to 1 million cells/mL. The cells were plated onto 96-well V-bottom microtiter plates, with 200 µL cell suspension per well. The cells were subjected to three distinct culture conditions to simulate normal physiological versus stressed tissue compartments: 1) Control (un-stressed) conditions, 2) Oxidative stress, induced by exposure to hydrogen peroxide (H_2O_2 200 µM), and 3) Inflammatory stress, induced by exposure to the bacterial lipopolysaccharide (LPS 5 µg/mL). The cultures for testing mitochondrial membrane potential were incubated for 1 hour, and the cultures for testing mitochondrial volume per cell were incubated for 2 hours.

After incubation, cells were washed in PBS to remove the stressors and were stained with two fluorescent dyes to evaluate mitochondrial parameters: 1) Mito-Tracker Green FM to quantify mitochondrial volume per cell. This dye accumulates in mitochondria regardless of membrane potential and provides a relative measure of mitochondrial volume per cell. 2) JC-1 dye to assess mitochondrial membrane potential. JC-1 exhibits potential-dependent accumulation in mitochondria, shifting from green fluorescence (monomeric form) at low membrane potential to orange fluorescence (aggregated form) in areas of the mitochondrial membrane that have a high membrane potential.

Flow cytometry was performed using an Attune® Nxt acoustic focusing cytometer (Thermo Fisher Scientific, Waltham, MA, USA). Forward scatter (FSC-A) and side scatter (SSC-A) parameters were used to electronically gate and analyze three major leukocyte populations: lymphocytes, monocytes, and PMN cells. Fluorescence intensity was measured for each cell type to determine mitochondrial volume per cell, based on MitoTracker fluorescence intensity, and mitochondrial membrane potential, based on the JC-1 orange fluorescence intensity in live cells, as indicated by the FSC/SSC properties and bright green fluorescence. This approach enabled within subject comparison of mitochondrial parameters across different stress conditions and time points, providing a relative measure of mitochondrial resilience.

Use of GenAI: Microsoft M365 Copilot was used to assist in generating summaries of selected literature during the initial drafting of the Introduction section. These summaries were critically reviewed and revised by the authors to ensure accuracy and relevance. The authors

take full responsibility for the final version. The authors confirm that all scientific content is original and authored by them.

Data analysis: Biomarker changes following consumption of the active products were evaluated in the context of each participant's circadian variation observed on the day where placebo was consumed. Data were analyzed using Microsoft® Excel® for Microsoft 365 (Microsoft Corporation, Redmond, WA, USA, version 2507). Changes from baseline to post-consumption time points were calculated using simple arithmetic calculations of the arithmetic mean ± standard error of the mean to summarize the data for changes after consuming an active test product compared to changes after consuming placebo. The difference in the change was calculated by subtracting the changes after consuming placebo to changes after consuming an active test product, to analyze for the difference introduced by an active test product on the background of each participant's normal circadian changes (Figure 3). Given the small sample size (n = 4), the dataset was not suitable for advanced statistical modeling, assumptions of normality, or multiparameter analyses. Within-subject comparisons of changes from baseline between active and placebo conditions were performed using two-tailed paired t-tests. Statistical significance was defined as $P < 0.05$, with high significance defined as $P < 0.01$.

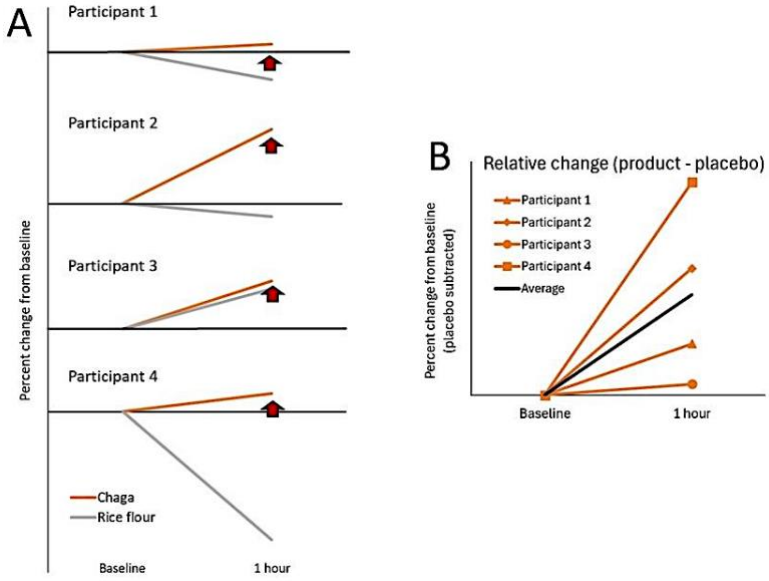


Figure 3. Analysis principles for calculating the difference in the change after consuming an active product versus the normal circadian changes captured on the clinic visit where placebo was consumed. A. The percent changes from baseline to 1 hour were calculated for the active product Chaga and for placebo (grey lines) for each participant. The circadian changes over this time of the morning showed decreases in Participants 1, 2, and 4, in contrast to an increase for Participant 3. However, the relative difference was an increase for all 4 participants (red arrows). B. The difference in percent change after consuming an active product compared to placebo was calculated by subtracting the change after consuming placebo. The average of those differences across all participants was calculated (black line).

RESULTS

Stem cell surveillance: Consuming each of the four nutraceutical ingredients rapidly affected stem cell numbers in the blood circulation (Figure 4 and Figure 5). The normal circadian changes during the morning hours on average showed a gradual reduction to the numbers of CD45dim $CD34^+$ stem cells. Relative to that gradual change, all four ingredients rapidly supported increased numbers of circulating CD45dim $CD34^+CD309^+$ pluripotential stem cells at 1 hour (Figure 4A and 4B). The increase from baseline was statistically significant after 1 hour for Ginseng extract and olive extract (Figure 4A).

When the changes were evaluated after subtracting the changes after consuming placebo, the increased levels of CD45dim $CD34^+CD309^+$ stem cells reached a statistical trend for Olive extract, statistical significance for Ginseng extract, and a high level of significance for Chaga extract. This increase was transitory, and after 3 hours the CD45dim $CD34^+CD309^+$ stem cell levels were comparable to the levels after consuming placebo. There was also an increase in the numbers of CD45dim $CD34^+CD309^-$ progenitor stem cells after consuming Ginseng extract (Figure 4C and 4D), reaching significance at 2 hours (Figure 4C), and when changes after consuming placebo were subtracted, the increase at 2 hours reached a high level of significance (Figure 4D). In contrast, Chaga consumption triggered a gradual decrease in the numbers of progenitor cells when compared to placebo, reaching statistical significance at 3 hours, suggesting increased homing (Figure 4C and 4D).

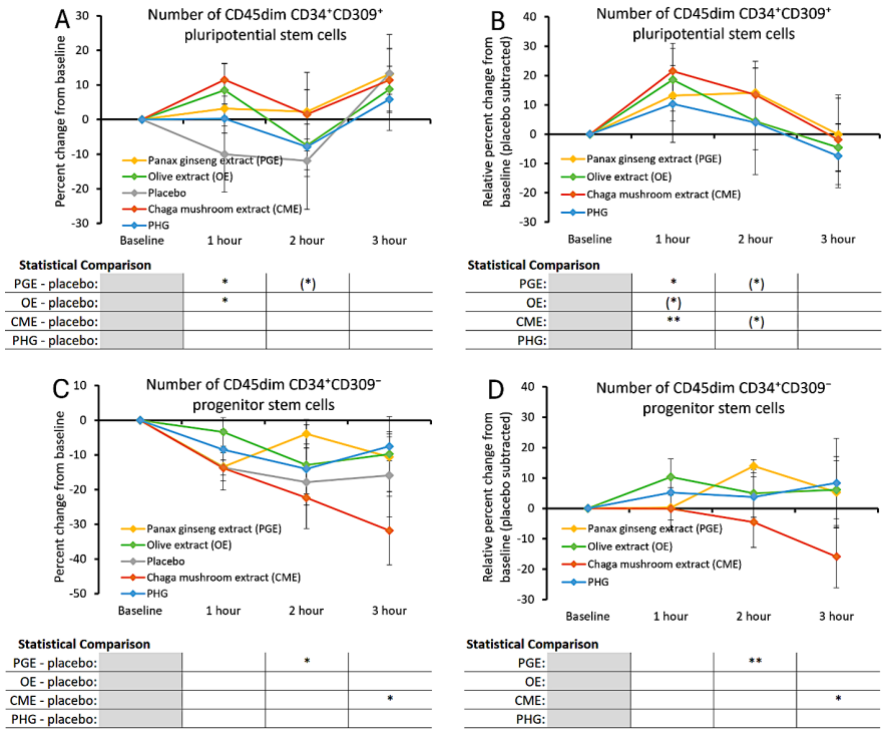


Figure 4. Changes to stem cell numbers within 3 hours after consuming a nutraceutical ingredient when compared to changes after consuming placebo. A. The percent change in the numbers of CD45dim $CD34^+CD309^+$ pluripotential stem cells when compared to baseline is shown for all four ingredients and for placebo. B. The relative percent change in the numbers of CD45dim $CD34^+CD309^+$ pluripotential stem cells when compared to baseline numbers after subtracting the changes after consuming placebo. C. The percent change in the numbers of CD45dim $CD34^+CD309^-$ pluripotential stem cells when compared to baseline is shown for all four ingredients and for placebo. D. The relative percent change in the numbers of CD45dim $CD34^+CD309^-$ pluripotential stem cells when compared to baseline numbers after subtracting the changes after consuming placebo. In A and C, the results are shown as the group averages ± standard error of the mean of the individual percent changes from baseline after consuming a product or placebo. In B and D, the results are shown as the group averages ± standard error of the mean of the individual percent changes from baseline after consuming a product where changes after consuming placebo are subtracted. The arithmetic averages and standard errors of the means are shown. Levels of statistical significance are shown where changes from baseline to a later time point are indicated by asterisks, where $p<0.10$: (*), $p<0.05$: * and $p<0.01$: **.

The numbers of $CD45^-$ $CD90^+$ lymphocytes, suggestive of a mesenchymal stem cell phenotype, increased at one hour after consuming potassium hydrogen glucarate (PHG) (Figure 5A and 5B), where the increase after subtracting the changes after consuming placebo reached statistical significance (Figure 5B). For Olive extract, a similar increase at 1 hour reached a statistical trend and was followed by a statistically

significant decrease at 3 hours, suggesting increased homing. The consumption of Chaga extract was associated with robustly increased numbers of $CD45^{-}CD90^{+}$ lymphocytes, reaching significance at 1 hour after subtracting changes after consuming placebo (Figure 5B), and continuing to increase, but due to individual variations in the participants' responses the strong 2-hour increase did not reach statistical significance, but showed a statistical trend (Figure 5B).

The numbers of $CD31^{++}CD34^{-}$ endothelial stem cells were increased by Chaga extract and PHG at 1 hour above the levels seen after consuming placebo (Figures 5C), reaching a statistical trend for olive extract after subtracting the changes after consuming placebo (Figure 5D). For Chaga extract, this increase was even more robust at 2 hours, reaching statistical significance when compared to changes after consuming placebo (Figure 5C) as well as after subtracting the changes after consuming placebo (Figure 5D). In contrast, at the 2-and 3-hour timepoints, there were reduced levels of $CD31^{++}CD34^{-}$ endothelial stem cells after consuming Olive extract and PHG, reaching statistical trends for olive extract at both 2 and 3 hours after consumption, after subtracting changes seen after consuming placebo (Figure 5D).

Consuming Ginseng extract did not affect the numbers of $CD45^{-}CD90^{+}$ lymphocytes or $CD31^{++}CD34^{-}$ endothelial stem cells when compared to placebo (Figure 5D).

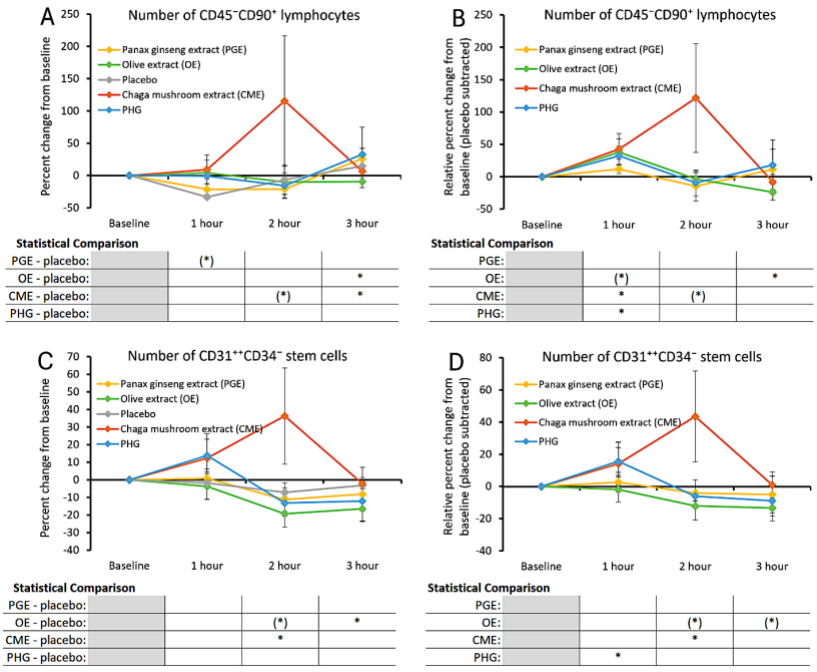


Figure 5. Changes to stem cell numbers within 3 hours after consuming a nutraceutical ingredient when compared to changes after consuming placebo. A. The percent change in the numbers of $CD45^{-}CD90^{+}$ lymphocytes when compared to baseline is shown for all four ingredients and for placebo. B. The relative percent change in the numbers of $CD45^{-}CD90^{+}$ lymphocytes when compared to baseline numbers after subtracting the changes after consuming placebo. C. The percent change in the numbers of $CD31^{++}CD34^{-}$ stem cells when compared to baseline is shown for all four ingredients and for placebo. D. The relative percent change in the numbers of $CD31^{++}CD34^{-}$ stem cells when compared to baseline numbers after subtracting the changes after consuming placebo. In A and C, the results are shown as the group averages ± standard error of the mean of the individual percent changes from baseline after consuming a product or placebo. In B and D, the results are shown as the group averages ± standard error of the mean of the individual percent changes from baseline after consuming a product where changes after consuming placebo are subtracted. The arithmetic averages and standard errors of the means are shown. Levels of statistical significance are shown where changes from baseline to a later time point are indicated by asterisks, where $p<0.10$: (*), $p<0.05$: * and $p<0.01$: **.

Mitochondrial responses to oxidative and inflamed stress: For the ex vivo challenges used for this study, the two stressors clearly affected mitochondrial volume and membrane potential in different ways (Figure 6). Relative changes to mitochondrial volume were assessed using the fluorescent reporter dye MitoTracker Green where the mean fluorescence intensities measured by flow cytometry are proportional to the relative mitochondrial volume per cell. Under H_2O_2-mediated oxidative stress, the mitochondrial volume per cell showed a mild increase above that in untreated control cultures, reaching high levels of statistical significance for lymphocytes (Figure 4A) and monocytes (Figure 4C), and a statistical trend for neutrophils (Figure 4E). This was in contrast to LPS-mediated inflammatory stress which triggered mild reduction to the mitochondrial volume, which was insignificant in lymphocytes (Figure 4A) and monocytes (Figure 4C), and reached a statistical trend for neutrophils (Figure 4E).

At the same time, changes to mitochondrial membrane potentials were documented using the fluorescent reporter dye JC-1 which forms J-aggregates in areas where the mitochondrial membrane potential is high, causing a shift from green to orange fluorescence. The stressor-induced changes to the mitochondrial membrane potential showed mild decreases for cells exposed to both H_2O_2- and LPS-induced stress for all three cell types, reaching high levels of significance for all treatments and cell types (Figure 4B, 4D, 4F), except for the H_2O_2-induced changes to monocytes that reached a statistical trend (Figure 4D).

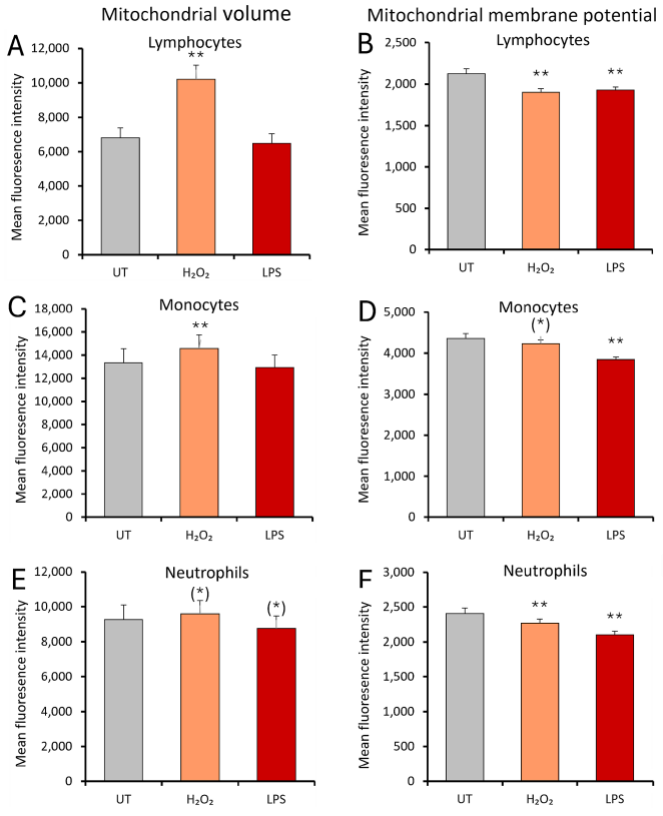


Figure 6. Mitochondrial responses to H_2O_2-induced oxidative stress (orange bars) and LPS-induced inflammatory stress (red bars), compared to untreated control cultures (grey bars). A. C. E. The relative mitochondrial volume per cell, as a function of the green fluorescence intensity of the MitoTracker dye, is shown for untreated cells, H_2O_2-treated cells, and LPS-treated cells, for lymphocytes, monocytes, and neutrophils. B. D. F. The relative mitochondrial membrane potential, as a function of the relative orange fluorescence intensity of the reporter dye JC-1. The arithmetic averages and standard errors of the means are shown. The levels of statistical significance for changes from baseline to a later time point are indicated by asterisks, where $p<0.10$: (*), $p<0.05$: * and $p<0.01$: **.

Nutraceutical modulation of the mitochondrial volume in response to stress: The four nutraceutical ingredients altered the mitochondrial volumetric responses to oxidative stress ex vivo (Figure 7). The normal circadian changes during the morning hours, documented on the visit where placebo was consumed, on average showed a gradual reduction to the mitochondrial volume under conditions of oxidative stress for all three cell types: Lymphocytes, monocytes, and PMN cells. The three ingredients Olive extract, Chaga extract, and PHG did not show changes to the mitochondrial volume under oxidative stress compared to baseline (Figure 7A), however, when compared to the placebo day—where oxidative stress was associated with a gradual decline in mitochondrial volume—all three nutraceutical ingredients supported higher mitochondrial volumes in lymphocytes at 2 and 3 hours. These increases reached statistical significance for Chaga extract and a high level of statistical significance for Olive extract (Figure 7B). This changed over time, and at 2 and 3 hours after consuming Ginseng extract the oxidative stress-induced mitochondrial swelling was mildly enhanced, but not to the same extent as after consuming the other three nutraceutical ingredients. Similar but milder effects were seen in monocytes (Figure 7C and 7D) and neutrophils (Figure 7E and 7F), reaching statistical significance for olive extract at 2 and 3 hours for monocytes (Figure 7D).

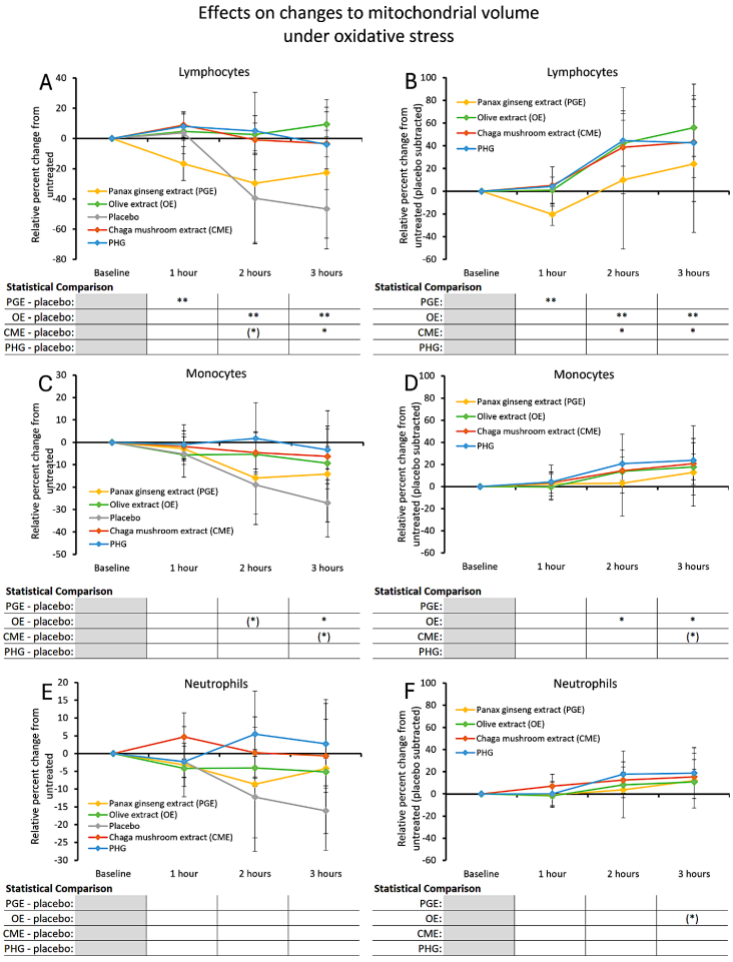


Figure 7. Effects on the mitochondrial volumetric responses to H_2O_2-induced oxidative stress after consuming nutraceutical ingredients when compared to changes after consuming placebo. The arithmetic averages and standard errors of the means are shown. In the tables below each chart the levels of statistical significance for changes from baseline to a later time point are indicated by asterisks, where $p<0.10$: (*), $p<0.05$: * and $p<0.01$: **.

In contrast to the changes to mitochondrial volumes under oxidative stress, consuming the four nutraceutical ingredients did not alter the mitochondrial responses to ex vivo inflammatory stress (Figure 8). The normal circadian changes during the morning hours, documented on the visit where placebo was consumed, on average showed a gradual reduction to the mitochondrial volume under inflammatory conditions for all three cell types: Lymphocytes, monocytes, and PMN cells. Relative to these normal circadian changes, mildly elevated mitochondrial volumes were seen after consuming the nutraceutical ingredients, especially for lymphocytes and monocytes after consuming Chaga, but the differences when compared to changes after consuming placebo did not reach or approach statistical significance, as can be seen by the complete lack of statistical indicators in the tables below Figures 8A-8F.

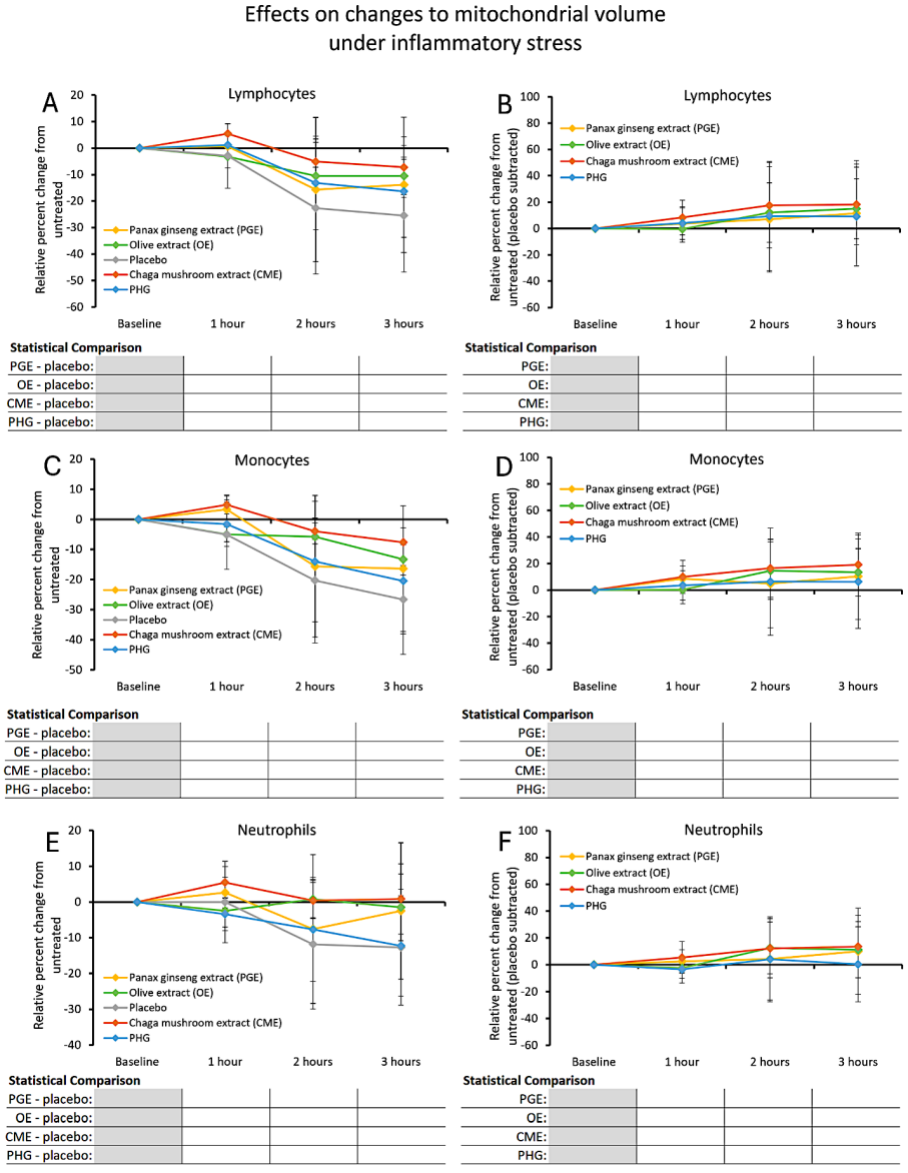


Figure 8. Effects on the mitochondrial volumetric responses to LPS-induced inflammatory stress after consuming nutraceutical ingredients when compared to changes after consuming placebo. The arithmetic averages and standard errors of the means are shown. In the tables below each chart the levels of statistical significance for changes from baseline to a later time point would have been indicated by asterisks, where $p<0.10$: (*), $p<0.05$: * and $p<0.01$: **, but none of the changes reached or approached statistical significance.

Nutraceutical modulation of the mitochondrial membrane potential in response to stress: The four nutraceutical ingredients altered the mitochondrial membrane potential in response to stress ex vivo (Figures 9, 10). The normal circadian changes during the morning hours, documented on the visit where placebo was consumed, on average showed a gradual increase in the mitochondrial membrane potential under conditions of oxidative stress for all three cell types: Lymphocytes, monocytes, and PMN cells. Relative to these normal circadian changes, mild changes to the mitochondrial membrane potential were seen after consuming the nutraceutical ingredients, All four ingredients further decreased oxidative stress-induced reduced membrane potential in lymphocytes (Figure 9A, 9B), with Ginseng extract's effect being the most robust, reaching a high level of significance at 1 and 2 hours, and remaining significant at 3 hours, after subtracting the changes after consuming placebo (Figure 9B). The reduction after consuming Olive extract and Chaga extract reached significance at 2 hours (Figure 9A, 9B), where PHG reached a statistical trend after subtracting the changes after consuming placebo (Figure 9B). Similar effects were seen in neutrophils where the reduced membrane potentials reached high levels of significance for Ginseng extract at 2 hours and olive extract and Chaga extract at 3 hours (Figure 9E, 9F). In contrast, the ex vivo oxidative stress-induced changes to mitochondrial membrane potential in monocytes were very minor, where a further reduction seen after consuming Chaga extract, after subtracting changes seen after consuming placebo, reached a statistical trend at 2 hours (Figure 9D).

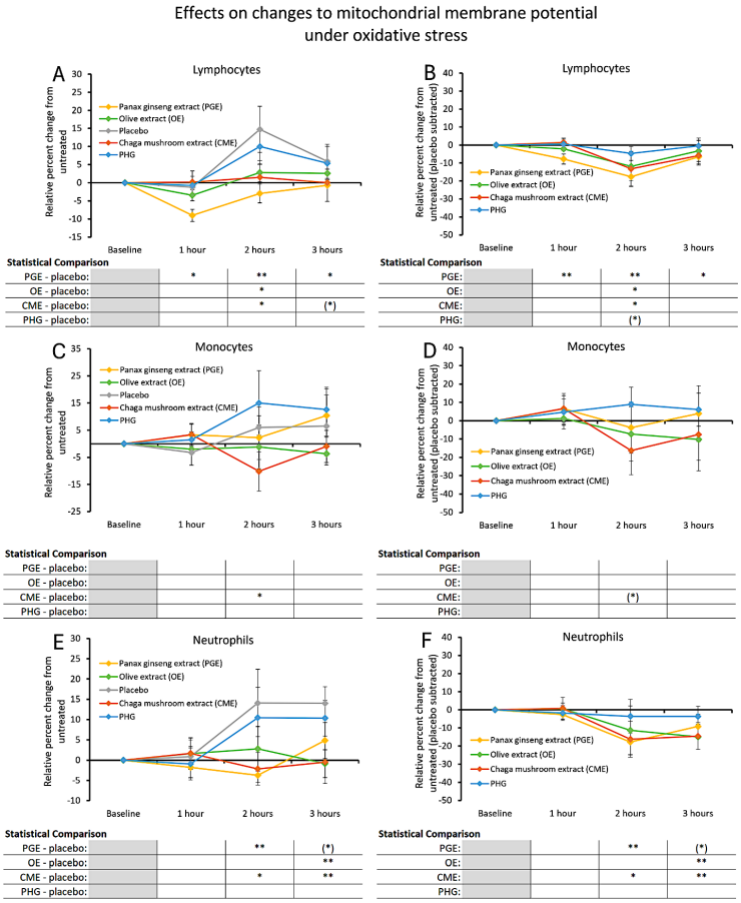


Figure 9. Effects on the mitochondrial membrane potential responses to H_2O_2-induced oxidative stress after consuming nutraceutical ingredients when compared to changes after consuming placebo. In the tables below each chart the levels of statistical significance for changes from baseline to a later time point are indicated by asterisks, where p<0.10: (*), p<0.05: * and p<0.01: **.

In context of ex vivo inflammatory stress-induced reduced mitochondrial membrane potential (Figure 10), the three ingredients Ginseng extract, Olive extract, and Chaga extract, were associated with lower membrane potential in lymphocytes than after consuming placebo (Figure 10A), reaching high levels of statistical significance at 2 hours for olive extract and Chaga (Figure 10B). In monocytes, Chaga extract protected the cells from inflammation-induced reduction in membrane potential at one hour followed by a reduction at 2 and 3 hours, where all changes reached statistical trends (Figure 10C, 10D). Similar, and more robust, biphasic effects of consuming all four nutraceutical ingredients were seen in neutrophils in context of inflammatory stress ex vivo, with an initial mild increase in membrane potential above that of placebo (Figure 10E). When these changes seen 1 hour after consuming placebo were subtracted, the relative increases reached a trend for Chaga extract, significance for PHG, and a high level of significance for olive extract (Figure 10F). At 2 and 3 hours, the membrane potentials were reduced by all four products, reaching a trend for Ginseng extract, significance for Olive extract, and high levels of significance for Chaga extract (Figure 10F).

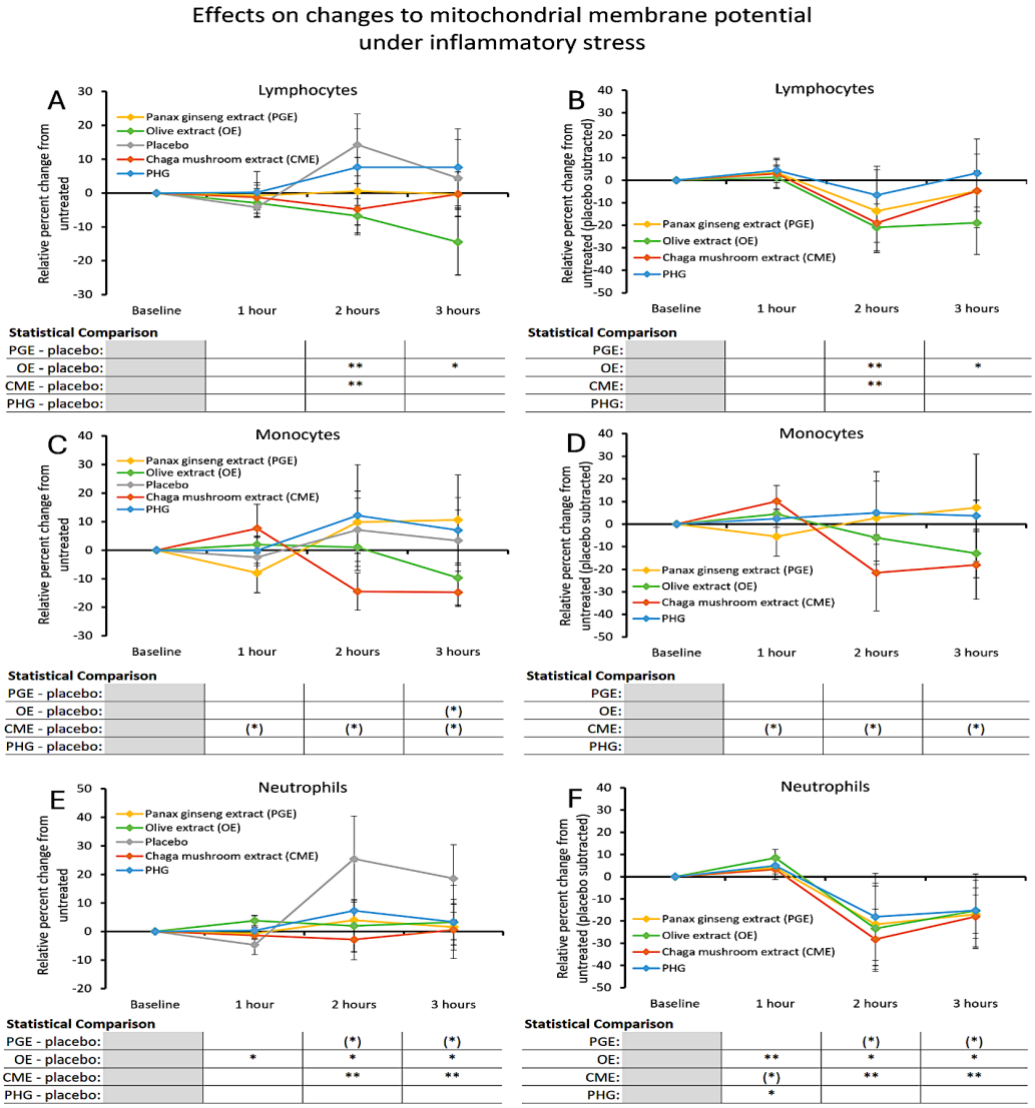


Figure 10. Effects on the mitochondrial membrane potential responses to LPS-induced inflammatory stress after consuming nutraceutical ingredients when compared to changes after consuming placebo. In the tables below each chart the levels of statistical significance for changes from baseline to a later time point are indicated by asterisks, where $p<0.10$: (*), $p<0.05$: * and $p<0.01$: **.

DISCUSSION

Natural compounds, including the nutraceutical ingredients reported here, have been studied for their potential anti-aging benefits, involving effects on stem cell biology and mitochondrial protection. This clinical proof-of-concept study was designed to document rapid effects following single-dose consumption. Our findings indicate that specific nutraceutical ingredients—PurGinseng (P. ginseng) extract, Oligen olive extract, MycoThrive Chaga mushroom extract, and CelluThrive potassium hydrogen glucarate (PHG)—can rapidly modulate stem cell trafficking and mitochondrial resilience in healthy adults. These preliminary results contribute to the growing body of evidence supporting the role of these natural compounds in promoting regenerative and anti-aging processes. All four ingredients showed distinct bioactive mechanisms of action that converge on key anti-aging processes: Supporting stem cell function and improving mitochondrial resilience against stress, thereby contributing to the 17-step functional food development model, specifically the steps pertaining to establishment of relevant biomarkers and providing initial clinical data for efficacy [19].

Mobilization of stem cells is a well-characterized phenomenon in other contexts – for example, pharmacological agents like granulocyte colony-stimulating factor (G-CSF) are used clinically to mobilize bone marrow stem cells after injuries [76], and exercise or stress can transiently increase circulating progenitor cells [77,78]. Previous reports on consuming nutritional supplements, leading to rapid changes in stem cell numbers, were associated with algae-based extracts, containing ligands for selectins involved in stem cell mobilization, including L-selectin ligands from the blue-green algae *Aphanizomenon flos aquae* [57]. Stem cell mobilization was also seen after consuming a high polyphenol-content extract from sea buckthorn berries [58], which led to the testing of other high polyphenol-content botanicals, such as the olive extract and Chaga mushroom extract reported here. While each of the four nutraceutical products reported here rapidly affected stem cell mobilization, the products differed in terms of the type of stem cells affected and the timing of this effect, suggesting some possible overlapping mechanisms, at least for the polyphenol-rich ingredients olive extract and Chaga mushroom extract. The consumption of each nutraceutical ingredient led to rapid, temporary changes to various stem cell populations in the blood circulation. All four ingredients increased the numbers of circulating CD45dim $CD34^{+}CD309^{+}$ pluripotential stem cells within one hour, returning to similar levels as after consuming placebo by three hours. Ginseng extract extract also elevated CD45dim $CD34^{+}$ $CD309^{-}$ progenitor stem cells at two hours, while the Chaga mushroom extract caused a reduction in this population at three hours. Consumption of Ginseng extract had selective effects on CD45dim $CD34^{+}$ hematopoietic stem cell types and did not significantly affect either $CD45^{-}$ $CD90^{+}$ mesenchymal or $CD31^{++}CD34^{-}$ endothelial stem cell populations. $CD45^{-}$ $CD90^{+}$ mesenchymal-like stem cells increased following intake of PHG and Chaga mushroom extract, with olive extract showing a similar trend followed by a decrease, possibly indicating stem cell homing. The numbers of $CD31^{++}$ $CD34^{-}$ endothelial stem cells were elevated at one hour after consuming Chaga, and PHG, with Chaga showing a sustained increase at 2 hours. Chaga had similar effects on the mobilization of hematopoietic cells compared to the other ingredients; this may possibly be related to increased levels of the stem cell-mobilizing growth factor G-CSF, that we reported previously after ingesting a nutraceutical blend containing the Poria cocos mushroom, reaching significance at 2 hours after consumption [59]. Furthermore, Chaga mushroom extract had a more pronounced effect on the mobilization of $CD45^{-}CD90^{+}$ lymphocytes and $CD31^{++}CD34^{-}$ endothelial stem cells than any of the other

ingredients, reaching a maximum change at 2 hours; the underlying mechanisms for this increase are yet unknown.

Three of the four ingredients tested are rich sources of polyphenols, which along with their metabolites, have been shown to modulate gut-brain communication through their effects on gut neurons and the vagus nerve [79]. These bioactive molecules can influence the activity of enteroendocrine and neuropod cells, located throughout the epithelial lining of the gastrointestinal tract, and serve as essential interfaces between the gut and brain [80]. Neuropods have direct synaptic connections to neurons, leading to altered release of neurotransmitters such as serotonin and dopamine. Through vagal afferent pathways, these changes can rapidly signal to the central nervous system, modulating neuroimmune and neuroendocrine responses [81]. Serotonin and dopamine are increasingly recognized for their roles in regulating stem cell dynamics, where they can differentially influence mobilization from the bone marrow and homing to target tissues [82]. Collectively, these observations support a plausible pathway by which nutraceuticals may indirectly influence stem cell trafficking via gut–brain neurochemical signaling.

The regenerative potential of stem cells is tightly associated with their mitochondrial function, and reduced mitochondrial function in stem cells is associated with declining health and accelerated aging [83,84]. While we evaluated the mitochondrial effects in broader cell populations and not specifically in stem cells, the selective impact of consuming the nutraceutical ingredients on the mitochondrial volume in lymphocytes under oxidative stress deserves attention, since this population includes the various types of stem cells. The relationship between mitochondrial volume and oxidative stress is complex and involves dynamic changes in mitochondrial structure, function, and signaling. A mild swelling is thought to be protective in some contexts, as it may help maintain mitochondrial membrane potential and ATP production under stress [85]. While none of the four nutraceutical ingredients triggered mitochondrial biogenesis in the absence of stress, they provided a mild support of this increased volume under oxidative stress, but not inflammatory stress. In situations where stress leads to a mild mitochondrial swelling, this may be associated with increased permeability of the inner mitochondrial membrane, which can lead to partial and temporary depolarization of the membrane potential. This may relate to the observations reported here where a mild increase in mitochondrial volume was accompanied by a temporary, mild reduction in mitochondrial membrane potential within 1–2 hours of consuming the nutraceutical ingredients. The implication of this rapid support of the mitochondrial stress-response suggests that these compounds may act as early modulators of cellular stress adaptations. This acute effect may reflect a priming of mitochondrial bioenergetics and redox buffering capacity, potentially improving cellular readiness to cope with inflammatory or metabolic challenges.

This study provides novel insights into the acute effects of select nutraceutical ingredients on stem cell mobilization and mitochondrial resilience. We propose that these rapid responses may offer mechanistic clues relevant to the established long-term regenerative and anti-aging associations of these natural products.That said, several limitations warrant consideration. First, the sample size was modest and limited to healthy adult participants, which may constrain the generalizability of the findings to broader populations, including those with age-related or chronic conditions of stress. Future studies should include larger and more diverse cohorts to validate and extend these observations and should evaluate responses to several doses of each bioactive compound, consumed at different times during the circadian cycle [19]. Also, the study observed distinct mobilization patterns for different stem cell subtypes and

relied on peripheral blood sampling to infer stem cell mobilization, which does not directly capture homing or engraftment into target tissues. Future research should incorporate imaging techniques to track stem cell migration and tissue integration, especially in models of injury or aging, to increase our understanding of the underlying molecular mechanisms.

Regarding the increased mitochondrial resilience under stress, further mechanistic studies are needed to document the signaling pathways and cellular targets engaged by each compound. Further research involving imaging of mitochondrial morphology is also necessary in context of improving the understanding of the increased resilience, since mitochondrial fusion and fission are dynamic processes that regulate the shape, function, and distribution of mitochondria within cells [86,87]. Fusion creates elongated, interconnected mitochondrial networks that are often more efficient at producing energy and resisting stress. In contrast, fission breaks mitochondria into smaller units, which can help isolate damaged regions but may reduce overall energy stability [88]. While the observed mitochondrial adaptations suggest enhanced resilience, documentation of the functional consequences of these changes, such as improved ATP production, reduced oxidative damage, or enhanced cellular repair, will be essential to fully characterize the bioenergetic impact of these nutraceutical ingredients. Lastly, the potential synergistic effects among these four bioactive compounds warrant investigation, given that multi-ingredient botanical blends have demonstrated enhanced efficacy in other clinical contexts [89].

Scientific innovation and practical implications: The results from this preliminary study are to the best of our knowledge the first evidence for almost-immediate systemic effects at the cellular level after consuming these four functional ingredients. While larger clinical trials are needed to validate this, the acute effects reported here may be contributing factors to the known long-term outcomes associated with daily consumption of these functional extracts. The research provides novel documentation of methodology to measure rapid changes to mitochondrial parameters in healthy people after consuming a single dose of botanical extracts, compared to placebo. The methodology presented here lays the groundwork for further documentation of fast-acting, regenerative functional ingredients in larger trials.

CONCLUSION

This clinical proof-of-concept study provides evidence that acute consumption of specific nutraceutical ingredients— PurGinseng P. ginseng extract, Oligen olive extract, MycoThrive Chaga mushroom extract, and CelluThrive potassium hydrogen glucarate—can rapidly influence key biological processes associated with healthy aging. Each compound demonstrated distinct yet converging bioactivities that support stem cell mobilization and mitochondrial resilience, underscoring their potential as natural modulators of regenerative health. The rapid mobilization of stem cells and early-phase mitochondrial adaptations observed within hours of consumption suggest that these ingredients are fast-acting modulators of the body's repair and stress-response systems. These preliminary findings expand the scientific understanding of how targeted nutraceuticals can engage core mechanisms of cellular renewal and stress adaptation, offering promising avenues for future research in anti-aging and regenerative interventions, not limited to chronological aging, but also encompassing stress-related accelerated decline of physical and mental health associated with nutrition insecurity in large parts of the world [90]. Future research should aim to expand the scope of investigation to include mechanistic depth, broader populations, and long-term functional outcomes, ultimately guiding the development of targeted interventions for healthy aging and regenerative medicine.

List of abbreviations: BMI, body mass index; CME, Chaga mushroom extract; FITC, fluorescein isothiocyanate; FSC, forward scatter; H_2O_2, hydrogen peroxide; LPS, lipopolysaccharide; OE, olive extract; PBMC, peripheral blood mononuclear cells; PE, phycoerythrin; PGE, *Panax ginseng* extract; PHG, potassium hydrogen glucarate; PerCP, Peridinin-Chlorophyll-Protein; PMN, polymorphonuclear cells; RPMI, Roswell Park Memorial Institute; SSC, side scatter.

Authors' contributions: GSJ designed the research; GSJ and KS performed the testing reported here and performed final audits of the data analysis; GSJ, DC, and KS prepared the visuals for the manuscript; GSJ, KS, DC, and CF prepared the manuscript. All authors have read and agreed to the published version of the manuscript.

Competing interests: The authors GSJ, KS, DC declare no financial interests or conflicts of interest. CF is employed as Chief Science Officer for the study sponsor, Applied Food Sciences Inc. The work was performed at NIS Labs, an independent contract research laboratory specializing in natural products research and clinical trials. NIS Labs received funding from Applied Food Sciences Inc. to conduct research on the nutraceutical products reported here but neither NIS Labs nor any of the coauthors GSJ, KS, and DC have other financial ties to the study sponsor or the nutraceutical products studied here.

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