Participant Information Sheet

Study title:	**Impact of the New Zealand pine bark extract (Enzogenol®) on sucrose metabolism and glycaemic responses in healthy adults – a single-blind, randomised, placebo-controlled, crossover trial**		
Sponsor:	**ENZO Nutraceuticals Ltd.**		
Locality:	**Massey University Albany Campus, Auckland**	Ethics committee ref.:	**Central Health and Disability Ethics Committees (Central)**
Lead investigator:	**Wen Xin Janice Lim**	Contact email:	**w.x.j.lim@massey.ac.nz**

Researcher Introduction

My name is Dr Janice Lim, a Postdoctoral Researcher at the Riddet Institute, Massey University, Auckland Albany campus.

Invitation to Participate in this Research Study

Thank you for your interest in our research on investigating the impact of the New Zealand pine bark extract (Enzogenol®) on sucrose metabolism and glycaemic responses in healthy adults. Whether or not you take part is your choice. If you don't want to take part, you don't have to give a reason. If you do want to take part now, but change your mind later, you can pull out of the study at any time.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide you may want to talk about the study with other people, such as family, whānau, friends, or healthcare providers. Feel free to do this.

If you agree to take part in this study, you will be asked to sign the Consent Form. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep.

This document is 10 pages long. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

Obesity and diabetes are epidemic in New Zealand (and in other Western countries), and many individuals now have problems controlling their blood glucose levels within normal levels. More alarmingly, epidemiological studies have shown that approximately 40% of individuals with normal glucose tolerance (NGT) may still eventually develop type 2 diabetes. Research has also revealed that 20% of NGT individuals already have a certain degree of insulin resistance.

Enzogenol® contains a high level of proanthocyanidins, which are part of polyphenols (normally found in fruits and vegetables), and they may be responsible for the inhibition of digestion enzymes including alpha-amylase, alpha-glucosidase and DPP-4 enzymes. It is hypothesised that Enzogenol® will be able to inhibit the enzymes involved in the digestion of sucrose (also known as white sugar, and typically found in most processed foods) such as the enzyme sucrase that breaks down sucrose into simpler units of glucose and fructose for absorption. The enzyme inhibition will reduce or delay the digestion of sucrose for subsequent absorption and may therefore aid in improving glycaemic (glucose) control in humans.

This study therefore aims to determine if Enzogenol® of two effective doses (50 and 400 mg) is able to improve postprandial (after-meal) glucose and insulin responses in healthy participants when consumed together with 75 g of sucrose solution. The treatments will be compared to a placebo (no treatment, only sucrose solution), and Reducose® (Phynova Group, Ltd.), which is a commercially available water extract of white mulberry (*Morus alba Linn*) leaf extract (standardised to 4.5-5.5% 1-deoxynojirimycin, DNJ), that has been used to regulate glucose metabolism in humans.

WHO CAN TAKE PART IN THE STUDY?

To take part in this study you must be:

- ✓ Healthy (either male or female)
- ✓ Aged 18-60 years old
- ✓ Body Mass Index (BMI) of 18.5-29.9kg/m^2 (BMI is calculated using formula body weight (kg)/ height (m) x height (m))
- ✓ Glycated haemoglobin A1c (HbA1c) <39 mmol/mol (According to American Diabetes Association (ADA) guidelines)
- ✓ Fasting blood glucose (FBG) <5.6 mmol/L (ADA guidelines)
- ✓ Able to communicate well in English

You are NOT eligible to participate if you:

- ✓ Body Mass Index (BMI) >29.9kg/m^2
- ✓ Glycated haemoglobin A1c (HbA1c) >39 mmol/mol (ADA guidelines)
- ✓ Fasting blood glucose (FBG) >5.6 mmol/L (ADA guidelines)
- ✓ Known food allergies or intolerance to pine bark extract or mulberry leaf extract
- ✓ Dieting or having dietary restrictions or dietary disorders
- ✓ Pre-existing medical conditions (e.g. cardiovascular disease (CVD), diabetes, hypertension (high blood pressure), gastrointestinal disorder or liver disease, or taking medications including anti-hyperglycaemic drugs and insulin known to affect glucose metabolism or regulation

- ✓ Use of steroids, protease inhibitors or antipsychotics medicines known to influence glucose metabolism and body fat distribution
- ✓ Pregnant or breastfeeding
- ✓ Smoking

HOW IS THE STUDY DESIGNED AND WHAT WILL MY PARTICIPATION INVOLVE?

The study will involve 40 people from the Auckland region. The study consists of **ONE** screening visit, followed by **FOUR** test visits over a period of four weeks.

Screening visit

The study will involve you coming to the Massey University Nutrition Research Facility, located at Albany campus, Auckland for the screening. The screening will be completed within an hour. You will be required to fast (i.e. no food or drink except water) for at least 10-12 h prior to your screening visit.

During the screening visit, you will be asked to complete a consent form, brief medical questionnaire, health screening questionnaire, an eating attitudes questionnaire, and a physical activity questionnaire. A finger prick blood sample will be taken from one of your fingers for fasting glucose, glycated haemoglobin A1c (HbA1c), and lipid profile measurements. Your weight and height, waist and hip circumference, Body Mass Index (BMI), body fat and muscle mass, blood pressure and heart rate will also be taken. You will be provided a copy of the measurements at the end of your screening visit.

Study visits

If you are eligible after the screening, you will need to be available for four mornings taking approximately 2.5 h each. Each study visit will be at least a week apart.

You will be required to fast overnight (i.e. no food or drink except water) for at least 10-12 h before each study visit. The day before each visit you will be asked to refrain from physical activity, and no alcohol, caffeinated tea or coffee formulations, and health supplement consumption 24 hours to each study visit. You will need to keep a constant diet and to refrain from consuming any products containing pine bark or mulberry leaf extract throughout the duration of the study.

During your study visit, you will be provided one of the four study treatments in a randomised and blinded manner. This means that you will not know which treatment will be allocated to you on the study visit. The treatment visits are as follows but in randomised order:

- 250 mL of water + 75 g of sucrose powder only
- 250 mL of water + 75 g of sucrose powder + 250 mg of Reducose®
- 250 mL of water + 75 g of sucrose powder + 50 mg of Enzogenol®
- 250 mL of water + 75 g of sucrose powder + 400 mg of Enzogenol®

A trained phlebotomist will be on site to obtain a baseline fasting capillary blood sample from you on your fingertip. After 10 minutes, another baseline blood sample at time 0 min will be obtained from your fingertip, after which you will be promptly provided

with the study treatment to consume. You will need to finish consuming the treatment within 5 minutes. Further blood samples will be taken at time points 15, 30, 45, 60, 90 and 120 min.

Refer to **Figure 1** below for an overview of the study visit. Blood samples taken will be used to measure blood glucose and insulin levels. At each visit, 2.7 mL (half a teaspoon) of blood will be obtained from the finger prick test, and a total of 11 mL (approx. 2 teaspoons) of blood will be collected for the whole study. You will need to remain in the research facility for 2.5 hours and not undertake any physical activity. Study and quiet activities are allowed, as are trips to the bathroom.

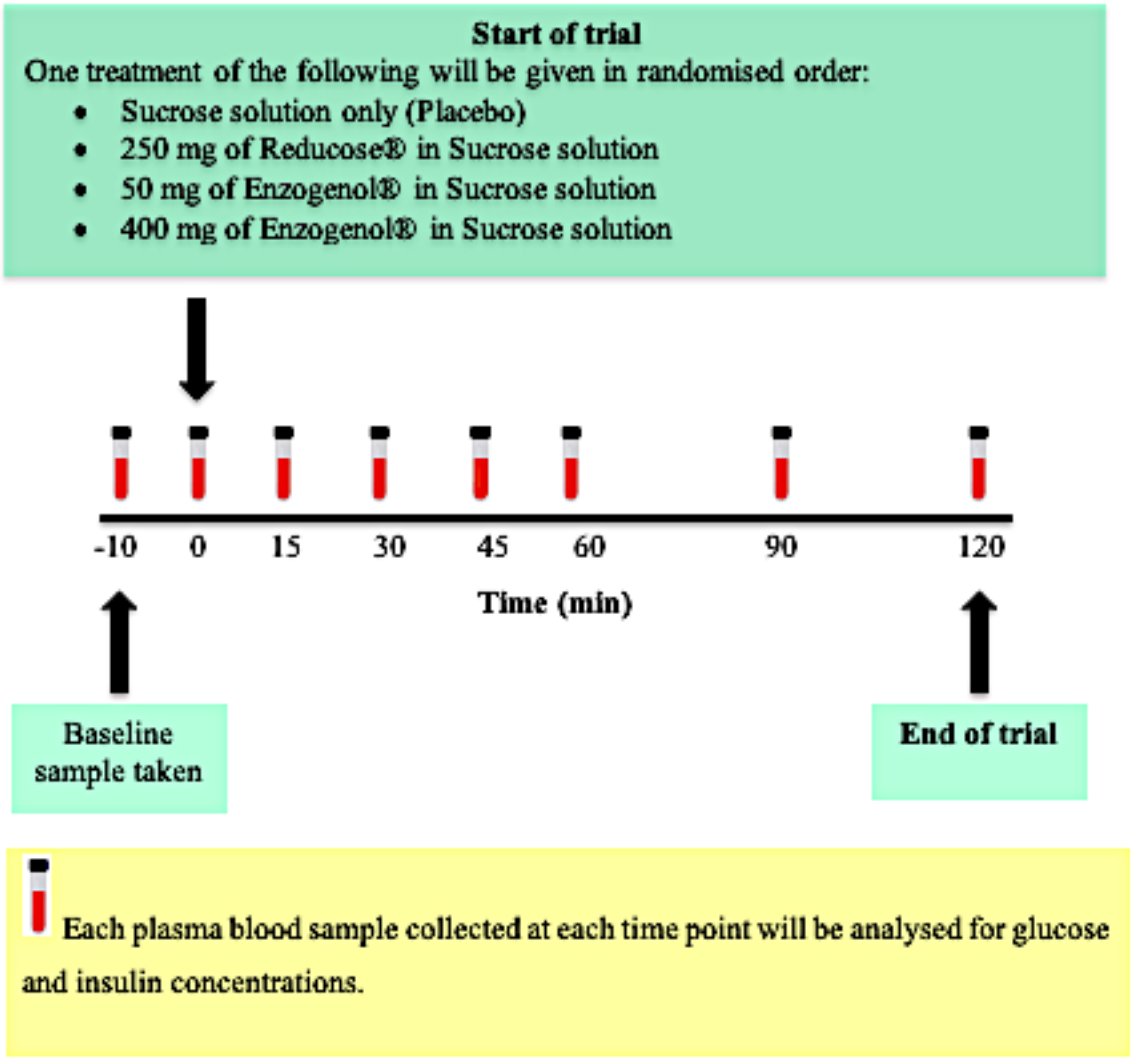

Figure 1. An overview of each study visit.

WHAT WILL HAPPEN TO MY BLOOD SAMPLES?

Your blood samples will be identified using a code unique to you. The samples will be sent to Waitemata DHB North Shore Hospital Laboratory and Massey University Nutrition Lab for the analysis of glucose and insulin levels.

Please note that subject to you giving consent to be part of this study, any stored blood samples may be used for additional testing related to this study including further markers of inflammation.

Blood samples will be stored at Massey University, Albany for a maximum of two years.

If you withdraw during the study your blood samples will be disposed of or returned to you upon request. If you have completed the study, you cannot withdraw the samples.

The cultural issues associated with storing your blood samples and analysis on them should be discussed with your family/whānau as appropriate. We are happy to meet with you and your family/whānau to discuss the study further. We also suggest that your family/whānau is involved with you at all stages of the study. You may hold beliefs about a sacred and shared value of all or any blood samples removed. There is a range of views held by Māori around these issues; some iwi disagree with storage of samples citing whakapapa and advise their people to consult prior to participation in research where this occurs. However, it is acknowledged that individuals have the right to choose.

WHAT ARE THE POSSIBLE BENEFITS AND RISKS OF THIS STUDY?

Research is a big part of medicine and healthcare and being involved can be very rewarding. You can learn a lot about the processes that are involved in research by actively participating and it can be satisfying to know that you are contributing to knowledge. Furthermore, by participating in the study you also obtain information about your general health status, HbA1c value, body composition and blood pressure measurement entirely at no cost to you.

It is highly unlikely that you will be injured during this study. Obtaining blood samples via the finger prick test is routinely used. Foreseeable risks, adverse-effects and discomforts that you may encounter by taking part in this study are minimal, but could include possible infection from the site in which blood is drawn and there may be some minor bruising at this site as well. A registered personnel will be available during each study session and researchers will be present to assess for adverse events (i.e. feeling nauseous, dehydrated or faint) during each blood sampling, and any event will be documented in alignment with Massey Code of Ethical Conduct.

WILL ANY COSTS BE REIMBURSED?

There is no cost to you, the participant, for taking part in this study.

In recognition of your participation in this study, you will receive a koha of $10 for screening and $50 for completion of each session. You will be given a total koha of $210 for completing the whole study (1 screening visit and 4 study visits) in the form of a gift voucher. If for any reason you are unable to complete the study, you will be reimbursed for the visits you completed.

WHAT IF SOMETHING GOES WRONG?

"Commercially sponsored" intervention studies:

As this research study is for the principal benefit of its commercial sponsor ENZO Nutraceuticals Ltd., if you are injured as a result of taking part in this study you **won't** be eligible for compensation from ACC.

However, ENZO Nutraceuticals Ltd. has satisfied the Central Health and Disability Ethics Committee that approved this study that it has up-to-date insurance for providing participants with compensation if they are injured as a result of taking part in this study.

New Zealand ethical standards require compensation for injury to be at least ACC equivalent. Compensation should be appropriate to the nature, severity and persistence of your injury and should be no less than would be awarded for similar injuries by New Zealand's ACC scheme.

Some sponsors voluntarily commit to providing compensation in accordance with guidelines that they have agreed between themselves, called the Medicines New Zealand Guidelines (Industry Guidelines). These are often referred to for information on compensation for commercial clinical trials. There are some important points to know about the Industry Guidelines:

- On their own they are not legally enforceable and may not provide ACC equivalent compensation.
- There are limitations on when compensation is available, for example compensation may be available for more serious, enduring injuries, and not for temporary pain or discomfort or less serious or curable complaints.
- Unlike ACC, the guidelines do not provide compensation on a no-fault basis:
- The Sponsor may not accept the compensation claim if:
    - Your injury was caused by the investigators, or;
    - There was a deviation from the proposed research plan, or;
    - Your injury was caused solely by you.

An initial decision whether to compensate you would be made the by the sponsor and/or its insurers.

If they decide not to compensate you, you may be able to take action through the Courts for compensation, but it could be expensive and lengthy, and you might require legal representation. You would need to be able to show that your injury was caused by participation in the trial.

You are strongly advised to read the Industry Guidelines and ask questions if you are unsure about what they mean for you.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT WILL HAPPEN TO MY INFORMATION?

During this study the researchers will record information about you and your study participation. This includes the results of any study assessments and questionnaires you have completed at screening. If needed, information from your hospital records and your GP may also be collected. You cannot take part in this study if you do not consent to the collection of this information.

Identifiable Information

Identifiable information is any data that could identify you (e.g. your name, date of birth, or address). Only researchers will have access to your identifiable information. Your usual doctor (your GP or specialist), if a study test gives an unexpected result that could be important for your health or well-being. This allows appropriate follow-up to be arranged.

De-identified (Coded) Information

To make sure your personal information is kept confidential, information that identifies you will not be included in any report generated by the researcher and any study information sent to the sponsor. Instead, you will be identified by a code. The researcher will keep a list linking your code with your name, so that you can be identified by your coded data if needed. The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you.

Future Research Using Your Information

If you agree, your coded information may be used for future research related to the study. If you agree, your coded information may also be used for other medical and/or scientific research that is unrelated to the current study.

This future research may be conducted overseas. You will not be told when future research is undertaken using your information. Your information may be shared widely with other researchers or companies. Your information may also be added to information from other studies, to form much larger sets of data.

You will not get reports or other information about any research that is done using your information.

Your information may be used indefinitely for future research unless you withdraw your consent. However, it may be extremely difficult or impossible to access your information, or withdraw consent for its use, once your information has been shared for future research.

Security and Storage of Your Information

Your identifiable information is held at Massey University during the study. After the study it is transferred to a secure archiving site and stored for at least ten years, then destroyed. Coded study information will be kept by the study researchers in secure, cloud-based storage indefinitely. All storage will comply with local and/or international data security guidelines.

Risks

Although efforts will be made to protect your privacy, absolute confidentiality of your information cannot be guaranteed. Even with coded and anonymised information, there is no guarantee that you cannot be identified. The risk of people accessing and misusing your information (e.g. making it harder for you to get or keep a job or health insurance) is currently very small, but may increase in the future as people find new ways of tracing information.

This research includes basic information such as your ethnic group, geographic region, age range, and sex. It is possible that this research could one day help people in the same groups as you. However, it is also possible that research findings could be used inappropriately to support negative stereotypes, stigmatize, or discriminate against members of the same groups as you.

Rights to Access Your Information

You have the right to request access to your information held by the research team. You also have the right to request that any information you disagree with is corrected.

Please ask if you would like to access the results of your screening tests during the study. You may access other study-specific information before the study is over, but this could result in you being withdrawn from the study to protect the study's scientific integrity.

If you have any questions about the collection and use of information about you, you should ask the researcher.

Rights to Withdraw Your Information

You may withdraw your consent for the collection and use of your information at any time, by informing the researcher.

If you withdraw your consent, your study participation will end, and the study team will stop collecting information from you.

If you agree, information collected up until your withdrawal from the study will continue to be used and included in the study. You may ask for it to be deleted when you withdraw, unless you withdraw after the study analyses have been undertaken.

Ownership Rights

Information from this study may lead to discoveries and inventions or the development of a commercial product. The rights to these will belong to ENZO Nutraceuticals Ltd. and the Riddet Institute. You and your family will not receive any financial benefits or compensation, nor have any rights in any developments, inventions, or other discoveries that might come from this information.

Māori Data Sovereignty

Māori data sovereignty is about protecting information or knowledge that is about (or comes from) Māori people. We recognise the taonga of the data collected for this study. To help protect this taonga:

- We have consulted with the Maori committee about the collection, ownership, and use of study data.
- We allow Māori organisations to access de-identified study data, for uses that may benefit Māori.

WHAT ARE MY RIGHTS?

Participating in this study is completely voluntary and you are free to decline to participate, decline to answer any particular question, or to withdraw from the research at any practicable time, without experiencing any disadvantage.

You, the participant has a right to access information about you, collected as part of this study. You will be told of any new information about adverse or beneficial effects related to this study which may impact upon your health.

It is important to us that we maintain your privacy throughout this study. Your name and contact information will be held electronically and stored on the Principal Investigators computer only for data recording purposes. Each participant in the study will be allocated a unique code. Staff involved in blood sampling and analysis will have access to participant codes only. All data from study sessions will be recorded against your participant unique code and your name will never be used in any report, correspondence or publication. Your involvement in this study is confidential.

WHAT HAPPENS AFTER THE STUDY OR IF I CHANGE MY MIND?

You are able to pull out of the study at any time, and will be compensated accordingly for your time. Further you are welcome to discuss any concerns you have with the research team at any time, and you have free access to your data. If you pull out of the study all of the data that was related to you will be shredded/destroyed. No study intervention will be provided after the study, and you will not be told what intervention you were provided with during the study.

The study data will be stored at a secure location at Massey University Albany Campus. Electronic data and records will be the responsibility of the Principal investigator. All data will be kept for ten years, at which point it will be destroyed using University Security methods for removal of confidential material.

CAN I FIND OUT THE RESULTS OF THE STUDY?

Participants are welcome to discuss the findings of this study with the researchers when data collection and analysis have been completed. It is very likely that the results of this study will be written up for publication in a peer-reviewed journal and/or presentation at a Nutrition conference within 12 months of completing the study. You will also be provided with a copy of the publication, if requested. If this happens no participant identification information will be included.

WHO IS FUNDING THE STUDY?

The funding is externally funded by ENZO Nutraceuticals Limited.

WHO HAS APPROVED THE STUDY?

This study has been approved by an independent group of people called a Health and Disability Ethics Committee (HDEC), who check that studies meet established ethical standards. The Central Health and Disability Ethics Committee (HDEC) has approved this study.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact the following researchers involved in the study:

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Dist/Prof Paul J Moughan: Distinguished Professor, Fellow Laureate of Riddet Institute, Massey University, Albany Campus, Auckland
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This project has been reviewed and approved by the Health and Disability Ethics Committees (HDEC). If you have any concerns about the conduct of this research, please contact the Health and Disability Ethics Committees (HDEC) Secretariat at hdecs@health.govt.nz or visit the website at www.ethics.health.govt.nz for more information.