RENAL FUNCTION OUTCOME IN ISOPRENALINE INDUCED MYOCARDIAL INFARCTION IN ALBINO RATS AND PROTECTIVE EFFECT OF METHANOL LEAVES EXTRACT OF *JATROPHA TANJORENSIS*

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ABSTRACT

Chronic kidney disease is prevalent among patients with myocardial infarction. There is positive correlation between renal dysfunction and myocardial infarction which could result to increase mortality in acute myocardial infarction patients. This present study evaluated the renoprotective effect of methanol leaves extract of Jatropha tanjorensis in isoprenaline induced myocardial infarction in albino rats. Seventy two male albino rats were used for the in vivo study and randomly divided into six groups of twelve rats per group. Group 1 served as the normal control, group 2 was the negative control (administered 85 mg/kg of isoprenaline only), group 3 served as the positive control (pretreated with 2 mg/kg carvedilol for 28 days, group 4 through 6 were pretreated with 200, 400 and 600 mg/kg of the extract respectively for 28 days. Myocardial infarction was induced in the rats using subcutaneous injection of 85 mg/kg isoprenaline (ISO) for two consecutive days (26th and 27th) at 24 hours interval. The result of the in vivo study showed that isoprenaline significantly ($p<0.05$) produced alteration in the renal function integrity because there was significant ($p<0.05$) increase in urea, creatinine and altered kidney morphology of the negative control group compared to the 400 mg/kg extract treated groups. The extract at the dose of 400 mg/kg significantly ($p<0.05$) decreased the urea and creatinine level and maintained the kidney morphology. This study suggested that the extract at moderate dose could serve as an agent for the prevention of isoprenaline induced renotoxicity followed myocardial infarction.

Keywords: Myocardial infarction, Renal, Isoprenaline, Carvedilol, *Jatropha tanjorensis*

INTRODUCTION

The significance of impairment of kidney function for cardiovascular outcome after myocardial infarction has been examined in patients with heart failure (Hillege *et al*., 2006). Impaired renal function is a risk factor for cardiovascular disease (CVD) and an adverse prognostic factor in patients with established CVD. Renal function is a crucial predictor of mortality in patients with myocardial infarction (Kümler *et al*., 2011).

The prevalence of cardiovascular disease rises with declining renal function. There is a close association between chronic kidney disease and myocardial function. The most common cause of death in chronic kidney disease patient is ischemic heart disease and it's associated with increased morbidity and mortality (Franczyk-Skóra *et al*., 2013). A good example of ischemic heart disease is acute myocardial infarction (MI) and it manifest due to inequality between coronary blood supply and myocardial demand. Myocardial damage due to free radicles is an imperative etiological mechanism that is linked with increased level of reactive oxygen species

and/or insufficient antioxidant defense system (Kharadi *et al*., 2016).

Over the years, herbs are used for combating several existing and newly spreading diseases. Medicinal plants/herbs have served as a constant source of medication with great efficacy and demand for the amelioration several diseases (Divya *et al*., 2017). One of the reported plants with numerous medicinal properties is *Jatropha tanjorensis* (Ellis and Saroja). *J. tanjorensis* belongs to the family Euphorbiaceae and is widely grown in southern Nigerian. *J. tanjorensis* has received a lot of attention due to its health benefit, availability and affordability (Omobuwajo *et al*., 2011). Its primary use is for fencing, and as medicine (Oboh and Masodje, 2009). This study seeks to evaluate the renal function at the time of isoprenaline induced myocardial infarction in albino rats and protective role of *J. tanjorensis* leave extract.

MATERIALS AND METHODS

Collection of Plant Leave: *J. tanjorensis* leaves were collected from the premises of Federal Polytechnic Nekede, Owerri and identified and authenticated by a Taxonomist in the Department of Plant Science and Biotechnology, Michael Okpara University of Agriculture, Umudike. The leave was washed with distilled water and dried to a constant weight for about seven days at room temperature. The dried leaves were pulverized into fine powder using Pulverizer (5126 TP) and preserved in cellophane bags until when used.

Phytochemical Screening: The qualitative phytochemical screening was carried out using the methods of Harborne (1973) and Trease and Evans (1989).

Experimental Animals: Seventy two (72) male albino rats of the Wistar strain aged 10 – 12 weeks and weighing 80 – 120 g and 18 mice weighing 16 – 22 g were procured from the Animal House of the Faculty of Veterinary Medicine, University of Nigeria, Nsukka. They were housed in standard transparent cages with wheat husk bedding, renewed every 24 hour. They were kept under controlled room temperature and humidity (25 to 29 °C; 30 to 70 %) in a 12 hour light-dark cycle. Animals were acclimatized for two weeks to laboratory conditions before starting the experiment. The animals were given standard rat feed (Vital Feeds with 18 % crude protein and 2800 kcal/kg metabolizable energy) and water *ad libitum*. Care of experimental animals was taken as per the guidelines given by NRC (2011) and the protocol was approved by Animal use Ethical Committee of Michael Okpara University of Agriculture Umudike with Ethical number BCM/EC/02/072.

Acute Toxicity (LD_{50}): The acute toxicity of the *J. tanjorensis* leaves was determined in two phases using Lorke's method (Lorke, 1983). Eighteen mice were used for the study. Phase one is divided into three groups of three mice per group and were orally administered the extract at the doses of 10, 100 and 1000 mg/kg respectively, and mortality was recorded at three hours intervals for 24 hours. After 24 hours, phase two was carried out with three groups of three mice per group and were orally administered the extract at the doses of 1600, 2900 and 5000 mg/kg respectively. Similarly, mortality was recorded at three hours intervals for 24 hours. LD_{50} was extrapolated from the regression plot of dosage against mortality.

Experimental Design: In a completely Randomized Design (CRD), the 72 male *Wistar* albino rats was allocated randomly into 6 treatment groups, replicated thrice with each replicate containing 4 rats. Myocardial infarction was induced in rats by giving Isoprenaline (ISO) (85 mg/kg) subcutaneously (s.c.) for two subsequent days, on day 26 and 27 at the interval of 24 hours. Distribution of study groups was as follow: Group 1 (normal control) rats were given distilled water orally for 28 days and normal saline s.c. on the day 26 and 27. Group 2 (negative control) rats were given distilled water orally for 28 days and ISO (85 mg/kg) s.c. on the day 26 and 27. Group 3 (positive control) rats were given carvedilol (2 mg/kg) orally for 28 days and ISO (85 mg/kg) s.c. on the day 26 and 27. Group 4 rats were given *J. tanjorensis* leaf extract 200 mg/kg orally for 28 days and ISO (85 mg/kg) s.c. on the day 26 and 27.

Group 5 rats were given *J. tanjorensis* leaf extract 400 mg/kg orally for 28 days and ISO (85 mg/kg) s.c. on the day 26 and 27. Group 6 rats were given *J. tanjorensis* leaf extract 600 mg/kg orally for 28 days and ISO (85 mg/kg) s.c. on the day 26 and 27. At end of the experiment, the rats were sacrificed and blood samples for biochemical assays were collected in plain tubes and allowed to clot before centrifugation and the sera were separated thereafter and used for the assays. The kidney was further harvested, fixed in 10 % buffered formalin and used for histopathological studies.

Histopathological studies

Tissue preparation: The method described by Palipoch and Punsawad (2013) with slight modification was used. The experimental animals were euthanized at the end of the study period. Tissue sections of the kidney from each group were collected for histopathological studies. The samples were fixed in 10 % phosphate buffered formalin for a minimum of 48 hours prior to tissue preparation. The tissues were subsequently trimmed, dehydrated in 4 grades of alcohol (70, 80, 90 % and absolute alcohol), cleared in 3 grades of xylene and embedded in molten wax. On solidifying, the tissue-containing wax blocks were cut into 5µm thick sections with a rotary microtome, floated in water bath and incubated at 60˚C for 30 minutes. The 5µm thick sectioned tissues were subsequently cleared in 3 grades of xylene and rehydrated in 3 grades of alcohol (90, 80 and 70 %). The sections were then stained with Hematoxylin for 15 minutes. Blueing was done with ammonium chloride. Differentiation was done with 1 % acid alcohol before counterstaining with Eosin. Permanent mounts were made on degreased glass slides using a DPX as mountant.

Slide Examination: The prepared slides were examined with a Motic Compound Light Microscope using x4, x10 and x40 objective lenses. The photomicrographs were taken using a Motic 9.0 Megapixels Microscope Camera at x100 and x400 magnifications.

Assay for Urea and Creatinine Level: Serum urea was estimated by a method described by Fawcett and Scott (1960) and creatinine was measured by an immunoturbimetric method as described by Hallan *et al.* (2003).

Statistical Analysis: Statistical analysis of the data was carried out with SPSS version 22.0 using one way analysis of variance (ANOVA). The results were reported as mean ± SEM. Significant difference was accepted at 95 % confidence level of probability ($p<0.05$).

RESULTS

Acute Toxicity: *J. tanjorensis* leaves extract was not toxic since no mortality was recorded at the highest dose of 5000 mg/kg though there was loss of appetite in mice administered 5000 mg/kg of *J. tanjorensis* leave extract.

The phytochemical screening of the *J. tanjorensis* leaves extract revealed the presence of alkaloid, tannin, flavonoid, saponin, phenolics terpenoid and steroid (Table 1).

Table 1: Phytochemicals present in methanol extract of *Jatropha tanjorensis* leaves

Phytochemicals	Inference
Phenolics	+
Flavonoid	++
Saponin	+
Alkaloid	++
Tannins	+
Terpenoid	+
Steroid	+

+ = present, ++ highly present

The body and kidney weights, and their relative ratios indicated that there were no significant ($p>0.05$) changes in the groups administered 200 and 400 mg/kg of extract compared to the 2 mg/kg carvedilol (positive) control for kidney to body ratio (Table 2). There was slight significant increase ($p<0.05$) in kidney to body ratio in the negative control.

There was significant decrease ($p<0.05$) in the urea level of the extract treated groups when compared with the negative control (85 mg/kg ISO only) group (Figure 1). There was significant increase ($p<0.05$) in the group treated with 600 mg/kg of the extract when compared with positive control.

Table 2: Body weight, Kidney weights and Kidney to body weight ratio in isoprenaline induced myocardial infarction in rats and protected methanol extract of *Jatropha tanjorensis*

Groups	Body Weight (BW) (g)	Kidney weight (KW) (g)	KW/BW (10^{-3})
Normal control	102.39 ± 2.43[a]	0.85 ± 0.03[a]	8.35 ± 0.24[b]
Negative control	122.81 ± 5.00[d]	1.29 ± 0.08[d]	10.50 ± 0.56[f]
Positive control	120.30 ± 9.26[c]	1.08 ± 0.13[b]	8.60 ± 0.50[c]
200 mg/kg extract	139.23 ± 6.22[f]	1.13 ± 0.05[c]	8.11 ± 0.26[a]
400 mg/kg extract	107.01 ± 4.63[b]	1.01 ± 0.06[b]	9.40 ± 0.39[d]
600 mg/kg extract	133.26 ± 7.36[e]	1.28 ± 0.09[d]	9.60 ± 0.22[e]

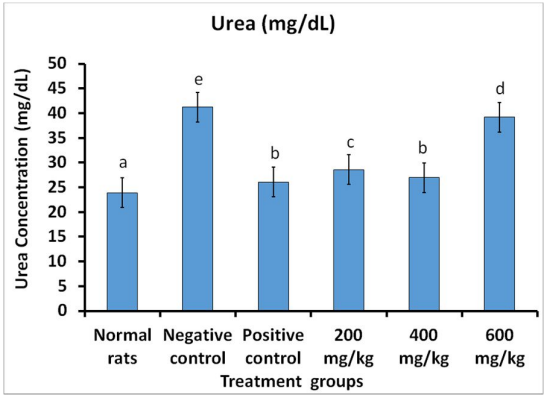

Figure 1: Urea level in isoprenaline induced renal injury followed myocardial infarction in rats and protected methanol extract of *Jatropha tanjorensis*

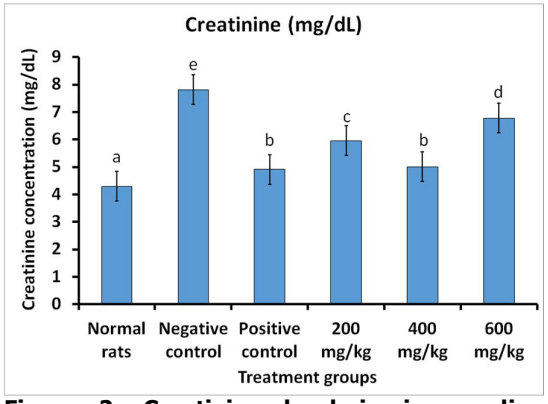

Figure 2: Creatinine level in isoprenaline induced renal injury followed myocardial infarction in rats and protected methanol extract of *Jatropha tanjorensis*

The group treated with 400 mg/kg extract had no significant difference ($p>0.05$) compared with the positive control groups.

There was significant decrease ($p<0.05$) in the creatinine level of the extract treated groups when compared with the negative control (85 mg/kg ISO only) group (Figure 2).

There was significant increase ($p<0.05$) in the group treated with 600 mg/kg of the extract when compared with positive control. The group treated with 400 mg/kg extract had no significant difference ($p>0.05$) when compared with the positive control groups.

The kidney histology of the rats from the groups administered 85 mg/kg ISO and 600 mg/kg of the extract showed a mild/moderate multifocal vacuolar degeneration of the renal tubular epithelial lining cells (Figures 3 and 4). The groups administered 200 and 400 mg/kg of the *J. tanjorensis* leaves extract as well as the positive and normal control showed the normal renal histomorphology for the laboratory rats (Figures 5 – 7).

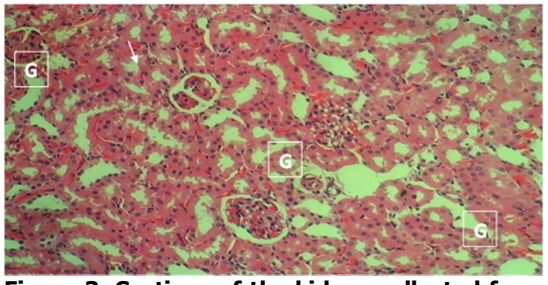

Figure 3: Sections of the kidney collected from the normal control group showed the normal renal histomorphology for laboratory rodents. Glomeruli (G); renal tubules (arrow). H&E x160

DISCUSSION

The phytochemical analysis of *J. tanjorensis* leaves revealed the presence of important bioactive compounds such alkaloid, tannin, flavonoid, saponin, phenolics terpenoid and steroid. The constituent phytochemicals of *J. tanjorensis* leaves could be responsible for the renoprotective effect of the leaf extracts on kidney function.

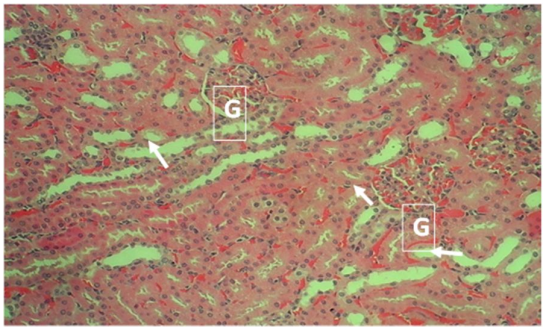

Figure 4: Sections of the kidney collected from rats in positive control group showed the normal renal histomorphology for laboratory rats. Glomerulus (G); Renal tubules (arrow), H&E x160

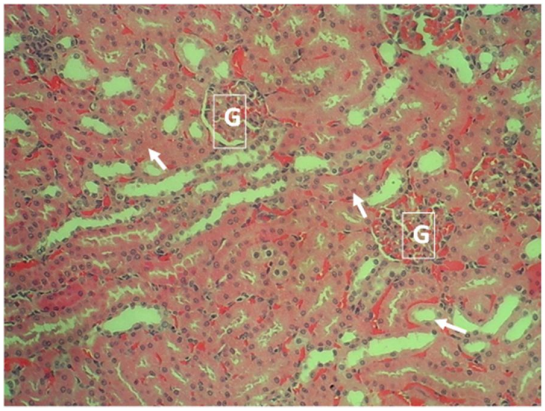

Figure 5: Sections of the kidney collected from rats in the group administered 200 mg/kg of the extract showed the normal renal histomorphology for laboratory rats. Glomerulus (G); Renal tubules (arrow), H&E x160

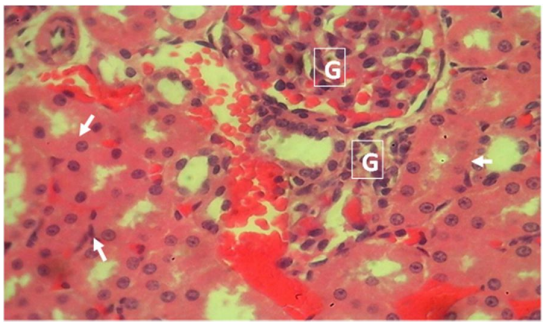

Figure 6: Sections of the kidney collected from rats in the group administered 400 mg/kg extract showed the normal renal histomorphology for laboratory rats. Glomerulus (G); Renal tubules (arrow), H&E x400

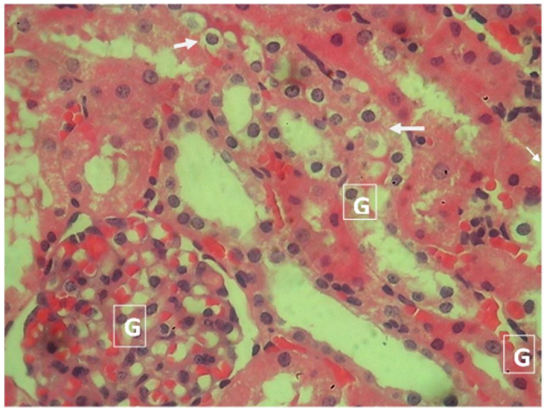

Figure 7: Sections of the kidney collected from rats in the group administered 600 mg/kg of the extract showed a mild multifocal vacuolar degeneration of the renal tubular epithelial lining cells. The affected cells appear swollen, with variably sized clear cytoplasmic vacuoles. Glomerulus (G). H&E x400

Saponins, terpenoid, flavonoids and tannins have been reported to have renoprotective properties (Chen *et al*., 2013; Dong *et al*., 2017; Vargas *et al*., 2018). Saponins are potent modulator of the renin-angiotensin-aldosterone system (RAAS), critical to kidney function. Saponin was reported to exert renoprotective effect via inhibition of intrarenal RAAS (Chen *et al*., 2013). Flavonoids could confer renoprotection against glomerulonephritis, diabetic nephropathy, and chemically induced kidney insufficiency (Vargas *et al*., 2018).

The methanol leaf extract of *J. tanjorensis* was not toxic to mice as no mortality even at a high dose of 5000 mg/kg of the extract was recorded. The use medicinal herbs in disease management have immense benefit. Plant medicine is relatively safe, more affordable and sometimes offers better therapeutic value than synthetic drugs. This is because human beings have co-evolved with plants over the past decades (Asuk *et al*., 2015). Igbinaduwa *et al*. (2011) reported no acute toxicity of methanolic extract of *J. tanjorensis* leave to Wistar albino mice at 8000 mg/kg body weight.

Cardiovascular diseases are globally known as the major cause of morbidity and mortality in the modern era (Syeda and Vasudeva, 2018).

Myocardial infarction is a situation whereby there is significant decrease or block in the blood oxygen supply to the part of the heart, leading to degeneration of a portion of the myocardium which triggers a caseade of cellular inflammatory and biochemical events, leading to the irreversible death (necrosis) of the muscle cells (Syeda and Vasudeva, 2018).

Myocardial infarction is one of the most common life threatening diseases that may lead to renal disorder via oxidative stress and inflammation (Tabl *et al*., 2019).

Hypothetically, when there is impairment in the hearts ability to pump efficiently, there will be congestion of blood which could lead to build up of pressure in the main vein connected to the kidney which consequently leads to congestion of blood in the kidney. A close pathophysiological interaction exists between kidney and the heart. It is worthy to remember that dysfunction of an organ may potentiate dysfunction of other organ under pathological condition (Přeček *et al*., 2018).

Lekston *et al*. (2009) reported that one of the risk factors of cardiovascular disease is impaired renal function. Chronic kidney disease is present in many patients with myocardial infarction with greater prevalence in those with severe symptoms (Hillege *et al*., 2006).

One of the renal function biomarkers is creatinine. The study revealed increase in the creatinine level in the group administered 85 mg/kg of isoprenaline only. The positive correlation between renal dysfunction and myocardial infarction which could result to increase mortality in acute myocardial infarction patients as reported by Granger *et al*. (2003) is validated in this study.

The result of the creatinine and urea level revealed significant decrease in the group administered 400 mg/kg of the extract as compared to the group administered 85 mg/kg of isoprenaline only (negative control). Although increase in blood urea nitrogen (BUN) may be as a result of neurohormonal activation and protein catabolism (Damman *et al*., 2012). BUN is an important predictor of morbidity and mortality in myocardial infarction and heart failure (Schrier and Bansal, 2008).

Marenzi *et al*. (2015) reported potential impaired renal function following acute coronary syndrome.

The heart is scheduled with the responsibility of pumping oxygenated blood to all parts of the body including the kidney, while the kidney removes waste products and excess water in the blood. In ischemic heart disease, there is limited supply of oxygenated blood to the kidney which alters the functionality of the kidney leading to elevation of kidney function parameters (Lekston *et al.*, 2009). This could be the mechanism of the elevated urea and creatinine level seen in the isoprenaline induced myocardial infarction untreated rats (negative control).

The kidney histology of 600 mg/kg extract and negative control groups showed mild multifocal vacuole degeneration of the renal tubular epithelial lining cells which mean that there is slight renal damage in both groups. Oyewole *et al.* (2012) reported that the prolong administration of *J. tanjorensis* leaf extract disrupted protein metabolism function of the liver and also interfered negatively with the filtration capacity of the kidney which might result in renal and hepatic dysfunction.

The 400 mg/kg and 200 mg/kg of the extract as well as the positive control group showed no renotoxicity. Oladele *et al.* (2020) reported that *J. tanjorensis* leaf extract at 500 mg/kg dose protected renal functionality. The protectective effect of *J. tanjorensis* leave could be as a result of its constituent phytochemicals such as saponin (Chen *et al.*, 2013), flavonoid (Vargas *et al*., 2018) and terpernoid (Dong *et al*., 2017). It is worthy to know that when treating cardiovascular disease, it is important to take into consideration this cardio-renal relationship.

Conclusion: The present study showed that isoprenaline which is an agent for the induction of myocardial infarction altered renal function integrity as proven in the histopathological study as well as elevated serum urea and creatinine levels, but the methanol leaf extract of *J. tanjorensis* at 400 mg/kg dose prevented renal dysfunction induced by isoprenaline.

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