



## A protective effect of curcumin on cardiovascular oxidative stress indicators in systemic inflammation induced by lipopolysaccharide in rats

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### ABSTRACT

**Objective:** Inflammation has been considered as an important factor in cardiovascular diseases (CVD). Curcumin has been well known for its anti-inflammatory effects. In current research, protective effect of curcumin on cardiovascular oxidative stress indicators in systemic inflammation induced by lipopolysaccharide (LPS) was investigated in rats.

**Material and methods:** The animals were divided into five groups and received the treatments during two weeks [1]: Control in which vehicle was administered instead of curcumin and saline was injected instead of LPS [2], LPS group in which vehicle of curcumin plus LPS (1 mg/kg) was administered [3-5], curcumin groups in them three doses of curcumin (5, 10 and 15 mg/kg) before LPS were administered.

**Results:** Administration of LPS was followed by an inflammation status presented by an increased level of white blood cells (WBC) ( $p < 0.001$ ). An oxidative stress status was also occurred after LPS injection which was presented by an increased level of malondialdehyde (MDA) while, a decrease in thiols, superoxide dismutase (SOD) and catalase (CAT) in all heart, aorta and serum ( $p < 0.001$ ). The results also showed that curcumin decreased WBC (doses: 10 and 15 mg/kg) ( $p < 0.001$ ) accompanying with a decrease in MDA ( $P < 0.01$  and  $P < 0.001$ ). Curcumin also improved the thiols and the activities of SOD and catalase ( $P < 0.05$ ,  $P < 0.01$  and  $P < 0.001$ ).

**Conclusion:** Based on our findings, curcumin can ameliorates oxidative stress and inflammation induced by LPS in rats to protect the cardiovascular system.

### 1. Introduction

Cardiovascular diseases (CVD) are consisting of disorders affecting the heart and the blood vessels. It represents one third of all deaths, and incidence is still growing [1]. Studies show that inflammation plays a crucial role in beginning and progression of CVD [2]. Chronic inflammatory situations also decrease endogenous antioxidant abilities because of constant production of high levels of reactive oxygen species (ROS). Patients with CVD are often with low blood levels of antioxidants and increased levels of oxidative stress indicators [3]. Some researches have shown that inflammation is related with change in signaling pathways, which results in increased levels of free radicals, inflammatory markers and lipid peroxides [4,5]. Therefore, the key mechanisms

of arterial damage and endothelial dysfunction are including oxidative stress and inflammation which both of them are associated with arterial stiffness and aging related vascular damage [6]. Released cytokines during inflammation are also play a key role in inducing atherosclerosis by attracting monocytes/macrophages to the vessel wall, which facilitates atherosclerotic lesions and plaque susceptibility. In addition, circulating levels of these proinflammatory cytokines rise in patients with acute myocardial infarction and unstable angina [7].

Lipopolysaccharide (LPS) is a endotoxin from a gram-negative bacteria and a major factor that is partly responsible for multiple organ failure, for example heart injury [8]. It is widely used to generate immune system responses [9]. While several mechanisms of LPS-induced myocardial injury have been hypothesized, the overproduction of

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auto-oxidation-induced cytotoxic free radicals is the most widely accepted [10]. LPS systemic administration can induce several organ disorder including heart damage [11]. Also it was shown that single dose of LPS induced a systemic inflammation and cardiovascular toxicity [12]. LPS exposure is thought to cause severe stress in cardiomyocytes, resulting in a loss of myocardial integrity due to a combination of oxygen deficiency, calcium overload, and the overproduction of free radicals [13]. The heart is one of the highest tissue oxygen consumption levels, and also poor antioxidant enzyme production and is thus highly vulnerable to ROS [14]. Increased production of ROS may result in myocyte hypertrophy, apoptosis, and interstitial fibrosis that may contribute to the development of depressed heart function and heart failure progression. It has been well known that in health and disease, endothelial function is a main factor of vessel wall and myocardial function [15]. For preventing the progression of heart diseases, modulation of oxidative stress-induced signaling pathways is effective [16].

Beneficial effects of dietary plants rich in antioxidants is proven to prevent free radical formation, remove free radicals before damage, healing oxidative damage, remove damaged molecules; studies showed their beneficial role in cardiovascular disease, and we can put them in our diet [17].

Although significant progress has been made in managing synthetic drugs for cardiovascular diseases, the search for indigenous cardioprotective agents is continuing. It has been shown that at least 30 food spices and herbs possess antioxidant properties such as *Boswellia serrata*, *Nigella sativa*, saffron and their major components such as thymoquinone, and safranin, [18–21]. Curcumin, the major yellow bioactive component of turmeric (*Curcuma longa* L., Zingiberaceae), is a more recent discovery [22,23]. Based on some investigations, curcumin supplement has indicated to be a safe and potential therapeutic agent against diseases, such as arthritis, pancreatitis, inflammatory bowel disease, as well as certain kinds of cancers [24]. It has many pharmacological effects for example: antioxidant, anti-inflammation, removing free radicals, anti-tumor, lipid regulation and anti-coagulation [25].

Curcumin plays a key role against oxidative stress mediated pathological conditions and it has anti-inflammatory activities when used as a therapy for treatment and prevention of chronic diseases [26,27]. The clinical trials did not indicate severe toxic or side effect [28,29]. It was shown that myocardial tissue from diabetic rats exhibited increased levels of eNOS and iNOS mRNA, and curcumin treatment prevented eNOS and iNOS mRNA upregulation showing a decrease in the oxidative DNA damage [30].

In current research, protective effect of curcumin on cardiovascular oxidative stress indicators in systemic inflammation induced by lipopolysaccharide (LPS) was investigated in rats.

## 2. Material and methods

### 2.1. Animals and treatments

The present study consisted of 35 male Wistar rats from the Central Animal House of Mashhad University of Medical Sciences which weighed  $250 \pm 10$ g. During the study, the animals were kept in a room with a cycle of 12h light/dark and standard temperature ( $22 \text{ }^\circ\text{C} \pm 2 \text{ }^\circ\text{C}$ ). The animals were randomly categorized into five groups:

1. Control: the rats in this group were intraperitoneally (IP injected with 2 ml/kg vehicle instead of Cur and 1 ml/kg saline instead of LPS.
2. LPS: the animals in this group received 2 mL/kg saline diluted Dimethyl sulfoxide (DMSO) as a vehicle instead of curcumin and 1 ml/kg LPS.
3. LPS-Cur 5: the animals in this group received 5 mg/kg Curcumin dissolved in saline diluted DMSO as vehicle and 1 mg/kg LPS.
4. LPS-Curcumin10: the rats in this group were injected with 10 mg/kg Curcumin dissolved in DMSO as vehicle and 1 mg/kg LPS.

5. LPS-Cur 15: the rats in the group were injected with 15 mg/kg Curcumin dissolved in DMSO as vehicle and 1 mg/kg LPS.

The daily IP injections took place in a period of two weeks. LPS was purchased from Sigma Aldrich Co. (purities  $\geq 97$ ). Also, curcumin powder (C1386) was purchased from sigma-aldrich Co. and we injected LPS 1 mg/ml. At the end of injections, the rats were injected with urethane to induce deep anesthesia. The blood samples were collected to be used for white blood cell (WBC) count and to be used for the oxidative stress indicators measurements in the serum. The heart and aorta of the rats were also collected to be used for oxidative stress criteria.

Malondialdehyde (MDA), thiol, catalase (CAT) and superoxide dismutase (SOD) were determined in the serum, aorta and heart.

The Animal Care and Use Committee of Mashhad University of Mashhad Sciences (IR.MUMS.MEDICAL.REC.1399.162) and also the National Institute of Health guidelines for the Care and Use of Laboratory animals approved this experimental protocol.

### 2.2. Biochemical measurements

#### 2.2.1. WBC count

Total WBC count was done in duplicate using a hemocytometer (in a Burkner chamber).

#### 2.2.2. MDA and total thiol concentration

The TBA-trichloroacetic acid-HCL reagent was initially applied to the tissue which we have already homogenized. The solution was then put in water and heated for 30 min. MDA reacts with thiobarbituric Acid [31] to form a red complex [32].

Besides, total thiol concentration was determined in the aorta, heart and serum. In this procedure, the reaction between DTNB (2,2'-dinitro-5,5'-dithiol benzoic acid) and thiol groups form a yellow complex. Absorbance was read at 412 nm [32].

### 2.3. SOD and CAT activities

SOD activity was measured by the procedure described by Madesh and Balasubramanian [33]. It was measured at 570 nm according to a colorimetric technique. One unit of SOD was equal to the amount of enzyme that should be inhibited by 50% of the MTT reduction rate. Aebi method was used to measure CAT activity using hydrogen peroxide (30 mM) as a substrate [32].

### 2.4. Statistical analysis

All the data is presented as mean  $\pm$  standard error of the mean. Data was evaluated by analysis of variance (one-way ANOVA) followed by Tukey post hoc test using Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc., Chicago, IL, USA). The differences were considered statistically significant when  $P < 0.05$ .

## 3. Results

### 3.1. Total WBC count

The results showed that the number of total WBCs were significantly increased in LPS group compared with Control group ( $p < 0.001$ ). Curcumin with doses 10 and 15 mg induced a significant reduction in total blood WBC count ( $p < 0.001$ ; Fig. 1) but 5 mg/kg of curcumin was not effective. In the rats treated by all doses of curcumin WBC count was still higher than the Control group ( $p < 0.001$ ,  $p < 0.001$  and  $p < 0.05$  for 5, 10 and 15 mg/kg doses respectively). In addition, WBC count in the rats treated by 10 mg/kg and 15 mg/kg curcumin was lower than that in the group treated by 5 mg/kg ( $p < 0.05$  and  $p < 0.001$  respectively). There was no significant difference between the effects of the medium and the highest dose of curcumin (Fig. 1).

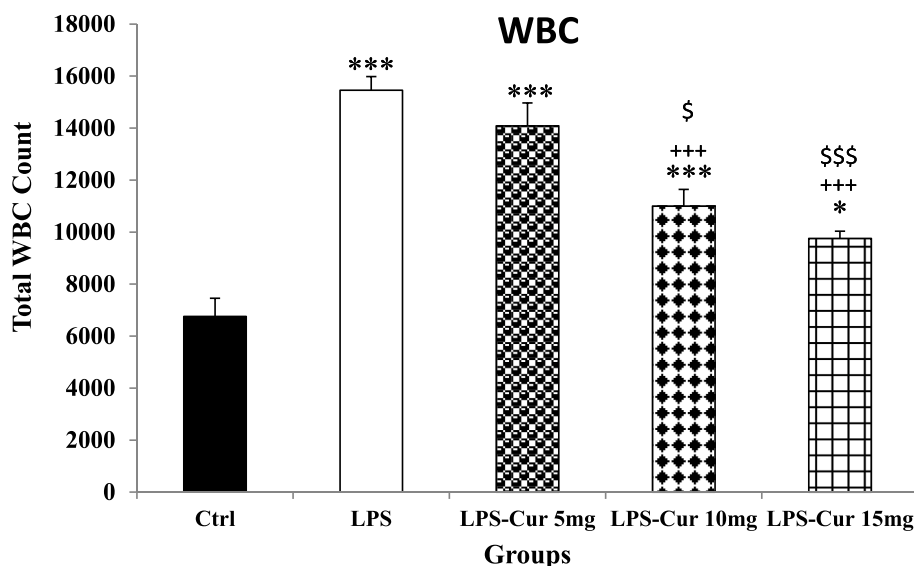


Fig. 1. WBC count. Data are shown as mean  $\pm$  SEM of 10 animals per group. \* $p < 0.05$  and \*\*\* $p < 0.001$  vs. Control group, +++ $p < 0.001$  vs. LPS group and  $^{\$}$   $p < 0.05$  and \$\$\$ $p < 0.001$  vs. LPS-Cur 5 mg group.

### 3.2. Total thiol and MDA concentration in the heart

Injection of LPS showed a significant decrease of thiol level in the heart of the LPS group compared to the Control group ( $p < 0.001$ ). Also we observed a significant increase in 10 and 15 mg/kg curcumin treated groups compared to LPS group ( $p < 0.001$  for both) but 5 mg/kg curcumin was not effective (Fig. 2A). The results also showed that thiol content in the heart tissue of treated groups by 5 and 10 mg/kg doses of curcumin was still lower than that in the Control group ( $p < 0.001$  for both) but there was no significant difference between LPS-Cur 15 mg and Control groups. There was no significant difference between three doses of curcumin.

Consequence of LPS injection was also seen as a significant increase in MDA level in the heart tissue of LPS group compared to the Control group ( $p < 0.001$ ). Another result was seen as a significant decrease of MDA in the heart of the groups treated with 10 and 15 mg/kg doses of curcumin compared to LPS group ( $p < 0.05$  and  $p < 0.001$  respectively) but 5 mg/kg curcumin was not effective (Fig. 2B). It was also observed that there was a more significant decrease in the group treated with dose of 15 mg/kg curcumin compared to 5 mg/kg treated group ( $p < 0.05$ ) but there was no significant difference between LPS-Cur 5 mg and LPS-Cur 10 mg groups and also between LPS-Cur 15 mg and LPS-Cur 10 mg groups (Fig. 2B). Finally, treatment by the highest dose of curcumin was able to attenuate MDA in the heart to the level of Control group and there was no significant difference between LPS-Cur 15 mg and the Control groups. In the heart of both LPS-Cur 5 mg and LPS-Cur 10 mg groups, MDA level was higher than in the Control group ( $p < 0.001$  and  $p < 0.01$  respectively).

### 3.3. Total thiol and MDA concentration in the aorta

Injection of LPS showed a considerable reduction of thiol concentration in the aorta of LPS group compared to the Control group ( $p < 0.001$ ). Administration of the medium and highest doses of curcumin showed a considerable increase in treatment groups compared to LPS group ( $p < 0.001$  for both) but the lowest dose was not effective. There was no significant difference between the three doses of curcumin. The results also showed that thiol content in the aorta of treated groups by 5 and 10 mg/kg doses of curcumin was still lower than that in the Control group ( $p < 0.001$  and  $p < 0.001$  respectively) but there was no significant difference between LPS-Cur 15 mg and Control groups (Fig. 3A).

Outcome of LPS injection was also seen as a considerable increase in

MDA in the aorta of LPS group compared to the Control group ( $p < 0.001$ ). A considerable reduction of MDA in the aorta of all curcumin treated groups was seen compared to LPS group ( $p < 0.001$  for all) but it was still higher than that in the Control group ( $p < 0.001$  for all). MDA level in aorta tissues of the rats treated by 15 mg/kg curcumin was lower than ones treated by 5 mg/kg and 10 mg/kg ( $p < 0.001$  and  $p < 0.05$  respectively) but there was no significant difference between the effects of 5 and 10 mg/kg doses of curcumin (Fig. 3B). MDA level in the aorta tissues of all LPS-Cur 5 mg, LPS-Cur 10 mg and LPS-Cur 15 mg was still higher than Control group ( $p < 0.001$  for all).

### 3.4. Total thiol and MDA concentration in the serum

Injection of LPS was accompanied with a reduction of thiol content in the serum of LPS group compared to the Control group ( $p < 0.001$ ). Administration of curcumin showed a noticeable increase in treated group with 15 mg/kg dose compared to LPS group ( $p < 0.001$ ) but there was no significant difference between LPS-Cur 5 mg, LPS-Cur 10 mg and the Control groups (Fig. 4A). Also it was indicated a more increase in group treated with 15 mg/kg dose of curcumin compared to other treatment groups ( $p < 0.01$ ). There was no significant difference between the effects of the medium and the lowest doses of curcumin. In addition, serum thiol content in the all groups treated by 5 mg/kg and 10 mg/kg curcumin was still lower than that in the Control group ( $p < 0.001$  for both) but there was no significant difference between LPS-Cur 15 mg and the Control group (Fig. 4A).

Result of LPS injection was seen as a noticeable increase in serum MDA level in LPS group compared to the control group ( $p < 0.001$ ). The result was also seen as a noticeable reduction of MDA in all curcumin treated groups compared to LPS group ( $p < 0.01$ ,  $p < 0.001$  and  $p < 0.001$  for lowest, medium and highest doses respectively). In addition, MDA level in the serum of LPS-Cur 15 mg group was lower than that in LPS-Cur 5 mg group ( $p < 0.05$ ) but there was no significant difference between LPS-Cur 5 mg and LPS-Cur 10 mg groups and also between LPS-Cur 10 mg and LPS-Cur 15 mg groups. In addition, serum MDA in LPS-Cur 5 mg group was still higher than that in the Control group ( $p < 0.05$ ) but there was no significant difference when MDA level in the serum of LPS-Cur 10 mg and LPS-Cur 15 mg groups was compared to the Control group (Fig. 4B).

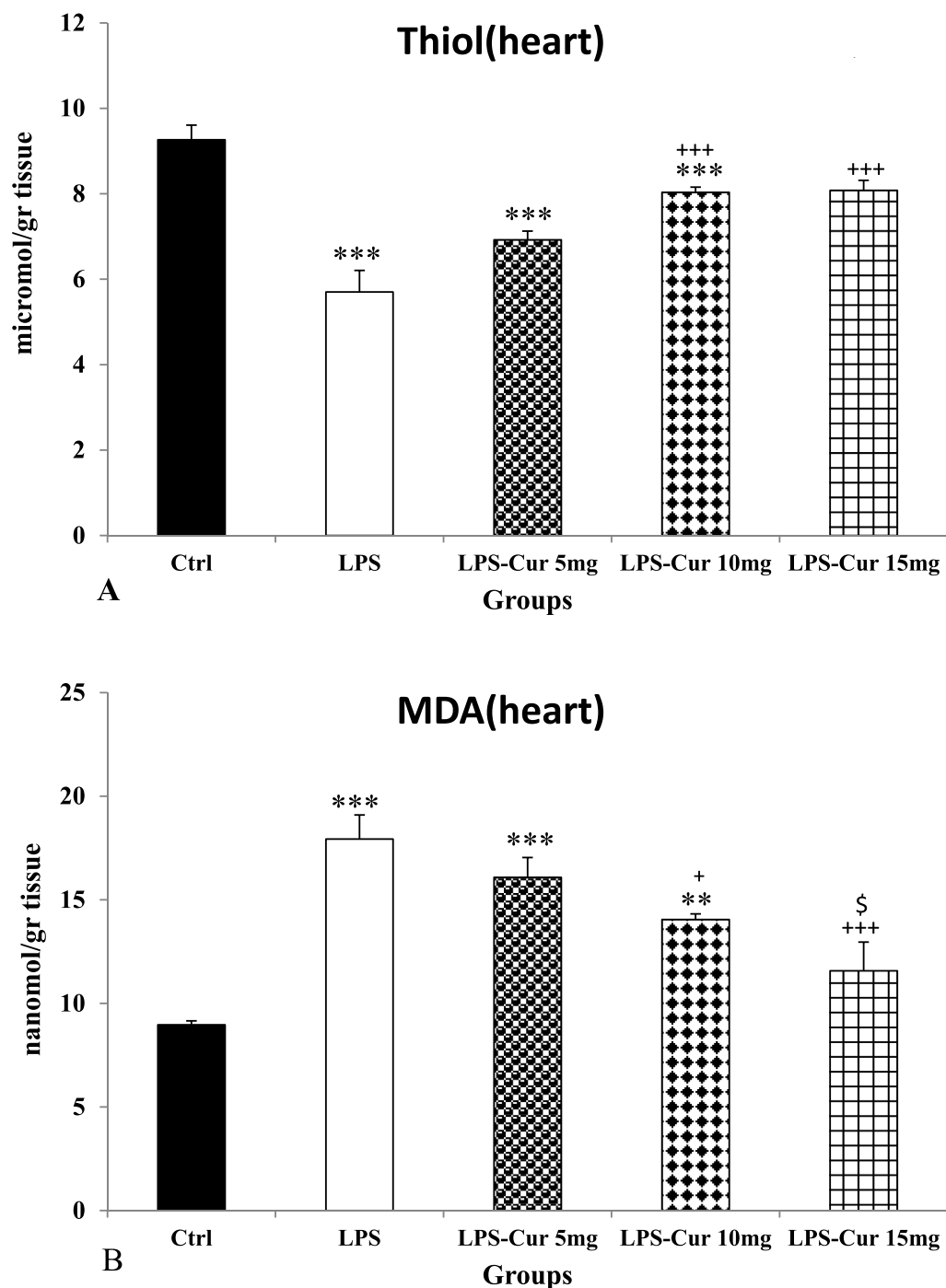


Fig. 2. Thiol (A) and malondialdehyde (MDA) (B) of heart tissues. Data are shown as mean  $\pm$  SEM of 10 animals per group. \*\* $p < 0.01$  and \*\*\* $p < 0.001$  vs. Control group, +  $p < 0.05$  and +++  $p < 0.001$  vs. LPS group and \$  $p < 0.05$  vs. LPS-Cur 5 mg group.

### 3.5. CAT and SOD activities in the heart

Administration of LPS caused a significant decrease in CAT activity in heart tissues of LPS group compared to control group ( $p < 0.001$ ). Also we found a significant increase in the CAT activity in the heart tissue of the rats treated groups 10 and 15 mg/kg curcumin compared to LPS group ( $p < 0.001$  for both) but 5 mg/kg curcumin was not effective. In the heart of the groups treated with both 10 and 15 mg/kg doses curcumin, CAT was higher than that in the group treated by 5 mg/kg

group ( $p < 0.05$  for both) but there was no significant difference between 10 and 15 mg/kg curcumin. CAT activity in the heart of all LPS-Cur 5 mg, LPS-Cur 10 mg and LPS-Cur 15 mg groups was still lower than that in the Control group ( $p < 0.001$ ,  $p < 0.01$  and  $p < 0.01$  respectively) (Table 1).

A significant decrease in SOD activity was observed following injection of LPS in LPS group compared to the Control group ( $p < 0.001$ ). In treated group by 15 mg/kg dose of curcumin we had a significant increase in SOD of LPS-Cur 15 mg compared to LPS group ( $p < 0.05$ ) but

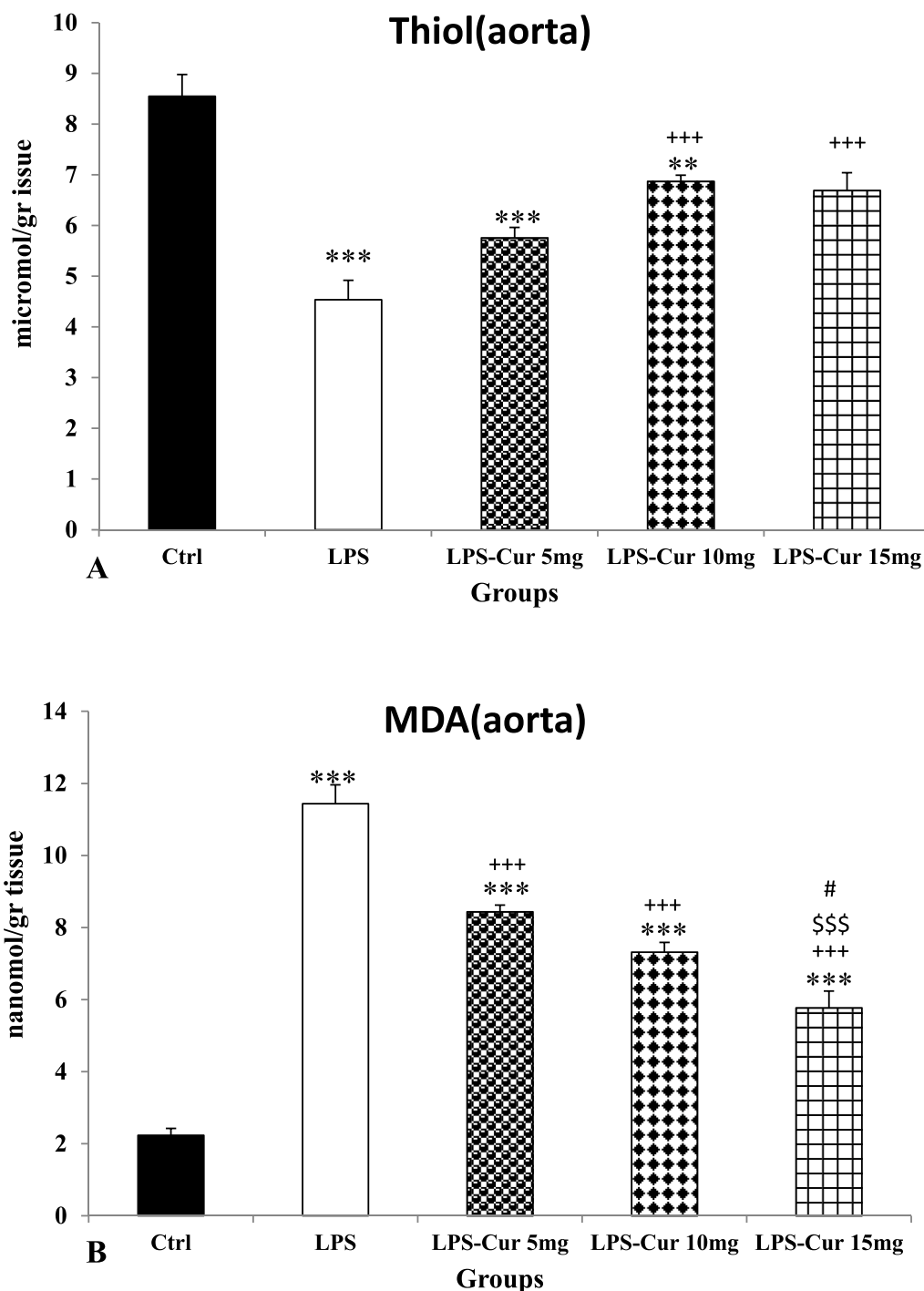
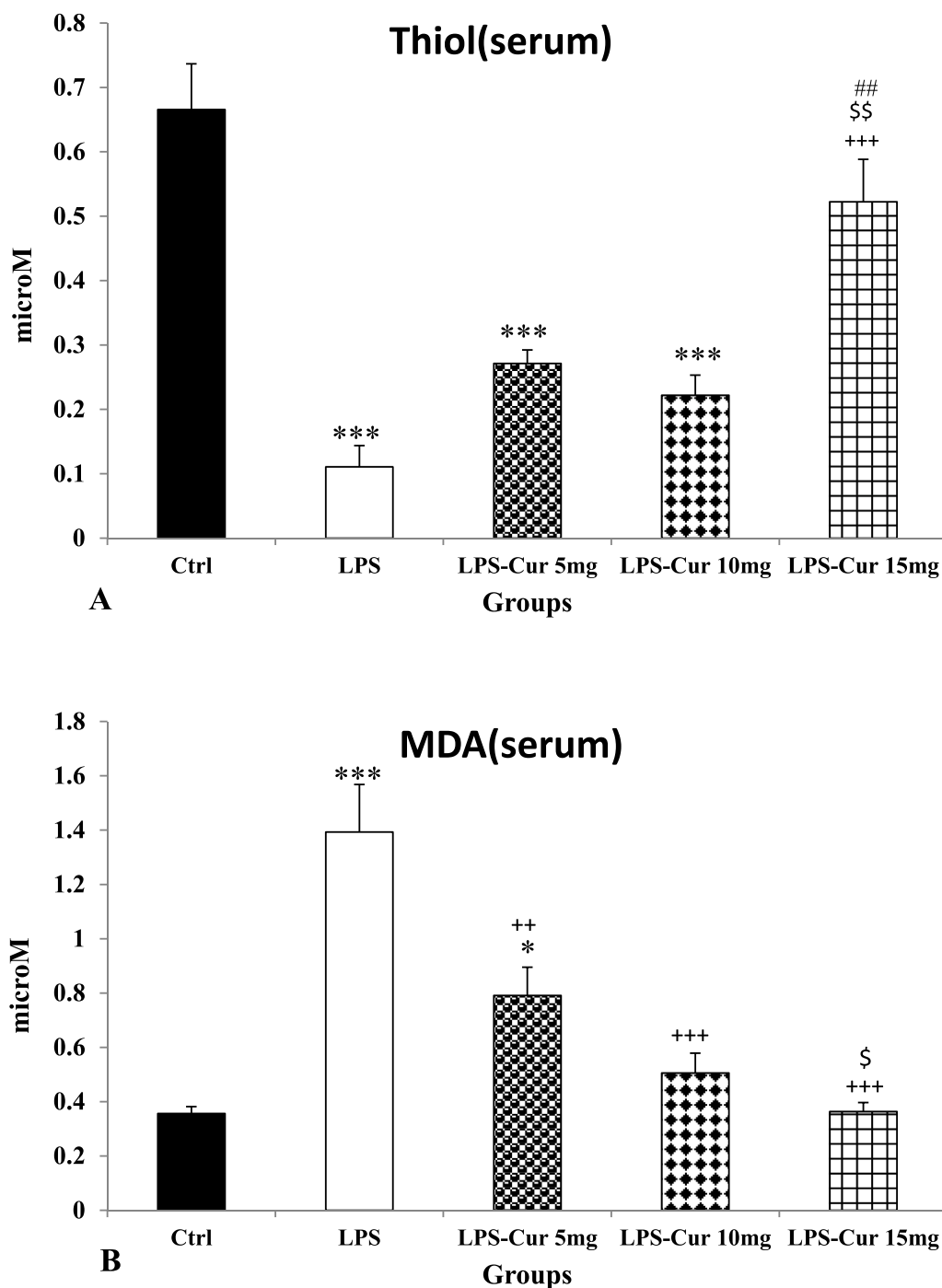


Fig. 3. Thiol (A) and malondialdehyde (MDA) (B) of aorta tissues. Data are shown as mean  $\pm$  SEM of 10 animals per group. \*\* $p < 0.01$  and \*\*\* $p < 0.001$  vs. Control group, +++  $p < 0.001$  vs. LPS group, \$\$\$  $p < 0.001$  vs. LPS-Cur 5 mg group, #  $p < 0.05$  vs. LPS-Cur 10 mg group.

there was no significant effect for 5 and 10 mg/kg of curcumin on SOD activity. In the heart of the groups treated by 15 mg/kg curcumin, SOD activity was higher than that in the group treated by 5 mg/kg ( $p < 0.05$ ) but there was no significant difference between LPS- Cur 15 mg and LPS- Cur 10 mg groups and between LPS- Cur 5 mg and LPS- Cur 10 mg groups. In the heart of all LPS- Cur 5 mg, LPS- Cur 10 mg and LPS- Cur 15 mg groups, SOD activity was still lower than that in the Control group ( $p < 0.001$  for all) (Table 1).

### 3.6. CAT and SOD activities in the aorta

Administration of LPS caused a considerable reduction in CAT activity in the aorta tissues of LPS group compared to the Control group ( $p < 0.001$ ). Also we had a considerable increase in all treatment groups (curcumin doses: 5, 10 and 15 mg/kg) compared to LPS group ( $p < 0.05$ ,  $p < 0.001$  and  $p < 0.001$  respectively). In curcumin treated groups with 5, 10 and 15 mg/kg doses a considerable increase in CAT in the aorta tissue was observed compared to the LPS group ( $p < 0.01$ ,  $p < 0.001$  and



**Fig. 4.** Thiol (A) and malondialdehyde (MDA) (B) of serum. Data are shown as mean  $\pm$  SEM of 10 animals per group. \* $p < 0.05$  and \*\*\* $p < 0.001$  vs. Control group, ++  $p < 0.01$  and +++  $p < 0.001$  vs. LPS group and \$  $p < 0.05$  and \$\$  $p < 0.01$  vs. LPS-Cur 5 mg group, ##  $p < 0.01$  vs. LPS-Cur 10 mg group.

$p < 0.001$  respectively; Table 1). In addition, CAT activity in the aorta tissue of LPS- Cur 10 mg and LPS- Cur 15 mg groups was higher than in LPS- Cur 5 mg group ( $p < 0.05$ ,  $p < 0.01$ ) but there was no significant difference between LPS- Cur 15 mg and LPS- Cur 10 mg groups. CAT activity in the aorta tissue of all LPS- Cur 5 mg, LPS- Cur 10 mg and LPS- Cur 15 mg groups was still lower than that in the Control group ( $p < 0.001$ ,  $p < 0.001$  and  $p < 0.01$  for all) (Table 1).

A considerable reduction in SOD activity was obtained from injection of LPS in LPS group compared to Control group ( $p < 0.01$ ). In the aorta of the group treated with 15 mg/kg dose of curcumin we observed a

considerable increase in SOD activity compared to LPS group ( $p < 0.01$ ) but 5 and 10 mg/kg of curcumin was not effective. Besides we observed another considerable increase with this group (dose: 15mg/kg) compared to other treatment groups ( $p < 0.05$  for both). There was no significant difference between LPS-Cur 15 mg and the Control groups but in the aorta of both LPS-Cur 10 mg and LPS-Cur 5 mg groups, SOD activity was lower than that in the Control group ( $p < 0.01$ ) (Table 1).



**Table 1**

The CAT (A) and SOD (B) activity of all tissues. Data are shown as mean  $\pm$  SEM of 10 animals per group. \* $p < 0.01$  and \*\*\* $p < 0.001$  vs. Control group, +  $p < 0.05$ , ++  $p < 0.01$  and +++  $p < 0.001$  vs. LPS group, \$  $p < 0.05$ , \$\$  $p < 0.01$  and \$\$\$  $p < 0.001$  vs. LPS-Cur 5 mg group, #  $p < 0.05$  and ##  $p < 0.01$  vs. LPS-Cur 10 mg group.

Tissues	Enzyme activity	Ctrl	LPS	LPS-Cur5mg	LPS-Cur10mg	LPS-Cur15mg
Heart	CAT(U/g tissue)	0.45 $\pm$ 0.03	*** 0.17 $\pm$ 0.02	*** 0.24 $\pm$ 0.02	**+++ $\$$ 0.33 $\pm$ 0.02	**+++ $\$$ 0.32 $\pm$ 0.03
	SOD(U/g tissue)	20.80 $\pm$ 2.65	*** 2.29 $\pm$ 0.99	*** 2.69 $\pm$ 0.94	*** 7.12 $\pm$ 1.62	**+ $\$$ 9.46 $\pm$ 1.41
Aorta	CAT(U/g tissue)	0.49 $\pm$ 0.03	*** 0.19 $\pm$ 0.01	***+ 0.27 $\pm$ 0.02	***+++ $\$$ 0.36 $\pm$ 0.02	**+++ $\$$ 0.38 $\pm$ 0.02
	SOD(U/g tissue)	9.92 $\pm$ 0.70	** 4.82 $\pm$ 0.70	** 5.51 $\pm$ 1.12	** 5.27 $\pm$ 0.90	+ $\$$ # 8.89 $\pm$ 0.33
Serum	CAT(U/ml)	66.21 $\pm$ 5.28	*** 21.21 $\pm$ 2.32	*** 44.84 $\pm$ 4.88	++ 58.76 $\pm$ 11.24	+ 49.68 $\pm$ 5.83
	SOD(U/ml)	0.61 $\pm$ 0.07	*** 0.08 $\pm$ 0.02	*** 0.13 $\pm$ 0.02	*** 0.22 $\pm$ 0.07	+++ $\$$ # 0.51 $\pm$ 0.03

### 3.7. CAT and SOD activities in the serum

Administration of LPS caused a noticeable reduction in CAT activity in serum of LPS group compared to control group ( $p < 0.001$ ). Also we had a noticeable increase in CAT activity in the serum of the treated groups by both 10 and 15 mg/kg curcumin compared to LPS group ( $p < 0.01$  and  $p < 0.01$  respectively) but there was no significant difference between LPS-Cur 5 mg and LPS groups. There was no noticeable difference between treatment groups. There was also no significant difference between curcumin treated groups and control group (Table 1).

A noticeable reduction in SOD activity resulted from injection of LPS in LPS group compared to Control group ( $P < 0.001$ ). In the group treated by 15 mg/kg dose of curcumin, SOD activity was significantly higher than LPS group ( $p < 0.001$ ). In the serum of LPS-Cur 15 mg, SOD activity was higher than that in both LPS-Cur 10 mg and LPS-Cur 5 mg groups ( $p < 0.001$  and  $p < 0.01$ ). In both LPS-Cur 10 mg and LPS-Cur 5 mg groups, the serum SOD activity was lower than Control group ( $p < 0.001$ ) but there was no significant difference between LPS-Cur 15 mg and Control group (Table 1).

## 4. Discussion

In the present study we showed that LPS injection was followed by an inflammation status and oxidative stress damage in aorta, heart and serum which was reversed by Cur. Using a bacterial endotoxin LPS, an extensive inflammatory response is occurred in the body which can be used to study the effects of inflammation in the experiments [34]. Inflammation status has been sometimes confirmed by WBC count [35] and it has been shown that WBC count can be a marker of inflammation [36]. The strong relation between WBC count, hypertension, and cardiovascular disease has been documented in several researches [37]. The association between WBC count and inflammatory factors in individuals with hypertension or complicating cardiovascular diseases has definitely been of crucial importance [37]. In spite of all these researches, the complete WBC count has not been studied and exploited for its usefulness in cardiovascular risk prediction.

In the current study injection of LPS induced an inflammation status which confirmed by increased number of WBC in LPS group (Fig. 1). Previously it was shown that the normal range of WBC count in normal

rat age 45–60 was 4000–10000 [38]. The WBCs count in LPS group was 15,400 and it showed inflammation status in this group.

In the current research, LPS induced inflammation was accompanied with an oxidative stress status in all heart, aorta and serum. Both inflammation and oxidative stress have been reported to be involved in the pathophysiology of CVD like congestive heart failure (CHF) [39].

In addition, oxidative stress can activate some factors, which can cause expression of several genes of inflammatory pathways [40]. On the other hand oxidative stress is sometimes occurred as a consequence of inflammation [41].

LPS as particle of gram negative bacteria has been reported to generate free radicals to cause lipid peroxidation of the membrane-bound polyunsaturated fatty acids, resulting in structural and functional integrity degradation of the membranes [8]. We assessed the effect of LPS on lipid peroxidation, which was measured in terms of MDA, a stable metabolite of the free radical-mediated lipid peroxidation cascade [42]. The MDA levels increased significantly following LPS treatment in rat serum (Fig. 4B) and heart (Fig. 2B) and aorta (Fig. 3B) tissues. The results also showed that total thiol concentration and CAT and SOD activity decreased in serum, heart and aorta tissues due to LPS injection (Table 1). These findings are consistent with previous study, which showed that LPS induced lipid peroxidation [43]. In agreement with these results, it was previously shown that the antioxidant capacity of the heart was decreased in myocardial injury induced by LPS in rats [8]. The data presented here clearly indicated how biochemical markers of the heart and aorta may be affected by the alteration in oxidative and anti-oxidative balance in the body following LPS administration. Additionally, LPS has been reported to have important roles in heart failure [44]. Researchers showed that LPS increased serum MDA and NO levels and decreased antioxidant enzymes activity [45].

It has been well known that the antioxidant and anti-inflammatory agents are useful for CVD. So polyphenols like curcumin are suggested [17]. Curcumin has been reported to have therapeutic potential for several chronic inflammatory diseases, essentially its anti-oxidative and anti-inflammatory properties against a huge of molecular targets [27]. Our results showed that the medium and the highest doses of curcumin decreased the WBC count to reach to the normal range but the lowest dose was not effective. Considering these results it seems that effect of curcumin on WBC was dose dependent and WBC count in the rats treated by 10 and 15 mg/kg was lower than that in ones treated by 5 mg/kg. This makes us realize that curcumin reduces inflammation in the body. In confirm with our results, another study showed that curcumin decreased WBC count elevation in collagen-induced arthritis and decreased the inflammation in this study [46].

Another mechanism studied for the effects of curcumin on the cardiovascular system is its effects on oxidative stress damage. The capacity of curcumin to prevent lipid peroxidation has been shown in many studies, a crucial factor in the development and progression of many diseases [47]. Curcumin's ability to stabilize the membrane was also documented [48]. In vitro, through activated macrophages, which play an important role in inflammation, curcumin significantly inhibited ROS generation such as superoxide anions, H<sub>2</sub>O<sub>2</sub>, and radical nitrite generation [49]. In addition, Venkatesan et al. observed a protective effect of curcumin against adriamycin-produced cardiotoxicity in rats, showing a reduction in parameters indicating lipid peroxidation [50]. Also, the results of our study showed that treatment with curcumin reduced the subsequent LPS damage in rat serum, heart and aorta tissues, demonstrated by a decreased level in lipid peroxidation (reduced MDA), an increased level in total thiol concentration and improvement in antioxidant enzyme status (increased activity of SOD and CAT). According to the results, the highest dose of curcumin had the best effect and it might be suggested that the effect of curcumin on oxidative stress indicators was dose dependent. In disease associated with increased oxidative stress, pharmacological increase of endogenous antioxidants has been established as a promising therapeutic strategy [51]. In the event of increased free radical generation, an increase in SOD activity

has been reported to be beneficial [31]. Nonetheless, an increase in catalase activity at the same time is important for an overall beneficial effect of an increase in SOD activity [52]. Protection may have been mediated by an increase in basal myocardial endogenous antioxidants induced by curcumin. Rao et al. [53] argued that the presence of phenolic groups in curcumin structure is important in understanding its ability to remove oxygen-derived free radicals from the medium that is largely responsible for cell lipid peroxidation. Ruby et al. reported it in 1995 while studying the antitumor and antioxidant activity of natural curcuminoids that inhibits curcumin in the production of superoxide radicals [54]. Our findings also corroborate the above findings. Other effect of curcumin on heart is modulation of vascular dysfunction and oxidative stress.

The results of the graphs show that in general, the level of MDA in heart and aortic tissues as well as in serum in curcumin-treated groups was decreased. The graphs also showed that the amount of total thiol groups as well as the activity of SOD and CAT enzymes in curcumin-treated groups was increased. However, due to the difference in the unit of measurement in tissues and serum, it is possible to make an accurate comparison to determine in which tissue curcumin has acted more effectively.

In this study, functional changes in cardiovascular tissue were not investigated. However, considering the oxidative damage and inflammation, it can be concluded that these can lead to CVD. Finally, it is proposed that other precise experiments at cellular and molecular levels should be carried out to explain the exact mechanism(s). Also it is suggested to examine inflammatory cytokines and the related signaling pathways.

Chronic inflammation has been shown to cause cardiovascular disease, and curcumin can prevent these diseases [55]. The results of this study can be examined in the people who suffer from cardiovascular dysfunction as a result of systemic inflammation. Curcumin with its antioxidant and anti-inflammatory properties can prevent these side effects however; it needs to be more investigated.

## 5. Conclusion

The results of current study showed that curcumin had protective effect against cardiovascular oxidative stress in a rat model of systemic inflammation induced by LPS. Considering these results, the beneficial effects of curcumin on cardiovascular disorders which are accompanied with oxidative stress and inflammatory conditions is suggested however, it needs to be more investigated.

## Declaration of competing interest

The authors declare no conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bbrep.2021.100908>.

## Author statement

Somaieh Ahmadabady: Analysis and/or interpretation of data.  
Farimah Beheshti: Drafting the manuscript, revising the manuscript critically for important intellectual content.  
Mahmoud Hosseini: Conception and design of study.  
Elnaz Khordad: Acquisition of data.  
Fatemeh Shahidpour: Drafting the manuscript.

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