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Original Article

Efficacy of *Sophora japonica L.* Pill in Subjective Memory Complaints in Healthy Adults: a protocol of randomized, double-blind, placebo-controlled, parallel-group, clinical trial

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Objectives: Subjective memory complaints, increasingly common among older adults, may indicate early cognitive decline or dementia. *Sophora japonica L.*, a herbal medicine in Korean medicine, has shown potential cognitive benefits in preclinical studies through neuroprotective and anti-inflammatory properties. Given limited efficacy of current pharmacological treatments for cognitive impairment and growing interest in natural products, investigating *S. japonica* extract in humans is warranted.

Methods: This randomized, double-blind, placebo-controlled trial will involve 100 participants aged 40-70 years with subjective memory complaints but without diagnosed cognitive impairment. Participants will receive either *S. japonica* extract (1,250 mg) or placebo daily for 8 weeks. The primary outcome is change in digit span test score, assessing short-term memory and attention. Secondary outcomes include changes in other cognitive function tests (visual short-term memory, visual learning, and verbal learning), as well as measures of depression (Beck Depression Inventory-II), anxiety (State-Trait Anxiety Inventory-Y), stress (Stress Response Inventory), heart rate variability, and quality of life (EuroQol 5-Dimension-3L). Assessments will be conducted at baseline and after 8 weeks, with safety monitoring throughout the study period.

Conclusion: This study will provide evidence on the efficacy and safety of *S. japonica* extract for improving cognitive function in adults with subjective memory complaints. If proven effective, this supplement could offer a new approach for supporting cognitive health in aging populations. The comprehensive assessment of cognitive, mood, and quality of life outcomes will allow thorough evaluation of its potential benefits.

Keywords: cognition, dietary supplement, clinical trial protocol, randomized controlled trial, *Sophora japonica L.*, memory disorders

INTRODUCTION

Dementia and cognitive decline are significant and growing public health challenges in our aging global society. As of 2019, the World Health Organization estimated that over 55 million people live with dementia worldwide, with nearly 10 million new cases annually. This number is projected to increase to 78 million by 2030 and 139 million by 2050, emphasizing the urgent need for effective interventions [1]. In the Republic of Korea, the prevalence of dementia among adults aged 65 and

older has been steadily increasing. According to the most recent Korean Dementia Observatory data, approximately 923,000 people had dementia in 2022, accounting for about 10.2% of the elderly population [2].

Moreover, the concept of subjective cognitive decline (SCD) has garnered attention as a potential early marker of future cognitive impairment [3]. A study by the United States Centers for Disease Control and Prevention found that, between 2015 and 2017, 11.7% of adults aged 65 and older and 10.8% of those aged 45-64 experienced subjective cognitive impairment [4]. In 2018, the Korea Disease Control and Prevention Agency initiated an investigation into subjective cognitive impairment in individuals aged 50 and over as a new health indicator [5]. A meta-analysis of long-term studies on cognitively unimpaired individuals with SCD revealed that, despite not initially meeting the clinical criteria for mild cognitive impairment (MCI) or dementia, 14% eventually developed dementia, and 27% progressed to MCI, indicating a heightened risk for future cognitive decline in this population [6].

As pharmaceutical research for dementia treatment encounters continuous challenges, with multiple high-profile drug trials showing disappointing results, the significance of prevention and early intervention has grown profoundly apparent. Cognitive decline begins as early as age 30 [7], and modifiable risk factors such as chronic stress, excessive alcohol consumption, lack of physical activity, poor sleep, and depression can expedite this process by increasing neuronal fatigue and impairing memory function [8].

The decrease in cognitive function, whether due to natural aging or neurodegenerative diseases such as dementia, not only affects an individual's quality of life and independence but also significantly affects healthcare systems and economies. In 2019, the global cost of dementia was estimated at US$1.3 trillion, and it is projected to exceed US$2.8 trillion by 2030, underscoring the societal impact of this condition [1].

While current pharmacological treatments for cognitive impairment have limited efficacy, there is an escalating interest in natural products that may support cognitive health and possibly delay or prevent cognitive decline. In recent years, research has increasingly focused on plant-derived substances for memory enhancement and potential dementia prevention or treatment [9, 10]. For example, Huperzine A, derived from the *Huperzia serrata*, has demonstrated promise in preclinical studies and clinical trials and is utilized in certain countries as a treatment for mild cognitive impairment and Alzheimer's disease symptoms [11-13].

Sophora japonica L., known as the "scholar's tree" in China, has been linked to cognitive benefits and longevity in traditional texts, such as the 'Compendium of Prescriptions from the Countryside (Hyangyakjipseongbang, 鄕藥集成方).' *S. japonica* has a long history of use in East Asian herbal medicine and has been traditionally utilized to address various health conditions. Our research team previously studied the pharmaceutical composition of *S. japonica* extract for dementia prevention and treatment, confirming its preventive effects against dementia caused by amyloid-beta peptide accumulation in preclinical models and suggesting potential cognitive benefits [14].

The current study aims to assess the efficacy and safety of *S. japonica* extract in improving memory and cognitive function in healthy individuals who have reported subjective memory issues. The primary objective of this study is to assess the efficacy of *S. japonica* extract in improving cognitive function, specifically memory and attention, in healthy adults who have subjective memory complaints compared to placebo after 8 weeks of treatment. The secondary objectives encompass evaluating the effects of *S. japonica* extract on other cognitive domains, mood, stress, and quality of life, as well as evaluating its safety. This research not only addresses a significant public health need but simultaneously investigates the potential of traditional herbal remedies for cognitive enhancement and neuroprotection.

MATERIALS AND METHODS

This study is a randomized, double-blind, placebo-controlled, parallel-group trial. Participants will be randomly assigned in a 1:1 ratio to receive either *S. japonica* extract or a matching placebo for 8 weeks. The 8-week intervention period for assessing the effect of *S. japonica* on subjective memory complaints is supported by prior studies which have demonstrated the effectiveness of this duration in the evaluation of cognitive improvements resulting from the use of natural supplements in controlled clinical trial settings [15, 16].

1. Study setting

The study will be conducted at two sites in the Republic of Korea: Kyung Hee University Korean Medicine Hospital in Seoul and Daejeon University Korean Medicine Hospital in Daejeon.

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2. Eligibility criteria

1) Inclusion criteria

The eligibility criteria are designed to include a relatively healthy population with subjective memory complaints, allowing for the assessment of *S. japonica L.* extract as a potential preventive or early intervention for cognitive decline.

The inclusion criteria are as follows: (1) Age 40-70 years; (2) Subjective memory complaints; (3) Clinical Dementia Rating (CDR) score of 0.5 or less; (4) Ability to read and understand Korean; (5) Minimum of elementary school education; (6) Voluntary agreement to participate with signed informed consent.

2) Exclusion criteria

The exclusion criteria are as follows: (1) Use of medications that may affect cognitive function within 4 weeks prior to enrollment; (2) Abnormal blood test results; (3) Diagnosis of dementia or other neurological disorders affecting cognition; (4) Uncontrolled hypertension, diabetes, or thyroid dysfunction; (5) History of unstable angina, myocardial infarction, or stroke within 6 months; (6) Severe head trauma with loss of consciousness within 6 months; (7) History of acute stroke within 3 months; (8) Participation in other clinical trials within 1 month; (9) Hypersensitivity to the study intervention; (10) Severe hearing or visual impairment; (11) Pregnancy or breastfeeding; (12) Women of childbearing potential who are not using appropriate contraception methods; (13) Difficulty with daily communication due to vision or hearing impairments, or difficulty writing due to physical disabilities; (14) Upper respiratory infections or other chronic diseases; (15) History of surgery under general anesthesia within the last 3 months; (16) Sensitivity to estrogen hormones; (17) Those deemed unsuitable for participation in the human application test by the investigator.

3) Criteria for discontinuing allocated interventions

Participants will be withdrawn from the study if they begin taking new cognitive-enhancing medications or foods, require hospitalization due to accidents or other illnesses, request to discontinue, withdraw consent, become pregnant, or exhibit a compliance rate below 70%. The principal investigator may also withdraw participants due to unforeseen circumstances hindering their study continuation.

3. Interventions

Participants will receive *S. japonica* extract pill, 1,250 mg, once daily. This pill comprises 558 mg of *S. japonica* extract, which is approximately 44.64%. This dosage was calculated from previous animal studies and then adjusted for human consumption [14]. The extract was standardized to contain a specific percentage of key bioactive compounds (e.g., quercetin, rutin) to ensure batch-to-batch consistency. The pill is administered daily without any particular scheduling restrictions.

A placebo was chosen as the comparator to assess the effect of *S. japonica L.* extract on cognitive function. The placebo is identical in appearance, smell, and taste to the active intervention to ensure blinding.

Both the intervention and placebo will be manufactured by Hanpoong Pharm Co., Ltd., a GMP-certified pharmaceutical company, and will be identically packaged. Participants will be instructed to take one pill once daily.

The study will include a screening visit, a baseline visit (Day 0), a mid-study visit (Week 4), and a final visit (Week 8) (Fig. 1).

4. Outcomes

1) Primary outcome

The primary outcome of this study is the change in the Digit Span Test (DST) score from baseline to 8 weeks. This test measures short-term memory and attention, key aspects of cognitive function that may be influenced by *S. japonica* extract. DST will be administered via a computerized neurocognitive function test (CNT 40; Maxmedica Inc., Seoul, Korea) [17]. This test consists of the forward DST, which presents sequences of 3-8 digits for immediate recall (maximum score: 8 points), and the backward DST, which presents sequences of 2-7 digits for reverse recall (maximum score: 7 points).

2) Secondary outcomes

Secondary outcomes include four cognitive tests administered through a computerized neurocognitive function test [17]. The visual span test, similar to the Corsi block tapping test, presents nine circles that flash sequentially on the screen [18]. Participants are instructed to click the circles in the corresponding sequence, with both forward and backward recall components (maximum scores: 8 and 7 points, respectively). The verbal learning test consists of 15 recorded Korean words presented in five immediate recall trials, followed by a delayed

	STUDY PERIOD			
	Screening	Medication		
	Visit 1	Visit 2	Visit 3	Visit 4
TIMEPOINT	-7 D	0W	4W±4D	8W±4D
Informed consent	X			
Vital signs and physical examination	X	X	X	X
Demographic survey / BMI	X			
Medical history and medication history survey	X	X		
Laboratory tests	X			X
Urine test	X			
ECG · Chest x-ray (PA)	X			
CDR	X			
Eligibility Screening	X			
Allocation	X			
S. japonica extract or placebo		←	—	→
CNT		X	X	X
BDI-II, STAI-Y, SRI		X		X
HRV		X		X
EQ-5D-3L		X		X
Adverse events			X	X
Concomitant treatment		X	X	X
Compliance				X

Figure 1. Standard Protocol Items: Recommendations for Interventional Trials Statement (SPIRIT). Overview of study process and outcome assessment. BDI, Beck Depression Inventory; CDR, Clinical Dementia Rating; CNT, Computerized neurocognitive test; ECG, Electrocardiogram; EQ-5D, EuroQol-5 Dimension; HRV, Heart Rate Variability; PA, Posteroanterior; SRI, Stress Response Inventory; STAI, State-Trait Anxiety Inventory.

recall trial after 20 minutes [19]. The visual learning test utilizes 15 target figures, each comprised of geometric elements (circles, squares, triangles, lines, and dots). The target figures are presented alongside 15 interference figures, and participants are instructed to recognize the original targets. This test comprises five immediate trials and one delayed recall after 20 minutes. These tests provide a comprehensive evaluation of various cognitive domains. The study will additionally examine changes in Beck Depression Inventory (BDI)-II scores to evaluate the potential influence on mood and depressive symptoms [20]. Changes in State-Trait Anxiety Inventory (STAI)-Y score will be measured to evaluate the impact on anxiety levels [21]. The impact on stress levels will be assessed by changes in the Stress Response Inventory (SRI) score [22]. Changes in Heart Rate Variability (HRV) will be monitored to indicate autonomic nervous system functionality and the potential physiological effects of the intervention. The variables include heart rate, total power, high frequency/low frequency (HF/LF), and standard deviation of normal-to-normal intervals (SDNN). HRV measurement is conducted using the SA-6000 (MEDICORE, Seongnam-si, Gyeonggi-do, Republic of Korea). Finally, changes in the EuroQol 5-Dimension (EQ-5D -3L) score will be analyzed to evaluate the overall quality of life [23]. These outcomes were selected to offer a thorough evaluation of the potential effects of *S. ja-*

ponica extract on cognitive function, mood, stress, and overall well-being. All outcomes will be evaluated at baseline and after 8 weeks of intervention.

3) Safety outcomes

Safety will be closely monitored throughout the study, with a focus on adverse events, vital signs, and clinical laboratory test results. Clinical laboratory tests entail hematological assessments (white blood cells, red blood cells, hemoglobin, hematocrit, platelets, erythrocyte sedimentation rate, white blood cell differential count) and blood biochemical tests (total bilirubin, direct bilirubin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides, alkaline phosphatase, total protein, albumin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, glucose, blood urea nitrogen, creatinine, sodium, potassium, chloride, lactate dehydrogenase, creatine phosphokinase). We will document these safety results at each visit. The safety evaluation will incorporate all participants who consume the study product at least once.

5. Sample size and recruitment

A total of 100 participants (50 per group) were recruited. This sample size was calculated to detect a standardized effect size of 0.63 with 80% power and a 5% significance level, allowing for a 20% dropout rate. This effect size is considered between medium and large, according to Whitehead et al. [24]. In studies with limited preliminary evidence, an effect size ranging from medium (0.5) to large (0.8) is commonly employed to achieve a balance between feasibility and clinical significance, as recommended by Cohen [25]. This approach aligns with the DELTA2 guidelines, which recommend effect size estimates that capture realistic, detectable differences without over- or underestimating impact in trials with limited prior data [26]. Due to limited evidence on the effects of *S. japonica* on memory improvement, this study selected a standardized effect difference of 0.63, representing a medium-to-large effect.

Participants will be recruited via advertisements in the hospitals and local community, as well as through online platforms.

6. Random allocation and blinding

The randomization ratio is set at 1:1 for allocation. An independent statistician not involved in the study or participant recruitment generated the random allocation sequence. This sequence was provided to pharmaceutical companies for packaging the *S. japonica* extract and placebo with corresponding random numbers. Participants will be sequentially assigned to these random numbers upon enrollment, ensuring allocation concealment throughout the process. The random allocation sequence will be securely stored within a locked chamber if unblinding becomes necessary.

Participants, investigators, and coordinators will be blinded to group assignments. To maintain blinding, the placebo and active intervention will be indistinguishable in appearance, smell, and taste. Unblinding should only be considered in instances of serious medical emergencies. Typically, unblinding should only occur when information about the treatment group might influence patient care. If the investigator or another researcher managing a medical emergency believes unblinding is absolutely necessary, the principal investigator will decide on unblinding the participant during a researcher meeting.

7. Data collection and data management

All outcome measures will be assessed at baseline and 8 weeks. The trained research staff will administer cognitive tests and questionnaires. To guarantee site uniformity, the Computerized Neurocognitive Function Test (CNT) will be administered via standardized computer software. Participants will complete self-report questionnaires (BDI-II, STAI-Y, SRI, EQ-5D-3L) under the supervision of research staff. Heart Rate Variability (HRV) will be measured using a validated device. To minimize distractions, all assessments will be conducted in a quiet, comfortable environment.

Adverse event data will be collected at each visit. In the event of an adverse event, we will record its onset and resolution dates, assess its severity, examine its potential causal relationship with the *S. japonica* extract, and record any interventions or actions taken.

Participants will regularly receive phone calls to encourage adherence and retention. Missed visits will be rescheduled within the permitted time window. Participants will be sent reminders via phone or text message prior to each scheduled visit. If a participant withdraws from the study, attempts will be made to collect outcome data with the participant's consent.

Data will be inputted into a Case Report Form (CRF) utilizing a secure, password-protected electronic database. Regular data quality checks will be conducted, including range checks

for data values and checks for missing data. A data management plan will be developed prior to the start of the study, highlighting procedures for data entry, coding, security, and storage.

8. Statistical methods

All statistical analyses will utilize two-sided tests with a significance level of 5%. To ensure a comprehensive assessment of the intervention's efficacy, both Intention-to-Treat (ITT) and Per-Protocol (PP) analyses will be conducted. The Full Analysis Set (FAS), closely related to ITT principles, will serve as the primary analysis set, where participants who never received the treatment specified in the protocol and were never assessed after randomization and, therefore, no data collected will be excluded from the analysis. The PP analysis will include only those participants who concluded the study without major protocol violations. Major protocol violations include dropouts during the study, inclusion/exclusion criteria violations, overall compliance of less than 70%, and other events that may be considered significant protocol violations. Missing values will be imputed using multiple imputation.

Demographic and baseline clinical data will be summarized separately for each group. Continuous variables will be expressed as means, standard deviations, and minimum and maximum values, while categorical variables will be reported as frequencies and percentages. Between-group comparisons will use t-tests or Mann-Whitney tests for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate.

For the efficacy analysis, differences in primary and secondary outcome measures from baseline to 8 weeks will be evaluated between the intervention and control groups. The safety analysis will include a comprehensive list of all adverse events with detailed descriptions. The frequency of adverse events, both related and unrelated to the intervention, will be documented. Adverse event incidence rates will be calculated for each group and compared utilizing chi-square tests.

9. Data monitoring

Data monitoring will be performed throughout the clinical trial to ensure study integrity. This process involves monitoring the progress of the human subject research and regularly verifying that the study is conducted and documented in accordance with the protocol, standard operating procedures, Good Clinical Practice guidelines, and relevant regulations. The monitoring activities will include periodic checks to ensure data collection, management, and reporting comply with established protocols and regulatory requirements. Given that *S. japonica* is a dietary supplement rather than a pharmaceutical agent, it was determined that a Data Monitoring Committee (DMC) was not necessary [27, 28].

10. Ethics and dissemination

1) Research ethics approval

The study was approved by the Institutional Review Board (IRB) of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2024-04-011-003) and adhered to the Declaration of Helsinki [29].

2) Protocol amendments

Any protocol modification will be made after thorough deliberation among the investigators at both sites. These amendments will be implemented only after receiving approval from the Institutional Review Board (IRB). The protocol is currently at version 1.3, dated August 13, 2024. All significant protocol modifications will be communicated to relevant parties, including investigators, the IRB, trial participants, and trial registries, as necessary.

3) Consent or assent

Informed consent will be obtained by the investigator or designated research staff at each study site. They will provide prospective participants with comprehensive information about the study, respond to inquiries, and ensure that participants fully understand the nature of the study, potential risks and benefits, and their rights as research participants prior to obtaining written consent.

4) Confidentiality

All participant information will be stored securely and identified solely by a code number. Personal identification data will not be input into the electronic Case Report Form (eCRF). Participant data will instead be collected and managed using screening and randomization numbers to maintain confidentiality.

5) Post-trial care

In cases of early withdrawal due to adverse events, we will

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complete an adverse event report and perform final clinical laboratory assessments. We will conduct follow-up evaluations on participants experiencing adverse events until their symptoms are completely resolved.

6) Dissemination policy

Clinical trial information and results will be submitted to the Clinical Research Information Service. The results will be published in peer-reviewed journals and presented at scientific conferences. Upon completion of the study, the participant-level data set will be uploaded to the Korean Medicine Clinical Research Data Hub. In addition, we will report the final data to the Ministry of Health and Welfare of the Republic of Korea through the Korea Health Industry Development Institute.

DISCUSSION

This protocol for a randomized controlled trial evaluating the efficacy of *S. japonica* extract on memory and cognitive function in individuals with subjective memory complaints addresses a crucial need in cognitive health and dementia prevention. As the global population ages and the prevalence of cognitive disorders becomes more prevalent, there is an urgent demand for safe, effective, and accessible interventions to maintain and enhance cognitive function.

The decision regarding *S. japonica* is deeply rooted in a rich historical and scientific context, seamlessly integrating traditional East Asian medicine with modern evidence-based practices [13]. In China, according to the 'Guideline for Diagnosis and Treatment of Chinese Medicine in Vascular Mild Cognitive Impairment' (2022 edition), a complex formulation contains *S. japonica* fruit extract called 'Tianzhi Granule' is suggested as a Grade C intervention for the treatment of vascular mild cognitive impairment, indicating a moderate level of evidence supporting its use in clinical practice [30].

S. japonica and its derivatives have demonstrated promising cognitive function and neuroprotection results in both clinical and preclinical studies, indicating potential therapeutic applications for various neurological disorders. Herbal medicines containing *S. japonica* have been broadly utilized in clinical settings, with a significant portion of published clinical studies (55.7%) concentrating on its use in treating cerebral infarction and vascular dementia [31]. *S. japonica* fruit enhanced cognitive function and mitigated Alzheimer's disease-like pathology in Aβ1-42-infused mice by reducing Aβ accumulation, preventing neuronal cell death, enhancing neurotrophic factors, and activating ERK-CREB signaling pathways. These findings suggest its potential as a therapeutic agent for neurodegenerative disorders [14]. *S. japonica* flower buds improved scopolamine-induced cognitive deficits in mice, thereby improving memory performance and modulating acetylcholine levels, acetylcholinesterase activity, and inflammation in the brain [32]. Sophoricoside, a compound derived from *S. japonica*, protects against isoflurane-induced neuronal injury and cognitive dysfunction in neonatal rats by enhancing cognitive function, reducing neuronal apoptosis, and modulating inflammatory responses [33].

This randomized controlled trial will offer valuable evidence on the efficacy and safety of *S. japonica* extract for improving cognitive function in healthy adults with subjective memory complaints. The comprehensive array of outcome measures, including assessments of various cognitive domains as well as measures of mood, stress, and quality of life, will provide a holistic perspective of the effects of *S. japonica* extract.

Limitations of the study include the relatively brief intervention period of 8 weeks, which may not provide adequate time to discern long-term effects on cognitive function. However, this duration was selected to balance allowing sufficient time for effects to manifest with maintaining feasibility in terms of participant retention and resource management. Future research could explore the long-term use of *S. japonica* extract. Furthermore, the study population is limited to healthy adults with subjective memory complaints. Thus, the results may not be generalizable to individuals with diagnosed cognitive impairment or dementia. This population was selected to focus on potential preventive impacts, but future research could investigate the effects of *S. japonica* extract in populations with mild cognitive impairment or early-stage dementia.

In conclusion, this study will provide evidence for the efficacy and safety of *S. japonica* extract in enhancing memory and cognitive function in individuals who report subjective memory complaints. The findings from this study will support the potential use of this herbal supplement as a preventive measure against age-related cognitive decline and a complementary approach to managing mild cognitive impairment.

AUTHORS' CONTRIBUTIONS

Conceptualization: Yunna Kim, Seung-Hun Cho; Methodology: Seung-Ho Lee, Seung-Hun Cho; Investigation: Yunna Kim, Yerim Jeon, Seung-Hun Cho; Resources: Seung-Hun Cho;

Writing - Original Draft: Yunna Kim, Seung-Ho Lee, Yerim Jeon; Writing - Review & Editing: Yunna Kim, Seung-Ho Lee, Yerim Jeon; Visualization: Yunna Kim; Supervision: Seung-Hun Cho; Project administration: Seung-Ho Lee, Seung-Hun Cho; Funding acquisition: Seung-Hun Cho.

ETHICAL APPROVAL

This research was reviewed and approved by the Institutional Review Board (IRB) of Kyung Hee University Hospital (registration number KOMCIRB 2024-04-011-003, approval date 2024.08.13) and Daejeon University (registration number DJDSKH-24-BM-06-2, approval date 2024.09.26).

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

CONFLICTS OF INTEREST

Seung-Hun Cho is an editorial board member of Journal of Pharmacopuncture but has no role in the decision to publish this article. No other potential conflicts of interest relevant to this aricle were reported.

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