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Protocol

A study protocol for assessing the efficacy of Guduchyadi Ghrita in mild neurocognitive disorder: a placebo-controlled trial with brain-derived neurotrophic factor evaluation

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ABSTRACT

Background: Mild neurocognitive disorder (mNCD), a preclinical stage of dementia, is becoming a significant public health concern, especially among the aging population. Brain-derived neurotrophic factor (BDNF) has emerged as a key biomarker for cognitive health. Guduchyadi Ghrita, an Ayurvedic formulation rich in nootropic, Rasayana, and antioxidant herbs, has shown promise in improving cognitive functions, including memory and attention, in preliminary studies. Pratimarsha Nasya, known for its brain-targeted therapeutic effects, may enhance the bioavailability of these compounds. This study aims to evaluate the efficacy of Guduchyadi Ghrita with Pratimarsha Nasya in improving cognition and BDNF levels in individuals with mNCD.
Methods: This randomized, placebo-controlled, open-label, single-centre clinical trial will involve 80 participants diagnosed with mNCD according to DSM-V criteria. Group A will receive 12 gm/day of Guduchyadi Ghrita orally and 2 drops per nostril of Pratimarsha Nasya for 60 days, following Deepana-Pachana and Mridu Virechana. Group B will receive a placebo (roasted semolina capsules) and cognitive stimulation activities for 60 days. Primary outcomes will include improvements in cognition, assessed using the Montreal cognitive assessment (MoCA). Secondary outcomes will involve changes in plasma BDNF levels, quality of life (QOL-AD), and daily functioning (Bristol ADL scale).
Conclusions: This study will assess the potential of Guduchyadi Ghrita and Pratimarsha Nasya in enhancing cognitive function and promoting neuroplasticity in individuals with mNCD, with a focus on BDNF as a biomarker.
Trial registration: The trial is registered with the Clinical Trials Registry of India (CTRI) (REF/2025/04104935).

Keywords: Guduchyadi ghrita, Mild neurocognitive disorder, Brain-derived neurotrophic factor, Pratimarsha nasya

INTRODUCTION

Mild neurocognitive disorder (mNCD), as categorized in DSM-5, refers to a level of cognitive decline that exceeds normal aging but does not significantly hinder daily functioning. With the global rise in life expectancy, the prevalence of mNCD and its potential progression to major neurocognitive disorders like Alzheimer's disease presents a significant public health challenge. India alone reports approximately 24 million people affected by mNCD, with nearly one in five adults over 60 exhibiting related symptoms.

Modern research identifies biomarkers such as brain-derived neurotrophic factor (BDNF) as important indicators of cognitive health and neural plasticity. Altered levels of BDNF are implicated in neurodegenerative diseases, and enhancing BDNF expression is emerging as a target for neuroprotective interventions.

In Ayurvedic medicine, although no exact nosological entity matches mNCD, the condition can be compared to Poorva Rupa of Smritibhramsha. Ayurvedic texts attribute the pathogenesis of such disorders to the vitiation of Prana, Udana, Vyana Vata, Sadhaka Pitta, Avalambaka and Tarpaka Kapha, and Rajas-Tamas involvement affecting the functions of Buddhi, Dhriti, and Manas.

Guduchyadi Ghrita, a polyherbal formulation processed in Ghrita (ghee), incorporates ingredients with proven nootropic, Rasayana, and antioxidant effects. Ghrita acts as an ideal medium due to its lipophilic nature, enhancing bioavailability and central nervous system delivery. In addition, Pratimarsha Nasya is a simple, safe, and effective method of drug delivery directly to the brain via the nasal route, as mentioned in Ayurvedic classics.

A recent departmental pilot study showed promising results using Ayurvedic interventions for mNCD, improving memory, attention, and quality of life. However, a larger randomized clinical trial is warranted to validate these findings scientifically and assess the cognitive, neurochemical, and quality-of-life outcomes.

Aim and objectives

Aim:

Aim of the study was to evaluate the efficacy of oral administration of Guduchyadi Ghrita along with its Pratimarsha Nasya in the management of mild neurocognitive disorder.

Objectives:

Objectives of the study were to assess the effect of trial drugs on cognition, mood and behavior assessed by Montreal Cognitive Assessment Scale (MoCA), and Neuropsychiatric Inventory Questionnaire; to assess the effect of interventions on BDNF biomarker level; to assess the effect of trial drugs in improving the quality of life of patients with mild neurocognitive disorder by Bristol activities of daily living scale - functional assessment measure and quality of life (quality of life instrument: AD).

METHODS

Patient & public involvement

Written consent will be taken in local language before enrolment of patients into the trial. Though public will not be involved directly in the conduct or data analysis of the study, the findings will be reported in a manner accessible to the public, and summaries will be shared with participants and relevant community groups to promote transparency and engagement.

Trial design

This study is a randomized, controlled, parallel-group clinical trial with an allocation ratio of 1:1. It follows a superiority framework to compare the effectiveness of the intervention against the control. The method of randomization will be computer-generated randomization using a random number table to ensure unbiased allocation.

Study setting

The study will be conducted in the Department of Kayachikitsa, Institute for Teaching and Research in Ayurveda (ITRA), Jamnagar. Eligible patients visiting the OPD/IPD of the Kayachikitsa and Manas Roga OPD of Kayachikitsa, and diagnosed with mNCD will be screened and enrolled. The total sample size will be equally divided between the two groups over the recruitment period.

Inclusion criteria

Participants of either gender, aged between 55 and 80 years, who fulfil the DSM-V diagnostic criteria for mild neurocognitive disorder, will be included.[1] They must score between 18 to 25 on the MoCA, indicating mild cognitive impairment.[2-6] Participants must demonstrate functional independence in daily living activities, i.e., the ability to perform most activities without significant external support. Only those who are willing to give written informed consent and comply with the study protocol, including follow-up visits and outcome assessments, will be enrolled.

Exclusion criteria

Participants will be excluded from the study if they are below 55 years or above 80 years of age, or if their MoCA score is less than 18 or greater than 25, indicating cognitive levels outside the mild impairment range. Individuals with major depression or other psychiatric disorders, or those currently receiving treatment for depression, will not be included. Cognitive impairment attributed to identifiable causes such as traumatic brain injury or acute infections will also be excluded. Subjects with neurological disorders including epilepsy, Parkinson's disease, or multiple sclerosis will not be eligible. Those using psychoactive medications that could interfere with reliable neurocognitive testing, or currently taking drugs known to impact cognition (e.g., benzodiazepines, anticholinergics), will also be excluded. A history of substance abuse (alcohol or drugs) within the past year, or the presence of malignant disease, HIV, or other serious infections, will disqualify a participant. Additionally, individuals with cardiovascular, renal, or hepatic disorders, as well as thyroid dysfunction, uncontrolled hypertension (BP >150/100 mm Hg), or uncontrolled diabetes (RBS >200 mg/dl) will be excluded. Participants who have experienced cognitive

decline because of surgery, or have visual or auditory impairments that could hinder compliance with the study protocol, will also not be considered for inclusion.

Intervention and comparator details

Intervention group (group A)

Participants in group A will receive Guduchyadi Ghrita, administered orally at a dose of 12 grams once daily, in the morning on an empty stomach, with lukewarm water as Anupana. In addition, they will receive Pratimarsha Nasya, with 2 drops administered in each nostril once daily in the evening. The duration of both interventions will be 60 days.

Comparator group (group B - placebo with cognitive stimulation)

Participants in group B will receive a placebo capsule containing 250 mg of roasted semolina, administered orally twice a day—30 minutes before breakfast and dinner, along with lukewarm water. Additionally, cognitively stimulating activities will be prescribed, based on the Global Council on Brain Health (GCBH) guidelines, as part of non-pharmacological support.[7]

Outcome

Primary outcome

Improvement in cognition, memory, and language will be assessed using the MoCA. Assessment Timepoints: At baseline (Day 0), Day 30 and at the end of the intervention (Day 60).

Secondary outcomes

Plasma BDNF levels assessment timepoints: Blood samples will be collected at baseline (day 0) and post-intervention (day 60) for BDNF quantification using ELISA.

Quality of life (QOL) will be assessed using the quality of life in Alzheimer's disease scale (QOL-AD). Timepoints: day 0 and day 60.

Daily functioning will be evaluated using the bristol activities of daily living (ADL) scale. Timepoints: day 0 and day 60.

Participant timeline

This table outlines the schedule of events throughout the clinical trial, from screening to the end of the treatment period. Participants undergo initial evaluations including informed consent, demographics, and baseline investigations. Follow-up visits occur at weekly intervals (±3 days) to monitor vitals, clinical signs, and scale-based assessments. Study drugs are dispensed post-randomization, with regular evaluations for safety, efficacy, and adverse events. Final assessments and biomarker analysis are performed at the end of the treatment period, which may include a telephonic visit. Details of timeline is given in Table 1.

Sample size calculation

For estimating the sample size, on the basis of previous research work regarding mild cognitive impairment, mean score of Montreal cognitive assessment scale was observed 20.14+-3.35(SD) in placebo group. It is assumed that the trial drug will improve further 12% of cognitive domain. Considering above assumption, sample size was calculated by software- https://clinical.com/stats/samplesize.aspx.

Allocation ratio- 1:1

Power of test- 80%

Level of significance- 95%

Error- 5%

In two side tests, number of patients calculated as 30 per group but considering 20% dropout, 40 patients in each group will be selected.

Recruitment strategy

Screening criteria

Participants suffering from symptomatology of mild NCD will be screened through Montreal Cognitive Assessment Scale and ad8 dementia screening interview. The Eight-item Informant Interview to Differentiate Aging and Dementia (AD8®) was developed as a brief instrument to help discriminate between signs of normal aging and mild dementia. The AD8 contains 8 items that test for memory, orientation, judgment, and function. Cut points are: normal cognition 0-1; impairment in cognition 2 or greater. The AD8 assesses intra-individual change across a variety of cognitive domains compared to previous levels of function and is sensitive to early signs of dementia regardless of etiology.[8]

Diagnostic criteria

Mild neurocognitive disorder diagnostic criteria as per DSM V.[9]

Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in

cognitive function; and a modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

Table 1: Participant timeline.

	Intervention phase										Follow-up	
Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit name	Screening	Randomization (Day 1)								End of the treatment period	Can be telephonically	
Visit window (in days)	1-7	7 days from screening	7±3	7±3	7±3	7±3	7±3	7±3	7±3	7±3	7±3	7±3
Screening	✓											
Informed consent		✓										
Demographics		✓										
Medical history	✓											
Physical examination	✓		✓	✓	✓	✓	✓	✓	✓	✓		
Vital signs	✓		✓	✓	✓	✓	✓	✓	✓	✓		
Assessment of signs and symptoms	✓		✓	✓	✓	✓	✓	✓	✓	✓		
Investigations BT (CBC, ESR,LFT,RFT, RBS, Lipid profile, S. TSH, Vit B12, Urine analysis)		✓										
Investigation BT& AT (Plasma BDNF Biomarker)		✓								✓		
Montreal cognitive assessment scale (MoCA)	✓	✓				✓				✓		
Neuropsychiatric inventory scale		✓				✓				✓		
Bristol Activities of Daily Living Scale		✓				✓				✓		
Quality of life (Quality of Life Instrument: AD)		✓				✓				✓		
Dispense *Deepana Pachana & Kosthasodhana* drugs		✓										
Dispense study drugs			✓	✓	✓	✓	✓	✓	✓	✓		
Adverse events			✓	✓	✓	✓	✓	✓	✓	✓		

The cognitive deficits do not interfere with the capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

The cognitive deficits do not occur exclusively in the context of delirium.

The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Allocation

The sequence generation for participant allocation in this study will be performed using computer-generated randomization to ensure unbiased distribution between

the intervention and control groups. Since the study is open-label, there will be no blinding or masking of the participants or researchers. As a result, both the participants and the investigators will be aware of the treatment assigned, making allocation concealment unnecessary (NA). This approach is designed to maintain transparency throughout the trial, although it may introduce potential biases due to the lack of blinding.

Data collection, management, and analysis

Data collection methods

Data will be collected by the scholar in a specially designed case report form.

Assessment criteria

Objective assessment criteria

For plasma BDNF biomarker enzyme-linked immunosorbent assay (ELISA) will be used as assessment Method at baseline and after the completion of treatment to evaluate change in plasma BDNF level.

For criteria for improvement a significant increase in plasma BDNF level compared to baseline, will be considered as an improvement.

Subjective assessment criteria

A special proforma will be adopted from the previous research work incorporating the signs and symptoms of mild neurocognitive disorder. A special scoring pattern for the assessment of subjective parameters will be given.[10] Symptoms of mild neurocognitive disorder will be observed at each follow-up on a weekly basis and assessed after 4 weeks. Changes in gradation of each symptom will be recorded before and after treatment and will be assessed in regards to baseline score. MoCA, neuropsychiatric inventory questionnaire quality of life Alzheimer's disease (QOL-AD) and Bristol activities of daily living scale. These questionaries will be assessed after 4 weeks. Changes in score of each question will be recorded before and after treatment and will be assessed in regards to baseline score.

Data management

Data will be entered in digital format in MS excel in form of master chart.

Data safety and monitoring

The study will be conducted under the supervision of the Institutional Ethics Committee (IEC), Institutional Review Committee (IRC), and Departmental Review Committee (DRC). All necessary approvals will be obtained prior to initiation. Regular monitoring will ensure participant safety, protocol compliance, and data integrity. Any serious adverse events (SAEs) or protocol deviations will be reported promptly to the IEC. At the end of the trial, the data will be disclosed to the IEC, IRC, DRC, and relevant regulatory authorities as required.

Data analysis

The information gathered based on the observation made about various parameters will be subjected to statistical analysis in terms of Mean, Standard Deviation (SD) and Standard Error (SE). General data will be subjected to suitable statistical analysis such as descriptive statistics for demographic data, Chi-square test or normal variate Z test will be used for testing associations of the baseline data. Paired t-test for paired continuous data i.e., within the groups, and unpaired t-test will be applied for between groups continuous data. Wilcoxon Signed-Rank Test will be used for non-parametric data within the groups and Mann-Whitney U Test for comparing between groups with non-parametric data. The data generated in the clinical study will be analyzed by applying appropriate statistical method also. After preparing the master chart of all the required data in a Microsoft Excel worksheet, statistical calculations will have made with the help of Sigma stat 3.5 software and in stat 3 software. The results will have interpreted as Significant $p<0.05$, Highly significant $p<0.01$, Very highly Significant $p<0.001$Insignificant $p>0.05$.

Safety monitoring in this study will be carried out through a comprehensive approach, which includes detailed physical examinations, regular monitoring of vital signs, and periodic clinical assessments throughout the trial. This ensures that any potential health concerns are promptly identified and addressed. In addition, any adverse events (AEs) or serious adverse events (SAEs) that occur during the study will be thoroughly documented. These events will be reported to the adverse drug reaction (ADR) Cell, which is the pharmacovigilance cell of ITRA, for further evaluation and management. This process ensures participant safety and adherence to regulatory requirements, while also providing an effective mechanism for managing any unforeseen risks associated with the interventions.

Ethics and dissemination

The study will commence only after obtaining approval from the Institutional Ethics Committee (IEC), ensuring that all ethical standards are met. Additionally, the study will be registered with the Clinical Trials Registry of India (CTRI) to maintain transparency and accountability. Written informed consent will be obtained from all participants in the local language, ensuring they fully understand the study's purpose, procedures, and potential risks. To protect participants' privacy, all personal data will be anonymized and coded. The results

of the study will be disseminated through publication in peer-reviewed scientific journals and presented at academic forums, allowing for broader sharing of findings within the scientific community. This approach ensures that the study adheres to ethical guidelines while promoting the transparency and accessibility of its outcomes.

DISCUSSION

The study protocol presented outlines a randomized, placebo-controlled clinical trial to assess the efficacy of Guduchyadi Ghrita and Pratimarsha Nasya in improving cognitive function in individuals with mNCD. mNCD, a condition that involves modest cognitive decline, is a growing public health concern, particularly as the global population ages. The aim of the study is to evaluate whether Ayurvedic interventions, known for their nootropic, Rasayana (rejuvenating), and antioxidant properties, can improve cognition and biomarkers such as BDNF, a key player in neuroplasticity.[3-5]

The study's design includes a comprehensive methodology with clear inclusion and exclusion criteria, aiming for participants aged 55-80 years diagnosed with mNCD based on DSM-V criteria. The intervention group will receive Guduchyadi Ghrita orally and Pratimarsha Nasya, a nasal administration of the therapy, while the control group will receive a placebo and cognitive stimulation activities. The primary outcome of the trial will be assessed using the Montreal Cognitive Assessment (MoCA), with secondary outcomes including plasma BDNF levels and quality of life measures.[6]

This trial is particularly significant in the context of integrating traditional Ayurvedic therapies with modern scientific frameworks, such as cognitive and biomarker assessments. Previous studies have shown promising results using Ayurvedic treatments for cognitive enhancement, but this trial seeks to provide rigorous scientific evidence. By using biomarkers like BDNF and focusing on cognitive assessments, the study aims to establish a more objective understanding of how Guduchyadi Ghrita and Pratimarsha Nasya may impact neurocognitive health in mNCD patients.[7-10]

If successful, this study could offer a novel adjunctive therapeutic approach to managing mNCD, blending traditional and modern medical practices. Furthermore, it could pave the way for future research on Ayurvedic interventions in neurodegenerative diseases, fostering broader acceptance and application of integrative medicine.

CONCLUSION

This study will advance the understanding of cognitive enhancement in individuals with mNCD by evaluating the effects of Guduchyadi Ghrita and Pratimarsha Nasya, traditional Ayurvedic interventions, on cognition and biomarkers like BDNF. The research combines modern diagnostic tools and Ayurvedic practices, offering insights into their potential therapeutic benefits for cognitive health. By focusing on objective biomarkers such as BDNF levels and incorporating subjective cognitive assessments like the MoCA, the trial will provide valuable data on the efficacy of these treatments in slowing or reversing cognitive decline associated with mNCD. Furthermore, this study will contribute to the integration of Ayurvedic methods within the broader context of neurodegenerative disease management, fostering a deeper understanding of how traditional medicine can complement contemporary approaches to cognitive health.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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