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The Effect of Saffron Supplementation with Aerobic Training on Inflammatory Factors and Cognitive Status in Elderly Men

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***Abstract*— the aim of this study was to evaluate the effect of 12 weeks of aerobic training and saffron supplementation on cognitive status and serum levels of IL-1β and TNF-α in elderly men. Forty men aged 60 to 70 years were purposefully selected and randomly divided into 4 groups: aerobic training, saffron, aerobic training + saffron and placebo (10 people in each group). Interventions were performed for 12 weeks. Aerobic training consisted of eight minutes of running with an intensity of 75 to 85% of the maximum reserve heart rate in the first session. Both sessions increased the running time by one minute until after 12 weeks, the running time reached 26 minutes. Saffron extract was taken as a capsule with a dose of 500 mg in two meals in the morning and after exercise. IL-1β and TNF-α levels were significantly reduced in both training and saffron groups, but in the training + saffron group, their decrease was greater (P<0.05). Cognitive status in the three intervention groups increased significantly compared to the placebo group, which was higher in the exercise + saffron group (P<0.05). It is possible that taking saffron supplement along with aerobic training for 12 weeks, by improving the cognitive status in older men by reducing inflammatory factors, can prevent cognitive disorders and eventually Alzheimer's.**

***Keywords*— Aerobic training, Saffron, Cognitive status, Inflammation, Elderly**

I. INTRODUCTION

The population aged over 60 years in Iran reaches around 10 million in 2020 and over 26 million up to 2050 that will be 23% of the total population (1). Cognitive impairment represents one of the common disorders in the elderly such that around 35% of them present with it at different severities and Alzheimer's disease is the progressive stage of this disorder (2). In cognitive impairment, attention, memory, language, orientation, actions, executive performance, judgement, and problem-solving are impaired mostly due to brain memory loss (3). The normal functioning of the various brain systems is responsible for cognitive function, and cognitive impairments arise as the age increases and the elements involved in these systems develop. Also, various inflammatory processes and cytokines play a key role in the pathogenesis of Alzheimer's disease (4). The expression of most cytokines in normal tissues is normal, but in neurodegenerative diseases, their

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expression is increased. For example, proinflammatory cytokine expression of tumor necrosis factor alpha (TNF-α) is increased in neurodegenerative diseases (5, 6). In this regard, it has been shown that the safety profile of patients with mild cognitive impairment changes (7).

It is important to consider interventions to prevent cognitive impairment and therefore Alzheimer's and measuring the inflammatory factors following these interventions can lead to a better understanding of the observed effects. Consumption of medicinal plants is one of such interventions that have attracted attention (8, 9). Meanwhile, saffron (Crocus sativus L.) is a perennial plant of the iris genus (Iridaceae) with a height of 10 to 30 cm and has a hard, round, fleshy onion covered with thin, brown membranes. The four major bioactive compounds in saffron are crocin, crocetin, picrocrocin and safranal, which are involved not only in the sensory characteristics of saffron (color, taste and aroma, respectively) but also in its health-improving properties (11). Numerous studies have shown that crocin and crocetin (which are the active compounds of saffron) are able to exert various protective medicinal effects that are attributed to the antioxidant capacity of these compounds (12). Several studies have reported that saffron extract and its two main components, crocin and crocetin improve memory and learning skills in mice whose learning behavior is impaired by ethanol induction. These results suggest that oral administration of saffron can be useful in the treatment of neurodegenerative diseases and related memory disorders (10). According to the results of Pitsikas et al. in 2006 and 2007, saffron-derived crocins fight diagnostic memory-related disorders in healthy rats, indicating the role of these carotenoids in memory (13). Saffron also has an anti-inflammatory effect (14) and as mentioned, the levels of inflammatory factors in cognitive disorders increase (4-7). In general, the effects reported for saffron include antioxidant, anti inflammatory, memory and learning improvements, anti tumor, anti depressant, reduces fat and lowers insulin resistance (15, 16). However, so far no research has investigated the effect of consumption of this plant on cognitive status and related factors in the elderly. On the other hand, exercise as a low-cost treatment method can have a positive effect on cognitive function, which may be achieved by reducing inflammatory factors; Because cross-sectional studies have shown that active individuals have better cognitive function than inactive counterparts (17), the anti-inflammatory effect of training has also been reported (18). Considering that cognitive disorders are one of the most common problems in old age and these disorders are the beginning of a path that will eventually lead to Alzheimer's and of course death and considering that no definitive treatment for Alzheimer's has been introduced yet, the use of preventive interventions is very important. Also in this field, the use of medicinal plants is of special importance due to its naturalness and no side effects (9). Since exercise and physical activity have a proven role in improving cognitive function (17) and inflammatory factors (18) has it, it is important to study the effect of combining training and plant in this field. However, so far no research has investigated the simultaneous effect of aerobic training and saffron supplementation on inflammatory factors and its relationship with the cognitive status in the elderly.

The aim of this study was to evaluate the effect of 12 weeks of aerobic training and saffron supplementation on cognitive status and serum levels of IL-1β and TNF-α in elderly men.

II. METHODOLOGY

This research was conducted by quasi-experimental method with pre-test and post-test design with control group. Eighty seven people aged 60-70 years volunteered to participate in the study after advertising our study among different elderly populations living in Shiraz County. Then, the Mini–Mental State Examination (MMSE) was administered to volunteers. The MMSE, developed by Folstein et al. in 1975, consists of 11 subscales: Orientation to time and place, registration, attention and calculation, memory, language, executive skills, reading, writing, and doing fine works (19). The subjects that do not have any problems in these subscales are given the score 30; the scores < 20 represent in-depth cognitive disabilities and the scores 20-25 represent partial cognitive damage. The reliability (Cronbach's alpha) of the MMSE has been reported 0.87 with sensitivity and specificity of 90% and 84%, respectively (20). Forty volunteers who attained the MMSE scores 21-25 randomly divided into 4 groups: aerobic training, saffron, aerobic training + saffron, and placebo (10 people in each group). Inclusion criteria included being a man, being 60 to 70 years old, being able to attend intervention sessions, being evaluated by a physician to determine general health and participating in aerobic exercise, and not being on medication to treat cognitive disorders. Exclusion criteria also included absenteeism in interventions, lack of independence in daily activities, having various physical or mental illnesses, medication use, unwillingness to continue research and treatment for various cognitive disorders. Interventions were performed for 12 weeks. Saffron supplement in the amount of 500 mg in two stages, after breakfast one capsule (250 mg) and immediately after the exercise session (250 mg) or at the same time in the afternoon for the saffron group without exercise to consumed with 100 ml of water. The placebo group also used empty but completely similar capsules with the same instructions. Preparation of saffron supplement was such that saffron flower heads and bottoms were collected from saffron orchards in Bidokht city located in Khorasan Razavi province in Iran in November. It was then dried in the shade for 10 days. Saffron was divided into flower and flower parts. Different parts of saffron were powdered with Chinese mortar. 250 mg of each part of saffron was encapsulated and prepared for consumption. Aerobic training was three sessions per week, each session consisting of eight minutes of warm-up and eight minutes of running with an intensity of 75 to 85% of the maximum reserve heart rate in the first session that both sessions increased the subjects' running time by one minute until later. From 12 weeks, the running time was 26 minutes and the last 5 minutes of each session were cooling (21). 24 hours before and 48 hours after the interventions, 5 ml of blood was taken from the brachial vein of the subjects in a 12-hour fasting state. In order to isolate the serum, blood samples were centrifuged at 2000 rpm for 10 minutes after clotting. Samples were stored in the freezer at -20 ° C until the variables were measured. IL-1β and TNF-α levels were measured with the sensitivity of 8 and 2 pg/ml, respectively, using a kit (Diaclone, France). Cognitive states were measured using the MMSE. Data were described by average and standard deviation. Inter- and intra-subject mixed ANOVA was used to investigate inter- and intra-group changes and tukey's test were used to compare the changes in the variables among the groups. To investigate the association between the changes in the variables, Pearson correlation coefficient was used to investigate the association between the changes in the variables. The level of significance (p) was considered ≤ 0.05. Data analysis was conducted in SPSS 16.

III. RESULTS

Descriptive data, the results of inter- and intra-subject mixed ANOVA and Tukey's test, and Pearson correlation coefficients are shown in Tables 1-3, respectively.

There was a significant difference between changes in weight, body mass index, cognitive status, TNF-α and IL-1β in the four groups over time (P=0.001). Weight and BMI in the two groups of training + saffron and training were significantly reduced compared to the two groups of saffron and control (P<0.05). There was no significant difference between weight and BMI changes between the two groups of training and training + saffron (P>0.05) and the two groups of saffron and placebo (P>0.05). Cognitive status was significantly increased in the three intervention groups compared with the placebo group (P<0.05). The increase in cognitive status in the training + saffron group was significantly more than the two groups of training and saffron alone (P<0.05), but the changes in cognitive status in the two groups of training and saffron alone were not significantly different (P=0.99). TNF-α and IL-1β were significantly reduced in the three intervention groups compared with the placebo group

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(P<0.05). The decrease in TNF-α and IL-1β in the training + saffron group was significantly greater than the two training and saffron groups alone (P<0.05), but changes in TNF-α and IL-1β in the two groups of training and saffron alone were not significantly different (P>0.05).

The results showed that there was a significant negative relationship between weight and BMI changes with cognitive status changes (P<0.05) and a significant positive relationship between weight and BMI changes with TNF-α and IL-1β changes (P<0.05). Regarding the relationship between cognitive status changes and changes in inflammatory factors, the results showed that with decreasing serum TNF-α levels in the elderly, their cognitive status increased significantly (r=-0.70 and p=0.001); And with decreasing serum IL-1β levels in the elderly, their cognitive status increased significantly (r=-0.65 and p=0.001).

Table1. Comparison of variables between four groups (ANOVA)

variables	groups	Before	After	F value	P value	Effect Size
Weight (kg)	training + saffron	78±3.80	75.10±6.04	13.36	0.001*	0.52
	training	76.90±5.50	74.50±2.75			
	saffron	79.40±6.48	79±5.56			
	placebo	78±5.79	78.50±5.81			
BMI (kg/m^2)	training + saffron	26.48±2.69	25.48±0.54	14.50	0.001*	0.54
	training	25.74±2.86	25.95±0.82			
	saffron	25.35±2.33	25.22±0.61			
	placebo	25.32±2.86	25.48±0.93			
Cognitive State (MMSE)	training + saffron	23.20±1.68	27±1.76	13.38	0.001*	0.52
	training	24.50±1.58	26.10±1.19			
	saffron	24.70±1.05	26.20±0.91			
	placebo	26.30±1.63	25.80±0.63			
TNF-α (pg/ml)	training + saffron	8.85±1.05	5.26±0.85	18.16	0.001*	0.60
	training	8.91±1.10	7.13±1.44			
	saffron	8.84±1.54	7.26±1.21			
	placebo	7.06±1.42	7.30±1.53			
IL-1β (pg/ml)	training + saffron	3.81±0.41	2.31±0.37	26.80	0.001*	0.69
	training	3.56±0.56	2.89±0.66			
	saffron	3.46±0.70	3.09±0.67			
	placebo	3.001±0.72	3.23±0.67			

*Significant at 0.05.

Table2. The results of Tukey's test regarding the points of significant difference

Pair wise Comparison	Weight	BMI	Cognitive State	TNF-α	IL-1β
training + saffron / training	0.85	0.75	0.013 *	0.007 *	0.001 *
training + saffron / saffron	0.002 *	0.001 *	0.009 *	0.002 *	0.001 *
training + saffron / placebo	0.001 *	0.001 *	0.001 *	0.001 *	0.001 *
training / saffron	0.014 *	0.012 *	0.99	0.98	0.46
training / placebo	0.001 *	0.001 *	0.019	0.002 *	0.001 *
saffron / placebo	0.48	0.48	0.028	0.006 *	0.021 *

*Significant at 0.05.

Table3. Pearson correlation coefficients to examine

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the association between the changes in variables

variables	Weight	BMI	Cognitive State	TNF-α	IL-1β
Weight	-	r= 0.99 p= 0.001 *	r= - 0.45 p= 0.003 *	r= 0.64 p= 0.001 *	r= 0.53 p= 0.001
BMI	r= 0.99 p= 0.001 *	-	r= - 0.46 p= 0.003 *	r= 0.66 p= 0.001 *	r= 0.56 p= 0.001
Cognitive State	r= - 0.45 p= 0.003 *	r= - 0.46 p= 0.003 *	-	r= - 0.70 p= 0.001 *	r= - 0.65 p= 0.001 *
TNF-α	r= 0.64 p= 0.001 *	r= 0.66 p= 0.001 *	r= - 0.70 p= 0.001 *	-	r= 0.68 p= 0.001 *
IL-1β	r= 0.53 p= 0.001 *	r= 0.56 p= 0.001 *	r= - 0.65 p= 0.001 *	r= 0.68 p= 0.001 *	-

*Significant at 0.05.

IV. DISCUSSION

After 12 weeks, both training and saffron groups showed a significant increase in cognitive status and a significant decrease in inflammatory factors (IL-1β and TNF-α). However, in the group that both exercised and took saffron supplements (training + saffron), a greater increase in cognitive status and a greater decrease in IL-1β and TNF-α were observed. Also, according to the findings of the present study, with weight loss and body mass index of the elderly, their cognitive status increases and their TNF-α and IL-1β levels decrease. In addition, the present results showed that with decreasing TNF-α and IL-1β, the cognitive status in the elderly increases. Therefore, although these relationships do not constitute the effect of cause and effect; however, a significant relationship between changes in cognitive status and inflammatory factors indicates that the reduction of inflammatory factors may play a role in increasing the cognitive status of the elderly following aerobic exercise and saffron consumption.

Studies have been done on the effect of saffron on cognitive status and memory. For example, in a study by Ghadami et al. (2009), intraperitoneal injection of crocin for six consecutive days improved the destructive effects of scopolamine on the learning and memory in rats in a dose-dependent manner (22). Also in the study of Khalili et al. (2012) the use of crocin as a treatment for three weeks in rats in which Alzheimer's disease was induced by intraventricular injection of streptozotocin, significantly improved spatial learning, memory and cognitive skills (23). In addition, in a study by Hosseinzadeh et al. (2012) in which saffron extract and its active ingredient crocin were selected as the treatment, it improved cognitive deficits induced by cerebral hypoperfusion in rats (24). Khalili et al. (2009) also observed similar results to Hosseinzadeh et al. (2012) in experimental Alzheimer's mice (25). In general, the beneficial effects of saffron extract on the brain have been reported (26, 27, 28). It has been suggested that the positive effect of saffron on learning and memory processes is due to the antioxidant activity of its active compounds (29). Crocin seems to be the main compound and antioxidant in saffron, the effect of improving the effects of saffron extract on cognitive status (24). Due to the reduction of inflammatory factors due to the consumption of saffron extract in the present study, it may be possible to attribute the improvement in the cognitive status of the elderly due to saffron extract to the reduction of inflammatory factors due to this extract. It has been observed that saffron has an anti-inflammatory effect (14). In any case, we need more detailed and controlled studies in this regard in the future.

Regarding exercise and consistent with the present findings, Farinha et al. (2015) evaluated TNF-α and IL-1β in 23 untrained women before and after 12 weeks of treadmill training without changing diet. Their results showed that a period of aerobic training significantly reduced serum levels of TNF-α and IL-1β (30). But Isanejad et al. (2015) reported that 8 weeks of endurance training resulted in a significant increase in IL-1β and a significant decrease in TNF-α (31).

Knudsen and Pedersen (2015) investigated the effect of training on inflammatory factors in patients with type 2 diabetes, reported that training leads to an increase in interleukin 6 by inhibiting TNF-α and by stimulating IL-1 receptor antagonist and thus limited IL-1β signaling leads to anti-inflammatory effects (18). In the present study, both a decrease in inflammatory factors and an increase in cognitive status were observed with aerobic training. In this regard, Miller et al. (2012) reported that there is a significant and positive relationship between cognitive status and physical activity (32) which it can be attributed to the reduction of oxidative stress and inflammation, increased angiogenesis, secretion of neurotrophins and catecholamines, and neurogenesis, especially in the hippocampal structure (33).

Regarding the effect of saffron consumption along with training on inflammatory factors and cognitive status, so far no research has been done, especially in the elderly. Therefore, the interpretation of the findings becomes difficult due to the impossibility of comparison with other findings. In any case, based on the present findings, it seems that two simultaneous interventions of saffron extract consumption and aerobic training can have a double effect on reducing inflammatory factors and increasing the cognitive status in the elderly; But as mentioned, this is the first time this research has been done and we need more research in this regard.

It is possible that both aerobic training and saffron supplementation, by improving the cognitive status of the elderly by reducing their inflammatory factors, can prevent or delay cognitive disorders and Alzheimer's disease in old age. It seems that the combination of two intervention methods (aerobic training + saffron supplement) leads to better prevention in this regard. Reducing inflammation may play an important role in this preventative measure, but other mediators should be considered in future research.

REFERENCES

1. Q.R Sharif-zadeh, M. Moudi, H. Akhbari, “Health situation of elderly supported by Imam Khomeini charity”. Iran Elderly Mag, 2010; 5(17), PP: 52-60.

2. M.B. Sohrabi, P. Zolfaghari, F. Mahdizade, et al, “Evaluation and comparison of cognitive state and depression in elderly admitted in sanitarium with elderly sited in personal home” Knowledge & health 2008; 3(2): 27. [Persian].

3. J.M. Torpy, C. Lynm, R.M. Glass, “JAMA patient page. Dementia” JAMA 2010; 304(17), PP: 972.

4. N.H. Greig, M.P. Mattson, T. Perry, et al, “New Therapeutic Strategies and Drug Candidates for Neurodegenerative Diseases: p53 and TNF-α Inhibitors, and GLP-1 Receptor Agonists” Ann NY Acad Sci, 2004; 1, PP: 290-315.

5. H. Jiang, H. Hampel, D. Prvulovic, et al, “Elevated CSF levels of TACE activity and soluble TNF receptors in subjects with mild cognitive impairment and patients with Alzheimer’s disease” Mol Neurodegener, 2011; 6: PP: 69.

6. W. Swardfager, K. Lanctôt, L. Rothenburg, et al, “A meta-analysis of cytokines in Alzheimer’s disease”. Biol Psychiatry, 2010; 68, PP: 930-941.

7. I. Ha, “Mild Cognitive Impairment (MCI): Pathogenesis and Treatments” Clin Psychopharmacol and Neurosci, 2009; 7(1), PP: 3-8.

8. R. Karamian, A. Mohammadian, E. Hassanimoghadam, et al, “Identification and comparison of the yield and composition of essential oil constituents of four Eucalyptus species adapted to the climatic conditions of Khorramabad”. J HerbMed Pharmacol, 2015; 4(1), PP: 25-28.

9. M.A. Kohanpour, M. Peeri, M.A. Azarbayjani, “The effects of aerobic exercise with lavender essence use on cognitive state and serum brain-derived neurotrophic factor levels in elderly with mild cognitive

impairment". J Herbmed Pharmacol, 2017; 6(2), PP: 80-84.

10. F. Abdullaev, J. Espinosa-Aguirre, "Biomedical properties of saffron and its potential use in cancer therapy and chemoprevention trials". Cancer Detection and Prevention, 2004; 28(6), PP: 426-432.

11. J.P. Melnyk, S. Wang, M.F. Marcone, "Chemical and biological properties of the world's most expensive spice: Saffron" Food Research International, 2010; 43(8), PP: 1981-1989.

12. A. Shati, F. Elsaid, E. Hafez, "Biochemical and molecular aspects of aluminium chloride-induced neurotoxicity in mice and the protective role of Crocus sativus L" extraction and honey syrup. Neuroscience, 2011; 175(23), PP: 66-74.

13. N. Pitsikas, N. Sakellaridis, L. Crocus sativus, "extracts antagonize memory impairments in different behavioural tasks in the rat" Behavioural Brain Research, 2006; 173(1), PP: 112-115.

14. M. Kamalipour, S. Akhondzadeh, "Cardiovascular Effects of Saffron:An vidence-Based Review" J Teh Univ Heart Ctr, 2011; 6(2), PP: 59-61.

15. M. Kamalipour, S. Akhondzadeh, "Cardiovascular effects of saffron: An evidence-based review" The J Tehran University Heart Center, 2011; 6(2), PP: 59-61. [Persian]

16. M. Modaresi, M. Messripour, "Effect of saffron extract on electrophoretic pattern of serum proteins in the male mice" Scientific J Kurdistan Uni of Med Sci, 2009; 13(4), PP: 23-9. [Persian]

17. C.H. Hillman, R.W. Motl, M.B. Pontifex, et al. "Physical activity and cognitive function in a cross-section of younger and older community-dwelling individuals" Health Psychol, 2006; 25, PP: 678-87.

18. S.H. Knudsen, B.K. Pedersen, "Targeting Inflammation Through a Physical Active Lifestyle and Pharmaceuticals for the Treatment of Type 2 Diabetes" Curr Diab Rep, 2015; 15(10), PP: 82.

19. J. Nillson, M.G. Parker, Z.N. Kabir, "Assessing Health – Relatel quality of life among older people in Rural Bangladesh". J of Trans Cultural Nursing, 2004; 15(4), PP: 298-307.

20. M. Frooghian, Z. Jafari, P. Shirinbaiani, et al, "Standardization of brief examination of cognitive status of elderly in Tehran". Advanced cognitive science Journal, 2008; 10(2), PP: 29-37. [Persian].

21. M.A. Kohanpour, M. Peeri, M.A. Azarbayjani, "The Effects of Glycyrrhiza glabra L. extract use with aerobic training on inflammatory factors and cognitive state in elderly with mild cognitive impairment" J Herbmed Pharmacol, 2017; 6 (4), PP: 178-184.

22. M.R. Ghadami, A. Pourmotabbed, "The effect of Crocin on scopolamine induced spatial learning and memory deficits in rats" Physiol Pharmacol, 2009; 12(4), PP: 287-295.

23. M. Khalili, F. Hamzeh, "Effects of Active Constituents of Crocus sativus L. Crocin on Streptozocin-Induced Model of Sporadic Alzheimer's Disease in Male Rats" Iranian Biomedical Journal, 2010; 14(1), PP: 59-65.

24. H. Hosseinzadeh, H.R. Sadegnia, V. Motamedshariaty, F.A. Ghaeni, S. Mohajeri, "Effects of saffron (Crocus sativus L.) and its active constituent, crocin, on recognition and spatial memory after chronic cerebral hypoperfusion in rats" Phytotherapy Research, 2012; 26(3), PP: 381-386.

25. M. Khalili, M. Roghani, M. Ekhlasi, The effect of aqueous Crocus sativus L. extract on intracerebroventricular streptozotocin-induced cognitive deficits in rat: a behavioral analysis. IJPR, 2009; 8(3), PP: 185-191.

26. J. Van Kampen, H. Robertson, T. Hagg, R. Drobitch, “Neuroprotective actions of the ginseng extracts G115 in two rodent models of Parkinson's disease” Experimental Neurology, 2003; 184(1), PP: 521-9.

27. M.S. Kim, J.I. Lee, W.Y. Lee, S.E. Kim, Neuroprotective effect of Ginkgo biloba L. extract in a rat model of Parkinson's disease. Phytother Res, 2004; 18(8), PP: 663-6.

28. B. Ghadrdoost, A.A Vafaei, A. Rashidy-Pour, R. Hajisoltani, A.R. Bandegi, F. Motamedi, et al, “Protective effects of saffron extract and its active constituent crocin against oxidative stress and spatial learning and memory deficits induced by chronic stress in rats” European Journal of Pharmacology, 2011; 667(1), PP: 222-229.

29. M.A. Papandreou, M. Tsachaki, S. Efthimiopoulos, P. Cordopatis, F.N. Lamari, M. Margarity, “Memory enhancing effects of saffron in aged mice are correlated with antioxidant protection” Behavioural Brain Research, 2011; 219(2), PP: 197-204.

30. J.B. Farinha, F.M. Steckling, S.T. Stefanello, et al, “Response of oxidative stress and inflammatory biomarkers to a 12-week aerobic exercise training in women with metabolic syndrome” Sports Med Open, 2015; 1(1), PP: 3.

31. A. Isanejad, Z.H. Saraf, M. Mahdavi, et al, “The effect of endurance training and downhill running on the expression of IL-1β, IL-6, and TNF-α and HSP72 in rat skeletal muscle” Cytokine, 2015; 73(2); PP: 302-8.

32. I. Miller, T. Vanessa, S.R. Patrick, et al, “Measuring the impact of exercise on cognitive aging: methodological issues” Neurobiology of Aging, 2012; 33, PP: 622-629.

33. P.A. Adlard, V.M. Perreau, V. Pop, et al, “Voluntary exercise decreases amyloid load in a transgenic model of Alzheimer’s disease” J Neurosci, 2005; 25, PP: 4217-4221.