Effects of *Lepidium sativum* seeds extract (Garden cress) on the kidney in sodium nitrite receiving rats

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ABSTRACT

This study was carried out to investigate the modulating effect of *Lepidium sativum* (LS) seeds aqueous extract consumption against sodium nitrite (SN) that induced the nephrotoxicity in male rats. Rats were divided into four groups. Group 1 (control): without any treatment; group 2: injected with a single dose of SN (50 mg/kg body weight) 24 h prior to decapitation intraperitoneally (i.p.); group 3: given orally 300 mg/kg body weight of LS for four weeks; group 4: treated orally with LS for four weeks, then injected with a single dose of SN, at 24 h prior to decapitation (i.p.) with the same doses. The results showed that, the treatment with sodium nitrite revealed a significantly increase in the levels of sodium, chloride, total calcium, ionized calcium, urea, creatinine and uric acid comparing to the control group. In respect to serum potassium, there is a significant decrease when compared to the control group. Also, the kidney tissue thiobarbituric acid reactive substances (TBARS) were significantly increased. But the superoxide dismutase (SOD), glutathione (GSH) and Catalase (CAT) enzymes were markedly decreased. The pre-treatment with LS before the injection of SN improved the harmful effects of SN caused in the serum levels of the biochemical parameters tested and the concentrations of GSH, SOD, CAT and TBARS in the kidney tissue comparing to SN-treated rats. It could be concluded that *Lepidium sativum* seeds act as a natural substance for ameliorating the alterations in serum electrolytes, kidney function and oxidative damage induced by sodium nitrite in the kidney tissue.

Keywords: Kidney function, *Lepidium sativum* seeds, Oxidative stress, Serum electrolytes, Sodium nitrite.

1. INTRODUCTION

Sodium nitrite is an inorganic salt, with the chemical formula NaNO_2 , is a white to slightly yellowish crystalline powder (Aboulgasem et al., 2015). It is used usually for the preservation of sausages and cooked meat (Helal et al., 2008). The daily food consumption of nitrite may be higher than the admissible level, by the use of several types of a preservative food (Bilczuk et al., 1991). Distinctly nitrites are formed slightly by endogenous synthesis, although the most with the dietary origin (Bartholomew and Hill, 1984). Sodium nitrite has been reported to have harmful effects due to increased oxidative stress that could cause harmful hazards to different organs including the kidney (Ibrahim et al., 1999), and the liver (Abdeen et al., 2015).

Numerous plant extracts have antioxidant activity which may be a critical property to these medical plants associated with the treatment of several diseases. So, the medical plants are considered as important resources to ameliorate and/or prevent certain disorders, such as diabetes, atherosclerosis, hepatotoxicity and other complications (Saggu et al., 2014). The plant seeds and leaves have been used in traditional medicine, as it has various biological effects. The garden cress (*Lepidium sativum*) belonging to Brassicaceae family is an annual herb, reported to have hypoglycemic, antihypertensive,

diuretic (Jouad et al., 2001), anti-inflammatory (Raval et al., 2013), hepatoprotective (Al-Sheddi et al., 2016), antioxidant (Zia-Ul-Haq et al., 2012), and anti-carcinogenic activities (Maghrani et al., 2005). Phytochemical investigations of *Lepidium sativum* showed the presence of flavonoids, triterpens, benzyl isothiocyanate, tannins, alkaloids, sterols and glucosinolates (Sakran et al., 2014), which have antioxidant, anti-inflammatory, analgesic activities and hepatoprotective properties (Raval and Ravishankar, 2010). The present research describes the effectiveness of garden cress seeds aqueous extract in the amelioration of sodium nitrite effects that induced the nephrotoxicity and oxidative damage in animal model.

2. MATERIALS AND METHODS

2.1. Materials:

Sodium nitrite (NaNO_2) was purchased from sigma Aldrich, St Louis, Mo .

The garden cress (*Lepidium sativum*) seeds were purchased from Agricultural Research Center, Giza, Egypt .

All using kits were purchased from Biodiagnostic Company, Giza, Egypt.

2.2. Methods:

The solution of sodium nitrite (NaNO_2) was prepared freshly by dissolving 5 g in 100 ml saline

solution, the rats were injected intraperitoneally (I.P) at 50 mg/kg body weight (1 ml dosing volume) according to Gluhcheva et al. (2012).

The garden cress seeds were washed, dried, crushed to powder using electric blender. The suspension of garden cress seeds powder were prepared freshly and administered to each rat orally by stomach tube at a dose 300 mg/kg body weight once daily for four weeks according to Raish et al. (2016).

2.3. Animals

Twenty four albino rats (*Rattus norvegicus*) weighing 125–150 g were used in the experiment. The animals were housed in metal cages in an air conditioned room at $22\pm 3^{\circ}\text{C}$, $55\pm 5\%$ humidity and were supplied with a standard laboratory diet and water ad libitum (Rogers, 1979). Rats were purchased from animal house colony of the National Research Center, Dokki, Giza, Egypt.

2.4. Experimental design

Animals were divided randomly into four groups (n=6). The first group is rats without any treatment as a control. The second group; rats received a single dose of sodium nitrite i.p. (50 mg/kg body weight), 24 h prior to decapitation. The third group; rats received *Lipidium sativum* seeds aqueous extract orally (300 mg/kg body weight) for four weeks. The fourth group; rats received *Lipidium sativum* seeds aqueous extract (300 mg/kg body weight) orally for four weeks and then injected with a single dose of sodium nitrite (50 mg/kg body weight) i.p. 24 h prior to decapitation.

2.5. Sample collection

The animals were starved overnight for 12h before the blood was collected. Rats were anaesthetized with diethyl ether and individual blood samples were collected and centrifuged for 15 minutes at 3000 rpm to separate the serum in sterilized vials by cervical dislocation for each rat for biochemical analyses. The serum was separated into clean tubes and kept frozen at -20°C till analysis. The kidney of each rat was homogenized in phosphate buffer solution (pH 7.4). The homogenate was centrifuged at 3000 rpm for 15 min and the supernatant was used for biochemical analysis. The supernatant was used for measuring the concentration of superoxide dismutase (SOD), glutathione (GSH), Catalase (CAT) and TBARS levels were estimated in the homogenate of kidney tissue.

2.6. Biochemical assays

Serum sodium and potassium were analyzed according to Tietz (1987); Calcium ion was determined according to Faulker and Meites method (1982); Chloride ion was estimated using the method of Skoog et al. (1996); Urea and uric acid were analyzed according to the method described by Young (2001). Creatinine was determined according to the method of Bartels and Bohmer method (1972).

2.7. Enzyme analysis

The extent of lipid peroxidation was assayed by the measurement of thiobarbituric acid reactive substances (TBARS) according to Yoshioka et al. (1979). Superoxide dismutase (SOD) and catalase (CAT) activity was estimated according to Sun et al. (1998) and Aebi (1984), respectively. The content of reduced glutathione (GSH) was determined according to Weckbercker and Cory (1988).

2.8. Statistical analysis

The obtained results were statistically analyzed by using SPSS program, version 16 according to the method of Glantz (1992). Significant differences among groups were determined by one-way analysis of variance (ANOVA) followed by post hoc test using Duncan's multiple range tests to compare the level of significance between control and experimental groups, significance between groups were considered when p-value < 0.05 .

3. RESULTS

Table 1 shows the changes in sodium, potassium, chloride, total calcium and ionized calcium serum levels in all groups. The results of the present study revealed a significant increase in the serum levels of sodium, chloride, total calcium and ionized calcium, and a significant decrease in the level of potassium comparing with the control group. In respect to, the garden cress seeds aqueous extract treated group, there were a non significant changes in all parameters when compared to the control group. The treatment with the garden cress seeds aqueous extract before the injection with sodium nitrite in group four, could restore the levels of sodium, potassium and chloride to control value and to some extent ameliorate the total calcium and ionized calcium levels.

Table 2 illustrates the effects of sodium nitrite, the garden cress seeds aqueous extract and their combination on the serum levels of urea, creatinine and uric acid in all groups. A significant increase in the serum levels of urea, creatinine and uric acid were observed in the sodium nitrite group with percent changes 38.7%, 28.95% and 28.6%, respectively from the control value. Whereas, the garden cress seeds aqueous extract obtained a non

significant changes in the values of urea, creatinine and uric acid comparing with the control values. When the rats treated with the garden cress seeds aqueous extract before the injection of sodium nitrite, the serum levels of urea and uric acid could restore to the control values; but to some extent it could ameliorate the level of creatinine that induced by sodium nitrite.

Table 3 shows that the daily treatment with the garden cress seeds aqueous extract before sodium nitrite injection alleviated significantly the sodium

nitrite-induced elevations in TBARS levels in the kidney tissue. Also, the results of the present study revealed that the treatment of rats with sodium nitrite induced a significant decrease in antioxidant enzyme activities in the kidney tissue, including GSH, SOD and CAT, when compared to the control group.

Whereas, the daily treatment with the garden cress seeds aqueous significantly ameliorated the alternation induced by the sodium nitrite in kidney antioxidant levels.

Table 1. Effects of sodium nitrite (Na NO₂), Garden cress seeds aqueous extract and their combination on the serum levels of sodium, potassium, chloride, total calcium and ionized calcium.

	Control	Na NO ₂	%D	Garden cress	% D	Na NO ₂ + Garden cress	%D	p-value
Sodium (mmol/L)	1.35 ^a ±0.3	1.42 ^b ±1.03	5.2	1.36 ^a ±0.73	0.74	1.34 ^a ±0.4	-0.74	*
Potassium (mmol/L)	4.9 ^a ±0.2	3.7 ^b ±0.2	-24.5	4.8 ^a ±0.1	-2.04	4.7 ^a ±0.2	-4.1	*
Chloride (mmol/L)	101.1 ^a ±0.6	107 ^b ±1.14	5.84	99.8 ^a ±0.9	-1.3	102.2 ^a ±0.4	1.1	*
Total Calcium (mmol/L)	8.9 ^a ±0.21	10.5 ^b ±0.21	17.9	8.8 ^a ±0.24	-1.12	9.7 ^c ±0.2	8.99	*
Ionized Calcium (mmol/L)	3.53 ^a ±0.1	4.6 ^b ±0.11	30.31	3.58 ^a ±0.105	1.42	4.1 ^c ±0.1	16.15	*

*Values are mean ± S.E (standard error) of six rats in each group. Different letters means in the same column not sharing a common superscript are significantly different (p < 0.05) between groups.

%% D: Percentage difference [(Treated value – Control Value) / Control Value] x 100 according to Bennett and Briggers (2005).

Table 2. Effects of sodium nitrite (Na NO₂), Garden cress seeds aqueous extract and their combination on the serum level of urea, creatinine and uric acid.

	Control	Na NO ₂	%D	Garden cress	% D	Na NO ₂ + Garden cress	%D	p-value
Urea (mg/dl)	27.2 ^a ±1.01	37.72 ^b ±1.3	38.7	28.03 ^a ±0.6	3.1	27.92 ^a ±0.6	2.65	*
Creatinine (mg/dl)	0.38 ^a ±0.01	0.49 ^b ±0.02	28.95	0.37 ^a ±0.02	-2.63	0.42 ^c ±0.01	10.53	*
Uric acid (mg/dl)	1.4 ^a ±0.1	1.8 ^b ±0.05	28.6	1.52 ^a ±0.12	8.6	1.5 ^a ±0.1	7.14	*

*Values are mean ± S.E. of six rats in each group. Different letters means in the same column not sharing a common superscript are significantly different (p < 0.05) between groups.

%% D: Percentage difference [(Treated value – Control Value) / Control Value] x 100

Table 3- Effects of sodium nitrite (Na NO₂), Garden cress seeds aqueous extract and their combination on the levels of antioxidants TBARS, GSH, SOD and CAT, in the kidney tissues.

	Control	Na NO ₂	%D	Garden cress	% D	Na NO ₂ + Garden cress	%D	p-value
TBARS (μmol/ g wet tissue)	18.3 ^a ±0.11	31.6 ^b ±0.43	72.7	18.4 ^a ±0.2	0.5	23.6 ^c ±0.2	28.9	*
GSH (μg/ g wet tissue)	12.1 ^a ±0.12	9.1 ^b ±0.2	-24.8	12 ^a ±0.15	-0.83	10.2 ^c ±0.11	-15.7	*
SOD (Unit/mg)protein	8.1 ^a ±0.11	4.2 ^b ±0.11	-48.14	8.3 ^a ±0.1	2.5	7.1 ^c ±0.11	-12.3	*
CAT (Unit/mg protein)	19.7 ^a ±0.42	15.3 ^b ±0.2	-22.33	20.3 ^c ±0.14	3.04	18.1 ^d ±0.1	-8.12	*

*Values are mean ± S.E. of six rats in each group. Different letters means in the same column not sharing a common superscript are significantly different (p < 0.05) between groups.

%% D: Percentage difference [(Treated value – Control Value) / Control Value] x 100

4. DISCUSSION

Sodium nitrite exists naturally in many foods, particularly vegetables and it is used as a preservative in cured meat products, fish and some types of cheese (Gluhcheva *et al.*, 2012). The toxicity to humans and animals is documented in the overexposure to the nitrite (RCHAS, 2000; WHO, 2007). The kidneys are very sensitive to the adverse effects of chemicals, as they are concerned with filtering and concentrating different chemicals and substances that may become toxic at high concentration (Loh and Cohen, 2009). Also, the kidneys work to keep the electrolyte concentrations in the blood constant despite changes in the body. So, the electrolytes values are commonly used as indicators for the renal functions or dysfunctions. Electrolytes and minerals are involved in the most cellular activities and have a major role in the metabolism. They assume multiple functions such as, holding fluids in compartments of the body and maintaining normal acid-base balance. Sodium nitrite consumption has major effects on the absorption, elimination and serum concentrations of many physiologically important electrolytes and minerals, including sodium, potassium, chloride, total calcium and ionized calcium. Electrolytes disturbance may lead to severe and even life-threatening metabolic abnormalities (Reddy *et al.*, 2018).

The present study investigated the protective effects of *Lipidium sativum* seeds aqueous extract administration against the nephrotoxicity induced by sodium nitrite (NaNO_2) in male rats. The results revealed that, when *Lipidium sativum* seeds aqueous extract given with sodium nitrite induced a decrease in the elevated serum levels of urea, creatinine, uric acid, sodium, chloride, total calcium and ionized calcium as compared with the sodium nitrite treated group. On the other hand, it induced an increase in potassium serum level comparing with sodium nitrite group. While no marked alterations was observed in the serum levels of these parameters in rats given *Lipidium sativum* seeds aqueous extract alone comparing with control rats. The serum levels of blood urea nitrogen, creatinine, and uric acid are indicator markers reflecting the adequate functions of the kidney (Gowda *et al.*, 2010).

The current results of the present study showed impaired kidney function in rats treated with sodium nitrite relative to the corresponding control ones as evidenced by the elevated levels of the assessed renal function indices. This is in agreement

with many authors (Zurovsky and Haber, 1995; Enovwo, 2010), who recorded that the toxicity of sodium nitrite on the serum urea, uric acid and creatinine concentrations. The adverse effects of sodium nitrite could be attributed to the changes in the threshold of tubular re-absorption, renal blood flow and glomerular filtration rate (Zurovsky and Haber, 1995; Enovwo, 2010). However, the garden cress seeds aqueous extract improved the deterioration in the kidney functions that induced by sodium nitrite in rats indicated by the increase the excretion of urea, creatinine, uric acid, sodium, chloride, total calcium and ionized calcium by increasing glomerular filtration rate. These results in agreement with many authors who reported the diuretic effects of the aqueous extract of garden cress seeds (Patel *et al.*, 2009; Halaby *et al.*, 2015), since it may be having nephroprotective and curative activity (Al Hamedan, 2010).

The diuretic effect of the garden cress seeds extract that may be due to the presence of several compounds which could be responsible for the plants diuretic effects such as flavonoids, saponins or organic acids (Maghrani *et al.*, 2005). Also, this effect may be produced by stimulation of regional blood flow or initial vasodilation (Stanic and Samarzija, 1993) or by producing inhibition of tubular reabsorption of water and anions (Pantoja *et al.*, 1993). This is indicative of ability of the garden cress seeds aqueous extract to improve the kidneys and restore electrolyte balance and renal functions in sodium nitrite treated rats.

Oxidative stress occurs when there is an imbalance between the generations of reactive oxygen species or reactive nitrogen species and the antioxidant defense system so that the latter become overwhelmed (Juránek and Bezek, 2005). Antioxidant enzymes, including SOD, CAT and GSH are the first line cellular defense enzymes against oxidative injury by scavenging the generated free radicals. Another indicator of oxidative stress in biological systems is the level of lipid peroxidation in the tissue based on the formation of thiobarbituric acid reactive substances (TBARS), that expressed as the extent of malondialdehyde (Wiland and Szechcinski, 2003; Karahan *et al.*, 2005).

Data of the present study revealed that sodium nitrite administration was related with oxidative stress as appeared by marked elevation of TBARS level accompanied with a marked decline in the activities of SOD, CAT and GSH enzymes in the kidney tissue. These changes were similar to the result of Ansari *et*

al. (2017), since NaNO_2 caused a decline in the activities of brush border membrane enzymes, increase in lipid peroxidation, protein oxidation, hydrogen peroxide levels. Also, several *in vivo* and *in vitro* studies have reported nitrite toxicity mediated through oxidative stress (Ansari and Mahmood 2016; Jia *et al.*, 2015). This is supported by reports that antioxidants can ameliorate nitrite toxicity (Sherif and Al-Gayyar, 2013). Özen *et al.* (2014), have reported degenerative changes in organs of nitrite-treated mice. The present study also revealed that garden cress seeds aqueous extract administration caused a significant decrease in the amount of lipid peroxidation and increase the level of antioxidant enzymes in the kidney tissues induced by sodium nitrite treatment. These results were in correlation with the study of Qusti *et al.* (2016), who reported a significant increase in the levels of GSH and a significant decrease in the levels of MDA in kidney tissue homogenate in rats received methanolic *lipidium sativum* extract for 4 weeks. Also, the garden cress seeds extract showed the antioxidant properties that increase in glutathione level and decrease in lipid peroxidation (Doke and Guha, 2014). The antioxidant effect of *lipidium sativum* may be attributed to its high content in antioxidants (vitamin C, E, carotenoids, polyphenols and flavonoids). Also, Choi *et al.* (2014) attributed the antioxidant activity of *lipidium sativum* to the presence of total polyphenolic compounds. These polyphenolic compounds include flavonoids, anthraquinones, anthocyanidins, xanthenes and tannins. These compounds can scavenge free radicals, superoxide and hydroxyl radical by single electron transfer. Based on our results, we suggest that the garden cress aqueous extract showed an improvement in the kidney functions against the damage caused by sodium nitrite treatment that could may be attributed to the antioxidant properties of the extract by increasing the antioxidant enzymes and by scavenging free radicals produced by sodium nitrite treatment.

5. CONCLUSION

The present study concluded that, sodium nitrite had adverse effects on the kidney. Garden cress seeds aqueous extract supplementation showed a remarkable amelioration of the nephrotoxicity induced by sodium nitrite in male rats. So, it is recommended that the use of sodium nitrite must be limited and using of garden cress seeds extract to alleviate the toxic effects of sodium nitrite.

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الملخص العربي

تأثير مستخلص جذور نبات حب الرشاد علي الكلي في الجرذان المعالجة بنيتريت الصوديوم

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لقد أجريت هذه الدراسة لمعرفة التأثير الوقائي لمستخلص جذور نبات حب الرشاد (LS) في ذكور الجرذان المستحثة للسمية الكلوية بواسطة نيتريت الصوديوم (SN). وقسمت الجرذان إلى أربع مجموعات، استخدمت المجموعة الأولى كمجموعة ضابطة ولم يتم معالجتها بشئ، والمجموعة الثانية تم حقنها بجرعة واحدة من SN (٥٠ مجم/ كجم من وزن الجسم) داخل الغشاء البريتوني قبل ذبحها ب ٢٤ ساعة، وتم اعطاء المجموعة الثالثة ٣٠٠ مجم/ كجم من وزن الجسم من LS يوميا عن طريق الفم لمدة أربعة أسابيع، وأعطيت المجموعة الرابعة مستخلص ال LS لمدة أربعة أسابيع. ثم حقنت بجرعة واحدة من SN قبل ذبحها ب ٢٤ ساعة بنفس الجرعات المستخدمة في المجموعة الأولى والثانية. وأظهرت نتائج هذه الدراسة أن استخدام نيتريت الصوديوم أدى الي زيادة ذو دلالة احصائية في مستوي الصوديوم والكلوريد والكالسيوم الكلي والكالسيوم المتأين واليوريا والكرياتينين وحمض اليوريك، بينما حدث انخفاض ملحوظ في مستوي البوتاسيوم مقارنة بالمجموعة الضابطة. وتم قياس مستوي حمض الثيوباربيتوريك (TBARS)، إنزيم السوبر أكسيد ديسميوتاز (SOD)، إنزيم الجلوتاثيون (GSH) و إنزيم الكاتاليز (CAT) في نسيج الكلي. ووجد أن معاملة ذكور الجرذان بنيتريت الصوديوم أدى الي زياده ملحوظة في مستوي حمض الثيوباربيتوريك (TBARS)، في حين أن إنزيم السوبر أكسيد ديسميوتاز (SOD)، الجلوتاثيون (GSH) والكاتاليز (CAT) قد انخفضت بشكل ملحوظ مقارنة بالمجموعة الضابطة. وقد أدت المعالجة المسبقة بـ LS قبل حقن SN الي الحد من الآثار الضارة لـ SN في المعايير البيوكيميائية المختلفة التي قياسها في مصل الدم ونسيج الكلي. لقد أظهرت نتائج هذه الدراسة أن المعالجة بمستخلص جذور نبات حب الرشاد أدى الي تحسن معظم التغيرات التي تم استحداثها في ذكور الجرذان عن طريق الصوديوم نيتريت.