



Camel Milk Mitigates Hemato- Immunotoxic Impacts of Fenpropathrin Oral Intoxication in Male Rat

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ABSTRACT

Key words:

Fenpropathrin, Type II pyrethroids, Camel milk, Hematology, Immunotoxicity, Spleen, Thymus

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Our present trial was carried out to investigate the hematological and immune related impacts of fenpropathrin (FNP) pyrethroid in male rats and to assess the ameliorating effect of camel milk (CM). Sixty male rats were randomly separated into six equal groups ($n=10$). 1st control (C), 2nd corn oil (CO), 3rd camel milk (CM) groups were orally gavaged physiological saline, CO, and CM respectively at doses of 2ml/rat day after day for 60 days. 4th (FNP treated group); orally received FNP 7.06 mg/kg B.W, 5th (CM+FNP pro/co treated group); received CM two weeks prior to and along with FNP, and 6th (FNP+CM co treated group); received FNP followed by CM with the same previous doses, route, and duration. FNP intoxication significantly decreased RBC counts, HCT, MCHC, Hb content, phagocytosis %, phagocytic index, serum lysozyme activity, and IgM levels. Also, FNP significantly increased leukogram, platelet count, TNF α and IL6 serum levels. CM significantly attenuates the altered indices more significantly in the (CM+FNP pro/co treated) group than the (FNP+CM co treated) group. Spleen tissues of FNP treated group revealed marked atrophy and lymphoid elements depletion with apoptosis. Furthermore; marked atrophy of thymic cortex, delineation of cortex and medulla with multifocal lymphocytic depletion. It is concluded that CM significantly attenuates both hematological and immunological toxic impacts induced by FNP oral intoxication in rats. Additionally CM pre and concurrent oral administration could lessen FNP induced alterations than CM concurrent administration only.

1. INTRODUCTION

In the developing nations, the use of pesticides has become "a necessary evil" considered as potential environmental hazards that injure non-target organisms. According to WHO, pesticides having an acute toxicity should not be used in developing countries (El-demerdash, 2007). However; in many countries, PYRs (pyrethroids) usage is still extensively increased; yielding more environmental problems and the likelihood of human exposure (Xu et al., 2008; Liu et al., 2009). Consequently; the toxicity of (PYRs) towards mammals has gained much attention in the past few decades (Sakr et al., 2002).

Pyrethrin and pyrethroids (PYRs) are the most common used insecticides worldwide; with over 3500

products registered to substitute the abandoning of more environmentally hazardous insecticides such as organochlorines (Amweg et al., 2005), organophosphates and carbamates (Shah et al., 2007; U.S. EPA, 2011). PYRs account for 30% of insecticides used globally (Shi et al., 2011); in agriculture, horticulture, forestry, public health, veterinary preparations and indoor home formulations for more than four decades and currently represent about one-fourth of the worldwide insecticide market (Amweg et al., 2005; Feo et al., 2010).

Fenpropathrin ((RS)- α -cyano- 3- phenoxybenzyl- 2, 2,3,3-tetramethyl cyclopropane carboxylate (FNP), is one of relatively new synthetic alpha-cyano PYRs. As a high neurotoxic and effective insecticide;

it has been used extensively (Soderlund et al., 2002). However, its constant use has produced worldwide environmental pollution problems. Recent research papers revealed that FNP residues have been detected in almost of the tested samples collected from agricultural and urban regions (lao et al., 2010; kuivila et al., 2012). This condition, moreover increased the hazard of human exposure, which may affect different body systems of human beings, including the reproductive, nervous, respiratory, and immune systems (Meeker et al., 2009). There is no concrete evidence that PYRs produce significant toxicities apart from their actions in the nervous system. Immune-insufficiency was studied with regard to PYRs insecticides (allethrin, cypermethrin, fenpropathrin, permethrin) (Descotes, 1988).

The modern onset of online pharmacies and increased knowledge about natural health products has increased the accessibility of camel milk (CM) for use in different populations (Yagil, 2013). In Egypt CM, obtained from free-ranging desert camels, is being consumed by chronic liver disease patients based on the confidence that it improves their liver function. The key scientific cause behind the traditional use of CM is the so called antioxidant potential as well as its high content of unsaturated fat, minerals, and vitamins (Konuspayeva et al., 2009). Also, contains protective proteins, like lysozymes and iron-saturated lactoferrin that exert its immunological potentials (Conesa et al., 2008).

CM exhibits a wide range of biological activities; antimicrobial, antioxidant, antithrombotic, antihypertensive and immuno-modulatory effect (FitzGerald and Meisel 2000; Kohonen and Pihlanto 2001; Saltanat et al., 2009). CM consumption helps in the treatment of diabetes, autism, cancer, various infections, heavy metal toxicity, colitis, and alcohol-induced toxicity (Alkoofee and Aljaber, 2018).

Overall, there is a paucity of data to raise conclusions on the relation between repeated low level of FNP exposure and its associated hematological and immuno-toxic potentials in rats. Therefore, the aim of the current sub-chronic toxicity trial was carried out to assess the hypothesis that FNP intoxication alters the histopathological, hematological and immune related indices in male rats and secondly to assess the ameliorative role of CM on the induced alterations.

2. MATERIALS AND METHODS

2.1. Animals

Sixty male albino rats weighing 150- 200 gm, were used in the present study. Rats were purchased from

the laboratory animal farm, Faculty of Veterinary Medicine, Zagazig University. The rats were accommodated under the suitable laboratory conditions; room temperature about 22- 28° C with a photoperiod of 12-h light/12-h dark cycle, a relative humidity of 50%.

2.2. Insecticide and chemicals

FNP was obtained in commercial form (Danitol) containing 20% EC (emulsion concentration). The insecticide was obtained from SUMITOMO CHEMICAL CO. Ltd (JAPAN). All other chemicals used in the current study were of analytical grade and purchased from Sigma

CM was collected from lactating Sudanese camels (*Camelus dromedaries*), of the same breed *Red sea Hills Bishari camels*. (Shalateen; Red Sea Governate). They were then stored frozen at -18°C until use without any further treatment.

2.3. Experimental protocol

Throughout the duration of this work a sub-chronic in vivo dosing model was used to examine FNP effects on hematological, histopathological and immune related indices in male rats, and to study the modulatory effect of CM. The experimental procedures were done according to the general guiding principles of the National Institutes of Health (NIH) for the Care and Use of Laboratory Animals in scientific research and approved by the Ethics of Animal Use in Research Committee (EAURC), Zagazig University, Egypt. The rats were accommodated for two weeks before being used. Rats were randomly divided into six groups (Gr I, Gr II, Gr III, Gr IV, Gr V, and Gr VI) comprising ten rats each (n=10). FNP and camel milk were given orally using rat stomach tube. Groups were designed as:

Group I: Control C (received physiological saline 2ml/rat for day after day for 60 days)

Group II: Corn oil CO (received CO 2ml/rat day after day for 60 days)

Group III: Camel milk CM (received CM 2ml*/rat day after day for 60 days)

Group IV: FNP Treated (received FNP 7.09mg/kg B.W "1/10 LD₅₀" of FNP* day after day for 60 days)

Group V: CM+FNP pro/co-treated; received CM firstly for 15 days then received CM+FNP day after day for 60 days by the same doses, route and duration)

Group VI: FNP+CM co-treated (received FNP followed by CM 1 hours later day after day

for 60 days by the same doses, route and duration)

(*): oral LD₅₀ of FNP in male albino rats is 70.6 mg/kg body weight (Manual 2004).

(*): oral dose of CM for male albino rats is 2ml/rat (Dallak, 2009).

2.4. Sample collection

2.4.1. Blood samples

At the end of the experimental period, rats from different groups were fasted all-night and blood samples were collected from the median canthus of the eye for each rat in all groups. Samples were collected in EDTA tubes. Another blood samples were taken into heparinized tubes and immediately used for assessment of a phagocytosis assay (percent and index assay), respectively. Additional blood sample was collected into clean, dry tubes without anticoagulant then centrifuged at 3000 RPM/15 min to collect serum samples and then stored at -20°C until biochemical measurements of serum oxidative stress related parameters and lysozyme levels.

2.4.2. Tissue samples

Rats were euthanized by CO₂ asphyxiation. Specimens from dissected spleen and thymus tissue from all experimental groups were taken and fixed at 10% buffered neutral formalin solution for histopathological investigations.

2.5. Hematological indices evaluation

All collected blood samples in EDTA tubes were immediately inspected using a Hemascreen 18 automatic cell counter (Hospitex, Osmannoro-Sesto Fiorentino, Italy) for obtaining hematological indices consisted of total erythrocytes count (RBC count; 10⁶/mL), hematocrit value (HCT), hemoglobin content (Hb) and mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC) and total leukocytes, granulocytes, lymphocytes, and monocytes were determined (Weiss and Wardrop, 2011).

2.6. Immune related indices

2.6.1. Phagocytosis assay

The white corpuscles were isolated from each collected heparinized blood sample to measure the phagocytic capacity. Heat-inactivated *Candida albicans* (*C. Albicans*; obtained from the Department of Bacteriology and Mycology, Zagazig University) which was prepared as summarized by (Wilkinson., 1977) for using in assessing leukocyte phagocytic activity. Lastly, the number of macrophages

(monocytes or neutrophils) with *C. Albicans* that attached or ingested were counted; a total of 100 phagocytes was examined each time to calculate phagocytic activity (showed as phagocytic %). Phagocytic index was calculated from the average number of engulfed/attached *C. Albicans* associated with phagocytically active cells (Muniz-Junqueira et al. 1992).

2.6.2. Lysozyme activity assay

The lysozymes activity in the serum was estimated according to the method mentioned by Mohrig, (1968) and Schlitz (1987). At the time of the assay serum samples and standard lysozyme solutions were brought at room temperature. Exactly 25 µl of each serum sample and standard lysozyme solutions were put in each poured well, then the plates were incubated at room temperature for 12-18 hours. The cleared zone rings diameters that have been developed in the plates were measured. The concentration of the standard was plotted on the logarithmic axis against the corresponding cleared-zones rings diameters on the linear axis of the semi logarithmic graph. The diameter of the samples was plotted against the standard for obtaining the lysozyme concentration in µMol

2.7. Serum biochemical estimations

Serum IgM levels were estimated using commercial IgM ELISA kit purchased from Invitrogen. Catalog number: KRC3011. Serum inflammatory cytokines; tumor necrosis factor (TNFα), and interleukin (IL) -6 levels were measured using ELISA commercial kit obtained from Invitrogen. Catalog number: KRC3011 and Invitrogen. Catalog number: BMS625 respectively.

Serum levels of total protein and albumin levels were determined according to BioMed Total protein kit, Invitrogen. Catalog number: TP116250 and BioMed Albumin kit, Invitrogen. Catalog number: ALB100250 respectively. Levels of serum globulin can be calculated by subtracting the amount of serum albumin from their correspondent total protein values. The values of A/G ratio were obtained by dividing the values of albumin on the values of globulin (Dumas and Biggs 1972).

2.8. Histopathological investigation

Tissue samples from spleen and thymus were taken from rats of different groups and then fixed at 10% buffered neutral formalin solution for 48 hours. Samples were then dehydrated in gradual ascending ethanol (from 70 to 100%), cleared in xylene, and embedded in paraffin. Five-micron thick paraffin were sliced using a microtome (Leica RM 2155, England).

The sections were prepared and routinely stained with hematoxylin and eosin (HE) dye for histopathology (Suvarna et al., 2013).

2.9. Statistical analysis

All the obtained data from the current study were analyzed using a one-way analysis of variance (ANOVA) test, followed by Duncan's multiple range tests for post hoc analysis. All data were analyzed using Statistics 21 software (SPSS, Chicago, IL).

The results are shown as mean \pm SE of means. Statistical comparisons were done to determine any significant differences between experimental groups. The difference was statistically significant when the p-value \leq 0.05.

3. RESULTS

3.1. Hematological indices

The modulating effect of CM on hematological indices in FNP orally intoxicated male rats is shown in **table 1**.

3.1.1. Total erythrocyte (R.B.C.) counts

FNP intoxication significantly decreased RBC counts in FNP treated group as compared with the C, CO, and CM groups. However, CM administration significantly increased R.B.C counts in (CM+FNP pro/co treated) and (FNP+CM co treated) groups as compared with the FNP treated one.

3.1.2. Red Blood Cell Indices:

In regard to HCT value; FNP significantly decreased HCT % in FNP treated group as compared with the C and CM groups. But the decrease was non-significant when compared with CO group. However, CM non-significantly increased HCT value in both groups either (CM+FNP pro/co treated) or (FNP+CM co treated) group as compared with FNP treated group.

Belonging to MCV and MCH values there were a non-significant change between all exposed rat groups. Meanwhile MCHC value showed significant decrease in FNP treated group as compared with the C and CO groups, but the decrease was non-significant as compared with CM treated group. Administration of CM non-significantly modulates the decreased values in the (CM+FNP pro/co treated) and the (FNP+CM co treated) group as compared with FNP treated group.

Concerning with the Hb level; FNP induced a significant decrease in Hb content in FNP treated group as compared with C, CO, and CM groups. Meanwhile, CM significantly increased Hb content in (CM+FNP pro/co-treated) group and non-significantly in the (FNP+CM co-treated) group as compared with FNP treated group.

The modulating effect of CM was non-significant between (CM+FNP pro/co treated) and (FNP+CM co treated) group for all examined hematological indices

3.2. Leukogram and platelet count

The mitigating effect of CM on total leukocyte (WBC) count, lymphocyte, neutrophils, eosinophil, basophils percentage, and platelets count in FNP treated male rats is shown in **table 2**. FNP induced significant increase in WBCs count in FNP treated group as compared with C, CO and CM groups. Administration of CM depicted a significant decrease of WBCs count in the (CM+FNP pro/co-treated) and the (FNP+CM co-treated) groups when compared with FNP treated group and also the modulating effect of CM was non-significant among them.

As regards to Lymphocytes %, FNP treated group showed a significant decrease in lymphocytes% as compared with the C, CO, and CM groups. Meanwhile; CM administration significantly restored the decrease in both (CM+FNP pro/co-treated) and (FNP+CM co-treated) groups as compared with FNP treated group.

In relation to monocytes %; FNP induced a non-significant increase in the FNP treated group as compared with the C and CM groups, meanwhile; the increase was more significant than the CO group. Administration of CM induced a non-significant increase in monocytes % in the (CM+FNP pro/co treated) and the (FNP+CM co-treated) groups as compared with FNP treated group.

Belonging to neutrophils %, exposure to FNP in FNP treated group induced significant increase in the neutrophils % than the C, CO, and CM groups. Meanwhile; CM administration significantly decreased neutrophils % in both (CM+FNP pro/co treated) or the (FNP+CM co-treated) groups as compared with FNP treated group (the modulating effect was a non-significant between them).

In regards to eosinophils %, obtained results showed that exposure to FNP in FNP treated group induced significant decrease in eosinophils % than the C, CO, and CM groups. Meanwhile; CM administration induced a non-significant increase in eosinophils % in (CM+FNP pro/co treated) group but significantly restored the decrease in (FNP+CM co treated) group as compared with FNP treated group, the modulating effect was a non-significant between them. In regards to basophils %, values showed non-significant changes between all the experimental groups.

Table 1: Shows the modulating effects of camel milk CM (2 ml/rat) on hematological indices in fenpropathrin FNP (7.06 mg/kg B.W) intoxicated male rats. (Results are expressed as mean ± SE) (n = 5).

Parameters	RBCs (x 10 ⁶ ml ³)	HCT (%)	MCV (fl)	MCH (pg)	MCHC (g/dl)	Hb (g/dl)
Group						
1 st group C	9.2± 0.012 ^a	42.44± 1.24 ^a	46.12± 1.27 ^a	16.72 ±0.62 ^a	36.28± 0.36 ^a	15.4 ±0.6 ^a
2 nd group CO	8.67± 0.01 ^{bc}	41.38± 1.23 ^{abc}	47.76± 1.49 ^a	17.26 ±0.55 ^a	36.3± 0.32 ^a	15.02 ±0.4 ^{ab}
3 rd group CM	8.81± 0.04 ^b	41.64± 1.02 ^{ab}	47.24 ±0.92 ^a	16.58 ±0.18 ^a	35.22± 0.31 ^b	14.64 ±0.2 ^{ab}
4 th group FNP treated	8.01± 0.10 ^e	38.58± 0.76 ^c	48.12 ±0.69 ^a	16.66 ±0.31 ^a	34.62± 0.18 ^b	13.36 ±0.27 ^c
5 th group CM + FNP pro/co-treated	8.57± 0.02 ^{cd}	40.9± 0.37 ^{abc}	47.72 ±0.49 ^a	16.96 ±0.02 ^a	35.54± 0.39 ^{ab}	14.5± 0.03 ^{ab}
6 th group FNP + CM co-treated	8.43 ± 0.03 ^d	39.22 ± 0.31 ^{bc}	46.46 ±0.22 ^a	16.54 ±0.20 ^a	35.6± 0.29 ^{ab}	13.96 ±0.2 ^{bc}

Means within the same column carrying different superscript letters are significantly different (p ≤ 0.05).

Table 2: Shows the modulating effects of camel milk CM (2 ml/rat) on leukogram and platelets count in fenpropathrin FNP (7.06 mg/kg B.W) intoxicated male rats. (Results are expressed as mean ± SE) (n = 5).

Parameter	WBCs x10 ³ /ml ³	Lymphocytes %	Monocytes %	Neutrophils %	Eosinophils %	Basophils %	Platelets ul
Groups							
1 st group C	9.53± 0.74 ^b	70.7 ±3.2 ^a	4.24± 0.11 ^b	19± 3.1 ^b	5.52± 0.97 ^{ab}	0.46± 0.08 ^a	589.4± 98.07 ^c
2 nd group CO	10.26± 0.25 ^b	59.6 ±3.4 ^b	2.38± 0.9 ^c	29.9± 2.5 ^b	5.64± 0.95 ^{ab}	0.36± 0.02 ^a	632.6 ± 76.48 ^c
3 rd group CM	10.07± 0.99 ^b	56.3 ±0.92 ^b	5.72 ±0.5 ^a	29.84 ±1.46 ^b	7.74± 0.16 ^a	0.38± 0.13 ^a	904.8 ± 49.87 ^b
4 th group FNP treated	22.62± 2.1 ^a	41.5 ±5.8 ^c	4.58± 0.31 ^{ab}	50.76 ±6.7 ^a	2.88± 0.58 ^c	0.28± 0.03 ^a	1179 ± 33.16 ^a
5 th group CM + FNP pro/co-treated	12.4± 0.1 ^b	62.68 ±0.41 ^{ab}	5.54± 0.14 ^{ab}	26.44 ±0.46 ^b	4.86± 0.02 ^{bc}	0.48± 0.07 ^a	865.4 ± 12.49 ^b
6 th group FNP + CM Co-treated	10.15± 0.058 ^b	60.08 ±3.2 ^b	4.94 ±0.15 ^{ab}	29.44 ±4.09 ^b	5.18± 2.3 ^b	0.36± 0.07 ^a	929.8 ± 47.53 ^b

Means within the same column carrying different superscript letters are significantly different (p ≤ 0.05).

Belonging to the platelet count; FNP induced a significant increase in platelet count in FNP treated group as compared with the C, CO, and CM groups. CM restored the increased values in both (CM+FNP pro/co-treated) or the (FNP+CM co-treated) groups as compared with the FNP treated group.

3.3. Immune related indices

The ameliorating effect of CM on immune related indices (phagocytosis, phagocytic index, lysozyme activity, IgM, TNF-α, and IL6) in FNP intoxicated male rats is shown in **table 3**. FNP treated group;

showed a significant decrease in phagocytosis %, phagocytic index, lysozyme concentration and IgM levels as compared with the C, Co, CM groups. CM induced a significant increase in phagocytosis %, phagocytic index, lysozyme concentration, and IgM levels in both (CM+FNP pro/co-treated) or (FNP+CM co-treated) groups as compared with the FNP treated group. The modulating effect of CM was more significant in (CM+FNP pro/co-treated) than (FNP+CM co-treated) group for phagocytosis %, phagocytic index, and lysozyme concentration while it was non-significant for IgM levels.

FNP induced a significant increase in levels of TNF- α and IL6 as compared with the C, Co, CM groups. CM induced a significant decrease in levels of TNF- α and IL6 in both (CM+FNP pro/co-treated) or (FNP+CM co-treated) groups as compared with the FNP treated group. The mitigating effect was more significant in (CM+FNP pro/co-treated) group than the (FNP+CM co-treated) group.

The modulating effect of CM on serum total protein, albumin, globulin levels, and A/G ratio in FNP intoxicated male rats is shown in **table 4**. FNP intoxication induced a significant decrease in serum total protein and globulin levels, while induced significant increase in the A/G ratio in FNP treated group as compared with the C, CO, and CM groups. In albumin levels, FNP induced significant decrease as compared with C and CO groups but the decrease was non-significant when compared with CM group. Administration of CM significantly restored the decreased values in total protein, albumin and total globulin levels, moreover; induced significant decrease in A/G ratio in both the CM+FNP (pro/co treated) or the (FNP+CM co treated) groups as compared with the FNP treated group. **Histopathological investigation**

The examined spleen sections of the C, CO, and CM groups showed a normal splenic architecture, including red pulp and white pulp (fig. 1.A and b). In regards to FNP treated group, the majority of the examined spleen sections revealed marked atrophy and hypo-cellularity of the lymphocyte follicles (fig 1. C). Characteristic apoptosis and necrosis of the lymphoid elements in both mantle and marginal zones of white pulp with marked tangible body (macrophages contain intra-cytoplasmic fragments of apoptotic lymphocytes) (fig 1. D). While spleen sections of CM+FNP (pro/co-treated) group revealed mild depletion of weight pulp due to hyper-cellularity with a few tangible bodies. A few follicles showed with germinal center formation (fig. 2 A and B). Finally, spleen sections of (FNP+CM co-treated) group showed normal with slight atrophy of a few lymphoid follicles due to slight hypo-cellularity and marked germinal center formation (fig.2 C and D).

The examined thymic tissue sections from the C, CO, and CM groups showed normal lobes architectures and both cortex and medulla were observed in the thymus sections (fig. 3.A). In regards to FNP treated group, the main lesions in thymic sections were marked atrophy of thymic cortex, delineation of cortex and medulla, multifocal district and sky stars appearance due to lymphocytic depletion, and marked atrophy and

hypo-cellularity of the lymphocyte follicles (fig 3. B). Sections of CM+FNP (pro/co-treated) group revealed normal histo-morphological structures. Mild sky stars appearance was observed in a few follicles (fig. 3. C). Finally, The thymic sections of (FNP+CM co-treated) group were within normal with activation cortex (fig.3 D).

4. DISCUSSION

Insufficient data are available in the literature regarding neurotoxic insecticide FNP impact on the immune system and hematological indices in male rats. Accordingly; our current study was conducted to identify the changes of hematological parameters along with the immune related indices in rats exposed to FNP and to search on the beneficial effects of CM administration in FNP intoxicated male rats.

Regarding to the effect of FNP on hematological parameters, the obtained results showed that FNP induced significant decrease in RBC counts, HCT, MCHC, Hb content. Also, induced a significant increase in TLC and platelet count. These results are in covenant with that obtained by (Bhelonde and Ghosh., 2004; Samia et al., 2008) who reported that orally administered FNP (1/100 and 1/1000 LD₅₀) in male rat for 10 weeks caused significant decrease in RBC counts, Hb content, packed cell value (PCV). Similar results in male rats induced by cypermethrin (Das et al., 2016) and by Lambda-cyhalothrin (Oularbia et al., 2015). Similar studies reported that PYRs intoxication induced alterations in hematological indices (Haratyma-Maj., 2002; El-Demerdash et al., 2004; Manna et al., 2005; Veness., 2007). The decreased RBCs may be due to the enhanced hemolysis of rat erythrocytes (Mandal et. Al., 1986) or may be due to impaired biosynthesis of heme in bone marrow (Rahman et al., 1990; Shakoori et al., 1992) or may be due to the disruptive action of FNP on erythropoiesis as mentioned by (Veness., 2007)) who reported that chronic exposure to PYRs insecticide resulted in the destruction of erythrocytes. Additionally, over-generation of ROS by FNP may exaggerate oxidative damage, other PYRs such as deltamethrin and cypermethrin have been reported to produce oxidative stress in cells as well (Giray et al., 2001; Liu and Shi., 2006). Similarly, (Makni et al., 2012) added that peroxidation led to a destruction of membrane protein, alteration of membrane bound enzymes as well as erythrocyte osmotic fragility. Furthermore; PYRs also cause hemolysis, resulted in a decrease in circulating RBC in blood (Mandal et al., 1986) The decrease in

PCV may be due to the decreased cellular counts in blood after pesticide exposure (Ahmad et al., 2009). As regards to the leucocytosis observed in the present study could be attributed to the activation of the

immunological system which results in a shift of the leukocytic pool from the bone marrow and spleen to the peripheral blood (Haratyma-Maj., 2002).

Table 3: Shows the modulating effects of camel milk CM (2 ml/rat) on immune related indices (phagocytosis, phagocytic index, lysozyme activity, IgM, TNF- α , and IL6) in fenpropathrin FNP (7.06 mg/kg B.W) intoxicated male rats. (Results are expressed as mean \pm SE) (n = 5).

Groups	Parameter	Phagocytosis %	Phagocytosis index	Lysozyme Conc. (ug/ml)	IgM (ng/ml)	TNF α (pg/ml)	IL6 (pg/ml)
1 st group	C	52.2 \pm 0.66 ^b	3.56 \pm 0.06 ^b	337 \pm 2.8 ^b	4.38 \pm 0.03 ^a	141.4 \pm 0.74 ^d	195 \pm 1.3 ^d
2 nd group	CO	51.4 \pm 0.5 ^b	3.44 \pm 0.05 ^b	314.6 \pm 4.45 ^c	4.72 \pm 0.22 ^a	143.6 \pm 0.5 ^d	205.2 \pm 1.8 ^c
3 rd group	CM	64.0 \pm 0.7 ^a	4.46 \pm 0.08 ^a	374.4 \pm 2.35 ^a	4.70 \pm 0.05 ^a	134.8 \pm 0.8 ^e	182.2 \pm 1.01 ^e
4 th group	FNP treated	32.0 \pm 0.7 ^c	2.00 \pm 0.07 ^e	249.9 \pm 4.73 ^e	3.34 \pm 0.07 ^c	178.2 \pm 0.73 ^a	249.8 \pm 0.58 ^a
5 th group	CM + FNP pro/co-treated	46.2 \pm 0.58 ^c	2.96 \pm 0.05 ^c	323.9 \pm 4.37 ^c	3.72 \pm 0.13 ^b	151.6 \pm 0.92 ^c	208.4 \pm 2.5 ^c
6 th group	FNP + CM co-treated	40.0 \pm 0.7 ^d	2.36 \pm 0.06 ^d	287 \pm 1.81 ^d	4.02 \pm 0.04 ^b	156.4 \pm 0.92 ^b	237.8 \pm 1.46 ^b

Means within the same column carrying different superscript letters are significantly different ($p \leq 0.05$).

Table 4: Shows the modulating effect of camel milk CM (2 ml/rat) on serum total protein, albumin, globulin levels, and A/G ratio in fenpropathrin FNP (7.06 mg/kg B.W) intoxicated male rats. (Results are expressed as mean \pm SE) (n = 5).

Groups	Parameter	Total proteins (g/dl)	Albumin (g/dl)	Total globulins (g/dl)	A/G ratio
1 st group	C	7.67 \pm 0.23 ^{ab}	4.22 \pm 0.014 ^a	3.45 \pm 0.21 ^{ab}	1.23 \pm 0.066 ^b
2 nd group	CO	8.1 \pm 0.18 ^a	4.16 \pm 0.087 ^a	3.93 \pm 0.19 ^a	1.06 \pm 0.062 ^b
3 rd group	CM	7.45 \pm 0.11 ^b	4.12 \pm 0.002 ^{ab}	3.31 \pm 0.012 ^b	1.24 \pm 0.004 ^b
4 th group	FNP treated	6.28 \pm 0.33 ^c	4.01 \pm 0.038 ^b	2.26 \pm 0.29 ^c	1.94 \pm 0.33 ^a
5 th group	CM + FNP pro/co treated	7.43 \pm 0.014 ^b	4.20 \pm 0.032 ^a	3.25 \pm 0.091 ^b	1.29 \pm 0.03 ^b
6 th group	FNP + CM co treated	7.23 \pm 0.008 ^b	4.17 \pm 0.011 ^a	3.05 \pm 0.006 ^b	1.36 \pm 0.004 ^b

Means within the same column carrying different superscript letters are significantly different ($p \leq 0.05$).

In addition, the increase in the total leukocytes may be attributed to stress caused by prolonged exposure to insecticidal chemical (FNP) (Samia et al., 2008). The significant decrease in lymphocytes induced by lymphocytes is in difference with that obtained by (Das et al., 2016) but in accordance with that obtained by (Basir et al. 2011) who reported that Lambda-cyhalothrin decreased lymphocytes in the female rabbits and by (Ibrahim et al., 2016); some of the inconsistent effects described for PYRs

insecticides on immune function may depend on species and strains of animals used and/or on PYRs vehicle, pure or commercial form, route, doses, type and schedules of exposure used (Righi and Palermo-Neto, 2005).

The results of this study investigated that CM can mitigate all the FNP altered hematological parameters. These results are in agreement with that obtained by (Zahran et al., 2018) by the virtue of its high Vit E content which play a crucial role in sustaining the

flexibility of RBCs and decrease its fragility and damage induced from RBCs membrane phospholipids oxidation (Kraus et al., 1997).

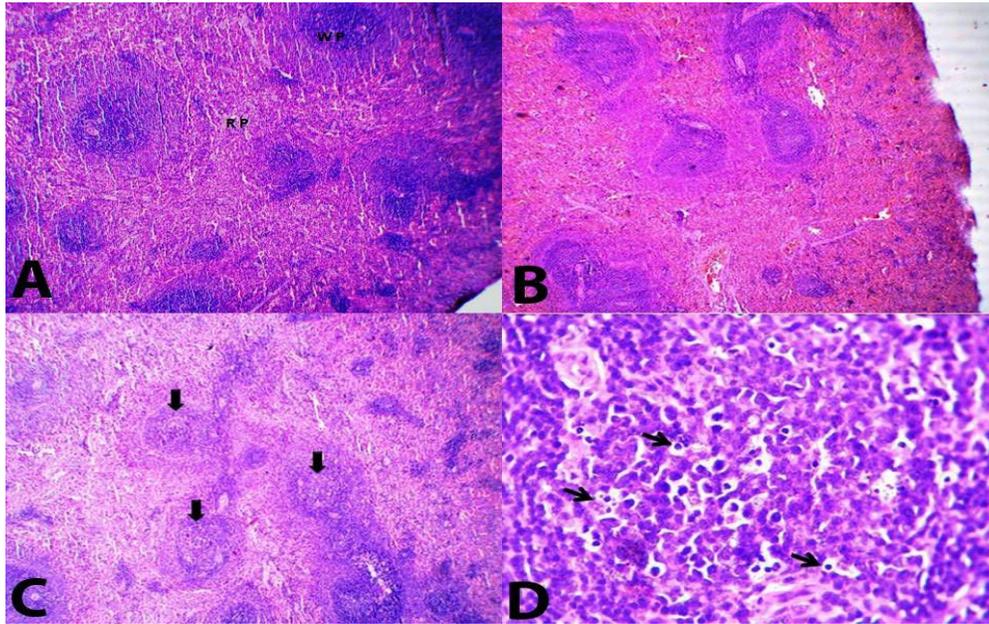


Figure 1. Photomicrograph of rat spleen A, B: spleen section from (C) and (CM) group showing normal architecture red pulp (RP) and weight pulp (WP). H&E X 100 C: spleen section from (FNP) group showing marked atrophy and hypocellularity of the lymphocyte follicles (arrows). H&E X 100. D: spleen section from FNP-treated group showing necrosis, apoptosis and tangible body macrophages contain intra cytoplasmic fragments of apoptotic lymphocytes in the weight pulp (thin arrows). H&E X 400.

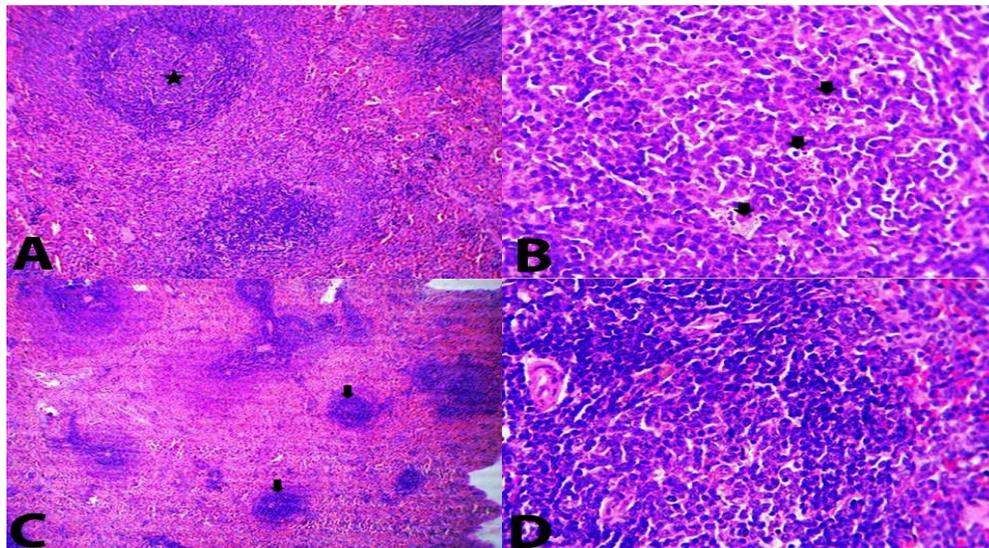


Figure 2. Photomicrograph of rat spleen. A: spleen section from (CM+FNP pro/co treated) group showing mild depletion of white (star) pulp H&E X 100. B: section from (CM+FNP pro/co treated) group showing mild hypercellularity with a few tangible bodies (arrows). H&E X 400. C: spleen section from (FNP+CM co-treated) group showing slight atrophy of lymphoid follicles with marked germinal center formation (arrows). H&E X 100. D: spleen section from

(FNP+CM co-treated) group slight hypo-cellularity of white pulp with the disappearance of tangible bodies. H&E X 400.

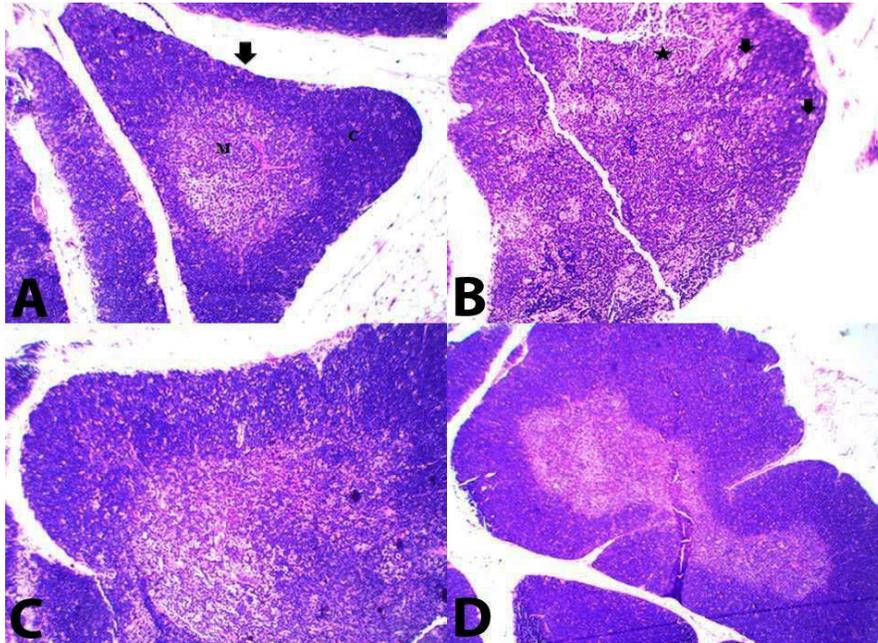


Figure.3. Photomicrograph of rat thymus. A: thymus section from the C group showing normal thymus lobe architecture (thick arrow) contained cortex (C) and medulla (M). H&E X 100. B: thymus section from (FNP treated) group showing marked atrophy of thymic cortex with delineation of both cortex and medulla with multifocal district due to lymphocytic depletion (thin arrow). H&E X 100. C: thymus section from (CM+FNP pro/co-treated) nearly normal thymus structures. H&E X 100. D: thymus section from (FNP+CM co-treated) group normal thymic lobes with mild hypertrophic cortex. H&E X 100.

This vitamin also has a direct impact on the formation of RBCs in the bone marrow (McDowell, 2000). Moreover; CM possesses hematopoietic activity since it is not hemato-toxic. According to (Kumarappan et al. 2010) camel milk also has antioxidative properties. Therefore, when CM was used as prophylactic agents in FNP, they can almost reverse negative features of hemotoxicity. Also, the obtained results are in harmony with that obtained by (Mohammad., 2009) who found that when rats orally treated with 2 mL of camel milk daily for 21 days with cadmium chloride (10 mg/kg body weight) in one solution, restored RBC's count, Hb, HCT value and RBC indices (MCV, MCH and MCHC) to their normal levels. This could be attributed to its high vitamins C, A, E, zinc and magnesium contents (Rahman et al., 2005). All these constituents are potent antioxidants can protect the cell against oxy-radical damage. Recent reports proposed that vitamin E and magnesium ions boosts glutathione levels "a main component of of RBCs" (Ray 1984). It has been noted that Zn has an association with several enzymes in the body and can hinder cell injury by means of enhancement of the

antioxidant system (Ozdemir and Inanc, 2005). Zinc could be a crucial constituent of the antioxidant system and their capacities at different levels (Sato and Bremner, 1993).

Regarding to immune related indices, the current study revealed a significant decrease in phagocytosis %, phagocytosis index, IgM with a significant increase in TNF α and IL6. These results are in harmony with those finding of (El Elaimy et al., 2012) who found that after oral administration of cypermethrin, a type II synthetic pyrethroid, to albino rats at dose of 1.0 mg/kg B.W. For 30 days, significantly decreased phagocytic index and the level of IgG. Aouey et al., (2017) found that Lambda-cyhalothrin induced a significant elevation in the levels of TNF α , IL6 in a dose of 31.1mg/kg B.W for 30, 45 and 60 days in male rats. In agreement with our result (Righi et al., 2009) found that after administration of cyhalothrin pyrethroid in a dose of (1.0 and 3.0 mg/kg B.W) to rats by oral dosing day by day for 7 days, resulted in a significant decrease of both the percentage and potency of phagocytosis in peritoneal macrophages.

Several mechanisms have been suggested for PYRs toxicity; including increased reactive oxygen species (ROS) generation and oxidative stress (Kale et al. 1999) with subsequent detrimental impacts, including lipid peroxidation (LPO), protein oxidation, and DNA damage. Former studies reported that treatment with various insecticides could speed up the synthesis of cytokines such as interferon gamma- γ (IFN) and tumor necrosis factor- α (TNF- α) (Wang et al., 2016). Moreover, TNF- α enhances the expression of different cytokines and other inflammatory mediators, including interleukin IL-1 β , IL-6, and IL-8 and cytokine inducible nitric oxide synthases (iNOS) that are believed to be a key elements in liver damage (Popa et al. 2007; Liedtke and Trautwein 2012).

Regarding to CM restored changes induced by FNP, several studies have shown that CM can decrease the level of TNF- α (Badr, 2013; Korish, 2014), therefore part of the valuable special effects of CM can be attributed to its reducing effect of inflammatory cytokine TNF α . CM has displayed characteristic anti-oxidant properties due to its high vitamins C and E along with zinc and selenium contents. The high lactoferrin content in CM can clarify its characteristic anti-inflammatory and anti-oxidant potentials (Legrand et al., 2005). Additionally, high amounts of IgA, IgM and nano antibodies have been detected in CM (El Agamy et al., 1992).

In relation to serum biochemical indices, the decreased protein content obtained in the current study is agreed with that obtained by (Kumar et al., 2012) which induced by cypermethrin in mice. Nearly similar results were recorded by (Baligar and Kaliwal, 2001) who noticed the alteration in plasma protein and decrease in albumin concentration in rats and mice exposed to the PYRs fenvalerate. Our results are in disagreement with that obtained by (Mansour et al., 2008) who reported that FNP 11.8 mg/k.g B.W for 28 days in male rats induced an increase in serum total protein content. The change in protein content might be due to the imbalance between the rate of protein synthesis and the rate of its degradation in the liver. These findings may be attributed to the impact of long term administration of PYRs on the liver and immune system activities. Belonging to the significantly restored levels of serum total proteins, albumin, and globulin concentration by CM. Similar results were obtained by (Nasr et al., 1996) who reported that CM administration restored the CCl₄ induced alterations. This could be due to their nutritional standards or due to its reduced lipid peroxidation and elevated plasma

protein thiol activities (Sadek et al., 2016; Al-Fartosi et al., 2012).

Regarding to the histopathological lesions in spleen and thymus of FNT treated rat. Similar results were induced by type II pyrethroid deltamethrin in rats thymus (Madsen et al., 1996). Similarly, significant lymphocyte depletion was observed in the thymus, spleen and lymph nodes of cypermethrin treated rats (Desi et al., 1986). Several studies reported immunosuppressive effects on humoral and cell-mediated immune responses in different species like adult mice, rats, and goats due to high doses of cypermethrin, supercypermethrin forte and deltamethrin (Desi et al., 1986; Siroki, 1994; and Tulinska et al., 1995). There was an increase in cells undergoing apoptosis when treated with cypermethrin which is in accordance with several other reports (Raszewski et al., 2015). Deltamethrin was reported to cause increased thymocyte apoptosis (Enan et al., 1996). Thymic atrophy and hypo-cellularity appeared to result, at least in part, from increased thymocyte apoptosis and from antiproliferative chemical effects on thymocytes. Antiproliferative effects in splenic T lymphocytes and reduced cell counts were demonstrated in this organ. In support of this hypothesis, Stelzer and Gordon (1984) previously reported inhibited proliferation of murine T cells exposed in vitro to pyrethroids. Antiproliferative effects may also contribute to thymic or splenic atrophy, thus were also evaluated as mechanisms that may lead to hypo-cellularity.

CONCLUSIONS

The present study shows that CM has the ability to reverse the FNP induced alterations in hematological parameters along with immune related indices in male rats. Our study established that CM pre and concurrent oral administration could lessen FNP induced alterations than CM concurrent administration only.

Conflict of Interest

No conflict of interest declared by the authors in the submission of this manuscript

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