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Evaluation of escitalopram induced reproductive toxicity in male Swiss albino mice

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ABSTRACT: Depression and anxiety are recognized as public health problems. For the treatment of major depressive disorder, antidepressant drugs are frequently prescribed worldwide. Antidepressants are a class of drugs that reduce the symptoms of depressive disorders by blocking the reuptake of neurotransmitter and by correcting chemical imbalances of neurotransmitters in the brain. The present study was carried out to evaluate the effects caused by escitalopram oxalate (an SSRI antidepressant) on male reproductive parameters of mice. The antidepressant drug was administered to *Swiss albino* male mice orally at the dose level of 10 mg/kg b.w./d and 20 mg/kg b.w./d for duration of 30 and 60 days. Body weight, relative sex organ weight, sperm parameters, biochemical parameters and marker of steroidogenesis were used as parameters to evaluate the toxicity of escitalopram oxalate on treated mice. The results showed significant decrease in body weight, weight of testis and epididymis. Escitalopram oxalate treatment also brought about marked reduction in sperm count, sperm motility and viability in exposed males. Testicular protein and sialic acid content reduced significantly whereas a significant increase in the glycogen and cholesterol content of testis was observed. In addition, 3 β-HSD and 17 β-HSD activity decreased significantly. In conclusion, escitalopram oxalate exerts toxic effects on testis of mice after 60 days of treatment at dose of 20mg/kg b.w./d.
KEYWORDS: Escitalopram oxalate; reproductive toxicity; biochemical parameter; male *Swiss albino* mice.

1. INTRODUCTION

Depression is the common psychiatric disorder, recognized as individual suffering from depressed or sad mood, loss of interest and energy and low self- worth [1] having high mortality and economic burden worldwide [2-5]. Approximately 3-4% of India's 100 crore plus population and 7–10% of the world population is affected by depression and anxiety and considered as common public health problems [6-7]. For the treatment of major depressive disorder, antidepressant drugs are frequently prescribed and are the third most commonly sold group of therapeutic agents worldwide and the goal of treatment with any antidepressant is to reduce symptoms at least by 50% [8-9].

Among antidepressants, selective serotonin reuptake inhibitors (SSRIs) are the newer antidepressant, first- line drug in treating depression and anxiety and now frequently used and prescribed due to the favorable side-effect profile and in year 2000, 65% of 20.5 million psychiatric patients are prescribed by SSRIs [10-12]. SSRI includes fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram and escitalopram. SSRIs act by blocking the uptake of serotonin into pre synaptic neuron and causing increased concentration in the synaptic space, resulting in the stimulation of post synaptic receptors. Sexual dysfunction, both male and female infertility, anorexia, weight loss, gastrointestinal disorders, diarrhea and palpitations are observed by treatment with SSRIs [13]. SSRI treatment are responsible for adverse effects on the reproductive system due to various hormonal and neurochemical changes in central and peripheral nervous system [14-15].

Escitalopram belongs to SSRI group of antidepressant and is the first antidepressant introduced according to chirality rules, which is an S-enantiomer of Citalopram. Mechanism of action of escitalopram is based on inhibition of serotonin transporter which leads to higher serotonin levels and a result of stimulation of serotonergic neurotransmission in the CNS [16]. It is one of the commonly prescribed SSRIs,

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used in the treatment of anxiety, and depression. Otherwise, it is noteworthy that there has been no published study on reproductive toxicity of escitalopram which is frequently used during reproductive ages in males. With this aim the study was designed to assess the effect of escitalopram (an antidepressant drug) on male reproductive parameters at repeated pharmacological doses in *Swiss albino* mice.

2. RESULTS

2.1. Effect on body weight and relative sex organs weight

Body weight: No significant changes were recorded in the body weight of mice when Escitalopram oxalate 10 mg/kg b.w. and 20 mg/kg b.w. was administered orally for 30 days as compared to the control mice. But when the treatment was continued for 60 days highly significant decrease (**P<0.01) was observed in both the treated groups as compared to their respective control group. No significant difference was observed within Group II and Group III (Table 1).

Testes weight: Escitalopram oxalate (20 mg/kg b.w./d) treated group for 30 days resulted in significant decrease (*P<0.05) in testes weight. But when the treatment was continued for 60 days, significant decrease (**P<0.01) was observed in both Escitalopram oxalate (10 mg/kgb.w. and 20mg/kg b.w. orally) treated mice as compared to the control mice. Significant reduction ($^{@}$P< 0.05) was observed when Group II compared with Group III after 60 days of treatment (Table 1).

Cauda Epididymis weight: Only Escitalopram oxalate (20 mg/kg b.w./d) treated group for 30 days showed significant decrease (*P<0.05) in epididymis weight. But when the treatment was continued for 60 days significant decrease (*P<0.05, **P<0.01) was observed in both Group II Group III treated mice when compared with control group. No significant difference was observed between Group II and Group III (Table 1).

2.2. Effect on sperm concentration, motility and viability

A significant decline (**P< 0.01, ***P< 0.001) was observed in the sperm count, motility and viability in cauda epididymis when mice were treated with both Escitalopram oxalate 10mg/kg b.w. and 20 mg/kg b.w. orally for 30 days and 60 days as compared to their respective control values. When mice were treated for 60 days, significant decrease ($^{@}$P< 0.05) was observed in sperm viability and sperm count when Group II compared with Group III (Table 2).

2.3. Effect on biochemical parameters

Protein content in the testes was found to decrease significantly (*P<0.05) in Group III treated mice after 30 days of treatment and highly significant decrease (**P<0.01) was observed in both the treated groups when compared with control group after 60 days of treatment. Significant reduction ($^{@}$P< 0.05) was observed in protein level when Group II compared with Group III after 60 days of treatment (Figure. 1)

Sialic acid content in the testes after 30 days of exposure showed highly significant decrease (**P<0.01) in Group III treated mice and after 60 days, significant decrease (**P<0.01) at both dose levels was observed when compared with control group. No significant difference was observed between Group II and Group III (Figure. 2).

Table 1. Body weight and relative organ weight of treated mice

Treatment	Body weight (g)		Testes weight (mg)		Cauda Epididymis weight (mg)	
	30 days	60 days	30 days	60 days	30 days	60 days
Group-I Control (vehicle)	30.25±0.69	31.67±1.02	123.7±0.57	124.56±0.69	18.39±0.09	19.5±0.42
Group-II Escitalopram oxalate (10mg/kg b.w./ day)	28.67±1.37	23.48±0.87**	118.20±1.28	90.45±1.19**	17.14±0.26	12.56±0.15*
Group-III Escitalopram oxalate (20mg/kg b.w./ day)	27.29±1.31	20.18±0.92**	114.58±1.15*	83.7±0.78**$^{@}$	13.64±0.21*	11.18±0.12**

The values are expressed as mean ± SEM (n=6).

*P<0.05, **P<0.01Escitalopram oxalate 10 mg/kg (Group II) andEscitalopram oxalate 20 mg/kg (Group III) treated groups compared with control group (Group I). @P<0.05 Group II compared with Group III.

Table 2. Cauda epididymal sperm analysis of treated

Treatment	Sperm count (Million / ml)		Sperm motility (%)		Sperm viability (%)	
	30 days	60 days	30 days	60 days	30 days	60 days
Group-I Control (vehicle)	42.35±1.21	41.12±1.75	83.67±0.82	82.12±1.24	67.06±1.96	70.43±1.46
Group-II Escitalopram oxalate (10mg/kg b.w./ day)	33.65±0.92**	23.8±0.22**	46.82±1.44**	27.06±1.19***	32±0.79**	22.41±1.19***
Group-III Escitalopram oxalate (20mg/kg b.w./ day)	26.43±0.79**	17.43±1.03**@	42.86±0.91**	25.83±2.15***	26.33±2.25**	19.67±1.25***@

The values are expressed as mean ± SEM (n=6).
**P<0.01, ***P<0.001 Escitalopram oxalate 10 mg/kg (Group II) and Escitalopram oxalate 20 mg/kg(Group III) treated groups compared with control group (Group I). @P<0.05 Group II compared with Group III.

The glycogen content increased significantly (**P>0.01, ***P>0.001) at both dose levels after 30 days and 60 days of treatment when compared with their respective control groups. Significant increase (@P> 0.05, @@P>0.01) in glycogen level was observed when Group II compared with Group III after 60 days of treatment (Figure. 3).

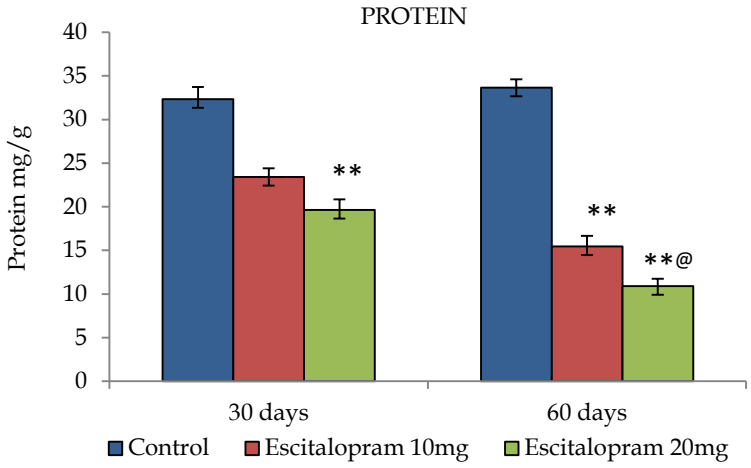

Figure 1. Effect of escitalopram oxalate on total protein level in mice.
The values are expressed as mean ± SEM (n=6).
**P<0.01 Escitalopram oxalate 10 mg/kg (Group II) and escitalopram oxalate 20 mg/kg (Group III) treated groups compared with control group (Group I). @P<0.05 Group II compared with Group III.

Statistical analysis was carried out by SPSS using one-way ANOVA, *post hoc tukey* test.

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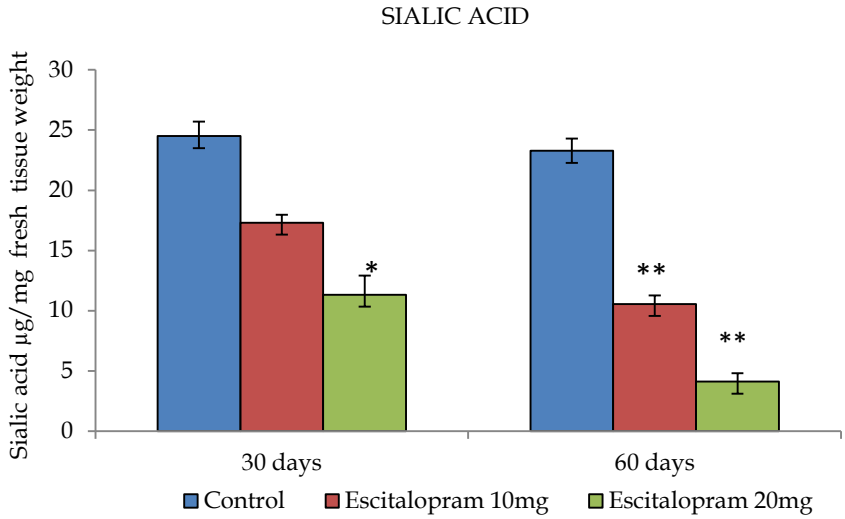

Figure 2. Effect of escitalopram oxalate on sialic acid level in mice.
The values are expressed as mean ± SEM (n=6).
*P<0.05, **P<0.01 Escitalopram oxalate 10 mg/kg (Group II) and escitalopram oxalate 20 mg/kg (Group III) treated groups compared with control group (Group I).

Statistical analysis was carried out by SPSS using one-way ANOVA, *post hoc tukey* test.

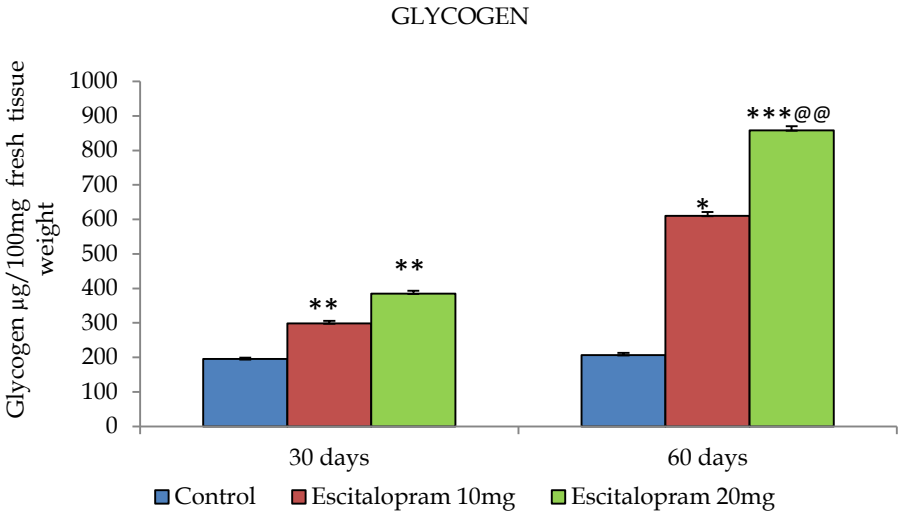

Figure 3. Effect of escitalopram oxalate on glycogen level in mice.
The values are expressed as mean ± SEM (n=6).
*P>0.05, **P>0.01, ***P>0.001Escitalopram oxalate 10 mg/kg (Group II) and Escitalopram oxalate 20 mg/kg (Group III) treated groups compared with control group (Group I). @@P>0.01 Group II compared with Group III.
Statistical analysis was carried out by SPSS using one-way ANOVA, *post hoc Tukey* test.

No significant difference was recorded in the cholesterol level of mice when Escitalopram oxalate 10 mg/kg b.w. and 20 mg/kg b.w. was administered orally for 30 days as compared to the control mice. But after 60 days of treatment, cholesterol content increased significantly (*P>0.05, **P>0.01) at both dose levels. Significant increase ($^{@}$P> 0.05) in cholesterol level was observed when Group II compared with Group III after 60 days of treatment (Figure. 4).

2.4. Effect on testicular steroidogenic enzyme activities

3βhydroxysteroid dehydrogenase (3β- HSD) enzyme activity in the testes was found to decrease significantly (*P<0.05) in Group III treated mice after 30 days of treatment. When the treatment was continued for 60 days, significant decrease (**P<0.01) was observed in both treated groups when compared with control mice. No significant difference was observed between Group II and Group III (Figure. 5).

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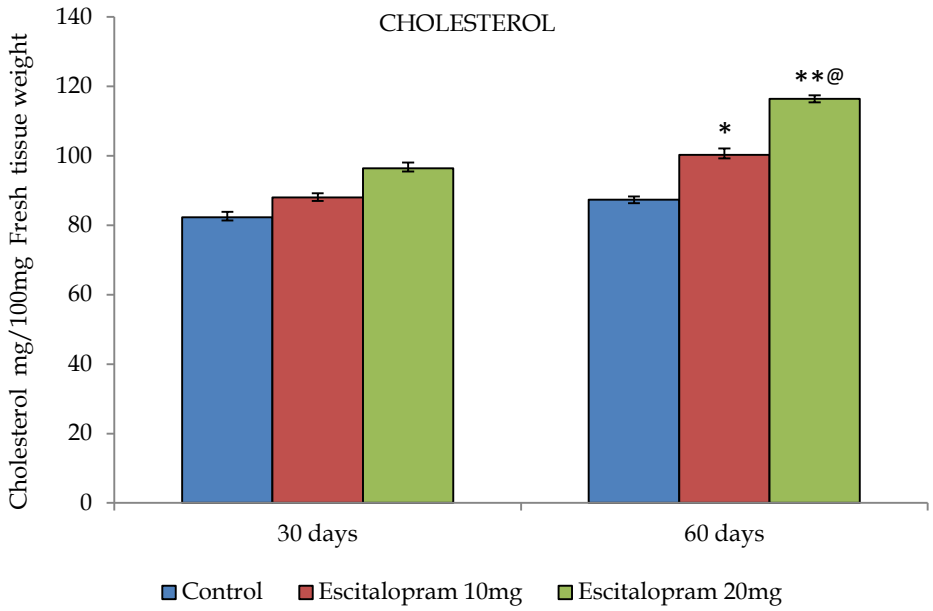

Figure 4. Effect of Escitalopram oxalate on Total Cholesterol level in Mice.

The values are expressed as mean ± SEM (n=6).

*P>0.05, **P>0.01 Escitalopram oxalate 10 mg/kg (Group II) and Escitalopram oxalate 20 mg/kg (Group III) treated groups compared with control group (Group I). @P>0.05 Group II compared with Group III. Statistical analysis was carried out by SPSS using one-way ANOVA, *post hoc Tukey* test.

No significant changes were recorded in the 17βhydroxysteroid dehydrogenase (17β-HSD) enzyme activity in the testes of mice when Escitalopram oxalate 10 mg/kg b.w. and 20 mg/kg b.w. was administered orally for 30 days as compared to the control mice. But when the treatment was continued for 60 days significant decrease (*P<0.05, **P<0.01) was observed in both treated groups as compared to their respective controls. Significant decrease (@P< 0.05) in 17β-HSD enzyme activity was observed when Group II compared with Group III after 60 days of treatment (Figure. 6).

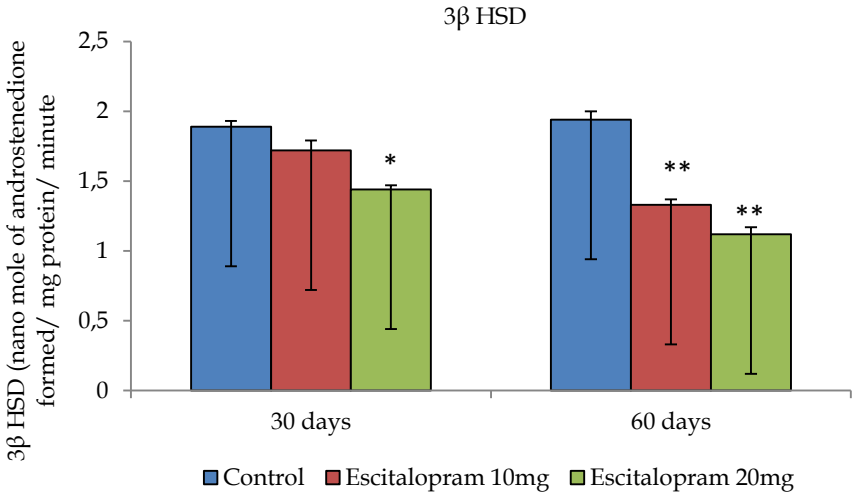

Figure 5. Effect of Escitalopram oxalate on Testicular 3β- HSD steroidogenic enzyme activities in Mice.
The values are expressed as mean ± SEM (n=6). *P<0.05, **P<0.01 Escitalopram oxalate 10 mg/kg (Group II) and Escitalopram oxalate 20 mg/kg (Group III) treated groups compared with control group (Group I). Statistical analysis was carried out by SPSS using one-way ANOVA, *post hoc Tukey* test.

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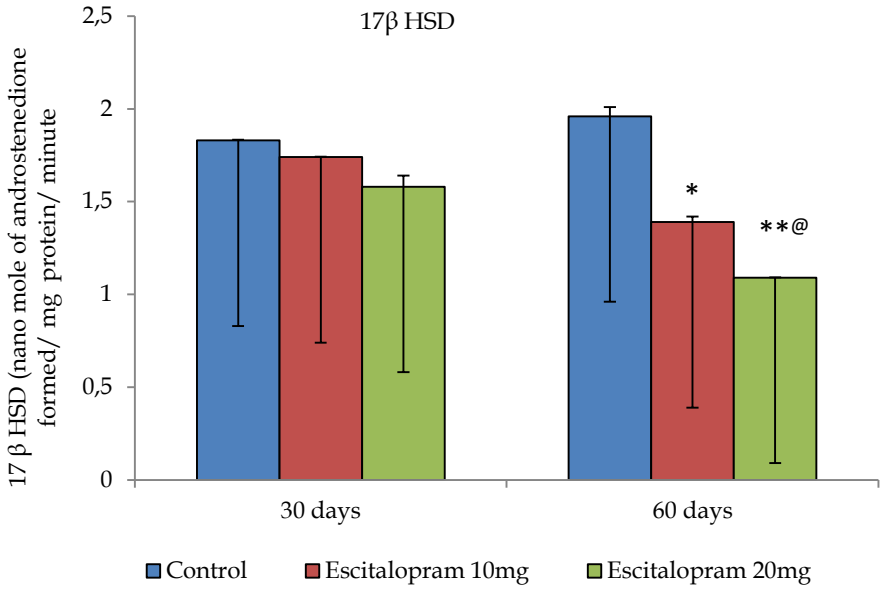

Figure 6. Effect of escitalopram oxalate on testicular 3β- HSD steroidogenic enzyme activities in mice.
The values are expressed as mean ± SEM (n=6). *P<0.05, **P< 0.01 Escitalopram oxalate 10 mg/kg (Group II) and Escitalopram oxalate 20 mg/kg (Group III) treated groups compared with control group (Group I). @P<0.05 Group II compared with Group III. Statistical analysis was carried out by SPSS using one-way ANOVA, *post hoc Tukey* test.

3. DISCUSSION

Testis is considered to be both an endocrine gland and most important male reproductive organ involved in spermatogenesis and steroidogenesis, responsible for hormones production and an important target for endocrine disruption [17-18]. Present study was conducted to access the effects of escitalopram oxalate exposure at two different concentrations on relative organ weight, sperm parameters, marker of steroidogenesis and biochemical parameters. In the present study, the control mice exhibited normal body weight throughout the study period. The mice treated with escitalopram oxalate revealed reduction in body weight as compared to control mice. The observed reduction in body weight might be due to direct cytotoxic effect of the antidepressant on somatic cells and regulation of endocrine functions, food and water intake by cental nervous system which is affected by the antidepressants [19-20] or may be due to metabolic disturbance or toxicity [21]. Similar decline in the body weight was also reported in various studies in mice treated with cyfluthrin [22], perchlorate [23] and manganese [24] intoxicated animals.

Testicular and accessory sex organ weight measurement is one of the end point tests for monitoring toxic effect of any test material on the reproductive organs. The mice treated with Escitalopram oxalate revealed reduction in organ weight as compared to control mice. Testicular weight and size are normally regulated by differentiated spermatogenic cell mass and the fluid secretion from the Sertoli cells [25]. Decreased number of germ cells and elongated spermatids [26], disruption of spermatogenesis and inhibition of steroid biosynthesis by Leydig cells [27-28] might be the reason for the reduction in testis and epididymis weight. These results are in agreement with earlier reports where similar decline in testes and epididymis weight has been reported in male rats treated with fluoxetine at a concentration of 200 mg/kg for 60 days [29]. Bellentani *et al* [30] concluded that sibutramine a monoamine reuptake inhibitor exposure to male rate at dose of 10 mg/kg b.w. for 28 days resulted in decrease in weight of reproductive organs.

Semen analysis like sperm count, motility and viability could be considered as marker for evaluating the fertilizing capacity of men. The present study showed decrease in sperm count, viability, and motility in mice given Escitalopram oxalate in dose dependent manner. This decrease in the concentration, motility, functionality, and morphology of spermatozoa might be due to disturbance in blood-testicular barrier [31] which reduce spermatogenic cells which disturbs spermatogenesis and result in declination of sperm count [32]. Our results are in agreement with study done by [29; 33] that showed oral administration of fluoxetine to male rats for 60 days resulted in significant decrease in sperm count and motility which leads to reduction in spermatogenesis. Similar study was done by Galal *et al* [34] who reported that rats treated with two different doses (9 mg/kg and 27 mg/kg) of fluvoxamine for 8 weeks resulted in decrease in semen

parameters, oxidative stress induction and apoptosis in the testes. Other studies examined the dose-dependent decrease in sperm count in animals when treated with 5, 10 or 20 mg/kg dose of sertraline and citalopram for 4 weeks [5;12].

Biochemical parameters are relevant marker indices of male testicular function which provide an insight of the internal milieu as well as structural and functional status of the organs. In the present work, total Protein, total cholesterol, sialic acid and glycogen were estimated to determine the functional capacity of testes.

Testicular proteins are crucial factor for proper development of testes, normal spermatogenesis and maturation of spermatozoa. In testis, the protein is considered as a marker of injury in the tissue, damage of cells and healing and a decrease value indicates toxicity in the animal [35]. In our study, mice treated with escitalopram oxalate resulted in a significant decline in testicular protein level. This may be a result of change in metabolism of protein or some formation of complexes with proteins or reduction in the number of germ cells in testis. These results are in agreement with earlier findings which also have shown decline of testicular proteins due to treatment of mice with fluoride, aluminum and its combination [36]. Similar studies were done by Pandey and Jain [28] who reported antispermatogenic and anti-androgenic activity of various metals in animals. Significant decline in protein content in testes of male rats administered with saponins isolated from *Albizia lebbeck* bark at the dose level of 50 mg/kg/b.w. per day for 60 days [37].

Sialic acid (N-acetylneuraminic acid) is a sialo mucopolysaccharide is a prime component of glycoproteins and glycolipids [38-39] and functions as a lubricant and immunoprotectant and helps in downward movement of sperms by reducing the friction among spermatozoa in the testis [40].The sialic acid is also involved in various processes such as stabilization of the plasma membrane, maintenance of ionic balance in epididymal plasma, keeping the sperms in decapitated state and interaction of antigen between sperm and epididymal epithelium [41]. In the present study, the testicular sialic acid concentration was decreased significantly in dose dependent manner in escitalopram oxalate treated mice. Decrease in sialic acid content in testes in mice suggest the deficiency of androgens and gonadotropins leading to inhibition of spermatogenesis and decrease in spermatozoal mobility and fertilizing ability [42]. Alteration in sialic acid content affects the functioning of gonads [43]. The results are in agreement with previous studies which also reported similar decline in testicular sialic acid content by fluoride treatment in mice [36], by aluminum treatment in rats [44], by treating the mice with cyfluthrin for 30 days [22].

Glycogen an energy producing source is the form of carbohydrates that are stored in the animal tissue. For maturation and proper functioning of gonads testicular glycogen content is crucial [45]. The increased level of glycogen in the testes observed in the present study reflects that Escitalopram oxalate interferes with the carbohydrate metabolism. Decrease in activity of glucose-6-phosphate dehydrogenase and glycogen metabolism might be changed due to accumulation of glycogen [46]. For ATP production, protein synthesis and for maintaining tissue integrity glucose acts as an essential substrate in the rat testis. Our results are in agreement with Patel et al, [36] who observed accumulation of glycogen in testis of mice treated with fluoride. According to Pandey and Jain; Das and Dasgupta [44; 47] mice treated with aluminum and nickel showed significant increase in the concentration of glycogen in testis.

Cholesterol an important constituent of the cell containing a mono atomic alcohol required for normal testicular activity, mass production of germ cells during spermatogenesis membrane biogenesis, cell signaling as well as precursor for androgen biosynthesis and bile acid synthesis [48]. Thus, male reproductive function has been clearly dependent on the cholesterol homeostasis. Accumulation of testicular cholesterol were interrelated with decline in the activities of steroidic enzymes (3β-hydroxysteroid dehydrogenase and 17β- hydroxysteroid dehydrogenase) which disturb the testicular steroidogenesis [49]. The results of the present study indicated a significant elevation in the testicular cholesterol levels in escitalopram oxalate exposed mice. Our results are in agreement with Kaur *et al* [50] who reported increased cholesterol content in testis in selenium treated rats. Similar elevation in testicular cholesterol content were also observed in rats treated with manganese chloride [51], chromium, mercury [52] and molybdenum [28].

3β-HSD and 17β-HSD are the two rate limiting enzymes which controls testicular androgenesis. In testosterone biosynthetic pathways, 3β-hydroxysteroid dehydrogenase (3β-HSD) and 17β-hydroxysteroid dehydrogenase (17β-HSD) plays an important role and as such are frequently targets for endocrine-disrupting chemicals [53]. In the current study, the analysis of intermediate enzymes in the pathway of steroidogenesis after escitalopram oxalate treatment observed a decrease in the activities of 3β hydroxysteroid dehydrogenase and 17β hydroxysteroid dehydrogenase. These results were interrelated with deposition of cholesterol in the testis. Similar studies are in agreement with Chakraborty [23] who concluded that when mice treated with perchlorate orally lead to decline in the levels of 3 β -HSD and 17 β -HSD in the

testis. Pant and Srivastava [54] also reported that the rats exposed to several xenobiotics leads to decrease in male reproductive potential with decline in the levels of 17 β hydroxysteroid dehydrogenase. Chang *et al* [55] reported decrease in the activities of testicular 3β- HSD and 17β-HSD in arsenic treated mice. Pogrmic *et al*; Abarikwu *et al* [56; 57] demonstrated that both short term or long term exposure of rat to atrazine. Dorman *et al* [58] concluded that exposure of manganese to Leydig cells of rat *ex vivo* downregulates steroidogenesis in Leydig cell through suppression of several genes responsible for 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase.

4. CONCLUSION

In conclusion, the results of present study provide evidence for adverse effects of Escitalopram oxalate antidepressant drug on male reproductive system. On the basis of the findings, it can be inferred that escitalopram oxalate 20mg/kg b.w./day exerts an adverse impact on steroidogenesis and sperm quality by varying the biochemical milieu of testis. It is assumed that these changes would interfere with the proper functioning of the testis. Thus, it may be concluded that escitalopram oxalate at dose of 20mg/kg b.w. per day for 60 days exposure induces male reproductive toxicity and may consequently contribute to male infertility.

5. MATERIALS AND METHODS

5.1. Drug

Escitalopram oxalate (Nexito) tablet each contained 10 mg and 20 mg which is manufactured by Sun Pharma laboratories ltd., India was obtained from Jaipur, India.

5.2. Experimental animal

The study was carried out on adult Swiss albino (*Mus musculus*) male mice approx weighing 25-30 g procured from the animal house of IIS (deemed to be University) Jaipur approved by the Ethical Committee CPCSEA Registration number No:1689/PO/9/13/CPCSEA. Clean properly ventilated cages were used for housing the animals and they were fed with standard laboratory diet and water *ad libitum*. 12 h light/dark condition was maintained in the animal house.

5.3. Experimental design

Animals were randomly divided into three groups.

Group I (control): animals received water orally through intubation tube for continuous 30 days (n=6) and 60 days (n=6) once a day

Group II: animals received escitalopram oxalate (10 mg/ kg b.w./ d) dissolved in water orally through intubation tube for continuous 30 days (n=6) and 60 days(n=6) once a day

Group III: animals received escitalopram oxalate (20mg/ kg b.w./ d) dissolved in water orally through intubation tube for continuous 30 days (n=6) and 60 days(n=6) once a day

The dose of escitalopram oxalate 10 and 20 mg/kg dose were selected for the experiment according to Waugh and Goa, 2003 [59]. On 31st and 61st day animals were weighed and anesthetized with an intraperitoneal injection of mild dose of sodium thiopental (30 mg/kg) followed by cervical dislocation. Then the testis, cauda epididymis was collected, weighed and used for estimation of sperm parameters biochemical parameters and markers of steroidogenesis.

5.4. Body and organ weight

The testes were removed from the animal body and weighed, the ratio of organ to body weight was calculated.

5.5. Assessment of sperm concentration, motility and viability

Cauda epididymal sperm motility and viability was recorded in percentage of motile and viable sperms was calculated per unit area. Sperm count (million/ml) were assessed using hemocytometer Neubauer's counting chamber [60].

5.6. Testicular biochemistry

Testicular tissues were assayed for total protein [61], sialic acid [62], total cholesterol [63], glycogen [64].

5.7. Markers of steroidogenesis

Testicular tissues were assayed for 3β hydroxy steroid dehydrohenase and 17β hydroxy steroid dehydrohenase enzyme activity [65].

5.8. Statistical analysis

The data obtained by present study was analyzed by SPSS using one-way ANOVA (Analysis of variance) followed by posthoc Tukey's test for comparison between all groups and were expressed as mean ± SEM (Standard error). Differences wereregarded as significant if P<0.05(*), highly significant if P <0.01(**) and very highly significant if P <0.001(***).

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Conflict of interest statement: The authors declared no conflict of interest in the manuscript.

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