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DINOTEFURAN INSECTICIDE EVOKES DISRUPTING OESTROUS CYCLE IN RAT FEMALE: THE AMELIORATIVE ROLE OF ROSEMARY EXTRACT

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ABSTRACT: Dinotefuran (DINO) is a third-generation neonicotinoid insecticide with extensive worldwide application, resulting in continued human exposure. The present study explored the reproductive toxicity of DINO on oestrous cycle stages in rat females and the ameliorative role of rosemary leaf extract (RE). Twenty rat females were exposed to DINO, RE, and their combination at 73.5 and 230 mg/kg for 14 days. The levels of estrogen and progesterone were measured, and the dysregulation of oestrous cycle stages was monitored. The exposure to DINO resulted in an imbalance in estrogen and progesterone levels. Also, the regulation of oestrous cycle stages was disrupted. These effects were mitigated when rats were administered RE. Altogether, these findings provide insights into the reproductive toxicity of DINO on rat females and the ameliorative effects of RE on DINO-induced toxicity.

Keywords: Dinotefuran, rosemary leaf extract, reproductive toxicity, pesticides.

INTRODUCTION

Dinotefuran is a third-generation neonicotinoid and contains two enantiomers, which has high insecticidal activity and selectivity (Raby *et al.*, 2018; Wang *et al.*, 2018). As a third-generation neonicotinoid insecticide, dinotefuran acts on target organisms through gastric poisoning and contact (Bass and Linda, 2007; Ran *et al.*, 2021). Given the strong endogenous penetration ability, efficient and long function time, wide insecticidal spectrum, and relatively low toxicity of dinotefuran on mammals, it is commonly used in agricultural production to control the number of various pests such as beetles, lacewings, and aphids (Bass and Linda, 2007; Wakita, 2011; Wang *et al.*, 2018; Ran *et al.*, 2021; Zhang *et al.*, 2022).

Dinotefuran inevitably enters the environment and is potentially toxic to non-target organisms and the ecosystem (Liu *et al.*, 2017; Chen *et al.*, 2019; Tang *et al.*, 2019; He *et al.*, 2021; Ran *et al.*, 2021; Zhou *et al.*, 2021). For example, dinotefuran is toxic to earthworms, honeybees, zebrafish, and *B. mori* (Bees, 2019; Chen *et al.*, 2019; Di *et al.*, 2021; Zhang *et al.*, 2022). Dinotefuran is more soluble in water than the first generation of neonicotinoid insecticides, causing more severe environmental pollution. In addition, dinotefuran is more potent and persistent than the first generation of neonicotinoid insecticides. Dinotefuran belongs to the newest generation of neonicotinoid insecticides, and its relevant risk assessment on non-target organisms is limited (Liu *et al.*, 2017, 2018)

Rosemary (*Rosmarinus officinalis*) is a well-known spice and medicinal herb belonging to the Lamiaceae family. At least 3% of the main constituents of rosemary are represented by phenolic acids such as rosmarinic, chlorogenic, and caffeic acids (Begum *et al.*, 2013). The predominant active compounds, carnosic acid and carnosol, and many other active polyphenolic compounds in rosemary can both scavenge free radicals directly and increase endogenous cellular antioxidant defences indirectly via activation of the redox-sensitive system Nrf2/Keap-1/ARE transcriptional pathway, as well as potentially via multiple other mechanisms (Satoh *et al.*, 2013).

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Rosemary was scientifically proven to possess antioxidant, anti-inflammatory, anti-nephrotoxic, anti-hepatotoxic, antimicrobial, and anti-tumor properties (Begum *et al.,* 2013). The safety of rosemary extracts for antioxidant use was first evaluated by the European Food Safety Authority (EFSA) in 2008 (Aguilar *et al.,* 2008).

Insufficient data exist about the reproductive toxicity of DINO in females. Consequently, this research endeavour aimed to evaluate the reproductive toxicity of DINO in *Rattus norvegicus* rats, female and the ameliorative effects of rosemary extract.

MATERIAL AND METHODS

1. Chemical

A commercially available of DINO (oshein 20%) CAS registry no: 165252-70-0, Molecular weight: 202.21 g/mol, has a formal name of [2-methyl-1-nitro-3-[(tetrahydro-3-furanyl) methyl] guanidine, 202.21 g/mol molecular formula and was obtained from Shoura Chemicals Company.

2. Preparation of rosemary leaf extract (RE)

Rosemary leaves were collected from a greenhouse in the Faculty of Agriculture, Menoufia University, Shibin El-Kom, Egypt. Rosemary leaf extract (RE) was prepared according to Yahia Bilto (2015). The dried leaves were ground in a blender with a particular size to ensure the powder was identical in size; 100 g of the powder was soaked for 5-7 days with 1000 ml of 80 % methanol at 25 °C. After filtration, the filtrate was evaporated with a rotary evaporator under reduced pressure at 50°C to remove the methanol. The dry crude extract of rosemary was stored in a dark glass bottle in a refrigerator until use. A 1mg/ml stock solution from the crude extract was prepared by dissolving 0.1g of dry crude extract/standard and diluting in 100 ml of 98% methanol. This stock solution was stored in the refrigerator until used for the *in vivo* study. A dose of 220 mg/kg of RE was utilized to study the potential ameliorative effects of RE on the toxicities provoked by DINO (El-Morsy *et al.,* 2015).

3. Tested Animals and Husbandry

Twenty adult sexually mature virgin female Wistar albino rats (*Rattus norvegicus*) aged 8–10 weeks (120-180 g in weight) were obtained from the Holding Company for Biological Products and Vaccines (VACSERA), Helwan, Egypt. They were maintained in the Animal House at the Department of Pesticides, Faculty of Agriculture, Menoufia University. Animals were housed in groups of 7 rats in polyacrylic cages (38 cm × 23 cm × 10 cm) and maintained under laboratory conditions at a temperature of 25±2 °C, regular photoperiod (12–12 h light-dark cycle). Also, they were fed standard pellets and allowed access to water *ad libitum* throughout the experimental period. The rats were acclimatized to laboratory conditions for two weeks before the commencement of the experiments. The institutional animal care and use committee (IACUC) at Menoufia University approved the experimental protocol (MUFAG/ S/ PS/ 3/ 23).

4. Determination of estrous cycle

Following physical restraint, a vaginal specimen was obtained by inserting a moist cotton bud into the vaginal opening. The swab was gently rotated within the vagina of the rat, ensuring it maintained contact with the vaginal wall. The swab was removed from the vagina and rubbed on a clean glass slide to transfer the vaginal specimen to the slide. It was allowed to air dry for 3-5 min, after which 0.1% aqueous solution of methylene blue was used to stain the vaginal smear. (Ajayi *et al.,* 2020)

The stained smear was allowed to dry for 3-5 min before viewing under the microscope at ×10 magnification. The cell types were used to determine the stage of the estrous as follows: 1) Proestrus: the presence of small round nucleated epithelial cells that are deeply basophilic either in clusters (grape clusters), sheath or strands. 2) Oestrus: the presence of nucleated keratinized epithelial cells and occasionally a few nucleated epithelial cells. 3) Metestrus: a combination of nucleated keratinized epithelial cells and neutrophils with small-sized multilobulated

nuclei. 4) Diestrus: few a nucleated keratinized epithelial cell combined with neutrophils, which are small and large nucleated epithelial cells and mucous. (Idris *et al.,* 2023).

For more certainty of the stage of the estrous cycle, the appearance of the vagina was observed before taking the smear according to the methods of Champlin *et al.* (1973). This method permits observations without mechanical manipulation of the vaginal tissue. 1) Proestrus: the vagina is gapping, and the tissues appear reddish-pink and moist. Numerous longitudinal folds or striations are visible on the lips. 2) Estrus: similar to proestrus, but the tissues are lighter pink and less moist, and the striations are more pronounced. 3) Metestrus: vaginal tissues are pale and dry. 4) Diestrus: vagina has a small opening, and the tissues are bluish-purple and very moist.

5. Experimental Design

The female animals were divided into five groups of 10 rats each and administered as follows: Group I: Untreated animals (Control) received Tap water daily by oral gavage without any treatment. Group II: Each animal received RE 220 mg/kg daily for 14 days by oral gavage. Group III: Each animal received DINO 73.5 mg/kg daily for 14 days by oral gavage. Group IV: Each animal received DINO 230 mg/kg daily for 14 days by oral gavage. Group V: Each animal received DINO 230 mg/kg, followed by RE with 220 mg/kg daily for 14 days by oral gavage.

6. Organ weights and gross necropsy

After blood collection, all animals were sacrificed by exsanguination, and the organs and tissues of the reproductive system were observed macroscopically. The reproductive system organs were removed and weighed. Relative organ weights were also calculated from the ratios of organ weights to body weight. The organs were fixed in 20% neutral-buffered formalin by Kayode *et al.* (2020)

7. Preparation of serum hormone

Blood samples were left to clot at room temperature and then centrifuged for about 15 min at ×3000 rpm. to obtain clear serum. The serum was stored in a deep freezer at – 70 C until just before other analyses.(Mokhtar *et al* ., 20713)

8. Determination of estradiol and progesterone hormones

The estradiol and progesterone levels in serum of female rats were analyzed by using immulte/immulite1000, and chemiluminescent enzyme immunoassay. Assay Kit (Catalog Mokhtar *et al.* / Journal of Applied Pharmaceutical Science 3 (12); 2013: 109-119 111 Number LKE21, DPC) of estradiol and assay Kit (Catalog Number LKPG1, DPC) of progesterone were used for assessment process (Bergquist *et al.,* 1983)

9. Histopathological analysis

The 10% formalin was used to fix tissue samples from the female uterus and ovaries. Fixed tissues were dehydrated for 30 min in ascending series of alcohol (70, 80, 90, 95, and 100%) with gentle shaking before being immersed in absolute ethanol overnight. The tissues were soaked in xylene (3 times) for 30 min before being paraffin at 56 °C (30 min, 3 times). The tissues were embedded in paraffin and cut into 4-µm sections using a digital semi-automatic microtome, Ambala (Haryana, India). The samples were mounted on microscope slides and then stained for 5 min with hematoxylin and eosin (H& E) (Bancroft and Gamble, 2013). The stained slides were examined and photographed using an Axiostar Plus (Carl Zeiss, Göttingen, Germany) microscope adapted with a Canon (Pc 1200 Power shoot A641) digital camera using Zoom Browser Ex software.

10. Statistical analysis

All assays were performed in triplicate.
Statistical analyses were conducted employing SPSS software (version 21.0; SPSS Inc., Chicago, IL, United States). The data sets were compared using One-way ANOVA and Tukey's test. The data were represented as mean ±SD. Values were deemed statistically significant when $p \leq 0.05$.

RESULT AND DISCUSSION

1. Body and relative organ weights of female rats

Table 1 displays the results of the body weight readings of female rats exposed to both DINO and RE extract and their combination following 14 days of exposure. The RE-treated group did not show a statistically significant change in body weight when compared to the control group. The administration of DINO for 14 days at two different doses (73.5 mg/kg and 220.5 mg/kg) did not significantly reduce body weight increments compared to the control group. Body weight increased non-significantly when RE extract was given in conjunction with DINO at a dose of 230 mg/kg compared to the high-dose DINO and the control groups (Table 1).

The RE-treated group did not demonstrate any statistically significant alterations in the absolute or relative weight of the ovary and uterus compared to the control group. Rats administered with DINO at doses of 73.5 mg/kg and 230 mg/kg were found to have significantly enlarged ovaries and uteruses than the control group ($p<0.05$) due to extensive hyperplasia. These results are in agreement with (Bhanot and Sangha, 2020). In contrast, the absolute/relative weights of the uterus and ovaries were dramatically lower in the co-administered RE (220 mg/kg) and DINO group 230 mg/kg than in the control group. (Table 2).

Table (1): Effects of oral administration of DINO, RE and their combination (DINO + RE) for 14 days on body weight of adult female albino rats.

Treatments	Initial body (gm)	Final body (gm)	Net body (%)
Control	172.53 ± 2.7	215 ± 9.5	24.62 ± 4.4
RE (220 mg/ kg)	180.87 ± 1.8	216.4± 3.6	22 ± 1.8
DINO (73.5 mg/kg)	169.23 ± 3.31	222.6 ± 2.5	26..02 ± 3.5*
DINO (230 mg/kg)	178.7 ± 3.3	225.2 ± 4.9	31.4 ± 5.9*
DINO (230 mg/kg)+ RE (220 mg/ kg)	169.23 ± 2.11	220.3 ± 2.5	23.8 ± 6.1

Values represent means ± SD. * $P = \leq 0.05$
DINO : Dinotefuran, RE : Rosmary extract

Table (2): Effects of oral administration of DINO, RE and their combination (DINO + RE) for 14 days on ovarian and uterine weights of adult female albino rats

Treatments	Ovary (gm)		Uterus (gm)	
	Absolute	Relative (%)	Absolute	Relative (%)
Control	0.05± 0.01	0.01	1.2± 0.02	0.83
RE (220 mg/ kg)	0.06± 0.01	0.04	1.3± 0.1*	0.83
DINO (73.5 mg/kg)	0.09 ± 0.01*	0.04*	1.95 ± 0.05*	0.86*
DINO (230 mg/kg)	0.1 ± 0.06*	0.06*	2.0 ± 0.01*	0.95*
DINO (230 mg/kg)+ RE (200 mg/ kg)	0.08± 0.01*	0.03*	1.7± 0.1*	0.83*

Values represent means ± SD. * $P = \leq 0.05$
DINO : Dinotifuran, RE : Rosmary extract

2. Stage of estrous cycle

The results of the stage of estrous cycle based on vaginal cytology are presented in Table 3 The RE-treated group did not demonstrate any statistically significant alterations in the proestrus, estrous, diestrus, and metestrus stage compared to the control group. Rats administered with DINO at doses of 73.5 mg/kg and 230 mg/kg were found to have significantly increase of proestrus and estrous stages and decrease in diestrus and metestrus than the control group ($p<0.05$).

Our results are similar to finding obtained by (Idris *et al.*, 2023), who reported that glyphosate significantly decreased diestrus and metestrus stages as well as increased proestrus and estrous stages in female rats treated with 250 and 500 mg/kg for consecutive 21 days . The increase of proestrus and estrous stage may be attributed to the ability DINO to either bind to estrogen receptors or mimic the effect of estrogen (Asthana and MA., 2006). Once the estrogen receptors are blocked or mimicked, it can lead to an increase in estrogen in the blood, which is the hormone that predominates during the estrus and proestrus stages of the cycle (Leigh, 2017) Moreover, the estrogenic effects of DINO may result in a decrease in the diestrus and metestrus stages. Progesterone is the dominant hormone during the metestrus and diestrus stages, and this hormone acts in synergy with estrogen to control the estrous cycle (Olurode., 2013) (Idris *et al.*, 2023). In contrast, the estrous and proestrus stages dramatically decreased, and diestrus and metestrus stages were substantially decreased in the co-administered RE (220 mg/kg) and DINO group 230 mg/kg than in the control group. (Table 3).

3. Estradiol and progesterone levels

The levels of estradiol and progesterone following exposure to DINO, RE extract, and the combination are presented in Table 4. When comparing the RE-treated group to the control group, there were non-significant alterations in estradiol and progesterone. The level of estradiol was substantially greater in groups exposed to DINO at 73.5 mg/kg and 230 mg/kg, respectively, compared to the control (Table 4). However, the level of progesterone was significantly lower in the DINO groups of 73.5 mg/kg and 220.5 mg/kg than in the control group. These results demonstrated that DINO treatments induced oxidative damage in the ovaries of female rats. A similar observation was reported by (Ren *et al.*, 2018) and (Schimpf *et al.*, 2022) in rats administered glyphosate herbicide. When estradiol level is maintained at a tonic level, it can result in persistent estrus (Feldman and Canine, 2004; Westwood, 2008). The prolonged periods of estrus in this study may be responsible for this. Low levels of progesterone are considered responsible for the maintenance of estrus (Vom Saal *et al.*, 1994). The persistent proestrus is also a result of an increase in estrogen levels but not high enough to move to the estrus stage (Feldman and Canine, 2004). Comparing the rats in the control group and those exposed to a high dose of DINO alone, the rats exposed to DINO (220 mg/kg) + RE (230 mg/kg) showed a considerably lower level of estradiol and a higher level of progesterone.

Tabel (3): Effects of oral administration of DINO, RE and their combination (DINO + RE) for 14 days on the stage of estrous cycle in adult female albino rats.

Treatments	Estrous	Proestrus	Diestrus	Metestrus
Control	5.2 ± 0.6	5.1 ± 0.5	5.0 ± 0.5	5.0 ± 0.57
RE (220 mg/kg)	5.3 ± 0.6	5.5 ± 1.7	5.0 ± 1.0	5.1 ± 0.7
DINO (73.5 mg/kg)	8.8 ± 0.6*	7.7 ± 0.5 *	3.3 ± 0.57*	3.7± 0.5*
DINO (230 mg/kg)	10.2 ± 0.6*	8.3 ± 0.5*	2.9± 0.1*	2.5 ± 0.2*
DINO (230 mg/kg+ RE (220 mg/kg)	6.2 ± 0.5*	3.9± 0.06*	4.2 ± 0.2*	4.5 ± 0.1*

Values represent means ± SD. * $P = \leq 0.05$
DINO : Dinotifuran, RE : Rosmary extract

Tabel (4): Effects of oral administration of DINO, RE and their combination (DINO + RE) for 14 days on the level of progesterone and estradiol in adult female albino rats.

Treatments	Estradiol (pg/ml)	Progesterone (ng/ml)
Control	30.30± 0.01	15.73±0.11
RE (220 mg/ kg)	32.01±0.82	14.91±0.31
DINO (73.5 mg/kg)	40.12±3.01*	12.60±1.80*
DINO (230 mg/kg)	57.10±1.80*	9.47±0.21*
DINO (230 mg/kg)+ RE (220 mg/ kg)	19.07±0.54*	10.64±1.32*

Values represent means ± SD. * $P = \leq 0.05$
DINO : Dinotefuran, RE : Rosmary extract

4. Histopathological examination

The ovaries collected from female rats that underwent 14 days of exposure to DINO, RE, and their combinations are illustrated in Fig 1 Ovarian tissues in the control and RE groups had a typical anatomical structure. Multiple clogged blood vessels and deteriorated germinal epithelium were observed in the DINO (73.5 mg/kg) group. Multiple constricted blood vessels and hyperplasia of the germinal epithelium were observed in the DINO (230 mg/kg) group. The group that received DINO (230 mg/kg) in combination with RE (220 mg/kg) exhibited developed graffian follicles and germinal epithelium that were in good health. Nonetheless, there continue to be obstructed blood vessels due to dino cause Potent endocrine disruptors typically cause histological changes in the ovary and uterus which induces ovarian atrophy in association with hyperplastic and hypertrophic changes in the uterus.

These findings agreed with (Madboli and Seif, 2021) who recorded that carbendazim toxicity in rat ovaries leads severe congestion. Moreover, Sakr *et al.* (2014) and Singh *et al.* (2016) recorded that in rats and mice, the CBZ causes ovarian toxicity as it induced severe congestion, dilatation, and hemorrhages due to damage in ovarian blood vessels and also the ovarian follicles showed degeneration and destruction of the oocyte granulosa cells and the atretic follicle numbers were increased. The histology of the uterus in female rats that received DINO, RE, and their combination for 14 days is presented in Fig 2 Both the control and RE groups exhibited typical endometrium and uterine gland anatomy. The endometrium exhibited hyperplasia in response to DINO (73.5 mg/kg). The administration of DINO (230 mg/kg) resulted in endometrial hyperplasia, endometrial structural disturbance, uterine diameter reduction, and muscle layer disruption. The uterus of the DINO (230 mg/kg) + RE (220 mg/kg) subject had endometrial glands and a marginally normal endometrial morphology.

The histopathological changes in the ovary and uterus were also found to be associated with increased lipid peroxidation in female rats due to Free radicals damage lipids. (Alchalabi *et al. 2016*) there were few researches . rosmary is rich in bioactive phytochemicals (tocols and phenolic compounds) with anti- radical and antihy perglycemic capabilities. Tocols and phenolics are active in radical.

Conclusion

The insecticide DINO exposure to female rats resulted in hormonal balance dysregulation, disrupting oestrous cycle stages. Furthermore, the RE alleviated the toxicity in rat females induced by exposure to DINO.

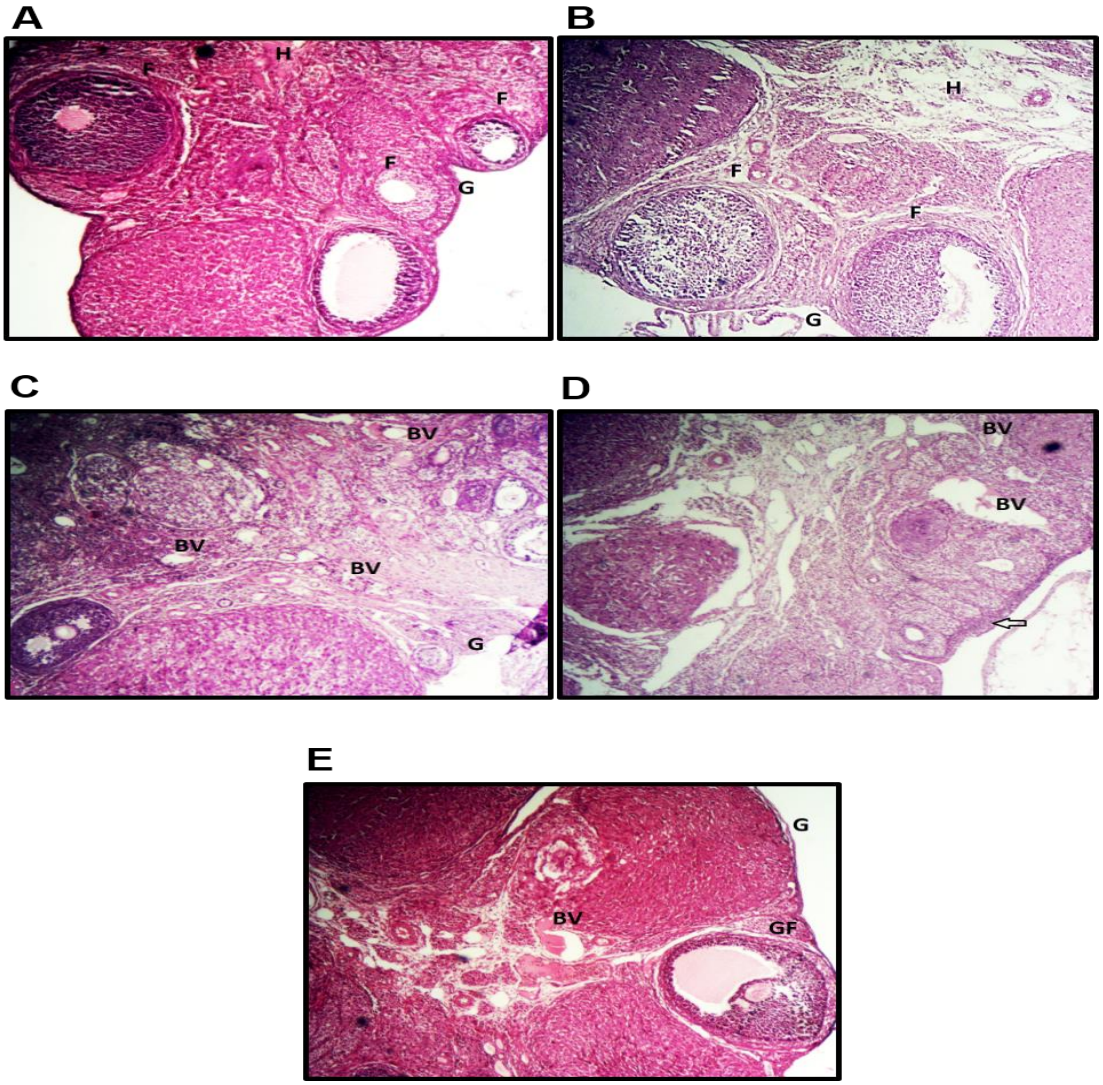

Fig. (1): Photomicrographs of ovary from control female rats and female rats treated with DINO, RE, and their combination for 14 days showing:

(A) A photomicrograph of the ovary of the control group shows smooth germinal epithelium (G), outer cortex formed of multiple ovarian follicles (F), and inner medulla (H). H&E x 100.

(B) A photomicrograph of the ovary of the RE (220 mg/kg) group shows smooth germinal epithelium (G), outer cortex formed of multiple ovarian follicles (F) and inner medulla (H) like control. H&E x 100.

(C) A photomicrograph of the ovary of the DINO (73.5 mg /kg) group shows degenerated germinal epithelium (G) and multiple congested blood vessels (BV). H&E x 100.

(D) A photomicrograph of the ovary of the DINO (230 mg/kg) group shows hyperplasia of germinal epithelium (G) and multiple congested blood vessels (BV) H&E x 100.

(E) A photomicrograph of the ovary of the DINO (230 mg/kg) + RE (220 mg/kg) group shows normal mature graffian s follicle (GF) and germinal epithelium (G). However, still there are congested blood vessels (BV) H&E x100.

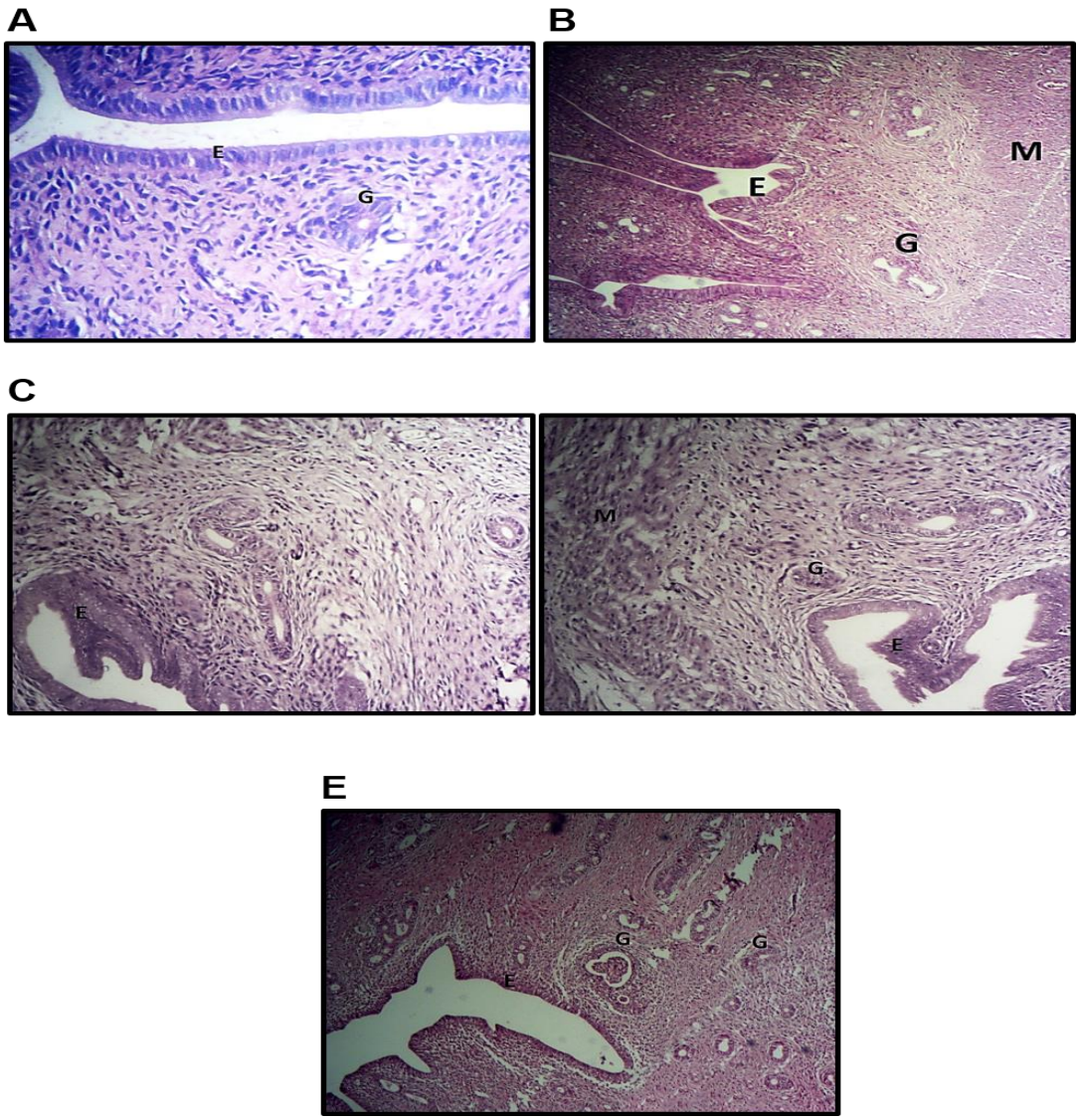

Fig (2): Photomicrographs of the uterus from control female rats and female rats treated with DINO, RE, and their combination for 14 days showing:

(A) A photomicrograph of histological sections of the control uterus shows a normal structure formed of endometrium (E) and uterine glands (G). H&E x 200

(B) A photomicrograph of histological sections of the RE (220 mg/kg) uterus shows a normal structure formed of endometrium (E) and uterine glands (G) and smooth muscle (myometrium) (M) like control. H&E x 200

(C) A photomicrograph of histological sections of the DINO (73.5 mg/kg) uterus shows hyperplasia of the endometrium (E). H&E x 200

(D) A photomicrograph of histological sections of the DINO (230 mg/kg) uterus shows the disturbed endometrial structure, hyperplasia of the endometrium (E), decreased diameter of uterine (G) and disturbed muscular layers (M). H&E x200

(E) A photomicrograph of histological sections of DINO (230 mg/kg) + RE (220 mg/kg) uterus shows slightly normal endometrial structure(E) and endometrial glands (G). H&E x 200

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يثير مبيد دينوتيفوران الحشري تعطيل دورة الشبق في أنثى الجرذ الابيض: الدور التحسيني لمستخلص إكليل الجبل

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الملخص العربى

إن مبيد الدينوتيفوران (DINO) هو من الجيل الثالث من مبيدات النيونيكوتينويد و الذى يعتبر واسع النطاق في جميع أنحاء العالم، مما يؤدي إلى استمرار تعرض الإنسان له. استكشفت الدراسة الحالية السمية الإنجابية لـ DINO على مراحل دورة الشبق لدى إناث الفئران البيضاء والدور التحسيني لمستخلص أوراق إكليل الجبل (RE). تم تعريض عشرين من إناث الفئران لـ DINO وRE ومزيجهما عند ٧٣,٥ و٢٣٠ ملجم/كجم لمدة ١٤ يومًا. تم قياس مستويات هرمون الاستروجين والبروجستيرون، وتم رصد خلل تنظيم مراحل دورة الشبق. أدى التعرض لـ DINO إلى خلل في مستويات هرمون الاستروجين والبروجستيرون. كما تم تعطيل تنظيم مراحل دورة الشبق. تم تخفيف هذه التأثيرات عندما تم إعطاء الفئران مستخلص أوراق إكليل الجبل. إجمالاً، توفر هذه النتائج نظرة ثاقبة حول السمية الإنجابية لـ DINO على إناث الفئران والتأثيرات التحسينية مستخلص أوراق إكليل الجبلعلى السمية الناجمة عن DINO.