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RECEIVED 03 June 2025  
ACCEPTED 25 July 2025  
PUBLISHED 15 August 2025

CITATION  
Yang Y, Koo M-S and Kwak YT (2025) Efficacy  
of *Ginkgo biloba* extract in amyloid  
PET-positive patients with mild cognitive  
impairment.  
*Front. Neurol.* 16:1639924.  
doi: 10.3389/fneur.2025.1639924

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# Efficacy of *Ginkgo biloba* extract in amyloid PET-positive patients with mild cognitive impairment

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**Background:** Mild cognitive impairment (MCI) with amyloid PET positivity represents a prodromal stage of Alzheimer's disease (AD), yet no disease-modifying therapies are currently approved. *Ginkgo biloba*, traditionally used in East Asian and European ethnomedicine as an oral decoction or standardized extract to support memory and cognitive function, is commonly utilized, however, its efficacy as monotherapy in biomarker-confirmed MCI remains uncertain. A $\beta$  oligomers, produced by abnormal cleavage of amyloid precursor protein, disrupt synaptic function and contribute to cognitive decline.

**Objective:** This study evaluated whether *Ginkgo biloba* alone, without adjunctive anti-dementia medication, could provide clinical and biomarker benefits in amyloid PET-positive MCI patients. Plasma MDS-Oa $\beta$  (Multimer Detection System–Oligomeric A $\beta$ ), a dynamic biomarker reflecting A $\beta$  oligomerization tendency, was used to explore mechanistic relevance.

**Methods:** In this retrospective cohort study, 64 amyloid PET-positive MCI patients were followed for 12 months. Participants received either oral *Ginkgo biloba* monotherapy (240 mg/day,  $n = 42$ ) or standard cognitive enhancers ( $n = 22$ ). Clinical outcomes included the Korean version of the Mini-Mental State Examination (K-MMSE), Clinical Dementia Rating–Sum of Boxes (CDR-SB), Korean Instrumental Activities of Daily Living (K-IADL), and Neuropsychiatric Inventory (NPI). Plasma MDS-Oa $\beta$  levels were assessed at baseline and at 12 months.

**Results:** At 12 months, the Ginkgo group showed significantly higher responder rates (100% vs. 59.1%,  $p < 0.001$ ), no conversion to AD dementia (0% vs. 13.6%,  $p = 0.037$ ), and greater improvement in K-MMSE and K-IADL scores. MDS-Oa $\beta$  levels decreased significantly in the Ginkgo group ( $p < 0.001$ ) but not in the control group. No significant between-group differences were observed in CDR-SB or NPI scores.

**Conclusion:** *Ginkgo biloba* monotherapy was associated with preserved cognition, improved daily functioning, and reduced plasma A $\beta$  oligomerization in amyloid PET-positive MCI patients. These findings suggest potential disease-modifying effects and warrant further validation in prospective, biomarker-based clinical trials.

## KEYWORDS

*Ginkgo biloba*, mild cognitive impairment, Alzheimer's disease, amyloid PET, MDS-Oa $\beta$

## Introduction

Alzheimer's disease (AD) is the most common cause of dementia, exerting a substantial global burden. Although the pathological roles of amyloid-beta ( $A\beta$ ) aggregation and tau have been increasingly clarified, translating these insights into effective treatments remains a major challenge (1). Mild cognitive impairment (MCI) is a transitional stage between normal aging and dementia, and individuals with amyloid PET-positive MCI are at particularly high risk of progressing to AD. Previous studies have characterized amyloid PET-positive MCI as prodromal AD (2, 3), with subtle impairments in memory and executive function that preserve functional independence. The annual conversion rate to AD among biomarker-confirmed MCI patients is estimated at 5–30% (4, 5). However, no disease-modifying treatments are currently approved for MCI. In South Korea and many other countries, standard anti-dementia drugs like donepezil, rivastigmine, galantamine, and memantine are not reimbursed for MCI (6), leading to widespread off-label use of cognitive supplements such as omega-3 fatty acids, choline precursors, and *Ginkgo biloba*.

*Ginkgo biloba* leaves have been traditionally utilized in East Asian ethnomedicine, particularly within Chinese and Korean medical traditions, as an oral decoction or herbal remedy to enhance memory, mitigate age-related cognitive decline, and alleviate circulation-related symptoms such as dizziness and tinnitus (7). Currently, standardized *Ginkgo biloba* extracts are widely employed both as prescription phytochemistry in Europe and as a non-prescription cognitive supplement globally. Despite their broad usage, the efficacy of *Ginkgo biloba* extracts as monotherapy in biomarker-confirmed mild cognitive impairment (MCI) remains uncertain.

At our institution, *Ginkgo biloba* extract has been occasionally prescribed depending on clinical context, and our accumulated clinical experience prompted a more systematic investigation. We employed Ginexin-F<sup>®</sup>, a standardized extract approved by the Korean Ministry of Food and Drug Safety (MFDS-199702183). Its composition is equivalent to EGb 761, a widely studied formulation in clinical trials. Ginkgo's neuroprotective effects have been attributed to antioxidative, anti-inflammatory, and vasodilatory properties, as well as modulation of neurotransmission and inhibition of  $A\beta$  aggregation (7–9). Although many studies have examined Ginkgo's effects in MCI, results remain mixed. A placebo-controlled trial showed cognitive benefits with good adherence (10), whereas the large GEM trial in cognitively normal elderly individuals failed to show preventive effects, likely due to low incidence of dementia and poor compliance (11). The GUIDAGE trial in patients with subjective memory complaints also yielded inconclusive results (12, 13). Early meta-analyses indicated modest cognitive improvements (14), but a Cochrane review in 2007 questioned their robustness (15). More recent randomized trials and meta-analyses suggest EGb 761 may offer symptomatic benefit in MCI. One 12-month trial in China reported reduced dementia incidence in amnesic MCI patients treated with Ginkgo (16), while others noted improvements in memory and neuropsychiatric symptoms (17, 18). Still, a recent systematic review concluded that definitive evidence for Ginkgo in MCI remains insufficient (19).

This inconsistency likely reflects the heterogeneity of MCI itself. While some patients harbor prodromal AD pathology, others may have non-AD causes of cognitive symptoms. This variability

complicates trials, as AD-targeting therapies may be tested on non-AD cases. Furthermore, the slow progression of early-stage AD challenges the sensitivity of conventional outcome measures. To address these issues, we integrated biomarker-based strategies for diagnosis and treatment monitoring. Our group previously reported a retrospective study combining donepezil and Ginkgo in amyloid PET-positive AD patients, using plasma MDS-Oa $\beta$  (Multimer Detection System–Oligomeric  $A\beta$ ) as a biomarker (20). This blood-based assay measures the oligomerization tendency of  $A\beta$  and has shown associations with cognitive scores, disease progression, and CSF tau levels (21). In that study, the combination group demonstrated improved cognition and greater reductions in MDS-Oa $\beta$ . However, all patients received donepezil, limiting evaluation of Ginkgo's independent effect. Because anti-dementia drugs are not reimbursed for MCI in Korea, *Ginkgo biloba*—being accessible and affordable—is often used as a practical alternative due to its accessibility and affordability. This creates a real-world setting to examine its effects without confounding treatments.

In this study, we focused on amyloid PET-positive MCI patients to enhance diagnostic specificity. We evaluated cognitive and functional changes as well as plasma MDS-Oa $\beta$  over 12 months. Unlike static biomarkers such as  $A\beta_{42}$  or total  $A\beta$ , MDS-Oa $\beta$  reflects the dynamic propensity for toxic oligomer formation, a key pathogenic step in AD (21). This study was designed to assess whether *Ginkgo biloba* monotherapy could provide both symptomatic and biomarker-level benefits in patients with amyloid-confirmed MCI. To this end, we analyzed real-world registry data and applied validated biomarker assays to evaluate its potential as a practical early intervention.

## Materials and methods

### Study design

This retrospective cohort study utilized data from the Soonchunhyang Dementia Registry, a longitudinal database capturing clinical, cognitive, and biomarker data from patients evaluated at the Dementia Clinic of Soonchunhyang University Cheonan Hospital. The registry includes detailed diagnostic evaluations and serial follow-ups since March 2020, offering a complete medical history, physical and neurological examinations, comprehensive neuropsychological testing, and routine laboratory tests including ApoE. Magnetic resonance imaging (MRI) is performed within 3 months, and <sup>18</sup>F-FC119S PET/computed tomography (CT) is performed when possible in the same period.

### Participants

Participants were eligible if they met the following criteria: (1) diagnosis of MCI according to Petersen et al. (22) criteria, which includes subjective cognitive complaints corroborated by an informant, objective impairment in one or more cognitive domains (typically memory), preserved global cognitive function, largely intact activities of daily living, and absence of dementia; (2) evidence of cerebral amyloid pathology confirmed by <sup>18</sup>F-FC119S PET (3) no

prior use of anti-dementia medications including cholinesterase inhibitors or memantine; (4) a minimum follow-up duration of 12 months; and (5) available plasma samples at baseline and 12 months for MDS-Oa $\beta$  analysis. Patients were excluded if they had major psychiatric illness, stroke, or other neurological conditions that could confound cognitive assessments.

## Group allocation and treatments

Patients were categorized into two treatment groups based on their initial post-diagnostic management. The Ginkgo group received 240 mg/day of a standardized *Ginkgo biloba*. The non-Ginkgo group received other commonly used cognitive enhancers, including omega-3 fatty acid supplements (with  $\geq 600$  mg DHA + EPA combined daily) or choline precursors. Importantly, no patients in either group received prescription anti-dementia drugs during the study period. Treatment decisions were made by the managing neurologist based on clinical judgment, patient preference, and insurance coverage limitations.

## Cognitive and functional assessments

Neuropsychological testing included the Korean version of the Mini-Mental State Examination (K-MMSE) to evaluate global cognitive function, and the Clinical Dementia Rating-Sum of Boxes (CDR-SB) to assess multidomain cognitive and functional abilities. Functional status was further assessed with the Korean Instrumental Activities of Daily Living (K-IADL) scale, with a K-IADL score (Sum of item scores/Number of items answered) of  $\geq 0.40$  indicating probable conversion to dementia (23). Behavioral symptoms were evaluated using the Neuropsychiatric Inventory (NPI), which covers 12 domains including depression, apathy, agitation, and hallucinations. All assessments were conducted at baseline and repeated after approximately 12 months. Due to the observational nature of the study, slight variations in follow-up timing were allowed, but all reassessments occurred within a 10–14 month window.

## Definition of clinical response

To assess treatment response, we applied the “no deterioration” criterion, commonly used in real-world studies. Patients were classified as responders if there was no decline in K-MMSE and no increase in CDR-SB over the 12-month period. Those who showed any decline in K-MMSE or any increase in CDR-SB during the same period were not classified as responders. Patients were considered to have converted to AD if their K-IADL score increased from  $< 0.40$  at baseline to  $\geq 0.40$  at 12-month follow-up, based on validated Korean criteria (23).

## Safety monitoring

Adverse events were monitored at each clinic visit by asking patients and caregivers about new symptoms and through direct

clinical observation. Events were recorded and categorized by severity. Discontinuation due to side effects was also noted.

## Plasma biomarker measurement

MDS-Oa $\beta$  was used to quantify the amyloid- $\beta$  oligomerization tendency in plasma. This assay measures how readily monomeric A $\beta$  peptides form soluble toxic oligomers under standardized conditions. At each measurement point, plasma samples were thawed and incubated with synthetic A $\beta$  peptides for 48 h at 37°C. Following incubation, samples were treated with a chemiluminescent substrate, and oligomerization levels were quantified using a Victor 3 luminometer. To ensure analytical reliability of the MDS-Oa $\beta$  assay, synthetic A $\beta$ 42 peptide was utilized as an internal standard, as previously described (24, 25). Reagents, including synthetic A $\beta$  peptides and capture antibodies, were consistently obtained from the same manufacturing lot to minimize lot-to-lot variability. Assay reproducibility was routinely monitored by assessing intra- and inter-assay coefficients of variation (CV), which were maintained below 10%. Plasma samples underwent a single freeze–thaw cycle; specifically, samples were thawed at 37°C for 15 min immediately prior to analysis, as previously validated (25, 26). All samples were analyzed concurrently to avoid inter-batch variability. The test has been validated in prior studies to correlate with CSF tau levels, cognitive scores, and PET findings, providing a dynamic and sensitive readout of early amyloid pathology (21, 24, 25, 27).

## Statistical analysis

Continuous variables were compared between groups using independent *t*-tests, and within-group changes were analyzed with paired *t*-tests. Categorical variables, including response status and conversion rates, were assessed using the chi-square test or Fisher’s exact test, as appropriate based on cell counts. All statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY), and a *p*-value  $< 0.05$  was considered statistically significant.

## Results

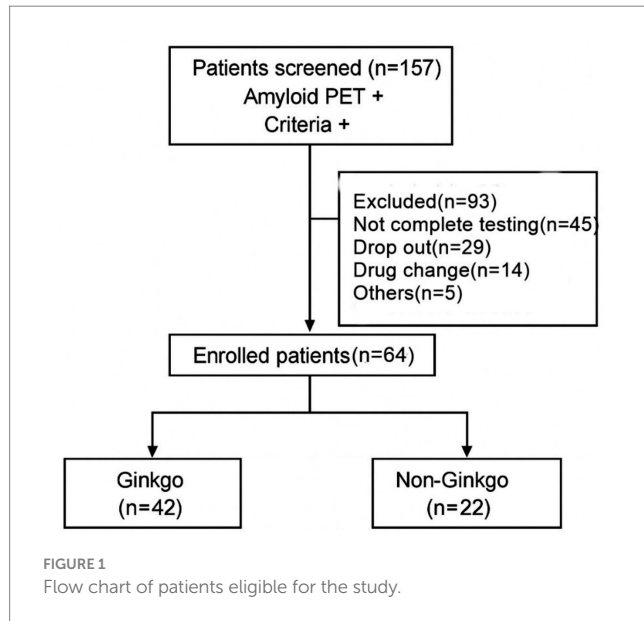
### Baseline demographic and clinical characteristics

A total of 157 patients who were amyloid PET positive and met inclusion criteria were screened. Among them, 93 patients were excluded due to incomplete testing ( $n = 45$ ), dropout ( $n = 29$ ), drug changes ( $n = 14$ ), or other reasons ( $n = 5$ ). Finally, 64 patients were enrolled, with 42 patients in the Ginkgo group and 22 in the Non-Ginkgo group (Figure 1). There were no significant differences between groups in age (65.8 vs. 68.6 years), sex distribution (73.8% vs. 81.8% female), education (12.6 vs. 11.1 years), or ApoE4 allele count (0.62 vs. 0.73). Baseline cognitive and functional measures, including K-MMSE (28.4 vs. 28.5), CDR (both 0.5), CDR-SB (0.8 vs. 0.9), and K-IADL (3.4 vs. 3.0), were similar between groups. Neuropsychiatric symptoms (NPI) and plasma MDS-Oa $\beta$  levels (0.88 vs. 0.89 ng/mL) also showed no significant differences (Table 1).

## Cognitive and functional response at 12 months

At the 12-month follow-up, all 42 patients in the Ginkgo group maintained stable cognitive status according to the responder criteria (no decline in K-MMSE and no increase in CDR-SB). In contrast, only 13 of the 22 patients (59.1%) in the non-Ginkgo group met the

responder criteria ( $p < 0.001$ ). Conversion to Alzheimer's disease was defined by a K-IADL score  $\geq 0.40$  at 12 months. No patients in the Ginkgo group met this criterion at 12 months, while three patients (13.6%) in the non-Ginkgo group did ( $p = 0.037$ ), indicating a statistically significant difference in functional outcomes between the groups (Table 2).



## Change in cognitive and biomarker outcomes over 12 months

Table 3 summarizes the changes in cognitive and biomarker outcomes from baseline to 12 months. K-MMSE scores increased slightly in the Ginkgo group (28.4 vs. 28.8), reflecting an average gain of 0.4 points ( $p = 0.008$ , within-group). In contrast, the non-Ginkgo group exhibited a mean decline of 0.8 points ( $p = 0.008$ , within-group). The between-group difference in MMSE change was statistically significant ( $p < 0.001$ ). CDR-SB scores remained unchanged in both groups, averaging 0.8 in the Ginkgo group and 0.9 in the non-Ginkgo group at both timepoints. K-IADL total scores improved in the Ginkgo group from 3.4 to 2.5 ( $\Delta - 0.8$ ,  $p = 0.001$ ), while they worsened in the non-Ginkgo group from 3.0 to 3.5 ( $\Delta + 0.6 \pm 0.9$ ,  $p = 0.013$ ). This between-group difference was statistically significant ( $p < 0.001$ ), indicating a meaningful functional benefit of Ginkgo therapy. There were no significant changes in NPI scores in either group over 12 months. Plasma MDS-Oa $\beta$  levels significantly decreased in the Ginkgo group, from 0.88 to 0.80 ng/mL, corresponding to a mean reduction of 0.08 ng/mL ( $p < 0.001$ ,

TABLE 1 Baseline demographics and clinical variables of study subjects.

Variables	Ginkgo (n = 42)	Non-Ginkgo (n = 22)	p-value*
Age, years	65.8 $\pm$ 10.4	68.6 $\pm$ 7.9	0.288
Female gender (%)	31(73.8%)	18(81.8%)	0.348
Education years	12.6 $\pm$ 4.7	11.1 $\pm$ 4.9	0.244
ApoE4 gene number	0.62 $\pm$ 0.73	0.73 $\pm$ 0.83	0.593
K-MMSE	28.4 $\pm$ 1.2	28.5 $\pm$ 1.2	0.763
CDR	0.5 $\pm$ 0.0	0.5 $\pm$ 0.0	NA
CDR-SB	0.8 $\pm$ 0.5	0.9 $\pm$ 0.5	0.894
K-IADL	3.4 $\pm$ 2.8	3.0 $\pm$ 1.4	0.477
NPI	3.7 $\pm$ 5.1	1.2 $\pm$ 3.3	0.149
MDS-Oa $\beta$ (ng/mL)	0.88 $\pm$ 0.15	0.89 $\pm$ 0.11	0.838

\*Between-group comparisons were conducted using independent *t*-tests. K-MMSE, Korean Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; CDR-SB, Clinical Dementia Rating Scale Sum of Box; K-IADL, Korean Instrumental Activities of Daily Living; NPI, Neuropsychiatric Inventory; MDS-Oa $\beta$ , Multimer Detection System-Oligomerized A $\beta$  assay; NA, not applicable due to zero variance.

TABLE 2 Clinical response at 12 months in Ginkgo and non-Ginkgo groups.

Outcome	Ginkgo	Non-Ginkgo	p-value
Stable cognitive status (responder)	42(100.0%)	13(59.1%)	0.000
Cognitive decline (non-responder)	0(0.0%)	9(40.9%)	
No conversion to AD (K-IADL < 0.40)	42(100.0%)	19(86.4%)	0.037
Conversion to AD (K-IADL $\geq$ 0.40)	0(0.0%)	3(13.6%)	

Stable cognitive status (Responder) was defined as no decline in K-MMSE and no increase in CDR-SB scores over 12 months. Conversion to Alzheimer's disease (AD) was defined as achieving a Korean Instrumental Activities of Daily Living (K-IADL) score  $\geq 0.43$  at 12 months. Values are number of patients (percentage within group). Statistical significance between groups was assessed using the chi-square test.

TABLE 3 Comparison of clinical outcome and MDS-Oa $\beta$  between Ginkgo and non-Ginkgo groups over 12 months.

Measure	Group	0 month	12 month	delta	P1*	P2*
K-MMSE	Ginkgo	28.4 $\pm$ 1.2	28.8 $\pm$ 0.9	0.4 $\pm$ 0.9	0.008	0.000
	Non-Ginkgo	28.5 $\pm$ 1.2	27.7 $\pm$ 0.9	-0.8 $\pm$ 1.2	0.008	
CDR-SB	Ginkgo	0.8 $\pm$ 0.5	0.8 $\pm$ 0.5	0.0 $\pm$ 0.1	0.323	NA
	Non-Ginkgo	0.9 $\pm$ 0.5	0.9 $\pm$ 0.5	0.0 $\pm$ 0.0	NA	
K-IADL	Ginkgo	3.4 $\pm$ 2.8	2.5 $\pm$ 2.7	-0.8 $\pm$ 1.3	0.001	0.000
	Non-Ginkgo	3.0 $\pm$ 1.4	3.5 $\pm$ 1.4	0.6 $\pm$ 0.9	0.013	
NPI	Ginkgo	3.7 $\pm$ 5.1	3.7 $\pm$ 5.1	0.0 $\pm$ 0.1	0.329	0.488
	Non-Ginkgo	1.2 $\pm$ 3.3	1.2 $\pm$ 3.5	0.0 $\pm$ 0.0	0.457	
MDS-Oa $\beta$ (ng/mL)	Ginkgo	0.88 $\pm$ 0.15	0.80 $\pm$ 0.11	-0.09 $\pm$ 0.10	0.000	0.000
	Non-Ginkgo	0.89 $\pm$ 0.11	0.91 $\pm$ 0.15	0.02 $\pm$ 0.07	0.255	

\*Within-group comparisons (P1) were conducted using paired *t*-tests, and between-group comparisons (P2) were conducted using independent *t*-tests. P1, Baseline vs Follow-up *p*-value (Within-group); P2, Ginkgo vs. non-Ginkgo *p*-value (Between-group); K-MMSE, Korean Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; CDR-SB, Clinical Dementia Rating Scale Sum of Box; K-IADL, Korean Instrumental Activities of Daily Living; NPI, Neuropsychiatric Inventory; MDS-Oa $\beta$ , Multimer Detection System-Oligomerized A $\beta$  assay, NA, Not applicable due to zero variance. Due to zero variance in the Non-Ginkgo group, statistical comparison was not applicable (NA). Hence, no conclusion can be drawn regarding group differences.

within-group). Conversely, the non-Ginkgo group exhibited a non-significant increase from 0.89 to 0.91 ng/mL ( $\Delta + 0.02$ ;  $p = 0.255$ ). The between-group difference in MDS-Oa $\beta$  change was statistically significant ( $p < 0.001$ ) (Figure 2).

## Analyzing the influencing variable for responder

In a linear regression model predicting responder status at 12 months, treatment group (Ginkgo vs. non-Ginkgo) was the only significant predictor ( $B = 0.319$ ,  $SE = 0.111$ , standardized  $\beta = 0.524$ ,  $t = 2.870$ ,  $p = 0.009$ ). No other variables—including sex, age, education, baseline MDS-Oa $\beta$ , CDR-SB, K-MMSE, K-IADL NPI, ApoE4 allele—were significantly associated with responder status (all  $p > 0.10$ ) (Table 4).

## Adverse events

Adverse events were generally mild and transient in both groups. In the Ginkgo group, the most commonly reported events were diarrhea (7.1%), headache (4.8%), nausea (4.8%), and dizziness (4.8%). The non-Ginkgo group experienced similar side effects, including nausea (9.0%), diarrhea (9.0%), and headache (4.5%). One case of skin rash occurred in the Ginkgo group. Importantly, no patient in either group discontinued treatment due to adverse events, suggesting favorable tolerability (Table 5).

## Discussion

This retrospective cohort study aimed to evaluate the efficacy of *Ginkgo biloba* monotherapy in patients with amyloid PET-positive MCI, using both clinical and biomarker endpoints. Our findings suggest that Ginkgo, when used alone without concomitant prescription anti-dementia medications, may offer measurable benefits in terms of cognitive stability, functional maintenance, and

reduction in plasma MDS-Oa $\beta$  levels over a 12-month follow-up period. In multivariate linear regression with responder status as the dependent variable, only Ginkgo group was significantly associated with being a responder, no other covariates reached statistical significance (Table 4). Our results are consistent with findings from recent studies that explored the use of EGb 761 in MCI and early dementia. For example, Tian et al. demonstrated a reduced incidence of dementia over 52 weeks in amnesic MCI patients treated with Ginkgo (16). Similarly, García-Alberca et al. found that Ginkgo in combination with acetylcholinesterase inhibitors improved cognitive and neuropsychiatric outcomes (28). While most studies have examined Ginkgo as an adjunct therapy, our study uniquely evaluates it in isolation, supported by biomarker evidence.

These results build upon our earlier study, which showed that the addition of Ginkgo to donepezil in amyloid PET-positive Alzheimer's disease (AD) patients led to better cognitive outcomes and a larger decrease in MDS-Oa $\beta$  (20). However, in that study, Ginkgo was not administered independently, and all patients received donepezil due to ethical standards. This limited our ability to isolate Ginkgo's effect. In contrast, the current study focused on MCI patients—a population where anti-dementia drugs are not reimbursed in Korea—allowing us to observe the standalone effects of Ginkgo in a real-world setting.

The cognitive preservation observed in the Ginkgo group is notable, especially considering that approximately 5–30% of amyloid PET-positive MCI cases convert to AD annually (4, 5). While the non-Ginkgo group showed mild decline in K-MMSE and modest functional worsening, the Ginkgo group not only maintained but slightly improved in both cognitive and functional outcome measures. These changes, though modest in magnitude, are clinically relevant given the context of early AD intervention, where even stabilization is a meaningful therapeutic target. The improvement in MDS-Oa $\beta$  levels further supports the potential disease-modifying effect of Ginkgo. This plasma biomarker reflects the dynamic propensity of A $\beta$  monomers to oligomerize, a process that is believed to play a critical pathogenic role in AD by disrupting synaptic function and triggering neuroinflammation. Traditional biomarkers like CSF A $\beta$ 42 and tau levels are static measures, whereas MDS-Oa $\beta$  offers insight into ongoing amyloidogenic activity. The observed reduction in MDS-Oa $\beta$

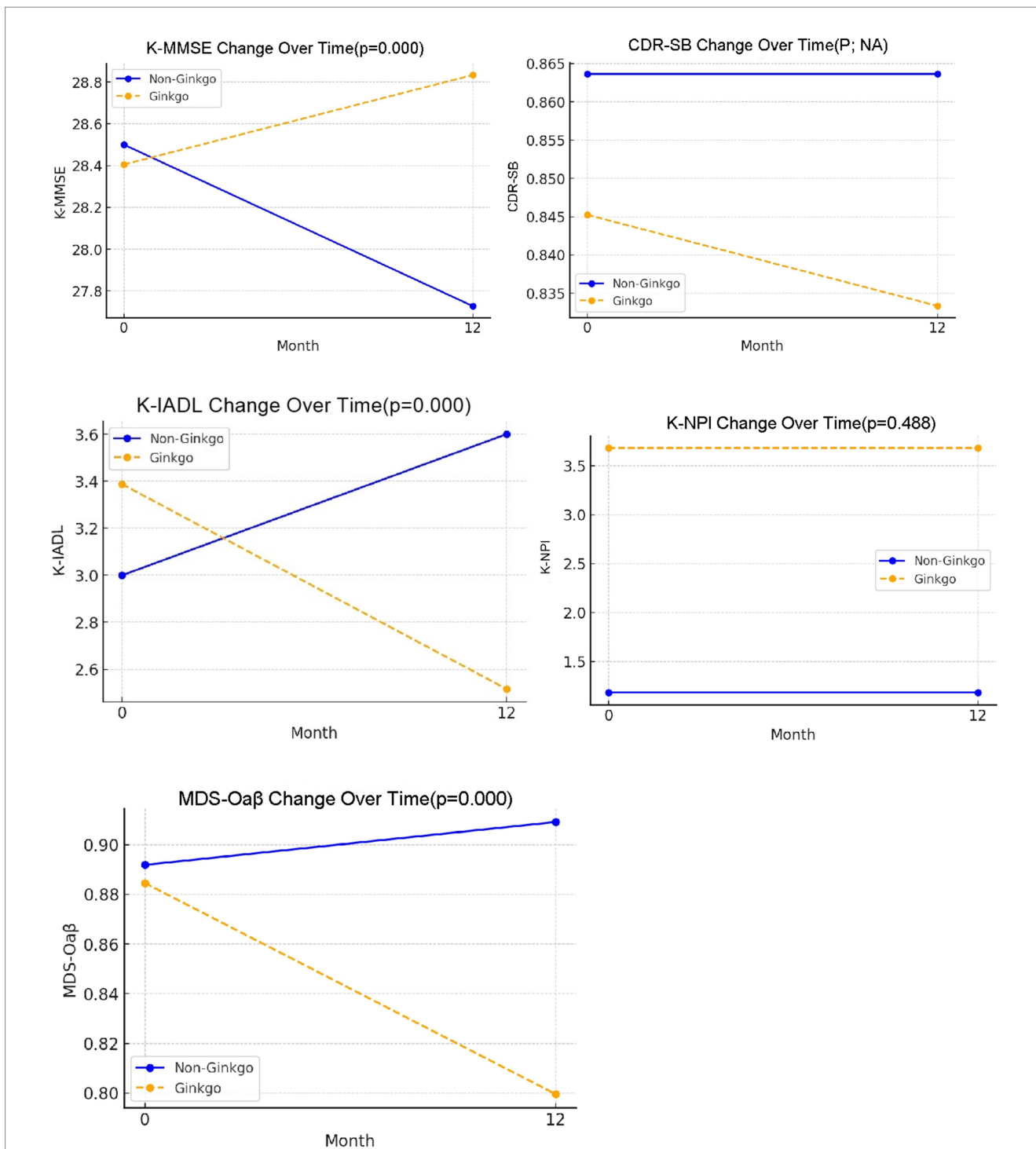


FIGURE 2 Change of K-MMSE, CDR-SB, K-IADL, K-NPI, and MDS-Oaβ in mild cognitive impairment patients with Ginkgo and Non-Ginkgo treatment.

in the Ginkgo group may indicate a suppression of toxic oligomer formation.

Mechanistically, standardized extracts of *Ginkgo biloba* contain bioactive components including flavonol glycosides (e.g., quercetin, kaempferol, and isorhamnetin) and terpene lactones (ginkgolides and bilobalide), which provide distinct yet complementary protective effects against amyloid-beta (Aβ) pathology. Flavonol glycosides

directly interact with Aβ peptides, disrupting the formation of β-sheet-rich oligomeric structures and inhibiting fibril nucleation, thus attenuating oligomer-induced synaptic toxicity. Additionally, their antioxidative activity mitigates oxidative stress-induced neuronal damage, a known accelerator of Aβ aggregation (8, 9). Ginkgolides, particularly ginkgolide B, have demonstrated potential inhibitory effects on β-secretase (BACE-1), the enzyme critically

TABLE 4 Linear regression analysis predicting responder status at 12 months.

Predictor	B	SE	Beta	t	p-value
Constant	-1.466	1.587	-	-0.924	0.366
Sex (male, female)	0.006	0.117	0.011	0.056	0.956
Age (years)	-0.007	0.007	-0.228	-1.002	0.327
Education (years)	0.002	0.014	0.029	0.138	0.892
MDS-Oa $\beta$	0.379	0.445	0.168	0.852	0.403
CDR-SB	-0.065	0.111	-0.134	-0.588	0.562
Baseline MMSE	0.083	0.057	0.305	1.443	0.163
NPI	0.021	0.013	0.342	1.709	0.102
Number of ApoE4	-0.030	0.097	-0.079	-0.306	0.762
K-IADL	-0.006	0.021	-0.056	-0.284	0.779
Group (Ginkgo vs. non-Ginkgo)	0.319	0.111	0.524	2.870	0.009

Linear regression was conducted to identify predictors of responder status, defined as the absence of decline in K-MMSE and no increase in CDR-SB over a 12-month period. Independent variables included demographic, clinical, and biomarker-related factors. A significant association was found between Ginkgo group membership and responder status ( $p = 0.009$ ). K-MMSE, Korean Mini-Mental State Examination; CDR, Clinical Dementia Rating Scale; CDR-SB, Clinical Dementia Rating Scale Sum of Box; K-IADL, Korean Instrumental Activities of Daily Living; NPI, Neuropsychiatric Inventory; MDS-Oa $\beta$ , Multimer Detection System-Oligomerized A $\beta$  assay.

TABLE 5 Adverse events in follow up study group.

Adverse event	Ginkgo ( $n = 42$ )	Non-Ginkgo ( $n = 22$ )
Diarrhea	3(7.1%)	2(9.0%)
Headache	2(4.8%)	1(4.5%)
Nausea	2(4.8%)	2(9.0%)
Vomiting	1(2.4%)	1(4.5%)
Dizziness	2(4.8%)	0(0.0%)
Skin lesion	1(2.4%)	0(0.0%)

In the Ginkgo group, 3 patients (7.1%) had multiple adverse events, and in the Non-Ginkgo group, 1 patient (4.5%) had multiple adverse events.

involved in amyloidogenic cleavage of amyloid precursor protein (APP), thereby reducing A $\beta$  generation at an early stage. Bilobalide further contributes neuroprotective effects through mitochondrial stabilization and promotion of autophagy-mediated clearance of misfolded proteins (29, 30). Collectively, these pharmacological activities likely synergize to reduce A $\beta$  oligomer formation and deposition, as reflected by decreased plasma MDS-Oa $\beta$  levels observed in our study. Importantly, these effects were achieved without the use of donepezil, rivastigmine, or memantine, highlighting the potential of Ginkgo as a monotherapy in the prodromal stage of AD.

The robustness of these findings is supported by two converging observations. First, our earlier add-on trial in amyloid-positive AD dementia showed that *Ginkgo biloba* produced a comparable magnitude of benefit when layered on top of donepezil, and that benefit tracked with a parallel reduction in plasma MDS-Oa $\beta$  levels (20). Second, in the present study, the non-Ginkgo group appeared to follow a clinical and biomarker trajectory similar to the natural course reported in longitudinal cohorts of amyloid-positive MCI: CDR-SB worsened over 12 months (4, 31), and MDS-Oa $\beta$  levels increased in a pattern consistent with previously reported biomarker trajectories in early-stage AD (27). The observation that the non-Ginkgo group showed clinical and biomarker trajectories similar to those reported in previous studies suggests that the likelihood of systematic bias or

measurement artefact may be low and provides some support for the interpretation of stability observed in the Ginkgo group. Nonetheless, because our design is retrospective and unblinded, these signals should be viewed as hypothesis-generating rather than confirmatory.

The study also holds significance in the context of current therapeutic limitations. Recently approved anti-amyloid agents such as lecanemab and donanemab have shown promise in modifying disease progression. While direct comparisons must be approached with caution due to substantial methodological differences, nonetheless the cognitive and functional outcomes in the Ginkgo group appeared relatively stable, and this observation may be of interest in the context of findings from recent monoclonal antibody trials. For example, in the Clarity AD study of lecanemab, all participants exhibited some degree of cognitive decline over 12 months, with a mean increase of approximately 1.2 points in CDR-SB despite treatment (32). A similar pattern of worsening was observed in the TRAILBLAZER-ALZ 1 trial of donanemab (33). In our study, however, no mean change in CDR-SB was observed and slight improvement in MMSE was noted over a comparable period. Moreover, their high costs, intravenous administration requirements, and limited availability hinder widespread adoption, particularly in countries without full insurance coverage. In contrast, *Ginkgo biloba* is accessible, affordable, and orally administered, making it a pragmatic option for early intervention. Furthermore, the ethical and logistical challenges of conducting large,

randomized trials in biomarker-confirmed MCI populations make real-world data increasingly valuable. Our study, based on registry-derived information and supported by biomarker assays, strengthens the internal validity of our findings.

Despite these promising results, several limitations must be acknowledged. First, the retrospective and non-randomized nature of this study inherently limits causal inference. Factors such as health behaviors, comorbidities, caregiver support, and other unmeasured variables might have influenced outcomes. Although we attempted to minimize these effects by comparing clinically similar groups, we did not apply formal statistical adjustments for baseline characteristics, and thus the possibility of residual confounding should be considered when interpreting between-group differences. Second, our sample size, while adequate for exploratory analysis, may not provide sufficient power to detect subtler subgroup effects or rare adverse events. Third, adherence to the assigned treatments was not objectively measured, although follow-up visits confirmed continued use in most cases. Fourth, while MDS-Oa $\beta$  is a promising biomarker, it should be acknowledged that MDS-Oa $\beta$  is not yet a globally standardized biomarker. To date, numerous peer-reviewed international studies have been published using MDS-Oa $\beta$ , demonstrating consistent analytic validity and substantial clinical utility in various contexts. Although its analytical performance can be sensitive to preanalytical factors—such as freeze–thaw cycles, sample handling, and storage duration—continuous efforts have been made to optimize and standardize these procedures. While there are currently no globally accepted regulatory standards or universal clinical thresholds for MDS-Oa $\beta$ , the method has already been approved by regulatory authorities in some countries (e.g., the Ministry of Food and Drug Safety, MFDS in Korea) and is actively utilized in clinical research. Thus, given its growing evidence base, MDS-Oa $\beta$  is emerging as a promising biomarker for Alzheimer's disease, warranting further prospective validation studies. Lastly, we did not assess other potential biomarkers such as plasma p-tau or neurofilament light chain (NfL), which could provide additional insights into disease progression. Nonetheless, the findings of this study carry practical implications. In healthcare systems where early AD treatments are not accessible or reimbursed, *Ginkgo biloba* may represent a viable first-line option for biomarker-confirmed MCI. Its tolerability profile and multi-mechanistic action make it especially suitable for early intervention strategies. For clinicians, the availability of real-world biomarker data may also encourage more personalized and proactive management of MCI. Future research should aim to validate these findings through prospective randomized controlled trials, ideally incorporating multimodal biomarkers (e.g., tau PET, digital cognitive tests, and CSF markers). Additionally, studies comparing *Ginkgo* to emerging AD treatments in head-to-head designs could clarify its position in the evolving therapeutic landscape.

## Conclusion

This study provides preliminary but compelling evidence that *Ginkgo biloba* monotherapy may offer clinical and biological benefits in amyloid PET-positive MCI. By stabilizing cognitive performance and reducing amyloid oligomerization in plasma, *Ginkgo* may represent a cost-effective and accessible option for early-stage intervention in the Alzheimer's continuum.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The study involving humans was approved by the Institutional Review Board of Soonchunhyang University Cheonan Hospital (IRB No. 2023-10-025) and conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants due to the retrospective nature of this study.

## Author contributions

YY: Data curation, Investigation, Writing – review & editing, Project administration, Writing – original draft. M-SK: Conceptualization, Investigation, Writing – review & editing. YK: Writing – review & editing, Formal analysis, Writing – original draft, Methodology, Data curation, Supervision, Conceptualization.

## Funding

The author(s) declare that financial support was received for the research and/or publication of this article. This research did not receive specific funding for its design or conduct. However, the publication fee was partially supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI22C0667).

## Acknowledgments

We would like to acknowledge the Soonchunhyang University Dementia Registry for providing the data used in this study. We also thank the staff of the Dementia Clinic at Soonchunhyang University Cheonan Hospital for their assistance in maintaining and managing the registry.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Generative AI statement

The authors declare that no Gen AI was used in the creation of this manuscript.

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