Ilam University of Medical Sciences

Journal of Basic Research in Medical Sciences

Online ISSN: 2383-0972
Print ISSN: 2383-0506

Homepage: https://jbrms.medilam.ac.ir

The response of the coagulation system and fibrinolytic factors to exercise and *saffron*: A systematic review

Narges Laghaei[1], Mehran Ghahramani[2]✉

[1] Department of Exercise Physiology, Kermanshah Branch, Islamic Azad University, Kermanshah, Iran.
[2] Department of Exercise Physiology, Gilan-E-Gharb Branch, Islamic Azad University, Gilan-E-Gharb, Iran.

Article Info

Article type:
Systematic review

Article history:
Received: 6 September 2022
Revised: 25 September 2022
Accepted: 16 November 2022
Published online: 25 September 2023

✉Correspondence to:
Dr Mehran Ghahramani, Department of Exercise Physiology, Gilan-E-Gharb Branch, Islamic Azad University, Gilan-E-Gharb, Iran.
Tel: +98 918 8342771
Fax: +83 43228483
Email: mehran.physiology@gmail.com

ABSTRACT

Introduction: Blood coagulation is an important physiological process in maintaining homeostasis that causes blood to clot. The two main components of the hemostasis process are fibrinolysis and coagulation and influenced by many factors including physical activity and diet. This study aims to evaluate systematic review on the response of the coagulation system and Fibrolytic Factors to Exercise and *Saffron*.

Materials and Methods: Search for studies on the response of coagulation and fibrinolytic factors to exercise and *saffron* extract in the reputable databases Springer, Hindawi, PubMed, Google Scholar, Scopus, SID and ISC using the keyword Exercise Training and *Saffron*, platelet count (plt), fibrinogen level, relative activated thromboplastin time (PTT) and prothrombin time (PT) and plasminogen inhibitor-activating antigen (PAI-1), activating antigen tissue plasminogen (tPA), tPA activity and D-dimer were performed.

Results: In studies related to *saffron* extract, its beneficial effects were observed during long-term interventions. However, *saffron* consumption during the short-term had no effect on coagulation factors. Also, in short-term aerobic and resistance training studies, some studies reported a transient improvement in coagulation indices. Both long-term aerobic and resistance training help to maintain of coagulation homeostasis.

Conclusion: Exercise and *saffron* and its effective substances on the coagulation and fibrinolysis processes in healthy people and in some diseases (such as myocardial infarction and diabetes) have benefits.

Keywords: Homeostasis, Exercise, *Saffron*, Coagulation factors

How to cite this article: Laghaei N, Ghahramani M. The response of the coagulation system and fibrinolytic factors to exercise and *saffron*: A systematic review. J Bas Res Med Sci. 2023; 10(1):49-58.

Publisher: Ilam University of Medical Sciences

Introduction

Disturbance of the blood homeostasis system impairs coagulation and fibrinolytic factors, so the increased events of cardiovascular disease is due to changes in blood coagulation. Blood coagulation is an important physiological process in maintaining homeostasis and causes blood to clot. This process converts fibrinogen to fibrin from both internal and external pathways, activating coagulation factors and platelet aggregation. Blood coagulation stops bleeding as blood clots, and defects in this process are fatal in diseases such as hemophilia, although abnormal blood coagulation can lead to heart attack (myocardial infarction), cerebral ischemia, and embolism. The belief that thrombosis is effective in the increase of plaque and the onset of acute coronary syndromes has attracted the attention of the blood-homeostasis apparatus and the two indicators of coagulation and fibrinolysis as contrasting physiological processes in hemostasis and thrombosis (1). Fibrinolysis and coagulation are influenced by many factors such as gender, menopause, physical activity and diet. Inactivity is a risk factor for cardiovascular disease and physical activity may be a strong predictor of cardiovascular disease. Physical activity can potentially reduce mortality by changing inflammatory markers and coagulation. On the other hand, the intensity and type of exercise, time and level of physical fitness of the subjects cause different reactions in the blood coagulation system. It is believed that moderate-intensity aerobic exercise reduces fibrinogen levels, so that higher levels of exercise are associated with lower levels of fibrinogen. In addition to environmental and pharmacological interventions, the use of some medicinal plants can play important role in the prevention and control of cardiovascular disease. *Saffron (Crocus sativus L)* is the most expensive traditional spice in the world, which is used as a food seasoning. *Saffron* has many medicinal and therapeutic properties. The stigma of *saffron* contains crocin, picrocrocin and safranal, which cause the pharmacological effects of *saffron*. The beneficial effects of *saffron* and its effective ingredients have been reported in in vitro and in vivo studies on the blood coagulation system (2, 3). It is important to identify prevention strategies which can reduce the risk of cardiovascular disease. Based on the benefits of exercise on coagulation, it seems necessary to use appropriate training methods. On the other hand, it may be possible to reduce and treat cardiovascular disease through combined intervention of exercise with the administration of *saffron* extract. According to previous studies, our knowledge is insignificant. Based on the above, this study intends to investigate the response of the coagulation system and fibrinolytic factors to exercise and *saffron*.

Mechanism of Changes in Coagulation Factors and Fibrinolysis

Some mechanisms have been suggested by researchers as factors affecting coagulation factors and fibrinogen, such as increasing plasma volume and improving the cardiovascular system, increase the activity of the sympathetic nervous system, and changing the fat profile of the subjects. Prothrombin time (PT) is an indicator of the external pathway at the beginning of coagulation and its amount depends on the concentration of prothrombin. Factors affecting on PT include the type of exercise, age, sex and initial condition of the subjects. Also, the Partial thromboplastin time (PTT) is one of the indicators of coagulation, which is much slower than PT and its mechanism begins with vascular damage and its contact with the collagen of the damaged vessel wall. The mechanisms regulating plasma fibrinogen are not well understood, although alteration of inflammatory factors appears to be an effective in fibrinogen content. Fibrinogen is the factor affecting blood viscosity and flow, so that high levels of fibrinogen are associated with high probability of cardiovascular disorders and other vascular obstruction diseases such as clots. Fibrinogen is synthesized by the cells of the liver parenchyma, and the breakdown products and cytokines, especially interleukin-1, affect its release into the bloodstream. In the acute phase of platelet activation, the increase in platelet volume may be due to deformation of cytoplasmic megakaryocyte fragments (4).

Crocus sativus L

Saffron - *Crocus sativus L (C. sativus)* - is one of the most expensive plants in market. *C. sativus* is used as a natural and healthy additive in cooking. *Saffron* is cultivated all over the world, especially in Iran. Good quality *saffron* is provided by sunlight or in a greenhouse. Also, *saffron* is called red gold due to its high price and low production. *Saffron* consists of water, nitrogenous substances, sugars, soluble extract, volatile oil and fiber. Some sterols such as Campesterol, Stigmasterol, β-sitosterol, oleanolic, ursolic, Palmitoleic, palmitic and oleic acids have been identified. Volatile compounds of *saffron* include terpenes, terpene alcohols and their esters and non-volatile compounds include picrocrocin, crostin, crocin and flavonoids (quercetin and kaempferol). The most important compounds in *saffron* stigmas are: carotenoids (such as crocetin, crocin, alpha), carotene, lycopene, zeaxanthin), monoterpene aldehydes (such as safranal picrocrocin), monoterpenoids (such as crococantins), isoferons and flavonoids. Riboflavin (vitamin B2) and thiamine (vitamin B1) are two essential vitamins found in *saffron*. The amount of *saffron* riboflavin is from 56 to 138 micrograms per gram, which is the highest amount among all foods. Other carotenoids such as beta-carotene, lycopene and zeaxanthin and vitamins, especially riboflavin and thiamine are found in *saffron*. Crocin, crocetin, picrocrocin and safranal are the main active components of *saffron*. These compounds of *saffron* contribute to its high value in food and medicine. Carotenoids such as crocetin and crocin are the main color-forming compounds in *saffron*, and monoterpene aldehydes cause the bitter taste and odor of *saffron*. The content of these active compounds varies in different regions. Crocins, which are glycosides composed of carotenoid called crocetin and sugars, are responsible for the color of *saffron*. Picrocrocin, the glycoside of safranal, is the cause of its bitterness, but safranal provides the characteristic aroma of *saffron* (5).

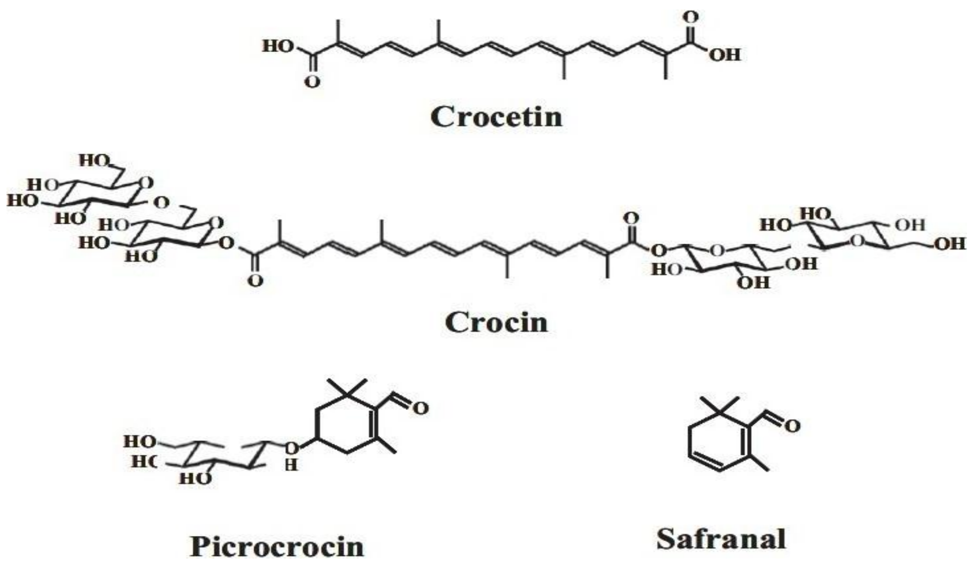

Figure 1. Chemical structure of crocin, crocetin, picrocrocin and safranal, the main active components of *saffron* (5).

Therapeutic Effects of *C. sativus L*

The beneficial properties of *saffron* in reducing fats, treating cancer, antioxidant, reducing inflammation and antidepressant have been considered (Figure 2). Also, because *saffron* has medicinal effects on the nervous system, it has been examined in clinical trials for depression, anxiety, Alzheimer's disease and other brain disorders. *Saffron* and its active components (crocin, crocetin and safranal) have inhibitory effects on free radicals. Given that radical inhibitory activity is strongly associated with anti-aging effect, it has been suggested that these extracts be used as a supplement in food and beverages. Also, Crocin is used to store sperm at very low temperatures due to its antioxidant effect. Daily prescription of *saffron* (100 mg) mixed with milk has improved the antioxidant status of patients with coronary heart disease (6). Crocin is associated with reduction of oxidative kidney damage in rats (7). Crocin and safranal protect the skeletal muscle in rats' leg against ischemic injury induced by occlusion of the femoral artery and vein (8). Crocin affects the storage and retrieval of information. Also, crocin administration before training of animal reduced scopolamine-induced animal performance deficiencies. The results of these studies confirm the cognitive enhancing effects of crocin, and also show that crocin has an effect on the mechanisms of recognition and spatial memory (9). Use of crocin has been shown to inhibit oxidative reactions in the cerebrovascular arteries and to destroy the microstructure of the prefrontal cortex endothelial cells by temporarily occluding the common carotid artery on both sides of the brain for 20 minutes. It has been suggested Crocin protect the brain against severe oxidative stress and is a therapeutic modality for local ischemia of the whole brain (10).

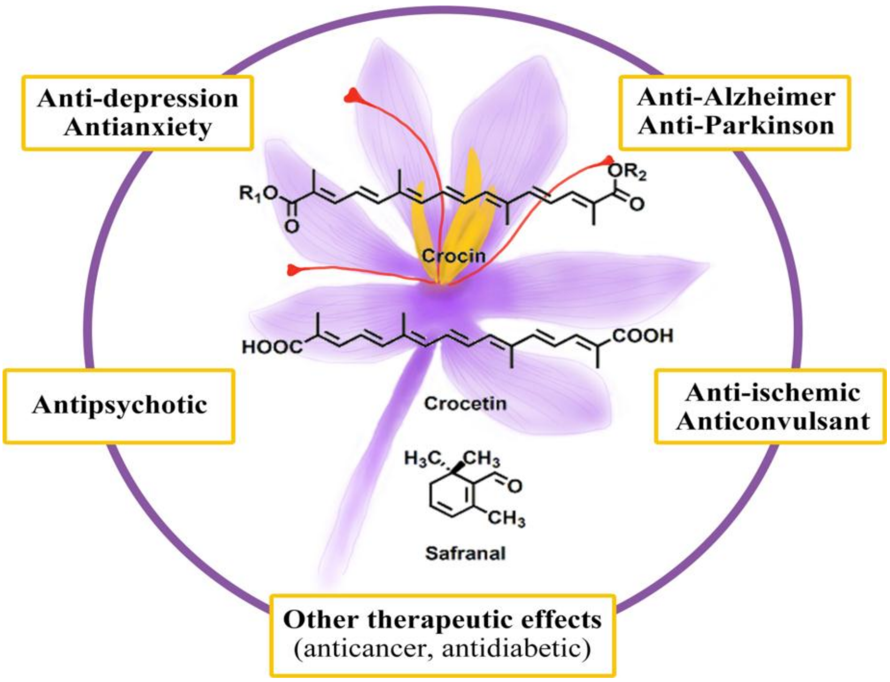

Figure 2. Therapeutic effects of *saffron* (5).

In general, in most studies has been reported antidepressant, antihypertensive effects, memory and learning enhancers, strong antioxidants, analgesics and anti-inflammatory, cardiac protector, hypoglycemic, anti-anxiety and hypnotic, anti-tumor, strengthening Sexual, anticonvulsant and cholesterol lowering of *saffron* components (5).

Cardiovascular Effects of *C. sativus L*

Cardiovascular diseases such as myocardial infarction, heart failure and stroke are known as the first cause of death worldwide. Inflammation is an influential factor in arteriosclerosis and the development of cardiovascular diseases. In the early stages of atherogenesis, inflammation in the lining of arteries increases proinflammatory cytokines, chemokines, and adhesion molecules. Oxidative stress is involved in the development of various types of CVD. Overproduction of reactive oxygen species (ROS) through the activation of nitric oxide synthase (NOS), xanthine oxidase, and nicotinamide adenine dinucleotide phosphate (NADPH) enzymes is associated with atherogenesis. In addition, due to its high oxidative metabolism and low antioxidant defense in heart tissue, this organ is exposed to oxidative damage. In addition to the antioxidant properties of *saffron*, its anti-inflammatory and anti-apoptotic capacity enhances the cardiac protective effects of *saffron*. The radical inhibitory properties of *saffron* play a role in its anti-inflammatory activities. This indicates that the anti-inflammatory effects of *saffron* compounds are due to its significant inhibitory effects against cyclooxygenase isoenzymes, COX-1 and COX-2 and the production of prostaglandin E2. In addition, the most important reasons for the anti-inflammatory properties of *saffron* are; Reduce endoplasmic reticulum stress signaling, inhibit the production of proinflammatory cytokines such as TNF-α, inhibit transcription factors such as NF-κB, which exacerbate chronic inflammation and suppress the expression of inflammatory genes by increasing histone diastylase activity. *Saffron* extract has a protective effect against cardiotoxicity in ischemic conditions. Crocin has been shown to protect platelets from oxidative stress-induced apoptosis and prevent platelet aggregation, thereby contributing to cardio protection (11).

Response of Coagulation Factors (platelet count (plt), fibrinogen level, PTT and PT and Fibrinolytic Agents (Plasminogen Inhibitor-activating Antigen (PAI-1), Activating Antigen Tissue Plasminogen (tPA), tPA Activity and D-dimer to One Session Aerobic and Resistance Exercise with *Saffron*

Acute exercise effects on coagulation and fibrinolysis as well as platelet aggregation and function (12). Most studies have examined plt, fibrinogen levels, PTT, and PT for evaluate coagulation factors. Also, Blood levels of PAI-1 antigen, tPA antigen, tPA activity and D-dimer level are measured to evaluate fibrinolytic activity. Therefore, the response of these indicators has been specifically investigated by researchers. Sub-maximal acute exercise with moderate duration and intensity on the treadmill leads to significant increase in fibrinogen levels (13). The results of Azimpour and Shahdadi (2016) showed that the PT and thromboplastin did not change significantly immediately after a session of resistance exercise, but the number of platelets immediately after training in isometric and eccentric exercise increased significantly compared to the control group (14). Also, Ghanbari and Tayebi (2011) showed that one session of eccentric resistance exercise had no significant effect on platelets and its indicators in inactive men (15). Increased PAI-1 concentration has been reported after acute sessions of aerobic exercise, although not significantly. However, these values decreased significantly 60 minutes after the end of exercise (16). So, it can be seen that exercise has temporary effect on coagulation status.

Effects of Long-term Aerobic Training and Saffron on plt, Fibrinogen Level, PTT and PT and Fibrinolytic Agents (PAI-1, tPA, tPA activity and D-dimer)

Increase of physical fitness as a result of exercise has significant effect on blood clotting time. A study on 722 men (mean age 54 years) found that people with higher fitness levels had shorter blood clotting times and increased blood clotting ability during maximal exercise. There was increase fibrinolytic activity in trained compared to untrained subjects after progressive training. The results showed that activating antigen Tissue plasminogen increased at rest and venous occlusion and plasminogen inhibitor decreased (17). Some studies have shown that aerobic training improves coagulation parameters and reduces fibrinogen levels¸ in healthy obese and overweight subjects (18, 19). In the study of El-Kader and Al-Jiffri. (2017) the obese group and aerobic training showed significant decrease in the mean values of PAI-1, while the mean values of the PTT, PT, PAI-1 and tPA significantly increased after 3 months of weight loss (18). However, the results of Podgórska *et al.* showed that regular physical activity modulates endothelial function but has no effect on platelets (20). Also, Bijeh *et al.* (2014) investigated the effect of aerobic exercise on platelets in sedentary middle-aged women. the platelet count increased significantly in the experimental group. These results indicate cardiac protection resulting from regular exercise in different populations (21). Gram *et al.* reported significant decrease in the potential of exogenous thrombin, PA and PAI-1 following daily endurance training in overweight men. Also, after 3 months of training, there was difference between groups for t-PA due to significant and lower values in the two training groups (22). Jahangard *et al.* Showed decrease in antigen and PAI-1 activity in sedentary healthy women after 10 sessions of sub-maximal aerobic cycling (3 times a week with 70% maximum heart rate for 25 minutes) (23). In addition, similar effects were observed in healthy men after 6 months of endurance training (3 times a week with 85% heart rate reserve for 45 minutes), which 37% reduced PAI-1 activity (24). Also, in a study, the effect of one week of treatment with 200 and 400 mg of *saffron* tablets on plasma fibrinogen and PT and PTT was evaluated in 60 healthy volunteers (age 20 - 50 years). No difference was shown between groups for plasma fibrinogen levels, PT and PTT. This study rejected the effect of *saffron* at doses of 200 and 400 mg for 1 week on the coagulation and anticoagulant system (25).

Effects of Long-term Resistance Training and *Saffron* on plt, Fibrinogen level, PTT and PT and Fibrinolytic Agents (PAI-1, tPA, tPA activity and D-dimer)

Some studies have reported that resistance training has better effect on reducing inflammation and improving cardiovascular risk factors than the aerobic training, and this may be due to reduction in fibrinogen. The results of some studies indicate that high-intensity resistance training reduces fibrinogen levels (26, 27). Amini *et al.* (2012) showed that changes Fibrinogen, PT, PTT, plt and D-dimer were significant in the post- training compared to the pre- training in the resistance training group (28). Amouzad *et al.* (2014) after 8 weeks of resistance training reported significant decrease in fibrinogen level, PT, PTT and platelet count and increase in fibrinolytic factor D-dimer in men (29). In study of Kohandelan *et al.* (2013) fibrinogen levels decreased significantly after four weeks of circular training in trained wrestlers (30). Also, Parsian *et al.* (2010) reported significant decrease in amount of fibrinogen in young untrained men following strength training with intensity of 70, 80 and 90% of maximum strength (31). On the other hand, the response of coagulation and fibrinolytic factors to the simultaneous intervention of exercise training and *saffron* has been limited. In this regard, it has been reported that *saffron* supplementation with resistance training reduces about 16% in healthy male subjects (32). More research should be done to determine the mechanism of changes in coagulation factors in response to resistance training and *saffron*.

Discussion

Long-term studies have shown a strong and obvious relationship between increased physical fitness with reduced risk of cardiovascular disease. Several studies have shown a positive effect towards antithrombotic state, especially at low plasma fibrinogen levels and improved fibrinolytic capacity with regular exercise. Studies show that there is no difference between the effects of aerobic and resistance training for improve fibrinogen and plasma viscosity, and both of these exercises are able to adjust the level of these factors after 3 months (33). It should be noted that most studies lacked a broad assessment of the two variables of homeostasis and fibrinolysis and thus provide incomplete information on the attribution of homeostasis to physical activity. According to Piccione et al. The different responses of coagulation factors to exercise indicate significant effect of exercise with age, sex, level of health and initial status of subjects on the response of the coagulation system. So, the response of the coagulation system depends on the intensity and duration of the exercise. High-intensity training is likely to shift the balance of the homeostatic system in favor of the coagulation system, and submaximal exercise training shifts this balance toward the fibrinolysis system (34). In association with the possibility of reduced fibrinogen synthesis from liver cells, we can point to the adaptation of the musculoskeletal system to exercise, which may reduce the activity of cytokines such as interleukin-1. Also, studies show that interleukin-1 responses decrease with increasing fitness level (35). The release of new platelets from the splenic vessel bed and the secretion of epinephrine after exercise have an effect on the increasing fitness level. The release of new platelets from the splenic vessel bed and the secretion of epinephrine after exercise have an effect on the number of platelets. This mechanism could explain the reason for the increase in platelet count in exercise in the above research. Also, fibrinolytic factor D-dimer increases after exercise. Fibrinogen level is directly related to the level of D-dimer fibrinolytic index, so that in activities where fibrinogen coagulation factor decreases, D-dimer fibrinolytic factor is likely to increase.

Conclusion

Reviewing the results of studies, it can be said that studies have shown the benefits of exercise and *saffron* and its effective component in healthy people at any age, especially in people who have a sedentary lifestyle. Also, the benefits of exercise and *saffron* on coagulation and fibrinolysis processes shown in patients, such as those suffering from myocardial infarction and diabetes. The findings of some studies are contradictory, which may be due to changes in training protocols or training programs used and the study population and homeostasis factors and lack of standardization in the analysis methods used for evaluate the factors of homeostasis.

Acknowledgments

We appreciate Islamic Azad University for assisting to complete this study.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Author Contribution

All the authors of this article participated in choosing the topic, searching, writing, submitting and revising.

Reference

1. Tanaka KA, Key NS, Levy JH. Blood coagulation: hemostasis and thrombin regulation. Anesth Analg. 2009;108(5):1433-46. doi: 10.1213/ane.0b013e31819bcc9c.
2. Razavi B, Imenshahidi M, Abnous K, Hosseinzadeh H. Cardiovascular effects of *saffron* and its active constituents: A review article. *Saffron* agronomy and technology. 2014;1(2):3-13. doi.org/10.1016/B978-0-12-818638-1.00030-7.
3. Kamalipour M, Akhondzadeh S. Cardiovascular effects of *saffron*: an evidence-based review. J Tehran Heart Cent. 2011;6(2):59-61.
4. Perneby C, Wallén NH, Hofman-Bang C, Tornvall P, Ivert T, Li N, et al. Effect of clopidogrel treatment on stress-induced platelet activation and myocardial ischemia in aspirin-treated patients with stable coronary artery disease. Thromb Haemost. 2007;98(6):1316-22. doi: 10.1160/th07-05-0323.
5. Srivastava R, Ahmed H, Dixit RK, Dharamveer, Saraf SA. Crocus sativus L.: A comprehensive review. Pharmacogn Rev. 2010;4(8):200-8. doi: 10.4103/0973-7847.70919.
6. Verma SK and Bordia A. Antioxidant property of *saffron* in man. Ind. J. Med. Sci. 1998; 52 (5): 204 - 7.
7. Hosseinzadeh H, Sadeghnia HR, Ziaee T and Danaee A. Protective effect of aqueous *saffron extract (Crocus sativus L.)* and crocin, its active constituent, on renal ischemia-reperfusion-induced oxidative damage in rats. J. Pharm. Pharmaceut. Sci. 2005; 8 (3): 387 - 93.
8. Hosseinzadeh H, Modaghegh MH, Saffari Z. Crocus sativus L. (Saffron) extract and its active constituents (crocin and safranal) on ischemia-reperfusion in rat skeletal muscle. Evid Based Complement Alternat Med. 2009;6(3):343-50. doi: 10.1093/ecam/nem125.
9. Pitsikas N, Zisopoulou S, Tarantilis PA, Kanakis CD, Polissiou MG, Sakellaridis N. Effects of the active constituents of Crocus sativus L., crocins on recognition and spatial rats' memory. Behav Brain Res. 2007 Nov 2;183(2):141-6. doi: 10.1016/j.bbr.2007.06.001.
10. Zheng YQ, Liu JX, Wang JN, Xu L. Effects of crocin on reperfusion-induced oxidative/nitrative injury to cerebral microvessels after global cerebral ischemia. Brain Res. 2007 Mar 23;1138:86-94. doi: 10.1016/j.brainres.2006.12.064.
11. Kemparaju K, Girish KS. Crocin, a dietary additive protects platelets from oxidative stress-induced apoptosis and inhibits platelet aggregation. Mol Cell Biochem. 2013;373(1-2):73-83. doi: 10.1007/s11010-012-1476-7
12. El-Sayed MS, Ali N, El-Sayed Ali Z. Haemorheology in exercise and training. Sports Med. 2005;35(8):649-70. doi: 10.2165/00007256-200535080-00001.
13. Eriksson-Berg M, Egberg N, Eksborg S, Schenck-Gustafsson K. Retained fibrinolytic response and no coagulation activation after acute physical exercise in middle-aged women with previous myocardial infarction. Thromb Res. 2002;105(6):481-6. doi: 10.1016/s0049-3848(02)00063-4.
14. Azimpour M, Shahdadi A. Response of Coagulation Indices to Two Types of Exercise of Eccentric and Isometric in Male Bodybuilding Athletes. Qom Univ Med Sci J . 2016; 10 (2) :13-21 doi: 20.1001.1.17357799.1395.10.2.5.7
15. Ghanbari A, Tayebi S. The effect of a single session eccentric resistance exercise on some blood coagulation factors of inactive male students. Sci J Iran Blood Transfus Organ. 2011;8(3):195-206

16. Antunes BM, Rossi FE, Oyama LM, Rosa-Neto JC, Lira FS. Exercise intensity and physical fitness modulate lipoproteins profile during acute aerobic exercise session. Sci Rep. 2020;10(1):4160. doi: 10.1038/s41598-020-61039-6.
17. El-Sayed MS, Davies B. A physical conditioning program does not alter fibrinogen concentration in young healthy subjects. Medicine and science in sports and exercise, Med Sci Sports Exerc. 1995;27(4):485-9.
18. El-Kader S, Al-Jiffri OH. Coagulation, Fibrinolytic and Cytokines Parameters Response to Weight Reduction in Obese Subjects. EUR J GEN MED. 2017; 5:179-185. doi:10.29333/ejgm/81730
19. Rashid Lamar A, Hashemi Javaheri AA, Jafari M. The effect of regular aerobic training with weight loss on concentrations of fibrinogen and resistin in healthy and overweight men. Tehran Univ Med J. 2011;68(12):710-717.
20. Podgórska K, Derkacz A, Szahidewicz-Krupska E, Jasiczek J, Dobrowolski P, Radziwon-Balicka A, et al. Effect of Regular Aerobic Activity in Young Healthy Athletes on Profile of Endothelial Function and Platelet Activity. Biomed Res Int. 2017;2017:8715909. doi: 10.1155/2017/8715909.
21. Bijeh Nahid, Sadat Jamali, Fahimeh Zabihi, Alireza Hejazi Keyvan. The effect of aerobic exercise with 55 to 65% of stored heart rate on C and S proteins and platelets in inactive middle-aged women Quarterly Journal of Evidence-Based Care. 2014; 11(4):57-64.
22. Gram AS, Bladbjerg EM, Skov J, Ploug T, Sjödin A, Rosenkilde M, Madsen DE, Stallknecht BM. Three months of strictly controlled daily endurance exercise reduces thrombin generation and fibrinolytic risk markers in younger moderately overweight men. Eur J Appl Physiol. 2015;115(6):1331-8. doi: 10.1007/s00421-015-3106-z.
23. Jahangard T, Torkaman G, Ghoosheh B, Hedayati M, Dibaj A. The effect of short-term aerobic training on coagulation and fibrinolytic factors in sedentary healthy postmenopausal women. Maturitas. 2009;64(4):223-7. doi: 10.1016/j.maturitas.2009.09.003.
24. Chandler WL, Schwartz RS, Stratton JR, Vitiello MV. Effects of endurance training on the circadian rhythm of fibrinolysis in men and women. Med Sci Sports Exerc. 1996;28(6):647-55. doi: 10.1097/00005768-199606000-00001.
25. Ayatollahi H, Javan AO, Khajedaluee M, Shahroodian M, Hosseinzadeh H. Effect of *Crocus sativus L.* (*saffron*) on coagulation and anticoagulation systems in healthy volunteers. Phytother Res. 2014;28(4):539-43. doi: 10.1002/ptr.5021.
26. Lowe G, Rumley A, Norrie J, Ford I, Shepherd J, Cobbe S, et al. Blood rheology, cardiovascular risk factors, and cardiovascular disease: The West of Scotland Coronary Prevention Study. Thromb Haemost. 2000;84(4):553-8.
27. Machado M, Koch AJ, Willardson JM, Pereira LS, Cardoso MI, Motta MK, Pereira R, Monteiro AN. Effect of varying rest intervals between sets of assistance exercises on creatine kinase and lactate dehydrogenase responses. J Strength Cond Res. 2011;25(5):1339-45. doi: 10.1519/JSC.0b013e3181d680d6.
28. Amini A, Kordi M R, Gaini A A, Ahmadi A, Ayoubian H, Lahoorpour F. The effects of aerobic exercises on coagulation and fibrinolytic factors in inactive aged men. SJKU. 2011;15 (4) :25-32
29. Amouzad Mahdirejei H, Aghababaeian A, Mirsaiedii M, Fadaei Reyhan Abadei S, Abbaspour Seyedii A. Effect of 8 weeks of resistance training on hemostasis indeces and lipid profile in

adult men. J Gorgan Univ Med Sci. 2014; 16 (2) :21-28

30. Kohandelan shahrenoei Y, Rashidlamir A, Ebrahimi atri A. Effect of 4 Weeks Circuit Training on Plasma Fibrinogen in Wrestlers. JRUMS. 2014;12(12):1003-1014 doi: 20.1001.1.17353165.1392.12.12.2.8
31. Parsian Heshmatollah, Seyedlangi Seyedeh Zahra, Ghazalian Farshad, Soheili Shahram, Khanali Fataneh, Shirvani Hossein. The effect of 12 weeks of endurance training on serum C reactive protein and plasma fibrinogen as predictors of cardiovascular disease. sjimu. 2010; 18 (3) :1-9
32. Ghanbari–Niaki A, Saeidi A, Aliakbari-Beydokhti M, Ardeshiri S, Kolahdouzi S, Chaichi MJ, et al. Effects of Circuit Resistance Training with *Crocus Sativus (Saffron)* Supplementation on Plasma Viscosity and Fibrinogen. Ann Appl Sport Sci. 2015; 3 (2) :1-10 doi: 10.18869/acadpub.aassjournal.3.2.1
33. Asaadi V, Azizbeigi K , Khosravi N, Haghnazari N. The Effect of Exercise Training on Fibrinogen and Viscosity of Plasma: Comparing Endurance Continuous, Circuit Resistance and High Intensity Interval Trainings in Young Obese Men. J Clin Res Paramed Sci. Online ahead of Print ; 2019;8(2):e97880 doi: 10.5812/jcrps.97880
34. Piccione G, Fazio F, Giudice E, Grasso F, Caola G. Exercise-induced Changes in the Clotting Times and Fibrinolytic Activity during Official 1600- and 2 000-Meters Trot Races in the Standardbred Horses. Acta Veterinaria Brno 2005; 74(4): 509-14. doi: 10.3390/ani11020447
35. Duncan BB, Schmidt MI, Chambless LE, Folsom AR, Carpenter M, Heiss G. Fibrinogen, other putative markers of inflammation, and weight gain in middle-aged adults--the ARIC study. Atherosclerosis Risk in Communities. Obes Res. 2000;8(4):279-86. doi: 10.1038/oby.2000.33.