ORIGINAL ARTICLE

The Effect of *Centella asiatica* and Aerobic Exercises on Estradiol, Cognition, and Balance in Menopausal Women

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ABSTRACT

Introduction: Menopause is a condition where there is a decrease in the hormones estrogen and progesterone in women which causes a reduction in balance and cognition. It is known that Centella asiatica and aerobic exercise enhance cognitive function and physical appearance, but their combination in menopausal women is undetermined. This study aimed to evaluate the efficacy of Centella asiatica and aerobic exercise on estradiol, cognition, and balance in menopausal women. **Materials and methods:** The research design consisted of a 12-week pre- and post-test period. There were 48 menopausal women, with an average age of 53.25 years, served as research subjects. Twelve participants were assigned to the CA group (Centella asiatica, 2x500 mg/day), the AE group (aerobic exercise, 2x90 minutes/week), the CA-AE combination group (n=12), and the control group (n=12). **Results:** The findings demonstrated that the combination of CA-AE caused an increase in plasma estradiol (p=0.041). The Mann-Whitney test revealed that CA was predicted to have the greatest effect on semantic fluency (Δ=4.44; p=0.001), forward digit span (Δ=0.6; p=0.015), and backward digit span (Δ=2.8; p=0.001). AE was expected to produce the greatest improvement in one-leg balance with eyes open (Δ=34.1; p=0.003). In the meantime, the combination of CA-AE resulted in the most significant improvement in MoCA (Δ=4.6; p<0.001), phonemic fluency (Δ=1.8; p=0.004), and visual recall (Δ=6.9; p<0.001). **Conclusion:** Centella asiatica and aerobic exercise have the potential to enhance plasma estradiol, cognition, and balance in postmenopausal women. A greater sample size will allow for more accurate results in future investigations.

Keywords: Aerobic exercise, Centella asiatica, Cognition, Estradiol, Physical fitness, Menopausal women

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INTRODUCTION

The improvement of health services in Indonesia has had a favorable effect, raising life expectancy from 71.8 years in 2018 to a projected 73.7 years in 2025, and women now have a longer life expectancy than men (1). Moreover, the average age of menopause for Indonesian women has increased to 50 years (2). It is anticipated that there will be 1.2 billion menopausal women by 2030 (3). Menopause is a biological event in the female reproductive system due to physiological aging (4).

Menopause occurs in women who are 50 or older. It is a universal and irreversible aspect of the entire aging process involving the reproductive system that, at this age, the monthly menstrual cycle begins to be disrupted and ultimately disappears. The disruption or cessation of menstruation in women is caused by a decrease in and loss of estradiol. This is a common issue that women experience throughout their lifetimes. Menopause is caused by the aging of the ovaries, which reduces the production of gonadotropins, estrogen, estradiol, and progesterone by the ovaries. The presence of inadequate levels of this hormone is associated with the development of a range of physical, vascular, sexual, and psychological symptoms that can cause distress (5). Premenopausal and menopausal syndromes are encountered by many women worldwide, including 70–80% in Europe, 60% in the United States, 57% in Malaysia, 18% in China, and 10% each in Japan and Indonesia. 40% of premenopausal women experienced hot flashes, 38% had trouble sleeping, 37% had more fatigue at work, 33% said they were irritable, 26% experienced joint pain, 21% said they had frequent headaches, and 35% said they forgot more frequently (6).

A decrease in the hormone estrogen is associated with memory loss in women. Reducing estrogen can also

disrupt the density of the spinal cord and the formation of synapses in the brain. In postmenopausal women, a lack of estrogen in the brain causes many undesirable symptoms, including impaired learning and memory, sleep and mood disturbances, hot flushes, and fatigue. Postmenopausal women typically experience a decline in verbal and semantic memory and information processing speed (7).

There are currently hormone replacement therapies, but they are costly and have long-term adverse effects such as heart disease, breast cancer, thrombosis, and stroke, so a safer alternative therapy is necessary (8). Indonesia is a tropical country with abundant natural resources, one of which is Centella asiatica. It is known that Centella asiatica contains phytoestrogens, which have estrogen-like properties in the human body (8). Isoflavonoids, flavonoids, stilbenes, and lignans are classified as phytoestrogens. Quercetin, kaempferol, catechin, rutin, and naringin are among the flavonoids found in Centella asiatica (9). These flavonoids have the capacity to enhance memory, learning, and cognitive function (10).

There are numerous Centella asiatica species in Indonesia that are traditionally used to improve blood circulation, reduce stress and depression, lower blood pressure, enhance memory, and function as diuretics when consumed as dry powders, extracts, teas, cosmetics, and fresh vegetables. Memory and mood improved in healthy seniors who ingested 500 mg and 750 mg of Centella asiatica daily for two months (11). In a different trial, 60 older adults (>65 years) showed improved cognitive performance after receiving Centella asiatica 2x500 mg/day for six months (12). In addition to enhancing cognition, taking 1x500 mg of Centella asiatica daily for two months increases leg muscle strength (13). Exercise is also known to enhance women's physical performance, but the effect of combining Centella asiatica with exercise has not been studied. This study was conducted to determine the impact of Centella asiatica and aerobic exercise on estradiol, cognitive function, and physical performance in menopausal women.

MATERIALS AND METHODS

This study employs a experimental pre- and post-test design. The Ethics Commission of the PPNI West Java Nursing College (No.III/001/KEPK-SLE/STIKEP/PPNI/JABAR/VIII/2020) has approved this study. The intervention lasted for twelve weeks. This study included premenopausal and postmenopausal women as respondents. The inclusion criteria for this study were women aged 45 to 60, who did not take cognitive-enhancing medications, and who had not exercised in the three months preceding the intervention. There were 48 respondents: 12 were willing to take CA 2x500 mg/day, 12 were willing to exercise twice weekly for 90 minutes each, 12 were willing to take CA 2x500 mg/day and exercise twice weekly for 90 minutes, and the remaining 12 were in the control group who did not receive the intervention. The control group engaged in only daily routines.

Each capsule of Centella asiatica contains 1.41 mg/g of asiaticoside. Each capsule is comprised of 500 mg of Centella asiatica extract. Twice a week, exercises are performed. Warm-up movements last for fifteen minutes, core exercises last for sixty minutes, and cool-down exercises last for fifteen minutes. The aerobic workouts in the core motions include breathing exercises, rheumatic exercises, and heart-healthy exercises. They are all performed to popular music, which makes the respondents excited about performing them. The actions performed also keep time with the musical beat. One gymnastics coach has thirty years of experience and a national certificate.

The data were analyzed using SPSS 24. To determine changes in the effect of Centella asiatica, aerobic exercises, and their combination from the start of the study to the 12th week on estradiol levels, cognition, and balance using the Wilcoxon test Meanwhile, to determine the differences between the four groups, the Mann-Whitney test was carried out.

Blood biochemistry examination

The estradiol level was measured by drawing 3 ml of blood from the brachial vein. The plasma was then extracted, and the estradiol concentration was determined using the HPLC apparatus and the ELISA technique. Before the intervention, 3 ml of blood was removed from the brachial vein of the fasting participants and put into EDTA tubes. The tubes were left at room temperature for 1 hour, then stored in a cool box (-8ºC) and brought to the laboratory. In the laboratory, the tubes were centrifuged for 10 minutes, then the plasma was separated and stored at -80ºC before further analysis.

Cognitive function measurement

All prospective research subjects underwent cognitive function tests consisting of verbal fluency tests (semantic and phonemic), digit span (forward and backward), and visual recall (14). Nurses who had received special training for this study administered the tests. The following is an explanation of each cognitive function test performed:1. Verbal fluency (semantic and phonemic). Semantic fluency was examined by asking respondents to name as many familiar animals as possible in one minute while the examiner recorded and counted the animals mentioned (15). Phonemic fluency was assessed by asking participants to name animals beginning with the letter S for one minute (16). This test measures verbal fluency and executive function (17); 2. Digit span (forward and backward digit span). Respondents were

asked to repeat the sequence of numbers mentioned by the examiner (digit span forward). After that, participants were asked to repeat the number mentioned by the examiner in reverse order (digit span backward). The examiner records and correctly counts the sequence of numbers mentioned by the participant (18). The purpose of this test is to assess attention and working memory (14); 3. Visual Recall (Memory Task). Within 20 seconds, respondents had to read and memorize 10 words that the examiner had given them, after which they had to name the words. The participants were then asked to memorize the same words in a different order within 20 seconds and then recite the words. This procedure was performed three times to memorize the same 10 words but arranged randomly, and then the examiner counted the number of words correctly mentioned by the respondents. This test serves to assess memory (14).

Balance measurement

The eye-open and eye-closed balance test is performed by standing on one leg as hard as possible, then recording the time to stand on one leg, both in a closed and open eye state (19).

RESULTS

This study was conducted on 48 menopausal women with an age range of 45-60 years. Almost all respondents have high education, married, postmenopause, and have a history of menarche age, number of children, and hormonal contraception. The characteristics of the respondents are shown in Table I.

Table I: Characteristics of Respondents

Characteristics	Centella asiatica/ CA (n=12)	Aerobic Exercise/ AE (n=12)	Combination of CA and AE (n=12)	Control (n=12)	p
Age, mean (sd), yr	53.3 (5.8)	53.0 (4.9)	53.0 (4.8)	53.3 (5.8)	0.999
Weight, mean (sd), kg	59.6 (6.5)	58.8 (8.9)	61.3 (8.9)	57.5 (6.9)	0.626
Height, mean (sd), cm	153.92 (4.5)	152.2 (5.0)	151.3 (6.1)	152.8 (3.9)	0.519
Sistole, mean (sd), mmHg	121.7 (14.0)	115.5 (11.3)	122.5 (14.2)	121.7 (15.3)	0.711
Diastole, mean (sd), mmHg	78.3 (7.2)	76.4 (6.7)	78.3 (7.2)	78.3 (7.2)	0.919
Education, n (%)					
Low	6 (35.3)	3 (17.6)	2 (11.8)	6 (35.3)	0.200
High	6 (19.4)	9 (29.0)	10 (32.3)	6 (19.4)	
Marital status, n (%)					
Married	12 (25.5)	12 (25.5)	11 (23.5)	12 (25.5)0 (0.0)	0.382
Widowed	0 (0.0)	0 (0.0)	1 (100.0)		
Menopause status, n (%)					
Perimenopause	3 (20.0)	5 (33.3)	3 (20.0)	4 (26.7)	0.785
Postmenopause	9 (27.3)	7 (21.2)	9 (27.3)	8 (24.2)	
Menarche age, mean (sd), yr	13.6 (1.9)	13.6 (2.3)	13.3 (1.3)	13.2 (1.8)	0.956
Number of children, mean (sd), score	3.1 (0.9)	3.0 (0.8)	2.7 (1.2)	3.1 (2.2)	0.718
Hormonal contraception, n (%)					
Yes	6 (24.0)	9 (36.0)	6 (24.0)	4 (16.0)	0.235
No	6 (26.1)	3 (13.0)	6 (26.1)	8 (34.8)	

*p<0.05; p-value were derived from Kruskal Wallis or ANOVA test and chi-square

The combination centella asiatica and aerobic exercise group demonstrated a significant difference in plasma estradiol levels before and after intervention (p = 0.041). The results of the three intervention groups differed significantly from those of the control group (see Table II).

Table II: Comparison of estradiol plasma, cognition, and balance between before and after intervention for 12-weeks

Variable	Centella asiatica/CA (n=12)	Aerobic Exercise/ AE (n=12)	Combination of CA and AE (n=12)	Control (n=12)	p[b]
Estradiol, ng/ml					
Pre	13.6 (9.7)	23.0 (15.4)	17.2 (12.7)	20.9 (22.5)	0.869
Post	22.4 (18.9)	43.7 (68.4)	25.7 (17.4)	13.2 (8.5)	
Δ	8.8 (16.1)	20.7 (63.9)	8.5 (11.3)	-7.8 (17.7)	
p[a]	0.177	0.239	0.041*	0.388	
Cognition					
MoCA, score					
Pre	22.8 (2.5)	22.6 (3.5)	23.3 (2.5)	23.4 (3.1)	<0.001*
Post	25.5 (2.4)	26.9 (2.8)	27.9 (1.5)	23.9 (3.3)	
Δ	2.8 (1.7)	4.3 (2.8)	4.6 (2.8)	0.4 (1.7)	
p[a]	<0.001*	<0.001*	<0.001*	0.312	

CONTINUE

Table II: Comparison of estradiol plasma, cognition, and balance between before and after intervention for 12-weeks (CONT.)

Variable	Centella asiatica/CA (n=12)	Aerobic Exercise/ AE (n=12)	Combination of CA and AE (n=12)	Control (n=12)	p[b]
Cognition					
Semantic fluency, score					
Pre	15.6 (5.3)	16.4 (1.6)	16.6 (4.2)	17.2 (5.3)	0.014*
Post	20 (5.6)	20.4 (5.4)	20.9 (3.6)	17.5 (5.7)	
Δ	4.4 (3.6)	4 (6.3)	4.3 (3.9)	0.3 (3.3)	
p[a]	0.001*	0.023*	0.001*	0.707	
Phonemic fluency, score					
Pre	2.1 (1.4)	2.6 (1.6)	2.9 (1.7)	2.3 (1.4)	0.002*
Post	3.4 (1.9)	4.2 (1.4)	4.6 (1.6)	2.2 (1.5)	
Δ	1.3 (1.3)	1.6 (1.7)	1.8 (1.9)	-0.1 (0.7)	
p[a]	0.005*	0.002*	0.004*	0.480	
Forward digit span					
Pre	7 (0.9)	7.6 (0.7)	7.6 (0.7)	7.3 (0.9)	0.004*
Post	7.6 (0.8)	7.9 (0.5)	8 (0)	7.1 (1.2)	
Δ	0.6 (0.8)	0.3 (0.6)	0.4 (0.7)	-0.2 (0.4)	
p[a]	0.015*	0.102	0.038*	0.083	
Backward digit span)					
Pre	1.9 (1.8)	3.6 (2.0)	2.9 (1.7)	3 (2.7)	<0.001*
Post	4.7 (1.9)	5.2 (1.8)	4.6 (1.6)	3.3 (2.4)	
Δ	2.8 (1.6)	1.6 (1.7)	2.6 (1.9)	0.3 (0.8)	
p[a]	0.001*	0.002*	0.001*	0.206	
Visual recall					
Pre	16.8 (6)	19.5 (4.6)	19.7 (3.3)	18.2 (5.2)	<0.001*
Post	22.2 (5.4)	24.9 (3)	26.6 (3.1)	19.9 (6.3)	
Δ	5.4 (3.2)	5.4 (4.5)	6.9 (3.1)	0.6 (1.2)	
p[a]	0.001*	0.001*	<0.001*	0.070	
Balance					
One leg balance with open eyes					
Pre	89.1 (65.9)	50.4 (29)	78.8 (56)	50 (30.1)	0.014*
Post	103.6 (95.6)	84.5 (57.6)	107.6 (63)	53.9 (36.8)	
Δ	11.8 (45.5)	34.1 (53.8)	28.8 (48.3)	4.6 (26.5)	
p[a]	0.007*	0.003*	0.001*	0.432	
One leg balance with close eyes					
Pre	11.8 (8.5)	12.1 (16)	11.9 (7.9)	11.4 (11.4)	0.082
Post	22.6 (25.8)	15.4 (10.8)	20.1 (13)	12.4 (10.9)	
Δ	10.4 (16.4)	3.3 (16.4)	8.1 (11.7)	1.7 (2.7)	
p[a]	<0.001*	<0.001*	<0.001*	0.270	

Δ: the difference between pre and post-intervention
p[a]: Wilcoxon test
p[b]: Mann-Whitney test
*Significant

The Mann-Whitney test showed that CA was to induce the highest increase in semantic fluency (Δ=4.44; p=0.001), forward digit span (Δ=0.6; p=0.015), and backward digit span (Δ=2.8; p=0.001). The results showed that AE was to induce the highest increase in one leg balance with open eyes (Δ=34.1; p=0.003). Meanwhile, the CA-AE combination led to the highest enhancement in MoCA (Δ=4.6; p<0.001), phonemic fluency (Δ=1.8; p=0.004), and visual recall (Δ=6.9; p<0.001) (see Table II).

DISCUSSION

Our study demonstrates that Centella asiatica alone and aerobic exercise alone do not increase plasma estradiol in perimenopausal and postmenopausal women; however, the combination of Centella asiatica and aerobic exercise for 12 weeks can increase plasma estradiol in these women. This is consistent with research on postmenopausal women, which indicates that aerobic exercise cannot increase estrogen because it decreases adipose mass, thereby decreasing estrogen levels (20). Aerobic exercise will reduce both fat mass and estrogen levels in postmenopausal women due to their increased body fat content (21). The combination of Centella asiatica and aerobic exercise increases plasma estradiol effectively. This is consistent with previous research indicating that Centella asiatica contains phytoestrogens that can increase estrogen levels in women. Aquatic aerobic exercise of 3x45 minutes per week for 8 weeks was effective in increasing estrogen levels and decreasing body mass index in obese and normal-weight postmenopausal women via the mechanisms of estrogen hydroxylation and catechol estrogen methylation by cytochrome P450 enzymes, according to a separate study (22). The other study found that exercise decreases estrogen purification and metabolism, resulting in elevated estrogen levels in the blood after exercise (23). Body fat in menopausal

women and variations in the type, length, and intensity of exercise can influence how a change in estrogen manifests itself (20).

Depending on age, type of menopause (natural versus induced), and stage of menopause (early versus late), current evidence suggests that estrogen may have beneficial, neutral, or detrimental effects on the brain (24). Estrogen acts as a neuroprotective agent by decreasing beta-amyloid and glutamate toxicity, enhancing synapse plasticity, preserving neurotrophic components, facilitating transcription factor initiation, reducing brain inflammation, and decreasing tau protein hyperphosphorylation (25). Estrogen affects hemodynamics and perfusion between the heart and brain regions, which may impact cognitive function. Through physical exercise, the rigidity of the elastic central arteries of the heart is reduced, so that hemodynamics and perfusion to the brain are improved, and cognitive function is also improved (26).

Previous research has demonstrated that gotu kola supplements of 750 mg/day and 1,000 mg/day can enhance memory function in healthy elderly individuals (11). The primary findings indicated that both exercise and combination exercise and CA enhanced global cognition, working memory, and executive function. Frequency and duration are critical moderators of effect size for multicomponent exercise, and higher frequency and longer duration are related to greater effects. In this study, exercise was performed three times for 90 minutes each (270 minutes weekly), which led to an improvement in cognitive performance (27). Aerobic exercise appears to be more beneficial for cognitive enhancement, as consistent aerobic physical activity increases cerebral blood flow by increasing the heart's oxygen supply. The intensity of exercise has a significant impact on cerebral blood flow regulation. Moderate to high-intensity aerobic exercise increases blood circulation in the cardiovascular and cerebrovascular regions more than low-intensity aerobic exercise (6). Exercise-induced enhancement of cerebral blood flow is closely associated with cognitive function and increased protein expression of neurotrophic factors, including brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1, and vascular endothelial growth factor (VEGF), in the brain and peripheral tissues (6). Compared to resistance training and continuous training, high-intensity interval training may be more effective in enhancing cognitive function in postmenopausal women, not only by reducing central arterial stiffness but also by facilitating neurotrophic factor production and increasing neurotrophic factor bioavailability. During aerobic exercise of high intensity, the hypoxic state increases VEGF production. Specifically, intermittent hypoxia during high-intensity interval training promotes the formation of BDNF, the most essential marker of neuroplasticity, in the cerebrovascular endothelium. Additionally, lactate, a byproduct of high-intensity exercise, can be used to facilitate the formation of BDNF and VEGF in peripheral tissues and is an additional source of energy for brain neuronal activity. After traversing the blood-brain barrier, both BDNF and VEGF produced in peripheral tissues can directly promote neuroplasticity in the central nervous system (26).

The research results found that CA, AE, and the combination of CA and AE could improve balance in menopausal women. This is in accordance with studies showing that physical fitness can increase with regular and programmed exercise for 60 minutes with a frequency of 2-3x/week (28). Another study showed that CA 500 mg can improve blood circulation and reduce oxidative stress and muscle degeneration, so that leg muscle strength and balance increase (13). By stimulating proprioceptors in the joints, aerobic exercise can be a useful method for enhancing stability and balance. Through enhanced proprioception, enhanced coordination, strengthened supporting muscles, quicker reflexes, and balance challenges, individuals can experience a variety of physical and psychological benefits that contribute to a healthier and more active lifestyle (27). The limitation of this research is that the number of respondents is small because it is difficult to get respondents who want to consume Centella asiatica because they are afraid of side effects.

CONCLUSION

Plasma estradiol can be increased in postmenopausal women via aerobic exercise and Centella asiatica. Since aerobic exercise decreases fat mass, it does not increase estrogen levels. These women can boost estrogen using Centella asiatica and exercise. Estrogen protects the brain by reducing beta-amyloid and glutamate toxicity, improving synaptic plasticity, preserving neurotrophic components, introducing transcription factors, reducing brain inflammation, and stopping tau protein from becoming too phosphorylated. Executive function, short-term memory, and global cognition are enhanced by physical activity. Gotu kola improves the memory of aging adults who are physically active. High-intensity interval training may enhance cognitive function in postmenopausal women by lowering cerebral arterial stiffness and increasing neurotrophic factor production and bioavailability. Aerobic exercise improves equilibrium by stimulating proprioceptors in the joints. This can enhance the health and activity of postmenopausal women. Centella asiatica aerobics aids postmenopausal ladies.

ACKNOWLEDGEMENT

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

REFERENCES

1. Mboi N, Murty Surbakti I, Trihandini I, Elyazar I, Houston Smith K, Bahjuri Ali P, et al. On the road to universal health care in Indonesia, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2018 Aug;392(10147):581–91. doi: 10.1016/S0140-6736(18)30595-6
2. Diyu IANP, Satriani NLA. Menopausal symptoms in women aged 40-65 years in Indonesia. Int J Heal Med Sci. 2022 Jun 7;5(2):169–76. doi: 10.21744/ijhms.v5n2.1896
3. Hill K. The demography of menopause. Maturitas. 1996 Mar;23(2):113–27. doi: 10.1016/0378-5122(95)00968-x
4. Wieder-Huszla S, Szkup M, Jurczak A, Samochowiec A, Samochowiec J, Stanisławska M, et al. Effects of Socio-Demographic, Personality and Medical Factors on Quality of Life of Postmenopausal Women. Int J Environ Res Public Health. 2014 Jun 26;11(7):6692–708. doi: 10.3390/ijerph110706692
5. Sharma S, Mahajan N. Menopausal symptoms and its effect on quality of life in urban versus rural women: A cross-sectional study. J Midlife Health. 2015;6(1):16. doi: 10.4103/0976-7800.153606
6. Nappi RE, Kroll R, Siddiqui E, Stoykova B, Rea C, Gemmen E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause. 2021 Aug;28(8):875–82. doi: 10.1097/GME.0000000000001793
7. Georgakis MK, Beskou-Kontou T, Theodoridis I, Skalkidou A, Petridou ET. Surgical menopause in association with cognitive function and risk of dementia: A systematic review and meta-analysis. Psychoneuroendocrinology. 2019 Aug;106:9–19. doi: 10.1016/j.psyneuen.2019.03.013
8. Echeverria V, Echeverria F, Barreto GE, Echeverria J, Mendoza C. Estrogenic Plants: to Prevent Neurodegeneration and Memory Loss and Other Symptoms in Women After Menopause. Front Pharmacol. 2021 May 20;12. doi:10.3389/fphar.2021.644103
9. Zheng C. Chemical components of Centella asiatica and their bioactivities. J Chinese Integr Med. 2007 May 15;348–51. doi: 10.3736/jcim20070324
10. Spencer JPE. Flavonoids and brain health: multiple effects underpinned by common mechanisms. Genes Nutr. 2009 Dec 15;4(4):243–50. doi: 10.1007/s12263-009-0136-3
11. Wattanathorn J, Mator L, Muchimapura S, Tongun T, Pasuriwong O, Piyawatkul N, et al. Positive modulation of cognition and mood in the healthy elderly volunteer following the administration of Centella asiatica. J Ethnopharmacol. 2008. doi: 10.1016/j.jep.2007.11.038
12. Tiwari S, Singh S, Patwardhan K, Gehlot S, Gambhir IS. Effect of centella asiatica on mild cognitive impairment (mci) and other common age-related clinical problems. Dig J Nanomater Biostructures. 2008.
13. Mato L, Wattanathorn J, Muchimapura S, Tongun T, Piyawatkul N, Yimtae K, et al. Centella asiatica improves physical performance and health-related quality of life in healthy elderly volunteer. Evidence-based Complement Altern Med. 2011. doi: 10.1093/ecam/nep177
14. Bossers WJR, van der Woude LHV, Boersma F, Scherder EJA, van Heuvelen MJG. Recommended Measures for the Assessment of Cognitive and Physical Performance in Older Patients with Dementia: A Systematic Review. Dement Geriatr Cogn Dis Extra. 2012. doi: 10.1159/000345038
15. Sabia S, Dugravot A, Dartigues JF, Abell J, Elbaz A, Kivimaki M, et al. Physical activity, cognitive decline, and risk of dementia: 28 year follow-up of Whitehall II cohort study. BMJ. 2017;357. doi: https://doi.org/10.1136/bmj.j2709
16. Shao Z, Janse E, Visser K, Meyer AS. What do verbal fluency tasks measure? Predictors of verbal fluency performance in older adults. Front Psychol. 2014; doi: 10.3389/fpsyg.2014.00772
17. Joubert S, Felician O, Barbeau EJ, Didic M, Poncet M, Ceccaldi M. Patterns of semantic memory impairment in Mild Cognitive Impairment. In: Behavioural Neurology. 2008. doi: 10.1155/2008/859657
18. Purpura DJ, Lonigan CJ. Early Numeracy Assessment: The Development of the Preschool Early Numeracy Scales. Early Educ Dev. 2015 Feb 17;26(2):286–313. doi: 10.1080/10409289.2015.991084
19. Jalali MM, Gerami H, Heidarzadeh A, Soleimani R. Balance performance in older adults and its relationship with falling. Aging Clin Exp Res. 2015. doi: 10.1007/s40520-014-0273-4
20. Razzak ZA, Khan AA, Farooqui SI. Effect of aerobic and anaerobic exercise on estrogen level, fat mass, and muscle mass among postmenopausal osteoporotic females. Int J Health Sci (Qassim). 2019;13(4):10–6. PMID: 31341450
21. Kim J-W, Kim D-Y. Effects of Aerobic Exercise Training on Serum Sex Hormone Binding Globulin, Body Fat Index, and Metabolic Syndrome Factors in Obese Postmenopausal Women. Metab Syndr Relat Disord. 2012 Dec;10(6):452–7. doi: 10.1089/met.2012.0036
22. Ketabipoor SM, Koushkie Jahromi M. Effect of Aerobic Exercise in Water on Serum Estrogen and C - Reactive Protein and Body Mass Index Level in Obese and Normal Weight Postmenopausal Women. Women's Heal Bull. 2015 Jul 18;2(3). doi:10.17795/whb-25048
23. Smith AJ, Phipps WR, Thomas W, Schmitz KH, Kurzer MS. The Effects of Aerobic Exercise on Estrogen Metabolism in Healthy Premenopausal Women. Cancer Epidemiol Biomarkers Prev. 2013 May 1;22(5):756–64. doi: 10.1158/1055-9965.

EPI-12-1325
24. Rocca WA, Mielke MM, Vemuri P, Miller VM. Sex and gender differences in the causes of dementia: A narrative review. Maturitas. 2014. doi: 10.1016/j.maturitas.2014.05.008
25. Uddin MS, Rahman MM, Jakaria M, Rahman MS, Hossain MS, Islam A, et al. Estrogen Signaling in Alzheimer's Disease: Molecular Insights and Therapeutic Targets for Alzheimer's Dementia. Mol Neurobiol. 2020 Jun 15;57(6):2654–70. doi: 10.1007/s12035-020-01911-8
26. Hwang MH. Cognitive Enhancement through Improved Central Artery Stiffness in Postmenopausal Women: Potential Benefit of HighIntensity Aerobic Exercise. Iran J Public Health. 2020 Aug 9.
27. Phoemsapthawee J, Ammawat W, Prasertsri P, Sathalalai P, Leelayuwat N. Does Gotu kola supplementation improve cognitive function, inflammation, and oxidative stress more than multicomponent exercise alone? – a randomized controlled study. J Exerc Rehabil. 2022 Oct 26;18(5):330–42. doi: 10.12965/jer.2244388.194
28. Lam FM, Huang MZ, Liao LR, Chung RC, Kwok TC, Pang MY. Physical exercise improves strength, balance, mobility, and endurance in people with cognitive impairment and dementia: a systematic review. J Physiother. 2018. doi: 10.1016/j.jphys.2017.12.001