Potential action of *Rumex vesicarius* (L.) against potassium dichromate and gentamicin induced nephrotoxicity in experimental rats

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Abstract: To determine the ameliorative potential of the active fraction from different extracts of *Rumex vesicarius* against potassium dichromate and gentamicin induced nephrotoxicity in experimental rats and its possible mechanism of action. Both sex wistar rats were divided into 6 groups (n=6/group) were fed with a control, potassium dichromate and gentamicin supplemented with different extracts at the doses of 200 and 400mg/kg respectively. Oral administration of EERV offered a significant ($p<0.01$ and $p<0.001$) dose dependent protection against PD and GN induced nephrotoxicity. Potassium dichromate and gentamicin nephrotoxicity assessed in terms of body weight, kidney weight, creatinine, urea, uric acid, BUN, albumin and total protein. Thus the present study revealed that EERV phytochemical constituents play an important role in protection against kidney damage.

Keywords: *Rumex vesicarius,* potassium dichromate, gentamicin, serum markers, nephrotoxicity, kidney protection.

INTRODUCTION

Kidney is a major target indispensable excretory organ for exogenous toxicants (Sun and Aree, 2012; Li and Douglas, 2013; Margaret and Stephen, 2012), foreign chemicals, detoxification (Swaran and Vidhu, 2010; Margaret, 2013) and elimination of endogenous waste metabolites. Like liver, the renal system also faces high risk of toxicity (Natasha and Kymberly, 2010; Bruna *et al*., 2012). Disclosure to drugs and chemical reagents like ethylene glycol (Tarek *et al*., 2013), carbon tetra chloride (Lamiaa, 2014), potassium dichromate (Mahmoud, 2013; José *et al*., 2013), sodium oxalate (Robert *et al*., 2014) and heavy metals such as cadmium, mercury, lead and arsenic also persuades nephrotoxicity leads to acute kidney injury (Hong and Yan, 2015; José *et al*., 2013). Most scientists delineate AKI as an unexpected decline in glomerular filtration rate (GFR) reflected by the doublings of serum creatinine and azotemia (David *et al*., 2012; Robert and Mark, 2011). The underlying pathogenesis of kidney damage involves down regulation of endothelial nitric oxide synthase (eNOS) and upregulation of inflammatory mediators in kidney tubular cells that result in high intracellular concentrations (Kashihara *et al*., 2010; Yashpal *et al*., 2011). The parent chemical or a metabolite initiates toxicity through its covalent or non covalent binding to cellular macromolecules or through their ability to produce reactive oxygen species (Yeong-Chul *et al*., 2014; Sabry, 2010). Furthermore, cell injury was occurred by changes in the activity of the macromolecule (Lobo *et al*., 2010). For instance, mitochondrion, lysosome, plasma membrane of proteins, lipids, cytosol and nucleus all are the objects of toxicants (Dean *et al*., 2010). The toxicant cause oxidative stress in both lipid per oxidation and protein oxidation has been shown to contribute to cell injury (Kanti and Syed, 2010). Predisposing factors such as age, pharmacokinetics, underlying disease, dose of the toxic substance, concomitant medication determine and influence the severity of nephrotoxic insult (David *et al*., 2012).

Rumex vesicarius (L.) is a valuable potent medicinal herb, which belongs to family Polygonaceae, commonly known as "Bladder dock or Chukkakura or Khatta palak". Leaves are rich in ascorbic acid, tartaric acids and citric acid (Ashok *et al*., 2013). The aerial parts of this plant and other species of rumex also contain anthraquinone derivatives and flavonoids like emodin, chrysophanol, chrysophanic acid, physcion, isovitexin, isoorientin, quercetin, kaempferol and luteolin glucosides have been detected (Zahed *et al*., 2012). A literature review discloses antibacterial (Tajdar *et al.,* 2014, antioxidant effect (Tajdar *et al.,* 2014), anti-hyperglycemic activity (Ashok *et al*., 2013), diuretic effect (Tajdar *et al.,* 2014), antimicrobial activity (Raid *et al*., 2014), antipyretic, anti emetic, spasmogenic and spasmolytic activity (Khalid *et al*., 2014). The high levels of phenolic compounds, omega 3-fatty acids are isolated and exhibited influential antioxidant activities (Sinéad *et al*., 2011; Mohammad, 2011). In vitro and in vivo study reported *R. vesicarius* against cytotoxicity, protection of kidney and liver (Asha *et al*., 2015). Therefore, the present study was designed to assure nephroprotective effect of phytochemical constituents of *R. vesicarius.* Hence, the attempt is made for the evaluation of different extracts of *Rumex vesicarius* in chemical induced kidney damage in rats.

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MATERIALS AND METHODS

Chemicals

Potassium dichromate was procured from Fisher Scientific, Mumbai, India. Gentamicin was obtained from Ranbaxy, Gurgaon, India. Creatinine, urea, uric acid, albumin and total protein kits were procured from Span Diagnostics, Surat, India. All other reagents and solvents were of an analytical grade.

Experimental animals

The study was approved by the institutional animal ethical committee of Ratnam institute of Pharmacy, Nellore, Andhra Pradesh. India (Ethical approval No.1558/po/a/11/CPCSEA). Wistar albino rats of either sex weighing between 150 to 200g were obtained from animal facility and housed (six animals per cage at 25± 5°C). The relative humidity maintained between 55-58%. The animals were allowed to have free access to tap water and standard laboratory pellet *ad libitum*.

Collection and identification of the plant materials

The fresh leaves of *R. vesicarius* were collected in the month of March and April 2014 from the village Pedur in Nellore district, Andhra Pradesh, India. The plant material was taxonomically identified and authenticated by expert botanist Dr. CVS Bhaskar, Principal in the department of botany, V.R College, Nellore. A voucher specimen of the plant is conserved under the reference number VRC/09/2014 and deposited at the college for further reference.

Preparation of the extracts

The crushed mass of leaves defatted with petroleum ether for 12 hours at 60 to 80°C and carried out in the process of continuous hot soxhlet extraction and decoction using organic solvents such as ethanol and water. Ethanol was recovered under reduced pressure by vacuum distillation at 350°C. The obtained resultant yield of dried ethanolic and aqueous extracts was 18.76% and 35.78% w/w respectively, and stored in refrigerator in an airtight container until use.

Phytochemical screening

The ethanolic and aqueous extracts of *Rumex vesicarius* were subjected to various phytochemical screening (Tajdar *et al*., 2014; Raid *et al*., 2014).

Acute toxicity study

After administration of 5mg/kg, 50mg/kg, 500mg/kg and until 2000 mg/kg dose of different extracts of *R. vesicarius*, the animals didn't show a behavioral abnormality, dyslipidemia, toxic or mortality in rats. Hence, *R. vesicarius* a dose of 200 and 400 mg/kg, p.o. was selected for further pharmacological investigations.

Potassium dichromate-induced nephrotoxicity in rats

Thirty six rats of either sex were allocated to six groups (n=6). A single dose of potassium dichromate (15 mg/kg/ml) administered subcutaneously in the neck region in a volume of 1 ml/kg, especially on the fourth day to all the animals except normal control. Group I served as a normal control, rats received normal food and water ad libitum orally; Group II considered as negative control, rats received potassium dichromate (15 mg/kg/ml, b.w/day, s.c) on the fourth day; Group III and IV rats received an ethanolic extract of *R. vesicarius* 200 and 400mg/kg b.w/day p.o for 5 consecutive days. Group V and VI rats received an aqueous extract of *R. vesicarius* 200 and 400mg/kg, b.w/day, p.o for 5 consecutive days. After 24h, each animal body weights were calculated. Blood samples were collected by retro orbital puncture under diethyl ether anesthesia and serum was separated by centrifugation. After blood collection animals were euthanasia and postmortem examination was performed (Sahu *et al*., 2014; Parveen *et al*., 2009; Yam-Canul *et al*., 2008).

Gentamicin-induced nephrotoxicity in rats

Thirty six rats were divided into 6 groups of six each. Group I served as normal control without any treatment. Group II served as negative control, rats received gentamicin sulphate injection (100mg/kg, b.w/day, i.p) for 8 successive days. Animals of group III and IV were administered gentamicin sulphate prior to ethanolic extract of different doses of *R. vesicarius* (200 and 400 mg/kg) was administered for 8 successive days. Animals of group V and VI served gentamicin sulphate prior to aqueous extract of different doses of *R. vesicarius* (200 and 400mg/kg) was administered for 8 successive days.

At the end of the study, all rats were euthanized by cervical dislocation after overnight fasting and postmortem examination was performed. Before the euthanasia, blood was collected from the retro-orbital sinus plexus under mild ether anaesthesia. (Jafarey *et al*., 2014; De *et al*., 2010; Patil *et al*., 2010)

Biochemical study

Serum biochemical parameters such as creatinine, urea, uric acid, blood urea nitrogen, albumin and total protein were analyzed.

STATISTICAL ANALYSIS

All the results were expressed as Mean ± standard error mean (SEM) for six animals in each group. Statistical significance was carried out using one way analysis of variance (ANOVA), followed by Dunnet's test using computer based fitting program and significance was set accordingly.

RESULTS

Phytochemical evaluation

Phytochemical evaluation of the ethanolic and aqueous extract of *Rumex vesicarius (L.)* showed the presence of

alkaloids, flavonoids, glycosides, saponins, sterols, triterpenoids, tannins, phenols, proteins, amino acids and quinones constituents (table 1).

Acute toxicity study

After administration of 5mg/kg, 50mg/kg, 500mg/kg, 1000mg/kg and until 2000mg/kg dose of different extracts of *Rumex vesicarius (L.)*, the animals didn't show a behavioral abnormality, dyslipidemia, toxic or mortality in rats. Hence, *Rumex vesicarius (L.)* a dose of 200 and 400 mg/kg, p.o. was selected for further pharmacological investigations.

Potassium dichromate induced changes on rat body weight, kidney weight and various serum biochemical activities

As shown in table 2 and 3, Potassium dichromate caused a significant decrease in rat body weight and increased kidney weight with potentially increased serum creatinine, urea, uric acid and BUN. Results have shown that decreasing the level of albumin as well as total proteins. EERV (200 and 400mg/kg) treated rats showed a dose dependent significant ($p<0.01$ and $p<0.001$) response against nephrotoxicity.

Gentamicin induced changes on rat body weight, kidney weight and various serum biochemical activities

Gentamicin caused a significant decreased rat body weight and increased kidney weight accompanying with increased in serum creatinine, urea, uric acid, blood urea nitrogen (BUN), decreased albumin and total proteins. *R. vesicarius* treated rat's attenuated significant response against gentamicin induced nephrotoxicity. Moreover, biochemical parameters such as creatinine, urea, uric acid, blood urea nitrogen, albumin and total proteins significantly reverse to normal range.

DISCUSSION

The present investigation was undertaken to assess the influence of *Rumex vesicarius* in phytochemical constituents of flavonoids (Walid *et al*., 2013), triterpenoids (Tajdar *et al*., 2014) and phenolic (Shreya *et al*., 2013) compounds play an important role of anti-oxidant and protective effect of kidney damage (Munehiro and Daisuke, 2013). As shown in table 4, potassium dichromate treated rats shown a decreased body weight and increased the kidney weight (Elshazly *et al*., 2015).

Paola et al (Paola *et al*., 2008) showed that the kidney is the principal route of Cr excretion and acute exposure of some chemicals elevation of serum Cr in experimental rats. It is characterized by the formation of hydrogen peroxide, ascorbate and glutathione induce oxidative stress (Scott and Malcolm, 2008). As shown in table 3, potassium dichromate treated rats showed an increase in the Cr level, which play a key role in the adverse biological effects (Khan *et al*., 2010).

Potassium dichromate alterations in renal function and down-regulate the renal brush border membrane (BBM) activity. Potassium dichromate induced nephrotoxicity was analyzed by serum creatinine, urea, uric acid, BUN, albumin and total proteins. A single dose of potassium dichromate resulted increase the serum enzymes like BUN and creatinine. After administration of K2Cr2O7 to increase lipid peroxidation and decrease in total sulfhydryl groups (Fatima and Mahmood, 2007)

Han et al study shown that tissue pathological abnormalities were observed in the liver of rats treated with K2Cr2O7 in a time-dependent fashion that correspond with the increase in the activity of plasma enzymes. The redox alterations caused by oxidative agents like Cr (VI) compounds have been shown to induce apoptosis and necrosis in hepatocytes and other cells (Behnam *et al*., 2008; Anita *et al*., 2009). Moreover, dichromate exposure damage in hepatocytes (Anita *et al*., 2009) and kidney (Boşgelmez and Güvendik, 2004). Kidney sections revealed degeneration of tubular epithelial cells, cystic dilatation of tubules, hyaline casts, congestion of blood vessels and dilation of bowman's space. Previous studies (Acharya *et al*., 2001; Da *et al*., 2006) shown that Cr VI induces free radical production by multiple mechanisms leading to peroxidation effect, which in the present study was revealed by a significant decrease in antioxidant markers such as SOD and GSH.

In the present study, we investigated nephro-protective and underlying mechanisms of *R. vesicarius* in rat model. Subcutaneous injection of potassium dichromate at single dose resulted in a significant increase serum creatinine and blood urea nitrogen. Earlier study documented, a single dose administration of potassium dichromate to produce the inflammation and apoptosis response (Sahu *et al*., 2014). Moreover, protective effect of *R. vesicarius* significantly restored the rat body and kidney weight. K2Cr2O7-treated rats showed significant increases in serum markers. Treated with *R. vesicarius* significantly decreased ($p<0.01$ and $p<0.001$) serum BUN, creatinine and uric acid. Parveen et al reported K2Cr2O7 treated rats showed a significant increase in serum markers like the ALP, Scr and BUN (Parveen *et al*., 2009). Our study evidenced that ethanolic extract of *R. vesicarius* preventing nephrotoxicity. K2Cr2O7 treated rats significantly increase in uric acid, malondialdehyde, superoxide dismutase and creatinine (Soudani *et al*., 2010). Mohammad et al demonstrated that fed with potassium dichromate showed a significant reduction in Albumin and total protein. Acute chemical exposure altered in normal albumin and total protein ratio levels. We investigated the EERV significantly increase the albumin and total proteins (Mohammad *et al*., 2014).

Table 1: Preliminary phyto-chemical studies of the different plant extracts of *R. vesicarius*

S. No.	Chemical Tests	Ethanolic Extract	Aqueous Extract
1.	Tests for alkaloids	+	+
2.	Tests for flavonoids	+	+
3.	Tests for glycosides	+	+
4.	Tests for saponins	+	+
5.	Tests for sterols and triterpenoids	+	+
6.	Tests for tannins	+	+
7.	Tests for phenols	+	+
8.	Tests for proteins and amino acids	+	+
9.	Test for quinones	+	+

Where, +: positive

Table 2: Effect of ethanolic and aqueous extract of *Rumex vesicarius* (L.) on body and kidney weight of potassium dichromate induced nephrotoxicity in rats.

Groups	Body weight (gm)	Kidney weight (gm)
Normal Control	179.5±2.141	0.410±0.012
Toxicity Control	130.2±2.386^{**a}	0.678±0.008^{**a}
EERV 200mg/kg	162.0±1.563^{**b}	0.503±0.015^{**b}
EERV 400mg/kg	171.2±2.124^{**b}	0.466±0.009^{**b}
AERV 200mg/kg	145.4±1.920^{*b}	0.581±0.022^{*b}
AERV 400mg/kg	158.5±2.545^{*b}	0.525±0.027^{*b}

Table 3: Effect of ethanolic and aqueous extract of *Rumex vesicarius* (L.) leaves on potassium dichromate induced nephrotoxicity

Groups	Creatinine (mg/dl)	Urea (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)	Albumin (g/dl)	Total protein (g/dl)
Normal Control	0.625±0.051	36.00±2.110	4.968±0.276	18.15±0.913	3.865±0.241	6.850±0.267
Toxicity Control	3.863±0.101^{**a}	87.11±3.950^{**a}	12.62±0.381^{**a}	38.59±2.571^{**a}	1.820±0.167^{**a}	2.842±0.373^{**a}
EERV 200mg/kg	1.350±0.136^{**b}	50.40±2.27^{**b}	7.090±0.332^{**b}	24.33±1.874^{**b}	2.938±0.185^{**b}	5.163±0.176^{**b}
EERV 400mg/kg	0.841±0.158^{**b}	42.15±2.14^{**b}	5.915±0.188^{**b}	20.84±0.900^{**b}	3.542±0.216^{**b}	6.224±0.291^{**b}
AERV 200mg/kg	2.072±0.181^{*b}	61.76±3.55^{*b}	9.262±0.297^{*b}	30.18±1.601^{*b}	2.676±0.154^{*b}	4.561±0.215^{*b}
AERV 400mg/kg	1.728±0.094^{*b}	52.82±1.59^{*b}	8.150±0.225^{*b}	26.11±1.997^{*b}	3.427±0.162^{*b}	5.989±0.160^{*b}

Table 4: Effect of ethanolic and aqueous extract of *Rumex vesicarius* (L.) on body and kidney weight of gentamicin induced nephrotoxicity in rats.

Groups	Body weight (gm)	Kidney weight (gm)
Normal Control	215.0±4.082	0.530±0.010
Toxicity Control	158.3±3.343^{**a}	0.814±0.009^{**a}
EERV 200mg/kg	194.2±3.005^{**b}	0.628±0.014^{**b}
EERV 400mg/kg	208.5±2.814^{**b}	0.571±0.015^{**b}
AERV 200mg/kg	178.7±3.071^{*b}	0.714±0.006^{*b}
AERV 400mg/kg	190.1±4.014^{*b}	0.656±0.012^{*b}

Table 5: Effect of ethanolic and aqueous extract of *Rumex vesicarius* (L.) leaves on gentamicin induced nephrotoxicity

Groups	Creatinine (mg/dl)	Urea (mg/dl)	Uric acid (mg/dl)	BUN (mg/dl)	Albumin (g/dl)	Total protein (g/dl)
Normal Control	0.940±0.144	33.69±2.841	6.285±0.227	16.83±0.974	4.737±0.127	8.314±0.105
Toxicity Control	2.852±0.125^{**a}	51.87±1.862^{**a}	10.31±0.202^{**a}	30.06±0.907^{**a}	2.732±0.195^{**a}	4.517±0.224^{**a}
EERV 200mg/kg	1.563±0.115^{**b}	39.91±1.425^{**b}	7.583±0.180^{**b}	20.92±0.788^{**b}	3.728±0.116^{**b}	6.392±0.229^{**b}
EERV 400mg/kg	1.182±0.1 38^{**b}	36.04±1.633^{**b}	6.710±0.188^{**b}	18.25±0.603^{**b}	4.045±0.157^{**b}	7.512±0.170^{**b}
AERV 200mg/kg	1.916 ±0.130^{*b}	43.80±1.226^{*b}	8.764±0.274^{*b}	25.12±0.941^{*b}	3.397±0.138^{*b}	5.635±0.216^{*b}
AERV 400mg/kg	1.684±0.122^{*b}	39.86±1.912^{*b}	7.905±0.302^{*b}	22.44±0.761^{*b}	4.422±0.139^{*b}	7.681±0.194^{*b}

Values are expressed as mean ± SEM; n=6 animals in a group; One Way ANOVA followed by Dunnet's t-test. *= p<0.01, ** = p<0.001; a = comparison to normal control group; b = comparison to potassium dichromate treated group.

Nanami Gotoh *et al* (Nanami *et al*., 2010) study demonstrates that gentamicin induces a significant degree of nephrotoxicity by entering into the tubular cell via the multi ligand receptor megalin and then uptake via a clatharin coated pit. Gentamicin complexes with iron, which catalyse the formation of ROS (Andrew *et al*., 2010) and the present study, may also express the same effect. Servais et al has found that the gentamicin causes release of the pro apoptotic condition. The study reflected that gentamicin directly or indirectly via ROS causes a key step in apoptosis (Servais *et al*., 2008). Previous studies showed ROS cause an increase in the gene expression of oxidative stress, which alters the decrease the GFR (Swaran, 2009). Past (Pradeep, 2010) report expressed, changes in the level of serum creatinine, urea, uric acid and blood urea nitrogen concentrations shown that impairment of kidney function in nephropathy as well as current study confirmed with this effect.

As shown if table 4, gentamicine treated animals significantly increased the kidney weight and decreased the body weight. The current results were strengthened by others which declared that gentamicine treated rats showed altering of oxidative markers with a significant increase in SOD, creatinine and urea levels, associated with a significant decrease in total proteins and albumin (Soudani *et al*., 2010). Our present study evaluated that ethanolic extract of *R. vesicarius* showed a dose dependent action against gentamicine induced nephro-toxicity. *R. vesicarius* supplemented rats resulted significant reduction in serum creatinine, urea, BUN and uric acid. Previous report expressed that gentamicine induced nephrotoxicity is a well known experimental model in rats (Rahul *et al*., 2014). Present study reported, rat kidneys protected by the plant extract of *R. vesicarius* from gentamicin-induced nephrotoxicity as evident from a decrease in the serum creatinine and urea level (Patil *et al*., 2010). Gentamicine induced nephrotoxicity rats markedly increased serum creatinine and urea, as well as decrease the kidney function and infiltration of inflammatory cells. Gentamicine induced nephrotoxicity characterized by acute tubular necrosis and diffuse hyaline cast formation in lumen (Gholamreza *et al*., 2013). Furthermore, *R. vesicarius* treated rats noticeably increased serum total protein and albumin when, compared with gentamicine treated animals (Kakalij *et al*., 2014). Gentamicine treated rats exhibited elevation of the nitric oxide level, therefore, increasing the inflammation leading to cellular damage (Ghaznavi and Kadkhodaee, 2007). As shown in table 5, Gentamicine treated animals significantly elevated the levels of serum creatinine, urea, uric acid, blood urea nitrogen, total proteins and albumin. The protective effect of EERV (200 and 400 mg/kg) significantly prevented the elevation of serum creatinine, urea, uric acid, blood urea nitrogen, total proteins and albumin in a dose dependent manner.

Vitamin E, a lipid soluble membrane localized anti-oxidant, protects cells and tissues from oxidative damage induced by a wide variety of free radicals. It functions as a chain breaking anti-oxidant that prevents the propagation of free radical reaction and preserves cell membranes by protecting against lipid peroxidation through reaction with lipid peroxyl radicals and conversion to a non-reactive tocopheroxyl radical (Chi-Ming *et al*., 2014). In the present study, the analysis of GCMS (Fig.1) is shows retention time 26.83 as considered vitamin E ($C_{29}H_{50}O_2$) when vitamin E was supplemented along with potassium dichromate and gentamicin, a remarkable resurgence was observed in all the parameters.

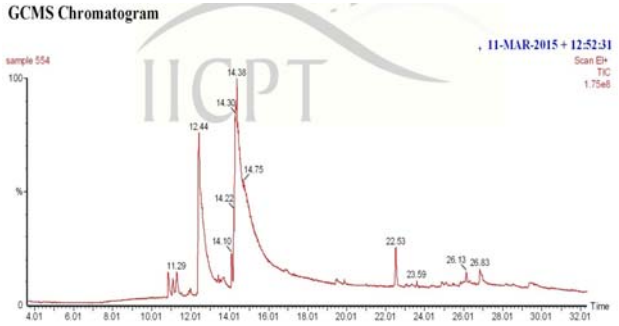

Fig. 1: GCMS of Ethanolic extract of *Rumex vesicarius*

The results of the present study agreed with earlier findings of a reduction in the anti-oxidant markers with simultaneous increase in peroxidation markers and functional markers in rats under the Cr influence (Samuel *et al*., 2012). In this study, it was clearly revealed that concurrent administration of ethanolic extract of *Rumex vesicarius* (L.) significantly satisfied with the physiological variations induced by potassium dichromate and gentamicin (Sang *et al*., 2013) as compared to water extract might be due to the phytochemical constituents like flavonoids, alkaloids, tannins, anthraquinones, etc. present in it. Omonhinmin et al study found that some of these phytoconstiuents have a potential nephroprotective activity which acts as antioxidants synergistically or individually (Omonhinmin *et al*., 2013).

CONCLUSION

Thus the present experimental study investigation, it is concluded that at the doses of 200 and 400mg/kg of EERV possessed potential useful nephro-protective activity since it gives a positive result in controlling kidney damage in potassium dichromate and gentamicin induced nephrotoxicity model in rats. The results reflected may have beneficial and reducing risk factors for nephropathy.

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