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RENOPROTECTIVE EFFECT OF *ERYNGIUM CAUCASICUM* IN GENTAMICIN-INDUCED NEPHROTOXIC MICE

S.H. ESLAMI[1], M.A. EBRAHIMZADEH[1], A. HAJIZADEH MOGHADDAM[2], S.F. NABAVI[1]*, N. JAFARI[2] and S.M. NABAVI[1, 2]

[1] *Pharmaceutical Sciences Research Center, College of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran*
[2] *Department of Biology, College of Sciences, University of Mazandaran, Babolsar, Iran*

Abstract - Recent studies show that hydrogen peroxide free radicals have an important role in the renal damage induced by Gentamicin. Previously we studied the hydrogen peroxide scavenging activity of *Eryngium caucasicum*. This work was conducted to evaluate the possible renoprotective effect of *Eryngium caucasicum* against Gentamicin-induced renotoxicity. Extracts at the doses 200 and 400 mg/kg/day for 10 consecutive days, by intraperitoneal route (i.p.) offered renoprotective action by change in the blood urea nitrogen (BUN), serum urea and creatinine. Results show that an extract at 400 mg/kg/day shows better activity than other tested samples. In conclusion, the extracts showed significant renoprotective activity compared with the control group.

Key words: Eryngium caucasicum, renotoxicity, Gentamicin, creatinine, urea, BUN

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INTRODUCTION

Aminoglycoside antibiotics are widely used in the treatment of gram-negative infections (Ho and Barza, 1987). Unfortunately, renal damage is a major side effects in 10-20% of patients using aminoglycoside antibiotics (Walker et al., 1999). It has been shown that aminoglycoside antibiotic-induced renotoxicity is recognized by direct tubular necrosis, which is localized mainly in proximal tubules (Pedraza-Chaverri et al., 2003). The exact mechanisms of aminoglycoside antibiotic-induced renotoxicity still remain unclear. Recent evidence shows that hydrogen peroxide (H_2O_2) radicals play an important role in aminoglycoside antibiotic mediated renotoxicity. Walker et al. (1999) have shown that the oxidative stress induced by gentamicin is responsible for renal damage. Some studies have reported that antioxidant administration alleviated nephrotoxicity that was induced by the antibiotic aminoglycoside (Pedraza-Chaverri et al., 2003). Free radical scavengers have been detected in a large number of natural products, including cereal grains, vegetables, fruits, plant extracts, etc (Milton, 2003; Mozaffarian, 2006). *Eryngium caucasicum* (Apiaceae) was found as a new cultivated vegetable plant in home gardens in northern Iran. Young fresh leaves are used as a food additive, cooked vegetable and for flavoring in the preparation of several local foods (Nabavi et al., 2008). A good antioxidant activity of *Eryngium caucasicum* Trautv. leaves has been reported recently (Moghaddam et al., 2010). Previously we reported potent free radical scavenging activity from different extracts of leaves and inflorescence of this plant (Nabavi et al., 2008; Ebrahimzadeh et al. 2009; Ebrahimzadeh et al., 2010). To the best of our knowledge there is no scientific report about the renoprotective effect of the aqueous extract of *Eryngium caucasicum* Trautv.

MATERIALS AND METHODS

Sample preparation

Eryngium caucasicum aerial parts were collected from the Sari Mountains, Mazandaran, Iran and identified by Dr. B. Eslami, assistant professor of plant systematics and ecology, Department of Biology, Islamic Azad University, Ghaemshahr, Iran. The materials were transported to the laboratory and kept at < 4°C within 24 h prior to sample preparation.

Preparation of extract

The material was oven dried at 38°C for 5 days. The dried material was coarsely ground (2-3 mm) before extraction. Materials were extracted by percolation method using methanol/water (80/20 w/w) for 24 h at room temperature. Extracts was filtered and concentrated under reduced pressure at 40°C using a rotary evaporator.

Animals

The study was performed on male NMRI mice of approximately the same age-group and body weight (2-3 weeks; 20-25 g), housed in ventilated cages at a temperature of 24 ± 2°C with a 12 h light/dark cycle and 60 ± 5% humidity. They were fed with standard laboratory animal feed, manufactured by the Pasteur Institute, Tehran, Iran. Water was provided *ad libitum*. All experiments were performed according to the norms of the Ethical Committee of the University of Mazandaran, Babolsar, which is in accordance with the national guidelines for animal care and use.

Renoprotective activity

Male NMRI mice were divided into six groups, each comprising ten mice. The groups and treatments were as follows. I) Control group: received isotonic normal saline intraperitoneally. II) Gentamicin-treated group: received 100 mg/kg/day GM intraperitoneal route for 8 consecutive days. III) GM and low dose extract treated group: received 100 mg/kg/day GM by intraperitoneal (i.p.) route and 200 mg/kg/day extract by intraperitoneal (i.p.) route for 10 consecutive days. IV) GM and high dose extract treated group: received 100 mg/kg/day GM by intraperitoneal (i.p.) route and 400 mg/kg/day extract by intraperitoneal (i.p.) route for 10 consecutive days (Moghaddam et al., 2010). After the last application, the animals were anesthetized with ketamine (60 mg/kg) and xylazine (5 mg/kg) given intraperitoneally. Blood samples were collected through retro-orbital puncture after 24 h (Moghaddam et al., 2010). The serum was rapidly separated and processed for determination of blood urea nitrogen (BUN), serum urea and creatinine using commercially available kits.

Statistical Analysis

The values are presented as means ± SD. Differences between group means were estimated using a one-way ANOVA followed by Duncan's multiple range test. Results were considered statistically significant when $p<0.05$.

RESULTS AND DISCUSSION

In this study we examined the possible renoprotective effect of an extract against renal injury induced by gentamicin (Table 1). The results show that administration of gentamicin at a dose of 100 mg/kg/day for 8 consecutive days brought about a significant increase in BUN, serum creatinine and urea and an extract in 200 and 400 mg/kg/day has recovery effects (Table 1).

The effects induced by gentamicin were significantly reduced by the extract, providing further evidence that this plant has the potential to be used in the treatment of renotoxicity induced by gentamicin. Recently, it has been shown that *Eryngium caucasicum* can act as a free radical scavenger (Liao et al., 2001). Free radicals play an important role in the renal injury induced by gentamicin (Kadkhodaee et al., 2005). Therefore, *Eryngium caucasicum* with its antioxidant and free radical scavenger properties may have the capacity to partially treat or eliminate the harmful effects caused by gen-

Table 1. Effect of extract on serum creatinine, serum urea, and blood urea nitrogen levels in gentamicin-induced renotoxic mice.

Groups	Serum creatinine μmol/l	Serum urea mg/dl	Blood urea nitrogen mg/dl
Gentamicin control (100 mg/kg, i.p.)	34.88 ± 8.54	119.56 ± 7.21	54.99 ± 3.31
Normal	24.05 ± 6.24	59.683 ± 6.30	27.45 ± 2.89
Extract-treated (200 mg/kg, i.p.)	30.90 ± 2.98 [A]	76.76 ± 6.42 [B]	35.87 ± 3.06 [B]
Extract-treated (400 mg/kg, i.p.)	26.19 ± 2.09 [B]	52.15 ± 3.83 [B]	24.37 ± 1.79 [B]

Values are mean ± SD (n = 10). Data for normal animals are considered as base-line data; there was no significant base-line difference between the groups.
[A] P>0.05 versus control group
[B] P<0.001 versus control group

tamicin. Results from many studies (Moghaddam et al., 2010) have shown that gentamicin produced an elevation in the concentrations of the biochemical parameters of kidney function i.e. BUN, serum creatinine and urea. BUN and serum creatinine and urea levels were augmented, indicating glomerular damage. However, the combined intraperitoneal administration of *Eryngium caucasicum* with gentamicin to mice resulted in a significant reduction in the elevated levels of BUN, serum creatinine and urea. These results could be in accordance with several other studies which reported that extracts with antioxidant properties like *Pleurotus porrigens* (Moghaddam et al., 2010) or garlic extract (Maldonado et al., 2003), partially prevented the increase in the BUN, serum creatinine and urea levels induced by gentamicin.

CONCLUSION

The tested extracts show the different effects on the biochemical parameters in gentamicin-induced renotoxic mice. These results can be beneficial for future studies of this plant and/or its constituents in pharmaceutical industries after performing clinical studies.

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