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Exercise and Gotu Kola Extract to Ameliorate Tumor Necrosis Factor - Alpha, Quality of Life, and Executive Function in Cognitive Impairment Women

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Abstract Increasing tumor necrosis factor-alpha (TNF-alpha) and decreasing quality of life (QoL) are associated with cognitive deterioration. Exercise and Gotu kola (Centella Asiatica) can improve memory and antiinflammation, but their combination has not yet been revealed. This study aimed to see how exercise and Gotu kola extract affected TNF-alpha, quality of life, and executive functions in women with cognitive impairment. This study used an experimental design with a control group with a 12-week pre and post-test in women with cognitive impairment. The Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairment. The participants in the study were 64 women with a mean age of 53.3 (4.8) years. The subjects were divided into four groups: Gotu kola/GK extract capsule (1x500 mg/day), exercises (2x75 minutes per week), a GK-exercise combination, and the control group. The WHO-QoL questionnaire was used to assess the quality of life. The Trail Making Test-B (TMT-B) was used to assess executive functions. The study found that Gotu kola might increase QoL in the physical domain (p=0.028) and environmental domain (p=0.016). Exercise and a GK-exercise combination could improve QoL: physical, psychological, social, and environmental domain (p<0.05). According to the Mann-Whitney test, the GK-exercise combination was the most helpful in enhancing TNF-alpha (Δ=-10.5; p=0.003), MoCA (Δ= 4.6; p=<0.001), and TMT-B (Δ=-21.4; p=0.023). Discussion: Physical activity is one of the factors that can play a role in cognitive function through several mechanisms. To conclude, exercise, Gotu Kola, and their combination can effectively decrease inflammation and increase the quality of life and cognitive function in women with cognitive impairment. This study expected that exercise and Gotu Kola could be priority interventions in treating cognitive impairment.

Keywords Gotu Kola, TNF-alpha, Executive Function, Quality of Life, GK-exercise Combination

1. Introduction

The elderly are one of the age groups that are very

vulnerable to various body function disorders due to degenerative processes that occur naturally and pathologically. Data shows that more than 35 million older people worldwide have neurodegenerative problems that trigger a decline in cognitive, emotional, and motor functions [1]. The cognitive impairment in the elderly is due to a progressive decline in the structure and function of neurons followed by death. Cognitive decline is associated with increased inflammation, one of which is Tumor necrosis factor-alpha (TNF-alpha). In Indonesia in 2016, the number of older people with cognitive decline was recorded at 1.2 million people and is estimated to be 4 million in 2050 [2].

TNF-alpha is a proinflammatory cytokine in Alzheimer's disease. TNF-alpha induces cell survival and cell proliferation via TNFR2. The proinflammatory function of TNF-alpha in the brain has a role in Alzheimer's disease [3]. TNF-alpha signaling exacerbates Aβ and tau pathology in vivo. Clinical trials have shown that TNF-alpha inhibitors can slow cognitive decline and improve daily activities in Alzheimer's patients [4]. Interestingly, both preventive and interventional anti-inflammatory strategies demonstrated decreased brain pathology and improved cognitive function in animal models of Alzheimer's.

Quality of life has been an essential outcome of studies in mild cognitive impairment patients. Many psychosocial and pharmacological strategies focus on features of behavioral therapy (cognitive-stimulation therapy, family care interventions) and the use of pharmaceuticals to improve quality of life. However, information about interventions incorporating several dimensions is lacking [5,6].

The decreased neurological function can be treated by various lifestyle changes, including exercise and the consumption of herbal plants. Exercise can improve cognitive function in the elderly by helping to release brain-derived neurotrophic factor (BDNF) [7,8]. Moderate and high-intensity training can reduce TNF-alpha in healthy rats [9]. Gotu Kola (Centella Asiatica) can improve cognitive decline by stimulating BDNF and lowering TNF-alpha [10]. Several meta-analyses and RCTs have reported that physical activity positively impacts the quality of life and executive functions in patients with mild cognitive impairment. Exercise in the elderly with mild cognitive impairment was better at the light intensity and more frequent [11]. Other studies have shown that moderate-intensity exercise can significantly improve cognitive function and quality of life [12-14].

Many specialists have validated the use of herbal medication to treat mild cognitive impairment. Alternatives such as Gotu Kola, Gingko Biloba, and Curcuma longa have to prevent or cure cognitive impairment. Gotu kola can prevent amyloid plaque formation, dopamine neurotoxicity, and oxidative stress [13]. Gotu kola is widely available in Indonesia.

Several studies have shown the positive effect of exercise and Gotu kola on cognitive impairment progression. However, the combination of these two types of therapy has not yet been revealed. Thus, this study investigates the effect of exercise and Gotu Kola on TNF-alpha, quality of life, and cognitive function in patients with cognitive impairment. Furthermore, this study is expected to develop a holistic approach to treating cognitive impairment women.

2. Materials and Methods

2.1. Design and Sample

This study was a pre and post-test experimental design study with the control group for 12 weeks. The research subjects consisted of 64 women with cognitive impairment in the Cibiru Community Health Center area, West Java, Indonesia. The Montreal Cognitive Assessment (MoCA) was used to recruit participants. Inclusion criteria included women aged 45-65, MoCA score <26, no bleeding disorder, no serious illness, no brain vitamins, and no exercise in the previous three months. The participants consisted of four groups: Gotu Kola/GK (1x500 mg/day with Asiaticoside levels of 1.41 mg/g per capsule), exercise (2x75 minutes/week consisting of warming up and stretching for 10 minutes, core exercise for 25 minutes, and cooling down for 10 minutes), the GK-exercise combination (1x500 mg/day and exercise 2x75 minutes/week), and the control group.

2.2. Measurement of Blood Plasma, Quality of Life, and Cognitive Function

The plasma TNF-alpha was measured by HPLC with the ELISA method. TNF-alpha plasma examination was carried out by taking 3 mL of blood from the brachial vein. Blood was taken before and after the intervention. Subjects fasted for 8-10 hours before having their blood drawn. Quality of life was measured by the WHO-QoL questionnaire consisting of 26 questions. The questionnaire is divided into seven physical domain questions, six psychological domain questions, three social domain questions, and eight environmental domain questions (14). Cognitive function was measured by MoCA and Trail Making Test-B (TMT-B). The MoCA consists of 30 questions regarding visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall, and orientation [15]. TMT-B serves to test executive function. TMT-B consists of numbers and letters arranged randomly [16]. Subjects were asked to draw lines alternately between numbers and letters as quickly as possible.

2.3. Procedure

Before conducting the research, subjects explained the

aims, objectives, procedures, uses, place, time, and the factors that would influence the research. Then the MoCA test was conducted to capture potential participants with mild cognitive decline. After that, subjects who met the inclusion criteria were asked about their willingness to become research participants voluntarily by signing an informed consent form, and subjects who were willing to be divided into four groups.

Screening examinations and initial tests were conducted for two months in the Cibiru Health Center area, West Java. The initial examination includes sociodemographic data and the mild cognitive impairment (MCI) screening test. Subjects were weighed and their height.

Afterwards, the subject was checked for pulse and blood pressure at rest, and then examined cognitive function and quality of life. After that, the subject was taken as much as 3 mL of blood for TNF-alpha examination.

After the initial test, the intervention was carried out for 12 weeks starting in September-November 2019. After the intervention was completed, the second examination of all study variables was carried out. 3 mL of blood was taken for blood biochemical examination by experts from the Laboratory of Molecular Genetics, Padjadjaran University.

2.4. Statistic Analysis

Shapiro-Wilk test was to determine the data distribution in this investigation. The Kruskal-Wallis test was used to see differences between groups. Different categorical data were tested using the Chi-square test. Wilcoxon's test was to see if the effects of GK, exercise and their combination have changed. The Kruskal-Wallis test was used to examine the difference in changes between the four groups after the intervention, followed by the Mann-Whitney test. Padjadjaran University granted ethical approval for this research (No. 1266/UN6.KEP/EC/2018).

3. Results

Age, MoCA examination, weight, height, blood pressure, education, marital status, menopausal status, and disease history did not differ significantly between the four groups, according to sociodemographic data (Table 1).

4. Discussion

This study showed a significant decrease in plasma TNF-alpha in the Gotu kola (GK), exercise, and GK-exercise combination compared to the control group. The Mann-Whitney found that TNF-alpha was the highest in the GK-exercise combination. It is consistent with a study that rats who received a Gotu kola dose of 600 mg/kg BW/day had a lower mean TNF-alpha than the control group [10]. Another study found that TNF-alpha increased and peaked at 14 minutes during exercise and then decreased [17]. The study showed that treadmill exercise could reduce TNF-alpha by 25.2% in Alzheimer's elderly [18].

Table 1. Sociodemographic characteristics

Characteristics	Gotu Kola (GK) n=16	Exercise n=16	GK-exercise Combination n=16	Control n=16
Age, years	53.9 (5.5)	52.9 (4.4)	53.5 (4.4)	52.7 (5.3)
MoCA, score	22.8 (2.5)	22.6 (3.5)	23.3 (2.5)	23.4 (3.1)
Weight, kg	57.8 (6.4)	58.8 (7.4)	59.8 (7.8)	57.4 (6.5)
Height, cm	153.3 (4.9)	152.6 (4.6)	152.3 (4.9)	153.1 (3.7)
Blood Pressure				
Systole, mmHg	121.9 (15.0)	120.6 (14.2)	123.8 (15.0)	121.2 (12.7)
Diastole, mmHg	78.1 (7.5)	78.1 (6.8)	79.5 (7.4)	78.8 (6.0)
Menopause Status n (%)				
Perimenopause	23.8	42.9	19.1	28.6
Postmenopause	76.2	57.1	81.0	52.4
Disease History, n (%)				
Gastritis	9.5	4.8	19.1	14.3
Hypertension	19.1	14.3	23.8	9.5
Diabetes mellitus	4.8	4.8	9.5	4.8

Table 2. Comparison of TNF-alpha, quality of life, and cognitive function between before and after intervention for 12-weeks

Variable	Gotu Kola/GK n=16	Exercise n=16	GK-exercise Combination n=16	Control n=16	p[b]
TNF-α					
Pre	12.4 (8.6)	14.9 (9.2)	25.1 (32.8)	10.0 (45)	0.026*
Post	6.0 (6.1)	11.7 (7.7)	14.5 (19.7)	26.7 (56.4)	
Δ	-6.4 (4.5)	-3.2 (4.4)	-10.5 (14.9) 0.003*	16.7 (55.0)	
p[a]	0.002*	0.012*		0.433	
Quality of Life					
Physical					
Pre	66.9 (7.9)	63.8 (14.6)	66.2 (13.1)	65.8 (12.2)	0.766
Post	75.1 (8.3)	74.6 (9.6)	76.7 (10.5)	72.6 (9.1)	
Δ	8.3 (8.9)	10.8 (14.4)	10.5 (14.7)	6.8 (10.1)	
p[a]	0.028*	0.009*	0.016*	0.059	
Psychological					
Pre	67.5 (8.0)	64.8 (12.2)	67.2 (11.8)	68.3 (8.9)	0.365
Post	72.5 (6.8)	72.8 (9.0)	76.6 (10.7)	74.6 (6.1)	
Δ	5.0 (10.2)	7.9 (9.5)	9.4 (13.0)	6.3 (10.3)	
p[a]	0.114	0.006*	0.022*	0.058	
Social					
Pre	61.9 (13.4)	65.7 (13.5)	57.4 (11.2)	62.8 (9.8)	0.132
Post	67.4 (7.9)	70.7 (12.3)	64.9 (16.5)	62.6 (8.9)	
Δ	5.6 (12.0)	5.0 (6.6)	7.5 (10.3)	-0.13 (9.1)	
p[a]	0.193	0.008*	0.014*	0.873	
Environmental					
Pre	60.3 (9.0)	63.3 (12.4)	62.1 (11.8)	61.6 (10.4)	0.314
Post	69.3 (11.1)	70.4 (10.4)	68.1 (6.4)	63.4 (11.9)	
Δ	9.0 (8.5)	7.2 (11.3)	6.0 (13.2)	1.8 (11.7)	
p[a]	0.016*	0.029*	0.033*	0.593	
Cognitive Function					
MoCA					
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	
TMT-B					
Pre	111.4 (43.4)	144.9 (77.0)	103.3 (55.9)	108.1 (65.0)	0.033*
Post	110.4 (51.3)	125.1 (61.0)	81.9 (57.4)	107.8 (60.3)	
Δ	-1 (32.2)	-19.8 (68.1)	-21.4 (43.3)	-0.25 (22.5)	
p[a]	0.587	0.074	0.023*	0.127	

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

Asiaticoside is one of the triterpenoid components found in Gotu kola that promise protective properties. Studies have shown that Asiaticoside treatment (20 and 40 mg/kg; intragastric) significantly decreased hippocampal IL-1β, IL-6, and TNF-alpha levels. Asiaticoside reduced nuclear factor (NF)-κBp65 phosphorylation and receptor protein expression, increased cAMP and protein kinase A (PKA specific), increased phosphorylation of the cAMP marker on vasodilator-stimulated phosphoprotein in serine 157, and activated the cAMP/PKA signaling pathway.

Asiaticoside may play a role as an antidepressant and anti-inflammatory agent in rat models by regulating the cAMP/PKA signaling pathway [19]. Asiatic acid treatment reduced TNF-alpha in AlCl3-induced Alzheimer's mice [20].

In this study, the exercise and the GK-exercise combination experienced a significant increase in all domains, namely physical, psychological, social, and environmental. Physical exercise, particularly aerobic exercise, is of global benefit, especially in cognitive aspects in patients with mild cognitive impairment [21]. Among various therapies, physical exercise as an extensive lifestyle of low intervention cost and low risk is more beneficial for improving brain health in elderly care practices [22].

Regular physical activity plays an important role in cognitive function and is a protective factor against dementia in the elderly [21]. Physical activity affects cognitive function. The more often and longer a person does physical activity, the smaller the risk of cognitive decline [23–26]. Physical activity can play a role in cognitive function through several mechanisms: increasing cerebral blood flow, reducing the risk of cardiovascular and cerebrovascular diseases, and stimulating nerve growth and neurogenesis, especially in the hippocampus area [27]. In addition, it is known that physical activity can increase brain-derived neurotrophic factor (BDNF) in the brain [28].

In the elderly, there are changes in the sensory, musculoskeletal, and central nervous systems. Changes that increase age lead to reduced balance control in the elderly, so the risk of falling increases. One of the causes of decreased postural control in the elderly is a decrease in the function of pressure receptors and a decrease in the stretch reflex of muscle spindles. Physical activity is thought to slow the decline in proprioceptive function so that the antigravity muscle can respond with a shorter latency. In addition, movement in physical activity also causes simultaneous stimulation of both sides of the vestibular afferents, thereby reducing the functional and anatomical asymmetry of the vestibular system. Physical activity increases central integration involving the vestibular reflex. These peripheral and central improvements increase precision in adjusting body position in response to environmental changes [29,30].

Other studies have found that physical activity slows cognitive impairment in patients with mild cognitive impairment by decreasing inflammatory cytokines and increasing peripheral neurotrophic factor concentrations [31–34]. Physical activity had a one-year delay in the onset of dementia in the elderly [29]. Physical activity can significantly improve cognitive abilities in general. Aerobic exercise, in particular, plays an essential role in cardiovascular health [34], which increases cerebral blood flow, the supply of oxygen and glucose to brain tissue, and the availability of neurotransmitters and the ability of nervous system [35]. Furthermore, aerobic exercise stimulates neurotrophic factor generation [36]. Quality of life is closely related to physical activity. Studies have found an association between cognitive functions, mainly executive function, with walking and balance [35]. Physical activity in nursing homes provides various benefits, including improving balance function, reducing the likelihood of falls, and improving quality of life [37].

One of the key achievements in improving the health of the elderly is improving their quality of life [38]. Various physical exercise programs carried out for the elderly in nursing homes 3x/week for 12 weeks showed an increase in the quality of life of the elderly [23]. A physical exercise program in older women improved the physical appearance of the knee muscles and joints and improved quality scores [22]. A regular physical exercise program significantly impacts the self-esteem and quality of life of the elderly.

Likewise, impacts in the environmental domain are significantly, especially on the availability of information for their lives, satisfaction with health services, and satisfaction with their place of residence. This situation shows that the elderly who participate in aerobic exercise feel that the availability of information, health services, and amenities must be fulfilled by the government. Physical activity is the movement of the limbs that results in energy expenditure and is essential for maintaining physical and mental health and quality of life to stay healthy and fit throughout the day [25].

Lack of physical activity causes chronic diseases in the elderly such as hypertension, stroke, heart disease, diabetes mellitus, and cancer. The regular exercise followed by an increase in aerobic fitness can reduce disease and disability, reduce mortality and improve the quality of life of the elderly [5]. Individuals' perceptions of physical health, psychological status, level of independence, social interactions, personal beliefs, and special relationships in society are referred to as quality of life [38]. The perspective of an individual's position in life, cultural background, value system, goals, expectations, standards, and concerns are all components of the quality of life.

In general, the quality of life decreases with age due to physical, mental, and psychosocial changes so that the elderly feel dissatisfied with their condition. Poor quality of life is also caused by the residence or home of the elderly who are far from children or other families. They often experience / feel lonely, which causes the elderly to be unable to carry out daily activities. Several interventions that can be done to improve the quality of life of the elderly in terms of psychological or mental health consist of physical activity, religion, family function, family support, peer and home-based intervention counseling as well as physical activity, respiratory regulation, psychology and cognitive behavioral therapy (CBT). Physical and religious activities are practical, simple, and friendly interventions that can help the elderly improve their quality of life [39].

Furthermore, high levels of physical activity are

associated with a high quality of life in the elderly, both on physical and mental health scales [40]. The physical activity carried out every day has a positive correlation which means the quality of life, meaning that the more independent the elderly are in doing physical activity, the quality of life of the elderly will increase [41]. High levels of physical activity are also associated with increased cognitive capacity. High levels of physical activity can maintain and even improve cognitive function in people without dementia [42].

A moderate-intensity aerobic exercise program can improve cognitive function and health-related quality of life in older people with mild cognitive impairment living in the community. Furthermore, lower depressive symptoms and improved sleep quality were associated with putative cognitive exercise-related mechanisms. Effectiveness and exercise programs can also help older people with mild cognitive impairment improve their cognitive capacity [43].

Gotu kola is a plant that has been used for generations to improve memory and cognitive function. It is used in traditional Chinese and Ayurvedic medicine. In this study, Gotu kola effectively improved cognitive function, especially executive function. Executive function is a series of processes related to self-regulation and other resources to achieve a goal. This function is the umbrella of thinking, which includes mind control and self-control. The cholinergic, antioxidant, and anti-inflammatory properties of Gotu kola extract contribute to its efficiency in enhancing cognitive function [44,45].

Gotu kola extract has in vivo cholinomimetic action and antioxidant properties [44]. The researchers also found that taking Gotu kola extract could increase neurite elongation and accelerate the regeneration of nerve cells in vitro. The effect of Gotu kola extract on improving working memory function delayed recall memory, and executive function may be due to modulation of dopamine production in the prefrontal cortex. In contrast, long-term effects on memory may be due to the modulation of norepinephrine, serotonin, and acetylcholine in the frontal cortex and hippocampus [44,45]. Combining Gotu kola with exercise improves executive function, including features such as impulse control, attention, planning, cognitive flexibility, and problem-solving.

5. Conclusion

Exercise, Gotu kola, and their combination can be an effective therapeutic modality to decrease inflammation and improve quality of life and executive function in women with mild cognitive impairment. Compared to other groups, the combination of Gotu kola and exercise had the highest effect in lowering TNF-alpha and improving cognitive function in women with cognitive decline. Further studies need to be conducted to determine the therapeutic use of other natural ingredients as anti-inflammatory agents to reduce cognitive impairment in both women and men.

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