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Protective Effects of Ethanol Tuber Extract of (Tigernut) *C. Esculentus* against Arsenic Trioxide-Induced Cardiotoxicity in Wistar Rats

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ABSTRACT: Therefore, the objective of this paper is to investigate the protective effects of ethanol tuber extract of (Tigernut) *C. esculentus* (ETECE) against Arsenic Trioxide (ATO)-induced cardiotoxicity in Wistar rats using appropriate standard procedures. Histological examination revealed that ATO exposure led to severe cardiac damage, characterized by coronary vascular ulceration, interstitial congestion, perivascular myocardial degeneration, and perivascular fibrosis. However, treatment with escalating doses of ETECE and vitamin C resulted in mild attenuation of these effects. Notably, the 200 mg/kg body weight dose of ETECE demonstrated a comparable protective effect to that of vitamin C. In summary, ETECE exhibited a moderate mitigating effect against ATO-induced cardiotoxicity, indicating that while ETECE may offer some level of cardioprotection, it is unlikely to be a complete safeguard against ATO-induced cardiac damage.

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The heart is a crucial muscular organ responsible for pumping blood throughout the body, providing tissues and organs with essential oxygen and nutrients. However, its function can be compromised when exposed to harmful environmental agents (Wang *et al.,* 2023). Cardiotoxicity, a condition characterized by the detrimental effects of substances, medications, or conditions on heart muscle or cardiac function, can lead to severe cardiac complications (Dong *et al.*, 2010).

For many years, arsenic-based compounds have been utilized in traditional medicine to treat a variety of ailments, including cancer, syphilis, and malaria (Zhu *et al.,* 2022). However, their global adoption was limited until the Food and Drug Administration (FDA) approved arsenic trioxide (ATO) as a treatment for relapsed and refractory acute promyelocytic leukemia (APL) (Fox *et al.,* 2008), marking a significant milestone in the modern application of arsenic-based therapies. The therapeutic use of arsenic trioxide (ATO) is limited by its potential to cause cardiac toxicity, which can manifest as QT interval prolongation, torsades de pointes (TdP), or even sudden cardiac death (Westervelt *et al.,* 2001). The underlying mechanisms of ATO-induced cardiotoxicity are multifaceted and primarily involve the induction of oxidative stress and calcium overload, leading to cardiac dysfunction (Vineetha *et al.*, 2014). *Cyperus esculentus*,

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commonly known as tigernut, earth almond, or yellow nutsedge, is a widely distributed crop belonging to the Cyperaceae family (Sanchez-Zapata *et al.,* 2012). As a nutrient-rich tuber, *C. esculentus* boasts a high energy content, comprising starch, fat, protein, sugar, and essential dietary minerals, making it a valuable food source (Zhang *et al.,* 1996). In Nigeria, *C. esculentus* is locally recognized by different ethnic groups, with the Hausas referring to it as "Aya", the Yorubas as "Imumu", and the Igbos as "Ofio" (Omode *et al.,* 1995). Nigerians utilize this versatile plant in various forms, consuming it fresh, dried, roasted, or as a key ingredient in the traditional beverage known as "Kunu" (Oladele and Aina, 2007). *C. esculentus* is predominantly cultivated in the middle belt and northern regions of Nigeria, where three distinct varieties - black, brown, and yellow - are grown. However, only the yellow and brown varieties are commonly found in markets. The yellow variety is particularly sought after due to its desirable characteristics, including its larger size, vibrant color, and fleshier texture, making it the preferred choice among consumers (Raphael *et al.,* 2010). *C. esculentus* offers several health benefits, including the reduction of cholesterol levels, which in turn decreases the risk of developing coronary heart disease and arteriosclerosis. In traditional medicine, *C. esculentus* is also valued for its digestive benefits, particularly in alleviating symptoms of heavy digestion, flatulence, and dysentery, making it a recommended remedy for individuals suffering from these conditions (Gambo and Da'u, 2014).

C. esculentus has been found to possess a rich nutritional profile, boasting an array of antioxidants, including vitamin E, vitamin C, and quercetin, as well as essential minerals such as zinc, potassium, and phosphorus (Allouh *et al.,* 2015). Furthermore, *C. esculentus* has been traditionally recognized for its potential to enhance male fertility and sexual wellness. Studies have reported that it can increase libido, improve sexual performance, and even restore sexual function in individuals with existing sexual abnormalities, making it a valuable natural remedy for promoting reproductive health (Saheed *et al.,* 2016). In addition to its numerous health benefits, *C. esculentus* has also been traditionally employed in the treatment of urinary tract and bacterial infections, as well as in reducing the risk of colon cancer when consumed (Adejuyitan *et al.,* 2009). Recently, there has been a growing interest among researchers in exploring the potential of medicinal plants with antioxidant properties, such as *C. esculentus*, to mitigate metal toxicity (Sudjarwo *et al.,* 2017). Therefore, the objective of this paper is to investigate the protective effects of ethanol tuber extract of (Tigernut) *C. esculentus* (ETECE) against arsenic trioxide (ATO)-induced cardiotoxicity in Wistar rats.

MATERIALS AND METHODS

*Collection, Authentication, and Preparation of Plant Specimens***:** *C. esculentus* tubers were sourced from new Benin market in Benin-City, Edo State. To confirm their authenticity, a sample was submitted to the Department of Plant Biology and Biotechnology at the University of Benin, where it was positively identified and assigned the herbarium number UBH-C419. After verification, the *C. esculentus* tubers were thoroughly washed with tap water, air-dried to remove excess moisture, and then pulverized into a fine powder to facilitate further processing. A total of 150g of the powdered tubers was then soaked in 1000ml of 50% ethanol for a period of 72 hours. The resulting crude ethanol extract was filtered using a Buchner funnel and Whatman No.1 filter paper to obtain a clear filtrate. This filtrate was subsequently freeze-dried, employing the method described by Kumar (2019), at the Natural Product Research Laboratory, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Benin, Benin-City. The freeze-dried extract was stored in a refrigerator at -4°C until further use.

*Experimental Animals and Administration***:** Forty-nine (49) adult Wistar rats weighing between 190 and 210 g were used for this experiment. The rats were bred in anatomy animal house in the School of Basic Medical Sciences, University of Benin, Benin City. The animals were provided with unrestricted access to food and water, and were housed in a controlled laboratory environment designed to ensure their optimal comfort and well-being. The laboratory conditions were carefully maintained within a narrow range, with a temperature of 28 ± 2°C, relative humidity of 50 ± 5%, and a 12-hour light-dark cycle, providing a stable and comfortable environment for the animals. The rats were randomly assigned to seven groups, each consisting of seven rats. Following an acclimatization period, the animals received the predetermined dosage of ETECE and ATO via oral gavage, using a modified version of the binge-drinking model developed by Carson and Pruett (1996). The dosages were determined based on the LD_{50} values obtained using Lorke's method (1983), and administered as groups A (control, 1ml of distilled water), B (10 mg/kg BW of ATO only), C (200 mg/kg BW of ETECE and ATO), D (400 mg/kg BW of ETECE and ATO), E (200 mg/kg BW of ETECE only), F (400 mg/kg BW of

ETECE only) and G (ATO and 100 mg/kg BW of Vitamin C)

Animals Sacrifice: The administration of the treatment lasted for 60 days. Following this period, the rats were humanely anesthetized using cotton wool soaked in approximately 30ml of ketamine, which was placed in an enclosed container for 2-5 seconds. Once anesthetized, each rat was positioned supine on the dissection table. A thoraco-abdominal incision was then made to expose the thoracic viscera, allowing for the careful harvesting of the heart. The excised heart was subsequently fixed in 10% formalin solution within a universal container, in preparation for histological analysis.

*Histological analysis***:** After fixation, the heart tissues were subjected to standard histological processing procedures. This involved a series of steps, including dehydration in a graded ethanol series (70-100%), followed by xylene clearing and paraffin wax embedding. Thin sections were then cut from the embedded tissues, stained with hematoxylin and eosin (H&E) using the protocol described by Drury and Wallington (1980), and subsequently examined under a light microscope to assess any histological changes.

RESULTS AND DISCUSSION

The heart of control group (Group A) showed normal bundles of cardiomyocytes, interstitial space and coronary artery (Plate 1). The heart of Group B (ATO only) showed coronary vascular ulceration, interstitial congestion, perivascular myocardial degeneration and perivascular fibrosis (Plate 2). The heart of Group C (200 mg/kg of ETECE and ATO) showed normal bundles of cardiomyocytes and mild perivascular fibrosis (Plate 3). The heart of Group D (400 mg/kg of ETECE and ATO) showed normal bundles of cardiomyocytes, interstitial infiltrates of inflammatory cells and interstitial congestion (Plate 4). The heart of Group E (200 mg/kg of ETECE only) showed normal bundles of cardiomyocytes, normal coronary arterioles and interstitial space (Plate 5). The heart of Group F (400 mg/kg of ETECE only) showed normal bundles of cardiomyocytes, coronary artery and interstitial space (Plate 6). The heart of Group G (Vit. C and ATO only) showed normal bundles of cardiomyocytes and mild perivascular fibrosis (Plate 7). The heart is a vital muscular organ that plays a pivotal role in sustaining overall bodily health by circulating blood, oxygen, and essential nutrients to various tissues and organs. However, exposure to harmful environmental factors can compromise its functional integrity, leading to adverse consequences for cardiovascular well-being (Wang *et al.,* 2023).

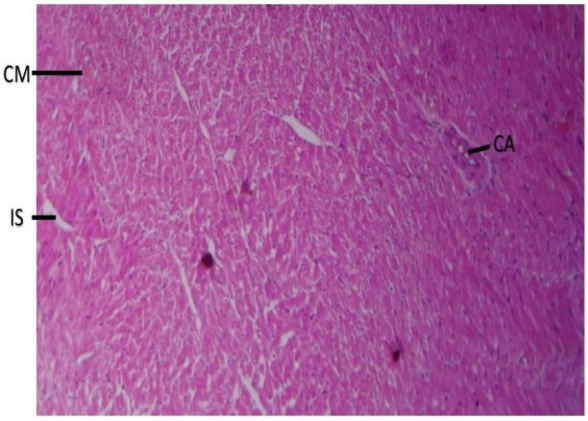

Plate 1. Photomicrograph of the heart of the control group (group A) showing normal architecture: bundles of cardiomyocytes (CM) interstitial space (IS) and coronary artery (CA). H and E 100x.

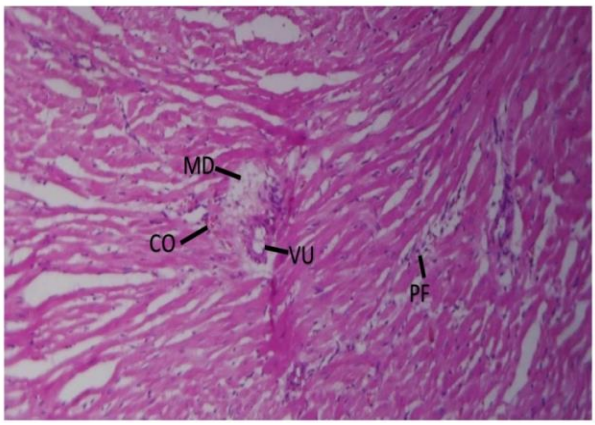

Plate 2. Photomicrograph of the heart of Group B (ATO only) showing coronary vascular ulceration (VU), interstitial congestion (CO), perivascular myocardial degeneration (MD) and perivascular fibrosis (PF). H and E 100x.

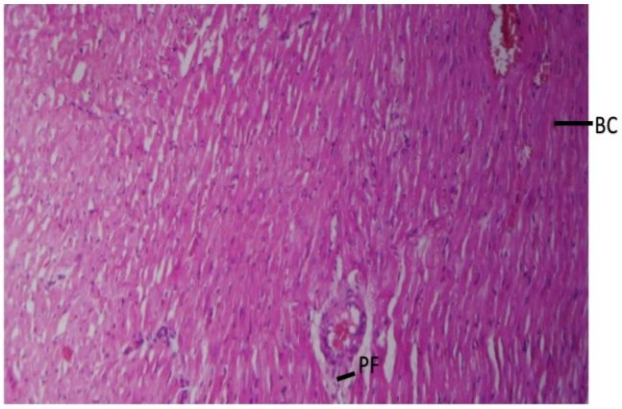

Plate 3. Photomicrograph of the heart of Group C (200 mg/kg of ETECE and ATO) showing normal bundles of cardiomyocytes (BC) and mild perivascular fibrosis (PF). H and E 100x.

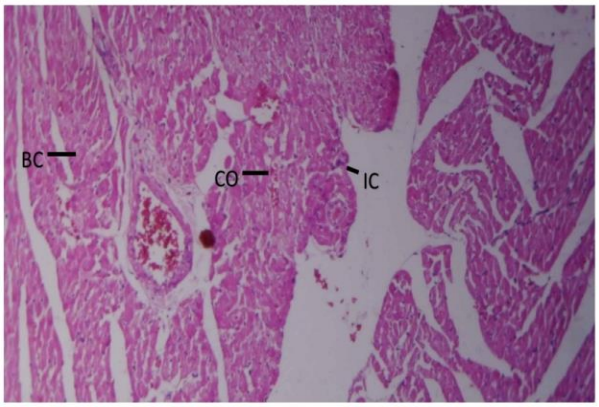

Plate 4. Photomicrograph of the heart of Group D (400 mg/kg of ETECE and ATO) showing normal bundles of cardiomyocytes (BC) interstitial infiltrates of inflammatory cells (IC) and interstitial congestion (CO). H and E 100x.

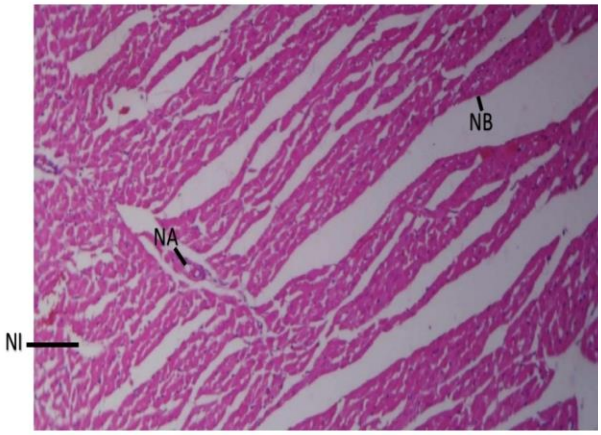

Plate 5. Photomicrograph of the heart of Group E (200 mg/kg of ETECE only) showing normal bundles of cardiomyocytes (NB), coronary arterioles (NA) and interstitial space (NI). H and E 100x.

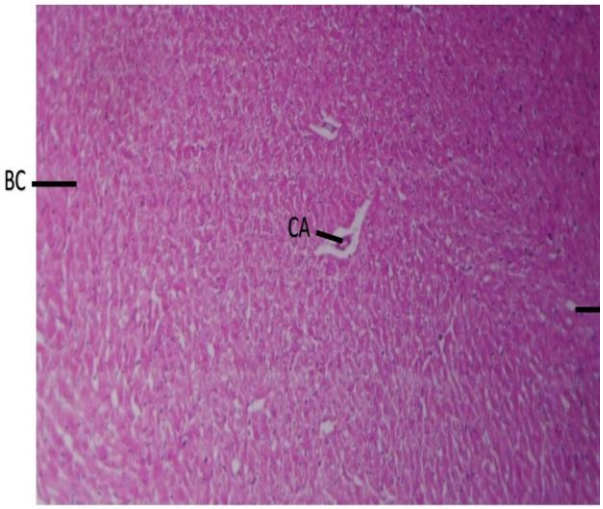

Plate 6. Photomicrograph of the heart of Group F (400 mg/kg of ETECE only) showing normal bundles of cardiomyocytes (BC), coronary artery (CA) and interstitial space (IS). H and E 100x.

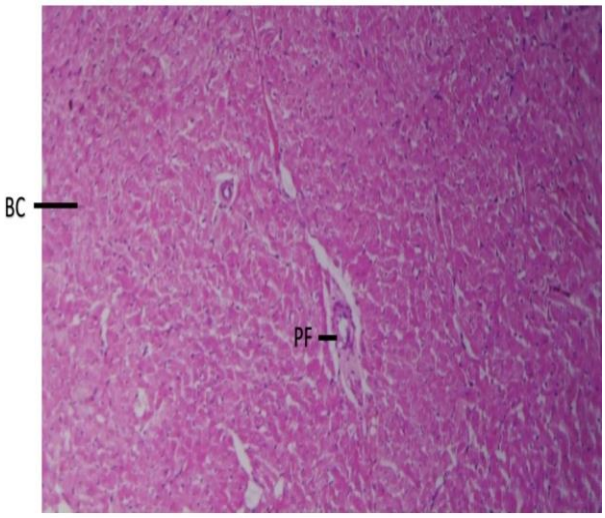

Plate 7. Photomicrograph of the heart of Group G (vitamin C and ATO) showing normal bundles of cardiomyocytes (BC) and mild perivascular fibrosis (PF). H and E 100x.

Cardiotoxicity refers to the detrimental effects of toxic substances on the heart, which can ultimately lead to various forms of myocardiopathy, including arrhythmia, myocardial infarction, and myocardial hypertrophy. The severe and often irreversible cardiac damage caused by certain therapeutic agents, such as anticancer drugs like ATO, is a major concern, frequently resulting in the termination of treatment and hindering the development of new drugs (Ewer and Ewer, 2015). Over the past few decades, a significant number of clinical drugs, exceeding 10%, have been withdrawn from the market due to unforeseen cardiovascular side effects. These adverse effects not only impede drug development but also compromise patient health outcomes. Research has shown that drug-induced myocardial damage often progresses in a stepwise manner, characterized by increased levels of cardiac biomarkers and structural deformation of the myocardium (Pistillucci *et al.,* 2015; Patel and Cornell, 2019). ATO has revolutionized the treatment of acute promyelocytic leukemia, yet its cardiotoxic effects remain a persistent concern. Extensive research over the past few decades has suggested that ATO-induced cardiotoxicity is primarily attributed to mitochondrial damage and cardiomyocyte apoptosis triggered by reactive oxygen species (ROS). Specifically, studies have shown that ATO increases ROS levels, leading to cardiomyocyte apoptosis (Raghu and Cherian, 2009; Vineetha *et al.,* 2015).

C. esculentus is a plant renowned for its rich antioxidant properties, rendering it a valuable medicinal herb. As a natural antioxidant, it exhibits

the capacity to neutralize free radicals and shield the heart from oxidative stress (Belewu, 1996). The therapeutic and biological effects of C. *esculentus* are multifaceted, encompassing anti-oxidative, anti-inflammatory, anti-cardiovascular, aphrodisiac, and anti-diabetic properties, ultimately contributing to enhanced overall well-being and improved health outcomes (Edo *et al.,* 2023). The oil extracted from *C. esculentus* has been shown to have a beneficial effect on lipid profiles, characterized by a reduction in low-density lipoprotein cholesterol (LDL-C) and a concomitant increase in high-density lipoprotein cholesterol (HDL-C) (Okafor *et al.,* 2003). Furthermore, it decreases triglyceride levels in the blood and mitigates the risk of thrombosis, thereby exerting a protective effect against the development of arteriosclerosis (Oladele *et al.,* 2009).

In this study, histological examination of heart sections from rats receiving standard feed and water (control), as well as those treated with graded doses (200 and 400 mg/kg body weight) of ETECE (groups E and F), revealed a normal architectural arrangement. The cardiomyocytes were organized into well-defined bundles, with distinct interstitial spaces, coronary arteries, and cardiac veins, indicating no apparent histological alterations, thus indicating that consumption of ETECE are safe at these doses. Histological sections from rats treated with ATO alone exhibited notable pathological changes, including vascular congestion, vascular ulceration, perivascular myxoid degeneration of myocardial fibers, and perivascular fibrosis. These alterations indicate localized areas of myocardial necrosis, accompanied by inflammation around blood vessels. These findings are consistent with previous research by Olukayode *et al*. (2024), who reported similar cardiac lesions in Wistar rats treated with ATO, including vascular distortion, perivascular inflammatory cell infiltrates, and focal myocardial degeneration, thereby confirming the cardiotoxic effects of ATO, and Varghese *et al.* (2017), who reported oxidative insults and pathological damages in the heart of Wistar rats induced with ATO. These findings further substantiate that ATO induces inflammatory reactions and causes ultrastructural damage to cardiomyocytes (Li *et al.,* 2017). The resultant inflammatory responses are believed to contribute, in part, to the cardiotoxic effects associated with heavy metal exposure (Lakkur *et al.,* 2015), highlighting the potential mechanisms underlying ATO-induced cardiac damage.

Histological sections from rats treated with 200 mg/kg body weight of ETECE in combination with ATO (group C) and Vitamin C, a well-established antioxidant, in combination with ATO (group G) displayed, to a significant extent, normal arrangements of cardiomyocyte bundles, accompanied by mild perivascular fibrosis. These findings suggest that both ETECE and Vitamin C offered a degree of protection against ATO-induced cardiotoxicity, although this protection was not absolute. This partial protection is likely attributed to the antioxidant properties of these two agents. Histological sections from rats treated with 400 mg/kg body weight of ETECE in combination with ATO (group D) revealed interstitial congestion and mild infiltrates of inflammatory cells. This suggests that while ETECE offered some protection, it was insufficient to completely prevent the inflammatory response. In comparison, the protection afforded by ETECE at this dose was not as robust as that provided by Vitamin C. However, the 200 mg/kg body weight dose of ETECE demonstrated a comparable degree of protection to Vitamin C against ATO-induced cardiotoxicity, indicating its potential as a protective agent.

*Conclusion:*This study provides evidence that ETECE possesses a minimal protective potential against ATO induced cardiotoxicity, comparable to vitamin C, a known antioxidant in Wistar rats. These findings suggest that ETECE could offer some degree of protection, but not absolute, for the heart.

Conflict of interest: The authors declare that they have no competing interests.

Data availability: The data supporting the findings of this study are available from the corresponding author upon request.

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