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Research Article

# Shen-Qi-Di-Huang Decoction Prevents Cisplatin-Induced Kidney and Liver Injury by Inhibiting Apoptosis

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**Abstract**

**Purpose:** This research delves into the procedure in the pathogenesis of Cisplatin (CIS)-caused liver and kidney impairment and check the defensive effect of shen-qi-di-huang decoction (SQDH).

**Methods:** It divides adult male Wistar rats into four groups of eight animals each: Regulation; SQDH; CIS and SQDH+CIS group. They performed multiple analysis to dissect the mechanisms constraining the implements of SQDH.

**Results:** The stems display that pretreatment with SQDH protects the rats from CIS-induced experience and kidney trauma, as disclosed by diminished degrees of serum ALT, AST, BUN and creatinine, improved histopathological damage in thriving and courage. SQDH significantly reverses CIS-induced dysregulation of apoptotic proteins in liver and kidney. In supplement, SQDH induces the activations of PI3K/AKT in kidney and p38/MAPK in liver, individually.

**Conclusion:** We confirm that SQDH protects against CIS-induced nephrotoxicity and hepatotoxicity, which is probably correlated with the activation of p38/MAPK in liver and PI3K/AKT in kidney.

**Keywords:** Cisplatin; Nephrotoxicity; Hepatotoxicity; Shen-qi-di-huang decoction; Apoptosis

## Introduction

Cisplatin (CIS) appears as one of the primary chemotherapeutic agents to use individual human malignancies, the broad treatment of CIS in clinical oncology, a large dosage and repeated courses of medication procedure has been reduced by its undesirable surface effects. Although being very impressive in reducing tumor burden, it is toxic and can make serious material impairment. Nephrotoxicity and hepatotoxicity are the most curious side-implements of CIS therapy [1,2]. The primitive formation of nephrotoxicity and hepatotoxicity caused by CIS remains incompletely recognized. For these reasons, several actions are ongoing to counter or downplay the toxicities and safeguard the efficacy of the platinum chemotherapy drugs.

Apoptosis is a crucial physical process for the progress and authority of tissue homeostasis [3]. Apoptosis ensures a surplus between nuclear proliferation and revolution in many goods. Cellular damage and death is a pivotal development in material damage generated by CIS. When fracture is moderate, the bruised tissue will ordinarily be rectified; however, excessive cell death may get to irreversible ruin and tissue fibrosis. I realize it that activation of the PI3K/AKT/Nrf2 signaling channel and p38/MAPK-mediated BCL2 down-regulation can protect cells from excessive apoptosis [4,5]. Therefore, we investigate the activity changes of PI3K and MAPK pathway, to explore the mechanism of CIS action in kidney and liver.

Shen-qi-di-huang decoction is a traditional Chinese medicine recipe recorded in the book of "Shen Shi Zun Sheng Book" by Jingo Shen during the Ming Dynasty, which is composed of Pilose Asia Cell Root (Radix Chaenopsis), Mongolian Milkvetch Root (Radix astragali mongols), cohesive Romanian Root Tuber (Radix Rumanian), Common Macrocarpa Fruit (Fructus macrocarpa), Common Yam Rhizome (Rhizoma Disagree papist), Tree Peony Root-bark (Cortex Mountain orders), Indian Bread (poria), Oriental Water plantain Tuber (Rhizoma Alismataceae), Cassiabarktree Twig (Romulus gonangium), Prepared Common Monkshood Daughter Root (Radix ancient lateralise Preparata). I have reported it that Shen-qi-di-huang decoction decreases proteinuria, protects kidney function, and improves histopathology in ADR-induced rats by preserving nephron expression [6].

In this study, we aim to investigate the protective effects of SQDH against CIS-induced nephrotoxicity and hepatotoxicity, and attempted to explain the antiapoptotic roles of SQDH and its modulation of the expression levels of Nrf2, PI3K/ AKT in kidney and BCL-2, MAPK/p38 in liver in a rat model induced by CIS.

## Methods

Male Wistar rats (180 ± 20 g) were purchased from the Experimental Animal Center of Dalian Medical University (Dalian, China). It allowed rats access to water and food ad libitum. All animal experiments are approved by the ethics committee of Dalian Medical University and performed in accordance with the institutional guidelines.

Rat models are induced by an intraperitoneal injection of CIS (6mg/kg) after fasting for 12h. Control rats are intraperitoneally injected with the same volume of a buffer carrier. We randomly divide rats are randomly into four groups (8 rats in each group; n = 8), as followed:

**Control group:** Receives an intraperitoneal injection of saline




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solution (vehicle of CIS) (1ml/100g body weight).

**SQDH group:** Orally treated with SQDH (1ml/100g body weight/day) for 14 consecutive days.

It gives CIS group a single intraperitoneal injection of CIS (6mg/kg body weight).

**SQDH+CIS group:** Through oral administration for 14 consecutive days, starting 7 days before CI receive SQDH (1ml/100g body weight/day) S injection. The rats were sacrificed by intraperitoneal injection of buffered and diluted barbiturates combined with local anesthetic (lidocaine) prior to injection.

### Preparation and administration of SQDH

**SQDH is composed of the following crude herbs:** Pilose Asia Cell Root (Radix Chaenopsis), Mongolian Milkvetch Root (Radix astragali Mongols), cohesive Armenian Root Tuber (Radix Armenian), Common macrocarpa Fruit (Fructus microcopy), Common Yam Rhizome (Rhizoma disagree Opposite), Tree Peony Root-bark (Cortex Mountain Radići), Indian Busad (poria), Oriental Water plantain Tuber (Rhizoma Alismataceae), Cassiabarktree Twig (Rumulus gonangium), Prepared Common Monkshood Daughter Root (Radix ancient lateralise Preparata). We purchase all herbs from the Dalian Metro Pharmaceutical Co., Ltd. (Dalian, Liaoning Province, China). They soak the mixtures in 8 volumes (v/w) of distilled water for 30 minutes and then boiled for 90min. The decoction is then concentrated to a final density of 0.99g/ml and stored at 4°C. During 2 weeks, SQDH group and SQDH+CIS group rats are orally administered SQDH at a dose of 1ml/100g body weight, while CIS group and control rats are orally administered an identical dose of ultra-pure water (Milli-Q Integral Water Purification System, Millipore Corporation, Billerica, MA, USA).

### Kidney and liver histology

Liver and kidney specimens are fixed in 10% buffered formalin and embedded in paraffin. Sections are cut at a thickness of 5 mm and stained with hematoxylin and eosin, and the stained sections are used to assess liver and kidney damage. Two independent blind observers grade the histological injury.

Detection of kidney injury in HE-stained tissues is based on the presence of tubular atrophy, hyaline cast, ischemic necrosis, vacuolization, and debris [7]. It scores damage intensity in the samples from 1 to 4, and we assign 0 to normal tissue (0, no damage; 1, 0-25% damaged tubules; 2, 25-50% damaged tubules; 3, 50-75% damaged tubules; and 4 >75% damaged tubules).

I give liver sections histological scores based on the extent of hepatocellular injury [8]: 0) Normal liver architecture; 1) Minimal injury (swelling, congestion, single cell necrosis); 2) Mild injury, with one or more minute foci of necrosis, the largest involving <1% of the examined sectional area of the lobule; 3) Moderate injury, as in 2, but the necrotic foci occupying 1-5% of the lobule; and 4) Severe injury, as above, but with necrotic foci covering >5% of the lobule.

We define necrosis when one or more of the following characteristics are seen: nuclear pyknosis, cytoplasmic hyper-eosinophilia, loss of distinct cellular borders, hemorrhage, and sinusoidal congestion. I take the percent area of necrosis from five randomly selected fields of each tissue section, and the average percent area of necrosis results from observing at least ten slides per group.

### Serum biochemistry measurements

After 7 days post-CIS injection, blood samples from sacrificed rats are collected in heparinized tubes. I centrifuge blood samples at 14,000g for 10 minutes to get plasma. The serum parameters Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Blood Urea Nitrogen (BUN) and Creatinine (Cré) levels are measured using detection kits according to the manufacturer's instructions (Nanjing Jiancheng Institute of Biotechnology, Nanjing, China).

### Immunohistochemical staining

Histological sections of rat kidneys and livers (4μm thick) are mounted on poly-L-lysine-coated slides. Slides are deparaffinized in xylene and rehydrated in graded alcohols. Sections are pre-treated with citrate buffer (0.01mol/L citric acid, pH 6.0) for 20min at 95°C. Then, at room temperature, sections are immersed in PBS containing 3% $H_2O_2$ for 10min. Afterward the sections are treated with 10% normal goat serum in PBS for 30 min at room temperature. The tissue sections are then incubated at 4°C overnight with rabbit polyclonal, anti-BCL2 or anti-Nrf2 (dilution 1:100). Then, sections are rinsed with PBS, incubated with biotinylated goat anti-rabbit IgG for 20min at room temperature and treated with 3,30-diaminobenzidine chromogen for 5min at room temperature. Finally, the sections are counter-stained with hematoxylin for 6min.

### Western blot analysis

Proteins are extracted from the rat kidneys and liver with a protein extraction kit (Kegen Biotech, Nanjing, China) according to the manufacturer's instructions and then measured using the bicinchoninic acid (BCA) assay (Solario, Beijing, China) with bovine serum albumin as the standard. Samples with 20μg of proteins are resuspended in electrophoresis sample buffer, separated by electrophoresis on a pre-cast 10% SDS-polyacrylamide gel (Bio-Rad, Hercules, CA) and electro transferred to a PVDF membrane (Millipore, Bedford, MA). They block the PVDF membranes for 2h at 37°C with 5% non-fat milk in Tris-buffered saline with 0.1% Tween-20 (TBST). β-Actin served as a loading control. Then, membranes are incubated overnight at 4°C with a 1:1000 dilution of a polyclonal antibody against Nrf2, caspase 3, caspase 9, Bax, Akt, P-Akt, BCL2, p-38, and P-p38 (Santa Cruz Biotechnology, Santa Cruz, USA; Beijing Biosynthesis Biotechnology, China) and with a 1:1500 dilution of monoclonal antibody for β-actin (Beyotime, China). After washing with TBST, it incubates the blots with the secondary antibodies. After another round of washing with TBST, they expose the membranes to enhanced chemiluminescence-plus reagents (ECL) from the Beyotime Institute of Biotechnology (Haimen, China). It documents emitted light with a spectrum-410 multispectral imaging system with a Chemi HR camera 410. Protein bands are visualized and photographed under transmitted ultraviolet light. Band densitometry is semi-quantitatively measured using the images.

### Data analysis

I perform significance testing between groups using the SPSS 13.0 software. Group data are expressed as the mean ± S.D. One-way analysis of variance is used to compare statistically significant differences of data between two sets. In all statistical analyses, it

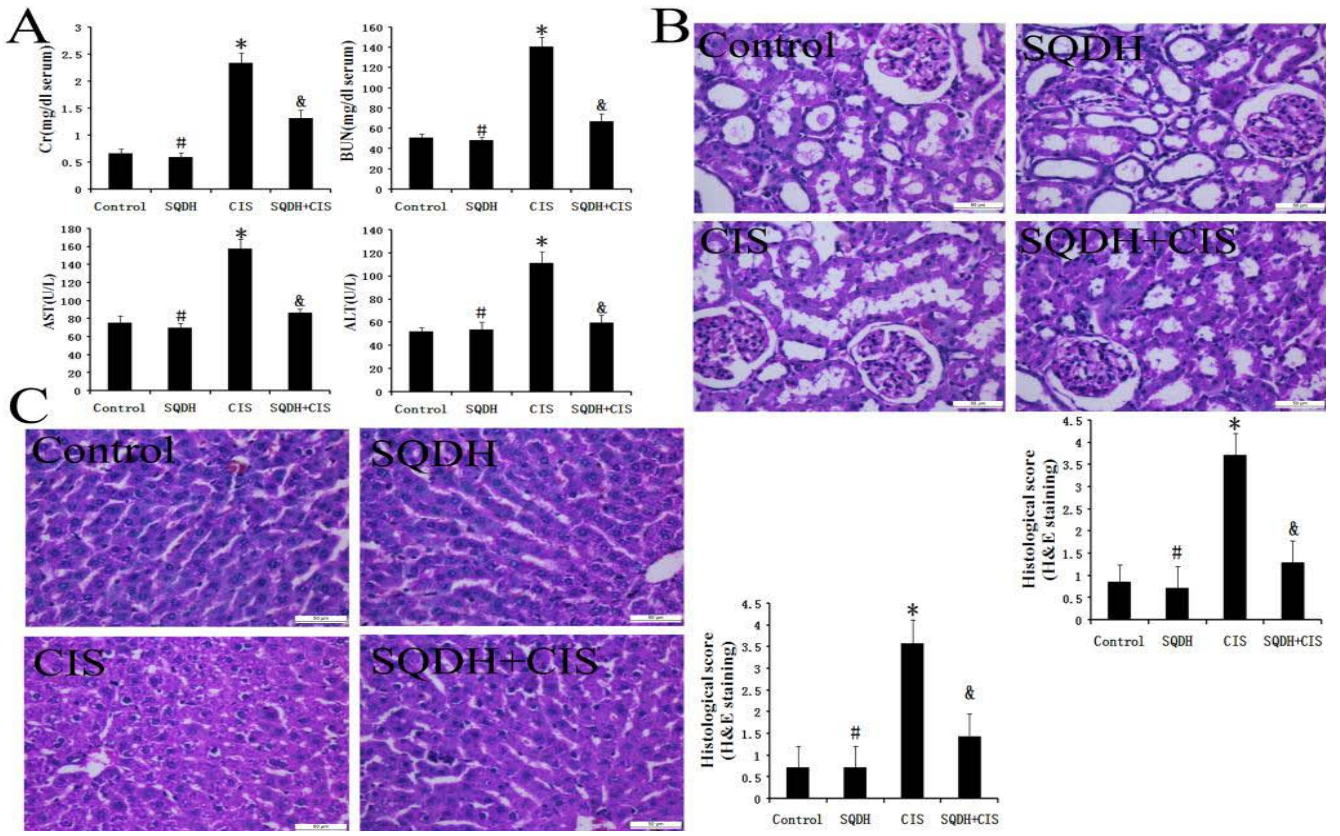


**Figure 1:** (A) SQDH significantly reduces renal injury-induced increase in serum Cr, BUN, ALT and AST. (B) CIS caused severe renal tissue damage, which were lightened after SQDH treatment. (C) CIS causes severe liver tissue damage, which were lightened after SQDH treatment (n=8 rat/group, values represent mean ± standard deviation in the histograms. #p >0.05 *vs.* control; *p <0.01 *vs.* control; &p<0.01 *vs.* CIS).

establishes the level of significance as $p < 0.05$ or $p < 0.01$.

### Animal and clinical studies

We conducted the research under the internationally accepted principles for laboratory animal use and care as found in the European Community guidelines (EEC Directive of 1986; 86/609/EEC) or the US guidelines (NIH publication #85-23, revised in 1985).

## Results

### SQDH eases serum parameters changed by CIS in rats

I test blood levels of CR and BUN for all groups. The blood levels of CR and BUN of the CIS group are higher than those of a control group on the 7th day after CIS injection. However, SQDH treatment improved blood Scr and BUN contents, which are significantly reduced (Figure 1A). I test blood levels of ALT and AST for all groups. The blood levels of AST and ALT of the CIS group are higher than those of a control group on the 7th day after CIS injection. However, SQDH treatment improves blood ALT and AST contents, which are significantly reduced (Figure 1A).

### SQDH eases renal and hepatic injury

HE stains of the groups also shows a protective role of SQDH against tissue damage. Tubular cell swelling, hyaline cast, vacuolization, and debris decrease with SQDH treatment (Figure 1B). I could observe tissue damage in the CIS-treated group, but it is milder in the group treated with SQDH. Histological scores assessed by two senior pathologists show a therapeutic effect of SQDH on real AKI (Figure 1B). HE stains of the groups also shows a protective role of SQDH against tissue damage in livers. Swelling, congestion, cell necrosis decrease with SQDH treatment (Figure 1C). I could observe tissue damage in the CIS-treated group, but it is milder in the group treated with SQDH. Histological scores assessed by two senior pathologists show a therapeutic effect of SQDH on liver injury (Figure 1C).

### SQDH promotes the activity of the PI3K/AKT signaling pathway in kidney and the p38/MAPK signaling pathway in liver

The phosphoinositide 3-kinase/serine-threonine kinase (PI3K/Akt) signaling pathway is upstream of Nrf2. Therefore, we investigate its activity after SQDH treatment. The phosphorylation levels of Akt in the CIS group is significantly decreased than that in the control group (Figure 2A). However, after SQDH treatment of CIS-injected rats, the phosphorylation levels of Akt are significantly higher than that of the untreated group (Figure 2A). These results suggest that SQDH can significantly promote the activity of the PI3K/Akt signaling pathway in CIS-injected rats. The p38 mitogen-activated protein kinase (p38/MAPK) signaling pathway is upstream of BCL2. Therefore, we investigate its activity after SQDH treatment. It significantly increases the phosphorylation levels of p38 in the CIS group is significantly than that in the control group (Figure 2B). However, after SQDH treatment of CIS-injected rats, the phosphorylation levels of p38

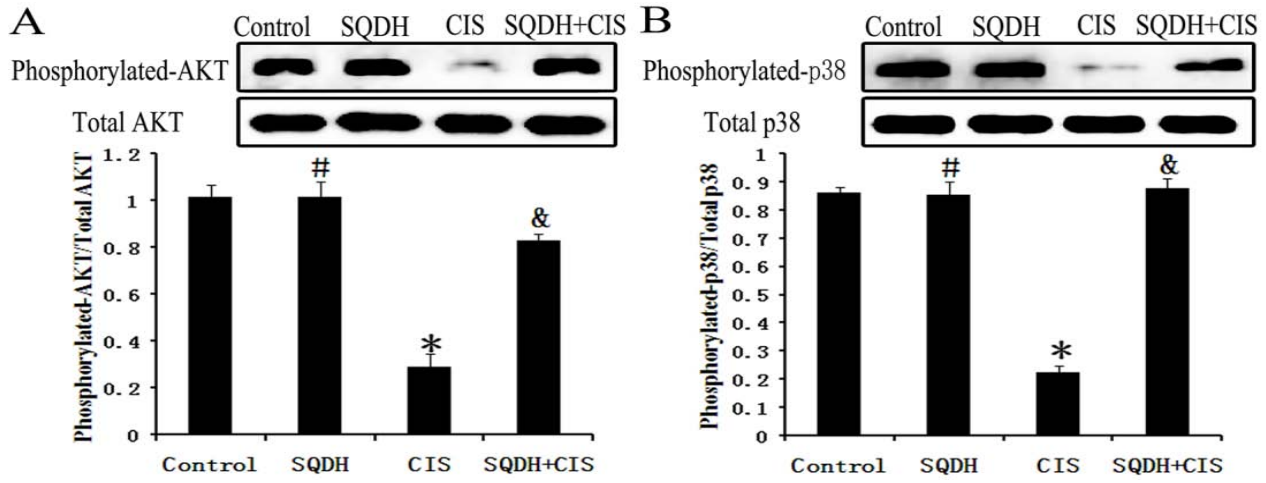


**Figure 2:** (A) SQDH significantly promoted the activity of PI3K/AKT pathway decreased in kidney. (B) SQDH significantly increased the activity of p38/MAPK pathway in liver (n=8 rat/group, values represent mean ± SD in the histograms. $^{\#}p > 0.05$ *vs.* control; $^{*}p < 0.01$ *vs.* control; $^{\&}p < 0.01$ *vs.* CIS).

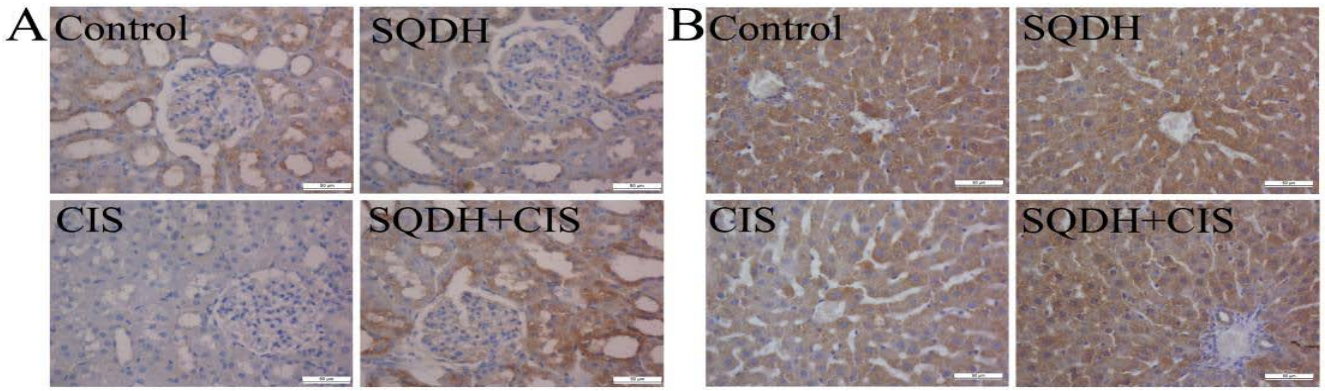


**Figure 3:** (A) Immunohistochemical analyses of Nrf2. Tissues in CIS group revealed significantly decreased expression of Nrf2 compared to control group. However, after SQDH treatment, expression level of Nrf2 is significantly increased compared with CIS group. (B) Immunohistochemical analyses of BCL2. Tissues in CIS group revealed significantly decreased expression of BCL2 compared to control group. However, after SQDH treatment, expression level of BCL2 is significantly increased compared with CIS group (n = 8 rat/group).

are significantly decreased than that of the untreated group (Figure 2B). These results suggest that SQDH can significantly suppress the activity of the p38/MAPK signaling pathway in CIS-injected rats.

### Evaluation of apoptosis

To determine the involvement of SQDH in intrinsic apoptosis, we probe the tissue sections of kidney and liver with antibodies specific for Nrf2 and BCL2, the expression levels are evaluated by immunohistochemistry (Figure 3). They also perform Western blot analysis is also to test the expression level of Nrf2, BCL2, Bax, caspase 3 and Caspase 9 (Figure 4 and 5). CIS group exhibited decreased expression of Nrf2 in kidney and BCL2 in liver, and increased expression of Bax, caspase 3 and caspase 9 both in kidney and liver. However, the expression of Nrf2 and BCL2 are increased in the CIS-injected group with SQDH treatment, whereas the expression of Bax, Caspase-3 and caspase 9 are reduced. Immunoblot analyses of these molecule proteins show the involvement of intrinsic apoptosis.

## Discussion

Despite its use as a chemotherapeutic agent, CIS exerts serious side effects involving tissues in several organs, including the kidneys and liver. The underlying mechanism of nephrotoxicity and hepatotoxicity induced by CIS remains incompletely understood.

Evidence of CIS-induced liver and kidney injury has been demonstrated by various studies [1,2,9-11]. Impaired kidney and liver functions are characterized by significant increases in serum BUN and creatinine levels with a concomitant reduction in calculated creatinine clearance values, and significant increases in serum ALT and AST levels compared with a control group. Histological evaluation of kidneys and livers reveal which is associated with pathologies, including significant nuclear pyknosis, cytoplasmic hyper-eosinophilia, loss of distinct cellular borders, hemorrhage in the CIS-treated group [12].

Apoptosis is a physiological process various factors can induce that and orchestrated through various cell death signaling pathways. In uncommon diseases, apoptosis can have different roles [13-15]. In this study, CIS induces excessive apoptosis in renal and hepatic tissues, and the apoptotic effect is reduced by treatment with SQDH. We have reported it that the anti-apoptotic protein Nrf2 and BCL2

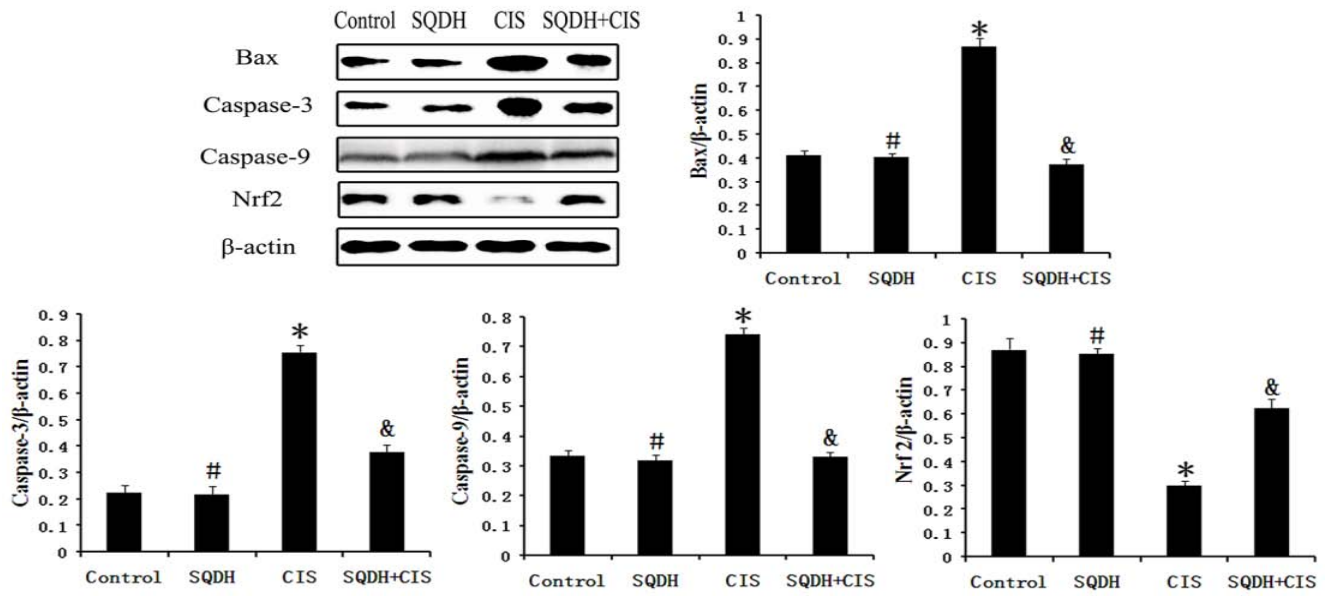


**Figure 4:** SQDH significantly reduces CIS-induced apoptosis in kidney (n=8 rat/group, values represent mean ± SD in the histograms. #p >0.05 *vs.* control; *p <0.01 *vs.* control; &p <0.01 *vs.* CIS).

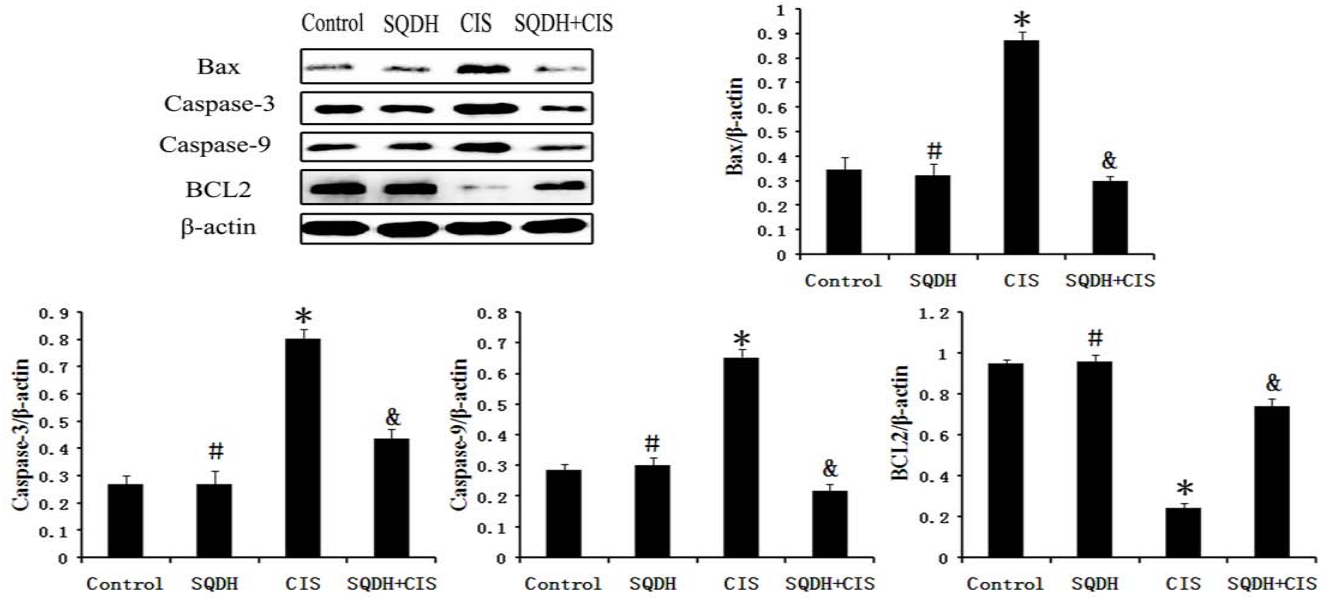


**Figure 5:** SQDH significantly reduces CIS-induced apoptosis in liver (n=8 rat/group, values represent mean ± SD in the histograms. #p >0.05 *vs.* control; *p <0.01 *vs.* control; &p <0.01 *vs.* CIS).

prevents abnormal apoptosis from causing damage to healthy tissues [16,17]. Amandla show the beneficial effects of Nrf2-activating agents on kidney injury [18]. Juanjuan Wu also reports that the activation of the PI3K/Akt signaling pathway could increase Nrf2 activity [19]. In this study, the expression of Nrf2 and the activity of the PI3K/Akt signaling pathway are significantly increased in SQDH-treated kidneys compared to those in untreated CIS-injured kidneys. It is also reported that activities MAPK and augmentative BCL2 promoting liver cell survival [20,21]. The expression of BCL2, in this study, is increased, and it significantly decreases the activity of the p38 in SQDH-treated livers compared to those in untreated CIS-injured lovers. In addition, the immunohistochemical expression levels of Nrf2 and BCL2 are both deceased in CIS-treated kidney and liver sections, and is increased upon treatment with SQDH. They have reported it that increased expression of Bax, caspase 3 and caspase 9 could induce apoptosis [22]. During cellular stress and extreme injury, such as during the injection of CIS, the increased expression levels of Bax, caspase 3 and caspase 9 lead to apoptotic cell death. In this study, the expression of Bax, caspase 3 and caspase 9 are significantly increased compared with the control groups. However, after treatment with

SQDH, the expression levels of Bax and caspase-3 in the rat kidneys and livers are both significantly decreased. Therefore, these results show that CIS induces cell apoptosis by decreasing the activity of the PI3K/Akt signaling pathway in kidney and increasing the activity of p38/MAPK pathway in livers, and then increasing the expression of Bax, caspase 3 and caspase 9 to trigger apoptosis. However, SQDH regulates excessive apoptosis, protecting the kidneys and liver from acute injury.

In summary, exposure of rats to CIS induce kidney and liver damage. The progression of apoptosis after CIS injection are mediated by multiple cell signaling factors. The most interesting and notable result is that distinct it involves mechanisms in CIS-induced nephrotoxicity and hepatotoxicity. SQDH increase the CIS-supersession expression of Nrf2 in kidney and BCL2 in liver, which both have a prominent role in anti-apoptosis process. The increased activity of PI3K/AKT signaling pathway in kidney and decreased activity of p38/MAPK pathway in liver after SQDH treatment show that SQDH regulates apoptosis, which is aberrant in CIS-induced tissues. The results the anti-apoptotic effect of ZWT in both kidney and liver. Therefore, it could be considered as a candidate drug to treat nephrotoxicity and hepatotoxicity induced by CIS.

## Conclusions

We conclude that SQDH protects against CIS-induced nephrotoxicity and hepatotoxicity, which is possibly associated with the activation of p38/MAPK in liver and PI3K/AKT in kidney.

## Declarations

**Ethics approval and consent to take part:** All animal experiments are approved by the ethics committee of Dalian Medical University and performed under the institutional guidelines.

**Author Contribution Statement:** Qi Liu, Lina Liang, Shouyu Hu and Shiying Li conceived and designed research. Shiying Li and Shouyu Hu conducted experiments. Qi Liu, Lina Liang contributed new reagents or analytical tools. Shiying Li and Shouyu Hu analyzed data. Qi Liu wrote the manuscript. All authors read and approved the manuscript.

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### References

1. Punithavathi R, Rania H, Riyaz M, et al. Histone deacetylase-mediated silencing of AMWAP expression contributes to cisplatin nephrotoxicity. KIDNEYINT. 2016; 2: 317-326.
2. Zeba F, Mohammad A, Sana R, et al. Oral administration of Nigella sativa oil ameliorates the effect of cisplatin on membrane enzymes, carbohydrate metabolism and oxidative damage in rat liver. Toxicology Reports. 2016; 3: 328-335.
3. Lee J, Yeganeh B, Ermini L, Post M. Sphingolipids as cell fate regulators in lung development and disease. Apoptosis. 2015; 20: 740-757.
4. Cam Ngoc Nguyen, Hye-Eun Kim, Seong-Gene Lee. Caffeoylserotonin Protects Human Keratinocyte HaCaT Cells against $H_2O_2$-Induced Oxidative Stress and Apoptosis through Upregulation of HO-1 Expression *via* Activation of the PI3K/Akt/Nrf2 Pathway. PHYTOTHER RES. 2013; 27: 1810-1818.
5. Shuyan Wang, Ping Ren, Xiaobo Li, et al. 17β-Estradiol Protects Dopaminergic Neurons in Organotypic Slice of Mesencephalon by MAPK-Mediated Activation of Anti-apoptosis Gene BCL2. J Mol Neurosci. 2011; 45: 236-245.
6. Chen H, Zhu Q, Tang X, et al. Effect of Shen-qi-di-huang decoction on reducing proteinuria by preserving nephrin in adriamycin-induced nephropathy rats. Afr J Tradit Complement Altern Med. 2011; 8: 467-476.
7. Ozkok Abdullah, Ravichandran Kameswaran, et al. NF-κB transcriptional inhibition ameliorates cisplatin-induced acute kidney injury (AKI). TOXICOLLETT. 2016; 240: 105-113.
8. Dora Catré MS, Joaquim S. Viana, António M. Cabrita, et al. Hydroxyethyl starch 130/0.4 attenuates early hepatic damage in ischemia/reperfusion injury. CAN J ANAESTH. 2014; 57: 439-445.
9. Yang M, Wang R, Sun J, et al. The liver X receptor agonist TO901317 protects mice against cisplatin-induced kidney injury. Exp Biol Med (Maywood). 2015; 240: 1717-1727.
10. Gizem Kursunluoglu, Hulya Ayar Kayali, Dilek Taskiran. The effect of cisplatin toxicity and capsaicin on electron transport chain in liver and kidney of sprague dawley rats. CELL BIOCHEM BIOPHY. 2014; 69: 707-716.
11. S Devaux, A Du Thanh, B Gallix, et al. Hepatic transarterial chemoembolization (HACE) with cisplatin in liver metastases from cutaneous melanoma: a prospective study of three patients. J Eur Acad Dermatol Venereol. 2013; 27: e261-e262.
12. Palipoch S, Punsawad C. Biochemical and histological study of rat liver and kidney injury induced by Cisplatin. J TOXICOL PATHOL. 2013; 26: 293-299.
13. Grazia Maria Virzì, Anna Clementi, Claudio Ronco. Cellular apoptosis in the cardiorenal axis. Heart Fail Rev. 2016; 21: 177-189.
14. Lebois M, Josefsson EC. Regulation of platelet lifespan by apoptosis. Platelets. 2016: 497-504.
15. Chang Seong Kim, Joon Seok Choi, Soo Yeon Joo, et al. Nicotine-Induced Apoptosis in Human Renal Proximal Tubular Epithelial Cells. PLoS One. 2016; 11: e0152591.
16. Susanne S, Iris B, Claudia G, et al. Inflammatory Macrophages Induce Nrf2 Transcription Factor-dependent Proteasome Activity in Colonic NCM460 Cells and Thereby Confer Anti-apoptotic Protection. J BIOL CHEM. 2011; 286: 40911-40921.
17. Akiko Iwata, R Angelo de Claro, Vicki L. Morgan-Stevenson, et al. Extracellular Administration of BCL2 Protein Reduces Apoptosis and Improves Survival in a Murine Model of Sepsis. PLoS One. 2011; 6: e14729.
18. Amandla AR, Xia W, Lauren MA, et al. Nrf2 activators as potential modulators of injury in human kidney cells. Toxicology Reports. 2016; 3: 153-159.
19. Juanjuan W, Devin W, Grant AW, et al. Estrogen increases Nrf2 activity through activation of the PI3K pathway in MCF-7 breast Cancer cells. Exp Cell Res. 2014; 328: 351-360.
20. Hany A. Omar, Wafaa R. Mohamed, Hany H. Arab, et al. Tangeretin Alleviates Cisplatin-Induced Acute Hepatic Injury in Rats: Targeting MAPKs and Apoptosis. PLoS One. 2016; 11: e0151649.
21. Panigrahi GK, Yadav A, Srivastav A, et al. Mechanism of Rhein induced apoptosis in rat primary hepatocytes: beneficial effect of Cyclosporine A. CHEM RES TOXICOL. 2015; 28: 1133-1143.
22. Qi Liu, Tianlei Si, Xiaoyun Xu, et al. Electromagnetic radiation at 900MHz induces sperm apoptosis through bcl-2, bax and caspase-3 signaling pathways in rats. REPROD HEALTH. 2015; 12: 65.