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Research Article

The Effect of Cinnamon Extract and Long-Term Aerobic Training on Heart Function, Biochemical Alterations and Lipid Profile Following Exhaustive Exercise in Male Rats

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Abstract
Purpose: Regular training is suggested to offer a host of benefits especially on cardiovascular system. In addition, medicinal plants can attenuate oxidative stress-mediated damages induced by stressor insults. In this study, we investigated the concomitant effect of cinnamon extract and long-term aerobic training on cardiac function, biochemical alterations and lipid profile following exhaustive exercise.
Methods: Male Wistar rats (250-300 g) were divided into five groups depending on receiving regular training, cinnamon bark extraction, none or both of them, and then encountered with an exhausted exercise in last session. An 8-week endurance training program was designed with a progressive increase in training speed and time. Myocardial hemodynamics was monitored using a balloon-tipped catheter inserted into left ventricles. Blood samples were collected for analyzing biochemical markers, lipid profiles and lipid-peroxidation marker, malondealdehyde (MDA).
Results: Trained animals showed an enhanced cardiac force and contractility similar to cinnamon-treated rats. Co-application of regular training and cinnamon had additive effect in cardiac hemodynamic ($P<0.05$). Both regular training and supplementation with cinnamon significantly decreased serum levels of total cholesterol, low-density lipoprotein (LDL), and increased high-density lipoprotein (HDL) level and HDL/LDL ratio as compared to control group ($P<0.01$). Furthermore, pre-treatment with cinnamon extract and/or regular training significantly reduced MDA level elevation induced by exhausted exercise ($P<0.01$).
Conclusion: Long-term treatment of rats with cinnamon and regular training improved cardiac hemodynamic through an additive effect. The positive effects of cinnamon and regular training on cardiac function were associated with a reduced serum MDA level and an improved blood lipid profile.

Introduction

Several studies have demonstrated that abnormal blood lipids and lipoproteins are the major risk factors for cardiovascular diseases including ischemic heart disease and atherosclerosis.[1,2] Dyslipidemia is one of the symptoms of metabolic syndrome that associates with obesity, diabetes and other co-morbidities. Dyslipidemia and hypercholesteromia result in endothelial dysfunctions, decreased nitric oxide production and increased reactive oxygen species (ROS) generation.[1-3]

It has been shown that long-term, regular exercise improved lipid profile by high-density lipoproteins (HDL) maturation and composition, cholesterol efflux and its delivery to the receptors.[4] The regular exercise can also result in decreased blood level of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG).[4,5] Therefore, regular exercise can reduce development of coronary heart disease, cardiac events and death. However, performing an exhaustive exercise by subjects who have inactive life style can be a precipitating factor for myocardial infarction and heart failure.[5] Long-term training benefits in cardiovascular health have been attributed, in particular, to myocardial, for example, enhanced oxidative capacity of the cardiac muscle and correction of endothelial dysfunction in the coronary vasculature adaptations in response to the stressor insults.[2,5] The alterations in response to short-term and exhaustive exercise may worsen cardiac left ventricle dimensions and contractile function. During exhaustive exercise, heart can subject to ischemic injury.[6-8] Ischemic injury of cardiomyocytes reduces a significant fraction of their function.[2] This myocardial injury can lead to primary pathological appearance of coronary artery disease.[2,8]

On the other hand, it is suggested that supplementation with antioxidant nutrients and other medicinal plants in humans and animals can attenuate ROS-mediated

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damage to the heart after an ischemic insult.[9-11] Some medicinal plants are potent antioxidants because of containing polyphenolic compounds. Cinnamon *(Cinnamomum Zeylancium*, from *Lauraceae* family*)* usually has been used as a popular condiment in meal of Asian people.[12,13] The excellent antioxidant activities of cinnamon bark, leaf and fruit extracts and essential oils have been reported in several in vitro and in vivo studies.[12-15] This plant also has positive effects on lipid metabolism.[12] However, there were no reports indicating concomitant effect of cinnamon supplementation and regular exercise on cardiac function and biochemical alterations.

The present study has evaluated the hypothesis that long-term regular aerobic training and supplementation by cinnamon bark extract (CBE) in rats can provide additive effects against alterations induced by an exhaustive exercise on cardiovascular system in male rat. For this purpose, we have assessed the hemodynamic activities of the heart and markers of tissue injury and oxidative stress in the serum. Additionally, this study has examined the effect of long-term regular training and supplementation with cinnamon bark on blood lipid profile in rats.

Materials and Methods

Animals

In this study, 30 male Wistar rats (8-week-old) weighing 250-300 g, were housed in a clean rodent room under a 12:12-h light- dark cycle, and maintained at a temperature of 24±1°C. The animals were fed with standard rodent laboratory diet and tap water *ad libitum*. All animal experimentations were approved by the Ethical Committee of the Tabriz University of Medical Sciences and carried out in an ethically manner according to the guidelines provided.

Experimental design

The rats were divided into five groups (6 rats in each) based on receiving regular training, exhaustive exercise and/or cinnamon bark extract (CBE) supplementation:

1. (**Con**): the control rats were in the rest status and received normal diet;
2. (**Con+Exst**): the rats received normal diet and performed a session of exhaustive exercise;
3. (**Cinn+Exst**): the rats supplemented with CBE for 8 weeks and performed a session of exhaustive exercise;
4. (**Train+Exst**): the rats performed regular aerobic training for 8 weeks, received normal diet and performed a session of exhaustive exercise in last session; and
5. (**Cinn+Train+Exst**): the rats performed regular training and supplemented with CBE for 8 weeks and performed a session of exhaustive exercise in last session.

Firstly, all rats were familiarized to the treadmill running for one week at 10m/min, 0% grade and 10min/day. Then, a chronic endurance training program was began with a progressive physical exercise such that training speed and time were gradually increased up to 22m/min for 90 min/day at fourth week. Training continued 90 min/day, 5 days/week for 8 weeks. In the last session, the trained and untrained rats ran on the treadmill to exhaustion such that running speed was began with 10 m/min, and then it was progressively increased up to 22m/min at 12th min and kept fixed to make the rats to be fully exhausted.[16] Furthermore, rats in the supplemented groups (i.e., groups 3 and 5) were received 200 mg/kg/day of cinnamon bark extract (CBE) for 8 weeks by oral gavages.[17]

Preparation of cinnamon barks extracts (CBE)

The powdered cinnamon barks (350 g) were extracted five times with methanol (90%), at room temperature overnight. Then the materials were dried using a vacuum evaporator. The extracts (50 g) were stored at -20°C until use.

Isolated heart protocol

After the exhaustions of animals at last session, they were immediately anesthetized by injection of ketamine (60 mg/kg) and xylazine (10 mg/kg). After opening the chest cavity, blood samples were collected from portal vein of rats, and then, their hearts were quickly excised and immersed in ice-cold krebs-Henseliet (K-H) solution. Then, the aorta was cannulated and the heart was retrogradely perfused via the aortic cannula in a Langendorff apparatus with K-H solution (pH=7.4) containing: 118 mM Nacl, 4.8 mM KCl, 1.2 mM MgSO4, 1.0 mM KH2PO4, 27.2 mM NaHCO3, 10 mM glucose and 1.25 mM CaCl2. The perfusate was bubbled with a mixture of 95% O2, and 5% CO2. The perfusate and bath temperatures were maintained at 37°C by thermostatically controlled water circulator (Satchwell Sunvic LTD). The isolated heart was perfused at a constant mean pressure of 75 mmHg.[18]

Myocardial hemodynamic parameters

Myocardial hemodynamic parameters were recorded and monitored using a latex balloon-tipped catheter inserted through an incision in the left atrium and advanced through the mitral valve into the left ventricle and connected to a pressure transducer and a recording system (Powerlab systems, Australia). The balloon was inflated and equilibrated to give an end-diastolic pressure of 5-10 mmHg. Left ventricular systolic and diastolic pressures and time derivatives of pressures were measured during ventricular contraction (+dP/dt) and relaxation (-dP/dt). Left ventricular developed pressure (LVDP) was calculated as the difference between the systolic and the diastolic pressures. The work index of the heart (LVDP×HR) was derived from the product of LVDP and heart rate (HR). Coronary flow (CF) rate was measured by collecting the effluent drained through the isolated heart.[18]

Blood markers analysis

Lipid profile

The blood samples were obtained and centrifuged at 3500 rpm for 10 min at 4°C and plasma was collected. The levels of triacylglycerol and very low density lipoprotein (VLDL) in serum were determined by enzymatic kits (Ziest Chem Diagnostic kits, Iran) with utilizing glycerol as a standard. Additionally, total cholesterol (Chol), high density lipoprotein (HDL) and low density lipoprotein (LDL) levels were determined based on enzymatic methods by diagnostic kits, (Ziest Chem, Iran), with utilizing cholesterol as a standard.

Creatine kinase and lactate dehydrogenase

Plasma creatine kinase (CK) and lactate dehydrogenase (LDH) activities were measured spectrophotometrically (UV-160, Shimadzu) in a blinded manner. The LDH and CK activity were measured by an automatic biochemistry analyzer using a commercially available kit according to the manufacturer's instructions. The absorbance of the solution for LDH was detected at 492 nm and for CK at 340 nm by a spectrophotometer. The results were reported in U/L.

Malondealdehyde content in blood

Malondealdehyde (MDA), as a marker of lipid peroxidation and oxidative stress, was estimated by measuring the thiobarbituric acid-reactive substances (TBARS) in blood sample. In this method, MDA was measured by its reactivity with TBA in acidic conditions to generate a pink coloured chromophore, which was read spectrophotometrically. In brief, the samples were mixed with 1 mL 10% trichloroacetic acid and 1 mL 0.67% thiobarbituric acid. Then, the samples were heated in boiling water for 15 min, and N-butanol (2:1, v:v) was added to the solution. After centrifugation (900g, 5 min), TBARS were determined from the solution absorbance at 532 nm.[19]

Statistical analysis

Data were expressed as mean±SD. Statistical analysis of data was carried out using SPSS 16 for windows software (SPSS INC, Chicago, IL, USA). A *One-way ANOVA* with *Tukey* post-hoc multi-comparison test was used to compare the differences between groups. A *P* values less than 0.05 were considered significant.

Results

There were no significant changes in body weight between all groups (Table 1). The plasma CK and LDH activity were also reported in Table 1. As shown, there were no significant differences in these biochemical markers between experimental groups.
Pretreatment of the animals with cinnamon extract and aerobic exercise together increased the systolic pressure of the myocardium in comparison with those of control animals (Table 2). Although the alterations of HR between groups were not statistically significant, it seems that pretreatment with cinnamon tends to reduce the fluctuations of HR induced by exercise. The coronary flow tended to increase (although statistically not significant) by regular training and its co-application with cinnamon as compared with those of control group (Table 2).

Table 1. The body weight and serum level of biochemical markers (CK and LDH) in rats submitted to an exhaustive exercise and pretreated with 200 mg/kg of CBE and/or performed regular aerobic training for 8 weeks.

Groups	Parameters		
	Body weight (g)	CK (U/L)	LDH (U/L)
Con	264 ± 35	605.2 ± 176.0	372.3 ± 52.5
Con+Exst	248 ± 34	683.2 ± 190.0	395.3 ± 62.5
Cinn+Exst	268 ± 54	511.4 ± 173.2	362.0 ± 65.1
Train+Exst	228 ± 65	609.0 ± 547.2	356.0 ± 35.7
Cinn+Train+Exst	223 ± 32	583.2 ± 231.7	407.0 ± 54.3

Result are expressed as mean ± SD (n=6 for each group). Con: Control, Exst: Exhausted, Cinn: Cinnamon, Train: Training, CK: Creatine kinase, LDH: Lactate dehydrogenase.

Table 2. The heart rate (HR), diastolic (Pd) and systolic (Ps) pressures and coronary flow (CF) in heart of rats submitted to an exhaustive exercise and pretreated with 200 mg/kg of CBE and/or performed regular aerobic training for 8 weeks.

Groups	Parameters			
	HR (bpm)	Pd (mmHg)	Ps (mmHg)	CF (ml/min)
Con	243 ± 22	5.6 ± 0.9	90 ± 12	12.4 ± 1.1
Con+Exst	260 ± 36	6.8 ± 2.4	108 ± 13	13.2 ± 2.4
Cinn+Exst	255 ± 15	5.8 ± 3.5	114 ± 10*	11.6 ± 1.9
Train+Exst	279 ± 50	6.3 ± 5.1	116 ± 8*	15.1 ± 1.9
Cinn+Train+Exst	246 ± 42	7.2 ± 3.4	118 ± 9*	14.7 ± 2.6

Result are expressed as mean ± SD (n=6 for each group). **P<0.05* compared to Con group. Con: Control, Exst: Exhausted, Cinn: Cinnamon, Train: Training.

Furthermore, the trained animals showed an enhanced cardiac force (LVDP; Figure 1) regarding the untrained animals (P<0.05). It is shown that the cinnamon supplementation has partly a positive inotropic effect and improves the performance of the heart. As it seen, the concomitant effect of both regular training and cinnamon on LVDP was similar to regular training effect (Figure 1). Co-application of both regular training and cinnamon significantly increased the indices of cardiac contractility (dp/dt; Figure 2) and cardiac work (HR×LVDP; Figure 3) (P<0.05); and these two treatment protocols had additive effect in this regard.

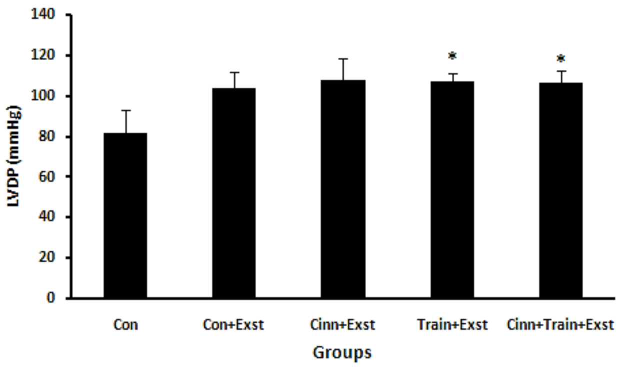

Figure 1. The changes of LVDP in rats submitted to an exhaustive exercise and pretreated with 200 mg/kg of CBE and/or performed regular aerobic training for 8 weeks. Result are expressed as mean ± SD (n=6 for each group). **P<0.05* compared to Con group. Con: Control, Exst: Exhausted, Cinn: Cinnamon, Train: Training.

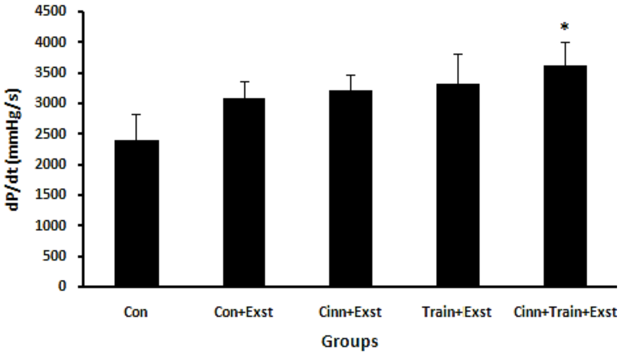

Figure 2. The changes of myocardial contractility (dP/dt) in rats submitted to an exhaustive exercise and pretreated with 200 mg/kg of CBE and/or performed regular aerobic training for 8 weeks. Result are expressed as mean ± SD (n=6 for each group). **P<0.05* compared to Con group. Con: Control, Exst: Exhausted, Cinn: Cinnamon, Train: Training.

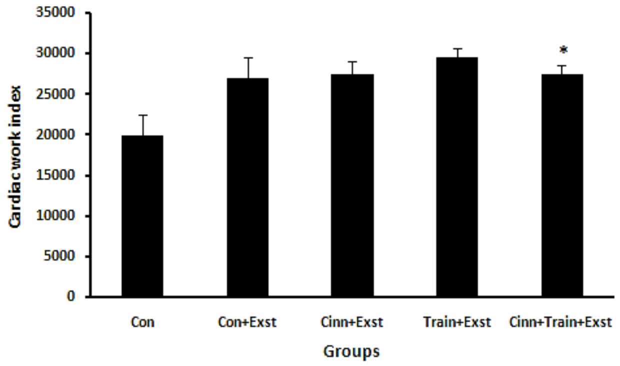

Figure 3. The changes of cardiac work index (HR×LVDP) in rats submitted to an exhaustive exercise and pretreated with 200 mg/kg of CBE and/or performed regular aerobic training for 8 week. Result are expressed as mean ± SD (n=6 for each group). **P<0.05* compared to Con group. Con: Control, Exst: Exhausted, Cinn: Cinnamon, Train: Training.

The alterations of lipid profile in animal groups were shown in Table 3. Both regular training and supplementation with CBE significantly decreased the total cholesterol (Chol) level as compared to control group (P<0.01). Cholesterol content in serum of Con+Exst group was also lower than those of Con group (P< 0.05). Serum level of LDL was significantly decreased in all treated groups in comparison to untreated control group (P<0.01). HDL level was significantly increased by regular training with or without CBE supplementation (P<0.05), and cinnamon alone had no effect on HDL level (Table 3). Furthermore, the ratio of HDL/LDL was significantly increased in Cinn+Train+Exst group as compared with control group (P<0.05). However, the elevation of HDL/LDL in other groups was not statistically significant. In addition, the serum level of VLDL was elevated in Cinn+Exst group as compared with those of other groups (P<0.05) (Table 3).

Finally, exhaustive exercise significantly increased the serum level of MDA as compared with those of control animals. Pre-treatment with regular training and/or cinnamon extract significantly reduced serum level of MDA as compared with those of Con+Exst group (P<0.01) (Figure 4).

Discussion

The findings of present study indicated that chronic cinnamon supplementation and regular aerobic training have additive effects on cardiac activities. This positive additive effect is also shown in some parameters of blood lipid profile. The improvement in cardiac function by both cinnamon supplementation and regular training was associated with a reduction in serum MDA level and improvement of blood lipid profile.

Table 3. The serum level of lipid profile in rats submitted to an exhaustive exercise and pre-treated with 200 mg/kg of CBE and/or performed regular aerobic training for 8 weeks.

Groups	Parameters				
	Chol (mg/dl)	**LDL-C (mg/dl)**	**HDL-C (mg/dl)**	**HDL/LDL (mg/dl)**	**VLDL (mg/dl)**
Con	73.0 ± 6.1	42.6 ± 5.7	17.3 ± 2.3	0.6± 0.2	5.3 ± 0.9
Con+Exst	57.0 ± 6.8*	23.6 ± 3.1*	28.0 ± 4.0*	1.2± 0.3	8.1 ± 2.1
Cinn+Exst	48.4 ± 8.1*	17.4 ± 5.5*#	19.9 ± 3.8	1.2± 0.8	11.8 ± 1.4*
Train+Exst	52.7 ± 7.5*	22.4 ± 4.1*	32.0 ± 4.0*	1.3± 0.9	7.6 ± 1.5
Cinn+Train+Exst	47.7 ± 8.4*	16.6 ± 1.5*#	25.3 ± 3.2*	1.4± 0.1*	7.5 ± 1.1

Result are expressed as mean ± SD (n=6 for each group). **P<0.05* compared to Con group. #*P<0.05* compared to Con+Exst group. Con: Control, Exst: Exhausted, Cinn: Cinnamon, Train: Training, Chol: Cholesterol.

The general population is frequently suggested to perform regular physical activity, with different types of training programs to maintain good cardiovascular health.[20] Therefore, the effects of training programs need to be evaluated. Many studies support the finding that regular training has a cardiac protective effect.[21-23] In consistent with previous studies, our results also confirmed that long term regular training enhanced the cardiac force and improved cardiac contractility.[20,24] In this study, although no significant changes were observed in some parameters including body weight, heart rate, coronary flow and enzymatic markers between untrained and trained supplemented rats, the exhaustive exercise increased the serum CK and LDH activities and MDA level regarding to control animals, indicating cellular damage and reflecting the stress on the cells. Training benefits on cardiovascular health have been attributed in particular to myocardial adaptations including enhanced oxidative capacity of the cardiac muscle and correction of endothelial dysfunction in the coronary vasculature.[25,26]

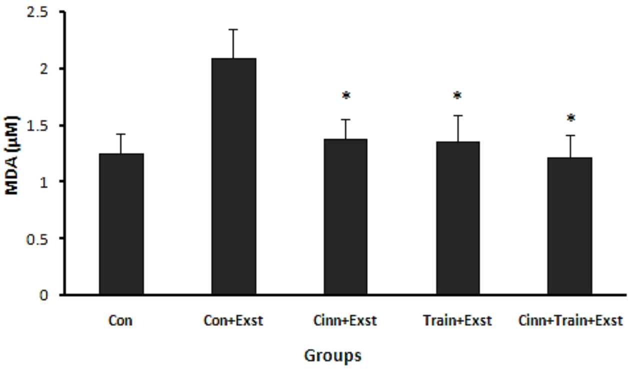

Figure 4. The changes of Malondealdehyde (MDA) in serum of rats submitted to an exhaustive exercise and pretreated with 200 mg/kg of CBE and/or performed regular aerobic training for 8 weeks. Result are expressed as mean ± SD (n=6 for each group). **P<0.05* compared to Con+Exst group. Con: Control, Exst: Exhausted, Cinn: Cinnamon, Train: Training.

In addition, the cinnamon supplementation had partly a positive inotropic effect and improves the performance of the heart, as well. The simultaneous applications of cinnamon and exercise have not been reported in the previous studies. The interesting data is that concomitant administration of both regular training and cinnamon pretreatment has additive effect in improving cardiac contractility. Although pretreatment with cinnamon did not showed significant chronotropic activity in heart; however, it seems that it tends to reduce the fluctuations of HR induced by exercise and thereby contributes to regular beating of the heart. It is more likely that cinnamon affects positively on hemodynamic responses of the heart to the exercise. It is expected that the coronary flow is also increased as the cardiac performance increases. In this study, the coronary flow was increased by cardiac performance enhancement through administration of long-term training or cinnamon, although this alteration was not statistically significant.

The most significant risk indicators for cardiovascular alterations are the increased serum cholesterol, triglyceride, LDL and decreased HDL which all of them are related to oxidative stress reactions.[3,19] The prolonged trained animals showed decreased LDL, increased HDL-cholesterol and HDL/LDL ratio. These effects were potentiated when the training was conducted with concomitant cinnamon pretreatment. It seems that co-application of cinnamon pretreatment with regular training may enhance the good effects of training on lipid metabolism and cardiac function. It has been suggested that a long-time exercise may increase the capacity to clear the cholesterol from circulation by enhancing lipoprotein lipase activity in plasma.[27] In agreement with our study, various studies have reported that prolonged moderate-intensity exercise increased serum level of HDL in hypercholesterolemia individuals.[28] Furthermore, there are reports indicating that chronic exercise in animal models including white rabbit,[29] guinea pig and rat[27] increases the serum level of HDL. The increase in serum level of LDL is lead to increased coronary vascular disease risk. HDL is the reverse cholesterol transporter that delivers cholesterol from the surface peripheral cells to the liver that finally results in decrease in serum level of LDL, and VLDL.[1,5,10,30] The cinnamon like as physical activity may increase the efficacy of HDL-mediated reverse cholesterol transport, leading to decreased risk of cardiovascular disease.

Various hypotheses have suggested that cardiovascular damage is the result of an oxidative stress process.[21,26,23] In our study in exhausted animals, increased malondialdehyde level could indicate the increased lipid peroxidation and overproduction of reactive oxygen species (ROS). Regular training as well as cinnamon supplementation seems to delay the accumulation of ROS-mediated cell damage by preventing the lipoperoxidation and MDA level elevation in the myocardium. Therefore, improvement in cardiac hemodynamic and function in trained and supplemented groups may be attributed to decreased MDA level and improved lipid profile.

Conclusion

Long-term supplementation with cinnamon bark and regular aerobic training induced beneficial effects on the serum lipid profile and lipid peroxidation following a stressor-exhaustive exercise. In addition, pretreatment of rats with cinnamon and regular training improved cardiac hemodynamic and there is additive effect in the condition of concomitant administration of them.

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Ethical Issues

All animal experimentations were approved by the Ethical Committee of the Tabriz University of Medical Sciences and carried out in an ethically manner according to the guidelines provided.

Conflict of Interest

The authors report no conflict of interests.

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