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Modulatory Effect of *Jatropha tanjorensis* Ethanol Leaf Extract and Vitamin E on Some Reproductive Hormone in Lead-Treated Male Wistar Rats

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Abstract:- Heavy metals such as Lead (Pb) in the environment could pose serious reproductive health issues resulting in infertility. *Jatropha tanjorensis* (JT) from previous studies has been proven to enhance reproductive parameters. This study examined the effects of *Jatropha tanjorensis* alongside vitamin E on some reproductive parameters in male rats. 40 rats male rats were assigned into 8 groups (n=5): Control, Lead treated group, low dose JT, high dose JT, Vitamin E control, lead + low dose JT, lead + high dose JT, lead + vitamin E groups. Administration was done for 14 days. Mean testosterone level was seen to significantly increase ($p<0.05$) in all treated groups and vitamin E group in combination with lead when compared to normal control group and Pb control. FSH levels was seen to increase significantly ($p<0.05$) in all JT treated groups and vitamin E treated group when compared to Pb control but no significant difference was observed when all treated groups was compared to normal control. Also from the study, LH level increased significantly ($p<0.05$) in high dose JT when compared with every other treated groups. JT and vitamin E administration was able to reduce the negative effect exerted by lead on the various reproductive parameters analyzed.

Keywords:- *Jatropha tanjorensis, Lead, Vitamin E, Hormones, Oxidative Stress, Testes, Wistar Rats.*

I. INTRODUCTION

The inability to conceive after one year of unprotected intercourse is referred to as infertility, which has been found out to affect 15% of couples worldwide approximately [1]. A combination of male and female infertility factors account for 30% of these cases while male infertility alone results to about 20% [2], [3]. Reproduction is a biological process that ensures the continuity of life. If reproduction in active male or female of reproductive age fails to occur, infertility ensues. Infertility has proven in recent times to cause serious health challenges across the globe. Reproductive hormones are extremely important to the process of fertility. Any disruption in the quantity or quality of these reproductive hormones may result in serious pathological conditions that may lead to infertility.

One of the heavy metal present in the environment is lead, which is mostly used in the production of car batteries, paints, ceramics, hair dyes, water pipes, cosmetics as well as in the manufacture of corrosion and acid resistant material by the building industry [4].High lead exposure can result due to consumption of vegetables, fruits and grains on soils with high lead content [5]. Absorption of lead into the human system can be either through food or weather [6], [7]. Body functions can be altered arising from exposure even to little amount of lead [8], [9]. According to [10], the main target of lead harmful effect in male reproductive system is situated at the pituitary-testicular axis which ensued in morphological alterations and decrease sperm count resulting in infertility.

The antioxidant activities of Vitamin E (a lipid-soluble antioxidant) have been reported over time. Vitamin E plays a role in controlling the synthesis of testosterone [11]. Vitamin E is recognized for improving erectile dysfunction associated with aging [12]. The main liposoluble antioxidant in humans is Vitamin E, which act by disintegrating the propagation chains which arise during lipid peroxidation of polyunsaturated fatty acids [13]. Vitamin E scavenges peroxyl radicals (RO2) produced during lipid peroxidation, leading to a tocopheroxylradical. Reduced glutathione, vitamin C and ubiquinol regenerate a-tocopherol [14], [15], [16]. According to [17] and [18], vitamin E expresses its antioxidant properties in lipoproteins and membranes respectively.

Most plants, apart from serving as food, have been reported to display some medicinal properties [19], [20]. *Jatropha tanjorensis* (JT) belongs to the family Euphorbiaceae [21], [22]. JT is a common field crop in the rain forest zones of West Africa [23]. In Nigeria, it is mostly referred to as “hospital too far”, “catholic vegetable” [24], the Yoruba’s refer to it as "Iyana-ipaja," and "Lapalapa" [25]. The leaves of JT are consumed locally as vegetable in most parts of Nigeria,

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and also employed in the treatment of diabetes mellitus believing it possesses anti-hyperglycemic properties [26].

In Nigeria and in many parts of the world, locals use traditional herbal medicines, since they can easily afford it to treat infertility and manage their reproductive health. *Jatropha tanjorensis* is one of such plants used by males and females of child bearing age for treating reproductive problems such as infertility. But there is paucity of literature on its effects on lead-acetate-induced testicular dysfunction. Thus, the aim of this study was to investigate the effect of ethanolic extract of *Jatropha tanjorensis* is on lead acetate-induced testicular dysfunction in Wistar rats.

II. MATERIALS AND METHODS

A. Purchase of Animals

Authority to conduct the study was obtained from Animal Research Ethics committee of the Faculty of Basic medical Sciences, University of Uyo. Upon approval of the study, forty male Wistar rats (weighing 150-170g) were purchased from the Faculty of Basic Medicals Animal House and Kept in spacious wooden cages. They were the allowed to acclimatize for on e week. Rat feed and water were freely assessable throughout the period of the research and they were exposed to 12/12-h light/dark cycle. They were handled in line with the guidelines prescribed by the ethical committee in regards to research animals.

B. Plant Material and Preparation of Extract

The leaves of *Jatropha tanjorensis* were obtained from the research farm of the Department of Natural Medicine and Pharmacognosy, Faculty of Pharmacy, University of Uyo. The leaf was identified by a taxonomist in the department of Botany and Ecological studies, University of Uyo and a voucher number was given. The samples were then deposited in the Herbarium and a voucher number [UUPH31(F)] was assigned. A method previously described was employed in the extract preparation [27]. The fresh leaf of the plant weighing 1kg was pulverized and macerated in ethanol (60%) for 72 hours, and the mixture was stirred every 24 hours, after which it was filtered and the filtrate concentrated to dryness in water bath at 45^{o}. The concentrated yield of the extract was then being preserved in the refrigerator at -4^{o} until when the research commenced.

C. Experimental Design and Study Protocol

Forty (40) male albino Wistar rats were used in this study. They were randomly distributed into eight groups of five rats each. The rats were fed graded doses of ethanol extract of *Jatropha tanjorensis*through orogastric gavage method for 14 days.

The rats were randomly divided into eight groups (n=5) and treatment with Pb, vitamin E and ethanolic extract was carried out for 2weeks (Table 1). Pb was administered intraperitoneally (i.p.) once daily for two weeks with dose being selected from previous study [28] due to the fact that this dose resulted in male reproductive impairment. We opted also for the intraperitoneal (i.p) route as this will prevent intestinal absorptions thus facilitating distribution of Pb to the tissues. Vitamin E was administered orally once daily for two weeks using orogastric tube with dose selected from a previous study [29]. Ethanolic leaf extract of JT was administered to the rats once daily via the oral route with its dosage base on the result of the acute toxicity study. All groups were allowed to feed freely without any water restriction as well in the entire duration of the research. At the end of the two weeks, the animals were sacrificed using ketamine as anaesthesia (60 mg/kg body weight) and blood samples were collected for laboratory analyses.

D. Collection of Blood Samples

On the 14th day, administration of *Jatropha tanjorensis* extract was stopped, and the rats were fasted for 24 hours. After which five animals were selected from each group and euthanized intraperitoneally with 1.5ml ketamine according to procedures acceptable by the Faculty of Basic Medical Sciences, University of Uyo.

E. Determination of Serum Reproductive Hormone Level

The collected blood samples were put into plain sample bottles and kept for 2 h undisturbed. The samples were thereafter be centrifuged for 15 min obtain sera. The sera obtained was now used to ascertain testosterone, FSH, and LH levels using ELISA kits (BioAssay Systems, Hayward, CA, USA) in accordance with the manufacturer's protocol.

F. Statistical Analysis

The datas are expressed as Mean ±Standard Error of Mean (SEM). Furthermore, the differences between mean values were analyzed using analysis of Variance (ANOVA), which was also followed by Tukey's post-hoc test for pairwise comparisons. Values of $P<0.05$ were considered statistically significant. Graph Pad Prism 7.0 software (Graph Pad Inc., USA) was used for statistical analysis.

III. RESULTS

A. Effect of Jatropha tanjorensis Ethanol Leave Extract on Sex Hormone Following Administration of Jatropha tanjorensis, Lead acetate and Vitamin E in male Wister rats.

- *Testosterone*

The mean values were: 0.86 ± 0.01, 0.51 ± 0.01, 1.57 ± 0.33, 0.92 ± 0.01, 0.88 ± 0.01, 0.59 ± 0.02, 2.83 ± 0.04, 1.66 ± 0.04 for normal control (NC), lead control (Pb_c), low dose *Jatropha tanjorensis* (JT10), high dose *Jatropha tanjorensis* (JT30), vitamin E control (VE_c), low dose *Jatropha tanjorensis* + lead (JT10+Pb), high dose *Jatropha tanjorensis*(JT30+Pb), and vitamin E + lead (VE+Pb) groups

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respectively. Mean testosterone level was seen to significantly increase (P <0.05) in JT10, (JT30+Pb), and (VE+Pb) groups respectively when compared to rats in (NC) group. But was significantly lower (P <0.05) in (Pb_c), and (JT10+Pb) groups when compared to (NC) group. However, little or no significant difference was observed in JT30 and (VE_c) groups when compared to (NC) group. A significant increase (P <0.05) in mean testosterone level was observed in rats in (JT10), (JT30), (VE_c), (JT10+Pb), and (VE+Pb) groups respectively when compared to (Pb_c) group. There was a significant increase in testosterone level in (JT30+Pb) group when compared to (JT10) group, but was seen to significantly decrease (P <0.05) in (JT30), and (JT10+Pb) groups when compared to rats in (JT10) group. Serum testosterone level was seen to significantly increase (P <0.05) in (JT30+Pb), and (VE+Pb) groups when compared to (JT30) group, but was significantly lower (P <0.05) in (JT10+Pb) group when compared to (JT30) group. However, little or no significant difference was seen in (VE_c) group when compared to (JT30) group. Testosterone level was significantly higher (P <0.05) in (JT30+Pb), and (VE+Pb) groups when compared to (VE_c) group, but was significantly lower (P <0.05) in (JT10+Pb) group when compared to (VE_c) group. There was a significant increase (P <0.05) in (JT30+Pb) and (VE+Pb) groups when compared to (JT10+Pb) group. Mean testosterone level was seen to significantly decrease (P <0.05) in (VE+Pb) group when compared to (JT30+Pb) group. (Figure1).

Table 1 Experimental Design and Animal Groups Treated with Lead Acetate, Hydroethanolic Leaf Ectract of *Jatropha tanjorensis* and Vitamin E.

S/N	Group	Treatment
1	Control (NC)	Normal saline
2	Lead acetate control (Pb)	Lead (20 mg/kg b.w.i.p.)
3	JT10 (LD)	Ethanolic extract of *J. tanjorensis*(Dose were based on LD50) 10% of(1118.03)= 111.8mg/kg
4	JT 30 (HD)	30% Ethanolic extract of *Jatropha* (Based on LD50)30% of (1118.03)= 335.4mg/kg
5	Vit E Control	100mg /kg of vitamin E
6.	Pb+LD	Lead + Low dose of the extract (111.8mg/kg +20 mg/kg)
7.	Pb+HD	Lead + High dose of the extract (335.4mg/kg + 20 mg/kg)
8.	Pb+Vit E	Lead (20 mg/kg) + 100mg /kg of vitamin E

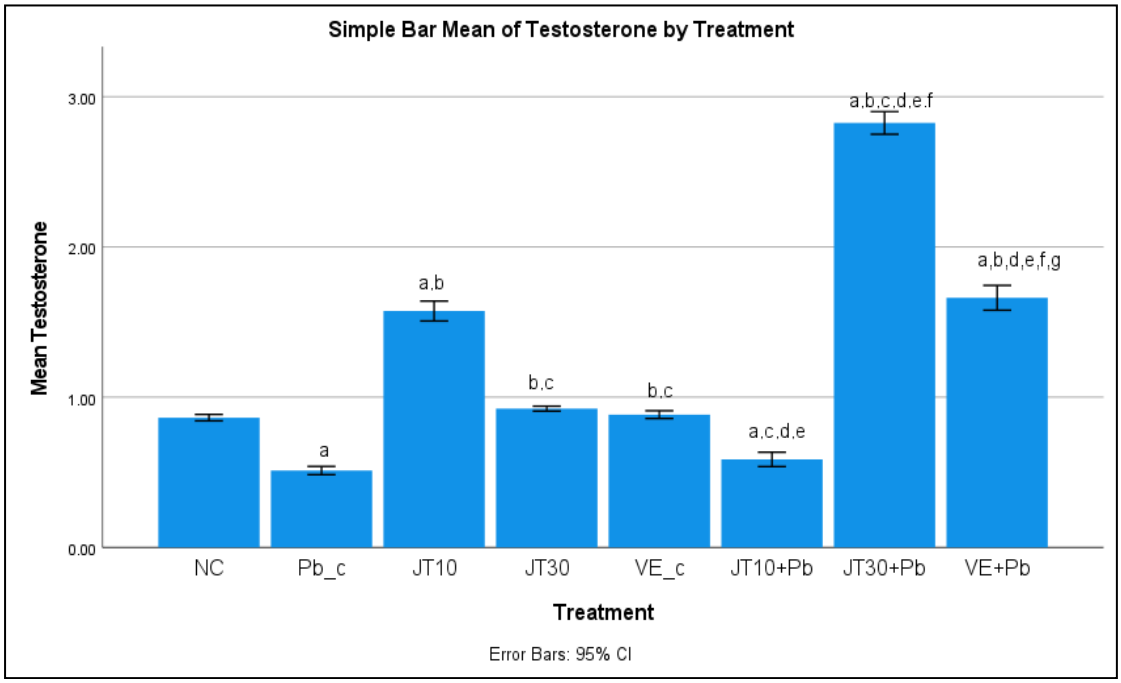

Fig 1: Testosterone Hormone Levels in Male Wistar Rats Treated with *Jatropha tanjorensis*leaf Extract, Lead (Pb), and Vitamin E.*a = Comparing with control group, b = Comparing with JT10, c= Comparing with JT30, d= Comparing with VE_c, f= Comparing with JT10+Pb,*g= *Comparing with JT30+Pb*

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B. Effect of Jatropha tanjorensis Ethanol Leave Extract and Vitamin E on Gonadotropic Hormones after administration

➢ *Follicle stimulating hormone (FSH)*

The average values were: 0.79 ± 0.02 (NC), 0.56 ± 0.01 (Pb_c), 0.83 ± 0.01 (JT10), 0.88 ± 0.02 (JT30), 0.83± 0.01 (VE_c), 0.75 ± 0.02 (JT10+Pb), 1.51 ± 0.04 (JT30+Pb), 0.86± 0.03 (VE+Pb). FSH level was significantly higher (P <0.05) in (JT30+Pb) group when compared to (NC) group, but was significantly lower (P <0.05) in (Pb_c) group when compared to (NC) group. There was significant increase FSH level in (JT10), (JT30), (VE_c), (JT10+Pb), (JT30+Pb) and (VE+Pb) groups when compared to (Pb_c). Serum FSH level was significantly higher (P <0.05) in (JT30+Pb) group, however, little or no significant difference was seen in (JT30), (VE_c), (JT10+Pb), and (VE+Pb) groups when compared to (JT10). FSH level was seen to significantly increase (P <0.05) in (JT30+Pb) when compared to (JT30), but was significantly lower (P <0.05) in (JT10+Pb) group when compared to (JT30) group. Mean FSH level was significantly higher (P <0.05) in (JT30+Pb) group, but little or no significant difference was seen in (JT10+Pb), and (VE+Pb) groups when compared to (VE_c) group. There was a significant increase (P <0.05) in (JT30+Pb) and (VE+Pb) groups when compared to (JT10+Pb) group. FSH level was significantly lower (P <0.05) in (JT30+Pb) when compared to (JT30+Pb) group (figure 2).

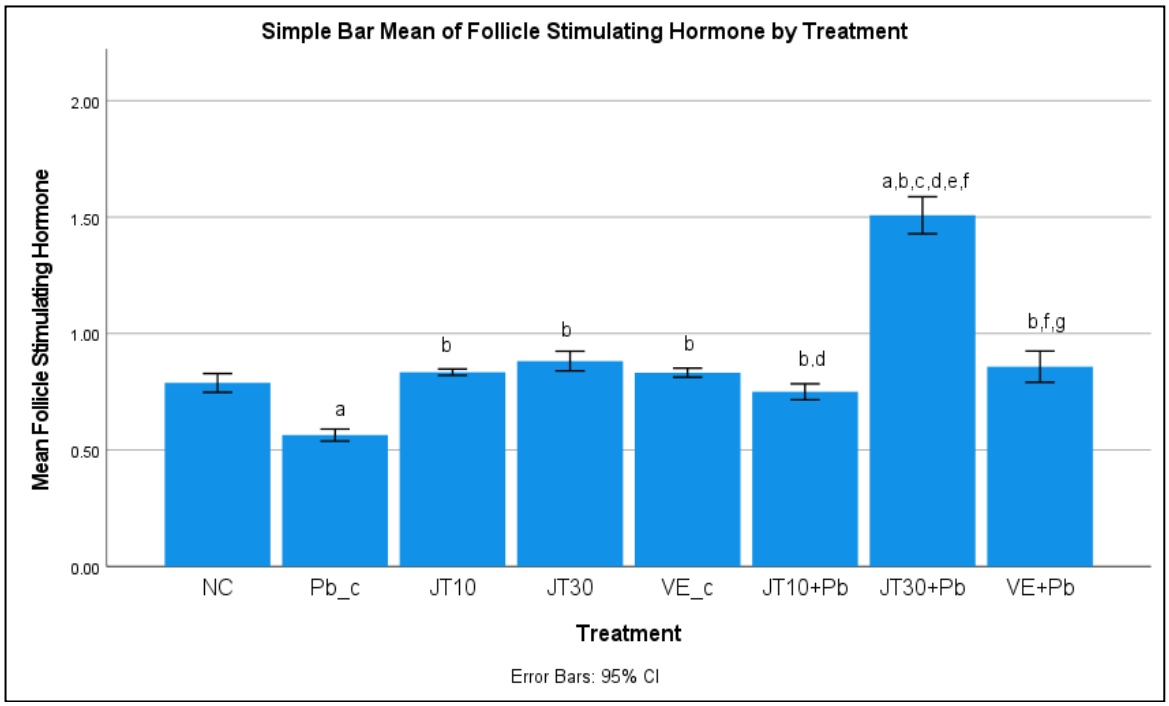

Fig 2: Effect of *Jatropha tanjorensis* Leaf Extract, Lead and Vitamin E on FSH Concentration of Male Wistar Rats.

➢ *Leuteinizing Hormone (LH)*

The mean values were: 1.94 ± 0.01, 1.26 ± 0.01, 1.73 ± 0.01, 2.40 ± 0.03, 1.78 ± 0.01, 1.52 ± 0.04, 1.80 ± 0.03, 1.77 ± 0.06 for normal control (NC), lead control (Pb_c), low dose *Jatropha tanjorensis* (JT10), high dose *Jatropha tanjorensis* (JT30), vitamin E control (VE_c), low dose *Jatropha tanjorensis*+ lead (JT10+Pb), high dose *Jatropha tanjorensi s* (JT30+Pb), and vitamin E + lead (VE+Pb) groups respectively. Mean LH level was significantly increased (P <0.05) in (JT30) group when compared to (NC), but was significantly decreased (P <0.05) in (Pb_c), (JT10), (JT10+Pb) groups when compared to (NC). There was a significant increase (P <0.05) in (JT10), (JT30), (VE_c), (JT10+Pb), and (VE+Pb) groups when compared to (Pb_c) group. Serum LH level was significantly higher (P <0.05) in (JT30), (JT30+Pb), and (VE+Pb) groups when compared to (JT10) group, but was significantly lower (P <0.05) in (JT10+Pb) group when compared to (JT10) group. A significant decrease (P <0.05) in LH level was observed in (VE_c), (JT10+Pb), (JT30+Pb), and (VE+Pb) groups when compared to (JT30) group. Likewise, LH level was significantly lower (P <0.05) in (JT10+Pb) group when compared to (VE_c) group, however, little or no significant difference was seen in (JT30+Pb), and (VE+Pb) groups when compared to (VE_c) group. Mean level of LH was seen to significantly increase (P <0.05) in (JT30+Pb), and (VE+Pb) groups when compared to (JT10+Pb) (Figure 3).

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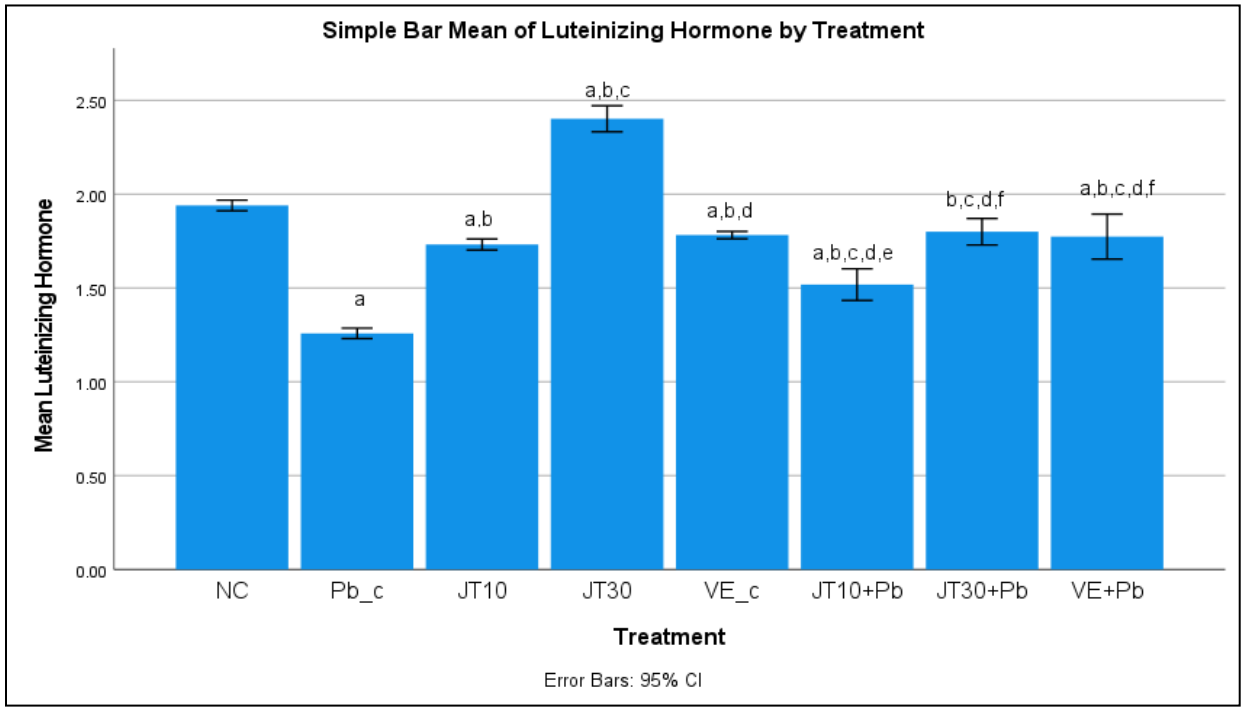

Fig 3: Effect of *Jatropha tanjorensis*leaf Extract, Lead and Vitamin E on LH Concentration of Male Wistar Rats.

IV. DISCUSSIONS

In this study, the effect of *Jatropha tanjorensis* and vitamin E was investigated on lead-induced oxidative stress on some reproductive parameters. Lead has been proven by various researches to cause most male infertility by either causing adverse reaction in the pituitary-testicular axis leading to alterations that might cause infertility [30] or by decreasing the level of androgens [31] or by also inhibiting the activities of steroidogenic enzymes [32]. *Jatropha tanjorensis* is a versatile plant that is grown for food and medicinal purposes. Almost every component of the plant has different nutritional and therapeutic properties. Depending on which portion of the plant is used, it has different benefits [33]. The antioxidant properties of Vitamin E has been widely reported with its antioxidant protective effect seen on testis exposed to L-thyroxine [34], fluoxetine [35], para-nonylphenol [36], cadmium [37], and lead-acetate [28] has been documented.

Testosterone which is secreted by the Leydig cells is a vital requirement for spermatogenesis, thus reduction in the quantity of testosterone could be an indicator of chemical toxicity in male reproduction [38]. From the study, serum testosterone level was at its lowest in the group treated with lead alone when compared with every other group, thus agreeing with the above research. The low-dose *Jatropha tanjorensis* group exhibited a significant increase in mean testosterone levels when compared to the normal control group and the lead-treated group. Likewise, the high-dose *Jatropha tanjorensis* group in combination with lead showed a significant increase in mean testosterone levels when compared with the low-dose *Jatropha tanjorensis* group. These results indicate that the effect of *Jatropha tanjorensis* extract and lead on testosterone levels is dose-dependent, with different responses observed in low-dose and high-dose groups. This position is in agreement with the conclusion of the research carried out by Osuchukwu *et al.* [39] who deduced that "*Jatropha tanjorensis* may have the potential of enhancing spermatogenesis when consumed for a short period of time", also, "the presence of some phytoconstituents such as flavonoids which can protect against cellular damage via inhibition of membrane lipid peroxidation and alteration in critical tissue biomolecules" as reported by Oladele *et al* [40] could be responsible for the increase despite the presence of lead. Additionally, the administration of Vitamin E had little or no impact on testosterone level as was seen in this study. This is in concordance with previous research by Udefa *et al* [29]. However, from the study, a significant increase in serum testosterone level was observed in the group treated with vitamin in combination with lead when compared to vitamin E control group. This could be as a result of the ameliorative effect presented by exogenous administration of vitamin E which also triggers a production of more endogenous antioxidant in response to a stressed condition. This agrees with previous work by Melcova *et al*, [41] and Hidayatik *et al*, [42].

The development, growth, pubertal maturation and reproductive process of the human body is regulated by Follicle stimulating hormone. The maturation of germ cells in both male and females is triggered by FSH. In males, androgen-binding protein (ABP) secretion is influenced by the

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FSH produced by the sertolic cells and controlled by a negative feedback mechanism embedded in the anterior pituitary. Specifically, activation of sertolic cell by FSH sustains spermatogenesis and stimulates inhibin-B secretion [43]. Lead has been proven by various research to be behind most male infertility by either causing adverse reaction in the pituitary-testicular axis leading to alterations that might cause infertility [30], or by decreasing the level of androgens [31], or by also inhibiting the activities of steriodogenic enzymes [32], thus, affirming the significant decrease observed in mean FSH hormone level in the lead control group. From the study, little or no significant difference was observe in the low dose *Jatropha tanjorensis* group, high *Jatropha tanjorensis* group and vitamin E control group when compared to normal control group, this however is in contrast with previous works by Akighir *et al*. [44] which states that the secondary metabolites, phytol and lupeol present in the leaf extract of *Jatropha tanjorensis* were responsible for the decrease in some of the gonadal hormones such as FSH. Serum level of FSH was seen to significantly increase in high *Jatropha tanjorensis* group in combination with lead when compared with low dose *Jatropha tanjorensis* group plus lead and vitamin E plus lead groups. This could be as a result of the presence of some phytochemical constituents such as flavonoid, alkaloid, saponins, etc which have been reported to enhance protection against cellular damage via inhibition of membrane lipid peroxidation and alteration in critical tissue biomolecules [40]. From the study little or no significant difference was observed in vitamin E plus lead group when compared to normal control group but was significantly higher when compared to the group that was administered lead alone. Vitamin E has been known to have antioxidant protective effect against toxins, such as L-thyroxine as reported by [34].Thus, despite the presence of lead, the vitamin E was able to maintain FSH level as that of normal control group due to its antioxidant activities.

Luteinizing hormone is also one of the gonadotropic hormones produced in the anterior pituitary gland. LH stimulates the Leydig cells to secrete testosterone. Furthermore, the quantity of testosterone secreted increases approximately in direct proportion to the amount of LH available, therefore LH acts through a feedback mechanism to maintain testosterone biosynthesis [46]. Lead toxicity in rats has been reported to cause a deformity in the pituitary gland and hypothalamus thus affecting LH secretion. It has been reported to directly damage the testis resulting in a low testosterone secretion from the Leydig cells [47], [48]. This was also the case in this study as a significant decrease in LH level was observed in lead control group when compared to normal control and every other treated groups. This study revealed a significant increase in mean luteinizing hormone level in high dose *Jatropha tanjorensis* extract (JT30) group when compared to normal control, lead control, low dose *Jatropha tanjorensis* extract (JT10), Vitamin E control (VE-c), low dose *Jatropha tanjorensis* extract + lead (JT10+Pb) group, high dose *Jatropha tanjorensis* extract + lead (JT10+Pb) group and Vitamin E + lead (VE+Pb) groups. This agrees with findings of Osuchukwu *et al.* [39] who deduced that *Jatropha tanjorensis* may have the potential of enhancing spermatogenesis when consumed for a short period of time, thus was dose dependent. A significant increase in mean LH level was also seen in high dose *Jatropha tanjorensis* extract + lead (JT10+Pb) group and Vitamin E + lead (VE+Pb) groups when compared to lead control group (Pb_c) respectively. This could be due to the presence of flavonoids and polyphenolic compounds in the plant extract which might have assisted in arresting the free radicals causing oxidative stress; this is consistent with the findings of Afsar *et al*. [48]. Vitamin E on the other hand is a known antioxidant [35], hence the significant increase observed above.

V. CONCLUSION

This study suggests that the leaf extract of *Jatropha tanjorensis* and vitamin E had modulatory effect against lead-induced testicular toxicity. The extract could possess this ability due to its rich supply of antioxidants such as tannins, flavonoids, and saponins. Vitamin E on the other hand is a known antioxidant which must have been behind some of the improvement seen in the study.

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