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Biochemical and Histopathological Effect of *Detarium microcarpum* Stem Bark Extract in Wistar Albino Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author YBB designed the study and wrote the protocol. Author ABM performed the statistical analysis and wrote the first draft of the manuscript. Author AIM managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aim: In this study, the methanol stem bark extract of *Detarium microcarpum* was evaluated for sub-chronic, biochemical and histopathological studies.
Methodology: Sub-chronic toxicity studies was investigated in rats administered with 35, 70 and 140 mg/kg doses of the extract orally for 28 days using standard laboratory procedures after the acute toxicity was carried out.
Results: The median lethal dose (LD_{50}) of the extract was calculated to be equal to (≥) 5000 mg/kg body weight in rats orally. Serological studies revealed significant (p<0.05) decrease in Alanine aminotransferase (ALT) at all doses tested, while at 140 mg/kg it caused a significant (p<0.05) increase in Alkaline Phosphatase (ALP). At doses of 70 and 140 mg/kg there was a significant (p<0.05) reduction in creatinine level. Histopathological studies on the liver showed moderate hepatocellular necrosis at doses of 35 and 70 mg/kg, while at 140 mg/kg there was intense hepatocellular necrosis, Kupffer cells and lymphocytes hyperplasia. The Kidney showed intense

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necrosis of tubules and glomerular necrosis with lymphocytes hyperplasia at all doses tested. The spleen also showed intense lymphocyte hyperplasia at all doses with sinusoidal congestion at the lowest dose of 35 mg/kg. The heart showed slight necrosis of cardiac muscle cells at all doses with blood congestion at 35 and 70mg/kg body weight.
Conclusion: The study indicates that prolong use of the extract in the management of disease conditions may be associated with some adverse effect of some vital organs.

Keywords: Detarium microcarpum; hepatotoxicity; medicinal plants; sub-chronic; histopathology and stem bark.

1. INTRODUCTION

The applications of medicinal herbs in the treatments and preventions of diseases are attracting the attention of scientist worldwide [1]. Scientific interest in medicinal plants has proliferated recently due to increase efficacy of plant derived drugs, rising concerns about side effects of modern medicine and the continuing emergence of drug resistant organisms. These problems made the search for new drugs from novel sources necessary [2] as they are costly effective, available and sustainable [3,4].

Tallo tree also known as *Detarium microcarpum* (D.M) Guill and Perr, belongs to *Caesalpiniaceae* family. *D. microcarpum* grow up to 10m high in dry areas and reach around 25m high in wet areas. The grayish bark severs into rectangular pieces to uncover an inner reddish surface and its twigs are covered with smooth or stripping orange bark [5]. D.M like other medicinal plants, its leaves, fruits, stem barks and roots or the whole plants can be used in various preparations as infusions or decoctions for prevention and treatments of certain disease and ailments [6,7].

The leaves and fruits of D. *microcarpum* are used in the treatment of diseases including itching and tuberculosis [7,8]. Locally, the stem bark extract is used for curing diarrhea including dysentery; amoebiasis, gonorrhea, hemorrhoids, rheumatism, venereal disease, urogenital infections and stomach ache [7]. The stem bark is also used in the treatment of pains and inflammations [6].

Due to the increase in search and uses of herbal and natural products, histopathological parameters determine the safety and toxicities of various alternative medicines. Liver, kidney and heart are vital organs in the human body and are the risk of damage by local herbs [9]. Further understanding of hepatotoxicity and kidney damages gives an insight on the efficacy and safety of the herb medicines.

Despite its prominent therapeutic properties of *D. microcarpum*, the plants need to undergo proper research and validation for safer usage and applications in herbal and traditional medicines. Thus in this present work, the sub-chronic and histopathologic effect of methanol extract of *Detarium microcarpum* were studied on Wistar strain albino rats.

2. MATERIALS AND METHODS

2.1 Plant Materials

The *Detarium microcarpum* plant sample was collected at Tsolonbashi village, Nigeria. The plant material was identified and authenticated by plant taxonomist in the Department of Biological Sciences, Bayero University Kano and deposited in the Herbarium with specimen voucher number 0071.

2.2 Experimental Animals

Wistar Albino rats (80-130g) of both sexes were obtained from Department of Pharmacology, Bayero University, Kano. The rats were freely allowed access to standard feed and water *ad libitum*. All Experiments with the Laboratory Animals were conducted in accordance with National Institute of Health Guidelines revised in 1996 (NIH Publication No. 80- 23).

2.3 Drugs and Chemicals

Methanol and Formalin solution were purchased from Sigma–Aldrich (Steinheim, Germany), Normal saline (Unique pharmaceuticals), and Distilled water.

2.4 Preparation of Extract

The stem bark collected was air dried pulverized using mortar and pestle and sieved. The powdered plant material was macerated in 70% methanol and kept for seven days with

occasional stirring. The extract was then sieved using mesh and filtered using Whatman filter paper. The filtrate was concentrated to dryness on water bath at 40°C until the solvent was completely evaporated. The resultant powdered extract obtained was stored in a desiccator until required.

2.5 Acute Toxicity Study

The LD_{50} of the extract was determined using Lorke's (1983) method. The study was carried out in two phases. Animals were deprived of food for 12-16 hours prior to administration of extract. In phase one, three groups of three Wistar rats per group were used. The extract was administered orally (p.o) in geometrical increasing doses (10, 100 and 1000 mg/kg). The treated experimental rats were observed four hours post administration and subsequently for 24 hours for signs of toxicity including death. In the second phase specific doses of (140, 225, 370 and 600 mg/kg) were administered according to the outcome of the first phase.

The LD_{50} was calculated using the formula as reported by [10]:

$$LD_{50} = \sqrt{(D_0 + D_{100})} \quad (1)$$

LD_0 lowest dose
LD_{100} highest

2.6 Sub-chronic Toxicity Studies

The study was conducted in accordance with WHO (1993) and Organization for Economic Cooperation Development OECD 407 (1995) guidelines. Twenty-four rats of both sexes were fasten for 16 – 18 hours, and divided in to four groups of six rats each. Group one served as control and received normal saline (1 ml/kg), whereas rats in groups two, three and four were subjected to oral graded dose of the extract at (35, 70 and 140 mg/kg) respectively for 28 days. The rats were allowed access to food and water throughout the duration of the experiment and were observed daily for general symptoms of toxicity and mortality. On the day 29th of the experiment, the animals were sacrificed, blood samples were collected for biochemical studies and their organs (kidney, heart, liver and spleen) were harvested for determination of organs weight ratio and histopathological studies.

2.7 Statistical Analysis

Data obtained were expressed as Mean ± Standard Error of Mean (Mean ± SEM) and presented as tables and plates where appropriate. Data were analyzed using one-way ANOVA followed by *Dunnett's post hoc test*. Values of $p< 0.05$ were considered statistically significant.

3. RESULTS AND DISCUSSION

3.1 Median Lethal Dose (LD_{50})

The oral median lethal dose of the extract was found to be (≥ 5000) in rats. Acute toxicity studies are usually carried out to determine the dose that will cause death or serious toxic manifestations when administered singly or severally at few doses in order to establish dose that should be use in subsequent studies [11].

3.2 Effect of Stem Bark Extract on Organ Weights after 28 Days Daily Oral Administration

There was no significant $p<0.05$ difference observed in the weights of the liver, spleen, kidney and heart of the animals in the extract treated groups when compared with control, as showed in the (Table 1).

Table 1. Effect of *Detarium microcarpum* stem bark methanol extract on organ weight after 28 days daily oral administration in rats

Treatment (mg/kg)	Mean organ weight (gram)			
	Liver	Kidney	Heart	Spleen
N/Saline (1ml/kg)	4.65±0.38	0.75±0.04	0.49±0.31	0.75 ±0.08
D.M (35)	5.17±0.11	0.73±0.02	0.52±0.32	0.77 ±0.04
D.M (70)	5.04±0.22	0.71±0.02	0.46±0.11	0.74±0.03
D.M (140)	4.83±0.18	0.74±0.37	0.45±0.10	0.75±0.04

Data were analyzed using one way ANOVA followed by Dunnet post hoc test. Values expressed as Mean ± SEM, n=6 /group. D.M = Methanol extract of Detarium microcarpum

3.3 Effect of *Detarium microcarpum* Stem Bark Methanol Extract on Some Liver and Kidney Function Parameters after 28 Days Daily Oral Administration in Rats

The extract at all doses tested (35, 70 and 140 mg/kg) did not produce significant changes in values of AST, Albumin, and Urea after 28 days daily oral treatment when compared with normal saline treated group. However, a significant (p<0.05) decrease in ALT was observed at dose of 70 and 140 mg/kg body weight when compared with control. Significant (p<0.05) increase in ALP was also observed at the highest dose of 140 mg/kg. The extract also at the dose of 70 and 140 mg/kg (108.3±1.9) and (106.8±1.4) body weight respectively significantly decreased serum level of creatinine when compared with normal saline treated group (Table 2).

Organ weight is an important index in physiological and pathological status in animals [12]. There was no significant change in organ weight in groups treated with extract when compared with the normal saline treated group, which indicated that the extract did not caused significant effects on in the animal organ weight.

Most of the orally consumed drugs undergo metabolism and excretion via liver and kidney, hence liver and kidney are always the target organs in oral toxicity [13]. Serum aspartate transaminase [14], Serum alanine transaminase (ALT), Serum alkaline phosphatase (ALP) are related to the hepatic cells functions, their measurement provides information on the nature of pathological damage to the tissue [15]. The daily oral administration of methanol extract of D.M stem bark for 28 days produce significant (p<0.05) decrease of ALT at all doses while ALP significantly (p<0.05) increased at 140 mg/kg. ALT catalyses the conversion of alanine and α-ketogluterate to pyruvate and glutamate and is more specific to liver and thus a better framework for discovering liver injury [16]. Reduction in the level of ALT at all doses could suggest inhibition or inactivation of the enzyme molecule [17]. ALP is a membrane bound enzymes, abnormal serum ALP level is important clinical diagnostic biomarker diseases of liver, kidney and cancer. ALP elevation in the serum is usually associated with disorders such as cholestatic liver disease, extrahepatic bile obstruction and infiltrative liver disease [18,19].

Urea and creatinine are considered as suitable prognostic indicators of renal dysfunction and kidney failure for any toxic compound [20], while urea did not significantly increase or decrease when compared with control group. Reduction in creatinine level is observed in cases of muscle wasting as seen in malnutrition [21]. The significant (p<0.05) reduction in creatinine concentration correlate with result found in body weight which suggest that the reduction in body weight is due to muscle wasting.

3.4 Effect of *Detarium microcarpum* Stem Bark Methanol Extract on Rats' Liver after 28 Days Daily Oral Administration

The group administered with normal saline (Fig. 1) showed normal liver cells, while the group administered 70 and 35 mg/kg showed moderate hepatocellular necrosis with vascular congestion and those administered 140 mg/kg showed intense hepatocellular necrosis, kupffer cells and lymphocytes hyperplasia.

Table 2. Effect of *Detarium microcarpum* stem bark methanol extract on some liver and kidney function parameters 28 Days' daily treatment

Parameters	Treatment (mg/kg)			
	N/Saline 1ml/Kg	D.M (35)	D.M (70)	D.M (140)
AST (U/L)	23.50±0.92	22.17±0.38	23.16±0.47	23.50±0.72
ALT (U/L)	33.00±0.78	30.67±0.56[a]	30.50±0.62[a]	29.67±0.42[b]
ALP (U/L)	32.67±0.49	32.50±0.62	33.50±0.61	34.50±0.62[a]
ALB (g/L)	44.83±1.20	37.17±0.93	45.18±0.70	47.12±0.42
Urea (mg/dL)	5.72±0.05	5.68±0.34	5.78±0.70	5.77±0.09
Creatinine (mol/L)	113.7±1.48	111.7±1.48	108.3±1.99[a]	106.8±1.40[b]

Data were analyzed using one way ANOVA followed by Dunnet post hoc test. Values expressed as Mean ± SEM, a, b, represent p<0.05, P < 0.01, n=6, AST= Aspartate transaminase, ALT= Alanine transaminase, ALP= Alkaline phosphatase, ALB = Albumin, D.M = Extract of Detarium microcarpum

The daily oral administration of methanol extract of D.M stem bark for 28 days on liver indicate normal hepatocytes in group treated with normal saline while the group administered 70 and 35 mg/kg showed moderate hepatocellular necrosis with vascular congestion and those administered 140 mg/kg showed intense hepatocellular necrosis, kupffer cells and lymphocytes hyperplasia. ALT is a key cytoplasmic enzyme present in liver and other cells. It is particularly useful in measuring hepatic necrosis, especially in small animals [22]. ALT is employed as a marker of hepatocellular damage and in general ALT is considered a more sensitive indicator of liver cell injury than AST. Though AST and ALT are not known to have any function in the plasma, but their increase level in the blood indicate cellular damage and increased membrane permeability and their altered metabolism [22]. Although hepatocellular necrosis was observed in histopathological studies of the liver the level of AST and ALT, was decreased this may be due to inhibition or inactivation of the two enzymes by the extract [23].

3.5 Effect of *Detarium microcarpum* Stem Bark Methanol Extract on Rats Kidney after 28 Days Daily Oral Administration

Animals treated with normal saline showed normal tubule and glomerulus while animals in group two, three and four (35, 70 and 140 mg/kg) showed intense destruction and necrosis of tubules with moderate glomerular necrosis and lymphocyte hyperplasia as depicted in (Fig. 2).

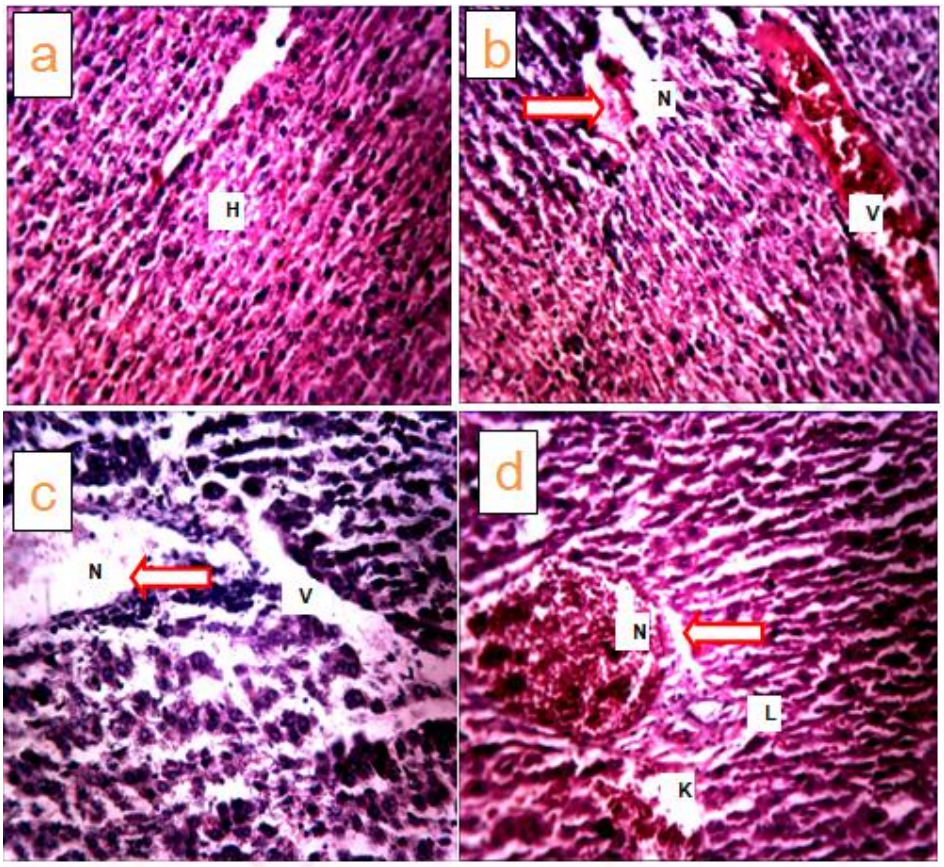

Fig. 1. Photomicrograph of a section of liver of a rat X 250. (a) Group administered with normal saline (b) Group administered with 35 mg/kg (c) Group administered with 70 mg/kg (d) Group administered with 140 mg/kg

H - normal hepatocytes, N- moderate hepatocellular necrosis, V - vascular congestion, K – kupffer cells, L -lymphocytes hyperplasia

Daily oral administration of methanol extract of D.M stem bark for 28 days on Kidney in group treated with normal saline showed normal tubule and glomerulus, while animals in group two, three and four (35 mg/kg, 70 mg/kg and 140 mg/kg) showed intense destruction and necrosis of tubules with moderate glomerular necrosis and lymphocyte hyperplasia, there increased but not significant level of urea which may be due to necrosis of glomeruli indicating renal dysfunction [24].

Daily oral administration of methanol extract of D.M stem bark for 28 days on Kidney in group treated with normal saline showed normal tubule and glomerulus, while animals in group two, three and four (35 mg/kg, 70 mg/kg and 140 mg/kg) showed intense destruction and necrosis of tubules with moderate glomerular necrosis and lymphocyte hyperplasia, there increased but not significant level of urea which may be due to necrosis of glomeruli indicating renal dysfunction [24].

3.6 Effect of *Detarium microcarpum* Stem Bark Methanol Extract on Cardiac Tissues after 28 Days Daily Oral Administration

The groups administered with (35mg/kg, 70 mg/kg and 140 mg/kg) showed slight necrosis of cardiac muscle cells with blood congestion at (35 mg/kg and 70 mg/kg) doses when compared with group administered with normal saline which showed normal cardiac cells.

All the doses tested showed slight necrosis of cardiac muscle cells with blood congestion at (35 mg/kg and 70 mg/kg) doses when compared with group administered with normal saline which showed normal cardiac cells which is an indication of cardiac toxicity and may cause a changes in lipid profile like decrease in LDL level due to impaired lipolysis [23].

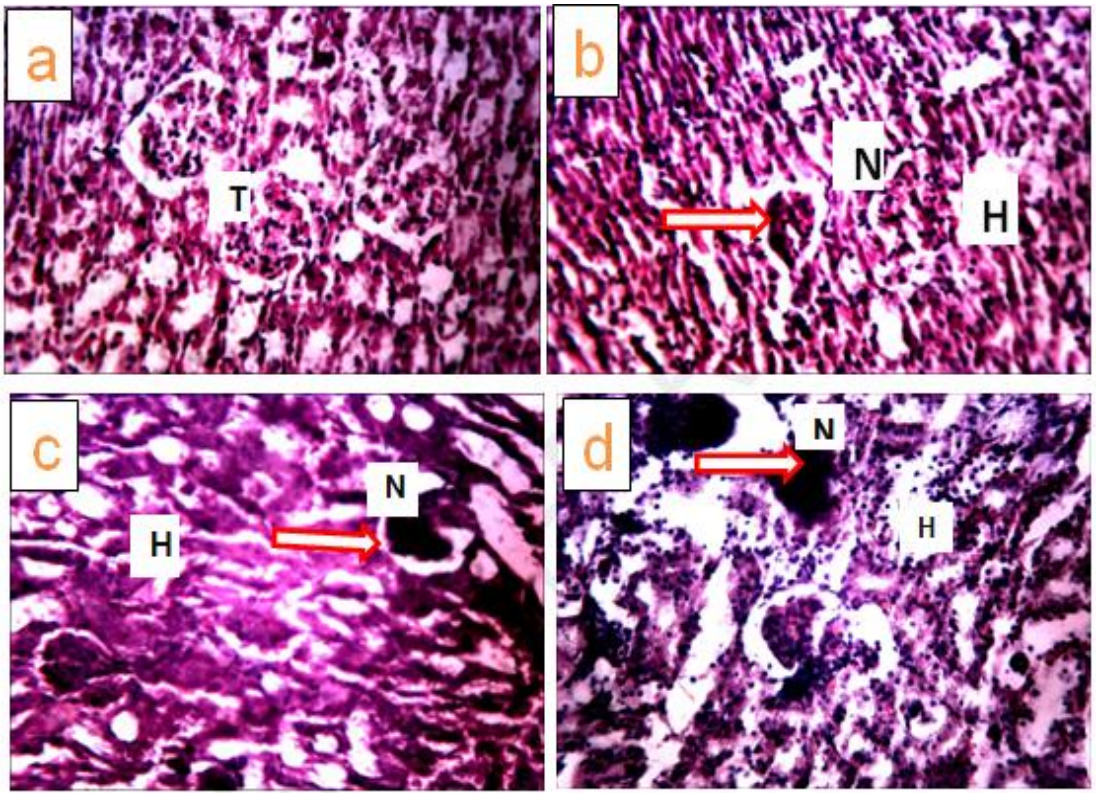

Fig. 2. Photomicrograph of a section of kidney of a rat X 250. (a) Group administered with normal saline (b) Group administered with 35 mg/kg (c) Group administered with 70 mg/kg (d) Group administered with 140 mg/kg

T - normal tubule and glomerulus, N - moderate glomerular, H - lymphocyte hyperplasia

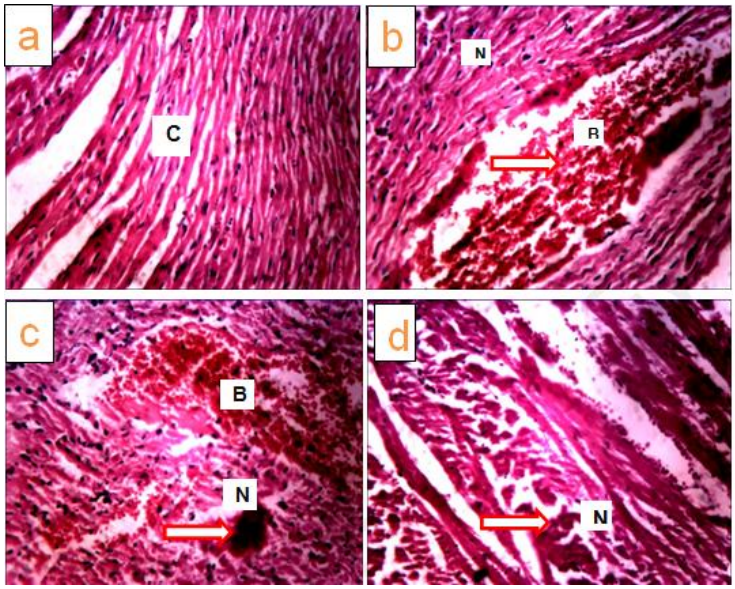

Fig. 3. Photomicrograph of a section of heart of a rat X 250. (a) Group administered with normal saline (b) Group administered with 35 mg/kg (c) Group administered with 70 mg/kg (d) Group administered with 140 mg/kg

Hyperplasia with sinusoidal congestion, C-normal cardiac cells, N-slight necrosis of cardiac muscle cells, B-necrosis with blood congestion

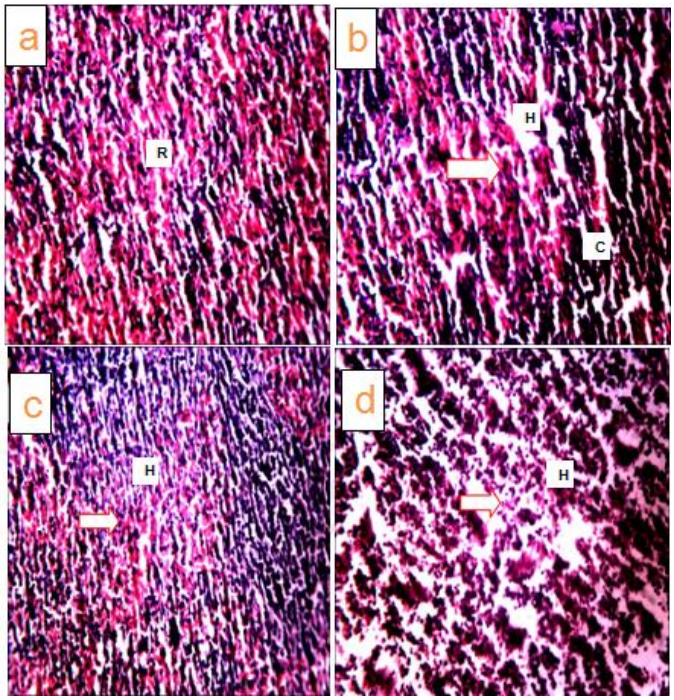

Fig. 4. Photomicrograph of a section of spleen of a rat X 250. (a) Group administered with normal saline (b) Group administered with 35 mg/kg (c) Group administered with 70 mg/kg (d) Group administered with 140 mg/kg

R- normal red with white pulp distribution, H- lymphocyte hyperplasia, C-lymphocyte hyperplasia with sinusoidal congestion, C-normal cardiac cells, N-slight necrosis of cardiac muscle cells, B-necrosis with blood congestion

3.7 Effect of *Detarium microcarpum* Stem Bark Methanol Extract on Spleen after 28 Days Daily Oral Administration

Animals treated with normal saline showed normal red and white pulp distribution while animals in group two, three and four (35 mg/kg, 70 mg/kg and 140 mg/kg) showed intense lymphocyte hyperplasia with sinusoidal congestion at (35 mg/kg).

The daily oral administration of methanol extract of D.M stem bark for 28 days on spleen showed normal red and white pulp distribution in group treated with normal saline, while animals treated with the extract showed intense lymphocyte hyperplasia with sinusoidal congestion at (35 mg/kg). Sinusoidal congestion is often as a result of venous out flow occurred due to the impairment of small hepatic vein, large hepatic vein and the heart. The impairments indicate the toxic effect of the methanol extract on the spleen [14].

4. CONCLUSION

Although *Detarium microcarpum* possessed significant therapeutic properties, prolong use of herb extract might lead to some adverse effect on the liver and kidney.

ETHICAL APPROVAL

All authors hereby declare that "Principles of laboratory animal care" (NIH publication No. 85-23, revised 1985) were followed, as well as specific national laws where applicable. All experiments have been examined and approved by the appropriate ethics committee.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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