Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2021.035

RESEARCH ARTICLE

Ameliorating Effect of Lycopene and N-Acetylcysteine against Cisplatin-Induced Cardiac Injury in Rats

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ARTICLE HISTORY (21-020)

Received: January 14, 2021
Revised: March 20, 2021
Accepted: March 27, 2021
Published online: April 09, 2021

Key words:
Cardiac toxicity
Caspase-3
Cisplatin
Lycopene
N acetylcysteine
Rats

A B S T R A C T

Cisplatin (CP) is one of antineoplastic agents with a broad range of anticancer activities. This research investigated the possible protective effects of lycopene (LP) and N acetylcysteine (NAC) in rats against CP-induced cardiac toxicity. Seven groups of rats (n=7); control vehicle group was administered saline, LP (10 mg/kg, PO), NAC (150 mg/kg, PO), CP group (7.5 mg/kg, IP) on the 27th day of the experiment, LP-CP group, NAC-CP group, and LP-NAC-CP group. Following injection of CP, concentrations of cardiac biomarkers, lactate dehydrogenase (LDH), creatine kinase (CK) and creatine kinase MB (CK-MB) were increased in serum of the treated groups. In addition, CP resulted in a significant increase in malondialdehyde (MDA), as well as significant decreases in glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) in rats' heart tissues. CP resulted in changes in cardiac histopathology and increased caspase-3 expression in cardiac tissues. Administration of LP and/or NAC ameliorated cardiac toxicity and apoptosis induced by CP, through their antioxidant properties.

To Cite This Article: Elsayed A, Elkomy A, Alkafafy M, Elkammar R, Fadl SE, Abdelhiee EY, Abdeen A, Shaheen H, Soliman A and Aboubakr M, 2022. Ameliorating effect of lycopene and N-acetylcysteine against cisplatin-induced cardiac injury in rats. Pak Vet J, 42(1): 107-111. http://dx.doi.org/10.29261/pakvetj/2021.035

INTRODUCTION

Cisplatin (CP) is used to treat a wide range of tumors and kills cells (anti-neoplastic drug) through different mechanisms, including, formation of reactive oxygen species (ROS), DNA damage, and induction of apoptosis (Almeer and Abdel Moneim., 2018; Jahan *et al*., 2018; Elkomy *et al*., 2020; Sallam *et al*., 2021). While cardiac toxicity is not known to be a common adverse effect of CP, a number of cardiac toxic findings produced during or shortly after CP injection have been reported. These involve moderate and extreme cardiac, vascular adverse reactions, such as cardiac failure, pericarditis, myocarditis, arrhythmia, hypertension, and occasionally, cardiac ischemia, cardiac tamponade, and endomyocardial fibrosis (Topal *et al*., 2018).

CP is known to be capable of producing reactive oxygen species (ROS). This ROS has caused tissue damage by interacting with biological macromolecules leading to the oxidized substance formation (Rosic *et al*., 2015).

Lycopene (LP) is found naturally in fruits and vegetables such as tomatoes, carrots, strawberries, and cherries (Hadley *et al*., 2003). Structurally, it is a carotenoid analogue, which function as a free-radical scavenger (Kara *et al*., 2016). Many epidemiological studies have suggested that consumption of food containing LP was inversely linked to the incidence of cardiovascular disease and prostate cancer. LP may provide some of the cardiovascular or cancer safety associated with tomato consumption, but is not likely to be the only bioactive ingredient in tomatoes. In this regard, a number of researchers have done relevant work to better understand the role of LP and its derivatives in the chronic disease phase (Antonuccio *et al*., 2020). LP has anti-inflammatory, immune-stimulant, anti-mutagenic

effects and protected against myocardial injury by inhibiting apoptosis and oxidative stress (Xu *et al*., 2015).

N-acetylcysteine (NAC), a compound has a wide range of actions, including antioxidant function, enhancement of intracellular glutathione levels and anti-inflammatory properties. NAC reduced the overproduction of cardiac ROS. NAC prevents the reaction of nitric oxide to superoxide radicals, hydrogen peroxide and hydroxyl radicals, and prevents the formation of peroxynitrite and its consequences (Krzyzanowska *et al*., 2016).

The goal of this research was to examine the protective function of LP and/or NAC in rats against CP-induced cardiac toxicity by exploring biochemical, markers of oxidative stress and caspase-3expressions.

MATERIALS AND METHODS

Chemicals: Cisplatin (CP) was purchased from EIMC Pharmaceuticals Company (Cairo, Egypt) in the form of parenteral vial with a concentration of 50 mg/ml. Lycopene (LP) has been received from Sigma Aldrich Company (Saint Louis, MO, USA). N acetylcysteine (NAC) were obtained from SEDICO (6 October City, Egypt). The analytical kits have been obtained from Bio-diagnostics Company (Giza, Egypt).

Animals and experimental design: From the Egyptian Organization for Biological Products and Vaccines, forty nine (49) male Wister Albino rats of 180-200 g body weight were obtained. All rats were then kept at 25±2°C and 12:12 h light / dark cycle with a standard pellet diet and free access to water. Treatment of rats, following the guide for the care and use of laboratory animals approved by the Research Ethical Committee of the Faculty of Veterinary Medicine, Benha University, Egypt (BUFVTM 030321). All rats were acclimatized for one week before starting the trial. Rats were divided into 7 groups (n=7). 1st group served as a control (saline only), once daily (vehicle control for LP and NAC); 2nd group; LP (10 mg/kg, PO) (Wang *et al*., 2018); 3rd group; NAC (150 mg/kg, PO) (Feng *et al*., 2015); 4th group; saline, PO and a single dose of CP on the 27th day of the study (7.5 mg/kg, IP) (Adeyemi *et al*., 2017) and served as CP toxic control; 5th group; LP+CP; the sixth group (NAC+CP), and the 7th group (LP+NAC+CP). Saline (1 ml/kg, PO), LP (10 mg/kg, PO) and NAC (150 mg/kg, PO) were administered once daily during the experiment (30 days).

Blood and tissues sampling: Rats were anesthetized by isoflurane, 24 h after the end of the study. From the retroorbital plexus, blood samples were taken and centrifuged for 15 minutes at 1200 g. At -20°C, the serum was preserved for further biochemical analysis. Heart was quickly excised and washed with saline and perfused with ice-cold 50 mmol/L sodium phosphate-buffered saline (100 mmol/L Na_2HPO_4/NaH_2PO_4, pH 7.4) containing 0.1 mmol/L EDTA to wash away the red blood cells and clots. Cardiac tissue (1 gram) was homogenized in 5 ml phosphate buffer pH 7.4. Tissue homogenates have been centrifuged at 1200 x g at 4°C for 20 min. The supernatants were stored at -20°C before further use in the assessment of oxidative stress biomarkers in cardiac tissues. A part of cardiac tissues were preserved immediately in formalin (10%) for histological and immunohistochemical (IHC) investigations.

Biochemical analyses: Indicators of heart injury in serum, creatine kinase CK (Abdel-Daim *et al*., 2017), lactate dehydrogenase LDH (Buhl and Jackson, 1978) and CK-MB levels (Abdel-Daim *et al*., 2017) were estimated using kits from Randox Laboratories Ltd., UK (for Lactate dehydrogenase) and kits from Stanbio™, TX, USA (for CK, and CK-MB).

Detection of the oxidative stress: Malondialdehyde (MDA) levels (Uchiyama and Mihara, 1978), catalase (CAT) activity (Aebi, 1984), superoxide dismutase (SOD) and glutathione reductase (GSH) activity (Abdellatief *et al*., 2017) were estimated using special diagnostic kits obtained from Laboratory Biodiagnostic Co, Egypt.

Histopathology and immunohistochemistry (IHC): Cardiac tissues were prepared and stained with hematoxylin and eosin for histopathological examination and the immunostaining using Caspase 3 was performed according to Aboubakr *et al*. (2020).

Statistical analysis: Obtained data in this study were viewed as mean±SE. One-way ANOVA using the statistical software package SPSS for Windows (Version 21.0; SPSS Inc., Chicago, IL, USA) was used for data analysis. For group comparisons, Duncan's post hoc test was used. Statistical significance was accepted at $P<0.05$.

RESULTS

Serum biochemical analysis: Cardiac toxicity was induced by CP as shown by increased serum biomarkers of the heart (Table 1). LDH, CK and CK-MP concentrations were significantly increased in response to treatment with CP compared to controls. Crucially, a significant decline in the value of these parameters was reported in CP-intoxicated rats when supplemented with LP and NAC compared LP or NAC treated rats. The decrease in these values was slightly lower relative to the controls. These data indicated that when LP and NAC were used in combination, they give better protection against CP-induced cardiac damage than either of them alone.

Parameters of oxidative damage: Results of CP toxicity and medication with LP and/or NAC on oxidative parameters and lipid peroxidation in the heart have been shown in Table 2. Significant rises in MDA levels with significant decline in CAT, SOD, and GSH levels in cardiac tissue in CP-intoxicated rats compared to control rats. Besides that, the damaging effects of CP on cardiac MDA, CAT, SOD and GSH were significantly lowered by the administration of LP or NAC alone, but these values were significantly different from the control values. In addition to these data, the LP+NAC+CP group treated showed an improvement in the oxidative damage caused by CP in cardiac tissue compared to the LP+CP and NAC+CP groups.

Histopathological findings: Cardiac sections of saline, LP and NAC treated rats showed normal arrangement of cardiac muscle fibers with branching pattern, central nuclei, and striated cytoplasm. In addition, Treated rats with LP or NAC also showed normal histological criteria of the heart. In contrast, in CP-treated rats, we observed severe degenerative changes myocardium; laceration in most of cardiac fibers, degranulation of cytoplasm and severe vacuolation, hyaline necrosis, pycnotic nuclei and blood vessels very congested and engorged with blood. Combination of LP or NAC, along with CP showed a myocardial moderate effect recorded by moderate congestion of cardiac blood vessels and laceration on some muscle fibers. Combined treatment of LP and NAC together with CP usually restore the normal myocardial architecture, leaving, mild myocardial adverse effect represented in mild congestion of cardiac vessels and little vacullation in some muscle fibers (Fig. 1).

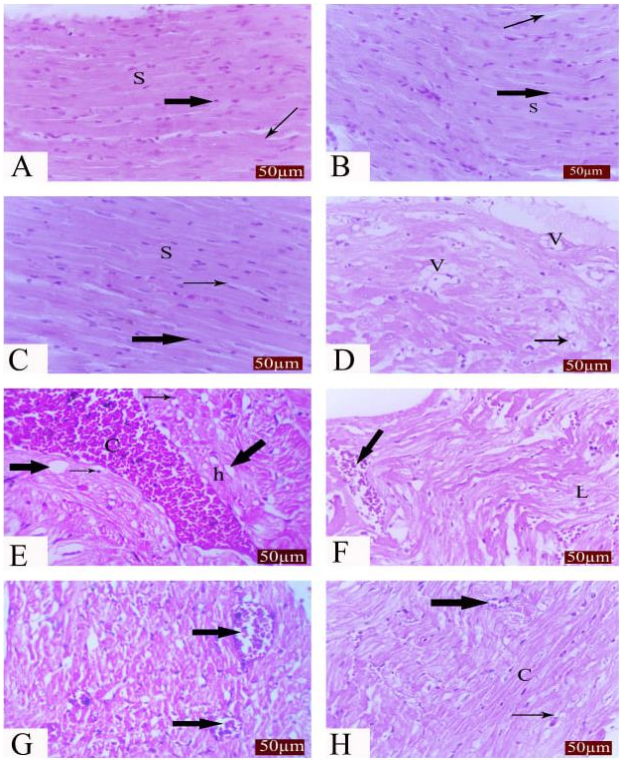

Fig. 1: Histopathological changes in cardiac sections. **A, B and C:** showing normal arrangement of cardiac muscle fibers with branching pattern (thin arrow), central nuclei (thick arrow) and striated cytoplasm (S), **(A)** control group, **(B)** treated group with LP and **(C)** treated group with NAC. **D:** Treated group with CP, showing severe degenerative changes in myocardium; laceration in most of cardiac fibers, dilated intercardial blood vessels (thick arrow), degranulation of cytoplasm (thin arrow) and severe vaculation (V). **E:** Treated group with CP showing severe effect on heart; cardiac blood vessels very congested and engorged with blood (C), vaculated cytoplasm (thick arrows), hyaline necrosis (h) and pycnotic nuclei (thin arrow). **F:** Treated group with CP and lycopene showing moderate effect on heart; moderate congestion of cardiac blood vessels (arrow) and laceration on some muscle fibers (L). **G:** Treated group with CP and NAC showing moderate effect on heart, congestion of cardiac vasculature (arrows). **H:** Treated group with CP**,** LP and NAC showing mild effect on heart; mild congestion of cardiac vessels (thick arrow),vaculation in some muscle fibers (thin arrow) and other cardiac fibers have normal appearance (C).

Immunohistochemical study: CP greatly enhanced caspase-3 expression in the cardiac tissues (Fig. 2). In the LP+CP and NAC+CP groups, a slight regulation of the caspase-3 expression in comparison with the control group. The combined therapy of LP and NAC greatly lowered the CP-induced up-regulation of caspase-3.

DISCUSSION

Cisplatin (CP), a commonly used cytotoxic antitumor drug. Numerous cytotoxic effects of CP in various types of cell lines have been shown (*in vitro*), but only a few studies (*in vivo*) have been performed (Rosic *et al*., 2015; Topal *et al*., 2018; Saleh *et al*., 2020). These studies are associated with our results, including oxidative stress and apoptosis pathways roles in CP-induced cardiac damage in rats, and the possible use of the LP and NAC as protecting agents against CP injuries, and these cardiotoxic conditions eventually lead to cardiac death.

Oxidative stress and apoptosis are key components of CP-induced cardiac toxicity (Qian *et al*., 2018). Serum levels of cardiac enzymes such as CK and CK-MB have gained prominence in cardiac damage detection in recent years.

In this research, CP-induced cardiac toxicity demonstrated by considerable alteration in serum cardiac enzymes (LDH, CK, and CK-MB). CP released intra-cellular proteins such as CK and CK-MB as CP interfered with cell membranes (Topal *et al*., 2018). In our study, significantly high LDH, CK, and CK-MB levels compared to the control group were observed in rats injected CP, which are in agreement with the findings of Wang *et al*. (2009); Rosic *et al*. (2015), Topal *et al*. (2018).

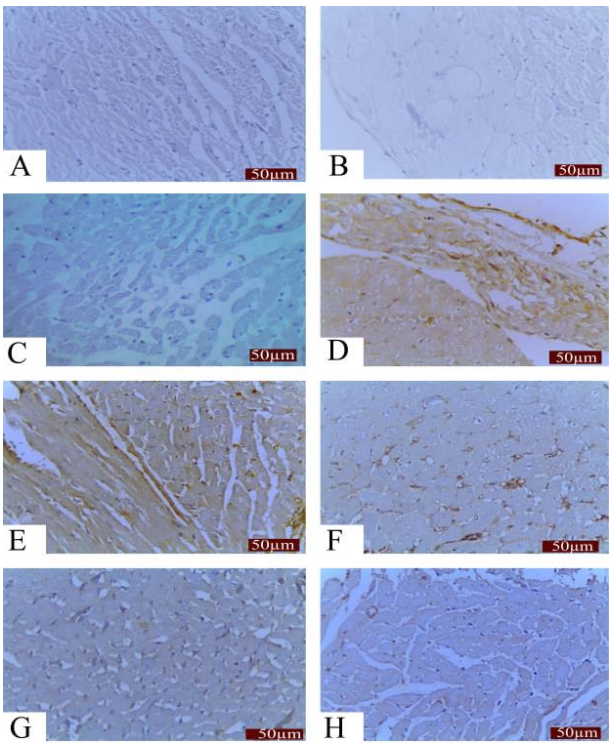

Fig. 2: Changes in cardiac caspase-3 expression, **A, B** and **C** showed negative immunostaining reaction for Caspase 3; (A) control group, **(B)** treated group with LP and **(C)** treated group with NAC. **D** and **E** treated groups with CP showing severe immunostaining reaction for Caspase 3. **F:** Treated group with CP and LP showing moderate immunostaining reaction for Caspase 3. **G:** Treated group with CP and NAC showing moderate immunostaining reaction for Caspase 3. **H:** Treated group with CP**,** LP and NAC showing mild immunostaining reaction for Caspase 3.

Table 1: Effect of LP, NAC and/or CP on biochemical parameters (n=7)

Parameters	Control	LP	NAC	CP	LYP+CP	NAC+CP	LP+NAC+ CP
LDH (U/L)	5.29±0.11^{d}	5.46±0.09^{d}	5.53±0.14^{d}	11.41±0.25^{a}	9.51±0.12^{b}	9.05±0.22^{b}	7.75±0.21^{c}
CK (U/L)	0.33±0.008^{e}	0.37±0.011^{de}	0.36±0.009^{de}	1.68±0.068^{a}	1.15±0.035^{b}	0.88±0.024^{c}	0.45±0.021^{d}
CK- MB (U/L)	31.75±0.66^{e}	33.15±0.67^{e}	33.67±1.12^{e}	67.18±1.15^{a}	56.53±1.29^{b}	50.24±1.74^{c}	42.28±0.73^{d}

Different superscript letters in the same row indicate statistical significance at P≤0.05.

Table 2: Effect of LP, NAC and/or CP on antioxidant parameters in cardiac tissues. (n=7)

Parameters	Control	LP	NAC	CP	LYP+CP	NAC+CP	LP+NAC+CP
MDA (nmol/g)	19.84±0.74^{e}	19.79±0.93^{e}	20.19±0.71^{e}	69.37±1.61^{a}	57.52±0.38^{b}	50.44±1.48^{c}	41.91±0.92^{d}
CAT (U/g)	58.08±0.64^{a}	57.96±1.33^{a}	60.04±2.03^{a}	22.26±0.61^{e}	27.90±0.33^{d}	34.18±0.67^{c}	45.03±0.63^{b}
SOD (U/g)	39.94±0.52^{a}	37.96±0.43^{b}	40.09±0.56^{a}	1434±0.28^{e}	23.62±0.52^{d}	28.05±0.57^{c}	36.66±0.88^{b}
GSH (mg/g)	13.08±0.25^{b}	13.21±0.24^{b}	14.03±0.36^{a}	4.46±0.12^{f}	6.51±0.16^{e}	7.85±0.16^{d}	11.58±0.27^{c}

Concerning oxidative stress/ antioxidant parameters, CP treated group revealed a significant increase of MDA level (increased lipid peroxidation) and decreased activities of the antioxidants (CAT, SOD and GSH) in the cardiac tissues. These results are compatible with Rosic *et al*. (2015) and Topal *et al*. (2018). These findings are attributed to oxidative stress induced by production of reactive oxygen species (ROS) (Qian *et al.*, 2018; Aboubakr *et al*., 2019). CP -induced apoptosis mainly involve the mitochondrial-mediated intrinsic pathway, death receptor-mediated pathway and endoplasmic reticulum pathway, the most closely related is an intrinsic pathway (Qian *et al*., 2018). Cardiac-myocytes with rich mitochondria is the power of energy metabolism. When CP accumulates in the mitochondrial matrix, it induces a large amount of ROS production and mitochondrial dysfunction that contributes to apoptosis (Qian *et al*., 2018).

LP is a lipophilic natural compound, and has been well studied due to its strong antioxidant properties. LP protects against cardiac toxicity by enhancing the role of cell antioxidant enzymes, inhibiting caspase-3, and scavenging oxygen free radicals (Abdel-Daim *et al*., 2018). LP administration reduced LDH, CK and CK-MB which agrees with the results of Abdel-Daim *et al*. (2018) and effectively reduced MDA production and increases of antioxidant enzyme expression including SOD, GSH and CAT (Abdel-Daim *et al*., 2018).

The potential benefits of the NAC are due to its function as a powerful free radical scavenger. NAC could be used to minimize cardiac ROS overproduction (Wang *et al*., 2017). NAC decreased CK levels comparable to CP group, although the CK levels remained significantly increased compared to control group. These results are compatible with Rosic *et al*. (2015). NAC reduced CK-MB levels and cell apoptosis in rats (Rosic *et al*., 2015; Wang *et al*., 2017).

Along with the LP or NAC scavenging ROS action of LP or NAC, the SOD and CAT activities and GSH levels could be restored in CP-intoxicated rats. We suggested that any improvement in biochemical parameters tested in this study may have been induced by ROS suppression (Aboubakr *et al*., 2020) and antioxidant up-regulation mechanisms of LP or NAC against CP-induced oxidative injury.

The histologic and immunohistochemical observations of this study were in accordance and confirmed the alterations oxidant/antioxidant and biochemical parameters in treated groups. Histological examination showed degenerative changes myocardium; laceration in most of cardiac fibers, degranulation of cytoplasm and severe vacuolation, hyaline necrosis, pycnotic nuclei and blood vessels very congested and engorged with blood (Topal *et al*., 2018; Bayrak *et al*., 2020). Our results showed CP treatment made highly expression of caspases-3 which indicates cell apoptosis, these data confirm the results of Topal *et al*. (2018) who mentioned that CP was converted to a more potent toxin that causes DNA injury, respiration damage and mitochondrial DNA which lead to initiation of inflammatory responses and activation of apoptotic pathways. These results go in hand with who reported that CP generates ROS, leading to apoptosis (Qian *et al*., 2018). Our results showed that treatment of rats with NAC alone has no adverse effect on cardiac muscle. Combined treatment of NAC with CP lowered the adverse effect of CP on heart. These results are consistent with Rosic *et al*. (2015) that mentioned NAC has cardio-protective effects by reducing oxidative damage on rat heart acting free radical scavenger protect against reactive oxygen species (ROS) caused by CP. Our results showed treatment of rats with LP alone has no adverse effect on heart. Combined treatment of LP with CP showed beneficial effect by lowering the histopathological lesions caused by CP. These findings agreed with Abdel-Daim *et al*. (2018); Duan *et al*. (2019) as they mentioned that LP considered as potent antioxidant anti-inflammatory agent provide protection against cellular damage caused by ROS of neoplastic drugs. LP administration reduced reaction of caspase 3 (Abdel-Daim *et al*., 2018). The results showed that combined treatment of LP and NAC together with cisplatin significant restore the normal histological architecture of the heart indicating that combined therapy of both NAC and LP was more effective than each monotherapy due to their synergistic cyto-protective actions and their ability to restore the activity of enzymatic antioxidants in myocardial tissue.

NAC may reduce cell apoptosis, manifested by the reduction of positive apoptosis cells, the Bax/Bcl-2 ratio, and the expression of cleaved-caspase-3, but has a more profound impact on autophagy because it may attenuate autophagy to a greater degree (Wang *et al*., 2017).

Pretreatment with LP and/or NAC conferred protection against CP induced cardiac toxicity, illustrated by the improved biochemical parameters, oxidative stress markers, histopathology, and caspase-3 expression. A dietary combination of LP and NAC would enhance the ROS scavenging capacity (Abdel-Daim *et al*., 2018). Our data revealed that co-administration of LP and NAC combination could elicit a better protective effect than their individual supplementations against CP damage.

Conclusions: Overall data suggest that CP may cause significant tissue damage in the heart due to oxidative stress and apoptotic mechanisms. LP and NAC in combination could be used as a potential protective agent against CP-induced damage in the heart.

Acknowledgments: Taif University Researchers Supporting Project number (TURSP-2020/57), Taif University, P.O. Box 11099, Taif 21944, Saudi Arabia.

Authors contribution: AE, MA, AE, HS, AS and MA; contributed in the study design, experimental work and statistical analysis and writing the manuscript. RE; performed the histopathological and immunohisto-chemical parts of the study. SEF, EYA, GY and AA analyzed the sera and tissue samples. All authors interpreted the data and approved the final version.

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