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RESEARCH ARTICLE

The Effectiveness of *Centella asiatica* Extract and Aerobic Exercise on Plasma Levels of Amyloid Beta-42 and Phosphorylated Tau in Older Women with Dementia

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Abstract

Urgency: Effect of Centella asiatica (CA) and aerobic exercise on Amyloid beta-42 (Aβ42) and phosphorylated tau (p-tau) as biomarkers of dementia is not yet known. **Objectives:** This study aimed to analyze the effect of CA, aerobic exercise, and their combination on Aβ42 and p-tau in older women with dementia. **Design:** It was a 24-week randomized, double-blind controlled trial. **Partisipant:** Subjects were divided into four groups: the Centella asiatica group (CA, 1x500 mg/day, n = 16), the aerobic exercise group (AE, 3x60 minutes/week, n = 16), the CA-AE combination group (1x500 mg/day and exercise, n = 15), and the placebo group (n = 15). **Instruments:** The dementia screening test used the Mini Mental State Examination (Intraclass correlation coefficients : ranging from 0.60 to 0.93, sensitivity of 88.3%) and Clinical Dementia Rating questionnaires (sensitivity 93.6% and specificity 100%). The Wilcoxon, Kruskal-Wallis, and Mann-Whitney tests were used to analyze the data. **Results:** Plasma amyloid beta-42 showed an increase in all groups: CA ($p<0.001$), AE ($p=0.001$), CA-AE combination ($p<0.001$), and placebo ($p<0.001$). Meanwhile, plasma p-tau also decreased in CA ($p<0.001$), AE ($p<0.001$), and CA-AE combination ($p=0.001$). The Mann-Whitney test showed that Centella asiatica caused the highest increase in Aβ42 ($\Delta=233.5$; $p<0.001$). **Conclusion:** This study indicate that Centella asiatica, aerobic exercise, and the CA-AE combination were effective in improving plasma Aβ42 and decreasing p-tau in older women with dementia. **Contributions:** This study can be an alternative therapy for the prevention and treatment of cognitive decline. Research with a larger sample size is recommended.

Keywords
Amyloid-Beta, Centella asiatica, Dementia, Exercise, P-tau

INTRODUCTION

The number of elderly individuals rises positively in response to increased health sector services. But dementia is also a major danger factor for the elderly. By 2050, there will be 89 million more people living with dementia (Prince et al., 2016; Burhaein et al., 2024). Alzheimer's disease is the most prevalent kind of dementia (Fitriana et al., 2021). Alzheimer's disease is typified by the loss of synapses and neurons as well as the development of intracellular neurofibrillary tangles (NFL) and extracellular amyloid plaques (Yu et al., 2014). The three main biomarkers for Alzheimer's disease are amyloid beta-42 (Aβ42), phosphorylated tau (p-tau), and total tau (T-tau). T-tau, P-tau, Aβ42, and NFL in cerebral fluid are employed in clinical treatment and clinical research because of their

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consistency (Olsson et al., 2016). Patients with mild amnestic cognitive impairment (aMCI) who are developing Alzheimer's disease may have low concentrations of Aβ 1-42 in their cerebrospinal fluid (CSF) or high ratios of T-tau protein to Aβ 1-42 in their CSF (Schneider et al., 2010). Compared to men, women are more likely to have Alzheimer's (Shimizu et al., 2019). There is evidence that women undergo brain atrophy at a faster rate than men because of variations in sexual hormones, life orientation, and estradiol deflation (Davey, 2013).

More efficient and affordable strategies are required because certain pharmaceutical medications are unable to prevent dementia from developing to a considerable degree (Lee et al., 2016). Exercise and Centella asiatica (CA) have been shown to enhance cognitive performance. Because of the active components asiaticoside and madecoside, CA is one of the traditional herbs that has been shown to have neuroprotective, antioxidant, memory-strengthening, and intelligence properties (Sari et al., 2019). By preventing beta-amyloid accumulation, acetylcholinesterase activity, and brain damage, CA enhances cognitive function (Soumyanath et al., 2012). In vitro, CA's antioxidant properties are demonstrated by its ability to scavenge free radicals, lower lipid peroxidation, prevent DNA damage, alter amyloid β pathology in Alzheimer's mouse brains, and modify elements of the oxidative stress response linked to the neurodegenerative changes associated with Alzheimer's disease (Dhanasekaran et al., 2009).

People with dementia benefit from aerobic physical activity (15 minutes of daily cycling for 15 months) because it enhances cognitive function (Cancela et al., 2015). Although the benefits of CA and exercise for enhancing cognitive function have been shown in numerous studies, their combined impact on various biochemical indicators in humans is not very significant. The purpose of this study was to ascertain how exercise, Centella Asiatica, and their combination affected the plasma levels of phosphorylation-tau (p-tau) and amyloid beta-42 (Aβ42) in older dementia-stricken women.

MATERIALS AND METHODS

Research Design

A 24-week, double-blind, randomized experiment with placebo control was the study design employed. The research was carried out in three Indonesian nursing homes. In this study, participants who satisfied the following criteria were included: MMSE value 10-26 (mild-moderate dementia) (Meyer et al., 2016), CSF Aβ42 levels <550 pg/ml (Jensen et al., 2016), absence from brain supplements for at least two weeks prior to the intervention; and exercise attendance of at least 80% of a total of 72 meetings.

After screening test used the MMSE and CDR questionnaires, respondents underwent a physical examination, medical history, daily activities (ADL), education level, and sociodemographic history. The screening results showed that 80 people met the criteria. After that, subjects who met the criteria were randomized and divided into four groups. The research flow chart is presented in Figure 1 as follows:

Participants

Eighty participants who met the eligibility requirements were split into four groups at random. Excel uses random selection to create a random list. The randomization group was unknown to the research staff members who analyzed the respondents. Of the 124 older people, 80 met the inclusion criteria. After that, respondents underwent a physical examination, medical history, daily activities (ADL), education level, and sociodemographic history.

Procedures

Strict standardization, conformance, and quality control procedures are followed in the production of centella Asiatica extract before a dry extract is obtained. By using HPLC, the asiaticoside level was determined to be 1.41 mg/g. Nurses in nursing homes administered up to 500 mg of CA extract every day to the respondents. A daily medication adherence list sheet is used to monitor medication compliance.

The three 60-minute workouts each week included a 10-minute warm-up and stretching period, a 40-minute core training session, and a 10-minute cool-down period. The core workout consist of breathing and some cardio movements together. The respondent's movements are tailored to their capabilities. The orphanage officer/nurse keeps track of attendance.

Participants in the Centella asiatica-exercise (CA-AE) combination group were told to exercise three times a week for 60 minutes and to take 500 mg of CA per day. The personnel of the senior home kept an

eye on adherence using CA diaries and exercise attendance lists. In the placebo group, subjects received 1x500 mg/day of a placebo medication containing starch.

Blood biochemistry was evaluated using HPLC and the ELISA technique. Prior to the intervention, the study participants who were fasting had their brachial veins drained of 3 ml of blood, which was subsequently placed into an EDTA tube. After being kept at ambient temperature for an hour, the tube was transferred to the lab and kept in a cool box at -8ºC. Prior to additional analysis, the tubes were separated and kept at -80ºC after being centrifuged for ten minutes in the lab.

Instruments

The dementia screening test used the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR) questionnaires. The MMSE test consists of 30 questions. The mild-moderate dementia category has an MMSE score of 10-26 (Meyer & O'Keefe, 2020). The test-retest reliability of the MMSE has been reported with intraclass correlation coefficients (ICCs) ranging from 0.60 to 0.93, indicating good to excellent reliability. In 14 studies, the MMSE had a sensitivity of 88.3% (95% confidence interval [CI], 81.3% to 92.9%) and a specificity of 86.2% (95% CI, 81.8% to 89.7%) for dementia Tsoi, 2015).

While the CDR consists of 5 questions with a five-scale rating score, namely 0: no cognitive impairment; 0.5: very mild dementia; 1: lightweight; 2: moderate; and 3: severe (Nam et al., 2020).

The CDR has high sensitivity (93.6%) and specificity (100%) for detecting dementia, making it a reliable tool for clinical assessments. The CDR exhibits excellent inter-rater reliability, with kappa values ranging from 0.77 to 1.00 across different domains, such as memory (0.95) and personal care (1.00) (Shwe, 2013).

Data Analysis

Data analysis was done using the Mann-Whitney, Kruskal-Wallis, and Wilcoxon tests.

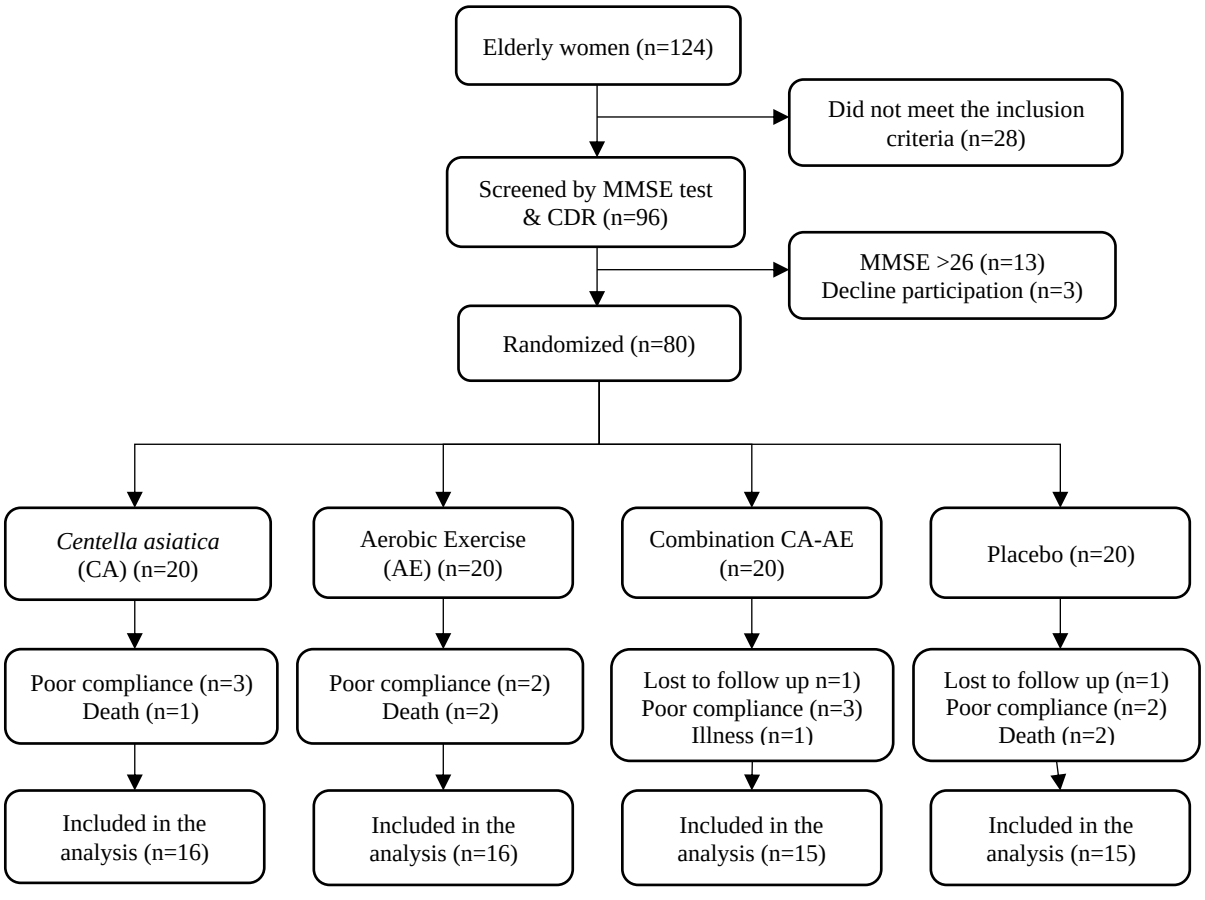

Figure 1. Research flow chart

RESULTS

Out of a total of 80, 62 people were able to complete the intervention over 24 weeks. Sociodemographic examinations including age, MMSE, CDR, blood pressure, weight, height, blood pressure, education, marital status, medical history, and blood biochemistry did not show differences in all groups (Table 1).

Table 1. Baseline data of older women with dementia

Characteristic	Centella asiatica/ CA, n=20	Aerobic Exercise/AE, n=20	Combination of CA-AE, n=20	Placebo, n=20	p-value
Age, mean (SD), yr	74.80 (10.10)	76.45 (8.67)	73.40 (8.79)	75.95 (10.06)	0.744
MMSE, mean (min-max), score	20 (10-25)	23 (12-25)	22 (10-25)	20 (13-25)	0.221
CDR, mean (min-max)	3 (2-8)	3.75 (2-7)	3 (2-7)	4 (2-7)	0.397
Weight, mean (SD), kg	46.50 (38-76)	49.5 (26-68)	47.5 (37-64)	41 (32-64)	0.555
Height, mean (SD), cm	145.50 (7.86)	145.95 (5.45)	146.15 (6.65)	143.80 (9.50)	0.751
Blood pressure, mean (SD)					
Sistole, mmHg	134.50 (19.05)	135.65 (15.13)	134.50 (18.07)	136.00 (1.20)	0.989
Diastole, mmHg	80 (70-90)	80 (60-100)	80 (60-100)	80 (70-90)	0.583
Education, n (%)					
Low	18 (26.5)	15 (22.1)	17 (25.0)	18 (26.5)	0.502
High	2 (16.7)	5 (41.7)	3 (25.0)	2 (16.7)	
Marital status, n (%)					
Unmarried	18 (25.4)	19 (26.8)	16 (22.5)	18 (25.4)	0.498
Married	2 (22.2)	1 (11.1)	4 (44.4)	2 (22.2)	
Disease history, n (%)					
Hypertension	4 (16.7)	8 (33.3)	6 (25.0)	6 (25.0)	0.592
Stroke	19 (25.7)	18 (24.3)	19 (25.7)	18 (24.3)	0.868
Rheumatic	17 (25.8)	14 (21.2)	17 (25.8)	18 (27.3)	0.374
Osteoarthritis	7 (50)	2 (14.3)	3 (21.4)	2 (14.3)	0.117
Blood biochemical, mean (SD), pg/ml					
Aβ-42	129.80 (45.68)	176.99 (105.01)	159.45 (122.26)	151.44 (54.09)	0.124
p-tau	413.17 (764.81)	115.28 (213.85)	170.12 (425.87)	342.40 (649.90)	0.261

*p <0,05

Plasma amyloid beta-42 showed an increase in all groups: CA (p<0.001), AE (p=0.001), CA-AE combination (p<0.001), and placebo (p<0.001). Examination of p-tau also decreased in all groups: CA (p<0.001), AE (p<0.001), CA-AE combination (p=0.001), and placebo (p=0.707). The Mann-Whitney test showed that there was a significant difference in Aβ-42 between the four groups (p = 0.007). CA caused the highest increase in Aβ-42 (Δ=233.5; p<0.001). Meanwhile, p-tau showed no difference between the four groups (Table 2).

Table 2. Comparison of amyloid beta-42 and p-tau between before and after intervention for 24-weeks

Variable	Centella Asiatica/CA (n=16) Median (min-max)	Exercise/E (n=16) Median (min-max)	Combination of CA-E (n=15) Median (min-max)	Placebo (n=15) Median (min-max)	p^b
Aβ-42, pg/ml					
Baseline	142 (65-229)	158.5 (90-209)	144 (62-182)	137 (90-264)	0.007*
After 24 weeks	362.5 (234-767)	315 (180-644)	343 (230-583)	321 (23-790)	
Δ	233.5 (102-671)	151.5 (90-449)	186 (86-495)	184 (-114-526)	
p^a	<0.001*	0.001*	<0.001*	<0.001*	
p-tau, pg/ml					
Baseline	60.5 (47-1682)	69.5 (51-941)	56 (48-277)	66 (49-291)	0.064
After 24 weeks	12.5 (7-998)	23.5 (8-324)	17 (7-197)	34 (9-500)	
Δ	-47.5 (-684-23)	-46 (-617-19)	-42 (-80-25)	-29 (-227-771)	
p^a	<0.001*	<0.001*	0.001*	0.707	

Δ: difference pre and post intervention, p^a: Wilcoxon test, p^b: Mann-Whitney test, *Significant

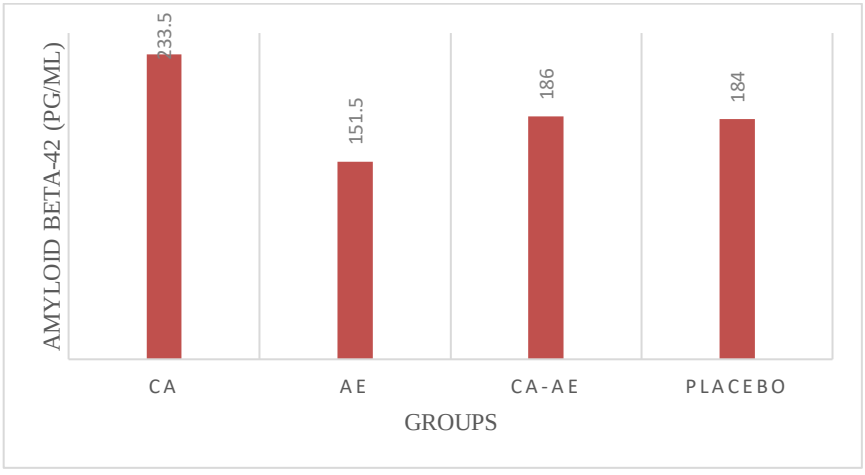

Figure 2. Change of Amyloid Beta-42 plasma after 24-weeks intervention

DISCUSSION

This study showed that all groups had increased plasma levels of amyloid beta-42. However, Centella asiatica scored the highest in elevated amyloid beta-42 in women with dementia. Another study found that Asiatic acid treatment reduced amyloid beta 1–42 in mice (Rather et al., 2018). Centella asiatica cannot inhibit Aβ aggregation of monomers and oligomers and cannot destroy preformed fibrils (Ramesh et al., 2010).

This study follows the study that found exercise for 5–30 minutes per week increased Aβ-42 levels in the elderly (Liang et al., 2010). Another study in mice showed that physical exercise reduced beta-amyloid by increasing the activity of enzymes responsible for regulating beta-amyloid clearance in brain tissue and suppressing apoptotic pathways such as the caspase-9, cytochrome c, Bax, and caspase-3 pathways (Ozbeyli & Cakir, 2017). Physical exercise for 3x60 minutes per week for 16 weeks had no positive effect on global beta-amyloid deposition in Alzheimer's patients (Frederiksen et al., 2015). The mechanism by which exercise affects amyloid deposition remains unclear. However, there is a direct effect on the metabolism of amyloid precursor protein and an indirect effect through the influence of neurotrophic factors, neuroinflammation, cerebrovascular function, and glucose metabolism (Head et al., 2012). The placebo group in this study also experienced a significant increase in plasma Aβ-42, presumably due to the suggestion given by the nurse or officer who gave the drug to the respondent and the positive effect of the placebo on the nervous system.

The results of this study showed that Centella asiatica, aerobic exercise, and a combination of Centella asiatica and aerobic exercise showed a positive effect on lowering plasma tau-phosphorylation levels in women with dementia. The asiaticoside content of 1.41 mg/g in this study is thought to reduce the formation of neurofibrillary tangles in women with dementia. This study in line with the results of a study on transgenic mice showed the effect of 12 weeks of exercise on reducing p-tau levels (Kang & Cho, 2015). Studies show that individuals who actively exercise for 5–30 minutes per week have lower levels of tau phosphorylation (Liang et al., 2010). Another study showed that exercising 3x60 minutes/week for 16 weeks showed no change in p-tau (Jensen et al., 2016). Centella asiatica may alleviate the etiology of dementia. Centella asiatica inhibits p-tau biosynthetic protein and maintains cytoarchitecture (Chiroma et al., 2019).

Respondents, who were all women, were also considered effective in giving positive results because of the homogeneity of the sexes. Based on research, women with Alzheimer's who were given the intervention had more positive effects than men with Alzheimer's (Mielke et al., 2012).

Conclusion

The results of this study showed that Centella asiatica, aerobic exercise, and a combination of Centella asiatica and aerobic exercise showed a positive effect on lowering plasma tau-phosphorylation levels in women with dementia. The results of this study can be an alternative therapy for the prevention and treatment of cognitive decline in women with dementia. The number of samples in this study is still limited therefore that further research can be carried out with a larger number of respondents, both women and men.

Conflict of Interest

We affirm that the article we have authored does not involve any conflict of interest.

Ethics Statement

The Health Ethics Commission of Universitas Padjadjaran has granted ethical permission for this research (No. 1266/UN6.KEP/EC/2018).

Author Contributions

Conception and design of the study, LAF, IKA, KA and IS; Data collection, LAF, ID, PTL; Data analysis and interpretation, LAF, IKA, KA, IS, and NF; Drafting article and critical revision, LAF, IKA, KA,I S, ID, PTL, NF, and EAS. All authors have read and approved the published version of the manuscript.

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