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EVALUATION OF *Abrus precatorius* ON REPRODUCTIVE FUNCTION OF MALE WISTAR RAT.

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ABSTRACT

Background: In recent times, attention has been shifted from synthetic drugs to the use of medicinal plants and this has greatly improved reproductive functions. *Abrus precatorious* plant has different parts which are used as diverse sources of naturally occurring chemicals that have a variety of therapeutic effects on the body. However, in this present study, we consolidated the reproductive property of *Abrus precatorius* in paroxetine-induced male reproductive dysfunction. **Methods:** Twenty four (24) male rats were divided into four (4) groups each containing six animals was used for this experiment following paroxetine-induced erectile dysfunction. Group one, received 1ml of distilled water, Group two received 20mg/kg of Paroxetine and 50mg/kg of sildenafil, Group three received 20mg/kg of Paroxetine and 300mg/kg of A. *precatorius* extract, Group four received 20mg/kg of Paroxetine and 900mg/kg of A. *precatorius* extract for 21 days. **Results:** Results from the studies reveal that there was significant decrease in the sperm motility of the rats administered with *Abrus precatorius* when compared with control. Interestingly, the high dose extract increased the serum testosterone levels significantly while the low dose extract significantly reduce the level of testosterone when compared with the control. Histological examination of the testes of treated rats displayed noticeable atrophy, which was characterized by disruption of the seminiferous epithelium and reduction in cell population of the Leydig cells. **Conclusion:** It appears that very high dose of *Abrus precatorius* may induce infertility by increasing serum testosterone levels.

Keywords: Abrus precatorius, Fertility, Sildenafil, paroxetine, Testosterone, reproduction
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INTRODUCTION

The ancient literature of indigenous systems of medicine has noted that plant preparations have a significant role in fertility management. Over the new era, researchers became interested in the function of these native plant compounds in the induction of male and female fertility in experimental animals (Bhakta and Das 2020).

The use of medicinal plants is on the increase as a result of the move away of focus from synthetic drugs to traditional medicine (Zhang *et al*., 2015). The majority of conventional drugs are based on herbs that are utilized by about 80% of the global population (Bhakta and Das 2020). One of the uses of medicinal plants is to improve reproductive functions. In general, while other herbal remedies are used to treat different reproductive issues, natural aphrodisiacs are consumed to improve sexual performance, such as erectile dysfunction, oligospermia, azoospermia, hormonal imbalance, etc. (Ogbuehi et al., 2015).

Abrus precatorius has been widely used in various traditional systems for its potential effects on reproductive health (Zhang *et al*., 2015). It contains several bioactive compounds, including abrin, precatorine, abraline, abrectine, abrusogenin, and flavonoids such as kaempferol, quercetin, and isorhamnetin. These compounds exhibit various pharmacological properties and may contribute to the effects on fertility (Anant and Maitreyi, 2012; Sharma *et al*.2020). Several studies have investigated the effects of Abrus precatorius on sperm parameters. Singh *et al.* (2018) demonstrated that Abrus precatorius extract significantly improved sperm count, motility, and morphology in male rats. Because of the antioxidant property of *A. precatorius*, it has the potential to mitigate oxidative stress-induced damage to sperm, since oxidative stress is known to be a contributing factor to male infertility (Mishra *et al.* 2017).

As part of its role in reproductive health, it has been found to modulate testosterone levels by increasing serum testosterone levels in male rats suggesting its potential role in improving reproductive functions (Kumar *et al.* 2019). This underpins the potential effects of *A.precatorius* in regulating hormonal imbalances associated with female infertility (Pardhi *et al.* 2019).

According to Nemeroff (1993), paroxetine is a representative SSRI chemical that has been widely utilized in clinical practice. It has also been documented to cause sexual dysfunction, like other compounds in its class (Montejo *et al*.,). It has the ability to prevent the production of nitric oxide (NO), a crucial mediator of smooth muscle relaxation and penile erection, both in vitro and in vivo (Finkel *et al*., 1996). When given either chronically or suddenly to rats, paroxetine reduces their ability to erect after being stimulated by the carvernosal nerve (Kim *et al*., 1991; Finkel *et al*., 1996).

A powerful and specific type 5 phosphodiesterase (PDE5) inhibitor, sidenafil (Viagra), improves the relaxation of the human corpus carvernosum brought on by NO as well as the penile erection in rats when NO is administered (Saenz, 2001; Angulo, 2001).

This study intends to investigate and consolidate reproductive property of *Abrus precatorius* in paroxetine-induced male reproductive dysfunction in male Wistar rat.

MATERIALS AND METHODS

ANIMALS

The study was carried out on twenty-four male wistar rats weighing between 180g-200g after it has been acclimatized for two (2) weeks under normal temperature and unrestricted access to water, food and ventilation. The rats were bred and housed in the Faculty of Basic Medical Sciences Animal house, University of Ilorin, Ilorin, Nigeria. The animal house was well ventilated and the normal day light cycle was maintained.

PLANTS MATERIALS AND EXTRACT PREPARATION

Abrus precatorius was obtained from Dongari Etile in the Asa local government area of Kwara state, Nigeria, and was authenticated in the Botany department (herbarium), University of Ilorin. The leave of A*. precatorius* was air-dried for three weeks and ground into powdered form (66g) for extract preparation. Powdered A. *precatorius* was soaked in distilled water for 48 hours and thereafter filtered. The filtrate was evaporated to dryness using a hot plate set at 50-degree margin. The weight of the extract after evaporation to dryness was 31.9g.

ANIMAL GROUPING AND INDUCTION OF SEXUAL DYSFUNCTION

The twenty four (24) experimental animals (Male Wistar rats) were randomly divided

into four groups (6 per cage). Group one (1) served as the control, while group two to four (2-4) were induced with sexual dysfunction using a daily oral administration of 20mg/kg body weight of paroxetine (Saraswathi, 2020) for three weeks (21days). Assessment of sexual behaviour was carried out on the 14th and 19th days respectively. The male rats were subjected to healthy female rats in order to achieve this, and mating behaviour was assessed.

ASSESSMENT OF MATING BEHAVIOUR PARAMETERS IN RATS

Mating test was assessed in all the groups on the 14th day of induction between the hours of 11pm to 1am and observed for 30minutes. Female albino rats were bought and introduced into each of the group (four female rats per group) and the following mating behaviour were observed: Mount frequency (MF), Intromission frequency (IF), Ejaculation frequency (EF) and Post-ejaculatory interval (PEI). Some of the animals from groups 2-4 displayed all these sexual behaviour on day 14 while some do not at all. By day 19th the test was repeated again using the same procedure and all the animals from groups 2-4 that displayed none of the sexual behaviour listed above were considered to have erectile dysfunction and thereby included in the study. Also there were physical manifestations as the testes of animals in groups 2-4 become smaller when compared to the period of acclimatization. Male rats were often classified as sexually impaired if they had a minimum 25% drop in MF, IF, and EF as well as a minimum 25% increase in mount latency (ML), intromission latency (IL), erectile latency (EL), and PEI (Malviya et al., 2011).

EXTRACT ADMINISTRATION

Twenty four (24) male albino rats were divided into four groups of 6 rats each and treated for 3 weeks (21 days) as follows: Group 1 (Control) were fed with normal animal diet and water throughout the experimental period, Group 2 rats received 20mg/kg of Paroxetine (for three weeks) plus 50mg/kg of sildernafil (Viagra), Group 3 rats received 20mg/kg of Paroxetine (for three weeks) plus 300mg/kg of A. *precatorius* extract (low dose) for three weeks (21days) via oral route, Group 4 rats received 20mg/kg of Paroxetine (for three weeks) plus 900mg/kg of A. *precatorius* extract (high dose) for three weeks (21days) via the oral route.

DETERMINATION OF SERUM TESTOSTERONE

At the end of the experiment, rats were dissected and sacrificed following ketamine anesthesia. Blood samples were collected in a well labeled heparinized bottle and immediately centrifuged. Serum was stored for further assay. The quantitative determination of Total Testosterone concentration in Serum by a Microplate Enzyme Immunoassay was performed using Monobind assay kit (Lake Forest, USA).

SPERM ANALYSIS

The testes and epididymis of the rats were isolated by incising the abdomen of the rat, and thereafter the distal end of the epididymis was dissected out. An incision of 1mm was made in the distal end of the epididymis to collect the semen used to estimate sperm motility, sperm morphology and sperm count. Motility was expressed as the percentage of motile spermatozoa and their mean speed, or motile quality (scale 1 to 6, where 1= motile and 6= very fast progressive motile, that is >100 μm/s).

HISTOLOGICAL STUDIES

The testes were removed, dissected, and preserved in neutral buffered formalin at a 10% concentration. These formalin-fixed tissues were embedded in paraffin, cut into 5 micrometers sections, stained with hematoxylin and eosin (H&E), and analyzed histologically under a light microscope.

STATISTICS ANALYSIS

Data collected were expressed as mean ± SEM and analyzed using a statistical Software; Graph Pad Prism (version 5.0). Statistical significance between the means was attained using unpaired student's t-test. p-value < 0.05 was considered statistically significant.

RESULTS

EFFECT OF A. PRECATORIUS AND SILDENAFIL ON SEMEN PARAMETERS IN MALE WISTAR RATS TREATED FOR TWENTY-ONE DAYS

Treatments with plant extract and sildenafil for 21 days cause a significant increase in sperm count (fig.1a), decrease in sperm motility (fig.1b) and changes in sperm morphology like abnormal head shape (such as bent tail, double head, small head); abnormal tail structure (such as bent tail, multiple bend tails); cytoplasmic droplets, head vacuoles (fig.1c) when compared with the control.

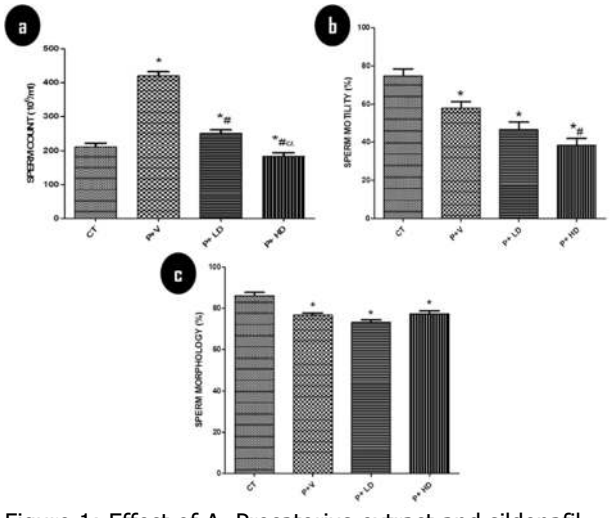

Figure 1: Effect of A. Precatorius extract and sildenafil on sperm parameter of male wistar rats. n=6; mean ± SEM, p<0.05 when compared with control group.
CT= Control, P +V = Paroxetine + Viagra, P + LD= Paroxetine + Low Dose extract, P + HD= Paroxetine + High Dose

EFFECT OF *ABRUS PRECARTORIOUS* ON SERUM TESTOSTERONE LEVEL OF MALE WISTAR RATS

Twenty one days treatment with A.Precatorius extract causes a significant increase in the high dose (HD) extract only when compared with the control. This might be the possible mechanism through which it improves sperm count.

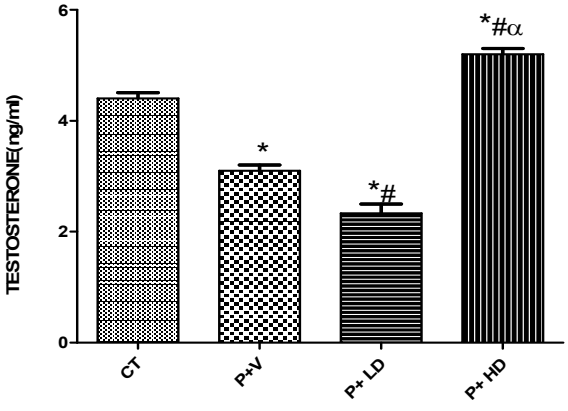

Figure 2: Effect of *Abrus precartorious* on serum testosterone level of male wistar rats. n=6; mean ± SEM, p< 0.05 when compared with control group. CT= Control, P +V = Paroxetine + Viagra, P + LD= Paroxetine + Low Dose extract, P + HD= Paroxetine + High Dose. NOTE: Values represent the Mean ± SEM (n=6); * p<0.05 significantly different from control, #p<0.05 significantly different from P + V, αp<0.05 P+HD significantly different from P+LD

HISTOLOGICAL OBSERVATIONS

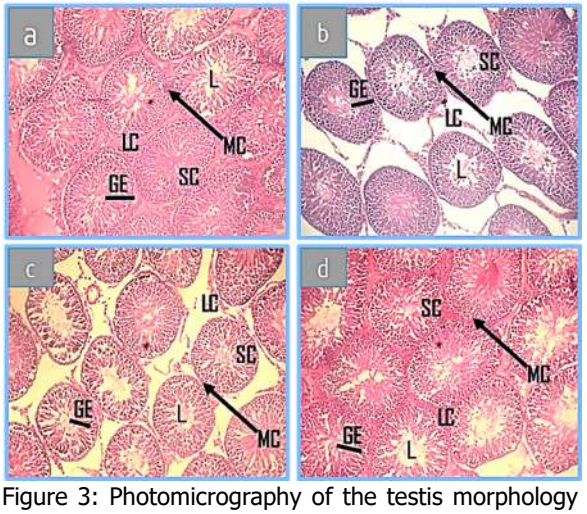

Figure 3: Photomicrography of the testis morphology stained with H&E at low magnification. The results show the Lumen (L), Leydig Cells (LC), Germinal Epithelium (GE), Myoid Cells (MC), and the Sertoli Cells (SC) across experimental groups.

The cellular assortment and the cytoachitecture of the group 1 (Control) reveals a well centralized lumen, sertoli cells with oval nucleus and dark nucleolus filled with abundant cytoplasm that extend from the basement membrane to the lumen. Furthermore, Leydig cells are properly arranged surrounded by connective tissues with the interstitial space. The germinal epithelium in these groups was properly arranged and myoid cells shows nucleus with dark pigmentation. The cellular assortments in the group 2 and 3 shows few vacuolated and decentralized lumen, with necrotic leydig and myoid cells and few pyknotic sertoli cells. Furthermore, there were few hypertrophy testes with germinal epithelium that are fragmented and disarrayed. The testicular histomorphology of the group 4 shows a slight similarity with that of Group 1 and only presented few hypertrophy testes and mild fragmentations in the germinal epithelium.

The cellular assortment and the cytoachitecture of the group 1 (Control) reveals a well centralized lumen, sertoli cells with oval nucleus and dark nucleolus filled with abundant cytoplasm that extend from the basement membrane to the lumen. The number of primary and secondary spermatocytes as well as spermatozoa decreased in the lumen of convoluted seminiferous tubules in group 2 and 3 respectively.

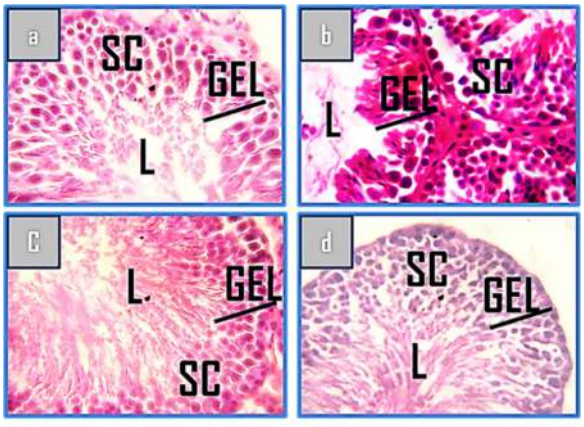

Figure 4: Photomicrography of the testis morphology stained with H&E at high magnification. The results show the Lumen (L), Germinal Epithelium (GE), and the Sertoli Cells (SC) across experimental groups.

The amount of seminiferous epithelium was reduced, with the majority of tubules being devoid of spermatids and just a small number of tubules harboring dead or degenerating tail pieces of spermatozoa. Around the tiny capillaries in the intertubular area, Leydig cells or interstitial cells were present, but their size and quantity were diminished. The interstitial cells displayed cytoplasmic atrophy and darkened nuclei. The same treated rats' epididymis displayed several empty tubules filled with degenerating spermatozoa or devoid of spermatozoa. The testes were normal, although there was cytoplasmic atrophy in the lining epithelial cells. The testicular histomorphology of the group 4 shows a slight similarity with that of Group 1 and only presented few hypertrophy testes and mild fragmentations in the germinal epithelium.

DISCUSSION

A.Precatorius extract has been reported to exhibit aphrodisiac property when administered chronically to experimental animals (Bhakta and Das 2020). Physical observation on mating performances such as mount latency (ML), mount frequency (MF), intromission latency and frequency (IL and IF), ejaculatory latency (EL) during the course of this present study shows that intake of this extract increases the libido of the experimental animals. They were more sexually active when compared with the control group; this could be attributed to the possible aphrodisiac property of *A.Precatorius.*

This result from this study shows that treatment with plant and Viagra increase significantly sperm count when compared to the control. However, there was a significant decrease of sperm motility

following treatment with plant extract across experimental group. The decrease in sperm motility seen in the high-dose extract group when compared with that of the control suggests that there is an alteration of sperm maturation in the epididymis and sperm production in the testis. This finding is corroborated by the report of Sinha et al., (1990) and Bhakta and Das (2015) in their studies that the *Abrus precatorius*' extract causes testicular anti-fertility effect and reduction of sperm motility in the cauda epididymis. Furthermore, methanol extract of *Abrus precatorius* seeds has been shown to deteriorate the motility of washed human spermatozoa with an EC 50 of 2.29 mg/ml irrevocably (Bhakta and Das, 2020). Sildenafil showed significant increase in the sperm motility when compared with LD and HD extract. This agrees with the study done by Glenn et al., (2007) which reported that Sildenafil citrate significantly increased both the number and velocity of progressively motile sperm.

The semen morphology when compared across experimental groups shows there is a considerable change in morphology like abnormal head shape, abnormal tail structure, cytoplasmic droplets and head vacuoles was noticed. These abnormalities can affect the sperm's ability to penetrate the egg, impair the sperm's motility making it difficult for them to reach and fertilize the and ultimately reduce fertility potential. However, there was an increase sperm count, decreases sperm motility in the treated group. This result is similar to Jahan et al., 2009 study. They reported that rats given *Abrus precatorious* showed decapitation, acrosome destruction, and swelling on the sperm at the midpiece region when observed under electron microscopy. The probable explanation of the observed morphological changes could be an alteration in energy metabolism caused by a decrease in ATPase and succinate dehydrogenase activity.

The result from the evaluation of serum testosterone shows an increase in serum testosterone in the high-dose (HD) extract when compared with the control. This might be the possible mechanism through which it improves sperm counts. Though, this increase looks contrary to other reports (Bhatt *et al*., 2007). While we used aqueous leave extract of *A. Precatorius* in the present study observe this increase in testosterone, Bhatt and colleagues used alcohol seed extract of *A. Precatorius* treated rats to describe its anti-fertility effect where it registered a significant reduction in testosterone levels that leads to functional sterility. There's however a study by Jahan et al (2009) that has also reported significant increase in serum testosterone levels after 60 days of *Abrus precatorious* administration. Additionally, Jahan and his team discovered an irreversible loss of sperm DNA integrity, which raised the possibility of teratogenicity. The increase observed in the high dose could be due to the negative feedback mechanism that stimulates the anterior pituitary gland to produce LH that act on the leydig cells to produce testosterone (Shama *et al*., 2022). It appears that very high dose of *Abrus precatorius* may induce infertility by increasing serum testosterone levels. Researchers have noted a decrease in testosterone levels, which may indicate that *A. precatorius* acts on the hypothalamus and pituitary (Bhakta *et al*., 2019). These findings may be related to gonadotrophin (LH, FSH) secretion that is below normal levels, which may result in fewer appropriate sperm in the lumen of convoluted seminiferous tubules. Also, the androgen starved effect could suggests that decreased testosterone is a possible cause of testicular and epididymal dysfunction (Khan *et al*., 2008). As a result, the mixed feeding had an impact on the development of sperm in each organ. This study demonstrated that a crude *A. precatorius*

mixture might produce functional infertility without causing harmful effects.

Tissue observation show normal testes in the control group when compared with the treated groups. In the treated groups there are mildly atrophied testes and degenerated cells. This could be due to the induction of paroxetine causing tissue dysfunctions. Tissue observation of control was compared with group two treated with sildenafil, it was observed that the control rat shows normal testis while the sildenafil showed some alterations in the seminiferous tubules of the testis and impaired spermatogenesis. This is due to the fact that sildenafil citrate induced abnormalities in sperm and an increase in sperm malformations, such as hypertrophic cells, necrosis of seminiferous tubules, testicular damage, and the presence of inflammatory cells. This observation is similar to the study of El-Kerdasy and Mohamed, 2019 who reported a comparable outcome. Furthermore, these consequences could result from modifications in the expression of different cGMP receptors or in the responsiveness of these receptors in the brain, damaging testicular tissue and impairing spermatogenesis (El-Kerdasy and Mohamed, 2019; Tocharus, 2005). Nitric oxide (NO) production may also vary as a result of the suppression of cGMP breakdown via negative feedback mechanisms (Kretschmann, 1999). NO may have varied effects on neurotransmitter activity in various brain systems.

Histology of the testis in group treated with HD and LD extract also show impairment in the testis specifically in the LD extract when compare with the control group as shown in fig 3. The number of primary and secondary spermatocytes as well as spermatozoa decreased in the lumen of convoluted seminiferous tubules. The amount of seminiferous epithelium was reduced, with the majority of tubules being devoid of spermatids and just a small number of tubules harboring dead or degenerating tail pieces of spermatozoa. Around the tiny capillaries in the intertubular area, Leydig cells or interstitial cells were present, but their size and quantity were diminished. The interstitial cells displayed cytoplasmic atrophy and darkened nuclei. The same treated rats' epididymis displayed several empty tubules filled with degenerating spermatozoa or devoid of spermatozoa. The testes were normal, although there was cytoplasmic atrophy in the lining epithelial cells. The implication of these could be that the treatment caused alterations in kinetics of spermatogenesis. Similar histological changes have also been reported in the work of Jahan *et al*., (2009) where they reported a significant reduction in the number of spermatozoa of animals treated with *A. Precatorius* extract which appear to be due to the suppressive effect of the treatment on spermatogenesis as it appears to possess a strong compound that decreases fertility mainly by decreasing the circulating androgen level.

CONCLUSION

Following the results of this research work, it can be suggested that A*. precatorius* extract at a very high dose may induce infertility by increasing serum testosterone levels, while at low dose a reduction in serum testosterone which could be linked to oxidative damage can possibly explicate the antifertility observed, although the mechanism of each dose appears dissimilar. Due to the fact that managing infertility and regulating fertility are two key aspects of reproductive health, crude extract of *Abrus precatorius* could be taken through clinical trials for possible therapeutic potentials.

RECOMMENDATION

It is recommended that further studies should be done to isolate the active ingredients of antifertility and aphrodisiac potentials of this plant.

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