Ayurveda therapeutic regimen as an Add-on to optimized conventional management of Parkinson's disease: Protocol for an exploratory RCT for assessment of Clinical, Cortical excitability, Neuroimmune and Autonomic function parameters

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Abstract

Background: Parkinson's disease (PD), a progressive neurodegenerative disorder, lacks disease-modifying treatments. Current therapies focus on symptomatic relief, highlighting the need for adjunctive neuroprotective strategies. Ayurveda, a holistic system, shows promise in improving PD clinical outcomes. This randomized, assessor-blinded trial will evaluate the efficacy and safety of integrating Ayurveda with standard PD treatment.

Objective: This assessor-blind randomized controlled study aims to systematically evaluate the efficacy of an add-on Ayurveda

therapeutic regimen compared to conventional treatment as usual in improving the clinical outcomes of PD.

Methods: Eighty PD patients, diagnosed by UKPDSBB criteria, will be randomized into two groups: Treatment as Usual (TAU) and Add-on Ayurveda. The intervention group will receive Ayurvedic therapy alongside conventional treatment for 180 days, while the control group continues TAU. Assessments will occur at baseline, 60, 120, and 180 days, evaluating motor and non-motor symptoms. Transcranial Magnetic Stimulation (TMS), Heart Rate Variability (HRV), and Pulmonary Function Tests (PFT) will assess cortical excitability, autonomic and pulmonary function respectively. Immunological parameters, including cytokine levels and telomere length, will be analyzed at baseline and 180 days to explore disease-modifying effects. Liver and renal function tests to monitor safety.

Results: As of August 2025, a total of 259 patients with Parkinson's disease have been screened for eligibility, of whom 58 participants have been successfully enrolled in the trial. Among these, 33 participants have completed the intervention and follow-up assessments, 14 have discontinued participation, and 11 are currently continuing in the study. Recruitment and follow-up are ongoing, and the trial is scheduled for completion in September 2026.

Conclusions: This study aims to address the lack of mechanistic evidence and robust data on Ayurveda in PD. By systematically evaluating clinical efficacy and potential bio-mechanisms, the findings will provide preliminary evidence for Ayurvedic interventions, potentially paving the way for their integration into comprehensive PD management. Clinical Trial: Clinical Trial Registry of India - CTRI/2022/01/039803 [Registered on: 28/01/2022].

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Parkinson's disease (PD), a progressive neurodegenerative disorder, lacks disease-modifying treatments. Current therapies focus on symptomatic relief, highlighting the need for adjunctive neuroprotective strategies. Ayurveda, a holistic system, shows promise in improving PD clinical outcomes. This randomized, assessor-blinded trial will evaluate the efficacy and safety of integrating Ayurveda with standard PD treatment.

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Conclusion:

This study aims to address the lack of mechanistic evidence and robust data on Ayurveda in PD. By systematically evaluating clinical efficacy and potential bio-mechanisms, the findings will provide preliminary evidence for Ayurvedic interventions, potentially paving the way for their integration into comprehensive PD management.

Keywords: Ayurveda; Parkinson’s Disease; Transcranial Magnetic Stimulation; Autonomic Function Test; Immuno-parameters.

Trial Registration: Clinical Trial Registry of India - CTRI/2022/01/039803 [Registered on: 28/01/2022].

1.0 INTRODUCTION

Parkinson's disease (PD), a progressive neurodegenerative disorder characterized by motor symptoms like tremor and rigidity, affects diverse populations worldwide (1). First described in 1817, PD's prevalence increases with age, impacting approximately 1% of individuals over 65 (2)(3). Regional variations in prevalence exist. Indian studies show a crude prevalence of 14.1 per 100,000 in rural Kashmir, with rates rising to 247 per 100,000 in those over 60 (4). Conversely, Bangalore reported a lower crude prevalence of 27 per 100,000 (3). Notably, a higher rate of 328.3 per 100,000 was observed among the Parsi community in Mumbai (5). Early-onset PD, occurring before 40, accounts for 3-5% of cases, and PD is generally twice as common in men (6). Beyond motor symptoms, PD presents non-motor challenges like sleep disturbances and cognitive impairment. Autonomic dysfunction also increases with age and disease progression. Patients face a six-fold increased risk of dementia (7).

Standard PD treatment focuses on symptom management using medications like levodopa and dopamine agonists (8). However, these treatments do not halt disease progression and can cause side effects (9)(10). Invasive procedures like deep brain stimulation are expensive and inaccessible to many, particularly in India. Consequently, many PD patients explore complementary and alternative medicine (CAM), including Ayurveda (11). Studies indicate that nearly half of PD patients use CAM, typically educated, younger, urban individuals with longer disease duration (11).

While CAM, including Ayurvedic interventions, shows potential for improving motor function, robust clinical evidence is lacking. Existing research consists of limited clinical trials, pilot studies, and case reports. There is a need for randomized controlled trials with objective measures to evaluate the mechanisms of Ayurvedic treatments. Specifically, the impact of comprehensive Ayurvedic therapies on cortical activity, neuroimmune function, autonomic function, telomere length, and neuropsychological function remains unexplored. Investigating these areas will provide crucial evidence for the efficacy and safety of Ayurveda in PD, and shed light on the neurobiological basis of its effects.

1.1 AYURVEDA and PARKINSON'S DISEASE

Parkinson's disease can be comprehended within the paradigm of Vāta Vyādhi (neurological disorders) as delineated in Ayurveda. It is primarily attributed to Vāta Dosha Prakopa (vitiation of Vata Dosha, a bodily humor that is primarily associated with movement), which manifest as tremors, rigidity, and bradykinesia. The chronicity and progressive nature of the disease necessitate a multidimensional therapeutic approach involving Vāta-pacifying strategies, Rasāyana (rejuvenating measures), and Panchakarma (detoxification therapies) for symptomatic relief and improving disease progress (12).

1.2 OBJECTIVES

This assessor-blind randomized controlled study aims to systematically evaluate the efficacy of an add-on Ayurveda therapeutic regimen compared to conventional treatment as usual in improving the clinical outcomes of PD.

The secondary objectives are to explore the effects of add-on Ayurveda therapy in comparison to conventional treatment as usual on multiple physiological and functional parameters, *viz*., cortical excitability, assessed through Single (MT, RC & SP) and paired pulse (SICI, LICI & ICF) Transcranial Magnetic Stimulation (TMS) measures; immune parameters, including Th1/Th2/Th17/T-regulatory cell population, plasma C-reactive protein (CRP), plasma levels of Th1/ Th2/Th17 pathway cytokines, and telomere length.

1.3 HYPOTHESIS

This study hypothesizes that Ayurveda treatment, when integrated with standard treatment as usual, will be safe and effective in improving clinical and cognitive outcomes in patients with Idiopathic Parkinson's Disease (PD). It is expected that these therapies will enhance the optimal response to levodopa, potentially leading to better symptomatic control. Ayurveda interventions are hypothesized to modulate cortical excitability measures, which will correlate with improvements in both clinical and cognitive parameters. Furthermore, it is postulated that add-on Ayurveda therapies may induce a significant shift in the Th1/Th2/Th17/T regulatory cell population, along with alterations in plasma levels of pro-inflammatory cytokines and telomere length, which will further correlate with clinical, cognitive, and neurophysiological outcomes. Lastly, it is anticipated that autonomic dysfunction, as measured through heart rate variability (HRV), will show significant improvement following Ayurveda interventions, aligning with overall clinical benefits observed in PD patients.

2.1 MATERIAL & METHODS

2.2 STUDY DESIGN DESCRIPTION

This study is designed as an assessor-blinded, randomized controlled trial (RCT) to be conducted at NIMHANS, Bengaluru.

Trial Design:

This study is a prospective, assessor-blinded, exploratory randomized controlled trial with a parallel-group design and a 1:1 allocation ratio. Participants will be randomized into either the add-on Ayurveda intervention arm or the TAU control arm, with each participant undergoing a 6-month study period.

Patients diagnosed with PD attending the Neurology and Integrative Medicine outpatient and inpatient services at NIMHANS will be screened for eligibility. Those meeting the inclusion criteria will be recruited after obtaining written informed consent. The study procedures, potential benefits, risks, and the right to withdraw at any stage will be clearly explained in the patient's language, and a copy of the consent document will be provided.

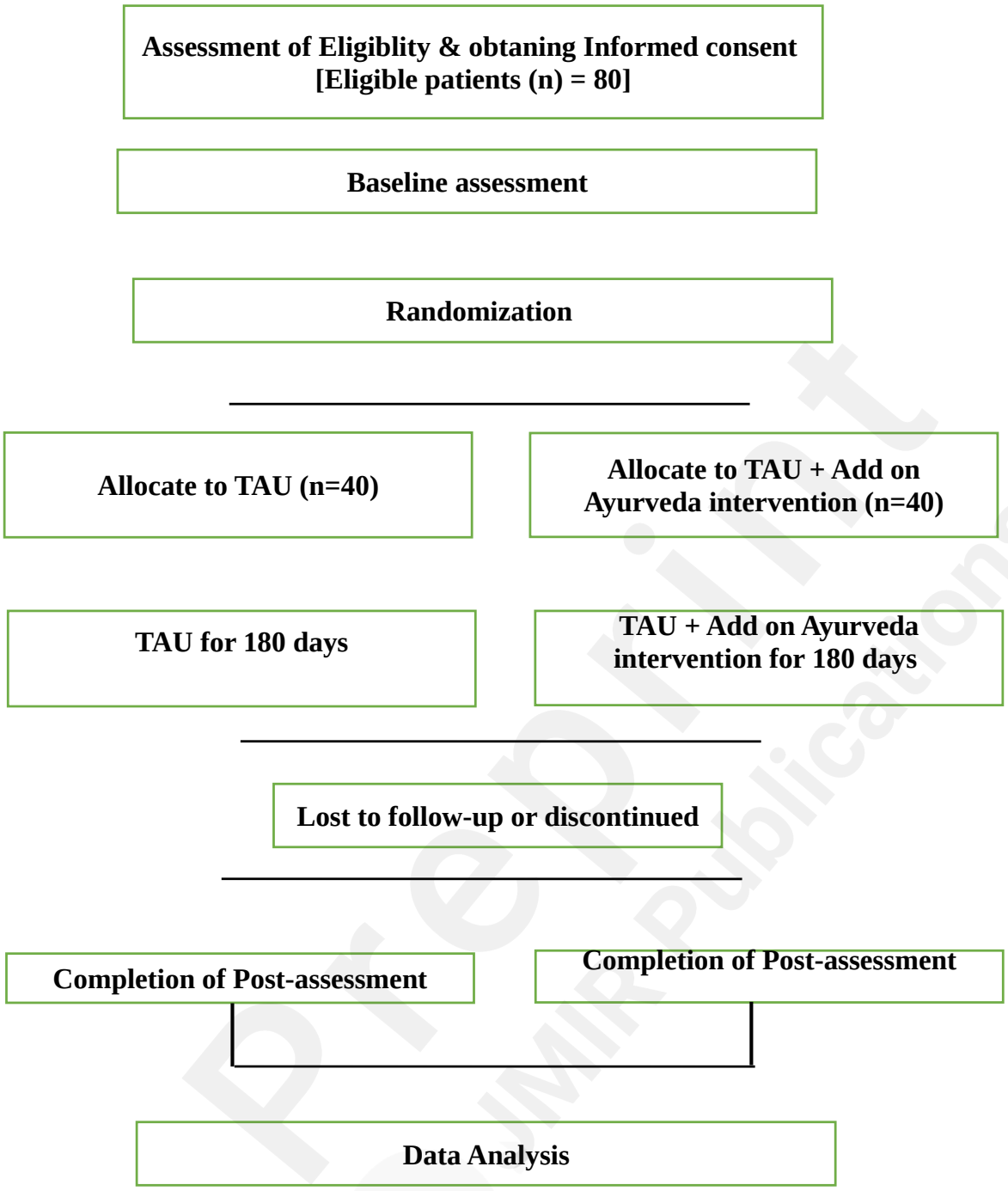

Figure 1: Study design

2.3 SELECTION OF SUBJECTS

Inclusion Criteria

Participants eligible for the study will be those diagnosed with Idiopathic Parkinson's Disease (PD) based on the UK Parkinson's Disease Society Brain Bank (UKPDSBB) criteria (13). The study will include individuals in Hoehn and Yahr (H&Y) stages 2 to 4, with a disease duration of more than

three years, experiencing severe motor fluctuations and suboptimal response to standard treatment, including dyskinesia and gait freezing. The eligible age range for participation will be 40 to 70 years.

Exclusion Criteria

Participants with Parkinsonism spectrum disorders or other neurodegenerative conditions such as motor neuron diseases and multiple sclerosis will be excluded from the study. Individuals with major cardiovascular disorders or those with hepatic, renal, or uncontrolled pulmonary dysfunction will not be eligible. Patients receiving concomitant medications that may interfere with Parkinsonian symptoms, including anticoagulants, neuroleptics, metoclopramide, Compazine, beta-blockers, fluoxetine, clozapine, quetiapine, olanzapine, buspirone, antipsychotics, and CNS stimulants such as sodium valproate, will also be excluded. Those with cognitive impairment, defined by a Mini-Mental State Examination (MMSE) score of less than 18, as well as individuals with evidence of malignancy or a history of substance abuse, will not be considered for participation. Additionally, patients who have participated in any other clinical trial within the past six months will be excluded to ensure unbiased study outcomes.

2.4 SAMPLE SIZE

The sample size estimation was based on the findings from a recent study which has used “Mucuna pruriens” in PD (14). The optimal sample size was estimated using the standard principles & methods (15). With an effect size of 0.43, for an allocation ratio of 1:1, it was estimated that a sample size of at least 40 Parkinson’s disease patients in add-on Ayurveda therapy group and 40 patients in TAU group (Total n=80, including 20% dropout) will be required to detect a two-tailed significant difference of α =0.05 with an estimated 90% power.

2.4 ASSIGNMENT OF INTERVENTIONS

Randomization will be conducted using computer-generated random numbers with allocation concealment, implemented via a serially numbered opaque sealed envelope (SNOSE) method. The study statistician, who is independent from the study would generate the randomization list in SPSS version 26.0 and would employ blocks of random block sizes. Given the nature of the intervention, double-blinding is not feasible; however, the assessor conducting the assessments will remain blinded to group allocation to minimize bias.

2.5 INTERVENTION

The interventions employed in this study consists of two arms: Group A (Control group) receiving conventional treatment as usual (TAU) and Group B (Intervention group) receiving add-on Ayurveda therapy along with TAU of Parkinson's disease, prescribed by the treating neurologist.

Group A (Conventional Treatment as Usual - Control Group): Participants will receive pharmacological treatment as prescribed by the treating neurologist. This would include T. Levodopa and carbidopa 125 mg or Tab Entacapone 200 mg or Tab Pramipexol 1 mg or Tab Selegiline 5 mg as appropriate per the assessment of consultant neurologist.

Group B (Conventional Treatment as Usual + Add-on Ayurveda - Intervention Group): Participants will receive Ayurveda intervention as an adjunct to the conventional treatment for a period of 180 days, comprising three cycles of Ayurveda therapies at 60-day intervals. The regimen is structured as follows:

- **Preparatory Phase (*Deepana-Pachana* Therapy):** To enhance digestion and metabolism, participants will be administered *Chitrakadi Vati* (250 mg/tablet), 2 tablets with warm water, three times daily before food for a duration of 5 days.
- **Shodhana Therapy** (Purification Phase – *Basti* (rectal administration of medicine) Therapy**):** This includes a Yoga Basti regimen, wherein a combination of *Niruha Basti* (therapeutic decoction enema) and *Anuvasana Basti* (oil enema), will be administered in a pre-specified regimen [in the form of *Basti* comprising one *Sneha Basti* initially, 3 decoction *Bastis* alternatively followed by 3 *Sneha Bastis* and one *Sneha Basti* in the end] aimed at pacifying *Vāta Dosha*.
    - Niruha Basti**:** Decoction of *Erandamoola* (made with root of *Ricinus Communis* Linn (450 ml**)** administered rectally on an empty stomach as per the protocol for *Yoga Basti*.
    - *Anuvasana Basti***:** *Bala Taila* (90 ml) administered immediately after food on five occasions as per the protocol for *Yoga Basti*.
- **Shamana Therapy (Pacificatory Phase):** Following purification, the participants will receive oral Ayurveda formulations for symptomatic relief and alleviation of vitiated *Vata Dosha* for 47 days in each cycle as follows:
    - *Mashabaladi Kwatha* **(**Decoction) - 15 ml, with two pinches of Asafoetida and Rock salt administered with warm water three times daily.
    - *Kalyanaka Ghrita* (Medicated Ghee) - 20 ml, taken early in the morning on an empty stomach.
- The complete Ayurveda intervention regimen will be repeated thrice over the study period,

with three cycles of 60 days each, totalling 180 days.

2.5 OUTCOME MEASURES

The primary outcome is the change in the total score of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) after six months of treatment, compared with the baseline.

The secondary outcome measures include a range of neurophysiological, biochemical, cognitive, and functional parameters. Cortical excitability assessed using Transcranial Magnetic Stimulation (TMS), evaluating both single-pulse (Motor Threshold [MT], Resting Cortical [RC], and Silent Period [SP]) and paired-pulse (Short Interval Cortical Inhibition [SICI], Long Interval Cortical Inhibition [LICI], and Intracortical Facilitation [ICF]) measures. Autonomic function will be analysed through Heart Rate Variability (HRV), while Pulmonary Function Tests (PFTs) will assess respiratory capacity.

Immunological markers, including changes in Th1/Th2/Th17/T regulatory cell populations, plasma levels of pro-inflammatory cytokines, and telomere length, will be measured to evaluate the immunomodulatory and anti-inflammatory effects of the intervention.

Functional and motor outcomes will be examined through reductions in dyskinesia severity using the Unified Dyskinesia Rating Scale (UDysRS) and improvements in gait parameters, measured using the 6-minute walk test and gait speed (10-meter walk test). Cognitive function will be assessed using the Montreal Cognitive Assessment (MoCA), and postural stability will be evaluated through the Balance Evaluation Scoring System (BESS). Changes in SCOPA-Sleep (Scales for Outcomes in Parkinson's disease - Sleep) will be monitored to assess improvements in sleep disturbances associated with Parkinson's disease.

Safety assessments will include monitoring for Treatment Emergent Adverse Events (TEAEs) throughout the study period. Liver Function Tests (LFT), Renal Function Tests (RFT), and Complete Blood Count (CBC) will be performed at baseline and at the end of the study (day 180) to detect any potential systemic adverse effects. For participants undergoing Basti therapy, adverse events will be monitored during the In-patient care.

2.6 Trial registration: The trial is registered with the Clinical Trial Registry of India - CTRI/2022/01/039803 [Registered on: 28/01/2022].

2.7 Ethics and dissemination:

The trial has been approved by the NIMHANS Human Ethics Committee for Research in

AYUSH and Integrative Medicine (NIMHANS/HECAIM/5th/MEETING/2021-22, Dated: 07.01.2022). All procedures in the trial will comply with the ethical guidelines outlined by the Indian Council of Medical Research (ICMR) and the Declaration of Helsinki. Participants will be recruited only after obtaining written informed consent, ensuring that they fully understand the study's objectives, interventions, potential risks, and benefits.

3.0 BRIEF DESCRIPTION OF SOME RELEVANT ASSESSMENTS

3.1 CLINICAL ASSESSMENTS:

MDS-UPDRS (Movement Disorder Society-Unified Parkinson's Disease Rating Scale): This scale assesses motor and non-motor PD symptoms. It includes four parts: non-motor experiences of daily living (Part I), motor experiences of daily living (Part II), motor examination (Part III), and motor complications (Part IV). Parts IA, IB, and II are conducted in the "ON" state, while Part III is assessed in both "ON" and "OFF" states. Part IV integrates patient-reported information with clinical observations (16).

UDyRS (Unified Dyskinesia Rating Scale): This tool evaluates involuntary movements (dyskinesia) associated with PD treatment. It includes historical (On-Dyskinesia, Off-Dystonia) and objective (Impairment, Disability) sections, focusing on choreic and dystonic movements (17).

SCOPA-S (Scales for Outcomes in Parkinson's disease - Sleep): This assesses nighttime and daytime sleep problems over the past month. It includes subscales for nighttime sleep (NS) and daytime sleep (DS), with a global assessment of nocturnal sleep quality (18).

MoCA (Montreal Cognitive Assessment): This tool evaluates cognitive function, assessing memory, language, executive functions, visuospatial skills, attention, abstraction, and orientation. It provides a Derived Memory Index score (MIS) to predict Alzheimer's dementia conversion (19)(20).

10-meter walk test and 6-minute walk test: These assess gait. The 10-meter walk test measures gait speed, while the 6-minute walk test evaluates aerobic capacity and endurance. Both are performed in the "OFF" state (21)(22).

BESS (Balance Error Scoring System): This measures postural stability using the Biodex balance system. It involves three stances (double-leg, single-leg, tandem) performed on firm and foam surfaces with eyes closed. Errors are scored, with lower scores indicating better balance (23).

TMS (Transcranial Magnetic Stimulation): This non-invasive technique assesses motor cortical function. TMS is conducted through "Magventure R30 with magoption" equipment using MCB -70 coil. It measures parameters like resting motor threshold (RMT), central motor conduction time (CMCT), silent period (SP), short intracortical inhibition (SICI), long interval cortical inhibition

(LICI), and intracortical facilitation (ICF). It is performed in the "OFF" state (24).

HRV (Heart Rate Variability): This assesses autonomic function using the "Chronovisor" HRV machine. Time-domain (SDNN, pNN50, RMSSD) and frequency-domain (LF, VLF, ULF, HF, LF/HF ratio) measures are acquired in the "OFF" state.

PFT (Pulmonary Function Test): This evaluates respiratory capacity using spirometry. Lung volume measures (FVC, FEV1, FEV1/FVC ratio) and respiratory muscle strength (MIP, MEP) are assessed in the "OFF" state.

3.1.2 NEUROIMMUNE PARAMETERS:

Objectives: To assess: (a) the proportions and activation status of human peripheral blood Th1/Th2/ Th17 cells. (b) Estimation of cytokine by Cytometric Bead Array (CBA).

Peripheral blood mononuclear cell (PBMC) isolation and cryopreservation: PBMCs and plasma samples will be separated from peripheral whole blood samples (10 ml) by density gradient centrifugation and cryopreserved.

Methodology:

(a) Staining with fluorescent antibodies for immunophenotyping of Th1/Th2/Th17 cells:

Cryo-preserved peripheral blood mononuclear cells (PBMCs) will be processed for multiparametric assessment of the frequencies of major adaptive immune T cells, namely Th1, Th2, Th17 and Treg cells. Briefly, 1 million PBMCs for each panel of immune surface markers will be stained with LIVE/DEAD Fixable green (Life Technologies) to exclude dead cells and with respective antibodies for 20 and 30 minutes respectively at 4°C. Cells will be washed and resuspended in 0.5% paraformaldehyde for fixation. Finally, the cells will be washed and resuspended in phosphate buffered saline (PBS) containing 1% FBS (fetal bovine serum). An unstained control will be included with all samples. Stained samples will be acquired using FACSLyric (BD Biosciences) flow cytometer. Analysis is done by using Flowjo software. Quality control of flow cytometry analysis will be ensured based on monitoring the performance of the instrument by using Cytometer Setup and Tracking (CS&T) beads. Compensation for fluorescence spectral overlaps will be calculated and applied for analysis of data for each of the different antibody cocktails. Data will be acquired through BD FACSuite interface and analyzed on Flow Jo software (BD Biosciences).

LASERS	Antibody Marker	Fluorochrome
Violet Laser-405 nm	Anti-CD4	BV 421
	Anti-CD25	BV 605
	Anti-CD127	BV 750
Blue Laser- 488 nm	Anti-CCR6(CD 196)	Alexa Fluor 488

	Anti- CD8	PE
	Anti-CCR4(CD 194)	PE CY 7
	Anti-FoxP3	BB 700
Red Laser-640nm	Anti-CD3	AF 647
	Anti-CXCR3(CD 183)	BD Horizon R 718

Table 1: Design of fluorescent antibody panel based on the LASERS and detection filters available in the FACSLyric Flow Cytometer for the identification of Th1, Th2 and Th17 cells

(b) Estimation of cytokine by Cytometric Bead Array (CBA):

Cryopreserved plasma specimens will be processed according to manufacturer's instructions for detection and quantification of the proposed cytokines by using the CBA kit (BD Biosciences). Data will be acquired on FACS Verse flow cytometer and analysed on FCAP Array software.

Table no 2: Participant enrolment and schedule of assessment

Sl. No	**Assessments**	**Baseline**	**60th day**	**120th day**	**180th day**
1	MDS UPDRS	✓	✓	✓	✓
2	UDyRS	✓	✓	✓	✓
3	SCOPA-S	✓	✓	✓	✓
4	MoCA	✓	✓	✓	✓
5	6-Minute walk test Gait speed (10-meter walk test)	✓	✓	✓	✓
6	BESS	✓	✓	✓	✓
7	**Laboratory parameters**				
	Haematology				
	Complete hemogram	✓			✓
	ESR	✓			✓
	Biochemistry				
	Liver function test	✓	✓		✓
	Renal function test	✓	✓		✓
	Lipid profile	✓			✓
	HbA1C	✓			✓
	FBS	✓			✓
	Sr. Uric acid	✓			✓
	Inflammatory markers				
	Plasma Cytokine Assay	✓			✓
	Immunophenotyping for	✓			✓

	Th1/Th2/Th17/T-regulatory cell population				
8	**TMS**				
	Single pulse measures	✓			✓
	Paired pulse measures	✓			✓
9	**Neurophysiological parameters**	✓			✓
	HRV	✓			✓
	PFT	✓			✓
10	Concomitant medication	✓	✓	✓	✓
11	Rescue medication		✓	✓	✓

4.0 Plans for data storage, handling, and statistical analysis:

Research investigators and study personnel will receive comprehensive, documented training on the protocol. Access to CRFs and electronic CRFs will be limited to trained individuals to ensure standardized data entry. MDS-UPDRS scores will be recorded on paper and cross-verified with electronic entries to minimize errors. Participant data will be coded, securely stored with password protection, and assigned unique identification codes for pseudonymization. The data analyst will be blinded to group allocation. Principal Investigators will ensure secure data-sharing mechanisms for privacy and confidentiality.

Statistical analysis will utilize SPSS software. Primary outcomes will be analysed using modified Intent-to-Treat (mITT) or Per Protocol (PP) approaches, with mixed-model repeated measures ANOVA. Sensitivity analyses will assess robustness in the under-treatment population. Secondary efficacy endpoints will be analysed in the mITT or PP population, while safety data will be assessed in the safety population. Qualitative variables will be presented as frequency and proportion, and quantitative variables using mean, standard deviation, median, interquartile range, and range. Descriptive analyses will be conducted for the overall and stratified study populations.

5.0 Monitoring and Oversight:

Data Safety Monitoring Board (DSMB) constituted by the Central Council for Research in Ayurvedic Sciences (CCRAS) comprising experts in neurology, clinical trials, ethics, and Ayurveda experts to oversee participant safety and trial integrity. The NIMHANS Ethics Committee will provide continuous ethical oversight. CCRAS will conduct independent monitoring for protocol, Good Clinical Practice (GCP), and regulatory compliance, ensuring objectivity. As an exploratory trial, no interim analysis is planned. However, the DSMB will periodically review safety data,

assessing serious adverse events (SAEs) and risks. The DSMB, in consultation with the Ethics Committee and CCRAS, will make final decisions on trial continuation or termination. The DSMB ensures participant well-being and maintains the trial's scientific and ethical standards through consistent monitoring and safety reviews.

6.0 Harms: **Adverse Event Collection, Assessment, Reporting, and Management**:

Participants will be assessed for Adverse events (AEs) at each scheduled follow-up visit (Day 60, 120, and 180) and during routine hospital visits. Each reported AE will be documented, categorized based on severity, relatedness to the intervention, and expectedness, following standardized guidelines. Laboratory safety assessments, including Liver Function Tests (LFT), Renal Function Tests (RFT), and Complete Blood Count (CBC), will be performed at baseline and at the final study visit (Day 180) to monitor any potential systemic effects. All recorded AEs will be reviewed by the DSMB, which will assess their clinical significance and provide recommendations for participant safety. Serious Adverse Events will be promptly reported to the NIMHANS Human Ethics Committee and the sponsor, CCRAS, in accordance with regulatory guidelines.

7.0 Protocol Amendments

The Principal Investigator will be responsible for communicating all significant protocol amendments. Substantial amendments will require approval from the accredited medical ethics committee before implementation, while non-substantial amendments will be documented and filed without separate notification. Any modifications impacting participant safety or study procedures will be promptly conveyed to enrolled participants, and, if necessary, a new informed consent process will be initiated.

8.0 Consent:

Informed consent will be obtained from all participants before enrolment, ensuring they fully understand the study's purpose, procedures, potential risks, and benefits.

9.0 Confidentiality

All participant data will be coded and securely stored with password protection to maintain confidentiality. Each subject will be assigned a unique identification code, ensuring pseudonymization in all study documents. Strict access controls will be implemented to safeguard personal information before, during, and after the trial.

10.0 Access to data

Access to the final trial dataset will be limited to the principal investigators, designated research staff, statisticians involved in the study, and the sponsor-collaborator, CCRAS, which will independently analyse the study data. Data sharing will be conducted in compliance with ethical and regulatory guidelines.

11.0 Ancillary and post-trial care:

Participants completing the trial will continue to receive routine medical care through the outpatient department of NIMHANS. Clinical trial insurance has been secured to provide coverage for any unforeseen adverse events, ensuring comprehensive risk mitigation and participant safety.

12.0 Dissemination policy: The trial results will be disseminated through peer-reviewed publications, and presentations at scientific conferences.

13.0 Results:

As of August 2025, a total of 259 patients with Parkinson's disease have been screened for eligibility, of whom 58 participants have been successfully enrolled in the trial. Among these, 33 participants have completed the intervention and follow-up assessments, 14 have discontinued participation, and 11 are currently continuing in the study. Recruitment and follow-up are ongoing, and the trial is scheduled for completion in September 2026.

14.0 Discussion:

The bio mechanisms of conventional medicines are well established. The biosynthesis and metabolism of dopaminergic drugs, dopamine agonist, Monoamine Oxidase B (MAO-B) inhibitors, Catechol-O-methyl transferase inhibitors, Anticholinergics and Amantadine used in the management of PD are established and well understood (8). levodopa-based preparations are designed to replace the dopamine in the depleted striatum. Levodopa is able to cross the BBB and gets converted into the neurotransmitter dopamine by DOPA decarboxylase(25). Dopamine agonists stimulate the activity of the dopamine system by binding to the dopaminergic receptors. Monoamine Oxidase B (MAO-B) inhibitors work by inhibiting the enzymes involved in dopamine metabolism, which preserves the levels of endogenous dopamine (26). Catechol-O-methyl transferase inhibitors offer a therapeutic means of preserving endogenous dopamine levels, by reducing its breakdown (27). Anticholinergics act through non-dopaminergic mechanisms. These reduce the activity of the neurotransmitter acetylcholine, by acting as antagonists at cholinergic receptors and offer some benefit in improving rigidity and tremor(28). Amantadine acts as a weak glutamate antagonist at the N-methyl-D-aspartate receptor (NMDAR) and is useful in the treatment of rigidity, rest tremor, and it can limit the severity

of levodopa-induced dyskinesias (29).

Despite Ayurveda's long-standing clinical application in managing neurodegenerative disorders, there is a lack of robust scientific evidence elucidating its mechanisms of action in comparison to conventional medicine. This study aims to bridge this gap by systematically evaluating the efficacy and safety of add-on Ayurveda therapy in Parkinson's disease and exploring its potential bio-mechanisms. By incorporating clinical, neurophysiological, immunological, and autonomic function assessments, this trial is expected to provide scientific validation for Ayurveda-based interventions in PD management.

The findings from this study could serve as critical evidence supporting the integration of Ayurveda in contemporary neurological care, potentially influencing clinical guidelines and policy decisions related to neurodegenerative disorders. Moreover, this research will provide preliminary data to guide future large-scale, multicentric trials and mechanistic studies exploring Ayurveda's role in neuroprotection and disease modification. Establishing the scientific basis for Ayurveda in PD management may also contribute to its global acceptance, fostering interdisciplinary research and collaboration in integrative neurology.

Declaration of interests: The study investigators have no competing or financial interest in conducting the trial.

Protocol version: 3-29/2021- CCRAS/Admn/Coll. The study was sanctioned on 9th April 2021.

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Authors contribution:

Project administrator is NS. The project was Conceptualized by U.C., P.K.P., B.H., K.K.R and S.J. Methodology: U.C., S.J., B.Y., B.H., K.K.R. Validation: S.J., M.M.V., K.U., R.N., K.K.R., B.C.S.R., S.B. Formal analysis: S.V., B.H., K.K.R., S.J., K.U., M.M.V., R.N., B.C.S.R., S.B. Investigation: S.V., B.H., K.K.R., S.J., U.C., M.M.V., K.U., S.G., S.M. Resources: U.C., P.K.P., N.K., R.R.M., V.V.H., R.V., K.U., S.G., M.M.V., S.J., B.C.S.R., S.B. Data curation: S.V., B.H., S.J. Writing-original draft: U.C., S.V., B.H., K.K.R., S.J., K.U., M.M.V., B.C.S.R., S.M. Writing- review and editing: B.H., K.K.R., U.C., S.J., K.U., M.M.V., B.C.S.R., S.J. Visualization: B.C.S.R., S.J., N.S., K.K.R., U.C. Supervision: U.C., S.K.V., B.H., S.J., K.K.R., K.U., M.M.V., B.C.S.R., S.B.

Role of Study Sponsor and coordinating center: The study protocol was jointly formulated by PIs

from NIMHANS and CCRAS and was peer-reviewed by the concerned subject experts before approval of the grant to the investigators. The primary and secondary data collected by the investigators will be analyzed and final report will be prepared and published jointly by NIMHANS and CCRAS. The coordinating center has procured and provided the trial drug and has formed the independent DSMB.

Availability of data and material: As this is a protocol and data collection are ongoing; the availability of data is not applicable.

Competing Interests: The authors are employees of NIMHANS, Bengaluru, an Institute of National Importance under the Ministry of Health and Family Welfare, Government of India & Central Council for Research in Ayurvedic Sciences under the Ministry of AYUSH, Government of India. No conflict of interest is declared.

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Appendices:

Informed consent materials – The patient information sheet and the consent forms are attached as Annexure-I

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Supplementary Files