AMERICAN JOURNAL OF BIOLOGY AND NATURAL SCIENCES
https://biojournals.us/index.php/AJBNS
ISSN: 2997-7185

Article

Evaluating the Effect of Curcumin and Vitamin C on Normalizing Oxidative Stress Levels and Immunological Markers Induced by the Use of the Drug Doxorubicin in Male Rats

Furat Latif Karim[1]
1. Tikrit University, College of Nursing, Clinical Nursing Sciences Branch, Tikrit, Iraq

Citation: Karim, F. L. Evaluating the Effect of Curcumin and Vitamin C on Normalizing Oxidative Stress Levels and Immunological Markers Induced by the Use of the Drug Doxorubicin in Male Rats. American Journal of Biology and Natural Sciences 2026, 3(11), 157-164.

Received: 28th Sep 2026
Revised: 15th Oct 2026
Accepted: 30th Oct 2026
Published: 24th Nov 2026

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Abstract: Doxorubicin is one of the most important chemotherapies for tumors, but the clinical use of it is hindered by the production of free radicals, loss of antioxidant defense and induction of inflammatory response. This study was designed to investigate the protection and therapeutic effects of curcumin and vitamin C on the normalization of markers of oxidative stress and inflammatory cytokines in male rats treated with doxorubicin. The experiment was designed for four weeks and 25 adult male Sprague-Dawley rats were divided into five different groups, each consisting of five rats: healthy control; injected with 20 mg/kg of doxorubicin twice a week; injected with doxorubicin and given oral curcumin 300 mg/kg; injected with doxorubicin and vitamin C 200 mg/kg; and injected with doxorubicin and a combination of curcumin and vitamin C. The analysis revealed significantly elevated ($P \leq 0.05$) malondialdehyde (MDA) and inflammatory cytokines (TNF-α and IL-6) concentrations along with significant decrease in the activities of catalase (CAT) and glutathione peroxidase (GPx) in doxorubicin treated group. On the other hand, therapeutic interventions brought about marked improvements; the combined treatment (curcumin + vitamin C) was associated with a decrease in MDA, increases in GPx and CAT activities and suppressed levels of TNF-α and IL-6 to close to the normal range. In conclusion, we propose that the synergistic outcome of curcumin and vitamin C is more effective in protecting against the toxic effects of doxorubicin on the body, suggesting that this combination could be used in the development of more effective and safer chemotherapy regimens.

Keywords: Doxorubicin, Oxidative Stress, Immune Response, Curcumin, Vitamin C

Introduction

Doxorubicin undergoes a redox cycle, producing semiquinone radicals and excess superoxide anions which ultimately neutralize primary defenses of the cells [1]. The continual exposure of reactive oxygen species (ROS) can damage polyunsaturated fatty acids in cell membranes and disrupt critical regulatory pathways like the Nrf2 pathway [2]. Malondialdehyde (MDA) is an elevated biomarker that is characteristic of membrane lipid peroxidation that ensues after a chain of free-radical reactions are initiated by anthracyclines [3]. In addition, the decrease in enzyme glutathione peroxidase (GPx), which

facilitates the removal of organic and inorganic hydroperoxides from the cells, aggravates the situation, and the depletion of glutathione reserves, which is required as a cofactor for the enzyme, further worsens things up [4].

Acute and chronic exposures to the drug doxorubicin cause a series of oxidative and inflammatory responses, with the release of key signaling proteins [5]. These systemic injuries are mainly mediated by the cytokines, "TNF-α and IL-6 [6]. Animal models and in vitro experiments have shown that doxorubicin can induce high plasma levels of both TNF-α and IL-6, as well as increased levels of these cytokines in specific tissues [7]. Such increases are correlated with increased oxidative stress and the decrease of antioxidant enzymes, as well as activation of the programmed cell death (apoptosis) pathways in the tissues [8]. In addition, the drug also triggers the formation of reactive oxygen species (ROS) and activates pathways that are mediated by nuclear factor-kappa B (NF-κB). As a consequence, there is increased circulating in the blood of both tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6)", which leads to severe cardiotoxicity and acute organ damage [5], [9].

The chemotherapy agent doxorubicin is known to induce high level of ROS, to deplete endogenous antioxidants and to trigger lipid peroxidation, which leads to significant organ toxicity [10]. On the other hand, curcumin's ability to reverse this oxidative damage is indicated by preclinical studies that found it decreases malondialdehyde (MDA) levels, increases glutathione peroxidase (GPx) activity and regulates the expression of catalase (CAT) [3]. Moreover, the beneficial effect of curcumin on pro-inflammatory cytokines, which includes tumour necrosis factor alpha (TNF-α), and interleukins 6 (IL-6), as demonstrated via animal studies (rats), in vitro cancer cell experiments, and pharmacological studies [3], [11]. Likewise, vitamin C (ascorbic acid) is known to strongly inhibit lipid peroxidation, replenish the levels of endogenous antioxidant enzymes and reduce the presence of tumour necrosis factor-alpha (TNF-α) [12]. Metwaly et al. [13] found in vitro a significant decrease in lipid peroxidation (doxorubicin) in normal human skin melanocytes.

Hence, the objective of this research was to assess and investigate the antioxidant and restorative effects of both curcumin and vitamin C against biochemical parameters which were changed by the drug doxorubicin. This was done by lowering the elevated levels of malondialdehyde (MDA) which is a marker of lipid peroxidation, and the inflammatory markers, such as TNF-α and IL-6. Moreover, the study aimed to restore and improve the functionality of the antioxidant defense systems found within the cells and organs (enzymes glutathione peroxidase (GPx); catalase (CAT)) to reduce the toxicity which chemotherapy causes to the cells and organs.

Materials and Methods

Materials

Doxorubicin was obtained from Pfizer (USA), curcumin was sourced from local markets, and vitamin C (ascorbic acid, chemical formula $C_6H_8O_6$) was procured from the Chinese company Macklin.

Animals

In this experiment, four-month-old male Sprague Dawley albino rats weighing 200 ± 10 g were employed. The rats were kept in specialised cages in a lab setting with a temperature of 22 ± 2°C and a light-dark cycle of 12 hours of light and 12 hours of darkness. The cages were cleaned and sterilised on a regular basis. The animals were given free access to food and water during their one-week acclimatisation phase. The animals were provided a typical diet for the whole four-week experiment.

Experimental Design

In this study, twenty-five adult male white rats with comparable body weights were split into five groups. Doxorubicin was given to groups 2 through 5. The following is how the groups were set up :

1. Group 1 "(Normal Control): Received a standard diet and was administered distilled water for four weeks".
2. Group 2 "(Doxorubicin): Injected intraperitoneally with Doxorubicin at a dose of 20 mg/kg, twice weekly for four weeks [14]".
3. Group 3 "(Doxorubicin + Curcumin): Injected with Doxorubicin (20 mg/kg) and administered Curcumin (300 mg/kg) [15] for four weeks".

4. Group 4 "(Doxorubicin + Vitamin C): Injected with Doxorubicin (20 mg/kg) and administered Vitamin C (200 mg/kg) [16] for four weeks".
5. Group 5 "(Doxorubicin + Curcumin + Vitamin C): Injected with Doxorubicin (20 mg/kg) and administered both Curcumin (300 mg/kg) and Vitamin C (200 mg/kg) for four weeks".

Serum Collection

The animals were starved for 12 hours at the conclusion of the four-week trial period. After that, an intramuscular injection of ketamine (5 mg/kg body weight) and xylazine (35 mg/kg body weight) was used to put them to sleep. After drawing blood from the heart, the serum was separated and kept at -20°C for the study's ensuing biochemical analysis.

Biochemical assays

The concentrations of MDA, GPx, and CAT, in addition to TNF-α and IL-6, were measured in blood serum following the instructions provided with the kits from the French company Biolabo, using the ELISA technique.

Statistical Analysis

"Using Duncan's multiple range test and SPSS software, the findings were statistically analysed at a significance level of ($P < 0.05$)".

Result

Serum Concentrations of MDA, GPx, and CAT

"The data shown in Figure 1 and Table 1 reveal a considerable decrease in GPx and CAT concentrations and a large increase in MDA concentration when comparing the doxorubicin-injected group to the normal control group. Conversely, the groups that received doxorubicin injections followed by treatment with either curcumin alone, vitamin C alone, or a combination of both (curcumin + vitamin C) demonstrated lower MDA concentrations and higher GPx and CAT concentrations than the group that received only doxorubicin. In the previously mentioned parameters, the group that took both curcumin and vitamin C showed the greatest improvement".

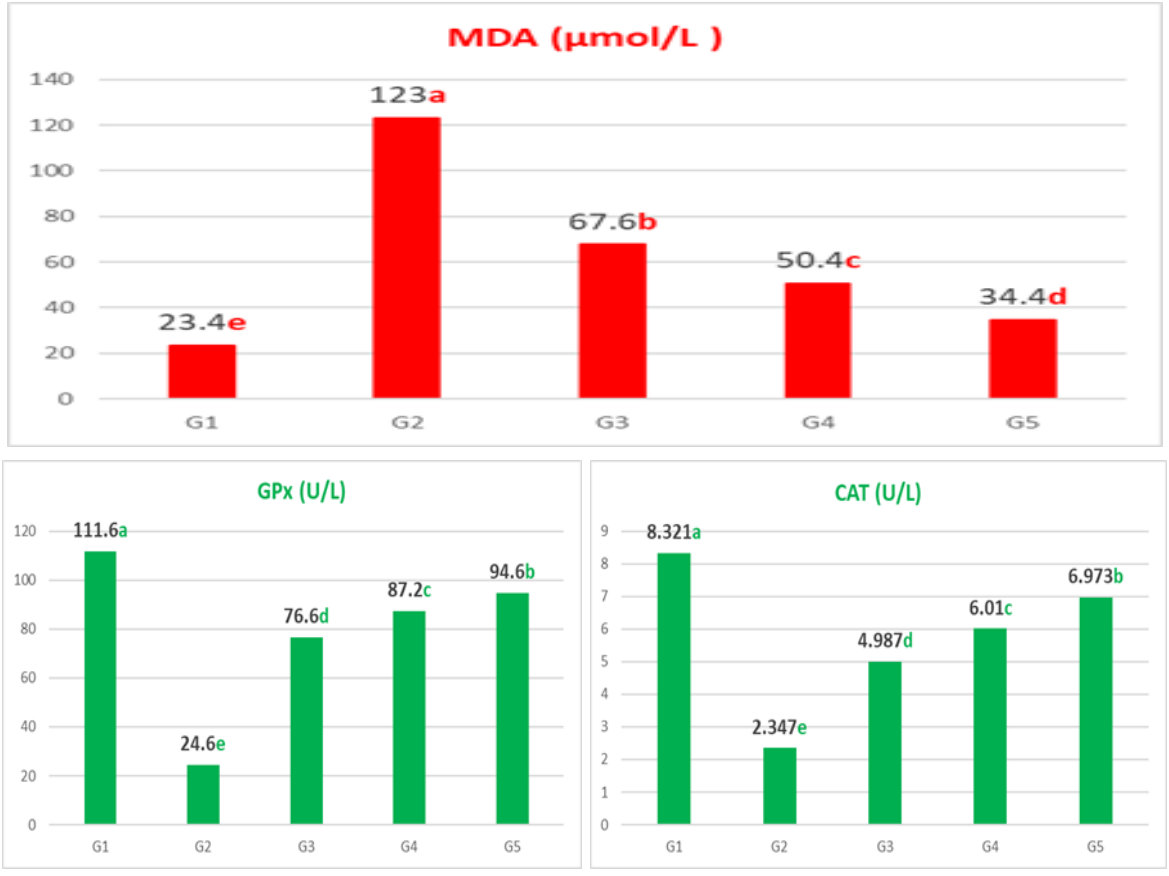

Figure 1. Serum MDA, GPx, and CAT measurements.

Table 1. Effects of curcumin and vitamin C on serum MDA, GPx, and CAT.

Group / Groups	MDA (µmol/L)	GPx (U/L)	CAT (U/L)
Control	23.40±3.65e	111.60±8.47a	8.321±0.385a
Doxorubicin	123.00±6.78a	24.60±3.65e	2.347±0.215e
Doxorubicin + Curcumin	67.60±6.19b	76.60±3.85d	4.987±0.221d
Doxorubicin + Vitamin C	50.40±3.85c	87.20±3.49c	6.010±0.224c
Doxorubicin + Curcumin + Vitamin C	34.40±3.65d	94.60±3.65b	6.973±0.180b
F	303.98	216.23	389.99
P-Value	<.0001***	<.0001***	<.0001***

Data are shown as mean ± SD.
Numbers with an asterisk marked with different letters in a column differ significantly at the probability level of (P≤ 0.05).

Serum Concentrations of TNFα and IL-6

Significant elevation in the level of serum tumor necrosis factor (TNFα) and interleukin (IL-6) was observed in the Doxorubicin injected group when compared with normal control as seen in the result presented in Figure 2 and Table 2. The groups that were injected with Doxorubicin and then treated with Curcumin alone, Vitamin C alone, or with a combination of both "(Curcumin + Vitamin C) had lower levels of the cytokines TNFα and IL-6 than the group that got Doxorubicin only. The group treated with the combination of Curcumin and Vitamin C showed the most favorable effect in improving these parameters.

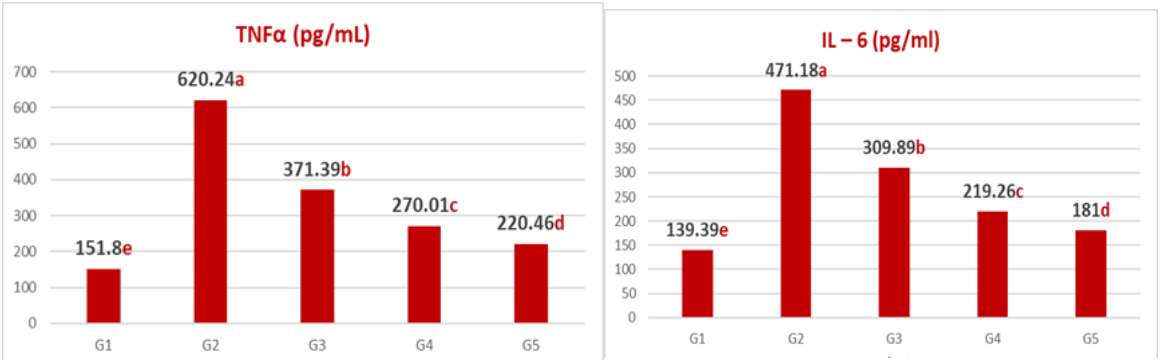

Figure 2. Serum TNF-α and IL-6 concentrations.

Table 2. Effects of curcumin and vitamin C on serum TNF-α and IL-6 concentrations.

Group / Groups	TNF-α (pg/mL)	IL-6 (pg/mL)
Control	151.80±29.43e	139.39±8.24e
Doxorubicin	620.24±21.61a	471.18±8.27a
Doxorubicin + Curcumin	371.39±24.55b	309.89±19.25b
Doxorubicin + Vitamin C	270.01±25.43c	219.26±12.13c
Doxorubicin + Curcumin + Vitamin C	220.46±19.64d	181.00±12.30d
F	280.59	539.20
P-Value	<.0001***	<.0001***

Discussion

Doxorubicin belongs to the anthracycline class of chemotherapeutic drugs, is an effective therapy in oncology, but its effectiveness is restricted from clinical use due to its dose-dependent toxicity in non-target tissues [17]. Doxorubicin-induced oxidative and antioxidant changes are both acute and chronic, and occur in a consistent manner in diverse in vivo rodent models as well as in vitro cell-based studies, with specific vulnerabilities present in different tissues [18]. The chemotherapy of doxorubicin causes massive oxidative stress in various organs, which are mainly characterized by elevated levels of lipid peroxidation products, and reduced levels of antioxidant defenses [19].

An increase in malondialdehyde (MDA) level and a simultaneous decrease in the enzymes glutathione peroxidase (GPx) and catalase (CAT) have been reported by many researchers in both clinical and preclinical studies [20]. The level of MDA is an overall marker of lipid peroxidation, which is significantly induced by doxorubicin administration in membranes of tissues, including heart, liver, nervous system and testes. In this context, the enzyme catalase converts hydrogen peroxide into water and molecular oxygen; this is an important protection from oxidative damage caused by anthracyclines. According to most studies, this enzyme activity in the liver and heart is decreased in the presence of doxorubicin [3], [21]. Moreover, it markedly exhausts the intracellular pool of reduced glutathione and affects the activity of glutathione peroxidase (GPx) which helps remove organic peroxides and hydrogen peroxide (H_{2}O_{2}) effectively [22].

At the molecular and inflammatory levels, the mechanisms mediating the release of TNF-α and IL-6 induced by doxorubicin involve a feedback loop between reactive oxygen species (ROS) and the transcription factor nuclear factor-kappa B (NF-κB) [5]. Doxorubicin reduces PTEN levels and increases AKT phosphorylation, which promotes the translocation of p65 into the nucleus, where it activates inflammatory genes [7]. Furthermore, transcriptomic evaluations indicate that doxorubicin upregulates the expression of various chemokines—all of which converge on the IL-17 and TNF-α signaling pathways [23]. Elevated local levels of TNF-α promote cellular necrosis or caspase-dependent apoptosis, while circulating IL-6 exacerbates endothelial cell injury and impairs tissue remodeling [24].

In the context of therapeutic interventions, treatment with either free curcumin or nano-curcumin significantly reduces the accumulation of MDA in tissues and blood serum, restoring it to normal levels. Curcumin also reactivates the enzyme catalase—though some protocols have observed compensatory increases in this enzyme's activity during states of acute stress [3], [21]. Furthermore, curcumin mitigates glutathione deficiency by upregulating antioxidant transcriptional pathways and preserving the activity of GPx in normal somatic tissues [25]. Furthermore, curcumin's anti-inflammatory capability has been demonstrated by the reduction of tumour necrosis factor-alpha (TNF-α) expression in the cardiac tissue of rats exposed to doxorubicin (DOX) during co-treatment [3]. Through antioxidant, anti-apoptotic, and anti-inflammatory effects, co-treatment with curcumin and doxorubicin reduces elevated levels of factors like NF-κB, COX-2, TNF-α, IFN-γ, IL-1β, IL-6, and IL-18 in the cardiac cells of doxorubicin-treated animals, according to a systematic review [26]. Tumour necrosis factor-alpha (TNF-α) levels in testicular tissue were significantly lower when nanocurcumin was used as opposed to the doxorubicin (DOX) group. It also lowered IL-6 levels by upregulating the expression of the SIRT1 gene, which in turn enhanced the production of superoxide dismutase (SOD) and glutathione (GSH). In this regard, the SIRT1/NF-κB signaling pathway is a key mechanism to support antioxidant capacity and reduce oxidative stress [22].

Likewise, ascorbic acid (vitamin C) scavenges free radicals to prevent this oxidative pathway in different tissue models, including the metabolism of doxorubicin which produces semiquinone intermediates and excessive ROS that react with unsaturated fatty acids in membranes resulting in severe lipid peroxidation. Doxorubicin administration caused a significant increase in tissue malondialdehyde (MDA) concentration, but vitamin C administration resulted in a significant decrease in the concentration of malondialdehyde (MDA) whether as a prevention or therapy in male Wistar rats. Notably, vitamin C administration is usually effective in complete histological and biochemical normalization; moreover, its concurrent administration maintains normal cell viability without impairing the antineoplastic action of doxorubicin against the cancer cells [12], [27]. Concomitant administration of vitamin C prevents the phosphorylation of IκB kinase (IKK) and c-Jun N-terminal

kinase (JNK) in the early phase and consequently the degradation of IκBα and the entry of NF-κB into the cell nucleus. The early removal of ROS by vitamin C also helps to re-activate low levels of antioxidant enzymes, including superoxide dismutase, glutathione, etc., which helps to maintain redox homeostasis in the heart [12], [28]. Nevertheless, while vitamin C inhibits tumour necrosis factor-alpha (TNF-α) and protects healthy cardiac cells, laboratory studies indicate that it can also protect cancer cells from death during anthracycline chemotherapy, which could ultimately help mitigate the success of anti-tumour drugs [11].

Based on the above, there is considerable research interest in studying the use of curcumin and vitamin C as therapeutic adjuncts towards reducing the tissue toxicity associated with the drug doxorubicin. In addition to leading to a dramatic alteration of the redox balance (increasing malondialdehyde (MDA) levels, decreasing antioxidant enzymes including glutathione peroxidase (GPx) and catalase (CAT) and inducing an inflammatory response through activation of NF-κB pathways and increased production of TNF-α and IL-6), intervention with curcumin and vitamin C shows a remarkable ability to normalize these markers. These inhibit the inflammatory cytokines (TNF-α and IL-6), restore MDA levels and antioxidant enzymes (GPx and CAT) to their normal levels and break the cycle of oxidative stress. This offers full coverage of healthy vital organs and makes therapeutic plans using anthracyclines safer.

Conclusion

The present study shows that the drug Doxorubicin causes acute physiological changes with high level of malondialdehyde (MDA) and high reduction in the activities of enzymes like catalase (CAT) and glutathione peroxidase (GPx) which indicate oxidative stress and the induction of inflammatory response with rise in the level of cytokines like tumour necrosis factor (TNF-α) and Interleukin (IL-6). The administration of Curcumin and Vitamin C alone or in combination proved to be highly effective in reducing and normalizing these physiological disturbances; both compounds were able to prove to inhibit oxidative and inflammatory pathways and to restore the efficiency of the endogenous antioxidant systems. However, combined treatment (Curcumin + Vitamin C) showed the best synergistic effect for normalization of these biomarkers and was effective for restoring oxidative and inflammatory balance, making this combination a promising protective shield against the tissue toxicity induced by chemotherapy treatment.

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