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Full Length Research Paper

Protective effect of the combination of exercise and curcumin supplementation on cardiac system in rats exposed to lead

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Effects of exercise training and curcumin supplementation, alone or combined on cardioprotective markers in left ventricle were investigated in rats during chronic exposure to lead acetate. Forty (40) male rats were randomly assigned to; sham (Sh), training + lead (TL), curcumin + lead (CL), training + curcumin + lead (TCL), and lead (L) groups. Heat shock protein (HSP_{72}) and enzyme activities were determined in rat hearts after receiving 20 mg/kg of lead acetate in the TL, TCL, CL and L groups and 30 mg/kg turmeric in the TCL and CL groups for 8 weeks, 3 times a week. In addition, the rats in the TL and TCL groups performed treadmill running at a speed of 15 to 22 m/min for 25 to 64 min, 5 times a week for 8 weeks. One-way analysis of variance (ANOVA) indicated that administration of lead can evoke a significant increase in HSP_{72} and malondialdehyde (MDA) in the left ventricle homogenates and a significant decrease in serum total antioxidant capacity (TAC). However, endurance training and\or curcumin supplementation resulted in a significant decrease in HSP_{72} and MDA levels and significant increase in the level of serum TAC (serum Total Antioxidant Capacity). These results can suggest that concomitant exercise and curcumin supplementation may have a more cardioprotective effect observed by amelioration of lead-induced cardiotoxicity.

Key words: Turmeric, endurance training, lead acetate, stress proteins, antioxidant.

INTRODUCTION

Cardiovascular disease (CVD) has remained the leading cause of morbidity and mortality worldwide, and therefore strategies that aim to improve prevention in people without existing disease (primary prevention) are important for managing the overall burden of disease (Heneghan, 2011). Although regulation of emissions has led to improvements in air quality, epidemiological data indicates clearly that air pollution continues to have widespread effects on human health. Literally, dozens of studies have demonstrated that poor air quality is associated with increased morbidity and mortality due to numerous causes. Air pollution is thought to be responsible for approximately 3 million deaths per year worldwide (Ritz, 2010). Lead is a persistent and common environmental contaminant. Like other commonly found, persistent toxic metals, –mercury, arsenic, and cadmium– lead damages cellular material and alters cellular genetics. The common mechanism of all these toxic

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metals involves oxidative damage. Toxic metals increase production of free radicals and decrease availability of antioxidant reserves to respond to the resultant damage (Patrick, 2006). Recent *in vivo* studies in lead exposed animals and workers showed the generation of reactive oxygen species, stimulation of lipid peroxidation and decreased antioxidant defense system, supporting the role of oxidative stress in lead toxicity (Haleagrahara et al., 2010).

Recent emphasis on the use of natural and complementary medicines has drawn the attention of the scientific community for the potential of these treatment options (Daniel et al., 2004; Kalpana et al., 2007). The lifestyle modification approach focuses on dietary control, regular exercise, weight reduction and stress management, aiming toward normalization of CVD risk factors (Srimahachota et al., 2010). Curcumin, a hydrophobic polyphenol, is the yellow pigment in the Indian spice turmeric derived from the rhizome of the herb *Curcuma longa*. Curcumin is also known as diferuloylmethane and chemically is a bis-α, β-unsaturated β-diketone. Differing in methoxy substitutions on the aromatic ring, turmeric contains three natural analogues, the so-called curcuminoids, with curcumin being the most abundant (77%) and the less common demethoxycurcumin (17%) and bisdemethoxycurcumin (3%). It has a long history as an herbal remedy for a variety of diseases. It has been ascribed a multitude of therapeutic activities and has been associated with suppression of inflammation, angiogenesis, tumorigenesis, and diabetes, and with therapeutic effects in diseases of the cardiovascular, pulmonary and neurological systems and of skin and liver. In general, most of these effects can be attributed to the antioxidant, anti-inflammatory and anti-cancer activities of curcumin. Curcumin is an effective scavenger of reactive oxygen species and reactive nitrogen species (Rajasekaran, 2011).

Epidemiological studies have shown that physical activity reduces the risk of various common diseases such as CVD, diabetes, and cancer; it also helps in reducing visceral adipose tissue (Aoi et al., 2011). A partial list of proposed mechanisms for exercise-induced cardioprotection include induction of heat shock proteins (HSP_{72}), increase in cardiac antioxidant capacity, expression of endoplasmic reticulum stress proteins, anatomical and physiological changes in the coronary arteries, changes in nitric oxide production, adaptational changes in cardiac mitochondria, increased autophagy, and improved function of sarcolemmal and/or mitochondrial ATP-sensitive potassium channels (Golbidi and Laher, 2011). Overall, more scientific evidence will undoubtedly encourage the widespread advocacy of the clinical benefits of exercise therapy in the prevention and treatment of CVD (Yung et al., 2009).

Despite the knowledge that lead can induce oxidative stress, studies have identified favorable effects of exercise training and/or antioxidants on certain cardiovascular biomarkers after acute exposure to air pollution (Kalpana et al., 2007). However, there are few data available with respect to concomitant effects of regular aerobic training and curcumin supplementation, particularly the oxidant/antioxidant equilibrium during chronic exposure to lead acetate. Therefore, the aim of the current study was to determine the effects of aerobic exercise with and/or without curcumin supplementation on cardio-protection related markers in left ventricle, including HSP_{72} and serum total antioxidant capacity (TAC). In addition, changes in malondialdehyde (MDA) level were studied in rats chronically exposed to lead acetate. It was hypothesized that these results would provide novel insights into the myocardial ameliorative potential of turmeric antioxidant and exercise training during chronic exposure to lead acetate.

MATERIALS AND METHODS

Forty (40) male Wistar rats, 8 weeks of age with body weight range of 240 ± 20 g were obtained from the Laboratory of Animal Bearing and Multiplying at the Pasture Institute of Iran. The animals were housed to a polycarbonate cage (20 × 15 × 15 cm), made at Pasture Institute of Iran. All rats were weighed on a weekly during the exercise training phase. Rats were provided with food, a standard rat chow provided by Pars Institute for animals and poultry with a daily regimen of 10 g/ 100 g body weight. Water was available *ad libitum*. The animals were maintained under standard conditions of temperature at 22 ± 2°C and 50 ± 5% humidity with an alternating 12 h light/dark cycle. The pollutant standard index (PSI) was in the acceptable range as determined by the Iranian Meteorological Organization.

The experimental protocol was approved by Department of Physiology, University of Mazandaran and was performed according to guiding procedures in the Care and Use of Animals, prepared by the Council of the American Physiological Society. Rats were acclimatized to ambient rearing conditions for 4 to 5 days (four rats per cage) and were familiarized with endurance running training on the treadmill, that designed to increase oxygen consumption and improve functioning of the cardiovascular and respiratory systems). A mild shock (0.75 mA, 500 ms duration, 0.5 Hz rate) was delivered through these loops to motivate the rats to continuously walk on the moving belt and thus avoid foot shock. The wire loops were activated during all exercise sessions, and an experimenter monitored all treadmill sessions. Rats quickly learned to stay on the belt and avoid shock, except for one rat, which would not stay on the moving belt, and thus, was quickly removed from the exercise group. They were randomly assigned to five experimental groups of 8 rats each. The groups were defined as follows:

Group 1: lead acetate (L), the animals received lead acetate at a concentration of 20 mg/kg in a water solution (for intra peritoneal injection, i.p.), 3 days in a week for 8 weeks.
Group 2: Endurance training and lead acetate (TL) - the rats in this group received lead acetate similar to that in Group 1, and in addition, they performed progressive running exercise of 15 to 22 m/min for 25 to 64 min, 5 times a week. The running speed and distance was gradually increased.
Group 3: Curcumin and lead acetate (CL) similarly received lead acetate, as well as curcumin 30 mg/kg 5 days weekly for 8 weeks (i.p.).
Group 4: Endurance training and curcumin and lead acetate (TCL);

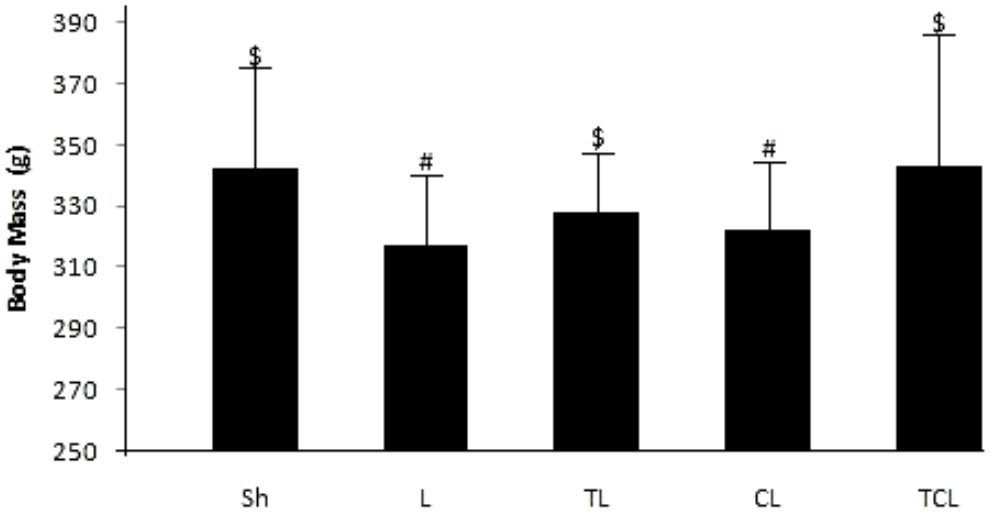

Figure 1. Body mass changes in rats during chronic exposure to lead acetate. Sh, Curcumin resolvent or ethyl oleate; TL, training + lead; TCL, training + curcumin + lead; L, lead acetate; CL, curcumin+ lead. Data are presented as mean ± SD; $, significantly different from lead group ($P < 0.001$); #, significantly different between combination (training + lead + curcumin) group with training and/or curcumin groups ($P < 0.05$).

the rats in this group performed an endurance training protocol similar to that in Group 2, and in addition, similarly received curcumin supplement and lead acetate, similar to that in Group 3.

Group 5: The sham-operate (sham); these rats received water and ethyl oleate in the same manner and for the same duration of time.

Lead acetate (Sigma) was solubilized in Milli-Q water, and curcumin was solubilized in 50% ethanol. In order to perform intra peritoneal (i.p) injections, curcumin was solubilized in ethyl oleate and was injected at a dose of 30 mg/kg. Turmeric was protected from light throughout the experiment (Daniel et al., 2004). We replicated a previously-reported lead dosing regimen that caused oxidative stress such that the doses of turmeric and lead acetate were 30 and 20 mg/kg, respectively (Asali et al., 2011; Daniel et al., 2004; Roshan et al., 2011).

Animals were decapitated after 12 to 14 h overnight fasting after anesthesia with ketamine and xaylozine. The chest cavity was then opened and the heart was rapidly removed from the aortic root. Heart tissues were weighed and placed into Petri dishes containing cold isolation medium (0.1 M K_2HPO_4, 0.15 M NaCl, pH = 7.4) to remove the blood. Left ventricular (free wall) tissue then was separated and were frozen immediately in liquid nitrogen and stored at -80°C for subsequent analysis of oxidant/antioxidant biomarkers. Frozen samples of heart tissue were thawed and homogenized in ice-cold 10 mM Tris-HC1, pH 8.2, containing 0.25 M sucrose, 2 mM 2-mercaptoethanol, 10 mM sodium azide, and 0.1 mM phenylmethylsulfonyl fluoride with a Polytron (4 vol/wt), and centrifuged at 50,000 g (20 min, 4°C). The homogenates were diluted with cold 20 mM Tris-HCl and centrifuged (10 min at 5°C, 3,000 g). The enzyme-linked immunosorbent assay (ELISA) method was used to determine the HSP_{72} content of the heart tissue homogenates, as described by Salo et al., (1991).

Lipid peroxidation (MDA) level in the left ventricular tissue was measured with the thiobarbituric-acid reaction using the method of Asali et al. (2011) and Roshan et al. (2011). The quantification of thiobarbituric acid reactive substances was determined at 532 nm by comparing the absorption to a standard curve of MDA equivalents generated by acid catalyzed hydrolysis of 1, 1, 3, 3 tetramethoxypropane. The value of MDA in left ventricle was expressed as nmol/mg tissue. Furthermore, serum TAC was measured using a commercially available kit (Randox Laboratories, Crumlin, UK) as previously described by Dabidi et al. (2011) and Asali et al. (2011). In this method, the most potent radical, hydroxyl radical, is produced. First, a ferrous ion solution is mixed with hydrogen peroxide. The sequentially produced radicals such as the brown colored dianisidinyl radical cations, produced by the hydroxyl radical, are potent radicals. The antioxidative effect of the sample against the potent free radical reactions is then measured. The assay has excellent precision values, which are lower than 3%. The results are expressed in µmol/ml. In accordance with the protocols of Asali et al. (2011), Daniel et al. (2004) and Roshan et al. (2011), we analyzed the lead acetate concentration using a spectrophotometer method only in the lead acetate group.

Statistical analysis was performed using a commercial software package (SPSS version 16.0 for Windows). Results are expressed as means $\pm$ SD. Data for HSP_{72} and oxidative stress-related biomarkers were normally distributed after log-transformation. A one-way analysis of variance (ANOVA) was used to detect statistical differences between groups. A post-hoc test (Tukey test) was performed to determine differences in the various markers between groups. The differences were considered significant at $P < 0.01$.

RESULTS

Data in Figures 1, 2 and 3 are shown, levels of body mass, heart mass, and heart- body mass ratio for the five groups, respectively. Lead acetate administration (20 mg/kg) caused significant decreases in body mass and heart mass were detected as compared to the other groups ($p< 0.01$) (Figures 1 and 2). Moreover, endurance training and curcumin supplementation protocols during chronic exposure to lead acetate caused preservation in body mass. However, aerobic training, but not curcumin supplementation significantly increased heart mass and

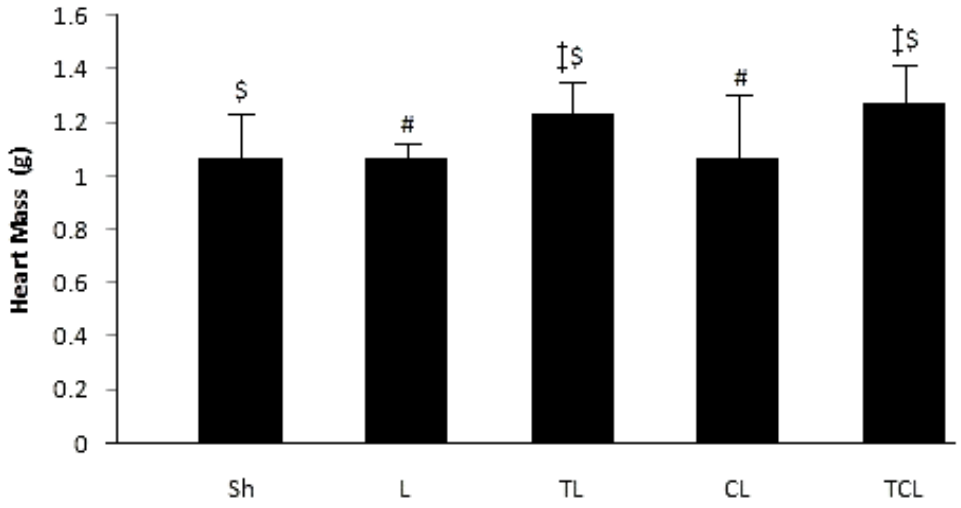

Figure 2. Heart mass changes in rats during chronic exposure to lead acetate. Sh, Curcumin resolvent or ethyl oleate; TL, training + lead; TCL, training + curcumin + lead; L, lead acetate; CL, Curcumin+ lead. Data are presented as mean ± SD; ‡significantly different from sham group ($P < 0.001$); $, significantly different from lead group ($P < 0.001$); #, significantly different between combination (training + lead + curcumin) group with training and/ or curcumin groups ($P < 0.05$).

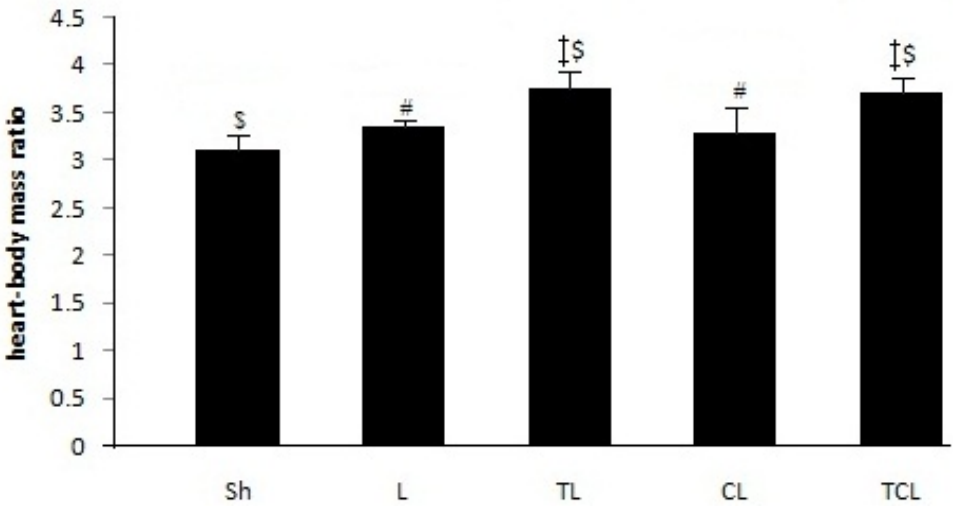

Figure 3. Heart mass and heart-to-body mass ratio in rats during chronic exposure to lead acetate. Sh, Curcumin resolvent or ethyl oleate;TL, training + lead; TCL, training + curcumin + lead; L, lead acetate; CL, curcumin+ lead. Data are presented as mean ± SD; ,‡ significantly different from sham group ($P < 0.001$); $, significantly different from lead group ($P < 0.001$); #, significantly different between combination (training + lead + curcumin) group with training and/or curcumin groups ($P < 0.05$).

heart-to-body mass ratio as compared to rats in the lead acetate group ($P < 0.01$) (Figure 3).

Data in Figures 4, 5 and 6 show changes in left ventricular HSP_{72} level, and oxidative stress-related biomarkers (MDA and TAC) in the rats exposed to lead acetate, respectively. Intra-peritoneal administration of lead acetate (20 mg/kg) caused a significant increase in the levels of left ventricle HSP_{72} and MDA by 15 and 70%, respectively, as compared to the sham (Sh) group ($P < 0.01$ and $p < 0.001$, respectively) (Figures 4 and 5). Furthermore, the administration of lead acetate for 8 weeks resulted in a decrease in TAC levels by 27%, in comparison to the Sh group ($P < 0.01$) (Figure 6). In contrast, curcumin supplementation, exercise training, and in particular their combination ($P < 0.001$) reversed MDA level, significantly. In other words, curcumin +

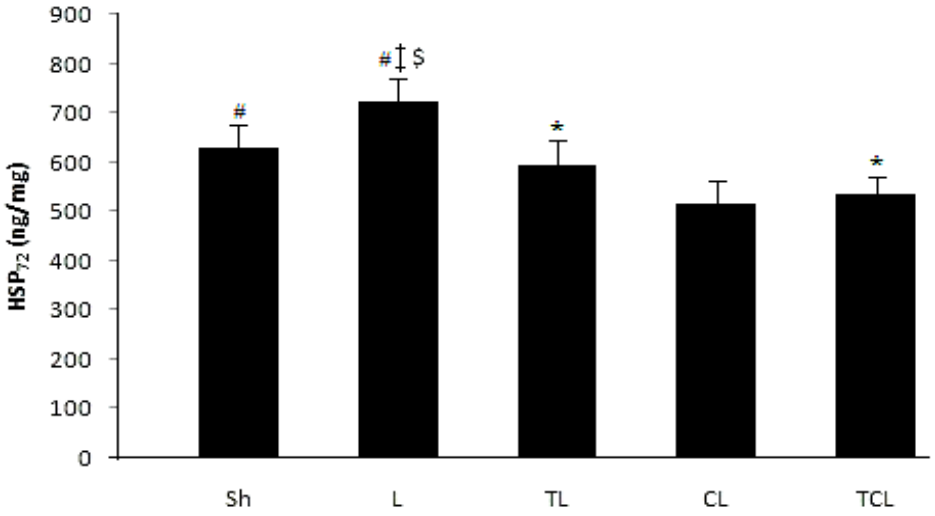

Figure 4. Left ventricle heat shock protein (HSP_{72}) levels in rats during chronic exposure to lead acetate. Sh, Curcumin resolvent or ethyl oleate; TL, training + lead; TCL, training + curcumin + Lead; L, lead acetate; CL, curcumin+ lead. Data are presented as mean ± SD; ‡, significantly different from sham group ($P < 0.001$);*, significantly different from Lead group ($P < 0.01$); $, significantly different from TL (training + lead) group ($P < 0.001$); #, significantly different between combination (training + lead + curcumin) group with training and/or curcumin groups ($P < 0.05$).

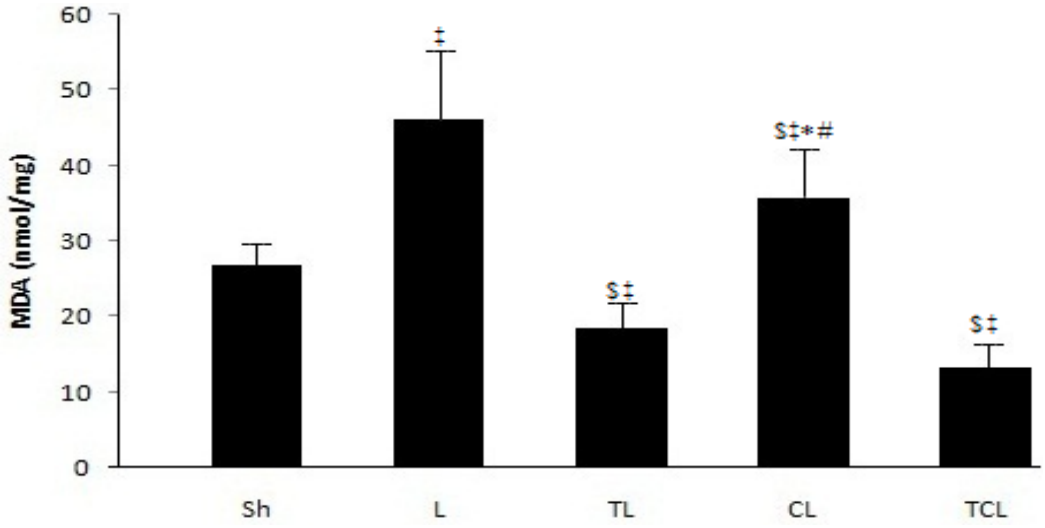

Figure 5. Left ventricle MDA levels in rats during chronic exposure to lead acetate. Sh, Curcumin resolvent or ethyl oleate; TL, training + lead; TCL, training + curcumin + lead; L, lead acetate; CL,(Curcumin+ lead. Data are presented as mean ± SD; ‡, significantly different from sham group ($P < 0.001$); $, significantly different from lead group ($P < 0.001$); *, significantly different from training group ($P < 0.01$); #, significantly different between combination (training + lead + curcumin) group with training and/or curcumin groups ($P < 0.05$).

training + lead treatment was more effective than curcumin + lead or training + lead alone treatments.

DISCUSSION

We investigated effects of endurance training and curcumin supplementation, alone and combined on HSP_{72} and serum TAC and MDA changes in male rats during chronic exposure to lead acetate. The present data showed intra-peritoneal administration of lead acetate (20 mg/kg) caused an increase in the levels of HSP_{72} and MDA in left ventricle and a decrease in the serum TAC concentration, by 15, 70 and 27%,

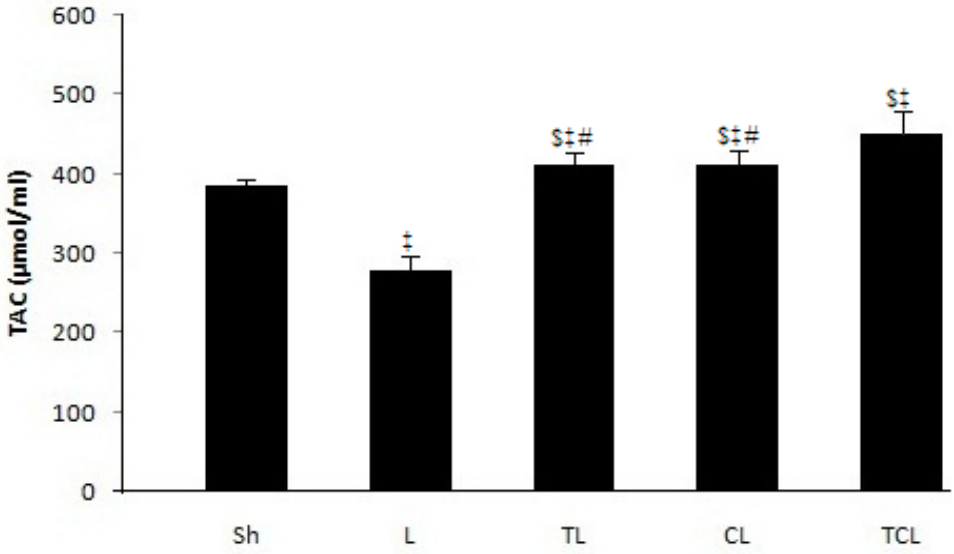

Figure 6. Serum TAC levels in rats during chronic exposure to lead acetate. Sh, Curcumin resolvent or ethyl oleate; TL, training + lead; TCL, training + curcumin + lead; L, lead acetate; CL, curcumin + lead. Data are presented as the mean ± SD for 8 rats; ‡, significantly different from sham group ($P < 0.001$); $, significantly different from lead ($P < 0.001$); #, significantly different between combination (training + lead + curcumin) group with training and or curcumin groups ($P < 0.05$).

respectively, as compared to the Sh group.

Lead is capable of inducing oxidative damage to brain, heart, kidneys, and reproductive organs and the results of this study support the hypothesis; lead acetate toxicity appears to affect organs with low antioxidant defenses such as the heart (Daniel et al., 2004; Gholam-Hosseini et al., 2009; Gurer and Ercal, 2000; Patrick, 2006), since our data stated that oxidative stress biomarker (MDA) levels in lead acetate group were higher than in the other treatment groups. Increased MDA and decreased antioxidant defense biomarkers in the lead acetate group suggests an increased myocardial lipid peroxidation. The mechanisms for lead-induced oxidative stress include the effects of lead on membranes, DNA, and antioxidant defense systems of cells (Ahamed and Siddiqui, 2007; Ashry et al., 2010; Somashekaraiah et al.,1992). In addition, one of the mechanisms by which lead can exert some of its toxic effects is through the disruption of the delicate proxidant/antioxidant balance that exists within mammalian cells (Gholam-Hosseini et al., 2009; Jackie et al., 2011). *In vivo* and *in vitro* studies suggest that lipid metabolism is altered both in acute and chronic exposure to lead. Lead inhibits antioxidant enzyme activity, and also, increasing lipid peroxidation. The HSP_{72} and serum TAC protect cellular membranes from peroxidative damage (El-Tohamy and El-Nattat, 2010). In contrast, endurance training and curcumin supplementation, particularly, their combination resulted in a significant increase in TAC, and a significant decrease in HSP_{72} and MDA, as compared to lead acetate and Sh groups. Training alone decreased the level of MDA in myocardial homogenates in rats exposed to lead acetate. Furthermore, training and curcumin together decreased the myocardial HSP_{72} and MDA levels, and actually restored lead-induced myocardial damage and tended to normalize these biomarkers suggesting a reversal of lead-induced cardiotoxicity and confirms the free radical scavenging property of curcumin.

Curcumin's protective function against peroxidative damage of biomembranes, known to be a free-radical-mediated chain reaction, has mainly been attributed to the scavenging of the reactive free radicals involved in peroxidation. These scavenging properties of curcumin have also been considered to be responsible for its protective role against oxidative damage of DNA and proteins, believed to be associated with a variety of chronic diseases such as cancer, atherosclerosis, neurodegenerative diseases and aging. In addition to its direct antioxidant activity, curcumin may function indirectly as an antioxidant by inhibiting the activity of inflammatory enzymes or by enhancing the synthesis of glutathione. The anti-inflammatory activity of curcumin seems to be comparable to steroidal drugs and non-steroidal drugs such as indomethacin and phenyl-butazone (Rajasekaran, 2011). When administered in the current study, curcumin effectively increased serum TAC levels during lead exposure. The result of present study is consistent with the hypothesis that a prolonged exercise and curcumin supplementation protocol is effective in preventing lead-induced myocardial oxidative stress and increases myocardial antioxidant defensive properties (Muhammad et al., 2011; Roshan et al., 2011;

Srivastava and Mehta, 2009).

Since activity of antioxidant enzymes depends on various essential trace elements for proper molecular structure and enzymatic activity, it is a potential target for lead toxicity (Patrick, 2006). The presence of the free -SH group is necessary for the proper action of antioxidant enzymes. Researchers have shown a decrease in the concentration of the free -SH groups in the blood as well as in the urine of rats exposed to lead (Tandon et al., 2003). The increase in the HSP_{72} and MDA in the heart and the decrease in TAC concentration in the serum of rats exposed to lead can be a result of this heavy metal-induced depletion in the free -SH groups noted in these animals. However, a second possibility that must be considered is that the rats with long-term exposure to lead acetate without treatment interventions were more prone to oxidative stress in organs with low antioxidant defense, which in turn increased the need for improved antioxidant defenses.

In conclusion, the present study demonstrates that chronic lead acetate administration can induce an imbalance in myocardial antioxidant defenses. In addition, we observed that training + curcumin + lead treatment was more effective than curcumin + lead and/or training + lead alone, that in turn, suggests that exercise training in concomitant with curcumin can potentially be more effective for inhibiting myocardial damage caused by lead in rats. These results suggest that exercise and curcumin supplementation may have a more cardioprotective effect by ameliorating lead-induced cardiotoxicity.

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