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The Effects of Aerobic Exercise and Crocin on Metabolic Indices, Oxidative Stress, and Blood Pressure in Overweight/Obese Women

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ABSTRACT

Introduction: Excess body weight is associated with increased oxidative stress, altered lipid profiles, and elevated blood pressure levels. This study aimed to investigate the effects of aerobic exercise combined with crocin supplementation on various indicators of metabolic syndrome, oxidative stress, and blood pressure in overweight or obese women.

Methods: Forty women, aged 30 to 40 years, with a BMI between 30 and 40 kg/m^2, were randomly assigned to one of four groups (n=10 per group): aerobic exercise, crocin supplementation, a combination of exercise and supplementation, and a placebo control group. Blood pressure measurements were taken in a fasted state 24 hours before the start of the intervention, followed by the collection of 5 mL blood samples from the brachial vein. Baseline assessments included metabolic syndrome markers and oxidative stress indicators. The exercise groups participated in an 8-week aerobic training program consisting of three 40-50 minute weekly sessions, performed at 65-80% of their maximum heart rate. The supplementation groups received 30 mg of crocin daily. Post-intervention measurements were taken 48 hours after the final exercise session. Statistical analyses were conducted using ANCOVA and ANOVA with Bonferroni post-hoc tests. Data were analyzed with SPSS version 26, and statistical significance was set at $p<0.05$.

Results: Significant differences were observed among the four groups for weight, body fat percentage, BMI, waist-to-hip ratio (WHR), glucose, insulin, triglycerides (TG), superoxide dismutase (SOD), malondialdehyde (MDA), glutathione peroxidase (GPX), systolic blood pressure (SBP), and diastolic blood pressure (DBP) (p=0.0001), as well as for high-density lipoprotein (HDL) (p=0.003), low-density lipoprotein (LDL) (p=0.023), and insulin resistance (IR) (p=0.049). Bonferroni's posthoc analysis revealed significant differences in weight, body fat percentage, BMI, WHR, glucose, insulin, MDA, GPX, and DBP between the control and all three intervention groups. Notable differences in SOD and SBP were observed not only between the control and intervention groups but also when comparing the exercise group with the exercise + supplementation group, as well as between the supplementation group and the exercise + supplementation group.

Conclusion: Aerobic exercise and crocin supplementation significantly improved metabolic syndrome indices, oxidative stress markers, and blood pressure in overweight/obese women. The combined approach of exercise and supplementation yielded enhanced benefits.

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Introduction

Obesity and overweight are associated with increased oxidative stress, lipid profile abnormalities, and hypertension. In the modern era, obesity and overweight are major global health concerns, with their prevalence rising significantly (1, 2). This growing trend has negative health implications and is linked to various diseases, including type 2 diabetes, dyslipidemia, cardiovascular diseases, hypertension, and cancer. These conditions reduce life expectancy and premature mortality, leading to substantial healthcare costs (1). Studies have shown that cholesterol reverse transport is impaired, and its clearance is reduced in obese mice, which may help explain some of the mechanisms underlying obesity-induced hypertension (3). Obesity increases systemic vascular resistance and causes triglyceride accumulation in blood vessels, which

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can lead to fibrosis of the vascular walls and an elevated risk of hypertension (4). Furthermore, it has been reported that the endogenous antioxidant system, including glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT), is primarily suppressed in obese individuals, making them more susceptible to disease (5). As a result, a heightened state of oxidative stress and inflammation, coupled with a compromised antioxidant defense system, is commonly observed (6). Although the complications of obesity may vary among individuals, the consequences are broadly similar across the population, particularly the presence of oxidative stress and inflammation in all obese patients (7). The Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC8) and the American College of Sports Medicine (ACSM) recommend aerobic exercise as a primary treatment for individuals with hypertension. Park et al. (2022) reported that moderate-intensity aerobic exercise may help reduce inflammation and oxidative stress independent of fat reduction, potentially lowering the risk of obesity-related disorders in middle-aged obese women (8). Krause et al. (2014) reported that 16 weeks of low- and moderate-intensity aerobic exercise, although not significantly affecting body composition, aerobic capacity, or inflammatory markers in obese individuals, improved oxidative stress by increasing muscle nNOS expression and tNOx levels in skeletal muscles (9). Another non-pharmaceutical, natural weight management approach is herbal supplements (10). Saffron (Crocus sativus L.), a perennial plant from the iris family, is rich in a compound called picrocrocin, with crocin being recognized as its main bioactive component. The beneficial properties of saffron, especially compared to its other compounds, are primarily attributed to crocin (11). Crocin has demonstrated various biological functions, including antioxidant, anti-inflammatory, and anti-obesity effects (12, 13). Studies have shown that crocin reduces high-fat diet-induced inflammation in brown adipose tissue through SIRT1 activation, which may help improve brown adipose tissue function in obesity (14). Saffron extract appears to reduce inflammation caused by a high-calorie diet (HFD) and the expression of microRNAs that negatively regulate SIRT1. It also prevents the nuclear translocation of NFκB in the brown adipose tissue of HFD-induced obese mice and inhibits the NFκB signaling pathway by modulating SIRT1 activity (15). Several meta-analyses have examined the effects of saffron extract supplementation on lipids, blood pressure, glucose, and insulin, but the results have been conflicting. For example, Sahebkar et al. (2017) reported that quercetin supplementation does not have a significant favorable effect on plasma lipids (16). In contrast, Huang et al. (2020) reported that after 8 weeks of quercetin supplementation, HDL-C and triglyceride (TG) concentrations improved significantly (17). Additionally, it has been reported that saffron extract supplementation significantly reduces blood pressure by modifying the renin-angiotensin and autonomic nervous systems, sensitizing the baroreflex's parasympathetic component, and reducing vascular resistance and compliance (18). However, a meta-analysis showed that quercetin supplementation has a relatively small effect on fasting plasma glucose, HOMA-IR, or hemoglobin A1c (19). Another study indicates that saffron extract increases cytosolic chloride concentration by activating the NKCC1 membrane transport protein, subsequently leading to an anti-hypertensive effect (20). Given that both aerobic exercise and crocin supplementation have independently shown a positive impact on metabolic syndrome indices, oxidative stress, and blood pressure in obesity, the present study aims to investigate whether the combination of crocin supplementation and aerobic exercise, compared to each intervention alone, has a more pronounced effect on overweight/obese individuals.

Methodology

Three experimental groups and one control group were included in this study, which employed a quasi-experimental design with a pretest-posttest format. The statistical population consisted of overweight/obese women (weight: 76.07 ± 7.11 kg, height: 162.4 ± 6.5 cm, age: 33.95 ± 4.75 years) from Ilam City, all of whom were either non-athletes or had not engaged in regular physical activity for at least six months before the study. Initially, a public summons was used to recruit interested participants, who voluntarily completed questionnaires detailing their medical history, personal characteristics, and level of physical activity and provided written informed consent.

Forty participants were randomly selected from eligible candidates and assigned to one of four groups: the control group, supplementation group, exercise group, or exercise plus supplementation group. Participants were instructed to maintain consistent communication with the researcher and refrain from altering their lifestyle or dietary habits during the study period. Following baseline measurements of height, weight, and body composition, participants attended training sessions three times weekly for eight weeks. They were required to fast for at least 10 hours before blood sample collection, performed before and after the 8-week training period. The ethics committee of Ilam University approved the study under the code IR.ILAM.REC.1403.002.

Blood Sampling

To measure blood variables during both the pre-test and post-test phases, 6 mL of blood was drawn from the left antecubital vein. Participants were required to fast for 10 hours to standardize metabolic conditions before blood sampling, which was performed 48 hours before and after the training protocol. To control for nutritional status, which could potentially influence specific measured parameters, a 24-hour food recall questionnaire was administered one day before both the pre-test and post-test (21). Superoxide dismutase (SOD), glutathione peroxidase (GPX), and malondialdehyde (MDA) were measured using research kits from Zellbio (Germany). Insulin levels were assessed using the ELISA method with Monobind kit protocols. Blood glucose was determined using the glucose oxidase method, and lipid profile analysis was conducted using photometric methods with Pars Azmoon kits (Iran). The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) was calculated using the formula: fasting insulin (μU/mL) × fasting glucose (mmol/L) ÷ 22.5 (22, 23).

Blood Pressure Monitoring

For resting blood pressure measurements, participants were instructed to refrain from physical activity for at least 30 minutes before measurement. A nurse subsequently measured blood pressure using an OMRON blood pressure monitor.

Crocin Supplementation

Based on previous studies, the supplementation groups received two 15 mg crocin tablets daily for eight weeks. The placebo group received an equivalent amount of starch, following the same protocol as the crocin supplementation group (24).

The Aerobic Exercise Protocol

The aerobic exercise protocol consisted of treadmill running three times per week at 65-80% of the maximum heart rate, as outlined in Table 1. Each session began with a 10-15 minute general warm-up, including stretching exercises, followed by the main treadmill exercise, and concluded with a 10-minute cool-down period (25).

Table 1. Protocol of aerobic training (25).

	Weeks							
	1st	2nd	3rd	4th	5th	6th	7th	8th
Intensity (HR_{Max})	65%	65%	70%	70%	75%	75%	80%	80%
Duration(Min)	20	20	24	24	28	28	32	32

Statistical Methods

In this study, data are presented as means with standard deviations. The Shapiro-Wilk test was used to assess the distribution of the data. Analysis of covariance (ANCOVA) was employed for factors where the assumption of homogeneity of regression slopes was met, including weight ($p = 0.25$), body fat percentage ($p = 0.67$), body mass index (BMI) ($p = 0.45$), waist-to-hip ratio (WHR) ($p = 0.93$), HDL ($p = 0.13$), LDL ($p = 0.06$), superoxide dismutase (SOD) ($p = 0.74$), malondialdehyde (MDA) ($p = 0.76$), glutathione peroxidase (GPX) ($p = 0.11$), systolic blood pressure (SBP) ($p = 0.40$), and diastolic blood pressure (DBP) ($p = 0.33$). One-way analysis of variance (ANOVA) was used for factors where this assumption was violated, including glucose ($p = 0.0001$), insulin ($p = 0.0001$), insulin resistance (IR) ($p = 0.001$), and triglycerides (TG) ($p = 0.0001$). When significant differences were detected by either ANCOVA or one-way ANOVA, Bonferroni post-hoc tests were performed, given the equal sample sizes across the four groups. Data analysis was conducted using SPSS software version 26 for Windows, with statistical significance set at $\alpha \leq 0.05$.

Results

The analysis revealed significant differences among the four groups for weight (p = 0.0001), body fat percentage (p = 0.0001), BMI (p = 0.0001), WHR (p = 0.0001), glucose (p = 0.0001), insulin (p = 0.0001), MDA (p = 0.0001), GPX (p = 0.0001), and DBP (p = 0.0001). Bonferroni post-hoc tests revealed significant differences between the control and all intervention groups (exercise, supplementation, and exercise plus supplementation groups). Significant differences were observed only between the control and exercise plus supplementation groups for insulin resistance, triglycerides, HDL, and LDL. For SOD and SBP, in addition to differences between the control group and the other three groups, significant differences were also observed between the exercise group and the exercise plus supplementation group, as well as between the supplementation group and the exercise plus supplementation group.

Table 2. Mean and standard deviation of the body composition in the four study groups.

Variables		Control	Training	Supplementation	training plus supplementation
Weight (kg)	Pre test	76.42 ± 3.98	75.83 ± 4.33	77.5 ± 4.3	74.55 ± 3.94
	Post test	76.6 ± 4.55	72.2 ± 4.34	75.01 ± 3.88	70.8 ± 3.98
Body fat percentage (%)	Pre test	38.4 ± 2.45	38.9 ± 1.85	37.5 ± 2.36	37.4 ± 2.17
	Post test	38.4 ± 2.31	36.01 ± 1.69	34.4 ± 1.89	33.60 ± 1.9
BMI (kg/m^2)	Pre test	29.98 ± 3.58	28.79 ± 1.83	28.58 ± 2.12	28.46 ± 2.82
	Post test	30.05 ± 3.67	27.42 ± 1.92	27.65 ± 1.93	27.01 ± 2.57
WHR (%)	Pre test	0.903 ± 0.09	0.924 ± 0.1	0.922 ± 0.09	0.938 ± 0.05
	Post test	0.892 ± 0.09	0.891 ± 0.09	0.893 ± 0.088	0.895 ± 0.06

Table 3. Results of ANCOVA analysis in oxidative stress parameters

Variables	Groups	Pre-test	Post-test	Paired sample t-test		ANCOVA	
		M±SD	M±SD	p	t	p	f
SOD U/ml	Control	65.5±16.7	65.3±15.6	0.86	0.17	P<0.001	32.96
	Training	69.7±9.9	75.2±9.5	0.0001	-14.73		
	Supplementation	61.26±12.7	65.7±12.5	0.0001	-11.72		
	T+S	66.6±9.8	75±9.3	0.0001	-23.34		
MDA µM	Control	27.9±9.1	28.4±8.1	0.28	-1.14	P<0.001	31.54
	Training	24.98±8.4	22.6±8	0.0001	7.88		
	Supplementation	23.6±6.5	21±5.9	0.0001	6.97		
	T+S	26.7±6.4	23±6	0.0001	7.82		
GPX U/ml	Control	202 ± 38	203 ± 36	0.85	-0.25	P<0.001	18.05
	Training	232 ±76	242 ± 77	0.0001	-11.54		
	Supplementation	230 ± 61	244 ± 62	0.0001	-13.46		
	T+S	220 ± 62	236 ± 65	0.0001	-0.9.92		

Discussion

This study demonstrated that aerobic exercise, crocin supplementation, and their combined effect (exercise plus supplementation) led to significant improvements in metabolic syndrome indicators among overweight/obese women, with the combined intervention group showing the most pronounced changes. These findings are consistent with previous research on the individual effects of crocin, such as studies by Taherifard et al. (26), Shirali et al. (27), and Javandoost et al. (24), as well as studies on aerobic exercise by Frączek et al. (28) and Davies et al. (29) in overweight and obese populations.

The mechanisms by which crocin and exercise improve metabolic syndrome indicators are multifaceted. Crocin has been shown to inhibit hepatic lipogenesis, enhance lipolysis, and upregulate genes involved in beta-fatty acid oxidation (30). Additionally, crocin's antioxidant properties may help reduce oxidative stress-induced lipid metabolism dysregulation, commonly observed in obesity (26). Conversely, aerobic exercise can increase lipoprotein lipase activity, an enzyme responsible for clearing triglyceride-rich lipoproteins, and enhance gene expression in reverse cholesterol transport, leading to increased high-density lipoprotein cholesterol (HDL-C) levels. Exercise-induced weight loss and improved insulin sensitivity may also contribute to the favorable changes in metabolic syndrome indicators observed in overweight and obese individuals (28). The synergistic effect observed in the combined intervention group appears to stem from crocin's ability to modulate lipid metabolism and the capacity of aerobic exercise to enhance lipid clearance and reverse cholesterol transport (31). The effects of crocin supplementation and aerobic exercise on insulin resistance in overweight/obese individuals have been extensively studied. Research indicates that crocin supplementation can significantly reduce fasting blood glucose, HbA1c, and insulin levels in obese individuals with type 2 diabetes (T2DM). Daily saffron supplementation combined with aerobic exercise over eight weeks has improved insulin levels and overall blood glucose control in middle-aged, overweight women with T2DM (32). Another study found that saffron consumption was associated with reduced insulin resistance, as measured by HOMA-IR, in diabetic mice, demonstrating its potential to enhance insulin sensitivity through various mechanisms, including modulation of oxidative stress and inflammation (33). Regular aerobic exercise has also been reported to significantly reduce insulin levels and improve metabolic markers in obese individuals. A 12-week study demonstrated significant reductions in insulin levels and inflammatory markers among participants (34). The combination of crocin supplementation and aerobic exercise appears to have synergistic effects. Studies have shown that when both interventions are applied together, more significant improvements in insulin sensitivity and reduced insulin levels are observed compared to either intervention alone. Rajabi et al. (2022) reported that participants who simultaneously used saffron extract and engaged in aerobic exercise exhibited more significant reductions in insulin and other metabolic markers compared to the other groups (35). Aerobic exercise has been reported to improve insulin sensitivity, which enhances the clearance of triglyceride (TG)-rich lipoproteins and promotes hepatic low-density lipoprotein cholesterol (LDL-C) uptake. This results in favorable changes in the lipid profile, including decreased TG and LDL-C levels (36, 37). Aerobic exercise can also influence the expression and activity of key enzymes involved in hepatic lipid synthesis and oxidation, such as acetyl-CoA carboxylase and carnitine palmitoyltransferase I. These adaptations reduce TG and low-density lipoprotein (VLDL) production, improving lipid profiles (38, 39). Additionally, weight loss from aerobic exercise can further enhance the lipid profile in overweight and obese individuals (40). This study revealed that both crocin supplementation and aerobic exercise significantly improved oxidative stress markers, yielding even more pronounced positive effects. Both interventions resulted in notable reductions in malondialdehyde (MDA), a marker of lipid peroxidation, while significantly enhancing the activity of antioxidant enzymes, superoxide dismutase (SOD) and glutathione peroxidase (GPX). Given that obesity is associated with increased oxidative stress, which can contribute to a variety of chronic diseases, including cardiovascular diseases and type 2 diabetes, the ability of crocin and aerobic exercise to mitigate oxidative stress in overweight/obese women is a significant finding. Previous research has demonstrated that crocin scavenges free radicals, inhibits lipid peroxidation, and regulates the expression of antioxidant enzymes. (41, 42). These mechanisms can help reduce the excessive production of reactive oxygen species (ROS) and restore the body's balance between oxidants and antioxidants (26). Additionally, aerobic exercise can stimulate endogenous antioxidant systems, such as superoxide dismutase (SOD) and glutathione peroxidase (GPX), through the activation of transcription factors like Nrf2 (43). Moreover, exercise-induced weight loss and improved insulin sensitivity can help reduce obesity-related oxidative stress (8). The combination of crocin supplementation and aerobic exercise appears to exert a synergistic effect on oxidative stress markers in overweight/obese women. In conjunction with the exercise-induced enhancement of endogenous antioxidant defenses, Crocin's antioxidant properties may significantly reduce lipid peroxidation and maximal increases in antioxidant enzyme activity. Crocin also enhances the activity of hormone-sensitive lipase and carnitine palmitoyltransferase I—enzymes involved in fatty acid mobilization and oxidation, respectively—contributing to reduced triglyceride (TG) levels and an improved overall fat profile (30). Studies have shown that aerobic exercise stimulates endogenous antioxidant enzymes, including SOD, catalase, and GPX. This exercise-induced enhancement of antioxidant defense mechanisms can help neutralize excessive reactive oxygen species (ROS) production associated with obesity (38, 44). Furthermore, aerobic exercise can stimulate mitochondrial biogenesis, leading to more efficient energy utilization and reduced electron leakage, decreasing ROS production (45). Additionally, since obesity is associated with low-grade chronic inflammation that contributes to oxidative stress, aerobic exercise has been shown to reduce the production of pro-inflammatory cytokines, such as TNF-α and IL-6, thereby mitigating inflammation-induced oxidative stress (46).

The results showed that aerobic exercise, crocin supplementation, and their combined effect led to significant changes in blood pressure among overweight/obese women, with the combination group showing the most substantial improvements. These findings aligned with studies by Chen et al. (47), Yang et al. (48), Wang et al. (49), and Razavi et al. (30). The beneficial effects of crocin on blood pressure can be attributed to its potent antioxidant and anti-inflammatory properties. Crocin has been reported to inhibit the renin-angiotensin-aldosterone system (RAAS), which plays a central role in blood pressure regulation (30). As a carotenoid compound derived from saffron (Crocus sativus), crocin has garnered increasing attention for its potential therapeutic applications in managing metabolic and cardiac disorders, including obesity. Crocin has been shown to improve endothelial function and enhance nitric oxide bioavailability, leading to vasodilation and reduced peripheral resistance (47). In addition, crocin's role in blood pressure reduction is partly due to its inhibition of key enzymes involved in RAAS, such as the angiotensin-converting enzyme (ACE) and the angiotensin II type 1 receptor (AT1R). This inhibition leads to reduced production and activity of angiotensin II, consequently decreasing peripheral resistance and lowering blood pressure. Aerobic exercise has also been shown to have favorable effects on blood pressure in overweight/obese individuals (50). Exercise can enhance baroreflex responsiveness, improve autonomic nervous system balance, and promote structural and functional adaptations in blood vessels, all contributing to blood pressure reduction (51) (52). The synergistic effect of crocin supplementation and aerobic exercise on blood pressure reduction observed in our study is supported by previous research. The combination of exercise and antioxidant supplements has been reported to be more effective in reducing blood pressure than either intervention alone in hypertensive individuals (44, 53). The underlying synergistic mechanisms may include improved endothelial function, reduced oxidative stress, and enhanced nitric oxide signaling (52). Obesity is associated with excessive sympathetic nervous system activation, which can contribute to hypertension. Aerobic exercise has been shown to improve autonomic nervous system balance by increasing parasympathetic activity and reducing sympathetic tone (54). This can reduce heart rate and peripheral vascular resistance, resulting in lower blood pressure (44). Regular aerobic exercise can also induce structural changes in blood vessels, such as increased arterial compliance and reduced arterial stiffness. These adaptations improve blood flow efficiency and decrease peripheral resistance, ultimately lowering blood pressure (25). Furthermore, aerobic exercise has been shown to regulate antioxidant defense systems and reduce the production of reactive oxygen species (ROS), thereby decreasing obesity-related oxidative stress. Exercise also reduces the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which have detrimental effects on vascular function (44). Additionally, aerobic exercise can promote weight loss and enhance insulin sensitivity in overweight and obese individuals. These metabolic adaptations contribute to blood pressure reduction, as excess body weight and insulin resistance are strongly associated with the development of hypertension (55).

Conclusion

In conclusion, overweight and obese women experienced significant improvements in metabolic syndrome indicators, oxidative stress, and blood pressure as a result of aerobic exercise and crocin supplementation. The combined use of these interventions may offer additional benefits, particularly for individuals with metabolic disorders such as type 2 diabetes (T2DM). To optimize the dosage and duration of these interventions for maximal efficacy, further research is needed to explore the underlying mechanisms.

Declaration

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Declaration of Interest

The authors declare no conflict of interest.

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Ethics Considerations

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants. The ethics committee of Ilam University approved the study using the code IR.ILAM.REC.1403.002

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