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THE STATE UNIVERSITY
OF NEW JERSEY

INTERVENTIONAL RESEARCH PROTOCOL

(HRP-503a)

STUDY INFORMATION

- **Title of Project:** Essential oils and delayed onset muscle soreness in older adults and the elderly; The effects of topical *Mentha x piperita* and *Eucalyptus globulus*

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1.0 Research Design

1.1 Purpose/Specific Aims

The purpose of this study is to find an alternative, low risk option for managing muscle soreness in the older adult and elderly population.

A. Objectives

This study aims to compare how the topical application of essential oils *Eucalyptus globulus* and *Mentha x piperita* impact delayed onset muscle soreness after eccentric exercises compared to one another and to control.

B. Hypotheses / Research Question(s)

It is hypothesized that application of *Eucalyptus globulus* or *Mentha x piperita* oil will reduce perceived muscle soreness in subjects compared to control.

1.2 Research Significance

Delayed onset muscle soreness (DOMS) is a common resultant of activity which exceeds one's typical range. Its effects linger, often beginning 8 to 24 hours after activity and peaking within 24 to 48 hours of repetitive eccentric exercises. [1] Elite athletes must frequently cope with this during the peak of their training, but the average person also experiences its effects following the initiation of an activity regimen or an increase in their routine. It is thought that this phenomenon is multifactorial in nature, with proposed mechanisms including lactic acid retention, damage to connective tissue, and local inflammation. [2] Swelling due to influx of fluid and immune cells into muscle tissue is also a contributing factor. [1] There are a multitude of proposed management strategies for DOMS, ranging from pharmacological approaches like NSAIDs and analgesics, exercise, stretching, cryotherapy, transcutaneous electrical nerve stimulation, ultrasound, fish oils, caffeine, and antioxidants, among others. [1] These methods have varying efficacy and consistency in improving the effects of DOMS, and furthermore they each have their potential for adverse effects or lack of accessibility.

Herbal and natural medicine has been around for many years, particularly in regard to inflammatory disorders and somatic symptoms. As more research into the efficacy of these alternative methods is performed, they become an even more viable option. Essential oils, through aromatherapy, topicals, or ingestion, have been employed for a wide variety of ailments including those of anti-bacterial, anti-oxidant, and anti-inflammatory nature. [3] These oils are generally regarded as safe to use as well, as is proclaimed by the U.S. Food and Drug Administration, particularly when used at appropriate diluted concentrations topically when the risks are minimized further. [4] These oils might be a potential alternative or additive to usual management of muscle soreness, particularly in patient populations like the elderly who are more susceptible to the side effects of medications like NSAIDs.

Oils under the genus *Eucalyptus* and *Mentha* have been shown to have anti-inflammatory and analgesic properties. [5,6,7] Both have been shown to have inhibitory effects on nitrous oxide and reduce the activity of various inflammatory markers. [5,8] *Eucalyptus globulus* is predominantly comprised of 1,8-cineole, which can inhibit neutrophil migration and thereby reduce edema and inflammation. [9] Rodent studies have even shown that *Eucalyptus* may have antinociceptive effects similar to that of morphine [8], which is supported by the subjective pain relief it brought to patients following a total knee replacement. [10] *Mentha x piperita* has been studied for its topical analgesic effects in headache patients, and application appeared to help suppress temporal muscle activity. [11] Local application has been shown to have a cooling effect through alteration of the calcium channels for cool-receptors, which may be soothing. [12] With these benefits in mind, this study aims to identify and compare the effects of topical *Eucalyptus globulus* and *Mentha x piperita* oils in delayed onset muscle soreness in the older adult and elderly population.

1.3 Research Design and Methods

This study is designed as a randomized controlled interventional study with a rolling enrollment over the course of 6 months, with each individual subject's participation spanning over 72 hours. 20 subjects will be recruited for participation. 10 subjects will be included in the *Eucalyptus globulus* intervention group, and the remaining 10 will be placed in the *Mentha x piperita* group. A blocked randomisation list will be generated using an online randomizer in order to allocate subjects to each treatment group randomly. Each subject will have one upper extremity serving as the control, and one upper extremity which receives the intervention.

A. Research Procedures

Subjects

Subjects 50 years old and above with no previous resistance training sessions within the past year will be recruited at The Manor Health and Rehabilitation, a subacute rehabilitation and long-term care facility. A verbal explanation will be provided to the potential subjects by Dr Asselstine or Dr Shah on-site at the facility, including the fact that their care at the facility will not be affected by their decision to participate or not, and if they are interested in proceeding they will be asked to complete a survey regarding the subject's demographics (gender, age, hand dominance), ensure there are no hypersensitivities to the oils being used, upper extremity injuries within 1 year, and that they have the functional capacity for exercise of 3.5 metabolic equivalents or greater based on the Duke Activity Status Index. Subjects will be required to sign a consent to participate in screening. If participants pass the screening process they will again be informed of the study and all potential risks/benefits prior to signing an informed consent to partake in research.

Materials

Eucalyptus globulus and *Mentha x piperita* essential oils will be obtained commercially from SunRose Aromatics (Morrill, Maine), and, individually, will be mixed with carrier oil for application. SunRose Aromatics is a recommended supplier from the RJ Buckle Clinical Aromatherapy for Health Professionals course. Fractionated coconut oil will be used as the carrier oil and also obtained from SunRose Aromatics. A 2% oil mixture for topical application will be made with essential oils diluted in fractionated coconut oil per guidelines from the RJ Buckle Clinical Aromatherapy for Health Professionals course recommendations. This mixture will be prepared directly before application of oils by Dr Asselstine or Dr Shah. The unmixed oils will be stored in a private room with no windows at room temperature at the Manor Health and Rehabilitation facility (689 W Main St, Freehold, NJ 07728).

Intervention

Participants will be divided equally into the *Mentha x piperita* or the *Eucalyptus globulus* group. A 2% oil mixture for topical application will be made with essential oils from SunRise Aromatics diluted in fractionated coconut oil per guidelines from the RJ Buckle Clinical Aromatherapy for Health Professionals course recommendations. Physician-supervised eccentric exercise of the elbow flexors will be performed based on an adaptation of the method described by Weber. [14] Free weight dumbbells will provide resistance. The subject will be instructed to prolong the extension aspect of the curl to be five seconds long. They will repeat this motion for 10 or more repetitions until exhaustion, either due to the participant feeling they can no longer tolerate the five second eccentric aspect of the exercise or the investigator identifying that their form has faltered. If subjects reach exhaustion after the 10 repetitions minimum, they will rest for 1 minute. If they are unable to complete 10 repetitions at this weight, the resistance will be decreased to the next lowest weight and they will continue until exhaustion. This will continue until subjects reach exhaustion with the lowest resistance weight. Immediately following exercise, the participants will have the respective oil applied topically to their left upper extremity by the investigator. Their right upper extremity will serve as the control and no essential oil will be applied. Investigators will apply the oil without any use of massage technique and to only apply very superficial pressure. This application will be repeated 8 hours after exercise, when DOMS has been known to initiate, and at 24 hours after exercise, when DOMS may begin to peak.

Subject Safety

Vital signs will be measured prior to the initiation of exercise, including temperature, heart rate, blood pressure, and oxygen saturation. A physician will be notified of any abnormalities and the subject must be medically optimized prior to exercising. All exercise will be supervised by a physician. After the intervention is applied, subjects will be directly observed for 15 minutes by a physician to ensure no immediate adverse reactions occur. Vital signs will be repeated at the end of the observation period.

Nursing staff will be on-site in their usual capacity and physicians available on-call throughout the duration of the study. Medications are available at the facility if needed for any adverse events.

B. Data Points

Subject outcomes will be based on a self-reported visual analog scale, which has previously been shown to have validity in subjectively quantifying perceived muscle soreness and used in prior studies. [14,16]. These outcomes will be recorded by investigators for both the intervention and control upper extremity at 24, 48, and 72 hours post-exercise.

C. Study Duration

Each subject will participate in this study for 72 hours. The overall study is anticipated to take place over a six month duration.

D. Endpoints

The primary endpoint will be a self-reported perceived muscle soreness using a visual analog scale. There are no secondary endpoints.

1.4 Preliminary Data

N/A

1.5 Sample Size Justification

We anticipate a sample size of 20 subjects, 10 subjects in the *Eucalyptus globulus* group and 10 subjects in the *Mentha x piperita* group. This is based on previous studies which have investigated interventions for perceived muscle soreness and utilized a similar sample size for a power of 80% and a 1 tailed level of significance of $p<0.05$. [15]

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Independent variables are whether the subject receives topical application of *Eucalyptus globulus* oil or *Mentha x piperita* oil. Additionally, each subject will have an intervention extremity that receives the essential oil, and a control extremity which receives no treatment. The subjects will be aware of which group they are in, as there is no way to mask the fragrance.

B. Dependent Variables or Outcome Measures

The dependent variable will be self-reported perceived muscle soreness based on a visual analog scale.

1.7 Drugs/Devices/Biologics

No drugs will be used during this investigation. Essential oils are not regulated under the U.S. Food and Drug Administration. The oils obtained commercially from SunRose Aromatics.

1.8 Specimen Collection

No specimens will be collected.

1.9 Data Collection

A. Primary Data Collection

Location: Data collection will occur at the Manor Health and Rehabilitation Center (689 W Main St, Freehold, NJ 07728). Permission has been granted by the director of this facility and by authorities with CentraState Healthcare System, which the Manor is owned by.

- **Process of Data Collection**: The investigators will oversee the collection of data in-person at the facility. Only Rutgers study staff will be involved in any research roles. Staff at the Manor Health and Rehabilitation will not be involved in the collection of data or treatment of subjects pertaining to this study, but will maintain their usual roles at the study site throughout the duration of this investigation.
- **Timing and Frequency**: Data collection will occur at the beginning of a subject's participation in order to collect demographic information, and then at 24, 48, and 72 hours following exercise to survey their perceived muscle soreness.
- **Procedures for Audio/Visual Recording**: There will be no recording of subjects.
- **Study Instruments**: Recruited subjects will complete a survey to collect demographic data, medical history, and allergies. Subjects will identify their perceived muscle soreness using a self-reported visual analog. They will complete this for both the control and intervention arm at 24, 48, and 72 hours post-exercise.
- **Ethnographic Studies, Interviews, Or Observation**: There will be no interviews or observational aspect to this study.
- **Subject Identifiers**: Each subject will be assigned to a random number associated with their name that will be stored in a password protected file on a secure drive. In a separate, also password protected, file the collected data will be stored with the associated subject's number

B. Secondary Data Collection: No secondary data collection will occur.

1.10 Timetable/Schedule of Events

T=0: Subjects perform supervised eccentric curl exercises.

T=1: Subjects have the intervention and control oils applied topically to their proximal arms immediately after exercise is completed and are monitored for 15 minutes.

T=1+ 8hrs: Subjects have a second application of the intervention and control oils applied topically to their arms.

T=1+ 24hrs: Subjects have a third application of the intervention and control oils applied topically to their arms. They complete the visual analog survey for perceived DOMS.

T=1+ 48hrs: Subjects complete the visual analog survey for perceived DOMS again.

T=1+ 72hrs: Subjects complete the visual analog survey for perceived DOMS for the final time.

2.0 Project Management

2.1 Research Staff and Qualifications

The research investigators consist of two board certified family medicine and geriatric physicians, Drs. Zeeshan Khan and Joshua Raymond. Both physicians are faculty within the Department of Family and Community Medicine at Rutgers. The team also consists of two resident physicians within the Rutgers RWJMS at CentraState Family Medicine Program, Dr Sydney Asselstine and Dr Anand Shah. Dr Shah will be transitioning into the geriatrics fellowship position through Rutgers RWJMS at CentraState for the 2021-2022 academic year. A certified aromatherapist will be available in consult for additional recommendations regarding the essential oils but will not be directly involved in any research activities. Each investigator has familiarity with the study site and patient population from working in this community.

2.2 Research Staff Training

All research staff will undergo a briefing of the protocol for this particular study and their respective roles. All investigators will be notified of any updates in protocol or procedures. All investigators have undergone CITI training.

2.3 Resources Available

At the facility there is a rehabilitation room available and weights that can be used to provide resistance for the exercise. There is also 24/7 nursing staff and physicians on-call that can assist in the event of any adverse consequences to participants. There is a medication room available that would have appropriate treatments for potential adverse outcomes such as rashes.

2.4 Research Sites

The research will occur at the Manor Health and Rehabilitation facility (under CentraState Medical Center, 689 W Main St, Freehold, NJ 07728), and the data will be analyzed at the Rutgers RWJMS at CentraState Family Medicine Residency Program office (597 Park Ave, Freehold, NJ 07728). CentraState Healthcare System and the Manor have provided an study site agreement indicating their support of this research. The Manor will not be engaged in research, and only Rutgers study staff members will engage in any research activities at this site.

3.0 Multi-Center Research

N/A

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Research staff will identify patients who are currently admitted at the facility for subacute rehabilitation or long-term care that meet the age criteria of 50 years or older

B. Recruitment Details

Potential subjects will be verbally informed of the opportunity to participate in the study by co-investigators Dr Asselstine and Dr Shah at the Manor Health and Rehabilitation center, and if interested full details allowing for informed consent would be provided by the investigators. Subjects will be informed that their decision to participate or not participate in the study would have no influence on their care at the facility.

C. Subject Screening

The co-investigators will administer a simple screening survey to interested subjects which identifies basic demographics, such as age, gender, and hand dominance, history of upper extremity injuries within the past 1 year, open proximal upper extremity wounds, any allergies/hypersensitivities to the oils involved. The patient's functional status for exercise based on the Duke Activity Status Index will also be assessed, and they must have a score equivalent to 3.5 or greater metabolic equivalents (METs). Potential subjects will sign a screening consent prior to partaking in this screening survey.

- **Inclusion Criteria**

Subjects 50 years or older with no previous resistance training sessions in the past year and who are currently admitted at the Manor Health and Rehabilitation facility will be recruited.

- **Exclusion Criteria**

Exclusion criteria included any history of musculoskeletal injury or weight bearing restrictions to the upper extremities within the past year. Participants cannot have any significant symptoms that would preclude them from exercising without medical clearance based on the American College of Sports Medicine's "Recommendations for Preparticipation Health Screening," [13] and those with an asymptomatic history of any cardiovascular, metabolic, or renal disease must have a functional capacity of at least >3.5 METs based on the Duke Activity Status Index to participate in the type of exercises that are part of this study, based on the American College of Sports Medicine's "2011 Compendium of Physical Activities." [20] Subjects with known adverse

reaction or allergy to the essential oils or hypersensitivities to fragrances, any open upper extremity wounds or history of upper extremity skin grafts are excluded.

4.2 Secondary Subjects
None

4.3 Number of Subjects

A. Total Number of Subjects
We anticipate enrolling 20 subjects to participate, 10 in the *Mentha x piperita* group and 10 in the *Eucalyptus globulus* group.

B. Total Number of Subjects If Multicenter Study
N/A

C. Feasibility
It is feasible to enroll this number of subjects given there is a consistent population of residents within this facility that would meet the age criteria and, after discussion with physicians at this facility, would also meet the criteria for exercise clearance. The nature of the facility also allows for a continuous influx of patients to the subacute rehabilitation facility, which will allow for rolling enrollment into our study.

4.4 Consent Procedures

A. Consent Process
- **Location of Consent Process**
  The consent process will take place at the Manor Health and Rehabilitation facility.
- **Ongoing Consent**
  N/A
- **Individual Roles for Researchers Involved in Consent**
  Co-investigator Dr Sydney Asselstine will obtain consent from participants. The principal investigator, Dr Khan, will be available to answer any questions or concerns from potential subjects if needed.
- **Consent Discussion Duration**
  Ten minutes of time will be allotted to discuss informed consent. Should the subject require any clarification or a longer timeframe, accommodations will be made.
- **Coercion or Undue Influence**
  Subjects will be informed this is an optional study and their medical care at the facility will not be influenced by their decision to participate or not. Subjects will be able to voice any concerns or questions they may have. Subjects will be able to leave the study at any point should they choose.

- **Subject Understanding**
  Subjects will be asked to repeat back what their role in the study would be. They will verbalize understanding prior to signing any consent forms.

B. Waiver or Alteration of Consent Process

N/A

C. Documentation of Consent

- **Documenting Consent**

All subjects will sign a form of informed consent. They will keep a copy and another copy will be stored in a secure file which only the research staff has access to.

- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**

N/A

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

N/A

B. Wards of the State

N/A

C. Non-English-Speaking Subjects

N/A

D. Adults Unable to Consent / Decisionally Impaired Adults

We will only be recruiting adults that have the decision-making capacity to consent.

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses

There will be no additional expense to the subjects participating in this research.

B. Compensation/Incentives

There will be no compensation or incentives for participating in this study.

C. Compensation Documentation

N/A

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**

Topical application of the essential oils carries a risk of a local dermatitis reaction. [17] In a German multicenter study with over 6000 subjects with pre-existing dermatitis, only 0.25% of subjects who received 2% topical *Eucalyptus* oil, and only 0.64% of subjects who received 2% *Mentha x piperita* oil experienced reactions. The maximum recommended dermal concentration for *Eucalyptus* is 20%, and for *Mentha x piperita* it is 5.4%, and so our study will utilize a concentration of 2%, well below those limits. [18,19]

Participating subjects will be performing exercises during the study which may put them at risk for musculoskeletal injury. Muscle soreness is an expected result of the study. Subjects will be monitored closely during exercise by a physician to ensure proper technique is used. If subjects experience any discomfort beyond the expected level of soreness medical attention will be available and alternative methods of pain or inflammation control will be provided.

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**

If a subject has a known hypersensitivity or allergy to peppermint, eucalyptus, or the carrier oil they are at increased risk for adverse reactions from the intervention, particularly local dermatitis and thus will be excluded from the study. Anyone with open proximal upper extremity wounds or a history of skin graft to the upper extremity will also be excluded. Those with known upper extremity injuries in the past year or upper extremity weight bearing restrictions that may predispose them to musculoskeletal injury from exercise will be excluded from participation as well.

- **Other Foreseeable Risks of Harm**

As with any research there is the risk of breach of confidentiality. All subject data will be stored in a secure file on a restricted drive that only investigators have access to. Subjects will be assigned a random identifier number. Names of subjects and their corresponding identifier number will be stored in one file, and a separate file will list the identifier number and the study data. Subject privacy will be ensured as well, as the exercise for this study will occur in a private room and only study staff will be aware of subject's participation in the study.

- **Observation and Sensitive Information**

N/A

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects

N/A

C. Risks of Harm to Non-Subjects

N/A

D. Assessment of Social Behavior Considerations

N/A

E. Minimizing Risks of Harm

Subjects will have vital signs taken prior to initiating any form of exercise, and a physician will review them to ensure that the subject is medically optimized. All exercise will be closely observed by a physician to ensure proper form and minimize risk for injury, and nursing staff will be available for any assistance needed. If subjects feel in any way they are being harmed through these exercises they will be encouraged to cease participation in the study. Medical care will be available if any injuries do occur.

Physicians will be directly observing subjects for 15 minutes after the first oil application to ensure there are no immediate adverse effects, and vital signs will be repeated at the end of this observation period. Subjects will have nurses available throughout the entire duration of the study. Subjects with known hypersensitivities or allergies to these substances, or pre-existing asthma, will be excluded from participating.

Medications are available on-site that will be able to address any potential adverse effects. Topical creams or antihistamines will be available for any dermatitis, and should any severe systemic allergic reaction occur there are epinephrine injectable pens available as well. Nursing staff is present at the facility 24/7 to care for the subjects, and physicians are on-call as well. On-call physicians have the ability to promptly notify investigators of any concerns with study subjects.

To reduce risk of breach of confidentiality, all subject data will be stored in a secure file on a restricted drive that only investigators have access to. Subjects will be assigned a random identifier number. Names of subjects and their corresponding identifier number will be stored in one file, and a separate file will list the identifier number and the study data. Subject privacy will be ensured as well, as the exercise for this study will occur in a private room and only study staff will be aware of subject's participation in the study.

- **Certificate of Confidentiality**

N/A

- **Provisions to Protect the Privacy Interests of Subjects**

All aspects of this study involving the research subject will take place in an area with only the subject and the investigators present in order to protect their privacy. Any information that they feel uncomfortable disclosing will be omitted.

F. Potential Benefits to Subjects

Potential benefits to subjects include identifying a natural alternative for managing muscle soreness.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

No identifiable health information will be utilized during this study.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

Review the following guidance to ensure you have sufficient information when specific populations are included in your research study.

A. Special Populations

N/A

5.4 General Data Protection Regulation (GDPR)

N/A

5.5 NJ Access to Medical Research Act (Surrogate Consent)

N/A

6.0 Data Management Plan

6.1 Data Analysis

Treatment analysis will involve a 1-way repeated measures ANOVA. Differences will be considered significant when p values are below an alpha level of 0.05.

6.2 Data Security

Subject data will be stored in a secure file on a restricted drive that only investigators have access to. Subjects will be assigned a random identifier number. Names of subjects and their corresponding identifier number will be stored in one file, and a separate file will list the identifier number and the corresponding study data.

6.3 Data and Safety Monitoring

A. Data/Safety Monitoring Plan

Subject's pain level following exercise will be monitored throughout the 72 hour data collection period and if the intervention does not seem to provide adequate relief of muscle soreness (to a functional level) alternative options will be offered to relieve discomfort.

B. Data/Safety Monitoring Board Details

N/A

6.4 Reporting Results

A. Individual Subjects' Results

Results will not be disclosed to individual subjects.

B. Aggregate Results

Aggregate research results will be available to subjects upon request.

C. Professional Reporting

We plan to publish any findings in a scientific peer-reviewed journal and/or present the data at a research conference to share with the scientific community.

D. Clinical Trials Registration, Results Reporting and Consent Posting

The investigation will be registered with Clinicaltrials.gov.

6.5 Secondary Use of the Data

N/A

7.0 Research Repositories – Specimens and/or Data

N/A

8.0 Approvals/Authorizations

Institutional Authorization Agreement has been obtained from CentraState Medical Center, which owns the Manor Health and Rehabilitation Center, for participation in research at this facility.

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