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Viagra exposure effects on learning and memory, some neurotransmitters and oxidative indices in male mice

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ABSTRACT

Background: Viagra is a white crystalline powder, with a molecular weight of 666.7, covered with a blue shell and takes the shape of a diamond or a rhombus. Male Swiss white mice were used to study the effect of Viagra on learning behavior, some neurotransmitters, and indicators of oxidative stress. In the Shuttle box, Water-maze, and *T*-Maze tests, Viagra -treated males showed decreased body weight and improved learning behavior.

Aim: The purpose of this study is to determine the effect of Viagra oral administration on learning behavior, neurotransmitters, and oxidative markers in male mice.

Methods: In this study, Dopamine (DA), 5-hydroxyanisole (5-HA) and acetylcholinesterase (AchE) were all downregulated. Biochemical assays such as glutathione (GSH) and enzyme activity of Glutathione S Transferase (GST), Catalase (CAT), and superoxide dismutase (SOD) and Thiobarbituric acid relative substances (TBARS) was studied.

Results: The results of this study show that the shuttle box test, Viagra exposure, water maize test, and *t*-maize test were all associated ($p < 0.05$). Exposure to Viagra decreased DA, 5-HT, AChE, GSH, GST, CAT, and SOD, although TBARS was significantly ($p < 0.001$) increased compared to their control groups.

Conclusion: This study contained the necessary explanations that explain the causes of the effect of Viagra on learning and other data, depending on the results obtained and other previous studies in this field. In general, Viagra still needs more studies to detect its harmful effects on other aspects of human and animal health.

1. Introduction

After the advent of Viagra, men considered this drug a legendary treatment for erectile dysfunction, which can solve all problems without side effects. Despite these dreams, the matter is still not without many concerns, especially since the results of recent scientific studies conflicted about the dangers of the drug (Yan et al., 2023; Aburawi et al., 2013). Viagra is a white crystalline powder, with a molecular weight of 666.7, covered with a blue shell and takes the shape of a diamond or a rhombus. The drug was produced commercially in three doses: 25, 50, and 100 mg given orally. Sildenafil, the active ingredient in Viagra, is used to treat erectile dysfunction in men (also called sexual impotence). PDE5 inhibitors, of which sildenafil is a member, are a class of drugs (Gadiya et al., 2019; Singh and Parle, 2003). Phosphodiesterase type-5 enzyme (PDE5) overactivity is prevented by these drugs. This enzyme can be found in the penis, one of the places where it is active. Men's bodies naturally respond to sexual stimulation by increasing blood flow to the penis, resulting in an erection. Sildenafil helps to maintain an erection after the penis is stroked by regulating the enzyme. Sildenafil does not work to produce an erection unless there is physical motion to the penis, such as that which occurs during sexual activity (Abdelsalam, 2018). Sildenafil was discovered as a treatment for angina pectoris (heart attacks), and Pfizer's laboratory decided to try this preparation in Britain on heart patients, but these people did not feel an improvement in their hearts, but all of them noticed a return to an active

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sexual life after a period of interruption of years due to their general condition. As of March 27, 1998, the FDA had given their approval to its use (Aburawi et al.,2013).

Sildenafil citrate or $C_{22}H_{30}N_6O_4S$ dilates the blood vessels in the pelvis and genital organs, which increases the strength and speed of blood flow in the body of the penis and causes enough force to complete the sexual process efficiently. The process of erection of the penis occurs as a result of blood congestion and its flow inside the penis and the increase in blood pressure inside it as a result of the increase in blood in the arteries feeding it with the contraction of the veins responsible for drawing blood from the penis to the blood circulation, which leads to an increase in the size and hardness of the penis, and the natural process of erection takes place as a result of excitement Sensory, mental or physiological sexuality, where signals arrive in the brain and sends nerve signals to the cells surrounding the penis, from which nitric oxide (NO) is released, which affects the penis in order to secrete the substance cyclic guanosine monophosphate, which expands the bloodstream in the penis It rushes inside and leads to an erection, and the erection continues as long as the excitement continues (Msiska et al., 2020; Kelly et al.,2008).

A multitude of biochemical and physiologic effects, as well as an impact on information processing, have been documented in existing studies that show sildenafil can penetrate the blood–brain barrier. According to previous research, NO synthase, PDE-5, and guanylyl cyclase are present at the highest levels in the parts of the brain that control behavior and sexual desire in male mice. The drug sildenafil has been linked to 274 adverse event reports, including forgetfulness and violent behavior, in addition to other neurologic abnormalities, including amnesia (Milman and Arnold, 2002). The purpose of this study is to determine the effect of Viagra oral administration on learning behavior, neurotransmitters, and oxidative markers in male mice.

2. Materials and methods

2.1. Mice

Swiss white mice were procured from the Animal House - Medical Research Center - College of Medicine - Jazan University and were between the ages of 10–12 weeks when they were adopted for the study. Animals have special environmental rooms, the ambient temperature ranges between 18 and 22 °C and the lighting duration is 12 h, from 22.30−10.30, followed by darkness for a similar period. The animals were placed in special plastic cages - their dimensions are $30 \times 12 \times 11$ cm, and they were provided with sawdust to absorb moisture and provide warmth to the mouse, in addition to helping to continuously clean the cages from time to time. Food (Pilsburyes Diet, Grain Silos, Jeddah) and water are available to animals ad libitum or as per experience. In addition, all animal care and care take place under the faint red light, in addition to all other behavioral studies.

2.2. Viagra administration and experimental design

Viagra was prepared at two doses (20 and 40 mg/kg). The experimental animals were separated into three groups, and distilled water or Viagra doses were administered orally through gastric tube for 30 days as follows:

1. The first group: Distilled water was given and this is the control group.
2. The second group: (20 mg / kg) was given of Viagra.
3. The third group: (40 mg / kg) was given of Viagra.

2.3. Mice body weigh

Weight is a good sign of the body's natural growth (Abu-Taweel,2020). In the current study, use the electronic scale (to determine the weights of animals in groups, so that the animals are weighed before exposure, then every-five days.

2.4. Behavioral assessment

2.4.1. Responses to avoidance

Using an automatic reflex conditioner called a "shuttle box," researchers monitored the animals' active avoidance behaviors (Ugo Basile, Comerio, and Varese, Italy). A stainless-steel wall with a gate allowing entrance to the adjacent compartment divided the rectangular shuttle-box into two equal-sized chambers. For two minutes prior to the commencement of the trials, each animal was permitted to adjust and become familiar with the shuttle box. As a conditioned stimulus, the light (21 W) and buzzer (670-Hz, 70-dB) were turned on at the same time for six seconds then shut off (CS). In order to test this hypothesis, we used a CS and an unconditioned stimulus (US). It was a shock to the grid floor delivered by an electric scrambler at a current of 1 mA for four seconds. A conditioned avoidance response was recorded by the shuttle box's microprocessor recorder if the animal ran into another compartment within 5 s of the commencement of the CS and avoided the electric shock. An inter-trial interval of 15 s was established for all of the animals. The total number of avoidances during the individual animal's 50-trial session were counted. Additionally, the total amount of time an animal spent in the other compartment in order to evade the shock treatment was recorded for each animal and the results were expressed for each group of animals. The number of crossings between chambers when no shock was present during UCS and CS was also used to assess the mouse's spontaneous migration to the opposite compartment between trials (inter-trial crossing). The automated shuttle box's recorder unit kept track of these variables throughout the duration of each animal's experiment (50 trials). An automated reflex conditioner "shuttle box" was utilized in previous studies to evaluate active avoidance reactions in mice [Abu-Taweels et al. (2012); Abu-Taweels et al. (2014); Ahmed et al. (2016); Abu-Taweels, 2018; 2020].

2.4.2. Morris Water-maze test

Rats (Rutten et al., 2002) and mice (Ahmed and Abu-Taweel 2018; 2019) have been extensively utilized to examine cognitive processes using the test (Morris, 1984). The mice were assessed for visual–spatial memory using a water-maze at the end of treatment (Morris, 1984). Galvanized white circular water tank (90 cm diameter, 50 cm height) filled with clear tap water (221 °C) to a depth of 15 cm was used to create this maze. At a depth of one centimeter below the surface of the water and 13 cms from the rim, an escape platform measuring 66 cm in stainless steel was installed. The platform couldn't be seen since the water was made opaque by adding 1 L of milk. The pool was divided into four sections by placing markers at the four corners of the rim in the directions of north (N), south (S), east (E), and west (W) (NW, NE, SE and SW). Animals could swim freely in a pool for 60 s without a platform on day one. The mice were able to acquire accustomed to the training environment because to the free swimming. It was on days 2–5 that animals were trained to identify and escape onto the submerged platform for 24 trials (six trials per day, inter-trial intervals of 30 s). The mouse was thrown into the water tank at the beginning of each experiment to ensure that it was completely submerged. Latency was measured between entering the pool and reaching the hidden platform (maximum trial duration of 120 s). After 120 s elapsed, if the mouse had not found the platform, a

glass rod directed it there manually, and a time was recorded for each of these experimenter-terminated trials. Each testing day's failure rate was calculated by totaling the number of failed trials. An interval of 30 s was provided for each mouse to relax and learn and remember the spatial clues that helped them get out of the platform. A wire mesh grid was set up at the end of the trials so that the animals could climb onto it and be taken back to their cages without additional intervention. The platform was removed from the pool for a 120-second probe trial on day 6 of the experiment with P 36 animals. An electronic time recorder recorded the amount of time spent in each of the four quadrants (during the 120-second probe test time). Normal animals often spend more time in the quadrant where the platform was previously positioned than in the other quadrants in this section of the probe trials in water-maze tests. The probe trial measures the strength of spatial learning, which is the closest human analog to episodic memory, and the testing procedures utilized during the four days of locating the hidden platform provide a measure of hippocampal-dependent spatial reference memory (Jeltsch et al., 2001; Spiers et al., 2001).

2.4.3. T-maze test

The animals in each of the three groups were denied food for the entire night preceding the examination. The raised *T*-maze was shaped like a T with three closed arms. a 100-by-10-by-20-centimeter main arm and two 40-by-10-by-20-centimeter side arms, all at a 20-cm height above the floor. The maze's arms are arranged in a *T*-shape. In the right lateral arm, we placed the rodent food. After each test, the maze was disinfected with a solution of 20 % ethanol. These carnivorous creatures were confined to the elevated *T*-main maze's arm, where they sat in an area facing the two lateral arms. The mice were allowed to roam the maze for one minute, after which the animal was taken out of the maze and placed in a cage for two hours. An experimenter who is unaware of the experiment's protocol observes the behavior of the mice in the main arm for five minutes. Under red illumination, the frequency and length of feeding and main arm visits were measured. In seconds, the amount of time spent searching for food and the amount of time spent in the food arm were calculated. According to Leret (2003), Maodaa et al. (2015), and Abu- Taweel (2015; 2020), the frequency and timing of food entry into the lateral arm was deemed a memory reflector.

2.5. Biochemical research

In order to conduct out biochemical experiments, liquid nitrogen was used to freeze the forebrain. Dopamine (DA) and 5-hydroxytryptamine (5-HT), two monoamine neurotransmitters, were measured in the manner reported by Patrick et al (1991). Using the Ellman et al (1961) technique, acetylcholinesterase (AChE) was determined. Oxidative stress indexes were also calculated. Using a UV–visible spectrophotometer, thiobarbituric acid-reactive substances (TBARS) were used to measure lipid peroxides (Ohkawa et al., 1979). The Mangino et al. (1991) method was used to measure the reduced glutathione (GSH) concentration. Catalase, GST, and SOD activity were all determined to be active in the body (Misra and Fridovich, 1972).

2.6. Analysis of statistical data

There was a one-way analysis of variance (ANOVA) performed on all of the experimental data (Khan et al., 2019). Students-Newman-Keuls multiple comparison exam was also performed. Various P levels such as $P < 0.05$, $P < 0.01$, and $P < 0.001$ were the three thresholds of significance (Abu-Taweel,2020).

3. Results

3.1. Mice bodies weight

Male mice administered with Viagra weighed substantially less than those in the control group ($P < 0.001$) at the end of the experiment (Fig. 1).

3.2. Behavioral evaluation

3.2.1. Reactions of actively avoiding

In shuttle box tests, exposure to Viagra significantly ($P < 0.001$) reduced the learning behavior of male mice compared to the control group (Fig. 2A-F).

3.2.2. Morris's water-maze

Fig. 3A-C shows that Viagra administration disrupted learning behavior in the Morris water-maze test significantly ($P < 0.001$) as compared to the control group (Fig. 3A-C).

3.2.3. T-Maze

A substantial ($P < 0.001$) learning deficit was observed in male mice exposed to Viagra in a *T*-maze test, compared to the controls (Fig. 4A-D).Fig. 5

3.3. Research in biochemistry

While TBARS (Fig. 6B) was elevated considerably ($P < 0.001$) compared to their control groups, exposure to Viagra reduced DA, 5-HT, AChE, GSH, GST, CAT, and SOD (Fig. 7A-C).

4. Discussion

Viagra is a white crystalline powder covered with a blue shell and takes the shape of a diamond or a rhombus (Singh and Parle, 2003). PDE-5 is inhibited by Viagra, preventing the breakdown of cyclic guanosine monophosphate (cGMP). As a result, it serves to extend the erection process. The summary of the action of this drug is that it inhibits the PDE-5 enzyme, so the result is a higher concentration of cGMP, which leads to a better expansion of the arteries, which leads to an improvement in the erection process, and through this property of this drug, it also helps to resume the erection even after ejaculation, but in the presence of sexual stimulus continuous. It is quickly absorbed (1–2 h), and takes effect within an hour or less (Aburawi et al.,2013).

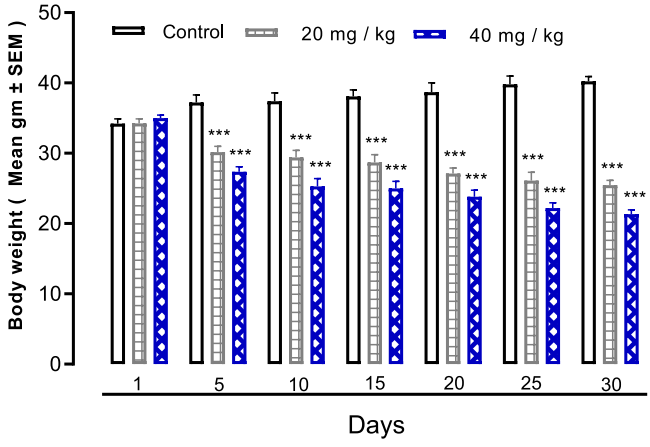

Fig. 1. Viagra exposure effects on body weight of male mice. ***represent statistically significant at $P < 0.001$ from the control by ANOVA and student's *t*-test.

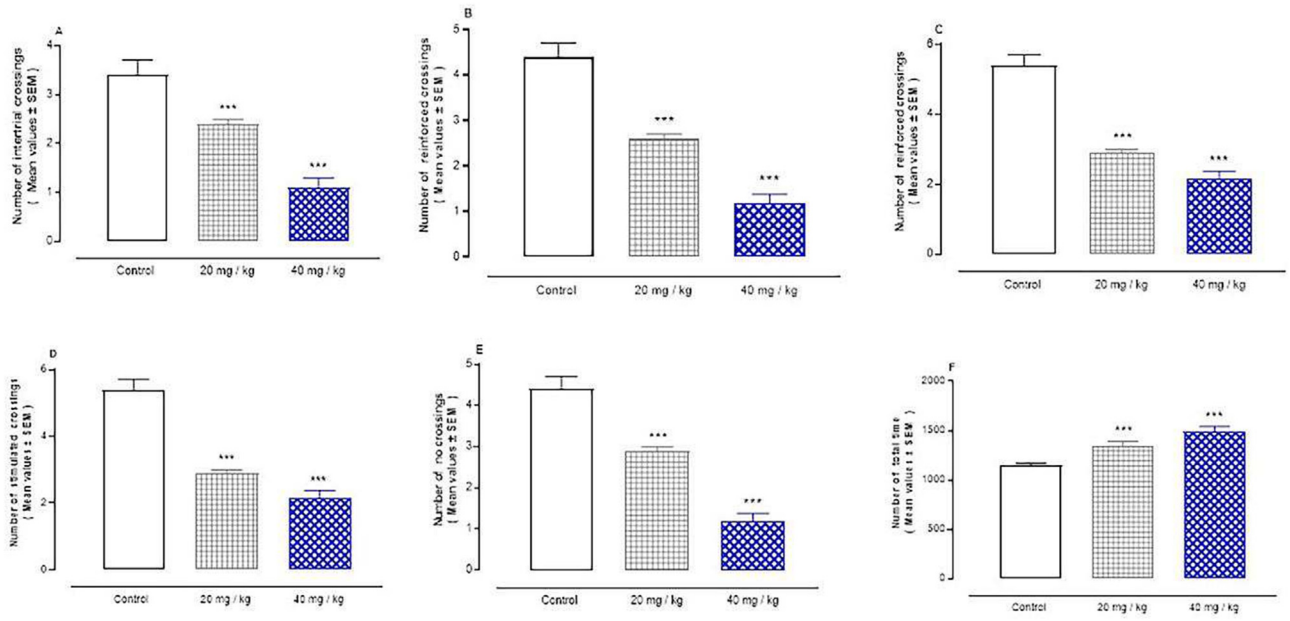

Fig. 2. A-F: Effects of Viagra exposure on learning behavior of male mice in shuttle box tests. *** represent statically significieant at P < 0.001 from the control by ANOVA and student's test.

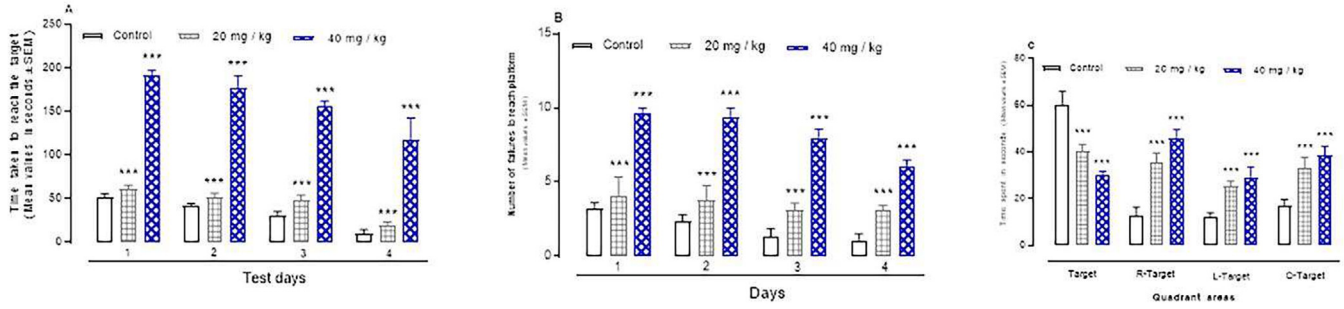

Fig. 3. A-C: Viagra effects on learning behavior of male mice in Mores water maze test. *** represent statically significieant at P < 0.001 from the control by ANOVA and student's test.

In the Shuttle box, Water-maze, and *T*-Maze tests, Viagra-treated males showed decreased body weight and improved learning behavior. 5 - hydroxyanisole (HA) and AchE were all downregulated. In comparison to the control, GSH and enzyme activity of GST, CAT, and SOD were decreased, while TBARS were elevated. According to the research of Hafez and El-Kazaz (2020), our findings are in agreement.

Body weight in treated male mice was significantly lower than in controls. Viagra's appetite suppressant effects have been reported for centuries (Mayo Clinic, 2021; Abebe et al., 2015). Side effects of Viagra include stomach upset, indigestion, dry mouth, nausea (severe or continuing), difficulty swallowing, stomach discomfort after meals, diarrhea, and tenderness in the stomach area. Abdominal or stomach pain, an increase in saliva, ulcers on the lips and in the mouth, rectal bleeding, a fast, irregular, or pounding heartbeat, and an increase in thirst are all symptoms of disorders that can reduce appetite and food intake (Mayo Clinic, 2021). In the Shuttle box, Water-maze, and *T*-Maze tests, who had taken Viagra showed reduced learning behavior. Learning and other behaviors are controlled by the brain and other variables, according to Abu-Taweel (2020). There are only a few pyramidal cell neurons left, and many of them have atrophied or deteriorated over time. With the vacuolation of their myelinated axons, their cytoplasm displayed varying degrees of cellular degeneration. Near-complete healing was evident in the pyramidal neurons of the recovery mice (Abdelhady, 2020). Viagra caused reversible alterations in the pyramidal neurons of the frontal cortex of adult male rats, according to the study's author. As revealed by Hafez and El-Kazaz (2020), sildenafil dramatically increased the levels of neurotransmitters in the brain's hippocampus region, including norepinephrine, serotonin (5-hydroxytryptamine), and GABA. There was an increase in malondialdehyde levels with a decrease in antioxidant parameters (reduced GSH, CAT, and SOD) activity) with the higher dose of sildenafil citrate (10 mg/kg) despite the fact that the lower dose of SC did not cause oxidative stress. SC treatments also elevated serum and brain hippocampus K, Cu, and Se concentrations. In addition, the raised plus maze test demonstrated that sildenafil had an anxiolytic effect. The effects of Viagra on the astrocyte cells that extend throughout the nerve ganglia and conduct numerous key roles, such as the learning process, are linked to the overall changes that happened in memory and learning in the treated mice. A problem that prevents these cells from carrying out their functions in organizing learning and influencing memory could be caused by structural or functional changes as a result of Viagra medication (Abdelhady,2020; Abu-Taweel,2019). Neuronal oxidative stress and programmed cell death, namely in that region, may be the root cause of the majority of learning difficulties (Safhi et al., 2014; Mohan et al., 2016). When aluminum and other oxidants such as metabolic products accumulate in the cell body or its branches, or when these branches are decreased,

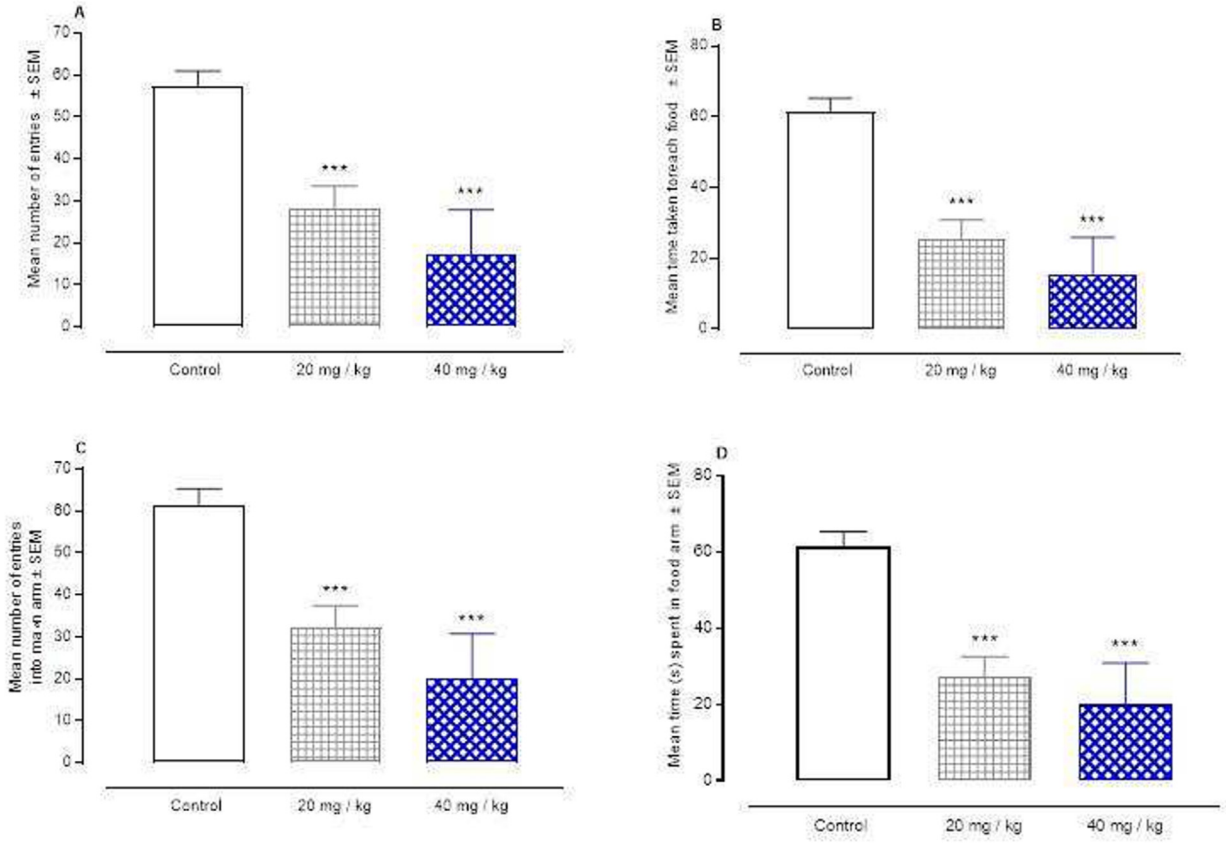

Fig. 4. A-C: Viagra effects on learning behavior of male mice *T*-maze test. *** represent statically significieant at P < 0.001 from the control by ANOVA and student's test.

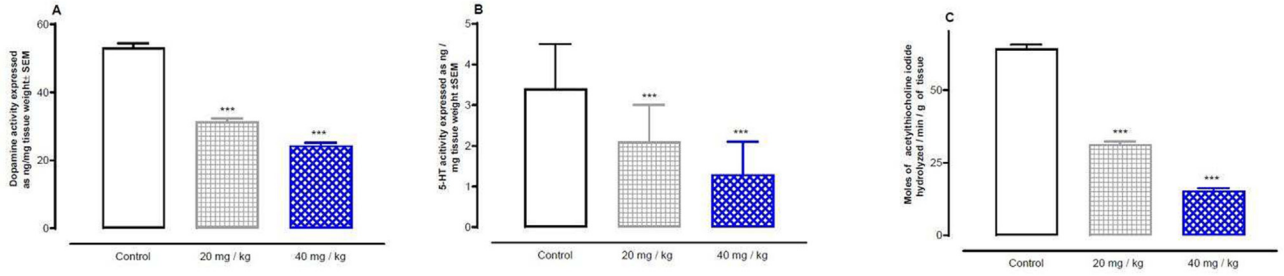

Fig. 5. A-C: Viagra effects on neurotransmitters,DA, 5-HT and ACHE of forebrain in male mice. *** represent statically significieant at P < 0.001 from the control by ANOVA and student's test.

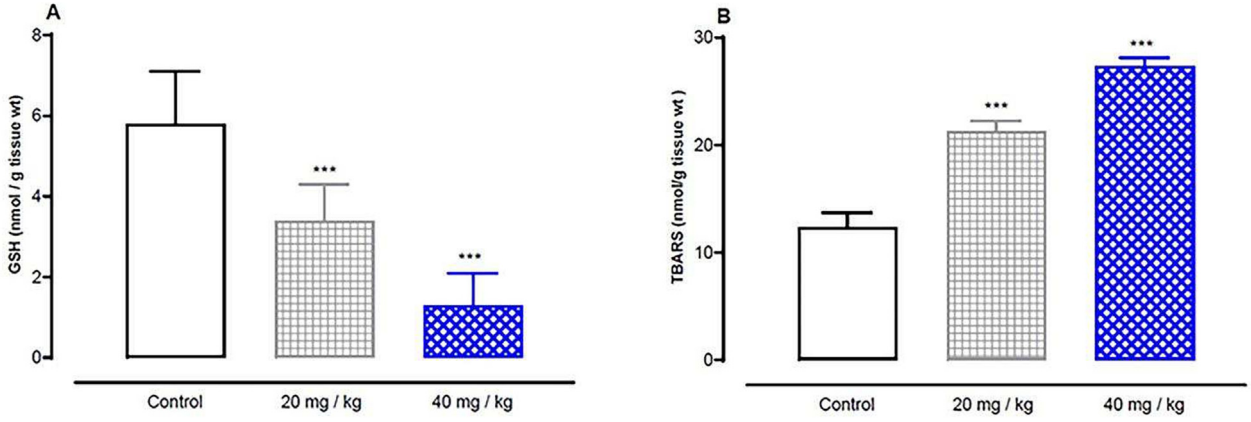

Fig. 6. A-B: Viagra exposure effects on non– enzymatic oxidative parameters, GSH and TBARS in forebrain of male mice. *** represent statically significieant at P < 0.001 from the control by ANOVA and student's test.

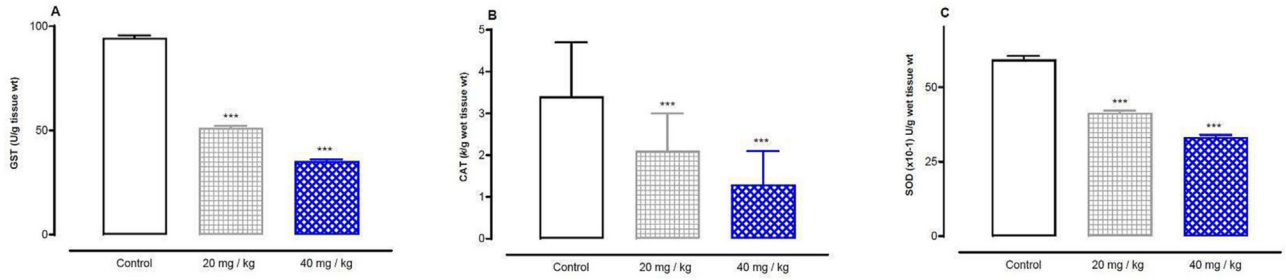

Fig. 7. A-C: Viagra exposure effects on enzymatic oxidative parameters, GST, CAT and SOD in forebrain of male mice. *** represent statically significieant at P < 0.001 from the control by ANOVA and student's test.

memory impairments can occur. Memory and learning are affected because the axons of the neurons are changed into a spherical or cordlike shape (Goncalves and Silva, 2007). One of the limitations of this study was missing out PCR and immunohistochemistry analysis.

5. Conclusion

The study results have established beyond a reasonable doubt the dangers of Viagra exposure on learning behavior and neurotransmitter levels in the body. Further prospective studies are needed to clarify and investigate Viagra's negative effects on behavior and biological aspects.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Further reading

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