EVALUATION OF SUB-CHRONIC TOXICITY, ANTI-INFLAMMATORY AND DIURETIC EFFECT OF ETHANOL LEAVES EXTRACT *FICUS CAPENSIS* IN ALBINO RAT

[1]OMODAMIRO, Olorunshola Dave, [1]AJAH, Obinna, [2]JIMOH, Mulikat Abiola and [1]EWA-IBE, Chigozie

[1]Pharmacology Unit, Department of Biochemistry, Michael Okpara University of Agriculture, Umudike, Umuahia, Abia State, Nigeria.

[2]Department of Plant Biology, Osun State University, Osogbo, Osun State, Nigeria.

Corresponding Author: Omodamiro, O. D. Pharmacology Unit, Department of Biochemistry, Michael Okpara University of Agriculture, Umudike, Umuahia, Abia State, Nigeria. **Email**: majekdamiro@yahoo.com **Phone:** +234 7064868550

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ABSTRACT

Ficus capensis is highly medicinal in nature and has been reported to possess pharmacological properties. Ethanol leaves of extract of F. capensis were evaluated for its sub-chronic impact on the hepatic biomarkers as well as anti-inflammatory and diuretic activity in male albino rat. Fifty four albino rats were randomly divided into six treatment groups of nine rats per group. Group A - received normal saline (normal control), Group B - received either 40 mg/kg of Furosemide (control for diuretic) or 50 mg/kg of Aspirin (control for anti-inflammatory), Group C - received 200 mg/kg F. capensis extract, Group D - received 400 mg/kg F. capensis extract, Group E - received 600 mg/kg F. capensis extract and Group F received 800 mg/kg F. capensis extract. The anti-inflammatory effect assessed using carrageen induced paw edema in rat was significantly affected by the extracts. The diuretic activity of the extract screened by quantification of urine volume and electrolyte concentration was significantly affected. The extract of F. capensis showed significant (p<0.05) increase in serum activity of aspartate aminotransferase (AST), alanine aminotranferarase (ALT), alkaline phosphatase (ALP), total and conjugate bilirubin in the 600 and 800 mg/kg extract treated groups on week 3 when compared to the normal control. The result suggested that ethanol leaves extract of F. capensis could be non-toxic to the liver at the doses of 200 and 400 mg/kg and has potential anti-inflammatory and diuretic properties, hence could be utilized at moderate doses in the treatment of inflammation and diuretic related health complications.

Keywords: Anti-inflammation, Diuretic effect, *Ficus capensis*, Hepatotoxicity, Potassium-sparing, Hepatic biomarkers

INTRODUCTION

Majority of the world's population in developing countries still rely on herbal medicines to meet their health needs. Many of the world's population are knowledgeable of the use of plants and herbs in their environs for the treatment, cure and or management of different diseases (Hansch *et al.,* 1990; Uzoekwe and Mohammed, 2015). Herbal medicines are often used to provide first-line and basic health services, both to people living in remote areas where it is the only available health service and to people living in poor areas where it offers the only affordable remedy (Ekor, 2014). Even in areas where modern medicine is available, the

interest in herbal medicines and their utilization have been increasing rapidly in recent years. Medicinal plants and herbal medicines account for a significant percentage of the pharmaceutical market (Harvey, 2008; Ekor, 2014). Medicinal plants are sources of raw materials for pharmaceutical drug formulation (Harvey, 2008). Medicinal plants contain numerous biologically active compounds such as nutrients and phytochemicals which have physiological actions on the human body (Olowokudejo *et al.,* 2008) and these inherent active ingredients are used to treat various ailments (Okigbo *et al.,* 2008). *Ficus capensis* (Thunb) commonly called "bush fig tree" belongs to the family Moraceae. In Nigeria, it is locally referred to as Akokoro (Igbo), Opoto (Yoruba) and Uwaraya (Hausa) (Otitoju *et al.,* 2014). Its leaves are broad, greenish and produce fruits all year round (Arnold and De Wet, 1993) and have been regarded as an underutilized plant. The leaves of *F. capensis* are used as vegetable both in soup and yam pottage in various parts of southeastern Nigeria (Otitoju *et al.,* 2014). Traditionally, *F. capensis* has been used for the treatment of dysentery and wound dressing (Igoli *et al.,* 2005). It is also used to treat circumcision wounds, leprosy, epilepsy, rickets, infertility, gonorrhea, edema and respiratory disorders (Olowokudejo *et al.,* 2008). Apart from its traditional uses, scientific investigations have reported its; pro-fertility in treating azoospermia (Gelfland *et al.,* 1985; Akomolafe *et al.,* 2016), anti-sickling effect (Mpiana *et al.,* 2008; Umeokoli *et al.,* 2013), antibacterial (Oyeleke *et al.,* 2008), antidiarrhoea (Ayinde and Owolabi, 2009), anti-abortifacient (Owolabi *et al.,* 2009), immune-stimulatory (Daikwo *et al.,* 2012), antioxidant (Ramde-Tiendrebeogo *et al.,* 2012) and blood-boosting effect (Otitoju *et al.,* 2014).

Liver plays a central role in the metabolism and excretion of xenobiotics, which makes it highly susceptible to their adverse and toxic effects. The liver is also involved in the synthesis of products like glucose derived from gluconeogenesis, plasma proteins, clotting factors and urea that are released into the blood stream. Liver injury caused by various toxic chemicals or their reactive metabolites (hepatotoxicants) is known as hepatotoxicity (Navarro and Senior, 2006; Papay *et al.,* 2009). Inflammation is part of the body's defense mechanism. It is the process by which the immune system recognizes and removes harmful stimuli and begins the healing process. Diuresis refers to increased urine production and excretion by the kidneys, and sometimes it is accompanied by loss of electrolytes such as sodium, chloride and potassium. In other to contribute to existing knowledge on the sub-chronic toxic impact of *F. capensis* on the liver as well as its anti-inflammation and diuretic effect, this study evaluated the sub-chronic toxicity, anti-inflammation and diuretic effect of *F. capensis* and validating its use as medicinal plant.

MATERIALS AND METHODS

Plant Material: Fresh leaves of *F. capensis* were harvested from a farm at Michael Okpara University of Agriculture, Umudike. The leaf was botanically identified (Akomolafe *et al*., 2016) and authenticated by a Plant Taxonomist in the Department of Plant Science and Biotechnology of same University. Voucher specimen number MOUAU/PSB/H/052 was kept in the Departmental Herbarium for reference purposes.

Preparation of Plant Extract: The fresh leaves of *F. capensis* were washed and allowed to shade dry to a constant weight and pulverized into powder using Pulverizer (5126 TP). 200 g of the grounded sample was macerated in 600 ml of 98 % ethanol and allowed for 72 hours (3 days) then filtered with Whatman No 1 filter paper. After which the ethanol filtrate obtained was evaporated to dryness using water bath at 45^{o}C.

Phytochemical Composition and Toxicity of *Ficus capensis* leaf Ethanol Extract

Phytochemical screening: The qualitative phytochemical screening *F. capensis* leaf ethanol extract was carried out using the methods of Harborne (1973) and Trease and Evans (1989).

Acute toxicity (LD_{50}): The acute toxicity of the *F. capensis* leaf ethanol extract was determined using Lorke's method (Lorke, 1983).

Experimental Animals: A total of 54 two months old male albino Wistar rats with the weight range of 100 – 130 g were obtained from the Animal House of the Faculty of Veterinary Medicine, Nnamdi Azikiwe University, Awka. They were housed in standard transparent cages with wheat husk bedding, renewed every 24 hour and kept under controlled room temperature (27 ± 2 °C) and humidity (50 ± 20 %) in a 12 hour light-dark cycle. Care of experimental animals was taken as per the guidelines for care and use of laboratory animals (NRC, 2011) and the protocol was approved by Animal use Ethical Committee of the University with Ethical number BCM/EC/03/107. Animals were acclimatized for two weeks to laboratory conditions before starting the study. The animals were given standard laboratory diet (Vital Feeds with 18 % crude protein and 2800 kcal/kg metabolizable energy) and water *ad libitum*.

Experimental Design for Anti-Inflammation: Using a complete randomized design (CRD), the albino rats were divided into six treatment groups replicated thrice with each replicate having three rats. Group A - animal received normal saline (normal control), Group B - animal received either 40 mg/kg of Furosemide (control for diuretic) or 50 mg/kg of Aspirin (control for anti-inflammatory), Group C - animal received 200 mg/kg *F. capensis* extract, Group D - animal received 400 mg/kg *F. capensis* extract, Group E - animal received 600 mg/kg *F. capensis* extract and Group F - animal received 800 mg/kg *F. capensis* extract.

Induction of Inflammation in Wistar Rat: Anti-inflammatory activity was investigated on the carrageenan inflammation model, which was induced by subplantar injection to the plantar fasciitis (aponeurosis) of the hind limb of Wistar rats using 0.1 mL of 1 % carrageenan (Omodamiro *et al*., 2017).

Determination of Inflammation: Inflammation of the hind limb of Wistar rat was determined. One hour after the administration of different concentrations of plant extract. Injection of 0.1 ml carrageenan into the hind paw induced a progressive edema reaching its maximum at three hours. The hind limb of each rat was measure using veinar caliper. Records were taken on each interval of 1^{st}, 3^{rd}, 6^{th} and 24^{th} hours (Okoli and Akah, 2000).

Determination of Diuretic Activity: Animals were fasted overnight with water before subjecting them to pharmacological studies. Before the treatments, all animals received physiological saline (0.9 % NaCl) at a dose of 25 ml/kg body weight (BW). The ethanol leaves extract of *F. capensis* was reconstituted using a method described by Omodamiro *et al*. (2017). After oral administration of the ethanol leaves extract of *F. capensis* and standard drug to the different groups, all the animals were placed in individual metabolic cages. Urine was collected and measured at 24 hours after the dose. The ratio of urinary excretion in the test group to that in the control group was used as a measure of the diuretic action for the given dose of the drug (Lipschitz *et al*., 1943). The diuretic activity was calculated by comparing diuretic action of extract to that of the standard. Sodium, potassium, chloride and HCO^{-3} levels in the urine were quantified by flame spectrophotometry (Systronics flame photometer-129) methods (Mukherjee, 2002).

Determination of Liver Function Activities: The administration of the extract was extended to 21 days and the liver function biomarkers were estimated at weekly interval. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were done using Randox limited commercial kits according to the method of Reitman and Frankel (1957), alkaline phosphatase (ALP) was assayed using a method described by Kochmar and Moss (1976). Total bilirubin and conjugated bilirubin were determined using a method described by Schachter (1959).

Statistical Analysis: Data collected were subjected to one way analysis of variance (ANOVA). The results were expressed as mean ± SEM, and LSD test was used to test for the significant difference between means with $p<0.05$ considered significant.

RESULTS

The qualitative phytochemical screening revealed the presence of phenol, flavonoid, saponin, alkaloid and tannin. The acute toxicity test the ethanol extract of *F. capensis* revealed no mortality although there was loss of appetite in the rats administered (orally) 5000 mg/kg of the extract (Tables 1 and 2).

Table 1: Phytochemicals present in ethanol extract of *Ficus capensis*

Phytochemicals	Inference
Phenolic	+
Flavonoid	++
Saponin	++
Alkaloid	+
Tannins	+

+ = present, ++ highly present

Table 2: Acute toxicity of ethanol extract of *Ficus capensis*

Groups	Concentration (mg/kg)	Mortality/signs of toxicity
Phase 1		
1	10	Nil
2	100	Nil
3	1000	Nil
Phase 2		
1	1600	Nil
2	2900	Nil
3	5000	No death but decrease in appetite

The ethanol extract of *F. capensis* showed significant increase ($p<0.05$) in the urine output in all the extract treated groups except 200 mg/kg when compared to the normal control. The 800 mg/kg extract effectively induced high urine output when compared to the standard drug (Figure 1).

The ethanol extract of *F. capensis* showed a significant ($p<0.05$) increase in Na^+ concentration in all the extract groups except the 200 mg/kg when compared to the normal control. The 800 mg/kg extract effectively competed with the standard drug (Figure 2).

The ethanol extract of *F. capensis* showed a significant ($p<0.05$) increase in Cl^- concentration in all the extract groups except the 200 mg/kg when compared to the normal control. The 800 mg/kg extract effectively competed with the standard drug (Figure 3).

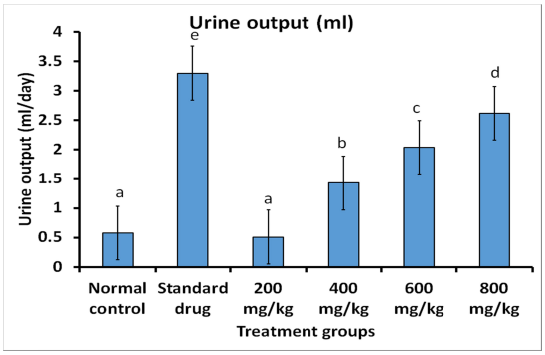

Figure 1: Effect of the ethanol extract of *Ficus capensis* on the urine output of albino rat

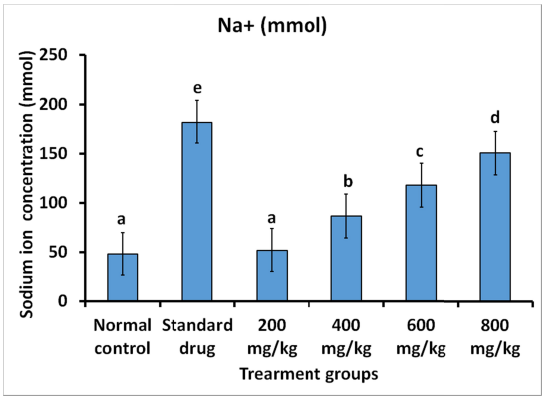

Figure 2: Effect of *Ficus capensis* on the 24 hour concentration of Na^+ (mmol) in urine of albino rat

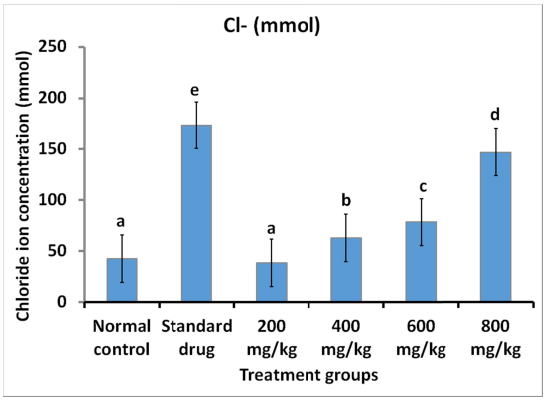

Figure 3: Effect of *Ficus capensis* on the 24 hour concentration of Cl^- (mmol) in urine of albino rat

The ethanol extract of *F. capensis* showed a significant decrease ($p<0.05$) in K^+ concentration in 200, 400 and 600 mg/kg extract treated groups when compared to the standard drug. There was non-significant difference ($p>0.05$) in K^+ concentration of the group orally administered 400 mg/kg of the ethanol extract of *F. capensis* when compared with normal control. The 800 mg/kg extract effectively competed with the standard drug (Figure 4).

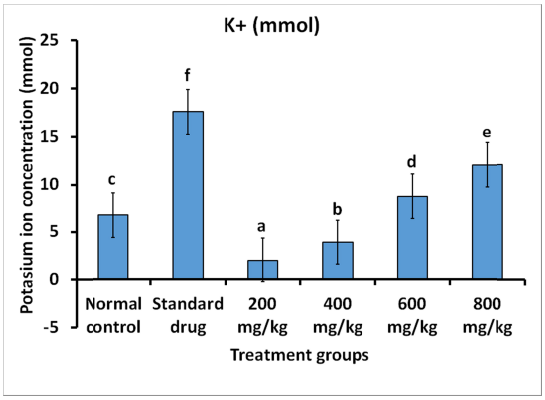

Figure 4: Effect of *Ficus capensis* on the 24 hours concentrations of K^+ (mmol) in urine of male albino rat

There was a significant increase ($p<0.05$) in the HCO^{-3} concentration in the group administered 800 mg/kg extract which favouraly compared to the standard drug, while group administered with 200, 400 and 600 mg/kg of the extract showed a significant decrease ($p<0.05$) in HCO^{-3} concentration when compared to the standard drug with non-significant difference ($p>0.05$) when compared to the normal control (Figure 5).

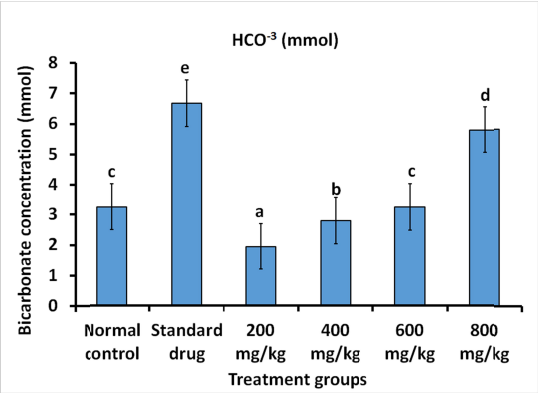

Figure 5: Effect of *Ficus capensis* on the 24 hours concentrations of HCO^{-3} (mmol) in urine of male albino rat

The ethanol extract of *F. capensis* significantly reduced ($p<0.05$) the inflammation of the paw of the rats in a dose dependent manner (Table 3). There was non-significant ($p>0.05$) different between the volume displacement method and venire caliper method of the 600 and 800 mg/kg of the extract.

The ethanol extract of *F. capensis* induced a significant increase ($p<0.05$) in the total bilirubin in the third week with the group treated with 800 mg/kg having the highest value compared to the normal control (Table 4). The ethanol extract of *F. capensis* induced a significant increase ($p<0.05$) in the total bilirubin in the third week with the group treated with 800 mg/kg having the highest value compared to the normal control.

The ethanol extract of *F. capensis* showed non-significant increase ($p>0.05$) in ALT of groups treated with 200 and 400 mg/kg of the extract when compared to the control at the first week. The ALT activity significantly ($p<0.05$) increased at the second and third week. There was also significant ($p<0.05$) increase in ALT of the groups treated with 600 and 800 mg/kg of the extract when compared with the both control groups in all the weeks (Tables 5).

The ethanol extract of *F. capensis* showed non-significant increase ($p>0.05$) in ALP of groups treated with 200 and 400 mg/kg of the extract when compared to the both controls at the first week. There was significant increase ($p<0.05$) in ALP of the groups treated with 600 and 800 mg/kg of the extract when compared with the both control groups in the second and third weeks (Tables 6).

The ethanol extract of *F. capensis* induced a significant increase ($p<0.05$) in the ALT in the third week with the group treated with 800 mg/kg having the highest value compared to the normal control (Table 7). There was non-significant increase ($p>0.05$) in the ALT of the extract treated groups in the first week.

There was a significant increase ($p<0.05$) in the conjugated bilirubin in the group treated with 600 and 800 mg/kg at the second and third weeks when compared with the normal control and standard drug (Table 8).

Table 3: Anti-inflammatory effect of *Ficus capensis* using volume displacement method (VDM) and venire caliper (VC) (percentage inhibition)

Treatment Group	Percentage Inhibition (%) (VDM)	Percentage Inhibition (%) (VC)
Distilled water	0.00 ± 0.00	0.00 ± 0.00
Aspirin (positive control)	52.10 ± 4.82*	51.19 ± 5.28
Extract 200 mg/kg	34.95 ± 5.93	34.51 ± 2.13
Extract 400 mg/kg	47.31 ± 1.53	44.81 ± 2.29
Extract 600 mg/kg	61.45 ± 3.08	61.60 ± 5.51
Extract 800 mg/kg	72.96 ± 6.09*	70.15 ± 6.59

Note: *Values are presented as mean ± standard error, * superscripts along a row represent significant mean difference at p<0.05*

Table 4: Sub-chronic toxicity effect of *Ficus capensis* on total bilirubin profile of albino rat

Groups	Week 1	Week 2	Week 3
Normal Control	12.50 ± 0.14^{2a}	11.50 ± 0.14^{1a}	12.40 ± 0.14^{2a}
Standard drug	12.60 ± 0.14^{1a}	14.45 ± 0.07^{2b}	14.72 ± 0.07^{2b}
200 mg/kg	12.80 ± 0.28^{1a}	22.80 ± 0.28^{2c}	32.80 ± 0.56^{3c}
400 mg/kg	14.85 ± 0.07^{1b}	24.85 ± 0.07^{2d}	34.15 ± 0.21^{3d}
600 mg/kg	16.50 ± 0.42^{1c}	26.50 ± 0.42^{2e}	36.20 ± 0.28^{3e}
800 mg/kg	17.30 ± 0.42^{1d}	27.30 ± 0.42^{2f}	37.55 ± 0.49^{3f}

Values are presented as mean ± standard error, different superscripts alphabet (column) and number (row) represent significant mean difference at p<0.05

Table 5: Sub-chronic toxicity effect of *Ficus capensis* on alanine aminotransferase profile of albino rat

Groups	Week 1	Week 2	Week 3
Normal Control	14.50 ± 0.14^{2a}	13.60 ± 0.14^{1a}	14.80 ± 0.14^{2a}
Standard drug	14.70 ± 0.14^{1b}	19.50 ± 0.18^{2b}	19.60 ± 0.14^{2b}
200 mg/kg	14.85 ± 0.71^{1c}	34.85 ± 0.07^{2c}	44.20 ± 0.28^{3c}
400 mg/kg	16.60 ± 0.28^{1d}	36.60 ± 0.28^{2d}	46.10 ± 0.14^{3d}
600 mg/kg	17.95 ± 0.07^{1e}	37.95 ± 0.07^{2e}	47.95 ± 0.49^{3e}
800 mg/kg	19.80 ± 0.28^{1f}	39.30 ± 0.42^{2f}	49.10 ± 0.14^{3f}

Values are presented as mean ± standard error, different superscripts alphabet (column) and number (row) represent significant mean difference at p<0.05

Table 6: Sub-chronic toxicity effect of *Ficus capensis* on alkaline phosphatase profile of albino rat

Groups	Week 1	Week 2	Week 3
Normal Control	79.50 ± 0.14^{2a}	82.20 ± 0.14^{3a}	74.50 ± 0.14^{1a}
Standard drug	82.45 ± 0.17^{1b}	83.95 ± 0.35^{2b}	84.64 ± 0.62^{3b}
200 mg/kg	86.95 ± 0.07^{1c}	96.95 ± 0.32^{2b}	91.71 ± 2.26^{3b}
400 mg/kg	89.60 ± 0.84^{1}d	100.60 ± 0.56^{2c}	106.00 ± 8.20^{3c}
600 mg/kg	99.40 ± 0.84^{1}e	108.40 ± 0.56^{2d}	118.25 ± 0.07^{3d}
800 mg/kg	102.10 ± 0.14^{1}f	112.12 ± 0.14^{2e}	122.65 ± 0.35^{3e}

Values are presented as mean ± standard error, different superscripts alphabet (column) and number (row) represent significant mean difference at p<0.05

Table 7: Sub-chronic toxicity effect of *Ficus capensis* on *aspartate aminotransferase* profile of albino rat

Groups	Week 1	Week 2	Week 3
Normal Control	13.50 ± 0.14^{1c}	14.50 ± 0.142^{2a}	13.50 ± 0.143^{3a}
Standard drug	13.20 ± 0.10^{1b}	14.70 ± 0.34^{2b}	14.80 ± 0.42^{3b}
200 mg/kg	11.75 ± 0.07^{1a}	31.75 ± 0.70^{1c}	41.30 ± 0.42^{3c}
400 mg/kg	14.15 ± 0.21^{1d}	34.15 ± 0.21^{2d}	44.30 ± 0.42^{3d}
600 mg/kg	16.0 ± 0.28^{1e}	36.00 ± 0.28^{2e}	46.20 ± 0.56^{3e}
800 mg/kg	17.30 ± 0.42^{1f}	37.50 ± 0.42^{2f}	47.40 ± 0.56^{3f}

Values are presented in mean ± standard error, different superscripts alphabet (column) and number (row) represent significant mean difference at p<0.05

Table 8: Sub-chronic toxicity effect of *Ficus capensis* on conjugated bilirubin profile of albino rat

Groups	Week 1	Week 2	Week 3
Normal Control	9.50 ± 0.14^{1f}	9.50 ± 0.14^{1}b	9.50 ± 0.14^{1}b
Standard drug	6.20 ± 0.28^{1b}	7.60 ± 0.28^{2a}	7.40 ± 0.28^{3a}
200 mg/kg	5.40 ± 0.28^{1a}	10.40 ± 0.28^{2c}	12.40 ± 0.28^{2c}
400 mg/kg	6.60 ± 0.28^{1c}	11.60 ± 0.28^{2d}	14.60 ± 0.28^{3d}
600 mg/kg	7.70 ± 0.14^{1d}	12.70 ± 0.14^{2e}	16.70 ± 0.14^{3e}
800 mg/kg	8.10 ± 0.14^{1e}	13.10 ± 0.14^{2f}	18.10 ± 0.14^{2f}

Values are presented in mean ± standard error, different superscripts alphabet (column) and number (row) represent significant mean difference at p<0.05

DISCUSSION

Medicinal plants have been reported to have therapeutic value and the prolong administration could be toxic at higher doses. This study evaluated the ethanol leaves extract of *F. capensis* for its anti-inflammatory, diuretic activity and possible toxic effect on the liver for a period of 21 days. The results on the toxicological effect of ethanol leaves extract of *F. capensis* showed that 600 and 800 mg/kg doses significantly ($p<0.05$) increase the AST, ALP, ALT, total and conjugated bilirubin on the week 3 when compared with the normal control. This suggested that prolong administration of the extract at high doses could be harmful to the liver. The *F. capensis* extract showed a significant anti-inflammatory activity ($p<0.5$) when compared with control at different time interval. The plant extract had similar effect as aspirin. The anti-inflammatory property of the extract could be because of some phytochemicals found in ethanol extract of *F. capensis* (Berg, 2000). The anti-inflammatory properties are due to inhibition of enzymes involved in inflammation, especially arachidonic acid metabolic pathway, and synthesis of prostaglandins (Harris *et al*., 2002). Tannins could affect the inflammatory response via free radical scavenging properties and inhibition of iNOS in macrophages (Gryglewski *et al.,* 1976). Saponins on the other hand, inhibit pain and inflammation via nitric oxide inhibition. Inhibition of these enzymes provides the mechanism by which the extract inhibits inflammatory disorders.

The diuretic effect in rats treated with furosemide and *F. capensis* extract indicated a significantly increase in urine volume at doses of 600 and 800 mg/kg respectively, there was a higher excretion of Na^+ in the groups treated with 600 and 800 mg/kg does of the extract than at the lower doses of 200 and 400 mg/kg body weight. Diuretics modulate the volume and composition of body fluids in variety of clinical conditions like hypertension (Zhao *et al.,* 2012). The increase natriuresis in response to acute treatment with ethanol extract of leaves of *F. capensis* may partly explain the increase in diuresis. Furosemide a loop diuretic increases urinary excretion of sodium by inhibiting $Na^+/K^+/2Cl^-$ symporter (co-transporter system) in the thick ascending limb of the Henley loop (Flower 1986). Thus, *F. capensis* could possibly act upon this part of the nephron to exert an inhibition of sodium chloride reabsorption and, hence, inducing a significant ($p<0.05$) urinary elimination of water (Zhu et *al.,* 2009).

The bicarbonate content was almost the same within the groups. The low level of bicarbonate among the treated group indicates that the extract suppresses the activity of the enzyme carbonic anhydrase which convert carbon dioxide and water to carbonic acid (Supuran *et al*., 2003). This suggests that *F. capensis* have similar mechanism of action to the carbonic anhydrase inhibitors that inhibit the transport of HCO^{-3} which leads to less sodium reabsorption. The levels of HCO^{-3} was statistical significant ($p<0.05$) when compared with standard control, except for 200 mg/kg dose which had no significant difference when compared with the normal control. The Na^+, Cl^- and K^+ output increased as the dose increased, indicating a significant increase in a dose dependent manner. The 200 and 400 mg/kg of the extract exhibited a weak excretion of potassium less than the standard drug which suggested that it has potassium sparing diuretic activity. Ntchapda *et al.* (2014) reported that the aqueous extract of the leaves of *F. glumosa* increased, in a dose dependent manner, the

excretion of Na^+, K^+, and Cl^- and caused a decrease in urine osmolarity.

Conclusion: The ethanol leaves extract of *F. capensis* shown significant diuretic activity and Anti-inflammatory properties activities in a dose dependent manner though prolong administration of the leaves extract of *F. capensis* at high doses could be toxic to the liver.

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