Pakistan Veterinary Journal

ISSN: 0253-8318 (PRINT), 2074-7764 (ONLINE)
DOI: 10.29261/pakvetj/2023.029

RESEARCH ARTICLE

Tectochrysin Attenuates Cisplatin-induced Hepatotoxicity by Restoring Biochemical, Inflammatory and Histological Profile in Rats

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ARTICLE HISTORY (23-022)

Received: January 21, 2023
Revised: April 8, 2023
Accepted: April 12, 2023
Published online: April 24, 2023

Key words:
Cisplatin
Tectochrysin
Oxidative stress
Antioxidants
Inflammation
Hepatotoxicity

ABSTRACT

Cisplatin is an efficacious anticancerous chemotherapeutic agent that is used to cure multiple types of malignancies. However, it has several hazardous effects on multiple organs, particularly liver. Tectochrysin is a naturally occurring flavonoid with extensive pharmacological properties. In this research, the potential anti-oxidant properties of tectochrysin against cisplatin-triggered oxidative stress in rats' hepatic tissues were investigated. 48 male albino rats were separated into 4 groups: control cisplatin (10 mg/kg), cisplatin + tectochrysin (10 mg/kg + 5 mg/kg), and tectochrysin (5 mg/kg). The trial executed for one month. The biochemical, inflammatory, histopathological and liver markers were evaluated. The results of the research suggested that cisplatin treatment remarkably lowered the activities of glutathione (GSH), superoxide dismutase (SOD), glutathione reductase (GSR), glutathione S-transferase (GST), glutathione peroxidase (GPx) as well as catalase (CAT) while escalated malondialdehyde (MDA) and reactive oxygen species (ROS) levels. Cisplatin administered rats exhibited significantly higher aspartate aminotransferase (AST), alanine aminotransferase (ALT) as well as alkaline phosphatase (ALP) levels. Furthermore, cisplatin administration significantly elevated the inflammatory indicators i.e., interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) as well as nuclear factor kappa-B (NF- κB) and cyclooxygenase-2 (COX-2) activity along with histopathological impairments. Conversely, co-administration with tectochrysin effectively reversed the cisplatin-triggered impairments and abnormalities in the hepatic tissue of rats. The current investigation demonstrated that tectochrysin lowered cisplatin-induced hepatotoxicity owing to its antioxidant, reactive oxygen species scavenging activities and anti-inflammatory effects.

To Cite This Article: Ijaz MU, Rafi Z, Hamza A, Tariq M, Alkahtani S, Alkahtane AA, and Riaz MN, 2023. Tectochrysin attenuates cisplatin-induced hepatotoxicity by restoring biochemical, inflammatory and histological profile in rats. Pak Vet J, 43(2): 366-370. http://dx.doi.org/10.29261/pakvetj/2023.029

INTRODUCTION

Cisplatin, a platinum-derived antineoplastic, DNA alkylating drug which is also known as cis-diamminedichloroplatinum (CDDP), with the molecular formula cis-[Pt $(NH_3)_2$ Cl_2] has a wide range of therapeutic uses (Ghosh, 2019). This chemotherapeutic agent is used to treat lung, head, neck, bladder, ovarian and testicular malignancies. Moreover, it also possesses therapeutic potential against a wide variety of tumors such as germ cell tumors, carcinomas, lymphomas and sarcomas (Aldossary, 2019). Cisplatin triggers cell death by covalently binding to biological molecules *i.e*., DNA and RNA. The potential of cisplatin to crosslink with DNA strands ultimately causes apoptosis as DNA replication is disrupted and gene expression is changed (Liu *et al*., 2022). Mounting evidences reveal that cisplatin has substantial toxicity and severe side effects (Qi *et al*., 2019). Cisplatin application has been significantly restricted due to its severe hazards such as gastrotoxicity, ototoxicity, nephrotoxicity as well as hepatotoxicity (Perše, 2021). Owing to its potentially lethal consequence, it causes substantial side effects on different organs especially the liver (Anbar *et al*., 2022).

Although the mechanisms of cisplatin-triggered hepatotoxicity have not been fully explored, various experimental models and several studies have linked cisplatin toxicity to reactive oxygen species (ROS) (Hassan *et al*., 2020) as well as an upsurge in lipid peroxidation (LPO) and alteration in glutathione (GSH) status (Akdemir *et al*., 2022). Cisplatin causes hepatocyte cell membrane breakdown and leakage of the enzymes from hepatocytes which is evident by the considerable upsurge in the concentrations of ALT, ALP and AST (Al-Yassen *et al*., 2022). Cisplatin disrupts hepatic lobule architecture and raises sinusoidal diameter in the liver (Esmat *et al*., 2022). Several anti-oxidant agents have been utilized to prevent cisplatin-induced hepatotoxicity (Abd Rashid *et al*., 2021).

Flavonoids, a broad group of naturally occurring hydroxylated phenolic compounds, found in fruits and vegetables are recognized as the scavengers of ROS (Ullah *et al*., 2020). Tectochrysin (5-hydroxy-7-methoxyflavone) is found in many plants, particularly edible plants like *Kaempferia parviflora*, *Alpinia oxyphylla*, *Muntingia calabura* and Carya genus (Hou *et al*., 2018). Tectochrysin has anti-oxidant, anti-diarrheal, anti-inflammatory as well as anti-cancer potentials (Niu *et al*., 2020). Despite the encouraging therapeutic effects of tectochrysin, its protective role against cisplatin-triggered hepatotoxicity remains undiscovered. The present research was intended to track the ameliorative role of tectochrysin against cisplatin-triggered hepatic dysfunction.

MATERIALS AND METHODS

Chemicals: Cisplatin and Tectochrysin were purchased from Sigma Aldrich, Germany.

Animals: For this experiment, 48 albino male rats (180 ± 220 g) were used. Animals were kept in the animal research station of University of Agriculture, Faisalabad (UAF). Animals were separated into groups and housed in steel enclosures in the laboratory at 26 ± 2°C, 12 h day/night, and given standardized feed and water during the whole trial.

Experimental design: Rats were separated into 4 groups (n=12) and handled in the following manner: 1st group was designated as the control group and was given regular feed and water. The second group was treated with cisplatin (10 mg/kg) orally, the third group was co-treated with cisplatin (10 mg/kg) plus tectochrysin (5 mg/kg) through oral gavage, and the fourth group was supplemented with tectochrysin (5 mg/kg) orally. Cisplatin at a dose of 10 mg/kg was selected according to the study of Soni *et al*. (2015). Tectochrysin at a dose of 5 mg/kg was administrated according to the earlier research conducted by Fang *et al*. (2021). The trial was executed for one month. The rats were anesthetized, decapitated, and blood was collected in sterilized tubes after the experiment. Normal saline was used to clean the liver after it had been removed. The liver was dissected into two parts, one of which was packaged in zipper pouches and preserved for biochemical examination at -80°C. For histological evaluation, the second part was kept in 10 percent formalin solution according to the study of Ibrahim *et al*. (2018).

Assessment of antioxidants: Chance and Maehly (1955) approach was followed to evaluate CAT activity. Nishikimi *et al*. (1972) method was used for measuring SOD activity. GST content was assessed using Couri and Abdel-Rahman (1979) method. Carlberg and Mannervik (1975) technique was followed to estimate GSR activity. The concentration of GSH in tissue homogenates was determined using Sedlak and Lindsay (1968) technique. GPx activity was determined by using the practice of Lawrence and Burk (1976).

Assessment of oxidative stress markers: Hayashi *et al*. (2007) technique was followed to estimate the ROS level in the homogenate. Ohkawa *et al*. (1979) technique was used for measuring the amount of malondialdehyde (MDA) in hepatic tissues. A spectrophotometer (UV-Noticeable/NIR-UH5700) was employed to take measurements.

Analysis of hepatic serum markers: The levels of ALT (ab285264), AST (ab263883) along with ALP (ab287823) were assessed via commercially available kits obtained from Wiesbaden (Germany).

Inflammatory markers assessment: The levels of inflammatory markers were evaluated by using commercially available kits. IL-6 (CSB-E04640r), TNF-α (CSB-E07379r), IL-1β (CSB-E08055r), NF- κB (CSB-E13148r) levels and COX-2 (CSB-E13399r) activity were measured via rat ELISA kit (Cusabio Technology Llc, Houston, TX, USA) by following the company's instructions.

Histopathological analysis: Hepatic tissues were washed in 0.9% cold saline solution and preserved in 10% formalin solution for 24 hours to examine histopathological changes. Following fixation samples were dehydrated using ascending grades of alcohol, cleared in xylene, and then fixed in paraffin wax. 4-5 µm thin slices were cut using a microtome machine (Leica RM 2155, England). Then the slides were stained using hematoxylin and eosin stain. The histological analyses of these sections were performed using an optical microscope (Nikon, 187842, Japan). The photos of tissues were taken using a Leica LB microscope-connected with a camera.

Statistical analyses: Results were displayed as Mean ± SEM. To compare the groups, one-way analysis of variance (ANOVA) was used, followed by Tukey's test. $P<0.05$ was set as statistically significant.

RESULTS

Effects of Cisplatin and Tectochrysin on anti-oxidant enzymes activities: Cisplatin exposure resulted in a considerable ($P<0.05$) reduction in anti-oxidant enzymes (GSH, GSR, GST, GPx, SOD as well as CAT) activities. However, the co-administration of cisplatin and tectochrysin noticeably ($P<0.05$) enhanced the activity of anti-oxidant enzymes in cisplatin-administered rats. Furthermore, only tectochrysin administration resulted in normal enzyme activity similar to the control group (Table 1).

Table 1: Effect of Cisplatin + Tectochrysin on the biochemical and oxidative stress markers of liver

Parameters	Groups			
	Control	Cisplatin	Cisplatin + Tectochrysin	Tectochrysin
CAT (U/mg protein)	9.33±0.27^{a}	4.11±0.20^{c}	7.46±0.33^{b}	9.38±0.32^{a}
SOD (U/mg protein)	8.18±0.14^{a}	3.23±0.10^{c}	6.03±0.27^{b}	8.21±0.13^{a}
GSR (nM NADPH oxidized/min/mg tissue)	6.46±0.26^{a}	1.89±0.20^{c}	4.41±0.09^{b}	6.48±0.29^{a}
GPx (U/mg protein)	17.29±1.66^{a}	4.52±0.57^{c}	12.30±1.01^{b}	17.44±1.99^{a}
GSH (µM/g tissue)	13.63±1.54^{ab}	4.73±0.59^{c}	10.52±0.79^{b}	13.99±1.75^{a}
GST (nM/min/mg protein)	24.34±2.18^{a}	9.92±0.79^{c}	19.55±0.74^{b}	24.72±2.71^{a}
MDA (nmol/g)	0.83±0.09^{b}	4.18±0.56^{a}	1.52±0.13^{b}	0.81±0.08^{b}
ROS (µmol/g)	1.14±0.09^{c}	8.82±0.32^{a}	2.94±0.18^{b}	1.11±0.11^{c}

Means that contain different superscripts in the same row are significantly dissimilar.

Table 2: Effect of Cisplatin + Tectochrysin on liver function markers.

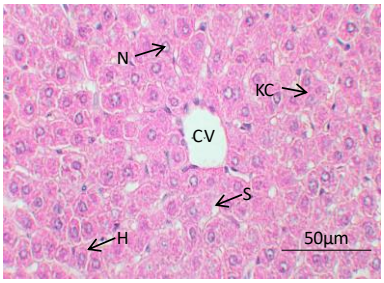
Parameters	Groups			
	Control	Cisplatin	Cisplatin + Tectochrysin	Tectochrysin
ALT (U/l)	44.47±4.47^{c}	117.85±4.00^{a}	73.56±1.82^{b}	43.19±3.48^{c}
AST (U/l)	80.77±2.73^{c}	183.15±5.79^{a}	104.97±9.18^{b}	79.48±3.43^{c}
ALP (U/l)	102.71±8.34^{c}	326.6±17.7^{a}	154.09±10.27^{b}	101.13±8.67^{c}

Means that contain different superscripts in the same row are significantly different.

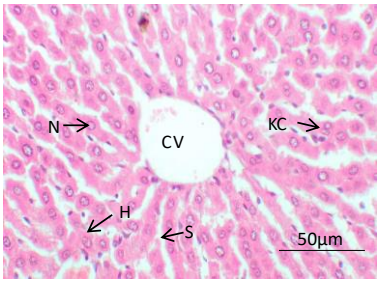
Table 3: Effect of Cisplatin + Tectochrysin on inflammatory markers of liver.

Parameters	Groups			
	Control	Cisplatin	Cisplatin + Tectochrysin	Tectochrysin
NF-kB (ng/g tissue)	14.33±2.21^{c}	76.22±3.23^{a}	28.04±2.95^{b}	14.18±2.26^{c}
TNF-α (ng/g tissue)	6.49±0.28^{c}	23.69±2.07^{a}	9.95±1.52^{b}	6.44±0.26^{c}
IL-1β (ng/g tissue)	23.54±2.30^{c}	92.25±3.07^{a}	35.65±3.77^{b}	23.37±2.11^{c}
IL-6 (ng/g tissue)	7.14±0.77^{c}	44.99±1.55^{a}	16.00±2.32^{b}	7.05±0.69^{c}
COX-2 (ng/g tissue)	15.62±1.83^{c}	77.79±3.94^{a}	31.54±1.92^{b}	15.36±1.87^{c}

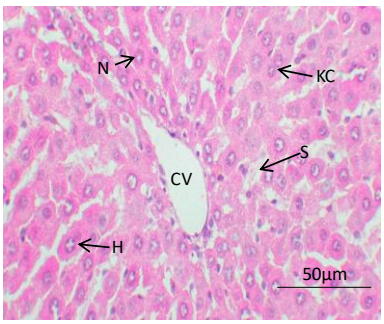
Means that contain different superscripts in the same row are significantly different.



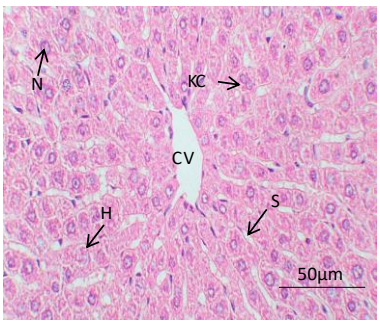
(A) Control



(B) Cisplatin (10 mg/kg)



(C) Cisplatin (10 mg/kg) + Tectochrysin (5 mg/kg)



(D) Tectochrysin (5 mg/kg)

Fig. 1: Light microscopy of liver tissues was obtained from different groups (H&E 400X). (A): Control (normal histoarchitecture). (B): Cisplatin (10 mg/kg.); Tissues showing extensive and marked necrosis. (C): Cisplatin (10 mg/kg) + Tectochrysin (5 mg/kg); decrease in necrosis throughout hepatic tissues as well as recovery of injured tissues. (D): Tectochrysin (5 mg/kg) supplemented; regular histoarchitecture almost as in control group. (S: sinusoids, CV: central vein, KC: kupffer cell, N: nucleus, H: hepatocytes).

Effects of Cisplatin and Tectochrysin on oxidative stress markers: Cisplatin treatment markedly (P<0.05) augmented MDA level along with ROS level in cisplatin-administered group when matched with the control group. Nonetheless, when cisplatin and tectochrysin were co-administered, MDA as well as ROS levels were substantially (P<0.05) lowered when matched with the cisplatin group. Moreover, only tectochrysin supplemented group showed MDA and ROS levels similar to the control group (Table 1).

Effects of Cisplatin and Tectochrysin on hepatic markers: The results of hepatic serum markers revealed that cisplatin intoxication caused profound liver damage, as evidenced by a considerable (P<0.05) upsurge in ALT, ALP as well as AST levels when matched with the control group. Although, in the co-treated rats, levels of liver markers were noticeably (P<0.05) lowered in contrast to cisplatin-intoxicated group. Furthermore, only tectochrysin administrated group displayed the levels of these markers close to the control (Table 2).

Effects of Cisplatin and Tectochrysin on hepatic inflammatory indices: Cisplatin administration noticeably (P<0.05) escalated the level of liver markers associated with inflammation (COX-2 activity, IL-6, TNF-α, IL-1β as well as NF-κB) in cisplatin-exposed group in contrast to the control group. Cisplatin and tectochrysin co-treatment, on the other hand, reduced the levels of inflammatory indices

in comparison with cisplatin-administered group. Only tectochrysin-treated group exhibited the same levels of inflammatory indices as in the control group (Table 3).

Effect of Cisplatin and Tectochrysin on histopathology: The histopathology of liver tissues is shown in photomicrograph 1. In comparison to the control group, cisplatin intoxication caused vacuolization, disruption of the central vein, nuclear aggregation, inflammatory cell infiltration, liver parenchyma disruption and necrosis. However, these injuries were remarkably reduced in the co-administered (Cisplatin + Tectochrysin) group. Only tectochrysin administered group showed a similar histological profile as in the control group.

DISCUSSION

The therapeutic efficacy of cisplatin in anti-cancer treatment has been well evaluated. However, its application is being questioned because of its toxic side effects, especially on hepatic tissues (Anbar *et al*., 2022). Histopathological changes such as elevation of hepatic serum enzymes, the decline in anti-oxidants and augmentation in oxidative stress as well as in inflammatory responses in liver tissues were observed after cisplatin administration (Ijaz *et al*., 2020). Thus, vast endeavors have been made to shed light on naturally derived hepatoprotective medicines, owing to their numerous therapeutic properties and low toxicity (Abd Rashid *et al*., 2021). Tectochrysin is identified as a potent anti-oxidant with anti-cancer as well as anti-inflammatory properties (Niu *et al*., 2020). Therefore, the current study was intended to examine the hepatoprotective potential of a natural flavonoid, tectochrysin against cisplatin-triggered liver damage.

Anti-oxidant enzymes are critical in protecting cellular components from oxidative damage (Pisoschi *et al*., 2021). According to our results, activities of SOD, GST, CAT, GSR and GPx were remarkably reduced in the hepatic tissue of cisplatin-administered rats owing to the constant and massive generation of reactive oxygen species such as hydroxyl radicals, peroxides as well as superoxides. Superoxide dismutase (SOD) converts oxygen-free radicals into H_2O_2, which is then transformed into H_2O and O_2 by CAT and GPx, therefore eliminating the fatal effects of OH radicals (Gharu, 2022).

We noticed that cisplatin administration remarkably augmented MDA and ROS levels in hepatocytes. The assessment of lipid peroxides confirmed the presence of liver anomalies. The most common cause of cisplatin-induced hepatotoxicity is increased ROS generation and oxidative stress. MDA level was upsurged due to enhanced lipid peroxidation (LPO), coupled with a lower GSH concentration (Akdemir *et al*., 2022). In the current study the supplementation of tectochrysin with cisplatin considerably reduced MDA as well as ROS levels in rats. Previous studies confirmed that cisplatin caused liver damage by increasing H_2O_2 concentrations, which elevated MDA and ROS levels, whereas reduced anti-oxidants in the liver (Bademci *et al*., 2021). The reduction in the activity of anti-oxidants and increased ROS generation instigates liver injuries. However, co-administration with tectochrysin relieved oxidative damage by removing free oxygen radicals and recovering the activity of anti-oxidants.

Following cisplatin treatment, serum ALT, ALP and AST levels were escalated dramatically in this experiment. These enzymes are released by hepatic mitochondria, indicating hepatic disorder (Al-Yassen *et al*., 2022). The findings of various studies have suggested that cisplatin-triggers significant ROS generation, which damages hepatic structural stability, as demonstrated by an aberrant increase in hepatic enzymes (Elsayed *et al*., 2021). Our results indicated that co-treatment with tectochrysin mitigated and alleviated cisplatin-triggered hepatotoxicity by reducing the levels of liver markers.

Inflammation is a major contributor to cisplatin-induced hepatotoxicity. In this experiment, cisplatin administration increased the activity of COX-2 and IL-6, NF- κB, IL-1β as well as TNF-α levels. NF- κB activity is indispensable for proinflammatory cytokines' expression that is associated with acute inflammatory responses (Oluranti *et al*., 2021). The release of IL-6, TNF-α and IL-1β is elevated by the activation of NF-kB, which correlates with acute liver damage (Cai *et al*., 2022). COX-2 is an inductive form of COX, a crucial inflammatory marker that performs a vital biological function in inflammatory response (Ju *et al*., 2022). In this study, COX-2 activity was enhanced in the liver of cisplatin-administered rats, indicating liver damage in cisplatin-administered rats. However, tectochrysin supplementation reduced the levels of inflammatory indices. Anti-inflammatory mechanisms of tectochrysin may be due to the C2-C3 double bond as well as a 7-OCH_3 on its A-ring (Hou *et al*., 2018).

Histopathological examination revealed that in cisplatin administered group, evident hepatic injuries were noticed such as lobule development, sinusoids dilatation, central vein rupture, biliary duct propagation, coagulation, obstruction, necrosis (Aboraya *et al*., 2022), and swelling of connective as well as supporting tissues (Esmat *et al*., 2022). However, the co-treatment of tectochrysin with cisplatin alleviated these severe anomalies. The alleviative attributes of tectochrysin may be linked to its possible anti-oxidant capacity, as evidenced by the suppression of LPO in the hepatic tissues.

Conclusions: Cisplatin administration resulted in oxidative stress due to excessive ROS generation, which caused a reduction in GSH, GPx, GST, GSR, SOD and CAT activities accompanied by an upsurge in MDA a well as ROS levels. Cisplatin administration augmented IL-6, TNF-α, IL-1β, NF- κB levels and COX-2 activity. In addition the levels of ALP, ALT as well as AST were elevated. Cisplatin disrupted hepatic lobule architecture and increased sinusoidal diameter in the liver. Our results indicated that tectochrysin exerted outstanding alleviation capacity against cisplatin-triggered hepatic oxidative stress. Tectochrysin therapy effectively regulated the levels of anti-oxidants and inflammatory markers as well as restored hepatic serum marker levels and histological abnormalities. The hepatoprotective role of tectochrysin may be attributed to its anti-oxidant and anti-inflammatory nature.

Authors contribution: MUI, ZR and AH perceived the idea of the study. AH, MT and SA performed the experiments. AAA and MNR helped in statistical analysis. MUI and ZR wrote the manuscript. All the authors approved the final version of manuscript.

Acknowledgements: This work was funded by Researchers Supporting Project number (RSP2023R26) King Saud University, Riyadh, Saudi Arabia.

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