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Oral Intake of Pomegranate Peels Extract Stimulate Glutathione Levels and Superoxide Dismutase Activity to Protect Against Cisplatin-Induced Nephrotoxicity

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Abstract

Cisplatin (CP) mediates the excessive generation of reactive oxygen species (ROS), and subsequently causes organ dysfunction; mainly in the kidney. Therefore the aim of this study is to test the ability of pomegranate peel methanol extract (PPME) to stimulate superoxide dismutase (SOD) activity and reduced glutathione (GSH) levels to protect against CP-induced nephrotoxicity. SOD activity and GSH level were colorimetrically evaluated in kidney tissue homogenate. Serum creatinine (Cr) and blood urea nitrogen (BUN) were also estimated. The results of this study showed that CP elevated both Cr and BUN levels. These were pathologically confirmed using histopathological examinations. On the other hand, oral intake of PPME significantly reduces these kidney markers. These may be due the successful enhancement in the SOD activity and GSH level. Again, the decrease in serum Cr, and BUN confirms this reparative effect of the oral intake of PPME. Thus it can be used to partially protect against CP-induced nephrotoxicity; at least in part, in rats..

Keywords: Cisplatin, Glutathione, Nephrotoxicity, Superoxide Dismutase, Pomegranate.

Introduction

CP is a potent antitumor and immune suppressive drug after organ implantation; including kidney. But CP has limited use in clinical practice as it is an AKI inducer despite the lack of even one of these co-morbidities, aging, and/or kidney conditions that already existed **(Fu *et al.*, 2019)**.

Nephrotoxicity is a diversified disease, characterized by a fundamental decline in glomerular filtration rate (GFR) leading to the preservation of metabolic wastes like Cr and BUN, in addition to deregulation of electrolytes, fluid, and acid-base balance **(Mortada *et al.*, 2023)**. Moreover, fast deterioration of kidney excretory systems, which enhances the buildup of waste materials caused by protein metabolism may also participate in CP-induced

nephrotoxicity **(McSweeney *et al.*, 2021)**.

Reactive oxygen species (ROS) and free radicals are frequent words used to describe the pathophysiology of many serious illnesses, including cancer, diabetes, hepatotoxicity, nephrotoxicity, osteoarthritis and many more **(Sacan *et al.*, 2021)**. An antioxidant enzyme called superoxide dismutase (SOD) is essential for physiological defense mechanisms in animals and plants against free radicals and reactive oxygen species (ROS). The addition of SOD from plants to the diet of mammals is a novel strategy for enhancing health and preventing pathological diseases **(Stephenie *et al.*, 2020)**.

The most prevalent thiol in cells, glutathione (GSH, -glutamyl-cysteinyl-glycine), is essential for many cellular processes, particularly those that control the redox state of live cells. Additionally, GSH protects cells by scavenging free radicals and acting as an antioxidant **(Aziz *et al.*, 2019)**. Therefore, it is recognized that GSH is essential for maintaining redox homeostasis, which entails the inter conversion of reduced sulfhydryl (GSH) into oxidized disulfide (GSSG) forms, in order to limit oxidative stress **(Dumont and Rivoal 2019)**.

The heavy burden of such condition should be avoided by taking all preventive measures because severe nephrotoxicity is linked to a high mortality risk **(Koza 2016)**. One of the strategies is making use of some natural plant extracts. In the current research, PPME was the choice. Pomegranate (*Punica granatum L*; POM), is an ancient fruit and one of the Lythraceae family and has been used, for a long history, as medicinal remedy. It has a great content of polyphenolic chemicals including anthocyanins, punicalagin, ellagic and gallic acids**(Cheng *et al.*, 2023)**.

Via suppressing the oxidative stress (OS), it was previously demonstrated that POM ameliorate nephrotoxicity in rats. The close relation between renal diseases mechanisms and protection gained by POM indicates that POM may be helpful in kidney protection against different renal diseases **(Makled *et al.*, 2021)**. This research sought to explore if PPME have the ability to stimulate the SOD activity and GSH level to protect against CP-induced nephrotoxicity or not.

Methods

Experimental design

This study included 24 Sprague Dawley rats. They were divided into 3 experimental groups. The negative control group (8 rats) received normal laboratory diet. The CP group (8 rats) which received a single intraperitoneal dose (4 mg/kg) of CP. The protection group (8 rats) they received PPME (200 mg/kg b.wt) for 4 days before administration of CP. They were also continually received this dose daily until the scarification day (at day 14).

Pomegranate peel extract preparation

POM peels were separated, dried by air, and powdered then mixed with methanol in a ratio of 1:4 (W/V) at 30°C for 1h. The mixture was left for 48 hrs the in refrigerator. Then, it was filtered and concentrated under vacuum at 40–50°C. After that, it was stored at 3- 4°C until its use **(Elwakf *et al.*, 2018).**

Samples collection

After all animals had been fasted for 12 hours, they were sacrificed. Blood samples were collected. Centrifuged and serum was separated. Half of the kidneys were removed and washed with saline solution (NaCl, 0.9 gm %). Then they were homogenized and used to estimate the SOD activity and GSH levels. For histopathological analyses, the second portion was rapidly placed in a container with neutral buffered formalin 10% for 24 hours and they were used for pathological confirmation of CP.

Estimation of antioxidant markers

Renal antioxidant markers in tissue homogenates; namely SOD and GSH were measured by colorimetrically assay kits (Bio-Diagnostics, Dokki, Giza, Egypt) according to their manufacturer instructions. SOD activity is defined in international units (U/g tissue).

Determination of kidney function tests

Serum Cr was colorimetrically determined by SPINREACT (Spain) as directed by the manufacturer. The estimation of BUN was done by BioMed-Urea, Enzymatic, Colorimetric Reagent Kit (Cairo, Egypt).

Histopathological analyses

After kidney tissues being cleaned, the

specimens were imbedded in paraffin and heated in a hot air oven for 24 hours at 56 degrees Celsius. They were then placed onto glass slides after being cutted into sections by a microtome at a thickness of 4 microns for the preparation of paraffin bees wax tissue blocks. The slides were then fixed using successively diluted alcohol. Then the tissues were dehydrate. The tissue sections were then deparaffinized and stained with hematoxylin and eosin (H&E) stains for histopathological analysis under a standard light microscope.

Statistical analyses

In this study, results were expressed as Mean ± standard error (SE) of the mean. Data were anatomized by one way analysis of variance (ANOVA) using the Statistical Package for the Social Sciences (SPSS) programme, version 17. The least significant difference (LSD) was used to compare significancy among groups. The difference was considered significant when P-value was < 0.05.

Results

1. Activity of SOD and GSH level

1.1. Activity of SOD and GSH level in control group

The data in **Table 1** represented the mean SOD activity and GSH levels in tissues of the control group. The mean SOD activity was 14±0.6 U/g.tissue while the mean GSH level was 75.2±2.8 mg/g.tissue.

1.2. Effect of CP on activity of SOD and GSH level in CP group

The SOD mean activity in CP-intoxicated rats was 7.2±0.3 U/g.tissue while the mean GSH level was 38.9±1.5 mg/g.tissue. The data illustrates that CP-exposed animals demonstrated significant decrease in GSH and SOD levels compared to the control group as shown in **Table 1.**

1.3. Effect of PPME on activity of SOD and GSH level in protection group

Data in **Table 1** shows that the SOD mean activity in the protected rats was 12.3±0.5 U/g.tissue while the mean GSH level was 63.6±2 mg/g.tissue. It is clear that the administration of PPME before CP-injection displayed adverse manner, in which high significant increases in both SOD activity and GSH levels were presented in protected animals compared to CP group.

Table 2. Values of serum Cr and BUN of the studied studied groups before and after PPME intake

	Control	CP-induction group	PPME Protection
SOD (U/g.tissue)	14±0.6	7.2±0.3	12.3±0.5
p values		p1<0.0001 p2<0.0001	p1<0.0001 p3<0.0001
GSH (mg/g.tissue)	75.2±2.8	38.9±1.5	63.6±2
p values		p1<0.0001 p2<0.0001	p1<0.0001 p3<0.0001

CP= cisplatin PPME= pomegranate peel methanol extract SOD= superoxide dismutase GSH= glutathione"**p1**" means relative to negative control groups, "**p2**" means comparison between CP and control groups, "**p3**" means comparison between PPME protection group and CP group, results are statistically **significant** if p <0.05 and **highly** statistically **significant** if p<0.001 & p<0.0001.

2. Serum Cr and BUN

2.1. Serum Cr and BUN in control group

The data in **Table 2** represented the mean ± standard deviation of serum Cr and BUN levels of the control group. The mean of serum Cr was 0.49±0.1 mg/dl while the mean of BUN was 723.8±3.8 mg/dl.

2.2. Effect of CP on Cr and BUN levels in CP group

The Cr mean value in the CP-intoxicated rats was 1.1±0.2 mg/dl while the mean value of the BUN was 45.9±7.5 mg/dl. The data illustrates that CP-exposed animals demonstrated significant increase in Cr and BUN levels compared to the control group as shown in **Table 2.**

2.3. Effect of PPME on Cr and BUN level in protection group

Data in **Table 2** shows that the serum Cr in the protected rats was 0.9±0.4 mg/dl while the mean value of the BUN was 40.6±3.8 mg/dl. It was noticed that PPME administration tended to protect the kidney from the pathogenic effect of CP compared to CP-induced nephrotoxicity rats even if it did not reach the complete nephrotic healing.

3. Correlations

Based on the correlation coefficients data which were presented in **Table 3** and **Figures 1-3,** one can conclude the following:

3.1. Correlations between SOD activity and GSH levels

Positive but not significant correlation was

found between SOD mean activity and GSH mean levels in all study groups (control group: r =0.16, P=0.71, CP group: r = 0.003, p=0.99, protection group: r =0.15, p=0.72).

Table 2. Values of SOD and GSH in tissue of the groups before and after PPME intake.

	Control	CP-induction group	PPME Protection
Cr (mg/dl)	0.49± 0.1	1.1±0.2	0.9±0.4
p values		p1<0.014 p2<0.001	p3<0.0001
BUN(mg/dl)	23.8±3.8	45.9±7.5	40.6±3.8
p values		p1<0.001 p2<0.0001	p1<0.021 p3<0.0001

CP= cisplatin PPME= pomegranate peel methanol extract Cr= Creatinine BUN= Blood urea nitrogen "**p1**" means relative to negative control groups, "**p2**" means comparison between CP and control groups "**p3**" means comparison between PPME protection group and CP group. Results are statistically **significant** if p <0.05 and **highly** statistically **significant** if p<0.001 & p<0.0001.

3.2. Correlations between SOD activity and Cr levels

The SOD mean activity correlate negatively but non-significantly with Cr mean levels in all rat groups (control group: r = -0.35, P=0.2, CP group: r = -0.14, p=0.17, protection group: r = -0.54, p=0.33).

3.3. Correlations between SOD activity and BUN levels

The data represents that there is a strong negative but non-significant correlation between SOD mean activity and BUN mean levels in both control and CP groups (control group: r = -0.51, P=0.39, CP group: r = -0.54, p=0.74). Also, a weak negative and non-significant correlation between SOD mean activity and BUN mean levels in PPME protection group (r = -0.39, p=0.16).

3.4. Correlations between GSH and Cr levels

A weak negative but non-significant correlation was found between GSH and Cr mean levels in all study groups (control group: r = -0.38, P=0.22, CP group: r = -0.26, p=0.79, protection group: r = -0.47, p=0.21).

3.4. Correlations between GSH and BUN levels

Also, a weak negative but non-significant correlation was found between GSH and BUN mean levels in all study groups (control group: r = -0.48, P=0.36, CP group: r = -0.11, p=0.54, protection group: r = -0.49, p=0.24).

3.4. Correlations between Cr and BUN levels

Conversely, a strong positive and highly significant correlation was found between Cr and BUN mean levels in all study groups (control group: r = 0.92, P=0.001, CP group: r = 0.66, p=0.07, protection group: r = 0.89, p=0.003).

Table 3: Correlation coefficient and P values between SOD, GSH, Cr, and BUN in all study groups

		Control		CP-induction group		PPME Protection	
		r value	p value	r value	p value	r value	p value
SOD GSH	/	0.16	0.71	0.003	0.99	0.15	0.72
SOD Cr	/	-0.35	0.2	-0.14	0.17	-0.54*	0.33
SOD BUN	/	-0.51*	0.39	-0.54*	0.74	-0.39	0.16
GSH Cr	/	-0.38	0.22	-0.26	0.79	-0.47	0.21
GSH BUN	/	-0.48	0.36	-0.11	0.54	-0.49	0.24
Cr BUN	/	0.92*	0.001*	0.66*	0.07	0.89*	0.003*

CP= cisplatin, PPME= pomegranate peel methanol extract, SOD= superoxide dismutase GSH= glutathione Cr=creatinie BUN= blood urea nitrogen. The values range from -1 to 1, where 1 represents a strong positive correlation, -1 represents a strong negative correlation, and 0 indicates no linear correlation. Results are statistically **significant** if p <0.05. The sign * means significance.

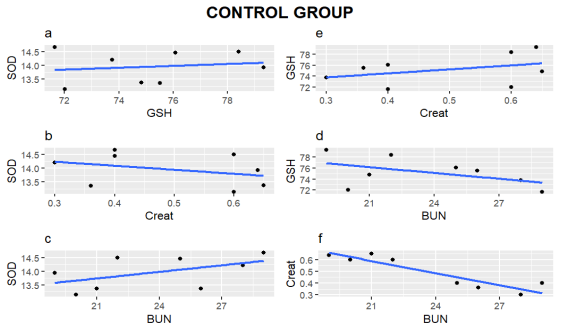

Figure 1: Correlation coefficient between SOD, GSH, Cr, and BUN in the control group
(a= SOD and GSH, b= SOD and Cr, c= SOD and BUN, d= GSH and Cr, e= GSH and BUN, f= Cr and BUN)

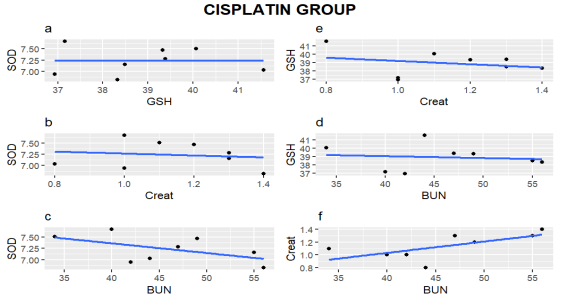

Figure 2: Correlation coefficient between SOD, GSH, Cr, and BUN in the CP-induction group
(a= SOD and GSH, b= SOD and Cr, c= SOD and BUN, d= GSH and Cr, e= GSH and BUN, f= Cr and BUN)

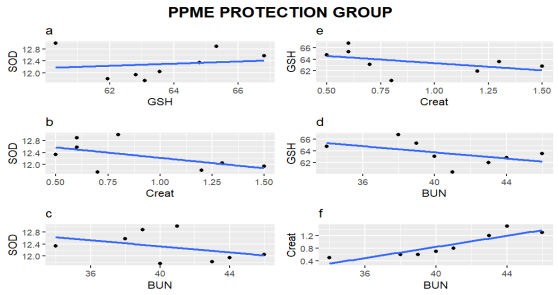

Figure 3: Correlation coefficient between SOD, GSH, Cr, and BUN in PPME protection group
(a= SOD and GSH, b= SOD and Cr, c= SOD and BUN, d= GSH and Cr, e= GSH and BUN, f= Cr and BUN)

Histopathological investigations

H&E examination of the medulla and cortex adrenal tissues

Kidney slices stained with H&E were collected from the control group for microscopic analysis (**Figure 4**) did not reveal any histopathological alterations.

On the other hand, at day 14 CP rats (**Figure 5**) showed severity in tubular dilation in cortical and also medullary parts of the kidney. Also, marked epithelial swelling and interstitial fibrosis was found in the cortex as well as tubular necrosis in the medulla which confirm CP toxicity.

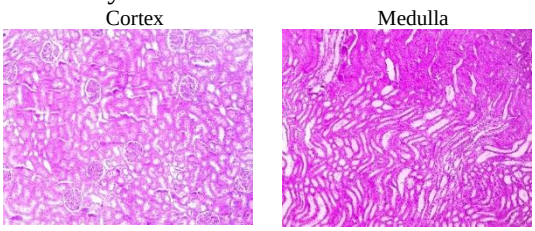

Figure 4: Microscopic pictures of H&E stained renal sections showing normal cortex and medulla in the control group from rats sacrificed at day 14. Low magnification X: 100 bar 100.

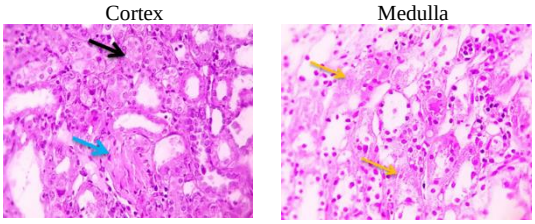

Figure 5: Microscopic pictures of H&E stained renal sections from the CP group on day 14 showing diffuse marked epithelial swelling (black arrows), and interstitial fibrosis (blue arrow) in the cortex.Tubular necrosis (orange arrows) in the medulla. Low magnification X: 100 bar 100.

Discussion:

Treatment with CP is frequently associated with cellular toxicity to various tissues including kidney pathophysiological alterations and dysfunction. The pathophysiology of the kidney induced by CP was attributed to the activation of both oxidative and endoplasmic reticulum stress which causes cellular damage via inflammation **(McSweeney *et al.*, 2021)**. Thus, the main goal of our research was to determine whether PPME can stimulate SOD activity and GSH level to reduce CP-induced nephrotoxicity in rats or not.

Renal dysfunction in CP-treated animals might be secondary to the oxidative tissue-damaging effect of this drug **(Taghizadeh *et al.*, 2020)**. Regarding our results, diminition in the activity of SOD and the reduction in GSH levels in CP-treated adult male rats confirmed the oxidative damage.

Our findings are consistent with previously published studies. In one of these, **(Aladaileh *et al.*, 2021)** observed significant decreases in the activity of the antioxidant enzyme, SOD, as well as GSH level in the kidney of rats after treatment with CP. Similar results have been reported in the kidneys of BALB/c mice following treatment with CP **(Zhang *et al.*, 2020)**.

Both SOD (an enzymatic antioxidant) and GSH (a non-enzymatic antioxidant) can stabilize the cells' redox state, as a result, they can play an important part in the defense mechanism against free radicals and reactive molecules-induced cell injury **(Jena *et al.*, 2023)**.This is because GSH acts as a reducing agent for oxidant molecules **(Ali *et al.*, 2020)**. SOD can also stimulate the superoxide radicals disputing ($O2^{\cdot-}$) into hydrogen peroxide(H_2O_2) **(Sachdev *et al.*, 2021)**. Consequently, a drop in both cellular GSH content and SOD activity in the kidney tissue of rats treated with CP can lead to an imbalance between cellular redox state and free radicals production which eventually lead to oxidative stress.

The increase in Cr and BUN values after CP intake vs the control group, in this study, confirmed the CP-nephrotoxic effect as presented in **Table2**. Also, the results of previous studies confirm the kidney damage after CP-induction; including **Chen *et al.*, 2020**.

In our experiment, oral administration of PPME repressed oxidative stress via stimulating SOD enzyme activity as well as elevating GSH content in the kidney tissue of the CP-treated rats. This result may lead one to conclude that POM may participate in renal function

enhancement via an-antioxidant mediated mechanism. A somewhat similar results were obtained by **Alkuraishy *et al.*, 2019** who observed that POM protects Sprague–Dawley male rats against oxidative damage induced by gentamicin-induced nephrotoxicity. The antioxidant properties and free radical scavenging activity of PPME could be due to its contents of flavonoid, phenolic, and hydrolysable tannins contents **(Kaderides *et al.*, 2021)**.

Ingestion of PPME before CP toxicity was found to cause a reduction in serum BUN and Cr when compared to the CP group as presented in **Table 2**. This result is consistent with the findings obtained by **Emam *et al.*, 2020** who emphasized that pomegranate peel extract (PPE) significantly suppressed BUN and Cr levels in the serum but in carbon tetrachloride-induced nephrotoxicity in adult male albino mice.

Regarding histopathological examinations, H&E sections exhibited that administration of CP in male rats induced renal tissue damage, as manifested by degenerative changes through morphological observation including glomerular degeneration, tubular dilation with degenerative changes interstitial edema and fibrosis, perivascular hemorrhage, perivascular and interstitial mononuclear cells infiltration. Further, marked tubular dilation with hydropic degenerative changes and cast formation in the outer medulla, in addition to apoptosis, tubular necrosis, and the majority of the tubular epithelial cells shed. Tubular dilation with degenerative changes and cast formation plus congested capillaries were found in the inner medulla.

Necrotic tubules and inflammatory cell infiltration of the interstices are further acute renal damage alterations. Obtained histopathological changes in the kidney which showed marked signs of tissue defects seems to be secondary to the induction of oxidative stress following injection with CP in adult male rats. Present histopathological findings as shown in **Figure 5** are in harmony with the outcomes of several prior research; including **Fang *et al.*, 2021** who reported that CP caused several histopathological alterations in the renal tissue of nephrotoxic patients leading to renal tubular dysfunction being compromised, leading to renal failure as well as kidney vascular injury.

Conclusion:

PPME oral intake can be used to protect against CP-induced nephrotoxicity in rats.

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الملخص العربي

عنوان البحث: قشر الرمان يحفز نشاط السوبر أكسيد ديسموتاز ومستوي الجلوتاثيون للحماية من سمية السيسبلاتين على الكلي

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وجد ان السيسبلاتين(CP) يحفز انتاج الشقوق الحرة(ROS) و بالتالي قصور في وظائف الاعضاء، بما في ذلك الكلي و لذلك كان هدف هذه الدراسة هو اختبار قدرة مستخلص قشر الرمان (PPME) علي تنشيط انزيم السوبر أكسيد ديسموتاز (SOD) و رفع مستوي الجلوتاثيون (GSH) المختزل لحماية الكلي من سمية السيسبلاتين. تعتبر هذه بمثابة خط الدفاع الأولي ضد ضرر الجذور الحرة للجزيئات الحيوية المهمة. تم تقدير نشاط انزيم السوبر أكسيد ديسموتاز وكذلك مستوي الجلوتاثيون المختزل بالطريقة اللونية في مطحون انسجة الكلي. اضف الي ذلك انه تم تقدير مستوي الكرياتينين (Cr) و نيتروجين اليوريا (BUN) في الدم.أظهرتالنتائج ان تناول مستخلص قشر الرمان عن طريق الفم ناجحًا في زيادة نشاط انزيم السوبر أكسيد ديسموتاز ورفع مستوي الجلوتاثيون المختزل و ربما يكون لهذين الارتفاعين دورا رئيسيا في تحسين ما تركه عقار السيسبلاتين من سمية بالكلي و مما يؤكد ذلك هو تحسن في مستوي الكرياتينين و نيتروجين اليوريا في الدم. ان تناول مستخلص قشر الرمان (او ربما القشر نفسه) يحمي ضد سمية السيسبلاتين في الكلي.