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Splenotoxicity of carbendazim and the role of date palm pollen as a therapeutic agent in male albino rats

Basma H. Hammad[1], Mohamed F. El-Sayed[1], Sary Kh. Abd El-Ghaffar[2], Ahmed Badr[1*]

[1*]Zoology Department, Faculty of Science, Sohag University, Sohag, Egypt.

[2]Pathology and Clinical Pathology Department, Faculty of Veterinary Medicine, Assiut University; Pathology and Clinical Pathology Department, School of Veterinary Medicine, Badr University Assiut, Egypt.

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Abstract: Fungicides are chemical substances used in agriculture to protect crops from pests. Among fungicides, carbendazim (CBZ) is a widely used fungicide that effective against a broad spectrum of fungal diseases. The extensive application of CBZ has prompted worries about its persistence in the environment and its possible toxic effects on organisms other than its intended targets, including humans. According to the existing information, the CBZ toxicity on spleen structure, plays a vital role in the lymphatic and immune systems, was not documented. Accordingly, we investigated the effects of chronic exposure to a sub-lethal dose of CBZ on the spleen's histological structure in rats. Moreover, we assessed the potential therapeutic role of date palm pollen (DPP) in mitigating CBZ-induced toxicity. Thirty-two male albino rats (*Rattus rattus*) were divided into 4 groups: control, CBZ (10 mg/Kg bw), DPP (100 mg/Kg bw), and CBZ with DPP; and the exposure experiment was lasted for 2 months. CBZ caused severe histopathological changes in the spleen structure as hemorrhagic infarction, severe congestion, dilatation of splenic sinuses, fibrosis and depletion in lymphoid cells in white pulp; and hemorrhage and hemosidrosis in the red pulp. Treatment with DPP alone showed normal spleen structure as control group; while it seems that DPP soothes the negative effects of CBZ when combined together, and shows mostly normal structure of spleen with exception of mild necrotic lymphoid cells in white pulp; hemosidrosis and infarction in red pulp. The ability of DPP to alleviate CBZ toxicity may be attributed to its chemical composition, which enhances detoxification processes by neutralizing reactive oxygen species (ROS) that could be produced during CBZ exposure. Nevertheless, further biochemical and physiological investigations are required to clarify CBZ toxicity and assess the therapeutic effectiveness of DPP.

Keywords: pesticides, natural products, date palm pollen, spleen, immune system.

Introduction

Pesticides are a diverse group of substances, including fungicides, essential for modern agriculture and public health, but their use requires careful management to minimize risks to humans and the environment (Tudi *et al*., 2021). Among fungicides, carbendazim (CBZ) that belongs to the benzimidazole class, primarily used in agriculture to control a variety of fungal diseases affecting crops. Its effective against a broad spectrum of fungal diseases making it suitable for a range of plants (Cuppen *et al*., 2000; Boudina *et al*., 2003; Daundkar & Rampal, 2014). Chemically, CBZ contains an aromatic hydrocarbon ring, which is predictable to be oxidized by cytochrome P450 (CYPs) (Manikandan & Nagini, 2018; Feng *et al*., 2021; Wu *et al*., 2021; Lv *et al*., 2022). CYP-mediated oxidation and reduction processes can lead to either detoxification or activation of compounds (Feng *et al*., 2021; Lv *et al*., 2022). Nevertheless, information remains limited regarding the specific metabolic enzymes, kinetic properties, and precise

* Corresponding author E-mail: ahmedbadr@science.sohag.edu.eg

metabolites involved in CBZ metabolism across different species. Compared to many other pesticides, CBZ displays relatively low acute toxicity in both humans and non-target organisms (Sandhu & Waters, 1980). Its LD50 values - the dose necessary to cause lethality in 50% of a test group - range from 2,000 up to more than 10,000 mg/kg body weight for oral and dermal exposure, reflecting a low level of acute toxicity in mammals (Pfeil & Dellarco, 2005; Hashim *et al*., 2023). Despite its low acute toxicity, the extensive use of carbendazim has sparked concerns over its environmental persistence, its potential to accumulate in soil, water, and food items, and possible toxic effects on non-target organisms, humans included (Boudh & Singh, 2019; de Souza *et al*., 2020; AbuQamar *et al*., 2024). Chronic exposure, especially at higher doses, has been associated with reproductive toxicity, liver damage, and slight immunotoxic effects in laboratory settings. In fact, carbendazim's toxic effects are well-documented; research has demonstrated its ability to induce oxidative stress, genotoxicity, carcinogenesis, and specific organ damage, particularly in the liver, kidneys, and reproductive system (Selmanoğlu *et al*., 2001; Lu *et al*., 2004; Jiang *et al*., 2015; Abdel-Rahman *et al*., 2022; Ebedy *et al*., 2022). These negative outcomes are mainly attributed to carbendazim's capacity to generate reactive oxygen species (ROS), interfere with cellular signaling, and disturb normal physiological processes (Hashim *et al*., 2023; Jiang *et al*., 2015; Ebedy *et al*., 2022). Although the lymphatic system, including the spleen, may be particularly vulnerable to CBZ toxicity, to our knowledge, there are no reports on the effects of CBZ on the spleen. The spleen, a vital organ within both the lymphatic and immune systems, is crucial for maintaining innate and adaptive immunity, filtering the blood, and regulating erythrocyte homeostasis (Bronte & Pittet, 2013; Aliyu *et al*. 2021). Histologically, the spleen consists of two main regions: the red pulp, which filters blood and removes defective cells, and the white pulp, rich in lymphocytes that mount immune responses. The organ is encapsulated by dense connective tissue and contains a network of sinusoids for blood filtration (Cesta, 2006; Suttie, 2006). Disruption in its structure or function due to toxicants as CBZ could diminish the body's ability to filter toxins and mount an effective immune response, and thus increasing susceptibility to infections and the harmful effects of circulating toxins (Schuurman *et al*., 1994; Vos, 2007).

Recently, researches have focused on using natural products to mitigate the pesticide-induced toxicity, because of their safety profile and multifaceted therapeutic properties (Yang *et al*., 2021; Zeng *et al*., 2021; Jabłońska–Trypuć *et al*., 2022). Among various natural substances, date palm pollen (DPP), the male gamete of the Phoenix dactylifera tree, has gained considerable recognition for its effectiveness in alleviating toxin-induced injuries (Sani *et al*., 2015; Shehzad *et al*., 2021; Abdelreheim *et al*., 2024). DPP is abundant in bioactive components such as flavonoids, phenolic acids, sterols, vitamins, and minerals, which together provide strong antioxidant, anti-inflammatory, and immunomodulatory effects. These properties enable DPP to scavenge free radicals, support cellular repair processes, and facilitate the restoration of damaged tissues (Ahmed *et al*., 2008; Alalwan *et al*., 2020). As a result, it serves as a promising protective agent against the harmful effects of various toxicants on the hematological parameters (Abdelreheim *et al*., 2024), anti-hepatotoxicity (Al-Qarawi *et al*., 2004), anti-nephrotoxicity (Hasan & Mohieldein, 2016), and anti-inflammatory (Rahmani *et al*., 2014). Accordingly, this study aimed to assess the impact of a sub-lethal dose of CBZ on the spleen, with particular attention to potential histological changes not previously described. In addition, the research sought to determine the potential therapeutic benefits of DPP in alleviating the toxic effects of CBZ on the spleen.

Materials and methods

Animals and experimental design

Male albino rats (*Rattus rattus*; n = 32; with mean weight 200 ± 20 g) were obtained from animal house of Faculty of Science, Sohag University, Egypt. In the University facilities, rats were maintained in clean stainless steel cages; in a well-ventilated room with optimum conditions (temperature 25 ± 1 °C; and under 12 h light: 12 h dark photoperiod). Each cage was covered with hardwood bedding that weekly changed. Animals were acclimated to these conditions for 2 weeks before starting the experiment. During the acclimation, rats were fed daily with standard rat's chow and drank tap water ad libitum. All experiments were done with the consent of the institutional ethical committee for animal experimentation (permission CSRE-30-24).

Rats were randomly divided into 4 groups (8 rats/ cage), and the exposure experiment was lasted for 2 months. First group (G1) was acted as a control group that provided with water and food only without any exposure; while the second group (G2) and the third group (G3) were orally treated with carbendazim (CBZ; 10 mg/Kg bw; (Muthuviveganandavel *et al*., 2008)) and date palm pollen grains (DPP; 100 mg/Kg bw; (Abdelreheim *et al*., 2024), respectively. Finally,

the fourth group (G4) was simultaneously treated with DPP (100 mg/Kg bw) and CBZ (10 mg/Kg bw). No mortality was observed during the experiment.

Chemicals

Carbendazim, methyl benzimidazol-2-ylcarbamate, (CBZ; Loba Chemie company, India) was prepared as a stock solution by dissolving in sunflower oil. Similarly, date palm pollen grains (DPP; obtained from the farm of Faculty of Agriculture, Sohag University, Egypt) were extracted from the date bark, washed, dried, blended, and the powder was kept in the fridge until use. The stock solution of DDP was prepared by dissolving the powder in the distilled water.

Histopathological studies

At the end of the experiment, rats were sacrificed and the spleen was excised and fixed in 10% of neutral buffered formalin (Sigma-Aldrich, St. Louis, MO) after washing with physiological saline (0.9% NaCl) solution. The spleen was prepared for histological examination and routinely processed for paraffin embedding technique. Embedded tissues were sectioned at 5 µm and stained with hematoxyline and eosin (H&E) as previously described in detail (Slaoui & Fiette, 2011; Cardiff *et al*., 2014). Histological sections were examined and captured by using Olympus CX43 light microscope with an Olympus SC52 camera adapted for the microscope (Olympus, Tokyo, Japan).

Results

Histological examination for G1 (control group) revealed normal histological structure of spleen with normal white pulp size and structure, red pulp, and splenic trabecules (Fig. 1). In G2 (CBZ group), CBZ caused severe histopathological changes in the spleen structure as hemorrhagic infarction, sever congestion, dilatation of splenic sinuses, fibrosis and depletion in lymphoid cells in white pulp (Fig. 2 A-D). Besides, thickening and hyalinization in the splenic artery of white pulp, necrotic lymphocytes in germinal center of white pulp, macrophage cells and megakaryocyte; hemorrhage and hemosidrosis in the red pulp (Fig. 2 E-H). Treatment with DPP (G3) alone showed normal splenic capsule, white pulp size and structure, red pulp, splenic trabecules, and normal red pulp as control group (G1) (Fig. 3A, B); while it seems that DPP almost soothed the negative effects of CBZ when combined together (G4), with exception of mild necrotic lymphoid cells in splenic white pulp, multiple megakaryocytes, hemosidrosis and infarction in red pulp (Fig. 3 C-E).

Discussion

Carbendazim is commonly utilized as a fungicide in agriculture; however, apprehensions have arisen about its toxicological effects, especially its influence on the immune system and lymphatic organs like the spleen. CBZ is known to possess teratogenic, mutagenic, and neurotoxic properties, with its harmful impact primarily mediated through the generation of ROS (Ebedy *et al*., 2022; Hashim *et al*., 2023; Zhou *et al*., 2023). CBZ promotes the oxidation of thiols, proteins, and lipids, while decreasing the activity of antioxidant enzymes (Sharma *et al*., 2022; Patil *et al*., 2023). In addition, it leads to hematological disturbances, impairments in liver and kidney function and structure, neurodegenerative conditions, and immune system disorders, as well as disruption of the body's antioxidant defense system (Selmanoğlu *et al*., 2001; Lu *et al*., 2004; Jiang *et al*., 2015; Abdel-Rahman *et al*., 2022; Ebedy *et al*., 2022; Sharma *et al*., 2022). Although numerous studies have highlighted the adverse effects of CBZ as a pesticide to control fungal diseases in agriculture, there are no reports specifically addressing CBZ toxicity on the spleen.

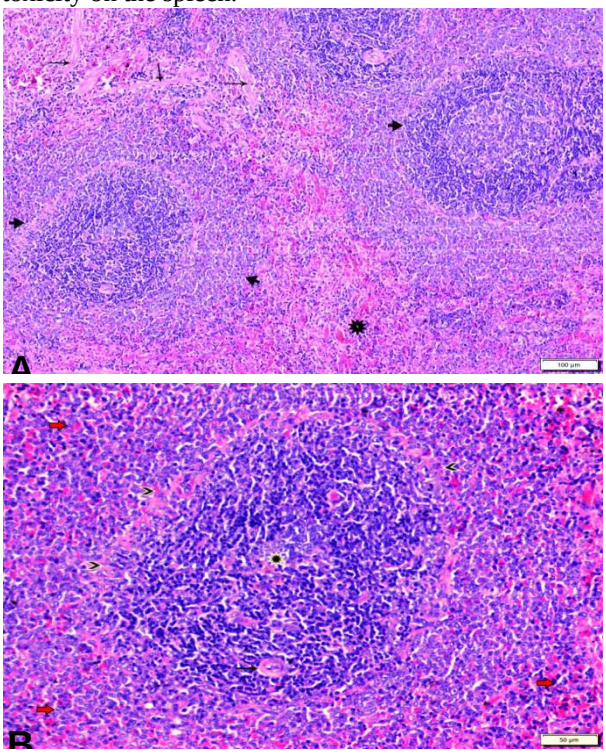

Figure (1): Photomicrograph of spleen tissue section from normal control group (G1) showing: **(A)** normal white pulp size and structure (arrow heads), normal red pulp (star), normal splenic trabecules (thin arrows). **(B)** Normal white pulp structure compromising in central germinal center with normal cellular density (star), follicular splenic artery (arrow), all surrounded by marginal zone (arrow heads), normal red pulp (red arrows). H & E stain. Bar equal 100 µm (A) 50 µm (B).

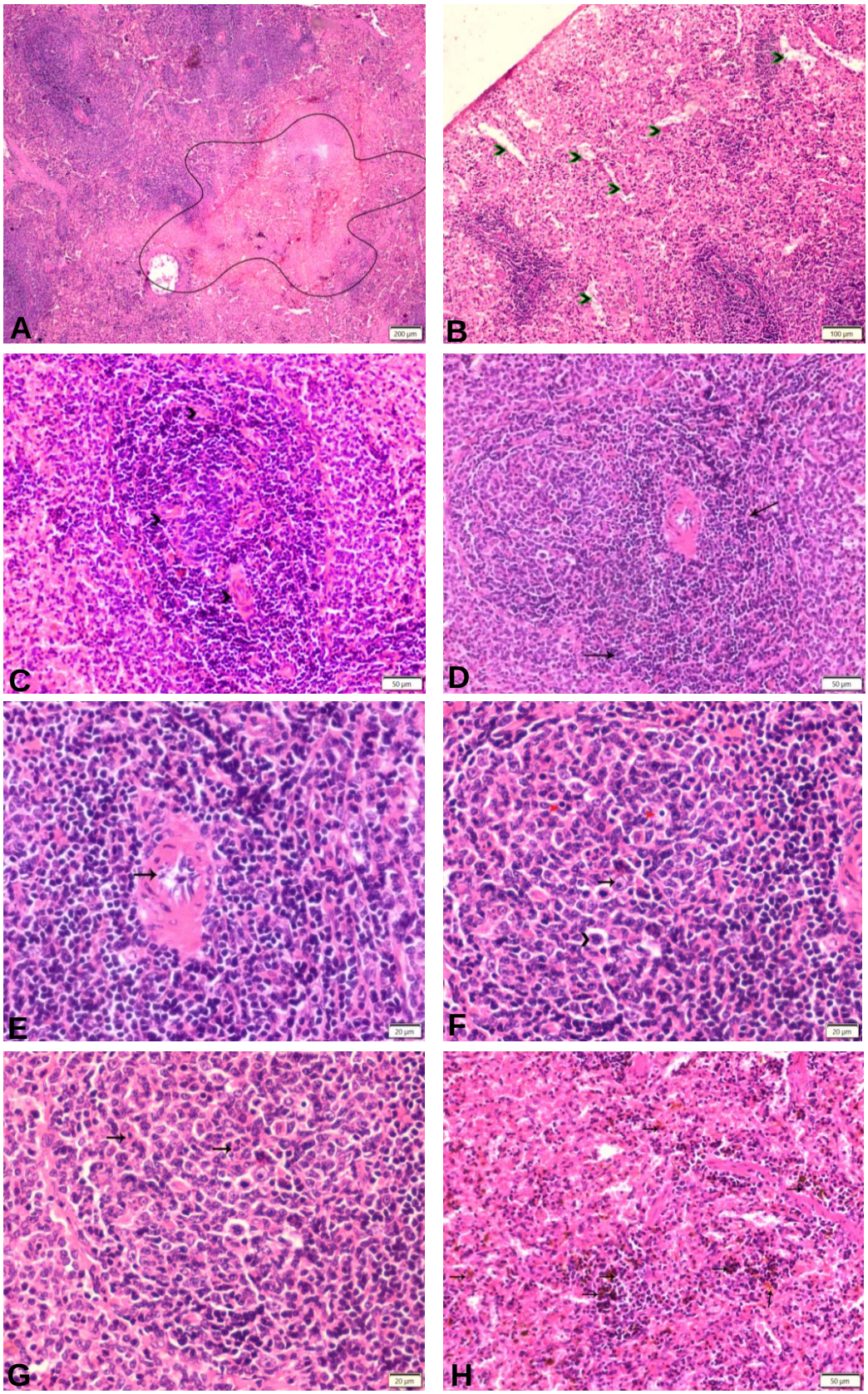

Figure (2): Photomicrograph of spleen tissue section from CBZ-treated group (G2) showing: **(A)** large area of hemorrhagic infarction (selected area); **(B)** sever congestion and dilatation of splenic sinuses (arrow heads); **(C)** fibrosis in white pulp (arrow heads); **(D)** depletion in lymphoid cells in splenic white pulp (arrows); **(E)** thickening and hyalinization in the splenic artery of white pulp (arrow); **(F)** necrotic lymphocytes in germinal center of white pulp (red arrow heads), macrophage cells (arrow), and megakaryocyte (black arrow head); **(G)** apoptotic cells in germinal center of white pulp (arrows); **(H)** hemorrhage and hemosidrosis in the red pulp (arrows). H & E stain. Bar equal 200 µm (A); 100 µm (B); 50 µm (C-D,H); 20 µm (E-G).

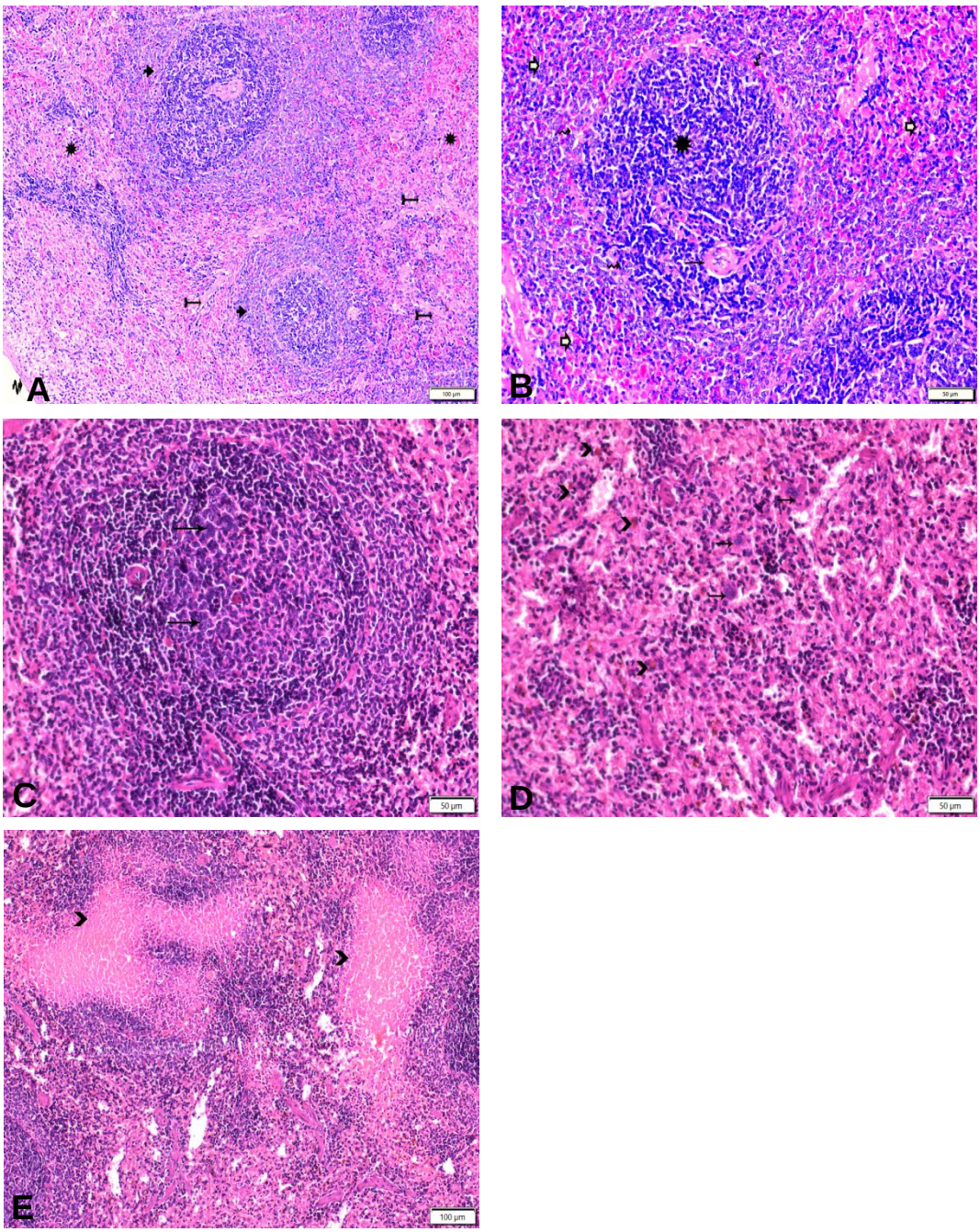

Figure (3): Photomicrograph of spleen tissue section from date palm pollen group (DPP; G3; A-B); and combination of CBZ with DPP-treated group (G4; C-E). (G3; A-B) showing normal splenic capsule (zigzag arrow), normal white pulp size and structure (arrow heads), normal red pulp (stars), normal splenic trabecules (arrows) **(A)**; normal white pulp structure compromising in germinal center with normal cellular density (star), follicular splenic artery (thin arrow), all surrounded by marginal zone (zigzag arrows) and normal red pulp (white arrows) **(B)**. (G4; C-E) showing splenic white pulp with mild necrotic lymphoid cells (arrows) **(C)**; multiple megakaryocytes (arrows), hemosidrosis (arrow heads) in red pulp **(D)**; infarction in red pulp (arrow heads) **(E)**. H & E stain. Bar equal 100 µm (A,E); 50 µm (B-D).

The spleen playing a vital role in the lymphatic and immune systems. It functions primarily as a blood filter, removing old or damaged red blood cells and pathogens from the bloodstream. Also it serves as a reservoir for blood and participates in both cell-mediated and humoral immunity, making it essential for protecting the body from infections and maintaining blood homeostasis (Bronte & Pittet, 2013; Aliyu *et al*., 2021). Recently, considerable focus has been directed toward investigating the capacity of naturally derived compounds, including date palm pollen, to mitigate the toxic impact of xenobiotics and

synthetic agents like pesticides (Sani *et al*., 2015; Abdelreheim *et al*., 2024). To our knowledge, this study is the first to demonstrate carbendazim-induced spleen toxicity and to highlight the protective effect of DPP as a natural remedy against carbendazim toxicity.

Carbendazim is considered to have low acute toxicity in mammals, with oral LD50 values in rats ranging from 2,000 to 10,000 mg/kg body weight, depending on the specific experimental conditions and methods used. This suggests that large doses are necessary to produce lethal effects (Pfeil & Dellarco, 2005; Hashim *et al*., 2023). Nevertheless, long-term or repeated exposure may result in significant health risks, such as liver toxicity, kidney toxicity, and reproductive toxicity (Selmanoğlu *et al*., 2001; Lu *et al*., 2004; Jiang *et al*., 2015; Abdel-Rahman *et al*., 2022; Ebedy *et al*., 2022). Histopathological analysis from previous studies has revealed marked kidney injury, characterized by infiltration of mononuclear cells, degeneration, and fibrosis of the renal tubules (Akbarsha *et al*., 2000; Selmanoğlu *et al*., 2001; Nwozo *et al*., 2017), as well as liver damage, which includes congestion, sinusoidal dilation, necrosis, and mononuclear cell infiltration within hepatic tissues (Akbarsha *et al*., 2000; Selmanoğlu *et al*., 2001; Muthuviveganandavel *et al*., 2008). Similarly, in the current study, oral administration of a few milligrams of CBZ (10 mg/Kg bw) for 2 months induced pathological changes in the splenic structure as sever congestion and dilation of splenic sinuses, fibrosis in white pulp, hyperplasia and dispersed lymphoid cells, thickening and hyalinization in the splenic artery of white pulp, necrotic lymphocytes, macrophages and megakaryocyte and apoptosis in germinal center of white pulp, hemorrhage and hemosiderosis. Indeed, different concentrations of CBZ resulted in reducing the spleen weight in male and female mice (Farag *et al*., 2011). Abolaji *et al*. (2017) reported that orally administration of 50 mg CBZ/Kg bw for 7 days caused neutrophilic infiltration with architectural degeneration characterized by multifocal cellular infiltration in female Wistar rats (Abolaji *et al*., 2017). Accordingly, a previous study revealed that CBZ induced hemorrhage and congestion in the splenic marginal among the white pulps and splenic artery (Madboli & Seif, 2021).

Date palm pollen (DPP) has recently drawn significant interest due to its wide range of uses and associated health advantages. It is rich in antioxidants, which can play a role in reducing oxidative stress linked to carbendazim toxicity. Thanks to its content of phenolic compounds and flavonoids, date palm pollen may support the body's natural detoxification processes by neutralizing reactive oxygen species (ROS), including those produced as a result of carbendazim exposure (Ahmed *et al*., 2008; Alalwan *et al*., 2020; Hashim *et al*., 2023; Al-Qarawi *et al*., 2024). By reducing oxidative stress, DPP may protect tissues from damage associated with pesticide toxicity. Previous studies have demonstrated that DPP can inhibit lipid peroxidation, a process that contributes to cellular damage during toxic exposure, which in turn is vital for maintaining cellular integrity and function in tissues affected by carbendazim (Daoud *et al*., 2017; Baagar *et al*., 2022). Studies have shown that treatment with date palm pollen (DPP) can help reduce liver injury triggered by a range of harmful substances, including toxins such as carbendazim (CBZ) (Selmanoğlu *et al*., 2001; Al-Asmari *et al*., 2020; Abdelreheim *et al*., 2024). Studies indicate that date palm pollen (DPP) can lessen tissue damage and inflammatory responses within the liver, pointing to its ability to help prevent liver toxicity associated with carbendazim exposure (Akbarsha *et al*., 2000; Selmanoğlu *et al*., 2001; Al-Asmari *et al*., 2020; Ebedy *et al*., 2022). Likewise, comparable protective benefits have been noted in kidney tissues. Date palm pollen (DPP) has been shown to improve renal function markers and reduce tissue damage in the kidneys, suggesting it may also aid in the recovery from carbendazim-induced toxicity (Akbarsha *et al*., 2000; Selmanoğlu *et al*., 2001; Nwozo *et al*., 2017; Al-Asmari *et al*., 2020; Ebedy *et al*., 2022). Consistently, the current study revealed that the administration of DPP before CBZ almost improve the splenic structure, with exception of hemorrhage, multiple megakaryocytes, and hemosidrosis in the red pulp. Hence, It might need more time for DPP treatment or higher concentration of DPP to remove the total negative impairs of CBZ toxicity, but further studies are needed to prove that. Thus, as an antioxidant, date palm pollen (DPP) may help prevent the formation of free radicals, thereby safeguarding the structural integrity of lymph nodes from carbendazim (CBZ) toxicity.

Conclusion

Prolonged exposure to even small amounts of carbendazim can lead to significant histopathological alterations in lymph node structure, potentially compromising immune function. In contrast, supplementing with date palm pollen may offer a natural means to counteract carbendazim-induced toxicity in the spleen. Due to its antioxidant capabilities and its role in diminishing oxidative stress, date palm pollen emerges as a promising subject for further investigation regarding its protective effects

against pesticide toxicity. Additional biochemical and physiological studies are required to further elucidate the harmful impact of carbendazim and to explore the safeguarding effects of DPP within biological systems.

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