Protocol

1. Project Title

Does dietary supplementation with curcumin maintain or improve physical and cognitive function in aging adults at increased risk for disability?

Short Title

Supporting Physical Independence and Cognition in Elders (SPICE)

2. Investigator(s)

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3. Abstract

Aging is associated with a progressive decline in cognitive and physical function leading to a loss of independence. A growing body of evidence strongly implicates chronic low-grade systemic inflammation as having a significant role in contributing to sarcopenia[1], functional decline[2-4], and ultimately disability[5]. To date, few therapies have been identified to reduce chronic systemic inflammation and improve functional performance in seniors. Natural compounds represent important and underexplored sources of potential new therapies for improving physical function because of their anti-inflammatory properties. In particular, the natural compound, curcumin, has been shown to have potent anti-inflammatory effects in recent clinical trials. The effect of these compounds on functional outcomes, particularly in older humans (age ≥ 70 years) at risk of functional decline, is not well documented. This placebo-controlled RCT tests whether dietary supplementation with curcumin maintains or improves cognitive and physical function in older adults who are at high risk of functional decline due existing (mild) functional impairments and elevated biomarkers of inflammation and explore the association between functional changes and changes in biological indicators of active inflammation.

4. Background

a. General Overview. The life expectancy of older Americans continues to increase, with persons aged ≥70 years representing the fastest growing segment of the US population[7]. While prolongation of life remains an important public health goal, of even greater significance is that extended life should involve preservation of the capacity to live independently and to function well[8]. Therefore, identification of proven interventions to maintain physical function and prevent disability is a major public health challenge[9]. Mobility and activities of daily living represent tasks that are necessary for the maintenance of basic independent functioning[10;11]. The inability to perform these activities marks a serious decline in functional health, conferring increased risk of institutionalization and death[12;13]. Many older adults are sedentary[14;15]. Among this population, many are mobile and free of disability but have elevated levels of pro-inflammatory markers and reductions in mobility marked by slower walking speed, which, in turn, is a key predictor of further decline and of increased risk of mortality[16]. These individuals represent the target population for the proposed intervention[17-19].

b. Causes of Physical Disability in Older Persons. Although physical disability can be directly caused or aggravated by acute events (stroke and hip fracture) and severe chronic conditions (heart failure, coronary heart disease)[20;21], a large proportion of mobility disability follows a progressive course over several years in older persons[22]. Specifically, a large and growing number of older adults experience progressive declines in physical function culminating in age-related physical disability with no clear connection to a single disease. Sarcopenia, the progressive loss of muscle mass and strength, has been identified as a common pathway associated with initial onset and progression of physical disability among adults with a variety of disease conditions[23;24]. This is noteworthy as recent estimates suggest that sarcopenia is present in one quarter of persons aged 65 years or older[25;26]. Chronic health conditions, such as diabetes and peripheral artery disease, and lifestyle factors, such as poor nutrition and physical inactivity, have strong potential to accelerate sarcopenia progression and ultimately physical disability[23;24]. This is particularly important as the number of older adults with chronic disease conditions associated with unhealthy lifestyle habits has increased dramatically over the past few decades[27].

As diverse as the etiologies of physical disability are, a growing body of evidence strongly implicates chronic low-grade systemic inflammation as playing a significant role in contributing to sarcopenia and associated functional decline.[1] In present study, systemic inflammation is defined based on elevations in key pro-inflammatory cytokines, specifically plasma C-reactive protein (CRP), tumor necrosis factor Alpha (TNF-ά), and particularly interleukin-6 (IL-6). Increased levels of systemic inflammation have been shown to be detrimental to skeletal muscle in humans[28] as well as in animal models[29] through direct catabolic effects or through indirect mechanisms (i.e., decreases in GH and IGF-1 concentrations, induction of anorexia)[24]. Chronic low-grade systemic inflammation has been found to be inversely associated with IGF-1[31], and reductions in IGF-1, a main messenger of growth hormone, and is associated with sarcopenia, frailty, and mortality in older adults[32]. Elevated levels of systemic pro-inflammatory cytokines have also been found to be positively associated with cachexia, which suggests inflammation may be involved in the process responsible for the anorexia of aging[33].

Apoptosis (i.e., programmed cell death) may play a key role in the development of sarcopenia, with cell loss occurring in post-mitotic tissues (such as skeletal muscle)[34]. An enhanced apoptotic process has been shown in several clinical conditions negatively affecting muscle mass and function[34-37]. A major mechanism leading to cellular apoptosis is promoted by the activation of specific signaling pathways, including the death receptor binding of TNF-α[38]**.** This receptor-mediated pathway promotes the activation of a cascade of caspases (e.g., caspase-8 activates capsase-3 and -7) leading to the proteolysis and cellular breakdown. Moreover, cytokines and reactive oxygen species (ROS) can stimulate cytosolic transcription factor nuclear factor-kappa B (NF-kB) to translocate to the nucleus. Translocation of this protein to the nucleus regulates various pro-oxidant enzymes, such as inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX), vascular cell adhesion molecule-1 (VCAM-1), and intercellular adhesion molecule-1 (ICAM-1). Hence, pro-inflammatory cytokine production in various tissues is known to be redox-sensitive and can be activated through an altered redox environment. Below, we review the biological mechanisms through which chronic low-grade systemic inflammation may contribute to functional decline.

c. Strategies to Reduce Inflammation and Improve Function in Seniors**.** Few therapies have been identified to reduce chronic low-grade systemic inflammation and improve functional performance in the elderly. There are currently no FDA-approved medications for the treatment of functional impairment in older adults. Given the increasing number of older adults with elevated levels of systemic inflammation who are at risk for functional decline, new therapies are urgently needed to reduce systemic inflammation levels and improve functional ability in

older adults, particularly among adults 70 years and older. In view of recent evidence from both basic and clinical research which identified chronic, low-grade inflammation as the major risk factor underpinning many diseases, a better understanding of the mechanisms of both natural and pharmaceutical anti-inflammatory agents is essential and beneficial beyond academic curiosity.

Natural agents that can modulate the inflammation process have the potential to improve both cognitive and physical function through a number of biological pathways. Long term treatment of inflammatory disorders with NSAIDs (non-steroidal anti-inflammatory drugs) has the potential of serious side effects such as increased risk of gastrointestinal and cardiovascular disease, increased susceptibility to fracture, opportunistic infections, and peptic ulcers. Given the increasing use of anti-inflammatory agents among older individuals, studies are needed to examine their safety and efficacy.

Some natural compounds, such as curcumin, may have multiple physiological effects due to their anti-inflammatory and anti-oxidant properties[39;40]. These findings are not unexpected given that curcumin has been found to activate a wide variety of targets, and produces broad, systemic effects that are very similar to caloric restriction, the only method to date that has been found to increase healthy lifespan in multiple species. Below we describe studies supporting the potential use of both of these compounds.

d. Curcumin. Curcumin is the bioactive polyphenolic extract of Turmeric, which has been used to treat inflammatory conditions in India for centuries. Findings over the past few decades indicate that curcumin has a broad range of biological properties, including anti-inflammatory and anti-oxidative properties, directly relevant to human health. In past clinical trials, doses ranging from 1000-2500 mg of curcumin per day have been found to be safe and well tolerated[41]. The anti-inflammatory role of curcumin is supported by both in vitro and in vivo evidence. For example, curcumin has been found to inhibit TNFα -activated NF- κ B signaling in adipocytes; thereby reducing cytokine expression[42]. Curcumin's anti-inflammatory effects may be due in part to its ability to upregulate expression of peroxisome proliferator-activated receptor gamma (PPAR-γ)[43]. Small scale pilot trials have found supplementation with low doses of curcumin (i.e., 20 mg per day) was effective in reducing plasma fibrinogen levels and apolipoprotein B in patients with elevated cardiovascular risk factors[44;45]. Most recently, supplementation with curcumin at a dose of 500 mg per day over an eight week period was found to significantly lower CRP levels in patients with rheumatoid arthritis[46].

5. Specific Aims:

Overall objectives:

(1) to demonstrate the feasibility, acceptability, and efficacy of the proposed intervention in older adults;

(2) to examine the biological effects of the intervention on functional performance and inflammatory processes (Specific Aims); and

(3) to determine the effect size of intervention on key outcomes for sample size calculations for future RCTs.

Specific Aims:

Specific Aim 1 - To examine the effects of dietary supplementation with curcumin on changes in physical function (walking speed, muscle fatigue, and grip strength) and in

self-reported physical activity

Hypothesis 1 – Dietary supplementation with curcumin will maintain or improve walking speed, muscle fatigue, strength, and physical activity compared to controls.

Specific Aim 2 – To examine the effects of dietary supplementation with curcumin on cognitive performance (attention, memory), and pain symptoms.

Hypothesis 2 - Dietary supplementation with curcumin will maintain or improve attention and memory and reduce pain symptoms.

Specific Aim 3 – To examine the effects of dietary supplementation with curcumin on markers of systemic inflammation

Hypothesis 3 - Dietary supplementation with curcumin will decrease levels of IL-6 and of other systemic and cellular biomarkers of inflammation

6. Research Plan

Design

The study will be a randomized, placebo-controlled, repeated measures clinical trial to examine whether supplementation with curcumin is associated with the following outcomes in 24 moderately functioning older adults (age ≥ 70 years) with elevated levels of inflammation (defined as IL-6 > 2.0 pg/mL):

(1) Improvement in physical function and increase in physical activity,
(2) Improvement in cognitive performance,
(3) Improvement in pain symptoms, and
(4) Reductions in systemic inflammatory biomarkers.

Study Population

The RCT will include 24 moderately functioning, sedentary adults age 70 years or older with elevated levels of systemic inflammation but without overt disease conditions. We estimate that up to 324 potential participants will undergo screening procedures to identify 24 persons eligible for enrollment in the RCT.

Based on our previous studies[47-49], we anticipate that the average age of participants will be approximately 77.0 years, and that approximately 20% will be African Americans. In general, participants will have a relative low prevalence of comorbid diseases.

The key inclusion criteria are the following:

(1) Age ≥ 70 years;
(2) Mild to moderate physical impairment (Short Physical Performance Battery score ≤ 10);
(3) Sedentary lifestyle (< 120 min per week of moderate intensity physical activity);
(4) Chronic low-grade inflammation measured by IL-6 >2.5 pg/ml. To minimize within person variability,[150, 156] IL-6 is the average of 2 measures taken 1-3 weeks apart at screening visits

See Table 1 for a complete list of eligibility criteria.

Table 1. Inclusion and Exclusion Criteria

Inclusion Criteria

- Age
- Mild to moderate physical impairment (Short Physical Performance Battery score ≤ 10);
- Sedentary lifestyle (< 120 min per week of moderate intensity physical activity);
- IL-6 > 2.5 pg/mL;
- Willingness and ability to give informed consent
- Willingness to be randomized to the intervention groups
- Availability for participation through duration of study

Exclusion Criteria (General)

- Failure or inability to provide informed consent
- Residence in a Skilled Nursing Facility (SNF); residence in an Assisted Living Facility (ALF) or independent housing is allowed
- Self-reported inability to walk one block;
- Unable to communicate because of severe hearing loss or speech disorder
- Clinically significant depression (CES-D score > 20)
- Severe cardiac disease, including NYHA Class III or IV congestive heart failure, clinically significant aortic stenosis, history of cardiac arrest, use of a cardiac defibrillator, or uncontrolled angina;
- Severe pulmonary disease, pneumonitis or interstitial lung disease;
- Severe rheumatologic or orthopedic diseases (e.g., awaiting joint replacement, active inflammatory disease);
- Neurological conditions that cause impaired muscle function or mobility (e.g., Parkinson's Disease, multiple sclerosis, ALS)
- Other significant co-morbid medical disease (e.g. renal failure with eGFR < 24 ml/minute or on hemodialysis) or severe psychiatric disorder (e.g. bipolar, schizophrenia);
- Terminal illness with life expectancy less than 12 months, as determined by a physician;
- Excessive alcohol use, defined as more than 5 drinks/day for males or more than 4 drinks/day for females, or more than 14 drinks per week;
- Current smoker or less than 3 years smoking cessation
- Participating in another clinical trial or receiving an investigational product within 3 months prior to screening/enrollment.

Exclusion Criteria (Curcumin-related)

- Diabetes mellitus currently taking medications to lower blood glucose (oral or by injection)
- Current use of anticoagulant or anti-platelet medications (aspirin 81 mg daily is allowed)
- Congenital or acquired bleeding disorders
- Cholelithiasis or other gall bladder or biliary tract disease
- Chronic gastrointestinal blood loss or iron deficiency (serum ferritin < 12 ng/mL, with or without anemia)
- History of estrogen-sensitive conditions including breast, uterine, and ovarian cancers; endometriosis; and uterine fibroids
- History of Tuberculosis (TB), HIV, Hepatitis B or C, or other disease potentially compromising immune function

- Current use of:
  - medications targeting immune or inflammatory function (e.g., sulfasalazine, systemic corticosteroids
  - anabolic medications (e.g., growth hormone, testosterone)
  - monoamine oxidase inhibitors (e.g., phenelzine, selegiline, tranylcypromine)
  - anticholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine

Temporary Exclusion Criteria

- Acute infection (urinary, respiratory, other) or hospitalization within 1 month
- Myocardial infarction, CABG, or valve replacement within past 6 months
- Pulmonary embolism or deep venous thrombosis within past 6 months
- Stroke, hip fracture, hip or knee replacement, or spinal surgery within past 4 months
- Receiving physical therapy for gait, balance, or other lower extremity training

Recruitment and Initial (Telephone) Pre-Screening

Potential participants will be recruited from the general population in the North/Central Florida region through:

(1) IRB-approved advertisements providing basic information about the study and inviting potential participants to call for additional information;

(2) Contact of potential participants who are enrolled in the Claude D. Pepper Recruitment Registry (IRB#417-2007) by Registry staff;

(3) Contact of potential participants who are enrolled in Community Engagement and Research Program – Health Street (IRB #265-2011) by Health Street staff; and

(4) Contact of participants in previous IOA studies who have given consent for re-contact about future studies by Study Coordinators.

Those who express interest will participate in a telephone pre-screening interview to assure basic eligibility criteria are met and exclusion criteria are identified. The interview is designed in a manner that does not collect specific PHI and is conducted by an IRB-approved script. Those who remain eligible after completing the telephone interview are invited to attend in-person screening visit prior to enrollment.

In-Person Screening (Screening Visits 1 and 2)

At Screening Visit 1, participants will be asked to give written informed consent for in-person screening tests and will then be evaluated for cardiovascular and other major diseases by a health review. The health review consists of a review of criteria in the telephone screen, medical and hospital admission history, medication inventory, and physical exam including blood pressure, pulse, weight, and waist circumference.

Short Physical Performance Battery (SPPB) will be performed and the Physical Activity Questionnaire will be administered.

Mini Mental Status Exam (MMSE) and Center for Epidemiological Studies – Depression Scale (CES-D) will be administered to identify potential participants with cognitive dysfunction or

clinically significant depression that would preclude participation. Participants will also provide a blood sample for additional eligibility requirements and participant safety measures.

Approximately 60 ml of blood will be drawn for laboratory tests to assure eligibility (complete metabolic panel, CBC with differential, serum ferritin, and IL-6).

Results of Screening Visit 1 will be reviewed by the PI or his designee. . At this time a copy of the Informed Consent document for the main study will be provided, to allow adequate opportunity for review and consideration before the baseline visit when consent for the main study is obtained. Ineligibles will be contacted by the Study Coordinator for an explanation of ineligibility and will receive a copy of abnormal laboratory results.

Enrollment and Randomization

24 eligible participants will be enrolled and randomized to allow for 6 participant failures or withdrawals

At the baseline visit, the Informed Consent document for the RCT will be reviewed with the potential participant and written consent obtained. Participants will undergo a battery of physical performance tests (400-meter walk; short physical performance battery, grip strength and endurance), formal tests of cognitive function, and a blood draw of about 60 ml (See Table 1). Quality of Life and pain will be assessed with the AM-PAC, the SF-36, and the Brief Pain Inventory (BPI). Self-report of physical activity and dietary fat intake will be obtained through brief questionnaires (RAPA and Block High Fat screen).

Participants will then be randomized to receive either curcumin (1000 mg/day; n = 15) or placebo (microcrystalline cellulose; n=15) for a three-month period. The study drug will be provided for the first month according to randomization.

Participants in both groups will be instructed to return to the research center every month for the duration of the three-month trial. At the monthly visits, compliance with the supplementation regimen for the previous month will be assessed by pill count and participants will be provided with another month's supply of study medication according to initial randomization. Participants will be queried about any adverse events they experienced since their previous visit and any medical history updates they may need to provide. Additionally, blood samples will be obtained (chemistry 15 panel and complete blood count) to ensure that no adverse changes have occurred since their previous visit.

To enhance retention and to ensure participant safety, participants will receive bi-weekly telephone calls throughout the intervention period to ascertain adverse events and express appreciation for participation.

Following the three month supplementation period (Month 3 visit), participants will complete a post-treatment assessment including the battery of physical performance tests (400-meter walk, short physical performance battery, grip strength and endurance); cognitive function tests; questionnaires for quality of life, pain symptoms, and physical activity; and a blood draw of approximately 60 ml (See Table 2).

Approximately 3-4 weeks after the Month 3 visit (at Week 15 – 16), participants will receive a final telephone call to ascertain any late adverse events, discuss any abnormalities from the final safety lab results, and express appreciation for participation.

Table 2. Study Visit Schedule Visit Type	Phone screen (pre-screening)	Screening visit 1		Baseline visit	Week 2	1-Month Visit	Week 6	2-Month Visit	Week 10	3-Month visit	Week 15-16
Basic eligibility screening	X	X									
Informed Consent (Screening)		X									
Health review and physical examination (including BP, pulse, weight, height, waist circumference)		X									
Medical History and Concomitant Medication		X									
Update Medical History and Concomitant Medication Info				X		X		X		X	
BP, pulse, height and weight, waist circumference		X		X		X		X		X	
MMSE, CES-D		X									
Physical Activity Questionnaire (RAPA)				X						X	
SPPB (including 4 m walk test)		X		X						X	
Phlebotomy		X		X		X		X		X	
IL-6		X								X	
Additional exploratory inflammatory markers (TBD)				X						X	
CBC and Comprehensive Metabolic Panel (CMP) (Safety blood tests)		X		X		X		X		X	
Informed Consent (Main Study), enrollment, and randomization				X							
400 m walk test				X						X	
Isokinetic dynamometry of knee flexors and extensors				X						X	
Isometric hand grip strength				X						X	
Cognitive Function Tests (NIH Toolbox)				X						X	
Quality of Life (AM-PAC, SF-36)				X						X	
Brief Pain Inventory				X						X	
Dietary Fat questionnaire (Block)				X							
Dispense study drug				X		X		X			
Scheduled phone call					X		X		X		X
Assess compliance, query adverse effects and events						X		X		X	X

Dietary Supplement Intervention

Participants will be given identical capsules containing either: (1) curcumin (1000 mg/day), or (2) placebo (microcrystalline cellulose) and will be instructed to consume two 500 mg capsules prior to breakfast every morning with a glass of water. Participants will be instructed to follow this dosing regimen throughout the entire three-month treatment period. Compliance with the dosing regimen will be monitored both through interview and by counting capsules left at monthly clinic visits.

Curcumin – C3 Complex (Sabinsa Corporation, Piscataway NJ) will be used as the curcumin preparation. Each 500 mg capsule of C3 Complex contains 450 mg of curcumin, 40 mg of desmethoxycurcumin, and 10 mg of bisdemethoxycurcumin. Based on findings from recent studies demonstrating supplementation with curcumin reduced systemic inflammation in middle-age adults[39], the selected dose will be 1000 milligrams per day in 2 divided doses. In safety studies, this dosage level has been determined to be safe for human consumption[41].

Placebo – Participants will consume microcrystalline cellulose in capsules identical to C3 Complex. There are no active ingredients in the placebo capsules.

Outcome Measures

a. Physical Function Measures.

400-meter walk test will assess gait speed. Participants will be asked to walk at their usual pace, without over-exerting. They can stop for up to 1 min for fatigue or other symptoms. Participants will be allowed to use a cane, but not a walker, to complete this test. The results from this test are directly related to whole body aerobic capacity, which has been found to be strongly associated ($r > 0.70$) with mitochondrial function in both younger and older adults[54-56].

Short physical performance battery (SPPB)[57]will assess functional performance on different tasks including timed short distance walk, repeated chair stands and a balance test. The battery will be administered by a trained and certified examiner.

We will conduct additional tests of isolated muscle function by performing unilateral knee extension and flexion maximal strength and endurance testing. This test involves using an isokinetic dynamometer set at 90 degrees per second. Methods similar to that previously described by our group will be used[58-61]. We have reported the reliability of strength testing to be very high (ICC=0.97; coefficient of variation=4.1%) when the testing sessions are separated by 4-weeks[62]. Participants will perform 50 maximal knee extension and flexion concentric repetitions, which will be administered by trained and certified research assistants. Maximal muscle strength will be summarized as peak torque achieved in Newton-meters. A muscle endurance index will be calculated as the decline in peak torque over the 50 repetitions. This will be calculated as a slope and be used to evaluate the effect of curcumin on muscle endurance.

Grip strength will be measured with a hand-held dynamometer as the average of three readings

b. Cognitive Function Assessments

Cognitive tasks. A valid cognitive battery (NIH Toolbox) will be used in this study to assess various aspects of cognitive performance including executive functioning, memory, language, and processing speed.

c. Self-Reported Function and Quality of Life**.** The Activity Measure for Post-Acute Care (AM-PAC) will be used to assess participants' level of perceived functioning. The total score on the AM-PAC is an excellent composite measure of disability or difficulty in performing basic and instrumental ADLs[63;64], especially those related to lower extremity function, and inability to move around (mobility limitations) which contribute the most to dependency, need for assistance from another person or a device, placement in an assisted care facility or a nursing home. It examines a set of functional activities that are likely to be encountered by most adults during daily routines during inpatient care, with outpatient post-acute services, or in the community

setting outside rehabilitation. Because functional activity is multidimensional, AM-PAC assesses multiple aspects (i.e., difficulty, assistance, limitations) of an individual's ability to perform specific daily activities in three functional areas: Basic Mobility (131 items), Daily Activity (88 items), and Applied Cognitive (50 items). AM-PAC is administered on a computer using software licensed by PAC-Metrix.

The Medical Outcomes Study Short-Form Health Survey (SF-36) will be used to provide a psychometrically valid measure of health-related quality of life (HRQOL)[65;66]. The SF-36 comprises a single multi-item self-report questionnaire that assesses 8 health concepts, yielding an overall score and individual scores for the eight subscales. Subscales assessing limitations in physical activities; limitations in usual role activities due to physical problems; bodily pain; vitality (energy and fatigue); and general health perceptions are particularly relevant to this study. The SF-36 has been utilized in many studies of HRQOL associated with a variety of medical conditions and it has often been used to measure changes in HRQOL associated with a variety of treatment interventions[67-69].

e. Pain Assessments. The Brief Pain Inventory (BPI)[70] will be used to assess the presence and location of daily pains, as well as pain severity and pain-related interference. The BPI measures pain severity using a series of 0 (no pain) to 10 (worst possible pain) scales, which assess average pain, worst pain, and least pain in the past week, as well as current pain at the time of testing. There are seven BPI interference questions, each ranging from 0 (does not interfere) to 10 (completely interferes), assessing the extent to which pain has interfered over the past 24 hours with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. This instrument has been validated for assessing outcomes in participants with non-cancer pain and has been used to quantify treatment outcomes.

f. Systemic Inflammatory biomarkers. Standard inflammatory biomarkers (i.e., IL-6, TNFa, and novel markers of inflammation) will be measured by ELISA at Baseline and the 3-month visit. All samples will be measured in duplicate and the average of the two measures will be used for data analyses.

g. Other measures

Dietary Fat (Block) questionnaire. Poor absorption of curcumin has been reported for various preparations, with enhanced absorption in high fat diets. This brief (13 item) “fat screen” identifies individuals with “high” fat intake, a potential confounder due to enhanced curcumin absorption.[71].

Self-reported physical activity. The Rapid Assessment of Physical Activity (RAPA) is a 9-item questionnaire developed to assess strength, flexibility, and level and intensity of physical activity among older adults[72].

Safety. As a safety check to ensure no adverse biological changes have occurred, the following measures will be completed at screening, baseline, and each monthly visit:

- Study Coordinator will review any changes in medication, ED visits or hospitalizations, or side effects since previous visit with the participant

- At monthly visits, 30 cc of blood will be drawn and analyzed for a CHEM-15 metabolic profile (Albumin, Albumin/Globulin Ratio (calculated), Alkaline Phosphatase, ALT, AST,

BUN/Creatinine Ratio (calculated), Calcium, Carbon Dioxide, Chloride, Creatinine with GFR Estimated, Globulin (calculated), Glucose, Potassium, Sodium, Total Bilirubin, Total Protein, Urea Nitrogen) as well as for a complete blood count (WBC, RBC, Hemoglobin, Hematocrit, MCV, MCH, MCHC, RDW, Platelet Count, MPV and Differential (Absolute and Percent - Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils).

Statistical Analyses

Sample size estimates for pilot studies are inherently difficult because by intent, a pilot study is meant to include a smaller sample than a fully powered study. The enrollment sample of 15 participants in the intervention group and 15 participants in the placebo group (allowing for at least 12 evaluable participants in each group after the expected 20% loss due to attrition) is intended to provide sufficient data to indicate feasibility of a larger study and to provide descriptive estimates of effects. Additionally, it will provide for nominal estimation (using a 95% confidence interval) of the mean changes in the inflammatory marker, IL-6, the primary outcome of this pilot.

Feasibility and acceptability of the proposed intervention in older adults will be evaluated by process variables including number of participants completing the study; medication compliance, number and severity of adverse events, and changes in Quality of Life attributable to study participation.

Efficacy will be assessed as effects of the intervention on functional performance (physical and cognitive measures; pain perception, and inflammatory processes (Specific Aims). The following outcomes will be evaluated: physical function (walking speed, muscle fatigue); cognitive function (attention, executive, and memory function); pain (self-report); and systemic inflammation (IL-6, CRP, TNFα, and novel markers)

For each outcome, we will take the value of that outcome after the 3-month supplementation period minus the value at baseline for each participant. Summary statistics and 95% confidence intervals will be provided for within group changes as well as between group differences.

Effect size of intervention on key outcomes for sample size calculations in the planning of a larger RCT Based on a sample size of 15 per group and 20% attrition, we have 80% power to detect a between group difference of effect size 1.2. Specifically, if we use the root mean squared error from LIFE-P (adjusted for baseline log(IL-6) and treatment) of 0.52 for log(IL-6), then we can detect a mean difference of 0.62 (on the log scale) or equivalently the difference between 4.20 and 2.26 pg/ml (or a 46% difference). And for selection based on walking speed change, we used a within group standard deviation of 0.25, which leads to a detectable mean difference of 0.3 m/s.

Compensation

Participants enrolled in the main study (RCT) will receive compensation of $50 for completion of the Baseline and 3-month visits, and $25 for the 1- and 2-month visits. Thus the maximum compensation for completing the main study is $150. Compensation will be provided at the completion of each visit.

Data Safety and Monitoring

Study Monitor: The study physician will serve as a Study Monitor to review all laboratory results, abnormal test scores (MMSE and CESD), and adverse events for individual participants.

Data Safety and Monitoring Board (DSMB): This project is funded as a Pilot Study through the UF Claude D. Pepper Older Americans Independence Center (OAIC) grant (NIH P24 AG028740) and thus uses the OAIC Data Safety Monitoring Board (DSMB).

The DSMB is an established board which has reviewed all studies conducted within the UF OAIC during for the past seven years. This board meets semi-annually. Membership comprises (1) Stephen Kritchevsky, Ph.D., Chair, an epidemiologist who has been involved in research for many years; (2) Jing Cheng, Ph.D., a biostatistician who has been involved with many clinical trials; and (3) John Meuleman, M.D., a physician who has been involved in the conduct of clinical research for many years. DSMB Reports will be provided to the UF IRB-01 with annual Continuing Review submissions.

7. Possible Discomforts and Risks:

General Approach.

All assessment visits will be conducted at a central location fully equipped with a semi-automated ECG and defibrillator.

All sessions are conducted by research staff trained to monitor potential adverse experiences and symptoms during the testing sessions. All personnel associated with the study have completed Basic Life Support (BLS) training and education on management of acute events including syncope, chest pain, acute dyspnea, focal neurological symptoms and abnormal vital signs. Contact numbers for emergency services are posted, and community EMS services will be activated if needed.

Participants will be instructed to talk with the investigators about any discomforts that occur during the study. If a participant reports an injury, chest pain, leg swelling, excessive shortness of breath, palpitations, or dizziness, he/she will be referred to medical attention (his/her doctor, or Emergency Department).

All research staff complete protection of human research subjects training required by the University of Florida institutional review board (IRB) and National Institutes of Health (NIH). This training includes education about the importance of maintaining confidentiality of personal health information.

Specific Potential Risks. Potential risks for this study are related to the following: (1) use of study product, (2) blood draw procedure, (3) blood pressure measurement procedure, (4) testing for depression and cognitive function; (5) the physical performance tests, and (6) potential loss of confidentiality related to study participation

1. Risks associated with curcumin. Curcumin and chemically-related “curcuminoids” are bioactive polyphenolic compounds extracted from turmeric. These compounds are used in large amounts in Eastern cooking (e.g., curry), as dietary supplements, and to treat inflammatory conditions in India for centuries. Findings over the past few decades indicate that curcumin has a broad range of biological properties, including anti-inflammatory and anti-oxidative properties,

directly relevant to human health. In recent clinical trials, doses ranging from 1000-2500 mg of curcumin per day have been found to be safe and well tolerated.[41]

C3 Complex (Sabinsa Corporation, Piscataway NJ) was chosen for this study due to reproducibility of the curcuminoid content and the curcumin dose. and is currently commercially available as a neutraceutical "bio-protectant."

Potential disease or drug interactions with curcumin have been suggested in animal studies and human case reports; however, the clinical implications of these findings are largely unknown[73].

- Curcumin may reduce levels of blood glucose and glycosylated hemoglobin (HbA1c), possibly through a PPAR-γ mechanism[43]. Persons currently taking medication to lower blood glucose are excluded from participation.

- Turmeric has been reported to have antiplatelet effects, so that concurrent use of curcumin with anticoagulants or antiplatelet drugs could theoretically increase the risk of bleeding. Persons with bleeding disorders or persons taking anticoagulant medications or antiplatelet agents (other than aspirin 81 mg daily) are excluded from participation. Participants taking low dose aspirin are monitored for increased bruising or bleeding and study medication is discontinued should this occur.

- Turmeric has been reported to cause gall bladder contractions. Persons with cholelithiasis or other gall bladder or biliary tract disease are excluded from participation.

- Curcumin may chelate iron and reduce its absorption. Serum ferritin will be checked at screening. Persons with chronic gastrointestinal blood loss or iron deficiency (serum ferritin < 12 ng/mL, with or without anemia) are excluded from participation

- *In vitro* evidence suggests that curcumin can competitively inhibit binding of 3H-estradiol or β-galactosidase to estrogen receptors and thus, theoretically, may have mild estrogenic effects. Persons with a history of estrogen-sensitive conditions including breast, uterine, and ovarian cancers; endometriosis, and uterine fibroids are excluded from participation.

- *In vitro* and animal studies suggest that curcumin may suppress cytochrome P450 1A1 (CYP1A1), cytochrome P450 1A2 (CYP1A2) cytochrome P450 3A4 (CYP3A4), so theoretically curcumin could increase levels of drugs metabolized by these enzymes. These interactions have not been reported in humans. However, persons taking MAO inhibitors or cholinesterase inhibitors are excluded from participation.

Specific information on side effects observed in clinical trials is limited due to the small size of most studies, the patient populations (ages and diseases studied), different doses and composition of curcumin, and the efficacy focus of the clinical research. The most commonly reported side effects include upset stomach, nausea, dizziness, and diarrhea. In a recently published multi-center clinical trial comparing ibuprofen to curcumin extract in the treatment of osteoarthriti[74], curcumin extract was associated with fewer adverse events than ibuprofen in all complaints except loose stools, although differences were statistically significant only for abdominal pain/distension (see Table 3 below).

Table 3. Adverse Events	Ibuprofen 1200 mg (n = 182)	Curcumin extract 1500 mg/day (n = 187)	P-value

	Mean age 60.9 yr	Mean age 60.3 yr	
Number of patients with AE	65 (35.7%)	55 (29.7%)	0.222
Number of events			
Abdominal pain and/or distension	33 (18.1)	20 (10.8)	0.046*
Dyspepsia	29 (15.9%)	21 (11.1%)	0.201
Nausea	15 (8.2%)	9 (4.9%)	0.091
Loose stools	16 (8.8%)	22 (11.9%)	0.324
Melena	2 (1.1%)	-	0.245
Pitting edema	13 (7.1%)	7 (3.8%)	
Kuptmiratsakul V et al. Efficacy and safety of *Curcuma domestica* extracts compared with ibuprofen in patients with knee osteoarthritis: a multicenter study. Clinical Interventions in Aging 2014:9 451-458 (Reference 74)			

Monitoring for Adverse Events (AEs). An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with a study intervention that *may* or *may not* be related to the intervention. At monthly study visits, participants will be queried about specific AEs as above and instructed to report any additional adverse effects they experience related to the study coordinator or other member of the investigative team. Basic blood chemistry and CBC from each visit will be reviewed by the Safety Monitor (study physician).

Grading scales found in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf) will be utilized for AE reporting. All AEs will be reviewed by the Safety Monitor (study physician) upon ascertainment.

- Grade 1 adverse events are mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 adverse events are moderate; minimal, local, or noninvasive intervention indicated; limit age-appropriate instrumental ADLs (preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
- Grade 3 adverse events are severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated disabling or limit self-care ADLs (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4 adverse events have life-threatening consequences, urgent intervention indicated
- Grade 5 adverse event are fatal, resulting in death.

Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) are defined for gastrointestinal side effects reported with curcumin in Appendix A.

Study medication will be stopped for the following reasons:

- Moderate to severe adverse effect symptoms limiting participant continuation in the study (Grade 3 or 4 toxicity)
- Elevation in liver function tests to 2x upper limits of normal or increase in serum creatinine to 1.5x baseline value
- Decrease in hemoglobin of > 1 g/dL from previous visit
- Development of medical problems listed as exclusion criteria
- Need for medications listed as exclusion criteria

As curcumin is well-tolerated, no Grade 3 or 4 toxicities are expected and no dose modifications are planned for this study.

This study will have a Safety Monitor (study physician) for continuous monitoring of individual participant results, and aggregate data will be reviewed semiannually by the Claude D. Pepper OAIC DSMB (see above).

2. Risks associated with blood draw. Risks include discomfort with the puncture and the possibility of a small bruise at the puncture site. To avoid these risks, research staff are trained in proper phlebotomy techniques

3. Risks associated with blood pressure measurement. The risks of placing a blood pressure cuff on a participant's arms are that it may cause pinching or slight bruising. To avoid this risk, research staff are trained in procedures for measuring blood pressure

4. Risks associated with cognitive function tests. Participants may experience fatigue and feelings of frustration while completing the cognitive function tests. Participation also includes a risk of loss of confidentiality of personal health information. To minimize these risks, research staff are trained in the conduct of the cognitive function tests and certified by Dr. Anton or his designee before they work with study participants.

6. Risks associated with physical performance tests. The 400-meter test may be associated with the risk of falling or development of chest discomfort due to coronary ischemia or dyspnea due to heart failure or lung disease. Rarely, falling during the 400-meter walk test may result in a fracture. Similar to the six-minute walk test, completion of the SPPB may be associated with the risk of falling or development of chest discomfort due to coronary ischemia or dyspnea due to heart failure or lung disease. Rarely, falling during the SPPB test may result in a fracture.

To minimize these risks, research staff are trained in the conduct of all physical performance tests and certified by Dr. Anton or his designee before they work with study participants. Study staff are instructed not to perform these tests if they feel that testing is unsafe for an individual participant or if the participant is concerned about safety. If safety concerns are identified by either the study staff or the participant during the testing procedures, testing is halted and the participant is not allowed to complete the test. In either case, the participant is assessed to determine the need for medical intervention and the cause for concern is evaluated. All study staff are trained in activating the emergency response system at The University of Florida facility.

7. Risks associated with questionnaire administration. Sensitive information collected for this study includes lifestyle factors (e.g., alcohol use) and personal health information (PHI) and are used predominantly in screening for eligibility and safety. Participation includes a risk of loss of confidentiality of this information.

To minimize risk, questionnaire data are collected in secure spaces where the interview cannot be overheard. Participants are reminded that they can decline to answer questions that are uncomfortable or concerning. All research staff members complete annual HIPPA for Researchers training as required by UF.

Collected data are maintained in locked computer files and file cabinets to which only study investigators have access. Only study investigators and key research staff (i.e. data manager and study programmers) have access to the study forms or database. Participants are assigned a unique study identifier; individual names will be removed from the study database and only the unique study identifier used to distinguish participants in the database. Collected data will be used only for research purposes, and publications will not contain any individual identifiers.

8. Possible Benefits:

Benefit to study participants. This study offers possible benefit to some participants (those receiving curcumin). Curcumin is categorized as "possibly effective" in improving symptoms of osteoarthritis by the Natural Medicines Comprehensive Database (NMCD)[73]. While preliminary clinical research suggests efficacy for other medical conditions (including Alzheimer's disease, type 2 diabetes mellitus, inflammatory bowel disease, and rheumatoid arthritis), NMCD considers "insufficient reliable evidence to rate" efficacy in these conditions.

Public health implications. Older participants with functional impairment are less likely to remain independent in the community, have higher rates of hospitalization, and have poorer quality of life than those without functional impairment. Thus simple effective interventions to improve functional capabilities or mitigate functional decline have important potential impact in public health and medical economics.

9. Conflict of Interest: None

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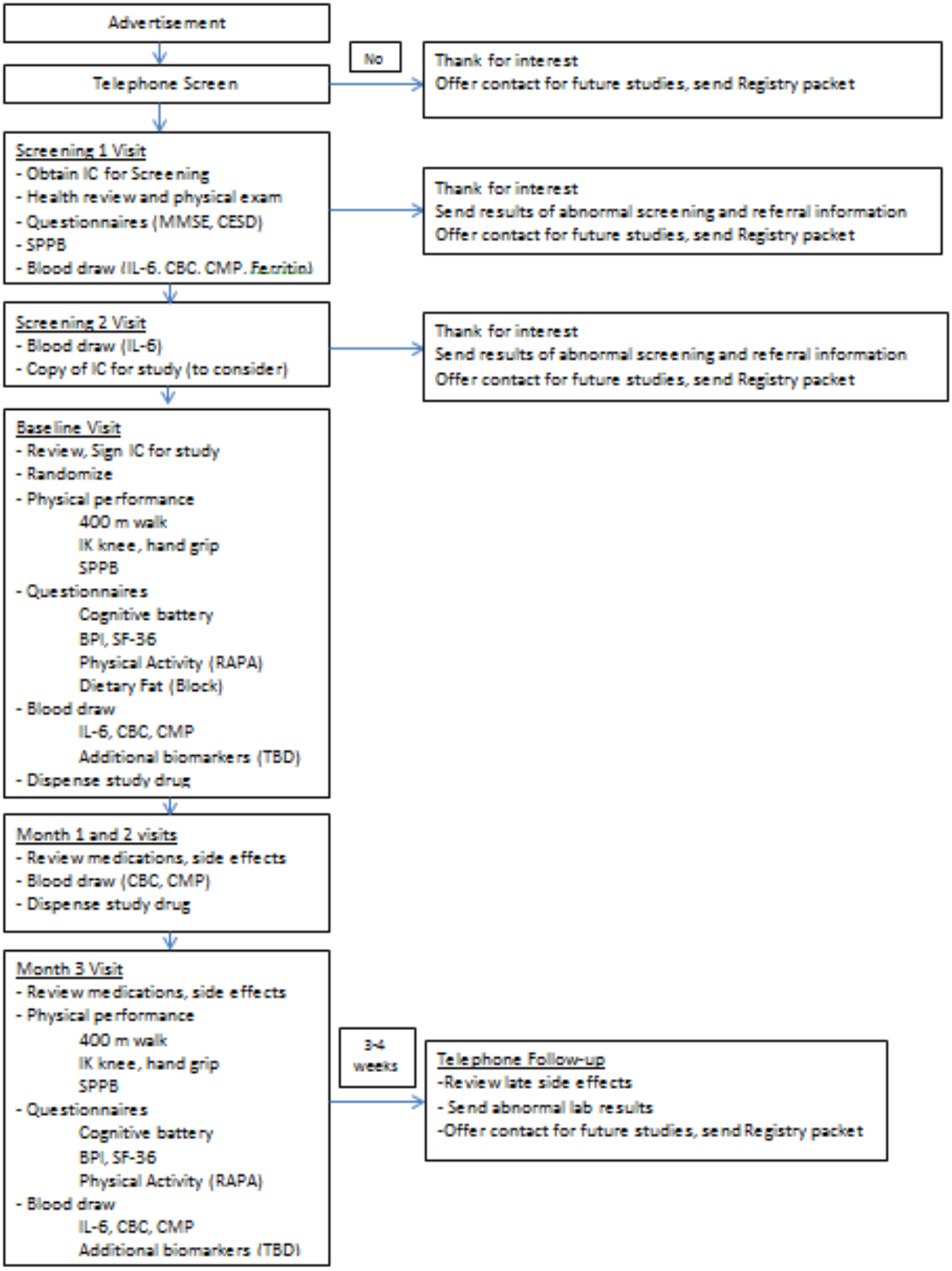
SPICE Study Schema



Appendix A: Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) for gastrointestinal side effects reported with curcumin

Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) Gastrointestinal Disorders relevant to Curcumin					
	Grade				
AE	1	2	3	4	5
Abdominal distension: A disorder characterized by swelling of the abdomen	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADLs	Severe discomfort; limiting self-care ADLs		
Abdominal pain: A disorder characterized by a sensation of marked discomfort in the abdominal region	Mild pain	Moderate pain; limiting instrumental ADLs	Severe pain; limiting self-care ADLs		
Bloating: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen	No change in bowel function or oral intake	Symptomatic; decreased oral intake; change in bowel function			
Diarrhea: A disorder characterized by frequent and watery bowel movements	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of ≥ 7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADLs	Life-threatening consequences; urgent intervention indicated	
Dyspepsia: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting	Mild symptoms, intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated		

Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.0) Gastrointestinal Disorders relevant to Curcumin (Cont.)					
AE	Grade				
	1	2	3	4	5
Flatulence: A disorder characterized by excessive gas in the alimentary canal.	Mild symptoms, intervention not indicated	Moderate symptoms; psychosocial sequelae			
Gastroesophageal reflux disease: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter and may result in injury to the esophageal mucosa. Symptoms include heartburn and acid indigestion.	Mild symptoms, intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated		
Gastrointestinal pain: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region.	Mild pain	Moderate pain; limiting instrumental ADLs	Severe pain; limiting self-care ADLs		
Nausea: A disorder characterized by a queasy sensation and/or the urge to vomit.	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration, or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated		
Stomach pain: A disorder characterized by a sensation of marked discomfort in the stomach	Mild pain	Moderate pain; limiting instrumental ADLs	Severe pain; limiting self-care ADLs		
Vomiting: A disorder characterized by the	1 – 2 episodes (separated by	3 – 5 episodes (separated by	≥ 6 episodes (separated by 5 minutes) in	Life-threatening consequences; urgent	Death

reflexive act of ejecting the contents of the stomach through the mouth	5 minutes) in 24 hours	5 minutes) in 24 hours	24 hours; tube feeding, TPN, or hospitalization indicated	intervention indicated	
Gastrointestinal disorders – Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADLs	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADLs	Life-threatening consequences; urgent intervention indicated	Death