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Curcumin as a Potential Therapeutic Agent for Mitigating Carbon Monoxide Poisoning: Evidence from an Experimental Rat Study

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Carbon monoxide (CO) is a poisonous gas and causes tissue damage through oxidative stress. We aimed to investigate the protective value of curcumin in CO poisoning.

Material/Methods: Twenty-four female Spraque Dawley rats were divided into 4 subgroups: controls (n=6), curcumin group (n=6), CO group (n=6), and curcumin+CO group (n=6). The experimental group was exposed to 3 L/min of CO gas at 3000 ppm. Curcumin was administered intraperitoneally at a dosage of 50 mg/kg. Hippocampal tissues were removed and separated for biochemical and immunohistochemical analysis. Tissue malondialdehyde (MDA) levels, nitric oxide (NO) levels, and superoxide dismutase (SOD) and catalase (CAT) activities were assayed spectrophotometrically, and serum asymmetric dimethylarginine (ADMA) were measured using the ELISA technique. Tissue Bcl-2 levels were detected by the immunohistochemistry method.

Results: Tissue CAT and SOD activities and NO levels were significantly lower, and MDA and serum ADMA levels were higher in the CO group than in the control group ($P<0.001$). The curcumin+CO group had higher CAT activities ($P=0.007$) and lower MDA than the CO group ($P<0.001$) and higher ADMA levels than the control group ($P=0.023$). However, there was no significant difference observed for tissue SOD activity or NO levels between these 2 groups. In the curcumin+CO group, the Bcl-2 level was higher than that in the CO group ($P=0.017$).

Conclusions: The positive effect of curcumin on CAT activities, together with suppression of MDA levels, has shown that curcumin may have a protective effect against CO poisoning.

Keywords: Carbon Monoxide • Neuroprotective Agents • Curcumin • Carbon Monoxide Poisoning

Abbreviations: **CO** – carbon monoxide; **MDA** – malonic dialdehyde; **SOD** – superoxide dismutase; **NO** – nitric oxide; **CAT** – catalase; **ADMA** – asymmetric dimethylarginine; **COHb** – carboxyhemoglobin; **OH** – hydroxyl radicals; **ROS** – reactive oxygen species; **H_2O_2** – hydrogen peroxide

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Introduction

Carbon monoxide (CO) is a non-irritating, tasteless, odorless, and colorless poisonous gas. It results from the incomplete combustion of molecules containing carbon. Asphyxia and cellular hypoxia, binding to hemoglobin, myoglobin, and cytochrome p450, and ischemia and reperfusion injury are all mechanisms by which carbon monoxide causes tissue damage. CO poisoning is believed to account for more than half of all fatal poisonings worldwide [1,2].

Although the carboxyhemoglobin (COHb) level is helpful in diagnosis, there is a weak correlation between the measured COHb level and clinical symptoms and findings [3]. Thus, clinicians can frequently face dilemmas in the treatment of patients considered to have CO poisoning [4]. The conventional treatment for CO poisoning is the injection of a large quantity of oxygen as soon as possible. Furthermore, hyperbaric oxygen therapy appears to be the preferred treatment for individuals with considerable CO exposure. The decision to commence hyperbaric oxygen treatment needs careful consideration of a number of parameters, such as the blood COHb level, comorbid disorders (including pregnancy), the patient's stability, and the proximity of the nearest facility with emergency hyperbaric capabilities [1].

Oxidative stress is characterized by an imbalance between reactive oxygen species (ROS), such as hydroxyl radicals (OH), ROS, and hydrogen peroxide (H2O2), which are produced during normal cellular metabolism, and antioxidants, which scavenge free radicals [5]. ROS, free radicals, and neuronal nitric oxide are thought to cause oxidative damage, which is one of the current hypotheses on the molecular mechanism of CO poisoning [6]. The natural compound curcumin, which is widely present in the *Curcuma longa* plant, is specifically suggested to serve as an anti-apoptotic enhancer or moderator against oxidative shocks. Its action may include its anti-oxidative effect and changes in signal targets [7].

The hypothesis of the study is that curcumin can prevent/reduce oxidative stress damage caused by CO poisoning. The objective of this study is to investigate the neuroprotective role of curcumin by measuring levels of superoxide dismutase (SOD), nitric oxide (NO), malondialdehyde (MDA), catalase (CAT), dimethylarginine (ADMA), and Bcl-2 in rats with CO poisoning.

Material and Methods

To biochemically detect oxidative damage, the levels of MDA, which is the final product of lipid peroxidation, as well as SOD and CAT, which are antioxidant enzymes, were measured. Additionally, the levels of NO and asymmetric ADMA, an inhibitor of the NO-synthesizing enzyme, were analyzed. Using immunohistochemistry, the anti-apoptotic marker Bcl-2 immunoexpression was detected.

Establishment of Experimental Groups

The study included 24 female rats (Sprague Dawley) with an average weight of 250 g. They were kept under standard conditions (at 21-23°C with 12 h/12 h light/dark cycles) and had free access to food and water. Carbon-monoxide gas of 3000 ppm concentration was obtained from the HABAS Industrial and Medical Gas Industry Company (İzmit, Turkey). Then, the rats were divided into 4 subgroups as follows (**Figure 1**).

Control group (group 1, n=6): Rats in this group were exposed to room air for 30 min. In this group, only room air was administered to the rats. CO gas and curcumin treatment were not administered. Subsequently, they were killed, and blood/tissue samples were collected.

Curcumin group (group 2, n=6): Rats in this group were administered curcumin (50 mg/kg) intraperitoneally. The rats in this group were treated only with curcumin; CO inhalation was not administered. After 30 min of room air, they were killed, and blood/tissue samples were taken.

CO group (group 3, n=6): Rats in this group were exposed to 3 L/min of CO gas at 3000 ppm concentration for 30 min. The rats in this group were exposed only to carbon monoxide inhalation. Subsequently, they were killed, and blood/tissue samples were collected.

Curcumin+CO group (group 4, n=6): Rats in this group were exposed to 3 L/min of CO gas at a concentration of 3000 ppm for 30 min. Following CO exposure, they were intraperitoneally administered curcumin at a dosage of 50 mg/kg. After an additional 30 min, the rats were killed, and blood/tissue samples were collected.

All rats were decapitated after intraperitoneal administration of ketamine (75 mg/kg) and xylazine (10 mg/kg). Intracardiac puncture was used to collect blood samples from the deceased rats for biochemistry analysis. Thereafter, parts of the hippocampus CA1 were surgically removed. One part of the tissue samples was used for biochemical analysis, while the other part was used for histopathological inspection. Although the tissues reserved for histological investigation were immersed in a 10% formaldehyde solution, processed through a series of graded alcohols and xylene, and ultimately embedded in paraffin blocks, the tissues reserved for biochemical analysis were kept at 80°C until analysis.

Tissue Homogenization and Biochemical Analysis

The tissues were homogenized using a glass-distilled water homogenizer. The supernatants of blood were centrifuged at 2500

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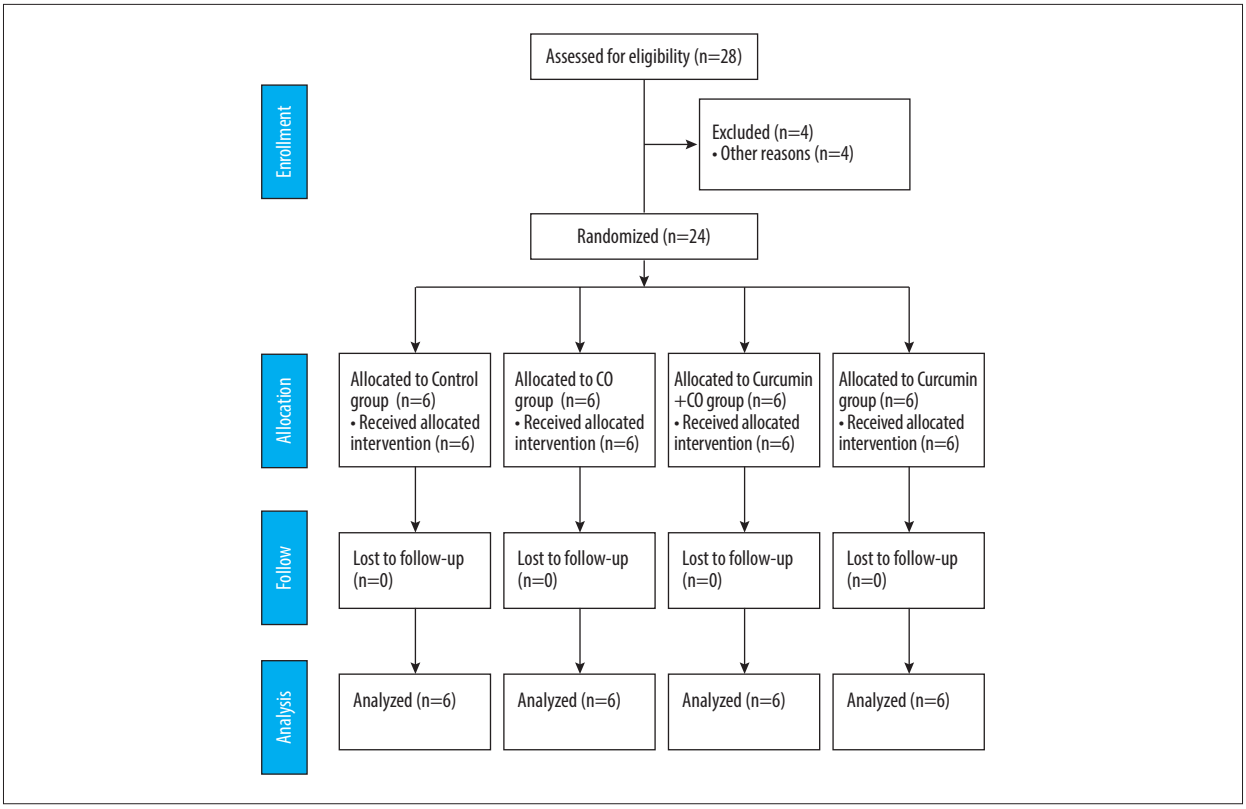

Figure 1. Consort diagram schema.

rpm after a 10-min resting period. Hippocampus tissues were rinsed with physiological saline after removal, and the right hemispheres were weighed, promptly frozen in liquid nitrogen, and stored at -80°C. For analysis, all tissue samples underwent homogenization using a blade homogenizer in a 1/6 phosphate buffer (pH: 7.4), followed by centrifugation at 20 000×g to isolate the supernatants. Total protein levels in all homogenates and supernatants were determined through spectrophotometric analysis, using the Bradford method (Shimadzu UV 1800 Spectrophotometer) [8].

Supernatant CAT activities were measured using Aebi's technique, and the maximal absorbance of hydrogen peroxide (H_2O_2) was at 240 nm. Catalase reduces ultraviolet absorption by converting H_2O_2 in the experimental environment into water and oxygen. The activity of the CAT enzyme is directly linked to a reduction in absorbance [9].

Supernatant SOD activities were measured by the method of Sun et al, based on the changes adapted by Durak et al [10]. This technique depends on the reduction of nitroblue tetrazolium by oxygen radicals produced by the xanthine oxidase system. Its reduction terminates with the formation of a blue color at 560 nm of maximum absorption.

Homogenate MDA levels were assayed by the method proposed by Placer et al and modified by Matkovics et al to measure lipid peroxidation [11]. This method is based on the reaction between butyric acid and MDA, an aldehyde made by lipid peroxidation that reacts with thiobarbituric acid to make a pink chromogen that can be measured at 532-535 nm on a spectrophotometer.

The NO production was assessed by the accumulation of nitrites by the modified technique of Griess, as described previously [12]. The optical density of the assay samples was measured spectrophotometrically at 540 nm.

Supernatant CAT, SOD, NO, and homogenate MDA results were expressed in proportion to gram protein. Serum ADMA levels were measured by the ELISA method using commercially available kits, according to the manufacturer's instructions (Thermo Scientific Multiscan GO, Finland).

Immunohistochemical Study

Bcl-2 is one of many important apoptotic regulators that are necessary for healthy development, tissue homeostasis, and defense against external pathogens. Many sets of genes control this pathway, but the Bcl-2 family is the best known [13]. The Bcl-2 family includes members that are proapoptotic (Bax, Bak, Bid, and Bad) and antiapoptotic (Bcl-2, Bcl-xL, and Bcl-w) [14].

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The paraffin blocks were cut into 5-m-thick sections using a microtome before being put on the slide. These sections were incubated for a whole night at 54°C before being deparaffinized twice for a total of 20 min. The sections were then rehydrated by allowing them to soak for 5 min in a series of alcohols with gradually lower concentrations (100%, 90%, 80%, and 70%). The sections were subjected to microwave irradiation (7+5+5 min) in 250 mL of freshly produced citric acid (pH 6.0) buffer, washed twice with phosphate-buffered saline (PBS), and then cooled at room temperature for 20 min to show antigenic epitopes. They were washed 3 times with PBS for 5 min at room temperature. The endogenous peroxidase activity in the tissues was then saturated by incubating them for 20 min at room temperature in a 3% H_2O_2 solution. The sections were held for 7 min at room temperature in blocking solution (Invitrogen, Carlsbad, CA, USA) to prevent non-specific binding. Following the removal of the blocking solution, bcl-2 primary antibodies (mouse monoclonal anti-Bcl-2, Dako) were added to the samples, which were then kept overnight at 4°C in a humid environment.

The sections were then incubated for 45 min at room temperature with biotin-labeled (Invitrogen) secondary antibodies. After the application of the secondary antibody, the streptavidin-peroxidase complex was introduced to the tissue samples and incubated for 30 min at room temperature. Following the PBS washing steps, dripping diaminobenzidine (DAB; Invitrogen) solution made antigen-antibody complexes visible. After DAB application, sections were rinsed with water and stained with Mayer hematoxylin. The samples underwent dehydration through a series of increasing alcohol concentrations, were cleared by passing through xylol, and were finally covered with a closure solution. Under a microscope, the resulting chromogenic reaction was examined.

Using the procedure described in the prior report, immunopositive cells were counted [15]. Hippocampal sections were examined under a 200×-magnification light microscope for immunostaining, and immunopositive cells per 1000 cells were counted. The evaluation was performed using a light microscope (Nikon Eclipse Ni), a digital camera (Nikon DS-R12), and software (NIS-Elements 4.50).

Statistical Analyses

The biochemical study was statistically analyzed using MedCalc (version 15.8), and the results were presented as the median and 25th percentile and 75th percentile. Kruskal-Wallis variance analysis was used to examine the median comparisons of more than 2 groups. Following the analysis of variance, post-hoc tests were used to determine the various groups, and the Bonferroni test was used for paired comparisons. The level of statistical significance accepted was 0.05.

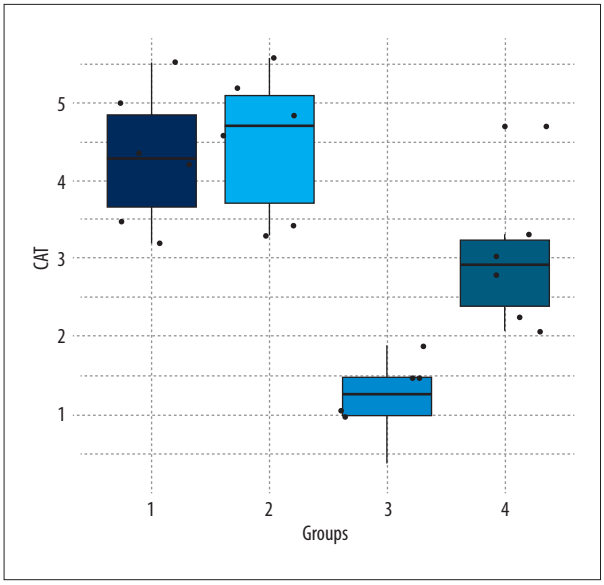

Figure 2. Box plot graphs of catalase (CAT). Group 1, control; Group 2, curcumin; Group 3, CO; Group 4, curcumin+CO.

SPSS was used to perform statistical analyses for immunohistochemistry (version 22.0, IBM Corp, Armonk, NY, USA). Descriptive statistics were reported as the mean±standard deviation. Shapiro-Wilk tests were used to analyze the group distributions. Since the data met the assumptions of normality, the differences between 3 or more groups were assessed using the ANOVA test. Post-hoc tests with Bonferroni correction or Games-Howell were applied for pairwise comparisons to identify specific group differences. A significance level of $P<0.05$ was considered statistically significant.

Ethics Statement

The study obtained approval from the Local Ethics Committee of Ankara Training and Research Hospital Animal Experiments (537; 13.08.2018).

Results

Our findings revealed that CAT values in the control, curcumin, and curcumin+CO groups were significantly higher than those in the CO group ($P<0.001$, $P<0.001$, $P=0.007$, respectively). Notably, the CAT value in the curcumin group was significantly elevated compared to the curcumin+CO group ($P=0.042$) (**Figure 2**). SOD values demonstrated a similar pattern, with the control and curcumin groups exhibiting significantly higher values than the CO group ($P<0.001$, $P=0.002$, respectively) (**Figure 3**). Regarding MDA levels, the control, curcumin, and curcumin+CO groups all showed significantly lower values than the CO group ($P<0.001$). Furthermore, MDA values in

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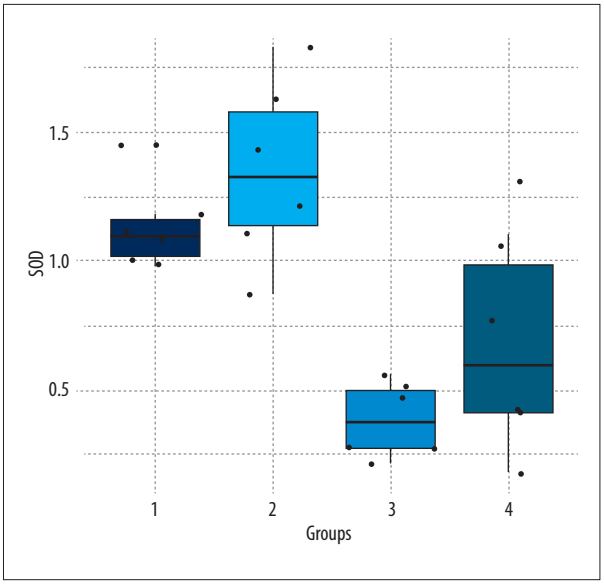

Figure 3. Box plot graphs of superoxide dismutase (SOD). Group 1, control; Group 2, curcumin; Group 3, CO; Group 4, curcumin+CO.

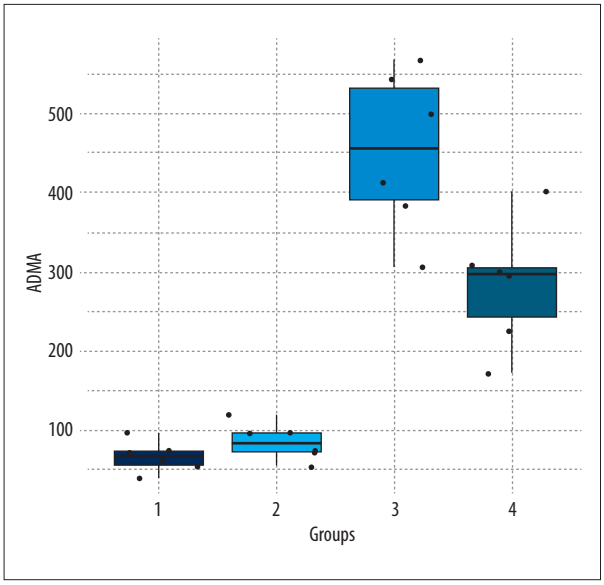

Figure 5. Box plot graphs of dimethylarginine (ADMA). Group 1, control; Group 2, curcumin; Group 3, CO; Group 4, curcumin+CO.

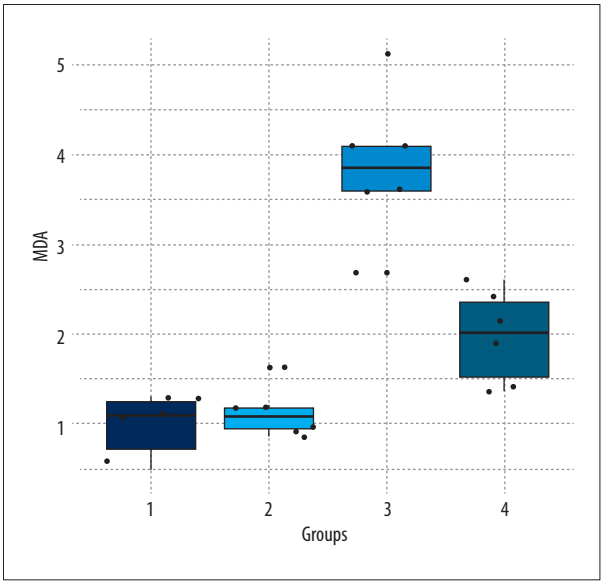

Figure 4. Box plot graphs of malondialdehyde (MDA). Group 1, control; Group 2, curcumin; Group 3, CO; Group 4, curcumin+CO.

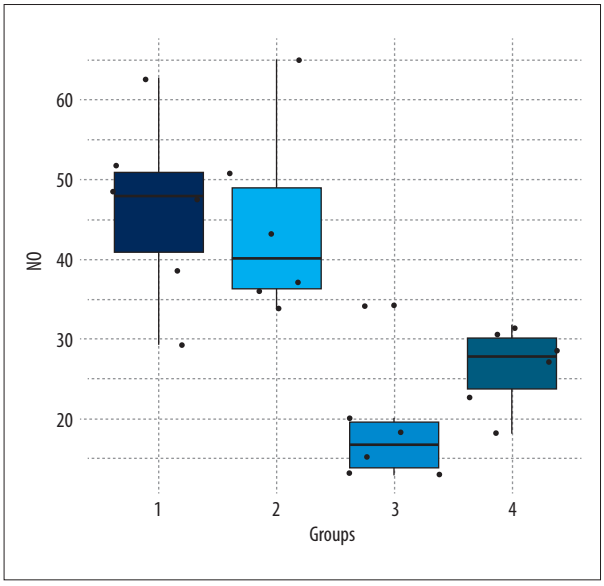

Figure 6. Box plot graphs of nitric oxide (NO). Group 1, control; Group 2, curcumin; Group 3, CO; Group 4, curcumin+CO.

the curcumin+CO group were significantly higher than those in the control group (P=0.023) (**Figure 4**). ADMA values in the control, curcumin, and curcumin+CO groups were all significantly lower than those in the CO group (P=0.001, P=0.001, P=0.041, respectively). Notably, in the control and curcumin groups, ADMA values were significantly lower than in the curcumin+CO group (P=0.003, P=0.004, respectively) (**Figure 5**). Additionally, NO values in the control and curcumin groups were higher than those in the CO group (P<0.001, P=0.010, respectively). Moreover, the NO value in the curcumin group was significantly higher than in both the CO and curcumin+CO groups (P=0.001, P=0.023, respectively) (**Figure 6, Table 1**).

The Bcl-2 value showed a significant increase in the control, curcumin, and curcumin+CO groups, compared with the CO group (P<0.001, P<0.001, P=0.017, respectively). Specifically, in the control and curcumin groups, the Bcl-2 immunopositive cell values were significantly higher than those in the curcumin+CO

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Table 1. Comparison of laboratory parameters according to rat groups with ANOVA.

	Control (1)	Curcumin (2)	CO (3)	Curcumin+CO (4)	p	Post-hoc p
CAT	4.29±0.88	4.47±0.93	1.20±0.52	3.02±0.94	**<0.001***	**1-3: <0.001[a]** **2-3: <0.001[a]** **2-4: 0.042[a]** **3-4: 0.007[a]**
SOD	1.14±0.17	1.35±0.35	0.38±0.14	0.69±0.43	**<0.001***	**1-3: <0.001[b]** **2-3: 0.002[b]**
MDA	0.98±0.35	1.13±0.28	3.87±0.80	1.98±0.51	**<0.001***	**1-3: <0.001[a]** **1-4: 0.023[a]** **2-3: <0.001[a]** **3-4: <0.001[a]**
ADMA	66.3±19.8	85.2±23.1	452.3±101.3	283.9±78.7	**<0.001***	**1-3: 0.001[b]** **1-4: 0.003[b]** **2-3: 0.001[b]** **2-4: 0.004[b]** **3-4: 0.041[b]**
NO	46.3±11.4	44.3±11.9	18.9±7.9	26.3±5.1	**<0.001***	**1-3: <0.001[a]** **1-4: 0.010[a]** **2-3: 0.001[a]** **2-4: 0.023[a]**

[a] Bonferroni correction, [b] Games Howel.

Table 2. Comparison of Bcl-2 immunopositive cells according to rat groups with ANOVA.

	Control (1)	Curcumin (2)	CO (3)	Curcumin+CO (4)	p	Post-hoc p
Bcl-2 Immunopositive cells	37.71±6.34	40.71±5.85	15.43±3.86	24.43±3.55	**<0.001***	**1-3: <0.001[a]** **1-4: <0.001[a]** **2-3: <0.001[a]** **2-4: <0.001[a]** **3-4: 0.017[a]**

[a] Bonferroni correction.

group ($P<0.001$, $P<0.001$, respectively). Moreover, within the curcumin+CO group, the Bcl-2 value was higher than that in the CO group ($P=0.017$) (**Table 2**).

In the immunostaining conducted with the anti-Bcl-2 antibody in the hippocampus, widespread expression (indicated by arrows) is evident in the control group (**Figure 7A**). Contrastingly, the presence of immunopositive cells notably decreased in the CO group (**Figure 7C**). In the Curcumin+CO group (**Figure 7D**), there was a significant increase in the presence of immunopositive cells, compared with the CO group. Notably, in the curcumin-treated group (**Figure 7B**), immune expression slightly increased when compared with that of the control group (scale bar: 100 µm) (**Figure 4**).

Discussion

Our study findings indicate that curcumin has a positive effect on serum ADMA levels and tissue CAT activities. We also found that it has suppressive effects on tissue MDA levels. However, curcumin had no effect on tissue NO levels and SOD activity. In addition, its effect on bcl-2, which is a crucial parameter in immune functions, was found to be quite interesting.

CO poisoning causes severe hypoxia in tissues and induces the overproduction of ROS, resulting in lipid peroxidation. If ROS are not effectively scavenged by antioxidant mechanisms, they lead to damaging effects on crucial biomolecules, such as nucleic acids, lipids, and proteins, causing neuronal cell death [16].

Curcumin has been reported to have preventive properties in many diseases, especially acute or chronic neurological

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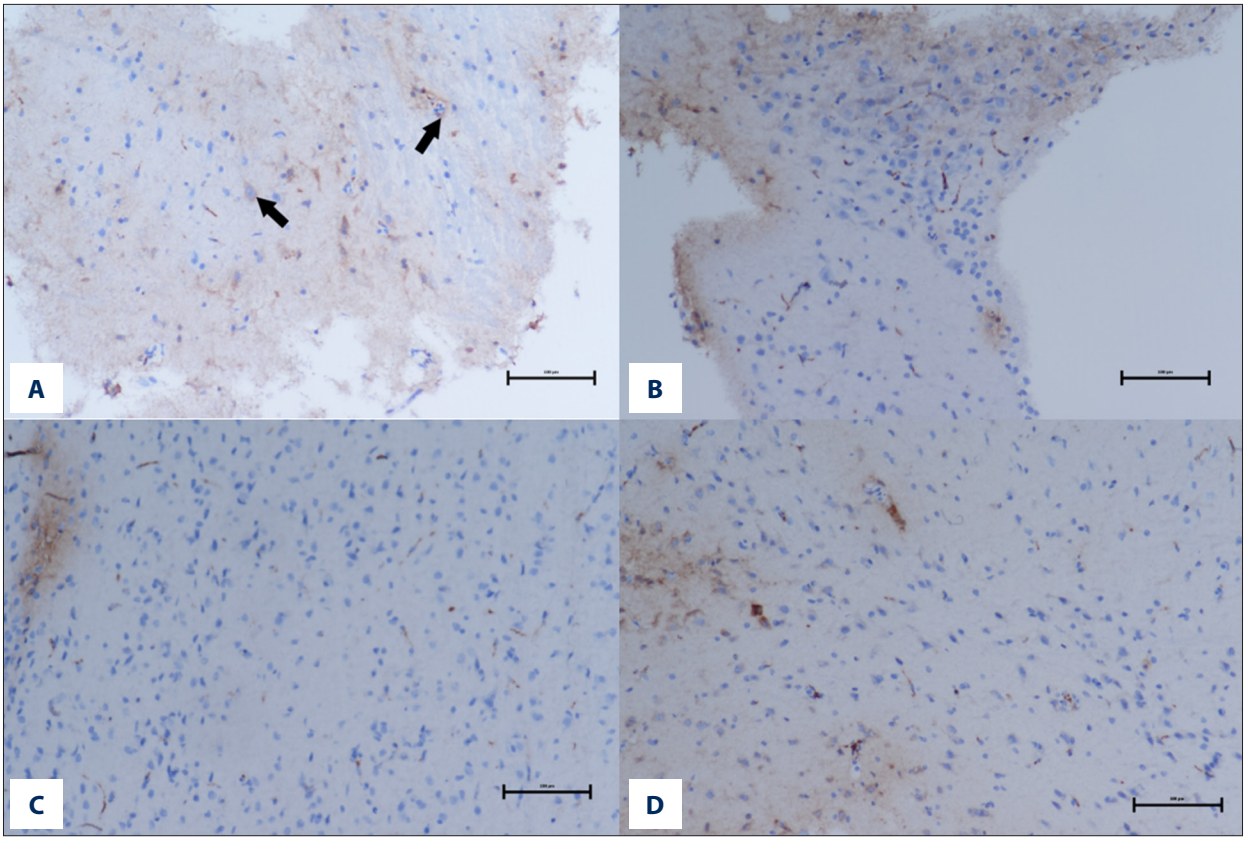

Figure 7. Micrograph of immunohistochemical staining with anti-Bcl-2 antibody in the hippocampus of rats for all groups. (**A**) Immunopositive cells (arrows) in the control group (Bar: 100 mm). (**B**) Bcl-2 immunohistochemical group of curcumin (Bar: 100 mm). (**C**) Bcl-2 immunohistochemical group of CO (Bar: 100 mm). (**D**) Bcl-2 immunohistochemical group of curcumin+CO (Bar: 100 mm).

diseases, due to its antioxidant and anti-inflammatory properties [17,18]. While the precise mechanism of action of curcumin remains incompletely understood, these beneficial effects of curcumin were found to be mainly associated with its ability in ROS scavenging [19]. The main proposed mechanisms of curcumin include hydrogen peroxide scavenging activity, which is attributed to the abstraction of hydrogen atoms from free hydroxyl groups, similar to α-tocopherol and vitamin C [20]. Additionally, curcumin demonstrates effective chelation of ferrous ions through its hydroxyl and methoxyl groups. Furthermore, it acts as a potent electron donor neutralizing free radicals, such as superoxide anions (O_2^-) and hydroxyl radicals (·OH) by forming stable products and has a restorative effect on glutathione depletion [21,22]. Curcumin has also been linked to the inhibition of NF-kappa B, which is a transcription factor that regulates many inflammatory genes, such as interleukin 6, interleukin 1β, and tumor necrosis factor α [23,24]. Therefore, investigating the effect of curcumin, an important antioxidant, on the structural and functional properties of proteins and enzymes involved in diseases has not only theoretical but also clinical applications.

In this study, we found significantly decreased CAT and SOD activities and increased MDA levels in the CO-treated group, as expected (P<0.01) (**Table 1**). CO-induced oxidative damage to antioxidant enzymes, particularly at the active site, can result in the progressive loss of enzyme activities [26]. However, following the administration of curcumin, we observed statistically significant increases in tissue CAT activities and decreased MDA levels (P<0.001) (**Table 1**). CAT is one of the earliest known and best characterized of the antioxidant enzymes that catalyse the dismutation of H_2O_2 to water and oxygen. The two most logical candidates that would benefit from this CAT activity are tissue (especially vascular) oxygen sensing and protection from ischemia and reperfusion injury [27]. Mofidi Najjar et al, in an experimental study evaluating curcumin and catalase activity, found that curcumin had a positive effect on catalase activity and reveals the nature of interactions between catalase and curcumin using computational methods and optical techniques [25]. In the present study, increased CAT activity following curcumin administration in the curcumin+CO group suggests that curcumin may have positive clinical effects on CO toxicity. Significant reduction in MDA levels in the curcumin+CO group further supports these findings

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(P<0.001). Because MDA is a measure of lipid peroxidation and an indicator of oxidative damage to tissues [6]. In another study, Alizadeh and Kheirouri stated that, in a meta-analysis, curcumin supplementation was effective in reducing MDA in diseased individuals under oxidative stress conditions and improving antioxidant levels [28]. This may be important in terms of preventing the inflammatory and tissue destruction caused by reactive superoxides, which is an important process in CO poisoning. The improvement in CAT activities and lower MDA levels following curcumin administration may have arisen primarily due to its prominent radical scavenging effect, consequently leading to protection against radical damage to these enzymes and membrane lipids. More studies are needed on changes in MDA levels after curcumin administration in CO poisoning. Extracellular SOD, another important antioxidant enzyme, protects against various oxidative stress-related diseases by scavenging reactive superoxides in the extracellular space [29]. Shen et al found that curcumin significantly extended the average lifespan of Drosophila causing increased SOD activity and decreased MDA levels [30]. We also detected significant reduction in SOD activity in the CO group, compared with controls (P<0.001); however, no improving effect was observed on SOD activity in the curcumin+CO group (**Table 1**). One possible reason for this could be associated with the relatively short duration after administering curcumin in observing changes in SOD activity.

Although oxidative stress is one of the main determiners for CO-related neuronal injury, limited literature is available about the curative role of antioxidants in CO poisoning. In one study, researchers showed that N-acetyl cysteine and melatonin reduced brain damage due to CO poisoning [31]. In another study, Wang et al stated that edaravone, a potent free-radical scavenger, reduced MDA levels and could improve delayed neuropsychological sequelae in rabbits after acute carbon monoxide poisoning [32].

CO toxicity does not show its effect only because of hypoxia. At the same time, the process triggered by CO causes an exaggerated inflammatory response. This triggers many mediators and disruption of hemostasis occurs at the cellular level. One of them, ADMA, is an endogenous inhibitor of endothelial nitric oxide synthase [33]. In our study, serum ADMA levels were notably higher in the CO group than in the control and curcumin groups (P<0.001). After curcumin administration, serum ADMA levels significantly decreased in the curcumin+CO group (P<0.001) but did not reach the control levels (**Table 1**). In this way, patients who have been exposed to CO gas may have endothelial dysfunction if their ADMA levels are high. This result indicates that curcumin has an ameliorating effect in inflammation-mediated serum ADMA levels. We also found lower tissue NO levels in the CO group (P<0.001), confirming results of a previous study conducted by Akyol et al. It has been shown that CO poisoning was found to reduce NO production in the rat striatum, and this decrease may be due to the suppression of NOS activity due to the lack of arginine, which is its substrate [6]. However, we did not observe any significant difference for tissue NO levels between the CO and curcumin+CO groups (**Table 1**). One possible reason could be the increased ADMA levels in the curcumin+CO group, because ADMA regulates the rate of NO formation and leads to a decrease in NO levels [34]. Another reason could be related to inhibition of inducible nitric-oxide synthase expression due to curcumin administration, as suggested previously [35]. Disruption of regulation between ADMA and NO may also be responsible.

Curcumin is reported to decrease apoptosis in brain tissue via upregulating Bcl-2 in pathological conditions. Overexpression of Bcl-2 can decrease ROS production and lipid peroxidation and increase resistance to apoptosis and neurodegeneration [36]. In the present study, the high Bcl-2 levels in the curcumin group indicate the neuroprotective role of curcumin in CO poisoning.

Despite curcumin's low oral bioavailability, combining it with piperine has been shown to increase bioavailability in both rats (150%) and humans (2000%). Various methods enhance its bioavailability, including nanoparticles and liposomes. Soleimani et al reviewed 26 studies on oral curcumin, finding minimal toxicity even at high doses [37]. Curcumin is generally recognized as a safe substance by the U.S. Food and Drug Administration.

Limitations of the Study

First, no measurements were conducted regarding the levels of curcumin in the plasma of the animals. Due to curcumin's poor bioavailability stemming from inadequate absorption, rapid metabolism, and quick systemic elimination, further studies are required to assess proper monitoring of both the administered dose and its effects. Second, this study exclusively focused on the short-term effects and single dose of curcumin at the tissue level. However, additional investigations exploring the long-term effects of curcumin at various doses may provide a better understanding of its potential therapeutic properties.

Conclusions

Curcumin can protect oxygen-dependent tissues from the toxic effects of CO gas. The positive effect on tissue CAT activities and serum ADMA levels, together with the suppression of MDA, are important mediators of the exaggerated inflammatory process that causes cell destruction. These findings support the hypothesis that the destructive effect of CO can be limited by curcumin. In addition, curcumin-mediated increased expression of Bcl-2 may limit the process leading to apoptosis and cell death.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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