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Hemato-biochemical toxicity induced by Carbendazim and the ameliorative impact of date palm pollen in female albino rats

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Abstract: Carbendazim (CARB) is a fungicide used worldwide for crop production and control of different pests and insects. It is a common environmental pollutant that contaminates food and water and severely damages human and animal health. Date palm Pollon (DPP) is an important source of natural antioxidants which is related to the presence of Phytochemicals such as flavonoids, Phenols, and vitamins. The current study aimed to investigate the ameliorative impact of DPP against the toxicity of carbendazim on the hematological parameters and the biomarkers of hepatorenal function for two months in female albino rats. Thirty-two female albino rats were allocated into four groups. The first group acts as a control group, the second group was exposed to 10 mg/kg body wt. of CARB, the third group was exposed to 100 mg/kg body wt. of DPP, whereas the fourth group was exposed to CARB before DPP. The results obtained indicated that DPP normalized the hematological and hepato-renal parameters. However, CARB induced a marked alteration in the hematological parameters and hepato-renal biomarkers. CARB combined with DPP induced a marked improvement, either increase or decrease in the toxicity of CARB on the hematological indices and the biomarkers of hepato-renal functions. So, it can be concluded that each DPP and the combination of CARB along with DPP have a beneficial impact in the improvement of the toxic effect of CARB on hematological indices and biomarkers of hepato-renal functions as an ameliorative impact, preventing the damage of hematopoietic organs and hepato-renal functions.

Keywords: Carbendazim, date palm pollen, hematological indices, hepato-renal biomarkers, female albino rats.

1. Introduction

Generally, pesticides are toxic chemicals that have been used to control insects, rodents, fungi, and bacteria. Cabindazim is one of these pesticides. Carbendazim C9H4N3O2 (methyl-1H-benzimidazol-2Carbamate "MBC") (CARB) is a fungicide **[1]**. It has been used to control fungal infections in fruits, vegetables, and cereals. Also, it has been used to improve the quality and quantity of agricultural products. In spite of its usefulness, it is highly toxic to natural resources and poses a severe threat to human and animal health **[2]**. Exposure to CARB takes place through inhalation, dermal contact, and ingestion of contaminated water, fruits, and vegetables **[3]**. CARB is classified as an environmental pollutant that causes potential threats to human and animal health **[4, 5]**. Administration of CARB to the experimental animals caused alterations in hematological parameters and the biomarkers of hepato-renal functions.

Oral administration of CARB at 200 mg/kg body wt. for one month led to a decrease in erythrocytes, hemoglobin levels, and Haemocrit (HCT%) value **[6]**. In female chickens, 25 and 50 mg/kg body wt. in the diet for 6th and 12 weeks resulted in a significant decrease in total erythrocyte count, haemoglobin, and total leukocytecount **[7]**. It has been documented that oral administration of 150 mg/kg body wt. of CARB to male albino mice for 5 weeks resulted in a significant reduction in erythrocytic indices and WBC count **[8]**. In male Wistar rats, oral treatment with 400 mg/kg body wt. for 7 days induced a significant decline in RBCs, hemoglobin (Hb), and PCV, while it induced a significant increase in WBC and platelet counts **[9]**. It has been stated that oral administration of 200 mg/kg body wt. to female Sprague-Dawley rats for two weeks led to a significant decline in the erythrocytic indices (RBCs, Hb, PCV, MCHC) and neutrophils. However, an elevation in HCV, WBC count, lymphocytes (LYM), and eosinophils (EOS) was observed **[10]**.

Exposure to CARB has been shown to impair liver and kidney functions. The liver is an important organ that performs numerous functions, including metabolism, detoxification, and glycogen storage. It has been reported that sub-chronic exposure to CARB at 100 mg/kg body wt. for 90 days in mice caused marked alterations in biomarkers of liver function **[11]**. In male albino rats, oral administration of CARB at doses of 100, 300, and 600 mg/kg body wt. elevated the hepatic enzymes in a dose-dependent manner [**12**]. Also, CARB at a dose of 150 mg/kg body wt. for 5 weeks, significantly enhanced the biomarkers of hepatic functions in male mice **[8]**. CARB at a dose of 50 mg/kg body wt. induced an elevation in the serum biomarkers of hepatic enzymes in male Wistar rats **[13]**.

The kidneys are the main organs that excrete and remove the waste products and the toxic metabolites, and xenobiotics through renal excretion. CARB disrupts the biological process

in vital organs such as the renal functions. It induced a significant increase in the serum urea and creatinine in male albino rats when applied for 8 weeks at a dose of 100 mg/kg body wt. [14]. Also, CARB led to an elevation in the serum levels of urea and creatinine in male Wistar rats at a dose of 100, 300, and 600 mg/kg body wt. for four weeks, in a dose-dependent manner [12].

Moreover, CARB at a dose of 150 mg/kg body wt. for 5 weeks in male albino mice induced a significant increase in the serum levels of uric acid and creatinine [8]. Furthermore, exposure to 50 mg/kg body wt. for 14 days caused a marked elevation in the serum levels of renal biomarkers (urea, blood urea nitrogen, and creatinine) [13].

Phytochemical studies have shown that DPP contains a wide range of biochemical and nutritional substances, such as flavonoids and phenols [15]. It has been stated that DPP is a good source of natural antioxidants [16]. Many studies have shown the DPP as an antioxidant that can be used as a protecting agent against the toxicity of xenobiotics on the hematological indices [17], anti-hepatotoxicity [18], and anti-nephrotoxicity [19].

Based on the action of CARB on hematological indices and the serum biomarkers of hepato-renal functions, this study was conducted to find out the role of DPP treatment in alleviating the toxicity of CARB on the hematological indices and hepato-renal enzymes in female albino rats.

2. Materials and methods

2.1. Chemicals

CARB was purchased from Loba Cherné Company, India. Date DPP, a small oval gametocyte with a fine park were sourced from the farm of the Faculty of Agriculture, Sohag University, Egypt. The grains were separated from the bark, washed, dried, and blended. The grain powder was kept in the refrigerator until use.

2.2. Animals

Thirty-two female albino rats (Rattus rattus) weighing between 200 - 220 g were used in the present study. The animals were procured from the Animal House of the Faculty of Science, Sohag University, Sohag, Egypt. During the experiment, the rats were housed in stainless steel cages in an air-conditioned room at a controlled temperature of 25±2°C, under a 12-hour light/dark photoperiod. Animals were provided with food and freshwater ad libitum. This study was carried out under the guidelines of the Animal Care Committee of the Faculty of Science, Sohag University, Sohag, Egypt, with approval number CSRE-29-24.

2.3. Experimental design

After two weeks of adaptation, the animals were arbitrarily allocated into four groups (n=8 animals/group). As follows, the first group acted as the control group which is provided with food and water, and the second group was treated with CARB by a stomach tube at a dose of 10 mg/kg body wt. [20]. The third group was treated with DPP at a dose of 100 mg/kg body wt. [17], whereas the fourth group was treated with CARB along with DPP.

2.4. Collection of blood sample

At the end of the experiment, the animals were fasted overnight prior to bleeding to reduce serum lipids. The rats were by cervical dislocation under light diethyl ether. The blood sample was collected from each rat and divided into two portions. The first portion was transferred directly into an anticoagulant sterilized tube and analyzed immediately for complete blood count (CBC), whereas the second portion was into another sterilized tube without anticoagulant for serum preparation. After centrifugation at 3000 rpm for 20 min, the serum obtained was stored at -20°C until used for the determination of biomarkers of hepato-renal functions.

2.5. Determination of hematological indices

A celtac hematological analyzer (Celtar, Japan) was used to evaluate all the erythrocytic indices, including the total red blood cells (RBCs) count, hemoglobin (Hb) concentration (g/dl), hematocrite (HCT%) value, mean red blood cell volume (HCV) (MCV/SL), mean corpuscular hemoglobin. MCH value (Pg), mean corpuscular hemoglobin concentration (MCH) value (g/d), red blood cell distribution width (ROW) value, Platelet count (PLT) (X103ML), mean platelet volume (MPV) (FL), and platelet distribution width (PDW) (FL). WBC count and the differential leukocyte count as total white blood cells (WBCs X103) count, neutrophils (NEUT X103), lymphocytes (LYM X 103), monocytes (MONO X 10^3), eosinophils (EOS X 103), and basophils (BASO X103) counts.

2.6. Serum biochemical analysis

The Prepared serum was used for the biomarkers of hepato-renal functions using commercial kits purchased from Biomed-Diagnostic Company, Giza, Egypt, according to the methods of the manufacturer's company.

2.6.1. Hepatic biomarker analysis

Serum glucose (Glu) was estimated according to the method of Hyvatinen & Nikkila [21], total protein (TP) was measured according to the method of Henry [22], albumin (ALB) was measured according to the method of Doumas & Biggs [23], serum alkaline phosphatase (ALP) was measured according to the method of Principato et al. [24], Serum aspartate trainsaminase (AST) and serum alanine aminotransferase (ALT) was measured according to the method of Reitman & Frankel [25]., Serum cholesterol (Chol) was estimated according to the method of Watsan [26], and triglyceride (TRIGs) according to the method of Bablok et al. [27].

2.6.2. Renal biomarkers analysis

Serum urea (SU) was analyzed according to the method described by Cheneg et al. [28], Serum uric acid (SUA) level was analyzed according to the protocol outlined by Barham & Trinder [29], and serum creatinine (Cr) levels were assessed using the method of Schvimeister et al. [30].

2.7. Statistical analysis

Results were presented as means ±SD, and they were statistically using one-way analysis of variances (ANOVA) at P ≤ 0.05 and least significant (LSD) used in the statistical analysis of data via the Statistical Package for Social Science (SPSS) version 17.0 in addition to Duncan's test to compare all groups.

3. Results

3.1. Hematological parameters

The obtained results indicated that DPP at a dose of 100 mg/kg body wt. for two months causes a slightly significant difference in all hematological indices, compared to the control group.

CARB induced a marked significant ($p \leq 0.05$) decrease in all RBC indices, including RBCs, Hb, HCT%, MCV, MCHC, and RDW, except MCH, which was significantly increased, with respect to the control group. On the other hand, CARB induced a highly significant (0.001) increase in the WBCs and the all-differential leukocyte counts. While CARB enhanced PDW and MPV significantly reduced ($p \leq 0.05$) the PLT count, with respect to the control (**Table 1**).

In comparison with CARB -treated group, DPP alone caused an improvement in all hematological parameters via an increase and/or decrease in the values of the hematological parameters, whereas combined CARB with DPP removed, the toxicity of CARB on the RBC indices by decreasing the values of RBC indices, significantly, with respect to CARB-treated group. CARB combined with DPP showed an improvement in the values of PLT, MPV, and PDW, WBCs, and NEUT and LYM via a significant ($p \leq 0.001$) decrease in the values of the above parameters, and a non-significant increase in the values of BAS and EOS counts (**Table 1**).

Relative to the DPP-treated group, of CARB along with DPP either decreased or increased significantly ($p \leq 0.05$) the values of RBC indices. However, PLT, MPV, and PDW showed a non-significant decrease. WBC count exhibited a highly significant ($p \leq 0.001$) increase. The values of Neut and LYM were the same as those of the DPP-treated group. Values of BAS and EOS showed a highly significant ($p \leq 0.001$) decrease, with respect to the DPP-treated group; however, Mon. exhibited a highly significant ($p \leq 0.0001$) increase (**Table 1**).

3.2. Hepatic biomarker

CARB induced a marked significant ($p \leq 0.004$) increase in the serum levels of all hepatic biomarkers (Glu., TP, ALB., AP., AST, ALT, TRIGs and Chol.) except ALP which showed a highly significant ($p \leq 0.0001$) decrease, in relation to the control (**Table 2**). Also, treatment with DPP and CARB along with DPP showed a significant ($P \leq 0.003$) increase in all biomarkers of hepatic functions with respect to the CARB-treated group. DPP and CARB, along with DPP, induced either a non-significant decrease or an increase in the serum levels of all biomarkers of hepatic functions. However, it induced a significant ($p \leq 0.004$) increase in the serum level of ALP and a significant ($p \leq 0.004$) decrease in the serum level of TRIGs (**Table 2**).

Relative to the DPP-treated group, CARB, along with DPP, induced a non-significant increase and decrease in all biomarkers of hepatic enzymes, except the serum levels of TP, which showed a significant ($p \leq 0.005$) increase. The serum levels of ALP and Chol, which shows a significant ($p \leq 0.002$) decrease (Table 2).

3.3. Renal biomarkers

CARB induced a significant ($p \leq 0.007$) increase in the serum levels of the biomarkers of all renal functions (UR, SUA, and Creat.) with respect to the control. However, DPP and CARB, along with DPP, induced a non-significant increase and decrease in the serum level of UR, while a significant ($p \leq 0.002$) increase in the serum level of UA was observed. On the other hand, DPP induced a significant ($p \leq 0.006$) increase in the serum level of Cr, while CARB, along with DPP, induced a non-significant decrease in the same parameter (**Table 3**).

Compared with CARB -treated group, DPP led to a significant ($P \leq 0.003$) decrease in the serum levels of SUA and Creat., while it led to a non-significant decrease in the serum level of UR. CARB, along with DPP, caused a non-significant decrease in the serum levels of UR and UA, whereas a significant ($p \leq 0.0002$) decrease in the serum level of Cr was documented (Table 3). In respect to the DPP-treated group, CARB, along with DPP, induced a non-significant increase in the serum levels of UR and UA, whereas a significant ($p \leq 0.007$) decrease in the serum level of Cr was documented (**Table 3**).

4. Discussion

CARB is known as a worldwide environmental pollutant. Humans and animals can be exposed to CARB via consuming contaminated water and food, such as fruits and vegetables. CARB, when entering the bodies of humans and animals, is carried by the bloodstream to the vital organs, which are responsible for detoxification, such as the liver and kidneys. Also, CARB as a fungicide induces a harmfull effect on blood-forming organs.

Recently, herbal medicine has been widely used for the prevention and treatment of many chronic diseases as they are cheap and has few side effects. Extraction and natural products from plants have been used for the treatment, cure, and prevention of many diseases. Date Palm Pollen, which is a male gametocyte of the palm tree (Phoenix dactylifera L.), has been used as a natural product for the treatment of many diseases for a long time in Egypt and China. It is classified in herbal medicines as a natural product due to the presence of polyphenolic and flavonoid compounds. Phenolic and flavonoid compounds were considered as antioxidants **[15]**, which alleviate the cellular damage and free radicals induced by toxicants.

4.1. Hematological Indices

It has been reported that exposure of experimental animals to CARB induced alteration in the hematological indices **[7, 32]**. The current study showed that the values of all erythrocytic were statistically decreased in rats treated with CARB. The reduction of RBCs, Hb, and HCT% values may be indicators of anemia,

coagulation, and hemorrhagic disturbances. The reduction in RBC count is considered due to the direct injurious action of the toxin on animals. This reduction may be attributed to the injury of organs and/or the destructive impact on RBCs membrane induced by CARB The decline in the hemoglobin concentration may be due to the elevated rate of breakdown of RBCs and/or reduction in the rate of RBC formation. The observed increase in MCH value may be due to the effect of Carb may be due to presence of high-quality older RBCs. So, the decreased values of erythrocytic indices and the increased MCH as a result of the administration of Carb may be attributed to the failure of the bone marrow, which leads to a deficiency of erythropoietin, which is essential to produce RBCs, consequently rendering the formation of RBCs, and finally causing microcytic anemia. Also, it can be concluded that the reduction in blood indices after exposure to Carb lowered the blood ability to carry oxygen and decreased the quantity of oxygen that reaches animal organs, which then led to anemia.

The obtained results indicated that administration of DPP alone or combined with Carb was either significantly lower or higher than that of CARB -treated group. It could be concluded that DPP (as an antioxidant) ameliorated the impact of Carb on the erythrotic indices via restoring the function of hematopoietic tissues. This suggestion is aligned with the studies, which indicated that the use of extractions and natural products from plants may ameliorate the toxicity of CARB on the erythrocytic indices **[8, 23]**. PLT plays a crucial role in blood clotting and cardiovascular health. Also, PLT acts as an indicator of selective immune stimulation properly and a protective response to the toxicants, since they are effector cells in the immune system. In the current study, CARB induced a significant reduction in the PLT count. This reduction may be attributed to the suppression of bone marrow caused by CARB MPV, which is an indicator of PLT size and activation. The elevation of the MPV value, in this study, as a result of the administration of CARB may be due to increased reactivity, which is linked with a higher risk of thrombosis. PDW is a measure of PLT size variability that can indicate the activation and dysfunction of PLT. The increased PDW value suggested elevated PLT turnover and activation, which is associated with an inflammatory and thrombotic state. So, it can be concluded that CARB affects PLT activation via suppression of bone marrow. Treatment with DPP and CARB along with DPP restored the values of PLT and PLT indices (MPV and PDW) to nearly the same as that of the control. So, DPP as a natural antioxidant may provide some protection and activate the bone marrow to compensate for the toxic effect of CARB on the hemopoietic organs. In this context, it must be stated that the ameliorative effect of DPP against the toxicity of CARB on erythrocytic indices, PLT, and PLT indices is rather wanted.

It is known that WBCs and differential leukocytes play an important role in immune function and inflammation. Alteration in WBC count indicates immune system activation or suppression. In this study, CARB induced a significant increase in WBC count. The increased WBC count suggests an immune response to CARB to alleviate the toxic effect of CARB on bone marrow. NEUT is a type of WBC essential for the immune response, especially for fighting infection and responding to inflammation.

In the current study, CARB induced an elevation in the NEUT count, in respect to the control, Elevated NEUT count indicates inflammation, infection, and oxidative stress, which is influenced by CARB LYM are a type of WBC, also, LYM are also essential for adaptive immunity, which plays a crucial role in identifying and neutralizing pathogens via antibody production and cell-mediated response. The increased LYM indicate that, as part of the immune system, attempts to shield itself against stress-induced inflammatory changes by CARB Moreover, MONO is a type of WBC that plays an important role in the immune system through differentiating into macrophages and dendritic cells, helping in pathogen elimination and repair of tissue. The elevated Mon. counts normally indicate chronic inflammation and immune activation influenced by xenobiotics. This seems to be the case in the current study, since CARB induced a marked elevation in Mon. counts. EOS and EOSO are types of WBCs that play a crucial role in allergic reactions and immune system regulation in response to inflammation and immune activation.

The increase and decrease in the EOS and BAS in response to CARB indicate strong immune activation to the toxicity of CARB on the immune defense system. So, it can be concluded that increased values of WBCs and differential leukocytic indices may act as a defense mechanism against the toxicity of CARB on the hematopoietic organs in a way to activate the bone marrow. Again, the impact of CARB on the WBCs and differential leukocytic indices is very scarce in the literature. The significantly decreased WBCs and differential leukocytic indices in DPP and CARB, along with DPP, may suggest that DPP (as a phytochemical natural product) was able to attenuate the toxic effect of CARB on these parameters and at the same time caused an increase in the immune response against the CARB toxicity.

4.2. Hepatic biomarkers

It has been demonstrated that the liver acts as a major toxic organ for several fungicides **[34]**. Several studies have indicated that pesticides could lead to liver toxicity in non-targeted organisms, which consequently might have adverse effects on hepatic tissue, such as liver disease and liver failure **[35, 36]**.

In the current study, it was found that CARB induced a marked increase in the serum level of Glu. This finding is aligned with the study, which revealed that CARB enhanced a significant elevation in Glu levels in male mice **[8]**. Glu is a critical biomarker that reflects carbohydrate metabolism and overall metabolic health. The increased serum level of Glu indicates impaired carbohydrate metabolism is due to the toxicity of CARB. Thus, the accumulation of Glu revealed that rats exposed to CARB became hyperglycemic.

The obtained results indicate that the damaging impact of CARB on the hepatic tissue is manifested by elevations in the serum ALT, AST, ALP, and ALB. The elevated transaminase enzymes (ALT and AST) are indicators of hepatocellular membrane injury and leakage in the bloodstream **[37]**. ALP is known ass an index enzyme for hepatobiliary system integrity **[38]**. So, the elevated serum level of ALP revealed hepatobiliary damage. Our results aligned with the study, which indicated that CARB induced a marked elevation of transaminase enzymes in male rats **[8, 12]**. ALB is the quantitatively most abundant

protein, and it is by hepatic parenchymal cells. So, the increased serum level of ALB may be related to the increased permeability of the hepatic membrane via liver function impairment and acute inflammation induced by CARB.

TP are essential biomarkers indicating the overall protein metabolism, liver function, and systemic inflammatory response. Changes in total protein levels may indicate alterations in nutrient absorption, liver function, and metabolic adaptation to the toxicants. So, the increased TP level induced by CARB may be attributed to the toxicity of this fungicide on the hepatic membrane, destroying hepatocytes' membranes, leading to spilled proteins in the bloodstream, resulting in increased total protein. This finding is not in accordance with the study, which indicated that CARB caused a significant decrease in the serum level of TP. in the female chicken **[7]**. TRIGs is a crucial type of lipid that acts as an energy source, and lipid metabolism. The increased TG serum level in the CARB-treated group may be attributed to vital interactions between the micronutrients and nutritional factors with CARB or hepatic membrane damage, leading to an increase in TG in the blood circulation. This finding is aligned with the previous studies **[39, 40]**. Cholesterol (Chol.) is a key lipid molecule that plays a crucial role in the cell membrane structure. The CARB - treated group showed a marked elevation in the serum level of Chol.. The elevated level of Chol. can be attributed to the stimulation of catecholamine in turn led to lipolysis and increased fatty acids production. Also, the increased serum level of Chol. indicated that the ability of CARB to inhibit cholesterol metabolism and upon rendering Chol synthesis. Moreover, CARB may interact with the integrity of the hepatic membrane, leading to increased Chol. in the bloodstream. This finding is in accordance with the previous studies on laboratory animals **[39, 41]**. DPP is usually used as an antioxidant referring to its composition of phenolic and flavonoid compounds, to alleviate the toxicity of xenobiotics on the vital organs. Oral treatment with DPP alone or along with CARB restored the hepatic biomarkers to be similar to or near those of the control. So, it can be concluded that DPP, as an antioxidant, could ameliorate the toxic effects of CARB on the hepatic biomarker enzymes.

4.3. Renal biomarkers

Renal biomarkers are generally used to assess renal function. The serum urea level is the key indicator of kidney function, as it reflects protein metabolism and renal clearance efficiency. In the current study, CARB induced a marked elevation in the serum level of urea. This finding is aligned with the previous studies **[13, 42, 43]**. The elevated serum urea level may be attributed to the impairment of kidney function associated with decreased reabsorption at the renal epithelium, which results in a marked rise in the urea level in the bloodstream. Also, the elevated serum urea level caused by CARB may be due to the breakdown of protein.

UA is the end product of purine degradation, which should be removed from the blood circulation to avoid its accumulation in the glomerular tubules, then excreted in the urine. So, the elevated SUA level induced by CARB may be attributed to the breakdown of purine and the inability of the kidney to excrete it in the blood circulation as a result of nephrotoxicity by CARB Cris freely filtered in the glomerulus, and small amounts are regularly discharged along the tubules. In the current study, CARB induced a marked elevation in the serum Cr level. This finding indicated renal impairment function, especially in the glomerular filtration rate. This aligned with the previous studies **[12, 13]**. So, it can be concluded that administration of CARB induced nephrotoxicity via elevated serum levels of UR, SUA, and Cr.

Administration of DPP alone or along with CARB normalized the renal biomarkers to be like that of the control, or close to it. This suggests that DPP (as an antioxidant) offers amelioration to the renal function against CARB induced impairment of kidney function.

5. Conclusion

This is the first study on the ameliorative effect of date palm pollen supplementation in rats exposed to carbendazim. The results indicated that the ameliorative effect of DPP is attributed to its chemical components. These chemical components act as antioxidant agents and improve of the hematological and hepato-renal alterations response in female albino rats exposed to CARB However, hematological and biomarkers of liver and kidney function investigation will be required to study the effect of different doses of DPP against the toxicity of CARB.

CRediT authorship contribution statement

Conceptualization, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa Abass; methodology, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed; validation, Heba Abd El Aziz Khalil, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa Abass.; formal analysis, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa Abass; resources, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa Abass; data curation, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa abass; writing—original draft preparation, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa Abass; writing—review and editing, Heba Abd El Aziz Khalil, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa Abass; Visualization, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed, Sary Kh. Abd El-Ghaffar, Doaa Abass; supervision, Heba Abd El Aziz Khalil1, Mohamed F. El-Sayed1, Sary Kh. Abd El-Ghaffar, Doaa Abass; project administration, Mohamed F. El-Sayed1.

All authors have read and agreed to the published version of the manuscript.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1: The impact CARB, DPP, CARB combined with DPP on the hematological parameters in female Albino rats (Rattus rattus); The sign (○) is used to show non-significant with p > 0.05, The sign (*) is used to show significant difference for control group with p > 0.05 and The sign (●) is used to show significant difference for CARB group with p > 0.05 and The sign (■) is used to show a significant difference for DPP group with p > 0.05.

Parameter	Control	CARB	DPP	DPP +CARB
RBCs (x10^6/UL)	7.33 ±0.266	6.74 ±0.377*	7.51 ±0.274○●	6.26 ±0.143*●■
Hemoglobin (g/dl)	14.37 ±0.457	13.09 ±0.72*	14.46 ±0.381○●	13.38 ±0.337*○■
Hematocrit (%)	47.79 ±1.063	44.46 ±1.915*	45.33 ±1.857*○	41.84 ±2.159*●■
MCV (fL)	64.63 ±2.875	55.5 ±1.195*	71.13 ±8.476*●	72.75 ±8.515○●○
MCH (Pg)	20.88 ±3.091	27 ±3.854*	23.88 ±5.139○○	25.38 ±4.502*○○
MCHC (g/dl)	36.13 ±1.885	28 ±3.162*	30.88 ±2.295*○	30.88 ±3.314*○○
RDW (%)	16.05 ±0.665	14.88 ±0.819*	16.11 ±1.192○●	16.26 ±0.292○●○
Platelets (x10^3/ UL)	85.59 ±3.462	71.41 ±7.034*	82.69 ±3.158○●	79.01 ±7.143*●○
MPV (fL)	8.36 ±0.245	12.5 ±0.273*	8.78 ±0.071*●	8.99 ±0.155*●■
PDW (fL)	10.9 ±0.053	14.41 ±2.814*	13.74 ±0.555*○	13.13 ±0.794*○○
WBCs (x10^3/ UL)	11.9 ±0.325	16.85 ±1.111*	12.36 ±0.412○●	16.81 ±0.442*○■
Neutrophils (%)	8.4 ±0.463	17.88 ±0.991*	14.88 ±2.357*●	14.88 ±2.357*●
LYM (%)	7.7 ±0.499	8.66 ±0.13*	8.3 ±0.351*●	8.3 ±0.359*●○
MONO (%)	0.885 ±0.025	0.569 ±0.231*	0.886 ±0.06○●	0.629 ±0.016*○■
EOSs (%)	0.38 ±0.011	0.25 ±0.101*	0.39 ±0.026○●	0.28 ±0.008*○■
EOSO (%)	0.07 ±0.005	0.04 ±0.018*	0.07 ±0.004○●	0.05 ±0*○■

Table 2: The impact of CARB, DPP, CARB combined with DPP on the biochemical activities (Hepatic biomarkers) in female Albino rats (*Rattus rattus*); The sign (○) is used to show non-significant p > 0.05, The sign (*) is used to show significant difference for control group with p < 0.05 and The sign (●) is used to show significant difference for CARB group with p < 0.05 and The sign (■) is used to show significant difference for DPP group with p < 0.05.

Parameter	Control	CARB	DPP	DPP +CARB
Glu. (mg/dl)	82.25 ±7.96	88.88 ±2.9*	88.38 ±5.999*○	91.38 ±3.159*○○
TP (g/dl)	5.1 ±0.765	8.99 ±1.945*	7.51 ±1.023*○	9.36 ±0.984*○■
ALB (g/dl)	4.09 ±0.155	4.56 ±0.338*	4.29 ±0.344○○	4.55 ±0.359*○○
ALP (IU/L)	96.58 ±3.124	48.31±1.51*	104.98 ±2.247*●	96.88 ±4.838○●■
AP (U/L)	0.37 ±0.048	0.58 ±0.066*	0.4 ±0.121○●	0.51 ±0.146*○○
AST (U/ml)	18.13 ±3.399	26 ±3.665*	24.4 ±5.464*○	25.63 ±4.779*○○
ALT (U/ml)	24 ±3.381	40.13 ±2.1*	28 ±6.633○●	26.5 ±2.777○●○
Chol.(mg/dl)	187.75 ±9.423	168.38±6.968*	193.75 ±11.511○●	170.25 ±8.43*○■
TG (mg/dl)	168.25 ±1.581	181 ±3.505*	172.38 ±5.706○●	170.25 ±8.464○●○

Table 3: The impact of Carbendazim (CARB), Date palm pollen (DPP), CARB combined with date palm pollen on Biochemical Activities (Renal biomarkers) in female Albino rats (*Rattus rattus*); The sign (○) is used to show non-significant p > 0.05, The sign (*) is used to show significant difference for control group with p < 0.05 and The sign (●) is used to show significant difference for CARB group with p < 0.05 and The sign (■) is used to show significant difference for DPP group with p < 0.05.

Parameter	Control	CARB	DPP	DPP +CARB
UA (mg/dl)	4.75 ±0.434	5.64 ±0.226*	5.16 ±0.262*●	5.45 ±0.363*○○
UR (mg/dl)	11.78 ±1.18	13.65 ±1.198*	11.21 ±4.591○○	12.49 ±5.031○○○
Creat. (mg/dl)	0.65 ±0.076	0.98 ±0.116*	0.76 ±0.092*●	0.66 ±0.119○●■

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