

## ORIGINAL ARTICLE

# Effect of Centella Asiatica and Aerobic Exercise in Older Women With Dementia: A Randomized Controlled Trial

Lisna Anisa Fitriana<sup>1,2</sup>, Irma Darmawati<sup>2</sup>, Lina Anisa Nasution<sup>2</sup>, Suci Tuty Putri<sup>2</sup>, Slamet Rohaedi<sup>2</sup>, Kusnandar Anggadiredja<sup>1</sup>, Iwan Setiawan<sup>3</sup>, Nur Fauziyah<sup>4</sup>, I Ketut Adnyana<sup>1</sup>

<sup>1</sup> Department of Pharmacology and Clinical Pharmacy, School of Pharmacy, Institut Teknologi Bandung, Jl Ganesha no 10 Bandung 40132, Indonesia

<sup>2</sup> Department of Nursing, Faculty of Sport and Health Education, Universitas Pendidikan Indonesia, Jl Setiabudhi no 224 Bandung, Indonesia

<sup>3</sup> Department of Basic Medical Sciences, Faculty of Medicine, Universitas Padjadjaran, Jl Prof. Eijkman no 38 Bandung 40161, Indonesia

<sup>4</sup> Department of Nutrition, Politeknik Kesehatan Bandung, Jl Prof. Eijkman no 30 Bandung 40161, Indonesia

## ABSTRACT

**Introduction:** Gotu kola (*Centella Asiatica*) and exercise have shown an increase in cognitive function. However, the effect of the combination on superoxide dismutase and quality of life in humans is not yet known. The purpose of this study was to determine the effect of *Centella Asiatica* and aerobic exercise on memory, superoxide dismutase (SOD), and quality of life (QoL) in women with dementia. **Methods:** This study used a randomized, double-blind, placebo-controlled trial that lasted 24 weeks in a nursing home. The Mini-Mental State Examination is used to screen for dementia. SOD was determined using ELISA, memory was assessed using a visual memory questionnaire, and quality of life was measured using the WHO-QoL questionnaire. The study involved 62 women with dementia ranging in age from 61 to 89 years. *Centella Asiatica* is given as much as 500 mg/day. Aerobic exercise was performed for 45 minutes 3x a week, and a combination of two interventions and one group as a control group with placebo pills. **Results:** *Centella Asiatica* helped improve SOD ( $P=0.009$ ) and memory ( $p=0.001$ ) in women with dementia. Meanwhile, aerobic activity significantly improved memory ( $p<0.001$ ), QoL-social relations ( $p=0.037$ ), and QoL-environment ( $p=0.004$ ). In addition, the combination of *Centella Asiatica* and aerobic exercise significantly improved SOD ( $p=0.031$ ) and memory ( $p=0.001$ ). **Conclusion:** The combination of *Centella Asiatica* and aerobic exercise can improve superoxide dismutase (SOD), memory, and quality of life in women with dementia, especially in the domain of social and environmental relationships. Nurses can do this in nursing care for the elderly.

**Keywords:** Aerobic exercise, *Centella asiatica*, Dementia, Superoxide Dismutase, Quality of Life

## Corresponding Author:

I Ketut Adnyana, M.Si., Ph.D  
Email: ketut@fa.itb.ac.id  
Tel: +62 813-2179-4375

## INTRODUCTION

Indonesia has a large elderly population, reaching 9.6% or 26 million people [1,2]. Statistical data shows that the proportion of female elderly is more significant, going 5%, while male elderly is 4.6% of the total population of Indonesia [1–3]. This is, of course, implies that the large population of older women requires attention, especially

older women with health problems. One of the health problems that most older women often experience is dementia [4,5].

Older women with dementia have difficulty performing daily activities [5–7]. Dementia causes the elderly to lose the ability to obtain information, make decisions and communicate. Some special conditions, such as losing the ability to recognize the surrounding world, can even lose the ability to eat, drink, bath, and even use the toilet without assistance [6,8].

Dementia is connected with reduced superoxide

dismutase activity and cognitive function. To combat ROS (reactive oxygen species) and oxidative stress, SOD catalyzes the creation of hydrogen peroxide. Cognitive function decrease in dementia patients due to a reduction in the volume of the hippocampus, which is a learning and memory center [9]. These conditions certainly impact the quality of life and cognitive function of older women with dementia [6–8,10].

Quality of life is one of the main domains measured in older women with dementia because they interpret their energy daily [10–13]. Quality of life includes a broad concept of biological, psychological, social, cultural, and spiritual domains [12,14]. In older women with dementia, the increased need for daily activities can decrease their quality of life. Reduced quality of life can increase morbidity and mortality [11,15]. Therefore, efforts are needed to improve the quality of life in older women with dementia.

Various interventions continue to be developed to improve the quality of life of the elderly, one of which is aerobic physical exercise [12,16,17]. Aerobic physical exercise positively impacts body function and structure, activity, and participation and can improve individual strength, endurance, and body mechanics [18–20]. Furthermore, this physical activity can improve motor skills and independence in the elderly so that it affects the quality of life [21,22]. Previous similar studies have shown that aerobic physical exercise can improve the quality of life in various age groups such as sick children, older men, and individuals in general [12,17,23,24].

Centella Asiatica also has a benefit in increasing cognitive function [25]. The Centella Asiatica (Apiaceae) plant, known in the United States as Gotu Kola, is used in traditional Chinese medicine and Ayurvedic medicine to improve cognitive function. Plant extracts have widely reported neuroprotective and antioxidant effects in vitro and in vivo [26]. Centella Asiatica boosts cognitive and mitochondrial performance while activating the nuclear factor erythroid 2-related factor 2 (NRF2)-regulated antioxidant response pathway. Centella Asiatica has been used as an active ingredient in nutraceutical products aimed at enhancing cognitive function. Centella Asiatica also plays a role in increasing levels of superoxide dismutase (SOD) [27]. SOD is the first detoxifying enzyme and the most potent antioxidant found in cells. This enzyme is the initial defense line against reactive oxygen species in the organism (ROS). SOD is essential for cellular health since it protects body cells against oxygen, free radicals, and other toxic compounds which cause cell death [28,29]. Centella Asiatica is believed to work as a secondary antioxidant, breaking the chain reaction of free radicals and increasing the level of SOD in the body as a primary antioxidant [27].

It has been demonstrated that both Centella Asiatica

and aerobic exercise increase cognitive performance. However, no previous studies have been conducted regarding the effects of combined aerobic exercise and Centella Asiatica on superoxide dismutase (SOD), memory, and quality of life in elderly women with dementia. The purpose of this study is to determine the effect of this combination on dementia-stricken older adults.

## MATERIALS AND METHODS

The study design was a randomized controlled trial with four arms and double-blind placebo control. Centella Asiatica (CA) capsules and placebo were administered in the same color capsule. This is done so that respondents feel they are getting the same drug. Randomization was done using Random Sampling Excel. CA, Aerobic exercise (AE), and placebo interventions were given in the three homes to the elderly who received the intervention according to the randomization.

This program was piloted in three nursing homes in Bandung and Garut, Indonesia, for 24 weeks from August 2019-January 2020. The inclusion criteria of this study were: older women aged more than 60 years, had no history of bleeding or other serious illnesses, did not participate in exercise for at least 6 months before the intervention, and attended exercise at least 80% of the total 72 meetings. Screening for dementia uses the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating (CDR). MMSE is an instrument that is used specifically to systematically assess mental status. This instrument consists of 11 questions measuring five areas of cognitive function [30,31]. These areas include orientation, attention, calculation, registration, memory, and language. The maximum score is 30. A total score below 23 indicates cognitive impairment. Meanwhile, the CDR consists of 5 questions with a 5-scale rating score, namely 0: no cognitive impairment, 0.5: very mild dementia, 1: mild, 2: moderate, and 3: severe. Researchers no longer conduct validity and reliability tests because the instrument has been validated and is widely used in research and clinical practice [30,31].

The WHO-QoL questionnaire was used to measure the quality of life. The WHO-QoL questionnaire consists of 26 question items. The range of answer scores for each question item is 1 (very dissatisfied/very poor) to 5 (very satisfied/very good). The assessment domain for this instrument consists of four domains, namely physical health (seven items), psychological health (six items), environment (eight items), and social relations (three items) [19,32]. This study no longer conducts validity and reliability tests because the instrument has been standardized. Item-internal consistency and item-discriminatory validity of the WHOQOL-Bref with a Pearson  $r$  of 0.4 [33-35].

The participants were randomly allocated into four

groups: Centella Asiatica (CA, n=20), aerobic exercise (AE, n=20), CA-AE combination (n=20), and placebo (n=20). In the first group, subjects were given Gotu kola as much as 500 mg/day. The second group was an aerobic exercise which was performed for 45 minutes 3x a week using nostalgic music or other types of entertainment music. The third group was a combination of two interventions (CA and AE). The last group, the control group, took a placebo pill of 500 mg/day. Participants in the study were asked to draw their blood for SOD analysis. SOD plasma examination using ELISA method with HPLC tool.

Descriptive statistics are used to explain the demographic data and the main variables. The Kruskal-Wallis test examined the differences in variables between the four groups. The Wilcoxon test was used to detect changes in the effects of CA, AE, and their combination on plasma SOD levels, cognitive function, and quality of life from trial entry to week 24. The Ethics Committee has approved this Padjadjaran University research with ethics number no. 1266/UN6.KEP/EC/2018.

## RESULT

This study was conducted on 80 older women with an age range of 61-90 years. Of the 80 people, 62 people were able to complete the intervention until it was finished. Almost all respondents have low education, are not married/widowed, and have a history of illness. The characteristics of the respondents are shown in Table I.

**Table I : Baseline data of older women with dementia**

Charac- teristics	Centella asiatica/ CA (n=20)	Aerobic Exer- cise/AE (n=20)	Combi- nation CA and AE (n=20)	Placebo (n=20)	p
Age, mean (SD), yr	74.80 (10.10)	76.45 (8.67)	73.40 (8.79)	75.95 (10.06)	0.744
MMSE, mean (SD), score	19.81 (4.81)	21.25 (3.91)	21.87 (2.53)	19.33 (3.33)	0.221
CDR, mean (SD)	3.75 (1.84)	3.85 (1.66)	3.38 (1.34)	4.13 (1.38)	0.397
Weight, mean (SD), kg	49.65 (10.47)	48.75 (9.71)	48.5 (8.29)	45.80 (9.77)	0.555
Height, mean (SD), cm	145.50 (7.86)	145.95 (5.45)	146.15 (6.65)	143.80 (9.50)	0.751
Sistole, mean (SD), mmHg	134.50 (19.05)	135.65 (15.13)	134.50 (18.07)	136.00 (17.20)	0.989
Diastole, mean (SD), mmHg	78 (8.34)	77.25 (10.06)	81 (10.08)	79.15 (8.38)	0.583

CONTINUE

**Table I : Baseline data of older women with dementia (CONT.)**

Charac- teristics	Centella asiatica/ CA (n=20)	Aerobic Exer- cise/AE (n=20)	Combi- nation CA and AE (n=20)	Placebo (n=20)	p
Education, n (%)					
Low edu- cation	18 (26.5)	15 (22.1)	17 (25.0)	18 (26.5)	0.502
High education	2 (16.7)	5 (41.7)	3 (25.0)	2 (16.7)	
Marital status, n (%)					
Unmar- ried/wid- owed	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 (%)					
Hyper- tension	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
Rheu- matic	17 (25.8)	14 (21.2)	17 (25.8)	18 (27.3)	0.374
Osteoar- thritis	7 (50.0)	2 (14.3)	3 (21.4)	2 (14.3)	0.117
Blood plasma, mean (SD)	2.29 (1.60)	4.97 (5.89)	2.32 (1.32)	3.37 (4.25)	0.249
SOD (ng/ ml)					
Cognitive function, mean (SD)	7.75 (6.66)	10.85 (5.90)	9.45 (6.34)	6.90 (5.12)	0.172
Memory (score)					
Quality of Life, mean (SD)	51.00 (17.43)	57.60 (15.30)	59.68 (17.54)	49.70 (18.46)	0.200
QoL-Phys- ical	53.35 (14.63)	61.60 (11.31)	63.84 (13.99)	53.85 (17.55)	0.055
QoL-Psy- cological	43.15 (14.62)	48.15 (14.98)	51.26 (14.59)	41.40 (14.89)	0.063
QoL-So- cial rela- tionship	57.20 (17.43)	58.75 (13.06)	65.58 (14.79)	51.43 (18.62)	
QoL-En- vironmen- tal					

\*p<0.05; p-value were derived from Kruskal Wallis test, chi-square

Table II shows the analysis of the effectiveness of Centella Asiatica, aerobic exercise, and its combination after 24 weeks of intervention. This study found that Centella Asiatica, aerobic exercise, and the two combinations improved cognitive performance in women with dementia ( $p < 0.05$ ). CA was more efficient in improving plasma SOD ( $p = 0.009$ ) and memory ( $p = 0.001$ ) in women with dementia than other parameters.

Meanwhile, aerobic exercise was effective in improving memory ( $p < 0.001$ ), the domain of quality of life-social relations ( $p = 0.037$ ), and the domain of quality of life-environment ( $p = 0.004$ ). Furthermore, the combination of CA and AE was shown to improve SOD and memory,  $p = 0.031$  and  $p = 0.001$ , respectively. In contrast, the control group showed no difference in all the measured parameters.

**Table II : Effectiveness of Centella asiatica, aerobic exercises, and its combination after 24 weeks intervention**

Variable	Centella asiatica/CA (n=16)		Aerobic Exercise/AE (n=16)		Combination CA and AE (n=15)		Placebo (n=15)	
	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
<b>SOD</b>								
Baseline	2.15 (1.54)	0.009*	3.63 (2.44)	0.865	2.41 (1.35)	0.031*	3.66 (4.45)	0.691
After 24 weeks	6.18 (4.32)		4.00 (3.39)		7.06 (5.43)		2.92 (1.98)	
<b>Memory</b>								
Baseline	6.69 (6.40)	0.001*	11.44 (5.37)	<0.001*	9.00 (6.43)	0.001*	5.60 (4.39)	0.348
After 24 weeks	14.31 (5.39)		16.88 (6.19)		18.40 (6.31)		6.73 (7.18)	
<b>QoL-Physical</b>								
Baseline	51.69 (21.45)	0.574	57.88 (15.80)	0.080	59.73 (16.44)	0.344	44.20 (17.97)	0.218
After 24 weeks	55.75 (17.53)		65.38 (14.57)		65.00 (14.12)		38.60 (16.80)	
<b>QoL-Psycological</b>								
Baseline	57.44 (14.12)	0.858	60.50 (10.86)	0.173	61.20 (13.85)	0.327	50.60 (14.22)	0.473
After 24 weeks	57.19 (10.23)		66.00 (13.87)		64.67 (9.66)		49.20 (12.02)	
<b>QoL-Social Relationship</b>								
Baseline								
After 24 weeks	42.19 (18.49)	0.944	43.81 (14.13)	0.037*	50.80 (14.21)	0.517	29.60 (14.59)	0.231
	42.19 (15.93)		53.75 (12.05)		47.07 (17.51)		36.13 (14.60)	
<b>QoL-Environmental</b>								
Baseline	59.75 (17.16)	0.055	55.88 (11.58)	0.004*	63.47 (15.70)	0.065	45.63 (17.12)	0.284
After 24 weeks	52.06 (12.13)		62.75 (8.26)		55.13 (11.25)		48.33 (13.54)	

\* $p < 0.05$ ; p-value were derived from wilcoxon test

## DISCUSSION

This study showed that Gotu kola can increase levels of superoxide dismutase (SOD). This is by previous research that Centella Asiatica can increase superoxide dismutase levels. SOD is the main antioxidant enzyme to fight free radicals [27,36]. The antioxidant effect of Centella Asiatica on increasing SOD affects the elimination of free radicals in various tissues [27,37]. This antioxidant effect is mainly found in the leaves and roots of Centella Asiatica, which have superoxide-free radical activity useful for Alzheimer's patients [37–39]. This study showed that the combination of Centella Asiatica and aerobic exercise was effective in improving memory function. Several studies support this result. CA improves memory and longevity [25,40]. Several studies have stated that CA can improve short-term memory, long-term memory, concentration, attention, and visual-spatial thinking skills [25,26,40,41]. The effectiveness of Centella Asiatica certainly increases further research on Centella Asiatica, including its combination with other substances such as Curcuma Longa, which also improves memory performance [42]. This study combines the beneficial effects of Centella Asiatica and aerobic exercise, both of which support cognitive function, particularly memory performance.

Aerobic exercise can help older people with dementia develop social skills and create a more pleasant environment for nursing home residents. Aerobic exercise effectively improves the quality of life in social and environmental domains in women with dementia. Subjective well-being is viewed as a quality of life and is described as an emotive and cognitive assessment of one's life. It has three distinctive elements: happiness with life, pleasant experiences, and negative experiences [43]. A retrospective study showed that frequent exercise in Honolulu, 2,263 elderly US men of Japanese descent, prevented dementia with a p-value of 0.022 for 30 minutes per day three times per week for six months. Fifteen weeks of exercise with 30 minutes per exercise performed by 16 older adults with dementia significantly improved cognitive function (p-value = 0.01) [44].

Exercise also slows the effects of pathological aging by maintaining and improving executive functions, including concentration, attention, and memory, which are defined as higher-order cognitive processes [45]. Exercise tolerated by the elderly is 30 minutes per session and a maximum of 3 times a week. This is believed to prevent dementia compared to exercising once a week. Exercises that are done regularly and correctly for 4-6 weeks or the same as 12-16 times, for 30 minutes per session will stimulate the brain. Exercise activates the Golgi tendon organ due to muscle contraction to the central nervous system in the form of muscle contraction. Sensory information from peripheral, visual, musculoskeletal, proprioception, vestibular system,

and constant blood flow assisted [46]. This condition will form the correct response and be stored in the inner brain to be integrated into the sensory system of cortical integration by the memory section, namely the amygdala, and then integrated into the cerebral cortex of the cognitive center into long-term memory.

Research shows that older adults who exercise (twice a week or more) will have better cognitive function than those who exercise less than three times a week. Exercise can also increase blood flow and supply of oxygen and nutrients to the brain to induce fibroblast growth in the hippocampus. Regular exercise by walking three times a week is also believed to reduce the risk of dementia in the elderly [8].

When the body exercise, the body will increase the need for oxygen. Increased oxygen demand will affect metabolic, cardiovascular, and ventilation functions to maintain adequate oxygen levels in the body. In addition, it will also affect components of the cardiovascular system, such as stroke volume, cardiac output, mean arterial pressure, and systolic blood pressure. So that when a person does exercise, the VO<sub>2</sub> max will indirectly increase along with the increase in the activity carried out. The increase in cardiac output is caused by the high demand for oxygen required by skeletal muscles. Muscles require large amounts of ATP to achieve maximum muscle contraction. ATP can be produced when the amount of oxygen in the body is sufficient. Even though the oxygen levels in the muscles are not enough, the muscles can still contract. This condition is called the anaerobic state. Under anaerobic conditions, muscles require ATP rapidly but produce waste products in the form of lactic acid. When oxygen demand is insufficient, muscles will still get ATP through pyruvic acid. If this happens within 1-3 minutes, lactic acid will build up in muscle cells in high amounts. If this continues, the muscles will experience fatigue or fatigue. The body feels the effects of lactic acid in a short time and within a few days. This is known as DOMS (Delayed Onset Muscle Soreness)[48].

This dementia condition affects the quality of life, the individual's perception of his life in the context of the culture, behavior, and value system in which they live and is related to the standard of living, expectations, pleasures, and the individual's assessment of his position in life. According to WHO, measurement of quality of life consists of physical, psychological, level of freedom, social relations, and environment [43].

The regular exercise followed by increased physical fitness can improve the quality of life of the elderly. Older people who engage in walking will benefit from the respiratory and cardiovascular systems to work harder to meet the increased demand for oxygen in the body. By walking, the elderly will be more active, so the elderly will also often meet with many people and socialize



again with many people. Thus the intervention given to the intervention group could significantly improve the quality of life of the elderly, but this was different in the control group. Aerobic exercise can help older people with dementia develop social skills and create a more pleasant environment for nursing home residents.

#### Limitations

The study was conducted in a nursing home, which has many factors that affect attendance in the program. Respondents in this study who were elderly had difficulty performing movements in a series of exercises. Movements cannot be regulated optimally and tend to be different for each respondent. Respondents did what they could. Furthermore, in this study the presence of a series of exercises is not always complete, some respondents are not present at the training session (total attendance is at least 80%).

#### CONCLUSION

In summary, based on data analysis, CA and AE and the two combinations significantly improved cognitive performance in women with dementia. CA is more efficient in increasing plasma SOD and memory levels. Aerobic exercise effectively improves the quality of life-social and quality of life-environment. Furthermore, the combination of CA and AE was also effective to improve SOD and memory. CA and AE interventions have been shown to improve cognitive function in dementia patients through increasing antioxidants. Future studies can increase the time of aerobic exercise intervention to increase plasma SOD levels in dementia patients, both female and male patients.

#### ACKNOWLEDGMENTS

We would like to express our gratitude to Ministry of Education and Culture of The Republic of Indonesia for funding of the research.

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