Universal Journal of Public Health 11(6): 861-868, 2023
DOI: 10.13189/ujph.2023.110610 http://www.hrpub.org

Centella asiatica (Indian Pennywort) Extract and Exercise Increase Brain-Derived Neurotrophic Factor Plasma, Cognition, and Physical Fitness among Menopausal Women

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Received February 6, 2023; Revised May 16, 2023; Accepted October 20, 2023

Cite This Paper in the Following Citation Styles

(a): *[1] Iwan Setiawan, Lisna Anisa Fitriana, I Ketut Adnyana, Kusnandar Anggadiredja, Nazhifa Ufamy, Irma Darmawati, Lina Anisa Nasution, Suci Tuty Putri, Upik Rahmi, Septian Andriyani, Komarudin, Ria Maria Theresa, Aih Cahyani , "Centella asiatica (Indian Pennywort) Extract and Exercise Increase Brain-Derived Neurotrophic Factor Plasma, Cognition, and Physical Fitness among Menopausal Women," Universal Journal of Public Health, Vol. 11, No. 6, pp. 861-868, 2023. DOI: 10.13189/ujph.2023.110610.*

(b): *Iwan Setiawan, Lisna Anisa Fitriana, I Ketut Adnyana, Kusnandar Anggadiredja, Nazhifa Ufamy, Irma Darmawati, Lina Anisa Nasution, Suci Tuty Putri, Upik Rahmi, Septian Andriyani, Komarudin, Ria Maria Theresa, Aih Cahyani (2023). Centella asiatica (Indian Pennywort) Extract and Exercise Increase Brain-Derived Neurotrophic Factor Plasma, Cognition, and Physical Fitness among Menopausal Women. Universal Journal of Public Health, 11(6), 861-868. DOI: 10.13189/ujph.2023.110610.*

Abstract Menopausal women are prone to cognitive disorders. Various therapies that have been developed to overcome this problem are the administration of Indian Pennywort (Centella asiatica) and exercise. Both have positive effects on cognitive function, but previous studies have not examined the combined effect of the two on the brain-derived neurotrophic factor (BNDF), cognition, and physical fitness among menopausal women. Methods: This study used a pre and post-test design. Subjects consisted of 64 people who were divided into four groups, consisting Indian pennywort/IP group (500 mg daily), an exercise group (2x90 minutes per week), a group combination of IP-exercise (IP 500 mg daily and exercise for 2x90 minutes per week), and the control group. The intervention was given for 12 weeks. Results: The study showed that Indian Pennywort, exercise, and its combination can increase plasma BDNF, cognition, and physical fitness in menopausal women ($p<0.05$). Mann-Whitney test showed that the combination of Indian Pennywort and exercise caused the highest increase in plasma BDNF ($\Delta=236$; $p=0.007$), MoCA ($\Delta=3.5$; $p<0.001$), right-hand strength ($\Delta=4.6$; $p=0.001$), left-hand strength ($\Delta=3.5$; $p=0.001$), and lower extremity strength ($\Delta=6$; $p<0.001$). Conclusion: Overall results showed that Indian Pennywort, exercise, and the combination of the two above were effective in ameliorated plasma BDNF, cognition, and physical fitness in menopausal women, but the combination provides a maximum effect compared to other groups.

Keywords BDNF, Cognition, Exercise, Centella Asiatica, Physical Fitness

1. Introduction

The elderly population continues to grow along with the increase in life expectancy. The life expectancy for women is higher than the life expectancy for men [1]. The increase in the number of older women certainly causes the need for attention to problems related to health problems in older women [2]. One of the risks of health problems in the elderly is cognitive impairment [3-4]. Mild cognitive impairment is a predementia phase characterized by a cognitive decline that is not severe and can still carry out daily activities [5]. The incidence of cognitive disorders in Indonesia was 1.2 million cases in 2015. By 2030 it is estimated to increase to 3.98 million [6]. Cognitive decline is a frequent complaint during the menopause transition and among post-menopausal women. Changes in memory correspond with diminished estrogen production. Having trouble remembering words or numbers, needing memory aides, and forgetting why one was engaging in a certain behavior were the most often reported problems [7].

Women have a higher prevalence of Alzheimer's than men. In addition, women with mild cognitive impairment tend to deteriorate more quickly than men [8]. This is related to the condition of older women experiencing menopause which reduces estradiol levels, which plays a major role in regulating nerve activity in several brain areas such as the hippocampus and prefrontal cortex [9]. Brain-derived neurotrophic factor (BDNF) is one of the neurotrophins with a high level of expression in the brain and its potent effects on synapses. The function of BDNF is to regulate synapses ranging from short-term to long-lasting in many brain regions [10].

BDNF plays an important role in improving cognitive power, memory, resilience, and nervous system development [11-12]. BDNF also plays a role in increasing neurogenesis and neuronal transmission at synapses, increasing synaptic growth, and modulating synaptic plasticity to form long-term memory [13]. Furthermore, one of the effects of menopause on older women is decreased cognitive function [14]. The decrease includes attention, calculation, orientation, and language ability [15]. These things affect the process of long-term memory and information. Decreased cognitive function will cause a decrease in the quality of life in older women.

Early interventions such as brain supplementations and exercises are thought to be able to prevent the progressive neurodegenerative process, including a decrease in cognitive function. Indian Pennywort is one of the plants known to have neuroprotective effects. The active compounds asiaticoside and madecoside in Indian Pennywort are known to strengthen memory and intelligence [16]. Indian Pennywort can induce positive modulation and increase BDNF in the prefrontal cortex so that cognitive function in male rats increases [17]. Another study found that the ethanol extract of Indian Pennywort increased memory and serum BDNF via TrkB-MAPK pathways in the hippocampus [18]. Indian Pennywort has a good effect on older women because of its cholinergic activity, antioxidant, and anti-inflammatory activity [19]. Indian Pennywort affects several cognitive domains such as attention and concentration, executive cognitive function, information processing speed, language, working memory, verbal memory, and visual memory [20].

Several studies showed the benefit of exercise in preventing the progression of cognitive impairment. Exercise stimulates the brain and increases BDNF. Aerobic exercise can reduce the possibility of memory loss in the elderly. Furthermore, aerobic exercise can improve cognitive function and increase BDNF concentration in the elderly [21]. A systematic review reported a higher BDNF response after moderate-intensity aerobic exercise in healthy older people [22]. The research facts above show that there are many positive effects of Indian Pennywort and exercise on BDNF, cognition, and physical fitness, but the combination of both in humans especially menopausal women was not been studied yet.

2. Materials and Methods

2.1. Study Design

This study used a pre and post-test design. The inclusion criteria of this study were premenopausal to postmenopausal women aged 45 to 65 years, who had no history of serious illness, had not done sports activities in the previous three months, and had not used brain-stimulating drugs in the previous two weeks. The Ethics Commission of the PPNI West Java Nursing College (No. III/001/KEPK-SLE/STIKEP/PPNI/JABAR/VIII/2020) has approved this study.

2.2 Intervention

The interventions were divided into four groups. The first group was given 500 mg of Indian pennywort/IP daily. The second group received exercise training twice a week for 90 minutes per session (15 minutes warm-up, 60 minutes core movement, and 15 minutes cool-down). The third group was a combined group that exercised twice a week for 90 minutes and required 500mg of IP daily. The fourth and final group served as the control group. The sample size of this study was 64 women. This intervention took 12 weeks to implement.

Exercise is done with a combination of cardiovascular and respiratory exercises (maximizing aerobic breathing), metabolic exercises (lipid metabolism), and

musculoskeletal strength (muscle strength and endurance). The movements in each type of gymnastics are carried out alternately and accompanied by music that sparks the enthusiasm of the participants. The choice of music is adjusted to the movements/exercise being performed.

CA extract is made through a standardized process by quality control until the dry CA extract is produced and packaged in capsule form. Each capsule contained 500 mg of CA extract with an asiaticoside level of 1.41 mg/g and was examined using the HPLC. Each participant consumed one capsule/per day. Compliance monitoring was carried out by observing the results of daily checklists which were checked every two weeks by nurses in the research team. Participants were also reminded via the WhatsApp platform every morning to consume CA extract capsules every day.

2.3. Measurement of Cognitive Function

Cognitive function was measured by the MoCA-Indonesian version. The MoCA consists of 30 questions regarding visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation. A specific biologically determined relationship between exercise and cognitive function can be detected using MoCA [23].

2.4. Measurement of Physical Fitness

Upper and lower extremity muscle strength was assessed as part of the physical fitness exam. A dynamometer was used to measure muscle strength in the upper extremities. Participants pull the handgrip with their left and right hands. Handgrip dynamometer readings recorded (in kilograms). Lower extremity muscle strength was measured by counting and recording the number of times the individual could squat and stand in 30 seconds [24]. Researchers also carried out a physical examination, which included anthropometric measurements, blood pressure checks, and a review of previous medical history.

2.5. BDNF Plasma Examination

In the Molecular and Genetics Laboratory, Faculty of Medicine, Universitas Padjadjaran, plasma levels of BDNF were tested using an ELISA technique and HPLC. Before the intervention, 3 mL of blood was drawn from the brachialis veins of fasting participants and placed in an EDTA tube. The tube was left at room temperature for one hour before being transferred to the laboratory in a cool box (-8°C). The blood was centrifuged for 10 minutes in the laboratory. Plasma was separated and stored at -8°C before further examination.

2.6. Statistical Methods

The Shapiro-Wilk test was used to determine the normality of the data. The Wilcoxon test was used to compare the differences between each group before and after the intervention. To identify differences across groups, the Mann-Whitney test was utilized. SPSS 25 was used to process and analyze data, with a significance threshold of $p<0.05$.

3. Results

The research subjects consisted of 64 menopausal women. Each group consists of sixteen people. The characteristics of respondents consisted of age, weight, height, blood pressure, education, menopause status, and marital status. From the characteristics of the respondents, there were no differences between the four groups ($p>0.05$) (Table 1).

Table 1. Characteristics of Respondents Based on Intervention

Characteristics	Indian Pennywort/IP (n=16) Median (min-max)	Exercise (n=16) Median (min-max)	Combination of IP-Exercise (n=16) Median (min-max)	Control (n=16) Median (min-max)
Age, yr	54 (44-62)	52.5 (44-61)	54.5 (47-62)	52.5 (45-60)
Weight, kg	56.5 (50-72)	57.5 (48-80)	60.5 (48-80)	56 (50-70)
Height, cm	152.5 (149-162)	151.5 (144-162)	150.5 (142-165)	152.5 (146-160)
Sistole, mmHg	120 (100-150)	120 (100-150)	120 (110-150)	120 (100-150)
Diastole, mmHg	80 (70-90)	80 (70-90)	80 (70-90)	80 (70-90)
Education, n (%)				
Low	8 (50)	6 (37.5)	2 (12.5)	7 (43.7)
High	8 (50)	10 (62.5)	14 (87.5)	9 (56.3)
Menopause status, n (%)				
Perimenopause	3 (20.0)	5 (33.3)	3 (20.0)	4 (26.7)
Postmenopause	9 (27.3)	7 (21.2)	9 (27.3)	8 (24.2)
Marital status, n (%)				
Married	16 (100)	16 (100)	13 (81.3)	16 (100)
Widowed	0 (0)	0 (0)	3 (18.7)	0 (0)

Table 2. Comparison of BDNF, cognition, and physical fitness between before and after intervention for 12-weeks

Variable	Indian Pennywort/IP (n=16) Median (min-max)	Exercise (n=16) Median (min-max)	Combination of IP-Exercise (n=16) Median (min-max)	Control (n=16) Median (min-max)	p^b
BDNF, pg/ml					
Pre	372.5 (63-890)	465 (136-1942)	241 (59-1387)	587.5 (90-2336)	0.002*
Post	700 (110-1749)	705 (140-1974)	622 (124-1974)	474 (108-1296)	
Δ	230 (-549-1317)	156 (-267-1467)	236 (-309-999)	-149.5 (-1843-570)	
p^a	0.034*	0.044*	0.007*	0.020*	
Cognition					
MoCA, score					
Pre	24 (10-26)	23.5 (17-26)	23.5 (19-26)	24.5 (15-26)	
Post	26 (21-29)	28 (21-30)	28.5 (25-29)	24.5 (15-27)	<0.001*
Δ	3 (-1-5)	3.5 (1-11)	3.5 (1-10)	0 (-2-5)	
p^a	<0.001*	<0.001*	<0.001*	0.312	
Physical fitness					
Righthand strength, kg					
Pre	13.1 (12-27)	19.9 (11-25)	15.5(11-25)	21.9 (13-23)	0.002*
Post	18.3 (14-28)	22.1 (11-27)	20.6 (15-29)	22.4 (12-24)	
Δ	1.1 (-2.4-7.4)	2.7 (-1.6-11)	4.6 (-36-11)	0.35 (-1.3-1.3)	
p^a	0.007*	0.003*	0.001*	0.432	
Lefthand strength, kg					
Pre	13.5 (12-24)	18.4 (10-25)	14.6(10-23)	21 (12-23)	
Post	17.4 (12-25)	19.9 (10-24)	18.3 (14-28)	22 (13-23)	0.010*
Δ	1.6 (-3.9-6.4)	1.3 (-3.5-6)	3.5 (-3.4-8)	0.5 (-1.7-1.5)	
p^a	0.013*	0.104	0.001*	0.229	
Lower extremity strength, score					
Pre	11 (9-16)	15.5 (9-20)	13.5 (9-16)	13 (11-16)	
Post	23 (14-29)	20 (11-26)	17.5 (14-27)	14.5 (10-18)	<0.001*
Δ	4.5 (1-15)	5.5 (-3-11)	6 (1-18)	1 (-2-2)	
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

Subjects that received Indian Pennywort extract, exercise, and a combination of Indian Pennywort and exercise had significant differences in BDNF plasma, cognition, and physical fitness before and after intervention ($p<0.05$). In the control group, BDNF plasma showed a significant decrease of -149.5 (-1843-570) ($p=0.020$) (Table 2).

The results of the Mann-Whitney test showed significant differences between the four groups ($p<0.05$). The combination of Indian Pennywort and exercise led to the highest increase in BDNF plasma ($\Delta=236$; $p=0.007$), MoCA ($\Delta=3.5$; $p<0.001$), righthand strength ($\Delta=4.6$; $p=0.001$), lefthand strength ($\Delta=3.5$; $p=0.001$), and lower extremity strength ($\Delta=6$; $p<0.001$) (Table 2).

Adverse events

Two subjects (Indian Pennywort group, n = 1; combination Indian Pennywort-exercise group, n = 1) experienced adverse events diarrhea, and urinated frequently but not related to the intervention. There were no other adverse events during Indian Pennywort and exercise treatment for 12 weeks.

4. Discussion

4.1. Effects of Centella asiatica (Indian Pennywort), Exercise, and Its Combination on BDNF plasma

The results showed that Indian Pennywort, exercise, and the combination of both could significantly increase plasma BDNF in menopausal women. Based on the three interventions, a combination of Indian Pennyworth and exercise gave the highest increase in BDNF plasma. This is following research showing that exercise for 2 years can

increase plasma BDNF in mild cognitive impairment elderly with an average age of 70.5 years [25]. Another study on 120 older adults showed that aerobic exercise improves memory function, serum levels of BDNF, and neurogenesis in the dentate gyrus mediator more than the control group [26]. Another study showed that a 1-year moderate-intensity walking intervention improved executive function and plasma BDNF compared to a control group [27]. Aerobic exercise increases BDNF production and consequently improves learning, memory, and executive function [28-29].

Regression analysis shows that BDNF and aerobic fitness are associated with hippocampal memory [30-31]. Animal models demonstrate the important role of brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I), and endothelial vascular growth factor (VEGF) in mediating exercise-induced hippocampal structural and functional changes [32].

The administration of Indian Pennywort improves cognitive performance by inducing an increase in BDNF in the prefrontal cortex in mice. Research shows Indian Pennywort 0.50 ug/ml can increase BDNF expression in young mice through the mechanism of neurogenesis [33]. BDNF effect on the brain synapses comes from downstream signaling pathways that are complex, and the diametrically opposite effect of pro and mature forms through a different receptor, TrkB, and p75NTR [11]. Studies show that Indian Pennywort induces positive modulation and increases BDNF in the prefrontal cortex so that cognitive function in male rats increases [19]. Another study found Indian Pennywort ethanol extract increased memory and serum BDNF via the TrkB-MAPK pathway in the hippocampus [20].

This study shows that BDNF decreased significantly in the control group. The hormone estradiol alters the function of memory circuits including BDNF during the menopausal transition. Decreasing estradiol in menopausal women has an impact on memory circuit aging, thus affecting the decrease in BDNF [34]. Other studies have shown that the climacteric period has nothing to do with BDNF [35].

4.2. Effects of Centella asiatica (Indian Pennywort), Exercise, and Its Combination on Cognition

Cognition examination results show Indian Pennywort, exercise, and their combination can improve cognitive function in menopausal women. Based on the Mann-Whitney test, the combination of Indian Pennywort-exercise gave the highest increase in cognitive function. This is following research showing that there is a significant improvement in memory in the Indian Pennywort 600 group in adult male rats compared to the control group [36]. In addition, Indian Pennywort has several active components that are thought to be anti-inflammatory. In addition, the results showed that Indian Pennywort can increase mitochondrial expression, antioxidant response in the brain and liver, and synaptic expression in the hippocampus and frontal cortex in healthy mice [37]. In addition, Indian Pennywort can improve memory and executive function in aged mice via a mechanism of increasing synaptic density in the hippocampus [38].

A meta-analysis of 11 Indian Pennywort intervention studies concluded that there was no significant effect of Indian Pennywort on human cognitive function. However, some studies with IP doses greater than 1000 mg/day can improve memory. The combination of Indian Pennywort with several other herbs has also been shown to be effective in improving cognitive function [19]. In late adulthood and the elderly, volume shrinking hippocampus causes memory impairment and increased risk of dementia. Several recent studies have shown that the effect of moderate-intensity aerobic exercise is effective in preventing hippocampal volume loss. Several meta-analyses have shown that physical activity is associated with increased attention, processing speed, and executive function in older adults with and without cognitive impairment [39].

4.3. Effects of Centella asiatica (Indian Pennywort), Exercise, and Its Combination on Physical Fitness

Studies show that a combination of Indian Pennywort and exercise is most effective in increasing right-hand strength, left-hand strength, and lower extremity strength. This is consistent with a systematic review study which showed that regular and programmed exercise for 60 minutes, 2-3x/week can improve leg muscle strength, balance, flexibility, walking speed, and 6-minute walking test in people with mild cognitive impairment or dementia [40]. Another study showed Indian Pennywort 500 and 750 mg can increase lower muscle strength in healthy elderly through the mechanism of increasing blood circulation which causes mitochondrial function and muscle capacity to use oxygen to increase, besides Indian Pennywort causes a decrease in ROS (reactive oxygen species) so that oxidative stress decreases and muscle degeneration also decreases [25].

Recent research has shown that physical exercise improves cardiorespiratory fitness and physical fitness in subjects who attend regularly a 16-week exercise intervention [41]. During aerobic exercise, there is an increase in muscle oxygen consumption, an increase in cardiac muscle contractility, and an increase in cardiac output. This results in an increase in systolic blood pressure and generalized vasoconstriction in muscles at rest. After exercising regularly, the efficiency of the work of the heart increases, indicated by a decrease in resting pulse rate.

5. Conclusions

Indian Pennywort, exercise, and the combination improve plasma BDNF, cognition, and physical fitness in

menopausal women. In addition, the Indian Pennywort-exercise combination showed the highest increase compared to other groups. This shows that the combination of the two modalities can provide maximum results compared to their own. Further clinical results are needed with larger samples and other biochemical tests in the different sexes.

Acknowledgements

We are very grateful to the Ministry of Research Technology and the National Agency for Research and Innovation of the Republic of Indonesia for funding this study.

REFERENCES

[1] I. K. Astina, W. I. Wan Ahmad, and B. Budiyanto, "Quality of Life of Older Persons in Indonesia: Sex Differences," *Mediterr. J. Soc. Sci.*, May 2015, doi: 10.5901/mjss.2015.v6n3s2p313.

[2] F. Y. Mardiyanto, D. S. Jahja, and Y. Limyati, "Factors Related to Cognitive Function in Elderly People," *J. Med. Heal.*, vol. 1, no. 6, Aug. 2017, doi: 10.28932/jmh.v1i6.547.

[3] N. L. K. A. Arsani, N. N. M. Agustini, and N. P. D. S. Wahyuni, "Impaired cognitive function and its relationship with menopausal onset and exercise intensity of elderly women," *Bali Med. J.*, vol. 9, no. 2, p. 419, Jun. 2020, doi: 10.15562/bmj.v9i2.1823.

[4] S. Pengpid, K. Peltzer, and I. H. Susilowati, "Cognitive Functioning and Associated Factors in Older Adults: Results from the Indonesian Family Life Survey-5 (IFLS-5) in 2014-2015," *Curr. Gerontol. Geriatr. Res.*, vol. 2019, pp. 1–7, Feb. 2019, doi: 10.1155/2019/4527647.

[5] K. M. Langa and D. A. Levine, "The diagnosis and management of mild cognitive impairment: A clinical review," *JAMA - Journal of the American Medical Association*. 2014, doi: 10.1001/jama.2014.13806.

[6] Y. Turana, J. Tengkawan, I. Suswanti, D. Y. Suharya, W. Riyadina, and J. Pradono, "Primary Prevention of Alzheimer's Disease in Indonesia," *Int. J. Aging Res.*, vol. 2, no. 3, pp. 40–44, 2019, doi: 10.28933/ijoar-2019-06-2506.

[7] J. R. Sliwinski, A. K. Johnson, and G. R. Elkins, "Memory decline in peri and post menopausal women: The potential of mind body medicine to improve cognitive performance," *Integr. Med. Insights*, vol. 9, pp. 17–23, 2014, doi: 10.4137/IMI.S15682.

[8] Y. Shimizu *et al.*, "Reproductive history and risk of cognitive impairment in Japanese women," *Maturitas*, vol. 12, no. 8, pp. 22–28, 2019, doi: 10.1016/j.maturitas.2019.06.012

[9] A. Hestiantoro, S. O. Jasirwan, M. Wiwie, A. Shadrina, N. Ibrahim, and B. P. K. Astuti, "Low estradiol levels escalate menopausal symptoms leading to mild cognitive impairment in postmenopausal women," *Med. J. Indones.*, 2019, doi: 10.13181/mji.v28i1.2447.

[10] B. Lu, G. Nagappan, and Y. Lu, "BDNF and synaptic plasticity, cognitive function, and dysfunction," *Handb. Exp. Pharmacol.*, 2015, doi: 10.1007/978-3-642-45106-5_9.

[11] J. Nettiksimmons, E. M. Simonsick, T. Harris, S. Satterfield, C. Rosano, and K. Yaffe, "The Associations between Serum Brain-Derived Neurotrophic Factor, Potential Confounders, and Cognitive Decline: A Longitudinal Study," *PLoS One*, vol. 9, no. 3, p. e91339, Mar. 2014, doi: 10.1371/journal.pone.0091339.

[12] T. Ng, C. Ho, W. Tam, E. Kua, and R. Ho, "Decreased Serum Brain-Derived Neurotrophic Factor (BDNF) Levels in Patients with Alzheimer's Disease (AD): A Systematic Review and Meta-Analysis," *Int. J. Mol. Sci.*, vol. 20, no. 2, p. 257, Jan. 2019, doi: 10.3390/ijms20020257.

[13] G. Weinstein *et al.*, "Serum Brain-Derived Neurotrophic Factor and the Risk for Dementia," *JAMA Neurol.*, vol. 71, no. 1, p. 55, Jan. 2014, doi: 10.1001/jamaneurol.2013.4781.

[14] D. M. Conde, R. C. Verdade, A. L. R. Valadares, L. F. B. Mella, A. O. Pedro, and L. Costa-Paiva, "Menopause and cognitive impairment: A narrative review of current knowledge," *World J. psychiatry*, vol. 11, no. 8, pp. 412–428, Aug. 2021, doi: 10.5498/wjp.v11.i8.412.

[15] R. Rismawaty and S. M. Adioetomo, "Determinants of Cognitive Impairment among The Elderly in Indonesia," *J. Berk. Kesehat.*, vol. 7, no. 1, p. 29, May 2021, doi: 10.20527/jbk.v7i1.9786.

[16] G. Sbrini *et al.*, "Centella asiatica L. Phytosome Improves Cognitive Performance by Promoting Bdnf Expression in Rat Prefrontal Cortex," *Nutrients*, vol. 12, no. 2, p. 355, Jan. 2020, doi: 10.3390/nu12020355.

[17] D. C. Ratna Sari, D. Juananda, M. Ar-Rochmah, M. Romi, and N. Arfian, "Ethanolic extract of the Centella asiatica (L.) Urb. leaf decreases cerebellar brain-derived neurotrophic factor (BDNF) levels in rats after chronic stress," *J. thee Med. Sci. (Berkala Ilmu Kedokteran)*, vol 50, no 2, 2018, doi: 10.19106/jmedsci005002201801.

[18] P. Puttarak *et al.*, "Effects of Centella asiatica (L.) Urb. on cognitive function and mood related outcomes: A Systematic Review and Meta-analysis," *Sci. Rep.*, vol.7,

no. 1, 2017, doi: 10.1038/s41598-017-09823-9.

[19] F. N. Kurdi and R. Flora, "The Impact of Physical Exercise on Brain-Derived Neurotrophic Factor (BDNF) Level in Elderly Population," *Open Access Maced. J. Med. Sci.*, vol. 7, no. 10, pp. 1618–1620, May 2019, doi: 10.3889/oamjms.2019.337.

[20] G. P. Rodrigues *et al.*, "Mineral status and superoxide dismutase enzyme activity in Alzheimer's disease," *J. Trace Elem. Med. Biol.*, vol. 44, pp. 83-87 2017, doi: 10.1016/j.jtemb.2017.06.005.

[21] M. Ihara, Y. Okamoto, Y. Hase, and R. Takahashi, "Association of physical activity with the visuospatial/executive functions of the montreal cognitive assessment in patients with vascular cognitive impairment," *J. Stroke Cerebrovasc. Dis.*, vol. 7, pp. 146-151, 2013, doi: 10.1016/j.jstrokecerebrovasdis.2012.10.007.

[22] L. Mato *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.

[23] K. E. Devenney *et al.*, "Acute high-intensity aerobic exercise affects brain-derived neurotrophic factor in mild cognitive impairment: A randomised controlled study," *BMJ Open Sport Exerc. Med.*, vol. 5, no. 1, 2019, doi: 10.1136/bmjsem-2018-000499.

[24] K. I. Erickson *et al.*, "Exercise training increases size of hippocampus and improves memory," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 108, no. 7, 2011, doi: 10.1073/pnas.1015950108.

[25] R. L. Leckie *et al.*, "BDNF mediates improvements in executive function following a 1-year exercise intervention," *Front. Hum. Neurosci.*, 2014, doi: 10.3389/fnhum.2014.00985.

[26] J. Hwang *et al.*, "Acute high-intensity exercise-induced cognitive enhancement and brain-derived neurotrophic factor in young, healthy adults," *Neurosci. Lett.*, vol 630, pp. 247-253, 2016, doi: 10.1016/j.neulet.2016.07.033.

[27] C. S. Mang, K. L. Campbell, C. J. D. Ross, and L. A. Boyd, "Promoting Neuroplasticity for Motor Rehabilitation After Stroke: Considering the Effects of Aerobic Exercise and Genetic Variation on Brain-Derived Neurotrophic Factor," *Phys. Ther.*, vol. 93, no. 12, 2013, doi: 10.2522/ptj.20130053.

[28] A. S. Whiteman *et al.*, "Interaction between serum BDNF and aerobic fitness predicts recognition memory in healthy young adults," *Behav. Brain Res.*, 259, pp. 302-312, 2014, doi: 10.1016/j.bbr.2013.11.023.

[29] A. Maass *et al.*, "Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults," *Neuroimage*, vol. 131, pp. 142-154, 2016, doi: 10.1016/j.neuroimage.2015.10.084.

[30] E. Kamelia, H. Miko, M. B. Karo, A. A. Islam, and M. Hatta, "Clinical Neurology and Neuroscience The Effect of Leaf Extract of Centella Asiatica on Neurogenesis and Bdnf Level in Hippocampus Cell Culture in Young Mice," *Clin. Neurol. Neurosci.*, vol. 1, no. 2, pp. 14-15, 2017, doi: 10.11648/j.cnn.20170102.11.

[31] K. Konishi *et al.*, "Impact of BDNF and sex on maintaining intact memory function in early midlife," *Neurobiol. Aging*, vol. 88, pp. 137–149, Apr. 2020, doi: 10.1016/j.neurobiolaging.2019.12.014.

[32] F. V. Ferreira *et al.*, "Brain-derived neurotrophic factor (BDNF) is not related to climacteric symptoms in healthy women: a cross-sectional study," *Maturitas*, vol. 124, p. 171, Jun. 2019, doi: 10.1016/j.maturitas.2019.04.161.

[33] A. Handayani, S. Yolanda, and R. Kodariah, "Centella asiatica ethanol extract increases hippocampal brain derived neurotrophic factor in male Wistar rats," *Universa Med.*, vol. 37, no. 2, pp. 143-149. 2018, doi: 10.18051/univmed.2018.v37..

[34] N. E. Gray *et al.*, "Centella asiatica increases hippocampal synaptic density and improves memory and executive function in aged mice," *Brain Behav.*, vol.8, no. 7, 2018, doi: 10.1002/brb3.1024.

[35] N. E. Gray *et al.*, "Centella asiatica attenuates hippocampal mitochondrial dysfunction and improves memory and executive function in β-amyloid overexpressing mice," *Mol. Cell. Neurosci.*, vol. 93, pp. 1-9, 2018, doi: 10.1016/j.mcn.2018.09.002.

[36] T. Suzuki *et al.*, "A randomized controlled trial of multicomponent exercise in older adults with mild cognitive impairment," *PLoS One*, vol. 8, no. 4, 2013, doi: 10.1371/journal.pone.0061483

[37] F. M. Lam, M. Z. Huang, L. R. Liao, R. C. Chung, T. C. Kwok, and M. Y. Pang, "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.

[38] N. A. Sobol *et al.*, "Effect of aerobic exercise on physical performance in patients with Alzheimer's disease," *Alzheimer's Dement.*, vol. 12, 2016, doi: 10.1016/j.jalz.2016.05.004.

[39] A. Zamfirescu, A. Capisizu, M. Slavila, A. A. Capisizu, and A. Romila, "Physical exercise training in older adults diagnosed with mild to moderate dementia," *J. Nutr. Heal. Aging*, vol. 12, pp.1207-1215, 2012.

[40] K. E. Devenney, B. Lawlor, M. G. M. Olde Rikkert, and S. Schneider, "The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment (MCI): study protocol for a randomised controlled trial," *BMC Geriatr.*, vol. 17, pp. 1, 2017, doi: 10.1186/s12877-017-0457-9.

[41] J. K. Morris *et al.*, "Aerobic exercise for Alzheimer's disease: A randomized controlled pilot trial," *PLoS One*, vol. 12, no. 2, 2017, doi: 10.1371/journal.pone.0170547.