DOI: https://doi.org/10.31351/vol32iss2pp112-119

Protective Effect of Cranberry Extract against Cisplatin-Induced Nephrotoxicity by Improving Oxidative Stress in Mice

Baidaa Ibrahim Mohammed[*,1] and Nada N. Al-Shawi[2]

[1]Ministry of Health and Environment, Diyala Health Directorate, Diyala, Iraq
[2]Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq

Abstract

Cranberry (Vaccinium macrocarpon) is a North American natural fruit. consumed as food and used for health promotion and prevention of various diseases. The present study was designed to evaluate the protective effect of cranberry fruit extract against nephrotoxicity induced by cisplatin in mice by measuring selected oxidative stress markers. Twenty-eight male albino mice were used in this study. The animals were divided into 4 groups as follows: **Group I** Control/Orally-administered normal saline for 7 successive days; **Group II** [Orally-administered cranberry fruit extract alone (200 mg/kg) for 7 successive days; **Group III**/Mice were orally-administered 0.25ml (0.9% NaCl) for 7 days by gavage tube, and cisplatin at a dose (12mg/kg) were intraperitoneally (IP) injected on day 7 and; **Group IV** [Orally-administered cranberry fruits extract for 7 successive days followed by single IP injection of cisplatin on day 7. After euthanization of each animal by diethyl ether (on day 8th), serum and renal tissue samples were collected for analysis; where the serum was used for assessing urea and creatinine and the renal tissue samples for determining oxidative stress markers (malondialdehyde and reduced glutathione). Administration of cranberry fruit extract resulted in a significant decline in serum creatinine level (0.87±0.120) and a significant elevation in renal reduced glutathione level (197.42±62.958) (P<0.05) with the improvement in the histological analysis of renal tissue of mice of **Group IV** compared to that in cisplatin intraperitoneally-injected **Group III** mice. Orally-administrated cranberry extract prior to cisplatin exerts a protective effect against nephrotoxicity induced by cisplatin via improving the oxidative stress process in mice.

Keywords: Nephrotoxicity, Oxidative stress, Cranberry, Cisplatin

التأثير الوقائي لمستخلص التوت البري ضد السمية الكلوية التي يسببها سيسبلاتين عن طريق تحسين الإجهاد التأكسدي في الفئران

بيداء ابراهيم محمد*[١] و ندى ناجي الشاوي[٢]

[١]وزارة الصحة والبيئة ، دائرة صحة ديالى،ديالى ، العراق
[٢] فرع الأدوية والسموم ، كلية الصيدلة ،جامعة بغداد ،بغداد، العراق

الخلاصة

التوت البري هو فاكهة طبيعية في أمريكا الشمالية يتم تناولها كغذاء وتستخدم لتعزيز الصحة والوقاية من الأمراض المختلفة.الهدف:صُممت هذه الدراسة لتقييم التأثير الوقائي لمستخلص فاكهة التوت البري على السمية الكلوية التي يسببها السيسبلاتين في الفئران عن طريق قياس علامات مختارة من الإجهاد التأكسدي.الطرق: تم استخدام ثمانية وعشرين من ذكور الفئران البيضاء في هذه الدراسة. حيث تم تقسيم الحيوانات إلى ٤ مجموعات على النحو التالي: المجموعة الأولى [التحكم السلبي] / تم أعطائها محلول ملحي طبيعي فموياً لمدة٧ أيام متتالية. المجموعة الثانية / مستخلص فاكهة التوت البري الفموي فقط (٢٠٠ ملغم / كغم) لمدة ٧ أيام متتالية. المجموعة الثالثة / تم حقن فئران هذه المجموعة بحقنة من السيزبلاتين داخل الصفاق (١٢ ملغم / كغم) في اليوم٧. المجموعة الرابعة / تم أعطائها مستخلص فاكهة التوت البري عن طريق الفم لمدة ٧ أيام متتالية متبوعًا بحقنة منفردة من السيسبلاتين داخل الصفاق في اليوم٧.وبعد القتل الرحيم لكل حيوان عن طريق اثيل الايثر في اليوم الثامن ، تم جمع عينات من المصل وأنسجة الكلي لتحليلها. النتائج. أدى تناول مستخلص فاكهة التوت البري إلى انخفاض كبير في مستوى الكرياتينين في المصل (٠,٨٧ ± ٠,١٢٠) وأرتفاع كبير في مستوى الجلوتاثيون الكلوي المنخفض (١٩٧,٤٢ ± ٦٢,٩٥٨)، مع تحسن التحليل النسيجي لأنسجة الكلى في الفئران من المجموعة الرابعة مقارنة بالمجموعة الثالثة من الفئران المحقونة داخل الصفاق بالسيسبلاتين. الاستنتاجات.أظهر مستخلص التوت البري الذي تم أعطائه عن طريق الفم قبل السيسبلاتين تأثيرًا وقائيًا ضد السمية الكلوية التي يسببها السيسبلاتين عن طريق تحسين عملية الإجهاد التأكسدي في الفئران.

الكلمات المفتاحية: السمية الكلوية ، الاكسدة ، التوت البري ، سيسبلاتين .

Introduction

Acute kidney injury (AKI) is defined as a sudden and reversible reduction in renal function or glomerular filtration rate (GFR) within a few hours to days after organ failure; this can cause retention of nitrogenous waste products, leading to a rapid increase in serum (or plasma) creatinine concentration(sCr) or blood/serum urea Nitrogen (BUN), and/or a decrease in urine output (oliguria) ([1]). Many important medications have been reported to behave as exogenous toxins and cause AKI, leading to acute tubular necrosis that limits their clinical usefulness. Among these agents is cisplatin (CP) [(2)], which is one of the platinum – containing antineoplastic drugs, and it is

[1]Corresponding author E-mail: ph.baidaaibrahem@gmail.com
Received: 20/7 /2022
Accepted: 21/9 /2022

extensively used to treat a variety of cancers perse or in combination with other drugs [3]. Despite its powerful anticancer properties and effectiveness, the clinical use of CP is restricted due to the severity of side effects, especially its dose-limiting factor (nephrotoxicity) [4], which can result from the preferential accumulation of such drugs in the renal tubules due to unbalanced absorption and outflow by protein transporters [5].

Oxidative stress is a redox imbalance that results in the production of reactive oxygen species (ROSs) as a part of the pathogenesis of cisplatin. Moreover, CP is also known to interfere with the mitochondrial electron transport pathway and thus. enhance the formation of (ROSs) (6). However, the excessive production of reactive oxygen species (ROSs) and decline in antioxidants such as reduced glutathione (GSH) and superoxide dismutase (SOD) enzyme contributed to kidney pathological damage, which in turn leads to oxidative stress (OS), mitochondrial dysfunction, and activation of the apoptotic pathway [7].

Cranberries, a fruit that originated in New England and is now grown throughout the East and Northeast regions of the United States and parts of Canada, were used by Native Americans to treat urinary tract infections (UTIs)and ingested as a food, as well as to treat wounds and blood poisoning [8] and to maintain the digestive system [9].

The berry is also considered unique among fruits due to its high concentration of vitamins, minerals, and polyphenolic substances such as flavonols, anthocyanins, proanthocyanidins (PACs), and others [10]; and it has a high potential for health promotion and prevention of chronic diseases [11].

In spite of the fact that no studies have yet tested the effects of cranberry supplementation in CKD patients, based on studies that were discussed in this research, there are reasons to hope that cranberries may have positive metabolic effects, reducing oxidative stress, and inflammation in CKD patients, especially where nowadays there is a great interest in identifying the potential benefits of medicinal plants, including cranberry. Therefore, this study was designed to be a novel work to evaluate the protective effect of cranberry fruit extract against cisplatin-induced nephrotoxicity via (OS) in mice.

Materials and Methods

Chemicals and kits

Chemicals utilized in this study included: Cranberry pure powder of the fruit extract from Hangzhou Hyper Chemicals Limited (China) [where a solution was prepared by dissolving it in distilled water and to be orally-administered to mice according to their weights]; Cisplatin (50mg/50ml) injectable solution from Accord Healthcare (Ireland); Diethyl ether liquid 98% from May and Baker (England); Reduced glutathione (GSH) and Malondialdehyde (MDA) Elisa kits from Bioassay Laboratory Technology (China); Urea kit/Linear Chemicals (Spain); Creatinine (Cr) kit Biolabo SAS (France); Formaldehyde solution 37% from Sinopharm chemical reagent Co., Ltd (China); Phosphate-buffered saline (FBS) from EuroClone Milan (Italy).

Laboratory animals and the experimental protocol

Twenty-eight (28) male Albino mice were used in this experiment they were provided from The Animal House at College of the Pharmacy/University of Baghdad. Their average weight was (25-30gm) and was kept at standard conditions of temperature (23–25°C) day/night cycle, they had unrestricted access to standard food (pellets) and water (*ad libitum*). This study was approved by The Ethical Committee of the Department of Pharmacology, and Toxicology, and the Scientific Committee of the College of the Pharmacy, University of Baghdad. The male mice used in the experiment were divided into 4 groups (7mice/group and each was kept in a separate plastic cage) as follows:

Group I (negative control)/ Orally-administered 0.25ml of 0.9% normal saline (NS) (NaCl) by gavage tube for 7 days [12].

Group II [Cranberry (CB)]/ Orally-administered cranberry (CB) fruit extract solution (200mg/kg/day) by gavage tube for 7 days [13].

Group III [(Cisplatin CP)]/ Orally-administered 0.25ml (0.9%NaCl) for 7 days by gavage tube followed by a single IP injection of cisplatin (12mg/kg B.W) on day 7 was given [14].

Group IV [Cranberry (CB)–Cisplatin (CP)]/Oral CB fruit extract solution (200mg/kg B.W) was given by gavage tube for 7 days, and a single dose of cisplatin (12 mg/kg B.W.) was injected intraperitoneally (IP) on day 7.

Samples collection and preparation of kidney tissue homogenate

Blood samples

Twenty-four (24) hours after the treatment period had ended (i.e., on day 8), the mice in each group were euthanized under diethyl ether anesthesia; and nearly 0.5-1.5ml of blood was obtained from each mouse by the retro-orbital route. The blood was sat in the Eppendorf tube and let to completely coagulate for 30 min at room temperature, then centrifuged in a cold centrifuge at 3000rpm for 20min at 4°C.

The serum then was collected and frozen at −20°C for analysis of the markers of renal function [Urea and Cr levels] [15].

Preparation of renal samples

At the end of the experiment period, each animal's group was sacrificed by (cervical

dislocation) under diethyl ether anesthesia and the abdomen was opened, then both kidneys were removed and rinsed in phosphate-buffered saline (PBS) to remove excess blood and other debris and were subdivided into two parts:

Part one was used for histopathological analysis. **Part two** was diced into little pieces, and each 100mg of tissue was placed in an Eppendorf tube containing 0.9ml of chilled PBS.

The Eppendorf containing the tissue and PBS was placed in an ice-containing beaker to keep it cold, then homogenized for 1 minute using a tissue homogenizer (Success, Techine industrial, Malaysia).

The tissue homogenate was then centrifuged at 4°C for 20 minutes at 3000 rpm in a refrigerated centrifuge.

The supernatant (serum) was extracted using a micropipette and stored at -20°C to be used for determining the indicators of OS [MDA, and GSH levels] [16-18].

Biochemical analysis

Biomarkers of kidney function [serum levels of urea and creatinine (Cr)] were determined through the utilization of commercial kits according to manufacturer guidelines [19,20]. Moreover, markers of OS (MDA and GSH), were quantified in the renal tissue homogenate *via* a sandwich enzyme-linked immunosorbent (ELISA) technique according to the kit manufacturer's instructions [21, 22].

Histopathological examination of the mice's kidney

At the end of the experiment (on day 8th), all the animals were sacrificed, and one kidney from each mouse was immediately-excised and fixed in a 10% formaldehyde solution for histological study using the paraffin sections technique as described by Junqueira LC. et al. (1995). Fixative tissues were paraffin-embedded, sectioned at 5µm thickness, and stained with hematoxylin and eosin(H&E) for light microscopy examination [23]; and the examination of renal histopathological parameters was done by the histopathologist Dr. Salem Rasheed Al-Obaidi; where parameters including cellular vacuolization and cellular architecture in the renal tubules.

The degree of renal tubular necrosis was evaluated using a semiquantitative scale, with 0 representing no necrosis, 1 representing 10%, 2 representing 10% to 25%, 3 representing 25% to 75%, and 4 representing more than 75% [24].

Statistical Analysis

All results were expressed as the values of mean ± standard deviation (SD). A computerized application from the Statistical Package for the Social Sciences (SPSS) was used to examine the data (version 25). A one-way analysis of variance was utilized to examine the statistical significance of differences between groups (one-way ANOVA). The differences were considered statistically significant at a P value of less than 0.05 ($P<0.05$).

Results

Effects on serum markers of kidney function

Orally administered CB fruit extract (200mg/kg) for 7 days did not significantly affect serum Cr level ($P>0.05$) in group II compared to the control group (Table 1 and Figure 1).

Furthermore, the serum Cr levels were considerably higher in male mice IP injected with a single dose of cisplatin (12mg/kg) (Group III) compared to such serum in the control (Group I). The levels were 1.01±0.140 and 0.80±0.081, respectively (1.26folds increase). Table 1 and Figure 1.

Additionally, results demonstrated a significant decline in serum Cr level in Group IV mice (CB prior to cisplatin) compared to such a serum level in male mice injected IP with a single dose of cisplatin (Group III); levels were 0.87±0.120 and 1.01±0.140, respectively. However, there was no significant difference ($P>0.05$) in serum Cr level in Group IV mice in comparison to serum level in control male mice (Group I). Table 1 and Figure 1

Regarding serum urea levels, orally administered CB fruit extract (200mg/kg) for 7 days did not significantly affect serum urea level ($P>0.05$) in group II compared to the control group (Table 1 and Figure 2).

Moreover, results showed that male mice IP injected with a single dose of cisplatin (12mg/kg) (Group III) resulted in a significant rise in the level of serum urea level ($P<0.05$) when compared to the corresponding serum level in the negative control (Group I) mice. Levels were respectively, 57.60±5.938 and 51.38±3.773. Table 1 and Figure 2 .Furthermore, there were non-significant differences ($P>0.05$) in serum urea level in Group IV male mice (CB prior to cisplatin) compared to the corresponding serum level in Group III/ CP IP-injected, and to that in male mice of Group I / (control). Table 1 and Figure 2.

Table 1. Effects of cranberry (CB) fruit extract treatment alone and prior to cisplatin on the serum levels of urea and creatinine (Cr).

Groups No	Names of groups	Creatinine (Cr) (mg/dL)	Urea (mg/dL)
Group I	0.9% Normal Saline (NaCl) (Negative Control)	0.80±0.081 b	51.38±3.773 b
Group II	Cranberry extract alone (200mg/kg/day)	0.77±0,089 b	48.35±4.006 b
Group III	Cisplatin (12mg/kg/day)	1.01±0.140 a	57.60±5.938 a
Group IV	Cranberry extract (200mg/kg/day) + Cisplatin (12mg/kg/day)	0.87±0.120 b	53.57±6.332 ab

* Data expressed as Mean ±SD; N=7 animals in each group.
*Values with non-identical small letters (a, and b) are significantly different (P< 0.05).
*Values with an identical small letter (a) are non-significantly different (P>0.05).
*A value with both (ab) letters in the renal urea column constituted that (a) is non-significantly (P<0.05) different compared to Group III mice; and (b) is non-significantly-different compared to Groups I and II mice.

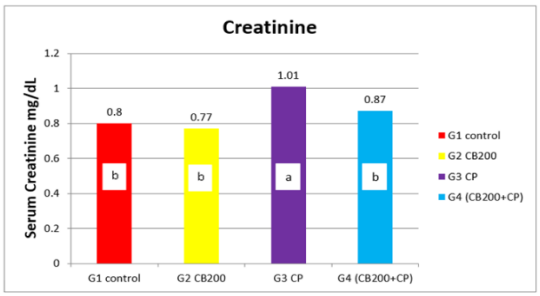

Figure 1. Effects of orally-administered cranberry (CB) fruit extract on Serum Creatinine (Cr) Levels

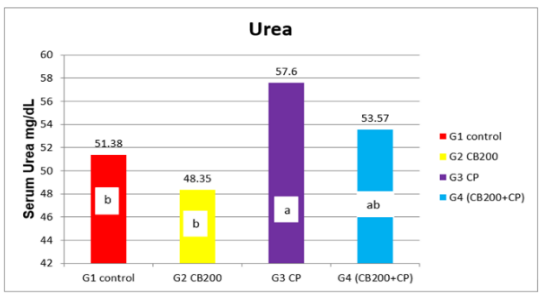

Figure 2. Effects of orally-administered CB fruit extract on Serum Urea Levels

Effects on renal antioxidant parameters

Oral administration of CB fruit extract (200mg/kg/day) alone by gavage tube to male mice for 7 days (Group II) did not produce a significant difference (P>0.05) in renal MDA level compared to the same renal level in negative control animals (Group I). Table 2 and Figure 3.

Moreover, the results showed that mice injected with a single IP dose of cisplatin (12mg/kg B.W) did not produce a significant difference (P>0.05) in the renal MDA levels in Group III compared to the control (Group I). Table 2 and Figure 3.

In addition, there was no significant difference (P>0.05) in the renal MDA level of male mice given CB fruit extract orally for seven days before a single IP injection of cisplatin (12mg/kg) (Group IV), compared to such a renal level in cisplatin-treated (Group III) and negative controls (Group I) mice. Table 2 and Figure 3.Regarding renal GSH levels, orally administered CB fruit extract (200mg/kg) for 7 days did not significantly affect renal GSH levels (P>0.05) in group II compared to the control (Group I) (Table 2 and Figure 4). Moreover, in mice IP injected with a single dosage of cisplatin (12mg/kg), there was a significant drop (P<0.05) in renal GSH levels in (Group III) compared to the equivalent renal level in the control (Group I). Levels were 153.65 ±76.773 and 203.17±61.027, respectively. Table 2 and Figure 4.Additionally, the result showed that orally-administered CB fruit extract for 7 days before a single injection IP of cisplatin (12mg/kg) resulted in a significant rise (P<0.05) in renal GSH level in Group IV compared to the level in Group III. Levels were 197.42 ± 62.958 and 153.65 ± 76.773, respectively (1.28folds increase). In contrast, there was no significant difference (P>0.05) in renal GSH levels between Group IV and control (Group I). Table 2 and Figure 4.

Table 2. Effects of cranberry (CB) fruit extract treatment alone and prior to cisplatin on the renal MDA and (GSH) levels.

No. of groups	Names of groups	Malondialdehyde (MDA) (nmol/ml)	Reduced glutathione (GSH) (mg/L)
Group I	0.9% (NaCl) Normal Saline (Control)	2.13±0.436 a	203.17±61.027 a
Group II	Cranberry extract alone (200mg/kg/day)	2.02±0.460 a	198.59±67.236 a
Group III	Cisplatin (12mg/kg/day)	2.37 ± 0.331a	153.65±76.773 b
Group IV	Cranberry extract (200mg/kg/day) + Cisplatin (12mg/kg/day)	2.24±0.365 a	197.42±62.958 a

* Data are expressed as Mean ± SD, n=7.
* Values with non-identical small letters (a, and b) are significantly different (P<0.05).
* Values with an identical small letter (a) are non-significantly different (P>0.05).

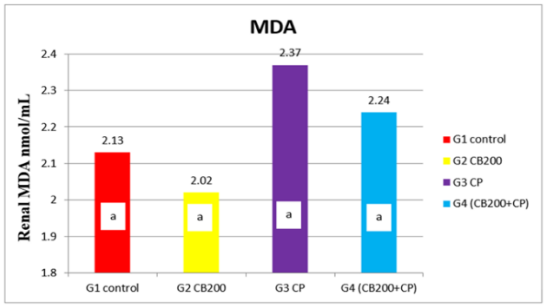

Figure 3. Effects of orally-administered cranberry (CB) fruit extract on renal Levels of malondialdehyde (MDA) in mice.

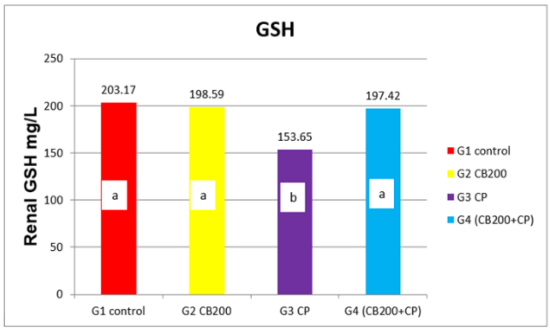

Figure 4. Effects of orally-administered cranberry (CB) fruit extract on renal Levels of reduced glutathione (GSH) in mice.

Histopathological analysis

Histological evaluation revealed normal histological structures of renal tissue which consists of glomeruli (red arrow marks), and renal tubules [proximal (PCTs) (yellow arrow marks) and distal convoluted tubules CTs (green arrow marks)] in kidney sections of control mice orally administered 0.9% NS once daily for 7 days (Group I) and orally-administered CB fruit extract (Group II) mice as shown in (Figure 5A and B).

Conversely, degenerative changes were noticed in the renal tubular cells mice IP injected with cisplatin (Group III); and the most prominent features were observed characterized by the loss of normal architecture of the renal tubules as well as inflammatory into the glomeruli with necrosis of renal epithelial cells (black arrow marks) (Figure 5C).

Interestingly, the evaluation of kidneys in mice, when administered oral CB prior to cisplatin (Group IV), showed an improvement in mice's renal histological architecture than those from Group III/ IP injected with CP, and such renal section was relatively similar to that of the control mice (Group I); although, degenerative changes in the epithelia of some renal tubules (orange arrow marks), the glomeruli looks-like normal (Figure 5D).

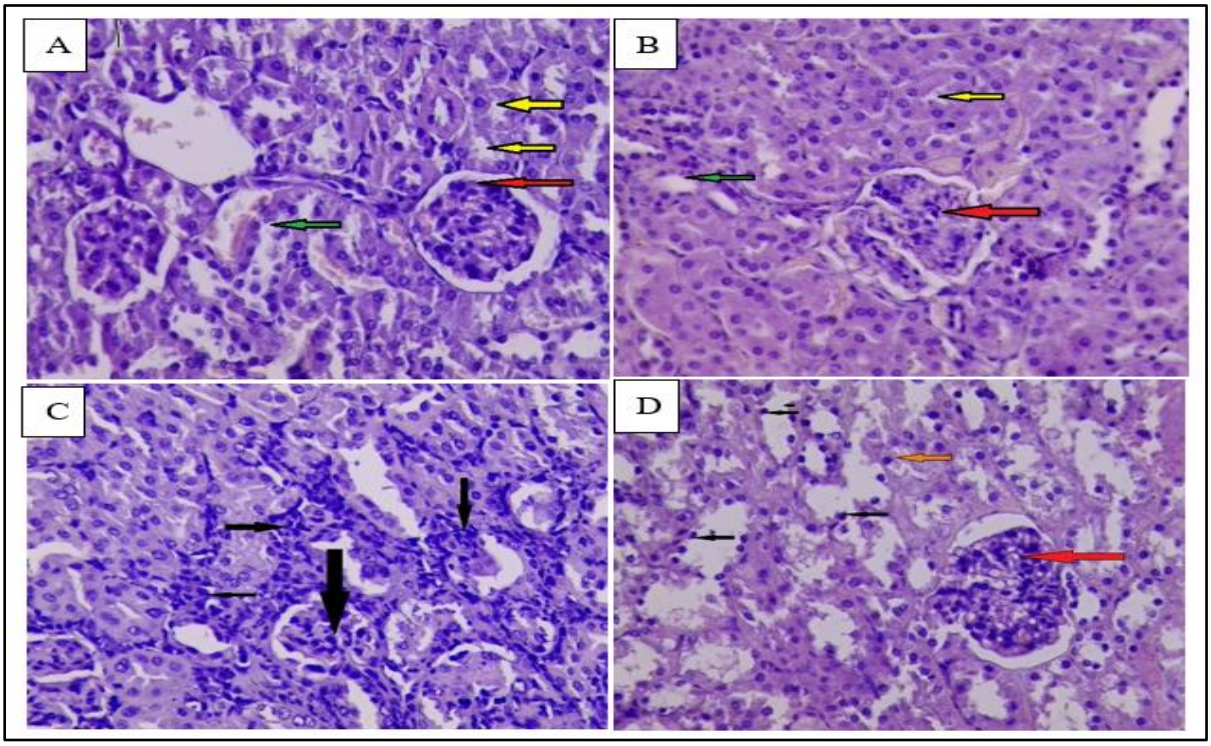

Figure 5. (A) Normal kidney section of mice orally-administered normal saline (Negative control, Group I). Score 0. (B) Normal Section of mice' kidney orally-administered cranberry (CB) fruit extract (200mg/kg/day) (Group II). Score 0. (C) Section of mice' kidney injected IP with a single dose of cisplatin (12mg/kg B. W) (Group III) showed necrosis. Score 4. (D) A cross-section of mice's kidneys orally - administered CB prior to cisplatin (Group IV) exhibited improvement with regenerative changes. Score 3. (H&E, X400).

Discussion

Nephrotoxicity is a sudden change in renal function that can result in changes in the glomerular filtration rate (GFR), blood urea nitrogen (BUN), serum creatinine (Cr), or urine output; and it resulting in renal impairment and possibly multi-organ disease by chemicals or drugs such as cisplatin, which can cause nephrotoxicity as a side effect [25].

Studies by Mcsweeney, *et al* (2021); and Jadon, *et al* (2019) reported that CP-induced nephrotoxicity is due to cellular uptake and accumulation of such chemotherapeutic drugs in proximal tubular epithelial cells (PTECs) resulting in acute tubular necrosis depending on the concentration and duration of exposure; moreover, its accumulation triggers increased production of ROSs, which played a significant part in the development of kidney injury and is involved in the key-clinical manifestation of nephrotoxicity (a reduction in GFR, elevated BUN, and plasma [Cr] resulting in nephrotoxicity [26,27]; and such manifestations were observed in Table 1 and Figures 1 and 2 of this study; where a single IP dose of CP injected on day 7 of the current study produced a significant increase in serum Cr and BUN levels.

Furthermore, researchers stated that elevated amounts of CP in PTECs also promote its deposition in mitochondria and this can consequently lead to mitochondrial dysfunction and damage, with the production of ROSs, through an impaired respiratory chain [28,29].

Additionally; other studies reported that CP disrupted the homeostasis between ROSs generation and the antioxidant defense system by increasing ROS production and a deficiency in antioxidant defense systems [such as superoxide dismutase (SOD), GSH, and catalase (CAT)] [30,31].

Thus, the reduction of key antioxidants leading to overexpression of OS following CP treatment [Soni H, *et al* (2014)] [32]; where a single IP dose of CP injected (12mg/kg) on day 7 of the current study resulted in a substantial reduction ($P<0.05$) in renal GSH levels compared to the level in the control. Levels being 153.65±76.773 and 203.17±61.027, respectively (Table 2 and Figure 4), and the results of this study [selected OS parameters (GSH)] levels are consistent with that of previously-mentioned studies.

Moreover, the histological results of the current investigation demonstrated that there were degenerative alterations in the renal tubular cells in mice injected with a single intraperitoneal dosage of CP as well as inflammation into the glomeruli with a marked loss of the normal architecture of the renal tubules (Figure 5C), and these results are similar to those obtained by other researchers [33,34].

Besides, Nemzer, et al (2022) & Wu, X, et al (2020) stated that CB possessed abundant nutritional components and many bioactive compounds mainly [polyphenol-rich antioxidants including anthocyanins, flavonols, and proanthocyanidins (PACs) which inhibit adherence of Escherichia coli to the UT; and it also contains hydroxycinnamic acid, ascorbic acid, triterpenoids, many vitamins (vitamin E, and vitamin K), trace elements, and others], which are well-known radical scavengers capable of preventing oxidative processes minimize cellular oxidative stress [35,36].

In the present study, oral administration of 200 mg/kg of CB fruit extract for 7 successive days before CP injection on day seven (Group IV) resulted in a considerable reduction in serum Cr level (0.87±0.120 b) (Table1 and Figure1) accompanied by a significant rise ($P<0.05$) in renal GSH concentration (197.42±62.958) (Table 2 and Figure 4) compared to serum level in CP-injected mice (Group III) with improvement in renal histological architecture (Figure 5).

Furthermore, Ledda *et al* (2015) confirmed that cranberries riched with proanthocyanidins (PACs) exert beneficial effects in the protection of UTIs caused by E. coli that can adhere to the uroepithelial cells; Moreover, dried cranberries and their extracts have a high concentration of polyphenols that can prevent bacteria from adhering to the mucosal and uroepithelial cells in the lower urinary tract [37].

Other studies reported that the natural products including cranberry were used as medicine and as food products that have nephroprotective effects and were used in treating or preventing UTIs and maintaining the digestive system, and are widely used in current clinical practice in many parts of the world [9,35]. In the present study, the administration of CB fruit extracts prior to CP significantly protected against nephrotoxicity induced by such chemotherapeutic drug via OS mechanism in mice and thus it shows a nephroprotective effect.

Conclusions

According to results obtained from this study, cisplatin produced considerable adverse effects on mice's kidneys; and the administration of oral CB fruit extract (200mg/kg/day) for 7 days has a protective effect against cisplatin-induced nephrotoxicity *via* the reduction of renal functions' markers, improvement of -OS mechanism (reduction of MDA/and elevation of GSH) and -in the histological analysis of renal tissue of mice.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflicts of Interest

The authors declare that there is no conflict of interest

Ethics Statements

This study was approved by The Ethical Committee of the Department of Pharmacology, and Toxicology, and the Scientific Committee of the College of the Pharmacy, University of Baghdad, according to decision (513) on 24/1/2022.

Author Contribution

The author 1/(Baidaa) contributed to a design; data gathering, analysis, or interpretation; drafting of the manuscript; and critical revising of the manuscript. The author 2/(Nada) gave final approval and agreed to be accountable for all aspects of the work in ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved**.**

Acknowledgment

The data of this article were abstracted from the M.Sc thesis submitted to the Department of Pharmacology and Toxicology, College of the Pharmacy University of Baghdad. The authors are extremely grateful to the College of the Pharmacy/University of Baghdad for supporting this work.

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