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Protective Effects of *Irvingia gabonensis* on Arsenic Trioxide-Induced Spleen Damage in Rats: A Histological and Haematological Study

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Abstract
Considerable attention from basic to clinical scientists has been given to the toxicity of drugs and other related agents, because of the passionate sourcing for the readily available and cheap agents against organotoxicity. We evaluated the protective effects of ethanol leaf extract of Irvingia gabonensis on arsenic trioxide-induced spleen damage in Wistar rats. In this study, rats received the plant extract at doses of 250 and 500 mg/kg body weight. Splenic damage was induced by administering 10 mg/kg body weight of arsenic trioxide for 28 days. The results revealed that arsenic trioxide significantly decreased ($P < 0.05$): red blood cell count, mean cell haemoglobin, mean corpuscular haemoglobin concentration, platelets, granulocytes and haematocrit level. The hematological alterations induced by arsenic trioxide suggest splenic damage, which is further confirmed by histopathological examination revealing severe follicular degeneration and sinus dilation. However, administration of Irvingia gabonensis extract exhibited protective effects, ameliorating both the histopathological changes in the spleen and hematological parameters, indicating its potential therapeutic value. In conclusion, the histopathological and haematological findings of this study demonstrate the damaging effects of arsenic trioxide on the spleen. Notably, the extract of Irvingia gabonensis exhibited protective effects, mitigating the splenic damage induced by arsenic trioxide, highlighting its potential therapeutic benefit.

Keywords: Follicular degeneration; sinus dilation; haemoglobin, arsenic trioxide; *Irvingia gabonensis*.

INTRODUCTION
Irvingia gabonensis, commonly known as bush mango or African wild mango, is a plant species native to Central and West Africa. The fruit, referred to as dika nut in Hausa, Ogbono in Igbo, and Oro in Yoruba, is widely consumed in these regions, and has garnered attention for its potential health benefits, and notably, virtually every part of the *I. gabonensis* plant has been found to have a significant use (Atangana *et al.*, 2001). *I. gabonensis* is a nutrient-dense fruit, boasting an impressive profile rich in dietary fiber, vitamins, minerals, and antioxidants. The seed nuts, in particular, are an excellent source of healthy fats and protein. In traditional medicine, *I. gabonensis* has been utilized for its medicinal

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properties, with various parts of the plant, including the bark, kernels, leaves, and roots, being employed to treat a variety of health conditions, demonstrating its versatility and potential therapeutic benefits (Agbor *et al.,* 2005). Specifically, the bark is traditionally mixed with palm oil to treat diarrhea and to facilitate weaning by reducing the breast-feeding period (Atangana *et al.,* 2001).

The shavings of the stem bark are consumed by mouth to treat hernias, yellow fever, and dysentery, and to reduce the effects of poison in French Equatorial Africa (Ejiofor and Okafor, 1997). The bark of *I. gabonensis* possesses antimicrobial properties, facilitating the healing of scabby skin and providing relief from toothache pain when boiled. Research has demonstrated that *I. gabonensis* leaf and root extracts exhibit robust antimicrobial activity, significantly inhibiting the growth of diverse bacteria and fungi. These findings suggest that the plant may serve as a valuable natural remedy for combating various infections (Ekpe *et al.,* 2007). Potential mechanisms of action include membrane disruption by terpenoids and inactivation of microbial adhesion, enzymes, and cell envelope transport proteins by ellagic acid-like compounds (Okolo *et al.,* 2015).**.** It contains various phytochemicals, including flavonoids and polyphenols, which are known to possess antioxidant activity (Okolo, 1994). *I. gabonensis* contains bioactive compounds with potent antioxidant properties, capable of scavenging and neutralizing free radicals. This helps mitigate oxidative stress and reduce potential cellular damage. Moreover, *I. gabonensis* may enhance the body's innate antioxidant defenses by boosting the activity of key antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx). These enzymes play a crucial role in neutralizing and detoxifying free radicals (Jemma *et al.,* 2017).

Arsenic trioxide (ATO) is a highly toxic white crystalline compound whose ingestion or inhalation of arsenic trioxide has been reported to have harmful effects such as vomiting, diarrhea, shortness of breath, and headache (Aphosian, 2016). Severe side effects may include acute promyelocytic leukemia differentiation problems and cardiovascular problems such as: hypertension, artherosclerosis, endothelial dysfunction, oxidative stress, inflammation and arrhythmias (Lee and Harrison, 2007), but with commercial applications limited by its toxicity. ATO is a precursor to most pesticides, in glass manufacture and also used as a wood preservative (Engel *et al.,* 2004). Prolonged ingestion of arsenic trioxide, historically used as an anticancer treatment, has been linked to severe health consequences, including an increased risk of skin cancer and reproductive issues. The adverse effects of ATO exposure can vary greatly, depending on factors such as the duration and concentration of exposure, as well as individual susceptibility and sensitivity. It's important to note that ATO is a highly toxic compound, and precautions should be taken to minimize exposure (Engel *et al.,* 2004). Prolonged exposure to ATO, particularly through consumption of arsenic-contaminated drinking water, poses significant health risks. Chronic exposure is associated with an elevated risk of developing various types of cancer, including lung, bladder, skin, liver, and kidney cancer, highlighting the importance of ensuring access to safe and clean drinking water. Chronic exposure may also contribute to the development of splenic disorders, cardiovascular diseases, neurotoxicity, and reproductive disorders (Wang *et al.,* 2020). Additionally, unintentional ingestion of ATO, or consumption of contaminated food or water, can result in acute poisoning. Symptoms of arsenic trioxide poisoning may include severe abdominal pain, nausea, vomiting, diarrhea, and dehydration. The gastrointestinal effects can be extreme, potentially leading to life-threatening complications if prompt medical attention is not sought. Direct skin contact with ATO can result in irritation and dermatitis (Wang *et al.,* 2020). Previous studies have demonstrated the occurrence of myocardial disorganization, interstitial oedema and infiltration of

inflammatory cells in the heart and liver following exposure to ATO in laboratory animals (Raghu *et al.,* 2009). It also resulted in a significant increase in the activity of certain relevant clinical enzymes for cardiac function and antioxidant mechanisms like the serum creatine kinase isoenzyme, lactate dehydrogenase, glutathione peroxidase and reduced glutathione (Raghu *et al.,* 2009). ATO has a long history and it is recognized as both poison and drug for more than two thousand years (Wang *et al.,* 2020). The increasing recognition of herbal therapy within the global healthcare system is attributed to the fact that many pharmaceutical medications are derived from plant-based active ingredients. This study aimed to investigate the histological and haematological effects of ATO on the spleen, as well as the potential protective effects of the ethanol leaf extract of *I. gabonensis* (ELEIG), highlighting the importance of exploring natural remedies in mitigating the toxic effects of certain substances.

METHODOLOGY

Collection of Sample Preparation of Plant Material

I. gabonensis leaves were collected from Ekosodin community, Ovia North-East local government area, Edo State. Taxonomic identification and authentication of the plant material were performed at the Department of Plant Biology and Biotechnology, University of Benin, Benin City, with herbarium number UBH-1153.

Preparation of Plant Material

Initially, the leaves were washed thoroughly with tap water to remove any impurities. The leaves were then air-dried to reduce moisture content, followed by pulverization into a fine powder using a grinder. A precisely measured quantity of the powdered leaf (120 g) was subsequently soaked in ethanol (500 ml of 50%) for a period of 72 hours. The resulting crude ethanol extract was filtered to remove any residual particulate matter, finally, the filtrate was freeze-dried (Kumar, 2019) to remove excess solvent and stored in a refrigerator at -4°C until further use.

Experimental Animals

Wistar rats with a weight range of 160-190g were obtained from the Animal House, Department of Anatomy, University of Benin. The animals had unrestricted access to food and water. To ensure optimal physiological conditions, they were housed in a controlled environment with a temperature of 28 ± 2°C, relative humidity of 50 ± 5%, and a 12-hour light-dark cycle.

Drugs Preparation

The administration of ATO was done orally to Wistar rats at a dose of 10 mg/kg body weight. ELEIG was administered orally to Wistar rats at the doses of 250 and 500 mg/kg body weight.

Animal Groupings

Rats were randomly divided into six groups (n=7).
Group A: Control, 1ml of distilled water only.
Group B: 10 mg/kg body weight of ATO only.
Group C: 250 mg/kg body weight of ELEIG only.
Group D: 500 mg/kg body weight of ELEIG only.
Group E: 250 mg/kg body weight of ELEIG and 10 mg/kg body weight of ATO.
Group F: 500 mg/kg body weight of ELEIG and 10 mg/kg body weight of ATO.

A 28-day treatment regimen was administered to the animals via orogastric tube. Upon completion of the treatment period, all animals were humanely euthanized. Euthanasia was performed by inducing anesthesia through inhalation of chloroform-soaked cotton wool (approximately 30ml) in an enclosed container for 2-5 seconds. Following anesthesia, each rat was placed in a supine position on a dissection table. An abdomino-thoracic incision was made to expose the abdominal viscera, facilitating the collection of blood samples through inferior vena cava and cardiac puncture using 5ml syringes. The collected blood samples were subsequently transferred into sample bottles for hematological analysis. The spleen was carefully excised, dissected, and immediately fixed in 10% formal-saline solution in a universal bottle for histological examination.

Histological analysis

The spleens of the dissected rats underwent gross examination, and then subjected to a series of histological processing steps, including dehydration in a graded ethanol series (70-100%), clearing in xylene, and embedding in paraffin wax. All tissue sections were examined under a light microscope after staining using Drury and Wallington techniques with hematoxylin and eosin (Drury and Wallington, 1980).

Haematology analysis

Blood was collected in EDTA bottles for the evaluation of red blood cell (RBC), white blood cell (WBC), lymphocytes, granulocytes, haemoglobin concentration, haematocrit, mean corpuscular volume, mean cell haemoglobin, mean corpuscular haemoglobin concentration and platelet counts using haematology (automated) analyzer (Abbott Cell-Dyn 3500).

Statistical Analysis

Statistical analysis was done using the GraphPad prism software (version 9) and data was expressed as mean with standard error of the mean (STEM).

RESULTS AND DISCUSSION

Table 1: Mean comparason of haematological indices in studied groups

Parameters	Control	ATO only (10mg/kg)	250mg/kg *I.gabonensis* only	500mg/kg *I.gabonensis* only	ATO + 250mg/kg *I.gabonensis*	ATO + 500mg/kg *I.gabonensis*	P-values
WBC ($x10^9$/L)	6.86 ± 0.445	6.65 ± 0.49	8.514 ± 1.05	7.200 ± 0.44	9.400 ± 0.83	8.100 ± 1.53	0.2465
Lymphocytes (%)	91.78 ± 1.08	94.15 ± 0.079	92.24 ± 1.13	93.76 ± 1.05	93.23 ± 0.63	92.43 ± 0.97	0.4680
Granulocytes (%)	3.24 ± 0.85	2.15 0± 0.11	2.586 ± 0.49	2.080 ± 0.28	2.000 ± 0.26	3.267 ± 0.75	0.3162
RBC ($x10^{12}$/L)	7.846 ± 0.23	5.085 ± 0.07	7.883 ± 0.06	8.190 ± 0.21	8.419 ± 0.23	6.000 ± 0.84	< 0.0001
Haemoglobin (mg/dl)	14.76 ± 0.50	8.400 ± 0.16	14.47 ± 0.13	15.54 ± 0.42	15.74 ± 0.52	10.77 ± 1.72	< 0.0001
Haematocrit (%)	42.12 ± 1.25	26.35 ± 0.49	39.26 ± 0.53	42.70 ± 1.08	42.91 ± 1.41	30.27 ± 4.46	< 0.0001
MCV (fl)	53.80 ± 1.27	51.90 ± 0.25	49.87 ± 0.53	52.18 ± 0.79	51.00 ± 0.59	50.03 ± 0.53	0.0050
MCH (pg)	18.78 ± 0.27	16.45 ± 0.08	18.31 ± 0.12	18.92 ± 0.20	18.63 ± 0.16	17.37 ± 0.57	< 0.0001
MCHC (g/dl)	35.00 ± 0.48	31.80 ± 0.03	36.84 ± 0.44	36.36 ± 0.23	36.64 ± 0.40	34.80 ± 0.75	< 0.0001
Platelet count ($x10^9$/L)	386.0 ± 29.90	193.5 ± 4.27	296.6 ± 50.28	389.0 ± 44.99	425.4 ± 59.19	310.0 ± 72.98	0.0438

*P<0.05 indicates significant difference compared with control.

The results show that administration of ATO caused significant (P<0.05) decrease in red blood cell count, mean cell haemoglobin, mean corpuscular haemoglobin concentration, platelets, granulocytes and haematocrit level, with no significant change in white blood cell

and lymphocytes counts after the administration of ATO. Treatment with ELEIG at doses of 250 and 500 mg/kg significantly increased these reductions.

The results from histopathological analyses and hematological parameters collectively indicate that ATO causes splenic damage, while the ELEIG exhibits ameliorative effects on ATO-induced splenic damage, as illustrated in Plates 1-4.

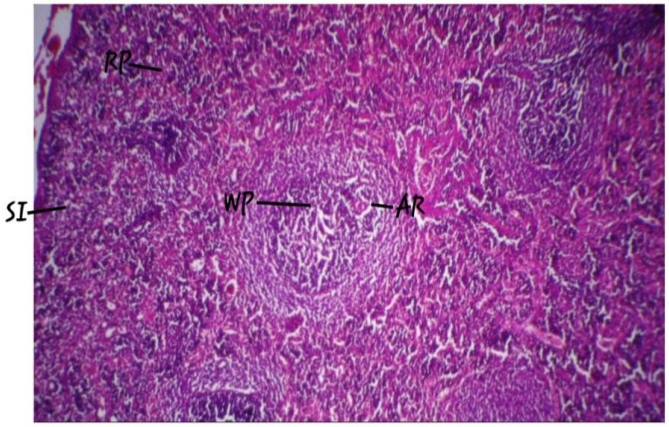

Plate 1. Rat spleen. Control. Composed of normal architecture: red pulp (RP), white pulp (WP), arteriole (AR), sinus (SI): H&E 100x

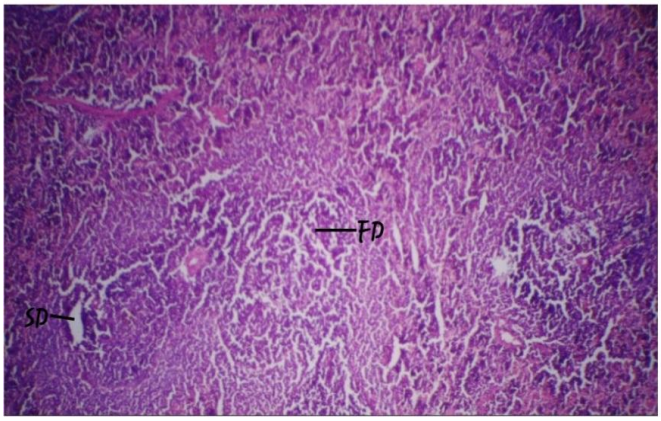

Plate 2. Rat spleen exposed to ATO only showing: severe follicular degeneration (FD), sinus dilatation (SD): H&E 100x

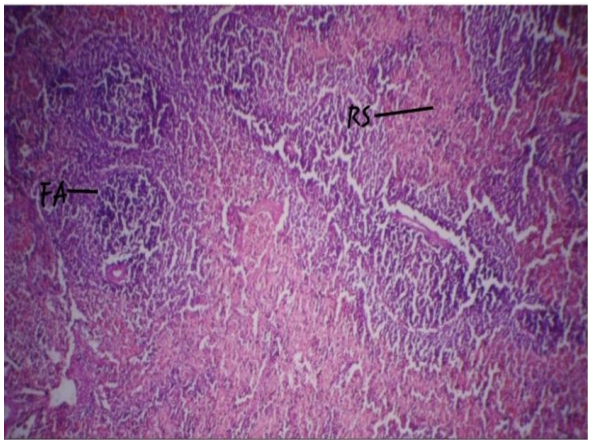

Plate 3. Rat spleen exposed to ATO + 200 mg/kg body weight of ELEIG showing: mild follicular activation (FA), increased red cell sequestration (RS): H&E 100x

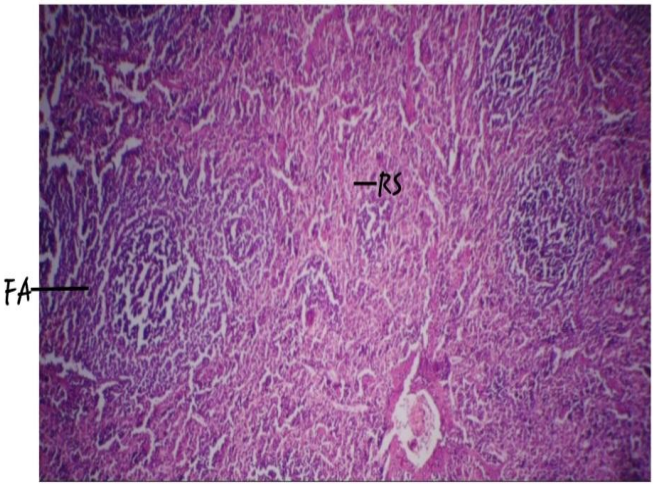

Plate 34. Rat spleen exposed to ATO + 500 mg/kg body weight of ELEIG showing: mild follicular activation (FA): increased red cell sequestration (RS): H&E 100x

The reduction in hematological parameters observed in this study indicates potential damage to organs such as the spleen, likely resulting from haemolysis of red blood cells. This is supported by significant reductions in red blood cell count, mean corpuscular volume, hematocrit level, and hemoglobin concentration. These findings collectively suggest the development of anemia, highlighting the adverse effects of arsenic trioxide on erythropoiesis and red blood cell integrity.

Anaemia is often accompanied by oxidative stress and toxicity, which impairs the blood's oxygen transport capacity, ultimately leading to symptoms of fatigue and weakness. This observation is consistent with previous research, which has also identified anaemia as a frequent outcome of arsenic trioxide (ATO) toxicity (Kile et al., 2016).

This work is also in agreement with studies where they observed the haematological variation due to arsenic trioxide that RBCs and haemoglobin levels decreased by exposure to arsenic trioxide (Breton *et al.,* 2006; Ferzand *et al.,* 2008). This is probably due to the binding effect of arsenic trioxide to haemoglobin which could lead to inhibition of haem synthesis pathway (Sulaimon *et al.,* 2015). The present study revealed a significant decrease in red blood cell (RBC) count and hemoglobin levels. Consequently, this reduction had a cascading effect on other hematological indices, including hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), as these parameters are directly dependent on RBC count and hemoglobin levels. The reduction in the red blood cells, white blood cells and platelets (pancytopenia) as revealed in this study further agrees with the previous report (Sofowora, 2015). This is probably because arsenic trioxide attacks the immune system as shown by follicular destruction of the splenic tissue.

In addition, the damage to the splenic tissue revealed in this study may again be due to overwhelming free radicals or availability of little antioxidant since free radical injury can affect many organs in the body irrespective of their origin and location (Joseph and Aworh, 1992; Ferzand *et al.,* 2008). These results corroborate existing evidence suggesting that the toxic effects of ATO are primarily driven by oxidative stress (Paithankar *et al.,* 2021). Previous investigations have revealed that ATO-induced oxidative stress arises from diminished activity of antioxidant enzymes (Zulfiqar and Ashraf, 2022) and elevated lipid peroxidation (Byeon *et al.,* 2021) in experimental animal models. Damage to the cellular

membrane can compromise its integrity, leading to the leakage of cellular contents into the bloodstream. The severity of membrane damage dictates the extent of cellular disruption. Furthermore, membrane damage can also impair the activity of essential enzymes, which are crucial for maintaining optimal cellular function. For example, it probably inhibited the activity of enzymes involved in DNA repair, causing DNA damage to accumulate and disrupted the functioning of enzymes involved in cellular energy production (such as the electron transport chain), leading to cellular dysfunction and organ damage (Ayuk *et al*., 1999). The observed alterations in hematological parameters and splenic architecture suggested that ATO induced splenic damage, which is further substantiated by histopathological findings of severe follicular degeneration and sinus dilation.

These findings suggest impaired blood flow, which can lead to tissue hypoxia and subsequent damage. As the spleen plays a crucial role in filtering blood, managing blood cells, and modulating immune responses, follicular destruction can compromise these functions. Moreover, sinus dilatation can damage the splenic vasculature, disrupting the integrity and function of blood vessels within the spleen. This can result in increased vascular permeability and hemorrhage. Consistent with these observations, previous studies have reported similar toxic effects of Arsenic trioxide (ATO) on various organ systems in experimental animals. For instance, ATO has been shown to induce endothelial dysfunction, contributing to cardiovascular disease, alter hematopoiesis, and impair immune responses (Mahmoud, 2022; Theofilis et al., 2021). However, administration of ELEIG was found to mitigate both the hematological and histopathological manifestations in the spleen, indicating its potential protective effects

CONCLUSION

The concurrent administration of graded doses of ELEIG significantly mitigated the adverse effects, with the 250 mg/kg dosage demonstrating the most pronounced ameliorative effect. These findings suggested that the ELEIG possesses splenoprotective activity, likely attributed to its bioactive constituents, which exhibit antioxidant properties, lipid-lowering capabilities, and potential splenoprotective effects.

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