Cover page with official title: ORAL SUPPLEMENT IN OLDER ADULTS TO SUPPORT PHYSICAL FITNESS AND MENTAL WELL-BEING (ID, 23767, PQQA)

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1) Introduction

Cucumbers have been anecdotally claimed to have anti-inflammatory activity for a long time, but the active principle was not identified. IdoBR1, (2R,3R,4R,5S)-3,4,5-trihydroxypiperidine-2-carboxylic acid, is an iminosugar amino acid isolated from fruits of certain cucumbers, Cucumis sativus (Cucurbitaceae), which has been shown to have anti-inflammatory activity in cells and ex vivo human blood.

We will explore if consumption of cucumber extract Q-actin when compared with placebo can have an impact on physical strength (measured by hand grip strength), finger dexterity (measured by Nine-Hole Peg Test (9HPT)) as well as quality of life (EQ-5D questionnaire), sleep quality (Pittsburgh Sleep Quality Index), hip and knee pain (WOMAC questionnaire), and diet (diet questionnaires are tailored to your eating habits, e.g., carnivore, vegetarian pescetarian, vegan etc). We will explore urine chemical composition of home-collected urine using high resolution metabolomics.

2) Statement of Purpose

A randomized, placebo controlled clinical human trial of Q-actin (2 x 10 mg gummies daily) or placebo (2 x 10 mg gummies, taken twice daily before bed), in middle aged and older adults (>50), is proposed for a period of 12 weeks. The aim is to explore whether consumption of Q-actin post intervention, and in comparison, to the placebo, has any impact on physical strength (measured by hand grip strength), finger dexterity (measured by Nine-Hole Peg Test (9HPT)), and hip or knee pain (WOMAC), as well as quality of life (EQ-5D questionnaire), sleep quality (Pittsburgh Sleep Quality Index (PSQI)), and diet (PDQS). Home-urine samples will be collected for the investigation into the chemical composition.

3) Investigational Product

3.1) Description

Q-actin is an imino-sugar (idoBR1, (2R,3R,4R,5S)-3,4,5-trihydroxypiperidine-2-carboxylic acid) isolated from fruits of certain cucumbers, Cucumis sativus (Cucurbitaceae). The daily dose will be 20mg, which will be divided into two vegan gummies (2x10mg) that are to be consumed before bed. The placebo is a gummy matching Q-actin in appearance, tase and texture, the ingredients for which are detailed in section 4.

3.2) Quality

Q-actin (and the matching placebo) will be consumed in the form of wax coated, square bottom gummies that are dark red in colour with natural raspberry flavouring. Vegan gummies were chosen as opposed to tablets because they are easier to consume than pills/capsules. Both Q-actin and the placebo have been manufactured by a fully licensed GMP site manufacturer. The gummies have been analysed and quality control screened for elemental elements and microbials and have passed, all according to guidelines..

3.3) Dose

The dose of Q-actin and the placebo will be 2x10mg gummies daily before bed, for a period of 12 weeks.

4) Investigational Product Safety

The Food Standards Agency have confirmed that Q-actin, can be used in clinical trials. A food grade statement for Q-actin has been obtained, and a GRAS document (Generally Recognised As Safe) status has been prepared for the producers in America (Gateway Health Alliances, Inc./IminoTech, Inc.) by Soni & Associates Inc. Gummy ingredients: Corn Syrup, Sugar, Purified Water, Pectin, Natural Flavours (raspberry), Citric Acid, MCT Oil, Natural Colors (vegetable concentrates), Carnauba Wax, Sodium Citrate

5) Study Design

5.1) Objectives of the Study

The aim is to compare physical strength, finger dexterity, hip and knee pain, quality of life, sleep quality, diet, and urine chemical composition between baseline and post intervention after Q-actin and placebo control.

5.2) Subject Selection

- 50 participants, over 50 years, mixed gender, mixed ethnicity

- Inclusion Criteria:
  - Consenting adults >50 y Age.
  - Commit to urine sampling.
  - Able to commit to attending WARU or the remote centre for measurements of physical strength, finger dexterity, quality of life, sleep quality, hip and knee pain, and diet choices.
  - Able to restrict from consumption of cucumber, gherkins, and melon for two days before coming to WARU or the remote centre.

- Exclusion Criteria:
  - Showing (or anyone within the household) any COVID-19 symptoms (see COVID-19 basic health screen).*
  - Higher risk or vulnerable from coronavirus or live with someone at a higher risk of a severe illness from COVID-19 (over 70, undergoing cancer treatment, high risk of getting infections).
  - Had a letter from the NHS advising you to shield (isolate).
  - Had been at risk of exposure to COVID-19 such as travel, contact with someone with COVID-19, been exposed to the virus, or has been asked to self-isolate by the track and trace system.
  - Serious health conditions that require daily long-term medication.
- *If the potential participant has had COVID-19 previously (and are fully recovered and not within isolation) then they are eligible to join the study

5.2) Study Design

This is a randomised, double-blinded, parallel study, where participants are asked to take the gummies (Q-actin or Placebo) twice a day for a period of 12 weeks. Within that 12 week period, participants will be required to make three visits to the Well-being and Health Assessment Research Unit (WARU) at Aberystwyth University, or to the remote facility in Trimsaran, following a pre-induction screening visit. Urine kits and study materials will be prepared (and stored) at the Well-Being and Health Assessment Research Unit (WARU) at Aberystwyth University. Urine samples will be assessed at AberInnovation and Aberystwyth University.

Pre-Induction
Participants are welcomed with tea or coffee and talked through how safe working practices are being conducted during coronavirus (COVID-19). Then they are introduced to the urine sampling boxes and provided with crib sheets and an email link to a video demonstration (if needed). They are talked through the logistics of study visits and the tasks that will be completed. They are asked to complete a medical health screening questionnaire, and height, weight, and BMI measurements are obtained. They are provided with the urine sampling kits complete with 1 needle, two sampling vacutainers and 1 collection cup for each visit (week 0, week 6 and week 12). A review of their continued right to withdraw, in addition to the data protection and storage of their personal data and biofluids, is provided, and the dates and times of visits 1, 2 and 3 are arranged. A consent form is signed. This pre-induction can also be done remotely and materials posted. Consent forms are to be received and stored prior to the first sample collection.

Visit 1
Participants arrive on their pre-organised day and time with 2 x 4ml of their first urine sample (after being stored between 3-5 degrees Celsius in participants home fridge), collected at home using our urine kits. Consent is obtained followed by the first assessment of physical strength, finger dexterity, quality of life (EQ-5D), sleep quality (PSQI), diet (PDQS) and hip and knee pain (WOMAC). They collect their gummies for the full 12-week period. The gummies are divided into 12 packets (labelled with the participants unique, pseudonymised code), with each packet consisting of 14 gummies (for 2 gummies x 7 days). On the first visit they will receive 6 packs (for the first 6 week, and on the second visit they will receive the remaining 6 packs)

Visit 2
On their pre-organized day and time, participants repeat the activities undertaken during visit 1. Second assessment of physical strength, finger dexterity, quality of life, sleep quality, diet choices, hip and knee pain, and week 6 urine drop off. On the second visit they will receive the remaining 6 packs of supplements.

Visit 3
On their pre-organized day and time, participants repeat the same activities as undertaken during visits 1 and 2. Final assessment of physical strength, finger dexterity, quality of life, sleep quality, diet choices hip and knee pain and week 12 urine drop off.

6) Participant Risks

The supplements have been tested for any adverse effects, so no risks are anticipated. However, participants are informed that if any negative effects occur, then they should refrain from continuing in the study and to inform the research team. The urine kits contain a needle, so care should be taken.

7) Benefits to participant

There is no financial incentive for participants if they decide to join this study. They will be allowing the researchers gain important insight into the anti-inflammatory properties of the cucumber supplement and the digestion and metabolism of the supplement within urine. This will be the first time this type of research will have been conducted and will be a valuable pilot study before the researchers can investigate further human health benefits in the future.

8) Ethical approval

Aberystwyth University Research Ethics Panel confirmed a favourable ethical opinion subject on the 27th October 2022.

9) Privacy/confidentiality

Participants are informed that only the researchers involved with the study will be able to look at the information they provide. Specific details and personal identifiers will only be available to the researchers. At the end of the study, any information relating to participants will be made pseudonymous (coded without their name associated). Participants will not be identifiable in any publication that may arise from this research. Electronic files will be kept in a logical manner and will always be kept grouped within specific folders and password protected, and backed up. There may be times when keeping paper forms are necessary (consent forms), but in this case the paper versions will be kept in a locked filing cabinet. All biofluids are stored in a locked freezer. Key is kept by the gatekeeper.

This research is being conducted in accordance with the GDPR guidelines. The AU Data Protection Manager provides oversight of AU activities involving the processing of UK GDPR and special category data, and can be contacted at infocompliance@aber.ac.uk. Personal data will be stored securely and processed for metabolomic analysis. The legal basis that would be used to process personal data will be 'a task in the public interest'. If participants are concerned about how personal data is being processed, AU can be contacted in the first instance at infocompliance@aber.ac.uk. If they remain dissatisfied, they may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/.

10) Safety Monitoring

Participant:
If a participant, or a member of their family/household become unwell during the study, then they are pre-warned to alert a member of the research team immediately using the contact information they

have been provided. Participation in the study will be suspended immediately until further discussion with the research team has taken place. If they become unwell at any point and need medical assistance, they are advised to contact 111 and seek advice from the NHS health sector or their doctor's surgery. We have a duty of care towards them and can help monitor their health remotely over 14 days and will help in any way we can.

Data:

See Privacy/confidentiality

In exceptional circumstances, confidentiality may have to be breached in cases where persons are considered to be at risk or if required by law.

11) **Data analysis and statistics**

The chemical composition of urine samples will be assessed at AberInnovation and Aberystwyth University using high resolution metabolomics. Self-report data will be analysed in WARU using appropriate methods.

12) Sponsors and contacts

Welsh Government is the sponsor. Gateway Health Alliances, Inc and Phytoquest are the companies. Main contact is Amanda Lloyd, Aberystwyth University abl@aber.ac.uk