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Toxicological Effect of Ficus musuco Leaf Extract onLiver andKidney Functions Variables of Male Rats

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Abstract:*Ficus mucuso is a plants whose various parts are employed traditionally in the treatment of different ailments. The decoction of the leaves is commonly used in the management of fever and anemia. The plant is consumed both as medicines and as vegetables with the trust that they are natural and safe without any side effects. Natural does not signify absence of adverse effects. Some plants are said to produce adverse effects that may not be immediate while others may be toxic but no investigation to prove and therefore not documented. The aim of this study was to examine the toxicological effects of the aqueous leave extracts of Ficus mucuso leaves on the kidney and liver functions of male wistar rats. A total of 56 adult male wistar rats were divided into seven groups of eight animals each. Group A; control received distilled water only, B, C and D that received Ficus mucuso 100mg/kg, 200mg/kg and 400mg/kg body weight respectively. Ficus mucuso leaf extracts was administered as a single dose orally for 21 days. Whole blood was collected by cardiac puncture after the animals were anaesthetized, the blood was centrifuged to get the plasma. Electrolytes (sodium and potassium) were analyzed using the ISE analyzer while urea and creatinine, AST, ALT, ALP and GGT were analyzed using chemistry standard spectrophotometric methods. The result shows that Ficus mucuso extract reduced significantly the plasma level of sodium and urea in the groups B, C and D respectively (P<0.005), and creatinine in group B (P<0.005) as compared to the control. AST was significantly reduced in groups C and D (P<0.005) Potassium, ALT, ALP and GGT remain significantly unchanged in all the groups (P>0.005). In conclusion Ficus mucusoextracts did not show toxic effect.*

Keywords: *Ficus mucuso, toxicity, kidney, liver, plant-extract.*

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I. Introduction

The use of plants and its products in the treatment and control of disease has been an old practice (Chukwuma et al., 2015 &Petrovaska, 2012). Herbal medicines are still used in the treatment of several disease conditions especially in developing countries (Khan et al., 2011). Several studiesadduced that medicinal plants have medicinal properties produced by the biochemical compounds contained in the different parts of the plants, (Alhadi et al., 2013 &Yadzani et al., 2011).

Plants and plant products are preferred in the treatment and control of disease based on the belief that herbal products are cheap and affordable with minimal side effects as compared to synthetic drugs (Akhigbe et al., 2009). However, some studies reported that for a drug to be effective it will have side effects that even herbal medicines may have side effects or may not be effective. Although several other studies considered majority of herbal medicines safe for human use but should be consumed with caution due to unrealized side effects that may lead to organ toxicity (Hamid and Hedayatollah, 2013).

The major organs affected by herbal or synthetic medicine consumption are the liver and the kidneys. These organs are referred to as organs of excretion as they function to get rid of harmful substances resulting from the body's metabolic activities.

The most useful part of the plant are the leaves.Ficus mucuso is a tree, mostly found in the tropical rainforest and in the mountain areas (Djemguo et al, 2009).

It is a specie of the genus Ficus belonging to the family Moraceae which has about 800 species distributed all over the world. It is grown in India, China, Uganda, Cameroon, Zimbabwe, Nigeria etc. Ficus genus is said to possess medicinal properties (Lansky et al, 2001), and is used in traditional medicine for the treatment of different ailments (Chukwuma et al, 2015).

Qualitative phytochemical analysis of the different useful parts showed the presence of chemical compounds that have protecting or disease preventive properties. Some of which are flavonoids, tannins, cardenolides, tritepenoides, steroids, saponins.

Ficus mucuso possesses properties that enable it to alter the cell activity of living organisms and is used in treatment of ailments. Studies showed it possess anti-malaria (Murgananthan et al., 2012) and antioxidant properties (Constant et al., 2012).

Several studies have shown that Ficus mucuso have been employed in traditional medicine in the treatment of different ailments. Powdered leave mixed with palm oil is used in the treatment of epilepsy in a village in Cameroon (Bankeu et al., 2009). Decoction of the stem bark is used in the treatment of insominia a sleeping disorder (Ugbogu et al.,2012, Chukwuma et al.,2015).

Over thousands of years, plants and its products have been used in the treatment of different ailments. Several plants have been identified to possess medicinal properties resulting from the bioactive compounds contained in them and have been employed in traditional medicine. But studies emphasize that natural does not signify being free from side harm. Though the side effects of herbal medicines are said to result from the misuse of the products. However, some researchers studied that plants contain medicinal properties as well as toxic chemicals. These toxic chemicals are responsible for the withdrawal of some of the herbal plants when discovered. Medicinal plants may produce side effects that may not be immediate. The phytochemical compounds contained in plants are the source of their pharmacological activities, these bioactive compounds according to studies can also be toxic as the dose increases. It is therefore necessary to investigate the toxicity of medicinal plants to generate information about the particular plant with respect to dosage.

Ficusmucuso is among the plants employed in the treatment of fever, anemia and several other ailments in some communities. It is used as the decoction of the leaves and also cooked as vegetables. It is believed and trusted to possess high medicinal values but the information about their toxicity has not been made known to the populace. Based on the trust that these plants are natural and safe, this research study has considered it necessary to investigate the toxicity of Ficus mucuso on the liver and kidney.

Though some pharmacological activities of the leaf extracts ofFicus mucuso has been investigated but there is paucity of data showing effect of increasing concentration of the leaf extracts on the liver and kidney. This study investigated the effect of different doses of their leave extracts on the liver and kidney function to justify their regular use based on the claim that they are safe for consumption.

II. Materials and Methodology

2.1 Experimental animals

Adult male wister rats weighing between 150g - 200g were used for this study.They were acclimatized in cages in the animal house for two weeks and fed with feed mash and tap water *adlibitum*.

2.2 Herbal plants

The Ficus mucuso leaf was harvested from a community forest .The leaves were identified by a certified botanist with herbarium number : EH/V/071.

2.3 Preparation of Plant Extracts

The fresh Ficus mucuso leaves were dried at room temperature for seven days. The dried leaves were grinded into fine powder using a blender and poured into a maceration jar. Maceration technique was employed for separation. Three liters of distilled water was added to blended powder, then placed in a maceration jar, kept in a tight cupboard with vigorous shaken and allowed to stand for twenty- four hours (24hrs). White handkerchief was used to filter and the filtrate transferred into a beaker. After five hours Whatman filter paper was used for a clear filtrate, the filtrate was poured into crucible plate and placed on a steam bath to evaporate at a temperature of 70ºC to obtain a semi-solid extract.

2.4 Acute Toxicity Study

Locke's method of determining effective dose was adopted. A total of 24 adult male wister rats were used for the acute toxicity studies of both the Ficus mucuso leaf extracts. Twelve animals were used for Ficus mucuso leaf extracts. The Locke's method has two phases:

2.5 Ficus mucuso Leaf Extract

Phase 1: Nine animals were divided into three groups of three animals in each group. The first group of three animals received 10mg/kg, the second group of three animals received 100mg/kg and the third group of three animals receive 1000mg/kg of the extracts respectively. The animals were observed for 24hrs.

Phase 2: Three animals were dived into three groups of one animal each. Higher doses of the extracts were administered. The first group received 1500mg/kg, the second group receive 2000mg/kg and the third group received 3000mg/kg of the extracts respectively. The animals were observed for 24hrs for changes.

2.6 Experimental Design

A total number of 56 adult male wister rats were recruited for the study. Simple random technique was adopted, theanimals were divided into seven groups of eight animals each, A B C D E. Group A served as the control group and received only distilled water. Group B, C and D received 100mg/kg, 200mg/kg and 400mg/kg doses of Ficus mucuso leaf extract respectivelyFicusmucuso leave extracts was administered as a single dose orally for 21 days. Whole blood was collected by cardiac puncture using needle and syringe after the animals were anaesthetized, the blood was centrifuged to get the plasma.

2.7 Determination of biochemical variables

Ion Selective electrode (ISE) electrode auto analyzer was used for the determination of sodium and potassium.Urea, creatinine (Cr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphate (ALP) and gamma-glutamyltransaminase were determined by spectrophotometric method.

2.8 Procedure for Histological Analysis of the Kidney

Tissue preparation: The kidney from the sacrificed animal was fixed in 10% formalin immediately after it was excised from the animal, processed and stained with Erlich's hematoxylin. The slide was cleaned, blotted and mounted in DPX under the coverslip.

2.9 Statistical Analysis

The mean and standard deviation was gotten using the Graph Prism Pad version 5.1. Turkey's Multiple Comparison Test was used to test for the statistical significant differences among the groups and between the two extracts. $P<0.05$ was taken as a significant value.

III. Results

Acute toxicity test of aqueous leaf extract of Ficus mucuso.

The highest doses administered for the aqueous leaf extract of Ficus mucuso was 3000mg/kg body weight. No death was recorded during the investigation.

Table 4.1 Result of phase 1 and phase 11 of acute toxicity test for Ficus mucuso

Phase 1		
Groups	Dosage (mg/kg body wt)	Mortality
1	10	0/3
2	100	0/3
3	1000	0/3
Phase 2		
1	1500	0/3
2	2000	0/3
3	3000	0/3

3.2 Mean ± Standard Deviations of Renal and Liver Function Indices of Group A, B, C and D

The details of the mean and standard deviations of renal and liver function parameters of groups A, B, C and D, are shown in table 4.2 and 4.3.

There were significant differences in Na levels between group A and B, Group A and C and group A and D ($p<0.005$; $F = 8.175$). There was no significant difference between group B and C, group B and D and group C and D for sodium. There were significant differences in urea among group A and B, A and C, and A and D respectively ($P = 0.0009$; $F = 7.715$). There was significant difference between group A and B for creatinine ($P = 0.0221$; $F = 3.840$). There was significant difference in group A andC, A and D for AST ($P = 0.205$; $F = 3.932$). No significant was observed for K ($P = 0.1622$; $F = 1.84$), ALT ($P = 0.27548$; $F = 0.1077$); ALP ($P = 0.3931$; $F = 1.039$) and GGT ($P = 0.0234$; $F = 2$.

Table 4.2 Mean± Standard Deviations of Renal Function Indices of Groups A, B, C and D.

	Na (mEq/L	K (mmol/L	Urea (mmol/L)	Creat (mmol/L)
GROUP A(N=7)	143.43 ± 4.61	5.4 ± 0.62	7.03 ± 1.56	61.85 ± 10.12
GROUP B (N=8)	136.37 ± 3.42	5.01 ± 0.45	4.91 ± 0.86	50 ± 7.29
GROUP C (N=7)	136.67 ± 3.01	5.05 ±0.45	4.8 ± 0.72	51.5 ± 4.76
GROUP D(N=7)	136.42 ± 2.07	4.88 ±0.51	5.2 ± 0.44	50.85 ± 6.71
F-values	8.178	1.84	7.715	3.849
p-values	0.0005	0.1627	0.0009	0.0221
Tukey's Multiple Comparison Test	Summary	Summary	Summary	Summary
GROUP A vs GROUP B	**	Ns	**	*
GROUP A vs GROUP C	**	Ns	**	Ns
GROUP A vs GROUP D	**	Ns	*	Ns

GROUP B vs GROUP C	Ns	Ns	Ns	Ns
GROUP B vs GROUP D	Ns	Ns	Ns	Ns
GROUP C vs GROUP D	Ns	Ns	Ns	Ns

Legend:
Group A – (Control) Distilled water only.
Group B – received 100mg/kg body weight of Ficus mucuso leaf extract
Group C - received 200mg/kg body weight of Ficus mucuso leaf extract
Group D – received 400mg/kg body weight of Ficus mucuso leaf extract.

Table 4.3 Mean ±Standard Deviations of Liver Function Indices of Groups, B, C and D.

	AST (U/L)	ALT (U/L)	ALP (U/L)	GGT (U/L)
GROUP A(N=7)	251 ± 27.47	107.14 ± 19.74	252.85 ± 55.40	9.57 ± 4.86
GROUP B (N=8)	203.5 ± 27.54	112.87 ± 32.25	319.65 ± 34.02	5.62 ± 1.21
GROUP C (N=7)	179.33 ±22.36	110.33 ± 21.82	374.5 ± 51.31	5 ± 1.54
GROUP D(N=7)	185 ± 26.99	103.57 ± 8.40	345.57 ± 57.51	6.14 ± 2.11
F-values	3.932	0.1077	1.039	2.629
p-values	0.0205	0.9548	0.3931	0.0734
Tukey's Multiple Comparison Test	Summary	Summary	Summary	Summary
GROUP A vs GROUP B	Ns	Ns	ns	ns
GROUP A vs GROUP C	*	Ns	ns	ns
GROUP A vs GROUP D	*	Ns	ns	ns
GROUP B vs GROUP C	Ns	Ns	ns	ns
GROUP B vs GROUP D	Ns	Ns	ns	ns
GROUP C vs GROUP D	Ns	Ns	ns	ns

Legend:
Group A – (Control) Distilled water only.
Group B – received 100mg/kg body weight of Ficus mucuso leaf extract
Group C - received 200mg/kg body weight of Ficus mucuso leaf extract
Group D – received 400mg/kg body weight of Ficus mucuso leaf extract.

Photomicrographs of Kidney tissue
Slide of group A (control)

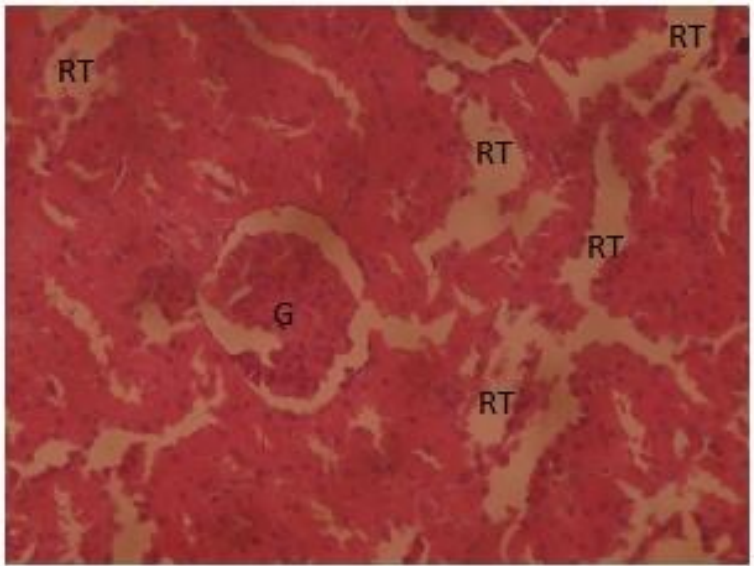

Fig. 4.1 The glomerulus was normal surrounded by patent bowman's capsule and renal tubules. G-GlomeruliRT-Renal Tubules

Slide of group B

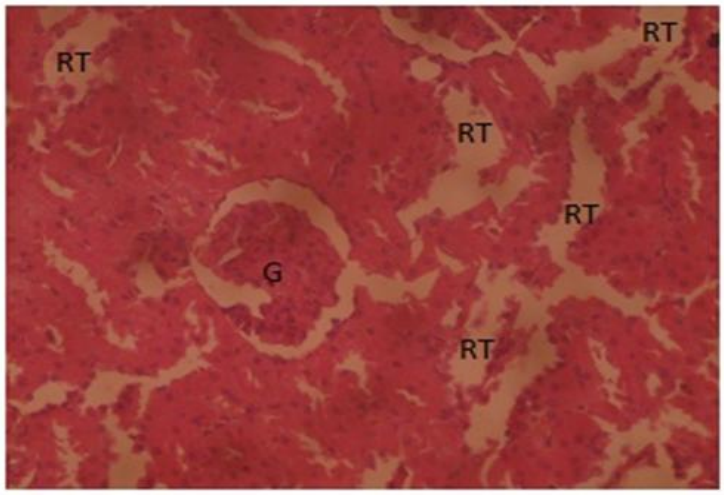

Fig. 4.2 Renal tubules lined by single layer of epithelial cells. This kidney tissue is histologically normal.

Slide of group C

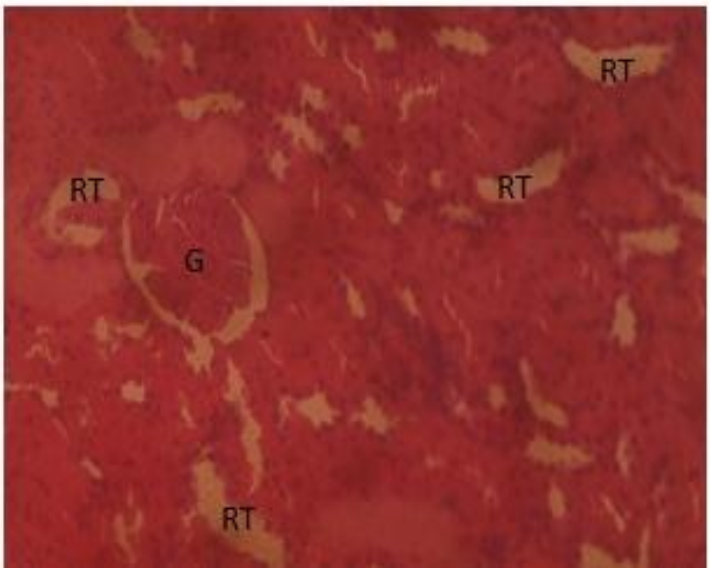

Fig 4.3 The glomerulus is surrounded by Bowman's capsular space, and renal tubules lined by simple epithelial cells. This shows histologically normal tissues

Slide of group D

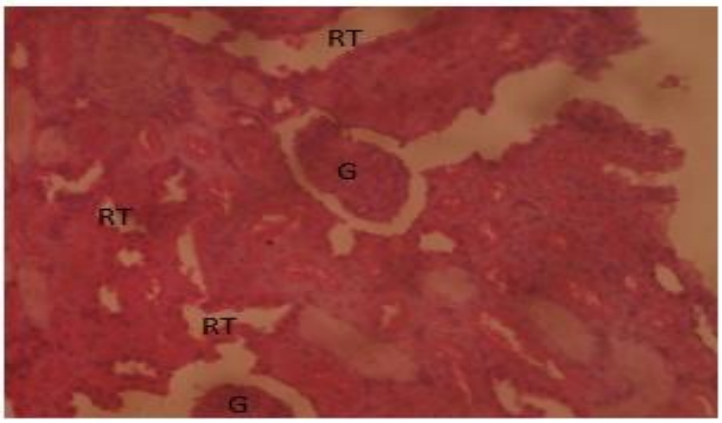

Fig. 4.4 Renal tubules lined by simple epithelial cells. This shows the kidney tissues are histologically normal.

IV. Discussion

In this study, Ficus mucuso aqueous leaf extract was not toxic to the body organs, the result of the acute toxicity test revealed Ficus mucuso could not cause death of the animals at a concentration of 3000mg/kg body. Ficus mucuso aqueous leave extract was administered at 100mg/kg, 200mg/kg and 400mg/kg body weight for group B, C and D respectively. For the effect of the extract on the kidney parameters, the mean value for sodium ion was significantly reduced in groups B, C and D as compared to the control ($P<0.005$; $F = 8.175$). No significant difference was observed in the mean value between the groups indicating the three different doses of Ficus mucuso leaf extract had same effect on plasma sodium level no variation as dose increases.Ficus mucuso leaf extracts reduction of sodium may be due to antidiuretic capacity of the extract but not below the lower limit of the reference range. This indicates that the extract may be useful in the moderation of sodium ion. Mean value of urea was also significantly reduced in groups B, C and D when compared to the control ($P= 0.0009$; $F =7.715$), no significant change between the groups, this also shows that at different doses of Ficus mucuso leaf extract the blood level of urea did not vary significantly. Urea is produced in the liver as a nitrogenous waste from the breakdown of protein and is eliminated from the body through the kidneys. The mechanism by which the extract reduces urea is not clear, rather could be adduced toFicus mucosa extracts improves the histoarchitecture of the kidney and by extension restores its functionality (Komolafe et al., 2013).Mean value for creatinine was significantly reduced between the control and the group B that received the 100mg/kg body weight of the extract ($P=0.0221$; $F = 3.840$). Creatinine is an end product of creatine breakdown in the muscles, it is also a nitrogenous waste that is removed from the body by the kidneys, it is marker of glomerular filtration rate (GFR) (Salazar, 2014), the concentration in the body depends on muscle mass (Hosten, 1990). Its concentration in plasma is used to investigate the ability of the glomerulus in filtering the blood flow (Micheal et al., 2008). Plasma potassium level was not affected significantly by the extract, no significant difference was observed between groups B, C and D as compared to the control ($P = 0.1627$; $F = 1.84$), and between the groups. Potassium is found more in the fluid inside the cells. Its reduction in plasma is associated with substances that increase the frequency of urination while increased plasma concentration may result from effects of drugs on one another and abnormal kidney function. In this study plasma concentration of potassium was not significantly affected. Harmful substances cause elevation of plasma urea and creatinine (Roy et al., 2015). The analysis carried out shows that Ficus mucuso aqueous leave extract was not toxic to the kidney cells. The electrolytes (sodium and potassium), urea and creatinine were not elevated on the administration of the extract rather sodium, urea and creatinine were reduced.

For the liver enzymes aspartate amino transferase has a significant change between the groups that received 200mg/kg and 400mg/kg body weight as compared to the control ($P=0.0205$; $F = 3.840$) it was significantly reduced, no significant difference was observed between groups B and C, B and D and C and D respectively. Alanine aminotransferase ($P = 0.27548$; $F = 0.1077$), alkaline phosphate ($P = 0.3931$; $F = 1.039$) and gamma-glutamyl transferase ($P =0.0234$; $F =2.267$) no significant difference was observed between the groups and control also between the groups. From the analysis carried out Ficus mucuso administered at 200mg/kg and 400mg/kg significantly decrease AST levels, the decrease observed in the 100mg/kg group was not significant. Variations observed in ALT, ALP and GGT were not significant. Adverse effect of a substance on the liver leads to cell injury and leakage of enzymes into the blood increasing their plasma concentration (Aragon, 2010). This increased concentration of liver enzymes has been associated with hepatocellular necrosis and cholestasis and it is seen in AST, ALT, ALP and GGT. (Han, et al., 2010) but in this study AST and GGT were insignificantly reduced in the three groups E,F and G.AST and ALP.

From this study, it appears that ficus mucosa leave extract has nephroprotective and hepatoprotective capacity.

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