https://doi.org/10.48047/AFJBS.6.15.2024.13288-13303

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Beneficial effects of natural antioxidants on reproductive toxicity and semen quality induced by subchronic oral exposure to organic solvents

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Volume 6, Issue 15, Oct 2024

Received: 15 Aug 2024

Accepted: 25 Sep 2024

Published: 21 Oct 2024

doi: 10.48047/AFJBS.6.15.2024.13288-13303

ABSTRACT

The aim of this research is to examine the potential protective effect of *Sesamum indicum* L (SS) against reproductive toxicity induced by Ethylene Glycol Monomethyl Ether (EGME) in male rabbits (*Oryctolagus cuniculus*). Twenty-four adult rabbits were split equally into four groups (n=6): control, SS (150 mg/kg bw), EGME (150 mg/kg bw), and combined group (EGME-SS). The rabbits were orally administered the respective treatments daily for a period of four weeks. The effects on sperm biology, serum testosterone levels, and oxidative stress markers in the testicular tissue were evaluated, along with the histology of the testis and epididymis. The findings showed that EGME had a deleterious effect, as seen by a marked drop in blood testosterone levels and spermatozoa motility, concentration, and speed. Nonetheless, the testosterone concentration and sperm biology of the SS group were significantly improved. Interestingly, the EGME-SS group exhibited markers that were nearly the same as the control group, except for significantly higher spermatozoa concentration, highlighting the beneficial use of sesame. The EGME treatment led to an increase in lipid peroxidation levels, while concentrations of GSH, GPX, and CAT in the testes decreased in contrast to the control group. However, the concurrent supplementation of sesame significantly alleviated testicular GSH, GPX, and CAT concentration. Histological analysis revealed changes and damage in the testes and epididymis tissues of EGME-treated rabbits, including the absence of spermatozoa in several seminiferous tubules. In contrast, the histology of organs in the EGME-SS group showed less deterioration, indicating the preventive activity of sesame against EGME-induced toxicity.

Keywords: *Ethylene glycol monomethyl ether, Reproductive toxicity, Sesamum indicum* L, *Reproductive protection, Male rabbit*

INTRODUCTION

Reproductive toxicity is mainly caused by various toxic products from the environment that disrupt the reproductive process, such as male and/or female infertility, spontaneous abortion, embryotoxic or fetotoxic effects (Michel *et al*., 2003). Ethylene glycol monomethyl ether (EGME), a common solvent used in the production of varnishes, textile dyes, printing inks, and jet fuel anti-icing additives, is one of these contaminated products. EGME exhibits a wide spectrum of toxic effects. It exerts its action after being metabolized by alcohol and dehydrogenase aldehyde into aldehydes and alkoxyacetic acids. The latter present toxicological properties similar to those of their precursor molecule because the ester bond is hydrolyzed very quickly. This suggests that these metabolites are responsible for the toxicity (Miller, 1987).

EGME is particularly harmful to organs including the liver, testes, thymus, and bone marrow in various animal species, including humans (Hardin, 1983; Beattie and Brabec, 1986; Li *et al*., 1996). EGME's reprotoxicity includes testicular degradation, impaired spermatogenesis, altered properties of spermatozoa, female infertility, and toxicity to embryonic development (including risks to pregnant females, data on fetal mortality, and malformations) (Lorente *et al*., 2000; Maldonado *et al*., 2003; Boatman, 2005; Cicolella, 2006).

Today, many ailments are treated with a variety of medicinal herbs, providing nutrition, and maintaining health due to their affordability, safety, and non-toxicity compared to synthetic drugs (Daglia *et al*., 2014; Selamoglu *et al*., 2017a; Selamoglu *et al*., 2017b). Researchers have suggested the use of natural products to reduce the toxic effects of EGME.

In this study, we propose the use of *Sesamum indicum* L, which is an annual aromatic plant that is considered one of the oldest crops known to humanity (Honjoya *et al*., 2021). It is part of the Pedaliaceae family of flowering plants and is distributed around the world. As an extensively grown member of the genus, sesame is well-known (Morris *et al.*, 2021). Since sesame seeds have been used by the Chinese for over 5,000 years, their oil has been burned to create soot for Chinese ink blocks. Sesame oil is used in industries for the production of various substances such as soap, paint, insecticide, etc. (Rasolofomanana, 2016). It is also used in the formulation of skincare and haircare preparations (Honjoya *et al*., 2021). Multiple studies have reported that sesame possesses antidiabetic (Manoj *et al*., 2020) , antimicrobial, anticancer (Wu *et al*., 2019), anti-aging and hypocholesterolemic effect. Additionally, sesame seeds have a potent emollient effect against constipation and are rich in

a valuable phosphorus compound called lecithin, which plays a vital role in the functioning of brain, nervous system, endocrine glands, heart, and sexual function (Rasolofomanana, 2016). Consequently, the purpose of this study is to look into how sesame may shield rabbits against oxidative stress brought on by ethylene glycol monomethyl ether (EGME), testicular tissue damage, and infertility.

MATERIALS AND METHODS

Chemical material

Ethylene glycol monomethyl ether

EGME was obtained from the Chemical department of Badji Mokhtar university (Annaba).

Biological material

Plant

In June 2024, seeds of *Sesamum indicum L.* were procured from Khenchela region in Algeria. After being cleaned, the fresh seeds were ground into a powder using a handmade mixer.

Animals

Twenty-four male rabbits from Pasteur Institute of Algeria were used in this investigation. The animals were housed in polypropylene cages with normal amenities, given commercial food pellets and unlimited water, and given a week's acclimatization period prior to the studies. The National Institutes of Health's Guidelines for Animal Care were followed during the experimentation process, and our institution's Ethics Committee gave its approval.

Experimental design

The rabbits weighing an average of 2362.3±177.5g at seven months of age, were split into four equal groups as they are:

- ***Control group (C):*** received 2ml physiological water
- ***Positive control group (SS):*** received 150 mg of sesame powder per kilogram of body weight.
- ***Group (EGME):*** received 150 mg/kg of EGME
- ***Group (EGME-SS)*****:** received a combination of SS with EGME (150+150 mg/kg bw)

The sesame seeds and EGME were administrated orally for four weeks. Upon the conclusion of the therapy duration, the rabbits belonging to the various groups were beheaded and slaughtered. To acquire serum for measuring testosterone levels, after being collected in tubes, blood samples were centrifuged for 15 minutes at 4000 rpm. For a histological examination, the testes and epididymis were excised, fat was removed, and they were kept in diluted formalin (10%).

Semen analysis

A tiny incision was performed in the caudal epididymis to collect a drop of sperm, which was then diluted in one milliliter of physiological saline (0.9% NaCl) in order to research the biology of sperm. Sperm concentration, motility, speed, and vitality were assessed using the World Health Organization's (1993) methodology.

Testosterone level

The commercial kit (ST AIA-PACK Testosterone Enzyme Immunassay) and equipment TOSOH AIA System Analizers (3-8-2 Shiba, Minato-ku, Tokyo, Japan) were used to measure the serum testosterone level. The amount of testosterone was stated in nanograms per milliliter.

Assessment of antioxidant defenses and oxidative stress

Lipid peroxidation, quantified as malondialdehyde (MDA), was established in testes tissue homogenates as described by Preuss *et al.* (1998) . Nitric oxide levels were calculated in the testes homogenates by measuring nitrite content using the Griess assay as detailed by Montgomery and Dymock, (1961). This colorimetric method involves a response from nitrite, N-(1-naphthyl) ethylenediamine and sulfanilamide to generate a pink chromophore with peak absorbance at 543 nm. Reduced glutathione (GSH) quantities were evaluated in the testicular homogenates via the protocol documented by Beutler *et a*(1963). The activity of glutathione peroxidase (GPx) in testicular tissue was quantified using the protocol documented by Matkovics *et al*(1998). Catalase (CAT) enzyme kinetics were evaluated spectrophotometrically following the methodology outlined by Aebi (1984), where the breakdown of hydrogen peroxide (H_2O_2) substrate in the testes preparations was tracked via absorption measurements at 240 nm over time.

Testes protein content determination

Using bovine serum albumin as a reference in Bradford (1976) method of measuring protein.

Histological evaluation

Testicular slices and sections of epididymis specimens preserved in 10% formalin and embedded in paraffin wax were subjected to histological assessment. Subsequently, hematoxylin and eosin-stained 4 µm-thick slices were cut, inspected under a light microscope, and any changes in histology were noted (Haoult, 1984).

Data analysis

The acquired data were displayed as mean ± SD. Student's *t-test* for comparison of two means was used in the statistical analysis of the data. At p≤0,05, the statistical test was deemed significant.

RESULTS

Testosterone level

When EGME was administered to rabbits, in contrast to the group under authority, they had considerably reduced serum testosterone levels. Although the effect was less strong, the testosterone level was lowered in the combined group (EGME-SS). In contrast to the other groups, the sesame-treated group's level was noticeably higher **(Table 1)**.

Sperm parameters

The spermatozoa in the EGME-treated group had significantly lower motility, concentration, speed, and vitality, according to the epididymal sperm assay results the group that received sesame (SS) shows a discernible improve in every sperm parameterment comparative to control group. In contrast to the EGME group, the combined treatment group (EGME-SS) exhibits a considerable improvement in spermatozoa concentration and a moderate enhancement in speed and mobility (Table 1).

Tab1.Effect of EGME and sesame treatment on testosterone level and spermatozoa biological characteristics (concentration, motility, speed and vitality).

	Control (C)	**SS**	**EGME**	**EGME-SS**
Hormone parameter				
Testosterone level (ng/ml)	1,80±0,122	1,98 ±0,210 **a^{NS}**	0,862±0,199 **a***,b*****	1,718±0,13 **a*,b***
Sperm parameters				
Concentration ($\times 10^6$/ml)	420,41± 9,01	463,5±19 **a****	310,1±23,9 **a***, b*****	411,5±30 **a^{NS}, b****
Mobility (%)	57,40±1,73	62,34±4,63 **a^{NS}**	35,67±6,41 **a***,b*****	54,86±5,35 **a^{NS}, b***
Speed (µm/s)	41,4±7,67	46,22±6,07	34,6±8,01 **a**,b*****	38,97± 6,77 **b***
Vitality (%)	59,07± 8,09 b*	64,5 ±4,62	41,87± 3,10 a***,b***	57,78± 4,7 b*

***a** : control Vs EGME. Control Vs SS Control Vs EGME-SS **b**:SSVs control SS Vs EGME SS vs EGME-SS*

*Data are expressed as M ± SD (n=7). ***P<0.001 **P<0.01 *P<0.05*

Effects of treatments on testes oxidative stress parameters

As observed in Figure 1, exposure to EGME resulted in a notable increase ($p<0.01$) in MDA levels (Figure 1-A), accompanied by a decrease ($p<0.01$) in both GSH concentration and CAT activity ($p<0.01$) in testes, in contrast to the control group and the positive control (Figure 1-B-D). These figures also demonstrate that the administration of sesame powder in combination with EGME reduced the toxic effects of EGME in testes. This was demonstrated by an increase in GSH concentration and a drop in MDA levels ($p<0.05$). Moreover, GPx activities were significantly decreased ($p<0.001$) after receiving EGME (Figure 1-C). Nevertheless, the concurrent addition of sesame powder resulted in a resurgence of these enzymes' activities within testes.

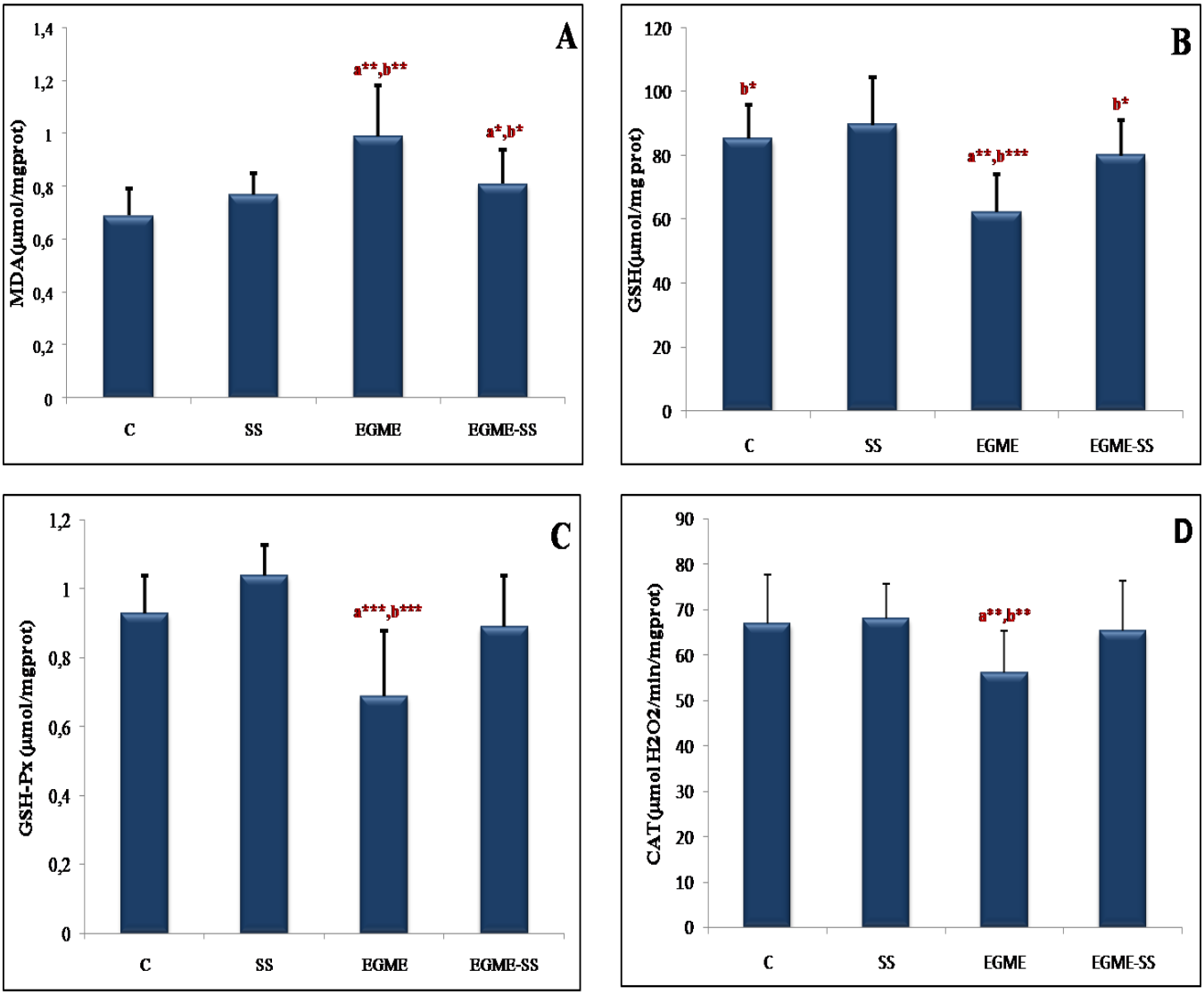

Fig.1. MDA, GSH, GPx and CAT concentration in the testes of control rabbits, treated with SS, EGME and EGME-SS after four weeks of treatment

*Values are given as mean± SD of six rabbits each group**P<0.01 and ***P<0.001*

Histological study

Testicular histology

The transverse slice of the seminiferous tubules in testes of treated and control rabbits is depicted in the photomicrograph in Figure 2. Seminiferous tubules with normal-looking spermatogenesis where mature spermatozoa occupy the majority of the lumen and preserve the proper diameter are shown in the control groups (C) and positive control (SS). Every step of spermatogenesis has a precise definition. As opposed to the control group, the EGME-treated group has less intense seminiferous tubules. Additionally, there is a change in the tissue structure, which may be brought on by the hazardous substance-induced apoptosis or necrosis of cells, which eliminates spermatogenic cells. In contrast to the (EGME) group, the (EGME-SS) group exhibits a restoration of the overall normal testis structure.

Epididymal histology

Both the control (C) and positive control (SS) groups demonstrated normal tissue with spermatozoa packed in the lumen of the epididymal tubules. In contrast to the control groups (C) and (SS), we observed a change and a decrease in the number of spermatozoa in the epididymal tubules in EGME-treated group. However, we noted a higher sperm density in the epididymal ducts in (EGME-SS) group (figure 3).

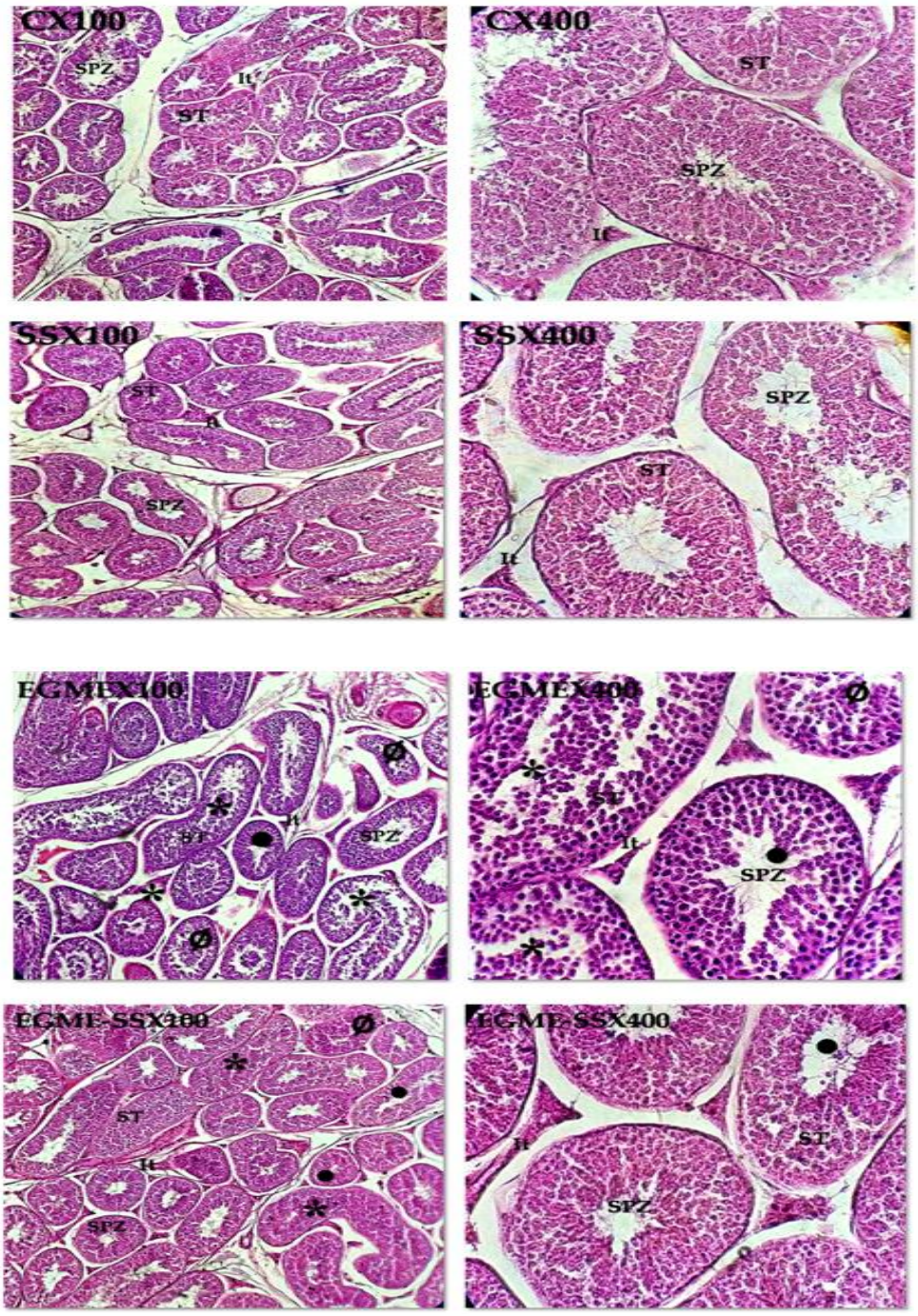

Fig.2. Photomicrographs (×100, ×400 magnifications) stained rabbit testicular longitudinal sections.**ST**. Seminal tube, **spz.** Spermatozoa, **It.** Interstitial tissue, (●) spz decrease, (*****) tissue degeneration (**Ø**) Absence of spz.

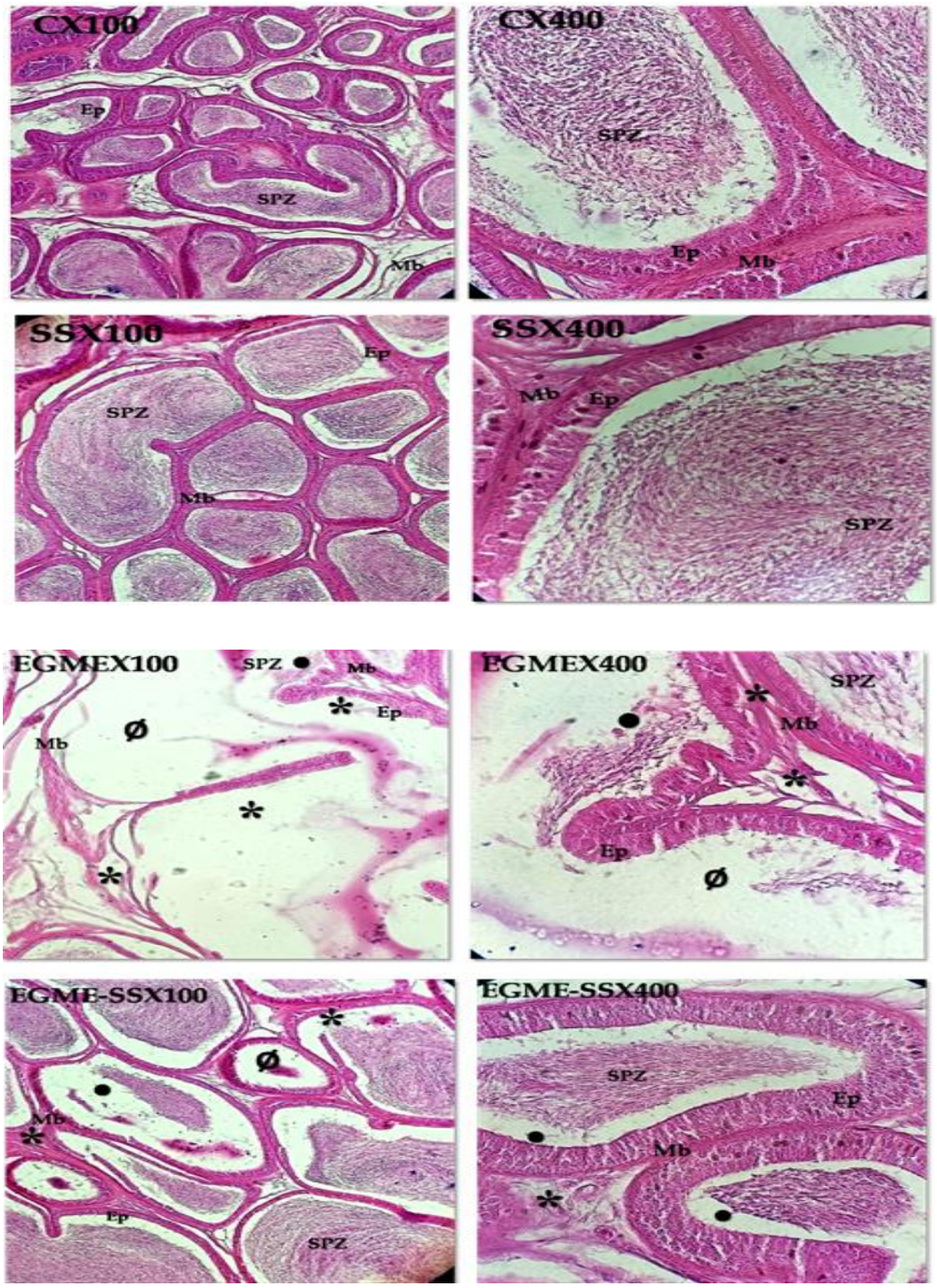

Fig.3. Photomicrographs stained rabbit epididyme longitudinal sections **() of** rabbits in the control and treated group (× 100, × 400 magnifications).**mb**. limiting membrane, **Ep**. epithelium, **Spz.** Spermatozoa. (●) spz decrease, (*) tissue degeneration (Ø) Absence of spz.

DISCUSSION

This study aims to evaluate the protective effect of the *Sesamum indicum* L against Ethylene Glycol Monomethyl Ether -induced reprotoxicity. Our experimental results indicate ,when EGME was taken orally, the testosterone concentration in the EGME group was notably less than in the control group. This decrease can be attributed to the depletion of testosterone plasma content caused by EGME. The metabolites of ethylene glycol monomethyl ether, as an endocrine disruptor, can affect the functioning of Leydig cells responsible for testosterone production. These molecules can bind to LH (Luteinizing hormone) receptors in Leydig cells, leading to an imbalance and/or blockage in testosterone production (Reader et al., 1991) . Other studies have demonstrated that this solvent can also impact LH levels and Sertoli cells structure and morphology (Tiradoet al., 2004). Djebaili (2009) reported that EGME reduces hormone levels, particularly testosterone, due to the histopathological changes in the testes induced by EGME in rats and dogs.

The results indicate that treatment with EGME alone resulted in a significant reduction in epididymal sperm speed, motility, vitality, and sperm concentration. These findings are consistent with previous studies by Adedara and Farombi, (2010) whose suggesting that the toxic effects of EGME on sperm count may be attributed to its impact on specific stages during spermiogenesis (de Rooji, 1998). EGME-induced inhibition of spermatogenesis and the selective loss of maturing and elongated spermatids may contribute to these effects, as evidenced by the dilation of seminiferous tubules in treated animals (PHS, 1996). Ethylene glycol monomethyl ether has been documented to have detrimental effects on both early and late pachytene and dividing spermatocytes. Further studies have shown that meiotic cells in the testis are mostly affected by EGME and its metabolites, whereas cells going through mitotic division seem to be spared. This lends credence to the idea that distinct processes underlie the testicular effects of EGME therapy (Lee & Kinney, 1989). Furthermore, this organic solvent also affects sperm mitochondria, leading to a decrease in motility and speed (Paul, 1984).

The EGME-treated group displayed seminiferous tubules with lower density compared to the control group. This decrease possibly attributed to cell necrosis or apoptosis induced by EGME, resulting in the absence of sperm in the lumen of certain seminiferous tubules. Moreover, there was a noticeable change and decrease in the number of sperm in the epididymal tubules' lumen in the EGME-treated group in contrast to the control (C) and positive control (SS) groups. These results are consistent with the research being conducted by Stenger *et al.* (1971), which reported histopathological changes in the testes of rats and

dogs exposed to EGME through various routes and for different durations. Interstitial edema and a decrease in the number of late maturation stages were among these alterations, which ultimately resulted in testicular atrophy, which was identified by a germinal epithelium with a single layer of cells made up of primary spermatogonia and Sertoli cells.

The administration of EGME resulted in a notable augmentation in MDA (malondialdehyde) levels and a decrease in GSH (glutathione), CAT (catalase), and GPX (glutathione peroxidase) concentrations in the testis, indicating the induction of oxidative stress. These changes in oxidative stress markers suggest damage to the testicular tissue and the potential for infertility. Our findings align with the studies conducted by Adedara & Farombi (2010), Oyinloye *et al*., (2016) and Somade *et al*., (2020). Previous research has demonstrated that oxidative stress in testicular tissue adversely affects reproductive function and can lead to infertility (Murugesan *et al*., 2005).

A noticeable improvement in all sperm parameters was observed when sesame was added to the rabbit's diet, indicating the protective role played by this plant. Sesame supplementation is essential for detoxifying EGME as it can neutralize free radicals and directly react with peroxide radicals. Positive results have been seen in studies looking into the ability of ethanolic extract from sesame cake and a combination of vitamin C and sesame extract to increase rat fertility. Increased sperm motility, serum testosterone levels, sperm counts, and the life-death ratio of sperm cells were among the results observed in all groups who were administered the extract (Ashamu *et al*., 2010) . Sesame not only serves as an important antioxidant by regenerating reduced GSH, nevertheless it's also a plentiful supply of antioxidants such as carotenoids, vitamins B-complex, flavonoids, phenols, and tannins. These secondary metabolites have the ability to act as antioxidant agents (Hsu &Liu, 2004 Saleem *et al*., 2013). Sesame contains various phenolic derivatives (such as Sesamol, Sesamolin, Sesamin, Sesaminoltriglucoside, Sesaminoldiglucoside, Rhamnetin, Mequelianin, Verbascoside, and Ferulic acid) as well as phytosterols (β-Sitosterol, Stigmasterol, Stigmasterolglucoside), which are powerful antioxidants that can react with free radicals generated by oxidative stress (Ajay *et al*., 2021). These antioxidant properties of sesame contribute to the protection of spermatozoa (Amini*et al*., 2013).

Conclusion

The reproductive function is essential for species survival and the prevention of extinction. This function is impacted by numerous external factors, including environmental

contaminants and specific chemical substances, which may result in infertility problems. Nutrition is necessary for protecting reproductive health. As a result, the application of sesame seeds has demonstrated advantages, as it protected male rabbits from infertility resulting from the chemical compound Ethylene Glycol Monomethyl Ether. This intervention increased biological indicators of sperm and testosterone levels, optimized oxidative markers related to testicular tissues, and protected testicular and epididymal tissues against damage induced by this substance.

ACKNOWLEDGMENTS

The authors would like to thank the Laboratory of Biotechnology, Water, Environment, and Health, which is housed in the the Faculty of Natural and Life Sciences. Additionally, the authors would like to acknowledge the Animal Ecophysiology Laboratory and the Chemistry Laboratory at the Faculty of Sciences, University of Annaba, Algeria, for providing the necessary reagents and chemicals for this research.

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