

Antidiabetic and Toxicological Potentials of the Ethanol Leaf Extract of *Annona muricata* (L.) (Annonaceae)

Tavs A. Abere¹, Ese A. Abere^{2,*}, Ifeanyi H. Osemenam³

¹Department of Pharmacognosy, Faculty of Pharmacy, University of Benin, Benin-City, Nigeria; ²Department of Medical Biochemistry, Faculty of Basic Medical Science, University of Benin, Benin-City, Nigeria; ³Department of Pharmacognosy, Faculty of Pharmacy, Maduka University, Ekwegbe, Nigeria

*Correspondence: eseabere@yahoo.com; +234-8023395616

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Abstract

Drug resistance and adverse effects plague conventional diabetic treatments. *Annona muricata* L. (Annonaceae) leaves have been reported to be relatively safe and possess antidiabetic activities amongst other medicinal uses. This study was aimed at confirming the antidiabetic activity of the leaf of *A. muricata* and evaluating its toxicological profile. Doses of the ethanol extract ranging from 100 – 500 mg/kg were evaluated in normoglycaemic rats. Wistar rats were induced with diabetes by a single intraperitoneal injection of freshly prepared streptozotocin (55 mg/kg body weight). The dose of 500 mg/kg of ethanol extract was administered to the diabetic rats with glibenclamide (1.25 mg/kg) as the reference standard. Acute toxicity of the extract (1-5 g/kg) was tested in Swiss albino mice. Animals were monitored for 10 min after 6 h and for 10 min every day for the next two days. Wistar rats were administered with 5 ml/kg of normal saline (vehicle) and 250 mg/kg of the ethanol extract, respectively for 30 consecutive days. The effects of the extract on the livers, kidneys, hearts, and testes were examined. Various doses of the extract produced a significant ($p < 0.05$) reduction in blood glucose levels in normoglycaemic and Streptozotocin-induced diabetic rats. The LD₅₀ in mice was above 5 g/kg body weight. Sub-acute evaluation in rats showed that the extract induced a mild chronic inflammation in the testes and epididymis, while in the tissues of the liver, kidney, and heart, the extract provoked a mild chronic inflammatory response, in addition to vascular reactions leading to rupture of the blood vessels and haemorrhage. It was concluded that *A. muricata* leaves have antidiabetic properties. The inflammatory and immune responses evoked in the sub-acute toxicological evaluation could be a protective response.

Keywords: *Annona muricata*, Annonaceae, Antidiabetic, Toxicological

Introduction

Herbal treatments are utilized worldwide, especially in developing nations. Medicinal plants synthesize secondary metabolites with pharmacological properties [1]. The World Health Organization (WHO) promotes medicinal plants because they are cheaper, more accessible, and easier to use, especially in developing countries [2].

Soursop, *Annona muricata* Linn (Annonaceae) (Fig. 1), is grown in tropical and subtropical climes, including Africa [3]. The fruit is called Graviola and Guanabana because it tastes slightly acidic when mature [4]. *A. muricata* leaves, barks, and roots have been used medicinally in the past, but the leaves are most commonly utilized ethno-medicinally [5]. The leaves are used as sedative, astringent, insecticide, pesticide, vermifuge, and analgesic. As an antioxidant, anticancer, antibacterial, and antimalarial, *A. muricata* leaf crude extract is utilized in chemotherapy [3]. The leaves have also been used to cure infections, coughs, weight loss, herpes, and nose-throat inflammation as a result of the

presence of bioactive acetogenins [6]. *A. muricata* also contains alkaloids (annonamine, coreximine, and reticuline) and phenolics (caffeoylquinic acid, quercetin, gentisic acid, gallic acid) [7-9].

Diabetes mellitus is a metabolic illness with elevated blood sugar, according to the WHO. Low insulin secretion impairs carbohydrate, lipid, and protein metabolism [10]. The prevalence of diabetes is high [11]. This is challenging in impoverished nations due to poor healthcare, dangerous orthodox medications, and low finance [12]. Even though synthetic hypoglycemic agents are used to treat diabetes, there is a need for research and development of innovative plant-based antidiabetic drugs due to drug resistance, adverse effects, and toxicity from prolonged therapy [13]. Many medicinal herbs have been tested for antidiabetic properties. These include *Lagenaria siceraria* juice [14], *Elaeagnus umbellata* essential oils [15], *Moringa oleifera* leaves [16], *Psidium guajava* [17], and *Secamone afzelii* [18].

Pharmaceutical research has moved to medicinal plants due to synthetic drug side effects and toxicity [19]. Some herbal medicines can harm the liver, heart, and kidneys [20]. They may be harmful, especially if the plant extract is used to treat chronic diseases such as hypertension and diabetes [21]. As therapeutic plants are natural, a larger amount is needed to cause harm than mainstream pharmaceuticals. Several biological studies on *A. muricata* Linn (Annonaceae) exist, but none on the crude ethanol extract's acute and sub-acute toxicity, which can aid herbal medicine practitioners and researchers [22]. *Annona muricata* leaf ethanol extract in this study was tested for toxicity and evaluated as a possible ethnomedicinal treatment for diabetes.



Fig. 1: Photograph of *Annona muricata* plant.

Methodology

Plant materials

The leaves of *A. muricata* were obtained in March 2023 at Evbuomere quarters in Benin City, Edo State, Nigeria. Identification and authentication were by using *Annona muricata* herbarium specimen MAU/057 from the Pharmacognosy Department Herbarium, Faculty of Pharmacy, Madonna University, Elele Campus, Nigeria. Leaves were powdered and sieved with an electric grinder and mesh screen after five days of room temperature desiccation.

Annona muricata extract

A certain quantity (1.86 kg) of *A. muricata* powdered leaves was successively macerated in 9 x 2 L of ethanol. The resulting 248 g crude extract was obtained and stored in a refrigerator after a rotary evaporator was used to evaporate the solvent.

Animals

Swiss albino mice (22.15 ± 0.88 g) and male Wistar rats (241.00 ± 9.54 g) were procured from the Animal House, Department of Pharmacology and Toxicology, Faculty of Pharmacy, Madonna University of Nigeria, Elele. International research

animal guidelines and standard environmental conditions were followed for all animals [23]. Regular pellets and limitless tap water were provided. Madonna University, Nigeria Animal Ethics Committee (approval number MAU/SREC/A/18) authorized the trial.

Diabetic screening

To induce diabetes, rats were given intraperitoneally 55 mg/kg of freshly generated streptozotocin (STZ) in 0.1 M acetate buffer, pH 4.5, after 16 hours of fasting [24]. Within 24 hours following STZ injection, diabetic rats received 5% glucose orally to minimize hypoglycemia. The study comprised diabetic rats with 250 mg/dl or greater blood glucose after 5 days. Normoglycemic rats received oral dosages of 100, 200, 300, 400, and 500 mg/kg *A. muricata* ethanol extract and 1.25 mg/kg glibenclamide dissolved in 1% aqueous Tween 80. Diabetic rats received 500 mg/kg crude extract and 1.25 mg/kg glibenclamide. Control group animals got 5 ml/kg vehicle [25]. STZ-induced diabetic rats had blood glucose levels measured at 0.5, 1, 2, 4, 6, 8, and 12 hours, while normoglycemic rats had them at 1, 4, 8, and 12. Blood was obtained from the tail tips of the rats.

Checking blood glucose

Glucose oxidase glucometer (AAU-CHEK, ROCHE, UK) was used to measure blood glucose levels (mg/dl) [18]. The glycaemic change percentage at any time was calculated using Eq. 1.

$$\text{Eq. 1: \% Glycemic change} = \frac{\text{FBG} - \text{GC} \times 100}{\text{FBG}}$$

where GC represents glucose concentration at different intervals and FBG represents the baseline fasting blood glucose concentration.

Toxicity Tests

Acute toxicity studies

A. muricata ethanol extract was orally given to five Swiss albino mice per group at 1, 2, 3, 4, and 5 g/kg. Normal saline (5 ml/kg) was administered to controls. Before treatment, each cohort of mice was acclimatized in the test cage for 30 minutes. After six hours, animals were monitored for 10 minutes daily for two days. Each group had death and toxicological symptoms (convulsions, diarrhoea, hyperactivity, piloerection) observed [26].

Investigations of sub-chronic toxicity

Two ten-rat groups of 20 male Wistar rats were randomly assigned. The control group (A) received 5 ml/kg of normal saline (vehicle), while the second group (B) received 250 mg/kg of crude extract orally daily for 30 days. Animals were monitored for toxicity (abnormal behaviour, writhing, convulsions, mood, motor activity, and general conditions) for 30 minutes daily. The animals were chloroform-euthanized after 30 days. The liver, kidney, heart, testis, and epididymis were removed and stored in 10% formaldehyde. The organ sections (6 μ m thick) were fixed in paraffin wax, and stained with Haematoxylin and Eosin [27].

Statistical analysis

Data are presented as mean $\pm$ SEM, with "n" representing the number of rats utilized. One-way analysis of variance assessed

mean differences. P-values below 0.05 indicate statistical significance.

Results

Antidiabetic examination

The ethanol crude extract of *A. muricata* hypoglycemic effects on normoglycemic and streptozotocin-induced diabetic rats are shown in Tables 1 and 2, respectively. In the normoglycaemic study, all *A. muricata* extract doses (100–500 mg/kg) lowered blood glucose, even more than glibenclamide, the positive control. The reduction in blood glucose was dose-dependent. After 12 h, the reduction of glycaemia ranges from 27.14% (for 100 mg/kg dose) to 46.40% (for the 500 mg/kg dose). Higher doses of the extract (≥ 200 mg/kg) produced significant ($p > 0.05$) reduction in the glycaemia of the normal animals relative to the control (Tween 80 group).

In streptozotocin-induced diabetes, glibenclamide and 500 mg/kg *A. muricata* crude ethanol extract significantly ($p < 0.05$) lowered blood glucose. The extract of *A. muricata* at 500 mg/kg caused the greatest blood sugar reduction at 12 hours (reduction of 40.47% from the baseline).

Acute toxicity assessment

At 5 g/kg body weight, mice did not die from *Annona muricata* leaf extract. Behaviour, posture, stool frequency, mood, and motor activity did not change. The animals did not convulse or die.

Subacute toxicity assessment

Ethanol extracts from *Annona muricata* leaves administered daily to rats for 30 days caused mild chronic inflammation in the testis (Fig. 3) and epididymis (Fig. 5), which was not seen in the control groups (Figs. 2 and 4). This may be a protective response by the body against the extract. In the tissues of the liver (Fig. 7), kidney (Fig. 9) and heart (Fig. 11), the extract provoked a mild chronic inflammatory response different from what happened in the control (Figs. 6, 8 and 10 respectively). There was in addition an intense vascular reaction leading to rupture of the blood vessels and haemorrhage. Moreover, in the heart, there was activation of the local immune response as evidenced by mild hyperplasia of the pericardial lymphoid aggregate.

Table 1: Hypoglycemic effects of ethanol extract from *A. muricata* in normoglycaemic rats

Experimental groups	Doses (mg/kg)	Mean ($\pm$ SEM) blood glucose level (mg/dl) (% blood glucose reduction in parenthesis)			
		1 h	4 h	8 h	12 h
1 % Tween 80	-	105.75 $\pm$ 2.44 (1.12)	103.32 $\pm$ 4.55 (3.53)	97.51 $\pm$ 3.35 (8.95)	98.47 $\pm$ 4.17 (8.06)
Glibenclamide	0.05	97.68 $\pm$ 2.57 (7.24)	94.28 $\pm$ 8.78 (10.47)	82.06 $\pm$ 12.41 (22.07)	83.06 $\pm$ 1.12 (21.08)
<i>A. muricata</i>	100	94.79 $\pm$ 10.13 (9.98)	86.74 $\pm$ 7.14 (17.63)	76.36 $\pm$ 7.19 (27.48)	76.72 $\pm$ 7.03 (27.14)
<i>A. muricata</i>	200	86.89 $\pm$ 13.04 (16.05)	72.16 $\pm$ 10.24 (30.28)*	63.22 $\pm$ 8.19 (38.92)	63.60 $\pm$ 4.50 (38.55)*
<i>A. muricata</i>	300	89.59 $\pm$ 19.21 (17.73)	74.88 $\pm$ 11.20 (31.24)*	60.85 $\pm$ 5.11 (44.12)*	61.16 $\pm$ 2.56 (43.88)*
<i>A. muricata</i>	400	91.72 $\pm$ 7.45 (18.47)	75.14 $\pm$ 4.26 (33.21)*	61.00 $\pm$ 5.70 (45.28)*	61.63 $\pm$ 6.42 (45.22)*
<i>A. muricata</i>	500	85.24 $\pm$ 10.10 (20.41)	69.34 $\pm$ 14.20 (35.26)*	55.03 $\pm$ 8.13 (48.62)*	57.41 $\pm$ 6.42 (48.40)*

*values are significant at $p < 0.05$ compared to the control group (1% Tween 80)

Table 2: The hypoglycemic effects of *A. muricata* ethanol extract on diabetic rodents induced by streptozotocin

Experimental Groups	Doses mg/kg	Mean ($\pm$ SEM) blood glucose level (mg/dl) (% blood glucose reduction in parenthesis)						
		0.5 h	1 h	2 h	4 h	6 h	8 h	12 h
1 % Tween 80	-	558.93 $\pm$ 23.45 (-1.66)	588.25 $\pm$ 35.46 (-3.46)	571.07 $\pm$ 53.23 (-3.87)	590.11 $\pm$ 77.48 (-7.33)	589.39 $\pm$ 90.50 (-7.20)	586.39 $\pm$ 45.53 (-6.59)	585.34 $\pm$ 34.10 (-6.46)
Glibenclamide	1.25	436.57 $\pm$ 23.75 (10.42)	425.16 $\pm$ 35.00 (12.76)	392.32 $\pm$ 29.03 (19.50)	309.27 $\pm$ 6.59 (36.54)*	291.78 $\pm$ 2.15 (40.13)	288.80 $\pm$ 14.44 (40.74)*	300.99 $\pm$ 12.08 (38.24)*
<i>A. muricata</i>	500	453.15 $\pm$ 11.25 (10.33)	432.18 $\pm$ 4.47 (14.48)	383.76 $\pm$ 41.01 (24.06)	322.62 $\pm$ 16.12 (36.16)*	302.10 $\pm$ 21.24 (30.22)	290.17 $\pm$ 32.21 (42.58)*	300.83 $\pm$ 10.68 (40.47)*

*values are significant at $p < 0.05$ compared to the control group (1% Tween 80)

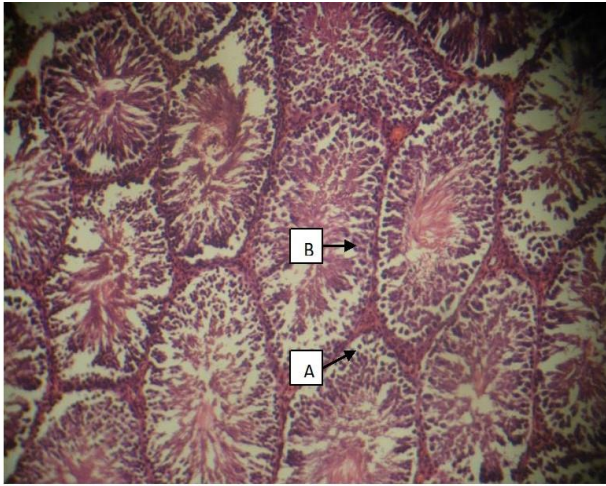


Fig 2: A photomicrograph of the rats given normal saline for 30 days showing seminiferous tubules (A) with spermatocytes (B) (H&E x 10).

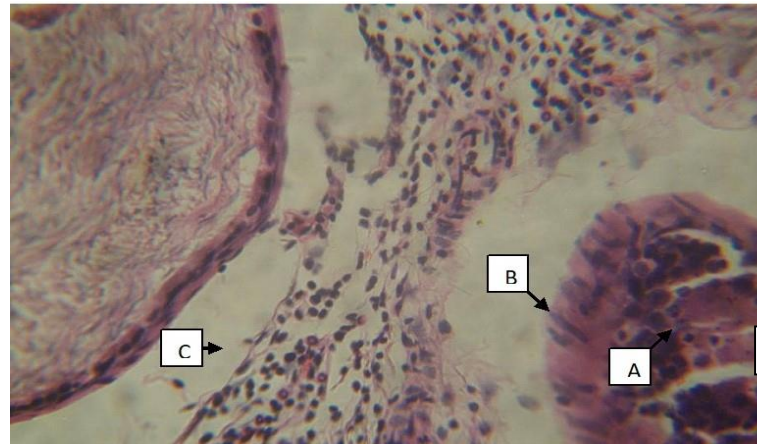


Fig 5: H&E x 40 shows interstitial vascular congestion (A), hypertrophy (B), and chronic inflammatory cell infiltrates (C) in rats' epididymis following 30 days of 250 mg/kg *A. muricata* extract.

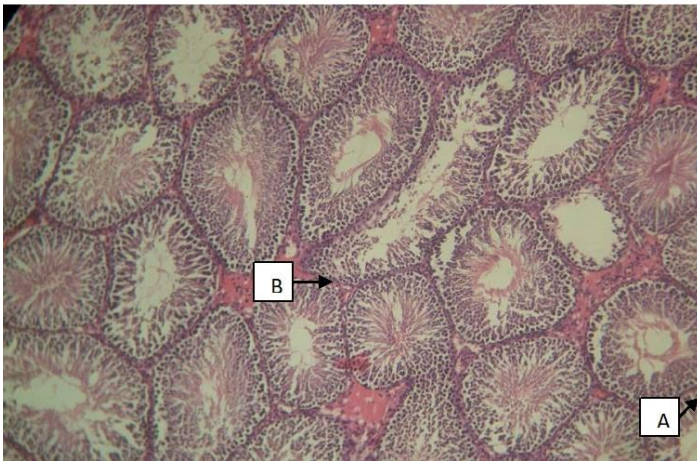


Fig 3: After 30 days of 250 mg/kg *A. muricata* extract, rats' testis photomicrographs show congestion (A) and bleeding (B) (H&E x 40).

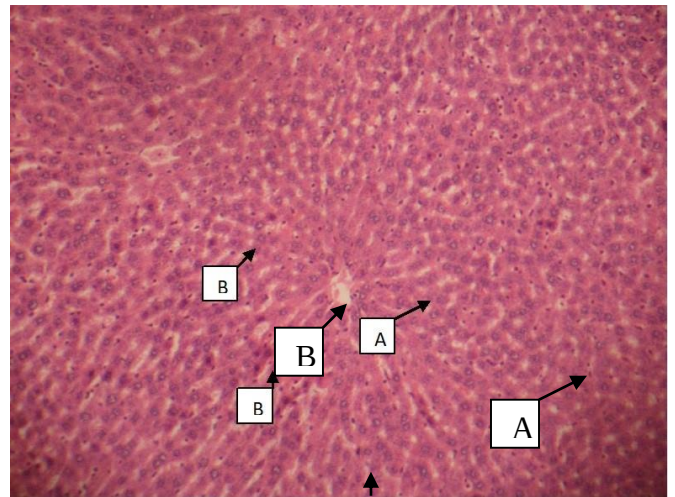


Fig 6: H&E x 10 rat liver photomicrograph showing hepatocytes (B) and central vein (A) after 30 days of normal saline.

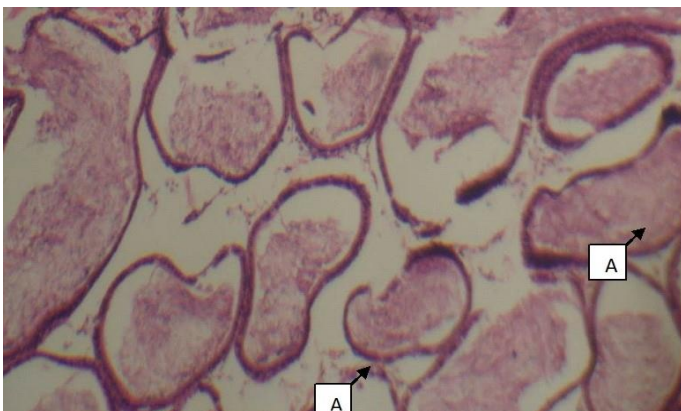


Fig 4: Rats' epididymis photomicrograph (A) (H&E x 40) after 30 days of normal saline shows tubules.

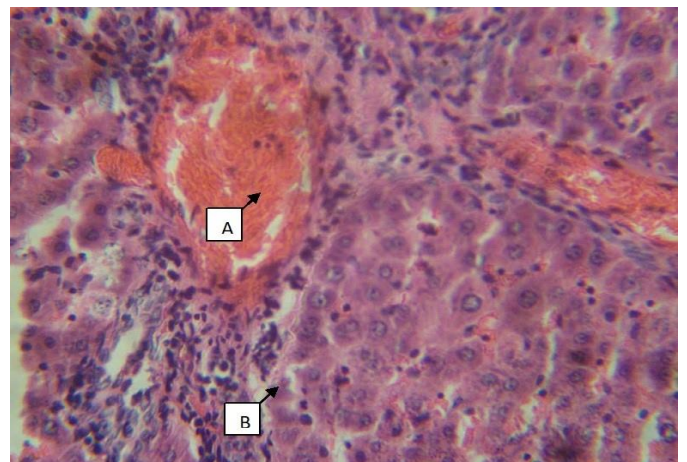


Fig 7: An H&E x 40 liver photomicrograph of rats given 250 mg/kg *A. muricata* extract for 30 days shows chronic inflammatory cell periportal infiltrates (B) and portal congestion (A).

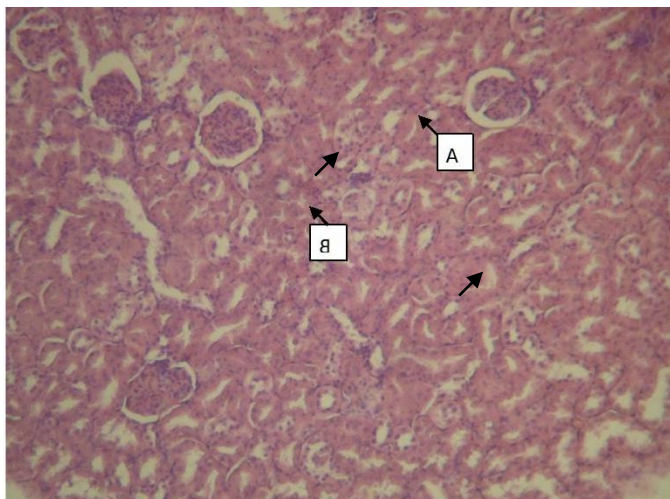


Fig 8: Rat kidney photomicrograph of glomeruli (A) and tubules (B) after 30 days of normal saline (H&E x 40).

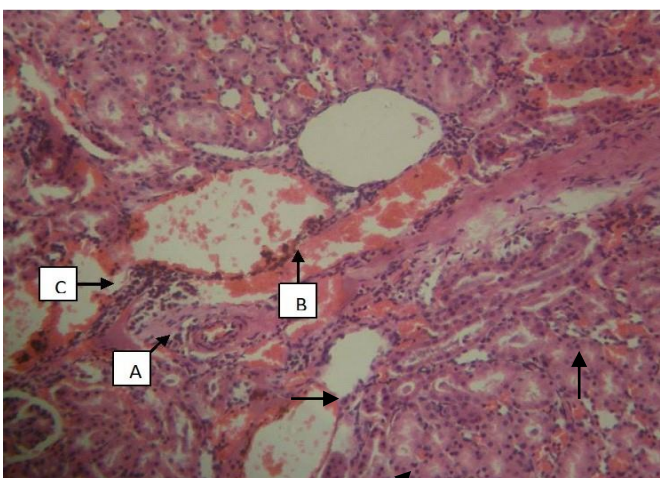


Fig 9: The kidneys of rats fed 250 mg/kg *A. muricata* extract for 30 days show chronic inflammatory cell infiltrates (C), haemorrhage (B), and interstitial congestion (A) (H&E x 40).

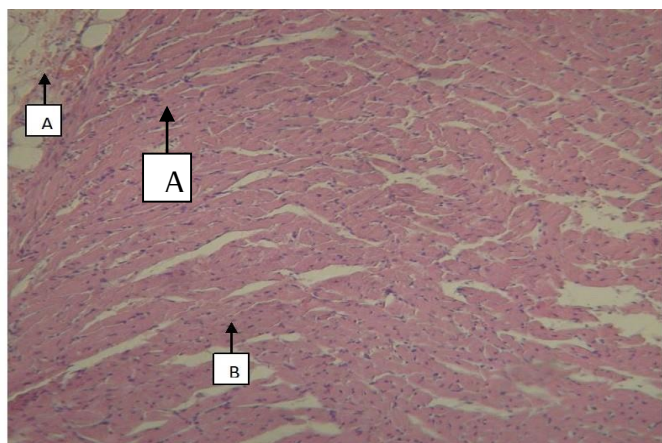


Fig 10: The pericardium (A) and myocardium (B) of rats administered normal saline for 30 days were imaged (H&E x 10).

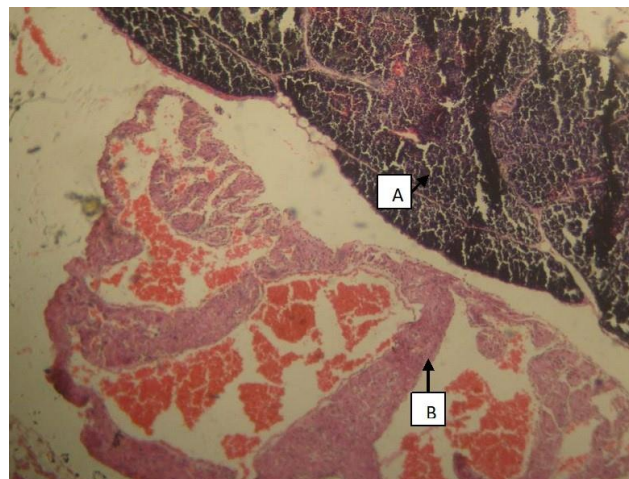


Fig 11: Rat hearts reveal myocardial bleeding (B) and pericardial activated lymphoid follicle (A) after 30 days of 250 mg/kg *A. muricata* extract (H&E x 40).

Discussion

Chemical constituents from nature have been reported to treat illnesses [7]. Prevalence of diabetes mellitus and paucity of healthcare resources in developing nations led most rural residents to use medicinal plants [28]. To investigate *A. muricata* crude ethanol extract's antidiabetic properties, Streptozotocin induced diabetes in rats were employed to resemble human diabetes [29]. Glibenclamide is one of the best positive control for comparing Streptozotocin-induced diabetic rats' hypoglycemia therapy [29]. The oral administration of *A. muricata* crude ethanol extract lowered blood glucose, suggesting antidiabetic potential. The crude ethanol extract of *A. muricata* reduced blood glucose levels in both normoglycemic and diabetic rats; however Florence *et al.*, observed that the aqueous extract did not lower blood sugar in normoglycemic rats, but a single 100 mg/kg treatment in diabetic rats reduced blood sugar by 75% [30]. This could be due to the fact that ethanol, being a semi-polar solvent, extracts both polar and non-polar components. *Momordica charantia* L. (Cucurbitaceae), *Laportea ovalifolia* (Schumach. & Thonn) Chew (Urticaceae) [31], *Acacia albida* [32], *Gongronema latifolium* Benth [33], and *Chromolaena odorata* [28] have been reported to reduce serum glucose in normoglycemic and diabetic rats.

There was indication of chronic inflammation in the toxicological evaluation of the crude extract of *Annona muricata*. Chronic inflammation is a protective response to fight against infection and cancer but when it becomes persistent, fibrosis will occur leading to tissue necrosis and eventually organ destruction. Inflammation of the liver cells can lead to chronic hepatitis due to the impairment in the production of clotting factors and this will eventually lead to bleeding/hemorrhage. In the heart, inflammation was indicated by mild hyperplasia of the pericardial lymphoid aggregate resulting in activation of the local immune response. This means that the extract is acting as an antigen, stimulating the lymphoid cells which are cells of the immune system. This could be the basis for the ethnomedicinal use of this plant in the management of various types of infections and cancer.

Conclusion

Ethanol leaf extract of *Annona muricata* (L.) (Annonaceae) has shown promising prospect as a potent source of

phytochemicals that can be used in lowering blood sugar levels, thereby justifying its use by traditional practitioners in the management/treatment of diabetes mellitus.

Although further toxicological evaluations may still be required to confirm safety, from the results obtained from the toxicological studies, the ethanol leaf extract of *Annona muricata* could be termed safe for usage via the oral route.

Conflict of interest

The authors declare no conflict of interest.

Contribution of authorship

Conceptualization and design of study as well as antidiabetic study: TAA, Toxicological study: EAA, Data analysis and proofreading: IHO

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