Protocol Title:
Feru-guard (ferulic acid and Angelica archangelica extract) for behavioral symptoms in dementia

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A. SPECIFIC AIMS:

Primary aims and Hypothesis

Dementia is a progressive neurodegenerative disease characterized by cognitive decline, with multiple possible etiologies. Some of the most common types of dementia include Alzheimer's disease (AD), vascular, and mixed. A common feature of dementia is the presence of behavioral and psychological symptoms, which can include agitation, anxiety, apathy, delusions, depression, irritability, hallucinations, and motor disturbance. Behavioral and psychological symptoms of dementia (BPSD) are associated with more rapid cognitive decline and impairment in daily activities [1, 2], diminished quality of life for the patients and caregivers [3-5], and lead to institutionalization [6, 7]. Identifying therapies that can ameliorate behavioral disturbances in dementia would have a direct benefit by improving the quality of life of patients and their caregivers. Glovia, Co. Ltd. has produced a proprietary dietary supplement containing ferulic acid and Angelica archangelica called Feru-guard 100M (Feru-guard). Feru-guard is a dietary supplement sold through health clinics and directly from Glovia, Co. Ltd., based on a doctor's recommendation in Japan. A study that evaluated ferulic acid in an AD mouse model showed behavioral and memory improvements after 6 months of oral treatment [8]. In an open-label study, participants with Lewy body and frontotemporal dementia showed improvement in BPSD after 4-weeks of oral Feru-guard supplementation [9]. The primary aim in this pilot study is to evaluate the safety and effectiveness of Feru-guard supplementation in decreasing BPSD in people with Alzheimer's disease, vascular and mixed dementias over 12 weeks. Secondary aims will evaluate if Feru-guard given to participants will decrease caregiver burden and increase caregiver quality of life.

Primary Aim 1.) Determine if Feru-guard (ferulic acid and Angelica archangelica) will improve behavioral and psychological symptoms of dementia.
We hypothesize that a 12-week supplementation of Feru-guard will improve behavioral and psychological symptoms in people with dementia.

The primary outcome measure will be a change in the total score on the Neuropsychiatric Inventory Questionnaire (NPI-Q) over 12-weeks. We expect the group receiving Feru-guard will have a greater improvement in total NPI score compared to the placebo group at 12-weeks.

Secondary Aim 2.) Measure the effect Feru-guard supplementation has on caregiver burden and quality of life, and global cognition in participants.
We will collect data on the effect of Feru-guard supplementation on caregiver burden (NPI-Q subscale of caregiver distress), the Zarit Burden Interview (ZBI) screening

version, and caregiver quality of life (SF-12) over 12 weeks. We will also collect data on changes in global cognition of participants over 12 weeks using the Montreal Cognitive Assessment (MoCA). We will compare secondary outcomes between Feru-guard and control group.

The data generated in this pilot study will be used to aid in the design of a larger clinical trial that can more definitively assess the effects of Feru-guard for BPSD in dementia.

B. BACKGROUND:

B.1. Behavioral and Psychological Symptoms of Dementia (BPSD)

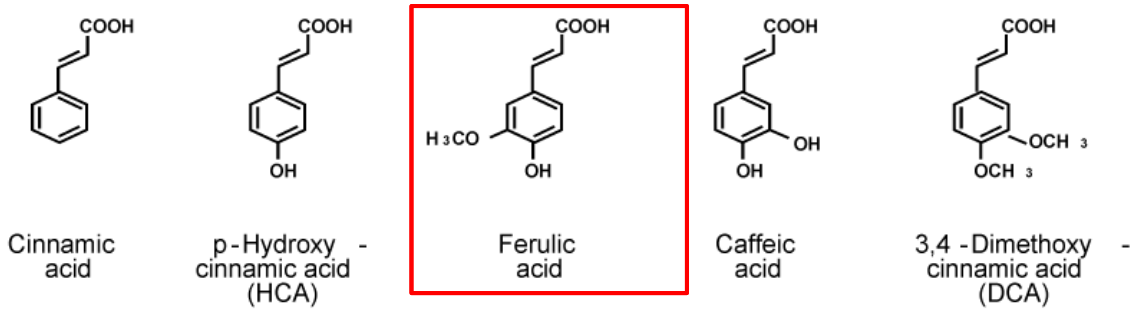
It is estimated that in 2050, 135 million people will suffer from dementia worldwide [10] and BPSD will affect up to 90% of patients [11]. BPSD is a constellation of symptoms that include disturbed behavior and mood (e.g. aggression, agitation, sleep problems, apathy, wandering) that are distressing for people with dementia and their caregivers. BPSD is associated with a more rapid progression of illness that affects cognition and activities of daily living that subsequently leads to an increase rate of institutionalization for patients [12, 13]. In addition, it is a major contributor to caregiver, societal, and economic burden, which carries treatment challenges for health providers and families [14]. Current therapies include non-pharmacologic (e.g. music therapy, exercise) and pharmacologic therapies [2, 14]. In a review of non-pharmacologic therapies for BPSD that included exercise, music therapy, light therapy, aroma therapy, cognitive rehabilitation, and a combination of exercise, art and music therapy, many of these therapies showed some benefit [2, 14]. The authors' report that the main limitation to studies reviewed was design heterogeneity (including non-randomized and randomized studies) and the majority with participants in nursing homes and facilitated care rather than community dwellers [2, 14]. Pharmacologic therapies for BPSD include antipsychotics for agitation/aggression and antidepressants for depression and anxiety [2, 15, 16]. Some recent evidence suggests higher mortality in demented patients with long-term antipsychotic drug use [16-18]. Given the negative impact BPSD has on patients and caregivers, and recent evidence that pharmacologic mood stabilizers produce undesirable side effects including mortality in fragile patients, identifying safe and effective non-pharmacologic therapies is highly warranted.

B.2. Ferulic Acid and Antioxidant Properties

Ferulic acid (FA) is a naturally occurring phenolic phytochemical found in fruits, vegetables, cereals, coffee, and some non-edible plants, with concentrations highest in cereal grains, reaching up to 2 gram/kilogram of dry weight in grains [19, 20]. Chemically, FA belongs to a broad class of phenolic compounds that are hydroxy derivatives of cinnamic acid [Figure 1. Chemical Structure: Hydroxycinnamic Acids] [19, 20]. Ferulic acid is a natural antioxidant and acts as a potent free-radical scavenger, the carboxylic acid groups can act as a lipid anchor protecting neuronal membrane fatty acids from lipid peroxidation [21-23]. Due to its antioxidant properties, FA has been used therapeutically for a wide range of chronic conditions that include, diabetes, cancer, aging, cardiovascular health, and has the potential for neuroprotective benefits [23, 24]. In addition, FA possess anti-inflammatory properties secondary to its ability to act as an anti-oxidant by mediating prostaglandin E_2 and tumor necrosis factor-alpha

(TNF-α) and iNOS expression and function [25]. In vitro and animals models evaluating FA and its metabolites vanillic and caffeic acids, are reported to exhibit anti-amyloid and protection against glutamate-induced cell death [26-28].

Figure 1. Chemical Structure: Hydroxycinnamic acids



B.2.1. Ferulic acid and anti-aggregation properties: Amyloid and Tau

Amyloid beta-peptide (Aβ) plaques are a central feature of the pathophysiology of Alzheimer's disease and in up to 38% of brains in frontotemporal dementia (FTD) [29, 30]. In a similar manner, tau protein aggregates also known are pathologic contributors in both AD and FTD [31]. Phenolic compounds, including FA have been shown to inhibit the formation, elongation, and stabilization of β-sheet structures like Aβ [32-33] and tau aggregates [34].

B.2.2. Ferulic Acid safety

Ferulic acid in Feru-guard is extracted from rice bran. It is naturally occurring in rice, wheat, oats, pineapple, grasses, grains, vegetables, flowers, fruits, leaves, beans, coffee beans, artichoke, peanut and nuts. In its extracted form, it can be found in cosmetics, sunscreens, food preservatives and a variety of therapeutic agents where strong antioxidants are beneficial. Ferulic acid has a low toxicity and is easily tolerated by humans [35].

B.3. Acetylcholinesterase and dementia

Acetylcholine is a neurotransmitter with a diverse set of roles within the central nervous system including involvement with brain plasticity, alertness, learning, memory, and apoptosis. Acetylcholinesterase is an enzyme that breaks down acetylcholine. In Alzheimer's patients, there is a progressive decline in the neurotransmission of acetylcholine, which contributes to the deterioration in cognitive function [36]. In addition to removing acetylcholine, acetylcholinesterase is linked to Aβ plaques by promoting its aggregation [37, 38]. The Aβ plaques, specifically soluble Aβ oligomers (AβOs), are toxic and induce oxidative stress to the surrounding brain tissue and cells. The presence of AβOs have been negatively correlated with cholinergic receptors, suggesting that AβOs induce impairment of cholinergic neurotransmission in Alzheimer's pathogenesis [39].

B.4. Angelica archangelica

Angelica archangelica is a biennial plant of the apiaceae family. Traditionally, Angelica archangelica has been used as an herbal remedy for anemia, flatulence, and to improve digestion.

B.4.1. Angelica archangelica and acetylcholinesterase

Acetylcholinesterase has been a target for the improvement of memory and cognition in dementia. Angelica archangelica contains the chemical imperatorin, which is known to inhibit acetylcholinesterase [40]. Oral administration of Angelica archangelica extracts that concentrate imperatorin levels, have demonstrated an ability to inhibit acetylcholinesterase and improve performance on memory tests in mice [41]. Interestingly imperatorin has also shown an ability to reduce oxidative stress in the hippocampus and cortex of mice [42]. Evidence from animal models gives a reasonable rationale for combining Angelica archangelica with ferulic acid in Feru-guard as a dietary supplement targeted to benefit older people with dementia.

B.4.2. Angelica archangelica safety

There is little published clinical trial data reporting on the safety of Angelica archangelica. We have included published and unpublished safety data supplied by Glovia, Co. Ltd., on Angelica archangelica as a component of Feru-guard at daily dose of 40.04 mg (see Section C1). There is one published double-blind, placebo controlled study by Sigurdsson et al. that evaluated Angelica archangelica in the product SagaPro for nocturia in men 45 years and older [43]. In this study, men (n=69) with nocturia were given a daily dose of 100 mg Angelica archangelica extract in SagaPro, for 8 weeks; there was no difference between the SagaPro and placebo groups in measure of nocturia. There were no SAE reported in either group and the AE possibly related to SagaPro was constipation [43].

B.5. Study Supplement - Feru-guard

Feru-guard is a dietary supplement commercially available in Japan in the form of a 1.5 g instant powder packet that is sold in health clinics and directly by Glovia Co. Ltd to patients on doctor's recommendation. The current study will use Feru-guard in the form of a 280 mg hard gel capsule that contains the same amount of the active ingredients (ferulic acid and Angelica archangelica) as the 1.5 g packets. Published and unpublished studies conducted in Japan have evaluated Feru-guard at 3.0 gram/day (two 1.5 gram packets). Table 1 shows the composition of the study supplement. Feru-guard capsules contains the following active compounds: ferulic acid and Angelica archangelica. Feru-guard also contains the inactive ingredient of ascorbic acid, d-α-tocopherol preparation, starch, calcium stearate, silicon dioxide (fine), and tricalcium phosphate.

Table 1. Feru-guard composition per one 280 mg capsule

Ingredients	mg	%
Ferulic Acid (Free Body)	80.08	28.6
Ferulic Acid (Cyclodextrin Clathrate)	100.24	35.8
Angelica Extract	20.02	7.15
Ascorbic acid	27.02	9.65
d-α-Tocopherol Preparation	5.012	1.79
Starch	28.028	10.01
Calcium Stearate	8.4	3.0
Silicon Dioxide (fine)	4.2	1.5
Tricalcium Phosphate	1.40	0.5
Food Flavor (Vanilla)	5.60	2.0
Total	280.0	100

B.5.1. Source of Product

Feru-guard will be supplied by Glovia, Co. Ltd., in Tokyo, Japan. This company follows the Ministry of Agriculture, Forestry and Fisheries of Japan guidelines for manufacturing procedures and verifies product quality and label claim by in-house and outside laboratory analysis.

Glovia, Co. Ltd., is applying for an IND for the proposed use of Feru-guard in dementia for BPSD prior to the study start date.

B.5.2. Rationale for product form and dose

The daily dose of Feru-guard in the proposed study will be 2 capsules a day, the same dose as in previously published studies with Japanese elders with MCI or dementia. Two 280 mg capsules are equivalent to a daily dose of 3 g of Feru-guard powder containing 360.2 mg of ferulic acid and 40.04 mg of Angelica archangelica [9, 44, 45].

In order to conduct a double-blind, placebo-controlled trial, Feru-guard is contained in opaque, hard gel capsules which allows for better matching of characteristics and improved blinding than studies using powder. The active study drug will be matched to the placebo in terms of appearance, smell, and taste.

B.5.3. Safety data

Clinical trials using Feru-guard supplementation (see Table 2) in Section C1.

C. Approach, Preliminary Studies

C.1. Summary of safety data on Feru-guard from published and unpublished data (unpublished data is confidential) – Table 2

Table 2. Summary of Adverse Events related to drop out from published and unpublished studies supplied by Glovia, Co. Ltd.

Year	2011	2014	2010-2013	2014-2017	2015-2016	2014-2016
PI	Dr. Kimura	Dr. Kimura	Dr. Yamaguchi	Dr. Yamaguchi	Dr. Yoshida	Dr. Yamamoto
Published	Yes	Yes	No	No	No	No
Number of participants	20	28	64	90	22	20
Design and Treatment Duration	Open Label 4weeks	Open Label 96 weeks	Open Label Cross Over 12 month (6 month cross over)	Double-Blind, Placebo controlled 24 months	Double-blind, placebo-controlled 48 weeks	Open Label 24 months
Participant population*	FTLD[1], DLB[2]	MCI3	AD[4], DLB[2]	MCI[3]	MCI[3]	MCI[3]
Number of dropouts	0	10	14	11	2	0
AE reported	0	0	14	11	2	0

[1] FTLD = Frontotemporal dementia
[2] DLB = Lewy body dementia
[3] MCI = Mild Cognitive Impairment
[4] AD = Alzheimer's disease

Summary of drop outs related to AEs supplied by Glovia, Co. Ltd.
PI: Yamaguchi, 2010-2014: AE listed by type and group (A or B), groups not identified (Table 3)

Table 3. Yamaguchi, 2014-2017 AE data

AE Reported	**Group A (n)**	**Group B (n)**
Personal reason	2	4
Symptom Progression	1	2
Death	3	1
Stroke	1	0
Total AE reported	7	7

All AEs reported related to drop out (no group assignment provided)
Skin rash (n=4)
Cholangitis (n=1)
Constipation/frequent urination (n=1)
Recurrent malignant tumor (n=1)
Recurrent cerebral infarction (n=1)
Dementia diagnosis (n=1)
High blood pressure (n=1)
Pituitary abnormality on MRI (n=1)
Total reported n=11

PI: Dr. Yoshida, 2015-2016 (Table 2)
AEs related to drop out

Chronic rash (n=1)
Diarrhea (n=1)

In summary, there were 27 AEs that include 4 SAE reported from the 244 total participants across studies; mean dropout rate across studies was 11.2% (27/244). Data provided for a double-blind, placebo controlled study that evaluated Feru-guard in AD and Lewy body dementia (PI: Yamaguchi, 2010-2014) found no significant difference between groups A and B in AE or SAE.

C.2. Feru-guard improves behavioral symptoms in frontotemporal dementia and Lewy body dementia in an open-label pilot study

Kimura et al. Effect of ferulic acid and Angelica archangelica extract on behavioral and psychological symptoms of dementia in frontotemporal lobar degeneration and dementia with Lewy bodies [9].

Twenty participants diagnosed with frontotemporal dementia (n=10) and Lewy body dementia (n=10) were given 3.0 grams/day of Feru-guard for 4 weeks. After four weeks, the total NPI score was used to evaluate baseline change of behavioral symptoms. The NPI reflects caregiver's rating on 10 behavioral symptoms common in dementia (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior), a higher score reflects a higher level of behavioral symptoms. Participants mean age was 81.6 years (SD $\pm$5.90) and 16/20 (80%) were female. Mean baseline NPI score was 28.3 (SD $\pm$ 9.6) and 4-week mean NPI score showed a significant decrease to 17.7 (SD $\pm$9.7), p <0.001. This finding suggests that Feru-guard may improve BPSD in older adults with dementia.

C.3. Summary of unpublished data evaluating Feru-guard for Behavioral symptoms in AD and Lewy body dementia in an open label pilot study.

Kanaya K, et al. Effect of ferulic acid and Angelica archangelica extract on Behavioral and Psychological Symptoms of Dementia (BPSD) of Alzheimer's Disease (AD) and Dementia with Lewy Body Disease. Poster presentation at the 27th International Conference of Alzheimer's Disease International, London, 2012.

Thirty two participants diagnosed with AD (n=18) and Lewy body dementia (n=14) were given 3.0 grams/day of Feru-guard for 8 weeks. After 8 weeks, the total NPI score was used to evaluate baseline change of behavioral symptoms. In addition, 22/32 participants underwent SPECT imaging at baseline and 8-weeks to evaluate Feru-guard's effect on cerebral blood flow. Participants mean age was 80.6 years and 18/32 (56.3%) were female. Mean baseline NPI score was 21.3 (SD $\pm$ 20.9) and 8-week mean NPI score showed a decrease to 15.9 (SD $\pm$14.9). SPECT imaging showed a significant increase in blood flow in the cingulate gyrus, right frontal lobe, left parietal lobe and brain stem (pons); and significant decrease in blood flow in the left and right occipital lobe. These finding suggests that Feru-guard may improve BPSD in older adults with

AD and LB dementia, changes in cerebral blood flow after 8 weeks on Feru-guard are observed in specific areas of the brain. The authors conclude that the relationship between blood flow changes and improvements in behavioral symptoms warrant further investigation.

C4. Summary of Preliminary data

Preliminary data suggest that that Feru-guard supplementation is relatively well tolerated in older adults with MCI and dementia. Pilot open-label studies suggests that taken for 4-8 weeks, Feru-guard has the potential to improve BPSD as measured by NPI-Q. This study will be the first double-blind, placebo-controlled study to evaluate Feru-guard for BPSD in people with AD, vascular, and mixed dementia and is unique in that it will prescreen for BPSD (at least 3 items on NPI-Q) as part of study inclusion.

D. STUDY DESIGN:

D.1. Overall Study Design

This is designed as a randomized, double-blind, placebo-controlled clinical trial with a 12 week intervention period. Seventy participants with a diagnosis of AD, vascular, and mixed dementia with at least 3 behavioral symptoms present from the Neuropsychiatric Inventory Questionnaires (NPI-Q) will be randomized to the Feru-guard (ferulic acid and Angelica archangelica) or placebo group. Participants will be screened first by a telephone interview or briefly in-clinic and then will be scheduled for an in-clinic screen to establish study eligibility prior to the baseline assessment visit. Clinical and biological outcome measures will occur at baseline and 12 weeks.

D.2. STUDY POPULATION:

D.2.1. Number of Participants

A total of 70 participants 55 years and older will be enrolled, this accounts for a 10% drop out rate. To achieve an enrollment of 70 participants, accounting for a 25% screen fail rate, we anticipate needing to screen 95 participants. Due to the study population being demented, each participant must have a committed caregiver who is able to act as their study partner. The study partner will be asked to accompany the participant to each onsite visit and complete some questionnaires pertaining to the participant's health.

D.2.2. Inclusion and Exclusion Criteria

Inclusion

- 55 years old or older.
- Diagnosis of AD, vascular, and mixed dementia
- Neuropsychiatric Inventory Questionnaire (NPI-Q) at least 3 items out of 12 items are rated as "present."
- Use of cholinesterase inhibitors, antidepressants and or antipsychotics medications is allowed, if on stable dosage for at least 2 months.
- Use of memantine and/or serotonin reuptake inhibitors is also allowed, if on stable dose for at least 2 months.
- Have a committed caregiver who is able and willing to assist them with medications, provide study participant information, and attend all study visits.

- Sufficient English language skills to complete all testing.
- MMSE score of 25 or lower.

Exclusion

- MMSE > 25
- Participants who started using antipsychotics or anticholinergics within the previous 2 months.
- Participants on blood thinners such as warfarin (Coumadin, jantoven), rivaroxaban (xarelto), fondaparinux (arixtra), dibigatran (pradaxa), apixaban (eliquis) dalteparin (fragmin), enoxaparin (lovenox). Aspirin use is allowed.
- Participants without an identified caregiver.
- Participants with delirium caused by medicinal poisoning or drug intoxication.
- Participants who have had the following diseases before the onset of cognitive impairment:
    1. Alcoholism
    2. Manic depression or bipolar disorder
    3. Schizophrenia
- Participants with malignancy or an acute inflammatory disease.
- Participants with critical circulatory, respiratory, kidney, or liver disease or diabetes.
- BMI of >30.
- Participants who have taken Feru-guard, ferulic acid, or Angelica archangelica supplementation within the last year.
- Enrollment in another clinical trial or treatment study within the previous 6 months.

D.2.3. Screen failure

In the event of a screen failure, all data that has been collected for that participant will be stored identically to data of participants who pass screen and are enrolled into the study. Data handling procedures of participants who are enrolled can be found in Section F of this protocol.

Screen Fail Procedure: Participants who are ineligible for study will be notified at in-clinic screening visit and provided an explanation for their ineligibility. The total number of screen failures and justification will be documented.

D.2.4. Vulnerable Populations

The current study will include participants who may be decisionally impaired adults. Dementia is a neurodegenerative disease, which is characterized in part by cognitive decline, so inclusion of decisionally impaired adults is necessary. To protect the rights and welfare of decisionally impaired adults in the study, when possible, informed consent will be obtained. Capacity to give informed consent will be ascertained via discussion and completion of the aid to capacity evaluation (ACE) between the participant, caregiver, and clinician. If it is determined that the participant is unable to give consent, their legally authorized representative (LAR) will be asked to give consent on behalf of the participant. In order to ensure the ongoing protection of the participant's

rights, they will have a committed caregiver accompany them to each visit and assist in the adherence to study procedures, ACE delivered at each onsite visit, and assured that they may withdraw or decline a measure at any time.

D.2.5. Inclusion of Women and Minorities

Including women and minorities in the study will be a priority. Due to the demography of the State of Oregon, we project that the majority of our participants will be "White," and "White not Hispanic or Latino." To maximize the inclusion of minorities, we will recruit from areas that have a high minority population (e.g. Northeast and Southeast Portland) within the Portland metropolitan area.

2010 Oregon Census Data
Gender: 50.5.% female, 49.5% male
Race: 83.6% White, 1.8% Black or African American, 1.4% American Indian and Alaska Native, 3.7% Asian, 0.3% Native Hawaiian and Other Pacific Islander
Ethnicity: 11.7% Hispanic or Latino, 88.3% Not Hispanic or Latino

2010 Portland Metropolitan area Census Data
Gender: 50.5.% female, 49.5% male
Race: 76.1% White, 6.3% Black or African American, 1.0% American Indian and Alaska Native, 7.1% Asian, 0.5% Native Hawaiian and Other Pacific Islander
Ethnicity: 9.4% Hispanic or Latino, 90.6% Not Hispanic or Latino

D.3. Setting

Recruitment will be done through the Layton Aging & Alzheimer's Disease Center and Portland VA geriatric clinics. All other data collection and study procedures will be completed at Oregon Health & Science University (OHSU) in the Oregon Clinical & Translational Research Institute (OCTRI).

Oregon Clinical and Translational Research Center (OCTRI): The OCTRI Clinical and Translational Research Center at OHSU is a dedicated research space for clinical studies at OHSU, and is equipped and flexibly staffed to support a broad range of protocols. OCTRI's pool of study coordinators, including dedicated pediatric RN/study coordinators, are available to perform study visits not only in OCTRI's units, but also off-site. These staff provide services throughout the life of a protocol, including study set-up, participant recruitment, clinical activities and data collection. Nursing staff are available at all OCTRI units to provide a full range of specialized procedures, such as phlebotomy, intravenous access, study drug administration, intensive blood drawing, and pharmacokinetic monitoring.

D.3.1. Recruitment Settings

OHSU's Layton Aging & Alzheimer's Disease Center: A multidisciplinary clinic offering comprehensive care to patients with Alzheimer's disease and related disorders. The clinic at Oregon Health & Science University is staffed by four neurologists, two neuropsychologists, nurses, and a psychiatrist experienced in providing both initial evaluations and second opinions, as well as offering ongoing care for individuals and

families affected by dementia. Opportunities for patients and families to participate in treatment trials for Alzheimer's disease, research on genetics, cognitive function, and family caregiving are offered through this clinic. The clinic is located at the Center for Health and Healing at the OHSU Medical Center and consists of 12 examination rooms, plus clinical support space. The Layton Aging & Alzheimer's Disease Center maintains direct contact for its ongoing longitudinal aging studies in over 50 aging centers, and retirement communities.

OHSU VA: Collaborative Dementia Care at the VA Portland Health Care Systems includes four geriatric neurologists, two geriatric medicine specialists and three geriatric psychiatrists. Patients are seen in five outpatient clinics during the week. Patients come from Veterans Administration clinics throughout Oregon and Southern Washington. In addition to clinic care, we provide Telehealth consultative dementia care with sites throughout Oregon and Washington. Physicians in our program have academic teaching and research appointments at OHSU.

D.4. Recruitment Methods

Prior to recruitment, the joint VAPORHCS-OHSU IRB will approve this study for human study. After receiving IRB approval, potential study participants will be found through database searches, and clinic referral for an estimated 6 month long enrollment period. Recruitment will be primarily focused on the Portland metropolitan area, though participants from outside the area will be enrolled if they are able to travel to OHSU. A blinded scan of the OHSU clinical database can identify potential participants that have visited OHSU in the last year that will meet the study's inclusion/exclusion criteria. Individuals identified through medical record scans will be sent an IRB approved letter describing their potential eligibility for the study. We will also utilize NeuroNext database of people that have consented to be contacted about clinical trial opportunities at OHSU. In addition, patients from the OHSU VA and NIA-Layton Aging & Alzheimer's Disease Center clinics who are potentially eligible for the study will be referred for screening. VA Portland Health Care System Neurology Dementia, geriatrics clinics, geriatric psychiatry clinic and Layton Aging & Alzheimer's Disease Center have over 20 patients per week with dementia diagnosis. We expect that we could obtain at least 5 participants per week on average who meet our inclusion criteria and consent to this study (20 participants per month). The last participant is expected to be enrolled at the end of 6 months from the start of the recruitment, which allows the last recruited participant to finish the trial within 1 year.

Study Timeline:

	Year 1												Year 2		
Month	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3
IRB Approval															
Study Enrollment															
Blinded Treatment Intervention															
Data Analysis															

D.5. Compensation

To compensate for cost of travel, time, and effort, each participant will receive $20 per onsite visit at OHSU. We believe a $20 compensation per visit is justified because travel to OHSU to complete visits will not present an undue burden for participants as they will be recruited from Portland VA and OHSU clinics. Travel to our study visits will require the participants to do more travel then they would for a standard trip for clinical care. The time commitment for participants per each onsite visit will not exceed 3hr. The effort required for onsite visits will consist of answering questions, a blood draw, and a physical/neurological examination. Our compensation is comparable to studies that require the same level of time commitment and effort on the part of the participant. $20 per onsite visit for a total possible compensation of $60 does not present a coercive influence for participation. The payments are prorated so there is no pressure for the participant to move through the study in order to receive a better payment.
Payments will be made through a ClinCard debit card, which will be assigned to them unless they have one registered to them from a previous study.

D.6. Consent Process

After potential participants have been identified through typical clinical contact, or response to recruitment letters, we will have a phone pre-screen. This will be done to prevent placing an undue burden on potential participants who may not be eligible to participate in the research by having them come in for an in-person visit to sign a consent form. We are requesting a waiver of HIPAA Authorization for the purpose of pre-screening potential participants. For participants referred from the VA, we will request a waiver of documentation of consent for the phone pre-screening portion of our study. We have limited our pre-screening questions to a list of things that would prohibit individuals from being in the study. The slight risk of breach of confidentiality in the phone screening is minimized by appropriate privacy protections specified in the protocol. We are using a consent script containing all required elements of consent except for the signature lines so we do not believe the waiver will adversely affect the rights and welfare of participants.

After a potential participant has passed the phone screening and has agreed to come in for an onsite screening visit, they will be mailed a copy of the IRB approved consent and HIPAA form so that they have a chance to review before the in clinic visit and be fully informed of all aspects of their participation in the study. At the in-clinic screening visit, a trained study coordinator will review the consent form with the participant and study partner and answer any questions they may have. After all questions regarding the study have been addressed, both the participant and their study partner will sign.
The capacity of potential participants to give consent will be assessed at the in-clinic screening. If the participant is determined unable to give informed consent, then a legally authorized representative (LAR) will need to give consent on behalf of the participant. We will identify appropriate LARs as stated in POLICY HRP-021. This policy details that a LAR is (in order or priority) a health care representative, legally authorized by a valid advance directive or health care power of attorney; court appointed guardian; spouse or registered domestic partner; adult child; either parent; adult sibling; adult

designated by others on list, if no one on the list objects; other adult relative or friend who has an established relationship with the potential participant.

D.6.1. Adults Unable to Consent/Decisionally Impaired

All participants will have a diagnosis of dementia, which is a progressive neurological condition. To ensure participant safety and ethical treatment, the signing of the consent form will follow guidelines from sections of the Code of Federal Regulation regarding protocols that involve decisionally impaired adults. Whenever possible, consent will be obtained from the participant. At every in-clinic visit the capacity to give informed consent will be ascertained via discussion and completion of the aid to capacity evaluation (ACE) between the participant, caregiver, and clinician. The ACE will address the capacity of the participant to give informed consent by asking potential participants and their study partners to describe key points in the consent: purpose of study, knowledge of placebo control group, length of study, risks of participation, alternatives to participation, and procedures to follow if he/she experiences discomfort or wishes to withdraw.

Participants who can answer these questions after going over the consent form and as determined by the clinician and study partner will sign the consent form along with their LAR.

Study assessments will only be started after the participant and study partner (LAR) have signed the consent form. Although unlikely, due to the nature of dementia's progression, if a participant previously unable to consent regains the capacity, they will be consented at whatever point they are in the study.

E. PROCEDURES:

E.1. VA vs OHSU activities/research

E.1.1. VA activities/research

A proportion of recruitment will take place at Portland VA geriatric clinics. Potential participants who are identified through typical clinical contact by their physician will be given a study flyer (approved by the joint IRB) with the study's details and contact information. The clinician will ask if the potential participant if they would like to be contacted by study staff.

No study data will be collected at the Portland VA clinic.

E.1.2. OHSU activities/research

All study data will be collected onsite at OHSU or over the phone by a research coordinator at OHSU, on OHSU time.

Both principal investigators, Dr. Sarah Goodlin and Dr. Lynne Shinto, have appointments at OHSU, and will participate in data collection.

E.2. Study Visits

Pre-Screen (phone): This visit will last approximately 0.5 hour.

Prior to the first screening visit, potential participants will be identified through routine clinical contact by clinicians or through OHSU data searches of potential participants. Potential participants will have a diagnosis of dementia and will be prescreened in-clinic or by a telephone interview to rule out medical exclusions, regular use of anti-psychotic medication, and any difficulties with participation (e.g. cannot travel to one of the study sites, does not have a study partner). The clinical trial coordinator or research assistant experienced in AD clinical trials will perform the phone or in-clinic pre-screens using the IRB approved script. If the potential participant passes the pre-screen evaluation, they will be scheduled for an in-clinic screening visit (Visit 1) and will be mailed a copy of the consent form to review before the in-clinic visit.

Screening Visit (Visit 1): This visit will last approximately 2 hours.

The visit takes place at OHSU, OCTRI. Participants will attend this visit with their study partner (LAR), and they will bring any medications that they are currently taking.
The visit will start with a trained research coordinator going over the consent form and participant rights with participant and their study partner, and answer any questions they have. After going through the consent form, the participant, study partner (who is also the LAR), and the study clinician will go through the ACE to determine the capacity to give consent. If the participant is determined to be unable to give consent, then the LAR will give consent on behalf of the participant. Both the participant and the study partner will sign a consent form if they agree to participate in the study. The study partner's signature is necessary because he/she will be answering questions as part of the study procedures.

Demographic information and general medical history, including mental health history, family history and history of allergies will be obtained. Participants will have a general physical and neurological exam, including vital measures (for example, weight and blood pressure).

To determine eligibility for participation, the Neuropsychiatric Inventory Questionnaires (NPI-Q) will be administered, with at least 3 items out of 12 being rated as "present" for inclusion. The NPI-Q is also the primary outcome measure and this will serve as a baseline measure of the participant's BSPD. Additionally, the Mini Mental State Exam (MMSE) will be administered to determine eligibility, with inclusion score of 25 or below. The MMSE will only be used to screen in potential participants.

Randomization will occur after this visit by OHSU Research Pharmacy. The participant will be scheduled for Visit 2 within 14 days.

Baseline (Visit 2): This visit will last approximately 1.5 hour.

This visit will be scheduled within 14 days of the screening visit at OHSU and take place at OHSU, OCTRI. Participants that have met all study inclusion/exclusion criteria will be assigned a study number. Since this visit will be performed close to the screening visit,

medical history, NPI-Q, and the physical and neurological examination from the screening visit will be used as “baseline” outcomes and will not be repeated at this visit.

A fasting blood draw will be performed for safety labs and will include: complete blood count, comprehensive metabolic panel, fasting lipid levels (cholesterol, triglycerides, HDL, LDL), prothrombin time (PT/INR), and for Apo E genotyping. About two tablespoons of blood will be collected. Food/light meal will be provided following the fasting blood draw and after all fasted blood draws throughout the study.
In order to establish baseline measures of cognitive function, the Clinical Dementia Rating (CDR) and Montreal Cognitive Assessment (MoCA) will be administered. SF-12 will be filled out by the study partner to establish baseline for general sense of health and ability to perform daily tasks. Because cereals are a source of ferulic acid, we will administer the Dietary Screener Questionnaire (DSQ) to establish a baseline for cereals in the participant's diet. In order to provide an additional measure of caregiver burden, the Zarit Burden Interview (ZBI) screening version will be administered.

Any recent changes in medications (prescribed, over-the-counter medications, nutritional supplements, herbals) and any recent changes in diet will be recorded at this visit. Adverse events will be collected at baseline for comparison throughout the study. The study coordinator will dispense a 12-week supply of medication and give both verbal and written instructions on medication dosing.

Week 6 (Visit 3 - Phone): This visit will last approximately 0.5 hour.
This visit will take place over the phone, six weeks after the baseline visit. The study coordinator will record adverse events and any recent changes in medications (prescribed, over-the-counter medications, nutritional supplements, herbals) and any recent changes in diet. Study supplement compliance will be assessed for by asking the participant how many capsules they take a day and have they stopped taking the capsules for longer than 24 hours. If possible, the coordinator will schedule the week 12 visit with the participant.

Week 12 (Visit 4): This visit will last approximately 2.5 hours
This visit will take place at OHSU, OCTRI, six weeks after the week 6 visit. Participants will have a general physical and neurological exam, including vital measures (for example, weight and blood pressure). A fasting blood draw will be performed for safety labs and will include: complete blood count, comprehensive metabolic panel, fasting lipid levels (cholesterol, triglycerides, HDL, LDL), prothrombin time (PT/INR). About two tablespoons of blood will be collected.

The NPI-Q, MoCA, CDR, ZBI, DSQ and SF-12 will be administered at this visit. In order to reduce the possibility or learning effects, a different version of the MoCa will be used at Visit 4. The study coordinator or research assistant will check compliance by capsule count and ask about any adverse events. Any recent changes in medications (prescribed, over-the-counter medications, nutritional supplements, herbals) and any recent changes in diet will be recorded. Participants, study partners, study investigators, and one of the principal investigators will fill out a “blindness evaluation” at this visit.

Visit schedule
The following chart summarizes the activities that will occur over the course of this study:

Table 4. Visit schedule

Visit Number	Pre-screen Phone	Visit 1 Screen	Visit 2 Baseline	Visit 3 Week 6-Phone	Visit 4 Week 12
Demographics	X				
Concomitant medications	X	X	X	X	X
Consent		X			
Aid to Capacity Evaluation (ACE)		X	X		X
Medical History		X			
Vitals		X	X		X
Physical / Neurological exam		X			X
Neuropsychiatric Inventory Questionnaire (NPI-Q)		X			X
Mini Mental State Examination (MMSE)		X			
Montreal Cognitive Assessment (MoCA)			X		X
Clinical Dementia Rating (CDR)			X		X
Caregiver Quality of life (SF-12)			X		X
Dietary Screener Questionnaire (DSQ)			X		X
Zarit Burden Interview (ZBI) screening version			X		X
Apo E genotyping			X		
Plasma Lipid levels			X		X
Metabolic panel			X		X
PT/INR			X		X
Complete blood count			X		X
Record adverse events			X	X	X
Dispense medication			X		
Capsule count					X
Blinding evaluation					X

E.3. Participant Withdrawal
If a participant decides to completely withdrawal from the study, any data collected will be stored identically to data of participants who complete the study and will be participant to the same data safety and confidentiality procedures (see Section F). They will be compensated for the visits they completed before deciding to withdraw.

Participants will be allowed to withdraw from taking the study supplement, and continue in the study completing non-interventional procedures.

E.4. Study Drug

This study will comply with all applicable Research Pharmacy policies and procedures and provide the Research Pharmacy with a manual for the study. One study capsule will be taken at breakfast and one at lunch. The study supplement will contain one of the following:

1. 280 mg hard capsule containing 180.32 mg ferulic acid and 20.02 mg of Angelica archangelica.
2. 280 mg hard capsule containing 268.8mg maltodextrin and 8.40 mg calcium stearate.

Group 1 – Active

Two 280 mg hard capsules per day (1 capsule am, 1 capsule pm). One capsule will be taken in the morning with a meal and one capsule will be taken in the afternoon with a meal.

Total daily dose of study supplement: 360.64 mg of ferulic acid and 40.04 mg of Angelica archangelica.

Group 2 – Placebo

Two 280 mg hard capsule per day (1 capsule am, 1 capsule pm). One capsule will be taken in the morning with a meal and one capsule will be taken in the afternoon with a meal. For full list of ingredients see Table 5 below:

Table 5. Placebo composition per 280 mg capsule

Ingredients	mg	%
Maltodextrin	268.8	96.
Calcium Stearate	8.4	3.0
Food Flavor (Vanilla)	2.80	1.0
Total	280.0	100

E.5. Blinding

This is a double-blind, placebo-controlled study. The placebos will be matched to the active supplement in both sensory and physical characteristics. The participants, study investigators, research associates, and study coordinators will have no knowledge of study assignment. Data analysis will be performed blinded to treatment status. The OHSU Research Pharmacy will be responsible for establishing a randomization scheme for newly enrolled participants. Additionally, the Research Pharmacy will ensure blinding of all study medications. We will also evaluate the effectiveness of our blinding by giving study evaluators, participants, study partners, and investigators a short questionnaire asking about knowledge of group assignment. The randomization code will be broken only after data analysis or if there are numerous serious adverse events before the end of the study.

E.6. Compliance
Compliance will be measured informally by a phone check week 6 (i.e., asking how participant is doing taking the supplement). If the participant is not taking the supplement in the appropriate dosage or stopped taking the capsules for longer than 24 hours, the coordinator will speak with the participant about finding ways to increase compliance. Official compliance will be measured in-clinic at Visit 4 via packet count. A participant will be considered compliant if they are ≥80%.

E.7. Description of Assessments and Procedures
E.7.1. Cognitive, Functional, Behavioral Assessments

Neuropsychiatric Inventory Questionnaire (NPI-Q)
The NPI-Q [46] is a structured interview with a caregiver or qualified study partner (defined as having direct contact > 2 days/week) that evaluates both presence and severity of 12 neuropsychiatric features which include: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability, lability, apathy, aberrant motor behavior, night-time behavior, and appetite/ eating changes [47]. If the response to the domain question is "No", the informant goes to the next question. If "Yes", the informant then rates both the Severity of the symptoms present within the last month on a 3-point scale ranging from 1 to 3 (mild to severe). Change in overall NPI-Q score between baseline and at 12 weeks will be the primary outcome measure. A modification of the original NPI is the addition of a Caregiver Distress Scale for evaluating the psychological impact of neuropsychiatric symptoms reported to be present. For each feature the caregiver distress score ranges from 1-5 (No distress to extreme distress). The caregiver distress subscale score is the sum of the distress scores for each of the 12 features. Change in overall NPI-Q subscale of caregiver distress score which is the between baseline and at 12 weeks will be a secondary outcome measure.

Clinical Dementia Rating (CDR)
The CDR [48] measures dementia severity and is a global rating of dementia with scores ranging from 0 to 3 (0, 0.5, 1, 2, and 3) rated by a semi-structured participant and informant interview [49]. A trained rater synthesizes information of cognitive performance and functional abilities based on 6 domains which include memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The scale has good inter-rater agreement [49].

Montreal Cognitive Assessment (MoCA)
A rapid screening instrument for assessing different cognitive domains [50]. Subjects are asked to do the following tasks: 1.) Join 10 randomly displayed numbers and letters in an alternating and sequential fashion. 2.) To measure visuoconstructional skills, accurately copy two drawings, a cube and a clock. 3.) Provide the names of three animals represented by drawings. 4.) Remember a list of 5 words. This is repeated 2 times. After a delay, subjects again recall as many words as possible. 5.) To measure

attention: repeat a five number sequence forward, and a separate three number sequence backwards, signal when a certain letter is read in a spoken sequence of varying letters, and count backwards from 100 by subtracting seven. 6.) Name as many words that start with the letter "F" in sixty seconds. 7.) Explain what pairs of words have in common, such as "Tell me how an orange and a banana are alike." 8.) To provide orientation, provide date, place, and city.

Mini Mental State Examination (MMSE)
The MMSE is among the most widely used screening instruments for cognitive impairment indicative of dementia [51]. This 30 point scale is helpful for comparing across diverse studies, as it has become a common way of communicating severity of dementia among clinicians. Participants must have MMSE score $\leq$ 25 to meet inclusion criteria, indicating a mild to moderate dementia severity.

SF-12
The 12-Item Short Form Health Survey (SF-12) is a 12-item validated shortened version of the SF-36 and was designed to provide a health-related quality of life (HRQL) measure that was quick and easy to administer in large population studies. The SF-12 contains a subset of the 12 items from the SF-36 and information from this subset of questions is used to construct a physical and mental component summary score (PCS and MCS, respectively). [52, 53]

Zarit Burden Interview (ZBI) screening version
The Zarit Burden Interview (ZBI) Screening Version is a popular caregiver self-report measure used by many aging agencies, and originated as a 29-item questionnaire. The revised screening version contains 4 items and has been validated. Each item on the interview is a statement, which the caregiver is asked to endorse using a 4-point scale. Response options range from 0 (Never) to 4 (Nearly Always). Change in overall ZBI score between baseline and at 12 weeks will be a secondary outcome measure.

Dietary Screener Questionnaire (DSQ)
The DSQ is a short 26 item questionnaire which asks about the frequency of consumption in the past month of selected foods and drinks. It captures intakes of fruits and vegetables, dairy/calcium, added sugars, whole grains/fiber, red meat, and processed meat. The DSQ can be administered by an interviewer, self-administered, or via the web. [56]

E.7.2. Other Evaluations

Serum Lipid Levels

Increased serum lipids levels (cholesterol, LDL) have been implicated as a risk factor for AD [57, 58]. Cholesterol in particular has been implicated in amyloid beta formation [58]. Serum cholesterol, triglyceride, LDL, and HDL will be measured in the Lipid laboratory at OHSU. Associations between serum lipid levels and clinical outcomes will be evaluated. Participants will be asked to fast the night before (10 hours). Measures will be taken at baseline and at 12 weeks.

Apolipoprotein E (Apo E)
Apo E genotype epsilon 4 allele will be collected due to its varied role in Alzheimer's disease and dementia [59]. The relationship between Apo E and the active ingredients of Feru-guard (ferulic acid and Angelica archangelica) remain unexamined and is worthy of investigation. Apo E genotyping will be performed in the Lipid laboratory at OCTRI using the protocol of Hixson and Vernier [60]. Blood draw for Apo E genotyping will occur only at Visit 2 (Baseline).

Safety labs
We will include a comprehensive metabolic panel (BUN, creatinine, sodium, potassium, bicarbonate, chloride, calcium, phosphorus, total bilirubin, direct bilirubin, alkaline phosphatase, SGOT, SGPT, GGT, LDH CPK, total protein, albumin, globulin, and glucose), complete blood count and prothrombin time (PT/INR). All three laboratory measures will be assessed at baseline, and 12 weeks.

Physical Exam
A complete physical exam will be performed by a medically qualified professional at screening and 12 week visits. A review of all major body systems will be performed. Vital signs (height, weight, blood pressure, pulse, temperature, and respiration) will also be performed at these visits.

Neurological Exam
A neurological exam will be performed by a medically qualified professional and will include assessment of cranial nerves, strength coordination, reflexes, sensation, and gait at screening and 12 week visits.

F. DATA AND SPECIMENS:

F.1. Handling of Data and specimens
Upon enrollment, each participant will be assigned a unique identification number by a study coordinator. This number will be used on all of the data collected for that participant, with no personal identifiers on the same source of data. All physical data including questionnaires, exam sheets, and lab reports will be placed in in a participant specific binder and stored in a locked room only accessible to study staff at OHSU in the Hatfield Research Center. The binder with all physical data will be stored in the locked room under the supervision of study staff until it is sent to the Iron Mountain storage facility for archiving once the study is completed.

F.2. Sharing of results with Participants
Research test results will only be shared with the participant, study partner, or the participant's primary care provider if the information is important to their health care. The determination of when to disclose incidental findings will be made by the investigators, or determined necessary by the DSMB. The lab where blood samples will be sent for analysis is CLIA certified.

F.3. Data and Specimen Banking
Data collected through questionnaires, lipid analysis, Apo E, and safety labs (CBC,

PT/INR, and CMP) will be stored to be used only for future analysis by Glovia, Co. Ltd., or the study PIs, Dr. Shinto and Dr. Goodlin.

G. DATA ANALYSIS:

G.1. Statistical Analysis

Aim 1: Determine if Feru-guard can improve BPSD in people with dementia.
This aim tests the hypothesis that Feru-guard supplementation over 12-weeks will improve common behavioral symptoms as measured by NPI-Q in people with dementia. Statistical analyses will be performed by OHSU.

Aim 2: Measure the effect Feru-guard supplementation has on caregiver burden and quality of life, and global cognition in participants.
This aim is exploratory and will be used to collect data on the study drug's effect on caregiver burden (NPI-Q subscale of caregiver distress), quality of life (SF-12 for caregiver) and Zarit Burden Interview (ZBI) screening version over 12 weeks. We will also collect data on changes in global cognition of participants over 12 weeks using the Montreal Cognitive Assessment (MoCA). Statistical analysis will be performed by OHSU.

G.2. Analytic approach

To compare the primary aim of total NPI-Q measure between the Feru-guard and placebo, we will use the mixed model approach to longitudinal data. This method allows for correlation between repeated observations on each participant and provides valid inference in the presence of missing data as long as the data is missing at random (MAR). Sensitivity analysis will be conducted, if warranted, to examine the impact of various assumptions regarding the reasons that parts of the data are missing. Our focus will be on the comparison of the 12 week changes from baseline to assess whether there is greater overall improvement in Feru-guard group compared to placebo. Descriptive information regarding the 12 week change for both groups and the differences in change between the groups will be obtained along with 95% confidence intervals. We will also examine the full profiles over the 12 week time period. In doing so, we will determine whether polynomial models, as opposed to unstructured models, provide a reasonable fit to the data. Given evidence of interaction between time and treatment--i.e. that the changes over time are different between the treatment groups--we will then use our fitted models to make follow-up comparisons between groups at individual time-points. In constructing our models, we will adjust for potential confounders such as dementia type, Apo E4 genotype, gender, and age. Subsequent analyses will incorporate compliance information. The same analysis will be used for outcomes in Aim 2, MoCA, SF-12, and caregiver burden (NPI).

G.3. Sample size estimation

The sample-size calculation was based on a previous open-label study published by Kimura et al. [9]. Since this study is an open-label study, estimated mean difference assumes that the placebo group will not have a change over 12-weeks and we are predicting that treatment will have a lowered NPI score, this effect size provides a reasonable estimate for contrasts between groups for the current study. For individual

contrasts between Feru-guard and placebo we will have a power with sample sizes of n = 32 in each group, and total n = 70 participants to detect a 7 point difference between placebo and Feru-guard, this sample size accounts for 10% participant drop out over 12-weeks.

Table 6. Sample sizes needed to detect differences in change in behavioral symptoms measured by NPI (total score) between groups with 80 % power using a significance level of 0.05.

Group comparisons	Estimated mean differences on NPI total score	Estimated standard deviation of change from baseline	Sample size needed for each group to detect a difference with 80% power and 0.05 significance
Placebo vs. Feru-guard	10.0	9.7	15
Placebo vs Feru-guard	7.0	9.7	31
Placebo vs Feru-guard	6.0	9.7	42

G.4. Randomization

Participants will be randomly assigned to study drug or placebo according to a randomization scheme developed by the Research Pharmacy at OHSU. The study participants, study investigators, research associates, and study coordinators will have no knowledge of study assignment.

G.5. Quality Control

The principal investigator will oversee the management of the participants, intervention, and analysis, which will be carried out by the clinical investigators, research statistician, and research assistant. Data entry, quality control and preparation, and participant management will be ongoing throughout the study.

The quality of data collection will be ensured by having all study staff up-to date on all data collection procedures, with a process of cross checking accuracy of data before and after entry into an online database. Quality of the study supplement will be checked and ensured by the Research Pharmacy at OHSU.

H. PRIVACY, CONFIDENTIALITY, AND DATA SECURITY:

H.1. Privacy and Confidentiality

All research records linked with personal information will be coded with a unique identification number; therefore will contain no personal identifiers. All records with identifying information and linked with identifying information will be physically locked or password protected so that only authorized study staff will have access to them.

H.2. Data Security

All physical data collected about participants will be locked so that only authorized study staff will have access. Data will be kept in locked cabinets separate from identifiers. Computer files will be password protected. No one other than the researchers will have access to identifiable data. All research staff with access to data will have gone through a background check and completed all relevant trainings on data safety and HIPAA compliance through OHSU.

I. MONITORING PLAN:

I.1. DSMB

The study will be monitored by the Data Safety and Monitoring Board (DSMB) of the Oregon Center of Complementary and Alternative Medicine in Neurological Disorders (ORCCAMIND) once a year to ensure participant safety. If a participant reports serious side effects related to the study medication and information on group assignment is believed to be necessary for the participant's safety and well-being, the blind will be broken for that participant. The randomization code will otherwise be broken only after data analysis or if there are numerous reports of serious adverse events before the end of the study. The DSMB has been and will continue to be compliant with NIH Policy for Data and Safety Monitoring.

I.2. Adverse Events

Adverse events (AEs) will be monitored at visits 2-4 as a part of the clinic visits and by phone. Although assessment of adverse events will also include solicitation of non-specific change (e.g., "Do you feel different since beginning the treatment?"), a 12 item adverse events checklist covering all major organ systems will be included to probe for adverse events. The nature of each AE, its severity (mild, moderate, or severe), its likely relationship to study treatment (definite, probable, possible, not related, or unknown), its duration and any necessary treatment modifications or adjustments will be recorded. In addition to recording of AEs, labs to assess basic metabolic function (including liver function tests), plasma lipid levels, a complete blood count, and prothrombin time (PT/INR) will be performed at visit 2 and 4. Participants will be reminded and encouraged during clinic visits and phone checks to contact the study coordinator or a study investigator as soon as a moderate or serious adverse event should occur.

J. RISKS AND BENEFITS

J.1. Potential Risks

Venipuncture: The risks are minimal and may include some pain, bleeding and transient hematomas.

Questionnaires: The risk from filling out questionnaires is minimal; there may be mild anxiety from filling out questionnaires.

Feru-guard: At a daily dose of 360.64 mg ferulic acid and 40.02mg Angelica archangelica per day, the risks are minimal. In previous studies, skin rash and gastrointestinal side effects (constipation, diarrhea) are included as potential side effects. Due to unknown interactions with pharmaceutical medications, we will exclude participants on blood thinning medications (e.g. warfarin) to mitigate risk.

Placebo: The placebo consists of maltodextrin, which is a common starch-based food additive. Possible side effects include allergic reactions, unexplained weight gain, bloating, and flatulence.

J.2. Study Limitations

We are not excluding over-the-counter medications (e.g. NSAIDS) and supplements (e.g. ginkgo, vitamin E). Excluding these types of OTCs may severely hinder recruitment. We will collect information on all prescription, OTC, and nutritional supplementation in participants, which will enable us to analyze association of medication use and outcomes. Our power analysis is limited to data from a published open-label study so estimates needed to be made on the placebo group. This study is a pilot with the intent of using the data collected to more definitively power a larger clinical trial.

J.3. Potential Benefits

Ferulic acid is a potent antioxidant which combats the oxidative stress/toxicity present in a wide range of chronic diseases such as diabetes, cancer, cardiovascular disease, aging of skin, arthritis, neurodegenerative diseases, and chronic inflammation. Though beyond the scope of the current study, it is possible the antioxidant properties of ferulic acid may benefit a participant that has a chronic disease with an oxidative stress/toxicity component, during their 12 weeks on the study supplement.

J.4. Importance of Knowledge to be gained

This study will test if the combination of ferulic acid and Angelica archangelica can improve or prevent further decline in the behavioral and psychological symptoms of demented older people. Currently, treatments designed to improve BPSD center around anti-psychotic medication, with recent growing interest in non-pharmacological therapies. It is an important public health issue to scientifically evaluate the potential benefits of a non-pharmacological therapy for BPSD.

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