Clinical Intervention Study Protocol and Consent

ClinicalTrials.Gov ID: 2010425	Bioavailability and Pharmacokinetic Measures of H. Procumbens Extract	NCT03641248

Date: 2.25.2020

PREFACE

Musculoskeletal conditions represent a major source of pain, loss of function, and health care expenditure that costs Americans many billions, yearly. People with conditions causing chronic pain turn to integrative health practices to supplement other conventional medical treatment, or when their pain is resistant to or in an effort to avoid side effects of medications. Clinical research has provided evidence that *Harpagophytum procumbens* (Devil's Claw) is an effective and safe treatment for patients suffering from arthritis and chronic low back pain. The variability in the natural products, however, and lack of a well-defined biological signature necessitate additional studies with well-characterized products, so that subsequent clinical studies of appropriate methodological rigor can be conducted. This study will use the best-characterized *H. Procumbens* product to assess a biological signature for a hypothesized mechanism of action that can provide the basis for subsequent definitive clinical efficacy studies.

The R21 phase of this project (PK Study: Study to Establish the Bioavailability and Pharmacokinetic Measures of *H. procumbens* Extract in Humans; Dosing Study: Study of Change in Systemic Inflammatory Markers after 4-Week Consumption of *H. procumbens* Extract by Humans) addresses the following objectives: (1) further define the bioavailability and short term pharmacokinetics of the principal secondary metabolites of a well-characterized aqueous-ethanolic extract of *H. procumbens* in non-enteric and enteric capsules; (2) define the biological signature and hypothetical mechanism of action of the *H. procumbens* extract in patients with knee osteoarthritis over four-week dosing; and, (3) develop protocol, data and safety monitoring plan and manual of operations/procedures and obtain all necessary regulatory approvals for the R33 phase. Following successful completion of the R21 phase, these objectives will be addressed during the R33 phase: (1) confirm and extend assessment of the impact of the *H. procumbens* extract upon the biological signature of the above referenced systemic inflammatory biomarkers and biomarkers in synovial fluid of patients consuming either of two doses over twelve weeks, as well as these markers in cultures of joint tissue; and, (2) evaluate the relationship between changes in systemic and local joint biomarker levels and clinical outcomes (pain, stiffness, functional difficulty). Completion of these studies will ensure that future clinical trials can be conducted with the methodological rigor and outcome measures needed to evaluate the effectiveness of such *H. procumbens* extracts.

FULL PROTOCOL TITLE

Study to Establish the Bioavailability and Pharmacokinetic Measures of H. procumbens Extract in Humans

Study Chairman or Principal Investigator:

William R. Folk, PhD
Professor
Department of Biochemistry
University of Missouri
Columbia, Missouri;
573-882-4857; folkw@missouri.edu

Supported by:

The National Center for Complementary and Integrative Health Grant Number: 7R21AT009086-03 and the University of Missouri

Study Intervention Product:

***Harpagophytum procumbens* aqueous ethanolic extract**

Sponsor of FDA-IND*127849* : Principal Investigator Dr. William R. Folk

Revision History

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STUDY TEAM ROSTER

William R. Folk, PhD (Principal Investigator)
University of Missouri
Biochemistry Department
117 Schweitzer Hall
Columbia, Missouri 65211
573-882-4857 (phone)
573-882-5635 (fax)
folkw@missouri.edu

Chokkalingam Siva, MD (Co-Investigator)
University of Missouri Health Sciences Center
Department of Medicine, Division of Rheumatology-Immunology

Columbia, Missouri 65211
573-882-8095 (phone)
SivaC@health.missouri.edu

Christine Spinka, PhD Co-Investigator and Study Biostatistician
Division of Plant Sciences
2-42 Agriculture Building
University of Missouri,
Columbia Missouri 65211
spinkac@missouri.edu

PARTICIPATING STUDY SITES

University of Missouri Health Sciences Center
Department of Medicine, Division of Rheumatology-Immunology
Chokkalingam Siva, MD (Co-Investigator)
Columbia, Missouri 65211
573-882-8095 (phone)
SivaC@health.missouri.edu

University of Missouri Health Sciences Clinical Research Center
N508 Medical Sciences Bldg
Dean Hainsworth, MD, Medical Director
Columbia Missouri 65211
Phone: 573-882-4894
Fax: 573-884-4779
ClinicalResearch@health.missouri.edu

PRÉCIS

Study Title: Study to Establish the Bioavailability and Pharmacokinetic Measures of *H. procumbens* Extract in Humans (PK Study)

Objectives

Primary Objective: To determine bioavailability and pharmacokinetic properties of harpagoside, harpagide, verbascoside, 8-p-coumarylharpagide and eicosanoids (product markers) after oral consumption of a daily dose of *H. procumbens* (i.e., capsules containing a total amount of extract yielding 100mg harpagoside) in patients with knee, hip, or hand osteoarthritis. We hypothesize that the pharmacokinetic properties of the *H. procumbens* aqueous - ethanolic extract as described in US Patent 6,280,737 B1 (Appendix 1; Example 2), will resemble the results obtained with healthy subjects without osteoarthritis, as reported by Loew et al.[1]

Secondary Objective: Compare the bioavailability and pharmacokinetic properties after dosing with an enteric coated capsule to changes found after dosing with a non-enteric coated capsule. We hypothesize the C_{max}, t_{max}, and AUC values for product

markers will be enhanced by the cellulose (enteric) coating.

Design and Outcomes

A one-dose design will be used to measure bioavailability and pharmacokinetic properties of the *H. procumbens* study product, which is an aqueous extract enriched in harpagoside from which pro-inflammatory mediators have been removed by precipitation with ethanol, as described in U.S. Patent 6,280,737 B1. Dosing level for this study will be extract containing 100mg harpagoside, previously shown to be safe.[2,3] Level of product markers will be measured for 24 hours following a single dose of *H. procumbens* study product, with blood collections taken at timed intervals.

Interventions and Duration

Dosing level for this study will be extract containing 100mg harpagoside (HP extract). Levels of product markers will be measured for 24 hours following a single dose of *H. procumbens* study product, with blood collections taken at timed intervals. Participants will be randomly assigned to receive HP extract in either enteric coated or non-enteric coated capsules.

Sample Size and Population

The study sample recruited into the study will consist of adults with knee osteoarthritis (n = 12 participants with complete data). Six of the participants will receive the HP extract in enteric coated capsules and the other six will receive the HP extract in non-enteric coated capsules.

The study size was determined based on a conservative estimate of the sample size needed based on the exemplar research used for comparison that used 6 healthy male volunteers.[1] We will balance both arms of the study with regards to sex (6 male and 6 female).

1. STUDY OBJECTIVES

1.1 Primary Objective

To determine bioavailability and pharmacokinetic properties of product markers after oral consumption of a daily dose of *H. procumbens* (i.e., capsules containing a total amount of extract yielding 100mg harpagoside) in patients with knee osteoarthritis. We hypothesize that the pharmacokinetic properties of the *H. procumbens* aqueous-ethanolic extract as described in US Patent 6,280,737 B1 (example 2), will resemble the results obtained with healthy subjects without osteoarthritis, as reported by Loew et al.[1]

1.2 Secondary Objectives

The secondary objective of the study is to compare the bioavailability and pharmacokinetic properties after dosing with an enteric coated capsule to changes found after dosing with a non-enteric coated capsule. We hypothesize the C_{max}, t_{max}, and AUC values for product markers will be enhanced by the cellulose (enteric) encapsulation.

2. BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

Musculoskeletal conditions represent a major source of pain, loss of function, and health care expenditure that costs Americans billions of dollars, yearly. Clinical research has provided evidence for safety and efficacy of the botanical dietary supplement *Harpagophytum procumbens* (*H. procumbens* or Devil's Claw) for many patients suffering from arthritis and chronic low back pain.[4-10] The variability in the natural products, however, and lack of a well-defined biological signature necessitate additional exploratory studies with well-characterized products, so that subsequent clinical studies of appropriate methodological rigor can be conducted.[8,10-17] For osteoarthritis (OA), there are currently no biomarkers qualified as surrogate clinical endpoints, and assessment of the efficacy of disease-modifying osteoarthritis drugs (DMOADs) in patients has provided only sparse understanding of the relationship between biomarkers and the effects of the medication.[18-20] These shortcomings may be due to the complex nature of deteriorating diarthrodial joints and the symptoms experienced by patients.

The study will use a well-characterized *H. procumbens* extract (HP extract) to assess the bioavailability and pharmacokinetic properties of product markers after oral consumption of a daily dose of *H. procumbens* (i.e., capsules containing a total amount of extract yielding 100mg harpagoside). Completion of this study will ensure that future clinical trials can be conducted with the methodological rigor and outcome measures needed to appropriately evaluate the effectiveness of this *H. procumbens* product.

2.2 Study Rationale

Commercially available Devil's Claw products may contain material from *H. procumbens* and *Harpagophytum zeyheri*, and both species may vary in their pro- and anti-inflammatory constitutents; this has undoubtedly contributed to the lack of agreement between published reports of efficacy of such products.[21-25] The anti-inflammatory and analgesic properties of *H. procumbens* have been ascribed to inhibition of eicosanoid and nitric oxide (NO) biosynthesis, by altering expression and inhibition of cyclooxygenases (COX1, 2) and lipoxygenases (LOX) and nitric oxide synthase (iNOS), and to altered expression of pro- and anti-inflammatory cytokines and other mediators (recently reviewed).[23,24] Harpagoside, 8-p-coumarylharpagide and related metabolites have been implicated as primary anti-inflammatory effectors.[22-24,26]

For these studies, we will use botanically verified *H. procumbens* plant material and an extraction procedure comparable to WS1531 extract used in the human clinical trial reported by Chrubasik and colleagues[27] and the in vivo and ex vivo studies reported by Loew et al.[1] In the former study, extract WS1531 extract was compared with placebo in a randomized, double blind study of 197 patients with chronic susceptibility to back pain. At four weeks, three pain-free patients occurred in the placebo group, six in the group receiving extract containing 50mg harpagoside/day, and ten in the group receiving extract with100mg harpagoside/day. This significant

dose-dependent pain relief was explored pharmacologically[1] where basal and A23187-induced synthesis of cysteinyl-leukotrienes (Cys-LT) was determined *ex vivo* to be dependent upon the content of harpagoside and the absence of pro-inflammatory components, as detailed in U.S. Patent 6,280,737 B1. This effect was supported by *in vivo* analyses, in which three subjects received, in a crossover fashion, 600mg, 1200 mg and 1800mg extract resulted in a statistically significant decrease (~58%) in Cys-LT levels in blood at 8hrs after treatment.

We have based our sample size on previous research published by Loew and colleagues[1] in which six healthy adult males received a single 150mg harpagoside dose through consumption of 600mg *Harpagophytum* extract HF 8858. The C_{max} value was reached within 1.3 hours following dosing and was calculated as 32.2 ng/mL; the half-life of this dose level was 5.6 hours. Given our plan to compare pharmacokinetic parameters between participants who are dosed with enteric versus non-enteric coated capsules, we doubled the sample size used by Loew and colleagues in order to do this comparison. We will collect complete data from 12 participants.

The PK Study will use HP extract with a daily harpagoside dose (100mg) that is equivalent to the dosing used in previous clinical studies that have demonstrated beneficial effects and been shown to be safe.[3,27] The study will provide data that can confirm the bioavailability and pharmacokinetic properties of harpagoside and 8-p-coumarylharpagide following a single dose administration. Oral administration of the study product was selected based on previous clinical research and based on the administration route that would be used in clinical practice.

Previous research indicates that risks of taking *H. procumbens* extracts are limited. Devil's Claw supplements are widely prescribed in Europe and available in the United States in grocery stores, health food stores, and pharmacies. Previous research using dose levels in the range of 50-100mg harpagoside daily dose has shown it to be at least as well tolerated as more traditional pain medication (e.g., nonsteroidal anti-inflammatory drugs)[8,9] and allergies have been rare.

We have established screening criteria to address any possible risks by excluding people with conditions that might be contraindicated. We will monitor possible side effects and adverse events throughout study participation, and participants will be given a phone number to contact study staff and/or the investigators to report side effects or adverse events, if needed. We will follow NIH guidelines for reporting adverse events to the Data Safety Monitoring Board (DSMB) and IRB. Any problems needing medical attention will immediately be triaged by Dr. Siva and when appropriate, referred to the participant's personal physician or other health care providers.

Other risks of participating in the study are minimal and include providing samples for clinical tests, having an electrocardiogram (ECG), and the inconvenience of completing questionnaires. The blood draws and ECG will be done following standard clinical guidelines to ensure no greater risk than what is expected with routine medical care. Study staff will be trained and will follow GCP and HIPAA guidelines in order to prevent any breach of participants' confidentiality and privacy

as a result of contacts with study staff.

3. STUDY DESIGN

Study Design - A one-dose randomized design will be used to measure bioavailability and pharmacokinetic properties of the *H. procumbens* study product, an aqueous extract enriched in harpagoside from which pro-inflammatory mediators have been removed by precipitation with ethanol, as described in U.S. Patent 6,280,737 B1 (HP extract). Dosing level for this study will be extract containing 100mg harpagoside, previously shown to be safe.[2,3] Level of product markers will be measured for 24 hours following a single dose of HP extract, with blood collections taken at timed intervals.

Primary Outcomes – pharmacokinetic metrics:

C_{max} (ng/mL) – first maximal concentration,

t_{max} (h) – time to reach the C_{max},

AUC (0-t) (ng/mL) – Area under the curve, and

Terminal $t_{1/2}$ (h) – terminal half-life.

Study Population - Adults with knee osteoarthritis (n = 12). Equal numbers of participants will be randomly assigned to receive study product in either enteric or non-enteric coated capsules.

Study Location - Participants will be recruited from MU Healthcare clinics that treat patients diagnosed with knee osteoarthritis. Participants will be treated at the University of Missouri Health Sciences Clinical Research Center (CRC). A letter of support from the Medical Director of the CRC is provided in the Appendix

Duration of Enrollment Period and Follow-up – Enrollment should be completed within 2 months after the final protocol is approved by the NIH, IRB and FDA. Each person enrolled in the study will be followed throughout the PK testing session and for the 24 hour period following the end of the testing session blood draw schedule.

Intervention and Administration - The study product will be packaged in either enteric or non-enteric capsules by Sonja Grinfeld, Pharm D, (MU-IDS Pharmacist). Participants will be randomly assigned to receive HP extract in either capsule type. At the PK testing session, all participants will receive capsules to deliver an oral dose of HP extract which provides 100mg of harpagoside.

Randomization, Blinding, and Stratification – Participants will be randomized to receive HP extract in either enteric coated or non-enteric coated capsules. Assignment to study group will be conducted double-blind. A pilot study indicated participants will not be able to distinguish between enteric and non-enteric capsules.

Other Protocol Specific Details - Analysis of all serum and urine samples will be processed using standard protocols following good clinical practices. Samples to measure study product markers will be processed at the University of Missouri (MU) and will be supervised by Dr. Folk (PI). Samples to measure safety endpoints

(complete blood count [CBC], basic metabolic panel [BMP], and liver function test [LFT]) will be processed by CLIA certified laboratories.

4. SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

To be eligible to participate, patients must meet all of the following inclusion criteria:

- adult (at least 18 years of age);
- diagnosed with knee osteoarthritis (OA);
- body mass index (BMI) of less than 40;
- willing to use only the *H. procumbens* (Devil's Claw) study product (HP extract) during study participation;
- able to use tramadol or Tylenol as a rescue pain medication during participation in the study;
- willing and able to monitor blood glucose levels if diabetic;
- willing to abstain from caffeine-containing drinks and food before participation in the study;
- able to read and understand English, and have the cognitive capacity to give consent; and,
- willing to abstain from use of the following during participation in the study: prescription and over-the-counter non-steroidal anti-inflammatory medications, (e.g., aspirin, ibuprofen, Advil, Motrin, Nuprin, Naproxen, etc.); any dietary supplements (St. John's Wort, etc.); and, grapefruit and/or products containing it.

4.2 Exclusion Criteria

Patients who have any of the following diagnoses or conditions will be excluded from participating:

- cardiovascular disease, previous myocardial infarction, stent, CABG, arrhythmia, high or low blood pressure;
- recurrent stomach upset, or gastric or duodenal ulcers;
- gallstones or gall bladder disease (cholelithiasis);
- liver or kidney disease; high alcohol use (more than two drinks per day on a regular basis);
- Coumadin or anti-platelet drug use;
- at risk for respiratory depression, history of seizures, or taking drugs that reduce the seizure threshold or may increase the risk for development of serotonin syndrome;
- pregnant or breast feeding, or intention to become pregnant during the study;
- pronounced allergies, or known allergy to *H. procumbens* or corn starch;
- have had an injection to treat OA within the past three months;
- currently taking NSAIDs, unless they are willing to stop for a 1-week wash-out period;
- currently on a SSRI but are poorly stabilized, or have evidence of suicidal ideation and/or suicide attempts in the past year; and,

- reported use during the 7 days prior to study drug administration of: prescription medicines, or over-the-counter medications; non-steroidal anti-inflammatory medications (e.g., NSAIDs); dietary supplements; grapefruit and/or its juice products; or products containing St. John's Wort.

4.3 Study Enrollment Procedures

The study team will work with MU Healthcare physicians to ensure that patients with qualifying diagnosis of knee osteoarthritis are identified and approached about participating in the study. Electronic medical records for potentially eligible patients will be reviewed for recorded information relevant to inclusion and exclusion criteria. A screening log will be maintained to track the patients who have been screened for eligibility, approached, and scheduled for a screening session; each individual will be assigned a screening identification (SID) number. The screening log will be used to document reasons for ineligibility and to record reason for non-participation for possibly eligible patients who decline to participate. These data will be collected in a manner to meet CONSORT guidelines.

Written informed consent (approved by the IRB) will be obtained at the screening session The study staff will ensure that the participant is given full and adequate oral and written information about the nature, purpose, and possible risk and benefit of the study. Participants will also be notified that they are free to discontinue from the study at any time. The participant will be given the opportunity to ask questions and allowed time to consider the information provided. The participant's signed and dated informed consent will be obtained before conducting any study specific procedure. The investigator will store the original, signed Participant Informed Consent Form and a copy will be given to the participant.

A Case Report Form (CRF) will be used to record the consenting and screening session procedures including determination of eligibility based on analysis and interpretation of laboratory, physical examination, and electrocardiogram (ECG) measurements. After eligibility is determined, patients will be contacted and the PK testing session will be scheduled.

Randomized assignment into enteric or non-enteric capsule study group will occur at the beginning of the PK testing session. All study staff who have direct contact with study participants and/or are involved in data collection or analysis will be blinded as to randomization assignment. Knowledge of random assignment will remain blinded until all preliminary data reviews and quality checks are completed.

The randomization procedures and assignment list will be the responsibility of Dr. Mojgan Golzy, Dept of Health Management and Informatics, and member of the DSMB. Dr. Golzy will have no direct involvement with the study participants, data collection, or statistical analysis of the study data.

Product capsules (i.e., enteric and non-enteric) will be labeled with a product code number; Dr. Golzy will be the only person with the master list that links the product code number to the type of capsule. Dr. Golzy will generate a participant list that identifies the product code associated with each participant identification (PID) number; this product/participant code match will be based on the randomization

process. Study staff who work with participants and study data will only know the match of participant and product code numbers and will not know the study product material encapsulation type.

5. STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The intervention to be tested in this study is oral doses of HP extract packaged in capsules prepared under GMP with extract containing approximately 25mg of harpagoside, without or with enteric coating. Comparison of enteric and non-enteric formulations is warranted by reports the anti-inflammatory and analgesic activity of HP extracts, and purified harpagoside, are sensitive to gastric acid.[28-30] A dose will consist of sufficient capsules to achieve consumption of 100mg harpagoside daily.

H. procumbens supplements are widely used in Europe and are widely-available in the United States in grocery stores, health food stores, and pharmacies. Previous research using dose levels in the range of 50-100mg harpagoside daily dose has shown it to be at least as well tolerated as more traditional pain medication (e.g., nonsteroidal anti-inflammatory drugs)[8,9] and allergies have been rare.

Screening criteria address any possible risks by excluding people with conditions that might be contraindicated. We will monitor possible side effects and adverse events during the PK testing session and at each post PK testing session contact. In addition, participants will be given a phone number to contact study staff and/or the investigators to report side effects or adverse events that occur following the testing session. Any problems needing medical attention will immediately be triaged by Dr. Siva and when appropriate, referred to the participant's personal physician or other health care providers. Diagnostic laboratory tests will be ordered as specified by the study physician.

Potential side effects of *H. procumbens* supplements include mild gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal pain; headaches; ringing in the ears; loss of appetite; and, loss of taste. It may also be related to allergic skin reactions, menstrual problems, and changes in blood pressure.[41] These were reported in less than 10% of people who took it in previous research; no serious adverse events were reported.[3] These side effects may be treated with an appropriate medication determined by Dr. Siva or the subject's personal physician.

5.2 Handling of Study Interventions

Aqueous-ethanolic extract of dried, milled secondary tubers of botanically verified *H. procumbens* as described in U. S. Patent 6,280,737 B1[31] were obtained from Parceval Herbal Pharmaceuticals, LLC, South Africa (Appendix II). Sufficient product for all planned studies have been obtained as a single batch. The product complies with the FDA Guidance for Industry-Botanical Drug Products and NCCIH Natural Product Integrity Policy, and with RSA biodiversity regulations, and has received an open IND by the FDA, which must be renewed upon approval of this protocol. The content of harpagoside has been determined by HPLC-MS to be the same as that when the

FDA provided the open IND. Since that time, more extensive toxicology studies in rats have been performed and published.[43]

Encapsulated study product will be prepared at the MU-IDS Pharmacy. Study product will be kept at room temperature in secure storage cabinets that are accessible only to authorized staff.

The dose of study product for the PK Study will be labeled with the appropriate participant identification (PID) number based on a list that links product code number to participant identification number. At the PK testing session, participants will be given one daily dose of study product. Any unused study product will be stored in the secured project storage cabinet until the completion of study data collection.

Study product accountability records will be maintained at the University of Missouri and will document: (1) the processing of the study product and packaging it with appropriate product code numbers; and, (2) the labeling of study product with participant identification number, based on the master list that documents the assignment of participant identification number for each product code.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

Participants will be allowed to use tramadol or Tylenol as a rescue medication for pain relief during the PK study data collection period; the prescription and dosing recommendations for the use of tramadol will be provided to the participant by his/her own physician. Participants will be asked to record the dates and times when they took tramadol, and the dose that was taken. This information will be provided to study staff at the follow-up contact.

5.3.2 Required Interventions

There are no required interventions in addition to the single dose of study product that each participant will receive.

5.3.3 Prohibited Interventions

Participants must agree to not use the following classes of medications while on study: medications prescribed to treat any of the exclusionary diagnoses or conditions; Coumadin or anti-platelet drug treatment; non-steroidal anti-inflammatory drugs; changes in SSRI treatment due to change in status; prescription and over-the-counter medications and dietary supplements; grapefruit and/or its products; and, St. John's Wort.

5.4 Adherence Assessment

Adherence will be documented through the CRF that will record the time of dosing. No additional dosing will be involved, and participants will not be responsible for any dosing.

6. STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Screening: Visit (2 – 14 days Before Testing Session)	PK Testing Session – Visit 1 (Time 0)	Follow-up - Visit 2 (24 hr)	Follow-up: Phone Contact (36 hr)
Informed Consent Form	X			
Demographics	X			
Medical History	X			
Current Medications	X	X		
Vital Signs	X	X	X	
General Physical Examination	X			
Electrocardiogram (ECG)	X		X	
Laboratory Values (CBC, CMP, LFT)	X		X	
Randomization		X		
Receive Daily Dose of Study Product		X		
Study Product Markers		X	X	
Measures of Side Effects		X	X	
Report of Adverse Events		X	X	X
Patient Reimbursement	**$50**	**$125**	**$50**	

6.2 Description of Evaluations

6.2.1 Screening Evaluation

The Screening Evaluation session to determine whether the patient is eligible to participate in the PK Study will occur from 2 to 14 days before the PK testing session. The Screening session will include the informed consent procedure and screening activities to ensure eligibility (described below).

Consenting Procedure

Prior to participants' participation in the study, written informed consent for the study, including screening and study procedures, will be obtained from each participant. CRC project staff or Dr. Siva will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. The participant's signed and dated informed consent will be obtained before conducting any study specific procedures. The CRC will store the original, signed Participant Informed Consent Form and a copy will be given to the participant.

Screening

Only volunteers who consent and pass all screening assessments will be scheduled for a PK testing session. Study participation will begin within 14 days of the Screening Evaluation session. At the screening session, the individual's SID number will be used to label all study data collected at the Screening session.

Following the completion of the informed consent procedures during the Screening session, a brief survey will be completed before other screening procedures are conducted. The survey will include items to record demographic information needed to describe the study sample (e.g., age, gender, race and ethnicity) and items to record contact information (e.g., address, phone number / email address).

The following eligibility screening evaluations will be completed.

- Medical history interview – Medical history will be collected via interviews. Participants will be asked about all previous diagnoses, allergies, procedures, and treatments to verify relevant inclusion/exclusion criteria (Section 4).
- Current medication use – Participants will provide a listing of all medications (prescription and over-the-counter) they are currently taking.. Anyone who reports using medications listed in Section 4.2 Exclusion Criteria will be asked to stop use of the product for 14 days before the PK testing session.
- Vital signs – The following vital signs will be recorded to verify they are within normal ranges: heart rate, blood pressure, respiration rate.
- General physical examination – A general physical examination will be conducted.
- Electrocardiogram (ECG) – Standard 12-lead ECGs will be performed at the Screening and 24-hour follow-up sessions. The site study physician will review

the recording and verify that the participant has a normal ECG.

- Laboratory values – Blood samples will be obtained for CBC, BMP, LFT and HCG (pregnancy) for baseline product marker assays. The study physician will review the CBC, BMP, LFT and HCG (pregnancy) results to verify eligibility.

6.2.2 Enrollment, PK testing, and/or Randomization

Enrollment

Participants who are judged to be eligible to participate by the study physician following all screening procedures will be contacted and scheduled for the PK testing session. At the testing session, participants will be assigned a participant identification number (PID). This PID is linked to their blinded randomization assignment, and linked to their SID.

PK Testing

During the PK testing session (Visit 1) the following assessments will be obtained.

- Current medication use – Participants will provide a listing of any and all medications (prescription and over-the-counter) they have taken since the Screening Session. Anyone who reports using any product listed in Section 4.2 Exclusion Criteria will have the PK testing session rescheduled to allow for a 7-day washout period during which they do not take any of the restricted medications.
- Vital signs – The following vital signs will be recorded as baseline values: heart rate, blood pressure, respiration rate.
- Study product markers – Blood samples will be obtained in order to assess product markers at timed intervals during the 10-hour testing session. Using an indwelling catheter that is inserted in the arm, two samples of blood will be collected at the following intervals following dosing: 0hr, 1 hr, 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, 8 hr, 10 hr. This data collection timing schedule is based on previous research.[1]

  An exploratory examination of the presence of study product markers in urine will be conducted by collecting random urine samples that are timed, to the extent possible, to blood collection time points. Examination of study product markers in urine is exploratory, and will be conducted with the goal of further informing our understanding of the PK parameters obtained from blood samples. Samples for the measurement of study product markers will be analyzed under the supervision of Dr. Folk.
- Side effects – Study staff will record occurrence of any side effects during the PK testing session.
- Adverse Events – Any occurrence of an adverse event noted by study staff or reported by a participant will be recorded and categorized by system.

Following all testing session assessments, the appointment time for the follow-up session will be confirmed and the participant will be paid for the testing session.

Randomization

Random assignment into study group will occur upon arrival at the PK testing session. Participants will be assigned to one of two study groups – enteric capsules or non-enteric capsules.

6.2.3 Blinding

All study staff who have direct contact with study participants and/or are involved in data collection or analysis, including the PI and the study biostatistician, will be blinded as to randomization assignment into study group. Knowledge of random assignment will remain blinded until all preliminary data reviews and quality checks are completed. Dr. Golzy will be authorized to break the blind for the DSMB as needed to respond to adverse events.

6.2.4 Follow-up Evaluations

24 hr Evaluation

The following measurements and procedures will be completed at the 24-hour follow-up session.

Visit 2 (24 hours following dosing during the PK Testing Session):

- Vital signs – The following vital signs will be recorded: heart rate, blood pressure, respiration rate.
- Electrocardiogram (ECG) – Standard 12-lead ECGs will be performed at the 24-hour follow-up session. A study physician will review the recording and interpret the findings.
- Laboratory values (CBC, BMP, LFT) – Blood samples will be obtained and CBC, BMP, and LFT assays will be assayed. Dr. Siva will review and interpret the lab results.
- Study product markers – Blood and urine samples will be obtained in order to assess level of product markers.
- Side effects – Study staff will record any side effects reported by the participant.
- Adverse Events – Any occurrence of an adverse event reported by a participant will be recorded and categorized by system (i.e., cardiovascular, dermatologic, endocrine/metabolic, gastrointestinal, hematologic, hepatic, musculoskeletal, neurologic, renal, reproductive, or respiratory).

36 hr Follow-up. A phone contact will be made at 36 hours following the dosing time at the PK testing session (i.e., 24 hours following the end of the testing session). During this contact, information regarding any side effects or adverse events that were experienced since the last study visit will be collected.

7. SAFETY ASSESSMENTS

Any occurrence of a self-reported adverse event will be recorded and categorized by system (i.e., cardiovascular, dermatologic, endocrine/metabolic, gastrointestinal, hematologic, hepatic, musculoskeletal, neurologic, renal, reproductive, or respiratory).

7.1 Specification of Safety Parameters

Safety and potential toxicity of HP extract ingestion will be evaluated by measuring vital signs; capturing adverse events; and, screening for potential renal, hepatic, metabolic, muscle, cardiac and hematological toxicity (by measuring biochemical and hematological parameters and by recording electrocardiograms (ECG). Based on previous research and standard practice regarding monitoring the use of NSAIDs, CBC, BMP, and LFT assay results will be evaluated as primary safety measures. Examples of parameters that will be indicative of safety concerns include: a clinically meaningful drop in hemoglobin which could indicate GI bleeding; clinically meaningful changes in creatinine; and, clinically meaningful changes in liver function test parameters.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

H. procumbens (Devil's Claw) is a widely-prescribed product in Europe and is widely-available in the United States in grocery stores, health food stores, and pharmacies. Numerous reviews provide a summary of safety-related information.[3,10,34-41] Previous research using dose levels in the range of 50-100mg harpagoside daily dose has shown it to be at least as well tolerated as more traditional pain medication (e.g., nonsteroidal anti-inflammatory drugs),[8,9] and allergies have been rare. Potential side effects of *H. procumbens* (Devil's Claw) include mild gastrointestinal symptoms such as diarrhea, nausea, vomiting, abdominal pain; headaches; ringing in the ears; loss of appetite; and, loss of taste. It may also be related to allergic skin reactions, menstrual problems, and changes in blood pressure.[41]

Screening criteria address possible risks by excluding people with conditions that might be contraindicated. We will monitor possible side effects and adverse events during the testing session and at each follow-up contact, and participants will be given a phone number to contact study staff and/or the investigators to report side effects or adverse events, if needed. Any problems needing medical attention will immediately be triaged by Dr. Siva and when appropriate, referred to the participant's personal physician or other appropriate health care providers.

Laboratory-based safety measures and the ECG will be assessed at the screening session to determine eligibility and at the 24-hour follow-up session (Visit 2) to assess health status following dosing. Vital signs will be collected at each study visit. Self-reported adverse events and side effects will be recorded at the follow-up sessions, and participants will be instructed to contact a member of the study team at any time during participation to report an adverse event.

7.3 Adverse Events and Serious Adverse Events

The following definitions will be used in the study when recording adverse events (AE), serious adverse events (SAE), and Unanticipated Problems.

An adverse event (AE) is any untoward medical occurrence to a subject during participation in the clinical study. This can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these regardless of relationship to participation in the study.

SAE will be defined as any untoward medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unanticipated Problems are those that involve risks to participants to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and,
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Laboratory values from CBC, BMP, and LFT assays will be examined. Any values that indicate a safety concern will be identified, reported to a study physician within 48 hours of the laboratory report being received by study staff, and followed-up by a study physician within 48 hours of notification. Abnormal laboratory values will be defined as values that are outside the reference range for a laboratory.

Participants will be given the name and phone number for study staff to report any adverse event that occurs. In addition, participants will be asked at the follow-up study session (Visit 2) and the follow-up phone contact to report any side effect or adverse event that might have occurred since the previous report. The timing of any reported adverse event will be recorded to ensure that an AE is not recorded as two separate events.

7.4 Reporting Procedures

Dr. Folk will review all AE/SAE related data within 24 hours of data collection. Any problems needing medical attention will be triaged by Dr.Siva, and when appropriate, referred to the patient's personal physician or other health care providers. Dr. Folk and Dr. Siva will determine whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for *H. procumbens*.

Dr. Folk will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Unanticipated Problems will be recorded in the data collection system throughout the study. At each study visit/contact, the investigator will inquire about the occurrence of AE/SAE since the last visit. Events will be followed for outcome information until resolution or stabilization.

Dr. Folk will report to the DSMB and IRB unanticipated problems using the following guidelines.

- Unanticipated AE/SAE resulting in death – within 24 hours of becoming aware of the event.
- Unanticipated SAE not resulting in death – within 24 hours of becoming aware of the event.
- All other AE that meet the definition of an Unanticipated Problem – within 5 business days of notification of the event.

Dr. Folk will report all AE/SAE to the DSMB, IRB, FDA and NCCIH in accordance with requirements.

- 7-day IND Safety Report (unexpected fatal or life-threatening AE related to HP extract); a copy of the report sent to the FDA will be submitted to the NCCIH Program Officer within 24 hours of FDA notification.
- 15-day IND Safety Report (any other serious and unexpected AE related to HP extract); a copy of the report submitted to the FDA will be submitted to the NCCIH Program Officer within 24 hours of FDA notification.
- All other AE documented during the course of the trial will be reported to NCCIH on an annual basis by way of inclusion in the annual report and in the annual AE summary which also will be provided to the FDA, IRB and the DSMB.

7.5 Follow-up for Adverse Events

Dr. Folk will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. Events will be followed for outcome information until resolution or stabilization.

7.6 Safety Monitoring

The DSMB will perform the following activities for the study: monitor participant

safety; assess study progress (including participant confidentiality, recruitment, and retention); and, monitor data quality and management. The DSMB members are not recent or active collaborators with any of the project investigators.

8. INTERVENTION DISCONTINUATION

HP extract will be delivered as a single dose; therefore, discontinuation of dosing is not relevant. All side effects and/or adverse events that occur following the single dosing will be recorded and tracked in order to identify a pattern of response that could have an impact on continued study enrollment.

9. STATISTICAL CONSIDERATIONS

9.1 General Design Issues

The primary objective of the PK Study is to determine bioavailability and pharmacokinetic properties of product markers after oral consumption of a daily dose of *H. procumbens* (i.e., capsules containing a total amount of extract yielding 100mg harpagoside) in patients with knee, hip, or hand osteoarthritis. We hypothesize that the pharmacokinetic properties of the *H. procumbens* aqueous-ethanolic extract as described in US Patent 6,280,737 B1 (Appendix 1, example 2), will resemble the results obtained with healthy subjects without osteoarthritis, as reported by Loew et al.[1]

Secondary Objective: Compare the bioavailability and pharmacokinetic properties after dosing with an enteric coated capsule to changes found after dosing with a non-enteric coated capsule. We hypothesize the C_{max}, t_{max}, and AUC values for product markers will be enhanced by the cellulose (enteric) coating.

Outcome measures: For each of the study product markers we will examine measures reflecting the pharmacokinetic properties of the HP extract. Specifically, we will measure and evaluate C_{max}, t_{max}, and AUC values.

The study will be conducted using a double-blind randomized control study design. Participants will be randomly assigned at the PK testing session to receive either enteric coated or non-enteric coated capsules containing HP extract.

9.2 Sample Size and Randomization

Sample size is based upon previous research published by Loew and colleagues[1] in which six healthy adult males received a single 150mg harpagoside dose through consumption of 600mg *Harpagophytum* extract HF 8858. The C_{max} value was reached within 1.3 hours following dosing and was calculated as 32.2 ng/mL; the half-life of this dose level was 5.6 hours. Given our plan to compare pharmacokinetic parameters between participants who are dosed with enteric versus non-enteric coated capsules, we doubled the sample size used by Loew and colleagues in order to do this comparison. We will collect complete data from 12 participants.

Treatment Assignment Procedures

Group assignment will be linked to the participant identification (PID) number that will be assigned at the start of the PK Testing Session. Study staff responsible for the PK Testing Session will be given the appropriate PID number to use for the participant attending the Testing Session; the PID number will not indicate specifics of the study product assigned to the individual.

All study staff who have direct contact with study participants and/or are involved in data collection or analysis, including the PI and the study biostatistician, will be blinded as to randomization assignment into study group (i.e., enteric or non-enteric capsules). Knowledge of random assignment will remain blinded until all preliminary data reviews and quality checks are completed.

The randomization procedures and assignment list will be the responsibility of Dr. Golzy, DSMB member. She will have no direct involvement with the study participants, data collection, or statistical analysis of the study data.

Study capsules (i.e., enteric and non-enteric capsules containing HP extract) will be labeled with a product code number; Dr. Golzy will develop the master list that links the product code number to the specifics of the capsule material. She will send this list to the University of Missouri Healthcare Inpatient Pharmacy which is responsible for preparing the study material. Dr. Golzy will also generate a list that identifies the product code associated with each participant study code (PID) number; this product/participant study code match will be based on the randomization list. Study staff who prepare the dosing of product to be given to each participant will only know the match of participant study identification code and product code numbers and will not know the study product capsule type (i.e., enteric or non-enteric). Study staff who are working directly with study participants and study data will only know the participant study identification code for an individual. Dr. Golzy will be authorized to break the blinding process as needed to evaluate SAE and/or Unanticipated Problems.

9.3 Definition of Populations

The PK Study will continue until complete data over the 24-hour period following dosing are collected from 12 participants. Analyses will be conducted on the data collected from these participants. Comparisons between values obtained from participants who received the dose of HP extract in the enteric coated capsules versus data from those who received HP extract in non-enteric coated capsules (6 in each group) will be compared.

9.4 Interim Analyses and Stopping Rules

No interim analyses are planned for the PK Study.

Monitoring of AE, SAE, and Unanticipated Problems will be conducted as described in Section 7. It is possible that enrollment in the study will be suspended based on a review of safety findings. Findings that might trigger a safety review include: the occurrence of SAE; AE or increased frequency of unexpected events.

9.5 Outcomes

9.5.1 Primary Outcomes

Blood samples will be collected on the time schedule listed in sections 6.2.2 and 6.2.5 above. These samples will be assayed in order to determine the following PK parameters for the study product markers.

C_{max} (ng/mL) – first maximal concentration,

t_{max} (h) – time to reach the C_{max},

AUC (0-t) (ng/mL) – Area under the curve, and

Terminal $t_{1/2}$ (h) – terminal half-life.

Measures of the study product markers obtained from the random urine collections will also be examined and compared to the pattern of change seen from the serum samples.

9.5.2 Secondary Outcomes

There are no secondary outcomes in the PK Study.

9.6 Data Analyses

Statistical analyses will be conducted to address the study objective to determine bioavailability and pharmacokinetic properties of product markers after oral consumption of a daily dose of HP extract. The analyses will follow the statistical method used by Loew and colleagues.[1]

The maximal concentration (C_{max}) and the time to reach C_{max} (t_{max}) will be computed for each study product marker using the assay values obtained from the repeated serum collections. The area under the curve (AUC) will be calculated using the trapezoidal rule. The terminal half-life ($t_{1/2}$) will be calculated using linear regression from the log-linear slope of at least three concentrations.

In order to test the hypothesis that these values will be enhanced for those who received the HP extract in the enteric coated capsules, the outcome measures for the two groups will be compared.

Analyses of the primary outcome measures (C_{max}, t_{max}, AUC, and $t_{1/2}$) will be conducted on the timed interval blood samples collected from 12 participants who complete the study protocol. Missing data, therefore, should not be a significant issue, resulting only from cases of an accident or assay problem with a specific sample. If there is a missing value for a specific timed interval sample for an individual, the missing value will be replaced in one of two ways in order to compute the primary outcome measures. (1) The missing value will be replaced with the average of the surrounding values if the missing value is a sample other than the first or last timed interval sample. (2) The missing value will be replaced with the immediately adjacent value if it is either the first timed sample or the last timed sample.

10. DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

All data collected for each participant by trained and authorized study staff will be labeled with the participant's study identification number. The association of study identification number and participant identity will be kept stored in secured project file storage that will be accessible only to authorized study personnel. Therefore, no identifying information will be directly associated with study data.

Study group assignment will be blinded until after all preliminary data quality reviews have been conducted and any decisions on handling of missing data have been completed. Therefore, any interpretation of clinical data will be conducted under blind conditions.

Source data will include: (a) records of clinical data results, including laboratory, ECG, and product marker data; and, (b) direct recording of data collected during study visits, including vital signs, physical examinations, reports of side effects, and adverse events.

10.2 Data Management

Study staff will work closely with Dr. Folk and Dr. Siva to coordinate study activities and data collection. All study-related data will be collected and will be part of the research study database. The project biostatistician (Dr. Spinka) and the PI (Dr. Folk) will be responsible for coordination and management of study data.

Case report forms (CRF) will be used for all study visits to record data that are collected at the session. In addition, CRF will be used to record laboratory and ECG data that are part of the study data record. An electronic database of all study data will be created using the REDCap (Research Electronic Data Capture)[42] system.

10.3 Quality Assurance

10.3.1 Training

All study personnel will complete human subjects training and good clinical practices (GCP) training.

10.3.2 Quality Control Committee

The project leadership team (PIs and Co-Investigators) will comprise the study quality control committee. Dr. Folk will have overall responsibility for quality control on the study as a whole. Dr. Folk and Dr. Spinka (study biostatistician) will be responsible for quality control related to management of the study database, data management, and statistical analysis.

10.3.3 Metrics

The analysis of HP extract marker samples will be performed under the supervision of Dr. Folk. These assays will be performed following analysis protocols, and quality measures (e.g., coefficient of variation) will be monitored to ensure quality control.

10.3.4 Protocol Deviations

Any protocol deviation that occurs will be recorded on the study visit CRF. The documentation will include a complete description of the deviation. Dr. Folk will review the deviation and will determine, in consultation with other members of the project leadership team as needed, how the deviation should be addressed.

10.3.5 Monitoring

The IRB and DSMB will review study protocols, consent forms, CRFs, and additional source documents.

11. PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

The study will be conducted with ethical oversight by the MU Health Sciences Institutional Review Board (IRB).

11.2 Informed Consent Forms

The study investigators will ensure that voluntary informed consent is provided by study participants indicated by signature on the informed consent document. The consent form includes a description of study procedures, the time involved, the right to withdraw at any time without penalty, procedures used to protect participant confidentiality, use of data, and potential benefits and risks of participating in the study. Consent procedures will include a verbal presentation of the information contained in the consent form and the opportunity for the volunteer to ask questions. Volunteers will indicate consent by signing the consent form; each participant will receive a copy of the consent form. Signed consent forms will be kept in a locked cabinet in the project office.

11.3 Participant Confidentiality

The project will use a database system that will support screening and recruitment, management and tracking, and data collection activities. To create a unified data management system, we will identify all participants with a study identification number. To ensure participant confidentiality, no names, social security numbers, hospital or clinic numbers will be included in the central study database. All computer files and systems will be password protected and accessible only by authorized study staff. Any records that contain identifying information that is needed for study activities (e.g., participant name and address so reminder cards for follow-up appointments can be sent) will be kept secured in the study locked file in the project office. All study staff will complete appropriate human subjects training, and HIPAA training.

11.4 Study Discontinuation

The study may be discontinued at any time by the DSMB, the IRB, the FDA, the NCCIH, or the OHRP.

12. COMMITTEES

The project leadership team (PI and Co-Investigators) will provide oversight and review of the study, including decisions regarding preparation of publications reporting the study.

13. PUBLICATION OF RESEARCH FINDINGS

Publication and presentation of the study and study results will be governed by procedures established by the project leadership team. Any presentation, abstract, or manuscript will be made available to the NCCIH at the time of submission.

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CONSENT FORM FOR PARTICIPATION IN A RESEARCH STUDY

INVESTIGATOR'S NAME: WILLIAM R. FOLK, PHD

PROJECT IRB #: 2010425

STUDY TITLE: Study to Establish the Bioavailability and Pharmacokinetic Measures of *H. procumbens* Extract in Humans

We invite you to take part in this research study. This consent form tells you why we are doing the study, what will happen if you participate in the study, and other information about the study.

Please take as much time as you need to read this consent form. You can discuss it with your family, friends, or personal doctor. If there is anything you do not understand, please ask us to explain. Then you can decide if you want to take part in the study or not.

The study Principal Investigator is Dr. William R. Folk, University of Missouri Professor of Biochemistry. The Study Physician is Dr. Chokkalingam Siva, University of Missouri Professor of Medicine. They and the nurses and other people working with them are the Study Team.

The U.S. National Institutes of Health (also called the sponsor) is paying for this study.

WHAT SHOULD I KNOW BEFORE I DECIDE WHETHER TO TAKE PART IN THIS STUDY?

- Medical research studies help us to learn new information about means of treating certain conditions/diseases.
- Taking part in this medical research study is voluntary. You decide if you want to take part, and you can stop taking part at any time.

- Your regular medical care at the University of Missouri Hospitals and Clinics will not be affected now or in the future if you do not participate in this study.
- This study is being conducted to find better ways to reduce pain and inflammation in people with osteoarthritis. We wish to learn about a dietary supplement from a plant called *Harpagophytum procumbens* (Devil's Claw) that is often used for pain and other inflammatory conditions.
- We invite you to take part in this study because you have been diagnosed with knee osteoarthritis.
- Twelve people will take part in this study at the University of Missouri Hospitals and Clinics.
- If you take part in this study, you will come to the University of Missouri Clinical Research Center (N508 Health Sciences Center) three times. You will be asked questions about your medical history and have vital signs measured, a physical exam and electrocardiogram (ECG), and blood and urine samples will be collected. A telephone follow-up call will occur after the third visit.
- If you take part in this study, you will have to stop taking anti-inflammatory pain medicines and dietary supplements you are taking for two weeks (fourteen days) before the study begins and while you are in the study.
- The total amount of time you could be in this study is thirty six hours.
- **There is no guarantee that taking part in this study will result in any improvement in your condition.**
- As with any research study, there are risks that we know about and there may be some risks we don't know about. We will explain these risks in this consent form.
- We will only include you in this study if give us your permission first, by signing this consent form.

WHY ARE WE DOING THIS STUDY?

In this study, we want to find out how quickly components of the dietary supplement (*Harpagophytum procumbens* (Devil's Claw) extract) appear in the blood and urine of patients with osteoarthritis. This study includes two groups of six individuals (twelve

total). One group will take capsules that release the dietary supplement into the stomach, and individuals in the second group will take capsules that release the dietary supplement after passing through the stomach. The ingredients in the dietary supplement that appear in the blood and urine will be determined. This information may be useful for treating future patients.

The study has been approved by the U.S. Food and Drug Administration (FDA); but not enough is known about how this dietary supplement can affect people. This study will likely not help you or your osteoarthritis. We hope the information we get from the study will help develop a better treatment for osteoarthritis.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

Screening Tests

If you decide to participate in this study, you will have these screening tests to see if you are eligible and that any risks are minimized:

- Medical Chart Review: The Study Doctor will review your medical chart to determine if it is safe for you to take part in the study.
- Physical Exam: You will have a physical exam, similar to what happens during regular doctor visits.
- Measurement of your heart rate and rhythm (ECG)
- Urine Sample: We will ask you to collect a sample of urine.
- Blood Tests: We will take about one and a half teaspoons of blood from a vein in your arm.
- Pregnancy Tests: If you are a female who can become pregnant (you have had your first period and have not reached menopause), a urine pregnancy test will be conducted to make sure you are not pregnant. (Pregnant and nursing women cannot take part in this study, because it is not known how the dietary supplement might affect them or their infants.)

If the screening tests indicate that you are eligible **and** you agree to participate, you will be scheduled for two test sessions and a follow-up telephone call. If you are not eligible to participate or decide not to participate, the study team will reimburse you for your time and trouble.

Study Test Sessions and Procedures

If you have recently used, or are using any of the following: prescription and over-the-counter non-steroidal anti-inflammatory medications, (e.g., aspirin, ibuprofen, Advil, Motrin, Nuprin, Naproxen, etc.); dietary supplements (St. John's Wort, etc.); and, grapefruit and/or products containing it; you will be asked to discontinue their use for 14 days before visit #2 and until after visit #3.

You should not drink coffee or tea or other drinks that contain caffeine on the morning of visit #2 (test session) and until after the visit #3 (follow-up test session), as these might affect the results.

Visit # 2 - Test Session

This will require visiting the research clinic for 13 hours. You will be given lunch and dinner meals during this visit, and may rest in a pleasant room. You may bring reading materials or other quiet activities to occupy your time.

These are the medical procedures that will occur:

- Vital signs will be measured: heart rate, blood pressure, and breathing rate will be monitored and recorded at several times during the visit.
- Study team will collect a blood sample from a catheter inserted into the arm.
- You will collect a urine sample.
- You will be given 3-4 capsules of dietary supplement to take with water.
- Study team will collect blood samples (approximately 2.5 teaspoons each time) at the following times after taking the capsules: 0 min, 1 hr, , 2 hr, 3 hr, 4 hr, 5 hr, 6 hr, , 8 hr, , 10 hr. (Approximately 21 teaspoons of blood will be collected during this test session.)
- You will collect a urine sample.
- Study team will remove catheter from arm and record information on any side effects (gastrointestinal disturbance, itching, etc.) you might have experienced.

Visit # 3 - Follow-up Session at the research clinic the next morning:
These are the medical procedures that will occur:

- Vital signs (heart rate, rhythm, blood pressure, and breathing rate) will be monitored.
- You will collect a urine sample.
- Study team will collect a blood sample (2.5 teaspoon) from the arm.
- Study team will collect information on any possible side effects (gastrointestinal disturbance, itching, etc.) experienced.

Phone Contact (approximately 36 hours after taking capsules during Visit #2)

- The study team will call you to ask about any side effects or other health symptoms that you experienced following last visit.

The results of the medical procedures can be made available to you and your doctor, if you request them.

HOW LONG WILL I BE IN THE STUDY?

If the screening tests indicate that you are eligible and you agree to participate, this study will take about one and a half days. After you arrive for visit #2 (test session) you will spend about 13 hours in the research clinic. The next morning you will return for a brief follow-up session (visit #3) and the study team will call you that afternoon to collect additional health information.

CAN I STOP BEING IN THE STUDY?

You can stop participating in the study at any time without giving a reason. This will not affect your future medical care at the University of Missouri Hospital or Clinics.

The Study Doctor may decide to take you off this study at any time. You will be told why - these reasons may be:

- If it is in your medical interest
- Your health has changed
- You are not able to follow the study rules
- The study is stopped

WHAT HEALTH RISKS OR PROBLEMS CAN I EXPECT FROM THE STUDY?

There are certain risks to taking part in any medical research study. This dietary supplement may cause health problems (side effects), some of which we do not know about. However, from what is known about this dietary supplement, we believe risks are very low. This dietary supplement have been sold in the U.S.A., Europe and Africa in grocery stores, health food stores, pharmacies, and over the internet for many years. Previous medical research has shown the dietary supplement to be tolerated as well as pain medications such as nonsteroidal anti-inflammatory drugs. In these studies, the side effects that people have experienced with various preparations of the dietary supplement have been rare, but include:

- Gastrointestinal (stomach) disturbances, including nausea, vomiting, stomach pain or diarrhea; loss of appetite or loss of taste.
- Allergies, including itching.
- Headaches or ringing in the ears.
- Menstrual problems.
- Changes in blood pressure.

The study screening session is intended to identify anyone who might experience such problems, and those people will not be eligible to participate in the study.

Medical procedures used in this study might also involve some risks. These include:

- Taking blood from you may cause some discomfort from the needle stick, bruising, or very rarely, infection. However, the study team is experienced in such procedures.
- The dietary supplement might affect an infant, before or after it is born, so anyone who might be pregnant or nursing an infant cannot participate in the study. If you are female, we will ask you to take a pregnancy test in the screening session to be sure you are not pregnant.
- Participation in the study might uncover health information that you might not wish to learn.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

This study is not likely to help you; but it is intended to provide information about future treatments for osteoarthritis that can help patients.

WHAT OTHER CHOICES DO I HAVE?

You can decline to participate or stop participating in the study at any time without giving a reason. This will not affect your future medical care at the University of Missouri Hospital or Clinics.

WHAT ABOUT PRIVACY AND CONFIDENTIALITY?

The study team needs to review your health/personal information. This information comes from questions we ask you, forms you fill out, and your medical record. We must ask your permission to obtain this health/personal information. We are committed to respecting your privacy and to keeping your health/personal information confidential.

If you agree to participate and sign this consent form, the form and any medical information that is obtained, including the results of tests and procedures, may also be entered into in your medical record.

Research information that does not become part of your medical record will be stored in the study electronic/computer or paper files. None of these records will contain your name or other information that could identify you. Computer files are password protected on University of Missouri computers. Paper files are kept in a locked office.

Certain people may see the study research information (without identifiable names or other information) include:

- Those on the study team.
- The study sponsor, the U.S. National Institutes of Health
- Members of the University of Missouri Institutional Review Board (IRB)

- The study Data and Safety Monitoring Board, a group that oversees the study to make sure it is being done safely
- Scientists at the U.S. Food and Drug Administration (FDA)

We may present the results of this study in medical science talks and publications and reports, but none of these results can identify you or your participation in the study.

This study is covered by a Certificate of Confidentiality from the U.S. National Institutes of Health. The Certificate assures that the researchers cannot disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use.

The Certificate allows use of research information by scientists of the U.S. National Institutes of Health needed for auditing or program evaluation or to meet the requirements of the U.S. Food and Drug Administration (FDA). Such research information will not include anything that can identify you.

The Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to the Principal Investigator.

The Certificate of Confidentiality will not prevent disclosure of your health history and other medical information required by the study to the study team.

CAN I SEE MY RESEARCH RECORDS?

If you participate in this study, you will be given one of two types of capsules with dietary supplement, without knowing which one. This is called a “blinded” study, which allows the researchers to compare capsules without other factors affecting the results. If

you ask to see your health records during this blinded study, the study team cannot tell you which capsule you are getting. You would have to wait until all participants have completed the study.

ARE THERE ANY COSTS TO BEING IN THE STUDY?

The sponsor (NIH) will pay for all research tests and procedures. You and/or your health plan/insurance will not be billed for any visits, tests and procedures that are part of this study.

Some costs to you from being in this study may include:

- transportation
- parking
- childcare
- time off work

The study will pay you $50 for study visit #1, $125 for study visit #2 and $50 for study visit #3 to cover these costs. The total amount that you will receive if you complete the study is $225.00.

If you decide to leave the study early, you will still receive a payment for each test visit you completed.

We will need your social security number in order to pay you. A check will be sent to you by the University through U.S. Mail. Any payment may need to be reported as income on your tax return. If you are not a resident/citizen (non-resident alien) of the United States, you may discuss with the MU Nonresident Tax Specialist at 573-882-5509.

WHAT HAPPENS IF I AM INJURED DURING THE STUDY?

It is not the policy of the University of Missouri to compensate human subjects in the event the study results in injury. The University of Missouri, in fulfilling its public responsibility,

has provided medical, professional and general liability insurance coverage for any injury in the event such injury is caused by the negligence of the University of Missouri, its faculty and staff.
The University of Missouri also will provide, within the limitations of the laws of the State of Missouri, facilities and medical attention to subjects who suffer injuries while participating in research studies of the University of Missouri.

In the event you have suffered injury as the result of participation in this research study you are to contact the Risk Management Officer, at (573) 882-1181, at the Health Sciences Center, who can review the matter and provide further information.
This statement is not to be construed as an admission of liability.

WHAT ARE MY RIGHTS AS A STUDY PARTICIPANT?

Taking part in this study is voluntary. You do not have to take part. Your present or future medical care at the University of Missouri Hospitals and Clinics will not be affected if you decide not to take part.

If you do decide to take part, you can change your mind and drop out of the study at any time. This will not affect your current or future care at the University of Missouri Hospitals and Clinics. There is no penalty for leaving the study and you will not lose any benefits that you are entitled to receive.

If the Study Doctor decides to take you off the study, you will be given the reason and the study team will help arrange for your continued care by your own doctor, if needed. We will tell you about any new information discovered during this study that might affect your health, welfare, or change your mind about taking part.

The Data Safety and Monitoring Board, an independent group of experts, will review the data collected during this study. We will tell you about any new information discovered

during this study that might affect your health, welfare, or change your mind about taking part.

Where Can I Get More Information About This Study?

A description of this clinical trial is available on www.ClinicalTrials.gov, as required by U.S. law. This site will not include information that can identify you. At most, the site will include a summary of the results. You can search this site at any time.

Who Can Answer My Questions About The Study?

If you have more questions about this study at any time, you can call the Principal Investigator, Dr. William Folk at 573-882-4857 or contact by email at: folkw@missouri.edu.

You may also contact the University of Missouri Institutional Review Board (IRB) if you:

- Have any questions about your rights as a study participant;
- Want to report any problems or complaints; or
- Feel under any pressure to take part or stay in this study.

The IRB is a group of people who review research studies to make sure the rights of participants are protected. Their phone number is 573- 882-3181.

If you want to talk privately about your rights or any issues related to your participation in this study, you can contact University of Missouri Research Participant Advocacy by calling 888-280-5002 (a free call), or emailing MUResearchRPA@missouri.edu.

We will give you a copy of this consent form. Please keep it where you can find it easily. It will help you to remember what we discussed today.

Signature Of Study Participant

My initials below indicate my choice about using the de-identified data and samples collected from my participation in the study for future research:

The de-identified data and samples may be stored and used for future research.

Yes _____ No _____

Consent to Participate in Research

By signing my name below, I confirm the following:

- I have read/had read to me this entire consent form.
- All of my questions were answered to my satisfaction.
- The study's purpose, procedures, risks and possible benefits were explained to me.
- I voluntarily agree to take part in this research study. I have been told that I can stop at any time.

Subject's Signature	**Date**

Signature of Witness (if applicable)*	**Date**

**A witness is required when a participant is competent to provide consent but is blind, or cannot read or write.*

Signature of Person Authorized to Obtain Consent*

I have explained the purpose of the research, the study procedures (identifying those that are investigational), the possible risks and discomforts and potential benefits of the study, and have answered questions regarding the study to the best of my ability.

Signature of Person Authorized to Obtain Consent	**Date**

**This signature is required for FDA regulated research and/or research that involves any medical procedure or surgical treatment.*

IF THE PARTICIPANT IS DECISIONALLY IMPAIRED, THE LEGALLY AUTHORIZED REPRESENTATIVE (LAR) SHOULD READ AND SIGN BELOW:

By signing my name below, I confirm the following:

- I have read/had read to me this entire consent form.
- All of my questions were answered to my satisfaction.
- The study's purpose, procedures, risks and possible benefits were explained to me.
- I voluntarily agree to this participant taking part in this research study. I have been told that they can stop participating at any time.

Signature of legally authorized representative

Relationship of LAR to Participant	**Date**

Signature of Witness	**Date**

**A witness is required when a legally authorized representative is blind, or cannot read or write.*

Signature of Person Authorized to Obtain Consent*	**Date**

**This signature is required for FDA regulated research and/or research that involves any medical procedure or surgical treatment.*

MO Rev Stat 431.064: Experimental treatment, tests, and drugs, consent to administer by third party — life-threatening emergencies, consent by whom. —
1. When an adult person, because of a medical condition, is treated by a teaching hospital for a medical school accredited by the American Osteopathic Association or the American Medical Association and such person is incapable of giving informed consent for an experimental treatment, test or drug, then such treatment, test or drug may proceed upon obtaining consent of a legal guardian, attorney-in-fact, or a family member in the following order of priority:
(1) Spouse unless the patient has no spouse, or is separated, or the spouse is physically or mentally incapable of giving consent, or the spouse's whereabouts is unknown or the spouse is overseas;
(2) Adult child;
(3) Parent;
(4) Brother or sister;
(5) Relative by blood or marriage.

2. Nothing in this section shall authorize such legal guardian, attorney-in-fact, or family member to consent to treatment in contravention to such incapacitated person's expressed permission regarding such treatment.

(L. 1993 H.B. 564 § 33, A.L. 2003 S.B. 431, A.L. 2006 H.B. 1601 merged with S.B. 765)