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Does Gotu kola supplementation improve cognitive function, inflammation, and oxidative stress more than multicomponent exercise alone? – a randomized controlled study

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A randomized control trial was conducted to investigate the synergistic effects of Gotu kola supplementation and multicomponent exercise on cognitive function, inflammation, and oxidative stress in older adults with mild cognitive impairment (MCI). Sixty participants aged 74.6±7.3 years with Mini-Mental State Examination (MMSE) scores of 20.7±2.6 were randomly assigned to one of three groups: a multicomponent exercise training group (EXE, n=20), a multicomponent exercise training with Gotu kola supplementation group (EXE+GK, n=20), or a placebo-controlled group (CON, n=20). Each participant received one capsule of placebo or 500 mg twice a day of Gotu kola extract. The multicomponent exercise program comprised of supervised resistance, aerobic, balance and dual-task training: three 80-min sessions/week for 12 weeks. The primary outcomes, such as cognitive function, inflammatory markers, and oxidative stress, were measured before and after the 12-week intervention. Following the interventions, the EXE and EXE+GK had significantly higher MMSE ($P<0.01$), Digit Span Forward test (DSF) ($P<0.01$), Digit Span Backward test ($P<0.01$) scores, and lower Trail Making Test parts A ($P<0.01$) and B ($P<0.01$) and lower 8-iso-prostaglandin F2α ($P<0.01$) and tumor necrosis factor alpha (TNF-α) ($P<0.01$) than the CON. The change in DSF and TNF-α in the EXE+GK had a negative correlation ($r=-0.504$, $P<0.05$). In conclusion, multicomponent exercise training with or without the supplement Gotu kola improves cognitive function, inflammation, and oxidative stress in older adults with MCI. Although supplementing with Gotu kola had no additional effects on cognitive function, it may improve the effects of multicomponent exercise on executive function by decreasing TNF-α levels.

Keywords: Cognition, Inflammation, Multicomponent exercise, Older adults, Oxidative stress

INTRODUCTION

Mild cognitive impairment (MCI) is a condition characterized by diminished cognitive function and the development of Alzheimer disease (AD) or the preclinical stage of other types of dementia. The ability to perform daily functional activities is preserved in this state, indicating that the patient is in an intermediate stage between normal aging and dementia (Petersen et al., 1999). Reducing or recovering from identified risk factors is critical for preventing the progression of MCI to AD or delaying the onset of dementia's prodromal symptoms. Therefore, early intervention at the stage of MCI can enable patients to maintain and improve their cognitive performance (Rodakowski et al., 2015).

Since AD is related to elevated levels of proinflammatory cyto-

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kines and lower levels of anti-inflammatory cytokines, there has been an increased focus on the role of inflammation in memory and learning deficits. Numerous proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), can activate microglia, which are readily triggered in response to immunologic stress and injury. Activation of glia, known as reactive gliosis, has been observed during the pathogenesis of AD (Krause and Müller, 2010; Shadfar et al., 2015). In addition, the generation and accumulation of amyloid-beta (Aβ) peptides caused by oxidative stress such as lipid peroxidation results in neuronal degeneration, which is commonly observed in AD (Krause and Müller, 2010).

Exercise has become an increasingly important non-pharmacological therapy in preventing cognitive function decline in patients with cognitive impairment (Huang et al., 2022). According to these findings, randomized controlled trials investigating the efficacy of exercise in subjects with MCI showed some positive cognitive outcomes, mainly on global cognition, executive function, or attention (Baker et al., 2010; Khanthong et al., 2021; Lam et al., 2011; Loprinzi et al., 2019; Nagamatsu et al., 2012; Nagamatsu et al., 2013; Suzuki et al., 2013; Varela et al., 2012). In addition, recent systematic review and meta-analysis studies have also discovered that multicomponent exercise is most likely to protect the global cognition and executive function of MCI patients (Huang et al., 2022; Wang et al., 2020). The multicomponent exercise programs consisted of aerobic exercise, strength training, and balance exercise since previous research found that combined aerobic exercise and strength training interventions improved attention and working memory more than aerobic exercise alone (Colcombe and Kramer, 2003; Smith et al., 2010). However, there is a lack of data on the effect of multicomponent exercise on biological markers for this in older adults with MCI (Wang et al., 2020).

Natural medicines are increasingly being used, particularly in their more effective herbal form, rather than the isolation of the pure compound (Dhanasekaran et al., 2009). *Centella asiatica* (L.) Urban, also known as Gotu kola, is a plant that has been utilized as a memory-enhancing substance (Puttarak et al., 2017). Triterpenes, which include asiaticoside, madecassoside, asiatic acid, and madecassic acid, are the primary components of Gotu kola and have antioxidant, anti-inflammatory, and antiapoptotic properties (Sun et al., 2020). A meta-analysis and systematic review revealed that Gotu kola may improve working memory. However, there is insufficient evidence to support Gotu kola's benefits in improving overall cognitive function, specifically attention and concentration, executive function, and information processing speed (Puttarak et al., 2017).

To the best of our knowledge, no evidence has been reported on the synergistic effects of Gotu kola and multicomponent exercise training on cognitive function. The present randomized trial was designed to test whether a combination of a 12-week supervised multicomponent exercise program with Gotu kola supplementation could improve cognitive function, especially in working memory and executive function, among older adults with MCI. We attempted to establish a causal relationship between changes in concentrations of 8-iso-prostaglandin F2α (8-iso-PGF2α), TNF-α, and IL-6 and improvements in cognitive domains.

MATERIALS AND METHODS

Participants

A total of 157 community-dwelling individuals aged 65 and up were recruited from senior citizen centers in Bangkok, Thailand. During the initial eligibility assessments, 82 potential participants with pre-existing memory difficulties were enrolled (Petersen et al., 2014). The participants were screened using the following inclusion criteria: being over 65 years old, living independently in the community (i.e., no impairment in activities of daily living), having sufficient hearing and visual acuity to participate in examinations, having Mini-Mental State Examination (MMSE) scores of 23 or lower, meeting the definition for the amnestic type of MCI, and having medical clearance to perform physical activities. Exclusion criteria included a history of major psychiatric illness, as well as other serious neurological or musculoskeletal diagnoses or kidney disease. Sixty participants (50 women and 10 men) aged 74.6±7.3 years old met the inclusion criteria and were randomly assigned to either the intervention or control groups.

The study was approved by the Ethical Review Committee for Research in Human Subjects, Ministry of Public Health, Thailand (Ref. no. 2/2558). Written and verbal informed consent were obtained from all participants; verbal consent was witnessed and formally recorded. This study was registered as a clinical trial with the Thai Clinical Trials Registry (TCTR20180228001). Sample size was based on the ability to detect a moderate to large effect (1.1) according to a previous report by Farhana et al. (2016). As a consequence, it was decided to require 80% power at 0.05 significance. Thus, having at least 11 participants in each group was required to complete the study. The demographic information of the participants in the study is presented in Table 1.

Study design

This was a 12-week, single-blind, placebo-controlled random-

Table 1. Baseline characteristics of the participants

Variable	CON (n=18)	EXE (n=20)	EXE+GK (n=20)	*P*-value
Age (yr)	73.7±8.3	73.2±4.9	77.7±7.7	0.100
Female sex	15/3 (83.3)	17/3 (85)	16/4 (80)	0.913
MMSE (score)	21.2±2.5	20.6±2.1	20.1±3.0	0.474
Level of education				
Unable to read and write	1 (5.6)	2 (10)	2 (10)	0.865
Incomplete primary school	6 (33.3)	5 (25)	6 (30)	0.850
Complete primary school	10 (55.6)	12 (60)	11 (55)	0.941
High school or university	1 (5.6)	1 (5)	1 (5)	0.996
Marital status				
Single	6 (33.3)	5 (25)	6 (30)	0.850
Married	11 (61.1)	13 (65)	12 (60)	0.943
Widowed	1 (5.6)	2 (10)	2 (10)	0.856
Underlying diseases				
Hypertension	12 (66.7)	14 (70)	12 (60)	0.795
Diabetes	10 (55.6)	12 (60)	10 (50)	0.816
Dyslipidemia	6 (33.3)	7 (35)	6 (30)	0.943
Heart disease	0 (0)	0 (0)	0 (0)	1.000
Pulmonary disease	0 (0)	0 (0)	0 (0)	1.000
Osteoarthritis	2 (11.1)	3 (15)	3 (15)	0.924

Values are presented as mean±standard deviaiton or number (%).
CON, placebo-controlled group; EXE, multicomponent exercise training group; EXE+GK, multicomponent exercise training with Gotu kola supplementation group; MMSE, Mini-Mental State Examination.

ized trial; measurements were taken at baseline and 12 weeks after the intervention. After baseline measurements, 60 participants were randomly assigned to one of three groups: a multicomponent exercise training group (EXE, n=20); a multicomponent exercise training with Gotu kola supplementation group (EXE+GK, n=20); or a placebo-controlled group (CON, n=20), and 58 participants completed the study. Two subjects in the CON withdrew prior to completion of the intervention, while no subject withdrew in the EXE and EXE+GK. The flowchart illustrates the procedure for selecting participants and carrying out the experiment (Fig. 1). Each participant received one capsule of placebo or 500 mg twice a day of Gotu kola extract. The color, texture, size, and smell of the placebo and Gotu kola extract capsules were identical.

The EXE and EXE+GK participants engaged in three 80-min sessions of multicomponent exercise training each week. Throughout the study period, all participants were instructed to continue their usual levels of physical activity, except for the interventions. They were instructed to maintain their food intake, i.e., the same intake levels as prior to the outset of the study. The participants' nutritional intake was tracked by monitoring their nutrition diaries. Participants were also notified not to take any other dietary supplements. The review of side-effect compliance was conducted independently by investigators who were also blind to group as-

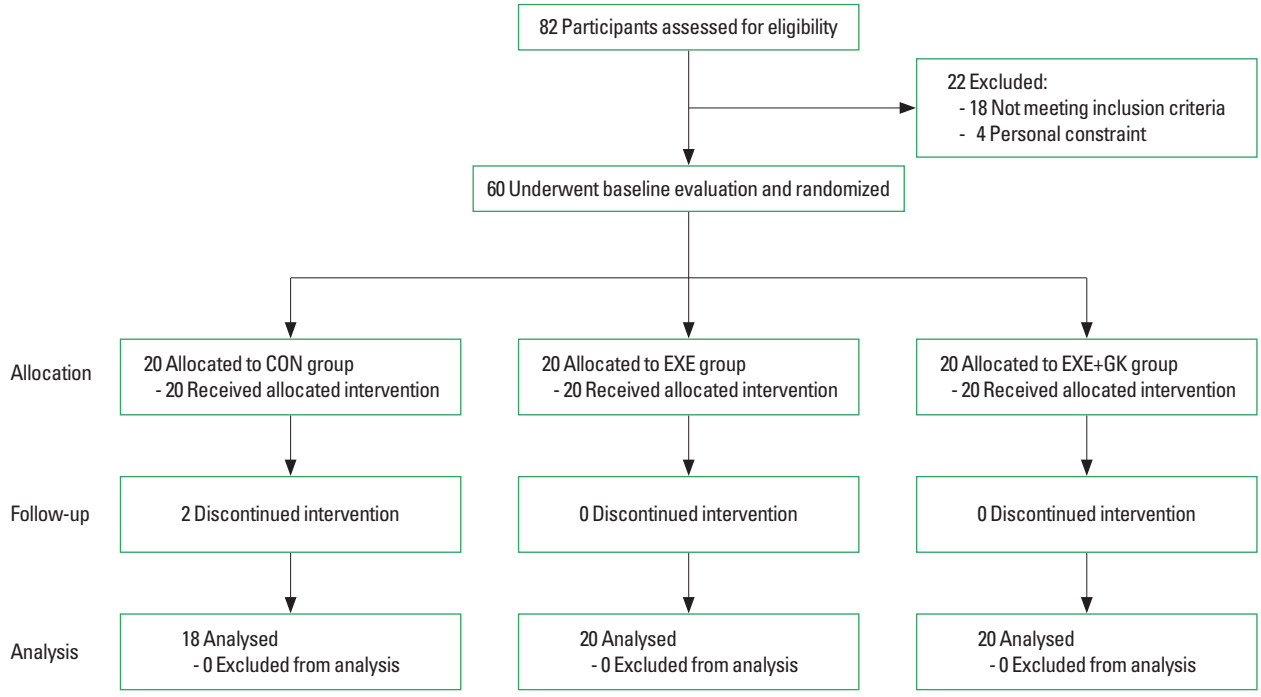

Fig. 1. CONSORT (consolidated standards for reporting of trials) flow diagram. CON, placebo-controlled group; EXE, multicomponent exercise training group; EXE+GK, multicomponent exercise training with Gotu kola supplementation group.

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signment. At each study visit, adverse effects were examined. During the period of this study, participants were instructed to contact the research center if they experienced any medical complications. To identify any contraindications, fasting blood glucose (FBG), aspartate transaminase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, and creatinine levels were measured and monitored prior to and throughout the trial. This study evaluates cognitive function, which consists of general cognitive function, executive function, and memory domains, oxidative stress, inflammatory markers, and functional mobility at baseline and after 12-week interventions.

Preparation of crude extracts

The crude extracts were prepared by the Bioresources and Biodiversity Section, Central Laboratory and Greenhouse Complex, Kasetsart University. Gotu kola was collected in Nakhon Pathom, Thailand. Only the leaf portion was used. The fresh leaves were dried at room temperature before being dried in a hot air oven at 70°C for 8 hr. The powdered dried leaves were finely ground. The leaf powder (500 g) was macerated after being extracted with 95% ethanol. To obtain the crude extracts (240 g), ethanol was removed using rotary evaporators under vacuum (Rotavapor R-205, BUCHI, Flawil, Switzerland). The leaf powder (500 g) and fresh leaves (500 g) were boiled in distilled water under reflux for one hour for the water crude extracts. The solution was then filtered and freeze-dried (Telstar Lyoalfa-6, Telstar, Terrassa, Spain) to obtain extract powder of 20 g and fresh leaves of 16 g, respectively. All crude extracts were stored at -20°C until they were used.

Exercise intervention

The participants exercised for 80 min per day, 3 times per week, for 12 weeks under the supervision of personal trainers. Each supervised session began with a 5-min warm-up period, followed by 30 min of muscle-strengthening exercise, and 40 min of aerobic exercise, postural balance retraining, and dual-task training, followed by a 5-min cool-down. The training program was designed according to the studies reviewed (Suzuki et al., 2012; Suzuki et al., 2013). Strengthening exercises were performed in a progressive sequence from seated to standing positions, with progressive resistance applied to increasing repetitions of each exercise or weight holding. Participants sat in a chair and performed toe raises, heel raises, knee lifts, knee extensions, sit to stand and other exercises. Participants then performed hip flexions, half squats, lateral leg raises, and repetitions of other exercises while standing upright behind the chair and holding the chair's back for stability. Participants completed circuit training in aerobic exercises and postural balance retraining, which included stair stepping, endurance walking, and postural balance retraining. The average intensity of the aerobic exercises was 65%–75% of the maximum heart rate. Throughout the aerobic exercise session, their heart rate was monitored by taking their pulse. Pulse rates and oxygen saturation were continuously monitored throughout the exercise session using a pulse oximeter (MD300C20 Pulse Oximeter, Beijing Choice Electronic Tech Co., Ltd, Beijing, China). These exercises were also carried out while multitasking. Participants were instructed to memorize a step pattern in consecutive square segments and to step as quickly and accurately as possible while walking. Following that, participants practiced postural balance retraining, which included standing on one leg, multidirectional weight shifts, and walking on balance boards. Throughout the program, researchers and personal trainers provided ongoing safety monitoring to prevent negative accidents such as falls.

Anthropometrics and body composition measurements

Body weight was measured via an electronic scale (Filizzola PL 150, Filizzola Ltda, São Paulo, Brazil). Height was measured minus shoes using a standard stadiometer (Health o Meter Professional, Sunbeam Products Inc., Boca Raton, FL, USA). Body mass index (BMI) was calculated as weight divided by height squared. Waist circumference was measured at the end of inspiration from the midpoint between the lower rib margin and the iliac crest with a flexible and inextensible measuring tape (Hoechstmass Balzer GmbH, Sulzbach, Hessen, Germany). Hip circumference was also measured at the level of the trochanter major, with a waist-to-hip circumference (W/H) ratio also calculated. Body composition, including % body fat, fat mass, and fat free mass, was measured using a bioimpedance analysis device (Inbody 720, Biospace Inc., Seoul, Korea) with light clothing and without shoes.

Blood samples collection

Blood samples for inflammatory markers were collected in standardized fasting conditions (12 hr) in the mornings between 7:00 and 9:00 a.m. at baseline and 7 days after the last training session to minimize any acute effects of exercise. Blood was collected in a vacuum test tube and centrifuged at 1,500 g for 15 min at 4°C. The plasma aliquots were then frozen at -80°C until they were analyzed.

Biochemical analysis

Total cholesterol (TC), high-density lipoprotein cholesterol

(HDL-C), and triglyceride (TG) concentrations (mg/dL) were determined using an automated colorimetric assay (BS-200, Shenzhen Mindray Bio-medical Electronics Co., Nanjing, China). Low-density lipoprotein cholesterol (LDL-C) concentration was calculated via the Friedewald equation (Friedwald, 1972). Atherogenic index of plasma (AIP) was computed by transforming the ratio of TG to HDL-C by a logarithmic scale. The non-HDL-C was computed by subtracting HDL-C from TC, and the atherogenic index (AI) was computed as the ratio of non-HDL-C to HDL-C. FBG levels were also measured using standard methods at Nakhon Pathom Hospital in Nakhon Pathom, Thailand.

Inflammatory markers and oxidative stress analysis

Plasma concentrations of IL-6 and TNF-α were measured using an enzyme-linked immunosorbent assay (ELISA) (Cayman Chemical Company, Ann Arbor, MI, USA) in accordance with the manufacturer's instructions. The plasma 8-iso-PGF2α concentration was analyzed by ELISA using commercial kits (Cayman Chemicals, Ann Arbor, MI, USA) in accordance with the manufacturer's instructions. The blood samples were run in duplicate. Researchers conducting ELISAs were blinded to all patient information.

Cognitive function assessment

Cognitive function, including general cognitive function, executive function, and memory domains, was assessed at baseline and 12 weeks following the intervention. Occupational therapists conducted cognitive evaluations using standardized methods, including the MMSE, Trail Making test (TMT), and Digit Span test (DST). The assessors introduced and demonstrated the assessments to facilitate understanding of the tests by the participants before they conducted the tests. The MMSE was used to assess general cognitive function. The TMT part A (TMT-A) and part B (TMT-B) were used to assess executive function. TMT-A requires participants to connect numbers ranging from 1 to 25 on a paper sheet. The TMT-B is similar to the TMT-A, except that participant connect numbers and letters alternately. Participants were asked to complete the tests as quickly and accurately as possible. The total time to complete the task is the score for each section. The DST, which consists of two subsections, the Digit Span Forward (DSF) test and the Digit Span Backward (DSB) test, was used to assess memory function. The DSF, which measures short-term memory, requires participants to memorize and repeat the numbers shown on a computer screen in the same order. In the DSB, measuring working memory, participants have to repeat the numbers in reverse order. The score for each test is determined by the number of correctly repeated sequences until participants are unable to reproduce two sequences of equal length.

Functional mobility assessment

Functional mobility and balance were assessed before and after the intervention using the 4-m timed walk test (4-MWT) and Timed Up and Go test (TUG). Participants were instructed to walk a straight 4-m distance at their normal ambulation pace for the 4-MWT. The mean duration of two trials was converted to walking speed (m/sec) (Miller et al., 2012). For TUG, participants were instructed to stand up from a chair with armrests without using their hands, walk for 3 m, and then return to their starting position (seated on the chair). The time required to complete the test was recorded. Assistive walking devices were only used at the participant's request or if the investigators observed a risk of falling.

Statistical analysis

The results were presented as the mean and standard deviation. The Shapiro–Wilk test was used to determine normality. A one-way analysis of variance or Pearson chi-square were used to compare baselines between groups. Covariates were used as baseline values. Prior to the analysis of covariance (ANCOVA), the data were transformed logarithmically to meet the normal distribution criterion. Aside from that, the measurement results were examined to see if they met the assumptions of normality, linearity, and variance homogeneity. ANCOVA was used to compare outcome variables between groups. The Bonferroni test was used for pairwise comparisons. The dependent *t*-test was used for within-group analysis. An effect size analysis was performed using eta-squared (η^2) for the ANCOVA, and interpreted 0.2, 0.5, and 0.8 as small, medium, and large, respectively. The Spearman correlation was used to examine correlations between changes (Δ; 12-week value - baseline value) in cognitive domains and oxidative stress and inflammatory markers. The level of statistical significance was set at $P < 0.05$. Statistical analyses were conducted by employing IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA).

RESULTS

The characteristics of the participants did not differ significantly between groups. Across all clinical parameters examined, all groups had similar profiles (Table 1). Participant adherence to the supervised training program was 100%. During the aerobic training sessions, participants completed more than 98% of the prescribed exercise duration and exercised at 100% of the prescribed exercise

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intensity. During the resistance training sessions, participants completed 98% of the prescribed sets and exercised at 100% of the prescribed weight. Aside from the intervention, there was no significant change in levels of habitual physical activity over time, and no difference was observed between groups. There were no significant changes in energy, fat, carbohydrates, or protein consumption. Throughout the study, there were no obvious side effects from Gotu kola.

Anthropometric and body composition parameters are shown in Table 2 before and after intervention. There were no significant differences in any anthropometric or body composition parameters in the CON group after the intervention. The EXE showed a significant reduction in W (-1% decrease, $P<0.01$) and H (-0.6%, $P<0.05$) following the intervention. After the intervention, BW (-0.9% decrease, $P<0.01$), BMI (-0.9% decrease, $P<0.01$), and W (-0.8% decrease, $P<0.05$) were significantly lower in the EXE+GK group. There was a significant difference in W ($F[2, 54]=7.841$, $\eta^2=0.225$, $P=0.001$) and H ($F[2, 54]=4.833$, $\eta^2=0.152$, $P=0.012$) between the groups, while adjusting for the baseline value. The EXE had significantly lower W ($P<0.01$) and H ($P<0.05$) than the CON, but there was no difference when compared to the EXE+GK. While W of the EXE+GK was significantly lower ($P<0.01$) than that of the CON, there was no difference when compared to the EXE. However, there was no statistically significant difference in % body fat, fat mass, fat free mass, or W/H ratio in the EXE and EXE+GK groups after the intervention.

As for lipid profiles, the CON showed a significant increment in FBG (16.8% increase, $P<0.01$) and TG/HDL-C ratio (16.1% increase, $P<0.05$), and a reduction in HDL-C (-3.3% decrease,

Table 2. Anthropometrics, body composition, and lipid profiles at baseline and post intervention

Variable	CON (n=18)		EXE (n=20)		EXE+GK (n=20)	
	Baseline	Posttest	Baseline	Posttest	Baseline	Posttest
BW (kg)	56.0±10.4	56.4±10.6	58.4±8.3	58.3±9.6	57.3±10.4	56.7±10.1**
BMI (kg/m^2)	24.5±5.1	24.7±5.2	24.1±2.3	24±2.8	25.4±3.4	25.1±3.3**
Body fat (%)	31.7±6.6	32±6.4	32.8±6.2	32±5.9	32±5.6	32.1±5.5
Fat mass (kg)	18.2±6.2	18.4±6.2	19.3±4.4	18.6±4.4	18.8±6.2	18.5±5.9
Fat free mass (kg)	37.8±5.6	38.0±5.7	39.1±6.8	39.7±8.1	38.6±5.3	38.3±5.2
W (cm)	82.5±11.6	83±11.3	89±7.9	88.1±7.8**,††	85.8±10.2	85.1±10.0*,††
H (cm)	93.4±9.5	94.3±9.8	97.3±6.4	96.7±6.1**,†	94.5±6.5	94.0±5.9
W/H ratio	0.88±0.1	0.88±0.1	0.91±0.1	0.91±0.1	0.91±0.1	0.91±0.1
FBG (mg/dL)	84.1±15.1	98.9±25.8**	94.9±11.6	92.2±11.9**,††	91.8±25.8	88.2±24.5**,††
TC (mg/dL)	190.2±43.1	186.4±35.3	208±37.3	197.9±32**	184.2±20.8	175.1±22.0**
TG (mg/dL)	99.1±56.7	115.2±61.1	98.4±28.2	88.6±26.0**,††	121.3±54.0	104.1±38.9**,††
HDL-C (mg/dL)	63.0±15.4	60.7±14.3*	57.8±14.2	60.3±14.3	57.6±17.2	61.4±16.2*,††
LDL-C (mg/dL)	106.3±37.2	104.7±53.6	130.7±36.6	119.2±31.8**	99.8±18.0	90.3±12.7**
Non-HDL-C (mg/dL)	127.2±39.8	125.7±34.9	150.2±36.2	137.6±35.6**	126.6±23.3	113.7±26.1**
TG/HDL-C ratio	1.8±1.5	2.2±1.8*	1.9±0.8	1.6±0.7**,††	2.3±1.3	1.8±1.0**,††
LDL-C/HDL-C ratio	1.8±0.8	1.8±0.8	2.4±0.9	2.1±0.8**	1.9±0.7	1.6±0.4**
AI	2.2±1.1	2.2±1.2	2.8±1.0	2.5±0.9**,†	2.4±1.0	2.0±0.9**,††
AIP	0.2±0.3	0.2±0.3	0.2±0.2	0.2±0.2**,††	0.3±0.2	0.2±0.2**,††
AST (U/L)	30.8±8	32.3±8.9	29.4±7.9	30.4±9.0	31.3±9.6	32.8±8.6
ALT (U/L)	18.2±7.8	17.1±8.8	17.1±6.4	16.8±7.5	22.8±15.3	22.3±15.5
ALP (U/L)	71.1±21.7	74.9±21.7	78.2±23.3	78.3±22.8	74.5±21.9	75.8±19.7
BUN (mg/dL)	18.2±7.8	16.9±5.5	13.3±3.1	13.9±4.6	14.2±4.3	14.8±3.8
Creatinine (mg/dL)	0.9±0.3	0.9±0.3	0.9±0.3	1.0±0.3	0.8±0.2	0.8±0.2

Values are presented as mean±standard deviaiton.
CON, placebo-controlled group; EXE, multicomponent exercise training group; EXE+GK, multicomponent exercise training with Gotu kola supplementation group; BW, body weight; BMI, body mass index; W, waist circumference; H, hip circumference; W/H ratio, waist-to-hip ratio; FBG, fasting blood glucose; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; AI, atherogenic index; AIP, atherogenic index of plasma; AST, aspartate transaminase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen.
*$P<0.05$ and **$P<0.01$ to within-group comparison (baseline vs. postintervention). †$P<0.05$ and ††$P<0.01$ to between-group comparison (vs. CON).

$P < 0.05$) following the intervention, with no significant differences between groups. Following the intervention, there was a significant decrease in FBG (-2.9% decrease, $P < 0.01$), TC (-4.5% decrease, $P < 0.01$), TG (-8.9% decrease, $P < 0.01$), LDL-C (-8.2% decrease, $P < 0.01$), non-HDL-C (-8.7% decrease, $P < 0.01$), TG/HDL-C ratio (-12.7% decrease, $P < 0.01$), LDL-C/HDL-C ratio (-12.1% decrease, $P < 0.01$), AI (-12% decrease, $P < 0.01$), and AIP (-55.2% decrease, $P < 0.01$) in the EXE group. In the EXE+GK, FBG (-3.4% decrease, $P < 0.01$), TC (-4.9% decrease, $P < 0.01$), TG (-10.5% decrease, $P < 0.01$), LDL-C (-8% decrease, $P < 0.01$), non-HDL-C (-10.5% decrease, $P < 0.01$), TG/HDL-C ratio (-16.3% decrease, $P < 0.01$), LDL-C/HDL-C ratio (-13.7% decrease, $P < 0.01$), AI (-16% decrease, $P < 0.01$), and AIP (-34.5% decrease, $P < 0.01$) were significantly reduced and HDL-C (7.8% increase, $P < 0.05$) was significantly increased after the intervention (Table 2).

There was a significant difference in FBG ($F[2, 54] = 17.164$, $\eta^2 = 0.389$, $P = 0.000$), TG ($F[2, 54] = 7.754$, $\eta^2 = 0.223$, $P = 0.001$), HDL-C ($F[2, 54] = 5.415$, $\eta^2 = 0.167$, $P = 0.007$), TG/HDL-C ratio ($F[2, 54] = 11.925$, $\eta^2 = 0.306$, $P = 0.000$), LDL-C/HDL-C ratio ($F[2, 54] = 6.791$, $\eta^2 = 0.201$, $P = 0.002$), AI ($F[2, 54] = 7.503$, $\eta^2 = 0.3217$, $P = 0.001$), and AIP ($F[2, 54] = 6.89$, $\eta^2 = 0.203$, $P = 0.002$) between the groups, while adjusting for the baseline value. The EXE had significantly lower FBG ($P < 0.01$), TG ($P < 0.01$), TG/HDL-C ratio ($P < 0.01$), AI ($P < 0.05$), and AIP ($P < 0.01$) than the CON. While the EXE+GK had significantly lower FBG ($P < 0.01$), TG ($P < 0.01$), TG/HDL-C ratio ($P < 0.01$), AI ($P < 0.01$), and AIP ($P < 0.01$) and higher HDL-C ($P < 0.01$) than the CON. However, no differences in FBG, lipid profiles, or AI variables were found between the EXE and EXE+GK groups. Furthermore, there were no significant differences in TC, LDL-C, non-HDL-C, or LDL-C/HDL-C ratio between groups (Table 2).

Cognitive function parameters before and after intervention are shown in Table 3. There were no significant differences in any of the cognitive function parameters in the CON group after the intervention. The EXE showed a significant increase in MMSE (10.4% increase, $P < 0.01$), DSF (22.3% increase, $P < 0.01$), DSB (44.9% increase, $P < 0.01$) scores, and a decrease in TMT-A (-8.8% decrease,

Table 3. Cognitive function at baseline and post intervention

Variable	CON (n = 18)		EXE (n = 20)		EXE+GK (n = 20)	
	Baseline	Posttest	Baseline	Posttest	Baseline	Posttest
MMSE (score)	21.2 ± 2.5	20.4 ± 2.8	20.6 ± 2.1	22.7 ± 2.8**,††	20.1 ± 3.0	22.2 ± 3.6**,††
DSF (score)	4.0 ± 1.5	3.9 ± 1.2	4.6 ± 1.1	5.6 ± 1.2**,††	4.5 ± 1.3	5.5 ± 1.6**,††
DSB (score)	3.1 ± 1.2	2.9 ± 1.1	3.6 ± 1.3	4.6 ± 1.2**,††	3.4 ± 1.4	4.5 ± 1.3**,††
TMT-A (sec)	99.6 ± 22.3	99.9 ± 20.1	91.8 ± 23.8	83.6 ± 20.9**,††	101.5 ± 29.0	87.1 ± 26.2**,††
TMT-B (sec)	172.4 ± 38.7	180 ± 39.6**	170.2 ± 35.5	145.2 ± 26.2**,††	170.5 ± 45.6	157.5 ± 39.3**,††

Values are presented as mean ± standard deviaiton.
CON, placebo-controlled group; EXE, multicomponent exercise training group; EXE+GK, multicomponent exercise training with Gotu kola supplementation group; MMSE, Mini-Mental State Examination; DSF, Digit Span Forward test; DSB, Digit Span Backward test; TMT-A, Trail Making test part A; TMT-B, Trail Making test part B.
**$P < 0.01$ to within-group comparison (baseline vs. postintervention). ††$P < 0.01$ to between-group comparison (vs. CON).

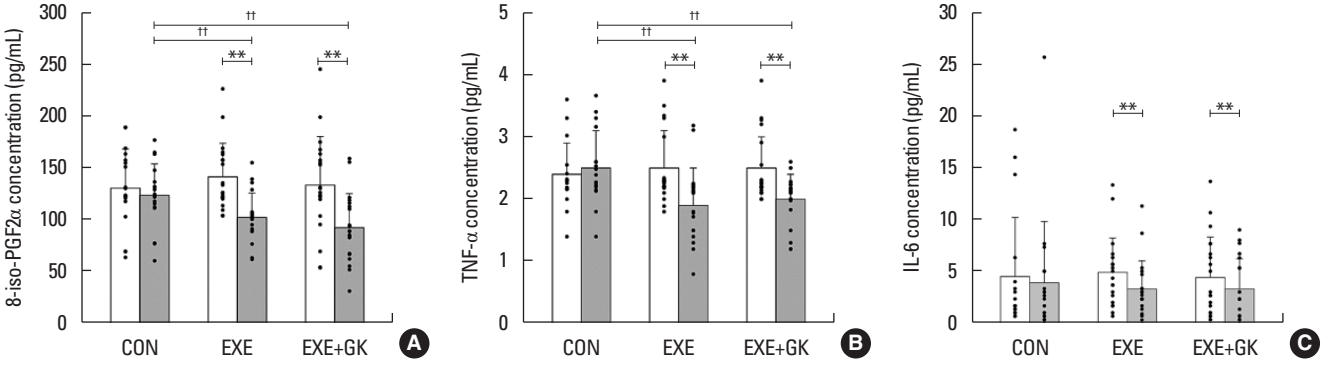

Fig. 2. Changes in levels of 8-iso-PGF2α (A), TNF-α (B), and IL-6 (C) at baseline and following the intervention. 8-iso-PGF2α, 8-iso-prostaglandin F2α; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; CON, placebo-controlled group; EXE, multicomponent exercise training group; EXE+GK, multicomponent exercise training with Gotu kola supplementation group. **$P < 0.01$ to within-group comparison (baseline vs. post interventions). ††$P < 0.01$ to between-group comparison (vs. CON).

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$P < 0.01$) and TMT-B (-12.4% decrease, $P < 0.01$) following the intervention. In the EXE+GK, MMSE (10.4% increase, $P < 0.01$), DSF (22.3% increase, $P < 0.01$), and DSB (50.5% increase, $P < 0.01$) scores were significantly higher, while TMT-A (-14.9% decrease, $P < 0.01$) and TMT-B (-8% decrease, $P < 0.01$) were significantly lower after the intervention. There was a significant difference in the scores of MMSE ($F[2, 54] = 13.158$, $\eta^2 = 0.328$, $P = 0.000$), DSF ($F[2, 54] = 17.208$, $\eta^2 = 0.389$, $P = 0.000$), DSB ($F[2, 54] = 26.505$, $\eta^2 = 0.495$, $P = 0.000$), TMT-A ($F[2, 54] = 30.142$, $\eta^2 = 0.527$, $P = 0.000$), and TMT-B ($F[2, 54] = 16.296$, $\eta^2 = 0.376$, $P = 0.000$) between the groups, while adjusting for the baseline value. The EXE and EXE+GK had significantly higher MMSE ($P < 0.01$ and $P < 0.01$, respectively), DSF ($P < 0.01$ and $P < 0.01$, respectively) and DSB ($P < 0.01$ and $P < 0.01$, respectively) scores, and lower TMT-A ($P < 0.01$ and $P < 0.01$, respectively) and TMT-B ($P < 0.01$ and $P < 0.01$, respectively) than the CON (Table 3). However, there were no significant differences in any of the cognitive function parameters between the EXE and EXE+GK groups.

The results for oxidative stress and inflammatory markers at baseline and after intervention are shown in Fig. 2. In the CON, there were no significant differences in 8-iso-PGF2α, TNF-α, or IL-6 concentrations following the intervention. Following the intervention, the EXE showed a significant decrease in 8-iso-PGF2α (-27% decrease, $P < 0.01$), TNF-α (-19.5% decrease, $P < 0.01$), and IL-6 (-35.4% decrease, $P < 0.01$) concentrations. After the intervention, the concentrations of 8-iso-PGF2α (-27.7% decrease, $P < 0.01$), TNF-α (-18% decrease, $P < 0.01$), and IL-6 (-21.3% decrease, $P < 0.01$) concentrations were significantly lower in the EXE+GK. There was a significant difference in 8-iso-PGF2α ($F[2, 54] = 13.08$, $\eta^2 = 0.326$, $P = 0.000$) and TNF-α ($F[2, 54] = 9.115$, $\eta^2 = 0.252$, $P = 0.000$) concentrations between the groups, while adjusting for the baseline value. The EXE and EXE+GK had significantly lower 8-iso-PGF2α ($P < 0.01$ and $P < 0.01$, respectively) and TNF-α ($P < 0.01$ and $P < 0.01$, respectively) concentration than the CON (Table 3). However, there were no significant differences in IL-6 between groups. Moreover, there was no significant difference in any of the oxidative stress and inflammatory markers between the EXE and EXE+GK groups. Following the intervention, there was a negative correlation ($r = -0.504$, $P < 0.05$) between the change in DSF and the change in TNF-α in the EXE+GK (Fig. 3). Despite this, there was no statistically significant relationship between the improvement in cognitive function parameters and inflammatory markers in the EXE following the intervention.

Table 4 demonstrates functional mobility before and after intervention. There were no significant differences in TUG or 4-MWT following the intervention in the CON. Following the intervention, the EXE resulted in a significant decrease in TUG (-8.6% decrease, $P < 0.01$) and an increase in 4-MWT (8.5% increase, $P < 0.01$). TUG (-10.9% decrease, $P < 0.01$) was significantly low-

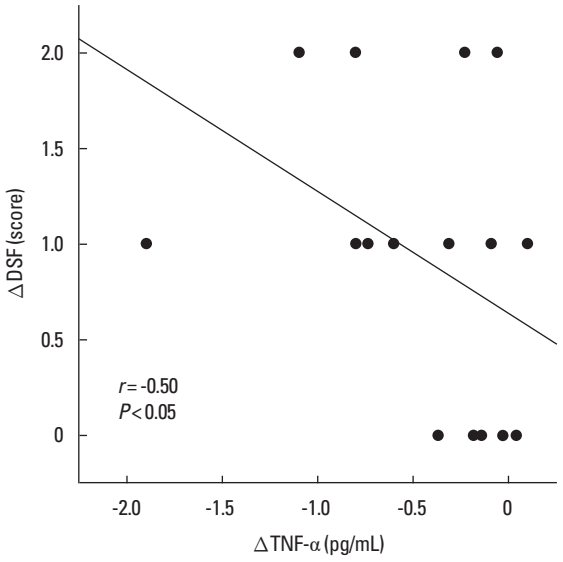

Fig. 3. The correlation between changes in DSF score and TNF-α concentration in the EXE+GK. DSF, Digit Span Forward test; TNF-α, tumor necrosis factor alpha; EXE+GK, multicomponent exercise training with Gotu kola supplementation group.

Table 4. Functional mobility at baseline and post intervention

Variable	CON (n = 18)		EXE (n = 20)		EXE+GK (n = 20)	
	Baseline	Posttest	Baseline	Posttest	Baseline	Posttest
TUG (sec)	16.6 ± 3.2	16.9 ± 3.1	17.1 ± 2.1	15.6 ± 2**,††	16.7 ± 3.2	14.8 ± 2.7**,††
4-MWT (m/sec)	0.82 ± 0.2	0.82 ± 0.1	0.8 ± 0.1	0.87 ± 0.1**,††	0.81 ± 0.1	0.84 ± 0.1**

Values are presented as mean ± standard deviaiton.
CON, placebo-controlled group; EXE, multicomponent exercise training group; EXE+GK, multicomponent exercise training with Gotu kola supplementation group; TUG, timed up and go test; 4-MWT, 4-m timed walk test.
**$P < 0.01$ to within-group comparison (baseline vs. postintervention). ††$P < 0.01$ to between-group comparison (vs. CON).

er after the intervention, while 4-MWT (4.8% increase, $P < 0.01$) was significantly higher in the EXE+GK. There was a significant difference in TUG ($F[2, 54] = 28.084$, $\eta^2 = 0.51$, $P = 0.000$) and 4-MWT ($F[2, 54] = 4.862$, $\eta^2 = 0.153$, $P = 0.011$) between the groups, while adjusting for the baseline value. TUG ($P < 0.01$) was significantly lower in the EXE and 4-MWT ($P < 0.01$) was significantly higher in the CON. TUG was significantly lower in the EXE+GK group ($P < 0.01$) than in the CON group, but 4-MWT did not differ significantly between groups. Furthermore, there were no statistically significant differences in any of the functional mobility parameters between the EXE and EXE+GK groups (Table 4).

DISCUSSION

This is the first study to demonstrate that multicomponent exercise training with or without the supplement Gotu kola improves cognitive function, inflammation, oxidative stress, lipid profiles, and functional mobility in older adults with MCI. This study found that both multicomponent exercise training with and without Gotu kola supplementation significantly improved MMSE, DSF, and DSB scores, TMT-A and TMT-B time scores, and 8-iso-PGF2α and TNF-α concentrations. No significant difference was found between the multicomponent exercise training with and without Gotu kola supplementation. Gotu kola supplementation had no additive effects when combined with multicomponent exercise. Although Gotu kola supplementation had no additional effects on increased cognitive function, the results revealed a significant relationship between the change in DSF and TNF-α after the combined intervention.

Recent systematic reviews and meta-analyses found that multicomponent exercise training improved global cognition, short-term memory, and executive function (Huang et al., 2022; Wang et al., 2020). Moreover, previous studies have shown that 750 mg/day and 1,000 mg/day of Gotu kola supplementation can improve memory function in healthy older adults (Wattanathorn et al., 2008) and patients with vascular cognitive impairment (Farhana et al., 2016), respectively. The primary finding showed that EXE and EXE+GK both enhanced global cognition, working memory, and executive function. EXE+GK had no added benefits over EXE. There is very little research on the effects of combined multicomponent exercise and Gotu kola supplementation on cognitive function. A previous study found that combining 500 mg/day of Gotu kola supplementation and aerobic exercise can improve memory performance in women with dementia, but there was no significant difference when compared to Gotu kola supplementation alone or aerobic exercise alone (Fitriana et al., 2021). The findings of the current study support the findings of the review, as supplementation with Gotu kola had no additional benefits over multicomponent exercise training in older adults with MCI.

Multicomponent exercise was the most effective exercise type for global cognition and executive cognition among MCI patients, according to a network meta-analysis (Huang et al., 2022). Multiple movement tasks characterized by perceptual motor adaptations and variable neuromuscular coordination have been proposed to improve executive function directly through cognitive stimulation (Forte et al., 2013). Moreover, motor skill training, such as balance and coordination, has a direct effect on a variety of cognitive domains, particularly attention, by promoting neuroplasticity through the production of brain-derived neurotrophic factor (BDNF) (Netz, 2019). Moreover, frequency and duration are important moderators of effect size for multicomponent exercise, and higher frequency and longer duration are associated with better effects (Huang et al., 2022). Participants in the EXE and EXE+GK groups completed three 40-min aerobic sessions and three 30-min resistance sessions per week (210 min per week), indicating that the duration and frequency of the program, particularly the aerobic component, are adequate and meet the dose recommended by the American College of Sports Medicine (Erickson et al., 2019). Overall, the improvement in global cognition, attention, short-term memory, and executive function in the present study may be attributed to the appropriate training intensity, duration, frequency, and/or complexity of the movements in the program.

In addition, multicomponent exercise is likely to induce beneficial biochemical changes via a variety of neurobiological mechanisms, including BDNF, insulin-like growth factor 1 (IGF-1), homocysteine, and inflammatory cytokines (Sanders et al., 2019). In addition, clinical studies have shown that Gotu kola may contribute to healthy aging, particularly as a neuroprotectant. It has been demonstrated that Gotu kola and its triterpenoids (asiatic acid, asiaticoside, and madecassoside) have antioxidative, anti-inflammatory, and neuron-regenerating properties. Its extensive multifunctional properties have the potential to promote general neuroprotection (Sabaragamuwa et al., 2018; Sun et al., 2020). TNF-α was reduced by both multicomponent exercise training with and without Gotu kola supplementation. It has been proposed that lowering proinflammatory cytokines may promote cognitive function improvement (Sanders et al., 2019; Wong et al., 2021). This hypothesis is supported by our findings, which show a significant relationship between the change in DSF and TNF-α ($r = -0.504$,

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$P < 0.05$) following the combined intervention. We suggest that the effect of multicomponent exercise training with Gotu kola supplementation on cognitive function, particularly executive function, may be mediated by a decrease in TNF-α. Although a link between changes in DSF and TNF-α was found, the correlation coefficient was low. More research into the combined intervention's protective effects on cognition is recommended. The correlation between cognitive domains and TNF-α in the EXE, on the other hand, did not reach statistical significance. Nonetheless, the EXE's cognitive enhancement mechanism should be distinct.

Oxidative stress may lead to cognitive impairments in older adults. Furthermore, oxidative stress may be exacerbated and associated with additional neuropathology in age-related neurodegenerative diseases (Head, 2009). Following the intervention, we found a significant decrease in 8-iso-PGF2α levels in the EXE and EXE+GK groups. This finding suggests that multicomponent exercise training with and without Gotu kola supplementation reduces oxidative stress. It may promote healthy brain aging and reduce the risk of developing AD. Nonetheless, the correlation between cognitive domains and 8-iso-PGF2α in the EXE and EXE+GK did not reach statistical significance, according to our findings. In addition to the mechanistic cognitive enhancement discussed above, other possible explanations why multicomponent exercise and Gotu kola supplementation can improve cognitive function may be achieved via other mechanisms such as stimulation of BDNF and IGF-1 production (Huang et al., 2022), modulation of the GABAergic system, and inhibition of acetylcholine esterase (Sabaragamuwa et al., 2018). However, these hypotheses must be tested in additional studies.

Regarding lipid profiles, multicomponent exercise training with or without Gotu kola supplementation decreased FBG, TG, the TG/HDL-C ratio, AI, and AIP, whereas multicomponent exercise training with Gotu kola supplementation enhanced HDL-C levels. Similar improvements in lipid profiles were observed in additional study (Bouaziz et al., 2016). The improvement in our lipid profile can be attributed to the aerobic and resistance activities in our multicomponent exercise program. Aerobic exercise promotes improvements in FBG, TG, and TC, whereas resistance training is also effective for altering the level of lipoproteins (Wewege et al., 2018). Moreover, resistance training can improve the ability of skeletal muscle to utilize fat, hence lowering plasma lipid levels (Ribeiro et al., 2015). TG improvements can be explained by an increase in muscle lipoprotein and a better clearance from the circulation after exercise due to an increase in blood flow (Kashiwabara et al., 2018). Additionally, Gotu kola proved capable of increasing blood flow (Incandela et al., 2001). It has been demonstrated that enhanced muscle blood flow has a significant role in the metabolic consequences and the improved potential for removal and utilization of fatty acids (Koch et al., 2005), which may offer the physiological basis for an increase in HDL-C concentration in trained subjects. The possible underlying mechanisms of multicomponent exercise training with and without Gotu kola supplementation to improve FBG, TG, the TG/HDL-C ratio, AI, AIP, and HDL-C are likely related to the chronic effect of exercise training and occur in part via the increase in blood flow to skeletal muscle. However, more research is needed to determine the precise underlying mechanism. As a result, both multicomponent exercise and Gotu kola supplementation should be recommended to promote a favorable lipidic health profile, which may be linked to cognitive performance (Jia et al., 2020).

Older adults with functional mobility preservation can sit, stand, and walk a few meters, which are essential functions for daily living activities. It has been demonstrated that MCI-induced cognitive impairment promotes a decline in functional mobility, particularly with TUG (de Oliveira Silva et al., 2019) and 4-MWT. Our findings showed that 12 weeks of multicomponent exercise training with and without Gotu kola supplementation resulted in significant improvements in TUG and 4-MWT. This study's exercise program combined strength training with either aerobic or balance training and resulted in significant improvements in functional mobility and walking speed, which is consistent with previous research (Bouaziz et al., 2016). Furthermore, the lower limb strength training program in this study was focused on the functional tasks of older adults. The exercise protocol, which includes sitting to standing, half squats, and progressing to holding objects that appear more functional, is normally required in their daily living activities. In addition, previous research found that Gotu kola supplementation resulted in significant improvements in functional mobility in older adults (Mato et al., 2011). The improvement in lower limb muscle strength could explain the benefits in functional mobility and walking speed (Bouaziz et al., 2016; Mato et al., 2011). Another reason for functional mobility could be the stimulation of proprioceptors in the joints, which promote stability or balance (Justine et al., 2012).

There are some limitations to the current study. Due to a low number of male vs. female participants, the study was unable to detect sex-specific differences. The small number of participants in our study was a significant limitation. As a result, a larger sample size may yield more precise effects and outcomes during inter-

vention. Such studies should be conducted with a larger study population in the future. Nonetheless, we believe that our findings can provide valuable insight for future studies exploring the synergistic effects of Gotu kola supplementation and multicomponent exercise training in different populations.

In conclusion, multicomponent exercise training with or without the supplement Gotu kola improves cognitive function, particularly working memory and executive function, as well as inflammation, oxidative stress, lipid profiles, and functional mobility in older adults with MCI. Although Gotu kola supplementation had no additional effects on cognitive function, it may enhance the effects of multicomponent exercise training on executive function by decreasing TNF-α levels. These findings suggest that multicomponent exercise training, with or without Gotu kola supplementation, may promote healthy brain aging and possibly reduce the risk of developing AD.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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