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EFFECT OF *SESAMUM INDICUM* L ON REPRODUCTIVE PERFORMANCE, BLOOD BIOCHEMICALS PARAMETERS, IN FEMALS RATS INTOXICATED WITH MERCURIC CHLORIDE

Tabbas Dalila*[1], Ait Hamadouche Nadia[2], Kharoubi Omar[3]

[1-3]Departement of Biology, University of Oran 1(Ahmed Benbella), Algeria. Laboratory of experimental Biotoxicology, Bio-Depollution and phytoremediation.

***Corresponding author*. e-mail:** daliladoct@gmail.com

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ABSTRACT:

This study evaluated the effect of aquous extract of *sesamum indicum* seeds (A.E.S) against mercuric chloride ($HgCl_2$) induced toxicity on females' reproductive system in rat. Forty female Wistar adult rats weighing (130-160 gr), divided into four groups (10 rats each): control group(C), intoxicated group (Hg), treated control group (C+A.E.S),intoxicated treated group(Hg^+ A.E.S) .Females adults rats were given $HgCl_2$ (2 mg/kg body weight) in drinking water for 45 Days .After the period of intoxication the rats are treated daily with (400 mg/kg body weight) of *Sesamum indicum* seeds extract given orally by gavage for (21) days. After the treatment period, each group subdivided into two groups (five rats each). One group of rats mated with unexposed males to study reproduction parameters, other group was sacrificed after treatment period; the Ovary and Uterus were taken for histopathology studies and blood samples were transferred to thel aboratory for biochemical analysis. Malondialdehyde (MDA), glycose levels and Serum activities of alkaline phosphatise (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), increased and serum levels of total protein, total cholesterol decreased in the intoxicated group (Hg) compared with control group(T). Whereas Body weight, ovaries and uterus weights, catalase, superoxide dismutase (SOD), glutathione peroxidise (GPX) activities, estrogen and progesterone levels were decreased in the intoxicated rats. There was no change in fertility index between groups. While, result of the number of newborns for the Hg group showed no significant decrease as compared with the others Group. Moreover, the percentage of weanlings from the intoxicated group showed a significant increase as compared with the control group. Also; $HgCl_2$ exposure resulted in histopathological changes in the ovaries. Our conclusion pointed out that *Sesame* seeds have an protective effect ondamages caused by $Hgcl_2$ and levels of some hormones.

Key words: Females rats, estrogen, progesterone, oxidatif stress, Ovaries, Uterus.

INTRODUCTION

Mercury (Hg) is a non-essential metal without biological function which can be found in three chemicals forms: elemental Hg (Hg^0), inorganic mercury (mainly $HgCl_2$) and organic mercury (mainlyMeHg) [1,**2**,3]. In females, mercury can accumulate in ovaries and can cause changes in reproductive behavior, infertility and ovarian failure [4].Human exposure to mercury occurs mostly through seafood

or sashimi consumption, and also to a lesser extent through dental amalgams, broken thermometers, fluorescent light bulbs, button cell batteries, and skin-lightening creams [5,6].Limited data are available from epidemiological studies showing that mercury disrupts female reproductive function[7].*Sesame* plant is one of the richest food sources of phytoestrogenic lignans, a valuable phytochemical known to man since the dawn of civilization [8].The major lignan of sesame seed is sesamin that possesses a myriad of beneficial effects on human health [9,10].Therefore, this investigation was directed to cast a light on the effect of *Sesame* seeds against oxidative stress and the deleterious effects induced by mercury chloride on the reproductive system of female rats.

MATERIALS AND METHODS

Reagents and chemicals

All of the chemicals and reagents used in the experiments were of analytical grade. Mercuric chloride ($HgCl_2$) was purchased From SIALCHI (expiry:2019). Nitrobluetetrazolium, methionine, reduced glutathione(GSH),ethylene diamine tetra acetic acid(EDTA) Sodium hydrogen phosphate (Na_2HPO_4), Ellmanreagent55dithiobis (2nitrobenzoicacid),Tris (2Aminohydroxymethyl propane1,3diol)+EDTA), salicylic acid, thiobarbituric acid, were obtained from SIGMA ALDARICH (expiry:2020). Potassium dichromate($K_2cr_2o_7$), Potassium hydrogen phosphate (K_2HPO_4), phosphate buffered saline (PBS)were procured From MERK (expiry:2019). Acetic acid was obtained from PROLABO CHEMICALS (expiry:2019). Dipotassium hydrogen phosphate (KH_2PO_4), Trichloroacetic acid (TCA) were obtained from BIOCHEMCHEM PHARM (expiry:2019). Riboflavin was purchased from LABOS (expiry:2020). Hydrogen peroxide were obtained from HONEYWELL (expiry:2021)

Plant materials

The brown seeds of *Sesamum indicum*were procured from the local market of Oran, Algeria, during April-May 2018.Then, the plant sample was identified at the plant ecology laboratory, University Oran1, Algeria.

Preparation of Aqueous Extract

The extraction method used to obtain the aqueous extract of the seeds of *Sesamum indicum* L is extraction under reflection. *Sesame* seeds are ground using an electric grinder.50 grams of vegetable powder are weighed and put in a glass flask containing 500 mL of distilled water (1: 10, w/v), so the mixture is put on heat (60 C°) for 30 min. The obtained decoction was frozen and then lyophilized (CHRIST ALPHA 2-4 LSC, Germany).

Animals and experimental conditions

Female Wistar rats were used in this study. They were born and raised in Animal House of the Faculty of Sciences in Oran1 Ahmed ben Bella University. All the procedure performed on animals were approved and conducted in accordance with the National Institute of health Guide (Reg. No. 488/160/1999/CPC-SEA). Before the experiment began, the animals were acclimatized in the experimental room for 7–14 days at room temperature (22 ± 1 °C) with the conditions of 12 h of light and 12 h of darkness with free access to standard laboratory rat water and food. Forty female Wistar adult rats weighing (130±30gr), divided into four groups

(10 rats each): control group(C), intoxicated group (Hg), treated control group (C+A.E.S), intoxicated treated group (Hg+ A.E.S) **.**Females adults rats were given $HgCl_2$ (2 mg/kg body weight) in drinking water for 45 Days .After the period of intoxication the rats were treated with a daily dose of (400) mg/kg body weight of Sesamum indicum seeds. Extract given orally by gavage for twenty-one (21) days. After the treatment period, each group subdivided into two groups of five rats each. One group of rats mated with unexposed males to study reproduction parameters**,** other group was sacrificed after treatment period**,** the Ovaries and Uterus were taken for histopathology studies and blood samples were transferred to the laboratory for biochemical analysis.

Biochemical examination

At the end of the experiment, the rats were anaesthetised with chloral hydrate 10% and then bled from the abdominal aorta using tubes. The blood samples were immediately centrifuged at 3000 rpm for 15 minutes, and the serum biochemical markers were subsequently evaluated. Activities of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea, creatinine, total protein, total cholesterol, glycose were assayed in the serum with a commercially available enzymatic kinetic kit (DiaSys respons®920). All the experimental protocols involving the use of laboratory animals were approved by the Institutional Animal Ethics Committee of Oran 1 ABB University (Reg.No.13/355/2015).

Estimation of oxidative parameters

The whole ovaries and uterus tissue was isolated immediately from the animals, weighed, and rinsed with 5 mL of 0.1 M (10% w/v) sodium phosphate buffer (pH 7.4). The tissue was then homogenised using a centrifuge (10,000 rpm, 4ºC) for 15 minutes. The supernatants of each uterus and ovary tissue homogenate were stored for the estimation of oxidative. Catalase (CAT) and Superoxide Dismutase (SOD) activity were determined by method described by [11] and [12] respectively. Glutathione peroxidase (GPX) activity was determined by the method of [13] The concentration of reduced glutathione (GSH) was measured using the Ellman method [14]. Lipid peroxidation was estimated by determining the level of malondialdehyde (MDA) [15].

Measurement of body and organ weights

Total body weight of each rat was measured weekly in the early morning over the experimental period of 45days. Rats were killed under anaesthesia at the end of the experimental period. The uterus and ovaries were removed and their wet weights were determined. The relative organ weight was then calculated using the formula (organ weight/body weight) x 100.

Reproduction parameters

Reproductive performance parameters are determined by: The number of newborns and the percentage of deaths as well as the fertility index which was determined as follows:

Fertility index = (total number of pregnant females/total number of mated females) x 100 [16].

Hormones determination

Serum progesterone and estradiol concentration was measured by the method of ELFA (Enzyme Linked Fluorescent Assay) using commercial kit from VIDAS®.

Histology

Part of the uterus and ovaries were fixed in 10% formalin for 24 h and then embedded in paraffin blocks, sliced into 5 μm sections, and stained with haematoxylin-eosin (H&E) for the histopathological evaluation. The sections were examined under a light microscope [17].

Statistical Analysis

All data were presented as mean ± SEM. For establishing significant differences, data were analyzed by one-way analysis of variance (ANOVA), followed by Turkey post hoc test using Statistical Package for the Social Sciences **(**spss) software version 23 (SPSS, Inc., Chicago, IL, USA). Values were considered statistically significant if P value is less than or equal to 0.05 ($p \leq 0.05$).

RESULTS AND DISCUSSION

Biochemical markers

Data are presented in (Fig. 1 and 2). The mercury-treated rats caused no significant elevation in the level of glucose, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP), and decrease in level of total protein and total cholesterol when compared to the control rats. On the Contrary, the results showed a decrease in the levels of urea, creatinine, AST, ALT, ALP and increase of total protein and total cholesterol of the Hg treated group (Hg+ A.E.S).The present work showed the increased levels of AST, ALT, ALP, urea and creatine in the serum of rat treated with mercuric chloride ($HgCL_2$).These results are in agreement with a previous study [18**].** The biological mechanism of associations between Hg exposure and liver dysfunction is mainly explained by oxidative stress, cell death, and impairment of metabolism [19]. The high levels of AST, ALT and ALP in serum of $Hgcl_2$ group were reverted to near normal levels due to plant extract treatment. Similarly, result of [20] reported that the plant extract significantly suppressed the increase of transaminases and MDA, suggesting a protective role of the plant extract against oxidative stress. Our data showed that *Sesamum indicum* extract significantly decreased the levels of blood alkaline phosphate is (ALP). A similar finding was revealed by [21]. Mercury exposed rats of the present study indicated a elevation in the concentration of creatinine and urea in intoxicated group. Such results are in agreement with [18]. The rise in creatinine level is strongly associated with kidney injury and oxidative stress [21]. Besides, in these experimental conditions, the treatment of rat by *Sesame* seeds extract has caused a significant reduction in creatinine and urea levels. Our data agree with what has been reported by [22]. This effect may be attributed to the prevention of degradation of proteins and nucleic acids. Our result showed a decrease in cholesterol and total protein level, these results are in agreement with the work of previous researchers [23, 24]. The depletion of protein content may be due to oxidative stress and possibly by indirectly inhibiting the protein synthesis [25]. The actual results show that the extract of *Sesamum seed* induced dimunition of cholesterol levels in treated rats. This finding is in line with the work of previous researchers **[**26]. The hypocholesterolemic effect of sesamin, relate to the component lignan in *sesame* seeds, which hinder the absorption of cholesterol in the intestinal region [27]. Mercury exposed rats of the present study indicated an elevation in the concentration of glucose. These findings are in

accordance with [18]. Peroxidation of poly unsaturated fatty acids (PUFA) caused by mercury may result in progressive loss of pancreatic beta cells, leading to hyperglycemia and glucose intolerance [28; 29]. In this study, treatment with plant extract did not reduce plasma glucose, as well, same results have been found by [30]. They suggested that enrichment of the diet with an unsaturated fatty acid supplement such as *Sesame* oil may worsen the metabolic disorders of diabetics.

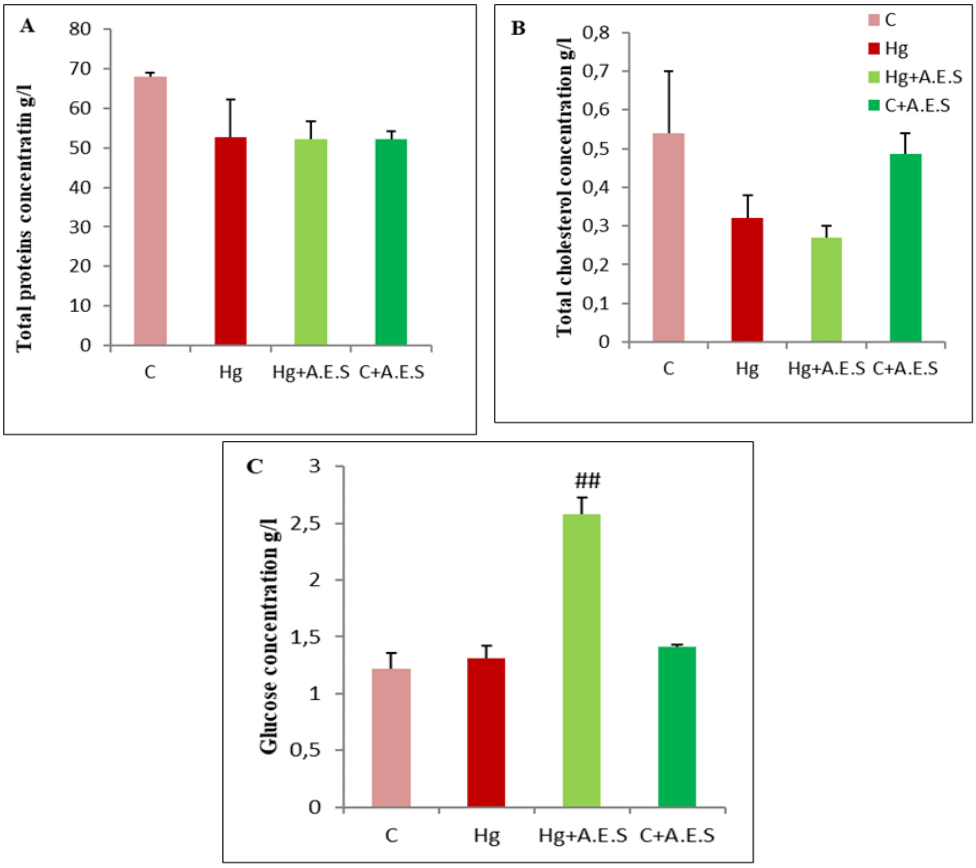


Fig. 1. Variation in the level of total proteins (A), total cholesterol (B) and glycose (C) in serum of rats in all groups.

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds; **Hg+ A.E.S:** rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds.

Data are reported as mean ± SE for 5 animals per group.(##p<0.0001) refer to hight significant differences between means .The comparison was made: C vs Hg, Hg vs Hg+ A.E.S, C vs C+A.E.S.

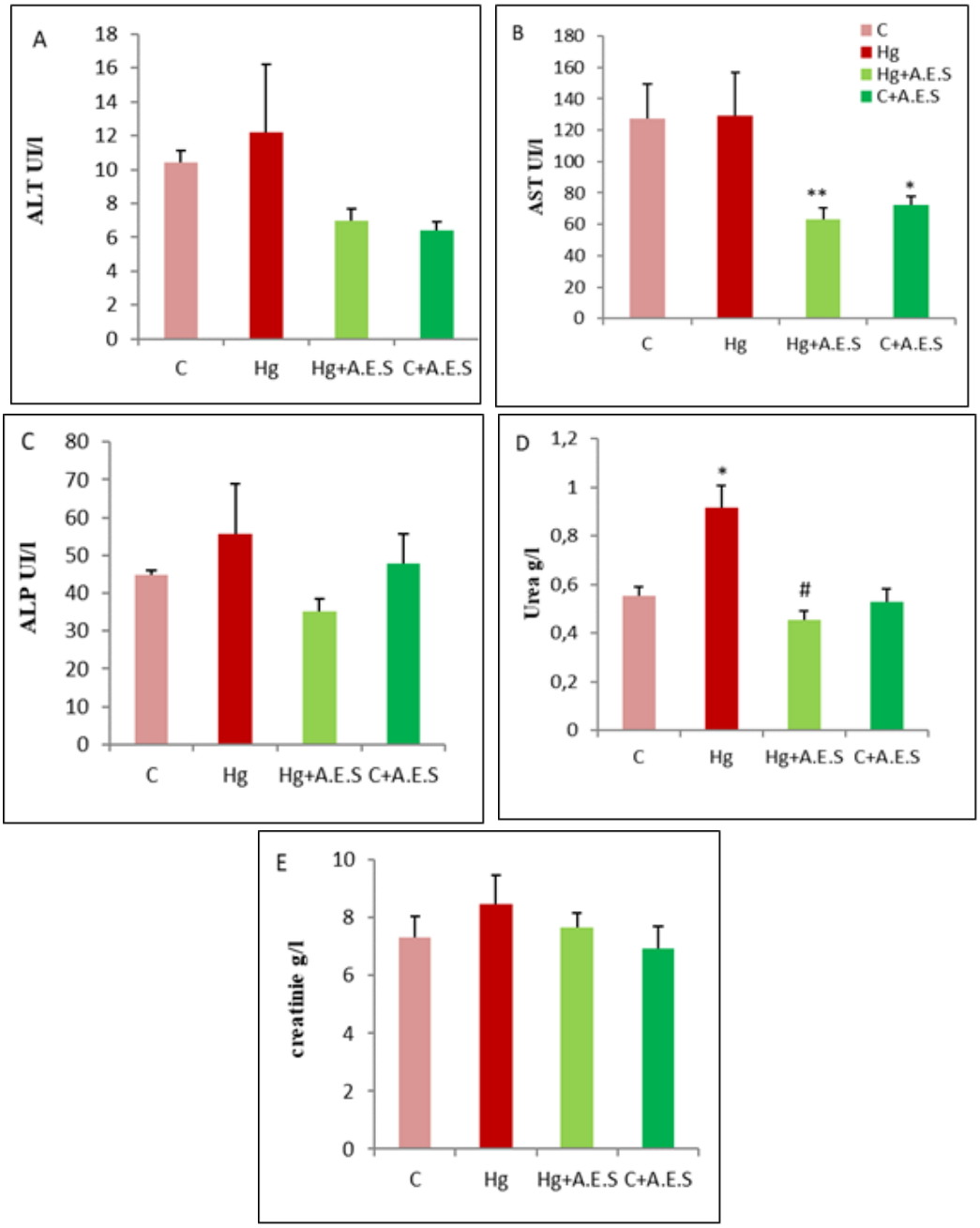


Fig.2. The level of ALT(A), AST (B), ALP(C), urea(D), and Creatinine (E)in serum of rats in all experimental groups.

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds; **Hg+ A.E.S:** rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds.

Data are reported as mean ± SE for 5 animals per group.(***** $p<0.05$) ,(**$p<0.03$) (#$p<0.009$) refer to Significant differences. The comparison was made: C vs Hg, Hg vs Hg+ A.E.S, C vs C+A.E.S.

Oxidative parameters

The findings exhibited that mercuric chloride treatment reduced the rate of ovaries and uterin SOD, CAT, GPX, GSH, and increased the rate of MDA in comparison with the control groups. Contrary, results showed an increase in the level of SOD, GPX, CAT, GSH and

decrease of MDA of the Hg treated group (Hg+ A.E.S) (Table1and 2). In the present study, $HgCl_2$ induced oxidative stress in tissus of intoxicated rats. These results are in agreement with the work of previous researchers [31]. Interactions occur between Hg and thiol groups of proteins, forming complexes that bind to important proteins as glutathione, cysteine, and superoxide dismutase, inactivating them reducing the antioxidant defences of cells [32]. In the present investigation, *Sesamum indicum* reduced MDA level and restored GSH level; and enhanced GPx, SOD and CAT in the treated group compared to Hg group. These results are in agreement with [33]. The study of [20] revealed that *Sesamum indicum* exercises its influence through the synergy between different present phytochemicals constituents. The presence of volatile terpenoids in Sesame oil such as carvone, carveol, farnesene epoxide E, and bisabolol which have anti-oxidant and anti-inflammatory effects [34].

Table 1. Effects of Sesamum indicum aqueous extract (A.E.S) and mercury chloride on the antioxidant enzyme activities (Catalase ,CAT ; superoxide dismutase SOD ;Glutathione peroxidise, GPX; malondialdehyde MDA, and Glutathione,GSH levels on uterus tissue in control and experimental groups.

Oxidative parameters	**C**	**Hg**	**Hg+A.E.S**	**C+A.E.S**
CAT(mmol H2O2 / mg of protein)	4.02± 0.13	3.22± 0.43	4.20±0.01	4.13±0.25
SOD(U/ mg of protein)	0.94±0.20	0.71 ±0.24	1.45±0.9	0.95 ±0.41
GPX(nmol GSH/mn/ mg of protein)	0.61±0.5	0.37± 01	0.6 ±0.1	0.81±0.2
GSH(nmol/mg of protein)	4.97±1.43	2.92±0.83	5.06±2.009	6.07±1.67
MDA(nmol/ mg of protein)	0.013±0.002	0.031±0.017*	0.015±0.0047$^{\#\#}$	0.012±0.0053

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds; **Hg+ A.E.S:** rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds

Data are reported as mean ± SE for 5 animals per group.(***** $p<0.05$) refer to Significant differences and (##$p<0.0001$) refer to hight Significant differences. The comparison was made: Cvs Hg, Hg vs Hg+ A.E.S, C vs C+A.E.S

Table 2. Effects of Sesamum indicum aqueous extract (A.E.S) and mercury chloride on the antioxidant enzyme activities (catalase CAT, superoxide dismutase SOD, Glutathione peroxidise GPX), malondialdehyde (MDA) and GSH levels on ovaries tissue in control and experimental groups.

Oxidative parameters	**C**	**Hg**	**Hg+A.E.S**	**C+A.E.S**
CAT(mmol H2O2 / mg of protein)	4.21± 0.13	3.95± 0.36	5.24±0.34*	4.84±0.07

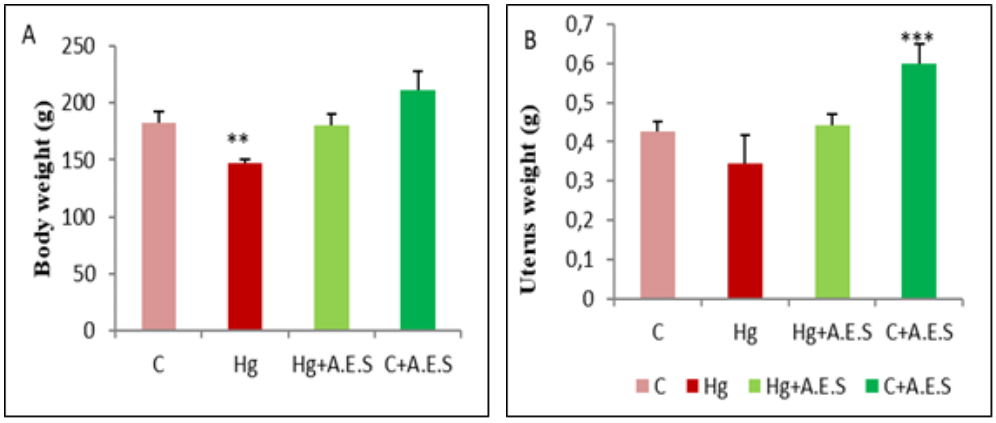
SOD(U/ mg of protein)	1.23±0.29	0.30 ±0.06	4.07±0.30***	2.25 ±0.90
GPX(nmol GSH/mn/ mg of protein)	0.62±0.3	0.36± 0.1	0.63 ±0.43	2.1 ± 0.7
GSH(nmol/mg of protein)	4.63±2.43	1.98±0.33	5.58±0.85	4.49±1.36
MDA(nmol/ mg of protein)	0.027±0.002	0.063±0.002*	0.009±0.0044##	0.016±0.0038

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds; **Hg+ A.E.S:** rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds

Data are reported as mean ± SE for 5 animals per group.(***** $p<0.05$) refer to Significant differences and (##$p<0.0001$) refer to hight Significant differences. The comparison was made: Cvs Hg, Hg vs Hg+ A.E.S, C vs C+A.E.S

Body and relative organ weight

In the present study, Hg group showed a decrease in body weight and absolute weight of the uterus and ovaries (Fig.3) compared with the other groups(*$p<0.05$), while relative weight showed no difference ($p>0.05$) (Fig. 4).Our data agree with that reported by [35].The possible cause of this result might be due to be adverse effect of mercuric chloride on hematopoietic system and on the absorption of essential vitamins and minerals from the gut and the destruction of the red blood cells [36].On the other hand, the treatment of rats with *Sesamum* seed extract causes the recovery of body weight. This effect may be due to increasing glucose uptake in peripheral tissues or inhibiting catabolism of fat and protein or by glycemic control [37].



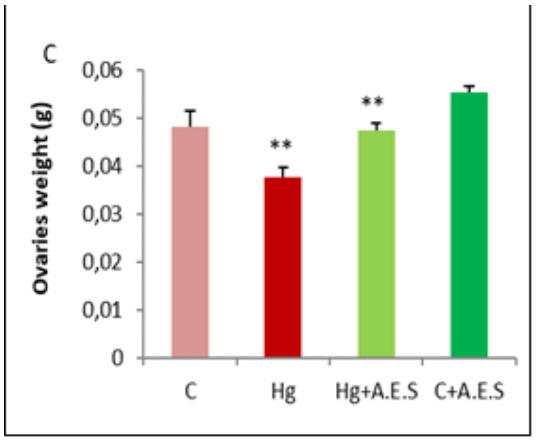


Fig.3 . Weekly mean body weights(A), absolute weight of uterus (B)and ovaries (C)of rats in all experimental groups.

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds; **Hg+ A.E.S:** rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds. Data are reported as mean ± SE for 5 animals per group.**p<0.03, ***p<0.01 refer to significant differences between means. The comparison was made: Cvs Hg, Hg vs Hg+ A.E.S, C vs C+A.E.S.

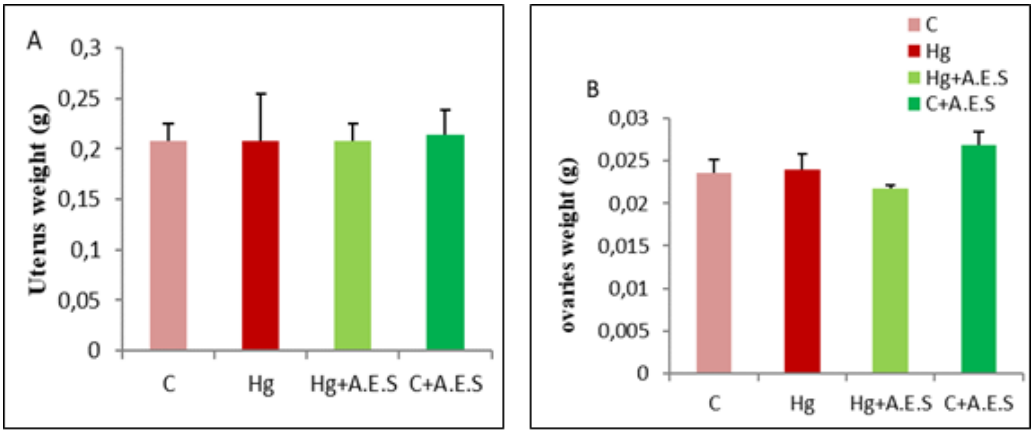


Fig.4 . Relative weight of uterus (A) and ovaries (B) in all experimental groups. Values are presented as Mean± SE. The comparison was made: Cvs Hg, Hg vs Hg+ A.E.S, C vs C+A.E.S.

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds;

Hg+ A.E.S: rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds.

Reproduction parameters

The effects of $HgCl_2$ on reproductive parameters are shown in (Fig.5). There was no change in fertility index between groups. Intoxication with $HgCl_2$ decreased the number of newborns (Fig. 5A), estradiol levels (Fig. 5B) and progesterone (Fig. 5C) and increased the percentage of deaths.

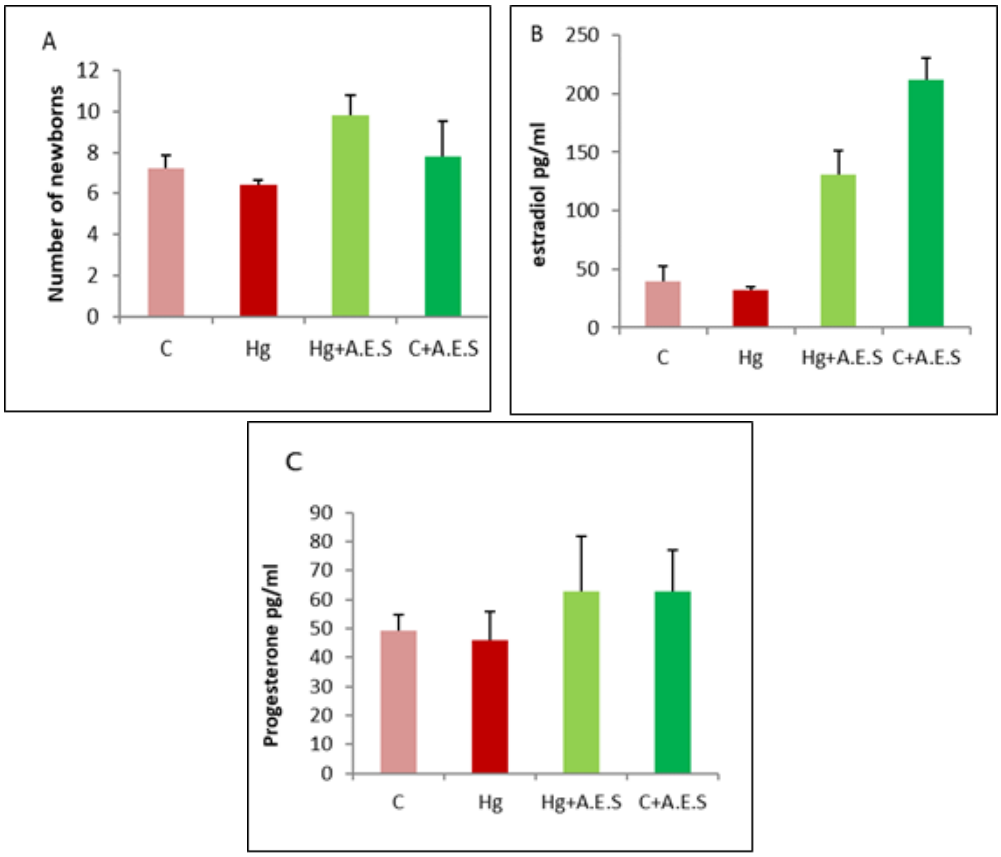


Fig. 5 . Number of newborn (A), level of estradiol (B) and progesterone (C) in serum,. Values are presented as Mean ±SE. The comparison was made: C vs Hg, Hg vs Hg+ A.E.S, C vs C+A.E.S.

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds; **Hg+ A.E.S:** rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds.

(Table 3) compared with the control group. However, treatment showed the opposite effect. The levels of these hormones were also reported to have decreased by [38]. This is achieved by interfering with the secretion patterns of LH and FSH, altering ovarian cyclicity, and causing atresia and apoptosis of follicular cells [39]. Furthermore, the decrease in the number of newborns and the increase in the mortality (25%) during lactation in pups from intoxicated females observed in the Hg group aligns with the findings of Donicova et al. [40]. These results are probably due to a more sensitive gland of the fetus and newborns to Hg exposure. This is due to their less effective blood-brain barrier, higher gastrointestinal absorption rate, less effective renal excretion and low body weight with a high food consumption rate per kilogram of body weight [41]. Sesame seed has positive effects on rats' hormonal markers that are consistent with observations [42]. Furthermore, sesame oil preserved serum estradiol and aromatase levels after bilateral ovariectomy in female rats [43]. In this study, supplementation of rats with sesame seed extract showed an increase in the number of newborns and the number of weanlings in the intoxicated treated group. Based on reports from [44], administration of the extract of S. *indicum* seed powder improved the reproductive indices and the gonadal-somatic index of cultured female African catfish. Study

showed that *Sesamum indicum* can enhance fertility with their antioxidants molecules such as sesame l, sesamolin, sesamin, and sesaminol triglucoside and sesaminol diglucoside [44].

Table 3. The effects of *sesamum indicum* aqueous extract (A.E.S.) and mercury chloride on the reproductive parameter (percentage of DEATHS) in all experimental groups

Reproductive parameter	**C**	**Hg**	**C+A.E.S**	**Hg+A.E.S**
Percentage of DEATHS	0%	25%	0%	0%

C: control rat; **Hg: rat** intoxicated with mercury; **C+A.E.S**: control rat treated with aqueous extract of *sesamum indicum* seeds; **Hg+ A.E.S:** rat intoxicated with mercury and treated with aqueous extract of *sesamum indicum* seeds

Histological Study

The results of histological observations showed normal architecture of the ovaries in C and C+A.E.S Groups as shown in (Fig.7D and E).while there were vascular congestion (VC), necrosis (N) and decrease in number of follicles in Hg group (fig.6 A and B).In the present study *sesame* showed positive impact to repair cells cause by mercury toxicity it was evident from the formation of normal ovaries(Fig.7C). Our data were in agreement with result of [45]. This deleterious effect observed in ovaries tissues are the result of suppressing the DNA repair mechanisms and molecular mechanisms by Hg resulting in cell damage, increased lipid peroxidation products and a decrease in the glutathione peroxidase enzyme activity [46]. Rats treated with A.E.S showed good evidence of protection against Hg-induced toxicity, as evidenced by ovary shape and increased follicle number. Sesame seed oil was found to be effective in preventing Penconazole toxicity [47]. These seeds are rich as minerals and trace minerals; vitamins and antioxidant lignan (phytoestrogens) and can improve the fertility potential of male reproductive tract [48]. A study has shown that sesamin can effectively protect spermatogenesis in male mice [49].

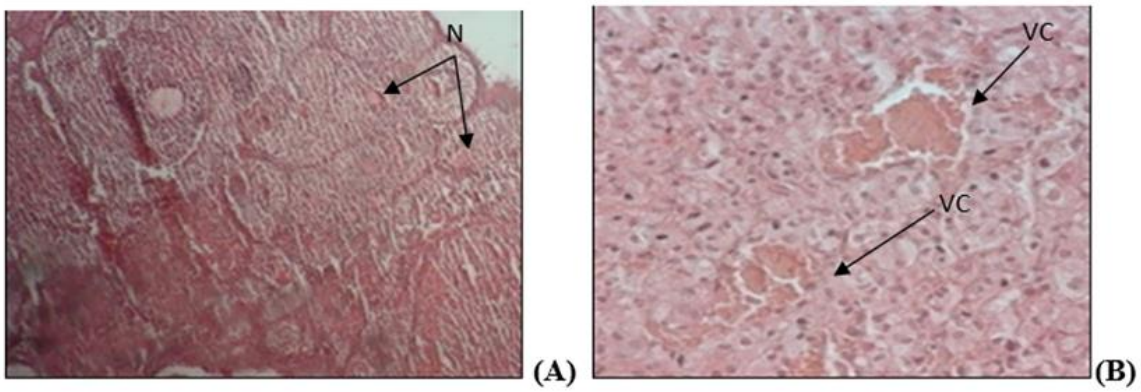
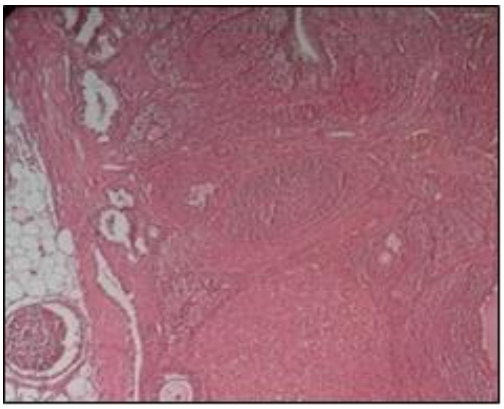


Fig. 6 . Light microscopy images of ovaries in the Hg group (A and B) showing hight decrease in the number of follicles, vascular congestion (VC) , necrosis (N) . H&Ex400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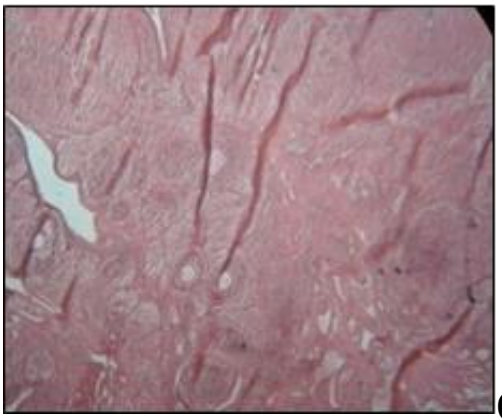
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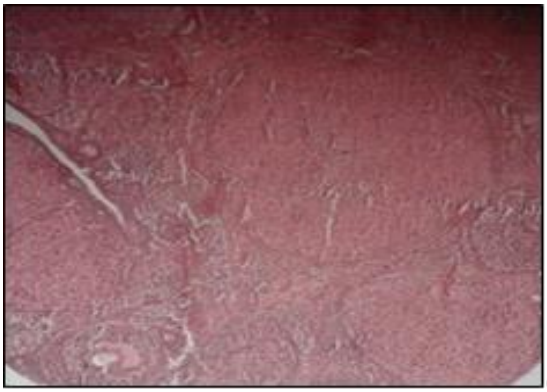
(E)

Fig. 7. Light microscopy Images of ovaries in the (Hg+ A.E.S) group (C) and control group (D) and C+A.E.S group (E). Showing healthy ovarian stroma and follicles in different stages of evolution. H&E x 400.

CONCLUSION

The present data showed that the exposure of females rats to mercuric chloride is capable of inducing alterations in some enzymatic activities, liver functions, renal functions and some biochemical parameters. The present findings showed significant disruption in reproduction parameters of female due to mercuric chloride toxicity including decrease in hormonal levels, number of newborns and increase percentage of weanlings. The histological structure of ovaries was also affected. Based our finding, *Sesame* is a key to protect the animals from mercury poisoning.

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