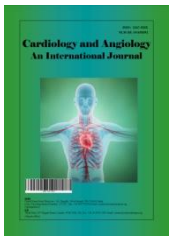

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Cardio-Protective Effect of the Leaf Extract of *Andrographis paniculata* in Isoproterenol-Induced Myocardial Infarction

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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ABSTRACT

Background: Nowadays, myocardial infarction has been regarded as one of the chronic diseases with increasing mortality rate worldwide. The use of medicinal plants in the treatment of this chronic disease is gaining wide acceptance globally.

Materials and Methods: This study was carried out to evaluate the cardio-protective effect of the leaf extract of *A. paniculata* in isoproterenol-induced myocardial infarction. Fresh green leaves of *A paniculata* were collected from the Faculty of Agriculture farmland, Nnamdi Azikiwe University, Awka, Nigeria. The plant was identified and authenticated at the Department of Botany, Nnamdi Azikiwe University and a voucher specimen was deposited at the herbarium accordingly. The shredded, air-dried sample was then pulverized and weighed. Solvent-solvent (ethanol and water) (7:3) was used for extraction via maceration for 72 hr. The filtrate was evaporated to dryness to obtain the ethanol extract which was used for further bioassay study. The bioactive constituents of the plant extract were quantitatively analyzed by Gas chromatography mass spectrometry (GC-MS). The animals were administered with the extract of *A. paniculata* orally for seven days at a divided dose of 100 mg/kg, 200 mg/kg and 400 mg/kg body weights. On the eight day, myocardial infarction was induced through subcutaneous administration of isoproterenol at a dose of 150 mg/kg/day diluted in 2 ml of saline on two consecutive days. Subsequently, the blood pressures were monitored and blood collected for bioassay studies.

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Results: The results of the study showed that the leaf extract of *A. paniculata* was rich in 2,5-Octadecadiynoic acid, methyl ester (28.21%); 1,2,3,5-Cyclohexanetetrol,(1à,2á,3à,5á)- (15.10 %) and 10-12-Pentacosadiynoic acid (13.05%). The findings also showed a significant decrease ($p>0.05$) in the Mean arterial blood pressure, heart rate, aspartate transaminase, alanine transaminase, creatinine kinase and lactate dehydrogenase activities of the treatment group compared with the untreated control group while the antioxidant (superoxide dismutase, catalase and glutathione) activities were significantly increased in the treatment group, compared with the untreated control group.
Conclusion: The findings of this work have shown that leaf of *A. paniculata* was rich in bioactive compounds which could be synthesized to produce plant based products to combat cardiovascular diseases especially myocardial infarction.

Keywords: Cardiovascular disease; myocardial infarction; medicinal plant; Andrographis paniculata; isoproterenol.

1. INTRODUCTION

Cardiovascular diseases (CVD) is currently the leading cause of morbidity and mortality worldwide with annual mortality rate of 17.5 million people, which constitute about 31% of all deaths worldwide [1], with more than 75% occurrence in low and middle income countries [2,3]. About 80% CVD deaths occur due to stroke and myocardial infarction [4]. Myocardial infarction (MI) is defined as the necrosis of the myocardium (heart muscle) following total occlusion of blood supply to the heart [5].

MI is now recognized as an overwhelming burden to the healthcare status of the human population and it is one of the significant type cardiovascular diseases [5]. MI is reflective when blood clot blocks the blood flow to the heart, resulting from decades of mismatched lifestyle choices. Addressing myocardial infarction in the populace will be a way to resolve chronic conditions of cardiovascular diseases.

Despite landmark achievement in medicine, the continuous use of synthetic cardio-protective drugs have been characterized with varying side effects ranging from joint pain to loss of memory [6]. Thus, the use of plants, abundant in our environment to combat cardiovascular diseases is a strategy that should provide an alternative approach to solve this perenial problem. Herbal medicine is gaining wide acceptance in the fight against chronic diseases especially myocardial infarction owing to better understanding of the mechanisms by which they positively influence health and improves quality of life [7].

Andrographis paniculata (Nees) is one of the promising plants that could help to ameliorate the negative impact of myocardial infarction. *A. paniculata* belongs to the natural order Acanthaceae and it is commonly known as king of bitters. It was reported to possess anti-inflammatory [8], anticancer [9], anti-hyperglycemic [10] and anti-oxidative [11] effects.

Despite several studies on *A. paniculata,* its potentials in ameliorating cardiovascular disorders have not been well explored and documented in the literature. Hence, the need for this study.

From the experience in this study, it could be possible to use this extract as a protective medicament in patients at high risk of myocardial infarction and those with stable and unstable angina. This could be life saving, cheaper and safer alternative to other conventional medications used for similar purposes.

2. MATERIALS AND METHODS

2.1 Sample Collection and Preparation

Fresh green leaves of *Andrographis paniculata* were collected from a farmland in Owerri, Imo-State, Nigeria. Identification and authentication of the plant was carried out at the Department of Botany, Nnamdi Azikiwe University, Awka and a voucher specimen was deposited at the herbarium of the Department for future references. The plant material was shredded with a knife and air-dried under shade for 21 days. The dried leaf was pulverized using a laboratory blender and the fine powders obtained was weighed and stored in an air-tight container at room temperature for further use.

2.2 Extraction of Plant Materials

The weighed powdered sample (245.79 g) was then used for the extraction with solvent

combination of ethanol and water (7:3) (2500 ml) for 72 hr via macceration. The mixture was decanted and filtered using sterile Whatman paper No. 1. The filtrate was thereafter evaporated to dryness with the aid of rotary evaporator to obtain crude ethanol extract which was carefully preserved for further analysis. The method of Nkafamiya et al. [12] was used to calculate the yield (12.36g) of the crude extract using the formula below:

$$\text{Percentage yield} = \frac{mass\ of\ crude\ extract\ (g)}{mass\ of\ powdered\ sample\ (g)} \times 100$$

2.3 GC-MS Elucidation

The method of Uchegbu et al. [13] was used to carry out GC-MS analysis at the Central Research and Diagnostic Laboratory, Ilorin, Kwara State, using Shimadzu GCMS-QP2010 SE.

2.4 Determination of Median Lethal Dose (LD_{50})

Lorke's [14] method was used to determine the median lethal dose of the extract.

2.5 Animal Studies

2.5.1 Procurement of study animals

Wistar albino rats (30) weighing approximately 180 g were purchased from Chris Farm Ltd Mgbakwu, Awka, Anambra State and were brought to the animal house of the Department of Applied Biochemistry, Nnamdi Azikiwe University, Awka. The rats were kept in standard cages with saw dust as bedding and standard housing conditions of 12:12 light: dark cycles and fed with standard rat pellets and water *ad libitum*. The animals were allowed to acclimatize to the new environment for seven days.

2.5.2 Dose Preparation and Treatment

The hydro-ethanolic leaf extract of *Andrographis paniculata* was prepared with distilled water in three divided dose (100, 200, and 400) mg / kg, Atorvastatin (10 mg/kg) used as a reference drug and distilled water was used as vehicle for the untreated group. The animals were administered the extract and drug for fourteen consecutive days prior to induction with water *per os* and feed *ad libitum*.

2.5.3 Experimental design

The animals were randomly grouped into five, with six animals in each group, and the treatment was as follows: Groups A, B and C animals were designated as *A. paniculata* treatment group and were pre-treated with the ethanol leaf extract at 100 mg/kg, 200 mg/kg and 400 mg/kg, respectively, for 14 days and thereafter 0.2 ml isoproterenol (ISO) at 150 mg/kg was injected subcutaneously at an interval of 24 h on the 15th and 16th day. Group D animals were designated as isoproterenol control and were administered 0.2 ml of 10 mg artovastatin for 14 days and thereafter 0.2 ml isoproterenol (ISO) at 150 mg/kg was injected subcutaneously at an interval of 24 h on the 15th and 16th day while group E animals (designated as vehicle control group) were administered 0.2 ml normal saline for 14 days; and on the 15th and 16th day, 0.2 ml isoproterenol (ISO) at 150 mg/kg was injected subcutaneously at an interval of 24 h [15].

2.5.4 Blood pressure measurement

Measurement of blood pressure of all the experimental animals was carried out the 17th day with the aid of a non-invasive tail cuff blood pressure monitor, the 6-channel CODA blood pressure monitor for rats and mice. Blood pressure parameters (the systolic, diastolic and mean arterial blood pressure) were all determined and recorded.

2.5.5 Collection of Blood Sample

At the end of the experimental period, the animals were anaesthetized with chloroform vapor, and sacrificed. 5 ml sterile syringe with needle was used for blood collection through cardiac puncture and the sera obtained were used for bioassay studies.

2.5.6 Preparation of tissue homogenate

The heart tissues of the rats were harvested on ice, rinsed with normal saline and homogenized in aqueous potassium buffer (0.1 M, pH 7.4). The homogenate was thereafter centrifuged at 12 000 rpm (4°C) for 15 min to obtain the supernatant fraction.

2.5.7 Biochemical assays

Assay of aspartate transaminase, alanine transaminase, creatinine kinase and lactate dehydrogenase activities were carried out with standard assay kit while glutathione peroxidase (GPx) activity was determined using the method of Rotruck et al. [16]. Superoxide dismutase (SOD) activity was carried out following the

method of Kakkar et al. [17] with slight modification while the method of Sinha [18] was employed in the assay of Catalase activity.

2.6 Data Analysis

The results obtained in this research were expressed as Mean ± S.D of triplicate determinations. One way analysis of variance (ANOVA) was carried out on the results and significance was accepted at $p<0.05$. GraphPad Prism5 Program (GraphPad Software, San Diego, CA, USA) was used for the graphical analyses of the results obtained.

3. RESULTS

The acute toxicological study of the plant extract on experimental rats is presented in Table 1. The plant extract showed a toxic effect at a dose of 5000 mg/kg when one mortality was recorded. The median lethal dose (LD_{50}) which is the dose required to kill half of the members of a tested population after specified test duration is calculated to be 3,807.88 mg/kg.

$$LD_{50} = \sqrt{(D_0 \times D_{100})}$$

Where:

D_0 = Highest dose that gave no mortality,
D_{100} = Lowest dose that produced mortality
$LD_{50} = \sqrt{(2900 \times 5000)}$
LD_{50} =3,807.88 mg/kg

The GC-MS analysis of the plant extract is presented in Table 2. The leaf extract of *A. paniculata* was found to be rich in 2, 5-Octadecadiynoic acid methyl ester (28.21%), 1,2,3,5-Cyclohexanetetrol, (1à,2á,3à,5á)- (15.10 %) and 10-12-Pentacosadiynoic acid (13.05%). Other compounds present include 1, 3-Propanediol, 2-(hydroxymethyl)-2-nitro-content (7.22%), 3-O-Methyl-d-glucose (6.02%) while Dibutyl phthalate (2.11%), Phytol (2.54%) and Hexanedioic acid, bis (2-ethylhexyl) ester (1.02%) are present in minute quantities.

The results showing the effect of *A. paniculata* leaf extract on the activity of aspartate transaminase (AST) in isoproterenol-induced myocardial infarction is presented in Fig. 2. Result showed a significant ($p>0.05$) decrease in AST activity in a dose dependent manner (100 mg/kg > 200 mg/kg > 400 mg/kg) in the extract treated group with marked activity increase in the untreated control.

The results showing the effect of *A. paniculata* leaf extract on the activity of alanine transaminase (ALT) in isoproterenol-induced myocardial infarction is presented in Fig. 3. Result showed a significant ($p>0.05$) decrease in ALT activity in a dose dependent manner (100 mg/kg > 200 mg/kg > 400 mg/kg) in the extract treated group with marked activity increase in the untreated control.

The result showing the effect of *A. paniculata* leaf extract on the activities of creatinine kinase (CK-MB) and lactate dehydrogenase (LDH) in isoproterenol-induced myocardial infarction is presented in Table 4. Result showed a significant ($p>0.05$) increase in CK-MB and LDH activities in a dose-dependent manner in the extract-treated groups compared with control group.

The results showing the effect of *A. paniculata* leaf extract on the activity of superoxide dismutase (SOD) activity in isoproterenol-induced myocardial infarction is presented in Fig. 4. Result showed a significant ($p>0.05$) increase in SOD activity in a group C animals (400 mg/kg) body weight compared with untreated control (group E).

Table 1. Acute toxicological study of hydro-ethanol leaf extract of *A. paniculata*

Phase 1

Groups	Number of animals	Dose (mg/kg)	Number of deaths
1	3	10	0
2	3	100	0
3	3	1000	0

Phase II

Groups	Number of animals	Dose (mg/kg)	Number of deaths
1	1	1600	0
2	1	2900	0
3	1	5000	1

Table 2. Bioactive compounds identified from the leaf extract using GC-MS

S/N	Compound	Molecular formula	Molecular weight (g/mol)	Retention time (min)	Content (%)
1	2,5-Octadecadiynoic acid, methyl ester	$C_{19}H_{34}O_2$	294.5	31.36	28.21
2	1,2,3,5-Cyclohexanetetrol, (1à,2á,3à,5á)-	$C_6H_{12}O_4$	148.20	10.56	15.10
3	10-12-Pentacosadiynoic acid	$C_{25}H_{42}O_2$	374.6	28.65	13.05
4	2H-Pyran, 2-(7-heptadecynyloxy)tetrahydro-2H-pyran	$C_{22}H_{40}O_2$	336.6	34.01	8.92
5	1,3-Propanediol, 2-(hydroxymethyl)-2-nitro-	$C_4H_9NO_5$	151.12	8.57	7.22
6	3-O-Methyl-d-glucose	$C_7H_{14}O_6$	194.18	9.75	6.02
7	Dibutyl phthalate	$C_{16}H_{22}O_4$	278.34	13.01	2.11
8	Phytol	$C_{20}H_{40}O$	296.53	14.5	2.54
9	Hexanedioic acid, bis(2-ethylhexyl) ester	$C_{22}H_{42}O_4$	370.6	19.30	1.02
10	Nitric acid, nonyl ester	$C_9H_{19}NO_3$	189.25	6.05	0.97

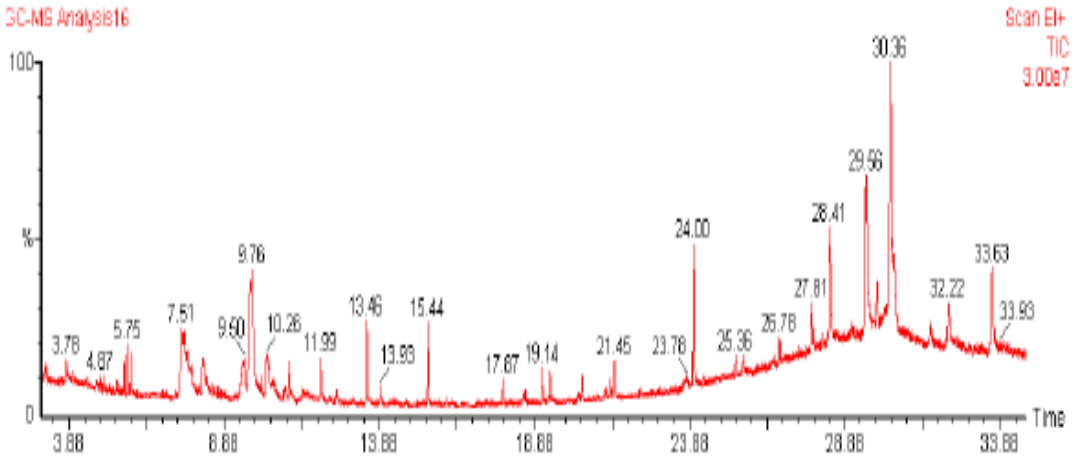

Fig. 1. GC-MS chromatogram of the leaf extract of *A. paniculata*

Table 3. Effect of the ethanol leaf extract of *Andrographis paniculata* on blood pressure (BP) and heart rate in isoproterenol-induced myocardial infarction

Group	Treatment	Mean arterial blood pressure (MAP) (mmHg)	Heart rate (HR)(beats/ mins)
A	Myocardial infarction plus 100 mg/kg extract sample	102.50^{d}	260^{d}
B	Myocardial infarction plus 200 mg/kg extract sample	118.00^{c}	300^{c}
C	Myocardial infarction plus 400 mg/kg extract sample	122.00^{b}	315^{b}
D	Myocardial infarction plus 10 mg/kg Atorvastatin	100.00^{d}	220^{e}
E	Myocardial infarction with distilled water	130.50^{a}	350^{a}

Columns with different alphabets superscript are significantly different at P< 0.05

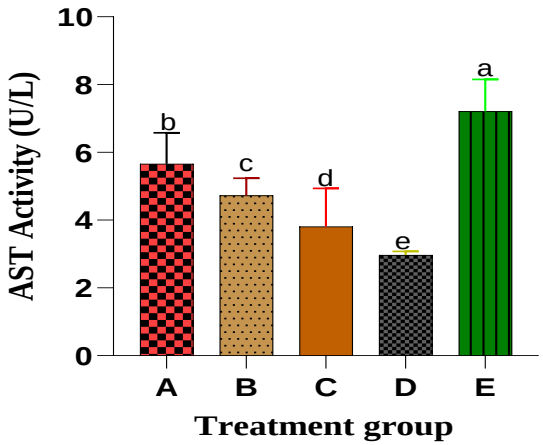

Fig. 2. Effect of *A. paniculata* leaf extract on the activity of aspartate transaminase (AST) in isoproterenol induced myocardial infarction

Columns with different alphabets are significantly different at P< 0.05

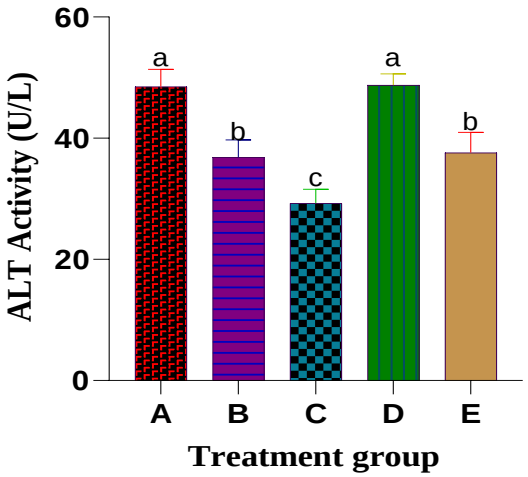

Fig. 3. Effect of *A. paniculata* leaf extract on the activity of alanine transaminase (ALT) in isoproterenol induced myocardial infarction

Columns with different alphabets are significantly different at P< 0.05

Table 4. Effect of the ethanol leaf extract of *Andrographis paniculata* on cardiac biomarkers in isoproterenol-induced myocardial infarction

Group	Treatment	CK-MB (IU/L)	LDH (IU/L)
A	Myocardial infarction plus 100 mg/kg extract sample	79.44^{d} ± 13.65	150.62^{d} ±31.44
B	Myocardial infarction plus 200 mg/kg extract sample	128.76^{c} ± 17.80	158.20^{c} ±28.55
C	Myocardial infarction plus 400 mg/kg extract sample	146.50^{b} ± 22.26	186.46^{b} ±23.27
D	Myocardial infarction plus 10 mg/kg Atorvastatin	152.40^{a} ± 14.63	208.40^{a} ± 7.32
E	Myocardial infarction with distilled water	57.58^{e} ± 15.77	76.54^{e} ± 1.45

Values are mean ±standard error of mean

Columns with different alphabets superscript are significantly different at P< 0.05

The results showing the effect of *A. paniculata* leaf extract on the catalase activity in isoproterenol-induced myocardial infarction is presented in Fig. 5. Result showed a significant (p>0.05) increase in the activity of catalase in a group C animals (400 mg/kg) body weight compared with untreated control (group E).

The results showing the effect of *A. paniculata* leaf extract on the activity of glutathione peroxidase (GPx) in isoproterenol-induced myocardial infarction is presented in Fig. 6. Result showed a significant (p>0.05) increase in GPx activity in a group C animals (400 mg/kg) body weight compared with untreated control (group E).

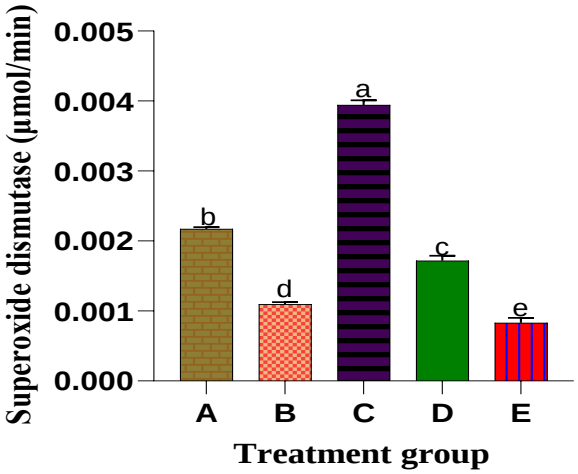

Fig. 4. Effect of *A. paniculata* leaf extract on the activity of superoxide dismutase in isoproterenol-induced myocardial infarction

Columns with different alphabets are significantly different at P< 0.05

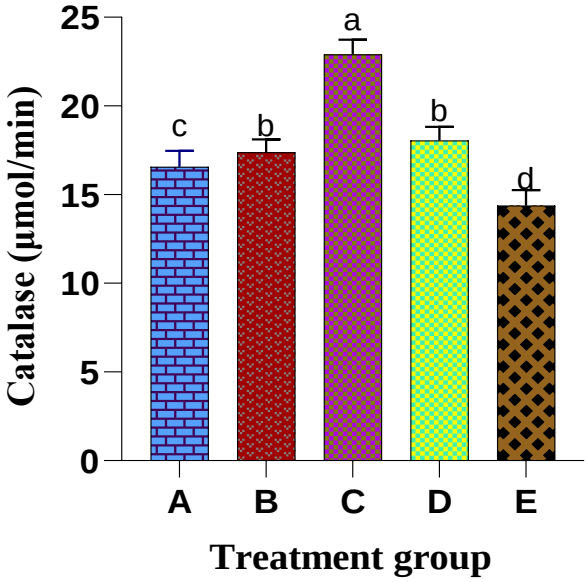

Fig. 5. Effect of *A. paniculata* leaf extract on the activity of Catalse in isoproterenol-induced myocardial infarction

Columns with different alphabets are significantly different at P< 0.05

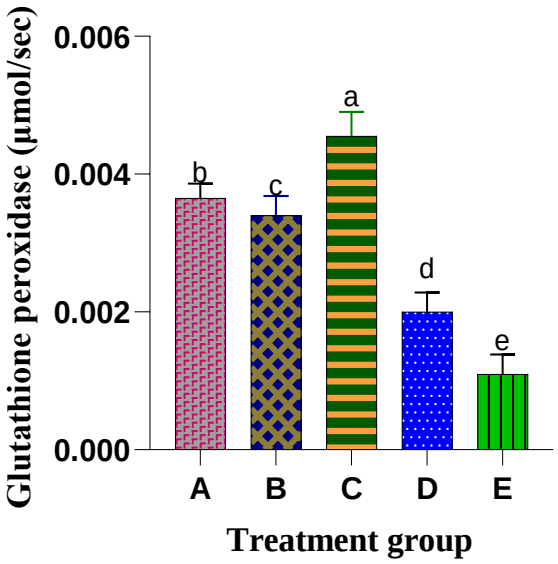

Fig. 6. Effect of *A. paniculata* leaf extract on the activity of glutathione peroxidase in isoproterenol induced myocardial infarction

Columns with different alphabets are significantly different at P< 0.05

4. DISCUSSION

Medicinal plants especially *Andrographis paniculata* has long been used for the treatment and prevention of many ailments [19] because they have been adjudged to be rich source of phytochemicals and other bioactive substances [20].

Phytochemical analysis of plants remains crucial in evaluating their therapeutic index. Hence, the quantitative phytochemical analysis of the leaves of *Andrographis paniculata* were carried out and a number of bioactive compounds including 2,5-Octadecadiynoic acid, methyl ester; 1,2,3,5-Cyclohexanetetrol, (1à,2á,3à,5á)-; 10-12-Pentacosadiynoic acid; 2H-Pyran, 2-(7-heptadecynyloxy) tetrahydro-2H-pyran; 1,3-Propanediol, 2-(hydroxymethyl)-2-nitro-; 3-O-Methyl-d-glucose; Dibutyl phthalate; Phytol; Hexanedioic acid, bis(2-ethylhexyl) ester as well as Nitric acid, nonyl ester were identified in the plant sample.

The plant was found to be rich in 2, 5-Octadecadiynoic acid methyl ester (28.21%) (Table 2). This is consistent with the report of Kalaiselvan et al. [21]. 2,5-Octadecadiynoic acid methyl ester is an unsaturated fatty acid which have been shown to play a significant role in the prevention and treatment of cardiovascular disorders, auto immune diseases as well as aiding learning ability [22].

The 1, 3-Propanediol, 2-(hydroxymethyl)-2-nitro-content (7.22 %) (Table 2) in the plant samples implies that its leaves could be used as a disinfectant. Clinical studies have reported that these health-promoting components could have an impact on the immune systems and thereby fight infectious diseases in a biological system [23].

3-O-Methyl-d-glucose (6.02 %) is another compound found in considerable quantity in the plant; a non-metabolizable glucose analogue that is not phosphorylated by hexokinase, 3-O-Methyl-d-glucose is used as a marker to assess glucose transport by evaluating its uptake within various cells and organ systems.

Other compounds such as Dibutyl phthalate (2.11 %), Phytol (2.54 %) and Hexanedioic acid, bis (2-ethylhexyl) ester (1.02 %) (Table 2) are present in minute quantities. This is in agreement with the findings of Imad et al. [24].

The present study has shown a significant cardiac dysfunction in the experimental animals as evidenced in the decreased mean arterial pressure (MAP) and heart rate (HR) after isoproterenol administration (Table 3).

Pre-treatment with *A. paniculata* significantly prevented the decrease in MAP and HR (determinants of myocardial oxygen demand); and hence, cause a decline in workload and also helped the heart to maintain myocardial oxygen balance in ischemic tissues. This aligns with the report of Ojha et al. [15]. Restoration of altered MAP and HR also increased blood flow through the sub-endocardial region, which bears the maximal burnt of ischemic insult in isoproterenol-induced myocardial infarction. The pretreatment with *A. paniculata* might have improved the perfusion to sub endo-cardium. Similar assertion was wade by Mohammad et al. [25] and Peng et al. [26] in their separate studies.

Although vast distribution of AST and ALT in a biological system made them to be non-specific enzymes for MI, they could however serve as an early predictor of tissue damage. In this study, we reported an increase in the serum activities of AST and ALT in rats induced with isoproterenol (Figs. 2 and 3). The leakage of cellular enzymes reflects the alterations in plasma membrane integrity and/or permeability as a response to α-adrenergic stimulation [27]. This could be as a result of the sarcolemma damage by the α-agonist which consequently rendered it leaky. Previous reports have shown that induction of isoproterenol generate free radicals via adrenoceptor mechanism which affects cell metabolism and consequently leads to myocardial necrosis [28]. The ability of the plant extract to cause a decrease in serum activities across and within the treatment groups showed the protective potential of the extract on the myocardium, thus reducing the cardiac damage thereby restricting the leakage of these enzymes.

Creatinine kinase (CK-MB) and lactate dehydrogenase (LDH), predominantly localized in the myocardium are released upon the induction of isoproterenol and caused myocardial injury [29]. As evidenced in the result above (Table 4), there was significant increase (146.50 ± 22.26 IU/L) in the activity of CK-MB in the heart tissue of animals treated with 400 mg/kg of the plant extract compared to the untreated control (57.58 ± 15.77 IU/L). This value falls within the reference activity range of CK-MB of 55-170 IU/L in healthy adults. Similarly, the activity of LDH significantly increased in the myocardium of the extract treated group (186.46 ±23.27 IU/L) (400 mg/kg) compared with the control group (76.54 ± 1.45 IU/L) (Table 4). Normal activity range of LDH in healthy adults has been reported to be between 105 to 333 IU/L. Since serum elevation of CK-MB and LDH is reflective of myocardial injury, the increased activities in the heart tissue of the treatment groups as observed in this study is indicative of the cardio-protective effect of the studied plant.

Various researches have reported the use of high concentration of isoproterenol in the induction of severe to chronic oxidative stress and this has been shown to result in necrotic lesions in the myocardium of rats [30]. Sawyer et al. [31] have reported that “increased generation of reactive oxygen species and/or depletion of the antioxidants in the defense system could contribute to oxidative stress, hence initiate the pathogenesis of MI”. “Free radical scavenging enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) serve as first-line cellular defence against oxidative stress” [32], “eliminating reactive oxygen radicals such as superoxide anion and hydrogen peroxide, and consequently arrest the formation of more reactive radical of hydroxyl ions” [20].

Figs. 4 to 6 present the effect of *A. paniculata* leaf extract on superoxide dismutase, catalase and Glutathione peroxidase activities in experimental animals induced with isoproterenol respectively. Researches have reported that approximately 3 to 5 % of the electron flow in mitochodria under normal physiological condition produces superoxide radicals and H_2O_2. This ratio is thus increased during diseases associated with oxidative stress. These frequently produced superoxide radicals (O_2^{*-}) and H_2O_2 are scavenged by SOD, GPx and catalase respectively. The higher activity of extracellular SOD in group C animals, as evident in Fig. 4 is indicative of the protective ability of the plant extract against oxidative damage.

Another distinctive antioxidant enzyme is the catalase (CAT) which catalyzes the decomposition of hydrogen peroxide to water and oxygen, thereby working on the product of the reaction catalyzed by SOD. Hence, in oxidative stress state, it is up-regulated alongside SOD. As evident in Fig. 5, there was a significant increase in catalase activity (23.05 ± 0.12 µmol/min) of the group C animals (400 mg/kg) when compared with group E (untreated) (13.12 ± 1.01 µmol/min). The increased activity of catalase in the treatment groups could be linked to its ability to regulate cellular level of hydrogen peroxide, thereby protecting the cells from oxidative damage.

As shown in Fig. 6, GPx activity was significantly increased in group C (400 mg/kg) animals compared to group E (untreated) animals. This is consistent with the findings of Hatai et al. [33] and strengthens the assertion of Sivakumar and Rajeshkumar [34] that *A. paniculata* enhanced antioxidant enzymes. Since GPx may be inactive under intense oxidative stress, its low activity observed in the untreated group may be attributed to enzyme inactivation.

5. CONCLUSION

The results from this research showed that the herbal plant as selected, is a potential protective agent on myocardial infarction induced by isoproterenol; hence, could serve as cheap alternative for the prevention of cardiovascular related disorders especially myocardial infarction.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All the experimental procedures and protocols used in this study were in accordance with the guidelines principles of animal Research Ethics Committee of the Nnamdi Azikiwe University (aREC-NAU) guide for the care and use of laboratory animals.

CONFERENCE DISCLAIMER

Some part of this manuscript was previously presented and published in the conference: ICPYDE 2022: International Conference on Pharmacy, Drugs and Efficacy on November 03-04, 2022 in Cape Town, South Africa. Web Link of the proceeding: https://publications.waset.org/abstracts/148881/pdf.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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