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Full Length Research Paper

Toxicological evaluation of the aqueous extract of *Felicia muricata* Thunb. leaves in Wistar rats

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The effect of the aqueous extract of *Felicia muricata* leaves at 50, 100 and 200 mg/kg body weight in Wistar rats was evaluated for 14 days. The extract caused significant increase in white blood cell (WBC) while it decreased the large unstained cells (LUC). The red blood cell (RBC), packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), neurophils, eosinophils and gamma-glutamyl transferase (GGT) compared favourably with the control. There was no significant difference in haemoglobin (Hb) and alanine aminotransferase (ALT) at both 50 and 100 mg/kg, but at 200 mg/kg, there was slight reduction in both parameters. The extract caused progressive significant increase in platelets concentration. The lymphocytes level was significantly higher at 50 and 100 mg/kg. The extract at all doses did not significantly alter the levels of Na, K, Cl, inorganic phosphorus, urea, creatinine, total bilirubin, globulin, total protein, total cholesterol, high density lipoprotein-cholesterol (HDCL-C) and low density lipoprotein-cholesterol (LDL-C). The liver- and kidney-body weight ratios were not altered by all the doses except an increase in kidney-body weight ratio by the 200 mg/kg body weight of the extract. The concentration of triacylglycerol was increased by the 50 and 100 mg/kg body weight, while that of alkaline phophatase did not follow any regular pattern. There was reduction in the concentration of aspartate aminotransferase (ALT) from 50 to 200 mg/kg body weight. The alterations on some hematological and liver function parameters were an indication that the extract possessed selective toxicity.

Key words: *Felicia muricata,* hematological parameters, serum lipids, function indices, selective toxicity.

INTRODUCTION

Plants are used for various purposes in this world. Their usefulness can be in the form of food, shelter, textile, medicine and many more (Fabeku, 2006). Exploring the pharmacological potentials of plants for both preventive and curative therapies is an age old concept. Records of indigenous knowledge from various parts of the world illustrate an age long tradition of plant being a major bioresources base for health care (Cowan, 1999; Stepp and Moerman, 2001; Yesilada, 2005). There are over a hundred chemical substances that have been derived from plants for drugs and medicines. For example, antimalaria drug, artemisinin from *Artemisia annua*, anti-inflammatory drug, aescin from *Aesculus hippocastanum* and many others. However, many plants have also been reported to be toxic to both human and animals. For example, *Vernonia molissima*, *Datura stramonium* and *Solanum aculeastrum* were reported to be highly nephrotoxic and hepatotoxic to livestocks and humans (Do¨ bereiner et al., 1976; Tokarnia et al., 1986; Ertekin et al., 2005; Koduru et al., 2006). It should therefore, be emphasized that the traditional use of any plant for medicinal purposes, by no means, warrants the safety of such plant, particularly with regard to mutagenicity, carcinogenicity, embryotoxicity, nephrotoxicity and hepatotoxicity, where the effects are rather complex and not easily recognized by the local/rural populations. Plants in folk medicine should therefore, be evaluated for safety or toxicity and necessary recommendations made on their use.

Felicia muricata Thunb., belongs to the family Asteraceae, which is a botanical family of enormous importance in the traditional medicine (Heinrich et al., 1998). The plant is a small, drought resistant, perennial, aromatic

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herb growing up to 0.2 m in height. In the Eastern Cape Province of South Africa, the rural dwellers use the species in the management of headache, pains, inflammation (Hutching, 1989a, b; Hutchings and Van Staden, 1994), as well as stomach, catarrh and cancer. According to McGaw et al. (1997), aqueous extracts from the plant showed 80 - 90% inhibitory activity against cyclooxygenase, an important enzyme in the prostaglandin biosynthesis pathway. *In vitro* studies of the extracts and essential oil from this herb have implicated the plant in the possession of strong antibacterial and antifungal activities (Ashafa et al., 2008a,b). Notwithstanding the widespread use of infusions, decoctions and poultices of *F. muricata* in the South African folk medicine, no study on the toxic effects of these preparations has been carried out before the commencement of this project. This study was therefore, undertaken to evaluate the toxic effect of the aqueous extract of *F. muricata* leaves.

MATERIALS AND METHODS

Plant material and authentication

The plant species was collected in March, 2008 from a single population of *F. muricata* growing within the premises of Alice campus of the University of Fort Hare, South Africa. The species was authenticated by Mr Tony Dold, Selmar Schonland Herbarium, Rhodes University, South Africa. A voucher specimen (AshMed.2008/2) was prepared and deposited in the Giffen Herbarium of University of Fort Hare.

Experimental animals

Twenty male Wistar rats weighing between 200 and 230 g were obtained from the Animal House of the Agricultural and Rural Development Research Institute (ARDRI), University of Fort Hare. The rats were housed in polypropylene cages placed in well-ventilated house conditions (temperature 23 ± 1°C, photoperiod: 12 h natural light and 12 h dark; humidity, 45 - 50%). They were maintained on Balance Trusty Chunks (Pioneer Foods (Pty) Ltd, Huquenot, South Africa) and tap water *ad libitum.* The study was carried out after the approval from the ethical committee on animal use and care of University of Fort Hare.

Assay kits and chemical reagents

The assay kits for creatinine, urea, calcium, sodium, magnesium, potassium, phosphorus, albumin, bilirubin, alkaline phosphatase, gamma glutamyl transferase, alanine and aspartate aminotransferases were obtained from Roche Diagnostic GmbH, Mannhein, Germany.

Preparation of extract

The leaves of *F. muricata* were carefully rinsed under running tap water, oven dried at 40°C and later pulverized before extraction. Powdered plant material (150 g) was extracted in water for 48 h on an orbital shaker (Stuart Scientific Orbital Shaker, UK). The extract was filtered through Whatman no. 1 filter paper and freeze-dried using Savant Refrigerated Vapor Trap, (RVT4104, USA). This was later reconstituted in distilled water to give the required doses of 50, 100 and 200 mg/kg respectively.

Animal grouping and extract administration

The animals were grouped into four consisting of five rats each. Group A (control) received orally, 0.5 ml of distilled water for 14 days while Groups B, C and D were treated like the control except that they received 50, 100 and 200 mg/kg body weight of the plant extract. The extract and distilled water were administered daily between 1000 – 1030 h using metal oropharyngeal cannula.

Preparation of serum

The method described by Yakubu et al. (2005), was adopted for the preparation of the serum. Briefly, under ether anaesthesia, the neck area of the rats was quickly shaved to expose the jugular veins. The veins after being slightly displaced (to avoid contamination with interstitial fluid) were cut with sterile scapel blade and an aliquot of the blood was collected into BD vacutainer sample bottles for the haematological analysis. The remainder was allowed to clot for 10 min at room temperature, and then centrifuged at 1282 *g* × 5 min using Hermle Bench Top Centrifuge (Model Hermle Z300, Hamburg, Germany). The sera were used within 12 h of preparation for the various biochemical assays. The liver and the kidney were thereafter removed from the animals and weighed for the determination of the organ-body weight ratio.

Determination of biochemical parameters

Adopting the method of Tietz et al. (1994), the levels of creatinine, uric acid, calcium, chloride, sodium and potassium ions, phosphorus and urea were determined. Cholesterol, LDL-C, HDL-C, triglyceride, albumin, bilirubin (total and conjugated), total protein, alkaline phosphatase, gamma glutamyl transferase, alanine and aspartate aminotransferases were determined in the serum using assay kits from Roche Diagnostics, GmbH, Mannhein, Germany on Roche modular (model P800) Mannhein, Germany. The atherogenic index was computed from the formular given by Panagiotakos et al. (2003). The Advia 2120 (Bayer, Germany) was used for the determination of hematological parameters.

Statistical analysis

Data were expressed as means of five replicates ± SD. They were subjected to one way ANOVA and means were separated by the Duncan Multiple Range Test. Percentage data were transformed to arcsine before analysis. Significant levels were tested at 5%.

RESULTS

The extract from the leaves of *F. muricata* at 50, 100 and 200 mg/kg body weight showed significant increase only in WBC. In contrast, there was significant decrease in the LUC at all the doses investigated. While the levels of RBC, PCV, MCV, MCH, MCHC, neutrophils and eosinophils were not significantly altered, there was dose specific effect on Hb, platelets, monocytes and lymphocytes. The highest dose (200 mg/kg body weight) decreased the Hb and platelets. In contrast, the 50 and

Table 1. Effects of aqueous extract of *F. muricata* leaf on the haematological parameters of Wistar rats.

Haematological parameters	Extract (mg/kg body weight)			
	Control	50	100	200
WBC (x 10^9/l)	7.246 ± 0.85^a	11.52 ± 0.88^b	11.37 ± 0.88^b	10.81± 0.59^c
RBC (x 10^{12}/l)	9.19 ± 0.29^a	8.51 ± 0.28^a	9.04 ± 0.57^a	8.00 ± 0.44^a
Hb (g/dl)	16.08 ± 0.41^a	15.12 ± 0.47^a	15.74 ± 1.0^a	13.55 ± 0.49^b
PCV (l /l)	0.528 ± 0.02^a	0.496 ± 0.03^a	0.51 ± 0.03^a	0.48 ± 0.01 ^{a}
MCV (fl)	57.4 ± 1.27a	59.3 ± 1.26^a	56.54 ± 2.05^a	57.85 ± 2.04^a
MCH (pg)	17.5 ± 0.42^a	17.78 ± 0.49^a	17.42 ± 0.73^a	18.2 ± 0.67^a
MCHC (g/dL)	30.48 ± 0.26^a	30.02 ± 0.51^a	30.84 ± 0.39^a	30.18 ± 0.70^a
RCW (%)	12.46 ± 0.65^a	13.34 ± 1.04^a	12.52 ± 0.58^a	12.18 ± 0.32^a
Platelet (x10^9/l)	913.8 ± 7.69^a	968.8 ± 9.63^b	1075.6 ± 8.82^c	1097.25 ± 8.27^c
Neutrophils (%)	3.72 ± 0.68^a	3.72 ± 1.30^a	3.7 ± 1.81^a	4.1 ± 1.69^a
Monocytes (%)	37.36 ± 1.49^a	27.96 ± 3.70^b	33.66 ± 1.04^a	43.05 ± 5.07^c
Lymphocytes (%)	46.64 ± 2.67^a	58.34 ± 6.31^b	53.8 ± 2.41^b	45.2 ± 4.19^a
LUC (%)	11.32 ± 1.86^a	9.98 ± 1.61^b	8.04 ± 0.13^b	6.88 ± 0.86^c
Eosinophils (%)	0.56 ± 0.07^a	0.58 ± 0.02^a	0.58 ± 0.01^a	0.53 ± 0.01^a
Basophils (%)	0.42 ± 0.03^a	0.34 ± 0.09^b	0.26 ± 0.01^c	0.25 ± 0.06^c

n = 5, $\overline{X}$ ± S.D. Means with the same letter across the rows are not significantly different (P > 0.05). WBC, White blood cell; RBC, red blood cell; PCV, packed cell volume; Hb, hemoglobin; MCV, mean corpuscular volume; MCHC, mean corpuscular hemoglobin concentration; LUC, large unstained cells

100 mg/kg body weight increased the lymphocyte level. The monocyte did not show any definite pattern as the blood index was decreased at 50 mg/kg body weight, whereas the 200 mg/kg significantly increase the monocyte level (Table 1).

Extract administration at all the doses did not significantly affect the serum concentrations of sodium, potassium, calcium, chloride, inorganic phosphorus, uric acid, urea and creatinine. Similarly, the total bilirubin, albumin, globulin and total protein and γ-glutamyl transferase activity were not significantly different from the control. Whereas the 50 mg/kg body weight produced reduction in conjugated bilirubin, the liver function index was elevated by the 100 mg/kg body weight of the extract (Table 2). There was increase in the activity of alkaline phosphatase at 50 mg/kg body weight of the extract; the 100 mg/kg body weight produced significant reduction. The activity of alanine aminotransferase was not affected except at 200 mg/kg body weight of the extract where it was increased. Generally, the extract produced decrease in aspartate aminotransferase activity (Table 2).

The extract of *F. muricata* did not produced any significant change in the serum total cholesterol, HDL-C and LDL-C of the Wistar rats, whereas the concentration of triacylglycerol increased by the 50 and 100 mg/kg body weight of the extract (Table 3).

The extract at all the doses investigated did not produce any significant change in the liver-body weight ratio (Figure 1). Similarly, there was no significant effect on the kidney-body ratio in the 50 and 100 mg/ml of the extract, whereas, the 200 mg/kg body weight dose increased the weight ratio (Figure 1).

DISCUSSION

Assessment of hematological parameters can be used to determine the extent of deleterious effect of foreign compounds including plant extracts on the blood constituents of an animal. It can also be used to explain blood relating functions of chemical compounds/plant extract (Yakubu et al., 2007).

The increase in WBC by the extract of *F. muricata* at all the doses (50, 100 and 200 mg/kg body weight) may indicate boost in the immune system (Yakubu et al., 2007). However, the non-significant effect of the extract on RBC, PCV, MCV, MCH and MCHC might be due to the fact that there was no destruction of matured red blood cells. The dose specific effect of the extract on Hb, platelets, monocytes and lymphocytes of the animals are indications of selective and localized toxicity. The decrease in Hb and platelets observed with the highest dose of 200 mg/kg, body weight may adversely affect the oxygen-carrying capacity of the blood (McLellan et al., 2003). The reduction in platelet level may equally have adverse effect on thrombopoietin (Li et al., 1999). The increase in the level of lymphocytes, the main effector cells of the immune system by the extract, may suggest stimulation of the immune system (McKnight et al., 1999; Yakubu et al., 2007). The non-definite pattern shown by the extract on the monocyte further supports the selective and localized effect on these blood parameters.

According to Moore and Dalley (1999), an increase in organ-body weight ratio is an indication of inflammation while a reduction in the same parameter can be adduced to cellular constriction. Therefore, the non-effect of the

Table 2. Effect of administration of *F. muricata* leaf extract on liver and kidney function parameters of Wistar rats.

Parameters	Extract (mg/kg body weight)			
	Control	50	100	200
Sodium (mmol/l)	134.6 ± 0.89[a]	135.2 ± 1.92[a]	134.2 ± 2.17[a]	135.75 ± 0.96[a]
Potassium (mmol/l)	6.14 ± 0.28[a]	5.88 ± 0.46[a]	6.12 ± 0.18[a]	6.45 ± 0.45[a]
Chloride (mmol/ l)	105 ± 2.24[a]	102.6 ± 1.14[a]	106.6 ± 0.55[a]	109.25 ± 2.22[a]
Inorganic Phosphorus (mmol/l)	3.66 ± 0.09[a]	3.48 ± 0.04[a]	3.04 ± 0.03[a]	3.2 ± 0.08[a]
Urea (mmol/l)	5.66 ± 0.46[a]	6.86 ± 0.77[a]	6.58 ± 0.31[a]	6.68 ± 0.38[a]
Creatinine (mmol/l)	45.2 ± 2.77[a]	45.8 ± 1.09[a]	46.00 ± 2.18[a]	45.75 ± 2.22[a]
Calcium (mmol/l)	2.37 ± 0.03[a]	2.40 ± 0.03[a]	2.37 ± 0.05[a]	2.39 ± 0.07[a]
Magnesium (mmol/l)	1.09 ± 0.10[a]	1.11 ± 0.09[a]	1.06 ± 0.07[a]	1.04 ± 0.09[a]
Uric acid (mmol/l)	0.10 ± 0.03[a]	0.10 ± 0.02[a]	0.10 ± 0.02[a]	0.10 ± 0.04[a]
Total bilirubin (µmol/l)	6.4 ± 0.52[a]	6.4 ± 0.52[a]	5.8 ± 0.17[a]	6.00 ± 0.37[a]
Conjugated bilirubin (µmol/l)	2.6 ± 0.34 [a]	1.6 ± 0.55[b]	3.00 ± 0.71[c]	2.25 ± 0.89[a]
Albumin (mmol/l)	17.4 ± 0.89[a]	16.8 ± 1.30[a]	17.60 ± 0.07[a]	16.5 ± 1.00[a]
Globulin (mmol/l)	40.6 ± 2.51[a]	41 ± 2.74[a]	42.8 ± 3.63[a]	41 ± 2.45[a]
Total protein (g/l)	58 ± 1.73[a]	57.8 ± 1.78[a]	60.4 ± 2.88[a]	57.5 ± 2.08[a]
Alkaline phosphatase (U/L)	338.4 ± 7.77[a]	414 ± 4.37[b]	295 ± 5.02[c]	345.25 ± 7.19[a]
γ- Glutamyl transferase (U/L)	5.02 ± 0.01[a]	5.04 ± 0.00[a]	5.01 ± 0.01[a]	5.00 ± 0.01[a]
Alanine aminotransferase (U/L)	53.4 ± 7.83[a]	52.8 ± 5.12[a]	50 ± 8.54[a]	44.5 ±7.85[b]
Aspartate aminotransferase (U/L)	181.6 ± 7.00[a]	157.2 ± 9.53[b]	167.2 ± 8.95[c]	158.5 ±5.05[b]

n = 5, $\overline{X}$ ± S.D. Means with the same letter across the row are not significantly different (P > 0.05).

Table 3. Effect of *F. muricata* leaf extract on serum lipid profile of Wistar rats.

Parameters	Extract (mg/kg body weight)			
	Control	50 mg/kg	100 mg/kg	200 mg/kg
Cholesterol (mmol/L)	1.16 ± 0.27[a]	1.28 ± 0.84[a]	1.10 ± 0.16[a]	1.15 ± 0.19[a]
TAG (mmol/l)	1.36 ± 0.27[a]	3.34 ± 0.71[b]	2.00 ± 0.58[c]	1.83 ± 0.62[a]
HDL-C (mmol/ l)	0.88 ± 0.13[a]	0.9 ± 0.16[a]	0.98 ± 0.11[a]	0.93 ± 0.22[a]
LDL-C (mmol /l)	0.40 ± 0.02[a]	0.44 ± 0.02[a]	0.42 ± 0.03[a]	0.41 ± 0.01[a]
Atherogenic index	0.45 ± 0.001[a]	0.49 ± 0.02[a]	0.43 ± 0.01[a]	0.44 ± 0.03[a]

n =5, $\overline{X}$ ± S.D. Means with the same letter across the rows are not significantly different (P > 0.05).

extract on the liver-body weight ratio in this study has suggested that the extract did not cause inflammation or constriction of the hepatocyte. This may also explain the non-effect of the 50 and 100 mg/kg body weight of the extract on the kidney-body weight ratio. However, the increase in the parameter observed with the 200 mg/kg body weight may be explained by the inflammation of the nephrons.

The concentrations of total proteins, bilirubin and albumin in the serum may indicate the state of the liver and the type of damage ((Yakubu et al., 2005). The fact that the total biliruin, albumin, globulin and total protein levels were not altered by the extract suggest that the secretory function of the liver was not impaired. However, the non-definite pattern shown by the extract on the conjugate bilirubin level may be explained as adaptation by the animals to the effect of the extract.

There are many enzymes such as phosphatases, dehydrogenases and transferases that are found in the serum which did not originate from the extracellular fluid. During tissue damage, some of these biomolecules find their way into the serum, probably by leakage (Panda, 1989), through disrupted cell membranes. Serum enzyme measurement therefore, provides a valuable tool in clinical diagnosis as well as toxicity studies. The increase in serum alkaline phosphatase activity at 50 mg/kg body weight and aspartate aminotransferase activity at all the doses in this study implied cellular damage to the plasma membrane of the rats' organs. Such tissue damage also suggests that the extract is not completely safe. The reduction in the serum enzymes may imply inhibitions at the cellular level by the component of the extract.

Renal function indices are usually required to assess the normal functioning of different parts of the nephrons

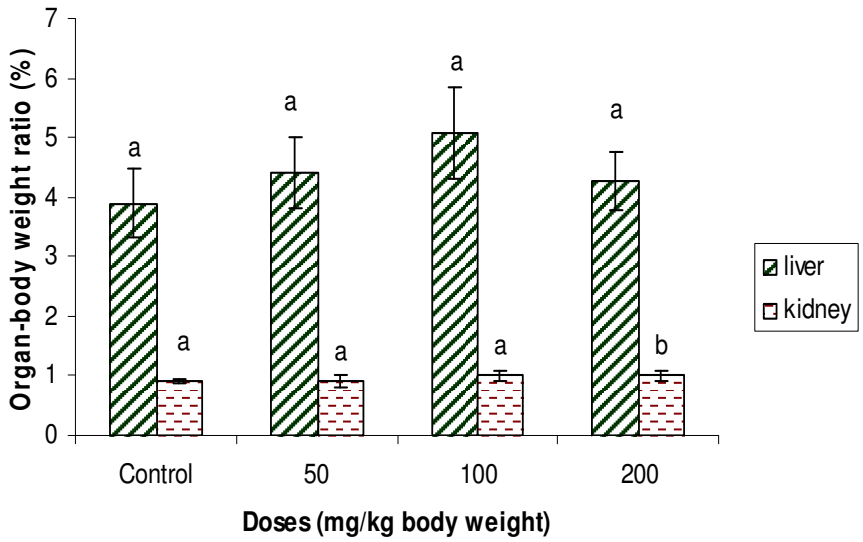

Figure 1. Effect of extract of *F. muricata* on organ-body ratio of Wistar rats.

(Abolaji et al., 2007). Similarly, the serum concentrations of electrolytes, urea, uric acid and creatinne could give an insight into the effect of a compound/plant extract on the tubular and or glomerular part of the kidney. Therefore, the non effect of the extract of *F. muricata* at all the doses investigated on the renal function indices may suggest that the normal functioning of the nephrons at the tubular and glomerular levels were not affected.

Alterations in the concentration of major lipids such as cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triacylglycerol can give useful information on lipid metabolism and predisposition of the heart to atherosclerosis and its associated coronary heart diseases (Yakubu et al., 2008; Rang et al., 1995). The non effect of the extract on the serum cholesterol concentration may be explained by non-impairment in the biosynthesis of cholesterol. Triacylglycerols are the storage form of fatty acid. The increase in the serum lipid at 50 and 100 mg/kg body weight of the extract may be attributed to accelerated lypolysis (Rang et al., 1995). This may imply depletion in the storage of fatty acids. HDL-C is known to have anti-atherogenic properties. The non-effect of the extract on HDL-C may imply that the anti-atherogenic property was not altered. LDL-Cs are primary carriers of plasma cholesterol which build up slowly in the walls of the arteries feeding the heart and the brain. As a result, it forms plaque that clots the arteries thereby causing atherosclerosis. The non significant effect of the extract on this serum parameter could imply that the extract may not predispose the heart to atherosclerosis. This is because the atherogenic index, a useful indicator of cardiovascular disease (Panagiotakos et al., 2003), was not altered in this study. It is inferred that the extract may not predispose the animals to atherosclerosis and its associated cardiovascular diseases despite the alterations in the serum triacylglycerol concentration.

This study has shown that *F. muricata* leaf extract possesses some slight toxicity and may not be completely safe for oral remedies.

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