Informed Consent Form

1. Study Information

Protocol Title:

Cardio-vascular protective effects of wolfberry in middle-aged and older adults

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Study Sponsor:

This study is sponsored by the Singapore Ministry of Education Academic Research Fund.

2. Purpose of the Research Study

You are invited to participate in this research study following your interest expressed during the phone interview.

It is important to us that you first take time to read through and understand the information provided in this sheet. Nevertheless, before you take part in this research study, the study will be explained to you and you will be given the chance to ask questions. After you are properly satisfied that you understand this study, and that you wish to take part in the study, you must sign this informed consent form. You will be given a copy of this consent form to take home with you.

An ageing population is a global phenomenon and likewise in Singapore, we are experiencing a rapid increase in our population average age as well. The process of aging results in a progressive decline of numerous physiological processes, leading to an increased risk of health complications such as cardiovascular disease (CVD). Since aging significantly affects the heart and vascular systems, it has been associated with an increased risk of developing CVD. CVD is one of the world's leading causes of death and in Singapore alone, 30 % of all total deaths or 16 deaths daily are attributed to CVD in 2016.

The American Heart Association recommends a healthy diet and lifestyle to help combat CVD and in Singapore, the Health Promotion Board (HPB) promotes a healthy eating pattern "My Healthy Plate", to help Singaporeans practice healthy eating habits that can aid in weight control and chronic disease protection. Additionally, enriching a healthy diet with wolfberry (goji berry), a familiar and easily incorporable ingredient in the Asian diet, may serve as an excellent complement to reduce the risk of CVD development.

Hence in this study, we aim to assess the effects of consuming a wolfberry as part of a healthy eating pattern diet on cardiovascular risk factors in the middle-aged and older adults. 40 to 50 participants from the general public will be recruited for this study which will span over a duration of 2 years.

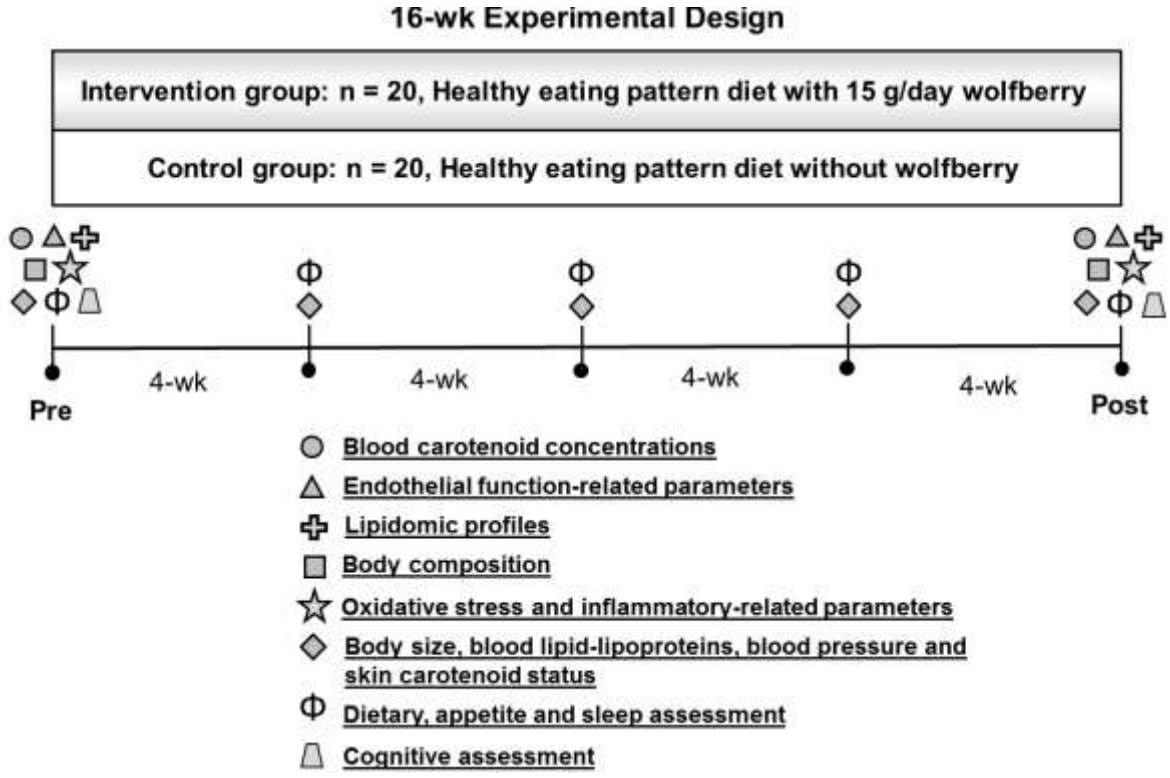
3. What procedures will be followed in this study

This is a 16-week prospective study, consisting of 6 visits in total to the National University Health System (NUHS) Investigational Medicine Unit, National University of Singapore Food Science and Technology Programme and Occupational Health Clinic including an initial screening visit (approximately 2 hr). Following which, each visit would be separated by a 4-week interval. The duration for each visit is estimated to be approximately 5 hr for the pre- and post-intervention visits and approximately 2 hr for the 3 visits in between. Details of the activities performed at each stage of the study are as follows.

Screening:

Under the guidance of trained study personnel, you will first be briefed about the study and given ample time to carefully read through this informed consent form. Take this opportunity to enquire more about the study and question any doubts before acknowledging the consent form. Upon acknowledgement, you will be further assessed in terms of your study eligibility. If you fulfill the criteria, you will be guided to complete a medical history questionnaire. Approval for participation will be finalised by either of the study investigators, Dr Khoo, Dr Chan or Dr Kim. Following this, you will be randomised to follow a healthy dietary eating pattern either with or without wolfberry. Randomisation means assigning you to one of 2 groups by chance, like tossing a coin or rolling dice.

Study visits:



Prior to each visit, you will be required to fast from the night before for approximately 10 to 12 hrs.

The following procedures will be conducted by trained research staff on the pre- and post-intervention visits (Visits 2 and 6):

1. Sampling of fasting-state blood (60 mL) through intravenous cannulation (Cannula (needle) insertion into the arm. The cannula will be left for around 10 to 20 mins in the arm)
2. Anthropometric measurements including height, weight and waist circumference
3. Blood pressure measurement
4. Skin carotenoid status measurement (Analysis of carotenoid level in the skin to indicate fruit and vegetable intake. Exposure of palm with visible light; 1 min procedure)
5. Brachial artery flow mediated dilation and carotid intima media thickness (Indicators of blood vessel health and function. Ultrasound scan of the arm; 15 min procedure)
6. Body composition assay by dual energy X-ray absorptiometry (Analysis of body fat distribution. Requires you to lie flat on an examination table for a scan with low levels of radiation; 10 min procedure)
7. Written questionnaires and assessment forms to assess your diet, sleep quality, stress, cognition and appetite

The following procedures will be conducted by trained research staff on the three visits in between (Visits 3, 4 and 5):

1. Sampling of fasting-state blood (20 mL) through intravenous cannulation
2. Anthropometric measurements including weight and waist circumference
3. Blood pressure measurement
4. Skin carotenoid status measurement
5. Questionnaires and assessment forms to assess your diet, sleep quality and appetite

Requests for meal photographs on pre-determined dates and other reminders will be disseminated to you via email, SMS or WhatsApp depending on your preference. Please inform the Study Coordinator if you lack access to all of the above mentioned communication platforms.

The total volume of blood to be extracted after all 6 visits of this study is 180 mL (approximately 36 teaspoons). Biological samples will be used in the current or future research in an individually non-identifiable form. Biological samples obtained during the course of this study will be stored for in freezers owned by the research group at NUS, for use in this research study and if agreeable, future nutritional research by NUS and/or NUS's collaborators for up to 10 years as long as they are not depleted. Biological samples will be shared with the collaborators in a de-identified manner. The samples will not be transferred outside of Singapore and will not be used for current or future restricted human biomedical research involving human animal combinations. For example, the introduction of human stem cells into an animal at any stage of the development (including prenatal animal fetus or animal embryo).

During the course of the study, there is a possibility that we might unintentionally come to know of new information about your health condition from your blood glucose and lipid profile, blood pressure and carotid intima media thickness that is conducted as part of the study. These are called "incidental findings".

"Incidental findings" are findings that have potential health or reproductive importance to research participants like you and are discovered in the course of conducting the study, but are unrelated to the purposes, objectives or variables of the study. These findings may affect your current or future life and health insurance coverage. Examples of potential incidental findings that may be discovered during the course of this study may include but are not limited to high blood glucose, hypertension, dyslipidemia and plaque build-up.

You will be asked to indicate whether you wish to be re-identified and notified in the case of a clinically significant incidental finding that is related to you.

If you agree to be re-identified and notified, a qualified healthcare professional will explain the incidental finding to you and discuss and advise you on the next steps to follow. For this purpose, please inform the Principal Investigator or any of the study contact persons listed in this document whenever there are changes in your contact details. You may wish to do more tests and seek advice to confirm this incidental finding. The costs for any care that will be needed to diagnose or treat an incidental finding would not be paid for by this research study. These costs would be your responsibility.

The research data and biological samples obtained during the course of this study will only be used for the current or future research purposes.

Provisions to ensure your privacy and confidentiality for any future research are described in *Section 12*.

4. Your Responsibilities in This Study

If you agree to participate in this study, you should follow the advice given to you by the Principal Investigator and study team. You should be prepared to visit the research venue six times and undergo all the procedures that are outlined above.

In addition, please refrain from the following activities/changes during these 4 months of intervention:

1. Vigorous exercise
2. Smoking
3. Intake of alcohol above 21 units per week (males) and 14 units per week (females): 1 unit = 360 mL of beer; 150 mL of wine; 45 mL of distilled spirits)
4. Pregnancy
5. Intake of over-the-counter dietary supplements (e.g. multivitamins, eye health supplements, fish oil supplements, Ensure nutritional shake etc.)

If you have been prescribed any medication or dietary supplements during the intervention, please inform the Principal Investigator, Co-Investigator or Study Coordinator.

5. What Is Not Standard Care or is Experimental in This Study

This study is being conducted because of the limited data from human clinical studies that observe the synergistic effects of wolfberry and healthy eating patterns on cardiovascular health in Singapore's middle-aged and older adults who are at risk for CVD.

The study intervention is practiced for the purpose of research and is not part of your routine care.

6. Possible Risks and Side Effects

There will be minimal risk/discomforts from participation apart from a slight pain and bruising associated with blood draw. Some people may also experience dizziness when drawing blood which will usually go away when the person lies down. In the unlikely event that you are injured, first aid and proper health treatment will be administered by an on-site study physician.

There is no known risk associated with the consumption of wolfberry or a healthy eating pattern diet according to earlier intervention studies of a similar nature but there is a possibility of the stomach or bowels becoming upset if there is a change in usual customary dietary intakes. If you experience these symptoms, you will be closely monitored and provided instructions to modify your diet. If the symptoms persist, the Principal Investigator and/or the Co-investigator of this study may stop your participation in the study at any time if they decide that it is in your best interests.

In terms of the analytical procedures, skin carotenoid status measurements involve only the exposure the palm to visible blue light with no risk associated. Brachial artery flow mediated dilation and carotid intima media thickness analyses uses non-invasive ultrasound and has been used for over 20 years with excellent record. It is generally considered safe when used by appropriately trained healthcare providers. Body composition measurements by dual energy X-ray absorptiometry involve exposure to radiation; however, it is very small. The average absorbed dose of radiation is less than or equal to one percent of the average exposure from a chest X-ray, and less than or equal to one-tenth of one percent of the average exposure from a full dental X-ray series.

7. Possible Benefits from Participating in the Study

No benefit is guaranteed and you may not derive any benefit from participating. However, you will be able to contribute to knowledge with regards to the effects of a wolfberry enriched healthy diets on improvements in cardiovascular health in the middle-aged and older population.

8. Important Information for Women Subjects

Women who are pregnant, planning pregnancy or breast-feeding may not take part in this study. For pre-menopausal female subjects, a pregnancy test kit will be provided during each visit to determine for pregnancy during the study duration. If you become pregnant during this study, inform the Principal Investigator, Co-Investigator or Study Coordinator immediately.

9. Costs & Payments if Participating in the Study

If you take part in this study, all tests and analytical procedures including the wolfberries will be provided at no charge to you. These costs will be borne by the Ministry of Education’s Academic Research Fund.

You will be reimbursed $ 610 for your time, inconvenience and transportation. However, the monetary stipend will be pro-rated depending on the number of visits completed if you decide to withdraw during the course of study. Even if you are deemed ineligible after today's screening, you will still be reimbursed $ 10 for your participation in this screening procedure.

Visit	**Financial payment/ incentive**
Screening	$ 10
Visit 1	$ 150
Visits 2 - 4	$ 50 each
Visits 5	$ 300
Total	**$ 610**

10. Voluntary Participation

Your decision to participate in this study is completely voluntary. You have the right to refuse and discontinue participation at any time in the research without reason by informing the Principal Investigator or Co-Investigator and all your data collected will be destroyed, unless otherwise agreed.

If you decide to discontinue your participation in this study, please notify Co-Investigator Dr. Jung Eun KIM at (65) 6516 1136; chmkje@nus.edu.sg or Study Coordinator Mr. Darel Wee Kiat TOH at (65) 9737 7263; dareltoh@u.nus.edu, and we will, according to your request terminate your further participation in the study and/or destroy any data that has not been analysed. Withdrawal of participation in the study will prevent your collected information from contributing to further research and analysis, but it will not be possible to remove your data from analyses that has already been done. Your biological samples collected will be considered to be gifted to NUS and will not be returned to you; however, you may request us to destroy any unused samples that could identify you.

You will also not have any right or claim to any share in the commercial gain derived from the research (if any). However, you retain your right to ask the Principal Investigator or Co-Investigator to discard or destroy any remaining samples if the biological samples have not been used for the research/future research or if it has been used for research/future research but it is practicable to discontinue further use of the biological samples for the research/future research.

In the circumstance that there are changes in the proposed research or serious adverse events that would lead to a change in the proposed research, you will be contacted for further consent. Your doctor, the Principal Investigator or the Co-investigator of this study may stop your participation in the study at any time if they decide that it is in your best interests. They may also do this if you do not follow instructions required to complete the study adequately. If you have other medical problems or side effects, the Principal Investigator and/or Co-Investigator will decide if you may continue in the research study.

In the event of any new information becoming available that may be relevant to your willingness to continue in this study, you will be informed in a timely manner by the Principal Investigator, Co-Investigator or his/her representative.

11. Compensation for Injury

In the unlikely event that you are physically injured during the process of this study despite following the directions of the Principal Investigator in charge of this research, NUS, without legal commitment, will compensate you for the injuries arising from your participation in the study without you having to prove NUS is at fault. By signing this consent form, you will not waive any of your legal rights or release the parties involved in this study from liability for negligence. There are however conditions and limitations to the extent of compensation provided. You may wish to discuss this with your Principal Investigator.

12. Confidentiality of Study and Medical Records

Information collected for this study will be kept confidential. Your records, to the extent of the applicable laws and regulations, will not be made publicly available. The records of this study will be kept strictly confidential with immediate access to your identifiable information (e.g. names, NRIC, contact, no. and email address) granted only to the Principal Investigator, Co-Investigator and authorised personnel. The original paper copies of all identifiable data will be kept in locked storage cabinets and rooms and electronic copies of all identifiable data will be kept on a secure website with access limited to the Principal Investigator, Co-Investigator and authorised personnel only. Identifiable information will never be used in publication or presentation and all your identifiable health information and research data will be coded (i.e. only identified with a code number) and kept separated from the data. The link between your identifiable information and the code number will be kept confidential by the Principal Investigator and Co-Investigator.

However, NUH, NUS and NHG Domain-Specific Review Board and Ministry of Health will be granted direct access to your original medical records to check study procedures and data, without making any of your information public. By signing the Informed Consent Form attached, you are authorizing (i) collection, access to, use and storage of your “Personal Data, and (ii) disclosure to authorised service providers and relevant third parties.

“Personal Data” means data about you which makes you identifiable (i) from such data or (ii) from that data and other information which an organisation has or likely to have access. This includes medical conditions, medications, investigations and treatment history. Research arising in the future, based on this personal data, will be subject to review by the relevant institutional review board. Any biological samples and/or information containing your “Personal Data” that is collected for the purposes described in this Informed Consent Form will not be transferred out of Singapore.

Data collected and entered into the Case Report Forms are the property of NUS. All research data collected will be retained by the PI and/or Co-Investigator for a minimum of 10 years in accordance to NUS’s Research Data Management Policy for use in this research study and if agreeable, future nutritional research in Singapore by NUS and/or NUS’s collaborators for as long as they are necessary. In the event of any publication regarding this study, your identity will remain confidential.

13. Consent to be contacted for future research

You are being asked for permission to be contacted in the future for participation in research studies that you may be suitable for. If you agree to be contacted, your information and contact details will be entered and stored in a secured database in NUS. Your information and contact details will not be released to any parties outside NUS without your permission. When investigators from NUS identify you to be suitable for a particular research study, the investigators or authorised personnel from NUS will contact you to inform you about the research study. Your decision to be contacted for future research studies is completely voluntary and separate from your decision to participate in this study. Your decision will not affect your medical care or any benefits to which you are entitled. You may change your mind at any time by contacting Co-Investigator, Dr. Jung Eun KIM at (65) 6516 1136; chmkje@nus.edu.sg or Study Coordinator, Mr. Darel Wee Kiat TOH at (65) 9737 7263; dareltoh@u.nus.edu.

14. Who To Contact if You Have Questions

Please contact Co-Investigator, Dr. Jung Eun KIM at (65) 6516 1136; chmkje@nus.edu.sg or Study Coordinator, Mr. Darel Wee Kiat TOH at (65) 9737 7263; dareltoh@u.nus.edu for all research-related matters and in the event of research-related injury; NUS Food Science & Technology Programme, Science Drive 2, S14 Level 5. Do not hesitate to contact us at any point before, during or after the research study.

The study has been reviewed by the NHG Domain Specific Review Board (the central ethics committee) for ethics approval.

If you want an independent opinion to discuss problems and questions, obtain information and offer inputs on your rights as a research subject, you may contact the NHG Domain Specific Review Board Secretariat at 6471-3266. You can also find more information about participating in clinical research, the NHG Domain Specific Review Board and its review processes at www.research.nhg.com.sg.

If you have any complaints or feedback about this research study, you may contact the Principal Investigator, Co-Investigator or the NHG Domain Specific Review Board Secretariat.

Consent Form

Protocol Title:

Cardio-vascular protective effects of wolfberry in middle-aged and older adults

Principal Investigator & Contact Details:
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I voluntarily consent to take part in this research study. I have fully discussed and understood the purpose and procedures of this study. This study has been explained to me in a language that I understand. I have been given enough time to ask any questions that I have about the study, and all my questions have been answered to my satisfaction.

By participating in this research study, I confirm that I have read, understood and consent to the NUS Data Protection Policy.

I hereby acknowledge that:

1. I have agreed to take part in the above research.

2. I have received an informed consent form which explains the use of my blood and data in this research. I understand its contents and agree to donate my blood and data for the use of this research.

3. I can withdraw from the study at any point of time by informing the Principal Investigator and/or Co-Investigator and all my blood/tissue/data will be discarded if they have not been anonymised.

4. I will not have any financial benefits from participating in this study.

Consent for the use of biological specimen and data for future research

☐ Yes, I agree to donate my biological samples and research data for future research as long as the research is related to nutrition.

OR

☐ No, I do not agree to donate my biological samples and research data for future nutrition-related research.

Consent to be re-identified and notified in the case of an incidental finding

☐ Yes, I agree to be re-identified and notified in the case of an incidental finding from this research.

In the event that I cannot be reached, please contact my next-of-kin

Name of next-of-kin: _____

Contact: _____

OR

☐ No, I do not agree to be re-identified and notified in the case of an incidental finding from this research.

Consent to be contacted for future research

☐ Yes, I agree to be contacted for future research that I may be eligible for.
I agree to be contacted via:

☐ Phone: _____

☐ Mail: _____

☐ Email: _____

☐ Others: _____

OR

☐ No, I do not agree to be contacted for future research.Your signature below indicates that you have decided to volunteer as a research participant for this study, and that you have read and understood the information provided above.

_____	_____	_____
Name of Participant	Signature	Date

Witness Statement
I, the undersigned, certify that:

- I am 21 years of age or older.
- To the best of my knowledge, the participant/ the participant's legally acceptable representative signing this informed consent form has the study fully explained in a language understood by him/her and clearly understands the nature, risks and benefits of his/her participation in the study.
- I have taken reasonable steps to ascertain the identity of the participant/ the participant's legally acceptable representative giving the consent.
- I have taken steps to ascertain that the consent has been given voluntarily without any coercion or intimidation.

_____	_____	_____
Name of Witness	Signature	Date

Investigator Statement
I, the undersigned, certify that I explained the study to the participant and to the best of my knowledge the participant signing this informed consent form clearly understands the nature, risks and benefits of his/her participation in the study.

_____	_____	_____
Name of Investigator / Person administering consent	Signature	Date