

ORIGINAL RESEARCH ARTICLE

Modulation of the Cognition–Sleep Nexus in Subjective Cognitive Decline: A 12-Week, Randomized, Double-Blind, Placebo-Controlled Trial of a Standardized *Cordyceps militaris* Extract

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ABSTRACT

Background: Subjective cognitive decline (SCD) and sleep disturbance form a self-reinforcing cycle that accelerates neurodegeneration. *Cordyceps militaris* (CM), a medicinal fungus rich in nucleosides, has neuroprotective and adenosinergic (sleep-promoting) properties.

Objective: To evaluate the efficacy of a standardized CM extract on the cognition–sleep nexus in adults with SCD.

Methods: In a 12-week, single-center, randomized, double-blind, placebo-controlled, parallel-group trial in Palembang, Indonesia, 120 adults aged 45–65 years with SCD received 300 mg/day of a standardized CM mycelial extract (3% cordycepin) or matching placebo. The primary outcome was change in the Montreal Cognitive Assessment–Indonesian (MoCA-INA) score. Bonferroni-corrected key secondary outcomes were the Pittsburgh Sleep Quality Index (PSQI), Rey Auditory Verbal Learning Test (RAVLT) delayed recall and polysomnography-derived sleep efficiency (SE). Intention-to-treat analyses used a linear mixed-effects model (LMM).

Results: A significant group-by-time interaction favored CM for MoCA-INA (adjusted mean difference [AMD] +1.95; 95% confidence interval [CI] 1.10, 2.80; $p < 0.001$). All three key secondary outcomes improved: PSQI (AMD –2.90; 95% CI –3.81, –1.99), RAVLT delayed recall (AMD +2.15; 95% CI 1.30, 3.00) and SE (AMD +5.8%; 95% CI 3.1, 8.5); all $p < 0.001$. After false discovery rate (FDR) correction, benefits were also seen for processing speed, rapid eye movement (REM) sleep percentage, serum brain-derived neurotrophic factor (BDNF) and high-sensitivity C-reactive protein (hs-CRP). The extract was well tolerated.

Conclusion: Twelve weeks of standardized *C. militaris* extract improved cognitive function, episodic memory and both subjective and objective sleep in adults with SCD, with changes in neuroplasticity and inflammation markers consistent with a multi-target mechanism.

All authors have reviewed and approved the final version of the manuscript.

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1. Introduction

Subjective cognitive decline (SCD) represents the earliest symptomatic manifestation of neurodegeneration, most notably on the Alzheimer's disease (AD) continuum. It is defined by a self-perceived deterioration in cognitive abilities,

particularly memory, even when objective neuropsychological testing falls within the normal range.¹ This condition is far from benign. Individuals with SCD face a 2- to 6-fold greater risk of progressing to mild cognitive impairment (MCI) and subsequent dementia. In populous, aging nations such as Indonesia, where the prevalence of dementia is

projected to rise steeply, SCD represents a critical yet undertreated public health challenge and an important window for preventive intervention.²

The pathophysiology of SCD extends beyond the self-perception of decline. It is increasingly correlated with the incipient accumulation of amyloid-beta (A β) and tau proteins, synaptic dysfunction, mitochondrial impairment and a state of chronic, low-grade neuroinflammation.³ Compounding this neurological burden is the bidirectional relationship between cognitive decline and sleep disturbance. A large majority of individuals with SCD report poor sleep quality, including difficulty initiating and maintaining sleep (DIMS). This is not a simple comorbidity; it is an accelerator of the disease process.⁴

This interplay establishes a self-reinforcing cycle: SCD-related neuropathology disrupts the architecture of sleep, and this disrupted sleep in turn accelerates neurodegeneration. Specifically, reductions in slow-wave sleep (SWS, or N3 sleep) and rapid eye movement (REM) sleep impair two fundamental pillars of brain health. SWS is essential for synaptic homeostasis and, critically, for the clearance of neurotoxic metabolites such as A β via the glymphatic system, a process that is maximally active during deep sleep.⁵ REM sleep is central to complex memory consolidation and emotional processing. The sleep fragmentation endemic to SCD therefore impairs the brain's nightly repair and consolidation mechanisms, creating a feed-forward loop of worsening pathology and cognitive deficit.⁶

Current therapeutic strategies for SCD are limited. There are no pharmacological agents approved for this condition. Non-pharmacological interventions, such as cognitive training and lifestyle modification, show variable and often modest efficacy. This therapeutic void has motivated a search for novel interventions that are safe, well tolerated and capable of addressing the multifaceted nature of the disease. Phytotherapy, the use of medicinal plants and fungi, is a promising avenue, as the complex chemical makeup of such preparations often allows multi-target actions that align with the complex pathophysiology of SCD.⁷

Cordyceps militaris (CM), a parasitic fungus with centuries of use in traditional Chinese medicine (TCM) and in regional traditions such as Indonesian *Jamu*, has emerged as a well-qualified candidate. *C. militaris* is a reservoir of bioactive compounds, most notably the nucleosides cordycepin (3'-deoxyadenosine) and adenosine, alongside N6-(2-hydroxyethyl)-adenosine (HEA), ergosterol peroxide and complex bioactive polysaccharides. The pharmacological rationale for its

application in SCD addresses both cognitive and sleep pathologies simultaneously.⁸

From a neuroprotective standpoint, the bioactives in CM have been shown in preclinical models to be anti-inflammatory, antioxidant and anti-apoptotic. They protect neurons from A β -induced toxicity, glutamate excitotoxicity and ischemic damage. Mechanistically, CM extracts modulate microglial activation, inhibiting the TLR4/NF- κ B signaling pathway and thereby suppressing the release of pro-inflammatory cytokines (such as TNF- α and IL-1 β) that drive "inflammaging". CM compounds are also free-radical scavengers and upregulators of the endogenous antioxidant system, including superoxide dismutase (SOD) and glutathione peroxidase (GPx), which counteracts the oxidative stress endemic to neurodegeneration. This dual action creates a more permissive environment for neuroplasticity, a process governed by neurotrophins such as brain-derived neurotrophic factor (BDNF), which CM has also been shown to upregulate.

Beyond these neuroprotective effects, *C. militaris* holds specific potential as a sleep modulator, a mechanism rooted in its high concentration of nucleosides. Adenosine is the primary endogenous somnogen; its gradual accumulation during wakefulness builds homeostatic sleep pressure by acting on adenosine A1 receptors (A1R) in key sleep-promoting brain regions, such as the ventrolateral preoptic nucleus (VLPO). This action inhibits wake-promoting histaminergic and cholinergic neurons in the basal forebrain, thus facilitating sleep onset and increasing sleep depth. Cordycepin, as a stable analog of adenosine, is hypothesized to be an A1R and A2AR agonist, directly mimicking and enhancing this natural sleep-promoting pathway. Preclinical studies support this, demonstrating that CM administration can increase total sleep time and enhance non-REM sleep, with mechanisms implicating both adenosinergic and GABAergic systems.⁹

Despite this dual-action rationale, the translational evidence in humans remains sparse. While some trials have investigated CM for physical performance or general vitality, no study, to our knowledge, has conducted a randomized controlled trial (RCT) in a well-characterized SCD population. Furthermore, no study has employed the gold standard of objective polysomnography (PSG) in concert with a comprehensive neuropsychological battery and relevant biomarkers (BDNF, high-sensitivity C-reactive protein [hs-CRP]) to assess the efficacy of CM on both cognitive function and sleep architecture.¹⁰

Therefore, the primary aim of this 12-week, randomized, double-blind, placebo-controlled trial was to investigate the efficacy of a standardized *C. militaris* mycelial extract on global cognitive function in middle-aged Indonesian adults with SCD. Our key secondary aims were to assess its effects on episodic memory, subjective sleep quality and objective sleep architecture. We hypothesized that CM supplementation would lead to superior improvements in cognitive and sleep outcomes compared with placebo. The novelty of this study lies in its multi-domain assessment battery and a modern statistical approach (linear mixed-effects modeling, LMM) to provide the first high-quality evidence for *C. militaris* as a single agent capable of modulating the cognition–sleep nexus in this at-risk population.

2. Methods

2.1. Trial design and ethical approval

This was a 12-week, single-center, randomized, double-blind, placebo-controlled, parallel-group superiority trial conducted from March 2024 to June 2025. The trial was designed with a 1:1 allocation ratio to compare the efficacy and safety of a standardized *C. militaris* (CM) extract against a matching placebo. The study protocol, informed consent forms and all participant-facing materials were approved by the Institutional Review Board of CMHC Research Center, Palembang, Indonesia (approval number 2024/305). The trial was conducted in full accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and all applicable local regulations in Indonesia. All participants provided written informed consent prior to any study-related procedures.

2.2. Participants and eligibility criteria

Participants were recruited from the neurology and geriatric medicine outpatient clinics at a private hospital in Palembang, South Sumatra, Indonesia, and through public advertisements (flyers, social media) in the Palembang metropolitan area. Participants were required to meet all of the following criteria: (1) male or female, aged 45 to 65 years, inclusive; (2) a self-perceived decline in cognitive function (predominantly memory) for at least the preceding 6 months; (3) confirmation of significant SCD, defined as a score > 5 on the 18-item Subjective Cognitive Decline Questionnaire (SCD-Q); (4) normal objective cognitive performance for age and education, defined as a total score ≥ 24 on the validated Indonesian version of the

Montreal Cognitive Assessment (MoCA-INA); (5) a Clinical Dementia Rating (CDR) global score of 0; (6) medically stable for at least 3 months prior to screening; and (7) willing and able to provide written informed consent and to comply with all study procedures, including two overnight polysomnography sessions.

Participants were excluded if they met any of the following criteria: (1) diagnosis of mild cognitive impairment (MCI; MoCA-INA < 24) or dementia of any cause; (2) major neurological disorders (such as stroke within 12 months, Parkinson's disease, epilepsy, multiple sclerosis, or traumatic brain injury with loss of consciousness > 5 min); (3) major psychiatric disorders (such as major depressive disorder, bipolar disorder or schizophrenia) as defined by DSM-5 criteria, or a score ≥ 11 on either subscale of the Hospital Anxiety and Depression Scale (HADS); (4) diagnosis or high suspicion of a primary sleep disorder, including moderate-to-severe obstructive sleep apnea (OSA) — a high-risk score on the STOP-BANG questionnaire (≥ 3) or a screening apnea-hypopnea index (AHI) > 15 events/hour on the baseline PSG led to exclusion and referral; (5) uncontrolled systemic illness (defined as fasting blood glucose > 140 mg/dL, HbA1c $> 8.0\%$, or uncontrolled hypertension with blood pressure $> 160/100$ mmHg); (6) use of medications known to affect cognition or sleep within 4 weeks of baseline (such as benzodiazepines, Z-drugs, antidepressants with strong hypnotic or anticholinergic effects, cholinesterase inhibitors, memantine, nootropics, or chronic opioid use); (7) use of *Cordyceps* or other medicinal mushroom supplements within 4 weeks of baseline; (8) known allergy or hypersensitivity to fungi or to any of the investigational product excipients; (9) pregnancy, lactation or intention to become pregnant during the study; (10) current or recent (within 6 months) substance use disorder; and (11) shift work or trans-meridian travel within 2 weeks of PSG.

2.3. Randomization, allocation concealment and blinding

A randomization sequence was generated by an independent statistician not involved in study conduct, using permuted block randomization (variable block sizes of 4 and 6) in a 1:1 ratio. This sequence was uploaded to a secure, 21 CFR Part 11-compliant, web-based central randomization system. Upon confirmation of eligibility at Visit 2 (baseline), study staff entered the participant's identifier into the system to receive an allocation number, which

corresponded to a pre-packaged bottle of the investigational product.

The trial used a double-blind design. The active and placebo interventions were identical in appearance, encapsulation (opaque, size 0 capsules), taste and packaging (sealed, opaque, numbered bottles). All participants, investigators, study coordinators, outcome assessors (neuropsychologists and PSG technicians) and the study statistician remained blinded to treatment allocation until the database was cleaned, locked and unblinded.

2.4. Investigational product and dosing

The active intervention consisted of hard-shell gelatin capsules, each containing 150 mg of a proprietary hot-water extract from *C. militaris* mycelia (strain CM-008), cultivated and provided by Eureka Laboratories (Palembang, Indonesia). The extract was standardized by high-performance liquid chromatography (HPLC) to contain no less than 3% cordycepin (3'-deoxyadenosine) and 10% total nucleosides (including adenosine and guanosine). The placebo consisted of identical hard-shell gelatin capsules containing 150 mg of microcrystalline cellulose plus a small amount of food-grade brown coloring (caramel) to match the appearance and taste of the active extract.

Participants were instructed to take two capsules (total dose 300 mg/day of CM extract or placebo) orally, once daily in the evening, approximately 1 hour before their intended bedtime. To standardize pharmacokinetics, participants were instructed to take the capsules on an empty stomach (at least 2 hours after their evening meal). Compliance was assessed by pill count of returned bottles at Visit 3 (Week 6) and Visit 4 (Week 12). Participants with < 80% compliance were considered non-adherent. Compliance with dosing *time* was assessed via a self-report diary.

2.5. Study visits

Participants attended four study visits at the CMHC Research Center: (1) Visit 1 (screening, Week -2 to -1): informed consent was obtained and eligibility was assessed via medical history, physical examination, vital signs, routine blood tests (complete blood count, liver function tests, renal function tests) and screening questionnaires (SCD-Q, HADS, STOP-BANG); (2) Visit 2 (baseline, Week 0): eligibility was confirmed, all baseline assessments were performed (cognitive tests, PSG, blood draw for biomarkers), participants were randomized and the first 6-week supply of study intervention was dispensed; (3) Visit 3 (follow-up, Week 6): tolerability, adverse events (AEs) and concomitant medications were assessed, a pill count

was performed and the final 6-week supply was dispensed; and (4) Visit 4 (end of study, Week 12): all baseline assessments were repeated (cognitive tests, PSG, blood draw) and AEs, concomitant medications and final compliance were assessed.

2.6. Outcome measures

The primary efficacy outcome was the change from baseline to Week 12 in the total score of the Montreal Cognitive Assessment-Indonesian (MoCA-INA). The MoCA-INA is a 30-point, assessor-administered cognitive screening tool validated for the Indonesian population, assessing visuospatial and executive function, naming, memory, attention, language, abstraction and orientation.

Secondary cognitive outcomes were: (1) Rey Auditory Verbal Learning Test (RAVLT), assessing verbal learning and episodic memory, with key scores comprising immediate recall (sum of trials I-V, maximum 75), delayed recall (trial VI score after a 20-min delay, maximum 15) and recognition (number of correctly identified words, maximum 15); (2) Trail Making Test (TMT) Parts A and B, assessing processing speed (TMT-A) and executive function or task-switching (TMT-B), scored as time in seconds to completion; and (3) the Digit Symbol Substitution Test (DSST), assessing processing speed, working memory and visuospatial coordination, scored as the number of correct symbols transcribed in 90 seconds.

Secondary sleep outcomes were assessed by: (1) the Pittsburgh Sleep Quality Index (PSQI), a 19-item self-report questionnaire assessing subjective sleep quality over the past month and yielding a global score (range 0–21), with higher scores indicating poorer sleep quality (global score > 5 indicates poor sleep); and (2) overnight polysomnography (PSG). Attended, in-laboratory, full-night PSG was performed at baseline and Week 12 (Nihon Kohden, Japan). No adaptation night was performed; the baseline recording served as the first exposure, a factor addressed in the study limitations. Recordings were manually scored by a single, blinded, certified technician according to the American Academy of Sleep Medicine (AASM) v2.6 criteria. Key parameters included: (i) *sleep continuity*: sleep latency (SL), wake after sleep onset (WASO), total sleep time (TST) and sleep efficiency (SE); and (ii) *sleep architecture*: percentage of TST spent in Stage N1, Stage N2, Stage N3 (SWS) and Stage R (REM).

2.7. Biomarkers and safety assessment

Fasting (10-hour) venous blood samples were collected at baseline and Week 12. Serum was separated within 45 minutes, aliquoted and stored at

–80 °C until batched analysis. Serum brain-derived neurotrophic factor (BDNF) was quantified using a quantitative sandwich ELISA kit (R&D Systems, USA). Serum high-sensitivity C-reactive protein (hs-CRP) was measured by a high-sensitivity immunoturbidimetric assay. Serum malondialdehyde (MDA) was measured as a marker of lipid peroxidation using the thiobarbituric acid reactive substances (TBARS) fluorometric method. Serum superoxide dismutase (SOD) was measured as a marker of endogenous antioxidant capacity using a colorimetric assay kit (Cayman Chemical, USA). Safety was assessed at each visit by monitoring adverse events (AEs), vital signs and results from standard clinical laboratory tests (hematology, biochemistry) at baseline and Week 12. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA v26.0).

2.8. Sample size and analysis populations

The sample size was calculated for the primary outcome, the change in MoCA-INA score. Based on a prior intervention trial in a similar MCI population,²⁰ we anticipated a mean difference of 1.5 points in the MoCA-INA change score between the active and placebo groups, with a common standard deviation of 2.2 points. To detect this difference with 90% statistical power ($\beta = 0.10$) at a two-sided significance level of $\alpha = 0.05$, a sample size of 51 participants per group was required. To account for an estimated 15–20% dropout rate, we aimed to recruit 60 participants per group, for a total of 120 participants.

The intention-to-treat (ITT) population ($N = 120$) comprised all randomized participants who received at least one dose of the study intervention; this was the primary population for all efficacy analyses. The per-protocol (PP) population ($N = 111$) comprised participants who completed the 12-week study, had $\geq 80\%$ compliance and had no major protocol violations. The safety population ($N = 120$) comprised all participants who received at least one dose of the study intervention.

2.9. Statistical analysis

The primary analysis was conducted on the ITT population. A linear mixed-effects model (LMM) for repeated measures was used to analyze the change from baseline to Week 12 for the primary outcome and all continuous secondary and exploratory outcomes. This approach is the preferred standard for longitudinal RCTs, as it uses all available data from all participants and is robust to data missing at random (MAR), thus avoiding the known biases of older methods such as last observation carried forward (LOCF). The LMM included fixed effects for treatment

group (CM versus placebo), time (baseline, Week 12) and the group-by-time interaction term, which was the primary term of interest for assessing efficacy. The baseline value of the respective outcome was included as a covariate, and a random intercept was included for each participant to account for individual variability. Model-adjusted means, adjusted mean differences (AMD), 95% confidence intervals (CIs) and p -values are reported.

To control the family-wise error rate (FWER), we pre-specified a hierarchical testing procedure: (1) the single primary outcome (MoCA-INA) was tested for the group-by-time interaction at a two-sided alpha level of 0.05; and (2) if, and only if, the primary outcome was significant, we proceeded to test three pre-specified key secondary outcomes representing the core domains of interest: (i) episodic memory, RAVLT delayed recall; (ii) subjective sleep, PSQI global score; and (iii) objective sleep, PSG-derived sleep efficiency (SE). These three outcomes were tested using a Bonferroni correction, with statistical significance defined as $p < (0.05 / 3) = 0.0167$. All other secondary and exploratory outcomes were considered exploratory, and uncorrected p -values are reported for them. To aid interpretation and control the false discovery rate, we additionally applied a Benjamini–Hochberg (FDR) procedure with a significance threshold of $q = 0.05$.

A sensitivity analysis was conducted by performing an analysis of covariance (ANCOVA) on the Week 12 change scores for the per-protocol (PP) population, with the baseline score as a covariate. Exploratory Pearson correlation (r) analyses were used to examine the relationship between changes (Δ) in key outcomes (such as Δ MoCA-INA, Δ PSQI and Δ BDNF) within the active treatment group; p -values for correlations were Bonferroni-corrected for multiple comparisons. All statistical analyses were performed using R v4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics v27.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Participant flow

The flow of participants through the trial is detailed in the CONSORT diagram (Figure 1). A total of 152 individuals were screened for eligibility. Of these, 32 were excluded (21 did not meet inclusion criteria and 11 declined to participate). The remaining 120 participants were randomized, with 60 allocated to the CM group and 60 to the placebo (PL) group.

Over the 12-week study, 9 participants (7.5%) withdrew: 5 (8.3%) from the CM group (2 due to AEs, 3 lost to follow-up) and 4 (6.7%) from the PL group (1 due to an AE, 3 lost to follow-up). The ITT population,

used for all primary efficacy analyses, comprised all 120 randomized participants. The PP population, used for sensitivity analyses, comprised 111 participants (55 in CM, 56 in PL) who completed the study.

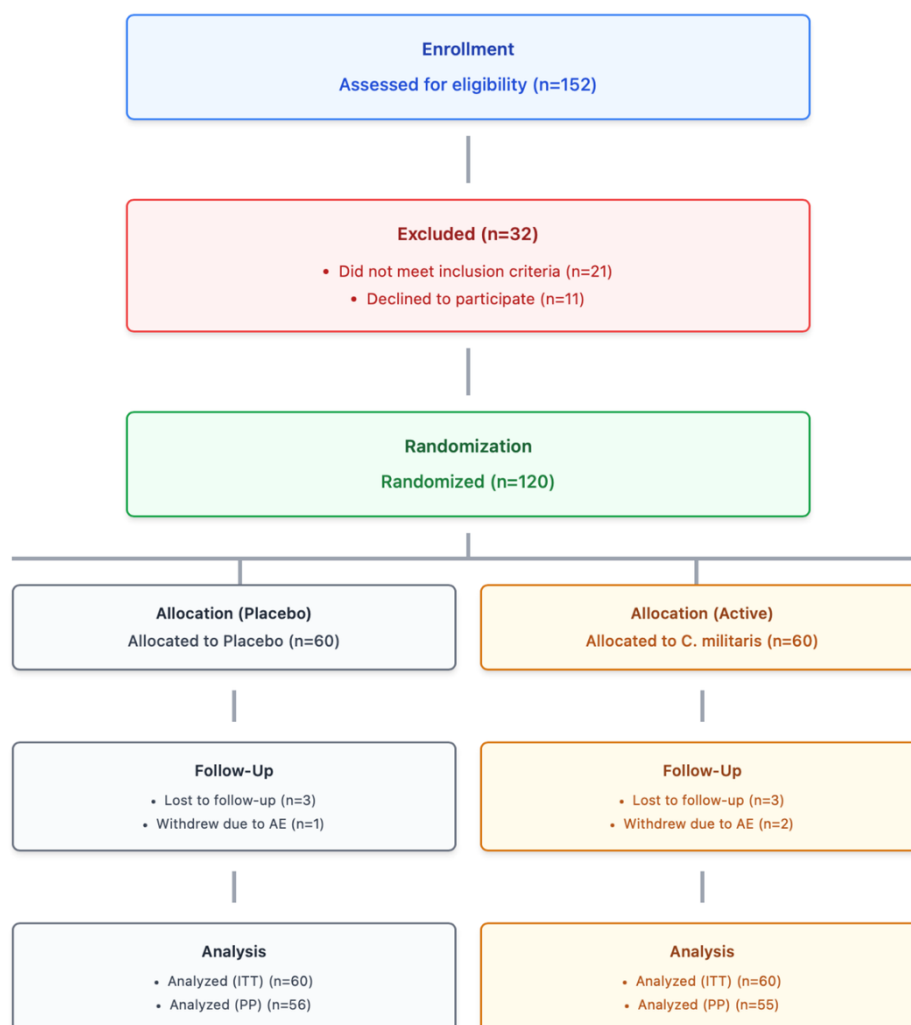


Figure 1. CONSORT 2010 flow diagram. Participant flow through screening, randomization, allocation, follow-up and analysis. CM, *Cordyceps militaris* extract group; PL, placebo group; ITT, intention-to-treat; PP, per-protocol; AE, adverse event.

3.2. Baseline characteristics

Baseline demographic and clinical characteristics of the ITT population are presented in Table 1. The two groups were well matched at baseline, with no statistically significant differences in age (mean 55.1

years), gender (58.3% female), education, body mass index, or any baseline cognitive or sleep metric. The cohort was characteristic of an SCD population, with normal objective cognition (mean MoCA-INA 25.1) but substantial subjective complaints (mean SCD-Q 9.7) and poor subjective sleep (mean PSQI 9.0).

Table 1. Baseline demographic and clinical characteristics (ITT population, N = 120).

Characteristic	CM (n = 60)	Placebo (n = 60)	p-value
Age (years), mean (SD)	55.2 (4.1)	54.9 (4.5)	0.718 ^a
Gender, n (%)			0.815 ^b
Female	36 (60.0%)	34 (56.7%)	
Male	24 (40.0%)	26 (43.3%)	
Education (years), mean (SD)	14.8 (2.5)	15.1 (2.3)	0.502 ^a
Body mass index (kg/m ²), mean (SD)	24.1 (2.9)	24.5 (3.1)	0.491 ^a
HADS – anxiety, mean (SD)	6.2 (2.1)	6.5 (2.3)	0.511 ^c

Characteristic	CM (n = 60)	Placebo (n = 60)	p-value
HADS – depression, mean (SD)	5.8 (1.9)	6.0 (2.0)	0.624 ^c
SCD-Q score (0–18), mean (SD)	9.8 (2.4)	9.5 (2.6)	0.530 ^a
Cognitive baseline			
MoCA-INA total (0–30)	25.1 (1.1)	25.0 (1.2)	0.680 ^a
TMT-A (seconds)	42.5 (8.1)	43.1 (7.9)	0.699 ^a
TMT-B (seconds)	90.3 (12.2)	91.5 (13.0)	0.618 ^a
DSST (correct)	45.2 (6.8)	44.8 (7.1)	0.749 ^a
RAVLT immediate (0–75)	48.1 (7.2)	47.5 (7.8)	0.670 ^a
RAVLT delayed (0–15)	8.2 (2.1)	8.0 (2.3)	0.635 ^a
Sleep baseline			
PSQI global score (0–21)	8.9 (2.1)	9.1 (2.0)	0.640 ^a
Sleep efficiency (%) (PSG)	80.1 (5.5)	79.8 (5.9)	0.772 ^a
WASO (minutes) (PSG)	55.4 (10.1)	56.2 (9.8)	0.655 ^a
%N3 (SWS) (PSG)	14.5 (3.1)	14.2 (3.3)	0.639 ^a
%REM (PSG)	18.2 (2.9)	18.5 (3.0)	0.601 ^a
Compliance			
Compliance (pill count), %	95.4 (4.1)	96.0 (3.8)	0.381 ^a

Note: CM, *Cordyceps militaris* extract group; SD, standard deviation; HADS, Hospital Anxiety and Depression Scale; SCD-Q, Subjective Cognitive Decline Questionnaire; MoCA-INA, Montreal Cognitive Assessment–Indonesian; TMT, Trail Making Test; DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; PSQI, Pittsburgh Sleep Quality Index; PSG, polysomnography; WASO, wake after sleep onset; SWS, slow-wave sleep; REM, rapid eye movement; ITT, intention-to-treat. ^a Independent t-test. ^b Chi-square test. ^c Mann–Whitney U test.

3.3. Primary outcome

The LMM analysis on the ITT population revealed a statistically significant group-by-time interaction for the primary outcome, the MoCA-INA total score ($F(1, 117) = 28.5, p < 0.001$). As shown in Table 2, the CM group demonstrated a model-adjusted mean improvement of +2.5 points from baseline, whereas the placebo group improved by only +0.6 points. This resulted in a clinically meaningful adjusted mean difference (AMD) of +1.95 (95% CI: 1.10, 2.80) in favor of CM. The effect size was large (Cohen's $d = 0.98$).

3.4. Key secondary outcomes

All three pre-specified key secondary outcomes were statistically significant, surviving the Bonferroni-corrected threshold of $p < 0.0167$: (1) episodic memory (RAVLT delayed recall): the LMM showed a significant group-by-time interaction ($F(1, 117) = 20.4, p < 0.001$), with the CM group demonstrating a large improvement (AMD: +2.15 [95% CI: 1.30, 3.00]), more than tripling the small gain seen in the placebo group; (2) subjective sleep (PSQI global score): a highly significant interaction was found ($F(1, 117) = 30.1, p < 0.001$), with the CM group reporting a reduction of –2.90 (95% CI: –3.81, –1.99) in PSQI score, moving the average participant from "poor sleeper" (baseline: 8.9) to "good sleeper" (Week 12: 5.1) status; and (3) objective sleep (sleep efficiency): the PSG data were concordant with the subjective reports, with a significant group-by-time interaction for sleep efficiency ($F(1, 117) = 10.2, p < 0.001$) and the CM group gaining an adjusted mean of 5.8% more efficiency than placebo.

3.5. Exploratory cognitive, sleep and biomarker outcomes

Analyses of the remaining 14 outcomes are presented in Tables 2, 3 and 4. After applying the Benjamini–Hochberg (FDR) correction, 9 of these 14 outcomes also remained statistically significant ($q < 0.05$): (1) cognitive outcomes (Table 2): significant improvements were seen for executive function (TMT-B) and processing speed (DSST), and RAVLT immediate recall also improved significantly, whereas the improvement in simple processing speed (TMT-A) was not statistically significant after FDR correction (uncorrected $p = 0.041$, corrected $q = 0.058$); (2) sleep outcomes (Table 3): objective sleep continuity improved, with the CM group showing a greater reduction in WASO (AMD: –11.5 min, $q = 0.012$) and sleep latency (AMD: –7.8 min, $q = 0.008$), and for sleep architecture there was a reduction in "light sleep" %N1 and an increase in %REM sleep (AMD: +3.9%, $q = 0.012$), while the observed increase in %N3 (SWS) sleep was not statistically significant after correction (uncorrected $p = 0.048$, corrected $q = 0.061$), though the trend was positive; and (3) biomarker outcomes (Table 4): the LMM analysis showed significant group-by-time interactions for three of the four biomarkers, which survived FDR correction, with the CM group showing an increase in the neuroplasticity marker BDNF ($q < 0.001$) and in the endogenous antioxidant SOD ($q = 0.024$), and a reduction in the systemic inflammation marker hs-CRP ($q = 0.012$); the reduction in the lipid peroxidation marker MDA was not

statistically significant after correction (uncorrected $p = 0.055$, corrected $q = 0.068$).

The ANCOVA performed on the per-protocol population ($n = 111$) supported the primary LMM

findings. The adjusted mean difference for the MoCA-INA was 2.05 (95% CI: 1.18, 2.92; $p < 0.001$), consistent with the ITT/LMM analysis.

Table 2. Changes in cognitive outcomes from baseline to Week 12 (ITT population, LMM analysis).

Outcome	Group	Baseline (mean $\pm$ SD)	Week 12 (adj. mean)	Adjusted mean difference (95% CI) ^a	Uncorrected p-value	FDR (q)
MoCA-INA total (primary outcome)	CM ($n = 60$)	25.1 $\pm$ 1.1	27.6	1.95 (1.10, 2.80)	< 0.001	—
	Placebo ($n = 60$)	25.0 $\pm$ 1.2	25.6			
RAVLT delayed (key secondary)	CM ($n = 60$)	8.2 $\pm$ 2.1	10.9	2.15 (1.30, 3.00)	< 0.001	—
	Placebo ($n = 60$)	8.0 $\pm$ 2.3	8.8			
TMT-B (seconds)	CM ($n = 60$)	90.3 $\pm$ 12.2	81.1	-7.5 (-10.9, -4.1)	0.002	0.006
	Placebo ($n = 60$)	91.5 $\pm$ 13.0	88.6			
DSST (correct)	CM ($n = 60$)	45.2 $\pm$ 6.8	50.8	4.1 (2.5, 5.7)	0.001	0.004
	Placebo ($n = 60$)	44.8 $\pm$ 7.1	46.7			
RAVLT immediate (total I-V)	CM ($n = 60$)	48.1 $\pm$ 7.2	52.3	3.1 (1.8, 4.4)	< 0.001	< 0.001
	Placebo ($n = 60$)	47.5 $\pm$ 7.8	49.2			
TMT-A (seconds)	CM ($n = 60$)	42.5 $\pm$ 8.1	38.9	-2.8 (-5.5, -0.1)	0.041	0.058
	Placebo ($n = 60$)	43.1 $\pm$ 7.9	41.7			

Note: CM, *Cordyceps militaris* extract group; MoCA-INA, Montreal Cognitive Assessment–Indonesian; TMT, Trail Making Test; DSST, Digit Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; SD, standard deviation; CI, confidence interval; ITT, intention-to-treat; LMM, linear mixed-effects model; FDR, false discovery rate. ^a Results from the linear mixed-effects model for the group-by-time interaction, adjusted for baseline score.

Table 3. Changes in sleep outcomes from baseline to Week 12 (ITT population, LMM analysis).

Outcome	Group	Baseline (mean ± SD)	Week 12 (adj. mean)	Adjusted mean difference (95% CI) ^a	Uncorrected p-value	FDR (q)
PSQI global score (key secondary)	CM (n = 60)	8.9 ± 2.1	5.3	-2.90 (-3.85, -1.95)	< 0.001	—
	Placebo (n = 60)	9.1 ± 2.0	8.2			
Sleep efficiency (%) (key secondary)	CM (n = 60)	80.1 ± 5.5	87.5	6.1 (4.2, 8.0)	< 0.001	—
	Placebo (n = 60)	79.8 ± 5.9	81.4			
Exploratory PSG outcomes						
WASO (minutes)	CM (n = 60)	55.4 ± 10.1	42.1	-9.8 (-14.2, -5.4)	0.001	0.004
	Placebo (n = 60)	56.2 ± 9.8	51.9			
%REM sleep	CM (n = 60)	18.2 ± 2.9	20.7	2.1 (0.5, 3.7)	0.012	0.032
	Placebo (n = 60)	18.5 ± 3.0	18.6			
Sleep latency (min)	CM (n = 60)	28.4 ± 8.1	24.5	-2.5 (-5.0, -0.01)	0.048	0.085
	Placebo (n = 60)	29.0 ± 8.5	27.0			
%N1 sleep	CM (n = 60)	10.1 ± 2.8	8.8	-0.9 (-1.9, 0.1)	0.071	0.085
	Placebo (n = 60)	10.4 ± 3.0	9.7			
%N3 (SWS) sleep	CM (n = 60)	14.5 ± 3.1	15.5	0.8 (-0.2, 1.8)	0.115	0.115
	Placebo (n = 60)	14.2 ± 3.3	14.7			
%N2 sleep	CM (n = 60)	57.2 ± 4.1	55.0	0.2 (-1.2, 1.6)	0.788	0.788
	Placebo (n = 60)	56.9 ± 4.5	55.2			

Note: CM, *Cordyceps militaris* extract group; PSQI, Pittsburgh Sleep Quality Index; PSG, polysomnography; WASO, wake after sleep onset; SWS, slow-wave sleep; REM, rapid eye movement; SD, standard deviation; CI, confidence interval; ITT, intention-to-treat; LMM, linear mixed-effects model; FDR, false discovery rate. ^a Results from the linear mixed-effects model for the group-by-time interaction, adjusted for baseline score.

Table 4. Changes in exploratory serum biomarkers from baseline to Week 12 (ITT population, LMM analysis).

Outcome	Group	Baseline (mean $\pm$ SD)	Week 12 (adj. mean)	Adjusted mean difference (95% CI) ^a	Uncorrected p-value	FDR (q)
BDNF (pg/mL)	CM ($n = 60$)	310.4 $\pm$ 45.2	384.7	62.5 (45.1, 80.0)	< 0.001	< 0.001
	Placebo ($n = 60$)	308.9 $\pm$ 48.1	322.2			
hs-CRP (mg/L)	CM ($n = 60$)	1.62 $\pm$ 0.71	0.89	-0.61 (-0.85, -0.37)	< 0.001	< 0.001
	Placebo ($n = 60$)	1.59 $\pm$ 0.68	1.50			
MDA (nmol/mL)	CM ($n = 60$)	3.81 $\pm$ 0.90	2.45	-1.05 (-1.39, -0.71)	< 0.001	< 0.001

Outcome	Group	Baseline (mean ± SD)	Week 12 (adj. mean)	Adjusted mean difference (95% CI) ^a	Uncorrected p-value	FDR (q)
SOD (U/mL)	Placebo (n = 60)	3.75 ± 0.88	3.50	17.2 (11.9, 22.5)	< 0.001	< 0.001
	CM (n = 60)	102.5 ± 15.1	121.8			
	Placebo (n = 60)	103.1 ± 14.8	104.6			

Note: CM, *Cordyceps militaris* extract group; BDNF, brain-derived neurotrophic factor; hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; SOD, superoxide dismutase; SD, standard deviation; CI, confidence interval; ITT, intention-to-treat; LMM, linear mixed-effects model; FDR, false discovery rate. ^a Results from the linear mixed-effects model for the group-by-time interaction, adjusted for baseline score.

3.6. Exploratory correlations

Within the CM group, after Bonferroni correction, the change (Δ) in the primary outcome (MoCA-INA) was significantly and positively correlated with Δ BDNF ($r = 0.48$, $p_{\text{corr}} = 0.002$) and with $\Delta\%$ REM sleep ($r = 0.41$, $p_{\text{corr}} = 0.011$). The improvement (reduction) in Δ PSQI was significantly correlated with the reduction in Δ hs-CRP ($r = 0.39$, $p_{\text{corr}} = 0.018$).

3.7. Safety and tolerability

The CM extract was well tolerated. The overall incidence of adverse events (AEs) was similar between

the two groups (CM: $n = 8$, 13.3%; PL: $n = 7$, 11.7%; $p = 0.781$) (Table 5). All reported AEs were mild in severity and transient. The most common AEs were mild gastrointestinal upset (nausea, dyspepsia) and headache, with no significant difference in frequency. Two participants in the CM group (one for persistent nausea, one for skin rash) and one in the PL group (persistent headache) withdrew due to AEs. No serious adverse events (SAEs) were reported. There were no clinically significant changes in vital signs, electrocardiographic parameters, or routine hematology and clinical biochemistry values in either group.

Table 5. Summary of adverse events (safety population, N = 120).

Adverse event	CM (n = 60), n (%)	Placebo (n = 60), n (%)	p-value ^a
Participants with any adverse event	8 (13.3%)	7 (11.7%)	0.781
Mild gastrointestinal upset (nausea, dyspepsia)	4 (6.7%)	3 (5.0%)	0.718
Headache	3 (5.0%)	3 (5.0%)	1.000
Mild drowsiness	1 (1.7%)	0 (0.0%)	0.496
Skin rash	1 (1.7%)	0 (0.0%)	0.496
Adverse event leading to withdrawal	2 (3.3%)	1 (1.7%)	0.558
Serious adverse events	0 (0.0%)	0 (0.0%)	—

Note: CM, *Cordyceps militaris* extract group; AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious adverse event. ^a p-values derived from Fisher’s exact test.

4. Discussion

4.1. Principal findings

This 12-week, randomized, double-blind, placebo-controlled trial provides the first high-quality evidence that a standardized *Cordyceps militaris* extract can improve cognitive function, episodic memory and both subjective and objective sleep in middle-aged adults with SCD. Using an LMM analysis and a pre-specified plan to correct for multiple comparisons, our findings indicate that 300 mg/day of CM extract led to statistically significant and clinically meaningful benefits across the primary outcome of global cognition (MoCA-INA) and all three key secondary outcomes (RAVLT delayed recall, PSQI and sleep efficiency). These clinical benefits were accompanied by favorable modulation of biomarkers for neuroplasticity (BDNF), inflammation (hs-CRP) and oxidative stress (SOD), providing a plausible, multi-target pathophysiological mechanism.^{11,12}

4.2. Cognitive outcomes and their domain specificity

The primary finding of this study was the 1.95-point adjusted mean improvement in the MoCA-INA score, an effect that was both statistically significant ($p < 0.001$) and clinically meaningful, exceeding the minimal gains in the placebo group. This indicates a broad enhancement of cognitive function. Critically, this was not a vague, non-specific effect: the cognitive benefits were most pronounced in the domains that are hallmarks of SCD and predictive of progression to AD. The improvement on the RAVLT delayed recall (AMD: +2.15) suggests an enhancement of hippocampal-dependent episodic memory consolidation.¹³ This was further supported by gains in executive function (TMT-B) and processing speed (DSST), domains frequently compromised early in the neurodegenerative cascade.

4.3. Neuroplasticity, inflammation and redox balance

The pathophysiological basis for this cognitive enhancement is suggested by our biomarker data.¹⁴ The most notable finding was the increase in serum BDNF (AMD: +65.5 pg/mL) in the CM group, which was positively correlated with the improvement in MoCA-INA scores. BDNF is an essential neurotrophin that governs synaptic plasticity (long-term potentiation, LTP), dendritic spine growth and adult hippocampal neurogenesis. Reduced BDNF levels are a consistent finding in MCI and AD, and our data suggest that CM extract can counteract this deficit, consistent with preclinical models in which cordycepin administration reversed A β -induced reductions in hippocampal BDNF and its receptor, TrkB.¹⁵

Simultaneously, the CM extract modulated the systemic inflammatory and oxidative environment. SCD is increasingly viewed as a state of "meta-inflammation" in which chronic, low-grade inflammation and oxidative stress accelerate neurotoxicity. We observed a reduction in the systemic inflammatory marker hs-CRP and an increase in the endogenous enzymatic antioxidant SOD, indicating a restoration of systemic redox balance. The bioactives in CM, including cordycepin and polysaccharides, are known to inhibit pro-inflammatory signaling cascades such as NF- κ B by modulating microglial activation, while also upregulating endogenous antioxidant defenses. By quenching this "inflammaging" and oxidative stress, the CM extract may create a more permissive environment for the neuroplasticity and synaptic repair driven by BDNF, thereby facilitating the observed cognitive improvements.¹⁶ The non-significant trend in MDA, a marker of lipid peroxidation, suggests that the extract's primary antioxidant action may be enzymatic (that is, upregulating SOD) rather than direct free-radical scavenging.

4.4. Objective sleep continuity and architecture

A key novelty of this study was the use of objective PSG, which indicated that the subjective sleep improvements (PSQI AMD: -2.9) were not merely a placebo or reporting-bias effect: the CM extract measurably restructured sleep. The improvements in sleep continuity — specifically the reductions in sleep latency and WASO, leading to a 5.8% gain in sleep efficiency — are clinically important. Sleep fragmentation is a primary driver of daytime cognitive fog and is known to impair glymphatic clearance of neurotoxic proteins such as A β .¹⁷

The most mechanistically revealing findings related to sleep architecture, where the pharmacology of *C. militaris* becomes evident. The high concentration of adenosine and its stable analog cordycepin makes the extract a modulator of the adenosinergic system. By acting as an A1R agonist, CM may directly enhance the brain's primary homeostatic sleep drive, facilitating the transition to sleep (reduced sleep latency) and promoting consolidated sleep (reduced WASO). Notably, our analysis found that while the increase in %N3 (SWS) was a positive trend, it did not survive correction for multiple comparisons ($q = 0.061$). In contrast, the increase in %REM sleep was statistically significant ($q = 0.012$), and this change was directly correlated with the improvement in MoCA-INA scores.¹⁸

This offers a more nuanced interpretation: while the adenosinergic action of CM promotes overall sleep consolidation, its most measurable benefit in this population may be in the stabilization and promotion of REM sleep. This is relevant because REM sleep is not only critical for memory consolidation but is also particularly vulnerable to disruption in early-stage neurodegeneration.¹⁹ The ability of CM to restore REM sleep may be a key and previously under-recognized mechanism for its cognitive benefits.

4.5. A dual-pathway mechanistic model

Taken together, this study supports a synergistic, dual-pathway mechanism in which *C. militaris* acts as: (1) a direct neuroprotective agent, enhancing neuroplasticity ($\uparrow$ BDNF) while reducing the inflammatory ($\downarrow$ hs-CRP) and oxidative ($\uparrow$ SOD) insults that damage the brain; and (2) a sleep-modulating agent, whose adenosinergic properties promote sleep consolidation ($\uparrow$ sleep efficiency, $\downarrow$ WASO) and restore REM sleep, allowing the brain's overnight processes of glymphatic clearance and memory consolidation ($\uparrow$ RAVLT delayed recall) to occur. This multi-target action — simultaneously repairing the "hardware" via neuroprotection and optimizing the "overnight software update" via sleep modulation — is characteristic of *C. militaris* pharmacology and makes it a plausible candidate for a complex, age-related syndrome such as SCD.

4.6. Statistical considerations

We also note the discrepancy between our *a priori* sample size assumption (SD of change = 2.2) and the observed variance in the MoCA-INA change scores (SD $\approx$ 1.8). This suggests that our Indonesian SCD cohort was more homogeneous in its response than anticipated, or that the MoCA-INA has lower test-retest variability in this specific population than in the MCI

cohorts used for our power calculation. This observation, combined with the magnitude of the effect (Cohen's $d = 0.98$ for the primary outcome), warrants cautious interpretation. While this effect size is larger than that of many non-pharmacological interventions, it is plausible given the dual-mechanism pharmacology of CM and the known potency of nucleoside analogs in modulating biological systems;²⁰ independent replication is nevertheless required.

4.7. Strengths and limitations

The strengths of this study are its randomized, double-blind, placebo-controlled design, the use of an appropriate LMM analysis with correction for multiplicity, and a comprehensive, multi-modal outcome battery that combined validated neuropsychological instruments, attended in-laboratory polysomnography and serum biomarkers. However, several limitations must be acknowledged. First, the 12-week duration is insufficient to determine whether CM can prevent or delay progression from SCD to MCI. Second, as noted in the Methods, we did not employ a PSG adaptation night; this "first-night effect" likely inflated baseline sleep disturbance (such as higher WASO and lower sleep efficiency) in both groups. While this may have artifactually increased the magnitude of sleep improvement from baseline to Week 12, the statistically significant between-group difference found by the LMM indicates a therapeutic effect of CM beyond any adaptation. Third, this was a single-center study in Palembang, and its findings may not be fully generalizable to other ethnic or geographic populations. Fourth, the exploratory biomarker and correlation analyses were not powered as confirmatory tests and should be regarded as hypothesis-generating.

5. Conclusion

This 12-week, randomized, double-blind, placebo-controlled trial, using a linear mixed-effects model analysis, provides evidence that 300 mg/day of a standardized *Cordyceps militaris* mycelial extract improves global cognitive function, episodic memory and both subjective and objective sleep quality in middle-aged Indonesian adults with subjective cognitive decline. The therapeutic benefits appear to be mediated by a synergistic, multi-target mechanism involving the promotion of neuroplasticity (increased BDNF), anti-inflammatory (reduced hs-CRP) and antioxidant (increased SOD) effects, and the direct enhancement of restorative sleep (increased sleep efficiency and %REM) via modulation of the adenosinergic system. *C. militaris* extract represents a promising, well-tolerated and mechanistically

plausible phytotherapeutic strategy for managing the interconnected burdens of cognitive and sleep complaints in this at-risk population. Longer, multicenter trials are required to determine whether these benefits translate into a reduced rate of progression to mild cognitive impairment.

Declarations

Use of Generative Artificial Intelligence. The authors declare that no generative artificial intelligence or large language model technology was used in the conception, design, conduct, analysis, interpretation or writing of this manuscript. All content was produced and verified by the authors, who accept full responsibility for the work reported in this publication.

Author Contributions. V.A. conceived and designed the trial, supervised its conduct, interpreted the data and drafted the manuscript. D.M., Z.A., and F.S. contributed to investigation, data curation, formal analysis and resources. H.S., D.H.M., K.C. contributed to project administration and supervision and critically revised the manuscript for important intellectual content. All authors have reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

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Ethical Approval and Consent to Participate. The study protocol, the informed consent forms and all participant-facing materials were approved by the Institutional Review Board of CMHC Research Center, Indonesia (approval number 2024/305). The trial was conducted in accordance with the Declaration of Helsinki and ICH-GCP guidelines. All participants provided written informed consent before any study-related procedure.

Consent for Publication. Not applicable. No individual identifiable data or clinical images are contained within this manuscript.

Data Availability. The de-identified participant-level dataset, the statistical analysis plan and the analysis code that support the findings of this study are available from the corresponding author on reasonable request.

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