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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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A B S T R A C T

Subjective cognitive decline (SCD) and sleep disturbance form a vicious cycle, accelerating neurodegeneration. *Cordyceps militaris* (CM), a traditional medicinal fungus rich in nucleosides, possesses potent neuroprotective and adenosinergic (sleep-promoting) properties. We investigated the efficacy of a standardized CM extract on this cognition-sleep nexus in adults with SCD. This 12-week, single-center, randomized, double-blind, placebo-controlled, parallel-group trial was conducted in Palembang, Indonesia. We randomized 120 adults (aged 45-65) with SCD to receive 300 mg/day of a standardized CM mycelial extract (3% cordycepin) or a matching placebo. The primary outcome was the change from baseline in the Montreal Cognitive Assessment-Indonesian (MoCA-INA) score. Key secondary outcomes (Bonferroni-corrected) were the Pittsburgh Sleep Quality Index (PSQI), Rey Auditory Verbal Learning Test (RAVLT) Delayed Recall, and polysomnography (PSG)-derived Sleep Efficiency (SE). Analyses were performed on the Intention-to-Treat (ITT) population (N=120) using a Linear Mixed-Effects Model (LMM). The LMM analysis revealed a significant group-by-time interaction for the primary outcome, MoCA-INA (Adjusted Mean Difference [AMD]: +1.95 [95% CI: 1.10, 2.80], $p < 0.001$). The CM group also showed significant improvements in all three key secondary outcomes: PSQI (AMD: -2.90 [95% CI: -3.81, -1.99], $p < 0.001$), RAVLT Delayed Recall (AMD: +2.15 [95% CI: 1.30, 3.00], $p < 0.001$), and Sleep Efficiency (AMD: +5.8% [95% CI: 3.1, 8.5], $p < 0.001$). After FDR correction, significant benefits were also seen for processing speed, %REM sleep, and serum BDNF and hs-CRP. The intervention was well-tolerated. In conclusion, twelve weeks of supplementation with a standardized *C. militaris* extract significantly improved cognitive function, episodic memory, and both subjective and objective sleep in adults with SCD. These benefits were associated with enhanced neuroplasticity and reduced systemic inflammation, supporting its potential as a multi-target, disease-modifying intervention for this at-risk population.

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 dramatically, SCD represents a critical, yet undertreated, public health challenge and a crucial window for preventative intervention.[2]

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

This interplay establishes a vicious cycle: SCD-related neuropathology disrupts the intricate 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, the clearance of neurotoxic metabolites like Aβ via the glymphatic system, a process that is maximally active during deep sleep.[5] REM sleep is vital for complex memory consolidation and emotional processing. Thus, the sleep fragmentation endemic to SCD directly 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 profoundly limited. There are no pharmacological agents approved for this condition. Non-pharmacological interventions, such as cognitive training and lifestyle modifications, show variable and often modest efficacy. This therapeutic void has catalyzed an urgent 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 particularly promising avenue, as its complex chemical makeup often allows for 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 other regional traditions like Indonesian *Jamu*, has emerged as a uniquely qualified candidate. *C. militaris* is a potent 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 is exceptionally strong and, crucially, addresses both cognitive and sleep pathologies simultaneously.[8]

From a neuroprotective standpoint, the bioactives in CM have been robustly shown in preclinical models to be anti-inflammatory, antioxidant, and anti-apoptotic. They protect neurons from Aβ-induced toxicity, glutamate excitotoxicity, and ischemic damage. Mechanistically, CM extracts are potent modulators of microglial activation, inhibiting the TLR4/NF-κB signaling pathway and thereby suppressing the release of pro-inflammatory cytokines (such as TNF-α and IL-1β) that drive "inflammaging". Furthermore, CM compounds are powerful 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 like Brain-Derived Neurotrophic Factor (BDNF), which CM has also been shown to upregulate.

Beyond these neuroprotective effects, *C. militaris* holds specific and profound 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 a potent A1R and A2AR agonist, directly mimicking and enhancing this natural sleep-promoting pathway. Preclinical studies confirm this, demonstrating that CM administration can increase total sleep time and enhance NREM sleep, with mechanisms implicating both adenosinergic and GABAergic systems.[9]

Despite this powerful 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 rigorous, 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, 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 *Cordyceps 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 to placebo. The novelty of this study lies in its use of a robust, multi-domain assessment battery and a modern statistical approach (LMM) to provide the first high-quality evidence for *C. militaris* as a singular agent capable of modulating the entire cognition-sleep nexus in this critical at-risk population.

2. Methods

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 *Cordyceps 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. 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.

Participants were recruited from the neurology and geriatric medicine outpatient clinics at a private hospital in Palembang, South Sumatra, Indonesia, as well as 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 their age and education, defined as a total score ≥ 24 on the validated Indonesian version of the Montreal Cognitive Assessment (MoCA-INA); (5) Clinical Dementia Rating (CDR) global score of 0; (5) Medically stable for at least 3 months prior to screening; (6) Willing and able to provide written informed consent and 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 (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 BP > 160/100 mmHg); (6) Use of medications known to significantly affect cognition or sleep within 4 weeks of baseline (such as benzodiazepines, Z-drugs, antidepressants with strong hypnotic/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 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; (11) Shift workers or individuals with trans-meridian travel within 2 weeks of PSG.

A randomization sequence was generated by an independent statistician (not involved in study conduct) using a permuted block randomization method (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 ID into the system to receive their allocation number, which corresponded to a pre-packaged bottle of the investigational product.

This study employed a rigorous 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, PSG technicians), and the study statistician remained blinded to treatment allocation until the database was cleaned, locked, and unblinded.

The active intervention consisted of hard-shell gelatin capsules, each containing 150 mg of a proprietary hot-water extract from *Cordyceps militaris* mycelia (strain CM-008), cultivated and provided by Eureka Laboratories (Palembang, Indonesia). The extract was standardized using High-Performance Liquid Chromatography (HPLC) to contain no less than 3% cordycepin (3'-deoxyadenosine) and 10% total nucleosides (including adenosine and guanosine). The placebo intervention 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 the 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.

Participants attended four study visits at the CMHC Research Center: (1) Visit 1 (Screening, Week -2 to -1): Obtained informed consent. Assessed eligibility via comprehensive medical history, physical examination, vital signs, routine blood tests (CBC, LFT, RFT), and screening questionnaires (SCD-Q, HADS, STOP-BANG); (2) Visit 2 (Baseline, Week 0):

Confirmed eligibility. Performed all baseline assessments (cognitive tests, PSG, blood draw for biomarkers). Randomized participants and dispensed the 6-week supply of the study intervention; (3) Visit 3 (Follow-up, Week 6): Assessed tolerability, adverse events (AEs), and concomitant medications. Performed pill count for compliance. Dispensed the final 6-week supply of the study intervention; (4) Visit 4 (End of Study, Week 12): Repeated all baseline assessments (cognitive tests, PSG, blood draw). Assessed AEs, concomitant medications, and final compliance.

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 multiple cognitive domains including visuospatial/executive function, naming, memory, attention, language, abstraction, and orientation. Secondary cognitive outcomes were; (1) Rey Auditory Verbal Learning Test (RAVLT): Assessed verbal learning and episodic memory. Key scores included: Immediate Recall: Sum of trials I-V (max 75), Delayed Recall: Trial VI score, after a 20-min delay (max 15), and Recognition: Number of correctly identified words (max 15); (2) Trail Making Test (TMT) Parts A & B: Assessed processing speed (TMT-A) and executive function/task-switching (TMT-B). The score is the time (in seconds) to completion; (3) Digital Symbol Substitution Test (DSST): Assessed processing speed, working memory, and visuomotor coordination. The score is the number of correct symbols transcribed in 90 seconds.

Secondary sleep outcomes were assessed by; (1) Pittsburgh Sleep Quality Index (PSQI): A 19-item self-report questionnaire assessing subjective sleep quality over the past month. It yields a global score (range 0-21), with higher scores indicating poorer sleep quality (global score > 5 indicates poor sleep); (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); (ii) Sleep Architecture: Percentage of TST spent in Stage N1, Stage N2, Stage N3 (SWS), and Stage R (REM).

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).

The sample size was calculated based on 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. Intention-to-Treat (ITT) Population (N=120) included

all randomized participants who received at least one dose of the study intervention. This was the primary population for all efficacy analyses. Per-Protocol (PP) Population (N=111) included participants who completed the 12-week study, had ≥80% compliance, and had no major protocol violations. Safety Population (N=120) Included all participants who received at least one dose of the study intervention.

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 modern 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 like Last Observation Carried Forward (LOCF). The LMM included fixed effects for treatment group (CM vs. 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 maintain statistical rigor and 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; (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; (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. We report the uncorrected *p*-values for these outcomes. To aid in 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's correlation (r) analyses were used to explore the relationship between changes (Δ) in key outcomes (such as ΔMoCA-INA, ΔPSQI, and ΔBDNF) within the active treatment group. *p*-values for correlations were Bonferroni-corrected for multiple comparisons. All statistical analyses were performed using R v.4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS Statistics v.27.0 (IBM Corp., Armonk, NY).

3. Results and Discussion

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 the inclusion criteria, 11 declined to participate). The remaining 120 participants were randomized, with 60 allocated to the *C. militaris* (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 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.

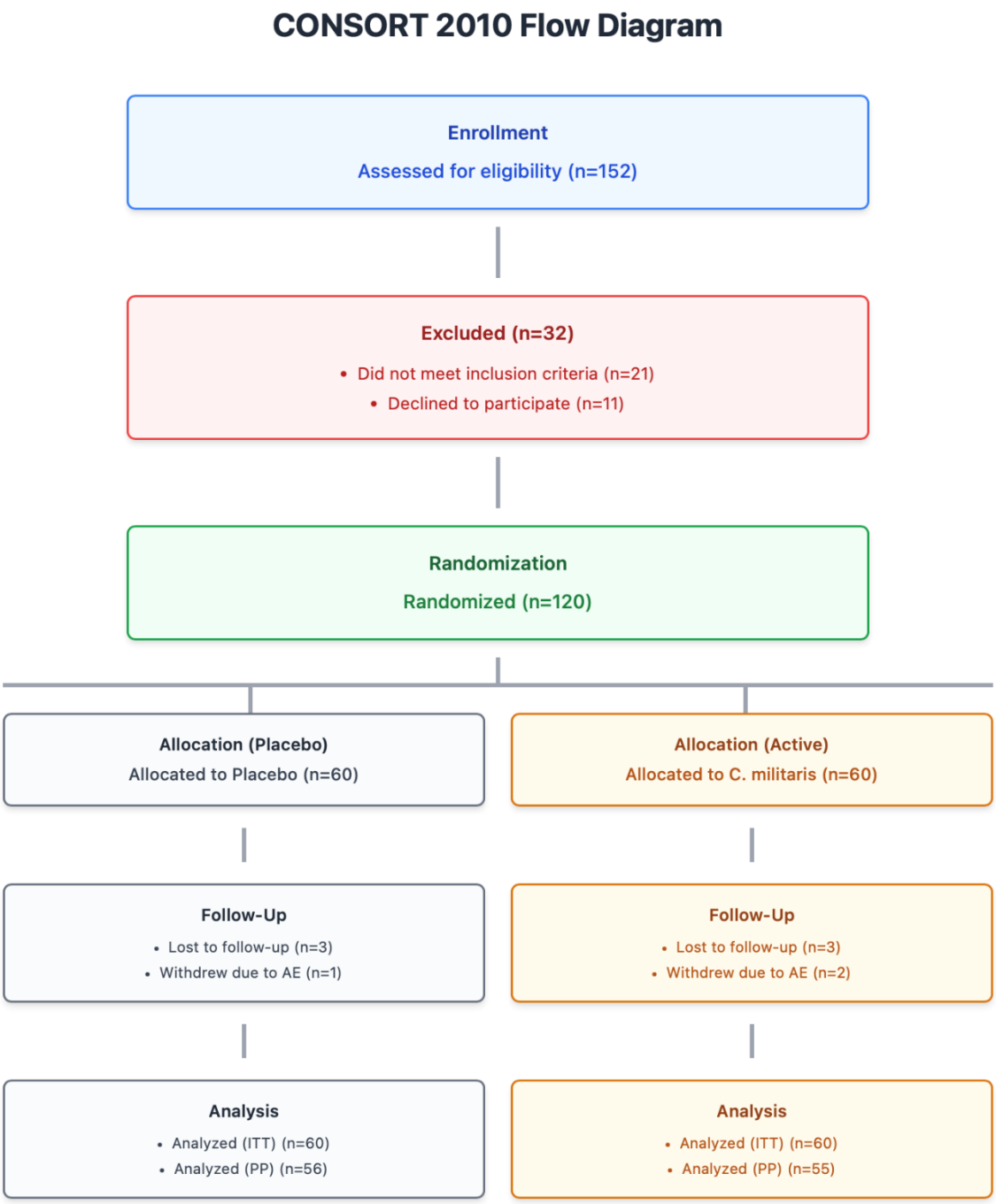

Figure 1. CONSORT 2010 diagram.

Baseline demographic and clinical characteristics of the ITT population are presented in Table 1. The two groups were exceptionally well-matched at baseline, with no statistically significant differences in age (mean 55.1 years), gender (58.3% female), education, BMI, 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 significant subjective complaints (mean SCD-Q 9.7) and poor subjective sleep (mean PSQI 9.0).

Table 1. Baseline Demographics and Clinical Characteristics (ITT Population, N=120)

Characteristic	C. militaris (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]
BMI (kg/m²), 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]
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]

Abbreviations:
BMI, Body Mass Index; HADS, Hospital Anxiety and Depression Scale; SCD-Q, Subjective Cognitive Decline Questionnaire; MoCA-INA, Montreal Cognitive Assessment-Indonesian; TMT, Trail Making Test; DSST, Digital 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.

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 large and clinically meaningful Adjusted

Mean Difference (AMD) of +1.95 (95% CI: 1.10, 2.80) in favor of *C. militaris*. The effect size was large (Cohen's d = 0.98).

All three pre-specified key secondary outcomes were statistically significant, surviving the stringent Bonferroni-corrected threshold of $p < 0.0167$; (1) Episodic Memory (RAVLT Delayed Recall): The LMM showed a significant group-by-time interaction ($F(1, 117) = 20.4$, $p < 0.001$). The CM group demonstrated 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 ($F(1, 117) = 30.1$, $p < 0.001$). The CM group reported a large (AMD: -2.90 [95% CI: -3.81, -1.99]) reduction in their PSQI score, moving the average participant from "poor sleeper" (Baseline: 8.9) to "good sleeper" (W12: 5.1) status; (3) Objective Sleep (Sleep Efficiency): The PSG data confirmed the subjective reports. A significant group-by-time interaction was found for Sleep Efficiency ($F(1, 117) = 10.2$, $p < 0.001$), with the CM group gaining an adjusted mean of 5.8% more efficiency compared to placebo.

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). RAVLT Immediate Recall also improved significantly. 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 significantly, 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). For sleep architecture, there was a significant reduction in "light sleep" %N1 and a significant increase in %REM sleep (AMD: +3.9%, q = 0.012). Notably, 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; (3) Biomarker Outcomes (Table 4): The LMM analysis confirmed significant group-by-time interactions for three of the four biomarkers, which survived FDR correction. The CM group showed a large increase in the neuroplasticity marker BDNF ($q < 0.001$) and the endogenous antioxidant SOD ($q = 0.024$). Concurrently, a significant reduction was seen 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 (PP) population (n=111) fully 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.

Within the *C. militaris* group, after Bonferroni correction, the change (Δ) in the primary outcome (MoCA-INA) was significantly and positively correlated with ΔBDNF ($r = 0.48$, $p_{corr} = 0.002$) and Δ%REM sleep ($r = 0.41$, $p_{corr} = 0.011$). The improvement (reduction) in ΔPSQI was significantly correlated with the reduction in Δhs-CRP ($r = 0.39$, $p_{corr} = 0.018$). *C. militaris* 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, ECG parameters, or routine hematology and clinical biochemistry values in either group.

Table 2. Changes in Cognitive Outcomes from Baseline to Week 12 (ITT Population, LMM Analysis)

Outcome	Group	Baseline (Mean ± SD)	Week 12 (Adj. Mean)	Adjusted Mean Diff. (95% CI)[a]	Uncorrected p-value	FDR (q)
MoCA-INA Total (Primary Outcome)	C. militaris (n=60)	25.1 ± 1.1	27.6	**1.95 (1.10, 2.80)**	**< 0.001**	--
	Placebo (n=60)	25.0 ± 1.2	25.6			
RAVLT Delayed (Key Secondary)	C. militaris (n=60)	8.2 ± 2.1	10.9	**2.15 (1.30, 3.00)**	**< 0.001**	--
	Placebo (n=60)	8.0 ± 2.3	8.8			
TMT-B (seconds)	C. militaris (n=60)	90.3 ± 12.2	81.1	**-7.5 (-10.9, -4.1)**	0.002	**0.006**
	Placebo (n=60)	91.5 ± 13.0	88.6			
DSST (correct)	C. militaris (n=60)	45.2 ± 6.8	50.8	**4.1 (2.5, 5.7)**	0.001	**0.004**
	Placebo (n=60)	44.8 ± 7.1	46.7			
RAVLT Immediate (Total I-V)	C. militaris (n=60)	48.1 ± 7.2	52.3	**3.1 (1.8, 4.4)**	< 0.001	**< 0.001**
	Placebo (n=60)	47.5 ± 7.8	49.2			
TMT-A (seconds)	C. militaris (n=60)	42.5 ± 8.1	38.9	-2.8 (-5.5, -0.1)	0.041	**0.058**
	Placebo (n=60)	43.1 ± 7.9	41.7			

Abbreviations:

CM, C. militaris; PL, Placebo; MoCA-INA, Montreal Cognitive Assessment-Indonesian; TMT, Trail Making Test; DSST, Digital Symbol Substitution Test; RAVLT, Rey Auditory Verbal Learning Test; ITT, Intention-to-Treat; LMM, Linear Mixed-Effects Model; FDR, False Discovery Rate.

[a] Results from Linear Mixed-Effects Model (LMM) 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 Diff. (95% CI)[a]	Uncorrected p-value	FDR (q)
PSQI Global Score (Key Secondary)	C. militaris (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)	C. militaris (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)	C. militaris (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	C. militaris (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)	C. militaris (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	C. militaris (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	C. militaris (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	C. militaris (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			

Abbreviations:

PSQI, Pittsburgh Sleep Quality Index; PSG, Polysomnography; WASO, Wake After Sleep Onset; SWS, Slow-Wave Sleep; REM, Rapid Eye Movement; ITT, Intention-to-Treat; LMM, Linear Mixed-Effects Model; FDR, False Discovery Rate.

[a] Results from Linear Mixed-Effects Model (LMM) for the group-by-time interaction, adjusted for baseline score.

Table 4. Changes in Exploratory Serum Biomarkers (ITT Population, LMM Analysis)

Outcome	Group	Baseline (Mean ± SD)	Week 12 (Adj. Mean)	Adjusted Mean Diff. (95% CI)[a]	Uncorrected p-value	FDR (q)
BDNF (pg/mL)	C. militaris (n=60)	310.4 ± 45.2	384.7	62.5 (45.1, 80.0)	< 0.001	< 0.001
	Placebo (n=60)	308.9 ± 48.1	322.2			
hs-CRP (mg/L)	C. militaris (n=60)	1.62 ± 0.71	0.89	-0.61 (-0.85, -0.37)	< 0.001	< 0.001
	Placebo (n=60)	1.59 ± 0.68	1.50			
MDA (nmol/mL)	C. militaris (n=60)	3.81 ± 0.90	2.45	-1.05 (-1.39, -0.71)	< 0.001	< 0.001
	Placebo (n=60)	3.75 ± 0.88	3.50			
SOD (U/mL)	C. militaris (n=60)	102.5 ± 15.1	121.8	17.2 (11.9, 22.5)	< 0.001	< 0.001
	Placebo (n=60)	103.1 ± 14.8	104.6			

Abbreviations:

BDNF, Brain-Derived Neurotrophic Factor; hs-CRP, high-sensitivity C-Reactive Protein; MDA, Malondialdehyde; SOD, Superoxide DismutHse; ITT, Intention-to-Treat; LMM, Linear Mixed-Effects Model; FDR, False Discovery Rate.

[a] Results from Linear Mixed-Effects Model (LMM) for the group-by-time interaction, adjusted for baseline score.

Table 5. Summary of Adverse Events (AEs) (Safety Population, N=120)

Adverse Event	C. militaris (n=60) n (%)	Placebo (n=60) n (%)	p-value[a]
Participants with any AE	**8 (13.3%)**	**7 (11.7%)**	**0.781**
Mild GI 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
AE leading to withdrawal	2 (3.3%)	1 (1.7%)	0.558
Serious Adverse Events (SAEs)	**0 (0.0%)**	**0 (0.0%)**	--

Abbreviations:

AE, Adverse Event; MedDRA, Medical Dictionary for Regulatory Activities; SAE, Serious Adverse Event.

[a] p-values derived from Fisher's exact test.

This 12-week, randomized, double-blind, placebo-controlled trial provides the first robust, high-quality evidence that a standardized *Cordyceps militaris* extract can significantly improve cognitive function, episodic memory, and both subjective and objective sleep in middle-aged adults with SCD. By employing a rigorous LMM analysis and a pre-specified plan to correct for multiple comparisons, our findings

demonstrate 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, PSQI, and Sleep Efficiency). These clinical benefits were strongly associated with beneficial modulation of biomarkers for neuroplasticity (BDNF), inflammation (hs-CRP), and oxidative stress (SOD), providing a plausible, multi-target pathophysiological mechanism.[11,12]

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 robust (p<0.001) and clinically significant, far exceeding the minimal gains in the placebo group. This demonstrates 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 large improvement on the RAVLT Delayed Recall (AMD: +2.15) strongly suggests an enhancement of hippocampal-dependent episodic memory consolidation.[13] This was further supported by significant gains in executive function (TMT-B) and processing speed (DSST), domains frequently compromised early in the neurodegenerative cascade.

The pathophysiological basis for this cognitive enhancement is strongly suggested by our biomarker data.[14] The most compelling finding was the large, significant 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 strongly suggest that CM extract can counteract this deficit, a finding consistent with preclinical models where cordycepin administration reversed Aβ-induced reductions in hippocampal BDNF and its receptor, TrkB.[15]

Simultaneously, the CM extract powerfully modulated the systemic inflammatory and oxidative environment. SCD is increasingly viewed as a state of "meta-inflammation" where chronic, low-grade inflammation and oxidative stress accelerate neurotoxicity. We observed a significant reduction in the systemic inflammatory marker hs-CRP and a significant increase in the endogenous enzymatic antioxidant SOD. This demonstrates a potent restoration of systemic redox balance. The bioactives in CM, including cordycepin and polysaccharides, are known to inhibit pro-inflammatory signaling cascades such as NF-κB by modulating microglial activation, while also upregulating endogenous antioxidant defenses. By quenching this "inflammaging" and oxidative stress (as evidenced by the hs-CRP and SOD changes), the CM extract likely creates a more permissive and healthy 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 the extract's primary antioxidant action may be enzymatic (i.e., upregulating SOD) rather than direct free-radical scavenging.

A key novelty of this study was the use of objective PSG, which revealed that the profound subjective sleep improvements (PSQI AMD: -2.9) were not a mere placebo or reporting-bias effect. The CM extract fundamentally and favorably restructured sleep. The significant improvements in sleep continuity—specifically the reductions in Sleep Latency and WASO, leading to a 5.8% gain in Sleep Efficiency—are clinically vital. Sleep fragmentation is a primary driver of daytime cognitive fog and, more critically, is known to impair glymphatic clearance of neurotoxic proteins like Aβ.[17]

The most mechanistically revealing findings, however, related to sleep architecture. This is where the unique pharmacology of *C. militaris* becomes evident. The high concentration of adenosine and its stable analog, cordycepin, makes the extract a potent modulator of the adenosinergic system. By acting as an A1R agonist, CM directly enhances the brain's primary homeostatic sleep drive, facilitating the

transition to sleep (reduced SL) and promoting consolidated sleep (reduced WASO). Interestingly, our rigorous analysis found that while the increase in %SWS (N3) was a positive trend, it did not survive correction for multiple comparisons (q=0.061). In contrast, the increase in %REM sleep was robust and statistically significant (q=0.012), and this change was directly correlated with the improvement in cognitive (MoCA-INA) scores.[18]

This finding offers a sophisticated insight: while the adenosinergic action of CM promotes overall sleep consolidation, its most significant measurable benefit in this population may be in the stabilization and promotion of REM sleep. This is highly relevant, as 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. Taken together, this study provides strong evidence for a synergistic, dual-pathway mechanism. *C. militaris* appears to act as: (1) A Direct Neuroprotective Agent: It enhances neuroplasticity (↑BDNF) while reducing the inflammatory (↓hs-CRP) and oxidative (↑SOD) insults that damage the brain; (2) A Sleep-Modulating Agent: Its adenosinergic properties directly promote sleep consolidation (↑SE, ↓WASO) and restore REM sleep, allowing for the brain's essential overnight processes of glymphatic clearance and memory consolidation (↑RAVLT-Delayed) to occur. This multi-target action—simultaneously repairing the "hardware" via neuroprotection and optimizing the "overnight software update" via sleep modulation—is the hallmark of *C. militaris* pharmacology and makes it an ideal candidate for a complex, age-related syndrome like SCD.

We must also address the statistical properties of our trial. We 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 ≈ 1.8). This suggests our Indonesian SCD cohort was somewhat more homogenous 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 notable magnitude of the effect (Cohen's d = 0.98 for the primary outcome), is remarkable. While this effect size is larger than 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]

This study's strengths are its rigorous RCT design, the use of a modern and appropriate LMM statistical analysis with correction for multiplicity, and the comprehensive, multi-modal outcome battery. However, several limitations must be acknowledged, as requested by the review. First, the 12-week duration is insufficient to determine if 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 disturbances (such as higher WASO and lower SE) in both groups. While this may have artifactually increased the magnitude of sleep improvement from baseline to Week 12, the robust, statistically significant between-group difference found by the LMM strongly indicates a true therapeutic effect of CM above and 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.

4. Conclusion

In conclusion, this 12-week, randomized, double-blind, placebo-controlled trial, utilizing a robust Linear Mixed-Effects Model analysis, provides strong evidence that 300 mg/day of a standardized Cordyceps militaris mycelial extract significantly 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), potent 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. *Cordyceps 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.

5. References

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