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Effect of Quercetin and Intermittent and Continuous Exercise on Catalase, Superoxide dismutase, and Malondialdehyde in the Heart of Rats with Colon Cancer

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ABSTRACT

Background: Colorectal cancer is the fourth leading cause of death globally, and the second most common cancer in Europe. About 8% of all cancer-related deaths occur due to colorectal cancer, and the highest prevalence has been reported in Asia and Eastern Europe.

Methods: In this experimental study, 80 rats were divided into two groups of cases (n=70) and controls (n=10). Colorectal cancer was induced weekly in rats by subcutaneous injection of 15 mg/kg Azoxymethane. The rats were then divided into 7 experimental subgroups of patients, saline, quercetin, intermittent exercise, continuous exercise, quercetin plus intermittent, and quercetin plus continuous exercise. Oxidative stress biomarkers, including superoxide dismutase (SOD), catalase (CAT), and malondialdehyde (MDA) were measured in the rats' heart tissue by the ELISA method. Data were analyzed using ANOVA by SPSS software.

Results: Oxidative stress in heart cells increased due to colorectal cancer. Quercetin alone or in combination with exercise significantly increased mean levels of CAT and SOD in the heart tissue of rats compared with patient and saline groups ($P<0.0001$). In contrast, the MDA level was significantly decreased ($P<0.05$).

Conclusion: Colorectal cancer increased the oxidative stress in cardiac cells. Quercetin alone improved oxidative stress in cardiac tissue, and its combination with exercise was more effective.

Keywords: Oxidative Stress, Colorectal Cancer, Intermittent and Continuous Exercise, Quercetin

INTRODUCTION:

Colorectal cancer is the fourth leading cause of death worldwide, and the second most common cancer in Europe (1). About 8% of all cancer-related deaths occur due to colorectal cancer. The highest incidence of colorectal cancer has been reported in Asia and Eastern Europe (2). Early detection of colorectal cancer in recent years has played a significant role in patients' survival, as chemotherapy medicines prevent the indefinite proliferation of cells in certain tissues of the organs and induce apoptosis in cancer cells (3). One of the problems is that current treatment methods for advanced colorectal cancer have harmful effects on the health system and individuals (4). In chemotherapy, as a common drug treatment for cancer, the effective substance is injected into the body. In addition to the cancer cells, it also affects other cells and tissues of the body and, more importantly, damages adjacent tissues (3). The efficiency of treatment is not satisfactory even with the development of new anticancer drugs so that the American Society of Clinical Oncology (ASCO) has emphasized the need for finding a new approach to treat cancer. The main goal of treating colorectal cancer should be the targeted use of cancer chemoprevention drugs (5). Therefore, Siddiqui et al. (2010) defined cancer chemoprevention drugs based on the extent of the effect on cancer by prescribing one or more natural or synthetic substances that can prevent cancer recurrence or delay cancer progression a chemical mechanism (6). The main mechanisms underlying cancer chemopreventive function of natural components of edible plants include modulation of the expression of genes regulating cell proliferation, differentiation, apoptosis, and suppression of angiogenesis and metastasis (7). The use of antioxidants and regular exercise are among the most critical factors that have attracted many researchers' attention to control and treat diseases (8).

Continuous exercise plays a crucial role in the treatment and prevention of low back pain, arthritis, obesity, cardiovascular diseases, hypertension, osteoporosis, respiratory disorders, and liver diseases, especially non-alcoholic fatty liver disease (NAFLD) (9). In a recent study by Hajighasem et al. (2018), intermittent and continuous exercise significantly increased the activity of superoxide dismutase (SOD) and catalase (CAT), as well as the levels of the anti-inflammatory mediator Interleukin-10 (IL-10) in the liver tissue. In contrast, the levels of the inflammatory mediator necrosis factor- α (TNF-α), the level of lipid peroxidation, and the number of apoptotic cells in the liver were significantly reduced (10). Polyphenols are secondary metabolites of plants that protect them against UV, oxidants, and pathogens. Flavonoids are the most abundant polyphenol in the human diet. Flavonoids include anthocyanins, flavonols, flavanols, flavonones, flavones, and isoflavones, among which quercetin (3, 5, 7, and 4-pentahydroxy flavone) is one of the most important (5,7). The main effects of quercetin include antioxidant properties, inhibition of muscle relaxation, platelet LDL, prevention of oxidation in vascular smooth muscle cells, lowering serum lipid levels, lowering systolic blood pressure, weight loss in animals, lowering plasma insulin levels, lowering levels of plasma inflammatory markers, and anticancer effects (5,11-13). One of the proposed anticancer molecular mechanisms of quercetin can be its direct effect on reducing the activity of Cyp1A7 in colorectal cancer, which is involved in the activation of carcinogens (11). Quercetin also affects estrogen-dependent receptors, has inhibitory effects on the expression and function of androgen receptors (called phytoestrogen-like activity) (12), induces apoptosis via mitochondrial pathway (activation of caspase 3 and 9), decreases the Bcl-xs/Bcl-xl ratio, increases Bax (13), affects DNA break, poly (ADP-ribose) polymerase, af-

fects Bcl-2 (anti-apoptosis), and reduces inflammatory cytokine synthesis and expression of inducible nitric oxide synthase (iNOS) (14). Since elevated levels of oxidative stress and inflammation are considered important factors in the progression of NAFLD and other related diseases, it seems that antioxidants and continuous exercise may help eliminate this condition (15). Despite the significant antioxidant and anti-inflammatory role of quercetin, the effect of this flavonoid with exercise has not been evaluated in the heart tissue of patients with cancer. This study aimed to investigate the effect of quercetin plus continuous exercise on the oxidative stress biomarkers, including SOD, CAT, and malondialdehyde (MDA) enzymes in rats' heart tissue with colorectal cancer.

METHODS:

In this experimental study, 80 male Sprague-Dawley rats (aged 4 to 5 weeks, 200-220 mg/kg) were selected from a laboratory animal center and were included. The sample size was determined based on previous studies. The rats were kept under controlled climatic condition (22 ± 2°C, 50 ± 5% humidity, and a 12:12 light-dark cycle) and standard laboratory conditions and received water ad libitum. First, animals were divided into control and patient (treated with Azoxymethane) groups. Rats in the control group were exposed to a standard diet (14% fat, 55% carbohydrate, 28% protein, and 3% others) for 3 weeks. Whereas after adjustment to the new environment, to induce colon carcinoma, all animals in groups 1-7 were injected subcutaneously with a weekly dose (15 mg/kg) of Azoxymethane (AOM) (5). All injections were performed twice a week with an equal interval for two weeks (weeks 4 and 5). In the sixth week, to ensure colon carcinogenesis induction, Dextran Sodium Sulfate 2% (DSS 2%) was added to the drinking water for 7 days until all rats were fed the basal diet before the fourth week. After that, animals in the patient group were subdivided into 7 subgroups (n=10 each) including (1) patient, (2) saline, (3) quercetin, (4) continuous exercise, (5) intermittent exercise, (6) continuous exercise plus quercetin, and (7) intermittent exercise plus quercetin groups. The continuous exercise protocol was set at a speed of 15 m/min for 5 min in the first week, while the speed was increased 1-2 m/min, and time increased 1-2 min each week. The exercise was performed at 5 sessions per week. The intermittent exercise consists of 8 weeks (3 sessions per week), and each session consists of 10 sets (a 1-min activity with 50% intensity + 2 min rest between each set), starting with a speed of 14 m/min and increased 2 m/min each week until it reached 28 m/min in the eighth week (16,17). Quercetin (10 mg/kg) (20) was dissolved in carboxymethyl cellulose to investigate the protective effects. The selected doses were based on the previous pharmacological studies on these two supplements. This procedure was performed for 8 weeks. After completing the study period, all animals were sacrificed through the injection of Sodium thiopental (100 mg/kg body weight) under completely similar conditions. The activity of SOD, CAT, and MDA enzymes was measured by diagnostic kits according to the manufacturer protocols. This study was approved by the Animal Ethics Committee of Kerman University of Medical Sciences (Ethical code: ir.kmu.rec.1398.034).

Statistical analysis

A quantitative description of data was performed as means and standard deviations. One-way ANOVA and Tukey's post-hoc tests were used to investigate the significant changes in each variable. Statistical significant level was considered at $P<0.05$. All statistical analyses were performed using SPSS 21 software.

RESULTS:

A The mean and standard deviation of the level of oxidative biomarkers are shown in **Table 1**. There was a significant difference in the concentration of MDA in

Table 1. Comparison of the mean and standard deviation of oxidative stress parameters in different groups

Group	CAT-unit/mg protein	SOD-unit/mg protein	MDA-nmol/g
Control	10.85± 157.6	36.47 ± 6.94	30.01 ± 4.28
Patient	117.5 ± 12.04	16.35 ± 5.39	58.92 ± 6.06
Saline	114.1 ± 14.29	16.35 ± 4.93	59.17 ± 5.23
Quercetin	143.2 ± 11.66	28.77 ± 5.51	43.52 ± 6.21
Continuous exercise	146.58 ± 8.37	30.01 ± 4.99	38.35 ± 4.89
Intermittent exercise	142.9 ± 11.66	29.25 ± 3.86	38.6 ± 6.88
Quercetin + continuous exercise	150.9 ± 10.13	33.05 ± 5.25	34.88 ± 5.54
Quercetin + intermittent exercise	148.61 ± 9.55	31.74 ± 6.17	36.37 ± 6.14
P-value	0.0001	0.0001	0.0001

*Statistical significant level was considered at P<0.05.

heart tissue between the groups (P=0.001). The concentration of MDA in the heart tissue was significantly higher in the patient (58.92 ± 6.06 nmol/g) and saline (59.17 ± 5.23 nmol/g) groups compared to the other groups (P=0.001). The use of quercetin, especially in combination with exercise, significantly decreased the mean MDA concentration in the rats' heart tissue compared to the patient and saline groups (P=0.0001) (**Figure 1**). Although there was no significant difference in the mean MDA concentration between the quercetin, exercise, and quercetin plus exercise groups, the use of quercetin plus exercise caused a slight decrease in MDA concentration (**Figure 1**). Mean levels of catalase and superoxide dismutase in the heart tissue of the patient (117.52 ± 12.04 and 16.35 ± 5.39 unit/mg protein, respectively) and saline groups (114.11 ± 14.29 unit/mg protein, respectively) were significantly lower than the other groups (P=0.000). The use of quercetin alone or combined with intermittent or continuous exercise significantly increased the mean activity of catalase and superoxide dismutase (**Figure 1**) in the rats' heart tissue compared to the patient and saline groups (P=0.001). There was no significant difference in the mean activity of CAT and SOD enzymes between quercetin, exercise, and quercetin plus exercise groups. However, the use of quercetin plus exercise increased the activity of these enzymes to some extent.

DISCUSSION:

In this study, we investigated the effect of quercetin alone and in combination with intermittent and continuous exercise on the oxidative stress biomarkers of heart tissue in cancerous rats. This study showed that the concentration of SOD and CAT in cancerous rats' heart tissue was significantly decreased compared to the control group. In contrast, the mean concentration of MDA increased significantly. We also showed that the increase in oxidative stress and the decrease in antioxidants are probably the effects of cancer on the heart tissue

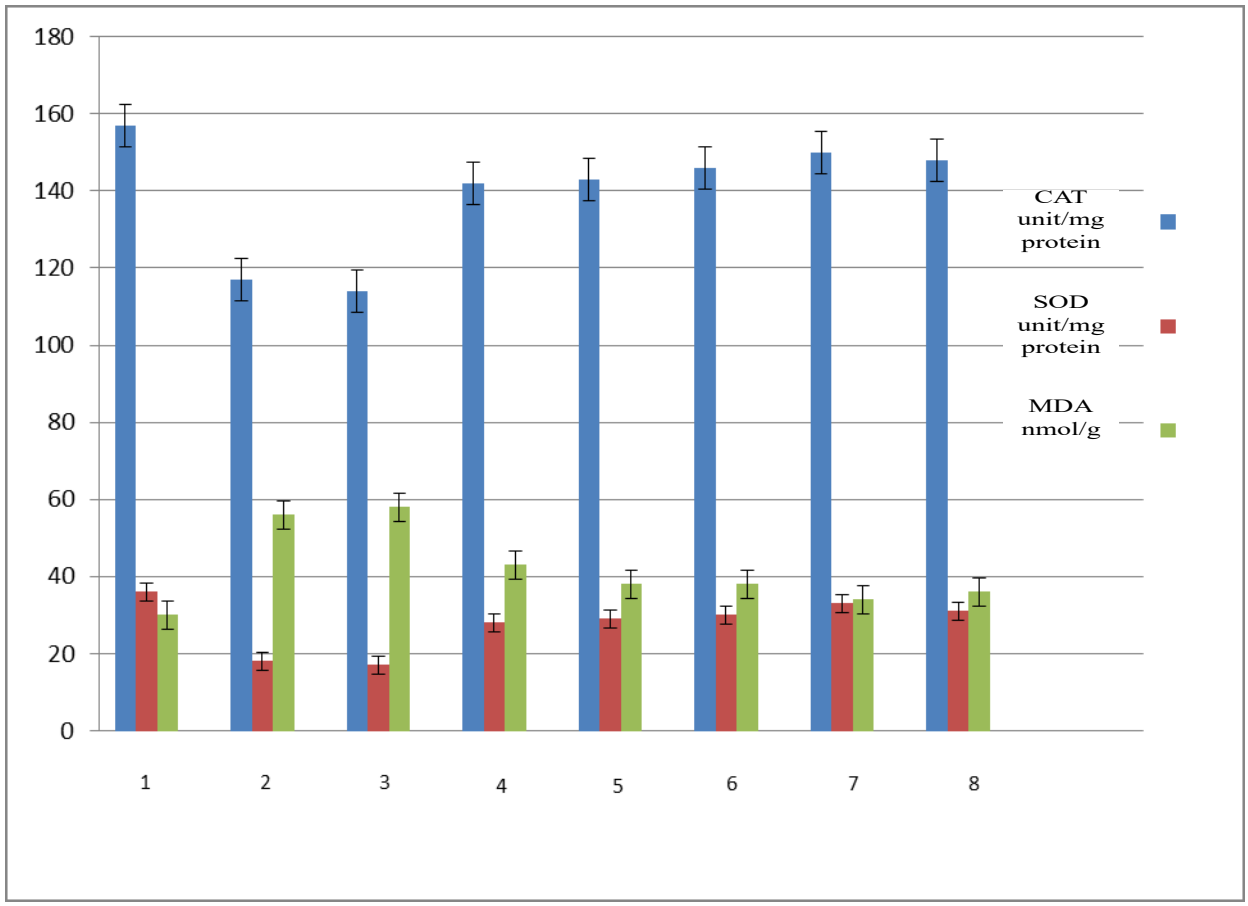

Figure 1. Comparison of the mean activity of oxidative parameters in different groups. **1.** Control, **2.** Patient, **3.** Saline, **4.** Quercetin, **5.** Continuous exercise, **6.** Intermittent exercise, and **7.** Quercetin + continuous exercise8.Quercetin + intermittent exercise

associated with apoptosis or cell death. Although the precise mechanism underlying this process is not well understood, it seems that an increase in free radicals in cancer results in damage to intracellular organelles, including the mitochondrial membrane, leading to the apoptotic activation pathway (18). Since mitochondria are considered as "the powerhouses of the cell" and control the amounts of intracellular free radicals, damage to the mitochondrial membrane leads to the release of apoptotic signals, including cytochrome C. The uncontrolled production of ROS throughout the electron transport chain is associated with more severe cellular damage and apoptosis (19). In a study by Schnider et al. (2001), the effect of resveratrol 0.01% for 7 weeks by gavage on APCmin/+ rats was investigated, and it was found that the rate of the small intestine and colon tumors production decreased in the resveratrol group. It was also revealed that Cyclin D1 and Cyclin D2 levels were decreased in the study group, indicating the reducing effect of resveratrol on the expression of genes directly involved in cell proliferation and cell cycle (20). In another study by Volate et al. (2005), entitled "Modulation

of aberrant crypt foci and apoptosis by dietary herbal supplements (quercetin, curcumin, silymarin, ginseng, and rutin)" on F344 rats with colorectal cancer induced by the injection of Azoxymethane, the use of quercetin (1.5%) in the diet of rats significantly reduced the abnormal colonic crypts (4-fold decrease). Still, no similar effect was reported for rutin alone. It was also revealed that the consumption of supplements containing all the compounds mentioned above reduced aberrant crypt foci (ACF) by 2, 1.8, 1.5, and 1.2 times, respectively. However, quercetin reduced ACF levels and increased apoptosis in the rats (3-fold increase) more than other compounds. Analysis of Caspase-9, Bax, and Bcl-2 using the western blot method showed that quercetin induces apoptosis through mitochondrial pathways. This effect was also reported for curcumin. This study suggests the role of quercetin and other herbal compounds in reducing the rate of precancerous lesions and inducing apoptosis in the colon (21). These results are highly similar to those of the present study. However, the biomarkers of oxidative stress in the heart tissue were examined in this study. Therefore, the present study indicates that cancer induces oxidative stress through ROS production and inflammation in the heart tissue, leading to apoptosis or cell death. According to these results, it seems that antioxidants or drugs, which protect cells against oxidative stress, can greatly improve the oxidative status and inflammation in the heart tissue of patients with cancer. Therefore, in this study, we investigated the therapeutic effects of quercetin alone or in combination with intermittent and continuous exercise on the reduction of oxidative stress and inflammation of the heart tissue in cancer patients. These results showed that the heart damage was significantly reduced in quercetin-treated rats compared to the patient group. These effects were associated with a significant decrease in the level of MDA peroxidative and a significant increase in SOD and CAT enzymes' levels. Although quercetin or exercise alone improved the oxidative and inflammatory status of the heart tissue cells, quercetin with intermittent or continuous exercise showed a stronger therapeutic effect. So far, several studies have investigated the therapeutic effect of antioxidants. In the previous study, the effect of resveratrol alone or in combination with exercise on the number of apoptotic cells of the liver, oxidative stress, and inflammatory markers was investigated (10). The results suggest that resveratrol, especially in combination with intermittent or continuous exercise, was associated with a significant increase in SOD and CAT activity and IL-10 levels in the liver. In contrast, the level of TNF-a, lipid peroxidation, and the number of apoptotic cells in the liver were significantly reduced (10). Several studies have also reported the increased expression of anti-inflammatory cytokines, such as IL-4 (22). Protective effect of resveratrol against other inflammatory mediators, such as IL-6, IL-1, IL-β, INF-γ, IL-5, IL-33 (23), nitric oxide (NO), inducible nitric oxide synthase (iNOS), Cyclooxygenase-2 (COX-2), and matrix metalloproteinases (MMPs) (24) were also reported in the previous studies. Many studies have also reported that resveratrol protects cells by its high antioxidant property (25). In a recent study, Elbe et al. (2017) showed that resveratrol decreases hepatotoxicity induced by Acetaminophen by decreasing MDA levels and iNOS activity and increasing the level of SOD, CAT, and GSH in the liver tissue (26). Several studies have examined the therapeutic effects of the combination of antioxidants and various exercises on improving the function of different tissues in patients. A clinical trial study by Faghihzadeh et al. (2014) showed that the use of resveratrol (500 mg/day for 12 weeks) along with exercise significantly decreased the levels of alanine aminotransferase (ALT), inflammatory cytokines, Nuclear Factor Kappa B (NF-κB) activity, serum levels of cytokine-18, and liver cirrhosis (27). In this study, intermittent and con-

tinuous exercise alone or in combination with quercetin reduced oxidative stress and inflammation in the heart tissue of rats with cancer, indicating the positive role of exercise in improving cardiac function. However, there was no difference between the intermittent and continuous exercise groups. Although the mechanism underlying the reducing effect of exercise on oxidative stress and inflammation has not yet been well understood, alteration in the expression of some genes, including increased antioxidant and anti-inflammatory genes, seems to be one of the possible mechanisms (10). Therefore, according to the present study and previous studies, combination therapy (quercetin plus exercise) may reduce the effects of cancer on other organs, especially on the heart tissue, through reducing oxidative stress by increasing the levels of free radicals, improving antioxidants, and reducing inflammation.

CONCLUSION:

According to the results, cancer is associated with increased oxidative stress and decreased antioxidants in the heart tissue. Although quercetin can be used as a compound with high antioxidant properties to reduce oxidative stress in the heart tissue of patients with cancer, combination therapy (quercetin plus intermittent or continuous exercise) may provide a better balance of oxidative status of heart tissues in patients with cancer.

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CONFLICT OF INTERESTS:

The authors declare that there is no conflict of interests associated with this work.

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