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ORIGINAL ARTICLE

Food Microbiology, Safety and Toxicology

Evaluation of Hematopoietic and Immune Toxicity in First-Generation (G1) Rats Following Maternal Thiacloprid Exposure During Gestation and Lactation, and the Protective Potential of Bitter Apricot Kernel Extract

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ABSTRACT

Background: Thiacloprid, a neonicotinoid insecticide, is known to accumulate in various fruits and vegetables, including fresh tomatoes. There is escalating concern about the potential health risks associated with its exposure, particularly during vulnerable periods such as gestation and lactation. While previous studies have indicated adverse effects of neonicotinoids on diverse physiological systems, information on their impact on the hematopoietic and immune systems at low doses remains limited.

Aims: The aim of this study was to evaluate the toxicity of thiacloprid at a microdose of 0.02 mg/kg and to assess the preventive effects of the hydroalcoholic extract derived from bitter almond apricot kernels (at a dose of 50 mg/kg) on the hematopoietic and immune systems during gestation (approximately 19 to 21 days) and lactation (approximately 3 to 4 weeks) in male and female Generation 1 (G1) rats.

Methods: The investigation employed several methodological approaches to examine the effects of thiacloprid and the putative protective potential of the extract. Hematological and immunological parameters were evaluated using automated systems and specialized kits. Rats were systematically allocated into distinct experimental groups, including those exposed to thiacloprid and those concurrently treated with the apricot kernel extract, to observe the impacts on blood and immune parameters. Furthermore, histological analyses of the thymic tissue were performed to assess structural alterations induced by thiacloprid exposure and to ascertain the potential protective effects of the extract.

Results: The results revealed a significant reduction in erythrocyte count, hematocrit, hemoglobin (HGB), and fibrinogen concentrations in rats exposed to thiacloprid. Conversely, a significant increase was observed in total white blood cell count, lymphocyte count, platelet count, mean corpuscular volume (MCV), reticulocyte levels, prothrombin time (PT), and activated partial thromboplastin time (aPTT). However, treatment with the apricot kernel extract led to notable amelioration of these perturbed parameters across the treated groups, indicative of a protective effect. Histological examination of thymic tissue from thiacloprid-exposed rats demonstrated severe histopathological damage, characterized by profound destruction of the thymic parenchyma, multifocal necrotic lesions, and the presence of numerous apoptotic bodies. In contrast, the thymic architecture remained intact in the extract-treated groups, with no significant histological abnormalities, thereby further corroborating the protective potential of the apricot kernel extract.

Conclusions: Exposure to thiacloprid, even at a microdose, can induce discernible toxicity within the hematopoietic and immune systems during critical development stages. Nevertheless, the hydroalcoholic extract of bitter almond from apricot kernels appears to safeguard the cellular integrity of blood and its parameters against the toxic effects of this insecticide, likely attributable to its beneficial phytochemical constituents.

Keywords: Thiacloprid toxicity; Bitter apricot kernel extract; Hematopoietic and Immune systems; Gestation and Lactation; Thymus histology.

ARTICLE INFORMATION

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1 INTRODUCTION

Neonicotinoids represent an emerging class of insecticides developed as an alternative to organophosphate and carbamate compounds, recognized for their established toxicity. This family of insecticides is extensively employed in agriculture for pest control due to its broad spectrum of action (Schaafsma *et al.*, 2015). Their mode of action involves binding to nicotinic acetylcholine receptors (nAChRs), leading to hyperexcitation, abnormal paralysis, and ultimately the demise of target organisms (Chen *et al.*, 2014). This class comprises seven chemical variants; imidacloprid, thiamethoxam, clothianidin, thiacloprid, acetamiprid, dinotefuran, and nitonpyrem (Pang *et al.*, 2020). Among these, Thiacloprid (THI) is predominantly utilized in Algeria. As a chloroprynydilic neonicotinoid, THI shares the common mechanism of blocking acetylcholine receptors (Galdikova *et al.*, 2019) and was registered in 2000 under the trade name Calypso® 480SC (480 $g.L^{-1}$) (Schwarzbacherová *et al.*, 2019).

Recent research indicates that THI exhibits toxicity in mammals, both acutely and chronically across a range of

dosages. Its adverse effects manifest as neurotoxicity (EFSA, 2019), hepatotoxicity and nephrotoxicity (Vivek & Jain, 2020), and endocrine disruptions (Sekeroglu *et al.*, 2014). Furthermore, this insecticide exerts deleterious effects on hematological parameters. Recent studies have demonstrated that thiacloprid exposure can lead to decreased red blood cells, white blood cells, hematocrit, hemoglobin, mean corpuscular volume, and platelet count, concurrently increasing the osmotic fragility of erythrocytes in equine and bovine blood samples (Arrigo *et al.*, 2023). It has also been associated with genotoxic and cytotoxic effects on bovine whole blood cells, inducing DNA damage, chromosomal aberrations, sister chromatid exchanges, and micronucleus formation (Galdíková *et al.*; 2015; Galdíková *et al.*, 2022). Additionally, THI interacts with calf thymus DNA, altering its structure and stability through direct binding (Verebová *et al.*, 2019).

Within the toxicopathological context, several medicinal plants are recognized for their cytoprotective properties, thereby possessing the potential to prevent or ameliorate various pathological aspects induced by insecticides and other environmental pollutants. These plants are conventionally employed in traditional medicine as whole plants or in the form of extracts. Bitter apricot kernels (*Prunus armeniaca L.*) are known to possess several traditional medicinal properties, including those related to pulmonary health, digestive regulation, and trauma management (Al-Juhaimi *et al.*, 2021). These kernels are notably rich in monounsaturated fatty acids, vitamin E, carotenoids and amygdalin, rendering them a valuable source of bioactive compounds (Al-Juhaimi *et al.*, 2018). Moreover, bitter apricot kernels extract has demonstrated neuroprotective potential against thiacloprid-induced toxicity, by restoring mitochondrial redox homeostasis, preventing cognitive impairment, and mitigating brain tissue damage (Djellal *et al.*, 2022).

Building on these preliminary findings that highlight the potential involvement of thiacloprid and bitter apricot kernels in mammalian health, the present study aimed to contribute to the assessment of thiacloprid's toxic effects particularly on the hematopoietic and immune systems, in rats exposed during the gestational and lactational windows. Concurrently, this search seeks to valuate the cytoprotective effect of the hydroalcoholic extract derived from bitter almonds of the apricot kernels against these documented toxicities.

2 Material and Methods

2.1 Harvesting, Drying of Plant Material and Extraction

The study utilized bitter almonds obtained from apricot (*Prunus armeniaca L.*) harvested in Ain-Elkhadra, M'sila, Algeria, between May and July 2022. Upon collection, the kernels were meticulously extracted, subsequently crushed, dried, and then ground into a fine powder. The extraction process was conducted in accordance with the method described by Minaiyan *et al.* (2014), which involved a 72-hour maceration period in aqueous ethanol. Following maceration, the mixture was filtered, and the filtrate was subjected to drying at 40°C to obtain the dry hydroalcoholic extract. The resulting residue was stored at 4°C for subsequent use.

2.2 Animal Husbandry

Wistar albino rats were procured from the Pasteur Institute in Algiers. Upon arrival, the animals underwent a two-week acclimatization period. Throughout the study, rats were maintained under standard laboratory conditions, with *ad libitum* access to food and water. Environmental controls included a controlled ambient temperature of 22±2∘C, a relative humidity of 50±10%, and a 12-hour light/dark cycle.

2.3 Chemical Agent, Extract Dose, and Animal Treatment Protocol

The study employed thiacloprid, a commercial-grade pesticide, for the experimental treatment of rats. The selected dose of THI was 0.020 mg/kg/day, determined based on its documented presence in biological matrices such as fresh tomatoes (Omirou *et al.*, 2009). This environmental concentration was converted to a daily dose for rats using a conversion factor of 0.05 (EFSA, 2011). A hydroalcoholic extract of bitter apricot kernels, at a dose of 50 mg/kg/day, was administered as a putative preventive treatment against thiacloprid toxicity (Kovacova *et al.*, 2020).

Following the 15-day acclimatization period, nulliparous female Wistar rats were mated with males (two females per male, overnight). The following morning, vaginal smears were microscopically examined to confirm evidence of gestation. This day was designated as gestational day 0. Pregnant rats were randomly assigned to one of four experimental groups:

- Control (CON) Group: Received distilled water orally throughout the gestation and lactation periods.
- Thiacloprid (THI) Group: Received 0.020 mg/kg/day of THI orally throughout the gestation and lactation periods.
- Extract (EXT) Group: Received 50 mg/kg/day of the hydroalcoholic extract of bitter apricot kernels orally throughout the gestation and lactation periods.
- Thiacloprid + Extract (THI+EXT) Group: Received concurrent oral administrations of 0.020 mg/kg/day of THI and 50 mg/kg/day of the hydroalcoholic extract throughout the gestation and lactation periods.

2.4 Evaluation of First-Generation (G1) Offspring

The study focused on evaluating the hematotoxicity of thiacloprid (THI) and the preventive effect of bitter almond extract from apricot kernels in first-generation (G1) adult male and female rats. At the conclusion of the experimental period, the G1 rats were sacrificed, and blood samples were collected for biochemical and hematological analyses. These analyses included a complete blood count (CBC), preparation and examination of blood smear, determination of reticulocyte count, measurement of prothrombin time (PT), activated partial thromboplastin time (aPPT), and fibrinogen levels. Additionally, histological examination of thymic tissue was performed to assess structural integrity. All specified parameters were evaluated using SPINREACT spectrophotometric reagent kits and automated analytical equipment. The experimental protocols adhered strictly to ethical guidelines and received approval from the committee of the ''Algerian Association of Sciences in Animal Experimentation'' under law No.88-08/1988, related to veterinary medical activities and animal health protection (N° JORA:004/1988).

Complete Blood Count (CBC)

The Complete Blood Count (CBC) was performed to ascertain the quantitative and qualitative composition of blood cellular components. Blood samples from G1 rats were collected into hematocrit capillaries and EDTA-anticoagulated tubes. To ensure accuracy, cytological and platelet count analyses were conducted within two hours of blood collection. Specialized automated devices were utilized to enumerate various blood cell types based on their specific characteristics (Diakite *et al.*, 2017).

Blood Smear Examination

The blood smear examination involved microscopic visualization of blood cellular elements (Cloutier *et al.*, 2014). A small blood sample obtained from orbital sinus of each rat was transferred to an EDTA-anticoagulated tube. A single drop of whole blood was then placed on a microscope slide, uniformly spread via capillary action, and air-dried. The prepared smear was then stained with May-Grünwald Giemsa (MGG) stain and examined under a light microscope (Piaton *et al.*, 2015). Interpretation takes into account cell size, shape, appearance, hemoglobin content, and white blood cell types and percentages (Ghosh *et al.*, 2016).

Reticulocyte Count

Reticulocytes represent immature erythrocytes released into the bloodstream from the bone marrow following erythropoiesis (Cowgill *et al.*, 2003). The reticulocyte identification is based on the presence of residual ribosomal RNA, which appears as bright blue filaments and granulations upon supravital staining. For analysis, whole blood was mixed with a specific reticulocyte dye, allowed to stand for 15 minutes, and then used to prepare a blood smear. The reticulocyte count was performed by enumerating reticulocytes among 500 red blood cells, as described by Bellier & Cordonnier (2010).

Prothrombin Time (PT)

Prothrombin time (PT) is a crucial essay employed to measure the extrinsic pathway of blood coagulation and identify deficiencies in extrinsic coagulation factors (Hafian *et al.*, 2003). This assay measures the time required for clot formation after the addition of thromboplastin—a tissue extract rich in tissue factor, phospholipids, and calcium—to platelet-poor plasma. Coagulation is initiated by the activation of Factor VII by tissue factor. The results of the Quick time were expressed in seconds relative to a control (Ref. 1709222. SPINREACT, 2015).

International Normalized Ratio (INR)

The International Normalized Ratio (INR) serves as a standardized measure for PT results, particularly relevant for comparative purposes across different laboratories. The INR was calculated as the ratio between the prothrombin time of the treated rat and that of the control group, utilizing the following formula by Laoudy *et al.* (2016):

$$\text{INR} = \left(\frac{\text{Patient PT}}{\text{Control PT}}\right) \text{ISI}$$

Kaolin Partial Thromboplastin Time (KPTT)

The Kaolin Partial Thromboplastin Time (KPTT) measures the clotting time of recalcified platelet-poor plasma in the presence of phospholipids (cephalin) and an activator, kaolin (Ignjatovic, 2013). This assay is employed to assess the integrity of intrinsic pathway of plasma coagulation and its results are expressed in seconds (Crighton, 2013).

Fibrinogen Measurement

Fibrinogen, a pivotal protein present in blood plasma and synthesized by the liver, is determined by the thrombin clotting time, which is inversely proportional to the concentration of fibrinogen within the plasma sample (Stang & Mitchell, 2013).

2.5 Histological study

Histological processing of thymic tissue involved a sequence of standard laboratory procedures: fixation, dehydration, clarification, paraffin baths, and mold creation. Initially, the excised thymus tissue was immersed in 10% neutral buffered formalin for an appropriate fixation period.

Subsequently, samples underwent dehydration through a graded series of ethanol solutions, followed by clarification in xylene baths. The processed samples were then placed in molten paraffin wax baths for one hour each to ensure complete infiltration, prior to being cast into metal molds to form tissue blocks. Blocks containing the embedded tissue fragments were then sectioned at a thickness of 7 µm using a microtome. The resulting sections were mounted on glass slides, dewaxed, rehydrated, and stained. After staining, the slides were air-dried and permanently mounted with a coverslip. The stained slides were subsequently photographed using a digital camera affixed to a light microscope (Houlot, 1984).

2.6 Statistical study

All quantitative results are presented as a mean ± standard deviation. Statistical analysis was performed using XLSTAT 2014.5.03 software. The significance of the differences between the control group and treated groups was assessed using a one-factor Analysis of Variance (ANOVA), followed by Tukey's honestly significant difference (HSD) post-hoc test for multiple comparisons. Statistical significance was interpreted as follows:

- **ns:** $p > 0.05$, indicating a non-significant difference;
- *: $0.01 < p \leq 0.05$, indicating a significant difference;
- **: $0.001 < p \leq 0.01$, indicating a highly significant difference;
- ***: $p \leq 0.001$, indicating a very highly significant difference compared to the control group.

Additionally, comparisons specifically against the thiacloprid (THI) group were denoted using the following alpha levels: $^{\#}p < 0.05$, $^{\#\#}p < 0.01$, and $^{\#\#\#}p < 0.001$. To illustrate these results, graphs and histograms were generated using Microsoft Office Excel 2016.

3 Results and Discussion

The methodological strategy of this study employed a pre- and postnatal exposure window, designed to highlight the susceptibility of offspring to the potential gestational and lactational transmission of thiacloprid (THI)-induced hematotoxicity. Human prenatal and postnatal exposure to environmental pollutants, including pesticides, has been associated with adverse developmental outcomes and the increased incidence of various adult-onset diseases (Gomez *et al.*, 2020). THI, one of the most widely utilized neonicotinoid insecticides globally, functions as an agonist of nicotinic acetylcholine receptors (nAChRs), identical to nicotine. Consequently, it possesses the potential to exert toxic effects on rat offspring (Kammoun *et al.*, 2019).

Several investigations underscore a significant correlation between pregnant women's exposure to certain agricultural pesticides and the subsequent physiological impairments observed in their fetuses (Zamora *et al.*, 2022; Albadrani *et al.*, 2024). Within this context, exposure to thiacloprid during critical developmental periods, such as gestation and lactation may induce significant alterations in hematological profiles, immune responses, and hemostatic parameters, particularly in mammalian systems. Despite these concerns, scientific research on this specific interaction remains limited. Therefore, this study aimed to investigate the potential hematotoxic effects of THI and its impact on key physiological systems, thereby contributing to a better understanding of its risks.

3.1 Complete Blood Count (CBC)

Erythroid Lineage

Our findings, detailed in Table 1 and 2, demonstrate significant alterations within the erythroid lineage in first-generation (G1) rats exposed to thiacloprid. Specifically, there was a significant decrease ($p < 0.05$) in both the red blood cell (RBC) count and hemoglobin (HGB) level in THI-treated male and female G1 rats compared to the control group. Concurrently, a significant increase was observed in mean corpuscular volume (MCV) and hematocrit (HCT) level. These results suggest that thiacloprid exposure, via pre- and postnatal maternal transmission, induces notable effects on erythropoiesis, potentially indicative of an anemic state characterized by larger, but fewer, red blood cells.

Table 1. Values of the different parameters of the red line of male control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT) of G1

Parameters Groups	GR 1012/L	MCV (fl)	HGB g/dl	HCT %
CON	8.69 ± 0.90	43.44 ± 1.49	15.51 ± 0.49	38.81 ± 2.21
THI	5.41 ± 0.48 *	69.94 ± 3.98 *	9.59 ± 1.50 *	56.06 ± 4.82 *
EXT	8.18 ± 0.59 ^{ns}	44.30 ± 2.81 ^{ns}	14.12 ± 1.03 ^{ns}	41.96 ± 1.18 $^{\#\#}$
THI+EXT	8.19 ± 0.61 ^{ns}	45.21 ± 2.13 ^{ns}	14.64 ± 1.30 *	42.02 ± 1.34 $^{\#\#}$

Note: Values are means ± SD, (n= 7); *$p \leq 0.05$: significant; ns $p > 0.05$: not significant groups compared to control group, $^{\#}p \leq 0.05$: significant; $^{\#\#}p \leq 0.001$: highly significant groups compared to Thiacloprid group. GR: Red blood cell; MCV: mean corpuscular volume; HGB: hemoglobin; HCT: hematocrit.

Table 2. Values of the different parameters of the red line of female control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT) of G1

Parameters Groups	GR 1012/L	MCV (fl)	HGB g/dl	HCT %
CON	6.84 ± 0.36	49.78 ± 1.43	15.51 ± 1.15	43.80 ± 1.27
THI	5.11 ± 1.10 *	72.00 ± 3.74 *	9 .89 ± 0.44 *	56.18 ± 3.49 **
EXT	6.91 ± 0.71 ^{ns}	50.72 ± 1.83 ^{ns}	16.04 ± 1.54 $^{\#}$	42.17 ± 1.26 $^{\#\#}$
THI+EXT	8.21 ± 0.25 $^{\#}$	51.52 ± 1.03 $^{\#}$	15.75 ± 1.15 $^{\#}$	44.67 ± 0.64 $^{\#\#\#}$

Note: Values are means ± SD, (n= 7); *$p \leq 0.05$: significant; **$p \leq 0.01$: highly significant; ns $p > 0.05$: not significant groups compared to control group, $^{\#}p \leq 0.05$: significant; $^{\#\#}p \leq 0.001$: highly significant; $^{\#\#\#}p \leq 0.001$: very highly significant groups compared to Thiacloprid group. GR: Red blood cell; MCV: mean corpuscular volume; HGB: hemoglobin; HCT: hematocrit.

Conversely, in male G1 rats, treatment with the apricot kernel extract (EXT) and the combined THI+EXT group demonstrated a highly significant decrease in HCT compared to the THI group ($p < 0.01$ for specific comparisons). In female G1 rats, the EXT and THI+EXT groups exhibited a significant increase in RBC count and HGB ($p < 0.05$ for specific comparisons) and a decrease in MCV and HCT when compared to the THI group. These observations indicate a protective and ameliorative effect of the apricot kernel extract against THI-induced erythroid toxicity, with gender-specific nuances in the restorative patterns. Our findings align with previous research; for instance, Chachoui *et al.* (2022) reported a significant decrease in HCT and hemoglobin concentration in animals following daily thiacloprid administration at a dose of 1 mg/kg/day for 90 consecutive days. Similar variations in hematological parameters were also reported by Kataria *et al.* (2016) after imidacloprid (another neonicotinoid insecticide) treatment, albeit over a shorter, 24-hour exposure period.

Leukocyte Lineage

The results of this study reveal a significant increase ($p < 0.05$) in the white blood cell (WBC) count in both male and female G1 rats treated with thiacloprid, relative to the control group (Figure 1). This observed increase leukocytosis could be attributed to an acute immune response triggered by pesticide toxicity, internal bleeding, or indeed, direct effects on bone marrow function and/or the pituitary-adrenal axis (Chachoui *et al.*, 2022). A comparable increase in leukocyte counts has been observed in laboratory animals following prolonged administration of other insecticides, suggesting a common mechanism by which thiacloprid may induce similar systemic inflammatory or stress responses (Singla & Sandhu, 2015).

Platelets

Data from this study demonstrate a highly significant increase ($p < 0.01$) in blood platelet count in male and female G1 rats exposed to thiacloprid when compared to the control group. Conversely, the groups treated with EXT and the combined THI+EXT intervention exhibited a highly significant decrease in platelet count relative to the THI-exposed group (Figure 2). This finding suggests that THI exposure may confer a risk of thrombosis through the promotion of platelet aggregation. This observation is corroborated by the work of Chakroun *et al.* (2016), who reported a significant increase in platelet count on rats

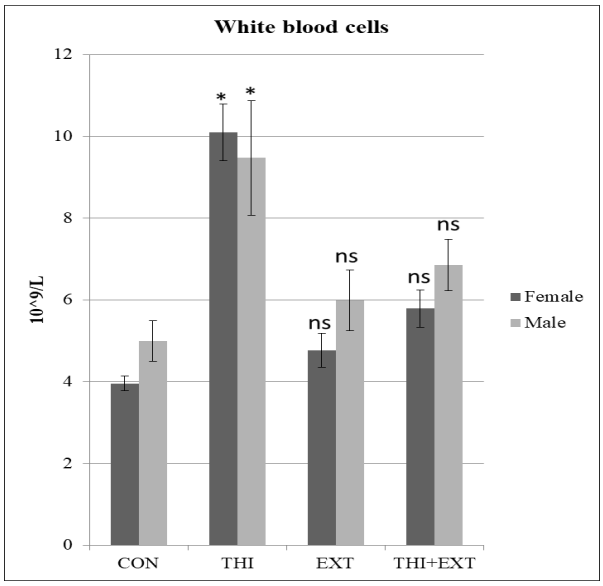

Figure 1. variation in white blood cell count of male and female control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT)
*Values expressed as means ± SD, (n= 7); *$p \leq 0.05$: significant; ns $p > 0.05$: not significant groups compared to control group.*

treated with various doses of acetamiprid (10.85 - 21.7 - 43.4 mg/kg) for 60 days.

Lymphocytes

Analyses of blood lymphocyte counts revealed a significant increase in the number of lymphocytes in both male and female G1 rats treated with thiacloprid, compared to the control group. In addition, a significant decrease in lymphocytes counts in female rats treated with the apricot kernel extract (EXT group), when compared to the

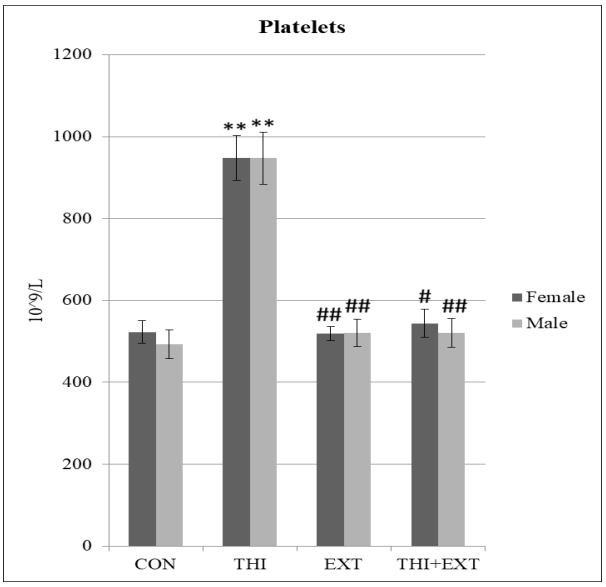

Figure 2. Variation of platelets of male and female control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT)

*Values are means ± SD, (n= 7); **p ≤ 0.01: highly significant compared to control group, #p ≤ 0.05: significant, ##p ≤ 0.001: highly significant groups compared to Thiacloprid group.*

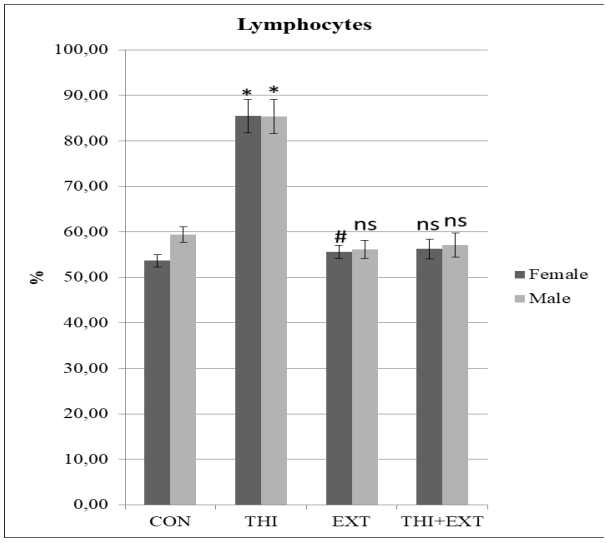

Figure 3. variation in lymphocytes count of male control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT)

*Values are means ± SD, (n= 7); *p ≤ 0.05: significant; ns p > 0.05: not significant groups compared to control group, #p ≤ 0.05: significant groups compared to thiacloprid group.*

thiacloprid-only group (Figure 3). These results collectively suggest that thiacloprid may induce modulation of white blood cell populations, including lymphocytes, likely as an immune system response to pesticide-induced toxicity. This observation implies an activation of the immune system in an attempt to counteract the deleterious effects of thiacloprid (Gavel *et al.*, 2019). Similar results have been reported following prolonged thiacloprid administration, as reported by (Aydin, 2011).

3.2 Blood Smear Evaluation

The results from the blood smear evaluation across the various experimental groups (THI, EXT, EXT + THI+EXT, and control groups (CON) are summarized in Tables 3 and 4.

In male G1 rats treated with THI, a significant increase was observed in the number of neutrophils (PN), monocytes, and atypical cells. A highly significant increase was also noted in basophils (PB) and eosinophils (PE) when compared to the control group. In contrast, the EXT and THI+EXT in male rats demonstrated a significant decrease in PN, PB, PE and atypical cells compared to the THI group.

For female Generation 1 rats exposed to THI, a significant increase was recorded in PB and monocytes, coupled with a highly significant increase in PN and atypical cells. Conversely, the EXT and THI+EXT groups in female rats exhibited a significant decrease in PB and PN, a highly significant decrease in monocytes and atypical cells, and a very highly significant decrease in PE when compared to the THI group (Figure 4).

Table 3. Percentage values of different cells obtained by blood smear analysis of male control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT)

Cells Groups	PN (%)	PB (%)	PE (%)	Mono	Abnormal cells
CON	7.76 ± 0.74	0.77 ± 0.16	0.24 ± 0.053	21.73 ± 0.85	0.00 ± 0.00
THI	17.86 ± 2.19*	4.57 ± 1.61**	1.71 ± 0.75 **	30.14 ± 1.76 *	3.86 ± 2.11*
EXT	8.57 ± 0.79#	0.88 ± 0.14##	0.12 ± 0.04 ##	20.41 ± 1.03 ns	0.00 ± 0.00#
THI+EXT	10.43 ± 0.97#	0.97 ± 0.05 ###	0.48 ± 0.13 ##	21.85 ± 1.06 ns	0.00 ± 0.00 #

Note: Values are means ± SD, (n= 7); *$p \leq 0.05$: significant; **$p \leq 0.01$: highly significant; ***$p \leq 0.001$: very highly significant; ns $p > 0.05$: not significant groups compared to control group, #$p \leq 0.05$: significant; ##$p \leq 0.001$: highly significant; ###$p \leq 0.001$: very highly significant groups compared to Thiacloprid group. Mono: monocyte cells, PN: neutrophils, PB: polynuclear basophils, PE: eosinophils.

Table 4. Percentage values of different cells obtained by blood smear analysis of female control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT)

Cells Groups	PN (%)	PB (%)	PE (%)	Mono	Abnormal cells
CON	9.6 ± 0.35	1.31 ± 0.39	0.18 ± 0.07	20.15 ± 1.04	0.00 ± 0.00
THI	18.70 ± 1.09 **	5.71 ± 1.11 *	1.57 ± 0.53 ***	27.57 ± 2.44 *	3.71 ± 1.38 **
EXT	9.37 ± 0.60 #	1.09 ± 0.47 #	0.12 ± 0.04 ###	20.85 ± 0.89 ##	0.00 ± 0.00 ##
THI+EXT	11.57 ± 0.53 #	1.71 ± 0.75 ns	0.30 ± 0.09 ###	21.85 ± 1.06 #	0.00 ± 0.00 ##

Note: Values are means ± SD, (n= 7); *$p \leq 0.05$: significant; **$p \leq 0.01$: highly significant; ***$p \leq 0.001$: very highly significant; ns $p > 0.05$: not significant groups compared to control group, #$p \leq 0.05$: significant; ##$p \leq 0.001$: highly significant; ###$p \leq 0.001$: very highly significant groups compared to Thiacloprid group. Mono: monocyte cells, PN: neutrophils, PB: polynuclear basophils, PE: eosinophils.

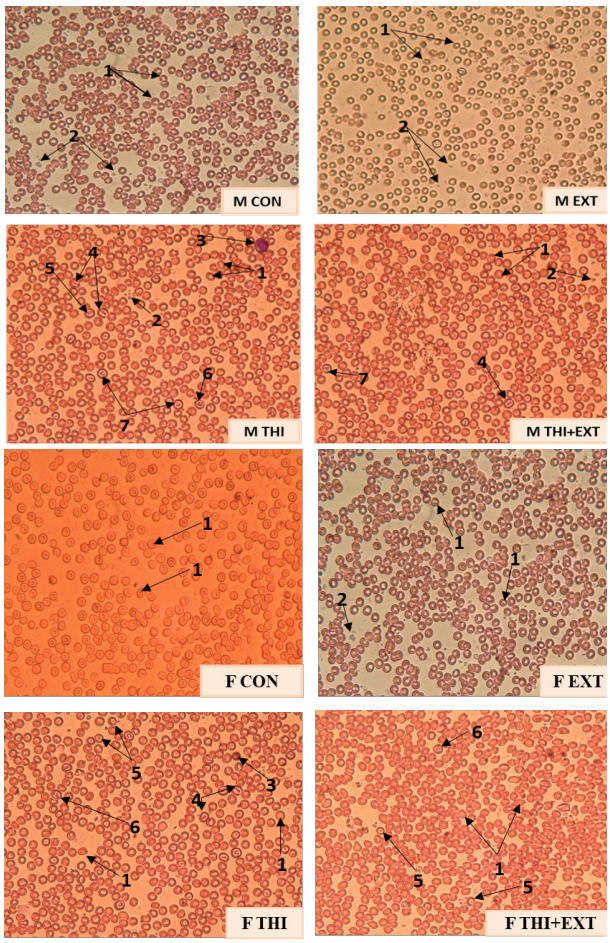

Figure 4. Blood smears from the different groups of males(M) and Female (F) rats

(CON: control; EXT: extract; THI: Thiacloprid; THI+EXT: Thiacloprid + Extract).1: red blood cells; 2: platelets; 3: lymphocyte; 4: eosinophil; 5: neutrophil; 6: monocyte; 7: basophil.

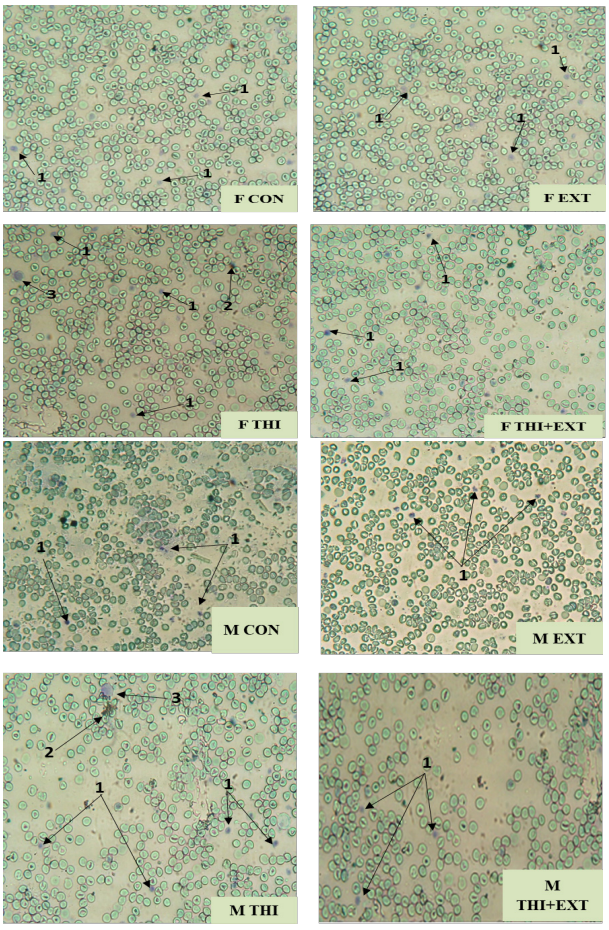

Figure 5. Reticulocytes from the different groups of males (M) and females (F) rats

(CON: control; EXT: extract; THI: Thiacloprid; THI+EXT: Thiacloprid + Extract). 1: reticulocytes; 2: platelet aggregate; 3: abnormal cell.

These findings align with those reported by Chelly *et al.* (2019), who observed similar alterations in rats with acetamiprid (20 mg/kg for 21 days). Such changes in leukocyte populations suggest that neonicotinoids exposure may induce an inflammatory response, possibly due to tissue necrosis, thereby activating the immune system. Similar ameliorative effects exerted by plant extracts were reported by Omer *et al.* (2020).

3.3 Reticulocyte levels

The results of this study indicated a significant increase in reticulocytes levels in both male and female Generation 1 rats treated with THI compared to the control group. Furthermore, a significant decrease in reticulocyte levels was observed in male rats treated with extract (EXT) when compared to the THI group (Figures 5 and 6). This elevation in reticulocytes in THI-exposed animals can be attributed to a compensatory hyperfunction of the bone marrow, which responds to the observed loss of hemoglobin and red blood cells by increasing the production of reticulocytes (Chelly *et al.*, 2019).

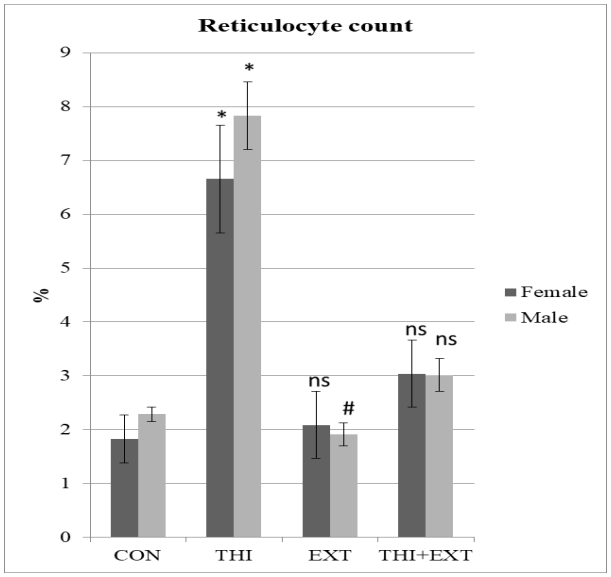

Figure 6. Variation in reticulocyte count of male and female control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT).

*Values are means ± SD, (n= 7); *p ≤ 0.05: significant; ns p > 0.05: not significant groups compared to control group, #p ≤ 0.05: significant groups compared to Thiacloprid group.*

3.4 Prothrombin level (PT)

The current study revealed a significant increase in prothrombin time (PT) in both male and female Generation 1 rats treated with (THI) compared to the control group. In contrast, male rats in the THI+EXT group exhibited a significant decrease in prothrombin time relative to the THI group (see Figure 7). This assay assesses the extrinsic and common pathways of the coagulation cascade. Prior research has indicated that thiacloprid exposure can prolong prothrombin time, indicating impaired clotting ability. Such prolongation may signify a deficiency in coagulation factors such as Factor I (fibrinogen), Factor II (prothrombin), Factor V, Factor VII or Factor X. To the best of our knowledge, an extensive review of various bibliographic databases did not yield studies specifically investigating the effect of thiacloprid and hydroalcoholic extract of bitter apricot kernels on hemostasis parameters. However, the rich content of phenolic compounds and amygdalin in the apricot kernel extract may confer its observed preventive effect against this insecticide's toxicity (Moradi *et al.*, 2017).

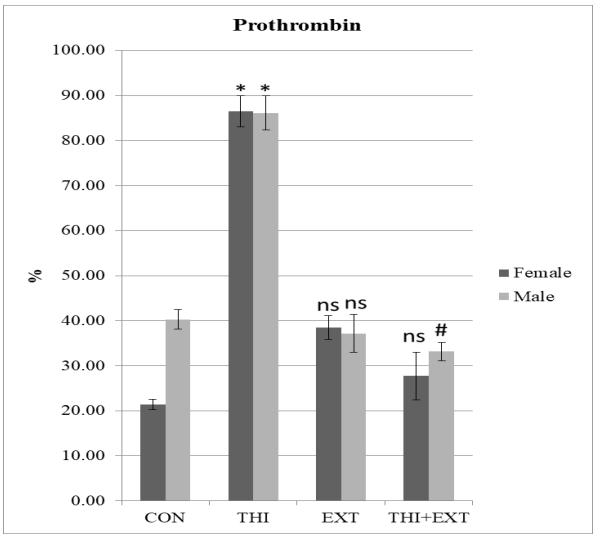

Figure 7. Variation of prothrombin of male and female control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT).

*Values are means ± SD, (n= 7); *p ≤ 0.05: significant; ns p > 0.05: not significant groups compared to control group. #p ≤ 0.05: significant groups compared to Thiacloprid group.*

3.5 International Normalized Ratio (INR)

Our results demonstrated a significant and highly significant decrease in INR in both male and female Generation 1 rats treated with thiacloprid respectively when compared to the control group, while the EXT and THI+EXT groups displayed a significant improvement in INR when compared to the THI group (Figure 8). While INR is a standardized indicator of blood clotting, there is currently no established evidence directly linking thiacloprid to INR variations in the existing literature. This highlights a gap in scientific research concerning the impact of this insecticide on human health, particularly regarding blood coagulation.

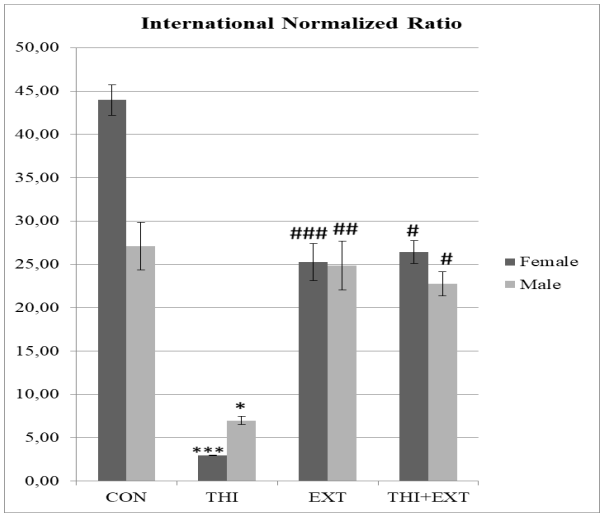

Figure 8. Variation of International Normalized Ratio of male control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT).

*Values are means ± SD, (n= 7); *p ≤ 0.05: significant, ***p ≤ 0.001: very highly significant groups compared to control group. #p ≤ 0.05: significant, ##p ≤ 0.001: highly significant, ###p ≤ 0.001: very highly significant groups compared to Thiacloprid group.*

3.6 Kaolin Partial Thromboplastin Time (KPTT)

The study also reported a significant increase in the level of KPTT in both male and female Generation 1 rats treated with THI compared to the control group. In contrast, a significant and very highly significant decrease in this parameter was noted in male and female rats, respectively, treated with the extract (EXT) when compared to the THI group (Figure 9). KPTT is an essential test employed to assess the intrinsic and the common pathways of coagulation. One study by Abdel Ghaffar *et al.* (2016), reported that thiacloprid exposure was associated with prolongation of KCT, which may indicate abnormalities in coagulation factors such as factors VIII, IX, XI and XII.

3.7 Fibrinogen

Regarding the fibrinogen assay, our results highlighted a significant increase in fibrinogen concentration in THI-treated male and female Generation 1 rats compared with the CON group, with no significant variation was observed in the other treated groups (Figure 10). These findings suggest that thiacloprid exposure may influence blood fibrinogen levels; however, specific data on this interaction remain limited. Such disturbances in fibrinogen synthesis can predispose to coagulation disorders; however, dedicated studies focusing on THI and fibrinogen levels following gestational and lactational exposure are necessary to draw definitive conclusions (Chachoui *et al.*, 2022).

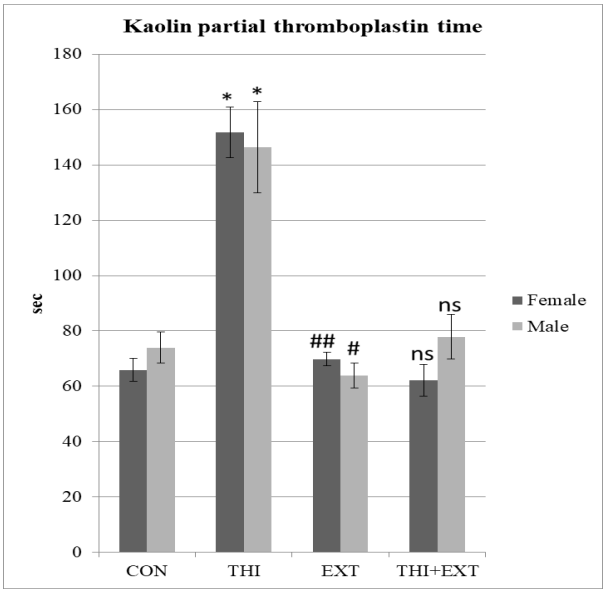

Figure 9. Variation of kaolin partial thromboplastin time of male control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT).

*Values are means ± SD, (n= 7); ns p > 0.05: not significant; *p ≤ 0.05: significant group compared to control group, #p ≤ 0.05: significant, ##p ≤ 0.01: highly significant groups compared to Thiacloprid group.*

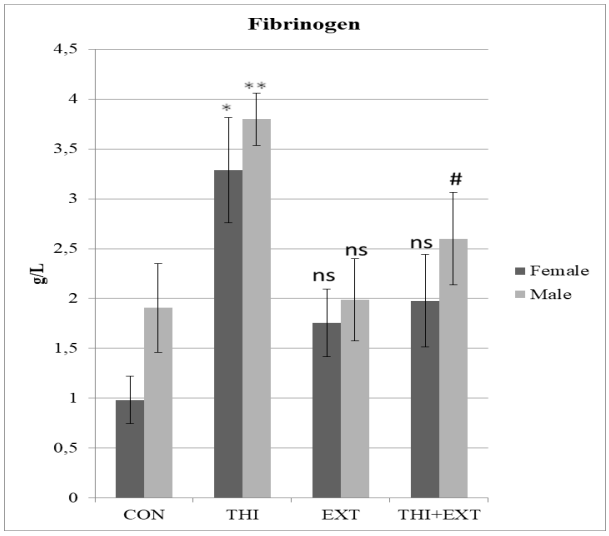

Figure 10. Variation of Fibrinogen of male and female control rats and treaties with thiacloprid (THI), Extract (EXT), and the combination (THI+EXT).

*Values are means ± SD, (n= 7); ns p > 0.05: not significant; *p ≤ 0.05: significant, **p ≤ 0.01: highly significant groups compared to control group, #p ≤ 0.05: significant groups compared to Thiacloprid group.*

3.8 Observation of Histological Changes in Thymus Tissue

Figures 9 and 10 illustrate the microscopic analysis of thymic tissue sections obtained from male and female rats subjected to different treatments during gestation and lactation. The control and extract-treated groups exhibited a well-preserved thymic parenchyma, encapsulated by a thin fibrous capsule that extended the septa to delineate the lobules. Each lobule comprised a distinct medulla, characterized by sparsely distributed lymphocytes, blood vessels, and epithelial cells forming Hassall's corpuscles, whereas the peripheral cortex was densely populated with small lymphocytes.

Conversely, the thymic parenchyma of rats exposed to THI exhibited pronounced histopathological alterations, including extensive necrotic foci, abundant apoptotic bodies, and notable fat involution. In addition, hemorrhagic lesions were evident in the thymic tissue of both male and female THI-exposed rats. Notably, no significant anatomo-histological variations were observed in the thymic sections of the THI+EXT group, indicating a potential protective effect of the extract against THI-induced thymic damage.

Leboffe *et al.* (2020) determined that the acceptable daily intake of THI is 0.03 g/kg BW/day. Research indicates that THI exposure may induce oxidative stress within thymic cells, resulting in increased levels of reactive oxygen species (ROS). Oxidative stress is well-established as a key mediator in apoptosis and cellular damage, operating by disrupting essential cellular components and initiating programmed cell death through procaspase activation (Akash *et al.*, 2020).

Microscopic examination of thymic tissue from THI-exposed rats revealed severe histopathological damage, characterized by the complete destruction of the thymic parenchyma, alongside the presence of necrotic foci and apoptotic bodies. In contrast, the thymic structure in the EXT-treated groups remained intact, exhibiting no significant histological abnormalities, suggesting a potential protective role of the extract against THI-induced toxicity. This cyto-protective and preventive potential is likely attributable to the presence of phenolic compounds, well-known for their antioxidants and antiradicals properties (Moradi *et al.*, 2017).

Comparable structural damage to thymic tissue has been previously documented following short-term exposure to high doses of THI (e.g., 1.5, 2, 3.5, …… 60 mg/kg), resulting in pronounced tissue degeneration (Abou-Zeid *et al.*, 2021; Şekeroğlu *et al.*, 2020). Given the essential role of the thymus in immune regulation, such alterations could exert profound effects on immune function, potentially compromising immune responses and increasing susceptibility to inflammation and disease. This may also account for the observed changes in lymphocyte populations in THI-exposed rats within the present study.

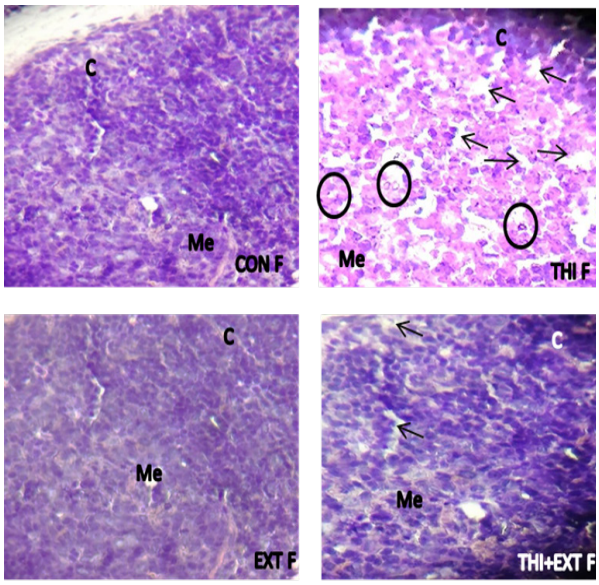

Figure 11. Histology of Female (F) rat thymus, of different groups of rats

(CON, THI, EXT, THI+EXT). Tissues coloration was performed using a combination of two dyes, hematoxylin and eosin. The Arrow indicates necrosis of thymus cells, and the circle indicates apoptotic cells (C: Cortex; Me: Medulla).

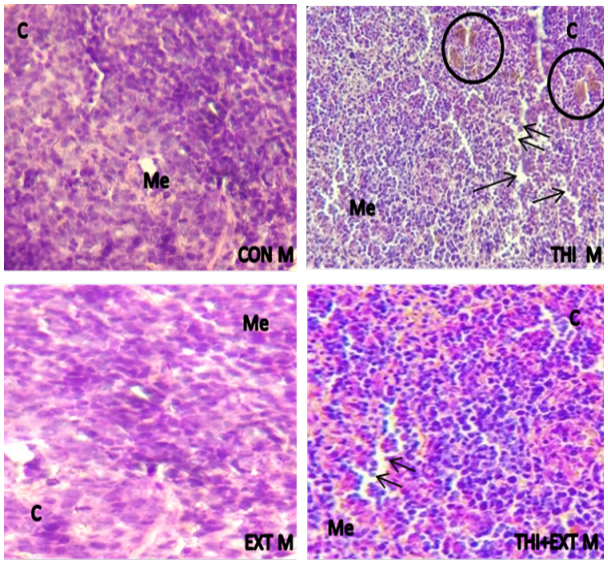

Figure 12. Histology of male (M) rat thymus, of different groups of rats

(CON, THI, EXT, THI+EXT). Tissues coloration was performed using a combination of two dyes, hematoxylin and eosin. The Arrow indicates necrosis of thymus cells, and the circle indicates Hemorrhages tissue (C: Cortex; Me: Medulla).

The apricot kernel extract (EXT) has demonstrated cytoprotective effects on both the hematopoietic and immune systems, primarily attributed to its rich composition of bioactive compounds, such as phenolic compounds (Okada *et al.*, 2013). Recent studies by Qin *et al.* (2019) have provided strong evidence that polyphenols play a crucial role in mitigating oxidative stress-related pathologies by enhancing endogenous antioxidant defense mechanisms, reducing cellular toxicity and preserving cellular integrity. This pharmacological efficacy can be attributed to the rich antioxidant composition of bitter apricot kernels, which contain essential constituents such as iron, potassium, amygdalin, and flavonoids. These bioactive compounds collectively exhibit a broad spectrum of biological activities, including antioxidants, anti-inflammatory, and antitumor effects (Li *et al.*, 2016). Furthermore, bitter apricot kernel extract constitutes a valuable source of magnesium, polyphenols and carotenoids, which contribute to its antioxidant, anticancer, anti-asthmatic, and anti-inflammatory properties (Moradi *et al.*, 2017; Kopčeková *et al.*, 2017; and Kovacikova *et al.*, 2019).

In summary, although bitter apricot kernels have unveiled beneficial effects on hematopoietic and immune functions, as demonstrated by Kovacikova *et al.* (2019), in a 14-day treatment study in rabbits at various doses, their consumption should be carefully monitored due to the presence of potentially toxic compounds.

3.9 Limitations of the study

The present investigation, while yielding valuable insights into the hematopoietic and immune toxicity induced by maternal exposure to thiacloprid during gestation and lactation in first-generation (G1) rats, as well as the potential protective effects of bitter apricot kernel extract, is subject to several inherent limitations that warrant acknowledgment.

Selection Bias: A potential limitation of this study resides in the possibility of selection bias. The selection of experimental animals and the allocation to treatment groups may not have been entirely randomized, this could compromise the external validity of the findings, thereby affecting their generalizability. Future studies should aim to prioritize the minimization of selection bias by employing more rigorous randomization methodologies and by ensuring a more diverse and representative sample.

Confounding Variables: Potential confounding variables include factors such as the genetic variability among the rats, prevailing environmental conditions (e.g., temperature and humidity), and variations in the standardized diet provided to the subjects. These factors possess the capacity to exert an independent influence on the observed outcomes related to the hematopoietic and immune systems, distinct from the effects of thiacloprid exposure or bitter almond of apricot kernel extract treatment. Subsequent studies should aim to control these variables more rigorously to isolate the effects of pesticide and protective intervention.

Limited Follow-Up Period: The duration of follow-up period in this study was limited to gestation and lactation. This relatively short timeframe may not fully capture the long-term effects of thiacloprid exposure or the sustained protective potential of bitter apricot kernel extract on the hematopoietic and immune systems. Such a limited timeframe prevents the assessment of chronic outcomes that may occur later in life. Future research should incorporate extended follow-up periods to evaluate the prolonged impacts and the enduring efficacy of the protective intervention.

Statistical Power: The statistical power of this study may be constrained by the relatively small sample size and the inherent biological variability observed within the experimental groups. A more modest sample size can reduce the capacity to detect significant differences or biological effects, especially when dealing with nuanced physiological variations.

4 CONCLUSIONS

In conclusion, this study unequivocally highlights the toxicological effects of thiacloprid on both the hematopoietic system and the immune system following exposure during critical gestational and lactational periods. Concurrently, the findings offer promising evidence of the preventive efficacy of the hydroalcoholic extract derived from bitter almond apricot kernels against these adverse systemic effects. The obtained results underline the critical imperative for continued research to deepen the understanding and minimize the adverse effects of pesticides on offspring health and development.

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Authors' Contribution: Djellal Dounia Conceptualization of the study, data collection, analysis and interpretation of results, manuscript writing. **Kebieche Mohamed** Supervision of the study, critical revision of the manuscript, methodological guidance, validation of results.

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