

## Ameilorative effect of lycopine against cisplatin toxicity in rats

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### Abstract

The following study aimed to investigate the hepato and neuro protective efficacy of Lycopine against Cisplatin which induced hepatotoxicity and neurotoxicity. Twenty Five male Wister rats were used for this experiment they were equally divided into 5 groups (5 rats per group): group (1) served as control group they were injected 1ml saline orally once daily for 20 day, group (2) served as Corn Oil group and they were administrated 1 mL Corn Oil orally once daily for 20 days, group (3) served as Lycopine group and they were administrated (10 mg/kg b.wt) Lycopine orally once daily for 20 days. , group (4) served as Cisplatin treated group and they were injected (6 mg/kg b.wt.) intraperitoneally once at day 10 of experiment and group (5) Lycopine+Cisplatin group and were administrated 10 mg/kg b.wt Lycopine orally once daily for 20 days and injected 6 mg/kg b.wt.) intraperitoneally once at day 10 . Result revealed that Cisplatin induced liver damage indicated by significant increase in liver biomarkers ALP, ALT, AST along with significant decrease in albumin, Moreover marked increase increase in tissue concentrations of malondialdehyde(MDA) and Total antioxidant(TAC) and reduce tissue Glutathione reductase(GSH),that indicated oxidative stress Also results revealed up regulation IL-6 and down regulation IL-10 in liver and brain tissue in compared to control group . However, interestingly concurrent administration of the Lycopine orally at dose level of 10mg/kg b.wt for 20 days with Cisplatin can mitigate these toxic effects caused by Cisplatin.So it is concluded that the antioxidant and the anti-inflammatory effects of Lycopine moderate the Cisplatin-induced hepato and neurotoxicity.

**Keywords:** Cisplatin; Lycopine; Liver.Brain.

### 1. Introduction

Cisplatin is an important anticancer drug. It kills cancer cells via various modes of actions beginning from oxidative stress, reactive oxygen species production, lipid peroxidation and activation of pro-inflammatory cytokines. These mechanisms of action may be an important way in the strategy of prevention of its side effects on normal cells Faten et al. 2021, On other way it as a useful and effective drug in the treatment of many solid tumors, in other side it has many hazard effects including hepatotoxicity; sever kidney injury, ototoxicity and cardiac toxicity Gaskell et al .2018.

Cisplatin destroys cell membrane and rise free oxygen and hydroxyl radicals and as a result of this and induces lipid peroxidation, inflammation and hypoxia Dhillon et al .2019. Cisplatin-induced hepatotoxicity is associated to oxidative damage and mitochondrial dysfunction Nagla and Basma (2017).

Antioxidants are substances used in breaking down reactive oxygen species (ROS) in food accordingly, many synthetic antioxidants have been used in nutrition caused harmful effects due to instability, and there is a hope to use antioxidant compounds from plant sources safe for clinical applications. These metabolites have been used to not only their antioxidant properties but also they have been proven to have anti-tumor, anti-inflammatory, nociceptive, hepatoprotective and nephroprotective effects Rjeibi et al.2017 and Lourenço (2019).

Lycopine is a phytochemical mainly found in tomato and tomato-based products. It is a tetraterpene compound consisting of eight isoprene units and 11 double linear bonds. Lycopine is a non-pro-vitamin A carotenoid Yin et al.2019. Lycopine is the most strong antioxidant. It is an important deactivator of ROS. For instance, it can remove singlet oxygen two and ten times more than beta-carotene and vitamin E Przybylska et al.2020. Now there has been more interest in Lycopine's health benefits. It is not only a potent antioxidant; its beneficial effects in the prevention and treatment of a different diseases Joshi et al.2020

The health effects of Lycopine may be related to the antioxidant effects of the native trans or Cisplatin structures and shortened by derivatives such as lycopineopenals, lycopineopenols, and lycopineopenoic acids Urbonaviciene and Viskelis 2017.

Lycopine is a natural neuroprotective agent. It seems that this carotenoid contributes to cognitive longevity Crowe-White et al .2019. and the treatment of several neuronal diseases, including cerebral ischemia, Parkinson's disease (PD), Alzheimer's disease (AD), subarachnoid haemorrhage, epilepsy, Huntington's disease, and depression Chen et al.2019. Therefore, in the current study, we focused on evalu-

ating the protective effects of Lycopine against Cisplatin-induced hepatic and brain injury in rats at both Molecular study and biochemical levels. However, hepatotoxicity is also encountered during low-dose repeated Cisplatin therapy Gedik et al. 2017.

In recent studies it has been reported that the mechanism of Cisplatin-induced hepatotoxicity can be multifactorial. Oxidative stress resulting from ROS may have a major role among these factors Veiga et al. 2020

## 2. Material and methods

### 2.1. Tested drugs:

Cisplatin (cytoplastin-50<sup>®</sup>) sterile solution, vial contains 50ml of 50mg(50mg/50ml) Cisplatin. It was obtained from cipla company, Egypt. Cisplatin was administrated at a dose of 6 mg/kg b.wt intraperitoneally (IP) once according to (Ammar et al. 2013).

Lycopine (Lycopine 5mg<sup>®</sup>) was obtained from puritans pride premium, USA. It was administrated at a dose of 10 mg/kg b.wt orally in corn oil once daily for 20 days according to (Sönmez et al. 2011)

### 2.2. Experimental rats:

The present study was carried out on a total number of 25 white Wister albinos male rats weighting 150-170 gm. Rats were obtained from Center of Laboratory Animal, Faculty of Veterinary Medicine, Benha University, Egypt. They acclimatized for one week prior to the experiment. All rats received standard laboratory balanced commercial diet and water ad libitum.

### 2.3. Experimental design and treatment protocol:

Twenty five male wistar rats were divided randomly into 5 groups (5 animals per group).

Group 1 :Rats in this group were served as control group and were administrated orally 1 mL saline once daily for 20 days.

Group 2: Rats in this group were served as corn oil group and were administrated orally 1 mL corn oil once daily for 20 days.

Group 3: Rats in this group were served as Lycopine group and were administrated orally (10 mg/kg b.wt) Lycopine once daily for 20days.

Group 4: Rats in this group were served as Cisplatin treated group and were injected (6 mg/kg b.wt.) intraperitoneally once at day 10 of experiment.

Group 5: Rats in this group were served as Lycopine+Cisplatin group and were administrated orally (10 mg/kg b.wt) Lycopine once daily for 20 days and injected (IP) (6 mg/kg b.wt.), once at day 10.

### 2.4. Blood sampling

Blood samples were collected by puncture of retro orbital plexus from 5 rats in each group after the end of the experiment . Blood sample was collected without anticoagulant for separation of clear serum for biochemical analysis. These serum samples were used for biochemical analysis of (ALT, AST,ALP and albumin).

### 2.5. Tissue samples

At the end of the experiment all rats were scarified, and tissue samples were taken from liver and brain for both biochemical oxidative stress markers ( MDA,TAC and GSH) and gene expression (IL-10 and IL-6).

### 2.6. Assay methods:

Serum biochemical analysis:

Serum was collected from blood after centrifugation at 3000 rpm for 10 min at 4 °C. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase(ALP) were detected .The absorbance of ALT,ALP and AST was read at 505 nm and the enzyme activity was calculated as U/L. ALT and AST were estimated according to Safety Data Sheet (2002) And albumin was estimated using a commercially available kit (Quimica Clinica Aplacada, Tarragona, Spain). All procedures were performed according to the manufacturer's instructions. Oxidative status was done by determination of the activity of Total Antioxidant activity (TAC), malondialdehyde (MDA), and glutathione reductase(GSH) levels according toKoracevic et al. (2001.) and Beutler et al. (1963) respectively

Preparation of liver homogenates: The tissue was dissected and washed with a PBS (phosphate buffered saline) solution, pH 7.4 containing 0.16 mg/ml heparin to remove any red blood cells and clots. One gram of each tissue was homogenized in 5 ml of 5-10 ml cold buffer (i.e., 50mM potassium phosphate, pH7.5 1mM EDTA) per gram tissue, using sonicator homogenizer. Aliquots of tissue homogenates was centrifuged by cooling centrifuge 4000rpm for 20 min then stored at -20 °C till do biochemical analysis.

Kits

For estimating ALT, AST, and ALP were supplied by Centronic GmbH Company

Germany by chem7, Kits for estimating of of Total Antioxidant activity (TAC),malondialdehyde (MDA), and glutathione reductase(GSH) in liver homogenate were purchased from BioDiagnostic Company, Cairo, Egypt by spectro nanodrop. Genes expression was made using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, CA, USA), and SYBR green master (Applied Biosystems, CA, USA).

Genes expression by real time PCR:

Total RNA was isolated from liver and brain tissue using the Total RNA Isolation System (Promega Co., Madison, WI, USA) according to the manufacturer's protocol. Briefly, RNA was extracted and re-suspended in 50 µL RNase free water, then stored at -80 °C. The total RNA concentration was determined spectrophotometrically (SPECTRO star Nano, BMG Labtech Co., Ortenberg, Germany) and then 1 µg of RNA was used for cDNA synthesis using the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems, CA, USA). The condition was achieved in line with the kit of cDNA reverse transcription as follow; step I (10 min/25 °C), step II (120 min/37 °C), step III (5 min/85 °C) and step IV (∞~ at 4 °C), then, 1 µg of the obtained cDNA with the SYBR green master mix were used in a total of

20 µl reaction volume 7 µl of nuclease-free water, 10 µl of master mix, 1 µl of forward primer, 1 µl of reverse primer, and 1 µl of DNA template) for HSP70 and β-actin gene amplification using the following primers:

IL 6 Forward GACTTCCAGCCAGTTGCCTTCTTG, IL 6

Reverse TGGTCTGTTGTGGGTGGTATCCTC, IL 10 Forward TGCCAAGC CTTGTCAGAAATGATCAAG, IL 10 Reverse TGCCAAGCCTTGTCAG AAATGATCAAG. GAPDH 5'-AACTCCCA TTCCTCCACCTT-3' forward, 5'-GAGGGCCTCTCTTGCTCT-3' reverse..

The genes were amplified then the expression levels were analyzed using a real-time PCR (7500 Fast Real-Time PCR System, Applied Biosystems, CA). The cycling condition was justified first the initial activation (3 min/95 °C), denaturation (3 s/95 °C), annealing/ extension (30 s/60 °C), and the number of cycles were 40 according to (Zhao FJ et al 2009). All gene expression level was normalized against the GAPDH gene.

### 2.7. Statistical analysis

The results were done as mean ± SE of the experimental groups using (one-way ANOVA) followed by Duncan's multiple range test. All analysis was performed by Statistical Package for Social science Software (SPSS (16) software (SPSS Inc., Chicago, USA).

## 3. Results

### 3.1. Effect on liver biomarker

Results revealed that intraperitoneal injection of Cisplatin at dose of 6 mg/kgb.wt once at day 10 showed significantly increased in ALP, ALT and AST by compared to control and corn oil group as well as significant decrease in albumin level ,while interestingly it was found that concurrent administration of Lycopine with Cisplatin result in significant in their levels ., also albumin return to normal level . all these data illustrated in table (1)

### 3.2. Effect on oxidative stress biomarker

The malondialdehyde (MDA) significantly increased by Cisplatin than control and corn oil group and grossly decreased by Lycopine with Cisplatin .Total anti-oxidant (TAC) increased by Cisplatin and down by given Lycopine with Cisplatin. Reduced glutathione GSH level reduced by Cisplatin and increased again by Lycopine with Cisplatin .Table (2)

### 3.3. Effect on gene expression

It was found that the expression of IL6 significantly increased in liver and brain tissue by Cisplatin than control and corn oil group and by the action of Lycopine genes expression regained to normal levels . IL10 down regulated in liver and brain tissue of Cisplatin group than what's happen in control group and corn oil group,while beneficially concurrent administration of Lycopine with Cisplatin leads to upregulation of genes expression again Table (3),(4)

**Table 1:** Effect of Lycopine on ALP, ALT, AST Concentration in Serum (IU/L) and Albumin Mg/ in Cisplatin Treated Rats. Data are Presented As (Mean ± S.E). S.E = Standard Error. Mean Values with Different Superscript Letters in the Same Column Are Significantly Different at (P<0.05)

Groups	N	Mean± Std. Error			
		ALP(U/L)	ALT(U/L)	AST(U/L)	Albumin(g/dl)
Control	5	320.1±1.63 <sup>e</sup>	48.67±1.3 <sup>e</sup>	89.56±1.58 <sup>e</sup>	2.93±0.23 <sup>a</sup>
corn oil	5	308.1±1.49 <sup>c</sup>	90.9±2.3 <sup>c</sup>	93.57±2.03 <sup>c</sup>	2.97±0.26 <sup>a</sup>
Lycopine	5	543.54±0.83 <sup>e</sup>	85.1±1.37 <sup>d</sup>	93.13±3.13 <sup>c</sup>	2.26±0.11 <sup>b</sup>
Cisplatin	5	999.7±0.70 <sup>a</sup>	209.9±1.37 <sup>a</sup>	222.8±1.05 <sup>a</sup>	0.98±0.33 <sup>c</sup>
lycopine + Cisplatin	5	602.63±2.07 <sup>b</sup>	102.27±0.72 <sup>b</sup>	128.55±1.95 <sup>b</sup>	2.08±0.06 <sup>b</sup>

**Table 2:** Effect of Lycopine on MDA, TAC and GSH Activity (Nmol/MI) in Cisplatin Treated Rats. Data are Presented as (Mean ± S.E). S.E = Standard Error. Mean Values with Different Superscript Letters in the Same Column are Significantly Different at (P<0.05)

Groups	N	Mean± Std. Error		
		MDA(nmol/gm)	TAC(µmol/g)	GSH(U/gm)
Control	5	125.35±1.45 <sup>d</sup>	24.78±1.6 <sup>a,b</sup>	135.2±1.21 <sup>a</sup>
corn oil	5	130.57±1.2 <sup>c</sup>	22.5±1.3 <sup>b</sup>	99.64±1.16 <sup>b</sup>
Lycopine	5	115.41±1.82 <sup>e</sup>	17.4 ±1.87 <sup>c</sup>	134.7±1.06 <sup>a</sup>
Cisplatin	5	504.8±1.59 <sup>a</sup>	27.09 ±1.43 <sup>a</sup>	87.97±1.08 <sup>c</sup>
lycopine + Cisplatin	5	298.83±0.81 <sup>b</sup>	21.06±0.67 <sup>b,c</sup>	137.4±1.57 <sup>a</sup>

**Table 3:** Effect of Lycopene on Fold Change in the Gene Expressions of IL6 and IL10 in Liver in Cisplatin Treated Rats. Data are Presented as (Mean ± S.E). S.E = Standard Error. Mean Values with Different Superscript Letters in the Same Column are Significantly Different at (P<0.05)

Groups	Mean ±Error of the gene expression in liver		
	N	IL6	IL10
Control	5	1.05±0.022 <sup>b</sup>	1.01±0.005 <sup>c</sup>
corn oil	5	1.02±0.06 <sup>b</sup>	1.38±0.05 <sup>b</sup>
Lycopine	5	0.98±0.03 <sup>b</sup>	1.4±0.15 <sup>b</sup>
Cisplatin	5	2.43±0.20 <sup>a</sup>	0.77±0.114 <sup>d</sup>
lycopine+Cisplatin	5	1.28±0.08 <sup>b</sup>	2.96±0.03 <sup>a</sup>

**Table 4:** Effect of Lycopene on Fold Change in the Gene Expressions of IL6 and IL10 in Brain in Cisplatin Treated Rats. Data are Presented as (Mean  $\pm$  S.E). S.E = Standard Error. Mean Values with Different Superscript Letters in the Same Column are Significantly Different at (P<0.05)

Groups	Mean $\pm$ Error of the gene expression in brain		
	N	IL6	IL10
Control	5	1.55 $\pm$ 0.132 <sup>c</sup>	1.2 $\pm$ 0.07 <sup>b</sup>
corn oil	5	1.85 $\pm$ 0.14 <sup>b,c</sup>	1.64 $\pm$ 0.183 <sup>a,b</sup>
Lycopine	5	2.81 $\pm$ 0.71 <sup>b,c</sup>	2.1 $\pm$ 0.14 <sup>a</sup>
Cisplatin	5	5.42 $\pm$ 0.30 <sup>a</sup>	0.49 $\pm$ 0.022 <sup>c</sup>
lycopine + Cisplatin	5	3.03 $\pm$ 0.02 <sup>b</sup>	2.05 $\pm$ 0.37 <sup>a</sup>

## 4. Discussion

Cisplatin is one of the most mostly used antitumor drug, however, it may cause liver and brain toxicity that depend on the dose and the duration of the drug administration Dasari and Tchounwou (2014). In the present study, lycopine is used in combination with Cisplatin as an antioxidant and anti-inflammatory agent to ameliorate Cisplatin-induced toxicity.

Cisplatin produced serious array of events of liver injury where significant increase in serum ALP,ALT and AST significantly increased by Cisplatin than control and corn oil group reach. These events were consistent with other studies who confirmed the changes related to the CP induced hepatotoxicity. Waseem et al., (2015) and Hanan et al., (2020) and grossly decreased by Lycopine with Cisplatin. Elevation of serum ALT and AST levels indicator of hepatotoxicity and indirectly reflects the failure of liver function Rabab and Fatma (2019).

Our results appeared to be consistent with many previous findings that indicated a hepatotoxic effect of cisplatin and its association with increased free radical formation and the subsequent oxidative and nitrosative stress. Omar et al.,(2016) In addition, our results appeared to agree with the study by Yousef et al.,(2009) who found increased oxidative stress markers in the liver of cisplatin-treated rats.

Cisplatin. can increase the generation of superoxide anion and NO by iNOS .The co-existence of both radicals forms peroxynitrite, a potent RNS. Both ROS and RNS are capable to activate the intrinsic apoptotic pathway to ultimately cleave Casp-3 Narayanan et al., (2015)

Cisplatin-associated alterations in liver and brain whether biochemical or inflammatory effects are attributed to the induction of cellular oxidative stress and endoplasmic reticulum stress that increase the level of superoxide anions and hydroxyl radicals. Yilmaz (2004). These free radicals can directly react with different cellular components causing their damage, inhibit mitochondrial respiratory chain functions, and increase mitochondrial permeability transition pore leading to ATP depletion and nucleus-independent apoptosis signaling. Dasari and Tchounwou (2014).

Lycopine is a natural pigment, synthesized by plants. Red fruits and vegetables are the most common sources of Lycopine, which had the strongest antioxidant activity among all dietary carotenoids. Therefore, nowadays, the potential role of Lycopine in human health is beginning to be noticed, and the most important health benefits are hypothesized to occur through their ability to protect against oxidative damage Urbonaviciene and Viskelis, P 2017. The aim of the present study was to demonstrate that Lycopine is an effective antioxidant. In this study, it was observed after Lycopine treatment that GSH and albumin level increased while AST, ALT,Alp,TAC and MDA levels decreased The results of Al-Salmi (2019) also revealed that the Administration of lycopine with ACR significantly decreased the ALT, AST and MDA level and increased GSH level when compared to ACR treated group. Jiang et al., (2016) found that treatment with Lycopine is able to inhibit the elevation of liver function markers, and liver damage. Moreover, Lycopine significantly raised GSH and reduced MDA, which suggesting that the activity of Lycopine as antioxidant play a role in the mechanism of its hepatoprotective effect and ameliorative effect against Cisplatin duced hepatotoxicity.

Increase in ROS levels in cells stimulated with Cisplatin. In previous studies on the antioxidant effect of lycopine, lycopine inhibited nitration of proteins and DNA strand breakage caused by peroxynitrite treatment Muzandu et al., (2006) and decreased the oxidative DNA damage caused by the redoxcycling of catechol-estrogens Muzandu et al.,(2005) and Liu et al. (2006) determined the subcellular localization of lycopene in prostate cancer cells and found that 81% of the lycopene was localized to the nucleus. These results support an antioxidant effect of lycopine in various cells the inhibitory effect of lycopine on Cisplatin-induced activation of interleukin 6 caused by the ROS as the obtained results from our research that Cisplatin causing increase level of the gene expression of IL6 decreased by lycopine.

Cisplatin causing reduction in IL-10 These results may be due to the decline in IL-10 exacerbates hepatic lesion that downregulate pro-inflammatory cytokine release. Faten et al.,(2021) Koppelman et al., (1997)

IL-10 is an important anti-inflammatory cytokine and plays essential role in controlling immune responses in the intestinal mucosa .It inhibits the synthesis of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IFN- $\gamma$  and blocks NF- $\kappa$ B activation. These results were nearly similar to those reported by El- Shaimaa et al. (2020), who revealed a significant rise in the inflammatory status of the injured colon with decreased levels of IL-10.

IL-10 is an anti-inflammatory cytokine that overturns the activation of leukocytes and the production of pro-inflammatory cytokines and chemokines (Miller et al., (2010). Deng and colleagues (2001) revealed that the administration of exogenous IL-10 prevents the upregulation of TNF- $\alpha$  and ICAM-1 expression and the influx of neutrophils into the tissues in reply to Cisplatininjection. Nowadays, it has become a strategic approach to use anti-inflammatory agents to ameliorate the Cisplatin-induced damage as lycopine.

## 5. Conclusion

It is concluded that lycopine has an ameliorating effect which minimizes the hepatic and neural toxicity induced by cisplatin,

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