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Original Article

The effect of eight-week resistance training and consumption of grape seed nanoparticles on mitochondrial biogenesis of heart tissue in the myocardial infarction model

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Abstract

Background and aims: The consumption of grape seed nanoparticles extract can control cardiovascular risk factors. Exercise plays a protective role against cardiovascular disease. Therefore, the aim of the present study was to investigate the effect of eight-week resistance training (RT) and the use of grape seed nanoparticles on mitochondrial biogenesis of heart tissue in myocardial infarction (MI) models.

Methods: In this experimental study, 25 rats were randomly divided into five groups including (1) control (C), (2) MI, (3) MI + RT, (4) MI + grape seed, and (5) MI + RT + grape seed. MI was induced by subcutaneous injection of isoprenaline (85 mg/kg). Grape seed nanoparticles were daily administered at a dose of 150 mg/kg for 8 weeks, and RT was performed 5 days a week. Finally, data were analyzed using the one-way analysis of variance (ANOVA) and Tukey's post hoc tests ($P \leq 0.05$).

Results: MI models showed decreased expression of PGC-1α, PPARγ, and UCP-1 genes in cardiac tissue ($P = 0.001$). However, RT combined with the use of grape seed nanoparticles had a significant effect on increasing the expression of PGC-1α ($P = 0.001$), PPARγ ($P = 0.002$), and UCP-1 ($P = 0.003$) genes in the heart tissue of MI model mice.

Conclusion: The consumption of grape seed nanoparticles along with RT has more effects on improving the expression of PGC-1α, PPARγ, and UCP-1 genes in MI than either alone. Therefore, the use of grape seed nanoparticles together with RT is recommended in case of MI.

Keywords: Resistance Training, Grape seed, PGC-1α, PPARγ, UCP-1, Myocardial infarction

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Introduction

Myocardial infarction (MI) is one of the most fatal forms of ischemic heart disease in the world. The number of people with MI worldwide reaches about 3 million, and about 50% of deaths from cardiovascular disease are related to MI (1). MI is caused by insufficient oxygen-rich blood flow to the heart, which causes an imbalance in the oxygen supply and ultimately damages the heart tissue (2). The central role of mitochondria in cardiac contractility involves specific regulations and adaptations of mitochondrial network structure and function (3). After MI, the heart muscle is impaired; therefore, mitochondrial abnormalities have been accepted to cause heart failure (4). Convincing evidence of a link between mitochondrial dysfunction and MI has been shown through mitochondrial respiratory dysfunction and decreased respiratory enzyme activity (5). The gamma peroxisome proliferator-activated receptor-activator-1α (PGC-1α) is a member of the nuclear cofactor family that has been studied the most. PGC-1α is found in tissues with high oxidative activity such as heart and brown adipose tissue (BAT), and it is rapidly induced under conditions of increased energy demand such as cold, training, and fasting. PGC-1α is associated with mitochondrial protein levels, mitochondrial mass, and cardiac oxidative capacity. The results suggest that PGC-1α is an important regulator of mitochondrial biogenesis and energy metabolism (6). Hearts lacking PGC-1α have normal mitochondrial volume density; however, mitochondrial gene expression, oxidative capacity, and fatty acid oxidation are decreased (7). In addition, PPARs are a family of proteins that play an important role in the proliferation of peroxisomes, organelles that work to remove toxins from the body. Peroxisomes are similar to mitochondria in that they have an internal crystalline structure, contain oxidative enzymes, and proliferate on their own. PARα regulates fatty acid homeostasis through the activation of transcription of genes encoding key enzymes in fatty acid metabolism (8). Moreover, white fat is a source of energy storage, while brown fat increases mitochondrial oxidation of fatty acids and heat production through uncoupling protein 1 (UCP-1), thereby reducing

storage in white adipose tissue (9). The role of PGC-1α in the conversion of white adipose tissue to brown fat has been confirmed (10). Increased expression of PGC-1α leads to the expression of FNDC5, a membrane protein that is secreted into the bloodstream as a newly identified hormone, irisin (10). PGC-1α-induced irisin increases the expression of UCP-1 protein and mitochondrial contents. UCP-1 is an important protein involved in the regulation of BAT thermogenesis and has the ability to convert white fat to BAT (10). Recent research has examined the effect of aerobic exercise on the regulation of mitochondrial biogenesis and the treatment of heart disorders and has assessed the positive effect of exercise on mitochondrial dynamics (11,12). The researchers showed that exercise on a treadmill increased the expression of PGC-1α (13) and UCP-1 (14). It is suggested that exercise has a protective role against various cardiovascular diseases, possibly by reducing cardiovascular risk factors, improving physiological growth of the heart, increasing antioxidant capacity, and improving mitochondrial function. If exercise is accompanied by nutritional interventions, it will undoubtedly have more effects, and in this regard, in recent years, much attention has been paid to medicinal plants. Meanwhile, black grape seed extract is one of the supplements that has flavonoid compounds with very high antioxidant effects. The biological properties of polyphenols include antioxidant, anti-cancer, and anti-inflammatory effects, among which proanthocyanidin is the most effective anti-oxidant compound of grape seed (15). Zarei et al in 2022 showed the positive and synergistic effects of co-administration of grape seed and regular exercise for 14 weeks to prevent acute and chronic cardiac protective phenomena in heart ischemia rat models (16). A study found that consuming grape seed reduced myocardial damage (17). Given the importance of time management in MI as well as the optimal role of each intervention (exercise and grape seed) in MI, there is limited information regarding the simultaneous effect of exercise training and consumption of grape seed nanoparticles on the subsequent PPARγ/PGC-1α/UCP-1 axis in the heart tissue following exercise. Therefore, the purpose of the present study was to investigate the effect of eight-week resistance training (RT) and consumption of grape seed nanoparticles on mitochondrial biogenesis of heart tissue in MI models.

Materials and Methods

Maintenance of laboratory animals

In this experimental study conducted in September 2021, 25 Wistar rats were obtained from Pasteur Institute of Iran and kept in a laboratory for one week for adaptation. During the study, the animals were kept in standard conditions including a 12-hour dark-light cycle, an ambient temperature of 20-22°C, a relative humidity of 55%, and free access to water and food. Additionally, all stages of the study were carried out in accordance with the ethical principles of working with animals based on the Helsinki Declaration and under the supervision of the Ethics Committee of the Islamic Azad University, Isfahan Branch (Khorasgan).

Modeling method and induction of myocardial infarction

MI was induced in laboratory mice after adaptation of the animals to the environment based on a study conducted by Sharma et al (18). Isoproterenol was dissolved in normal saline (1 mg/mL) and injected subcutaneously at a dose of 85 mg/kg for two consecutive days with 24 hours of intervals. One day after injection, four animals lost their lives and were replaced immediately; therefore, the induction of MI was conducted based on the standard protocols. In this study, several mice were randomly anesthetized two days after MI, and samples of cardiac tissue were extracted from their left ventricle and examined by hematoxylin and eosin staining using histochemical techniques. Finally, 25 rats were included in the study. In other words, 25 rats with MI were randomly assigned to five groups, including: 1) control, 2) MI 3) MI + RT, 4) MI + grape seed, and 5) MI + RT + grape seed.

Preparation of grape seed

The active ingredient of grape seed extract was obtained in pure form from Sigma Company and then dissolved in DMSO. After preparation of the supplement in the form of nanoparticles, 150 mg daily was gavaged to the supplement groups (19).

Training protocol for rats

RT began 1 week after MI. The RT program was selected based on the results of a previous study by Lee et al (20). Resistance exercises were performed using a 1-m ladder with 2-cm handrails and a slope of 85°. 1RM was defined as the heaviest weight lifted. 1RM included climbing a ladder with a slope of 85° and using 50 to 130% g/body weight with 20% weight increments per climb to reach the maximum weight. RT included a starting climb weight of 50% 1RM, incremental weight increase of 5% per climb, 8–10 climbs per session, and 2-minute rest between climbs (Table 1) (21).

Molecular evolution of heart tissue by real time PCR

Initially, RNA was extracted from the tissues of all study groups according to the protocol (Qiagen, Germany).

Table 1. Resistance training protocol

Factor week	Intensity	Repetition	Rest time (min)	Number of days per week
First	50%	8	2	5
Second	60%	8	2	5
Third	65%	10	2	5
Fourth	75%	10	2	5
Fifth	85%	10	2	5
Sixth	95%	10	2	5
Seventh	110%	10	2	5
Eighth	130%	10	2	5

Then, 200 µL of qiazol was added to the samples and incubated at 80°C for 24 hours. The plaque inside the cryotube was crushed in a semi-frozen state and 100 µL of chloroform was added to the samples to lyse the cells. This solution was in contact with the cells for 1 minute. The resulting solution was centrifuged at 12000 rpm for 10 minutes. The clear liquid at the top of the tube containing the RNA was slowly extracted and placed in a DEPC microtube. Then, 1 mL of isopropanol was added to the clear RNA and stirred by hand for 1 minute. The samples were centrifuged at 12 000 rpm for 10 minutes. The supernatant was then discarded and 1 mL of 70% alcohol was added to the precipitate. Next, cDNA synthesis was done in line with the manufacturer's protocol (Fermentas, USA), and the synthesized cDNA was used for reverse transcription. The expression of PPARα, PGC-1α and UCP1 in heart tissue was measured by real time-PCR (Table 2).

Statistical analysis

In the descriptive part, the mean and standard deviation were used. Data normality was confirmed using Shapiro-Wilk test. One-way analysis of variance (ANOVA) and Tukey's test were used to compare the differences between groups. The required data were collected and analyzed by SPSS version 22.0 at $P \leq 0.05$. Microsoft Excel was used to draw the graphs.

Results

Figures 1, 2, and 3 show the expression of PPARα, PGC-1α, and UCP-1 genes in rat heart tissue. The results of ANOVA showed that there was a significant difference in the expression of PPARα ($P=0.001$), PGC-1α ($P=0.002$), and UCP-1 ($P=0.003$) genes in the heart tissue of rats in different research groups (Table 4).

The results of Tukey's post hoc test indicated that PGC-1α gene expression was significantly lower in the MI, MI + RT, and MI + GS groups compared to the control

Table 2. Sequence of primers

Gene name	Oligo sequence
PPARα	F: AGTGCCCTGAACATCGAGTGT
	R: AAGCCCTTACAGCCTTCACATG
PGC-1α	F: TCATACATGACATGGAGACCTTG
	R: ACTGGCAGCAGTGGAAGAATC
UCP-1	F: CAATGACCATGTACACCAAGGAA
	R: GATCCGAGTCGCAGAAAAGAA
GAPDH	F: AAG TTC AAC GGC ACA GTC AAG G
	R: CAT ACT CAG CAC CAG CAT CAC C

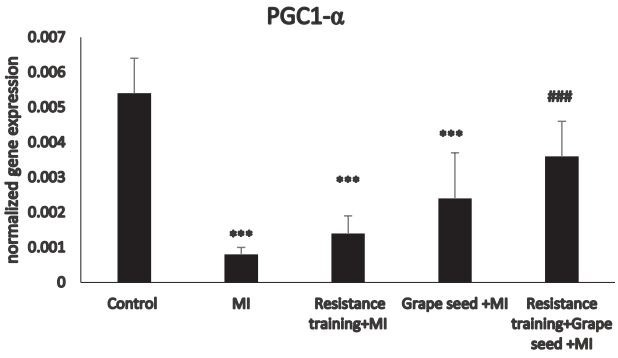

Figure 1. PGC-1α gene expression in the cardiac tissue of different study groups. Values are displayed as means and standard deviation (mean ± SD). Statistically significant differences between the mean values were evaluated at $P<0.05$. ***$P \leq 0.001$: significant decrease compared to the control group. ### $P \leq 0.001$: significant increase compared to the MI group.

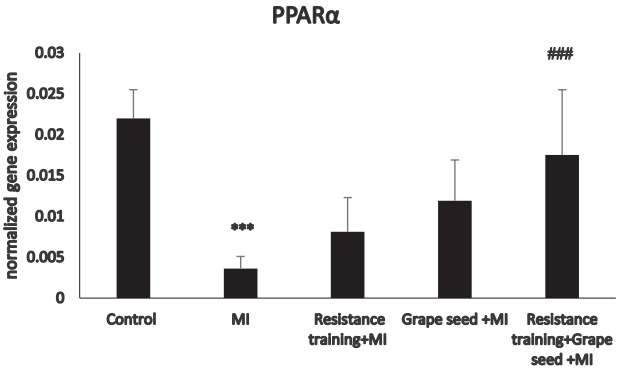

Figure 2. PPARα gene expression in the cardiac tissue of different study groups. Values are displayed as means and standard deviation (mean ± SD). Statistically significant differences between the mean values were evaluated at $P<0.05$. ***$P \leq 0.001$: significant decrease compared to the control group. ### $P \leq 0.001$: significant increase compared to the MI group.

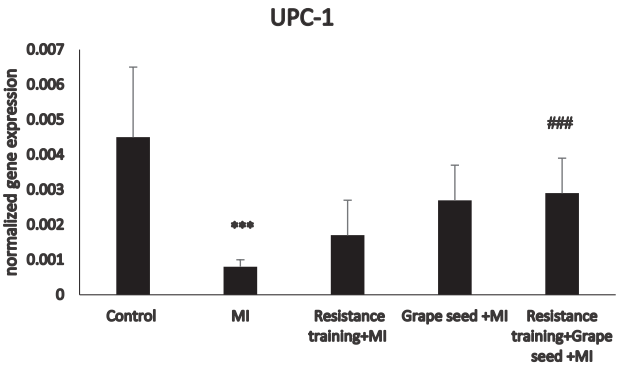

Figure 3. UPC-1 gene expression in the cardiac tissue of different study groups. Values are displayed as means and standard deviation (mean ± SD). Statistically significant differences between the mean values were evaluated at $P<0.05$. ***$P \leq 0.001$: significant decrease compared to the control group. ### $P \leq 0.001$: significant increase compared to the MI group.

Table 3. Mean and standard deviation of body weight and age

Variable	Group				
	Control	MI	MI + RT	MI + GS	MI + RT + GS
Body weight (g)	301 ± 13.44	300.5 ± 8.97	310.75 ± 11.50	307.25 ± 9.11	303 ± 10.02
Age (wk)	8	8	8	8	8

Abbreviations: RT, resistance training; MI, myocardial infarction; GS, grape seed.

Table 4. One-way ANOVA for PGC-1α, PPARα, and UCP-1mRNA

Variable	Group	Mean ± SD	Mean square	F	*P* value
PGC-1α	C	0.0054 ± 0.001	0.001	14.065	0.001
	MI	0.0008 ± 0.0002			
	MI + RT	0.0014 ± 0.0005			
	MI + GS	0.0024 ± 0.0013			
	MI + RT + GS	0.0036 ± 0.001			
PPARα	C	0.022 ± 0.0035	0.001	6.168	0.002
	MI	0.0036 ± 0.0015			
	MI + RT	0.0081 ± 0.0042			
	MI + GS	0.0119 ± 0.005			
	MI + RT + GS	0.0175 ± 0.008			
UCP-1	C	0.0045 ± 0.002	0.001	5.694	0.003
	MI	0.0008 ± 0.0002			
	MI + RT	0.0017 ± 0.001			
	MI + GS	0.0027 ± 0.001			
	MI + RT + GS	0.0029 ± 0.001			

Abbreviations: RT, resistance training; MI, myocardial infarction; GS, grape seed; SD, standard deviation.

group ($P = 0.001$). Nevertheless, PGC-1α gene expression in the MI + RT and MI + GS groups did not show significant changes compared to the MI group ($P = 0.1$). PGC-1α in the MI + RT + GS showed a significant increase compared to the MI group ($P = 0.001$) (Figure 1).

The results of Tukey's post hoc test indicated that PPARα gene expression was significantly lower in the MI group compared to the control group ($P = 0.001$). Nevertheless, PPARα gene expression in the MI + RT and MI + GS groups did not show significant changes compared to the MI group ($P = 0.3$). PPARα gene expression in the MI + RT + GS showed a significant increase compared to the MI group ($P = 0.001$) (Figure 2).

The results of Tukey's post hoc test indicated that UPC-1 gene expression was significantly lower in the MI group compared to the control group ($P = 0.001$). Nevertheless, UPC-1 gene expression in the MI + RT and MI + GS groups did not show significant changes compared to the MI group ($P = 0.2$). UPC-1 gene expression in the MI + RT + GS showed a significant increase compared to the MI group ($P = 0.001$) (Figure 3).

Discussion

The results of the present study indicated that 8 weeks of RT along with the consumption of grape seed significantly increased the levels of PGC-1α, PPARα, and UPC-1 gene expression compared to the MI group in the cardiac tissue of rats with MI. Mitochondria are organelles that directly affect homeostasis because their role in ATP production is important for the whole organism. Five protein complexes (CI-CV) in the mitochondrial electron transport chain are involved in ATP production. Therefore, mitochondrial damage directly affects energy production and cell activity. In addition, PGC-1 plays a major role in controlling the transcription of mitochondrial biogenesis and respiratory function (22). Mitochondrial function is compromised due to increased ROS in MI conditions. Removing damaged mitochondria or ROS-producing mitochondria and producing new mitochondria are vital for maintaining their normal function (23). We hypothesize that PGC-1α actively regulates downstream factors through mitonuclear communication during MI and, by reducing ROS, ensures mitochondrial homeostasis, leading to activation of mitochondrial biogenesis and mitophagy. Studies have shown that PGC-1α plays a role in adaptation and response to exercise as one of the most important regulators. In this regard, acute exercise led to an increase in PGC-1α expression (24). The results of a study by Cartoni et al showed that acute training increased Mfn1, Mfn2, PGC-1α, and NRF -2 mRNA levels (25). Both AMPK and the silencer regulatory protein (Sir2) homologue to SIRT1 are PGC1 α activators. Natalia et al reported that prolonged exercise increased the pAMPK/AMPK ratio and SIRT1 expression in BAT, which could be responsible for increasing PGC1 expression (26). In line with these findings, the data indicate that contraction-activated PGC-1α signaling pathways in skeletal muscle are redox sensitive and that nonmitochondrial ROS play a major role in stimulating mitochondrial biogenesis (27). Consistent with the present research, Laurindo et al showed that RT enhanced PGC-1α gene expression (28). In the present study, RT increased PGC1-α gene expression in the heart tissue of MI animals and confirmed the role of RT in mitochondrial homeostasis. Botta et al reported that short-term and moderate-intensity training upregulated PGC-1α gene expression (29). The results show that a decrease in the calcium cycle, calcium calmodulin kinase (CaMK) activity, and a decrease in sirtuin 1 (Sirt1) expression can lead to inhibition of PGC-1α activity. In general, it seems that induction of MI can reduce PGC-1α expression. In contrast, RT can stimulate

PGC-1α activity by modulating calcium, increasing CaMK, and increasing Sirt1 expression. Tao et al showed that three weeks of swimming training significantly decreased autophagic activity and apoptosis in rat heart. In addition, mitochondrial biogenesis increased with increasing expression of mtDNA levels. PGC-1α acts as a key mitochondrial regulator that can be affected by exercise and plays a vital role in improving the metabolism of the heart and cardiovascular disease (30). Induction of MI resulted in decreased PGC1 expression in cardiac tissue compared to healthy controls. Moreover, decreased PGC1 expression could impair mitochondrial function in the heart tissue of MI mice. RT with 50% to 130% of body weight increased the expression of PGC-1 in the RT group compared to the MI group. In addition, increased PGC1 expression following RT improved mitochondrial function in MI tissue (27). While interacting with PPARs, PGC-1α plays a vital role in regulating BAT function. PPARα is a transcription factor that controls the expression of genes related to lipid metabolisms, such as mitochondrial biogenesis, β-oxidation, peroxisomal β-oxidation, fatty acid uptake, binding, assembly, and lipoprotein transport (31). In addition, a decrease in PPARα leads to impaired fatty acid metabolism with a significant reduction in serum short-chain acylcarnitines and increase in long-chain acylcarnitines (32). The present study showed that trained mice had an increase in PPARα mRNA. It can be considered that the type of exercise performed for this study led to PPARα compatibility. In line with the present study, Gasparotto et al showed that aerobic exercise increased PPARα and UCP1expression (33). Additionally, Askari et al demonstrated that eight weeks of cardiac rehabilitation exercise can increase PPAR-α gene (34). Some lines of evidence indicate that agonist PPARα is beneficial in protecting the heart from MI injury (35). These data suggest that RT can effectively improve glucose and cardiac fatty acid metabolism in MI, although the potential role of PPARα needs to be further elucidated. The induction of MI decreased PPARα expression in the MI group compared to the healthy group. In addition, decreased PPARα expression is associated with impaired glucose and fat metabolism in mitochondria. RT with 50% to 130% of body weight increased the expression of PPARα in the RT group compared to the MI group. In addition, PPARα mediates the transcriptional regulation of UCP 1 and UCP 3 genes of mitochondrial uncoupling proteins in BAT. UCP1 contains approximately 10% of the mitochondrial protein content and plays a thermogenic role by catalyzing proton leakage. In this experimental study, trained animals had high levels of Ucp1 and Ucp3 mRNA in BAT. The results showed that exercise increases body fat oxidation and reduces obesity (36). Mitochondrial content and respiratory capacity can be altered by exercise. Under standard conditions, mitochondrial respiration is associated with ATP production and is the major source of ATP. However, since the coupling of respiration to ADP phosphorylation is less than 100% energy efficient, respiration also releases heat. UCP1 plays a key role in the physiology of BAT as it enables brown fat cells to dissipate oxidation energy as heat. As previously published, our study shows an enhanced UCP1gene expression, indicating that exercise increases UCP1 to produce heat. Picard showed that increased expression of PGC-1α plays an essential role in the induction of UCP-1 expression by aerobic training (37). The researchers showed that aerobic training increased the PGC-1α and UCP-1 gene expression (13,14). Mice with MI experienced a decrease in UCP-1 expression. This decrease in UCP expression leads to decreased fat metabolism and calorific value in mitochondria. RT with 50% to 130% of body weight increased the expression of UCP-1 in the RT group compared to the MI group. In addition, the polyphenols in grape seed extract include flavonoids, gallic acid, and dimeric, monomeric, and polymeric proanthocyanidins. Proanthocyanidins are a group of polyphenolic compounds, which are widely distributed in the human diet. Proanthocyanidins are considered bioactive compounds because they affect physiological and cellular processes and therefore can have beneficial effects on health. In addition, proanthocyanidins have antioxidant and anti-inflammatory properties and can act as lipid-lowering agents (38). Studies show that grape seed extract has a high potential to eliminate free radicals and inhibit oxidative stress, and in MI and tissue regeneration, its inhibitory role against oxidative stress has been proven (39). The results of the present study indicated that consumption of grape seed and RT enhanced PGC1-α, UCP-1, and PPARα. In line with the present study, the consumption of grape seed increased mitochondrial biogenesis (40). PGC1 is the upstream signaling cascade of UCP-1 and PPARα genes in biogenesis and mitochondrial differentiation in the heart tissue. Induction of MI and activation of ROS disrupts the mitochondrial biogenesis signaling cascade. Stroke induction reduces the expression of PGC1 in heart tissue, and the decrease in PGC1 reduces the expression of UCP-1 and PPARα as downstream genes. Decreased UCP-1 and PPARα are associated with impaired fat metabolism and BAT in mitochondrial biogenesis. RT with 50 to 130% of body weight and consumption of grape seed as an antioxidant can increase the expression of PGC1-α, UCP-1, and PPARα in the heart tissue of MI models and thus improve mitochondrial function in damaged heart tissue. In addition, one of the limitations of the present study is the control of the received diet. Additionally, considering the role of PGC1-α, UCP-1, and PPARα isoforms in mitochondrial biogenesis and their importance in exercise, as well as failure to measure different isoforms, the use of different measurement methods such as Western blotting in future studies is recommended.

Conclusion

In conclusion, it can be stated that grape seed

nanoparticles along with exercise training, especially RT (regularly), are effective in mitochondrial biogenesis by positively regulating PGC1-α, UCP-1, and PPARα in the heart tissue. Therefore, grape seed nanoparticles and RT are recommended in case of MI.

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Authors' Contribution

EK carried out tests and collected the data. KJD, FT, SAH designed the study and analyzed the data. EK and KJD wrote and revised the manuscript. All authors approved the final version of the manuscript.

Conflict of Interests

The authors of the article have no conflict of interest to disclose.

Ethical Approval

The study protocol was approved by the Research Ethics Committee of Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran(IR.IAU.KHUISF.REC.1400.289).

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