DOI: 10.48305/jrrs.2021.30849 Published by Vesnu Publications

The Effect of Eight Weeks of Aerobic Exercise and Ferulic Acid Supplementation on the Oxidative Stress Indices of the Experimental Model of Breast Cancer in Mice

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Original Article

Abstract

Introduction: Ferulic acid is a phenolic compound found in various cereals and studies show that this compound has antioxidant, anti-apoptotic, and differentiating effects on nerve cells. The aim of this study was to evaluate the effect of eight weeks of aerobic exercise and ferulic acid consumption on the oxidative stress indices of the experimental model of breast cancer in mice.

Materials and Methods: In this experimental experiment, 30 female Balb/C mice weighing 220-250 g with breast cancer were divided into 1) control+, 2) control-, 3) ferulic acid supplementation, 4) exercise, and 5) exercise + ferulic acid supplements. By induction of breast cancer 14 days after injection of 1×10^6 T14 cells subcutaneously in the groin of four-week-old female Balb/C mice, a sample model of breast cancer in mice was obtained. For eight weeks, groups 3 and 5 daily consumed a dose of 200 microliters by gavage, and groups 4 and 5 performed aerobic exercise five days a week. One-way analysis of variance (ANOVA) with Tukey post-hoc test was used to analyze the findings at significance level of 0.05.

Results: Eight weeks of ferulic acid supplementation significantly increased the amount of superoxide dismutase (SOD) ($P \leq 0.01$). Catalase (CAT) levels increased significantly after eight weeks of aerobic exercise with ferulic acid supplementation and ferulic acid supplementation alone ($P \leq 0.01$). Moreover, aerobic exercise with ferulic acid supplementation and ferulic acid consumption alone significantly reduced malondialdehyde (MDA) ($P \leq 0.01$).

Conclusion: It seems that aerobic exercise with ferulic acid supplementation has more favorable effects on improving SOD, CAT, and MDA levels in breast cancer than any other alone. Therefore, the use of ferulic acid with aerobic exercise is recommended in cases of breast cancer.

Keywords: Exercise; Ferulic acid supplement; Superoxide dismutase; Catalase; Malondialdehyde; Breast cancer

Citation: Pira M, Jalali-Dehkordi K, Taghian F, Nasiri R. **The Effect of Eight Weeks of Aerobic Exercise and Ferulic Acid Supplementation on the Oxidative Stress Indices of the Experimental Model of Breast Cancer in Mice.** J Res Rehabil Sci 2021; 17: 126-33.

Received: 24.01.2021 Accepted: 14.04.2021 Published: 05.05.2021

Introduction

Breast cancer is a major health concern among women, the most common type of cancer in Western countries, accounting for approximately one-third of all women's cancers. It has different molecular subtypes, classified as estrogen receptor-dependent or non-estrogen receptor-dependent cancers (1). Most breast cancers are epithelial tumors that originate from the lining cells of the ducts or lobules of the breast and are called estrogen receptor alpha (ERα) positive due to the expression of the alpha estrogen receptor gene (2).

Over the past decade, there has been a significant focus on the role of physical activity in preventing and treating breast cancer. Doctors, sports physiologists, and patients have all recognized the potential benefits of exercise in improving the quality of life of patients with breast cancer. Research has shown that aerobic exercise, in particular, can help reduce cancer complications, ultimately decreasing mortality rates (3). Studies

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conducted on rodents have also found that the intensity of physical activity can either accelerate or prevent the development of breast cancer (4). Furthermore, aerobic exercises have been linked to decreased tumor volume in mice with breast cancer (4). A recent study by Betof et al. investigated the effects of aerobic exercise as a treatment modality for breast cancer (4). They found that groups that exercised after cancer had a slower tumor growth rate than those who did not exercise. Although these results show that aerobic exercise can have anti-tumor properties for patients with breast cancer, further research is needed to investigate the details of these findings (5).

The imbalance between oxygen species production and antioxidant mechanisms results in oxidative stress, which damages macromolecules like membrane lipids, proteins, and nucleotides through reactive oxygen species (ROS). The brain is particularly vulnerable to oxidative stress because of its high oxygen consumption, low antioxidant levels, and high phospholipid levels. Lipid peroxidation creates oxidized phospholipids (OxPL) and reactive aldehydes, which increase blood-brain barrier (BBB) permeability (6). Antioxidant enzymes like glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT), and non-enzymatic antioxidants like glutathione, tocopherol, ascorbic acid, uric acid, beta-carotene, and bilirubin are the first line of defense against oxidative stress. Recent studies suggest that GPx, SOD, and CAT play an essential role in cancer pathogenesis by protecting against ROS (7). However, the sensitivity of oxidative damage indicators increases with the expression of antioxidant enzymes, and secreted macrophages and astrocytes can defend themselves by producing androgen antioxidant enzymes (8).

Ferulic acid is a phytochemical found in plant cell walls. Phytochemicals are chemical compounds produced by plants that aid in their growth. These compounds have numerous health benefits, including anti-cancer, anti-inflammatory, anti-mutation, and antioxidant properties. Ferulic acid is a phenolic compound found in several cereals that has been shown to inhibit the growth of breast cancer cell lines. Research also suggests that it has antioxidant, anti-apoptotic, and differentiation effects on nerve cells. The study conducted by Al-Mutairi et al. found that ferulic acid and thymoquinone, separately, had anti-cancer properties in all cancer cells (10). Furthermore, the study examined the combined effect of thymoquinone and ferulic acid, which showed favorable results. The present study investigates the simultaneous development of eight weeks of aerobic exercise and ferulic acid consumption on oxidative stress indicators in the brain tissue of mice with breast cancer. The study aims to provide more information regarding the role of time management in cancer conditions.

Materials and Methods

Maintenance of laboratory animals: In this experimental trial, 30 female BALB/c mice weighing 220-250 grams were obtained from the Animal Breeding and Reproduction Center of Royan Research Institute in Tehran, Iran. After being transferred to this academic unit's specialized sports physiology laboratory, they were kept in this environment for a week for adaptation. Notably, during the entire research period, the animals were kept under standard conditions, including a 12-hour light-dark cycle, ambient temperature of 20-22 degrees Celsius, relative humidity of 55%, and free access to water and food. Besides, all the ethical principles of working with animals were carried out according to the Declaration of Helsinki and under the supervision of the Ethics Committee of the Islamic Azad University, Khorasgan Branch, Isfahan, Iran, with the code IR.IAU.KHUISF.REC.1400.293.

Generation of breast cancer mouse model: After 14 days of injecting 1×10^6 4T1 cells subcutaneously in the groin of four-week-old BALB/c female mice, a mouse model with breast cancer was obtained, confirmed by pathology slides. Hematoxylin and eosin (H&E) were taken from the chest of mice and analyzed (Figure 1).

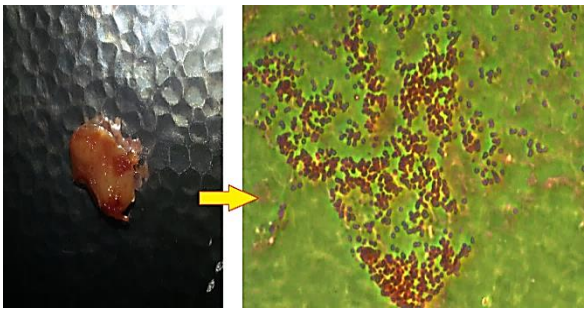

Figure 1. Pathology slide with hematoxylin and eosin (H&E) staining of mouse cancer cells

Cells used in this research: T14 cancer cells were purchased from the cell bank of Mashhad University of Medical Sciences, Mashhad, Iran. It was cultured in Dulbecco's Modified Eagle Medium (DMEM) with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. The cell line growth conditions were 37 °C and 92% humidity with 5% carbon dioxide (CO2). All cell tests were performed in the exponential growth phase of the cells. Thirty

mice with breast cancer were randomly divided into six groups: positive control, negative control, aerobic exercise, ferulic acid supplement, and aerobic exercise + ferulic acid supplement.

Aerobic exercise protocol: To prepare for the main exercise, a 5-minute warm-up was performed on a treadmill with a 0-degree incline and 6 meters per minute speed, both before and after the training. The main exercise was carried out with slight modifications based on the report by Shalamzari et al. (11) and table 1. The electric shock was set to the minimum amount to prevent any stress.

Table 1. Exercise program designed in the present study

Length of each session (week)	Running speed (meters per minute)	Duration of each session (minute)	Number of sessions per week (day)
First	10	20	5
Second	14	25	5
Third	14	25	5
Forth	16	30	5
Fifth	16	30	5
Sixth	18	30	5
Seventh	18	30	5
Eighth	18	30	5

Ferulic acid supplement injection method: The ferulic acid supplement injection was administered through an insulin syringe via intraperitoneal injection at an angle of 45 degrees. The volume injected was 200 microliters.

Measurement of hippocampal tissue's antioxidant activity: The heads of the mice were separated using a guillotine, and the brain and hippocampus were immediately washed with 9% cold sterile saline and then frozen in liquid nitrogen. Each sample was mixed with a cold solution of 1.15% potassium chloride to create homogenate. The hippocampal tissue homogenate was prepared using a mechanical homogenizer. After centrifugation at 1000 rpm for 10 minutes at four degrees Celsius, the supernatant was used for biochemical analysis.

Determination of brain SOD activity: The SOD radicals were produced in this method using xanthine and xanthine oxidase. The radicals reacted with 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyl-1H-tetrazole and formed a formazon red color which was measured at a wavelength of 505 nm (12).

Determining brain CAT activity: The CAT levels in the brain were determined using 2, 2'-Azino-bis (3-ethylbenzthiazoline-6-sulfonic acid) (ABTS+). The ABTS+ free radicals were produced near hydrogen peroxide. The activity of brain CAT levels was investigated by measuring the reduction of hydrogen peroxide absorption at a wavelength of 240 nm by the spectrophotometric method. The blue-green color produced was measured at a wavelength of 600 nm. The presence of antioxidants in the sample weakened the production of this color (12).

Measuring the concentration of malondialdehyde (MDA): 0.2 grams of brain tissue was taken from a freezer that was stored at -80 degrees Celsius. The tissue was then stabilized using a homogenizer while maintaining a standard temperature. 5 ml of trichloroanisole (TCA) was added to the tissue to make it uniform, after which it was centrifuged at 10000 rpm for 5 minutes. The resulting supernatant was mixed with 4 ml of 20% TCA solution containing 0.5% thiobarbituric acid (TBA). The reaction mixture was then heated for 30 minutes at 95° C and immediately chilled in an ice bath. After 10 minutes, the combination was mixed at 10000 rpm and centrifuged. The absorption intensity of the solution was measured using a spectrophotometer at a wavelength of 532 nm (13). MDA concentration was calculated by considering the absorption results at zero time and using equation 1. The extinction coefficient of 155 mM^{-1} $cm^{-1}$was used to calculate the concentration.

Equation 1: $$\text{MDA concentration} = \frac{\text{absorption changes}}{\text{quenching coefficient}}$$

To begin with, we utilized the Shapiro-Wilk test to check the normality of the data distribution. Once the normality was determined, we performed the One-way analysis of variance (ANOVA) test to compare the groups. Lastly, the data were analyzed using GraphPad Prism software version 6. A significance level of $P < 0.05$ was considered.

Results

One-way ANOVA test results showed a significant difference between the groups' mean SOD, CAT, and MDA indices ($P = 0.010$). Tukey's post hoc test compared two groups (Table 2).

According to the Bonferroni post hoc test results, the SOD levels in the positive control group significantly decreased compared to the negative control group ($P = 0.010$). Only the ferulic acid group showed significant improvement in the SOD index compared to the positive control group ($P = 0.010$). However, the training + ferulic acid group and the training group alone did not present significant changes compared to the positive and negative control groups ($P > 0.050$) (Figure 2).

Table 2. One-way analysis of variance (ANOVA) test results of oxidative stress indices

Index	Negative control	Positive control	Ferulic acid	Exercise	Exercise + ferulic acid	F-statistics	P value
SOD	32.24 ± 3.42	26.33 ± 1.73	30.58 ± 1.93	29.31 ± 3.52	27.25 ± 7.62	1.003	0.400
CAT	3.24 ± 0.57	2.41 ± 0.18	3.00 ± 0.20	2.20 ± 0.31	2.98 ± 0.14	5.569	0.010
MDA	23.92 ± 3.86	40.65 ± 2.30	25.74 ± 3.76	35.78 ± 2.35	25.53 ± 2.14	18.643	0.001

Data are presented as mean ± standard deviation (SD)
SOD: Superoxide dismutase; CAT: Catalase; MDA: Malondialdehyde

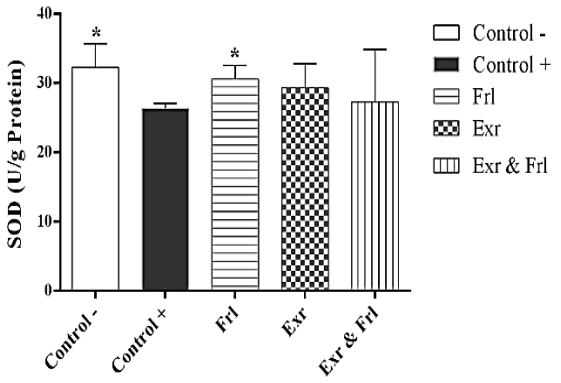

Figure 2. Superoxide dismutase (SOD) levels in the brain tissue of the studied rats

After conducting the Bonferroni post hoc test, a significant decrease in the CAT level was observed in the positive control group compared to the negative control group (P = 0.010).

Compared to the positive control group, the groups treated with ferulic acid and exercise + ferulic acid displayed a significant increase in CAT value (P = 0.010). However, the exercise group did not show significant changes in the CAT level compared to the positive and negative control groups (P > 0.050), as illustrated in figure 3.

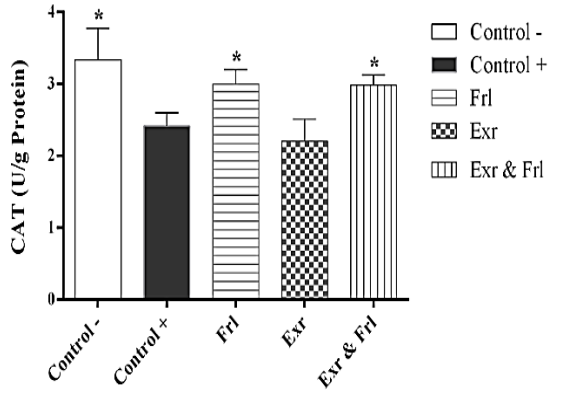

Figure 3. Catalase (CAT) levels in the brain tissue of the investigated mice

The results of the Bonferroni post hoc test showed that the MDA index in the positive control group had a significant increase compared to the negative control (P = 0.010) (Figure 4).

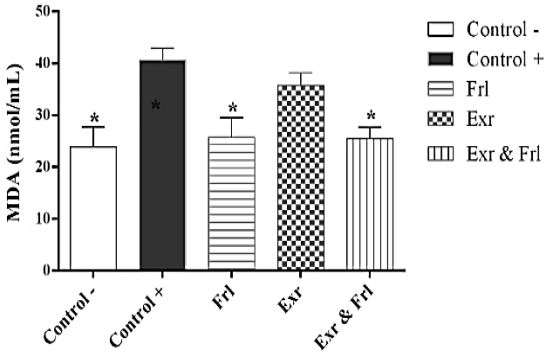

Figure 4. Malondialdehyde (MDA) levels in the brain tissue of the investigated mice

Compared to the positive control group, ferulic acid + exercise and ferulic acid alone showed a significant decrease in MDA level (P = 0.010). This was even though the training group did not show significant changes in the amount of MDA compared to the positive and negative control groups (P > 0.050) (Figure 4).

Discussion

The study results indicate that aerobic exercise and ferulic acid supplementation can enhance the antioxidant capacity and decrease lipid peroxidation in the brain tissue of rats with breast cancer. The carcinogenesis process can be triggered by various endogenous and environmental factors that cause complex cellular and molecular changes. Due to the high consumption of oxygen and concentration of unsaturated fatty acids, the human brain is vulnerable to free radical attacks. Additionally, compared to other organs, the brain has a lower antioxidant capacity, which makes it more susceptible to oxidative damage (14).

According to the study's findings, the levels of antioxidant enzymes, SOD and CAT, decreased in the

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brains of mice with breast cancer. However, the group treated with ferulic acid showed a significant increase in SOD levels compared to the positive control group. Similarly, the groups treated with ferulic acid and combined exercise significantly increased CAT compared to the positive control group. The study's results are consistent with the findings of Nouri et al., who suggested that 15 weeks of combined exercise could increase enzymatic antioxidant defense by enhancing SOD and GPx levels in postmenopausal women with breast cancer (15). Additionally, Nabi et al.'s research indicated that sports activity could lower MDA levels and increase antioxidant enzyme activity in the hippocampus. Thus, sports activity can help protect against damage and disorders caused by cerebral ischemia by increasing the activity of antioxidant enzymes (16).

In cancer model mice, ROS damage in brain tissue involves different mechanisms. ROS is essential for most cellular regulatory processes, but when the rate of free radical production exceeds the cellular antioxidant capacity, oxidative stress occurs. This leads to ROS-induced damage to macromolecules such as membrane lipids, essential proteins, and nucleotides. However, the body activates a compromising mechanism to protect cells against ROS-mediated toxicity and to maintain tissue redox balance. This mechanism involves increasing the expression of androgen antioxidant enzymes. The antioxidant activity of SOD and CAT also increases as a response to stress (17). The transcription of genes that encode most antioxidant enzymes is regulated through a transcription factor called nuclear factor erythroid-2-related factor 2 (Nrf2) and antioxidant response elements (ARE) in these genes. Under physiological conditions, Nrf2 is usually attached to Keap1 protein in the cytoplasm. However, under oxidative stress conditions, Nrf2 dissociates from Keap1 and translocates to the nucleus, activating ARE-mediated coordinated gene transcription. So far, over 200 genes involved in detoxification and antioxidant defense system, including the genes encoding SOD and CAT (18), have been identified under the control of Nrf2-ARE.

The present study indicates that combining ferulic acid extract and aerobic exercise can help mitigate oxidative stress indicators. The experiment involved administering 200 microliters of ferulic acid extract and conducting aerobic exercise. The results showed increased SOD and MDA capacity in the brains of mice with breast cancer. Previous studies have reported no significant change in hippocampal SOD values after four weeks of intermittent aerobic training (19). A separate survey by Camiletti-Moiron et al. also reported no change in brain SOD activity after 12 weeks of high-intensity exercise (20). In contrast, the present study found a positive difference in brain SOD activity.

The study conducted by Rami et al. revealed that endurance training effectively increased the antioxidant role of the CAT enzyme and reduced the amount of MDA in the hippocampus tissue (21). This finding is consistent with the results of the present study. The intensity of sports training can produce free radicals that activate the metabolic pathways of antioxidants. When sports activities begin with low power, free radical production is lower. At this stage, SOD is the first line of defense and works by rapidly dismutating superoxide anions into hydrogen peroxide. As long as the exercise is performed at an intensity that does not require the elimination of more free radicals, SOD continues to work. However, as the intensity of the exercise increases, GPx and CAT are activated and neutralize hydrogen peroxide. Therefore, high activity of GPx and CAT is associated with a lower rise in SOD (22). The difference in gender and species of the investigated animals, the method of treatment, the dosage of ferulic acid, and the intensity of activity are among the possible causes of the difference between the results of the mentioned studies and the present research. Ferulic acid, a caffeic acid derivative found in vegetables, grains, and coffee, has antioxidant and neuroprotective properties. This plant compound is widely used in Chinese medicine, and Angelica sinensis is one of its main therapeutic properties (23).

In bipolar patients, there is a negative correlation between the concentration of brain-derived neurotrophic factor (BDNF) and serum TBA reactive substances (TBARS). The upregulation of BDNF-tropomycin receptor kinase B (BDNF-TrkB) has an antioxidant effect by inhibiting p47phox phosphorylation. The activation of extracellular signal-regulated kinases (ERK) can reduce the activity of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1 (NOX1) and can suppress the production of superoxide anion (free radical). ERK from the same pathway can play a role in BDNF-TrkB signaling activity. Additionally, BDNF improves mitochondrial function, and mitochondria are the source of many free radicals during cerebral ischemia (24).

After eight weeks of aerobic exercise and ferulic acid consumption, the amount of MDA decreased in the present study. The results suggest that the intensity and duration of the sports activity increased

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the antioxidant defense system and reduced the lipid peroxidation index. This adaptation optimized fat oxidation to provide the required energy and prevented complications caused by excess oxygen in the oxidation pathway. The reduction of MDA in the present study seems to be due to the increase in antioxidant defense caused by regular aerobic activity. Administration of ferulic acid reduced lipid peroxidation and improved the antioxidant status, mainly due to antioxidant function of ferulic acid (25). This was consistent with the findings of Valado et al. (26) and Gupt et al. (27) but inconsistent with some other studies. The inconsistency of the results may be related to the intensity of the exercise, the type of treatment, and the dose of ferulic acid (28-29). Acikgoz et al. reported that acute retinol activity did not significantly affect brain MDA (29). Phenolic compounds act as antioxidants by increasing exercise capacity, and ferulic acid is a phenolic compound and an effective free radical scavenger that reduces lipid peroxidation by inhibiting cytochrome (26). The present study showed that ferulic acid supplementation and exercise + ferulic acid supplementation increased antioxidant capacity and decreased lipid peroxidation (26). Faraji et al. concluded that reducing the antioxidant defense system in stroke effectively increased the damage caused by free radicals, and perhaps consuming more food and medicine containing antioxidants effectively controls and reduces brain tissue destruction (30). You et al. found that ferulic acid led to increased sports performance improvement. It increased the antioxidant capacity and reduced fatigue in mice (31).

Limitations

Among the limitations of the present study, we can mention the lack of control of nutrition and diet during eight weeks of sports activity and the lack of measurement of oxidative stress.

Recommendations

It is suggested that in future studies, careful control of nutrition and evaluation of oxidative stress in mice with breast cancer should be done.

Conclusion

The findings of the current research indicate that after eight weeks of aerobic exercise coupled with ferulic acid supplementation, there was a significant increase in the levels of SOD and CAT and a decrease in MDA. This is further evidence of an increase in antioxidant capacity, a reduction in tissue damage, and an increase in the survival of healthy cells in the brain tissue of mice with breast cancer who underwent aerobic exercise and were given ferulic acid supplements.

Acknowledgments

The present study is taken from the doctoral dissertation in Physical Education and Sports Science-Sports Physiology with ethics code IR.IAU.KHUISF.REC.1400.293 approved by the Islamic Azad University of Isfahan (Khorasgan). The study was conducted without financial support.

Authors' Contribution

Study design and ideation: Khosro Jalali-Dehkordi, Farzaneh Taghian, Rozita Nasiri, Maryam Pira

Attracting financial resources for the study: Maryam Pira

Study support, executive and scientific services: Khosro Jalali-Dehkordi, Maryam Pira, Farzaneh Taghian, Rozita Nasiri

Providing equipment and study samples: Khosro Jalali-Dehkordi, Farzaneh Taghian, Rozita Nasiri, Maryam Pira

Data collection: Maryam Pira

Analysis and interpretation of results: Khosro Jalali-Dehkordi, Farzaneh Taghian, Rozita Nasiri, Maryam Pira

Specialized statistics services: Khosro Jalali-Dehkordi, Rozita Nasiri, Maryam Pira

Handwritten arrangement: Khosro Jalali-Dehkordi, Rozita Nasiri, Maryam Pira

Specialized evaluation of manuscripts in terms of scientific concepts: Khosro Jalali-Dehkordi, Maryam Pira, Farzaneh Taghian, Rozita Nasiri

Confirmation of the final manuscript to be sent to the office of the magazine: Khosro Jalali-Dehkordi, Maryam Pira

Responsibility for maintaining the integrity of the study process from the beginning to the publication and responding to the opinions of the judges: Khosro Jalali-Dehkordi, Farzaneh Taghian, Rozita Nasiri, Maryam Pira

Funding

The present study is taken from the doctoral dissertation in Physical Education and Sports Science-Sports Physiology with ethics code IR.IAU.KHUISF.REC.1400.293 approved by the Islamic Azad University of Isfahan (Khorasgan). The study was conducted without financial support.

Conflict of Interest

Authors have no conflict of interest.

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