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RESEARCH ARTICLE

Toxicopathological assessment revealed expanded tissue tropism of fipronil in experimental Wistar albino rats

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ABSTRACT

Fipronil is a widely used phenylpyrazole insecticide known primarily for its neurotoxic action, however, increasing evidence suggests that its toxic effects extend beyond the nervous system in non-target mammals. The present study was undertaken to evaluate the expanded tissue tropism of fipronil in Wistar albino rats with particular emphasis on organs that have received limited attention in earlier studies. Twenty-four healthy male Wistar albino rats were randomly divided into four groups (n = 6). Group I served as control, Group II received fipronil (10 mg/kg) orally for 45 days, Group III received *Punica granatum* peel extract (200 mg/kg) alone, and Group IV received *Punica granatum* concurrently with fipronil. Histopathological evaluation of fipronil treated rats revealed distinct toxic alterations in multiple organs, including the heart, spleen, pancreas, adrenal glands, thymus, lymph nodes and gastrointestinal tract. Cardiac lesions were characterized by myocardial degeneration, inflammatory infiltration and fibroblastic proliferation and lymphoid organs exhibited lymphoid depletion and vascular congestion indicating immunosuppressive effects. Pancreatic tissue showed ductular hyperplasia, acinar degeneration and islet atrophy. Intestinal and gastric sections revealed mucosal degeneration, inflammatory infiltration and villous disruption, while adrenal glands demonstrated cortical vacuolar degeneration and medullary haemorrhages. In contrast, rats receiving *Punica granatum* supplementation along with fipronil showed marked attenuation of these lesions, with near-normal histoarchitecture in most tissues. The findings of the present study demonstrate that fipronil exhibits expanded tissue tropism involving cardiovascular, immune, endocrine and gastrointestinal systems in rats. These results highlight the need for comprehensive multisystem toxicological evaluation of fipronil in non-target organisms.

Keywords: Adrenal, fipronil, heart, pancreas, *Punica granatum,* wistar rats

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INTRODUCTION

Over the past several decades, numerous arthropod species have progressively developed resistance to conventional insecticides[1]. This growing resistance necessitated the development and global introduction of newer insecticidal compounds, including fipronil (FIP). Fipronil is a synthetic, second-generation phenylpyrazole insecticide that primarily targets the central nervous system of invertebrates[2]. Nevertheless, evidence suggests that FIP may also exert effects on other physiological systems, such as the reproductive system, as documented in ticks[3]. As a phenylpyrazole class insecticide, fipronil (FIP) exerts its toxic effects by inhibiting γ-aminobutyric acid (GABA) gated receptors and by promoting oxidative stress through the excessive generation of reactive oxygen species[4,5,6]. Fipronil may exert adverse effects beyond its primary neurotoxic action by targeting non-neuronal organs such as the liver, kidney, thyroid, and by disrupting reproductive functions in non-target species[6]. Chronic exposure to fipronil in rats has been shown to predominantly affect the liver, kidney, and thyroid, where marked toxic alterations were observed[7]. Additionally, short-term fipronil exposure has been reported to induce oxidative stress in the kidney, brain, and liver of mice[11].

Although it primarily exerts its insecticidal action by blocking γ-aminobutyric acid (GABA) gated chloride channels in invertebrates, increasing evidence suggests that FIP is not selectively neurotoxic and can adversely affect multiple organ systems in non-target mammals[8,9]. Experimental studies have demonstrated that FIP exposure induces oxidative stress, mitochondrial dysfunction and apoptotic signalling, mechanisms that may contribute to its systemic toxicity[10]. Among mammalian organs, the liver has been identified as a major target of FIP toxicity, with several rodent studies reporting hepatotoxic effects following acute, sub-chronic and chronic exposure[11,12]. Similarly,

nephrotoxicity has been consistently documented, indicating that the kidney is highly susceptible to FIP induced oxidative and metabolic disturbances[13,14]. Neurotoxicity remains one of the most well-established outcomes of FIP exposure, affecting both central and peripheral nervous systems[15,16], while pulmonary involvement has also been described in experimental models[17]. Collectively, these findings indicate that FIP exhibits a broad toxicological profile rather than being restricted to neural tissues. In contrast, information regarding the effects of FIP on other vital tissues involved in cardiovascular function, immune regulation, endocrine balance and metabolism is sparse. Organs such as the heart, spleen, adrenal glands, thymus, pancreas and gastrointestinal tract play critical roles in maintaining physiological homeostasis, and toxic insults to these tissues may have far-reaching systemic consequences[18,19]. However, systematic toxicopathological evaluations of these organs following FIP exposure are lacking.

In this context, the present study was undertaken to investigate the expanded tissue tropism of FIP in Wistar rats by examining its potential toxic effects on the heart, spleen, adrenal glands, thymus, pancreas and gastrointestinal tract. By focusing on these relatively under-explored tissues, the study aims to provide a more comprehensive understanding of fipronil induced multisystem toxicity and to bridge existing gaps in the toxicological assessment of this widely used insecticide.

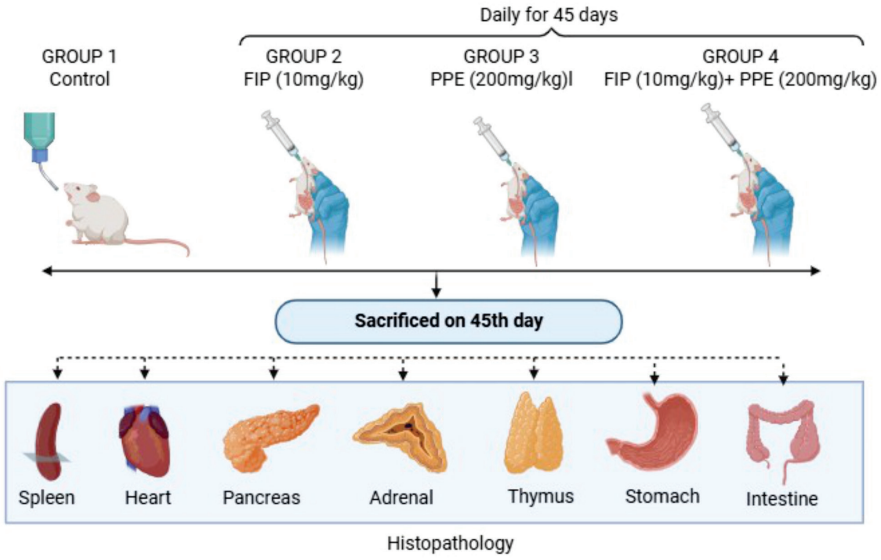
MATERIALS AND METHODS

Source and Management of Experimental Animals and Test Compounds

Healthy male Wistar albino rats weighing between 100 and 120 g were utilized for the present investigation. The animals were obtained from Sri Venkateshwara Enterprises, Bengaluru. Following procurement, the rats were allowed a two-week acclimation period before initiation of the experimental protocol. Animals were maintained in polypropylene cages under controlled environmental conditions, with three rats housed per cage. The animal room temperature was regulated at 25 ± 1 °C, and a consistent 12-hour light and 12-hour dark photoperiod was maintained throughout the six-week study duration. Standard laboratory animal feed and potable water were provided ad libitum, and appropriate hygienic and management practices were followed in accordance with laboratory animal care guidelines. The test toxicant, fipronil (technical grade, 99% purity; Batch No. FIP92B5266), was sourced from Gharda Chemicals Ltd. The *Punica granatum* (pomegranate) peel extract used in the study (Product code: Dadim LC23030077) was procured from Chemiloids Life Science Pvt. Ltd., Andhra Pradesh

Ethical approval: Prior approval for the experimental design was obtained from the Institutional Animal Ethics Committee (IAEC approval No. 281/GO/ReBi/S/2000/CPCSEA/CVSc/TPTY/010/Veterinary Pathology/2023, dated 08-05-2023), and all procedures were conducted in compliance with CPCSEA regulations.

Experimental design: Twenty-four clinically healthy young male Wistar albino rats were enrolled in the study and randomly allocated into control and treatment groups. The animals were divided into four experimental groups, each comprising six rats. Fipronil was administered orally by gavage, using distilled water as the vehicle, once daily throughout the 45-day experimental period. The experimental grouping and dosage regimen followed in the present investigation are depicted below. All rats were maintained for 6 weeks and animals were sacrificed by overdose of inhalational



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anaesthetic agent in a closed chamber at the end of the research study (45th day).

Histopathology

A comprehensive postmortem examination was carried out on all animals sacrificed from each experimental group. Representative tissue samples from the heart, spleen, pancreas, intestine, thymus, lymph nodes and gastro-intestinal systems were collected and fixed in 10% neutral buffered formalin for histopathological evaluation. The fixed tissues were routinely processed using the paraffin embedding technique. Tissue sections of 5–6 µm thickness were prepared and stained with Haematoxylin and Eosin (H&E) following standard procedures[20]. Special histochemical stains were applied wherever required to aid in diagnosis.

RESULTS

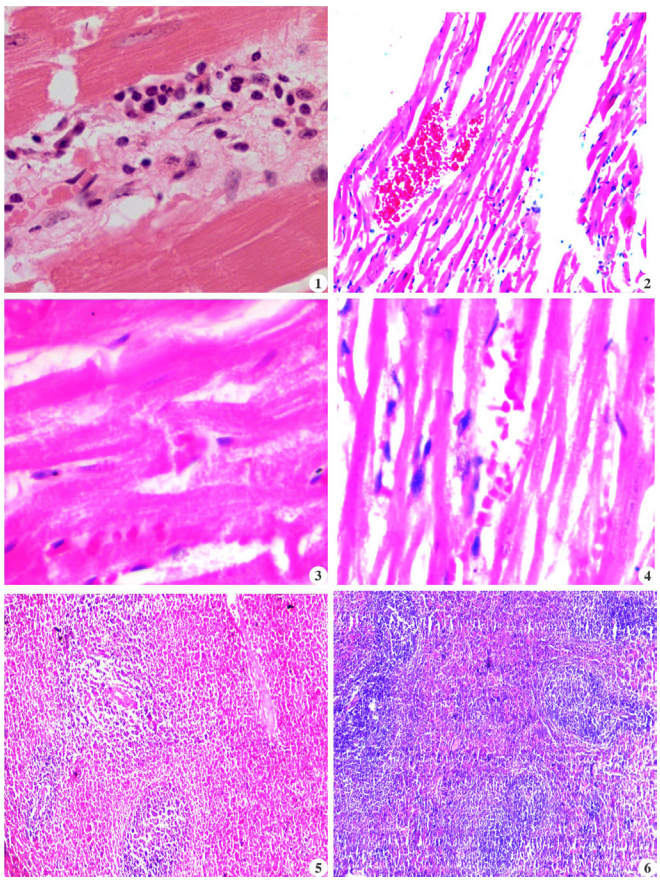

Fig. 1. Heart: Group II: showing mixed inflammatory cell infiltration and fibrin in the cardiac interstitium. H&E X400; **Fig. 2.** Heart: Group II: Section showing pockets of hemorrhages in between cardiac muscle fibres. H&E X100; **Fig. 3.** Heart: Group II: Section showing swollen and granular cytoplasm of cardiac muscle fibres. H&E X400; **Fig. 4.** Heart: Group II: Note reduced thickening of cardiac muscle fibres. H&E X400; **Fig. 5.** Spleen: Group II: Section showing mild to moderate depletion of lymphocytes in the white pulp. H&E X40; **Fig. 6.** Spleen: Group IV: Section showing normal appearance of white pulp and presence of more lymphoid follicles. H&E X40

At the completion of the experimental duration (sixth week), rats belonging to the control group (Group I) and the *Punica granatum* control group (Group III) did not exhibit any gross or histological alterations of pathological relevance. In contrast, histological examination of the heart in Group II (fipronil-treated) rats revealed moderated mononuclear inflammatory cell infiltration, proliferation of fibroblasts (Fig. 1), and focal interstitial haemorrhages between cardiac muscle bundles (Fig. 2). Additionally, several regions showed swollen myocardial fibres with granular cytoplasm and features consistent with coagulative necrosis (Fig. 3). In

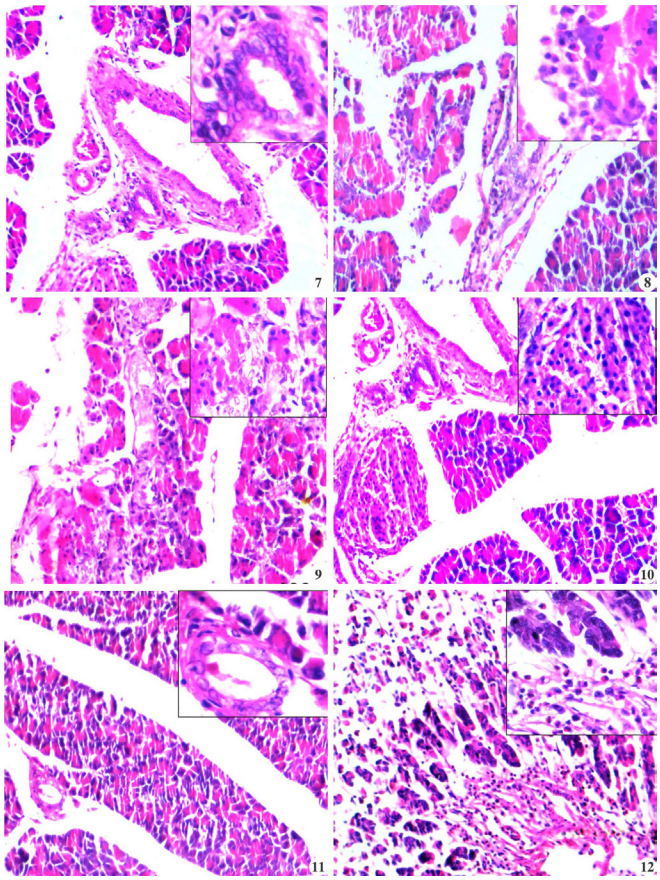

Fig. 7. Pancreas: Group II: Note thickened interlobular ducts with fibrous tissue deposition and hyperplasia of ductular epithelium. H&E X100, (Insight microphotograph X400); **Fig. 8.** Pancreas: Group II: Section showing infiltration of eosinophils and MNC's in inter-acinar spaces. H&E X100, (Insight microphotograph X400); **Fig. 9.** Pancreas: Group II: Section showing degenerated and complete architectural loss of pancreatic acini with replacement of acinar cells by fibrous tissue and MNC's. H&E X100 (Insight microphotograph X400); **Fig. 10.** Pancreas: Group II: Section showing congestion and degeneration with focal loss of islets of Langerhans. H&E X100 (Insight microphotograph x 400); **Fig. 11**. Pancreas: Group IV: Section showing normal appearance of lining epithelium of pancreatic ducts. H&E X100 (Insight microphotograph X400); **Fig. 12.** Stomach: Group II: Section showing moderate degenerative changes with desquamation of mucosal lining and severe infiltration of inflammatory cells mainly eosinophils in mucosa. H&E X100 (Insight microphotograph X400)

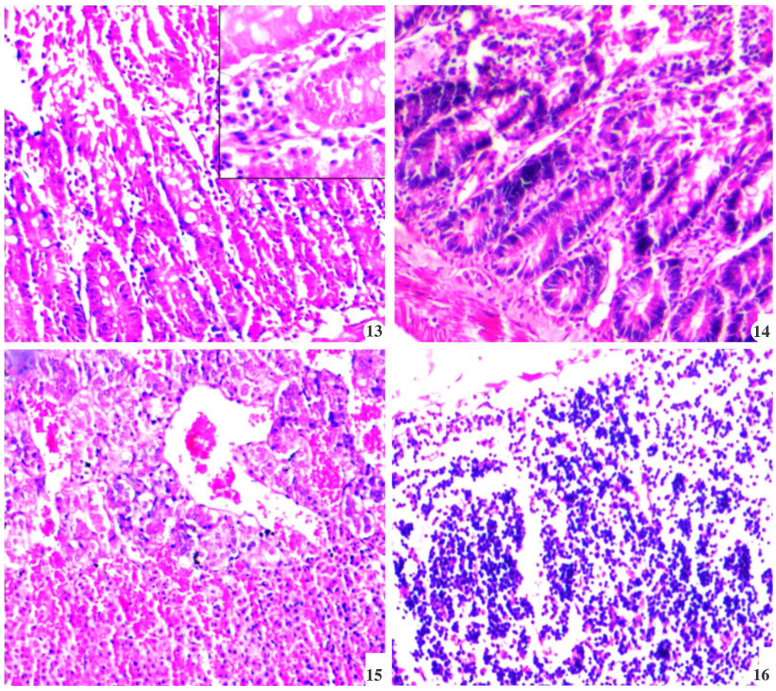

Fig. 13. Intestine: Group II: Section showing increased number of goblet cells in the mucosa and severe infiltration of eosinophils and MNC's in submucosa. H&E X100 (Insight microphotograph X400); **Fig. 14.** Intestine: Group IV: Section showing mild degenerative changes and less MNC's infiltration in the villous structure. H&E X100; **Fig. 15.** Adrenal: Group II: Section showing congestion and haemorrhages in adrenal medulla. H&E X100; **Fig. 16.** Lymph node: Group II: Section showing mild to moderate depletion of lymphocytes in the cortex. H&E X100.

a few animals, myocardial atrophy characterized by thinning of muscle fibres and expansion of intermuscular spaces was evident (Fig. 4). Mild to moderate sarcolytic degeneration accompanied by fibroblastic proliferation was also observed, along with congestion and thickening of myocardial blood vessels, which became more pronounced by the end of the sixth week. Conversely, the cardiac tissue of Group IV (ameliorated) rats exhibited only mild degenerative alterations, minimal haemorrhage, and slight inflammatory infiltration, with an overall preservation of myocardial architecture. The heart of *Punica granatum* treated rats displayed normal histomorphology comparable to that of control animals.

Microscopic evaluation of the spleen in fipronil-exposed rats demonstrated mild to moderate lymphoid depletion within the white pulp (Fig. 5), prominence of splenic trabeculae, and congested, thickened blood vessels at the end of the experimental period. In the ameliorated group, similar splenic changes were present but with reduced severity, including mild lymphocytolysis, minimal congestion, reactive hyperplasia of the white pulp, and an increased number of lymphoid follicles. The splenic architecture in *Punica granatum* treated rats remained comparable to that observed in the control group (Fig. 6).

Histopathological examination of the pancreas in Group II animals revealed thickening of interlobular ducts with deposition of fibrous connective tissue, ductular epithelial hyperplasia (Fig. 7), vascular congestion, and infiltration of eosinophils and mononuclear cells within the inter-acinar regions (Fig. 8). The islets of Langerhans showed prominent congestion, degenerative alterations, and atrophy in most animals (Fig. 9). Multifocal areas exhibited moderate to severe degeneration of pancreatic acini with disruption of normal lobular architecture, wherein acinar cells were replaced by fibrous tissue and inflammatory cells (Fig. 10). Intralobular ductular hyperplasia was consistently noted in all fipronil-treated rats. The pancreas of Group IV rats showed similar lesions but of lesser magnitude, characterized by mild acinar degeneration with preservation of normal ductal structures and islets. Pancreatic sections from *Punica granatum* treated rats appeared histologically normal and comparable to controls (Fig. 11).

Examination of the stomach in fipronil-treated rats showed moderate degenerative changes, sloughing of the gastric mucosal epithelium, and intense inflammatory cell infiltration predominantly eosinophils within the mucosal glands. These alterations were also observed in the ameliorated group but with diminished severity (Fig. 12). Microscopic assessment of the intestine in Group II rats revealed marked goblet cell hyperplasia within the mucosa, dense infiltration of eosinophils and mononuclear cells between the mucosal glands, and focal necrosis of the mucosal layer (Fig. 13). Structural disruption and desquamation of intestinal villi were also evident by the end of the sixth week. The ameliorated group exhibited similar intestinal lesions but with noticeably reduced intensity. Intestinal histology of *Punica granatum* treated rats was comparable to that of the control group (Fig. 14).

Histological examination of the adrenal glands in fipronil-exposed rats demonstrated vacuolar degeneration within the adrenal cortex, along with congestion and focal haemorrhages in the medulla (Fig. 15). The ameliorated group showed similar adrenal changes, albeit milder in nature. Lymph nodes from Group II rats exhibited mild to moderate cortical lymphoid depletion and vascular congestion, while the ameliorated group displayed the same lesions with reduced intensity (Fig. 16). Thymic sections from fipronil-treated animals showed mild

to moderate haemorrhages and congestion of blood vessels, whereas the ameliorated group demonstrated comparable but less pronounced changes.

DISCUSSION

In the current study, histological evaluation of the cardiac tissue in most fipronil exposed rats showed moderate mononuclear inflammatory infiltration, fibroblastic proliferation, focal hemorrhages and swollen myocardial fibers exhibiting granular cytoplasm. Sarcolytic degeneration and necrotic alterations, along with focal fibroblast proliferation were consistently observed. In addition, myocardial atrophy characterized by thinning of muscle fibers and widening of intermyocardial spaces was evident in all treated animals. Comparable myocardial alterations following fipronil exposure have been reported in earlier studies[18,22]. These pathological changes may be attributed to mitochondrial dysfunction in cardiomyocytes, resulting from excessive mitochondrial reactive oxygen species (ROS) generation, loss of mitochondrial membrane potential, and subsequent release of cytochrome-c, ultimately leading to cardiomyocyte injury [18]. Rats belonging to the *Punica granatum* ameliorated group (Group IV) exhibited only minimal histological alterations in the heart when compared with the fipronil-treated group (Group II). This protective effect may be associated with the potent antioxidant and free radical scavenging properties of *Punica granatum* [23,24,25,26], which likely neutralize excess ROS generated within cardiac mitochondria and thereby mitigate oxidative damage to myocardial tissue.

Microscopic examination of the spleen from fipronil treated rats revealed mild to moderate lymphoid depletion in the white pulp, prominence of trabecular structures, and marked vascular congestion with thickened vessel walls. These findings corroborate earlier findings in the literature[19,27,28]. The observed lymphocytolytic changes may be linked to the immunosuppressive action of fipronil on lymphoid tissues. Fipronil induced ROS can directly damage cellular lipids, proteins, and DNA in immune cells, while also activating stress responsive intracellular signalling pathways that compromise immune function[29].

In the *Punica granatum* supplemented group, similar splenic alterations were evident but with markedly reduced severity when compared to the fipronil only group. This improvement may be attributed to the immunomodulatory potential [30] and antioxidant capacity of *Punica granatum*[23-26.]

Histopathological assessment of the pancreas in fipronil treated rats showed thickening of interlobular ducts due to fibrous tissue deposition, hyperplasia of ductular epithelium, vascular congestion, and infiltration of eosinophils within inter-acinar spaces. The islets of Langerhans exhibited degenerative and atrophic changes. Marked disruption of pancreatic acinar architecture was evident, with extensive degeneration and replacement of acinar structures by fibrous tissue and desquamated epithelial cells. Hyperplasia of intralobular ductular epithelium was consistently observed across all treated animals. As comparable reports were unavailable in the literature, these pancreatic alterations are likely attributable to the direct cytotoxic effects of fipronil. In contrast, pancreatic tissue from the ameliorated group appeared largely preserved and near normal when compared with fipronil fed rats.

Microscopic examination of the intestine in fipronil exposed rats revealed severe necrosis of intestinal villi, loss and desquamation of villous architecture, goblet cell hyperplasia, and dense infiltration of eosinophils and mononuclear cells between mucosal glands. Similarly, gastric sections showed moderate degenerative alterations, sloughing of the mucosal epithelium, and intense inflammatory cell infiltration predominantly eosinophils at the base of mucosal glands. Due to the absence of comparable studies in the literature, these findings could not be directly correlated. However, only minimal histological changes were observed in the intestine and stomach of *Punica granatum* ameliorated rats, which may be attributed to its established anti-inflammatory properties[31].

In the present study, adrenal sections from Group II rats demonstrated vacuolar degeneration of the adrenal cortex along with hemorrhages within the medulla. As no comparable reports were available, these findings appear novel. The adrenal glands of ameliorated rats showed near to normal histological features by the end of the experimental period. Microscopic evaluation of lymph nodes from fipronil treated animals revealed mild to moderate cortical lymphocyte depletion accompanied by vascular congestion, consistent with previous findings[19]. These alterations may result from fipronil induced immunosuppression and oxidative injury to immune cells[29]. Although similar lesions were observed in the ameliorated group, their severity was considerably reduced, possibly due to the immunomodulatory effects of *Punica granatum*[30]. Histological examination of the thymus in Group II animals showed mild to moderate hemorrhages and congestion of blood vessels. In the absence of comparable literature, these findings could not be directly contrasted. However, the ameliorated group exhibited similar thymic changes with reduced severity, which may again be attributed to the immunomodulatory action of *Punica granatum*[30.]

CONCLUSION

The present toxicopathological study clearly demonstrates that fipronil is not restricted to neurotoxicity but exhibits expanded tissue tropism affecting the cardiovascular, immune, endocrine, pancreatic, and gastrointestinal systems in Wistar albino rats following sub-chronic exposure. The consistent histological alterations observed in the heart, spleen, pancreas, adrenal glands, thymus, lymph nodes, and gastrointestinal tract indicate a broad multisystem toxic potential of fipronil, likely mediated through oxidative stress–induced cellular and mitochondrial damage. Importantly, concurrent administration of *Punica granatum* peel extract significantly attenuated the severity of these lesions, suggesting its protective antioxidant and immunomodulatory role. These findings underscore the necessity for comprehensive multisystem toxicological evaluation of fipronil in non-target mammals and highlight the potential of *Punica granatum* as a natural ameliorative agent against fipronil-induced toxicity.

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