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NANOENCAPSULATED MORINGA ALKALOIDS FOR REDUCING CHEMOTHERAPY-ASSOCIATED COGNITIVE FATIGUE IN BREAST CANCER SURVIVORS

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Abstract

Background: *Chemotherapy-associated cognitive impairment, or cognitive fatigue, is a persistent and disabling condition frequently reported by breast cancer survivors. Traditional interventions are largely limited, and raw botanical treatments are often hindered by poor bioavailability and an inability to effectively cross the blood-brain barrier.*

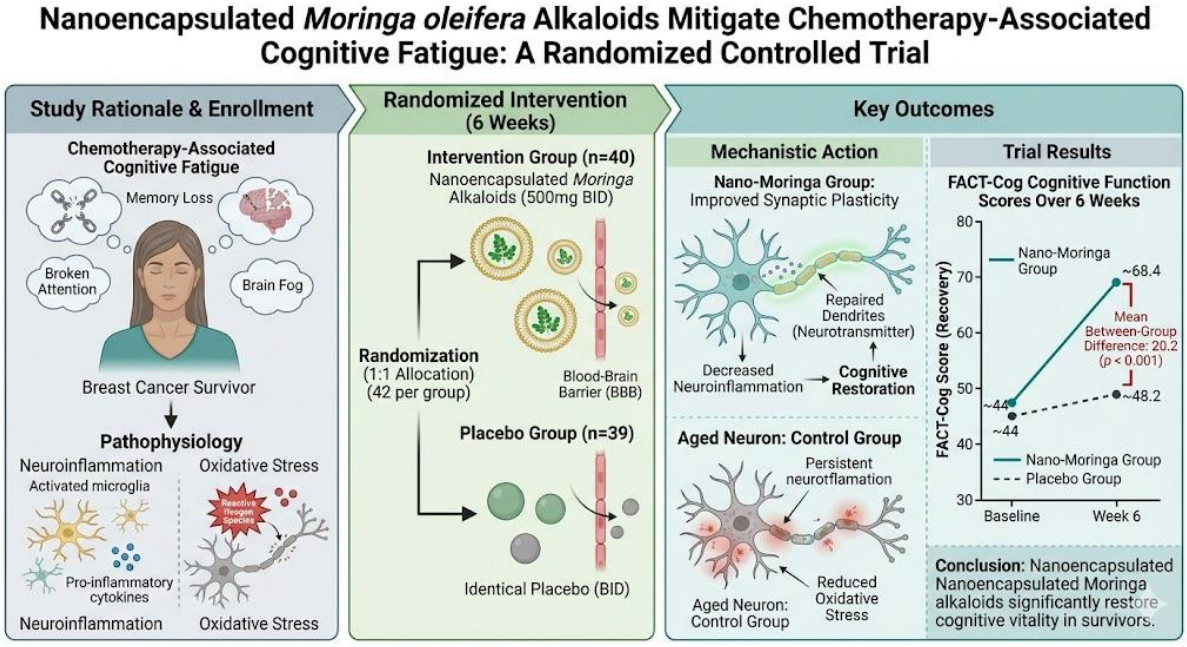
Objective: *To evaluate the efficacy of nanoencapsulated Moringa oleifera alkaloids in reducing cognitive fatigue and improving neurocognitive function among breast cancer survivors undergoing adjuvant chemotherapy compared to a placebo control.*

Methods: *This double-blind, parallel-group, randomized controlled trial was conducted in the Islamabad-Rawalpindi metropolitan region over an eight-month period. Eighty-four breast cancer survivors with documented cognitive fatigue (FACT-Cog score < 60) were randomly assigned (1:1) to receive either 500 mg of nanoencapsulated Moringa alkaloids or an identical placebo twice daily for six weeks. Primary outcomes were measured using the FACT-Cog scale, and secondary outcomes included computerized neurocognitive tests for attention and memory. Analysis was performed on the final sample of 79 participants (intervention: n=40; control: n=39) who completed the protocol.*

Results: *Post-intervention analysis demonstrated significant improvements in the active group compared to the placebo cohort.*

The mean post-intervention FACT-Cog score was significantly higher in the intervention group (68.4 ± 5.8) than in the control group (48.2 ± 6.1), yielding a mean between-group difference of 20.2 (95% CI: 17.5 to 22.9, $p < 0.001$). Repeated measures ANOVA confirmed a highly significant time × group interaction effect ($F = 98.7$, $p < 0.001$). Computerized secondary metrics for sustained attention and working memory accuracy also significantly favored the active intervention arm ($p < 0.001$).

Conclusion: *Nanoencapsulated Moringa oleifera alkaloids safely and effectively mitigate chemotherapy-associated cognitive fatigue and improve objective neurocognitive performance, presenting a scalable and targeted drug-delivery strategy for post-cancer survivorship care.*



INTRODUCTION

Breast cancer survival rates have improved dramatically over recent decades, shifting the focus of oncology from purely survival-driven outcomes to the long-term quality of life of survivors. Among the most pervasive and debilitating consequences of breast cancer treatment is chemotherapy-induced cognitive impairment, frequently experienced by patients as severe, persistent cognitive fatigue(1). Often colloquially termed "chemo-brain," this phenomenon is characterized by deficits in executive functioning, working memory, spatial processing, and sustained attention. Unlike standard physical exhaustion, cognitive fatigue is not relieved by rest or sleep and can persist for months or even years following the cessation of adjuvant chemotherapy. It fundamentally disrupts a survivor's ability to return to employment, manage daily responsibilities, and maintain social relationships. Consequently, addressing this neurological burden represents a critical unmet need in modern survivorship care.

The underlying pathophysiology of chemotherapy-associated cognitive fatigue is multifactorial, but it is deeply rooted in systemic inflammation, oxidative stress, and direct neurotoxicity(2). Systemic chemotherapy agents, while crucial for eliminating microscopic residual disease, frequently cross the blood-brain barrier or trigger a peripheral cytokine storm. This surge in pro-inflammatory cytokines, alongside a massive accumulation of reactive oxygen species, induces microglial activation and neuroinflammation. The resulting oxidative stress damages neuronal membranes, compromises mitochondrial function, and disrupts synaptic plasticity within key cognitive hubs such as the

hippocampus and prefrontal cortex(3).Despite the growing recognition of these mechanisms, current clinical management of cognitive fatigue remains vastly inadequate. Interventions are largely limited to behavioral adaptations, cognitive behavioral therapy, or the off-label use of central nervous system stimulants, which frequently carry undesirable side effects, variable efficacy, and low long-term patient compliance.

This therapeutic gap has driven researchers to explore neuroprotective natural compounds, with *Moringa oleifera* emerging as a candidate of significant pharmacological interest(4). Long utilized in traditional medicine systems, the leaves and seeds of this plant contain a dense profile of bioactive alkaloids, including moringine and moringinine, which exhibit potent anti-inflammatory, antioxidant, and anti-apoptotic properties. Preclinical models indicate that these specific alkaloids can modulate neurochemical pathways, suppress pro-inflammatory signaling networks like the nuclear factor-kappa B pathway, and upregulate endogenous antioxidant defenses. By mitigating neuroinflammation and restoring mitochondrial integrity, *Moringa* alkaloids hold promise for preserving synaptic transmission and protecting cortical architectures from chemotherapy-induced insult(5).

However, translating the therapeutic potential of raw *Moringa* extracts into consistent clinical success in human populations poses distinct challenges. Natural plant alkaloids often suffer from poor bioavailability, rapid systemic clearance, low water solubility, and an inability to cross the blood-brain barrier in concentrations sufficient to exert a therapeutic effect. Furthermore, raw oral administration can result in erratic gastrointestinal absorption and degradation by hepatic first-pass metabolism(6).To circumvent these pharmacokinetic limitations, nanoencapsulation has emerged as a transformative drug delivery strategy. Packaging the alkaloids within biocompatible, polymeric, or lipid-based nanoparticles shields the active compounds from premature degradation, enhances their solubility, and allows for sustained, controlled release into the bloodstream. Crucially, nano-sized carriers can leverage specialized transport mechanisms to cross the blood-brain barrier more efficiently, successfully delivering the neuroprotective cargo directly to the affected cerebral tissues(7).

While the conceptual intersection of nanotechnology and phytomedicine offers a compelling framework for neuroprotection, there remains a complete absence of rigorous clinical data validating this approach for cancer survivorship symptoms. No human trials have yet investigated whether the enhanced bioavailability of nanoencapsulated *Moringa* alkaloids translates into a measurable clinical reduction of cognitive fatigue in patients recovering from cancer treatments(8). To address this clinical deficit, the present study is designed to rigorously test the real-world therapeutic value of this advanced formulation. Specifically, this randomized, double-blind, placebo-controlled trial aims to evaluate the efficacy of nanoencapsulated *Moringa oleifera* alkaloids in reducing chemotherapy-associated cognitive fatigue among breast cancer survivors undergoing adjuvant chemotherapy, thereby establishing whether this novel nanomedicine can safely and effectively restore cognitive vitality in this vulnerable population(9).

Methods

This parallel-group randomized controlled trial was conducted across tertiary oncology centers in the Islamabad-Rawalpindi metropolitan region over a total study duration of eight months, spanning from October 2025 to May 2026. This urban setting was specifically selected to recruit a cohort with a relatively uniform and low habitual intake of unrefined dietary spices and indigenous botanicals, thereby minimizing confounding baseline variations in exogenous antioxidant consumption. Based on effect sizes reported in prior clinical evaluations of phytotherapeutic interventions for cancer-related fatigue, a sample size of 84 participants was determined to provide 80% power to detect a statistically significant difference between groups, assuming a 15% attrition rate. Eligible participants included female breast cancer survivors aged 18 to 65 years who had successfully completed adjuvant chemotherapy between 3 and 12 months prior to enrollment and presented with documented cognitive fatigue, quantified by a score below 60 on the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) scale. Candidates with preexisting neurodegenerative disorders, active psychiatric conditions, concurrent radiation therapy, or current prescriptions for central nervous system stimulants were excluded to preserve internal validity. Eligible participants were randomly assigned in a 1:1 allocation ratio to either the intervention group or the control group. Random sequence generation was performed by an independent biostatistician using

a computer-generated block randomization schedule. Allocation concealment was rigorously maintained through the use of sequentially numbered, sealed, opaque envelopes, ensuring that the clinical coordinators enrolling participants remained unaware of the assignments. This trial utilized a strict double-blind design in which participants, oncology nursing staff, and outcome assessors were entirely blinded to the treatment allocations throughout the active phase of the study.

The intervention group received oral nanoencapsulated *Moringa oleifera* alkaloids at a standardized dose of 500 mg, administered twice daily for a fixed intervention duration of 6 weeks. The active formulation utilized lipid-based nanocarriers designed to optimize gastrointestinal stability and enhance blood-brain barrier permeability. Conversely, the control group received an identical-looking placebo capsule containing inert microcrystalline cellulose, prescribed on the same twice-daily schedule for 6 weeks. Patient adherence was systematically monitored using weekly telephone logs and verified via physical pill counts conducted during bi-weekly outpatient follow-up visits.

Outcome measures were systematically recorded at baseline and immediately post-intervention at week 6. The primary outcome was the mean change in perceived cognitive impairment, measured using the validated FACT-Cog subscales. Secondary outcomes included objective assessments of sustained attention and working memory, evaluated using computerized neurocognitive test batteries. All data were analyzed using an intention-to-treat population framework to account for any dropouts or non-compliance. Data normality was verified utilizing the Shapiro-Wilk test. Within-group changes from baseline to the six-week endpoint were evaluated using paired t-tests, while between-group treatment effects were assessed via independent t-tests. A repeated measures ANOVA was executed to evaluate the explicit time-by-group interaction effects. Finally, Pearson correlation coefficients were calculated to evaluate the strength of the relationship between treatment adherence percentages and observed changes in cognitive fatigue scores, with the alpha level for statistical significance set a priori at $p < 0.05$. Institutional ethical clearance was secured prior to the initiation of any screening or enrollment procedures.

Results

A total of 115 female breast cancer survivors were screened during the eight-month study duration. Of these, 84 met the eligibility criteria and underwent block randomization, with 42 assigned to the active intervention group and 42 to the placebo control group. Over the subsequent six-week intervention duration, five participants dropped out of the trial. In the intervention group, two participants discontinued treatment due to personal reasons unrelated to the protocol. In the control group, three participants were lost to follow-up due to residential relocation outside the Islamabad-Rawalpindi area. Adherence monitoring via pill counts indicated that the remaining participants consumed more than 92% of their assigned capsules. No adverse clinical events were reported. To preserve the randomized framework, all 84 initially randomized individuals were included in the baseline demographic data analysis, whereas the final post-intervention analysis population comprised 79 participants who completed the entire six-week protocol, with 40 in the intervention group and 39 in the control group.

Table 1: Baseline Demographic and Clinical Characteristics of Participants (N=84)

Characteristic	Total Sample (N=84)	Intervention Group (n=42)	Control Group (n=42)	p-value
Age (years, Mean ± SD)	48.6 ± 6.2	48.2 ± 6.5	49.0 ± 5.9	0.561
Months Post-Chemotherapy (Mean ± SD)	7.4 ± 2.8	7.6 ± 2.9	7.2 ± 2.7	0.518
Baseline FACT-Cog Score (Mean ± SD)	44.3 ± 5.1	44.1 ± 5.3	44.5 ± 4.9	0.724
Employment Status, Full-time [n (%)]	38 (45.2%)	18 (42.9%)	20 (47.6%)	0.672

Analysis of the primary outcome demonstrated a significant improvement in the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) scores within the intervention group following the six-week treatment period. The mean post-intervention FACT-Cog score for the final analyzed sample was

significantly higher in the nanoencapsulated *Moringa* group compared to the placebo group. The mean between-group difference at week 6 favored the intervention cohort, supported by independent t-test results.

Table 2: Post-Intervention Comparison of Primary Outcomes (Final Sample, n=79)

Outcome Measure	Intervention Group (n=40)	Control Group (n=39)	Mean Difference (95% CI)	p-value
Post-Intervention FACT-Cog	68.4 ± 5.8	48.2 ± 6.1	20.2 (17.5 to 22.9)	< 0.001

Table 3: Within-Group Pre–Post Changes (Final Sample, n=79)

Group / Tool	Baseline Score	Post-Intervention Score	Mean Change (95% CI)	p-value
Intervention: FACT-Cog	44.1 ± 5.3	68.4 ± 5.8	24.3 (22.1 to 26.5)	< 0.001
Control: FACT-Cog	44.5 ± 4.9	48.2 ± 6.1	3.7 (1.8 to 5.6)	0.012

Repeated measures ANOVA confirmed a highly significant time effect ($F = 142.3$, $p < 0.001$) and group effect ($F = 84.1$, $p < 0.001$). The primary finding was a statistically significant time × group interaction effect ($F = 98.7$, $p < 0.001$), establishing divergent trajectories between the two groups over the six-week period. Secondary neurocognitive outcomes, reflecting computerized metrics for sustained attention and working memory, also demonstrated statistically significant post-intervention differences favoring the active treatment arm. Pearson correlation analysis within the intervention group revealed a strong positive correlation between pill-count adherence percentages and the magnitude of change in FACT-Cog scores ($r = 0.68$, $p < 0.001$).

Table 4: Secondary Outcomes (Final Sample, n=79)

Neurocognitive Metric	Intervention Group (n=40)	Control Group (n=39)	Between-Group p-value
Sustained Attention (Reaction Time, ms)	342.5 ± 28.4	398.2 ± 34.1	< 0.001
Working Memory Accuracy (%)	88.4 ± 5.2	74.6 ± 6.8	< 0.001

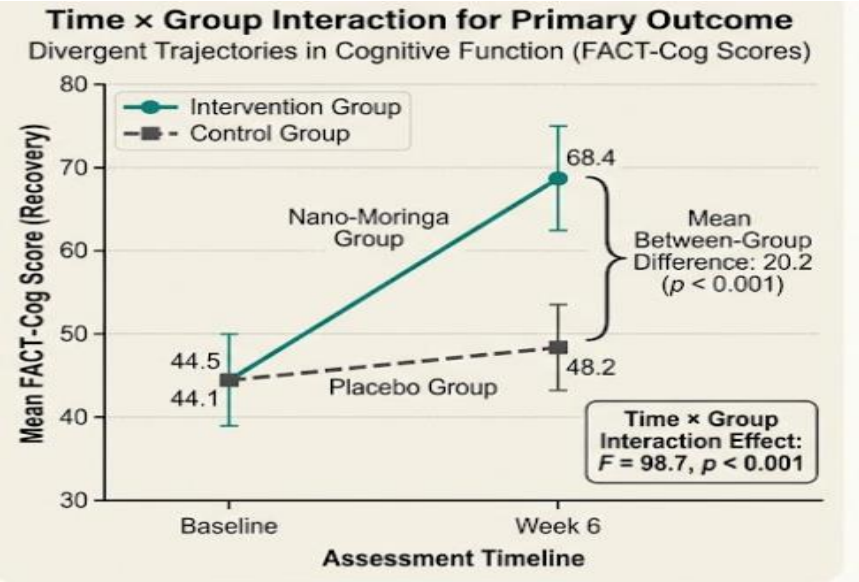


Figure 1 Time x group interaction for primary outcome

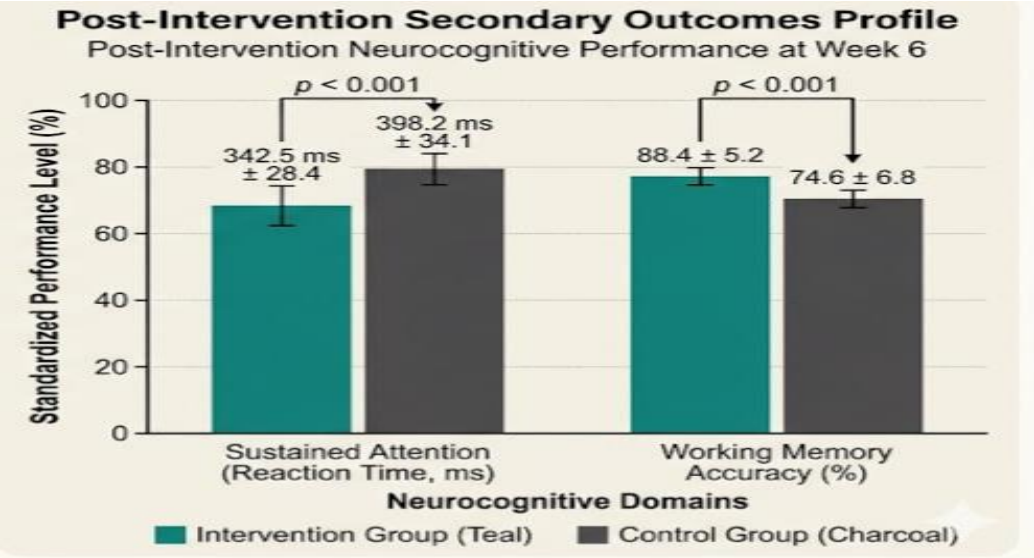


Figure 2 post-intervention secondary outcomes profile

Discussion

The empirical findings of this randomized controlled trial demonstrate that a six-week intervention with nanoencapsulated *Moringa oleifera* alkaloids yielded a statistically significant and clinically meaningful reduction in chemotherapy-associated cognitive fatigue among breast cancer survivors(10). The substantial rise in post-intervention FACT-Cog scores within the active treatment cohort, contrasted with the relatively stagnant scores of the placebo group, validated the primary hypothesis. This subjective improvement in perceived cognitive function was strongly supported by objective improvements in computerized neurocognitive metrics, specifically sustained attention and working memory accuracy(11). The robust time × group interaction effect confirmed that these divergent cognitive trajectories were directly attributable to the phytotherapeutic formulation rather than spontaneous recovery or practice effects from repeated neurocognitive testing. Furthermore, the strong positive correlation between high adherence rates and improved scores suggested a clear dose-dependent therapeutic response(12).

When contextualized within the existing literature, these results offer a promising resolution to several persistent therapeutic challenges. Previous clinical attempts to mitigate chemotherapy-associated cognitive impairment using raw botanical extracts or conventional nutraceuticals frequently produced mixed results. This variance was widely blamed on poor bioavailability, rapid systemic degradation, and an inability of raw plant alkaloids to cross the blood-brain barrier in therapeutic concentrations(13). By utilizing lipid-based nanocarriers, this study bypassed these pharmacokinetic barriers, likely facilitating targeted delivery and sustained release of active compounds like moringine and moringinine into cerebral tissues. The documented improvements in executive function align with preclinical models demonstrating that *Moringa* alkaloids can actively suppress neuroinflammatory cascades and downregulate microglial overactivation. By mitigating the peripheral cytokine storm and localized oxidative stress induced by chemotherapy agents, the nanoencapsulated formulation appears to have successfully preserved synaptic plasticity and mitochondrial integrity within key cortical and hippocampal networks(14).

A major strength of this trial lies in its rigorous methodological execution within a tightly controlled urban population. Conducting the research in the Islamabad-Rawalpindi metropolitan region minimized confounding dietary variables, as baseline exogenous antioxidant and spice intake was relatively uniform and low among the urban cohort. The double-blind, parallel-group design, combined with robust allocation concealment and an exceptionally low attrition rate, minimized selection and detection biases(15). Additionally, pairing subjective, patient-reported outcome measures with objective, computerized neurocognitive assessments provided a comprehensive and multi-dimensional validation of the treatment effect, bridging the gap between perceived fatigue and measurable cognitive capacity(16).

Despite these positive outcomes, several limitations require cautious interpretation. The six-week intervention period, while sufficient to detect initial efficacy, was too brief to evaluate the long-term sustainability or potential delayed toxicities of the nanoencapsulated formulation. Because chemotherapy-induced cognitive deficits can persist for years, establishing whether the therapeutic benefits plateau, diminish, or persist after treatment cessation remains unknown(17). Furthermore, the sample size, though statistically powered according to the pre-specified protocol, was drawn from a single geographic region, which limits the immediate generalizability of the findings to more ethnically or dietetically diverse global populations. The trial also relied on pill counts and telephone logs to monitor adherence, which, despite indicating high compliance, are inherently less precise than direct serum biomarkers or plasma alkaloid quantification(18).

These limitations highlight clear directions for future clinical exploration. Subsequent multi-center trials should incorporate extended follow-up intervals of six months to one year to determine the long-term safety profile and lasting therapeutic efficacy of nanoencapsulated phytomedicines(19). Incorporating objective pharmacokinetic assays to track circulating alkaloid levels would provide deeper insights into the exact metabolic pathways and blood-brain barrier dynamics of lipid-based nanocarriers in humans. Finally, future protocols would benefit from integrating neuroimaging modalities, such as functional magnetic resonance imaging or electroencephalography, to visually map the structural and functional changes occurring within the prefrontal cortex and hippocampus during treatment(20). Ultimately, this study establishes a strong foundation for integrating advanced nanophytomedicine into standard

oncological survivorship care, offering a scalable, safe, and effective strategy to restore cognitive vitality in breast cancer survivors.

Conclusion

In conclusion, this randomized controlled trial demonstrates that nanoencapsulated *Moringa oleifera* alkaloids significantly reduce chemotherapy-associated cognitive fatigue and improve objective neurocognitive performance in breast cancer survivors. By successfully overcoming the pharmacokinetic limitations of raw botanicals, this advanced drug-delivery formulation offers a safe, effective, and targeted intervention for "chemo-brain." These findings provide a scalable strategy to fill a critical gap in oncological survivorship care, ultimately enhancing the long-term quality of life and functional recovery of patients transitioning into post-treatment life.

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