ISRCTN14647763 https://doi.org/10.1186/ISRCTN14647763

A study to compare the acute immune effects of a herbal blend compared to a placebo

Submission date
18/03/2022

Recruitment status
No longer recruiting

Registration date
12/04/2022

Overall study status
Completed

Last Edited
03/05/2024

Condition category
Other

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[X] Individual participant data

Plain English summary of protocol

Background and study aims
Unigen, Inc. focuses on identifying and studying the unique bioactive natural products of medicinal botanicals and then developing them into proprietary standardized extracts for use as novel ingredients in cosmeceutical and nutraceutical products. Based on the market need for products that support immune health, there is a high interest in science-based natural products with documented rapid effects on the human immune system. This clinical proof-of-concept study aims at documenting the acute effects of consuming a test product through evaluation of immune cell activation, cell trafficking, cytokine changes, antiviral peptides, and restorative growth factors. Data on immune cell trafficking and surveillance will be collected. The testing will show whether consuming the novel blend leads to a rapid change in the alertness of the immune system to search for and attempt to eliminate microbial invaders, and to collaborate effectively between immune cell types. Data on immune cell trafficking and surveillance will be collected. The goal of this study is to compare the rapid immune-modulating effects of a natural blend of plant extracts UP360 to a placebo. This data is important to verify immune-related effects.

Who can participate?
Healthy volunteers aged 18-75 years (inclusive)

What does the study involve?
Participants will be tested on four different clinic days. The sequence in which each person will consume the different products will be randomized. On each clinic day, immediately after a blood draw, participants will be given a single dose of either the active test product or a placebo (dummy product) in the presence of the clinic staff. They will consume the capsules with water and a few bland soda crackers to stimulate digestive function.

What are the possible benefits and risks of participating?
There is no direct benefit to participants. There are no known discomforts from the test product, except if participants have certain allergies to foods contained in the test product such as aloe, rosemary, or mushrooms. Blood samples can cause discomfort and a slight risk of bruising.

Where is the study run from :
Natural Immune Systems (USA)

When is the study started and how long is expected to run for?
February 2021 to October 2021

Who is funding the study?
Unigen Inc. (USA)

Who is the main contact?
Lidia Alfaro Brownell
lbrownell@unigen.net

Contact information

Type(s)
Scientific

Contact name
Ms Lidia Alfaro Brownell

ORCID ID
https://orcid.org/0000-0002-5328-0152

Contact details
2121 South State Street
Tacoma
United States of America
98405
+1 (0)2532747166
lbrownell@unigen.net

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
181-002-R3

Study information

Scientific Title
Rapid immune-modulating effects: proof of concept study

Study objectives

This clinical proof-of-concept study aims at documenting the acute effects of consuming a test product through the evaluation of immune cell activation, cell trafficking, and cytokine changes to pro- and anti-inflammatory cytokines, antiviral peptides, and restorative growth factors. Data on immune cell trafficking and surveillance, cytokine profile, and immune cell reprogramming towards bacterial and viral challenges will be collected.
The testing will show whether consuming the novel blend leads to a rapid change in the alertness of the immune system to search for and attempt to eliminate microbial invaders, and to collaborate effectively between immune cell types.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 13/08/2021, Argus Independent Review Board (6668 S. Hidden Flower Way, Tucson, AZ 85756-5111, USA; +1 (0)520 299 7494), ref: 181-002

Study design
Placebo-controlled randomized double-blinded cross-over study

Primary study design
Interventional

Study type(s)
Other

Health condition(s) or problem(s) studied
Immune cell activation, cell trafficking, and cytokine changes to pro- and anti-inflammatory cytokines, antiviral peptides, and restorative growth factors

Interventions
For this clinical study, human subjects will be tested following an established placebo-controlled, randomized, double-blinded, cross-over study design. Specifically, the study design has been used in previous clinical studies on immune-modulating products including the yeast-based fermentate Epicor, a bovine colostrum-based peptide- and oligosaccharide-rich extract Immunel, the algae-based extract for stem cell support StemEnhance, and an aloe-based folk medicine formulation from Madagascar. Recently, the NIS Labs' team also published on changes to lymphocyte trafficking, specifically stem cell subsets, using this study design when consuming a placebo versus a polyphenol-rich extract from Sea Buckthorn from Tibet.

There will 2 visits 7 days apart. After visit one there will be a 7 day washout period. The product will be consumed only once per visit. Samples will be collected at each visit. On each clinic day, participants will rest quietly for 1h prior to the baseline blood draw to ensure representative baseline data. During this period participants will complete questionnaires on previous meals, snacks, exercise, stressors, and recent sickness. Immediately after the baseline blood draw, subjects will be given a single dose of either the active test product UP360 or a placebo in the presence of the clinic staff. Subjects will consume the capsules with water and a few bland soda crackers to stimulate digestive function. 3 more samples will be drawn at 1, 2, and 3 h after consumption of the product or placebo.

The sequence in which each person will consume the different products (active test product versus placebo) will be randomized. The test parameters evaluated do not necessarily stay

constant, even over a few hours, since they are related to people's metabolism, individual circadian rhythms, and other normal physiological parameters. Therefore, studies of this nature must include a placebo test day, allowing a within-subject analysis of changes between the test days for each person. This very much strengthens the data analysis from this type of pilot study. In the absence of a placebo test day, the data is considered inconclusive since changes cannot be interpreted as being related to product intake. In light of previous data on products such as Epicori and Immunel, some differences were seen at 1 versus 2 h, and it is ideal to perform testing at both time points, in the current study a 3 h time point is added.

Intervention Type
Supplement

Primary outcome(s)
Immune surveillance, trafficking, and activation of immune cells in vivo, measured using flow cytometry to evaluate immune cell movement in and out of tissue and absolute numbers immune cell populations in the circulating blood. as well as the activity of immune cells showing signs of a higher level of function from blood samples (1 EDTA vial, a total of 6 ml blood) collected at baseline, 1, 2, and 3 h for the first clinic visit (0 days) and at baseline, 1, 2, and 3 h at the second clinic visit (7 days). In order to make these measurements, cells will be stained with a monoclonal antibody towards the CD3/ γδ T Cell Receptor,vii viii and co-stained with CD5. The cells are also stained for CD56 which may be expressed on some γδ T cells.ix The 2 activation markers CD69 and CD25 will also be used. This allows analysis of numbers of the following types of immune cells in the blood circulation at each time point in the study:
Add-on panel for numbers of gamma-delta (γδ) T cells (γδTCR+ CD5-):
1. CD3/ γδ T Cell Receptor+ CD5- CD56+
2. CD3/ γδ T Cell Receptor+ CD5- CD56-
3. CD3/ γδ T Cell Receptor+ CD5- CD69+
4. CD3/ γδ T Cell Receptor+ CD5- CD25+
Cells are stained with the T cell markers CD4 and CD8, the B cell marker CD19, and co-stained with monoclonal antibodies towards CD45Ra and CD45R0 isoforms.vi CD45Ra is expressed on naïve T cells and resting B cells. CD45R0 is expressed on memory T cells and recently activated B cells. Cells expressing both isoforms have recently been through an immune activation event. This allows analysis of numbers of the following types of immune cells in the blood circulation at each time point in the study:
1. CD4 T lymphocytes
2. CD8 T lymphocytes
3. CD19 B lymphocytes
Each type of lymphocyte will be analyzed for:
1. CD45RA expression
2. CD45Ra and CD45R0 co-expression
3. CD45R0 expression

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
30/10/2021

Eligibility

Key inclusion criteria

1. Healthy adults
2. Age 18-75 years (inclusive)
3. BMI between 18.0 and 34.9 kg/m² (inclusive)
4. Veins easy to see in one or both arms (to allow for the multiple blood draws)
5. Willing to comply with study procedures, including:
5.1. Maintaining a consistent diet and lifestyle routine throughout the study
5.2. Consistent habit of bland breakfasts on days of clinic visits
5.3. Abstaining from exercise and nutritional supplements on the morning of a study visit
5.4. Abstaining from use of coffee, tea, and soft drinks for at least 1 hour prior to a clinic visit
5.5. Abstaining from music, candy, gum, computer/cell phone use, during clinic visits

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
75 years

Sex
All

Total final enrolment
12

Key exclusion criteria
1. Previous major gastrointestinal surgery (absorption of test product may be altered) (minor surgery not a problem, including previous removal of appendix and gall bladder)
2. Taking anti-inflammatory medications on a daily basis
3. Currently experiencing intense stressful events/life changes
4. Currently in intensive athletic training (such as marathon runners)
5. Cancer during the past 12 months
6. Chemotherapy during the past 12 months
7. Currently treated with immune suppressant medication
8. Diagnosed with autoimmune disorders e.g. systemic lupus erythematosus, hemolytic anemia
9. Donation of blood during the study or within the 4 weeks prior to study start
10. Have received a cortisone shot within the past 12 weeks
11. Immunization during last month
12. Currently taking anxiolytic, hypnotic, or anti-depressant prescription medication
13. Ongoing acute infections (including teeth, sinus, ear, etc)
14. Participation in another clinical trial study during this trial, involving an investigational product or lifestyle change
15. An unusual sleep routine (examples: working graveyard shift, irregular routine with frequent late nights, studying, partying)

16. Unwilling to maintain a constant intake of supplements over the duration of the study
17. Anxiety about having blood drawn
18. Women of childbearing potential: pregnant, nursing, or trying to become pregnant
19. Known food allergies related to ingredients in the active test product or placebo
20. Prescription medication will be evaluated on a case-by-case basis

Date of first enrolment
14/08/2021

Date of final enrolment
21/10/2021

Locations

Countries of recruitment
United States of America

Study participating centre
Natural Immune Systems
1437 Esplanade Ave
Klamath
United States of America
97601

Sponsor information

Organisation
Unigen Inc.

Funder(s)

Funder type
Industry

Funder Name
Unigen Inc.

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from Lidia A Brownell (lbrownell@unigen.net).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		12/09/2023	03/05/2024	Yes	No
Dataset		12/09/2023	03/05/2024	No	No
Participant information sheet	version 1.0	01/07/2021	05/04/2022	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol (other)		12/09/2023	03/05/2024	No	No
Protocol file		08/07/2021	16/08/2022	No	No