

RESEARCH ARTICLE

On the Benefit of Nanocurcumin on Aluminium Phosphide-induced Cardiotoxicity in a Rat Model

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ABSTRACT

Objective(s): Cardiotoxicity is considered the main cause of death in aluminum phosphide (ALP)-poisoned cases. Curcumin, an active ingredient of turmeric, is a potent protective polyphenol compound against cardiac diseases including cardiotoxicity. This study aimed to examine the probable cardioprotection potential of nanomicelle curcumin in a rat model of ALP-induced cardiotoxicity.

Methods: The rats were orally intoxicated with ALP (12 mg/kg, p.o.; 1/4 LD₅₀). In treatment groups, curcumin (50 mg/kg, i.p.) and nanocurcumin (10, 20 and 50 mg/kg, i.p.) were administered intraperitoneally 30 min following ALP administration. Twenty four hrs subsequent to ALP intoxication, the hearts were dissected out for evaluation of oxidative stress and lipid peroxidation (LPO) markers such as thiol, reactive oxygen species (ROS), superoxide dismutase (SOD), glutathione (GSH) levels, malondialdehyde (MDA) and the ferric reducing ability of plasma (FRAP).

Results: In fact, ALP increased MDA as well as ROS and SOD levels. On the other hand, ALP significantly lowered thiol, GSH and FRAP markers. In contrast, nanocurcumin successfully could reverse the increases in MDA as well as SOD, ROS and GSH. Simultaneously, it significantly enhanced thiol, GSH and FRAP markers. Moreover, curcumin markedly lowered MDA, ROS and SOD levels while increased thiol and GSH contents.

Conclusions: Overall, the present data demonstrated the cardio-protective effects of nanocurcumin in this model of cardiotoxicity. Further, it suggested that this cardioprotection is possibly mediated by the ability of nanocurcumin to confront the oxidative stress and LPO resulting from ALP intoxication of the heart tissue.

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INTRODUCTION

Phosphides have been utilized throughout the world as pesticides to protect stored grains [1]. Nevertheless, solid phosphides include aluminum phosphide (ALP) form toxic phosphine gas, phosphine (PH₃) following direct contact with water, the air moisture, or stomach hydrochloric acid [1, 2]. The majority of deaths take place within the first 12-24 hrs., commonly owing to cardiovascular arrest [3, 4]. As soon as its systemic absorption, either subsequent to inhalation or via the gastrointestinal route, phosphine hurts the cell membranes and enzymes of the mitochondrial respiratory system. In animal studies, phosphine inhibited mitochondrial cytochrome oxidase. Consequently, it led to fluctuations in the glucose levels secondary to alterations in electrolyte and hormones [5].

ALP as a solid pesticide, is frequently used to protect stored food products and during the processes of food transformation as well [6]. This lethal pesticide does not have any influence on seed viability and remains minimal residues on food products. Besides, its utilization is cost-effective with great effectiveness against all life stages in insects [6, 7]. Unfortunately, over 70% of ALP-exposed individuals pass on from its toxic consequences in various body organs and cardiotoxicity is the primary culprit. The most important cardiovascular disturbances consist of dysrhythmias, congestive heart failure and refractory hypotension [8]. Animals Studies demonstrated that ALP probably acts by inhibiting cytochrome oxidase in the mitochondria [9]. It is suggested that the harmful effect of ALP on heart in rats is mediated by both decline in the myocardium cellular metabolism and necrosis of the cardiac tissue leading to the release of intermediates of reactive oxygen [10]. The malondialdehyde (MDA) level is raised in the cardiac tissue of ALP-poisoned rats [10]. ALP-poisoned individuals displayed considerably higher superoxide dismutase (SOD) and MDA levels and lower catalase (CAT) levels in the serum [11].

Unluckily, no specific antidote or effective drugs do exist to manage its cardiotoxic effects. The protective effects of some drugs such as triiodothyronine, [12], vasopressin [13], iron sucrose [14], Mg nanoparticle [15], acetyl-l-carnitine [16] and melatonin [17] on phosphine-induced cardiac and mitochondrial toxicity have been previously investigated.

Curcumin (diferuloylmethane), a natural phenolic compound, is isolated from turmeric (*Curcuma longa*) as a yellow pigment, which is generally employed as a spice, additive, and food colorant [18]. It has been stated that this compound possess a diversity of biological and pharmacological properties consist of antioxidant [19, 20], anti-inflammatory [21], anti-microbial [22], and anti-cancer [23]. It has been revealed that curcumin is a potent scavenger of a variety of reactive oxygen species (ROS) such as superoxide anion, hydroxyl radicals [24], and nitrogen dioxide radicals [25]. Curcumin was capable to improve mitochondria-induced ROS production and lipid peroxidation (LPO) in various oxidant damage models [26, 27] in the cardiac tissue [28, 29]. Curcumin played an important role in protection against cardiovascular dysfunction in humans and animals, which is always the underlying cause of serious cardiovascular diseases such as atherosclerosis, aortic aneurysm, myocardial infarction (MI) and stroke [30, 31]. Furthermore, anti-oxidant, anti-inflammatory and anti-apoptotic characteristics of curcumin have been demonstrated to be beneficial in improvement of cardiac hypertrophy, heart failure, and cardiotoxicity [32, 33]. Curcumin was effective in reversing the cardiotoxicity induced from some chemotherapeutic compounds including doxorubicin, cyclophosphamide, cisplatin, irinotecan and methotrexate mainly by balancing the oxidative stress [34-36].

Curcumin is considered a golden spice protecting against cardiovascular diseases nowadays [37]. However, low bioavailability of curcumin is limited its clinical application [38]. Therefore, curcumin potential for therapeutic translation has been impeded by its weak aqueous solubility, and rapid degradation as well [39]. To overcome these obstacles, different formulations of curcumin have been suggested [40-42], and proper drug combinations recommended [35, 43, 44]. In addition, by structural modifications, researchers have found several synthetic derivatives, which have better bioavailability, some of them show comparable or even improved pharmacokinetic/ pharmacodynamics profile in comparison to curcumin [45, 46]. Curcumin encapsulation in a nanoparticle form is a possible and advantageous tool enabling an improved delivery. Considering small size and high surface-to-volume ratio of nanoparticles, they are able to cross the skin barrier [39]. Nano-formulations of curcumin have been

established for preclinical investigations on cancer, inflammation, wound healing, and other disorders, which prove its heightened therapeutic efficacies [39, 47]. Liposomal nanoparticles of curcumin for example, illustrate enhanced permeability and stronger resistance in metabolic processes [48].

In our previous study, acute systemic administration of curcumin C3 complex nanoparticles revealed dose-dependent anticonvulsant property on pentylenetetrazole-induced seizure at the doses 20, 40 and 80 mg/kg, i.p. in mice [49]. This study was designed to investigate whether nano-formulation of curcumin in the form of nanomicelles was able to increase the antioxidant and anti-inflammatory capacities of curcumin against cardiotoxicity resulted from ALP, a lethal solid pesticide, in male rats.

MATERIALS AND METHODS

Animals

Sixty male Wistar rats weighing 200–250 g were used in this experiment. The rats were kept in standard polycarbonate cages in a temperature-controlled room (22 °C) with a 12 h light/12 h dark cycle. They were familiarized with the animal room conditions at least three days before experiments with free access to food and water. The experiments were performed between 09:00 and 13:00 a.m. All the experimental procedures were conducted in line with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised 1978) with the approval of Research and Medical Ethics Committees of Tehran University of Medical Sciences, Tehran, Iran. The groups consisted of at least eight rats and each was used only once. Furthermore, the efforts were made to reduce the animal suffering and use only the necessary number of animals to obtain reliable scientific outcomes.

Chemicals

Aluminum phosphide (ALP) > 95 % purity was prepared from Samiran Pesticide Formulating Co. (Tehran, Iran). Nanocurcumin (curcumin C3 complex-loaded nanoparticles) and native curcumin were bought from Exir Nano Sina Co., Tehran, Iran. In relation to dynamic light scattering analysis, the mean diameter of nanomicelles is about 10 nm. The efficiency of encapsulation curcuminoids in nanomicelles is virtually 100%. The curcuminoid content and the size distribution of nanomicelles remain constant at least 24

months. According to a published paper, the oral absorption of SinaCurcumin was at least 59 times higher compared to the conventional powder of curcumin in mice [50]. The other chemicals were purchased from Aldrich Chemical Co. Sigma Chemical or Co. (St Louis, Missouri, USA).

Determination of ALP LD100

The LD50 and LD100 of ALP were reported to be 12.5 [13] and 20 mg/kg of rat body weight, respectively [7]. We also determined the LD100 of ALP for each experiment in our study. In this regard, different doses of ALP 12- 20 mg/kg were selected. Then a straight line was drawn between the probit values (mortality %) and ALP concentrations by linear regression analysis, which displayed a direct relationship. Accordingly, oral LD50 of ALP was calculated as 11.59 mg/kg in male rats, and in this experiment 0.25 LD50 was used as the test dose.

Study Groups

Fifty-eight rats were randomly divided into six study groups of 8-10. The control group received ALP (12 mg/kg, p.o.) + saline (i.p.); the vehicle group received almond oil (p.o.) as the solvent for ALP + saline (i.p.); treatment groups received either ALP (12 mg/kg, p.o.) + curcumin (50 mg/kg, i.p.) or ALP (12 mg/kg, p.o.) + nanocurcumin (10, 20 and 50 mg/kg, i.p.).

Assessment of oxidative stress and lipid peroxidation (LPO) biomarkers:

Assessment of malonedialdehyde (MDA)

MDA is an end-product of polyunsaturated fatty acids oxidation and to produce a complex which can be determined spectrophotometrically, it can react with thiobarbituric acid (TBA). LPO in the samples was assessed regarding thiobarbituric acid reactive substances (TBARS) [51]. Lipid peroxides as oxidation by-products of polyunsaturated fatty acids, form a complex with TBA called TBARS, which make a pink color of a 532 nm absorbance. [52]. The principle for the LPO assessment is according to a method in which the amount of the produced MDA corresponds to the peroxidation extent and determined using a spectrophotometer, as LPO end-product [53].

Assessment of reactive oxygen species (ROS)

The amount of peroxides was measured using fluorescent dichlorofluorescein diacetate (DCFDA) assay kit. DCFDA (5 µm) of was added to the

supernatant and incubated at 37 °C for 30 min. After that, the amount of DCF as the fluorescent end-product was calculated at excitation and emission wavelengths of 488 and 525 nm, respectively [54].

Assessment of superoxide dismutase (SOD) Activity

To calculate the activity of the enzyme SOD, the production of a red formazon dye functioned as an indicator of its activity [55].

Measurement of total thiol

To measure total thiol (SH), 0.2 ml of the sample was mixed with 0.6 ml of Tris-EDTA buffer (Tris base [0.25 M], EDTA [20 mM], pH 8.2) in a 10-ml test tube, and then mixed with 40 ml of DTNB (10 mM) in methanol. By adding 3.16 ml of methanol, the final volume was made up to 4.0 ml. The test tube was centrifuged at 3000 g for 10 min at the ambient temperature. Following 15– 20 min, the color showed up. The supernatant absorbance was measured at 412 nm [52].

Determination of Ferric Reducing/Antioxidant Power (FRAP)

The FRAP test is performed based on the antioxidant power of plasma to deoxidize Fe³⁺ to Fe²⁺. The reagents comprised 300 mM acetate buffer (pH 3.6) with 16 ml acetic acid per liter of buffer solution, 10 mM 2,4,6-tripyridyl-striazine (TPTZ) in 40 mM HCl and 20 mM FeCl₃. Working FRAP reagent was prepared as required by mixing 25 ml

of acetate buffer, 2.5 ml of TPTZ solution and 2.5 ml of the FeCl₃ solution. At that time, ten µl of H₂O diluted sample was freshly added to 300 ml reagent warmed at 37 °C. The complex between TPTZ and Fe²⁺ makes a blue color with 593 nm absorbance [56].

Glutathione (GSH) assay

GSH was determined in the supernatant (3000×g, 10 min and 4 °C) as described [57]. The GSH-400 kit (OXIS Health Products, Inc., Portland, OR) was employed. GSH content in homogenates of the heart tissue was measured (nmol/g tissue) [58].

Statistical analysis

The statistical software Sigma Plot (Version 12) was employed. The results were expressed as the mean ± SEM. The data were analyzed by one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. A P value <0.05 was regarded as the significant change in all the experiments.

RESULTS

Fig. 1 illustrates MDA levels (µmol/mg protein) in experimental and control groups. As can be observed, the amount of MDA was significantly increased 24 hrs following ALP administration (12 mg/kg, p.o.) compared to the vehicle group (P<0.001). On the other hand, curcumin at dose

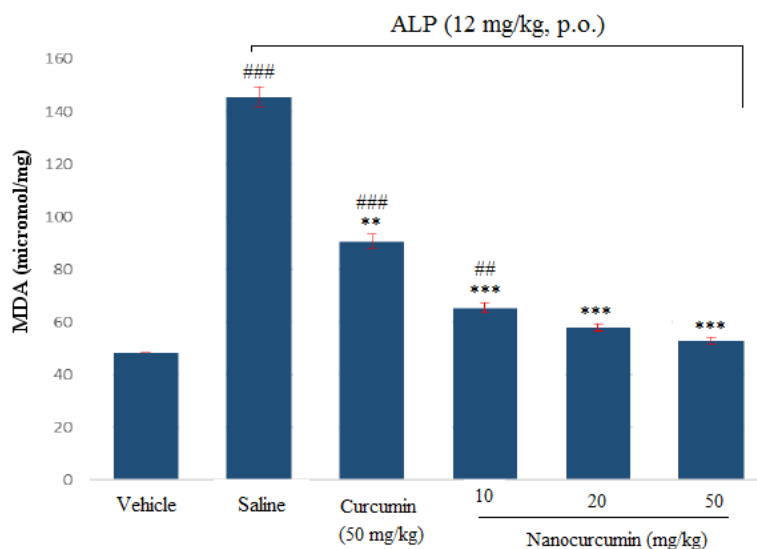


Fig. 1. Effects of curcumin and nanocurcumin on MDA levels in ALP-intoxicated rats. ## P<0.01 and ### P<0.001 significantly different from vehicle. ** P<0.01 and *** P<0.001 significantly different from control group (ALP + saline).

of 50 mg/kg, i.p. could markedly lower MDA level in ALP-intoxicated rats compared to saline treated intoxicated rats ($P < 0.01$). However, its amount is still significantly different compared with normal vehicle-treated group ($P < 0.001$). Similarly, nanocurcumin at doses 10, 20 and 50 mg/kg, i.p. decreased MDA level in a significant manner ($P < 0.001$) in comparison to saline-treated group in ALP-intoxicated rats. Although nanocurcumin

at doses 20 and 50 mg/kg could lower MDA to levels similar to normal vehicle-treated group, at dose of 10 mg/kg is still markedly different from it ($P < 0.01$).

Fig. 2 illustrates ROS levels (u/mg protein) in experimental and control groups. As can be observed, the amount of ROS was significantly increased 24 hrs following ALP administration (12 mg/kg, p.o.) compared to the vehicle group

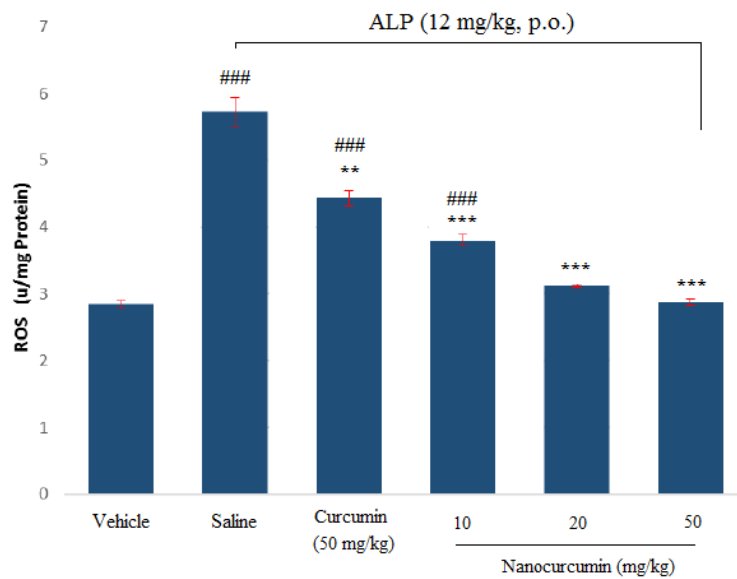


Fig. 2. Effects of curcumin and nanocurcumin on ROS levels in ALP-intoxicated rats. ### $P < 0.001$ significantly different from vehicle. ** $P < 0.01$ and *** $P < 0.001$ significantly different from control group (ALP + saline)

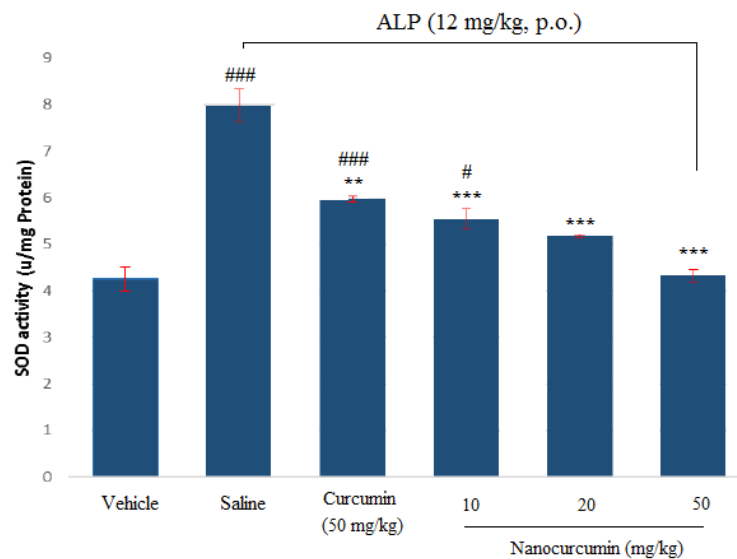


Fig. 3. Effects of curcumin and nanocurcumin on SOD levels in ALP-intoxicated rats. # $P < 0.05$ and ### $P < 0.001$ significantly different from vehicle. ** $P < 0.01$ and *** $P < 0.001$ significantly different from control group (ALP + saline).

($P < 0.001$). On the other hand, curcumin at dose of 50 mg/kg, i.p. could markedly lower ROS level in ALP-intoxicated rats compared to saline treated intoxicated rats ($P < 0.01$). However, its amount is still significantly different compared with normal vehicle-treated group ($P < 0.001$). Similarly, nanocurcumin at doses 10, 20 and 50 mg/kg, i.p. decreased ROS levels in a significant manner ($P < 0.001$) in comparison to saline-treated group in ALP-intoxicated rats. Although nanocurcumin at doses 20 and 50 mg/kg could lower ROS to levels similar to normal vehicle-treated group, at dose of 10 mg/kg it is still markedly different from it ($P < 0.001$).

Fig. 3 illustrates SOD activity (u/mg protein) in experimental and control groups. As can be observed, the amount of SOD was significantly increased 24 hrs, following ALP administration (12 mg/kg, p.o.) compared to the vehicle group ($P < 0.001$). On the other hand, curcumin at dose of 50 mg/kg, i.p. could markedly lower SOD level in ALP-intoxicated rats compared to saline treated intoxicated rats ($P < 0.01$). However, its amount is still significantly different compared with normal vehicle-treated group ($P < 0.001$). Similarly, nanocurcumin at doses 10, 20 and 50 mg/kg, i.p. dose-dependently decreased SOD levels in a significant manner ($P < 0.001$) in ALP-intoxicated rats in comparison to saline-treated group. Although nanocurcumin at doses 20 and 50 mg/kg could lower SOD to levels similar to normal vehicle-treated group, at dose of 10 mg/kg it is still

markedly different from it ($P < 0.05$).

Fig. 4 illustrates thiol levels (μM) in experimental and control groups. As can be observed, the amount of thiol was significantly decreased 24 hrs following ALP administration (12 mg/kg, p.o.) compared to the vehicle group ($P < 0.001$). On the other hand, curcumin at dose of 50 mg/kg, i.p. could markedly enhance thiol level in ALP-intoxicated rats compared to saline-treated intoxicated rats ($P < 0.05$). However, its amount is still significantly different compared with normal vehicle-treated group ($P < 0.001$). Similarly, nanocurcumin at doses 20 and 50 mg/kg, i.p. increased thiol level dose-dependently in a significant manner in comparison to saline-treated group in ALP-intoxicated rats, $P < 0.01$ and $P < 0.001$, respectively. Nevertheless, nanocurcumin at doses 10, 20 and 50 mg/kg are still significantly different from normal vehicle-treated group $P < 0.001$, $P < 0.001$, $P < 0.01$, respectively.

Fig. 5 illustrates FRAP levels ($\mu\text{M}/\text{mg}$ protein) in experimental and control groups. As can be observed, the amount of FRAP was significantly decreased 24 hrs following ALP administration (12 mg/kg, p.o.) compared to the vehicle group ($P < 0.001$). Moreover, curcumin at dose of 50 mg/kg, i.p. is still significantly different compared with normal vehicle-treated group ($P < 0.001$). On the other hand, nanocurcumin at doses 10, 20 and 50 mg/kg, i.p. increased FRAP levels dose-dependently in a significant manner in comparison to saline-treated group in ALP-intoxicated rats, $P < 0.001$. Nevertheless, nanocurcumin at doses 10, 20 and 50

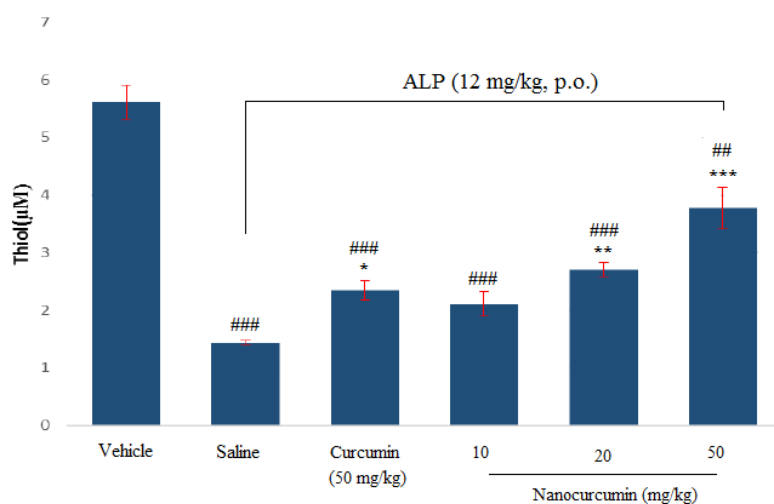


Fig. 4. Effects of curcumin and nanocurcumin on thiol levels in ALP-intoxicated rats. ## $P < 0.01$ and ### $P < 0.001$ significantly different from vehicle. * $P < 0.05$, ** $P < 0.01$ and *** $P < 0.001$ significantly different from control group (ALP + saline).

mg/kg are still significantly different from normal vehicle-treated group $P < 0.001$, $P < 0.001$, $P < 0.05$, respectively.

Fig. 6 illustrates GSH levels (nmol/g tissue) in the experimental and control groups. As can be observed, the amount of GSH was significantly decreased 24 hrs following ALP administration (12 mg/kg, p.o.) compared to the vehicle group ($P < 0.001$). Moreover, curcumin at dose of 50 mg/kg, i.p. is still significantly different compared with normal vehicle-treated group ($P < 0.001$). On the other hand, curcumin at dose of 50

mg/kg profoundly increased GSH level in ALP-intoxicated rats, $P < 0.01$. In the same way, nanocurcumin at doses 10, 20 and 50 mg/kg, i.p. increased GSH levels in a significant manner in comparison to saline-treated group in ALP-intoxicated rats, $P < 0.001$.

DISCUSSION

In the current investigation, effects of nanomicelle curcumin on ALP-induced cardiotoxicity were studied in a rat model. The results demonstrated that ALP induced oxidative

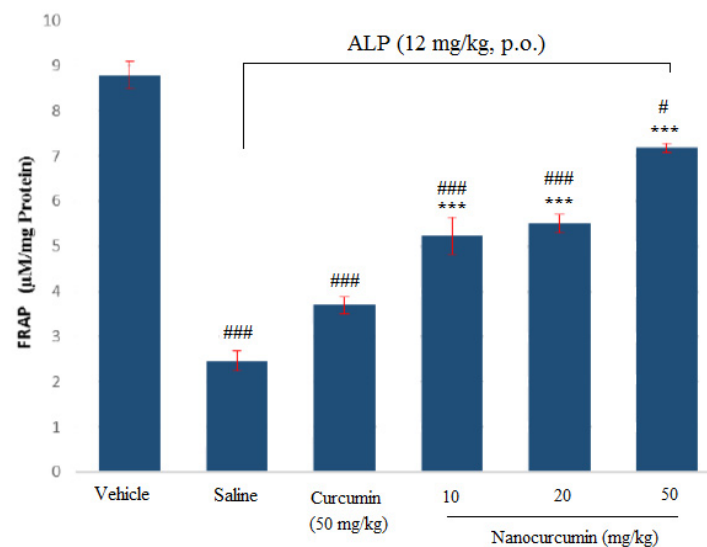


Fig. 5. Effects of curcumin and nanocurcumin on FRAP levels in ALP-intoxicated rats. # $P < 0.05$ and ### $P < 0.001$ significantly different from vehicle. *** $P < 0.001$ significantly different from control group (ALP + saline).

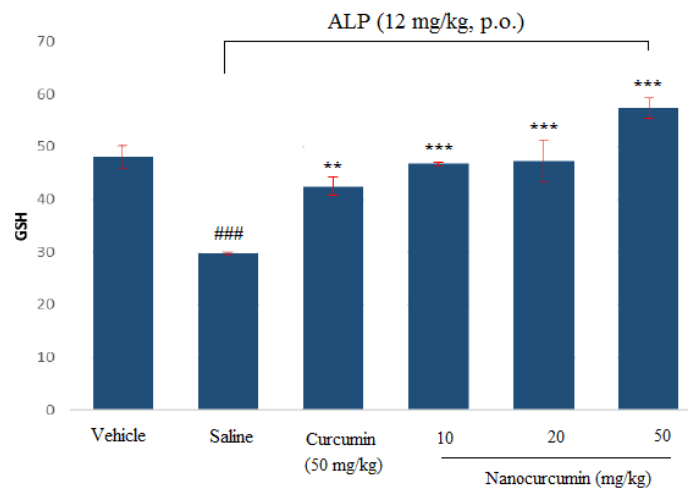


Fig. 6. Effects of curcumin and nanocurcumin on GSH levels in ALP-intoxicated rats. ### $P < 0.001$ significantly different from vehicle. ** $P < 0.01$ and *** $P < 0.001$ significantly different from control group (ALP + saline).

stress and LPO in the heart tissue, which were documented by marked increases in ROS, SOD and MDA as well as significant decrease in thiol, GSH and FRAP. On the other hand, curcumin at dose of 50 mg/kg, i.p. could ameliorate the ALP damage to the heart tissue lowering ROS, SOD and MDA levels and enhancing thiol and GSH markers in a significant manner. Notably, nanomicelles curcumin ameliorated the ALP damage to the heart tissue much more powerfully in comparison to curcumin in a dose-dependent manner (10, 20 and 50 mg/kg, i.p.) and its effect was comparable with vehicle-treated group. In fact, it reduced ROS, SOD and MDA and raised thiol, GSH and FRAP levels considerably.

Effect of curcumin administration (50 mg/kg, p.o.) was explored on acute myocardial infarction in a rat model. Data showed the serum decrease of lactate dehydrogenase (LDH), creatine kinase (CK), and cardiac troponin I (cTnI) after curcumin intake. Curcumin was proved to modify oxidative status by lowering SOD and MDA contents [59].

Virtually consistent with our study, the effect of chronic supplementation of curcumin (200 mg/kg, p.o.) on cisplatin -induced cardiotoxicity was assessed. Oxidative stress markers including MDA, SOD, and CAT, and pro-inflammatory cytokines like IL-1 β , IL-6, and TNF- α , and the histological and immune-histochemical alterations were evaluated in rat cardiac tissues. Curcumin has shown beneficial influence on cisplatin, by improving oxidative status and attenuating morphological changes in the tissue [34].

In line with our research, chronic oral curcumin treatment (100 and 200 mg/kg, seven days) ameliorated doxorubicin-induced cardiotoxicity in rats. Curcumin ameliorated doxorubicin-induced LPO, glutathione depletion, decrease in antioxidant (SOD, CAT, and GPx) enzyme activities, and cardiac toxicity markers [creatin kinase isoenzyme-MB (CK-MB), LDH, and cTn-I]. In addition, curcumin diminished activities of caspase-3, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and levels of nuclear factor kappa-B (NF-kB), TNF- α , and IL-1 β , and cardiac tissue damages [60]. Additionally, curcumin attenuated doxorubicin-induced cardiotoxicity in mice via suppressing oxidative stress and preventing mitochondrial dysfunction mediated. Curcumin treatment reduced LDH, ROS and CK activities while increased cell viability [61]. Similarly, curcumin (100 mg/kg-1, p.o.) protected

the heart tissue against irinotecan-induced damage concerning TNF and IL-4, oxidative stress parameters TBARS, SOD, CAT, GSH, and GPx levels, and histological damage in rats [36].

Curcumin attenuated chronic oxidative stress and mitochondrial dysfunction induced by aluminum in rat brain. Curcumin long-term supplementation (50 mg/kg, i.p.) was able to normalize markedly the activities of the three mitochondrial complexes as well as to reduce GSH content in the brain of aluminum-treated rats [62]. Curcumin pretreatment (50 or 100 mg/kg, p.o.) protected against acute acrylonitrile-induced oxidative damage in rats. Chronic curcumin administration reversed the acrylonitrile effects, reducing the levels of MDA and enhancing CAT activity and increasing GSH content in the brain and the liver [63].

Curcumin pretreatment (200 mg/kg, p.o.) attenuated the ischemia and reperfusion (I/R) injury as supported by loss of the cardiac mechanical work, raise in LPO and reduction in GSH content, and the activity of SOD and glutathione reductase (GR) in the cardiac tissue and isolated mitochondria, and decline in capacity of mitochondrial respiratory. The protective effect of curcumin was related to the diminution of oxidant stress and mitochondrial dysfunction [64].

In a similar study, the impacts of curcumin against cardiotoxicity of two commonly used anti-diabetic drugs namely pioglitazone and metformin were evaluated. Quantitative assays for cell growth, ROS generation, LPO and mitochondrial permeability followed by anti-oxidant enzymes and caspases activity assays were carried out. Curcumin (4-16 μ M), being an anti-oxidative molecule, could suppress these toxic effects in the cardiomyoblasts [65].

Protective effect of a novel 25 Mg Zn -carrying nanoparticle (25 Mg PMC16) on parameters such as energy depletion, oxidative stress, and electrocardiographic (ECG) has shown on the heart tissue of ALP-poisoned rats. 25 Mg PMC16 significantly increased the blood pressure (BP) and heart rate (HR). [15].

Recently, the protective activity of chronic administration of nanomicelle curcumin in bisphenol A-induced cardiotoxicity subsequent to sub-acute exposure was shown in rats. Curcumin (25 and 50 mg/kg, p.o.) significantly reversed elevation of body weight, BP, and MDA and decreased in GSH [66].

Similarly, dietary curcumin reversed enhanced MDA level and reduced GSH levels in the in the colon mucosa and the liver of rat [67].

To conclude, this study demonstrated that administration of curcumin in the form of nanomicelle could enhance its cardioprotective effect in a rat model of cardiotoxicity resulted from oral ALP treatment. It should be noted that curcumin exerted this cardioprotective effects due to its anti-oxidant, anti-inflammatory, and anti-apoptotic properties. Nanoformulation of this naturally occurring agent may be beneficial in ameliorating toxicity of phosphides including cardiotoxicity. Nonetheless, studies that are more specific will be needed to extend the results.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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