

## Amelioration of Chlorpromazine-Induced Sexual Dysfunction in Male Rats by *Mucuna Pruriens* Seeds Extract.

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### Abstract:

**Background:** Sexual dysfunction in men is a common problem of antipsychotic drugs for the treatment of schizophrenia. *Mucuna pruriens* seeds extract has a significant effect in enhancing sexual function and reproductive parameters. Furthermore, it may have a therapeutic impact on the damage induced by hormonal changes and reactive oxygen species (ROS) to the structure and function of sperm.

**Aim of the study:** The current study aims to assess the effect of *Mucuna pruriens* seeds extract on sperm parameters and oxidative stress in chlorpromazine-induced sexual dysfunction in male rats.

**Methodology:** Thirty male Wistar rats with average weight (150-200g) were divided into five groups (n=6). Group 1: Negative control group, rats that received distilled water for 52days; Group 2: Induction group, rats that received (20mg/kg) of chlorpromazine for 52 days; Group 3: treatment group with a low dose of *Mucuna pruriens* 500mg/kg for 22days Group 4: treatment group with a medium dose of *Mucuna Pruriens* 1000mg/kg for 22 days Group 5: treatment group with a high dose of *Mucuna Pruriens* 2000mg/kg for 22 days. A serum sample was collected to measure glutathione (GSH) and malondialdehyde (MDA) serum levels using the ELISA technique. Semen samples were collected to determine Sperm count, morphology, and motility.

**Results:** This study revealed that chlorpromazine administration deteriorated the testicular function of rats, resulting in a significant[P<0.05] decrease in GSH serum level(6.37±0.29IU/ml), an increase in MDA serum level(9.57±0.16nmol/ml), and a reduction in sperm parameters (count, motility, and morphology) in the induction group compared to the control group. Treated groups with *Mucuna Pruriens* showed a significantly increased GSH serum level, significantly decreased MDA serum levels, and improved sperm parameters (count, motility, and morphology) compared to the induction group treated with chlorpromazine.

**Conclusion:** The study concluded that *Mucuna pruriens* improves reproductive toxicity and testicular damage induced by chlorpromazine through oxidative stress reduction, increased antioxidant activity, and improved sperm parameters.

**Keywords:** Chlorpromazine, *Mucuna pruriens*, Sexual dysfunction, Oxidative stress.



## تحسين العجز الجنسي الناجم عن عقار الكلوربرومازين في ذكور الجرذان بواسطة مستخلص بذور الميقونة الشهوانية.

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### خلاصة

**خلفية البحث:** يعد العجز الجنسي لدى الرجال أحد الآثار السلبية الشائعة للأدوية المضادة للذهان لعلاج الانفصام. مستخلص بذور نبات الميقونة الشهوانية له تأثير كبير في تعزيز الوظيفة الجنسية والمعايير الانجابية. علاوة على ذلك، فإن له تأثيراً علاجياً على الضرر الناجم عن أنواع الأكسجين التفاعلية وتغير الهرمونات في بنية ووظيفة الحيوانات المنوية.

**الهدف من الدراسة:** تهدف الدراسة الحالية إلى تقييم تأثير مستخلص بذور الميقونة الشهوانية على مؤشرات الحيوانات المنوية والإجهاد التأكسدي في العجز الجنسي الناجم عن عقار الكلوربرومازين في ذكور الجرذان.

**منهجية العمل:** تم تقسيم ثلاثين ذكراً من فئران البيضاء الغير معالجة بمتوسط وزن (150-200 جرام) عشوائياً إلى خمس مجموعات كل مجموعة تحتوي ستة من ذكور الجرذان. المجموعة الاولى تلقت الماء المقطر عن طريق الفم لمدة 52 يوم، المجموعة الثانية تلقت (20 ملغم/كغم) من الكلوربرومازين عن طريق الفم لمدة 52 يوم، المجموعة الثالثة تم معالجتها باعطاء جرعة منخفضة من مستخلص بذور الميقونة الشهوانية (500 ملغم/كغم) عن طريق الفم لمدة 22 يوم، المجموعة الرابعة تم معالجتها باعطاء جرعة متوسطة من مستخلص بذور الميقونة الشهوانية (1000 ملغم/كغم) عن طريق الفم لمدة 22 يوم، المجموعة الخامسة تم معالجتها باعطاء جرعة عالية من مستخلص بذور الميقونة الشهوانية عن طريق الفم لمدة 22 يوم. وايضا تم جمع عينات السائل (ELISA) في الدم بواسطة تقنية (MDA) و (GSH) جمعت عينات المصل لقياس مستويات المنوي لتحديد عدد الحيوانات المنوية وشكلها وحركتها.

**النتائج:** كشفت هذه الدراسة اعطاء عقار الكلوربرومازين أدى الى تدهور وظيفة الخصى لدى الجرذان، مما أدى الى انخفاض كبير في مستوى مصل (GSH) وزيادة في مستوى مصل (MDA) و انخفاض مؤشرات الحيوانات المنوية (العدد، الحركة، الشكل) في المجموعة التي تلقت عقار الكلوربرومازين مقارنة بالمجموعة التي تلقت الماء المقطر. أظهرت المجموعات المعالجة بمستخلص بذور الميقونة الشهوانية ارتفاع في مستوى (GSH) و انخفاض ملحوظ في مستوى (MDA) وتحسين في مؤشرات الحيوانات المنوية (العدد، الحركة، الشكل) مقارنة الى المجموعة التي تلقت عقار الكلوربرومازين.

**الاستنتاج:** أظهرت هذه الدراسة عمل الميقونة الشهوانية على تحسين وظائف جهاز التناسلي الذكري و تلف الخصى الناجم عن عقار الكلوربرومازين من خلال تقليل الاجهاد التأكسدي و زيادة فعالية مضادات الاكسدة و تحسين مؤشرات الحيوانات المنوية.

**الكلمات المفتاحية:** كلوربرومازين، الميقونة الشهوانية، العجز الجنسي، الاجهاد التأكسدي.

## Introduction

Psychiatric disorders affect millions of people worldwide. According to the World Health Organization (WHO), mental disorders are projected to become the primary cause of the burden of disease worldwide within the next 20 years (1). Phenothiazines, such as chlorpromazine, are widely used antipsychotic medications for controlling and managing mental disorders, including schizophrenia (which is a chronic severe disease that affects 21 million people

worldwide), and treating manic episodes of bipolar disorder (1,2).

Psychoactive drugs cause male sexual dysfunction and reproductive impairment by the inhibition of D2 dopamine receptors, which leads to a decrease in dopamine activity in the brain (3). Chlorpromazine treatment leads to notable alterations in many reproductive hormones, such as prolactin, gonadotropin, and steroidogenic enzymes, due to the removal of the inhibitory effect of dopamine on prolactin secretion (4). Hyperprolactinemia inhibits the secretion of



gonadotropin-releasing hormones (GnRH) from the hypothalamus, thereby resulting in hypogonadism, decrease libido, and infertility due to changes in the activity of gonadotropin (luteinizing hormone, LH, and follicle-stimulating hormone, FSH). Therefore, the decreased serum levels of LH, FSH, and testosterone that result from chlorpromazine have been linked to alters in spermatogenesis, granulosa cell function, fertilization problems, and decreased sperm motility, semen quality, and alterations in testicular morphology(5,6).

Antipsychotic drugs can promote the generation of reactive oxygen species (ROS). Oxidative stress is the result of an imbalance between various oxygen species, which can cause damage to sperm and semen, which have been linked to male infertility(7).Chlorpromazine increased lipid peroxidation and reduced the superoxide dismutase protein content and activity (8,9). *Mucuna pruriens* commonly known as (Cowhage plant) is the most widely used drug in the Ayurvedic and Unani systems of medicines in China and India. Seeds of *Mucuna Pruriens* are used for managing male infertility (10) *Mucuna pruriens* is a rich source of L-DOPA, which increases the level of dopamine in the brain. It plays an important role in mediating male sexual behavior and function (11). Furthermore, *Mucuna pruriens* seeds contain rich natural sources of bioactive antioxidant compounds that reduce ROS level lipid peroxidation and reactivate the antioxidant defense system, improving male infertility(12,13).

**Aim of study:** The current study aims to assess the therapeutic effect of *Mucuna pruriens* seeds extract on sperm parameters and oxidative stress in chlorpromazine-induced reproductive toxicity in male rats.

**Conclusion:** *Mucuna Pruriens* seeds extract improved rats' testicular damage and reproductive toxicity induced by chlorpromazine by increased antioxidant

activity and improved sperm parameters through increased levels of sex hormones and reduced oxidative stress.

## Materials and Methods

All chemicals and kits utilized in this study have high purity. Their origin was as follows: chlorpromazine (Sanofi -French), *Mucuna pruriens* (Echemi-China), Malondialdehyde (MDA)(MyBioSource—USA), and glutathione (GSH) (MyBioSource—USA). All measurements relied on the enzyme-linked immunosorbent assay (ELISA) technique.

## Animals

Thirty male Wistar rats weighing (150-200g) were used to conduct this study. Rats were purchased from the Animal House of the College of Pharmacy/ Mustansiriyah University, and housed in big, comfortable cages. For 12 days, rats were allowed to acclimate in a controlled environment, including temperature, humidity, and a light schedule of 12 hours of light and dark cycles. They were allowed food and water *ad libitum*. The study commenced following approval from the Scientific and Animal Ethics Committee within the Department of Pharmacology and Toxicology.

## Experimental design

The rats were randomly assigned to five groups, each consisting of six rats. The doses of chlorpromazine and *Mucuna Pruriens* were selected according to the previous studies(14,15) as below.

**I. Group 1 (n=6): Negative control group,** rats received distilled water P.O. for 52 days.

**II. Group 2 (n=6): The positive control or induction group** included rats that received 20mg/kg of chlorpromazine orally by gastric gavage once daily for 52 days.



**III. Group 3(n=6): Low-dose Mucuna Pruriens**, pre-treated with chlorpromazine 20 mg/kg orally once daily for 22 days. Then, from days 23 to 52, rats were treated with Mucuna Pruriens (500mg/kg b.wt, P.O.) with a continued daily dose of chlorpromazine.

**IV. Group 4(n=6): Medium dose of Mucuna Pruriens**, pre-treated with chlorpromazine 20 mg/kg orally once daily for 22 days. Then, from days 23 to 52, rats were treated with Mucuna Pruriens (1000mg/kg b.wt, P.O.) with a continued daily dose of chlorpromazine.

**V. Group 5(n=6): High dose of Mucuna Pruriens**, pre-treated with chlorpromazine 20 mg/kg, orally once daily for 22 days. Then, from days 23 to 52, rats were treated with Mucuna Pruriens (2000mg/kg b.wt, P.O.) with a continued daily dose of chlorpromazine.

#### Samples collection

To measure the levels of MDA and GSH in the serum, blood samples were collected from the left ventricle of the heart using a 5ml syringe with a gauge 23 needle. The samples were then placed in gel tubes and allowed to clot at room temperature for 15 minutes. After clotting, the tubes were centrifuged at 3000 RPM for 15 minutes. The resulting serum was frozen in Eppendorf tubes(1.5ml) at -20 °C. The sandwich ELISA technique measures MDA and GSH.

Semen samples were collected to determine sperm count, motility, and morphology. Cauda epididymides were dissected and cut into three parts by scissor, then immediately minced in 5 mL of normal saline, and then incubated at 37 °C for 30 minutes to facilitate the release of spermatozoa from the epididymal tubules. Thereafter, the percentage of motile sperm and sperm count were recorded using a phase contrast microscope at a magnification of 400 ×. The total sperm number was determined by using a Neubauer hemocytometer(16).

#### Statistical analysis

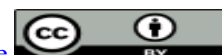
The collected data were presented as mean  $\pm$  standard error of the mean (M $\pm$ SEM). The results were analyzed by SAS (Statistical Analysis System - version 9.1). The statistical tests of one-way ANOVA, two-way ANOVA, and least significant differences (LSD) post hoc test were conducted to evaluate significant variations among the means. The results were considered as statistically significant differences when P-value  $\leq$  0.05.

#### Results

The results from table (1) clarify the levels of glutathione and malondialdehyde in rats exposed to chlorpromazine and the potential effects of different Mucuna pruriens doses.

**Table (1): Effect of Mucuna pruriens seeds extract on oxidative stress biomarkers of rats exposed to chlorpromazine.**

| Groups                                  | GSH<br>IU/ml      | MDA<br>IU/ml      |
|-----------------------------------------|-------------------|-------------------|
| Control                                 | 9.61 $\pm$ 0.52ab | 8.50 $\pm$ 0.12cd |
| Induction                               | 6.37 $\pm$ 0.29c  | 9.57 $\pm$ 0.16a  |
| Treatment with 500mg of Mucuna Pruriens | 9.39 $\pm$ 0.18b  | 8.87 $\pm$ 0.11b  |

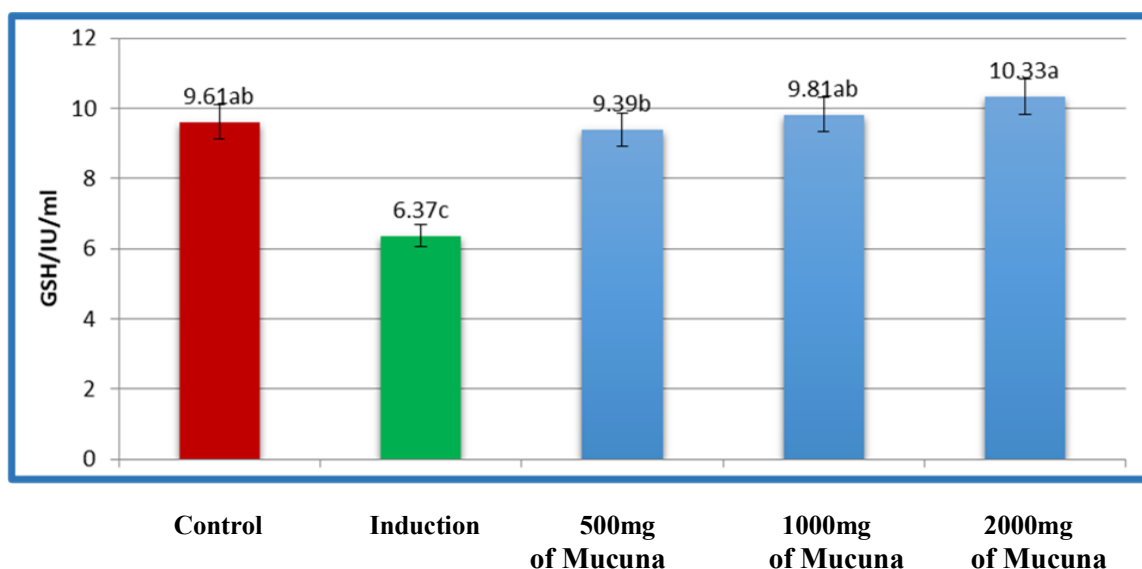


|                                          |             |             |
|------------------------------------------|-------------|-------------|
| Treatment with 1000mg of Mucuna Pruriens | 9.81±0.11ab | 8.81±0.11bc |
| Treatment with 2000mg of Mucuna Pruriens | 10.33±0.30a | 8.26±0.09d  |
| LSD                                      | 0.89        | 0.36        |

The data were represented as the Mean  $\pm$  SEM. Different small letters indicate statistically significant differences among groups. P-value  $\leq 0.05$  is considered a statistically significant variation. M.P=Mucuna pruriens, GSH=glutathione, MDA= malondialdehyde.

The levels of GSH significantly decreased ( $6.37 \pm 0.29$ ) in the induction group compared to the control group. Although there was no significant difference between the treatment groups with doses of 500mg and 1000mg of Mucuna pruriens significantly increased when compared to the induction group, while

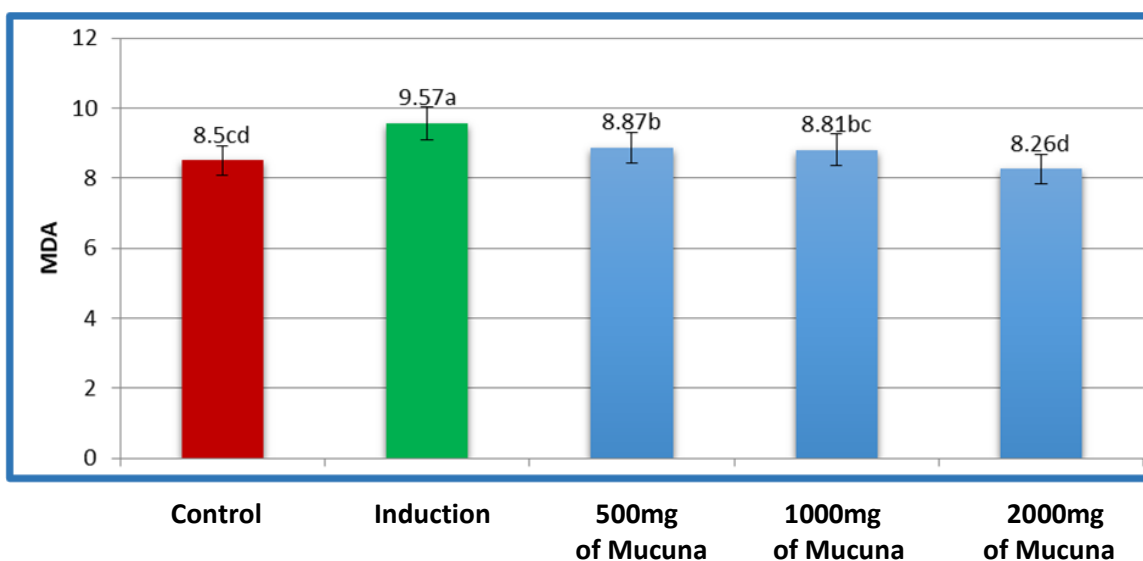
the treated group with 2000mg of Mucuna pruriens was increased significantly (p-value  $\leq 0.05$ ) ( $10.33 \pm 0.30$ ) when compared to induction group and treated group with 500mg of Mucuna pruriens. Still, no significant difference was observed with a control group, as illustrated in the figure (1).



**Figure (1): Effect of Mucuna Pruriens seeds extract on GSH in serum level of rats exposed to chlorpromazine.**

Figure (2) illustrates the effect of chlorpromazine and Mucuna pruriens on serum level of MDA. The induction group showed significant elevation ( $9.57 \pm 0.16$ ) in serum MDA levels when compared to the control group. A treated group with 500mg of Mucuna pruriens significantly diminished when compared to the induction group. Still, the level of MDA was higher than the control

group, while the treated group with 1000mg showed no significant difference between the control group and the treated group with 500mg of M.P. Treated group with 2000mg of M.P showed significantly diminished (p-value  $\leq 0.05$ ), ( $8.26 \pm 0.09$ ) when compared to the induction group and treatment groups with 500,1000mg of M.P but no significant difference with the control group.



**Figure (2): Effect of Mucuna Pruriens seeds extract on MDA in serum level of rats exposed to chlorpromazine.**

Semen analysis showed a significant improvement in the sperm parameters (sperm count, motility, and morphology) when rats

exposed to chlorpromazine received Mucuna pruriens (p-value  $\leq 0.05$ ), as shown in table (2).

**Table (2): Effect of Mucuna pruriens seeds extract on the sperm parameters of rats exposed to chlorpromazine.**

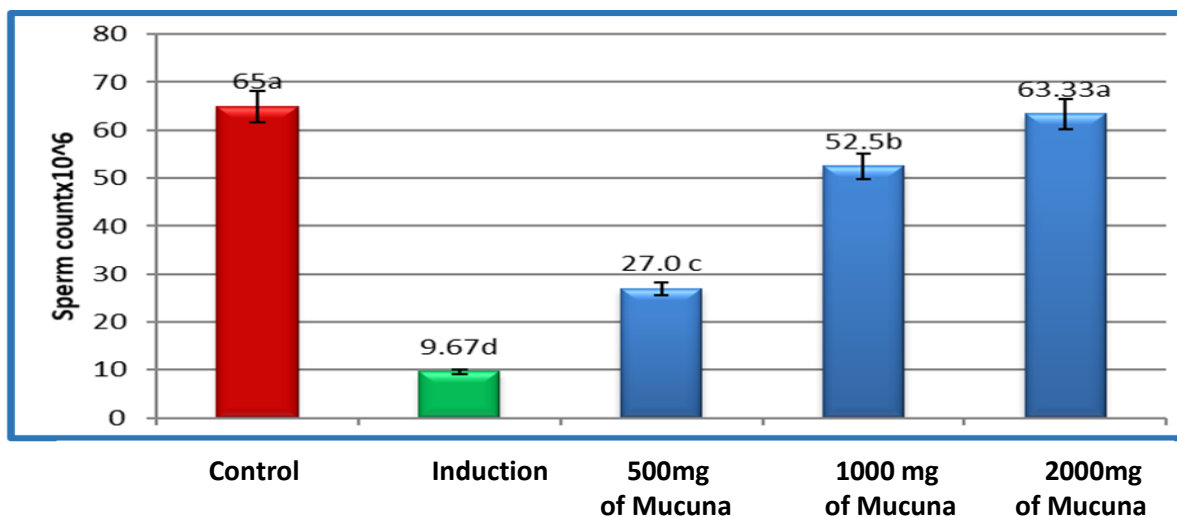
| Groups                        | Sperm count<br>*10 <sup>6</sup> | Motility     |              | Morphology    |               |
|-------------------------------|---------------------------------|--------------|--------------|---------------|---------------|
|                               |                                 | Active%      | Inactive%    | Normal %      | Abnormal %    |
| Control                       | 65.00±6.26a                     | A65.72±3.84a | B34.28±3.84c | A62.48±3.75a  | B37.52±3.75c  |
| Induction                     | 9.67±1.33d                      | B13.66±4.48c | A86.34±4.48a | B18.83±3.78c  | A81.17±3.78a  |
| Treatment with 500mg of M.P   | 27.00±1.91c                     | B37.16±5.32b | A62.84±5.32b | A47.50±5.73b  | A52.50±5.73b  |
| Treatment with 1000mg of M. P | 52.50±6.92b                     | A55.72±4.14a | A44.28±4.14c | A57.85±4.14ab | A42.15±4.14bc |
| Treatment with 2000mg of M. P | 63.33±2.47a                     | A65.72±3.84a | B34.28±3.84c | A60.85±3.71a  | B39.15±3.71c  |
| LSD                           | 13.44                           | 12.41        |              | 12.05         |               |

Data were expressed as Mean  $\pm$  SEM, and means with a different small letter in the same column are significantly different ( $P < 0.05$ ). The statistical analysis was done by using one-way, ANOVA and Least significant differences (LSD) estimated in one value.



The group that was treated with chlorpromazine alone showed that significant low in the count of seminal fluid sperms ( $9.67 \pm 1.33 \times 10^6$ ) when compared to the control group. Meanwhile, the administration of 500mg and 1000mg of M.P for rats exposed to chlorpromazine significantly elevated the sperm count ( $27.00 \pm 1.91 \times 10^6$ )

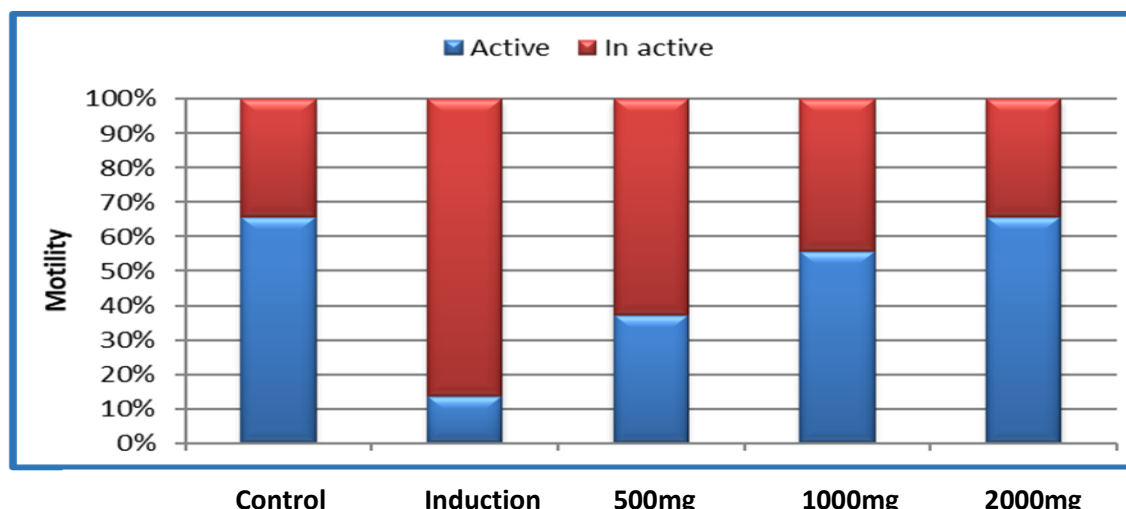
and ( $52.50 \pm 6.92 \times 10^6$ ) respectively, compared with rats on just chlorpromazine ( $p$ -value  $\leq 0.05$ ), while the sperm count for rats given high dose of M.P(2000mg) there was no significant difference to control group and significant difference to other doses of M.P and induction group as shown in figure (3).



**Figure (3): Effect of *Mucuna pruriens* seeds extract on the sperm count of rats exposed to chlorpromazine.**

Regarding sperm motility, all results showed a significant difference between active and inactive. The induction group treated with chlorpromazine alone showed a significant ( $p$ -value  $\leq 0.05$ ), decline ( $13.66 \pm 4.48$ ) in the percent of active sperm and an increase ( $86.34 \pm 4.48$ ) in the percent of inactive sperm when compared to the control group, while the treated group with 500mg of *Mucuna pruriens* showed significant improvement when compared to induction group but fewer

than other doses of *Mucuna pruriens* and control group. Meanwhile, the treatment with 1000,2000mg of *Mucuna pruriens* showed significant ( $p$ -value  $\leq 0.05$ ), increases ( $55.72 \pm 4.14, 65.72 \pm 3.84$ ) in the percent of active sperm and a decrease ( $44.28 \pm 4.14, 34.28 \pm 3.84$ ) in the percent of inactive sperm when compared to induction group and no significant difference with the control group that illustrated in figure (4).

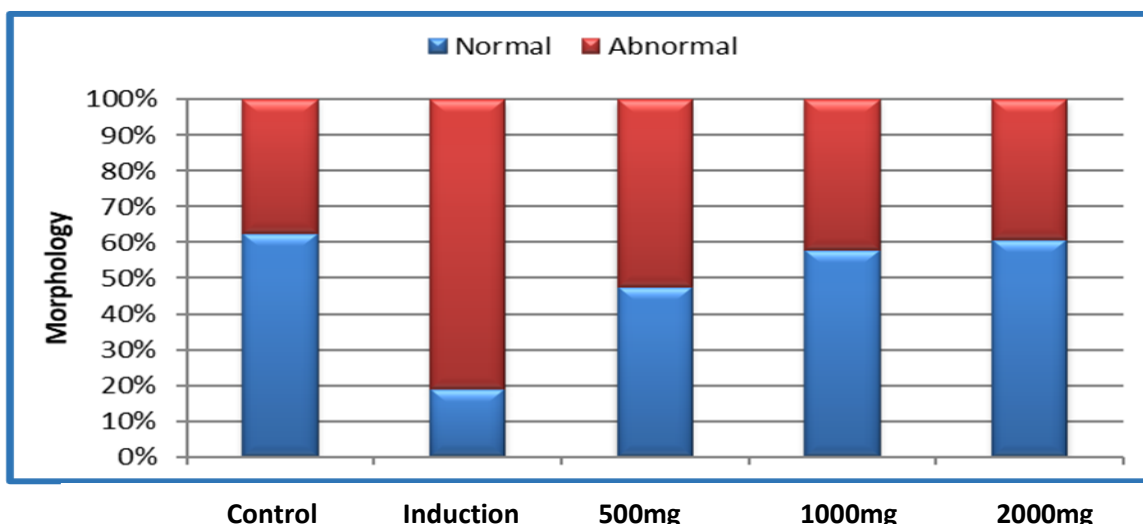


**Figure (4): Effect of *Mucuna pruriens* seeds extract on the sperm motility of rats exposed to chlorpromazine.**

The percentage of morphological alterations in sperms demonstrated in figure (5) shows a significant difference between normal and abnormal sperm of each group. In the induction group that was treated with chlorpromazine alone, that indicates the percent of normal sperm morphology was significantly ( $p\text{-value} \leq 0.05$ ) decreased ( $18.83 \pm 3.78$ ), and the percent of abnormal sperm morphology significantly increased ( $81.17 \pm 3.78$ ) when compared to the control group. The treated group with 500, 1000mg of *Mucuna pruriens* showed significant

improvement in the morphology of sperm when compared to the induction group, while the treated group with 2000mg of *Mucuna pruriens* showed a significant ( $p\text{-value} \leq 0.05$ ) increased ( $60.85 \pm 3.71$ ) in the percent of normal sperm morphology and significantly ( $p\text{-value} \leq 0.05$ ) decreased ( $39.15 \pm 3.71$ ) in the percent of abnormal sperm morphology when compared to the treated group with 500mg of *Mucuna pruriens* and induction group, but no significant difference with the control group.





**Figure (5): Effect of *Mucuna pruriens* seeds extract on the sperm morphology of rats exposed to chlorpromazine.**

## Discussion

Antipsychotic drugs can negatively affect sexual function. Spermatogenesis, the most prolific replicative process, demands the highest level of oxygen consumption and generates high quantities of reactive oxygen species. ROS has significant implications in biological systems, exerting either positive or negative effects depending on their nature, concentration, location, and duration of exposure. Male infertility is linked to a reduction in the antioxidant activity in semen (17,18).

The current study showed that chlorpromazine significantly reduced serum levels of GSH in the induction group compared to the control group. These results agreed with Nikolić-Kokić et al. 2022(19) Elmorsy et al. 2017(19,20). Chlorpromazine induced depletion in the GSH reservoir, causing oxidative stress and reproductive damage in males; glutathione deficiency can cause impaired sperm motility due to the susceptibility of spermatozoa to reactive oxygen species (ROS). This susceptibility is attributed to the high levels of

polyunsaturated fatty acids found in the plasma membrane and cytoplasm of sperm, which leads to a decrease in sperm motility. This decrease could be caused by a rapid depletion of intracellular ATP(21,22).

The serum levels of GSH dramatically increased when treated with *Mucuna pruriens* is rich in several bioactive compounds, such as alkaloids, phenols, flavonoids, and alkylamines, which play an important role in enhancing the antioxidant capacity and therapeutic effects against free radicals and oxidative stress(23).

This study demonstrated a significant increase in MDA levels in the induction group compared to the control group. Lipid peroxidation (LPO) has been recognized as a mechanism of sperm damage induced by chlorpromazine, resulting from chain oxidation mediated by free radicals. This agrees with previous studies (24,25). The elevation of MDA levels indicates the presence of oxidative stress and tissue toxicity(26). LPO of the membrane lipid of sperm may disturb the functions, inhibit mitochondrial function, and reduction of membrane fluidity affecting the sperm concentration, motility, morphology, and

survival of sperm (27,28). Treated groups with *Mucuna pruriens* showed a substantial decline in MDA serum levels in the rats. *Mucuna pruriens* suppress ROS production, increase free radical scavenging before they interact with the plasma membrane of sperm, and prevent membrane damage by impeding LPO production because they contain Phytochemicals and functional compounds with antioxidant activity (29,30).

According to the guidelines provided by the World Health Organization (WHO), conventional semen analysis is very important in identifying male infertility by estimating sperm parameters that include the determination of sperm total count, motility, and morphology(31,32).

In this study, chlorpromazine significantly restricts sperm motility and reduces sperm count. Also, it increases abnormal sperms, as shown in table (2) and figures (3,4,5). Oyovwi et al. (2021)(5) identified an analogous observation. who revealed that chlorpromazine decreased sperm count and reduced sperm motility and morphology. chlorpromazine-induced modification in sperm production, maturation, and motility is associated with decreased testicular dehydrogenases, such as luteinizing hormone (LH)(33,34). Moreover, chlorpromazine induced an excess of ROS that caused impairment of the motility machinery and flagellum of sperm (33,34) Sperm cells, which contain high levels of polyunsaturated fatty acids (PUFAs), play an essential role in ion transport and maintaining the fluidity of the sperm membrane. ROS causes oxidation of sperm membrane PUFA that leads to deficiency in membrane function of sperm and sperm death(35).Furthermore, high levels of ROS cause cellular injury by damaging DNA, lipids, and proteins in the cells, causing lipid peroxidation and increasing mitochondrial membrane permeability, interrupting the respiratory chain and ATP production that leads to ATP

consumption. The alterations in sperm membranes will cause injury to the membrane fluidity and affect motility, count, and morphology(17,36). Moreover, oxidative imbalance may be associated with increased immature sperm count(37).

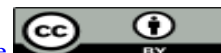
In the current investigation, *Mucuna pruriens* showed a significant decrease in the damage of sperm produced by chlorpromazine. *Mucuna pruriens* contains many bioactive constituents that play an important role in enhancing antioxidant levels and significantly decreasing lipid peroxide levels; it also inhibits hydroxyl radical and superoxide anion, nitric oxide radical scavenging (38). As a result, increasing sperm count motility and reducing structural and functional abnormalities further protect the mitochondrial membrane potential (MMP) in rat sperm from oxidative stress, reducing sperm cell apoptosis in testis and improving epididymal sperm maturation (39,40).

### Conclusion:

This study has clarified reproductive toxicity and testicular damage generated by chlorpromazine (synthetic antipsychotic drugs). Chlorpromazine disrupts the equilibrium between the production of ROS and antioxidants, leading to an increased level of oxidative stress that affects spermatogenesis and sperm parameters. Due to its antioxidant activity, *Mucuna Pruriens* can improve reproductive toxicity and testicular damage in rats.

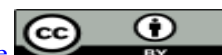
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