Protocol #: MHICC-2020-003

A phase 2, randomized, double-blind, placebo-controlled study of hesperidin therapy on COVID-19 symptoms:
The Hesperidin Coronavirus study (Hesperidin)

NCT #: NCT04715932

Informed Consent Form v3

21-Jan-2021

APPROUVÉ / APPROVED
Comité d'éthique ICM
MHI – Research Ethics Board
Date : 21 janvier 2021

INFORMATION AND CONSENT FORM

RESEARCH PROJECT: 2021-2841

A phase 2, randomised, double-blind, placebo controlled study of hesperidin therapy on COVID-19 symptoms: The Hesperidin Coronavirus study

Hesperidin

Principal Investigator and Co-Investigators
Jocelyn Dupuis MD, PhD; Jean-Claude Tardif MD.

Sponsor
Montreal Heart Institute

Granting agencies
Montreal Heart Institute Foundation
Ingenew Pharmaceuticals Inc.

PREAMBLE

We are inviting you to take part in this research project because you have been diagnosed with COVID-19 without having more than one high risk criteria of complications from COVID-19.

You are entirely free to accept or refuse to participate.

Before you agree to take part in this project and sign this information and consent form, please take the time to carefully read, understand and consider the following information.

This form may contain words that you do not understand. We invite you to ask the investigator in charge of the project or the other staff members involved in the research project any questions you consider useful and ask them to explain any word or information that is not clear to you.

Taking part in several research projects at the same time may be dangerous. If you are already taking part in a clinical study, please notify the study doctor.

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NATURE AND OBJECTIVES OF THE RESEARCH PROJECT

COVID-19 is due to an infection by the beta-coronavirus SARS-CoV-2. The outbreak of COVID-19 disease started in December 2019 in Wuhan, Hubei Province, China, has spread to other parts of China and Asia, and is now a pandemic that has reached Europe and North America. The number of confirmed cases has reached 12 507 849, including more than 560 460 deaths, as of July 12, 2020.

Patients often present with fever with or without respiratory symptoms, but a large number of patients later develop various degrees of pulmonary abnormalities visible on chest imaging. Although the vast majority of patients only have a benign form of the illness, approximately 15% of the patients will develop a severe form of the disease, with requirement of assisted ventilation and oxygenation. These patients suffer from acute respiratory distress syndrome.

The main aim of this study is to determine the effects of short-term treatment with hesperidin on COVID-19 symptoms in comparison with a placebo. Treatment effects will be observed through a symptoms diary that will be completed by participants throughout the study and by taking the oral temperature daily.

This research study involves the use of hesperidin at a dose of 1000 mg once a day (2 capsules of 500 mg once a day) or of a placebo. The use of hesperidin in the treatment of COVID-19 has not been approved by regulatory health bodies such as Health Canada and that is why the usage in this research project is experimental.

In addition, hesperidin is a natural flavonoid naturally present in citrus fruits. It is readily available in consumer products such as orange juice and natural products from citrus extracts.

NUMBER OF PARTICIPANTS AND LENGTH OF PARTICIPATION

A total of 216 participants will be recruited in Quebec to participate in this trial and the Montreal Heart Institute which is conducting the study is the only participating site.

Your individual participation in this study will be of approximatively 14 days.

RESEARCH PROJECT FUNDING

The investigator in charge of this research project has received funding from the Montreal Heart Institute Foundation to carry out this project. Hesperidin and placebo used in this study are provided by the company Ingenew Pharmaceuticals Inc.

RESEARCH PROJECT PROCEDURES

If following a telephone interview with a member of the research team, you meet all the eligibility criteria to participate in this research project, you will be randomized, this means that you will be randomly assigned to one of the 2 treatment groups in this study. You will have the same chance of receiving hesperidin (1000 mg once a day) as placebo (a product apparently similar to the study product, but which does not contain any active ingredient).

This is a double-blind study, which means that neither you nor your study doctor will know whether you are receiving the study product or the placebo until the end of the study unless an emergency occurs. Over the course of the study, you will continue to receive all the standard medical care that you may require.

Your participation in this study will be of approximatively 14 days. In addition to the phone interview during which the study selection criteria will be verified and the randomization completed, you will have 4 phone visits to assure follow-up as well as complete your study participation. During these calls, on day 3, 7, 10 and 14, the study team will ask you questions about the symptoms you have and that you need to enter in the symptoms diary provided to you. Your participation in the study will end with the fourth follow-up call which will take place on day 14 of your participation.

If you meet the inclusion criteria, and do not meet any of the exclusion criteria, we will send you the consent form by email which you must read and sign electronically via your cell phone, your tablet or your computer.

You will receive your bottle of hesperidin or placebo at the door of your home by the services of a delivery man hired by the Montreal Heart Institute. The delivery person will contact you to inform you of the arrival of your product. In addition to the study product, you will also receive an electronic thermometer to take your oral temperature everyday, as well as a symptoms diary that you will need to complete everyday.

During your participation, you will need to take 1000 mg of the study product once a day, meaning 2 capsules of 500 mg at the same time, in the evening, at bedtime, with a little bit of water. The study product should be taken in a fasting condition, meaning at least 1 hour before and at least 2 hours after a meal. If in doubt, do not hesitate to contact the research team.

Moreover, we will ask you for an emergency phone number to reach you if you are hospitalized, in the purpose of the study objectives. This phone number will be kept confidential by the research team and will not be provided to any third party.

The following table summarizes your participation in the research project.

	Screening/ randomization phone call	**Phone call***	**Phone call (±1 day)**	**Phone call (±3 days)**	**Phone call (±3 days)**
Day	***0***	***3***	***7***	***10***	***14***
Length	***1h15***	***30 minutes***	***30 minutes***	***30 minutes***	***30 minutes***
Consent form	***X***				
Demographics	***X***				
Medical and surgical history	***X***				

	Screening/ randomization phone call	Phone call*	Phone call (±1 day)	Phone call (±3 days)	Phone call (±3 days)
Day	*0*	*3*	*7*	*10*	*14*
Length	*1h15*	*30 minutes*	*30 minutes*	*30 minutes*	*30 minutes*
Concomitant medication	X	X	X	X	X
COVID-19 symptoms and temperature	X	X	X	X	X
Inclusion/exclusion criteria	X				
Urinary pregnancy test	X				
Adverse effects and complications		X	X	X	X
Study product, symptoms diary and electronic thermometer shipping	X				
Study product compliance		X	X	X	X
Symptoms diary return					X

*If day 3 occurs on the weekend, the phone call will be done on previous Friday or following Monday, whichever is the closer to day 3.

Here are a few explanations about the preceding table:

Consent form: Before beginning the study, we will ask you to read, understand and sign the present consent form.

Demographics: We will ask you for personal information such as your age, sex and ethnicity.

Medical and surgical history: We will collect information on the medication you are taking or have taken as well as past medical and surgical procedures.

Concomitant medication: We will ask whether you are taking medications, under prescription or over the counter. If you are taking anticoagulant or antiplatelet medication, you cannot participate in the study.

COVID-19 symptoms and temperature: We will ask you about your symptoms related to your COVID-19 infection. In order to facilitate the daily evaluation of the COVID-19

symptoms, you will receive a symptoms diary in which you will have to check the symptoms you are suffering each day. Furthermore, we will ask you to take your temperature orally everyday, using the electronic thermometer that will be provided to you. You will need to enter the temperature obtained in the patient-log-book.

Inclusion/Exclusion criteria: We will ask you questions to make sure you meet all the study inclusion criteria and none of the exclusion criteria. For example, to participate in the study, your regular consumption of orange juice should not exceed one glass per day.

Pregnancy test (urine): This test will be carried out only on women who can become pregnant. If the nurse considers it necessary for the participant to take a pregnancy test, the pregnancy test will be sent with the study drug following her randomization. In this case, the product will only be started after the home test confirming the absence of pregnancy.

Adverse effects and compilations: We will ask you if you have experienced any side effects related to the study product or complications related to your COVID-19 infection.

Study product, symptoms diary and electronic thermometer shipping: Thanks to a home delivery service, you will receive the study product, the symptoms diary, the electronic thermometer, and a pregnancy test if it has been determined that you need to have one. You will receive the needed number of capsules for the duration of your 14-day treatment. A pre-addressed, pre-paid envelope will also be added to this shipping in order to return the symptoms diary to the study team.

Study product compliance: Follow-ups about the study product compliance will be done at each phone call to make sure you take the study product adequately.

Symptoms diary return: You will need to return the symptoms diary to the study team using the pre-addressed, pre-paid envelope provided to you.

PARTICIPANT'S RESPONSIBILITIES

In order to be able to take part in this study, you will be asked to DO the following:

- Take the study product and store it as per the instructions that you will be given by the study staff;
- Throw the bottle and unused capsules away in the garbage at the end of the study;
- If you forget a dose of the study product, you must not under any circumstances double the following dose;
- Not share the study product with other people;
- Tell the study doctor about any other medications you are taking or plan to take including any prescription or nonprescription drugs, medicinal herbs or supplements;
- Record the symptoms you have on a daily basis in the symptoms diary provided to you;

- Take you temperature orally each day with the electronic thermometer provided to you and record it in the symptoms diary;
- Inform the study team if you are unavailable for a phone follow-up appointment. A new phone follow-up appointment will be scheduled;
- Inform the study doctor if you think you are pregnant;
- Inform the study doctor if you take anticoagulant/antiplatelet medications, if you have bleeding disorders (blood capacity to form clots), or if you had a surgery 2 weeks before the start of the study or if you plan to have one in the following 2 weeks after the end of the study;
- At the beginning of the study, in the same package as the study product, you will receive an information card with details on the study and how to contact the study doctor in case of an emergency. You should keep this card with you at all time during your participation in this study.
- In order to be able to take part in this study, you will be asked NOT to take on a daily basis the natural product containing more than 150 mg of hesperidin or drink more than a glass of orange juice per day.

RISKS ASSOCIATED WITH THE RESEARCH PROJECT

By participating in this research project, you may be exposed to products that involve particular unknown, unexpected or unforeseeable risks. The purpose of this section is to describe the foreseeable risks associated with your participation in this research project. Consequently, the risks associated to your COVID-19 infection are not detailed here.

Hesperidin-related risks

Orally, hesperidin is generally well tolerated. However, you may experience some side effects from taking hesperidin.

For example, hesperidin may have effects on blood clotting and thus increase the risk of bleeding. This is why people with bleeding disorders, people taking anticoagulant or antiplatelet medications and people who are scheduled or who have had surgery within 2 weeks before or after the study are not allowed to participate in the study. **Please inform the study doctor without delay if you are in any of these groups of people.**

As well, some patients who took hesperidin have experienced headaches, physical fatigue, muscle cramps and gastrointestinal disorders such as abdominal pain, nausea, diarrhea and dyspepsia (discomfort in the upper region of the abdomen originating in the stomach or nearby structures).

Risks related to placebo:

Some participants in this study will receive a placebo. Taking a placebo is equivalent to being treated in accordance with standard practices. If you are one of the research participants receiving the placebo, your condition could stay the same or get worse like it would have been the case without any additional treatment.

Risk of breach of confidentiality:

During this study, the study product will be delivered to you by a third party mandated by the Montreal Heart Institute. Your name and telephone number will be entrusted to this agent so that he can proceed with the delivery. These exceptional measures are taken to avoid any contagion but may affect the confidentiality of your personal information and the protection of your identity. The company that will deliver the study product has signed a confidentiality agreement.

RISKS RELATED TO PROCREATION

Participation in this research project may involve known or unknown risks for pregnant women, unborn children or breastfed infants. Consequently, pregnant or nursing women cannot participate in this project.

Women of childbearing potential must undergo a pregnancy test before they start participating in the project. In the event that the nurse deems it necessary for the participant to take a pregnancy test, the test will be shipped in the same package as the product under study. Additional pregnancy tests will be performed throughout the research to ensure that you have not become pregnant during your participation in the project.

The investigator in charge or the research project staff will check your birth control method to ensure that it is medically acceptable.

If you think that you have become pregnant during your participation in this project, you will need to notify the investigator in charge of the research project immediately in order to discuss the various options.

INCONVENIENCES ASSOCIATED WITH THE RESEARCH PROJECT

You may experience some inconvenience from participating in this study, especially because of the time you will have to devote to it.

BENEFITS

You may personally benefit from your participation in this research project, but this cannot be guaranteed. However, the results obtained will contribute to furthering scientific knowledge in this field.

PROCEDURE IN THE EVENT OF DEATH

In the event of your death while participating in this research project, it may be useful for the research project investigator and the sponsor to know information about your health condition at the time of your death and the causes of your death. For this purpose, you may authorize the project investigator to obtain a copy of your medical record from another health care or extended care facility. This may include a copy of your record from the emergency department or from any department of another hospital, nursing home or medical clinic. The information collected will only be used for the purposes of this research and will remain confidential. It may be shared with the sponsor or granting agency of this study.

VOLUNTARY PARTICIPATION AND THE RIGHT TO WITHDRAW

Your participation in this research project is voluntary. Therefore, you may refuse to participate. You may also withdraw from this project at any time, without giving any reason, by informing the research team.

Your decision not to participate in this research project, or to withdraw from it, will have no impact on the quality of care and services to which you are otherwise entitled, or on your relationship with the teams providing them.

The doctor in charge of this research project, the Research Ethics Board, the granting agency, or the sponsor may end your participation without your consent. This may happen if new findings or information indicate that your participation is no longer in your interest, if you are not following the study instructions, or if there are administrative reasons to terminate the project.

However, before your withdrawal from this research project we suggest, that you contact the study team for a final evaluation, for safety reasons.

If you withdraw or are withdrawn from the project, the information and material already collected during this project will nonetheless be retained, analyzed or used to ensure the integrity of the project.

Any new findings during the course of the project that could influence your decision to stay in this project will be shared with you quickly.

CONFIDENTIALITY

During your participation in this research project, the doctor in charge of this project and the research staff members will collect information in a study file about you which is required to meet the scientific goals of this research project.

This may include information concerning your past and present state of health, your lifestyle, as well as the results of all tests, exams, and procedures that will be performed.

Your file could also contain other information, such as your name, sex, date of birth and ethnic origin.

All the information collected will remain confidential to the extent provided by law. You will only be identified by a code number. The key to the code linking your name to your study file will be kept by the doctor in charge of this research project.

This research data will be stored for at least 25 years by the doctor in charge of this research project.

The research data may be published or shared during scientific meetings; however it will not be possible to identify you.

For monitoring, control, safety, security, and marketing of the study product, your study file as well as your medical charts may be examined by a person mandated by regulatory authorities, in Canada or in other countries, such as Health Canada, as well as by

representatives of the sponsor, the institution, or the Research Ethics Board. All these individuals and organizations adhere to policies on confidentiality.

You have the right to consult your research file in order to verify the information gathered,

However, in order to protect the project's integrity, accessing certain information before the project is ended may require that you be withdrawn from the project.

SHOULD YOU SUFFER ANY HARM

Should you suffer harm of any kind following administration of the study product or any other procedure related to this research project, you will receive any care and services required for your health condition.

By agreeing to participate in this research project, you are not waiving any of your rights nor discharging the doctor in charge of this research project, the sponsor or the institution, of their civil and professional responsibilities.

COMPENSATION

If, exceptionally, you had to travel to the Montreal Heart Institute during your participation in this study, your travel, meals, parking costs related to your participation in the research project will be paid by a coupon which you will be given when you return to the study site.

CONTACT PEOPLE

If you have any questions or if you have a problem related to the research project, or if you would like to withdraw, you may contact the doctor in charge or someone on the research team at any time at the following numbers:

Montreal Heart Institute

Jocelyn Dupuis MD, PhD, Investigator:	Tel.: 514 376-3330 (ext. 3542)
Research team:	Tel.: 1 (833) 917-3369

For any question regarding your rights as a participant in this research project or if you have a complaint or comment to make, you may contact:

The Local Complaints and Service Quality Commissioner of the Montreal Heart Institute at the following number: 514 376-3330, ext. 3398.

APPROVAL BY THE RESEARCH ETHICS BOARD

The Montreal Heart Institute Research Ethics and New Technology Development Board has approved this research project and will be monitoring it. It will approve any revisions and any amendments made to the information and consent form and the research protocol.

APPROUVÉ / APPROVED
Comité d'éthique ICM
MHI – Research Ethics Board
Date : 21 janvier 2021

CONSENT FORM

RESEARCH PROJECT: 2021-2841

A phase 2, randomised, double-blind, placebo controlled study of hesperidin therapy on COVID-19 symptoms: The Hesperidin Coronavirus study

Hesperidin

Principal Investigator and Co-Investigators
Jocelyn Dupuis MD, PhD; Jean-Claude Tardif MD.

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I have reviewed the information and consent form. Both the research project and this information and consent form were explained to me. My questions were answered, and I was given sufficient time to make a decision. After consideration, I consent to participate in this research study in accordance with the conditions stated in this form.

In the event of my death, I consent to any health care or long term care facility, including a hospital, nursing home or medical clinic providing a copy of my medical record to the investigator of this study, should this be requested.	☐ I agree	☐ I refuse

In the event that the results obtained in this research lead to the development of an additional research project (substudy or new research directly resulting from this project), I agree to be contacted again to be asked whether I am interested in taking part in this substudy or this new project.	☐ I agree	☐ I refuse

Name of participant ***Signature*** ***Date (dd-mm-yyyy)***

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Signature of the person who obtained the consent

I have explained the research project and the information and consent form to the research participant, and I answered all his/her questions.

Name of the person obtaining consent	*Signature*	*Date (dd-mm-yyyy)*

Commitment of the principal investigator

I certify that the terms of this information and consent form were explained to the participant, that all the participant's questions were answered and that it was clearly explained that the participant is free to end his or her participation.

I undertake, together with the research team, to respect what was agreed upon in the information and consent form, and to give a signed and dated copy of this form to the participant.

Name of the principal investigator	*Signature*	*Date (dd-mm-yyyy)*

WITNESS' SIGNATURE

☐ **YES** ☐ **NO**

A witness's signature is required for the following reasons:

- ☐ Difficulty reading or inability to read – The person (impartial witness) signing below certifies that the consent form was read and the project was explained precisely to the participant, who seems to have understood it.
- ☐ Lack of understanding of the language used in the consent form – The person signing below served as an interpreter for the participant during the consent process.

Name of witness	*Signature*	*Date (dd-mm-yyyy)*

N.B.: A signed and dated copy of this information and consent form will be kept by the principal investigator and a copy will be given to the participant.