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Research Article

EFFECT OF AQUEOUS LEAF EXTRACT OF *EUPHORBIA HETEROPHYLLA* ON KIDNEY, LIVER AND PANCREATIC FUNCTIONS AND PLASMA ELECTROLYTES IN RABBITS

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ABSTRACT

Although the use of *Euphorbia heterophylla* as herbal laxative in Nigeria is associated with severe and sometimes life-threatening side effects, not much is known about the toxic effect of the herb. This study was designed to assess the effect of aqueous leaf extract of the plant on some vital organ functions in rabbits. Three groups of rabbits (six rabbits/groups) were used. Two groups received either 10 mg or 20 mg of aqueous extract/kg body weight for 18 days via oro-gastric route. Members of the third group received saline and served as controls. On the 18th day, the rabbits were sacrificed following an overnight fast and blood samples were collected via the ear veins in heparinised bottles for plasma preparation. The kidney, liver and pancreas were quickly dissected out and weighed portions were used in preparation of tissue homogenates for biochemical analysis. Using standard procedures, alkaline phosphatase (ALP), aspartate transaminase (AST) gamma glutamyl transferase (GGT), alanine transaminase (ALT), electrolytes (Na^+, K^+ and Cl^-), blood urea nitrogen (BUN), creatinine, total proteins and albumin were assayed either in tissues or in plasma or both. The results obtained showed that the extract significantly and dose-dependently decreased plasma Na^+, urea and creatinine, while plasma Cl^- and K^+ were significantly elevated relative to control ($P < 0.05$). The extract also significantly increased fasting blood glucose and plasma amylase ($P < 0.05$). On the other hand, pancreatic protein and pancreatic amylase were significantly decreased. The plasma levels of GGT, AST and ALP were significantly higher in the extract-treated rabbits, while the activities of the enzymes were significantly decreased in the liver ($P < 0.05$). ALT did not follow a definite pattern, initially significantly decreasing in plasma and then increasing at the higher extract dose, while the activity of the enzyme significantly increased dose-dependently in the liver ($P < 0.05$). The extract significantly decreased liver and kidney total protein as well as plasma total protein and plasma albumin ($P < 0.05$). These results suggest that *E. heterophylla* may have toxic effects on vital organs and may provide a basis for rationalizing the adverse health effects frequently associated with the use of this herbal laxative.

Keywords: *Euphorbia heterophylla*, toxicity, liver, pancreas, kidney, plasma electrolytes.

INTRODUCTION

Euphorbia heterophylla (spurge weed) is a medicinal shrub that grows freely in the savannah and tropical forest zones. The leaves of the plant serve diverse ethno-medicinal purposes in many cultures[1]. In India, the leaves are used for treating diabetes[2]. In Nigeria, the plant is employed in the treatment of bronchitis, asthma and constipation[3]. The plant is also used for as a lactogenic agent[4] and for curing gonorrhea[5]. Studies have shown that *E. heterophylla* exhibits antibacterial activity[6,7], as well as laxative activity[8]. Indeed in Nigeria, the plant is more popular for its laxative properties than for any other use. Results from phytochemical screening have shown that *Euphorbia heterophylla* is rich in alkaloids, flavonoids and tannins, but low in saponins[9]. The laxative property of *E. heterophylla* has been ascribed to synergistic effect of phorbols and bulk-forming disaccharides in the plant[8]. This laxative effect is so strong that amongst the Igbo ethnic group in Nigeria it has earned the cautionary sobriquet *mere nga 'le ri*, which literally warns consumers to be careful over the dose of the herb taken due to serious health consequences of over-dose. This warning probably arose from the frequent incidents of mortality and severe debilitation observed in rural dwellers that use aqueous extracts of the herb as laxative. Incidents of victims being unable to walk home on their own, or collapsing and dying in the bushes from too frequent defecation are indeed not uncommon. Nevertheless the laxative uses of the herb has not stopped, due probably to poverty of rural dwellers and the problem of high cost of orthodox healthcare. In view of the health hazards associated with this herb, this study was carried out to assess the effect of its aqueous leaf extract on plasma electrolytes and some vital organ functions in an experimental animal model. This is with a view to exploring the scientific basis for the perceived toxic effects of the plant.

MATERIALS AND METHODS

Collection of plant material and preparation of extract

Fresh aerial parts of *Euphorbia heterophylla* were collected from the bush in Asaba, Delta State, Nigeria. The plant was identified by a Taxonomist at the Department of Plant Biology and Biotechnology, University of Benin, and a voucher specimen (voucher number UBHe0152b) was deposited at the herbarium of the Department. The leaves were washed in running water to remove sand and debris and oven-dried at 50^{o}C for 7 days. Subsequently the dried leaves were pulverized in a blender and extracted in boiling water. In essence, 50 g of pulverised material was soaked in 1L of hot water (100^{o}C) in a beaker and allowed to stand at room temperature (27^{o}C) for 1 h. It was then filtered through a Buchner funnel, and the extract obtained was evaporated to dryness at reduced pressure in a rotary evaporator. The residue obtained was kept refrigerated at 4^{o}C and used within two days.

Acute toxicity studies

The LD_{50} of the extract was determined by the method of Miller and Tainter as elaborated by Randhawa[10]. Six groups of rabbits (6

rabbits/groups) were separately given by oro-gastric route, six graded doses of the extract i.e. 50 mg, 100 mg, 200 mg, 300 mg, 800 mg and 1600 mg/kg body weight. The animals were observed closely in the first 2 h and subsequently at 6 h and 24 h for signs of toxicity such as writhing, loss of coordination, mortality, convulsion and loss of fur. The number of dead rabbits at each dose and the mortality were obtained, and the % mortalities were converted to probits. The LD_{50} was calculated from a plot of probit against log dose.

Experimental animals, grouping and treatment

A total of 18 mixed breed English rabbits, aged about two months were purchased from a breeder at Aduwawa, Benin City, Edo State, Nigeria. The rabbits were maintained in clean rabbit hutches on grower's mash (Guinea Feeds Ltd, Benin City) and acclimatized to laboratory conditions for two weeks prior to the experiment. They were then randomly assigned to three groups, each having 6 animals. Rabbits in one group received the extract at a dose of 10 mg/kg body weight, while another group was given a higher dose of 20 mg/kg body weight. Extract administration was via oro-gastric tube. The third group of rabbits received saline in place of extract and served as controls. The experiment lasted for 18 days, during which the animals were maintained on grower's mash (Guinea Feeds Ltd, Benin) and drinking water *ad libitum*. The study was carried out in strict compliance with the ethics in Guidelines and Specifications on Experimental Animal Care[11]. On the 18th day, the rabbits were sacrificed after an overnight fast and blood was collected via the ear veins in heparinised bottles for preparation of plasma samples. The liver, pancreas and kidney were quickly dissected out and used for preparation of tissue homogenates for biochemical analysis.

Biochemical analysis

Fasting blood glucose was determined colorimetrically using Randox assay kits. Amylase was assayed colorimetrically using Randox kits, based on the ability of the enzyme to hydrolyse p-nitrophenyl-D-maltoheptoside (PNPG). AST and ALT were assayed colorimetrically by measuring the hydrazone derivatives of their keto acid products, according to manufacturer's instructions contained in Randox assay kits. AlP assay was carried out in a colorimetric reaction using Quimica Clinica Applicada assay kits, based on measurement of the amount of p-nitrophenol liberated from p-nitrophenyl phosphate, pNPP by the enzyme. GGT assay was carried out by monitoring the amount of 5-amino-2-nitroanilide released from gamma-glutamyl-3-carboxy-4-nitroanilide at 405 nm, as described in Randox assay kits. Protein was assayed using Randox assay kits according to manufacturer's instruction. Randox assay kits were also used for albumin determination, based on the quantitative binding of the protein to the indicator bromocresol green to form a colored complex which absorbs strongly at 578 nm. Plasma urea was estimated using Randox assay kits as per manufacturer's instruction. The assay is based on the Bethelot reaction, in which ammonia liberated from urea by urease reacts with phenol and hypochlorite to yield a blue-colored solution that absorbs at 630 nm. Creatinine was also assayed with Randox kits, based on the reaction of creatinine with alkaline picric acid. Cl^- was determined titrimetrically using $AgNO_3$ and K_2CrO_4 as indicator[12]. Na^+ and K^+ were estimated by flame photometry using appropriate standards.

Statistics

All data were expressed as Mean ± SEM of 6 replicates. Differences between means were analyzed with paired sample Student's t-test using SPSS package (version 15). P values < 0.05 were taken as significant.

RESULTS

Results for the effect of the extract administration on plasma and hepatic levels of ALP, AST, ALT and GGT are shown on Table 1A and Table 1B respectively. The *E. heterophylla* extract significantly and dose-dependently increased plasma activities of ALP, GGT and AST, with significant decreases in the liver activities of the three enzymes relative to control values ($P < 0.05$). A reverse trend was seen in ALT activity, which was significantly decreased in the plasma and significantly increased in the liver ($P < 0.05$).

Table 1A: Plasma levels of ALP, AST, ALT and GGT in the extract-treated groups and controls (U/L)

	Group 1	Group 2	Group3
ALP	3.25 ± 0.10^a	4.91 ± 0.02^b	10.15 ± 0.10^c
AST	26.83 ± 0.90^a	87.17 ± 0.30^b	48.87 ± 0.50^c
ALT	51.80 ± 1.00^a	23.39 ± 0.70^b	34.83 ± 2.00^c
GGT	2.93 ± 0.01^a	10.27 ± 0.30^b	13.43 ± 0.50^c

Values are mean ± SEM (n = 6). Those with different superscripts across differ significantly ($P < 0.05$)

Table 1B: Liver levels of ALP, AST, ALT and GGT in the treated rabbit groups and controls (U/g fresh weight)

	Group 1	Group 2	Group 3
ALP	127.07 ± 0.50^a	125.03 ± 0.03^b	79.05 ± 7.00^c
AST	218.33 ± 3.00^a	137.00 ± 3.00^b	169.67 ± 5.00^c
ALT	195.00 ± 1.00^a	201.33 ± 0.50^b	237.00 ± 0.50^c
GGT	15.73 ± 0.09^a	11.00 ± 0.01^b	13.44 ± 0.50^c

Data are expressed as mean ± SEM (n = 6). Those with different superscripts across differ significantly ($P < 0.05$)

Plasma urea was dose-dependently and significantly increased by the extract ($P < 0.05$) but the changes in plasma creatinine were not statistically significant (Table 2). The extract also brought about significant decreases in total protein in kidney ($P < 0.05$). Fasting blood glucose and plasma amylase activity were significantly higher in the extract-treated rabbits than in controls ($P < 0.05$). Pancreatic amylase levels increased initially but decreased significantly at the higher extract dose; however pancreatic total protein was significantly decreased in a dose-dependent manner by the extract ($P < 0.05$). Plasma total proteins and albumin were also significantly decreased in a dose-dependent manner in the two groups that received the extract ($P < 0.05$).

Table 2: Effect of *E. heterophylla* extract on plasma amylase, urea, creatinine, pancreatic amylase, fasting blood glucose and total protein content of pancreas, kidney and liver

	Group 1	Group 2	Group 3
Plasma urea (mg/dL)	1.86 ± 0.20^{a}	1.92 ± 0.20^{a}	3.49 ± 0.50^{c}
Plasma creatinine (mg/dL)	0.68 ± 0.06^{a}	0.61 ± 0.07^{a}	0.71 ± 0.08^{a}
Plasma glucose (mg/dL)	55.81 ± 0.07^{a}	69.14 ± 0.30^{b}	228.43 ± 3.00^{c}
Plasma amylase (U/L)	41.01 ± 5.00^{ac}	17.69 ± 2.00^{b}	47.44 ± 6.02^{c}
Pancreatic amylase (U/g tissue)	68.34 ± 0.50^{a}	99.02 ± 2.00^{ac}	77.99 ± 0.89^{ac}
Pancreatic protein (mg/g tissue)	83.92 ± 2.00^{a}	64.69 ± 0.70^{ab}	49.83 ± 0.70^{ac}
Kidney protein (mg/g tissue)	420.67 ± 1.00^{ac}	341.33 ± 0.40^{bd}	349.67 ± 6.67^{cd}
Liver protein mg	29.11 ± 0.80^{a}	24.49 ± 2.00^{b}	15.32 ± 1.11^{c}
Plasma total protein (mg/dL)	19.17 ± 0.40^{ac}	17.50 ± 0.80^{a}	13.00 ± 0.40^{c}
Plasma albumin (mg/dL)	4.21 ± 0.01^{a}	3.49 ± 0.10^{b}	2.12 ± 0.30^{c}

Values are mean ± SEM (n = 6). Those that have different superscripts across differ significantly ($P < 0.05$)

Table 3 shows the effect of the extract on some key plasma electrolytes. There was a significant reduction in plasma Na^+ concentration, and significant elevation of plasma K^+ and Cl^- ($P < 0.05$).

Table 3: Effect of aqueous extract of *E. heterophylla* on plasma levels of Na^+, K^+ and Cl^-

	Group 1	Group 2	Group 3
Na^+	132.00 ± 00^{a}	$125.46 \pm .23^{b}$	123.13 ± 0.40^{c}
K^+	4.82 ± 0.02^{a}	5.39 ± 0.01^{b}	5.60 ± 0.01^{c}
Cl^-	$115.60 \pm 0.30a$	133.21 ± 4.71^{c}	124.36 ± 2.33^{c}

Results are mean ± SEM (n = 6). Values with different superscripts across differ significantly ($P < 0.05$)

DISCUSSION

Constipation is one of the most common gastrointestinal problems known to man[13-15]. The disease has been linked to many factors such as inadequate water intake, physical inactivity and low fiber diets[16]. Constipation results in increased intestinal transit time due to decreased intestinal motility, which leads to less frequent evacuation of faecal matter[17]. Although the use of herbal purgatives for alleviation of constipation has gained acceptance in many cultures, this practice is not without some toxic consequences. It has been shown that although plants of *Euphorbia* species possess medicinal properties, they are also toxic[18]. Indeed *Euphorbia heterophylla* is listed as one of the toxic species of *Euphorbia* species[19]. In the present study, the LD_{50} of the *Euphorbia heterophylla* extract was 208 mg/kg. Arising from the fact that substances with LD_{50} below 5000 mg/kg have been classified as toxic[20], the LD_{50} value of 208 mg/kg, and the dullness, loss of fur, loose watery stools and weakness observed in the rabbits during the acute toxicity study strongly suggest that the extract is toxic. The loose, watery droppings are evidence of the laxative effect of the plant. The toxicity of the extract is further manifested in the significant and dose-dependent increases in plasma levels of AST, ALP and GGT, which were accompanied by significant, though not commensurate decreases in the hepatic activities of these enzymes. Elevation of plasma levels of transaminases, ALP and GGT are associated with cellular lesions due to hepatotoxic agents[21]. ALT is very abundant in the cytoplasm of hepatocytes, and so is more specific for predicting liver damage than AST. Although the extract significantly decreased plasma ALT, the elevation of AST, ALP GGT and the significant reduction in plasma protein suggest that the extract is hepatotoxic. Elevations in plasma AST, ALT, AST, GGT and lowered plasma proteins are included in current clinical biomarkers of hepatic injury[21]. Moreover, the extract-induced significant reduction in liver protein, plasma total protein and plasma albumin indicate likely impairment of liver synthetic ability. The extract at a dose of 20 mg/kg body weight, raised the fasting blood glucose to a level 4 times the control value, and significantly increased plasma amylase and pancreatic protein levels. These results suggest that the use of the extract may predispose consumers to acute pancreatitis and hyperglycemia. Elevation of blood amylase is a marker of acute pancreatitis[22]. In addition, the extract-induced increase in blood urea nitrogen suggest impairment of kidney function, and is in agreement with a previous report of herbal laxative-induced changes in serum urea, electrolytes and creatinine in *Aloe vera*-treated rats[23]. The extract-induced significant decreases in plasma Na^+ and increases in plasma Cl^- and K^+ is not surprising. Many natural laxatives bring about accumulation of fluid and increased colonic motility by decreasing Na^+ absorption and increasing Cl^- secretion[24]. Sodium ion depletion in blood has been associated with the laxative effects of some *Aloe vera* species in rabbits[25], and in humans[26]. Thus the decrease in plasma Na^+ might have arisen from increased loss of the electrolyte via the loose, watery stool due to the laxative effect of the extract. Decreased Na^+ and water absorption during the use of some laxatives have been attributed to disruption of colonic epithelial cell ion gradient due to inhibition of Na^+-K^+-ATPase and decreased ATP[27,28]. This is true especially for anthranoid herbal laxatives. Anthranoids are absent in *E. heterophylla* but the plant contains phorbols to which its laxative effect has been ascribed[8]. Phorbol esters inhibit Na^+-K^+-ATPase[29]. Na^+ is a major and very important extracellular electrolyte[30]. Its depletion in blood leads to dehydration and hypotension[31,32]. Since the extract significantly decreased plasma Na^+, and since phorbol esters inhibit Na^+-K^+-ATPase, it is likely that *E. heterophylla* may exert its laxative effect through a mechanism related to that of the anthranoid herbal laxatives.

CONCLUSION

Taken together, it seems reasonable to suggest that the results obtained in this study indicate that the extreme weakness and fatalities associated with the use of *E. heterophylla* as a laxative may be due to dehydration and toxic effect of the herb on some vital organs. Thus it would appear that the traditional admonition for caution in the use of this herbal laxative may not be misplaced, especially for individuals whose overall health status and medical history are uncertain.

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