

Toxicological profile of hydro-ethanolic extract of the leaf of *Solenostemon monostachyus* (P. Beauv.) (Lamiaceae) in rats

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ABSTRACT

The rapid increase in consumption of herbal remedies worldwide has been stimulated by several factors, including the notion that all herbal products are safe and effective. However, over the past decade, several news-catching episodes in developed communities indicated adverse effects, sometimes life-threatening, allegedly arising as a consequence to taking herbal products or traditional medicines from various ethnic groups. Therefore, this present study aimed to carry out extensive toxicological evaluation of hydro-ethanolic extract of the leaf of *Solenostemon monostachyus* (P. Beauv.) Lamiaceae. In an acute toxicity tests of five groups of mice ($n = 5/\text{group}$), male albino mice were orally treated with aqueous extract of *S. monostachyus* up to 25000 mg/kg and general behavioral activity, adverse effects, and mortality were recorded for up to 14 days. A sub-chronic toxicity test was performed by daily administration with the extract at 75, 112.5 and 225 mg/kg orally ($n = 6/\text{group}$) for 49 days, while control rats received distilled water. Haematological and biochemical (liver enzymes, proteins and bilirubin) parameters were determined and histopathological examination was carried out. The LD₅₀ was estimated to be 22,500 mg/kg, with acute behavioural manifestations of reduced locomotion and calmness. The extract showed statistical significant difference ($P \leq 0.05$) in haematological and biochemical parameters in the treated rats compared to the control in subchronic treatment. While, subchronic administration of the extract affected some vital organs evident by slight distortion in histo-architecture, degeneration and fat deposits. Results obtained in this study suggest hydro-ethanolic extract of the leaf of *S. monostachyus* is relatively safe when administered orally in traditional medicine.

Keywords: *Solenostemon monostachyus*, haematology, liver and biochemical function, sub-chronic toxicity.

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INTRODUCTION

Herbal medicine is still considered to be the most abundant, affordable, reliable, trusted and well understood form of health care in virtually all African villages (Abalaka et al., 2009) and 80% of African populations use some form of traditional herbal medicine (Willcox and Bodeker, 2004). Before the advent of orthodox medicine, larger African population relied on herbs growing in and around them to take care of their health problems and, in some cases, as a simultaneous source of food (Abalaka et al., 2009). Orthodox medicine somewhat minimizes the herbal health care system but

the development of resistance against orthodox medicine by pathogens, high costs as well as lack of availability of some of these drugs has, in recent times, begun to reverse this trend (Lee, 2006; Lam, 2007; Ogbunugafor et al., 2008), fortified by the notion that all herbal products are safe and effective (Farnsworth and Soejarto, 1985; Soejarto, 1989). However, several adverse effects, sometimes life-threatening, arose after the consumption of herbal products or traditional medicines from various ethnic groups, putting into question the safety of such herbal remedies (Soejarto, 1989; Elvin-Lewis, 2001). In

some cases, adulteration, inappropriate formulations, or a lack of understanding of plant and drug interactions or their uses led to adverse reactions that were sometimes life-threatening or lethal to patients (Ernst, 1998). Therefore, contrary to popular belief, the use of herbal remedies can pose serious health risks (Wood, 2002). Traditional herbal medicines do not receive sufficient attention in global health debates even though the worldwide annual market for traditional herbal medicine products approaches US\$ 60 billion (Adelaja, 2006). China, India, Nigeria, the USA and WHO have all made substantial research investments in traditional herbal medicines (WHO, 2002). Industry has also invested hundreds of millions of US dollars looking for promising medicinal herbs and novel chemical compounds (Zamiska, 2006). Herbal drugs are often bulky, doses are not quantified and most importantly toxicity is largely unknown (Galati and O'Brien, 2004; Sa'ad et al., 2006). Although a substantial number of scientific research papers have revealed activities of so many African plants, not many venture into studying the toxicity of this plant material (Abalaka et al., 2009). Wood (2002) recommended that in the quality assurance research of herbal remedies, determination of the efficacy and safety are important aspects to consider.

S. monostachyus is an important herb that is native to West and Central Africa. The plant is commonly called Monkey's potato. The leaves have been traditionally used for various medicinal purposes. This plant has significant abilities to scavenge hydrogen peroxide and hydroxyl radicals, and also significant ability to reduce ferric ions *in vitro*. The extract also possesses significant abilities to reduce lipid peroxidation and haemolysis in erythrocytes induced by hydrogen peroxide when compared with the ability of ascorbic acid to do the same. This is ascribed to the presence of antioxidant phytochemicals which acted in synergy (Okoko and Ere, 2012). Therefore, the present study was aimed at ascertaining the safety of this plant in traditional medicine and evaluating certain deleterious effects that may emanate from it prolong usage. This was undertaken by conducting acute toxicity in mice and sub chronic toxicity in rats.

METHODOLOGY

Plant collection

The fresh young leaves of *S. monostachyus* were collected from Itumoro area of Ikenne town, Ogun. Botanical identification and authentication was performed by Mr O.O Oyeboji of the Department of Botany, Faculty of Science, University of Lagos. A voucher specimen (LUH 5910) was deposited in the herbarium of the University of Lagos, Akoka, Yaba, Lagos.

Extract preparation

S. monostachyus leaves were air dried until a constant weight was obtained and the dried material was ground to fine powder.

One hundred g of the plant material was macerated in 1000 ml of hydroethanol (1:1) for 48 h, after which the liquid was decanted and filtered twice to remove all debris. The residue from the process was re-macerated in same volume of hydroethanol to ensure exhaustive extraction (x2). The filtrate from each extraction process was combined and evaporated to dryness at 40°C under reduced pressure. The solid extract obtained was reconstituted in distilled water before each experimental session.

Animals

Male Wistar albino mice (average weight 20 g) and male albino rats (average weight 100 g) used in this study were obtained from the Laboratory Animal Centre of the College of Medicine, University of Lagos, Lagos, Nigeria. The animals were maintained under standard environmental conditions (23 to 25°C, 12 h/12 h light/dark cycle) and were fed on Pfizer standard rodent pellet diet and water *ad libitum*. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health (NIH Publication No. 85-23, revised 1996) for studies involving experimental animals. The use of mice in the acute toxicity study and rats in the chronic toxicity study is a standard toxicological/experimental procedure.

Phytochemical analysis

Phytochemical screening of the hydroethanolic leaf extract of *S. monostachyus*, to determine the presence or absence of various phytochemicals, was carried out according to the methods of Sofowora (1993) and Edeoga et al. (2005).

Acute toxicity study

Oral acute toxicity

Mice were randomly divided into five groups of five animals per group. Graded doses of the extract (5000, 9000, 10000 and 25000 mg/kg) were administered to the animals orally *ad libitum*. The control group was administered 0.5 ml distilled water orally. Mice were observed for 24 h post-treatment for mortality, behavioural changes (restlessness, dullness, agitation) and signs of toxicity.

Sub-acute toxicity study

Rats were randomly allotted to four groups of 10 animals per group. The animals were orally administered hydro-ethanolic extract of the leaf of *S. monostachyus* at doses of 75, 112.5, and 225 mg/kg daily for 49 days. The control group was orally administered 0.2 ml of distilled water daily. The rats were weighed weekly throughout the course of the experiment. The animals were closely observed for behavioral activity such as restlessness, hyperactivity, dullness and general morphological changes.

Collection of blood and organ sample

The animals were sacrificed on the 61st day of the experiment and blood samples were collected via cardiac puncture with the aid of a capillary tube into EDTA (ethylenediaminetetraacetic acid) bottles and non EDTA containing bottles to obtain serum for haematological and blood chemistry analysis, respectively. The vital organs (kidneys, liver, lungs and stomach, heart, testes, ovary) were carefully isolated for histopathological examination.

Haematological parameters and serum chemistry analysis procedures

The white blood cell (WBC), red blood cell (RBC), hemoglobin (HGB), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and platelet (PLT) were determined using a fully automated haematology analyzer (Swelab Auto counter 910^{EO+, USA}). For biochemical analysis, the parameters determined were aspartate phosphatase (AST), alanine phosphatase (ALT), alkaline phosphatase (ALP), total-cholesterol (T.CHOL), triglyceride (TG), HDL-cholesterol, total bilirubin and total protein using commercially available kits (RANDOX, United Kingdom) and an auto biochemical analyzer machine (Rayto). The serum activities of liver enzymes alkaline phosphatase (ALP) was estimated by method of Sigma Diagnostics (1987), while those of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were estimated by colorimetric method (Sigma Diagnostic, 1985). The LDL-cholesterol was determined using the formulae of Friedewald et al. (1972).

Histopathological examination of selected vital organs

Briefly, laparotomy was done to harvest the internal structures (kidneys, liver, lungs and stomach, heart, testes, ovary) were fixed in 10% formalin in labeled bottles.

Tissues were processed routinely and embedded in paraffin wax. Sections of 5 μ m thickness were cut, stained with haematoxylin and eosin (H&E) and examined under the light microscope by a pathologist.

Statistical analysis

The data were subjected to one-way analysis of variance (ANOVA) test and differences between samples were determined by Dunnett's multiple comparison test, using the Graph Pad Prism (statistical) software. Results were considered to be significant at $P \leq 0.05$ and were expressed as mean \pm SEM.

RESULTS

Phytochemical analysis

The results of the chemical tests performed in the preliminary phytochemical screening revealed the presence of flavonoids, saponins, alkaloids (strongly present), cardenolides, anthraquinone, phenolics and tannins in the hydroethanolic leaf extract of *S. monostachyus*. Phlobatamins and oils were found to be absent.

Acute toxicity test

S. monostachyus did not cause any mortality and visible signs of toxicity when administered orally up to 22.2 g/kg and observed for fourteen days. Behavioural manifestations observed for 2 h post-oral treatment included reduced locomotion and calmness. The LD₅₀ of the extract administered orally was estimated to be 22500 mg/kg (Table 1).

The t-test $\alpha = 0.05$ showed statistically significant differences between doses within each parameter.

The effect of SM on body weight in rat shows significant increase in weight during the first (4 weeks) of treatment and a subsequent reduction during the last 3 weeks of treatment ($P < 0.05$) in all administered doses while there were significant increase in the weight of the control throughout the 7 weeks ($P > 0.05$) (Table 2).

Table 3 shows significant changes on all biochemical parameters ($P < 0.05$) of the treated groups, except in direct Bilirubin and HDL ($P > 0.05$).

Table 4 shows significant changes on all haematological parameters ($P < 0.05$) of the treated groups, except in monocyte ($P > 0.05$).

Histological changes observed in liver, kidney, lungs, stomach, testes and heart of control and treated rats with *Solenostemon monostachyus* are shown in Figures 1 to 6, respectively.

DISCUSSION

The phytochemical screening of the crude plant of *S. monostachyus* revealed the presence of anthraquinone, alkaloids, flavonoids, saponin, tannins and cardenolides.

Anthraquinones are aromatic organic compounds and is a derivative of anthracene. It has the appearance of a yellow or light-gray to gray-green, solid, crystalline powder. It is fairly stable under normal conditions. It naturally occur in some plants, fungi, lichen and insects, wherein they serve as a basic skeleton for their pigments. It is used in the production of dyes and also used as a laxative (Samp, 2008).

Alkaloids are naturally occurring chemical compounds containing basic nitrogen atoms and are produced by a large variety of organisms including bacteria, fungi, plants, and animals. Many alkaloids are toxic and often have a pharmacological effect, which makes them to be used as medications and recreational drugs. Some alkaloids have a bitter taste.

Flavonoids are derived from 2-phenylchromen-4-one (2-phenyl-1-4-benzopyrone) and are commonly known for their antioxidant activities. Flavonoids, which are widely distributed in plants, fulfill many functions including producing yellow, red or blue pigmentation in flowers and protection from attacks by microbes and insects. Compared to other active plant compounds, they are low in toxicity. Flavonoids are referred to as nature's biological response modifiers because of their inherent ability to modify the body's reaction to allergens, viruses and carcinogens. They show anti-allergic, anti-inflammatory, antimicrobial and anticancer activity (Spencer, 2008). Flavonoids exhibit potent antioxidative and free radical scavenging activities (Urquiaga and Leighton, 2000).

Tannins have antioxidant properties, they are

Table 1. Acute (oral) toxicity study in mice after 24 h of administration of hydro-ethanolic leaf extract of *Solenostemon monostachyus*.

Group	Dose (mg/kg)	D/TA	Signs of toxicity observed
A	0.2 ml (H ₂ O)	0/5	No toxic changes observed
B	5000	0/5	No toxic changes observed
C	9000	0/5	No toxic changes observed
D	10000	0/5	Slight dullness was observed in 2 Animals in the first 2 h
E	25000	3/5	Slight dullness was observed in 2 animals in the first 2 h

D/T: Number of mice deaths/total number of mice (n = 5).

Table 2. Effects of hydro-ethanolic leaf extract of *Solenostemon monostachyus* on the body weights of rats after 49 days administration (N = 10).

	0WK	1WK	2WKS	3WKS	4WKS	5WKS	6WK	7WKS
Control distillate water (0.5 ml)	186.50 ± 1.64*	189.50 ± 2.47*	192.83 ± 2.99	197.50 ± 2.43	201.83 ± 2.02	204.00 ± 2.03	209.00 ± 5.72*	212.50 ± 3.15*
SM 75 (mg/kg)	133.33 ± 3.27*	141.33 ± 3.13*	148.66 ± 3.35*	153.00 ± 4.69*	158.00 ± 4.49*	153.66 ± 3.87*	143.50 ± 3.56*	140.33 ± 2.38*
SM 112.5 (mg/kg)	154.50 ± 2.97*	161.00 ± 2.95*	168.83 ± 3.59*	173.83 ± 3.72*	180.60 ± 4.62*	153.66 ± 3.87*	143.50 ± 3.56*	140.33 ± 2.38*
SM 225 (mg/kg)	165.33 ± 1.28*	173.33 ± 2.21*	184.50 ± 2.82	191.00 ± 2.20	195.83 ± 2.78	153.66 ± 3.87*	143.50 ± 3.56*	140.33 ± 2.38*

Key: * = difference considered statistically significant.

Table 3. Biochemical parameters in rats after 49 days treatment with *Solenostemon monostachyus*.

Parameter	Control distilled water (0.5 ml)	SM 75 mg/kg	SM 112.5 mg/kg	SM 225 mg/kg
AST (U/l)	38.02 ± 2.35	107.49 ± 0.47**	83.28 ± 4.45*	62.63 ± 1.10*
ALT (U/l)	16.60 ± 0.41	28.72 ± 1.56*	26.66 ± 1.54*	16.88 ± 0.71
ALP (U/l)	145.32 ± 2.32	210.68 ± 7.15*	226.32 ± 9.23*	198.72 ± 3.49*
T.PRO (mg/dl)	47.13 ± 0.26	34.78 ± 0.64*	42.42 ± 0.59*	41.90 ± 0.55*
T.BIL (mg/dl)	0.46 ± 0.20	0.44 ± 0.27	0.47 ± 0.11	0.59 ± 0.09*
Direct bilirubin (mg/dl)	0.12 ± 0.01	0.11 ± 0.008	0.12 ± 0.01	0.15 ± 0.01
TG (mg/dl)	25.77 ± 1.06	97.69 ± 5.23*	71.53 ± 1.92*	27.30 ± 1.06
T.CHOL (mg/dl)	73.40 ± 1.31	78.56 ± 3.27	118.67 ± 2.48*	92.05 ± 4.09*
HDL(mg/dl)	32.17 ± 1.18	30.35 ± 0.43	32.7 ± 0.66	30.89 ± 0.55
LDL (mg/dl)	36.25 ± 2.09	28.67 ± 2.33	71.64 ± 1.86*	55.70 ± 3.43*

Key: * = difference considered statistically significant; ** = difference considered extremely statistical significant.

Table 4. Haematological parameters in rats after 32 days treatment with *Solenostemon monostachyus*.

Parameters	Control distilled water (0.5 ml)	SM 75 mg/kg	SM 112.5 mg/kg	SM 225mg/kg
Packed cell volume (%)	37.00 ± 0.36	25.66 ± 1.64*	38.33 ± 0.55	38.66 ± 1.44
RBC ($\times 10^{12}/L$)	3.94 ± 0.04	2.91 ± 0.22*	4.36 ± 0.16	4.51 ± 0.19
WBC ($\times 10^9/L$)	6750 ± 245.62	5766.66 ± 453.62*	6033.33 ± 480.04	6816.66 ± 458.37
HGB (g/L)	12.24 ± 0.14	8.27 ± 0.42*	12.67 ± 0.21	12.78 ± 0.47
MCV (fl)	93.92 ± 0.25	88.68 ± 1.63	88.16 ± 2.06	85.80 ± 1.71*
MCH (pg)	33.07 ± 0.10	32.37 ± 0.43	33.04 ± 0.88	33.06 ± 0.10*
MCHC (g/dl)	33.07 ± 0.10	32.37 ± 0.43	33.04 ± 0.88	33.06 ± 0.10*
Neutrophil	22.00 ± 2.89	32.33 ± 2.34*	27.00 ± 1.31	20.66 ± 1.28
Lymphocyte	76.33 ± 3.04	67.33 ± 2.48*	71.66 ± 1.72	78.00 ± 1.09
Monocyte	1.00 ± 0.36	0.33 ± 0.21	0.00 ± 0.00	1.33 ± 0.21

Key: * = difference considered statistically significant; ** = difference considered extremely statistical significant.

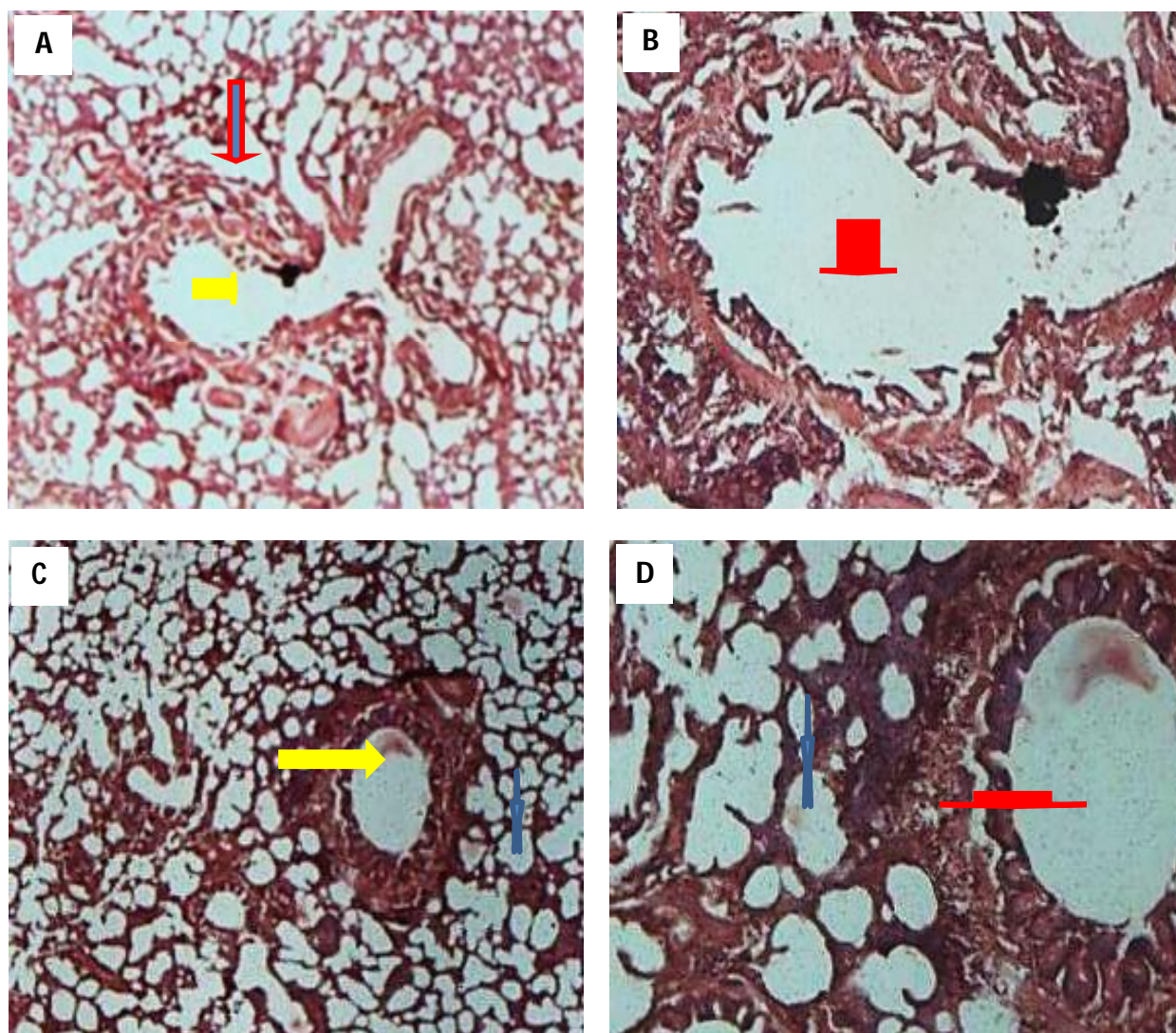


Figure 1. Micrographs of the lung tissue sections obtained from rats untreated and rats treated with various doses of hydro-ethanolic leaf extract of *Solenostemon monostachyus*. Magnification H&Hx40; (A) Rats untreated (control). (B) Rats treated with 75 mg/kg. (C) Rats treated with 112.5 mg/kg. (D) Rats treated with 225 mg/kg. Alveolar sac (star), Alveolus (red arrow), and Bronchiole (yellow arrow). The treated groups show increase micro-steatosis and collapsed alveolar septa.

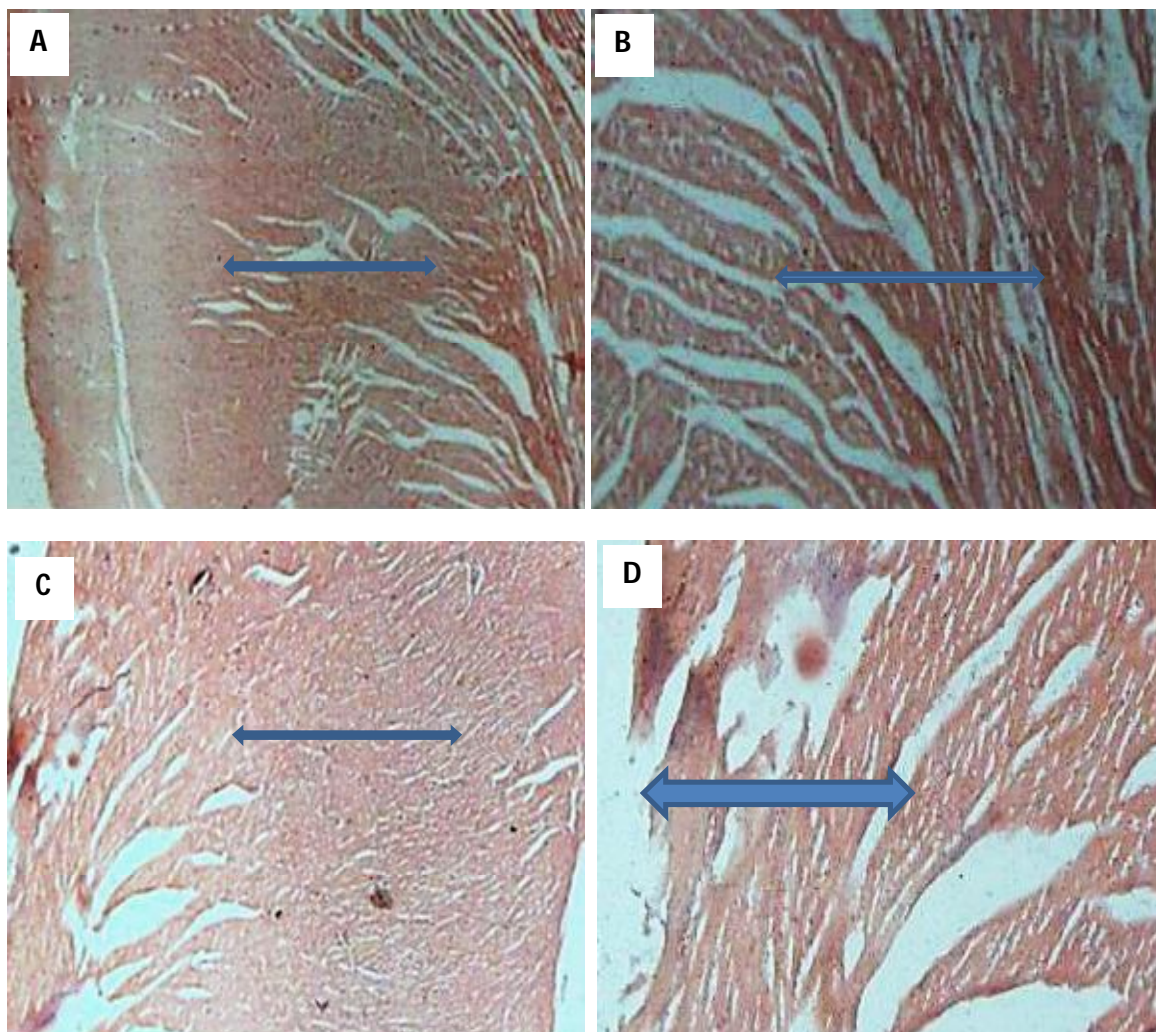


Figure 2. Micrographs of the heart tissue sections obtained from rats untreated and rats treated with various doses of hydro-ethanolic leaf extract of *Solenostemon monostachyus*. Magnification H&Hx40.; (A) Rats untreated (control). (B) Rats treated with 75 mg/kg. (C) Rats treated with 112.5 mg/kg. (D) Rats treated with 225 mg/kg cardiac muscle (blue arrow).The cardiac muscle of the treated groups is slightly hypertrophied.

astringent and excessive amount could damage the mucosa lining of the digestive tract (Hemingway et al, 1989). Tannins have shown potential antiviral (Lin et al., 2004), antibacterial and antiparasitic effects (Akiyama et al., 2001).

Saponins are being promoted commercially as dietary supplements and nutraceuticals. There is evidence of the presence of saponins in traditional medicine preparations where oral administrations might be expected to lead to hydrolysis of glycoside to aglycone (sapogenin) and glycone component.

Saponins are the glycosides of 27 carbon atom steroids, or 30 carbon atom triterpenes in plants. They are found in various plant parts; leaves, stems, roots, bulbs, flowers and fruits. They are characterized by their bitter taste and their ability to haemolyze red blood cells. They are used medically as expectorant, emetic and for the treatment of

excessive salivation, epilepsy, chlorosis and migraines. They are used in Ayurvedic medicine as treatment for eczema, psoriasis and for removing freckles. Saponins are believed to be useful in the human diet for controlling cholesterol. Digitalis-type saponins strengthen the heart muscle causing the heart to pump more efficiently. Saponins also inhibit cancer tumor growth in animals, particularly, lung and blood cancers, without killing normal cells. They are the plant's immune system acting as an antibiotic to protect the plant against microbes and fungus

Cardenolides (cardiac glycosides) are secondary metabolite of plant, have therapeutic activity involved in the treatment of cardiac failure. Their utility results from an increased cardiac output by increasing the force of contraction.

The acute oral toxicity study showed no mortality at

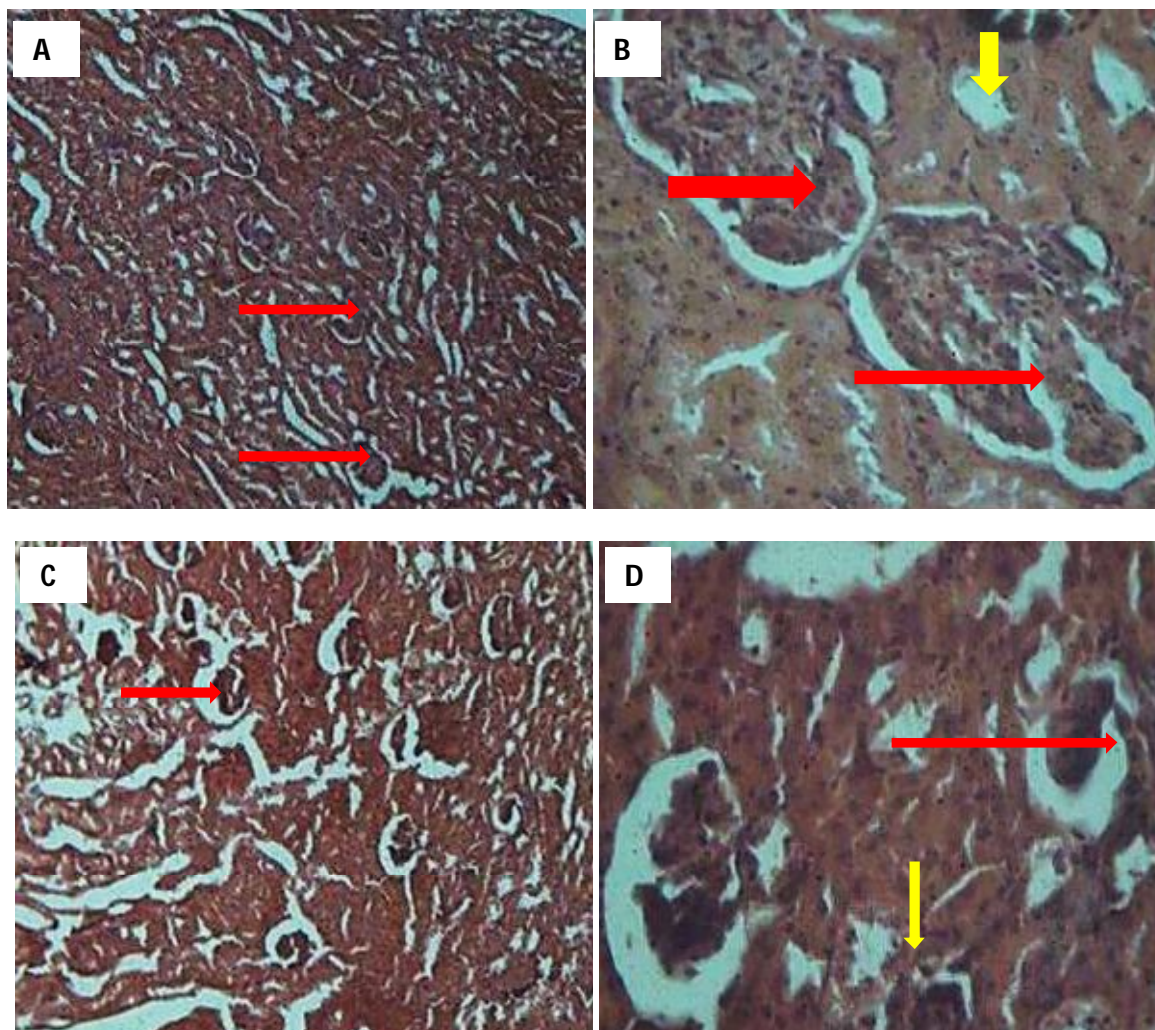


Figure 3. Micrographs of the kidney tissue sections obtained from rats untreated and rats treated with various doses of hydro-ethanolic leaf extract of *Solenostemon monostachyus*. Magnification H&H \times 40.; (A) Rats untreated (control). (B) Rats treated with 75 mg/kg. (C) Rats treated with 112.5 mg/kg. (D) Rats treated with 225 mg/kg; Glomerulus (red arrow), and renal tubule (yellow arrow). The treatment causes slight histoarchitectural distortion, glomerular degeneration resulting in enlarged urinary space.

dose of 1000, 5000, 9000, 10000 and 25000 mg/kg body weight. A modification of method which was done to modify the LD₅₀ also showed no mortality at 5000, 9000, 10000 mg/kg but 60% mortality was recorded at 25000 mg/kg. The result of acute toxicity under this condition of study shows that LD₅₀ of *S. monostachyus* by the oral route is 22500 mg/kg.

The underlying principle of toxicology is that dose makes a poison. According to Clarke and Clarke (1977), any plant extract with an estimated LD₅₀ greater than or equal to 1000 mg/kg through the oral route is considered safe.

In the sub-acute toxicity study, no deaths were recorded during the seven weeks treatment with *S. monostachyus* through the oral route except on day 19 when one animal in group II died due to hyperactivity. The extract induced a 'bulimia-like' disorder (a massive

over eating and drinking) on the experimented animals. Thus there was statistical significant difference between the initial and final weight of the animals at all doses of administration during the 49 days period

Haematological profile of the treated and control groups showed that *S. monostachyus* significantly increase RBC ($P < 0.05$), HGB ($P < 0.05$), and PCV ($P < 0.05$) at doses of 75 mg/kg, MCV ($P < 0.05$) and MCH ($P < 0.05$) at 225 mg/kg, while WBC values have no statistical difference with the control. The increase in RBC, HGB, MCV, PCV and MCH suggests that *S. monostachyus* has haemopoietic function and can be used in management of anaemia.

The biochemical profile (liver function test and lipid profile) of the treated and control groups are represented in Table 3. Biochemical markers (e.g. alanine transferase, alkaline phosphatase and bilirubin) are often

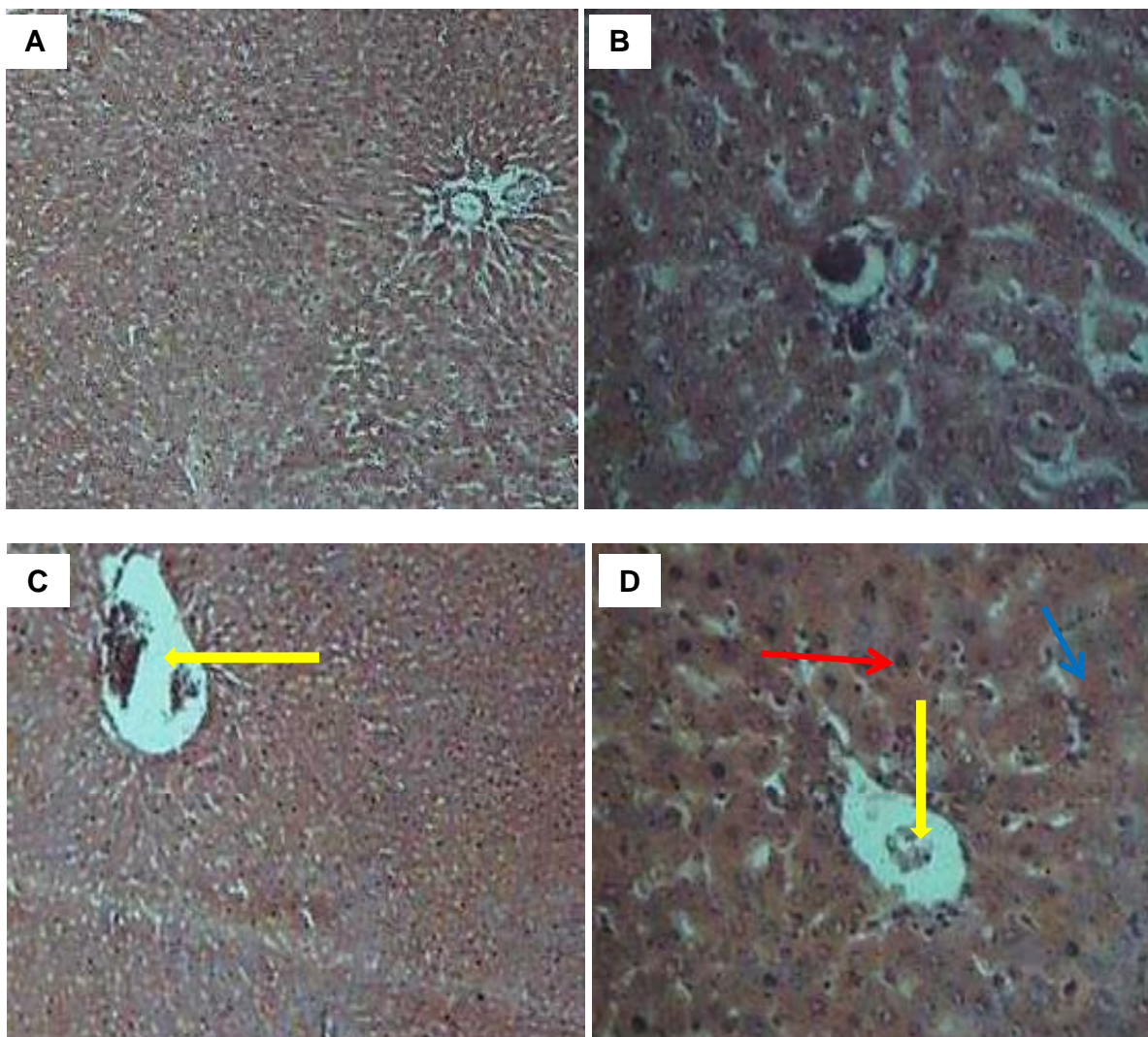


Figure 4. Micrographs of the liver tissue sections obtained from rats untreated and rats treated with various doses of hydro-ethanolic leaf extract of *Solenostemon monostachyus*. Magnification H&Hx40.; (A) Rats untreated (control). (B) Rats treated with 75mg/kg. (C) Rats treated with 112.5 mg/kg. (D) Rats treated with 225 mg/kg Hepatocytes (red arrow), Central vein (yellow arrow) and Sinusoid (blue arrow). The treatment causes slight histoarchitectural distortion, enlarged central vein, collapsed sinusoids and increased picnotism.

used to indicate liver damage. The result reveals significant decrease ($P < 0.05$) in the hepatic enzymes (ALT at doses of 75 and 112.5 mg/kg) while AST and ALP at all doses) of the treated groups compared with the control in a dose dependent manner and may be indicative of low hepatotoxic profile of the extract. Results of the lipid profile revealed that *S. monostachyus* significantly reduce (T.CHOL, LDL at doses of 112.5 and 225 mg/kg while TG at doses of 75 and 112.5 mg/kg). This might justify the use of the plant extract in management of obesity and cardiovascular diseases.

Histological investigation of some vital organs revealed slight distortion of histo-architecture of the liver and kidney which were not seen in the control.

The liver plays a central role in transforming and

clearing chemicals and is susceptible to toxicity from these agents. There was enlarged central vein collapsed sinusoids and increased picnotism (cell apoptosis) in the liver of treated groups. This condition may suggest right heart failure, shock liver, hepatic infarction, chronic passive congestion, Pylephlebitis, Hodgkin's disease or a total shutdown of hepatic system (Mitros, 2010). The kidney of treated animals revealed degenerated glomerulus which resulted in enlarged urinary space in the kidney of treated groups a condition involving a group of pathologies in which the renal excretory function is chronically compromised. In most cases the situation are progressive and irreversible, pathological syndromes that start silently (that is, no functional alterations are evident), continue through renal dysfunction and ends up in renal

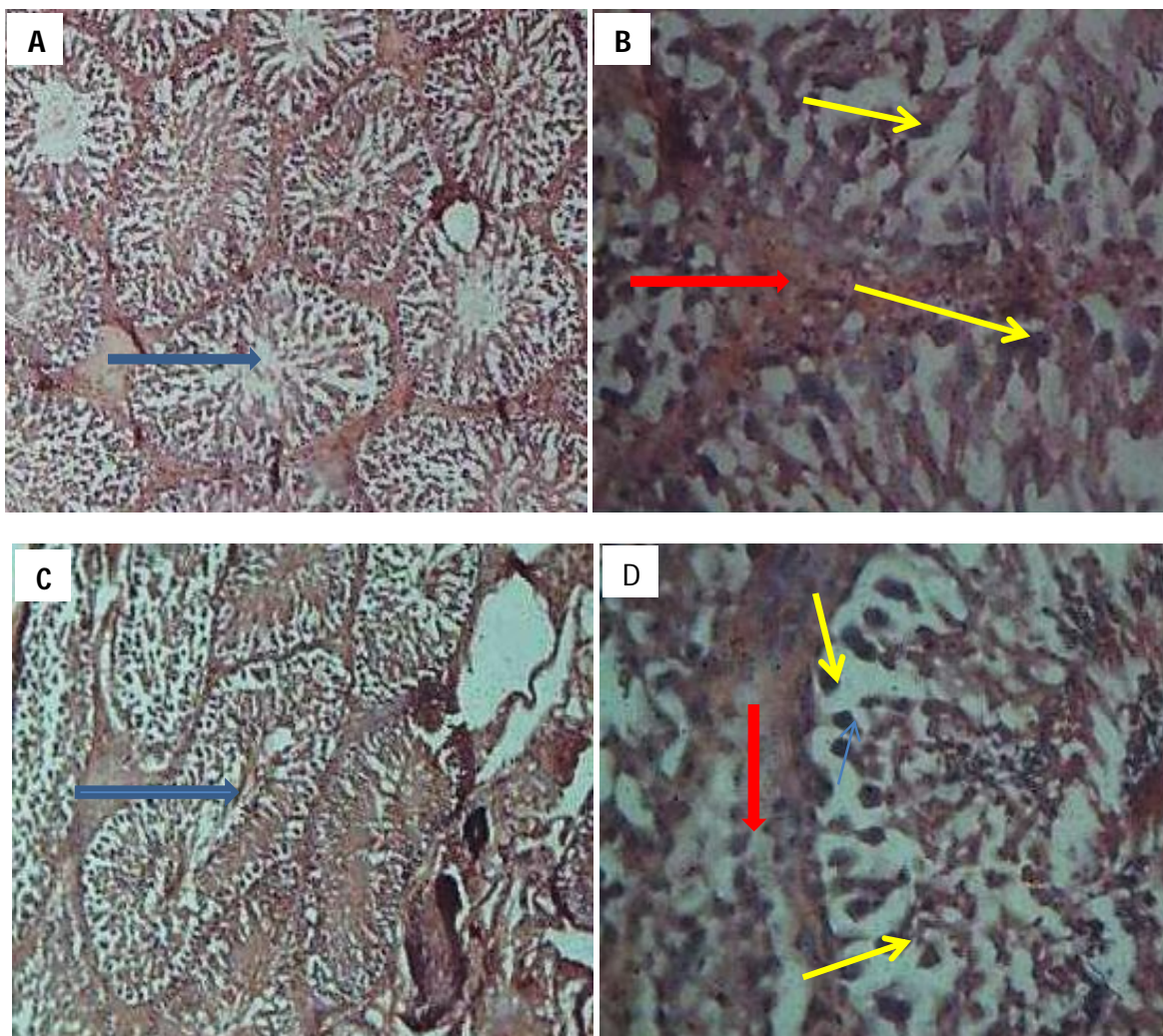


Figure 5. Micrographs of the testis tissue sections obtained from rats untreated and rats treated with various doses of hydro-ethanolic leaf extract of *Solenostemon monostachyus*. Magnification H&E \times 40.; (A) Rats untreated (control). (B) Rats treated with 75 mg/kg. (C) Rats treated with 112.5 mg/kg. (D) Rats treated with 225 mg/kg Leydig cells (red arrow), Sperm cells (yellow arrows) and Seminiferous tubules (blue arrow). The treatment causes distortion in the shape of the seminiferous tubules, apparent increased in the population of leydig cell and deranged spermatogenic cells.

failure. At this point, kidney transplant or dialysis (renal replacement therapy) becomes necessary to prevent death derived from the inability of the kidneys to cleanse the blood and achieve hydroelectrolytic balance, an undesirable condition that can emanate in chronic usage of *S. monostachyus* (López-Novoa et al., 2011).

Histological examination of the lungs revealed collapsed alveolar septa, and increased micro steatosis in the lungs of treated groups. This results in marked airspace enlargement with reduction of alveolar capillary exchange area. The pathological condition has been thought to bring about alveolar destruction by the interaction of apoptosis, oxidative stress, and protease/antiprotease imbalance (Tuder et al., 2006). Examination of the stomach reveals hypertrophy of the muscularis mucosae, muscularis externa and the

connective tissue of the submucosa. A new finding shows that intradiverticular carcinomas are often associated with a hypertrophic layer of muscularis mucosae, this can potentially confound tumor staging and consequently leads to malignant tumour (Zhong et al., 2014). Further, histological investigation of the heart revealed cardiac muscle being slightly hypertrophied in the heart of treated group, implicated by hypertension and Hypertrophic cardiomyopathy. The testicular tissue revealed distortion in the shape of the seminiferous tubules, apparent increased in the population of leydig cell and deranged spermatogenic cells in the testes of treated groups. This however may suggest reason for the use of *S. monostachyus* leaves extract in traditional medicine as herbal remedy for female infertility secondary, to hyperprolactinemia.

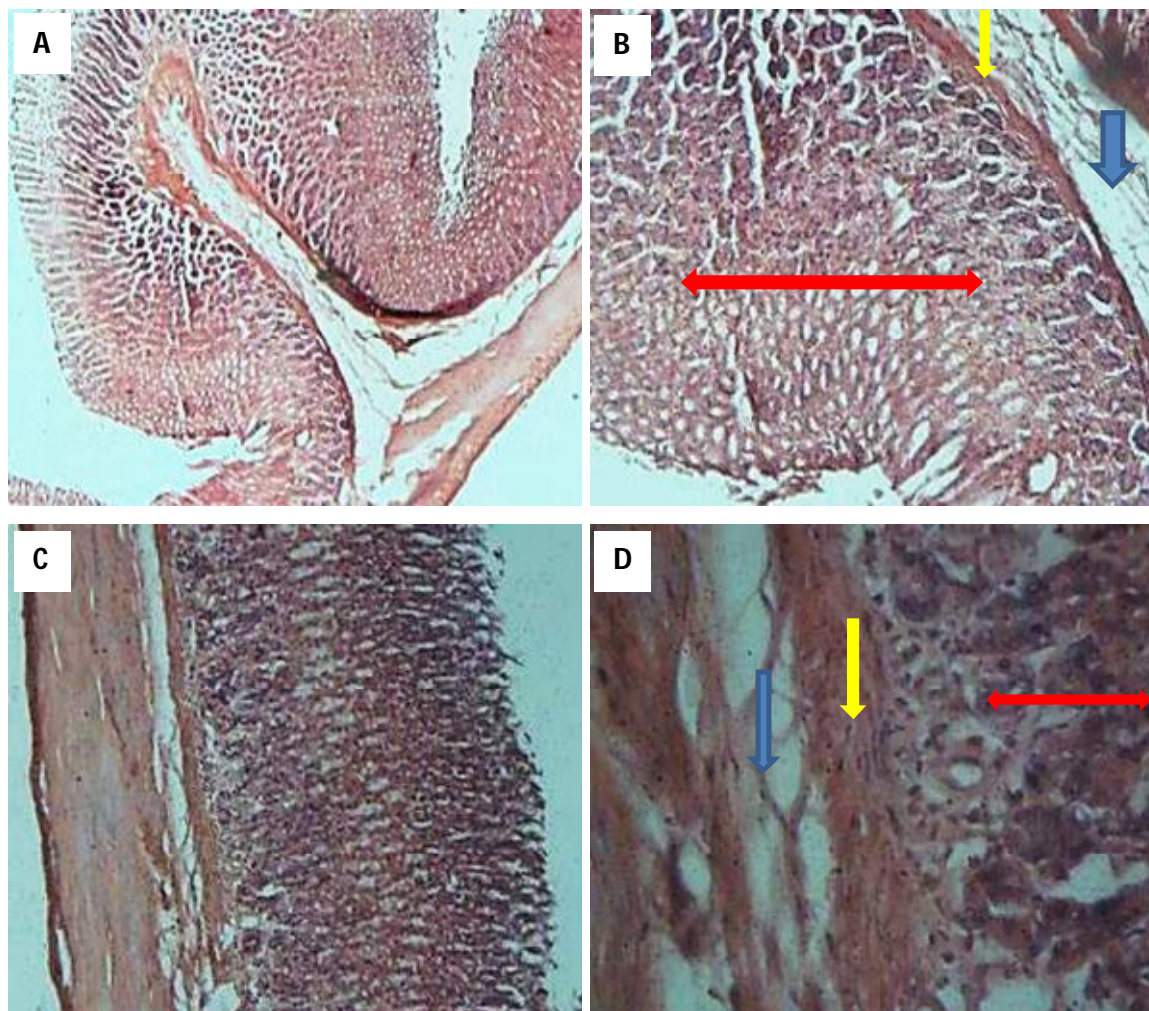


Figure 6. Micrographs of the gastric tissue sections obtained from rats untreated and rats treated with various doses of hydro-ethanolic leaf extract of *Solenostemon monostachyus*. Magnification H&H \times 40.: (A) Rats untreated (control). (B) Rats treated with 75mg/kg. (C) Rats treated with 112.5 mg/kg. (D) Rats treated with 225 mg/kg. Gastric glands (red arrow), Muscularis mucosae (yellow arrow) and Submucosa (blue arrow). The treatment causes hypertrophy of the muscularis mucosae, muscularis externa and the connective tissue of the submucosa. There is also a decrease in the gastric glandular height.

CONCLUSION

Chronic administration of hydroethanolic extract of *S. monostachyus* affected some vital organs evident by slight distortion in histo-architecture and degeneration. Thus, continuous administration of *S. monostachyus* leaf extract, use in herbal medicine for the treatment of various medical conditions should be employed with caution for safety purposes.

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