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REVIEW ARTICLE

The Combined Effects of Saffron (*Crocus sativus* L.) and Exercise on Body Health: A Review Study

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KEYWORDS

Saffron;
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ABSTRACT: Researchers have always been looking for a suitable combination of nutrition and physical activities to prevent and treat diseases, increase well-being and improve physical performance. Saffron (*Crocus sativus* L.) is a valuable plant in traditional medicine. The properties of this plant are attributed to its effective and bioactive compounds such as crocins, crostin, picrocrocin, safranal, and glycosides. This study provides a review of the effects associated with saffron consumption and its effective compounds along with various sports exercises on body health. Scientifis database such as Scopus, PubMed, Sciencedirect and Scientific Information Database (SID) were used to search for articles, and finally 106 articles were selected based on relevance to the topic and novelty. Saffron has a positive effect on the secretion of male sex hormones and IGF-1, causes an increase in muscle contraction during stimulation and increases the number, mobility and ability of sperm. It also strengthens the female reproductive system, such as reducing the symptoms of dysmenorrhea, premenstrual syndrome, polycystic ovary syndrome, menopause, and sexual dysfunction by regulation of hormones, folliculogenesis, ovulation, and protection of the ovary and uterus. Saffron supplement and exercise are known as two effective factors in preventing complications of type 2 diabetes, reducing appetite, improving glycemic indices, fasting glucose control and lipid profile. Saffron has beneficial effects on oxidative stress, inflammatory reactions, apoptotic indices, muscle strength, body mass index, metabolism regulation, leptin serum levels, blood pressure, lung function, liver, cardiovascular, digestive, chronic renal, neurological diseases, metabolic syndrome and cancer have a preventive and therapeutic role.

INTRODUCTION

Physical activity and exercise stimulate the generation of free radicals and make an increase in reactive oxygen species (ROS) because of the enhancement in the process of cell oxidation, which in the long run leads to tissue destruction. Oxidative stress occurs when there is an imbalance between the efficiency of the antioxidant defense system and the generation of free radicals. For this reason, athletes and active people need to take antioxidant supplements. In recent years, the use of food and natural supplements to improve strength, performance and hypertrophy has become popular among athletes. Saffron extract, tablet or powder is used as a supplement along with various sports exercises. The aim of this study is the review of the effects of saffron and its effective compounds along with various exercises on body health.

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MATERIALS AND METHODS

In this review research, Scientific Information Database (SID), Scopus, PubMed and ScienceDirect scientific databases were used and finally 106 articles were selected. 33 % of articles were retrieved from SID and 77 % of articles were retrieved from international databases. Three key words including saffron, crocin and exercise in Farsi and English were searched. The criteria for including articles in the study were their novelty and relevance to the subject under study, preferably involving human samples. In total, 88 of the articles (about 85 %) are from 2018 to 2024 and 16 articles (about 15 %) are from 2004 to 2017.

RESULTS

Saffron

Saffron (Crocus sativus L.) is a sterile and highly valued male triploid plant that has a warm nature and is used in traditional medicine as a pain reliever, expectorant, sexual stimulant, diuretic, and euphoric. The stigma is the most important part of the saffron flower from which edible saffron is obtained. The color of the stigma depends on the amount of carotenoid and lycopene present in it [1]. Saffron contains more than 150 compounds, including lipophilic and hydrophilic compounds such as protein, amino acids, Minerals, vitamins (notably riboflavin and thiamine), along with pigments like crocin, carotene, anthocyanin, flavonoids, lycopene, starch and other chemical compounds [2]. Crocin, crostin and monoterpene aldehyde compounds such as picrocrocin and safranal are among the most important carotenoid active metabolites of saffron [3]. Consuming saffron along with physical activity improves body systems and regulates metabolism. The reason for these effects is the correlation and synergism of saffron metabolites, especially crostin and crocin, and increasing the strength of the body's defense-antioxidant system [4]. Crocin, as the main pigment of saffron, has antioxidant, anticancer and memory enhancing properties [5]. By inhibiting the activity of ROS, crocin and crocetin help prevent the oxidation of fatty acids within the cell membrane and increase the motility and improve the sperm morphology and sexual performance of men [6]. Saffron demonstrates its anti-inflammatory and antioxidant specification by decreasing levels of cytokines. Some properties of saffron plant are presented in Figure 1.

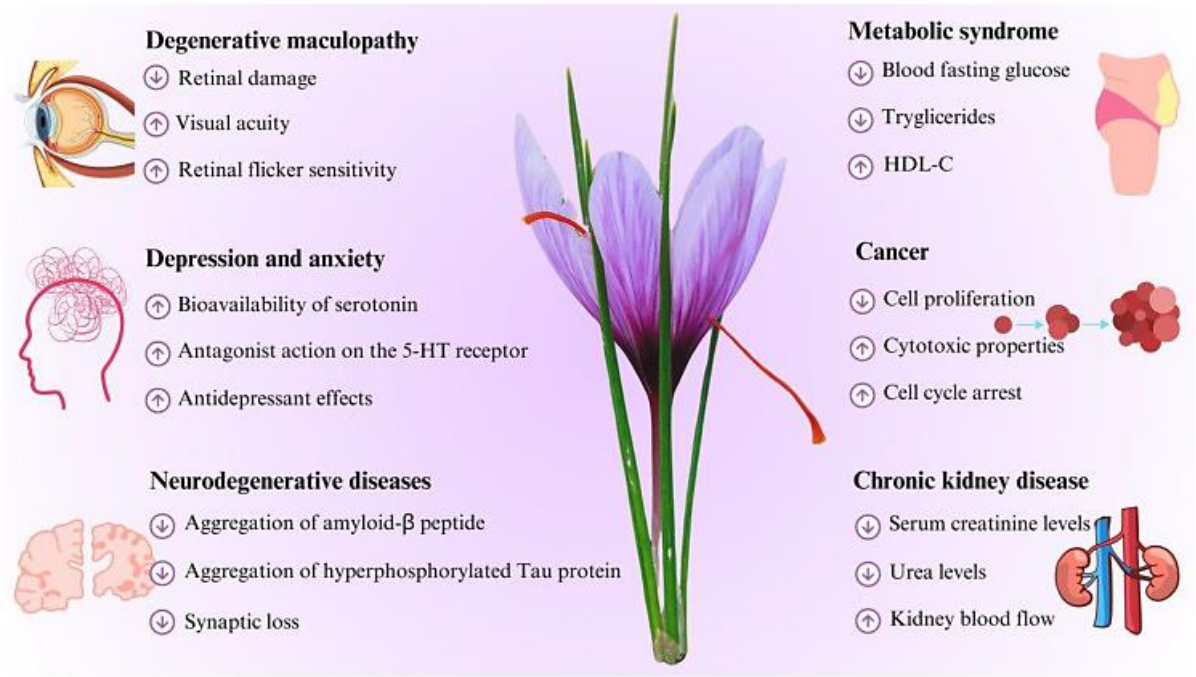

Figure 1. The beneficial effects of saffron in medicine. Abbreviations including: 5-HT: serotonin, HDL-C: high-density lipoprotein-cholesterol, ↑: increase, ↓: decrease [7]

Consumption of saffron with resistance exercises

Resistance exercises with saffron supplement have many interactive effects on improving body health, which

related studies are presented in Table 1.

Consumption of saffron along with aerobic exercises

Research related to the effect of aerobic exercises with saffron extract or supplement on body health can be seen in Table 2.

Consumption of saffron along with endurance exercises

Studies related to the effect of endurance exercises, endurance training and swimming with saffron extract or supplement on body health can be seen in Table 3.

Consumption of saffron along with interval training

Studies related to the effect of interval training with saffron extract or supplement on body health can be seen in Table 4.

Table 1. Effects of resistance training with saffron extract or supplement on body health

Exercise	Experiment	Result	Ref.
Resistance	The effect of resistance training and aqueous saffron extract (25 mg kg^{-1} daily) on testosterone, LH (Luteinizing hormone) and FSH (Follicle-Stimulating Hormone) five days a week during six weeks in rats	1. The levels of testosterone, FSH, and LH in the extract combined with exercise group were notably higher compared to the control group. 2. Levels of FSH and LH in the extract + exercise group are higher compared to the extract group. 3. FSH levels in the extract combined with exercise group are higher compared to the exercise group	[8]
Resistance	The simultaneous effect of crocin with two doses 12.5 and 25 mg kg^{-1} daily and resistance training including climbing a 1-meter ladder consisting of 26 steps and an 85-degree incline, 3 sessions/week for 8 weeks on pituitary-gonadal (PG) axis hormones in male rats after nanderlone induction (10 mg kg^{-1} deep injection in gluteal muscle)	1. Consumption of crocin and resistance training each alone causes a decrease in LH and FSH. 2. The combination of crocin + resistance training causes a significant increase in testosterone and dihydrotestosterone. 3. Increase in the secretory function of the testis in crocin + exercise group and independent of changes in pituitary hormones	[9]
Resistance	The effect of the combination of crocin (12.5 and 25 mg kg^{-1} daily) and resistance training (3 sessions of climbing a ladder/week) for 8 weeks on liver damage in rats poisoned with nanderlone (10 mg kg^{-1})	1. Crocin + exercise causes a significant decrease in Alanine Transaminase (ALT), Gamma-Glutamyl Transferase (GGT), albumin and total protein and no significant effect on Alkaline Phosphatase (ALP) and Aspartate Aminotransferase (AST). 2. The combination of crocin + exercise prevents the increase of some enzymatic and non-enzymatic markers of hepatocyte damage caused by nanderlone	[10]
Resistance	The effect of resistance training (three sessions/week) with and without consumption of crocin (12.5 and 25 mg kg^{-1}daily) for two months on Catalase (CAT) and Glutathione Peroxidase (GPx) in heart tissue of rats poisoned with nandrolone.	1. Dose of crocin 25, exercise + crocin-12.5 and exercise + crocin-25 cause a significant decrease in CAT activity. 2. Exercise + crocin-12.5 and exercise + crocin-25 has a more significant effect on the reduction of CAT than the exercise group. 3. Crocin-12.5 causes a significant elevated GPx activity.	[11]
Resistance	The combined effect of saffron supplement (one 150 mg tablet daily) and resistance training 4 sessions/week with 60-70% intensity of one maximum repetition for six weeks on the levels of IGF-1 (Insulin-like Growth Factor-1), testosterone and growth hormone in young men	1. Significant increase in testosterone, growth hormone and IGF-1 levels in control (exercise) and experimental (exercise + saffron supplement) groups after six weeks. 2. Significant enhance in testosterone levels was observed in the experimental group, while no significant changes were detected in the levels of growth hormone and IGF-1 when compared to the control group.	[12]
Resistance	The effect of saffron (one 150 mg tablet daily) along with resistance training (4 sessions/week with 60-70% of a maximum repetition) on leptin levels, body composition and muscle strength of young non-athletes men	1. Significant difference between exercise group + saffron supplement consumption and exercise group in serum leptin level, body fat percentage and fat-free mass. 2. No significant difference in upper body and lower body strength between two groups	[13]
Resistance	The interactive effect of saffron supplement (one 150 mg tablet per day) and resistance training (six weeks of selected protocol with 60-70% RM1) on the sex hormone levels in young men	1. Significantly increase in testosterone, LH and FSH levels in exercise and exercise+supplement groups. 2. Significant difference between the levels of testosterone, LH and FSH in exercise and exercise + supplement. 3. Saffron supplement + resistance exercise increased more testosterone, FSH and LH hormones	[14]
Circular	Effect of circular resistance training (including 12 stations of 30 seconds with 40% intensity, a maximum	1. No significant difference was observed in cortisol levels between groups. 2. A significant increase in testosterone	[15]

resistance	repetition of five sessions/week) along with different parts of saffron (stigma and petals) supplements (500 mg daily in two meals in the morning and immediately after training) for a period of 2 weeks on plasma testosterone and cortisol	levels in all test groups and a significant reduction in cortisol levels just in the saffron stigma+exercise group. 3. A significant enhancement in the ratio of testosterone to cortisol in the saffron stigma+exercise and saffron petals +exercise groups and no significant changes in other groups. 4. Circular resistance training + saffron supplement improves hormones more.	
Resistance	The Effect of resistance training including 3 sessions/week and daily consumption of crocin with two doses (12.5 and 25 mg kg^{-1}) for eight weeks on GPx and catalase in kidney tissue of rats poisoned with nandrolone	1. All the doses and their combination with exercise decrease CAT. 2. The group of exercise and exercise + crocin 25 caused a significant increase in GPx. 3. The training group + crocin 25 has a greater effect on increasing GPx than the training group + crocin 12.5.	[16]
Resistance + Aerobics	Effect of aerobic exercise (intensity 50-70% of maximum heart rate) and resistance exercise (intensity 65-70% of one repetition maximum) combined with daily consumption of saffron supplement (3 mg/kg) for eight weeks on GPx and Malondialdehyde (MDA) in men type 2 diabetes	1. Before the intervention: a significant reduction in the resting of MDA level in the placebo and aerobic exercise+ saffron groups. 2. After the intervention: a significant enhancement in GPx levels in the groups of aerobic exercise + saffron, resistance exercise and resistance exercise + saffron.	[17]
Resistance	The effects of saffron (200 mg daily) along with resistance training for 12 weeks on reducing hypertension in elderly men suffering from high blood pressure	Resistance training combined with saffron consumption helps improve blood pressure in older adults with hypertension by influencing the factors that contribute to changes in vascular endothelial resistance.	[18]
Resistance	Effect of resistance training (4 times/week, 3 sets using 60-70%, maximum 1 repetition) and saffron supplement (150 mg tablet, daily) for six weeks on indicators involved in the level of depression and happiness in untrained young men	1. Resistance training + saffron supplement improves the concentration of 2-Arachidonoylglycerol (2-AG), dopamine, N-Arachidonoyl Ethanolamine (AEA), beta-endorphin and serotonin. 2. Addition of saffron supplement to chronic resistance training resulted in greater improvement in happiness level than resistance training alone.	[19]

Table 2. Effects of aerobic exercise with saffron extract or supplement on body health.

Exercise	Experiment	Result	Ref.
Aerobics	Effect of saffron aqueous extract (25 mg kg^{-1} daily) and aerobic training (running on a treadmill at a speed of 12 m/min, with zero incline for 30 minutes durind two weeks, five consecutive sessions/week) on antioxidant concentration. Liver non-enzymes in streptotocin-treated diabetic rats	1. A significant difference was observed in the MDA and GPx levels and total antioxidant capacity between groups. 2. Significant reduction of MDA concentration in saffron + exercise, exercise + diabetic and saffron+diabetes compared to diabetic and healthy groups. 3. The lowest increase of GPx concentration in saffron + exercise and the highest increase in diabetic control. 4. The greatest increase of the total antioxidant capacity was in saffron + exercise group and the least enhanceent was in the diabetic group	[20]
Aerobics	Effect of the combination of saffron aqueous extract and aerobic exercise (two weeks) on some hepatic oxidative stress indicators in diabetic male rats	1. Exercise + saffron causes a decrease in GPx and an enhancement in superoxide dismutase (SOD) compared to the diabetic control group. 2. The aerobic exercise and saffron consumption causes no significant change in liver CAT activity	[21]
Aerobics	Effect of saffron supplement (100 mg) on the activity of antioxidant enzymes during a session of extroverted activity (running at intensity of 70% of the maximum oxygen consumption on a treadmill with a negative slope of 10% for 45 minutes) in active men for 14 days	1. Saffron supplementation significantly increased SOD activity. 2. In the placebo group compared to the saffron and vitamin C (1000 mg capsule) groups, an extrovert activity showed a clear increase in the concentration of malondialdehyde, but there was no significant change in the activity of the catalase enzyme.	[22]
Aerobics	Effect of saffron consumption (one 30 mg capsule of saffron head powder daily) and periodic aerobic training (for three months) on spirometric, physiological and blood pressure indicators of non-athlete boys	1. Saffron + aerobic exercise increases lung volumes and capacities and decreases systolic and diastolic blood pressure, heart rate and breathing rate in one minute. 2. No significant difference was observed between the exercise + saffron and saffron groups in cases of high-pressure vital capacity, maximum expiratory flow, high-pressure expiratory volume in the first second, high-pressure inspiratory volume in the first second. 3. No significant difference was observed between the exercise + saffron and exercise + placebo groups at maximum voluntary ventilation and peak inspiratory flow	[23]
Aerobics in water	The simultaneous effect of six weeks of aerobic training in water and crocin supplementation on cardiomyocyte caspase 3 gene expression in male rats poisoned with hydrogen peroxide or hydrogen peroxide (H2O2) by subcutaneous injection 30 minutes before training	1. Induction of hydrogen peroxide causes a significant enhancement in the caspase 3 gene expression. 2. Six weeks of water activity lead to a significant reduction in caspase 3 gene expression in myocardial tissue. 3. Six weeks of activity in water and induction of crocin have a synergistic effect in reducing caspase 3.	[24]
Aerobics	Adaptation of irisin serum levels, lipid profile including Triglyceride (TG), Low-Density Lipoprotein (LDL-C), Total Cholesterol (TC), and insulin resistance index or	1. In the post-test phase, reduction of TC, TG, LDL-C, HOMA-IR and body fat percentage were observed in the saffron groups and non-significant change in the placebo	[25]

	HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) to an aerobic training period (with an 60-75% intensity of the maximum heart rate) and the oral consumption of saffron (400 mg daily) for two months and its persistence after that in type 2 diabetic obese women	group. 2. Increase in HDL-C (High-Density Lipoprotein-Cholesterol) and irisin in the groups receiving saffron and non-significant change in the placebo group). 3. A significant difference in weight and BMI (Body Mass Index) wae observed between the groups and was reduced in the saffron, exercise + saffron and exercise + placebo groups.	
Aerobics	Effect of eight weeks of saffron supplementation (400 mg of sorghum powder daily) and aerobic exercise with an 60-75% intensity of maximum heart rate, three sessions a week, on changes in blood pressure, pulmonary function such as VO2max (Maximal Oxygen Consumption), PEF (Peak Expiratory Flow), FVC (Forced Vital Capacity), FEV1 (Forced Expiratory Volume in One Second), FVC/FEV1, MVV (Maximal Voluntary Ventilation) and spirometric indices of type 2 diabetic obese women	1. A significant enhancement in pulmonary function and a significant decrease in systolic blood pressure and anthropometric indices in all three groups of saffron alone, placebo + aerobic exercise and saffron + aerobic exercise and a significant difference in the above variables between the saffron group + exercise with saffron alone and placebo + groups exercise. 2. The combination of aerobic exercise with saffron consumption causes a more effective improvement in increasing lung volumes and capacities as well as lowering blood pressure compared to the effect of each one alone.	[26]
Aerobics	Effects of six weeks of aerobic training in water (5 days/week, 60 minutes each time) and crocin supplement (12.5 mmol/kg by intraperitoneal injection) on the expression of BAX (Bcl-2-Associated Protein X) and BCL-2 (B-Cell Lymphoma 2) and genes in cardiomyocytes in male rats treated with hydrogen peroxide (1 mmol/kg)	1. Induction of H2O2 causes a significant enhancement in BAX expression. 2. Activity in water leads to a decrease in BCL-2 expression and crocin causes a significant reductionn in BAX expression. 3. The interaction between crocin induction activities and H2O2 induction has a reducing effect on BAX expression and an increasing effect on BCL-2 expression, which indicates the protective effect of regular activity in reducing cardiomyocyte apoptosis. 3. Regular activity in water and consumption of crocin separately leads to a significant reduction in the expression of BAX and a significant enhancement in the expression of BCL-2. 4. The combination of regular activity and crocin has a synergistic and synergistic effect in inhibiting the expression of BAX and increasing the expression of BCL-2 in rats poisoned with H2O2	[27]
Aerobics	The combined effect of aerobic training (8 weeks of endurance training) with extract of saffron (100 mg) on regulatory factors of soleus muscle apoptosis in male rats after aerobic exercise includes four groups: G1 (placebo, no training), G2 (no training) + saffron extract), G3 (exercise) and G4 (exercise + saffron extract)	1. Before implantation, bcl-2 protein expression and Bax/bcl-2 ratio in G3 and G4 groups were significantly higher and lower than other groups, respectively. 2. Subsequently, the expression of bcl-2 and Bax proteins in the soleus muscle of all groups except G4 showed a significant increase and decrease, respectively, and the ratio of Bax/bcl-2 enhanced. 3. Aerobic training and saffron prevent the increase in Bax and Bax/bcl-2 protein expression following a bout of restorative activity.	[28]
Aerobics	The effect of a therapeutic exercise program (three sessions/week for 8 weeks, aerobic exercise with an intensity of 60-75% of the maximum heart rate) and oral consumption of saffron (daily 400 mg of saffron head powder) on the levels of TNF-α (Tumor Necrosis Factor Alpha), IL-6 (Interleukin 6) and control Glycemic in obese type diabetic women	1. Significant decreasing of IL-6, TNF-α, blood glucose and HbA1c (Hemoglobin A1c) in the post-test stage in comparison with pre-test groups. 2. There was a significant difference between the saffron + training, training + placebo, saffron and placebo groups in the post-test stage. 3. There is a significant difference in BMI and weight between the saffron + training and other groups.	[29]
Aerobics	Meta-analysis of the efficacy of saffron medicinal plant on enzyme markers of antioxidant defense in aerobic exercise	1. Significant increase of antioxidant enzymes in the supplement and supplement + exercise in comparison with the control group. 2. The estimate of antioxidant defense through catalase enzyme in the supplement group was significant in comparison with the control group, but the supplement + exercise group was not significant in comparison with the control group. 3. Estimation of antioxidant defense through superoxide dismutase in the supplement and supplement+exercise was significant in comparison with the control group. The most effective of saffron was in the superoxide dismutase enzyme and this effectiveness was not confirmed on the amount of catalase.	[30]
Aerobics	Investigating the effects of aerobic exercise, running (60 minutes) at an intensity of 40-60% of maximum speed, five days a week and consumption of 10 mg kg^{-1} crocin for 8 weeks on oxidative stress caused by 2 mg kg^{-1} per day doxorubicin (doxorubicin by increasing oxidative stress destroys tumor and healthy cells, especially heart tissue) by intraperitoneal injection) in the cardiac tissue of rats	1. Doxorubicin injection significantly increased the level of malondialdehyde in heart tissue and significantly decreased the activity of catalase and superoxide dismutase. 2. Aerobic exercise, consumption of crocin and the combination of crocin + aerobic exercise significantly significantly reduced the levels of malondialdehyde in rats treated with doxorubicin and increased the activity of catalase and SOD enzymes in heart tissue.	[31]
Aerobics	Antioxidant effects of aerobic exercise and consumption of crocin (10 and 50 mg per day) on doxorubicin-induced testicular toxicity in rats	The increase in the level of antioxidants in the exercise + crocin group is dose-dependent. The oxidative stress was reduced in both the crocin and exercise groups, but its effect was dose-dependent in the crocin group.	[32]
Aerobics	Effect of aerobic training (five days a week for 8 weeks) and daily consumption of saffron extract (100 mg) on TNF-α and C-reactive protein and in the serum of mice	1. After supplementation, the levels of C-reactive and TNF-α in the serum of all groups increased significantly. 2. Aerobic exercise alone and combined with the saffron extract leads to	[33]

	following acute aerobic activity	the reduction of inflammatory reactions following a burst of residual activity.	
Aerobics	The effect of aerobic exercise (the first session includes 20 minutes of activity, 40-45% intensity of the maximum heart rate, which was added 5 minutes to the duration every week and 5% to the intensity of the activity every two weeks) and the oral consumption of Sargol Iranian saffron powder (200 ml daily) on omentin-1 and nesfatin-1 in type 2 diabetic fat women	1. There is a significant difference between pre-test and post-test omentin-1 and nesfatin-1 in all groups except the placebo group. 2. Significant difference was obseved in omentin-1 and nesfatin-1 between all groups receiving saffron in the post-test stage with the placebo group. 3. More increase of omentin-1 and nesfatin-1 was observed by saffron extract combined with exercise.	[34]
Aerobics	The effect of 9 weeks of aerobic training (including 15 minutes of warm-up, 20 minutes of activity with an intensity of 50 to 55% of the maximum heart rate, with 5 minutes added to the training time every week and 5% to the activity intensity every two weeks) with and without saffron supplementation (daily 200 mg of powder) on liver enzyme AST and HOMA-IR in type 2 diabetes obese women	1. Aerobic exercise simultaneously with saffron supplementation after 9 weeks had a significant effect on reducing AST and HOMA-IR indices in fat women with type 2 diabetes. 2. Aerobic exercise and saffron supplement alone can reduce AST liver enzyme and insulin resistance. Combination of these two factors has a more effective role in reducing these indicators.	[35]
Aerobics	Effect of aerobic exercises (eight weeks) and saffron extract on the expression of Caspase-3, Bcl-2 and Bax genes (by Real Time PCR method) in the hippocampal tissue of male Alzheimer's rats (with injection of amyloid beta 42-1 in the hippocampus)	1. Bax gene expression was significantly decreased in the intervention groups in comparison with the AD group. 2. Significant reduction of caspase 3 in AD group + aerobic exercise and AD group + aerobic exercise + extract extract in comparison with AD group. 3. Significant increase in Bcl-2 gene expression in AD group + aerobic exercise and AD group + aerobic exercise + extract in comparison with AD group.	[36]
Aerobics	Interactive effects of crocin and aerobic training (3 sessions/week with an 60-70% intensity VO2max) and supplementation (50 mg kg^{-1} per day) for eight weeks on some markers of kidney apoptosis in rats exposed to doxorubicin (2 mg kg^{-1} per day)	1. Bax/BCL2 and Bax values in doxorubicin + exercise + crocin and doxorubicin + crocin groups are less than doxorubicin and BCL2 level are more than doxorubicin group. 2. The values of Bax/BCL2 and Bax in the doxorubicin + exercise group are lower than in the doxorubicin group. 3. The values of Bax/BCL2 and Bax in the doxorubicin + exercise + crocin group are lower and the BCL2 values in this group are higher than the doxorubicin + crocin group. 4. The values of BCL2 in the doxorubicin + exercise + crocin group are more and Bax/BCL2 are less than the doxorubicin + exercise group.	[37]
Aerobics in water	Effect of aerobic water exercise and consumption of crocin (12.5 mg by subcutaneous injection) for 6 weeks on the prevention of cardiac muscle tissue cell death	Aerobic training in water, consumption of crocin supplement and the combination of both decreased the genes expression of the internal apoptosis pathway in male rats.	[38]
Aerobics	The effect of 8 weeks of aerobic training, (three sessions/week with 60-75% HRmax (Maximum Heart Rate) and saffron powder supplementation (400 mg daily) on inflammation and metabolism in middle-aged obese women with type 2 diabetes	1. Aerobic exercise, saffron supplement and their combination had an effect on body mass index, insulin resistance index and serum adiponectin, insulin, IL-6, HDL-C, triglyceride and cholesterol. 2. Body fat percentage, body weight and serum levels of TNF-α, glucose, irisin, resistin and LDL-C showed significant changes only in the saffron + exercise group. 3. Saffron supplement + aerobic exercise can improve metabolism, inflammation, lipid profile and glycemic status in type 2 diabetes and the changes are stable up to two weeks of non-exercise.	[39]
Aerobics	Effect of aerobic exercise (eight weeks), crocin and treadmill on heart damage and oxidative stress in diabetic rats	1. Diabetes increased lipid peroxidation and MDA levels, decreased SOD (Superoxide Dismutase) and GPx levels, decreased Bcl-2 expression, enhanced Bcl-2 related Bax expression and induced apoptosis in heart tissue. 2. Crocin and continuous exercise significantly decreased lipid peroxidation, blood sugar levels, and increased Bcl-2 gene expression and antioxidant enzymes activity in comparison with diabetic group. 3. Aerobic exercises simultaneously and separately with treadmill and crocin prevent apoptosis in heart tissue.	[40]
Aerobics	Effect of aerobic exercise (three sessions/week with mild to moderate intensity for 12 weeks) with or without saffron powder supplementation (200 mg) on specific markers of diabetes and inflammation in type 2 diabetic women	1. A significant decrease in HOMA-IR, serum levels of glucose, Fibrinogen (FIB), Homocysteine (HCY), IL-6 and TNFα in saffron groups + exercise, placebo + exercise, and saffron were observed compared to the placebo group. 2. The saffron + exercise group was more effective than all groups	[41]
Aerobics	The interaction of crocin and aerobic exercise improves memory, learning and hippocampi tau and neurotrophin gene expression in mice treated with trimethitine as a model of AD	1. Alzheimer's induction caused a significant decrease in memory, learning, expression of NGF (Nerve Growth Factor), TrkB (Tropomyosin Receptor Kinase B) and BDNF (Brain-Derived Neurotrophic Factor) genes and increased tau gene expression. 2. Crocin consumption and endurance training separately significantly enhanced learning, memory, expression of TrkB, BDNF and NGF genes and decreased tau gene expression.	[42]

Table 3. The effects of endurance exercise, relaxation and swimming along with saffron extract or supplement on body health

Exercise	Experiment	Result	Ref
Endurance (swimming)	The effect of subchronic administration of aqueous (intraperitoneal injection doses of 50, 100, 400, 800 and 1200 mg kg^{-1}) and hydroalcoholic extracts (100, 200, 400, 800 and 1600 mg kg^{-1}) of saffron stigma of Estehbanat Fars in swimming test (immobility, climbing and swimming) in mice	1. Aqueous extract with doses of 50 and 100 significantly decreased immobility and increased climbing. 2. The hydroalcoholic extract in all doses did not significantly change immobility, swimming and climbing behaviors in comparison with control group. 3. Aqueous extract in all doses and hydroalcoholic extract only in dose of 1600 decreased motor activity. 4. Saffron has an anti-depressant effect in chronic administration and probably works through the effect on the norepinephrine system.	[43]
Endurance (swimming)	Interactive hypoglycemic effects of aqueous saffron extract (daily 25 mg kg^{-1} intraperitoneal injection) and swimming training (five sessions/week, each session: 30 minutes) for four weeks in diabetic rats injected with 60 mg kg^{-1} streptozotocin	1. Swimming training has a significant effect on decreasing fasting glucose in diabetic rats. 2. Saffron extract has a significant effect on reducing fasting glucose, insulin and insulin resistance. 3. Saffron + swimming has a significant effect on decreasing fasting glucose, insulin and insulin resistance. 4. Saffron + swimming, compared to swimming, has a greater effect on reducing fasting glucose, insulin and insulin resistance. 5- Compared to swimming, saffron has a greater effect on decreasing insulin and insulin resistance.	[44]
Acute exhaustive endurance	The effect of short-term consumption of aqueous extract of saffron stigma (50 mg) on antioxidant system and MDA level of the liver of young male rats after a session of acute residual activity	As a result of residual activity, there was no significant change in the amount of MDA and the activity of CAT, SOD and GPX in the liver tissue of experimental group mice, unlike the control group.	[45]
Exhaustive endurance	The effect of aqueous extract of saffron stigma (50 mg of extract dissolved in 2 ml of distilled water) on cardiac troponin T and cardiac creatine kinase isozyme in the serum of male rats following endurance exercise (rotating band)	1. An increase in cardiac troponin T and cardiac creatine kinase isozyme was observed in all groups after restimulation. The lowest increase was observed in the exercise + extract and the highest enhancement was observed in the group without exercise. 2. Consumption of saffron extract + aerobic exercise is more effective in modulating the increase of troponin T and serum creatine-kinase cardiac isoenzyme following a bout of inhibitory activity than either of them alone.	[46]
Endurance	The effect of eight weeks of endurance training with moderate intensity (3 sessions/week, each session lasting 15-30 minutes and at a speed of 15 to 20 m/min on the treadmill) along with the consumption of aqueous saffron extract (25 mg) on the process of memory and learning with Y-Maze device and passive avoidance memory with shuttle box) in TMT (Trimethyltin) Alzheimer's mice	1. Endurance training combined with saffron aqueous extract significantly improves working memory and passive avoidance memory in Alzheimer's rats. 2. The interaction of endurance training and saffron extract was significant in reducing the time spent in the dark house, but the interaction of training and saffron extract in enhancing the duration of entering the dark house and increasing the percentage of intermittent behaviors was not significant.	[47]
Endurance	The effect of endurance training (treadmill running) on inflammation, mitochondrial biogenesis, capacity, antioxidant and metabolic and endurance biomarkers in Wistar rats	1. mtDNA copy number and NRF-1 gene expression enhanced in the training + saffron group significantly compared to the training and control groups. Endurance capacity time enhanced in the training + saffron group compared to the training group. 2. MDA, CPK (Creatine Phosphokinase), IL-6 and AST reduced and antioxidant parameters including GPx and glutathione increased in the exercise + saffron group compared to the athlete rats. 3. Saffron enhanced mitochondrial biogenesis, modulated metabolic biomarkers and reduced inflammation in exercised rats.	[48]
Endurance	Pretreatment with100 mg kg^{-1} crocin combined with exercise on a treadmill, with anti-inflammatory and antioxidant mechanisms, reduced movement and memory deficits in hemiparkinsonian rats induced by 6-OHDA (6-Hydroxydopamine)	1. Pretreatment with crocin and combined with exercise reduced the total number of rotations in comparison with the 6-OHDA-treated group. 2. Crocin treatment combined with exercise improved bad and spatial memory. Crocin and exercise reduce TNFα levels in the striatum. Crocin treatment reduced hippocampal lipid peroxidation levels, while training enhanced total thiol concentrations.	[49]
Endurance	Effect of endurance exercise with crocin on the expression levels of MFN2 (Mitofusin-2) and DRP1 (Dynamin-1-like) genes, glucose and insulin indices in the muscle tissue of diabetic rats	Exercise and crocin, combination or separately, have a beneficial effect on diabetes and mitochondrial dynamics by improving the mitochondrial fission and fusion indices (Mfn2 and Drp1), and improving glucose homeostasis and insulin resistance index.	[50]
Endurance	A comparative study of the protective effects of crocin (30 mg daily) and exercise (treadmill running) for three weeks on long-term potentiation (LTP) in the hippocampal CA1 region of rats subjected to chronic unpredictable stress (CUS)	1. Groups of crocin + exercise + stress and crocin + stress led to a significant enhancement in the slope and amplitude of post-synaptic field stimulating potential. 2. Crocin was more effective than exercise. 3. The interaction of crocin consumption and exercise had no synergistic effect and the observed protective effect was due to crocin administration rather than exercise	[51]

Endurance	Effects of four weeks of high-intensity exercise and saffron aqueous extract on the expression of genes related to breast cancer (induced by 4T1 cell line) including Sirtuin-1 (SIRT1), human telomerase reverse transcriptase (hTERT) and Tumor Protein p53 (p53)	1. The mRNA level of SIRT1 enhanced in the saffron + training group compared to the training and control groups. 2. The amount of p53 mRNA in the tumor tissue in the training group increased compared to the control and saffron + training groups. There were no changes in hTERT mRNA expression between the groups. 3. Exercise may decrease tumor burden through upregulation of p53 associated with the tumor suppressor pathway. The combination of saffron and exercise did not change the expression levels of p53 and hTERT and may inhibit tumor growth by other mechanisms.	[52]
Endurance	The effect of 40 mg kg^{-1} saffron combined with endurance exercise (treadmill) on the increase of NT-3 (Neurotrophin-3), serotonin and BDNF in Wistar rats	1. Significant increase in BDNF and hippocampal serotonin in saffron treatment + exercise compared to control and saffron groups. 2. Enhancement of NT-3 mRNA in soleus muscle in saffron + exercise group compared to other groups. 3. The significant high level of 5-HIAA (5-Hydroxy indoleacetic acid) in the hippocampus and short-term memory in the intervention groups compared to the control.	[53]
Endurance	Effect of moderate intensity endurance training (3 sessions/week, each session lasting 15-30 minutes at a speed of 15-20 m/min on the treadmill for eight weeks) and daily consumption of crocin (25 mg kg^{-1}) on the expression of hippocampal MAP-Tau genes. and NGF in hippocampal degeneration model rats with intraperitoneal injection of 8 mg kg^{-1} of trimethyltin (TMT).	1. TMT injection increases MAP-Tau gene expression in Alzheimer's group in comparison with healthy control group. 2. There was a significant decrease in MAP-Tau gene expression in the exercise, crocin and exercise + crocin groups in comparison with the control group with AD, and this decrease was the most in the exercise + crocin group. 3. Injection of TMT decreases the level of NGF in the Alzheimer's group in comparison with the healthy control group. 4. The significant increase in NGF gene expression in the exercise, crocin and exercise + crocin groups in comparison with the control group with AD and this increase was the highest in the crocin group. Endurance training improves the Alzheimer's process in mice and crocin supplement also strengthens this improvement.	[54]

Table 4. The effects of interval exercise with saffron extract or supplement on body health.

Exercise	Experiment	Result	Ref
High-intensity interval	The simultaneous effect of eight weeks of intense interval training (starting with 2 intense intervals in the first week and ending with 8 intense intervals in the last weeks) and crocin on the oxidative stress of heart tissue of male rats exposed to doxorubicin	1. A significant enhancement in malondialdehyde and a significant reduction in SOD and catalase activity in the heart tissue of the group receiving doxorubicin in comparison with the healthy control group. 2. A significant decrease in the level of malondialdehyde in the training, crocin and training + crocin groups and a significant increase in superoxide dismutase and catalase activity in the training, crocin and training + crocin groups. 3. No significant difference was observed between the effect of interval exercise and crocin alone, but a significant difference observed between their combined effect and the effect of each of these two alone.	[55]
Interval	Effect of interval training (five sessions/week, respectively 16, 24, 32, 40 minutes of running on the treadmill for 8 weeks) and daily consumption of crocin (50 mg kg^{-1}) on the apoptotic indices of the testicular tissue of male rats subjected to apoptosis induction with doxorubicin (2.5 mg)	1. The continuous training group + crocin + doxorubicin had a significant effect on the decrease of Bax/Bcl-2 ratio and Bax and the increase of Bcl-2 compared to other groups. 2. Continuous exercise and crocin injection reduce the toxicity caused by doxorubicin, reduce free radicals and create beneficial adaptation in the antioxidant system of the testicular tissue.	[56]
sprint interval	Effect of intermittent speed training (4 sessions/week on a treadmill for eight weeks) along with daily consumption of saffron extract (30 mg kg^{-1}) on muscle PGC-1α (Peroxisome Proliferator Activated Receptor Gamma Coactivator-1 Alpha) and SIRT3 (Sirtuin 3) levels in aged male rats	1. Although the levels of PGC-1α and SIRT3 increased in all experimental groups in response to saffron consumption and intermittent speed training, only a significant increase in PGC-1α levels was observed in the intermittent-speed training group in comparison with the control group. 2. The consumption of saffron supplement causes a decrease in the adaptation of speed interval training and its consumption should be avoided during this training period.	[57]
Interval and Continuous	Effect of continuous and interval training (3 sessions/week with an intensity of 80-85 and 50-55% of the maximum running speed on the treadmill eight weeks eight weeks for eight weeks) along with daily consumption of crocin (25 mg kg^{-1}) on the expression of BDNF and NGF genes. in heart tissue of diabetic rats	1. Internal training and continuous training + crocin had a significant effect on enhancing BDNF. 2. Continuous training + crocin compared to continuous training, crocin, intermittent training and intermittent training + crocin had a greater effect on enhancing BDNF. 3. Continuous training + crocin had a significant effect on enhancing NGF and in comparison with continuous training, crocin, intermittent training and intermittent training + crocin had a greater effect on enhancing NGF.	[58]
High-intensity interval	Effect of high-intensity interval training (five days a week, with 2-minute intervals and with an 80-90% intensity of maximum speed for eight weeks) and consumption of crocin (2 mg kg^{-1}) on the oxidative stress of the liver tissue of male rats under induction	1. Doxorubicin caused a significant increase in the level of MDA and a significant decrease in the activity of SOD and catalase in liver tissue in the groups receiving doxorubicin in comparison with the healthy control group. 2. The application of all three interventions caused a significant decrease in the level of MDA and a significant enhancement in the activity of SOD	[59]

	chronic doxorubicin (2 mg kg^{-1})	and catalase. 3. The effect of training + crocin is better than the effect of each one alone.	
High-intensity interval	Effect of high-intensity interval training (five days a week, with 2-minute intervals and running with an 80-90% intensity of the maximum speed for eight weeks) and consumption of crocin (10 mg kg^{-1}) on the expression of apoptotic genes in liver tissue male rats under doxorubicin (2 mg kg^{-1}) induction	1. Doxorubicin significantly reduced Bcl-2 expression and enhanced Bax expression and Bax/Bcl-2 in liver tissue of patient groups. 2. In contrast to exercise, crocin and the combination of exercise + crocin decreased the expression of Bax, the ratio of Bax/Bcl-2 and increased the expression of Bcl-2 in the experimental groups in comparison with the doxorubicin group.	[60]
Interval	The interactive effect of high-intensity and low-intensity interval exercises (three sessions/week with an intensity of 80-85 and 50-55% of the maximum running speed on the treadmill) and daily consumption of crocin (25 mg kg^{-1} orally) for eight weeks on the expression of PGC-1α and UCP1 (Uncoupling Protein 1) genes in cardiac tissue of diabetic male rats	1. High-intensity and low-intensity interval exercises and crocin consumption had a significant effect on increasing gene expression of PGC-1α and UCP1. 2. Also, training with crocin consumption had interactive effects in increasing gene expression of PGC-1α and UCP1, and high-intensity intermittent training and low-intensity interval training have the same effects on increasing UCP1 gene expression.	[61]
Interval	Effect of saffron supplementation combined with different intensities of exercise on the metabolic balance of overweight and obese women for 12 weeks	1. A significant difference in fat percentage, BMI and weight was observed between the control group with exercise interventions and saffron. 2. A significant difference in visfatin was observed between all groups with exercise + saffron group. 3. A significant difference in visfatin was observed between training + saffron and control group. 4. A significant difference in irisin was observed between the periodic training + saffron, training + saffron and training with the control group. 5. A significant difference in the ghrelin was observed only between the training + saffron and all groups. Intense interval exercise with saffron supplement is a good strategy for gaining health and preventing diseases related to obesity.	[62]
Interval	Apoptosis of tumor cells caused by treatment with saffron aqueous extract and high-intensity interval training in mice with breast cancer	1. Tumor volume in the training, saffron and combination groups was significantly lower than the control. 2. Caspase 3 protein level in the training and saffron groups was higher than the control and combination. 3. Bax protein level in the saffron group was higher than the control and lower than the training + saffron group. 4. Bcl-2 protein level was higher in exercise + saffron than others and Bax/Bcl-2 in exercise and saffron groups was significantly higher than exercise + saffron and control.	[63]
Interval	Effect of interval training (for five sessions/week on a treadmill with 80-85% for eight weeks) and crocin supplementation (25 mg kg^{-1} daily) on mitochondrial biogenesis and redox-sensitive transcription factors, AP1 (Activator Protein 1), LCAD (Very Long Chain Acyl CoA Dehydrogenase Deficiency), NF-κB, SIRT1, SIRST3 and PGC1-α) in the liver tissue of type 2 diabetic rats	1. Continuous training, interval training and crocin decreased AP1 and increased LCAD. 2. Crocin increased SIRT1 and continuous training + crocin and interval training + crocin decreased AP1 and increased NF-κB and LCAD. 3. Intermittent training + crocin increased SIRT1, SIRST3 and PGC1-α. Intermittent training + crocin compared to continuous training + crocin has a more favorable effect on mitochondrial biogenesis factors.	[64]
High-intensity interval	Effect of high-intensity interval training (5 days a week and every day of 2 intervals of 2 minutes and intensity of 80% in the first week and 8 intervals in 2 minutes and intensity of 90% of maximum speed in the final weeks) and daily oral consumption of crocin 14 mg kg^{-1}) on serum markers of heart tissue toxicity caused by injection of anticancer drug doxorubicin (subperitoneal injection 7 times and each time at the rate of 2 mg kg^{-1}) in male Wistar rats	1. Induction of doxorubicin caused a significant increase in lactate dehydrogenase and creatine kinase-MB in comparison with the healthy control group. 2. Intense intermittent training causes a significant decrease in lactate-dehydrogenase and creatine kinase-MB in comparison with doxorubicin group. 3. Exercise + crocin causes a significant decrease in lactate dehydrogenase and creatine kinase-MB compared to doxorubicin and no difference was between exercise and exercise + crocin groups	[65]

Consumption of saffron combined with corrective exercises

A research was conducted to examine the effects of 12 weeks of saffron consumption combined with corrective exercises on quality of life and depression levels in women diagnosed with Multiple Sclerosis (MS). The mean scores of depression in all groups (corrective exercises, saffron and exercises combined with saffron) indicated a notable difference compared to the control group. The corrective exercises combined with saffron resulting in a more pronounced effect than the other groups. The average scores of life scores, both physical and mental, in the experimental groups differed significantly from those in control group. Notably, the saffron group exhibited a remarkable improvement in the physical dimension, while the combined corrective

exercises and saffron group showed a marked difference in the mental dimension. Both exercise programs and saffron consumption independently proved effective in reducing depression and improving the quality of life for MS patients. However, their combined use yields even greater benefits [66].

Consumption of saffron combined with simultaneous exercises

The effects of saffron (100 mg daily) along with simultaneous exercise on glycemic status, inflammatory markers and body composition in type 2 diabetic obese men showed that both of them significantly reduced the concentration of insulin, IL-1β, IL-6, TNF-α, hs-CRP (High-Sensitivity C-Reactive Protein), FBG, HOMA-IR and HbA1c, and the increase of IL-10 concentration. There was a positive correlation between BFP changes with TNF-α, IL-1β, IL-6, IL-10 and hs-CRP concentrations in the intervention groups. The interaction effect of saffron supplement combined with exercise has a more effective effect on anti-inflammatory status when compared to using each individually [67].

Consumption of saffron combined with recreational activities

The effects of saffron extract (28 mg daily) in recreationally active adults showed that saffron has beneficial effects in men and increases the enjoyment of exercise and heart rate changes, and such benefits were not detected in women [68].

Consumption of saffron with dry sauna

The effect of saffron aqueous extract (5 mg kg^{-1} daily for 4 days) on maximum aerobic capacity, total antioxidant capacity and lipid peroxidation of the serum of young male athletes after a dehydration session in a dry sauna leading to a 4% decrease in body weight was investigated. A significant decrease in maximum aerobic power was observed after dry sauna in both groups receiving and not receiving the extract. There was a significant decrease in total antioxidant capacity and an enhancement in serum malondialdehyde in the control group. Saffron improved the serum total antioxidant capacity and prevented the significant increase in serum malondialdehyde after sauna, but it did not have a significant effect in preventing the reduction of maximum aerobic power after sauna [69].

Effects of crocin and physical activity in adolescents

Exercise as a non-pharmaceutical intervention and crocin supplementation during pre-puberty can protect against behavioral and morphological abnormalities caused by adolescent stress in adulthood [70]. The combination of crocin and exercise stop adolescent stress-induced spatial navigation disorder and dendritic contraction in CA3 region of hippocampus. Adolescent stress increases corticosterone levels and tends to decrease BDNF levels in the CA3 region. Adolescent stress causes disturbances in spatial memory and learning and reduces the apical dendritic length of CA3 pyramidal neurons. Exercise, crocin and both together improves spatial disorder and learning and caused by stress and dendritic length contraction of CA3 pyramidal neurons and significantly reduces corticosterone and increases CA3 BDNF levels [71].

New findings about the therapeutic effects of saffron

New research has been conducted on the efficacy of saffron and its compounds on the heart and blood vessels [72], nervous system [73] and digestive [74] diseases, and positive therapeutic effects have been observed. Saffron supplement can probably improve glycemic parameters and lipid profile such as glucose level, HbA1c, triglyceride, total cholesterol and LDL [75]. Kaempferol in the petals of saffron flower shows anti-inflammatory, anti-cancer and anti-depressant properties [76]. Crocin is the most important anticancer compound of saffron due to changes in the gene level and inducing of apoptosis in cancer cells [77]. Saffron strengthens the reproductive system of women such as reducing the symptoms of dysmenorrhea, premenstrual syndrome, menopause, polycystic ovarian disease and reducing sexual dysfunction through the regulation of sex hormones, folliculogenesis, ovulation, and protecting the ovary and uterus against Oxidative stress becomes [78, 79]. Saffron extract has shown more advantages than saffron powder because it is effective in more parameters and does not cause side effects. Saffron powder

decreased AST enzyme and increased body mass index (BMI), but crocin decreased HbA1c, FBG, creatinine and total cholesterol. Crocin decreased HbA1c, FBG and systolic blood pressure but increased creatinine levels [80]. The effects of saffron were lower than conventional drugs for the treatment of depression, cognitive disorders, anxiety, obsessive-compulsive disorder (OCD) and attention deficit/hyperactivity disorder (ADHD), but it showed good effects and few side effects [81]. Saffron and its components have shown a positive role in improving the inflammatory symptoms of non-autoimmune and autoimmune diseases like MS [82]. Also, saffron improves mild to moderate age-related macular degeneration (AMD) [83]. Crocin has shown a neuroprotective effect on cognitive memory disorders and cell death in the hippocampus of the Fetal Alcohol Syndrome model against ethanol toxicity [84]. Saffron has shown positive effects on Alzheimer's disease (AD) or mild cognitive impairment [85]. Crocin (15 mg twice a day for 12 weeks) improved the pulmonary function tests (PFT) and 6-minute walking distance test (6MWD) in chronic obstructive pulmonary disease and increased IL-6 serum levels and decreased TNF-α exerted preventive effects compared to the placebo group [86]. The voluntary exercise and crocin increase cardiac angiogenesis through ERK1/2 (Extracellular Signal-Regulated Kinase 1/2) and Akt (Akt Kinase) signaling in type 2 diabetic rats. ERK1/2 and Akt levels were higher in the exercise and crocin groups than in the diabetic group. The levels of ERK1/2 and Akt proteins and CD31 (Cluster of Differentiation 31) immunohistochemistry were significantly higher in the group of voluntary exercise + crocin compared to other groups. Treatment with voluntary exercise and crocin have a synergistic effect on angiogenesis and it is probably through the activation of ERK 1/2 and Akt signaling pathways in the heart [87]. The cardioprotective effect of voluntary exercise combined with crocin for 8 weeks in rats and the function of Mir-126 and Mir-210 in cardiac angiogenesis were investigated. The levels of ERK1/2 and Akt in the heart tissue were higher in the group treated with the exercise group, crocin group and the combined group. The expression of CD3, miR-210 and miR-126 in the heart of both exercise and crocin groups increased compared to the control group. Crocin and exercise improve cardiac angiogenesis probably through increasing the expression of miR-210 and miR-126 [88]. The effect of 12 weeks of crocin supplementation (30 mg kg^{-1}) on exercise capacity and oxidant/antioxidant markers with 6-minute walking distance test (6MWD), and pulmonary function tests in Chronic Obstructive Pulmonary Disease (COPD) patients. showed that crocin decreases the serum level of NF-kB (Nuclear Factor-kappa B) and total oxidant status, and increases total antioxidant capacity. 6MWD test showed the improvement of exercise capacity. Crocin supplementation efficaciously restored the oxidant/antioxidant balance and ameliorated inflammatory conditions [89].

Mechanism of action of saffron

Saffron provides neuroprotection by inhibiting excitotoxic pathways and neuroinflammation, modulating autophagy, apoptosis, activating defensive antioxidant enzymes and reducing oxidative damage [90]. Saffron compounds have neuroprotective effects through various mechanisms such as modulating neurotransmitters, increasing neurogenesis, reducing neuroinflammation, turning on the modulating epigenetic factors, Nrf2 (Nuclear Factor Erythroid 2–Related Factor 2) signaling pathway and improving cognitive function and nervous mood [91]. Crocin reduced methylphenidate-induced cognitive impairment and hyperactivity and increased P-CREB (cAMP-Response Element Binding Protein) and BDNF levels. Crocin probably causes neuroprotection through the P-CREB/BDNF signaling pathway [92]. The active compounds and crocins derived from saffron have protective effects against ischemic stroke and cerebral ischemia. Crocin has an effect on signaling pathways and multiple mechanisms involved in ischemic stroke, including inhibitor of nuclear factor kappa light chain in B cells, mitochondrial apoptosis, calcium-binding protein B S100, VEGF-A (Vascular Endothelial Growth Factor A) and interleukin-6. Crocin has poor bioavailability and must be converted to crostin to cross the blood-brain barrier [93]. By limiting the synthesis of RNA and DNA in cancer cells, stopping the chain reactions of free radicals and the antioxidant activity of its compounds,

saffron helps in preventing and curing cancer. Also, carotenoid compounds interact with topoisomerase 2 enzyme, which is related to the cytotoxicity of saffron and causes apoptosis of cancer cells [94]. Saffron acts against breast cancer and induces apoptosis, inhibits cell division and modulates signaling pathways involved in cancer development, such as PI3K (Phosphoinositide 3-Kinases)/AKT, NF-κB and MAPK [95]. Crostin also inhibits the growth of a number of cancer cells by inhibiting RNA polymerase II in neoplastic cells, decreacing the synthesis of DNA, RNA, protein and interfering with the structure of histone H1 and DNA-H1 [96, 97]. Unlike the toxicity of saffron on cancer cells, it has been assessed as non-toxic on normal cells and in oral administration [98]. Crocin and safranal present in saffron have the same effect as fluoxetine and prevent the reabsorption of dopamine, norepinephrine and serotonin [99, 100]. By preventing serotonin reabsorption, crocin and safranal lead to an enhancement in serotonin levels and a reduction in depressive symptoms in women with premenstrual syndrome (PMS). Since depression is one of the most important factors in reducing sexual desire, improving depression and increases sexual function [101]. The function of crocin in reducing oxidative stress includes reducing malondialdehyde and increasing GPx, CAT and SOD [102]. The role of saffron in the death of human cervical cancer cells (HeLa) and human liver cancer cells (HepG2) has been proven [103]. Two mechanisms have been introduced for the anticancer activity of saffron: 1- inhibition of cell multiplication in the primary stages of cell growth by modulating gene expression, inducing cell cycle arrestment or targeting DNA sequences and 2- destroying cancer cells through apoptosis. [104].

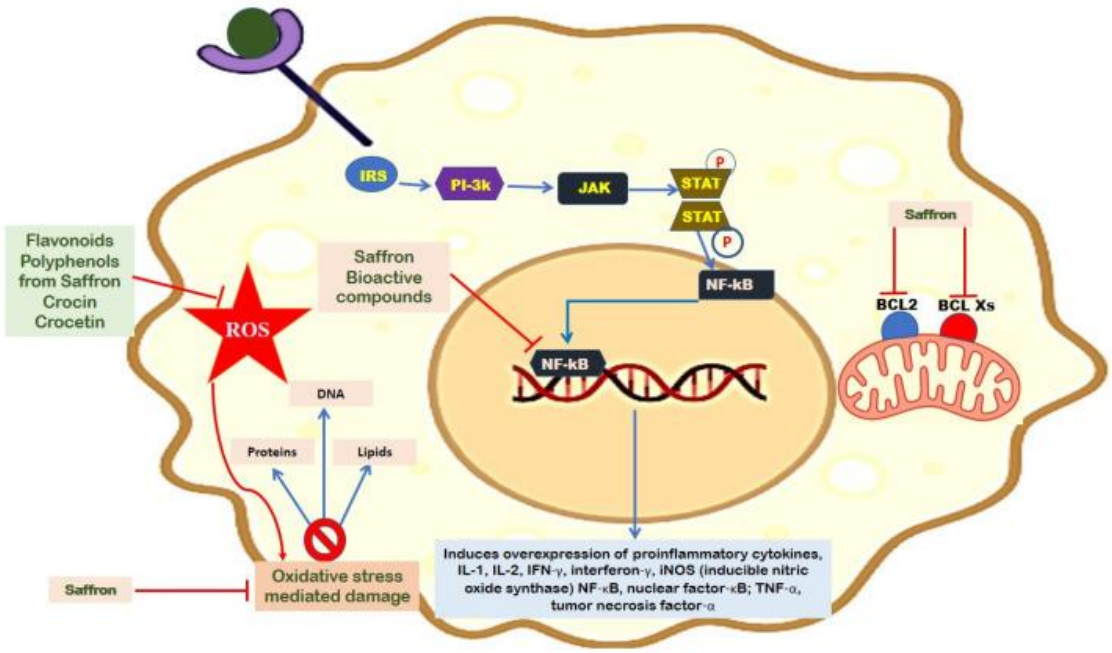

Figure 2. Schematic picture of the inhibitory action of saffron, which leads to a reduction in the production of ROS, IL-1β, IL-17, NF-κB, TNF-α and NO. Also, saffron suppresses apoptosis by preventing the function of BCL-2 [105].

Saffron, exercise and sexual activity

Saffron combined with sports activity improves male body composition and endocrine function of the pituitary-testicular axis, sperm parameters and spermatogenesis; increases the serum levels of FSH, LH, testosterone, the number of spermatocytes, the epithelium diameter of the seminiferous tubules and sperm viability rate and also by reduction of varicocele indicators can strengthen male reproductive activities [105]. In women, saffron and its effective compounds can increase the serum levels of FSH, LH, beta-estradiol, the number of peri-antral and antral follicles, oocytes, the percentage of fertilization and blastocysts, and a significant reduction in the number of aborted embryos, improving the process of embryonic development before

implantation, the quality of embryos obtained from in vitro fertilization, reducing the number of cystic follicles in polycystic ovary syndrome (PCOS) and removing melasma of pregnancy and strengthening the female reproductive system [106].

CONCLUSIONS

The interaction of saffron consumption and short-term and long-term sports activities increases testosterone, FSH, LH, estradiol hormones, improves body composition, reduces cardiovascular risk factors, controls fasting glucose and increases the function of the reproductive system. Consumption of long-term aerobic exercise along with saffron has strengthened the antioxidant system, improved respiratory diseases and improved glycemic indices. Consumption of aqueous saffron extract and resistance training alone do not have a significant effect on the reproductive system of male rats, but their combination has a significant effect on increasing the performance of this system and increasing the testosterone hormone in young men. Resistance training along with saffron supplementation can improve body composition in non-athletic men, but it does not improve upper and lower body strength. Supplementing with saffron before performing outdoor activities is a preventive measure to reduce the incidence of oxidative stress made by activity. The combination of saffron extract and aerobic activity is a suitable method to strengthen the liver's non-enzymatic antioxidant system in diabetes. Aerobic and resistance training and their combination with saffron consumption is an effective method in reducing the peroxide balance and increasing the antioxidant. It is suggested to use the combination of aerobic exercise in water and crocin supplement to reduce the apoptosis of the heart tissue, less cell damage and ultimately the health of the heart tissue. Regular vigorous intermittent exercises, crocin supplement or a combination of the two can have protective effects against the oxidative damage of heart tissue made by doxorubicin and reducing the malondialdehyde level and oxidative index and enhancing the catalase and superoxide dismutase activity of heart tissue. The consumption of stigma supplement of saffron and sports activities can have beneficial effects for clinical applications in the prevention and treatment of blood pressure and respiratory diseases.

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Conflict of interest

The author declare that she has no conflict of interest.

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