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Hydroalcoholic extract of Capparis spinosa seeds reduces cisplatin-induced nephrotoxicity in rats

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Acute kidney injury (AKI) is a common problem in many clinical conditions associated with increased mortality and morbidity. AKI is a common complication of distinct chemotherapy drugs, including cisplatin. Cisplatin induces nephrotoxicity in 20-30 percent of patients by a single dose, which is also increased by prolonged and repeated doses. Plant-derived phytochemicals have been considered to show beneficial effects against several toxic conditions. Capparis spinosa encompasses high amounts of bioactive antioxidant components. Therefore the current study aimed to evaluate its seeds potential nephroprotective effects against cisplatin-induced nephrotoxicity in vivo. The protective effects of the seeds of this plant have rarly been evaluated before. In this study, 40 male Sprague Dawley rats with weights 230±20 gr in 8 groups were assessed: Control group, cisplatin single dose 7 mg/kg intraperitoneally injected group, high dose Capparis spinosa hydroalcoholic extract 200 mg/kg group, and 5 treatment groups with cisplatin 7 mg/kg IP single dose and different doses and days of treatment by extract (50 and 100 mg/kg of extract for 1 day and 12 days and one post-treatment group).
Significant protective effects of the extract lowering serum creatinine and uric acid levels were seen. Anti-oxidative and anti-inflammatory effects of CSE were seen in the kidney tissue. In this research study, we compared pre and post-treatment by CSE. Good nephroprotective effects were seen in post-treatment groups by CSE. Capparis spinosa is an ancient therapeutic which could be used for kidney protection in patients with AKI. However, more clinical studies are needed to detect the proper doses of therapeutic and commercial products preparations.

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KEYWORDS

Capparis spinosa; kidney; cisplatin; seeds; Persian medicine.

Introduction

Acute kidney injury (AKI) or acute renal failure (ARF) is a prevalent clinical challenge connected with high mortality and morbidity. Kidney function failure leads to disturbed disposing of waste materials, toxins, and excess body fluid, thus inducing life-threatening conditions [2]. Moreover, AKI is a common complication of specific anti-cancer drugs. Cisplatin is a wieldy used chemotherapy agent against solid tumors of the head, neck and breast, lung, ovary, testis cancers, and many others. However, it is toxic for kidneys, and nephrotoxicity due to cisplatin administration occurs in 20-30 percent of patients after a single dose [8]. Cisplatin-induced AKI can turn into chronic renal failure (CRF) if non-treated [13,21,7]. The underlying mechanism of this kidney

injury mainly involves inflammation and oxidative stress [9].

Plant-derived natural products have been considered potential complementary or conventional therapy for the treatment and prohibition of oxidative and inflammatory conditions of the kidney due to the presence of high bioactive antioxidant and anti-inflammatory components in their structure. Also, the proper use of phytochemicals has been associated with lower serious side effects in comparison with synthetic drugs [2]. Capparis spinosa with names wild watermelon in China, Alcapparo in Spain, Cappero in Italy, capper (kebar), Lagaji, Shaflaj, Gebara, kebbara, Alaf-e Mar in different areas of Iran is an ancient traditional plant with several medicinal applications in Persian Medicine [16]. Different parts of the plant such as root, fruit, and flower have served as medicines used to treat different diseases in the ancient traditional medicine of Egypt, Iran, Roman, and Greek [20,16]. It has been used as an enforcement therapeutics for the liver, kidney, spleen and other organs in Persian medicine [16]. Capparis genome contains more than 250 species worldwide, and Capparis spinosa l. is a common type of genum Capparaceae growing in the Mediterranean region [25,20]. Capparis spinosa l contains a high amount of flavonoids, phenols, glucosinolates and can serve as an essential source of antioxidants [25]. Although several experimental studies have evaluated its beneficial effects [19,25,24,22,16,15,17,18,5,6] literature search fetches with scanty investigations regarding the nephroprotective effects of Capparis spinosa especially on seed-derived extract [24,16]. Also, the fruit of this plant that was processed in vinegar were used as ingredients of food or species many times ago [1, 25,6,4]. Therefore, the current study aimed to investigatethe possible protective effects of the ethanolic extracts of Capparis spinosa through different biochemical assays.

Materials and methods

Chemicals

Cisplatin solution vials Mylan (France) 50 mg/50 mL was prepared for intraperitoneal injection. Ethanol 96% was purchased from SIMIN TAAK.CO. (Zanjan-Iran) for ext. preparation.

Seeds

Capparis spinosas whole ripe fruits from the Moghan province of Iran were collected. Herbarium confirmation of the plant species was obtained from Shahid Beheshti pharmacology faculty lab. Seeds of fruit were extracted, spread in the shade, and dried. Seeds of the plant were kept in a dry and cool place at 4 °C until the experiment's starting time.

Preparing seeds extracts

Three approaches were evaluated to choose the extracting method that gives a higher antioxidant level. The cold press method and n-hexane oil were used for obtaining oil content, and the hydroalcoholic extract was also prepared. Total antioxidant levels of three samples were measured in Shahid Beheshti pharmacology laboratory by the BBPH method. Total antioxidant levels of hydroalcoholic extract were higher ($P < 0.001$) than expected. Thus were selected for the experiment. The total phenolic amount of hydroalcoholic extract was 25.12±1.2 µg/mL, total flavonoid 13.93±1.8 µg/mL, and rutin 4.00 ±1.1 µg/mL.

Capparis spinosa l. seeds hydroalcoholic extract (CSE) production

Powder prepared from seeds by grinder (KEEP grinder model KG-250 Made in Korea) and dissolved in ethanol and distilled water with a 70/30 concentration ratio, preserved at room temperature. After 48 h, the extracted fluid was dried, and then the extract was

collected. This action was repeated three times for preparing the whole extract.

Animals and experimental groups

Forty male Sprague Dawley rats with weights 230±20 gr were prepared from Pasture Institute (Tehran- Iran). Five days before the experiment, animals were maintained in the standard situation (at 22 °C, 12 h light/dark cycle, and free access to standard food and water). Then rats were randomLy divided into 8 groups: Group A: sham or control, gavage of distilled water without any cisplatin or CSE administration, Group B: Cisplatin 7 mg/kg one dose intraperitoneal (IP), Group C: high dose CSE 200 mg/kg BID orally (by gavage) for 12 days, Group D: Cisplatin 7 mg/kg one dose (IP) fallowed CSE 50 mg/kg BID for 12 days, Group E: Cisplatin 7 mg/kg one dose (IP) fallowed CSE 100 mg/kg BID for 12 days, Group F: Cisplatin 7 mg/kg one dose (IP) then CSE 50 mg/kg BID for 1 day, Group G: Cisplatin 7 mg/kg one dose (IP) then CSE 100 mg/kg BID for 1 day, Group H: CSE 100 mg/kg pre-treatment for 12 days and then injection of cisplatin 7 mg/kg one dose (IP) on day 12th. The proper doses of CSE were obtained from other studies [19]. Also, cisplatin injection dose was obtained from previous studies [11].

Serum and tissue sampling

Sampling was done two days after the ending of the experiment. Blood samples were obtained from the eye sinusoid and, after clotting at room temperature, centrifuged at 9000 rpm for 20 min. Serum separated and froze at -20 °C for subsequent analysis. Then the left kidney of rats was removed and divided into two parts. The upper zone was preserved at -70 °C for later analysis.

Serum Parameters analysis

The serum urea, creatinine, and uric acid levels were measured using the commercial kits. Urea levels by Pars Azmoon kit no: 129400 and Creatinine by Pars Azmoon kit no: 109400, and uric acid with kits of Man. A company under license ELITech Group.

Tissue parameters analysis

The upper half of left kidney tissue was homogenized and prepared for tissue parameters measurements. The lipid peroxidation levels were assessed by the malondialdehyde (MDA) ZellBio GmbH MDA assay kit. Ant oxidative parameters include superoxide dismutase (SOD) by ZellBio GmbH(Germany), glutathione peroxidase (GPx) by SIGMA-ALDRICH NO: CS0260, total antioxidant capacity (TAC) by manual method of RANDOX products, catalase activity (CAT) by ZellBio GmbH(Germany), reactive oxygen species (ROS) by SIGMA-ALDRICH fluorometric intracellular ROS kit no: MAK142 and inflammatory parameters include tumor necrosis factor-α (TNF-α) by DuoSet ELIZA Rat TNF-α kits, interleukin -1B (IL-1B) by DuoSet ELIZA Rat IL-1B kits, interleukin-6 (IL-6) by DuoSet ELIZA Rat IL-6 kits.

Statistical analysis

All data were presented as meam± SD. Data were analyzed by software Spss and the one-way ANOVA test and followed by post hoc LSD multiple comparison test between the study groups with acceptable significance $P<0.05$ as set for all data.

Results and discussion

Kidney function analysis

Serum urea

Serum urea means level in the cisplatin-administrated group was 52 ±10.51 mg/dl, compared to the control group significantly increased to 166±109.66 ($p<0.04$). Twelve days of treatment with CSE at concentrations 50 and 100 mg could significantly reduce serum urea level to 59.2±13.37 and 61.2±24.47, respectively ($p< 0.05$). Also,

groups F and G, which received CSE for one day post-cisplatin injection, demonstrated a lower urea level than cisplatin-received animals. However, pre-treatment with CSE (100 mg/kg) increased the urea level compared to the cisplatin-received group and induced a significant upward trend in urea level compared to the other groups, including normal control (Table 1).

Creatinine

Serum creatinine mean level from 0.33 mg/dl in the control group increased to 1.84 mg/dl in the cisplatin group. However, the result was not statistically significant (p<0.06). Mean serum of creatinine level in the groups treated with cisplatin then 50 and 100 mg/kg CSE For 12 days, were 0.39 mg/dl and 0.40 mg/dl, respectively, which were not again statistically significant compared to the cisplatin group (p<0.07). The mean serum creatinine level in groups treated with cisplatin in addition 50 and 100 mg/kg CSE for one day was 1.43 mg/dl and 1.59 mg/dl with respective p-values of p<0.6 and p<0.7. Moreover, the creatinine level of the group that was pre-treated with CSE 100 mg/kg for 12 days and then received cisplatin was significantly higher than the cisplatin group (Table 1).

TABLE 1 renal function biochemical markers in experimental groups

	Urea Mean±SD* (mg/dl)	**Creatinine Mean±SD* (mg/dl)**	**Uric Acid Mean±SD* (mg/dl)**
1)Control (received distilled water by gavage)	52 ±10.51	0.33±0.11	3.66±1.40
2)Cisplatin (7 mg/kg IP*) single dose	166±109.66	1.84±1.58	8.96±5.46
3)CSE** 200 mg/kg BID for 12 days	55.2±10.99	0.30± 0.107	3.10±1.11
4)Cisplatin (7 mg/kg IP*) single dose +CSE 50 mg/kg BID for12 days	59.2±13.37	0.39± 0.41	4.20±0.37
5)Cisplatin (7 mg/kg IP*) single dose +CSE 100 mg/kg BID for 12 days	61.2±24.47	0.40±0.30	4.92±3.63
6)Cisplatin (7 mg/kg IP*) single dose +CSE 50 mg/kg BID for 1 day	130.6±102.7	1.44±1.59	10.28±5.52
7)Cisplatin (7 mg/kg IP*) single dose +CSE 100 mg/kg BID for 1 day	135.2±139.91	1.59±1.71	12.16±11.53
8)CSE 100 mg/kg BID12 days+Cisplatin (7 mg/kg IP*) single dose	248±118.95	3.39±2.03	23.28±18.17
	P<0.007	p<0.004	p<0.008

IP*=intraperitonealy. CSE**= Capparis spinosa hydroalcoholic extract. Values were expressed as the mean ± SD. one-way ANOVA test was used and followed by post hoc LSD multiple comparison test between the study groups. P<0.05 was considered for significance.

Uric Acid

When serum uric acid level was compared with studied groups, it was shown that mean serum uric acid level in the cisplatin group was 8.96 mg/dl, which is up to two-folds of the control group. However, the difference statistically was not significant (p<0.31). Serum uric acid means in the groups that had received cisplatin and 50/100 mg/kg CSE for 12 days were 4.20 and 4.92 mg/dl, respectively that compared to cisplatin group was not statistically significant. Also, the serum level of uric acid in the CSE pre-treated group sharply increased (23.28 mg/dl) in comparison with the control and even cisplatin groups (p<0.01 and p<0.001, respectively) (Table 1).

Lipid peroxidation

In the group that received cisplatin, MDA level (0.54 nmol/mg pr) was non-significantly

higher than sham (0.45 nmol/mg pr) in the cisplatin-received group was 0.54 nmol/mg pr) that was non-significantly higher than sham (0.45 nmol/mg pr). Also, none of the CSE treatment groups showed a significant effect despite reversing effects. In contrast, the pre-treatment group exhibited a MDA level similar to the cisplatin group (Table 2).

TABLE 2 Lipid peroxidation and oxidative markers in kidney tissue

	MDA Mean nmol/mg pr±SD	**SOD Mean IU/mg pr±SD**	**GPX Mean IU/mg pr ±SD**	**CAT Mean IU/mg pr ±SD**	**ROS Mean±SD**	**TAC Mean µmol/mg pr ±SD**
1)Control (received distilled water by gavage)	0.45±0.10	1.65±0.33	32.96±6.86	2.27±0.42	1.0±0.21	2.15±0.44
2)Cisplatin (7 mg/kg IP*) single dose	0.54±0.17	1.23±0.33	30.30±3.90	2.32±0.42	1.39±0.32	1.96±0.18
3)CSE** 200 mg/kg BID for 12 days	0.52±0.11	1.53±0.30	28.89±5.08	1.84±0.53	1.23±0.39	1.87±0.33
4)Cisplatin (7 mg/kg IP*) single dose +CSE 50 mg/kg BID for12 days	0.45±0.09	1.64±0.17	31.75±2.36	1.97±0.63	1.66±0.22	2.06±0.15
5)Cisplatin (7 mg/kg IP*) single dose +CSE 100 mg/kg BID for 12 days	0.41±0.12	1.43±0.37	31.58± 3.14	2.42±1.18	1.03±0.35	2.05±0.20
6)Cisplatin (7 mg/kg IP*) single dose +CSE 50 mg/kg BID for 1 day	0.55±0.12	1.27±0.32	30.63±3.19	2.10±0.46	1.37±0.41	1.99±0.21
7)Cisplatin (7 mg/kg IP*) single dose +CSE 100 mg/kg BID for 1 day	0.45±0.16	1.30±0.41	34.80±5.51	2.64±0.99	1.23±0.35	2.14±0.57
8)CSE 100 mg/kg BID12 days+Cisplatin (7 mg/kg IP*) single dose	0.53±0.07	1.12±0.23	32.10±3.31	1.98±0.54	1.41±0.31	2.06±0.57
	P<0.52	P<0.09	P<0.67	P<0.64	P<0.35	P<0.94

Values were expressed as the mean ± SD. one-way ANOVA test was used and followed by post hoc LSD multiple comparison test between the study groups. IP*=intraperitonealy. CSE**= Capparis spinosa hydroalcoholic extract. MDA= malondealdehyde, SOD=superoxide dismutase, GPX=glutathione peroxidase, CAT=catalase activity, ROS=reactive oxygen species, TAC=total antioxidant capacity. P<0.05 were considered for sighnificancy.

TABLE 3 Inflammation markers in kidney tissue

	IL6 Mean pg/mL±SD	ILβ1 Mean pg/mL ±SD	TNF-α Mean pg/mL ±SD
1)Control (received distilled water by gavage)	1176.52±162.58	234.76±38.64	49.38±6.27
2)Cisplatin (7 mg/kg IP*) single dose	1344.88±434.53	298.76±105.67	84.80±41.37
3)CSE** 200 mg/kg BID for 12 days	1205.95±203.50	245.12±43.33	51.30±7.80
4)Cisplatin (7 mg/kg IP*) single dose +CSE 50 mg/kg BID for12 days	1231.62±244.24	217.54±64.22	53.50± 17.58
5)Cisplatin (7 mg/kg IP*) single dose +CSE 100 mg/kg BID for 12 days	1144.03±331.47	243.68±75.11	58.40±23.83
6)Cisplatin (7 mg/kg IP*) single dose +CSE 50 mg/kg BID for 1 day	1556.37±763.08	324.86±168.66	87.28±60.25
7)Cisplatin (7 mg/kg IP*) single dose +CSE 100 mg/kg BID for 1 day	1023.01±380.84	256.46±80.67	64.36±27.08
8)CSE 100 mg/kg BID 12 days+Cisplatin (7 mg/kg IP*) single dose	2086.27± 627.73	389.68±132.09	102.88±47.47
	P<0.01	P<0.13	P<0.13

Values were expressed as the mean ± SD.one-way ANOVA test was used and followed by post hoc LSD multiple comparison test between the groups of study. IP*=intraperitonealy. CSE**= Capparis spinosa hydroalcoholic extract. IL6= interleukin-6, ILβ1= interleukin- β1, TNF-α= tumour necrosis factor-α. P<0.05 were considered for sighnificancy.

Antioxidant activity

To investigate Capparis spinosa seeds' antioxidant effects in kidney tissue, SOD, GPX, Catalase, ROS, and TAC levels by standard methods.

SOD

SOD levels in the sham group were 1.65 IU/mg pr while cisplatin plummeted its amount to 1.23 IU/mg pr. CSE treatment could increase SOD levels, although non-significantly. In addition, the mean SOD level in the pre-treated group by 100 mg of CSE was 1.12 IU/mg pr, which was lower than sham (Table 2).

GPX and TAC

Kidney tissue GPX and TAC levels in the cisplatin group decreased compared to sham, whereas treatment with CSE could reverse these effects (Table 2).

Catalase and ROS

CAT levels were not significantly altered between study groups (Table 2). ROS levels in the cisplatin group were 1.39 (DCF fold of control) compared to sham 1.0 (DCF fold of control). Only in the group treated with 100 mg/kg CSE for 12 days ROS level (1.03 DCF fold of control) showed a fall nearly to sham (Table 2).

Anti-inflammatory effect

IL-6

Kidney tissue IL-6 level as an essential inflammatory index evaluated in study groups. A significant increase was observed in cisplatin group 1344.88 pg/mL compared to sham 1176.52 pg/mL. CSE treating in groups which received cis then treated with 100 mg/kg of extract both 12 and 1 day and 50 mg/kg for 12 days, the levels of IL-6 were 1144.03 pg/mL, 1023.01 pg/mL, and 1231.62 pg/mL respectively. In CSE pre-treated, IL-6 level increased compared to all groups of study statistically (Table 3).

IL-β1

The mean level of kidney tissue IL-β1 mean levels were increased from 234.76 pg/mL in the control group to 298.76 pg/mL in the cisplatin received group. Also, that was

declined to 217.54 pg/mL and 243.68 pg/mL by doses 50, 100 mg/kg of CSE in the groups that received cisplatin and CSE for 12 days. Also, IL-β1 mean level was 256.46 pg/mL in the group that received CSE. 100 mg/kg for one day (Table 3).

TNF-α

TNF-α means level in the sham group was 49.38 pg/mL and increased to 84.80 pg/mL in the cisplatin group. TNF-α mean levels in the groups treated with CSE by doses 50 and 100 mg/kg for 12 days decreased to 53.50 pg/mL and 58.40 pg/mL, respectively. Also, the mean of TNF-α in the group treated with cisplatin and CSE 100 mg/kg for one day decreased to 64.36 pg/mL (Table 3).

Discussion

Cisplatin induces toxicity by inducing ROS production and mitochondrial dysfunction in renal tissue. ROS act on multiple cell components such as lipids, proteins, and DNA. Also, injured mitochondria increases ROS generation. Because of the critical role of mitochondrial dysfunction in apoptosis induction, antioxidants protect against mitochondrial impairment and thus might reduce apoptosis in drug/xenobiotic-induced renal toxicity [13]. Previous research has reported potential antioxidant and anti-inflammatory effects of Capparis spinosa, which are supported by ancient therapeutic properties of this plant [14,12]. Many analytical studies have evaluated the ingredients of different parts of Capparis spinosa [25]. Different parts of Capparis spinosa such as leaves, flowers, fruit, and root have been used in some studies for several purposes [19,16,12,20,21,23,24]. In the studies regarding the seeds of Capparis spinosa, the number of phytochemicals (quantitatively and qualitatively) has been in relation to the size of seeds, harvest time, region of growth, and maybe many other conditions [25,14]. However, most studies have evaluated phytochemical levels in the fruit, Leaf, and root [25,14,1]. Contents of various plant parts are different and depend on several factors [25]. Moreover, a different extraction method has ended in different results about the contents [25]. Recent analytical studies using the chromatography method on the seed of Capparis spinosa l. have shown that the main glycosinolates ingredient of the seeds is glucocapparine [20,25]. Also, the oil amount of seeds is high (about 30%) [20,25], and mainly contains linoleic acid and, to a lesser extent, oleic acid, linolenic, and other saturated and unsaturated fatty acids [20,25]. Meristic acid is a rare and valuable fatty acid in Capparis spinosa seeds [25]. Other essential components of seeds are tocopherols, including γ-tocopherol and δ-tocopherols that are the main components of vitamin [25]. Thus, Capparis spinosa seeds could be a potential source of antioxidants [25].

In the present study, we used the best antioxidant product of Capparis spinosa seeds, hydroalcoholic extract (CSE), confirmed by a pilot study. We used cisplatin as a nephrotoxic agent and investigated the possible renal protective effects of Capparis spinosa seeds extract by several assays in vivo. The CSE showed protective effects on the kidneys in cisplatin-treated rats by enhancing kidney function. Moreover, the anti-oxidative and anti-inflammatory activities of CSE that were investigated through evaluation of MDA, GPX, TAC, IL-6, and TNF-α were shown. Our findings align with the results of other studies proposing the potential restorative effects of Capparis spinosa extracts. It has been reported that the alcoholic ext. of leaves and seeds of Capparis spinosa improves kidney function, reduces oxidative stress, and reverses the pathological changes in vivo nephrotoxic models [21,10]. As the most crucial critical ingredient of Capparis spinosa extract, it is deemed that rutin is responsible for its protective effects [3,25].

It has been demonstrated that the administration of rutin (one of the main components of this extract) [25] can significantly improve kidney injury through modulation of oxidative hazard, inflammatory response, and apoptosis machinery [3].

In our study, to find the best dose and the proper extract administration time and elongations of treatment for yielding the best protection, we used two different doses and two different administration times. It was shown that administration of CSE after cisplatin injection had good kidney protective effects, especially in reversing kidney function parameters. However, pre-treatment with CSE failed to show protective effects and increased nephrotoxicity markers. In other studies with extracts of other parts of the plant, protective effects in kidney, liver, and some other organs pre- and post-cisplatin administration have been observed [19,21,23]. In a study conducted by [19] administration of seed extract 7 days before cisplatin continued after induction of nephrotoxicity, protective effects were observed [19]. Thus, more studies are required to determine whether pre-treatment with Capparis spinosa seed extract is protective. It has been shown that high doses of Capparis spinosa have toxic effects on the kidney and liver in terms of dose and time. We found that CSE 200 mg/kg for 12 days in vivo showed slightly malicious effects on tissue MDA, SOD, GPX, ROS, and TAC levels. These toxic effects should further be studied for possible underlying mechanisms.

Conclusion

Due to the excellent safety profile of seed extracts of Capparis spinosa in our study in therapeutic doses, clinical trials are recommended to investigate the possible kidney protective effects of this natural product with could be used in cancer patients that are under cisplatin-therapy and would save kidney capacity for better therapy and life quality. Also, more studies are needed to investigate mechanisms of unfavorable results in the pre-treated groups by CSE.

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