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Small Intestinal Toxicity Induced by Imidacloprid in Rats and The Protective Role of Berberine and Resveratrol

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Abstract
Imidacloprid is one of the insecticides in the neonicotinoid group. Resveratrol and berberine are powerful antioxidants known to alleviate the adverse effects of toxicity caused by oxidative stress. The aim of this study was to investigate the potential toxic effects of imidacloprid in the small intestinal tissues of rats and the protective effects of berberine and resveratrol against these effects. In the study, rats were divided into 7 groups. The groups were as follows: control group, resveratrol (20 mg/kg), berberine (100 mg/kg), imidacloprid (9 mg/kg.), imidacloprid plus resveratrol, imidacloprid plus berberine, imidacloprid plus resveratrol plus berberine. Test compounds were administered to rats by gavage for 28 days. At the end of the experimental period, antioxidant enzyme activities (SOD, CAT, GST and GPx) and MDA levels were evaluated in small intestinal tissues obtained from rats. At the end of the 28-day treatment period, it was determined that MDA level increased, and antioxidant enzyme activities decreased in the intestinal tissue of rats treated with imidacloprid. However, when imidacloprid plus resveratrol plus berberberine treated group, imidacloprid plus resveratrol treated group and imidacloprid plus berberine treated group were compared with imidocloprid group, a significant decrease in MDA level and a significant increase in antioxidant enzyme activities were observed. Histological findings support the protective properties of resveratrol and berberine. The results of this study showed that berberine and resveratrol, which were administered to prevent damage caused by imidacloprid in the small intestine tissue of rats, showed a positive effect and improved the studied parameters.

Keywords: Imidacloprid, Berberine, Resveratrol, Small intestine, Oxidative stress

1. INTRODUCTION

Pesticides are widely used to control pests, but they can cause toxic effects on humans and non-target organisms. The use of pesticides harms food safety and economy and also pollutes water resources [1]. Pesticides damage ecosystems and cause contamination of soil, food and water. They show their most important effect on health [2]. Living things can absorb pesticides, causing chronic and fatal health conditions such as infertility, cancer, and DNA damage [3]. However, pesticides are also known to trigger asthma, diabetes and Alzheimer's disease [4].

Imidacloprid (IMI) is the first representative of neonicotinoid insecticides, introduced in 1991 [5]. It has been frequently used in recent years due to its mode of action. These insecticides can be used in agricultural control and control of vector diseases [6]. IMI cannot be completely washed out of food, and humans are exposed to IMI through residues in food [7]. IMI caused adverse effects on the nervous, immune, reproductive and metabolic system in rats [8-10]. IMI has also been reported to have a negative effect on the digestive system [11]. Since the intestines have the longest and largest surface area of the digestive system, they are exposed to a lot of these substances [12].

Berberine (BBR) is a plant alkaloid isolated from plants. It is frequently used due to its broad antimicrobial activity against viruses, fungi and protists that damage the intestinal microbiota [13]. Berberine has shown to have various beneficial effects such as preventing inflammation, suppressing tumors, improving the circulatory system and maintaining homeostasis [14, 15].

Resveratrol (RES, $C_{14}H_{12}O_3$) is isolated from the roots of *Polygonum cuspidatum* and *Viburnum grandiflorum* and is also found in plants such as grapes, raspberries and strawberries. [16, 17]. It is stated that RES has therapeutic properties in central nervous system disorders

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such as depressive and bipolar disorder, Alzheimer's disease and autism, and also has anti-oxidative stress and anti-inflammatory effects [18-20].

In this study, the effect of imidacloprid toxicity and the protective effect of berberine and resveratrol on the small intestine of rats were investigated. For this purpose, MDA levels and antioxidant enzyme activities (SOD, CAT, GPx and GST) in the small intestine tissue were measured. However, pathological changes in the small intestine tissue were examined with a light microscope.

2. MATERIAL AND METHODS

2.1 Animals and Application

Permission for animal experiments was obtained from G.U. Animal Experiments Local Ethics Committee. 7 experimental groups were created, with 6 Wistar rats in each group. The application to experimental animals was continued for four weeks (28 days). Experimental groups are given in Table 1.

Table 1. Application schedule and doses of substances to rats

Groups	Application
1. Control group	Rats were given 1 ml/kg body weight (bw) of corn oil.
2. Berberine treated group	Rats were given 100 mg/kg bw of berberine dissolved in distilled water.
3. Resveratrol treated group	Rats were given 20 mg/kg bw resveratrol dissolved in corn oil.
4. Imidacloprid-treated group	Rats were given 9 mg/kg bw (1/50 LD_{50}) of imidacloprid dissolved in corn oil.
5. Imidacloprid plus berberine treated group	Rats were given 9 mg/kg bw of imidacloprid dissolved in corn oil. Then, 100 mg/kg bw berberine was administered by dissolving in distilled water.
6. Imidacloprid plus resveratrol treated group	Rats were given 9 mg/kg bw of imidacloprid dissolved in corn oil. Then, 20 mg/kg bw resveratrol was administered by dissolving in distilled water.
7. Imidacloprid and berberine plus resveratrol treated group	Rats were given 9 mg/kg bw of imidacloprid dissolved in corn oil. Then, 100 mg/kg bw berberine and 20 mg/kg bw resveratrol was administered by dissolving in distilled water.

2.2 Measurement of Biochemical Parameters

For biochemical analyses, tissue samples taken from the small intestine were homogenized by centrifugation. Protein concentrations were determined [21]. Then, MDA levels [22], SOD [23], CAT [24], GPx [25] and GST [26] enzyme analyzes were measured on a spectrophotometer using appropriate methods.

2.3 Preparation of Tissues for Light Microscopy

Tissues were fixed in formaldehyde, stained with hematoxylin-eosin and examined under a light microscope.

2.4 Statistical Analysis

One-way analysis of variance and Tukey test were used in the statistics used in the study. The significance limit was accepted as $P<0.05$.

3. RESULTS AND DISCUSSION

3.1 Evaluation of Malondialdehyde (MDA) Levels

MDA levels in the small intestinal tissues of all groups was measured. No statistically significant difference was observed between the control group, BBR and RES treated groups. When the control group and the IMI, IMI plus BBR, IMI plus RES and IMI and BBR plus RES treated groups were compared in terms of MDA level, a statistically significant increase was observed. A statistically significant decrease in MDA level was observed when the IMI-treated group was compared with the IMI plus BBR, IMI plus RES and IMI and BBR plus RES treated groups ($P<0.05$), (Figure 1).

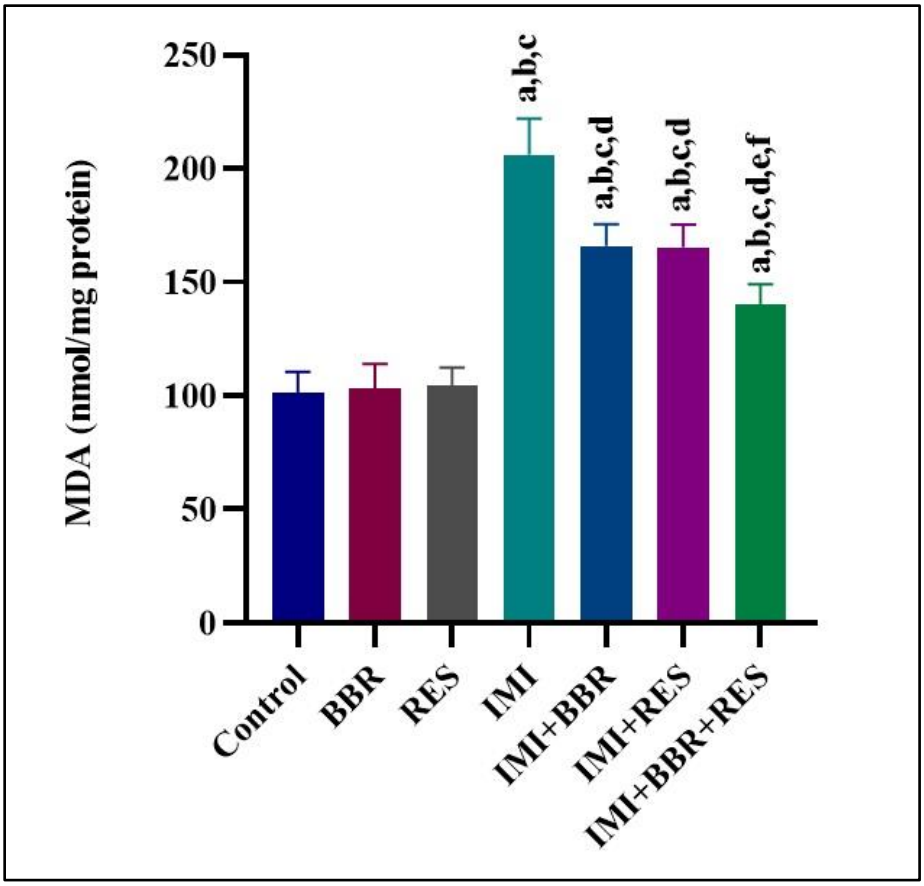

Figure 1. MDA levels. Comparison of [a]control group, [b]BBR-, [c]RES-, [d]IMI-treated group, [e]IMI+BBR and IMI+RES treated group comparison IMI treated groups. [f]IMI+BBR and IMI+RES treated group comparison IMI+BBR+RES treated. Mean±Standard deviation ($P<0.05$)

3.2 Evaluation of Antioxidant Enzyme Activities

At the end of the experiment, which lasted for four weeks, antioxidant enzyme activities (SOD, CAT, GPx and GST) levels in the small intestinal tissues of all groups was measured. No statistically significant difference was observed between the control group, BBR and RES treated groups. When the control group and the IMI, IMI plus BBR, IMI plus RES and IMI and BBR plus RES treated groups were compared to antioxidant enzyme activities, a statistically significant decrease was observed. A statistically significant increase in antioxidant enzyme activities was observed when the IMI-treated group was compared with the IMI plus BBR, IMI plus RES and IMI and BBR plus RES treated groups ($P<0.05$), (Figure 2).

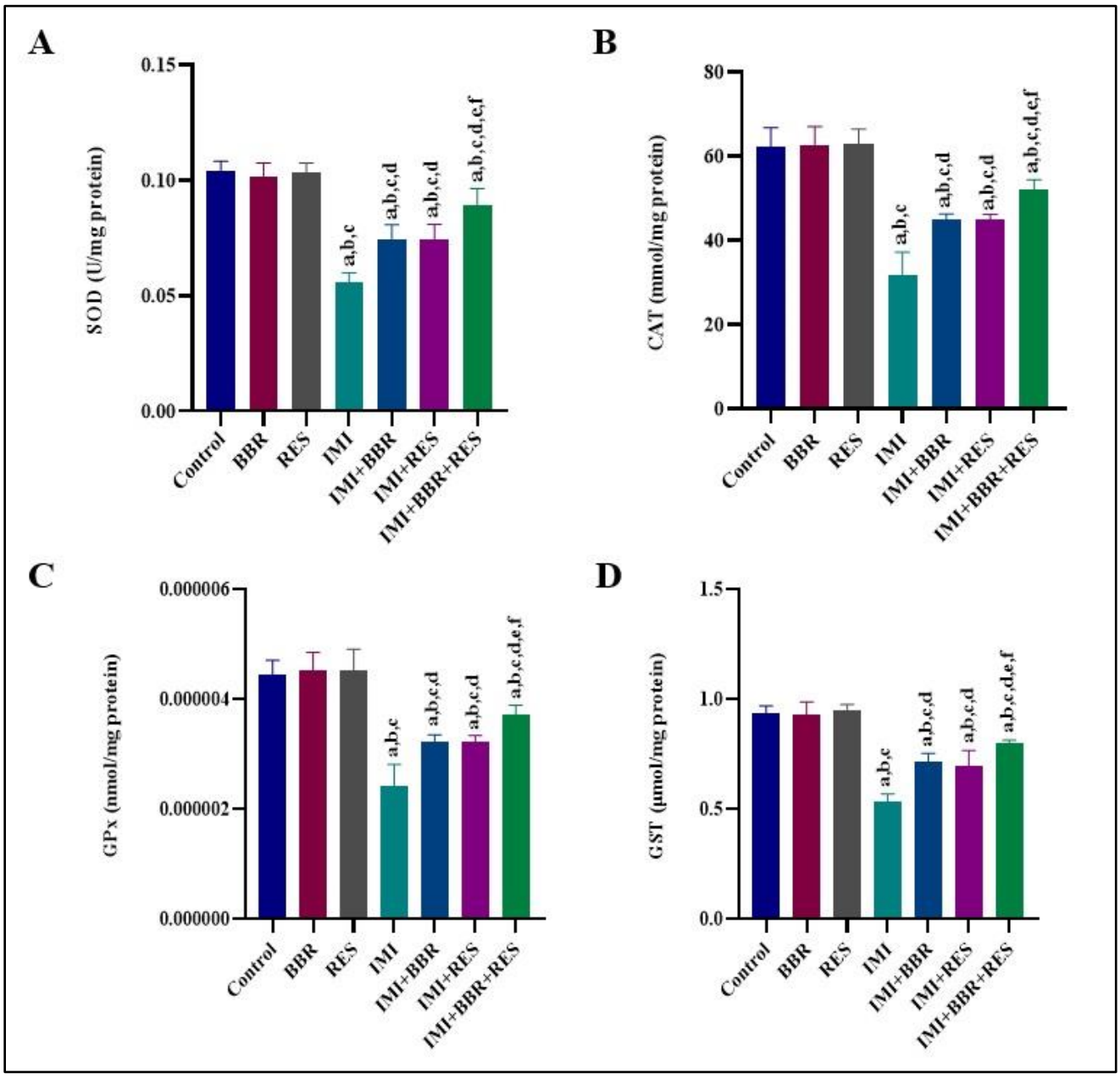

Figure 2. SOD, CAT, GPx and GST antioxidant enzyme activities. Comparison of [a]control group, [b]BBR-, [c]RES-, [d]IMI-treated group, [e]IMI+BBR and IMI+RES treated group comparison IMI treated groups. [f]IMI+BBR and IMI+RES treated group comparison IMI+BBR+RES treated. Mean±Standard deviation ($P<0.05$)

3.3 Light Microscope Findings

In our examinations with light microscopy, the small intestine tissue of the control, BBR and RES treated groups was observed to have a normal structure. No pathological findings were found in the villi in the intestine and the cells lining the villi. The villi were of normal length. The muscle tissue surrounding the intestine was also observed to have a normal structure (Figure 3a, b, c). In the intestinal tissue of rats administered IMI, shortening and blunting of the villi occurred. Additionally, irregularity and shortening of the villi were observed. Cell infiltration was observed in some areas (Figure 3d). In intestinal tissue, IMI plus BBR and IMI plus RES treated of rats, blunting and expansion of villi were observed. However, these effects were found to be milder (Figure 3e, f).

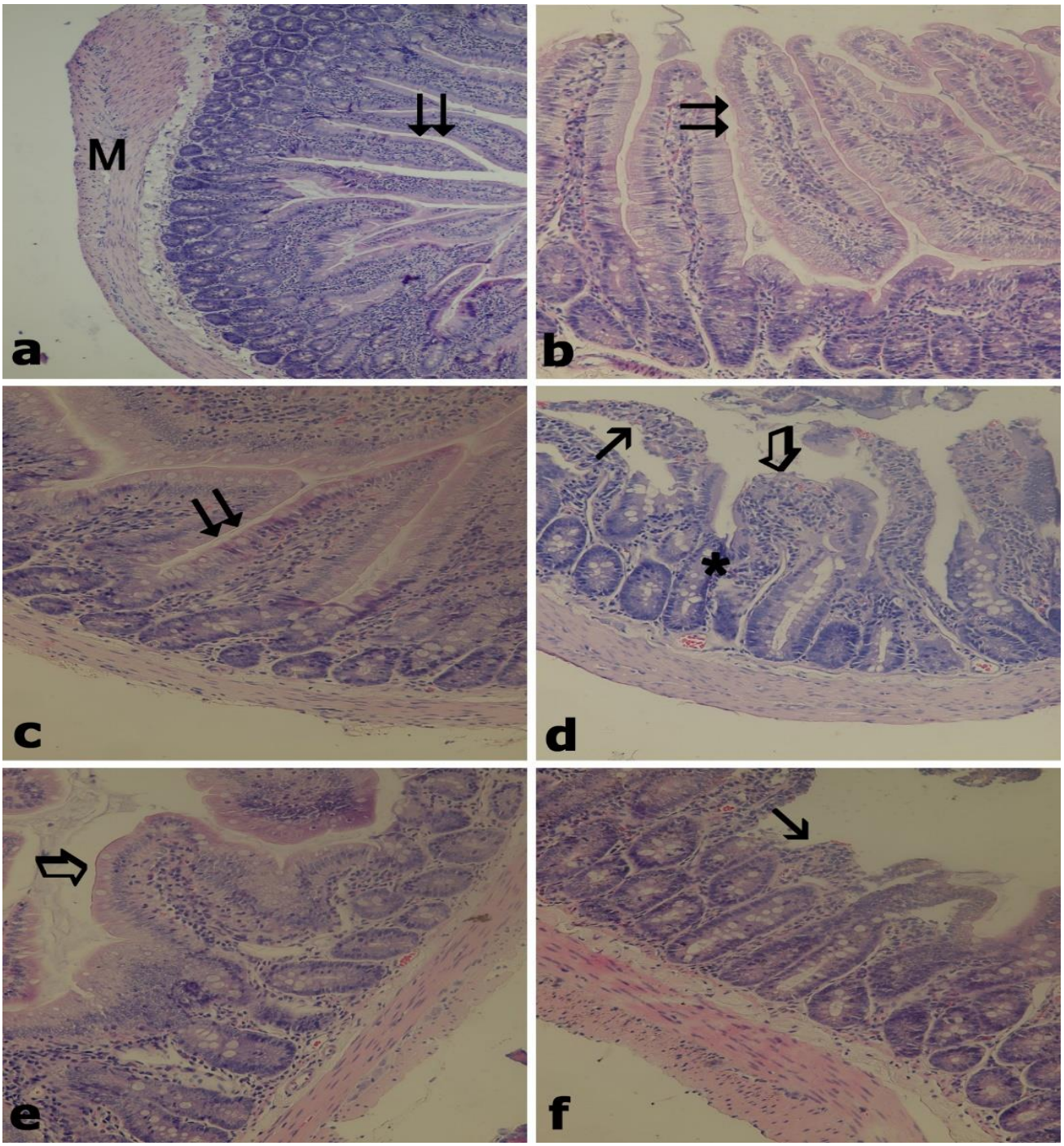

Figure 3. No pathological findings were observed in the small intestine tissue of the control, b. BBR, c. RES treated groups. d. IMI treated group, villus shortening, blunting, (⇨) irregularity (→) and infiltration (✱). e. IMI+BBR treated group, villus shortening, blunting, f. IMI+RES treated group, villus irregularity. H&E, X200

Environmental pollutants such as heavy metals, plasticizers and pesticides are increasingly causing negative effects on ecosystems and living things [27-30]. Pesticides are among the most frequently used substances in agricultural control. IMI is a pesticide derived from nicotine, which is among the widely used pesticides in the world [31]. IMI has very high water solubility. For this reason, it spreads very quickly in nature. As a result, it has been reported that it may harm non-target organisms and their biodiversity [32]. There are many studies showing the toxic effects and harms of IMI on non-target organisms. These studies are generally on aquatic creatures and arthropods [33]. However, studies showing the toxic effects of IMI on mammals are limited. In this study, the toxic effect of IMI on the intestinal tissues of rats was examined. In our study, IMI was administered orally to experimental animals for 28 days and its subacute effect on the intestines was examined.

Luo et al., [34] investigated the effect of IMI on zebrafish (*Danio rerio*, Hamilton, 1822). The researchers noted that low-dose IMI exposure triggered oxidative stress in the zebrafish intestine and increased superoxide dismutase and catalase enzyme activities. Malondialdehyde is the end product of lipid peroxidation and is an important marker of cell damage [35, 36]. Changes in antioxidant enzyme activities are other indicators of tissue damage [37]. Disruption of the antioxidant enzyme system may cause disruption of hemostasis in cells and disruption of other physiological activities. Accordingly, loss of work and function may occur in the cells. As a result, the cell may be damaged. In a study by Apaydin et al. [38], bendiocarb, a carbamate group pesticide, caused pathological changes in the small intestine tissue of rats. Atrophy, infiltration and necrosis occurred in the intestinal tissue. In our study, while IMI caused an increase in MDA level in the intestinal tissue of rats, it also caused a decrease in antioxidant enzyme activities. In our study, IMI caused an increase in MDA level in the intestinal tissue of rats and a decrease in antioxidant enzyme activities. Our histological examinations showed damage to the intestinal tissue.

Luo et al, investigated the effect of IMI on zebrafish. The researchers stated that low-dose IMI exposure caused thickening and inflammation in the intestinal wall of zebrafish [34]. Miao et al. showed that IMI changes the composition and function of the intestinal microbiota, disrupts the integrity of the intestinal structure and increases intestinal permeability. The researchers stated that melatonin protects the damage that occurs in the intestines [31]. Zhao et al, administered IMI orally to rats for 90 days. They observed that IMI increased intestinal permeability by disrupting tight junctions. As a result, they noted a response in the intestinal tissue [39]. In our histological studies, IMID caused inflammation in intestinal tissue. Pathological findings decreased in IMI plus berberine and IMI plus resveratrol treated groups.

It is known that some vitamins and flavonoids prevent the formation of free radicals in the cell and reduce oxidative stress [40, 41]. In this study, RES and BBR, potent antioxidants, were used to reduce/prevent IMI toxicity.

4. CONCLUSION

As a result of our study, it was determined that IMI had a toxic effect on the small intestine tissue of rats. Both our biochemical and histopathological findings showed this. BBR and RES reduced the toxic effect of IMI on the intestinal tissue of rats.

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AUTHOR'S CONTRIBUTIONS

The authors contributed equally.

CONFLICTS OF INTEREST

There is no conflict of interest.

RESEARCH AND PUBLICATION ETHICS

The author declares that this study complies with Research and Publication Ethics.

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