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Moringa Oleifera Mitigates the Fluoxetine-Induced Damage to the Histological Architecture of the Seminiferous Tubules in Adult Male Rats

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[1]Substantial contributions to the conception and design of the work Agreement to be accountable for all aspects of the work
[2,4]Final approval of the version to be published, Analysis and interpretation of data for the work 3Drafting the work and revising it critically for important intellectual content, [5]Final approval of the version to be published
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ABSTRACT

Objective: To observe the ameliorative changes of Moringa oleifera on the gross and histological architecture of fluoxetine-treated adult rat testis.

Methodology: A laboratory-based experimental study was conducted at Department of Anatomy, Army Medical College, Rawalpindi in collaboration with the National Institute of Health (NIH), Islamabad and Pathology Lab Pak Emirates Military Hospital Rawalpindi, Pakistan, from October 22 to April 2023. Thirty male Sprague Dawley rats were randomly divided into three groups (n=10). Rats were kept at the animal house of NIH Islamabad. Group A (control), Groups B and C (experimental) were given doses dissolved in distilled water through oral gavage once daily. The experimental period was 08 weeks. Group B was administered fluoxetine in a dose of 10 mg/kg body weight. Group C rats were treated with two chemicals, same dose of fluoxetine as in group B and concomitantly received 50 mg/30 grams body weight of Moringa Oleifera. After dissection, testes were fixed and staining was done with Hematoxylin & Eosin for histological study. Analysis of data was done on SPSS version 22. A p-value ≤ 0.05 was considered statistically significant.

Results: The present study concluded that amelioration caused by Moringa Oleifera was statistically significant (p-value <0.05) when compared to the other groups.

Conclusion: Moringa Oleifera has ameliorative effects on the testicular toxicity induced by Fluoxetine in male rats by showing improvement in the diameter of the seminiferous tubules.

Keywords: Fluoxetine, Moringa Oleifera, Seminiferous tubules, SSRI, Testicular Toxicity.

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Introduction

Depression is a chronic, recurrent mood disorder that affects the physical, psychological, economic and social statuses of a person.[1] According to American Psychiatric Association, depression is considered a mood swing characterized by a persistent sense of melancholy and lack of ambition [2] It affects the appearance, thinking and actions of an individual and can cause several mental and physical difficulties. Like other chronic diseases, depression can be debilitating and even fatal however, it is poorly acknowledged and stigmatized.[3]

Depression directly affects the way a person thinks by receiving attention and altering memory.[4] In this era, climatic changes, technological changes, globalization and

the spread of social media have boosted economic gains but affected the mental health especially among youth.[5] Various surveys have shown that of 20% to 30% of men suffer from sexual dysfunction.[6] The high impact and high prevalence of this percentage raises an urge to protect against the problems. [7]

Fluoxetine is member of the SSRI (Selective Serotonin Reuptake Inhibitors).[8] It is one of the most potent antidepressant used worldwide [9]. It is used to treat neurological disorders, such as bulimia nervosa, obsessive-compulsive disorders and depression.[10] Despite its miraculous effects in treating depression, it also has some untoward effects on human health. Fluoxetine (FLX) increases the levels of serotonin in the brain. [11] Increased levels of serotonin in the cerebrum affect the release of FSH and LH, thereby inhibiting the secretion of gonadotrophin releasing hormone (GnRH) in the hypothalamus.[12] This ultimately affect spermatogenesis and steroidogenesis in the adult rats [13]. This drug induces oxidative stress in various tissues that ultimately affects its function. Reactive oxygen species (ROS) which are formed as a result of oxidative stress in the testes affects spermatogenesis and lower sperm counts, which can result in infertility. [14]

Moringa Oleifera (MOL) is a naturally occurring medicinal herb, having a rich constitution of antioxidants that can combat the effect of this injury in testicular tissue.[15] Moringa Oleifera has exceptional nutritional and therapeutic properties. It is abundant in macro- and micronutrients as well as other bioactive substances that are crucial for the body's regular operation and the prevention of specific disorders. Nearly all components of this tree, including the leaves, blossoms, and seeds, are edible and have powerful medicinal properties, including antidiabetic, anticancer, antiulcer, antibacterial and antioxidant properties. [16]

Numerous researches have demonstrated the harmful effects of fluoxetine on the testis, but there hasn't been any prior information on how Moringa Oleifera can help. Consequently, the goal of this investigation was to ascertain how Moringa Oleifera can lessen the fluoxetine-induced testicular toxicity in male Sprague Dawley rats.

Methodology

The study was conducted in partnership with the National Institute of Health (NIH), Islamabad, and the Pak Emirates Military Hospital (PEMH), Rawalpindi, in the department of anatomy at the Army Medical College Rawalpindi Pakistan. The ethical committee of Army Medical College gave its clearance before any animal care and handling operations were carried out.

Inclusion Criteria: All male rats ranging between 3-4 months of age, having an average weight ranging between 300± 50g comprised of the study.

Exclusion Criteria: Male rats with any gross genital or testicular abnormality were dropped out of the study.

Thirty male Sprague Dawley rats were taken from NIH, Islamabad. The rats were housed in the NIH's animal facility under conventional lab conditions. The rats had unrestricted access to standard laboratory food as well as clean drinking water. The animals were randomly divided into three groups, each group having 10 rats each and 5 rats lodged in one cage. [17] All the animals were weighed at the start and end of the experiment using a digital analytical balance. In Group A, no intervention was performed to maintain it as control. Group B and C were kept as experimental groups. All drugs were given in a single daily dose through oral gavage. Group B received fluoxetine 10 mg/kg body weight [18]. Group C was also administered same dose of fluoxetine but concomitant administration of Moringa Oleifera (MOL) 50mg/30 grams body weight [19] was also administered.

Rats were euthanized and then sacrificed through proper dissection incision techniques at the end of the experimental period. The right testis was dissected out to set as a standard and selected testes were weighed in grams (g). The testes were preserved in labeled plastic containers with 10% formalin solution. Sectioning was done in PEMH histopathology lab Rawalpindi. Two distinct levels of each testis were used to derive cross sections: one from the upper one-third and one from the lower one-third. After that, the tissues were put into cassettes with the proper labels. Blocks were created by embedding the processed tissue in molten paraffin wax after it had been processed automatically with a Leica TP 1020 tissue processor. Using a rotary microtome, sections with a thickness of 5 µm were produced, and the slides were stained with hematoxylin and eosin.

Histomorphometric analysis of slides was done under light microscope using 10X lens. Ten round cross sections were selected in one histological section. The diameter was calculated by taking two perpendicular diameters D1 and D2. The average of both these readings was taken as the final diameter for that seminiferous tubule. The mean of all the readings was taken as the final diameter for that histological section. A comparison of the diameter of the

seminiferous tubule was observed between the groups. The findings of both the parameters were compared at the end.

The data was analyzed using SPSS version 22. The variable was described using descriptive statistics, such as mean and standard deviation. To examine differences between the groups, one-way analysis of variance (ANOVA) was used, followed by a post-hoc Tukey's test. P-values less than 0.05 were regarded as statistically significant.

Results

Table I presents the mean values of the Diameter of the Seminiferous Tubules (µm) across three groups The p-value for the comparison among the groups was found to be less than 0.001, indicating significant differences. Table-II illustrates the intergroup comparison of the mean values of the Diameter of the Seminiferous Tubules among the three groups using a post hoc Tukey test.

The testis weight for each group was measured in grams, The differences in testis weight between the groups were found to be statistically significant, with a p-value of less than 0.001. (Table III) Post hoc Tukey tests were conducted to further analyze the intergroup comparisons. (Table IV).

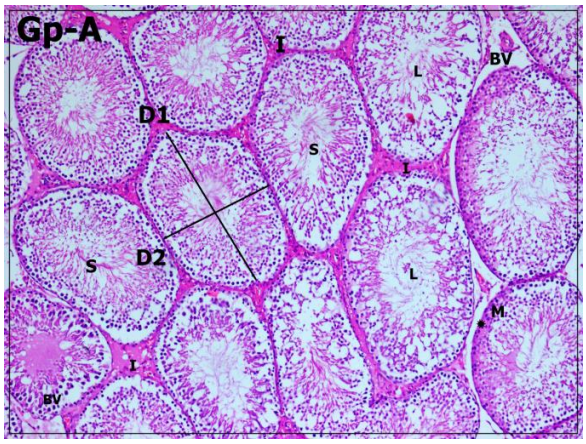

Figure- II: A photomicrograph of control group A showing the diameter of the seminiferous tubules DST (10X, H&E). Two perpendicular diameters D1 and D2 are taken from one basement membrane to the other. Section showing a normal architecture with lumen (L) filled with mature spermatozoa (S). Peritubular myoid cells (M) can be seen below the basal lamina. The Interstitial connective tissue space (I) is dense with normal sized blood vessels (BV) seen.

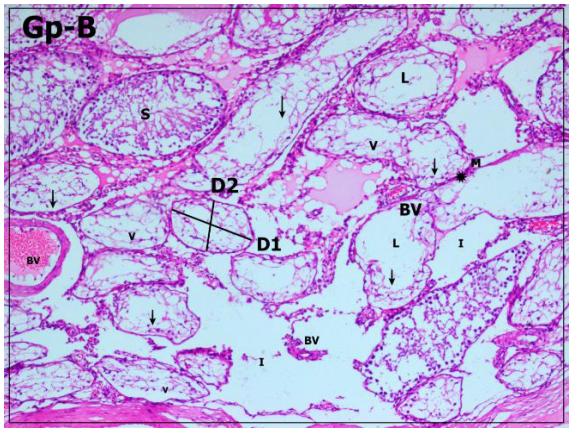

Figure- III: A photomicrograph showing the diameter of the seminiferous tubules DST of fluoxetine-treated experimental group B at (10X, H&E). Two perpendicular diameters D1 and D2 are taken from one basement membrane to the other. Section showing a distorted architecture of the seminiferous tubules (↓) caused by Fluoxetine with disintegrated germ cell layer and an empty lumen (L) having few spermatids (s), cytoplasmic vacuolations (v) are also seen. The interstitial connective tissue space (I) is widened with congested blood vessels (BV). Peritubular myoid cells (M*) are also scanty.

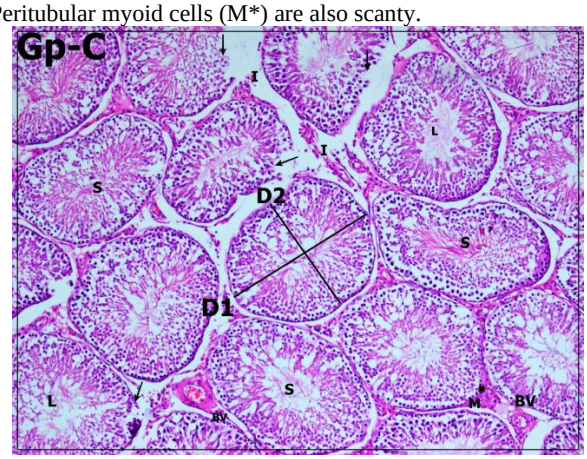

Figure- IV: A photomicrograph of experimental group C showing the diameter of the seminiferous tubules DST taken by two perpendicular diameters D1 and D2 at (10X, H&E). MOL has significantly ameliorated the toxicity induced by Fluoxetine. Improved architecture of the seminiferous tubules is observed by reduced distortion (↓). Lumen (L) contains abundant spermatids (s). The interstitial connective tissue space (I) is less widened, with normal sized blood vessels (BV). Peritubular myoid cells (M*) can also be seen.

Table I: Mean values of the Diameter of the Seminiferous Tubules between control group A and experimental groups B and C.

Histological Parameter	Group A (n=10)	Group B (n=10)	Group C (n=10)	p-value
Diameter of the Seminiferous Tubule (µm)	392.63 ± 4.26	301.60 ± 8.14	377.61 ± 3.48	<0.001

Table III: Mean values of the weight of the testis of control group A and experimental groups B and C.

	Group A (n=10)	Group B (n=10)	Group C (n=10)	p-value
Weight of the testis (gm)	2.70 ± 0.14	1.92 ± 0.13	2.35 ± 0.21	<0.001

Table II: Inter Group comparison of the mean values of the Diameter of the Seminiferous Tubules between the three groups by applying post hoc Tukey test.

	Group A vs B	Group A vs C	Group B vs C
Diameter of the Seminiferous Tubule DST (µm)	<0.001	<0.001	<0.001

Table IV: Inter Group comparison of the mean values of the weight of the testis between the three groups by applying post hoc Tukey test.

	Group A vs B	Group A vs C	Group B vs C
Weight of the testis (gm)	<0.001	<0.001	<0.001

Discussion

The testicular weight was also noted in this study. The testis seemed pink, spongy, smooth, and soft upon physical examination. An analysis of the intergroup comparison revealed a statistically significant difference in testicular weight between the experimental groups B and C and the control group A. The testes weight significantly decreased in experimental group B. This conclusion is corroborated by a study done by Camara[20] that described how significant dissociation and loss of germ cells led to decreased tubular and epithelial regions, which in turn caused the testes weight to decrease. El-Roghy [10]also conducted studies showing a decrease in testicular weight in response to fluoxetine, however, the distinction between their study and this one is the use of albino rats. Elsedawi[21]conducted a study that validated this finding by demonstrating that fluoxetine can inhibit steroidogenesis by blocking serotonin reuptake and decrease the release of LH from the anterior pituitary lobe.

However, mature albino rats were selected here. Another study done by Mojtaba [22] where maternal exposure to fluoxetine during lactation significantly reduced the diameter and epithelial height of the seminiferous tubules thereby supporting a favorable correlation between the volume of seminiferous tubules, the population of Sertoli cells, and sperm production and testicular weight. Study conducted by Hanif[23] showed a significant reduction in testicular weight of Wistar albino rats when given fluoxetine by causing vacuolation, sloughing and degeneration of germ cells, leading to distortion of seminiferous tubules. When compared to group B, there was a statistically significant increase in testicular weight in experimental group C, which was taking both fluoxetine and Moringa oleifera. This is consistent with a study by Nayak[24] where moringa herb significantly ameliorated the cyclophosphamide induced testicular toxicity by showing an improvement in the testicular weight of mouse testis. Improvement in the testicular blood flow and hormonal levels were suggested as the key factors for enhancing spermatogenesis. In our work, we employed Sprague Dawley rats, but Obeme and Raji[25] used extract from Moringa Oleifera seeds and saw a similar pattern of increase in testicular weight in male Wistar rats where toxicity was induced by cadmium. Regarding the histological parameter, in control group A, the diameter was within the normal range and no significant variations were observed. The seminiferous tubules were nearly circular with a very symmetric architecture. Group B was exposed to fluoxetine, which induced testicular injury and disrupted the testicular architecture. The cellular components were disorganized. The sloughing of the germ cells was also observed. The shape of the seminiferous tubules was distorted resulting in reduced diameter of the tubules. Many sperms were not observed in the lumen. The interstitial connective tissue space between the tubules increased and appeared scanty with less cellular content. This finding coincides with the study conducted by El-Roghy[10] which postulated that fluoxetine induces testicular toxicity by lipid peroxidation, which results in the release of free radicals that ultimately lead to membrane disruption causing tissue damage.

Another study supporting the present study was done by Lauren A. Beeder in which fluoxetine demonstrated gonadotoxic effects by disrupting the process of spermatogenesis which caused a decrease in the diameter of the seminiferous tubules.[26] This finding is also in accordance with a similar study conducted by Madlool [27] in which reduced diameter caused by the distortion of the seminiferous tubules was observed by the antidepressant fluoxetine. It explained its occurrence due to oxidative stress producing reactive oxygen species (ROS). In lipid peroxidation, plasma membrane fats are the primary target of ROS. As sperm membrane contains many unsaturated fatty acids, they are particularly vulnerable to ROS damage, which is consistent with our findings.

Histological findings of experimental group C showed that Moringa Oleifera significantly ameliorated the damage caused by fluoxetine on testes of Sprague Dawley rats and improvement was seen in the diameter of the seminiferous tubules with ($p < 0.05$). Our study is consistent with similar research conducted by Prabsattrro and B. Ogunlade in which Moringa Oleifera improved the diameter of the seminiferous tubules of the Wistar rats damaged by the oxidative stress induced by 12hr immobilization.[7] This study established that M. Oleifera leaf extract possesses

antioxidant and Monoamine oxidase-B (MAO-B) suppressing properties. The predominant amino acid included in the extract was phenylalanine, which prevented the decrease in the interstitial cells of Leydig and blood testosterone levels brought on by stress exposure. The study also showed that dopamine, which is an important factor in enhancing male sexual behavior is increased by the leaf extract of Moringa Oleifera by suppressing MAO-B. This in turn causes the cavernosal nerve to release nitric oxide, increasing oxytocin release from the paraventricular nucleus (PVN) of hypothalamus and cause an increase in cGMP in the penis. Nitric oxide's cGMP-dependent vasodilation action may be improved by elevation of cGMP by Moringa Oleifera extract and reduction of PDE-5, which can improve penile blood flow and erection thereby improving reproductive function. The later research supports that the radical scavenging abilities of Moringa Oleifera and the distinctive and substantial diversity of phytochemicals responding individually with diverse free radicals should be credited for the ameliorative potential displayed by the herb.

Moringa Oleifera has substantial antioxidant properties that are attributable to a wide range of substances, including anthocyanins and reductones.[28] Another research in favor of the present study was conducted by Lilibeth[19] in which effect of Moringa Oleifera was observed on the reproductive system of mice. Similar kind of result was also observed by another study where use of Moringa Oleifera significantly improved the diameter of the seminiferous tubules, however, gentamicin induced the testicular toxicity in male rats of *Rattus norvegicus*. The presence of antioxidants in moringa leaves like flavonoids, vitamin C, vitamin E and quercetin is responsible for its ameliorative effect.[29] Amelioration by moringa herb is the topic of discussion in medical science these days but its effect on fluoxetine was not addressed before. So, this study is providing a track to explore it further.

Conclusion

The study supports the fact that spermatogenesis directly impacts the histological architecture, in terms of diameter of the seminiferous tubules bearing a strong correlation with the weight of the testis. Our study infers that by combination of antidepressant drug, fluoxetine with moringa herb, offers higher testicular protection due to its antioxidant properties. Thus, it may help to mitigate these structural alterations and will safeguard the fertility of the patient using it.

Limitations of the study: Further extension in experimental period will disclose more potent effects both in terms of toxicity and amelioration. Serum markers and immunohistochemistry are the gold standards for research which were left due to limited finance.

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