Evaluation of Some Biomarkers and Histological Alterations of Selenium and 6-Shogaol Against Permethrin Toxicity in Male Laboratory Rats

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***Abstract*—** The current study was designed to investigate some biological effects of the pesticide Permethrin in male white rats. As a result of the present study revealed a significant increase in the concentrations of liver enzymes (AST, ALT, and ALP), malondialdehyde (MDA), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) at a probability level of ($P < 0.05$) in the treated group (T1) which was administered Permethrin at a concentration of 75mg/kg for 45 day. Additionally, the findings revealed a significant decrease in the concentrations of antioxidants (SOD and CAT) in the treated group Tat the aforementioned probability level.

On the other hand, the results demonstrated a significant decrease in the concentrations of liver enzymes (AST, ALT, and ALP), MDA, TNF-α and IL-6 in the groups T2, T3, and T4 (treated with Permethrin + Selenium, Permethrin + 6-Shogaol, and Permethrin + Selenium + 6-Shogaol simultaneously, respectively) compared to the treated group T1. A significant increase in the concentrations of SOD and CAT was observed compared to T1 at the specified probability level . As for the histological study of the liver of male rats in the treated group T1, it revealed severe adipose steatosis with infiltration of inflammatory cells, particularly macrophages, and dilation of hepatic sinusoids. Conversely, the results of groups T2, T3, and T4 showed a clear improvement in hepatocytes, which appeared radially arranged around the central vein with mild adipose degeneration

***Keywords* —** Permethrin, Selenium, 6-Shogaol .

INTRODUCTION

Permethrin (PER) is a synthetic pyrethroid insecticide formulated to mimic natural pyrethrins extracted from chrysanthemum flowers (*Chrysanthemum cinerariaefolium*) (1). Permethrin was identified in 1949 as the first synthetic pyrethroid compound used as an insecticide (2). Since then, with continuous developments in chemistry and agricultural technology, a large number of pyrethroid compounds have been developed, most notably: cypermethrin, deltamethrin, fenvalerate, PER , pyrethrin, resmethrin, and sumithrin (3).Structurally, pyrethroids are divided into two main types based on the presence of an alpha-cyano group:

Type I: Does not contain anal pha-cyano group and includes compounds such as permethrin and allethrin.
Type II: Contains an alpha-cyano group, such as cypermethrin and deltamethrin (4-6).

Numerous Research has demonstrated that Permethrin has systemic toxic effects extending to the blood, liver, kidneys, heart, and lungs reflecting an inflammatory response (7). Moreover, MDA levels increased as a marker of oxidative stress, accompanied by a disruption in the activity of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione (GSH), particularly in liver and gill tissues. Recent studies have shown increasing interest in the hepatotoxic effects of Permethrin, particularly through the mechanism of oxidative stress and the disruption of antioxidant balance in hepatocytes. Permethrin caused a decrease in the activity of CAT, glutathione peroxidase (GPx), and glutathione S-transferase (GST), indicating a clear inhibition of cellular defense systems. It also led to a significant increase in liver damage markers, represented by a significant increase in ALT, AST, and ALP levels, along with elevated MDA concentrations as a marker of lipid peroxidation (8). Furthermore, (9) in their study on the effect of Permethrin on liver fish such as carp and Nile tilapia, stated that exposure to Permethrin may cause multiple physiological and histological disturbances, particularly in the liver, which is the primary organ responsible for metabolism and detoxification in fish.

These disturbances include histological changes such as hyperplasia and necrosis, indicating that the liver's vital functions and its ability to resist toxins are affected. Under physiological conditions, cells maintain balanced levels of reactive oxygen species (ROS). However, exposure to internal factors such as oxidases or external factors like radiation, drugs, pollutants, and smoking leads to an abnormal increase in ROS concentrations. ROS target essential cellular components, including cell membrane lipids (lipid peroxidation), proteins, and DNA, causing cellular damage that may lead to chronic diseases such as tissue inflammation, cancerous tumors, cardiovascular diseases, diabetes, and nervous system disorders (10). Intracellular antioxidant systems constitute the primary line of defense and include

non-enzymatic components such as glutathione (GSH), ascorbic acid, and lipid peroxides, in addition to key enzymatic systems including SOD, CAT, GPx, and GST. These enzymes efficiently regulate the degradation of superoxide and peroxide, while GSH acts as a regenerating agent CAT by GPx and GST (11). The enzyme defense systems involving superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) further contribute to cellular protection against oxidative damage. Specifically, superoxide dismutase converts superoxide radicals (O_2^-) into hydrogen peroxide (H_2O_2), which is subsequently broken down into water (H_2O) and oxygen (O_2) by catalase (12).

MATERIALS AND MTHODS

1. Study Design

The current study was designed to evaluate the effect of Selenium and Shogaol on some biomarkers of male laboratory rats against Permethrin toxicity. In this experiment, (40) adult male albino rats aged 14-16 weeks and weighing between 150-160 g were used. They were divided into 5 groups .The experimental design was as follows:

1. Control group (C) : Animals were given normal water and diet throughout the experimental period, which lasted 45 days.
2. Second treated group (T1): Animals were orally administered Permethrin pesticide at a dose of 75 mg/kg body weight daily for 45 days.
3. Third treated group (T2): Animals were orally administered Permethrin pesticide at a dose of 75 mg/kg body weight daily, concurrently with Selenium solution at a dose of 50 mg/kg body weight for45 days.
4. Fourth treated group (T3): Animals were orally administered Permethrin pesticide at a dose of 75 mg/kg body weight daily and 6-Shogaol at a dose of 20 mg/kg body weight concurrently for 45 days.
5. Fifth treated group (T4): Animals were orally administered Permethrin pesticide at a dose of 75 mg/kg body weight daily, Selenium solution at a dose of 50 mg/kg, and 6-Shogaol at a dose of 20 mg/kg daily concurrently for 45 days.

2. Estimation of Liver Enzymes Levels in Serum

To estimate liver enzyme activity, the colorimetric method of Reitman and Frankel (1957) was followed, using kits supplied by the Italian company Giesse.

3. Enzyme-Linked Immunosorbent Assay (ELISA)

An ELISA reader was used according to the manufacturer's instructions (Sunlong, China) for several tests, including (oxidative stress markers and antioxidants, IL-6, and TNF-α.

4. Histological Study

Tissues were fixed in a 10% formalin solution, dehydrated in ethanol, embedded in paraffin wax, sectioned at a thickness of 5 µ, and stained with Hematoxylin and Eosin (H&E) according to the method of Humason et al. (1997) .

STATISTICAL ANALYSIS

The results were statistically analyzed to determine significant differences between the means of the studied parameters across various groups. Significant differences were determined at a probability level of ($P < 0.05$). The statistical analysis included a Completely Randomized Design (CRD) to determine differences between parameter concentrations among study groups. Significant differences between means were also tested using the Least Significant Difference (LSD) test at a probability level of ($P < 0.05$).

RESULT

1.Serum Liver Enzymes Level

The results of the statistical analysis in Table (1) showed a significant increase ($P < 0.05$) in the concentration of liver enzymes (AST, ALT, and ALP) in the (T1) group after treating the animals with Permethrin for 45 days in comparison to the control group and other treatments. The results also recorded a significant decrease ($P<0.05$) in the treated groups (T2, T3, and T4) when in comparison to the first treated group T1 administered Permethrin. A clear improvement and significant increase were observed in the treated groups (T2, T3, and T4) in comparison to the control group at the probability level of ($P < 0.05$), with significant differences among the treated groups (T2, T3, and T4) when in comparison to each other at the significance probability level.

Table 1. Effect of Selenium and 6-Shogaol treatment on liver enzymes levelsin male white rats treated with Permethrin

Group	AST (IU/L)	ALT (IU/L)	ALP (IU/L)
C	31.32 ±0.31 e	25.05 ±0.36 e	80.73 ±0.19 d
T1	98.73 ±0.76 a	109.12 ±3.07 a	211.29 ±4.36 a
T2	72.72 ±1.19 b	65.32 ±0.34 b	110.44 ±2.57 b
T3	57.36 ±1.01 c	49.69 ±0.38 c	94.86 ±0.65 c
T4	40.95 ±0.22 d	35.06 ±0.31 d	89.27 ±0.67 cd
L.S.D	1.99	3.39	5.64

Different letters indicate significant differences ($P < 0.05$).

2. Oxidative Stress Markers and Antioxidants

2.1 Serum Malondialdehyde (MDA) Level

The result of MDA levels in table (2) recorded a significant increase ($P < 0.05$) in the level of MDA concentration in the (T1) group after treating the animals with Permethrin for 45 days compared to the control group and other treatments. Treated groups(T2, T3, and T4) showed a clear improvement and a significant decrease ($P < 0.05$) compared to the first treated group T1. Results also showed a significant increase in

MDA concentration in groups (T2, T3, and T4) compared to the control group. Significant differences were observed when comparing groups T2 and T3 with each other. Concurrently, results Recorded a non-significant decrease in the treated group T4 when compared to the fifth treated group (T3) at the aforementioned probability level.

.2 Serum Superoxide Dismutase (SOD) and Catalase (CAT) Levels

According to the results in table (2) witnessed a significant decrease ($P < 0.05$) in the concentration level of SOD and CAT in the T1 group after treating the animals with Permethrin for 45 days in comparison to the control group and other treatments. The table results showed a significant increase ($P < 0.05$) in the treated groups T2, T3, and T4 in comparison to the first treated group T1 with Permethrin. The second treated group (T2) showed a significant decrease ($P<0.05$) compared to the control group. Simultaneously, the table results witnessed a clear improvement and a non-significant increase ($P > 0.05$) in the two treated groups T3 and T4 in comparison to the control group. Results also showed the absence of significant differences when comparing both groups with each other at the above probability level.

Table 2. Effect of Selenium and 6-Shogaol treatment on MDA, SOD, and CAT levels in male white rats treated with Permethrin s

Group	MDA (U/mL)	SOD (U/mL)	CAT (U/mL)
C	2.3750 ± 0.04 d	4.3262 ± 0.036 a	0.7168 ± 0.008 a
T1	7.8437 ± 0.218 a	1.2563 ± 0.38 d	0.2432 ± 0.004 d
T2	4.8150 ± 0.465 b	3.0975 ± 0.694 c	0.3845 ± 0.006 c
T3	3.8988 ± 0.80 5 bc	3.7150 ± 0.465 ab	0.5690 ± 0.017 ab
T4	3.3475 ± 0.909 c	4.7875 ± 0.63 a	0.6077 ± 0.011 ab
L.S.D	0.55	0.45	0.15

Different letters indicate significant differences ($P < 0.05$).

3. Inflammatory and Immunological Parameters

3.1 Serum Interleukin-6 (IL-6) Level

The results shown in table (3) a significant increase ($P <0.05$) in the concentration level of IL-6 in the T1 group after treating the animals with Permethrin for 45 days compared to the control group and other treatments. In contrast, treated groups (T2, T3, and T4) showed a significant decrease ($P <0.05$) compared to the first treated group (T1) exposed to Permethrin, while simultaneously showing an increase compared to the control group at the probability level of ($P < 0.05$). The results also indicated a large significant decrease as evidence of a massive improvement in the level of IL-6 when comparing the treated group T4 with the Permethrin-treated group T1 at the significant probability level.

3.2 Serum Tumor Necrosis Factor-alpha (TNF-α) Level

Results of the current study in Table (3) indicated a significant increase ($P < 0.05$) in the level of TNF-α in group T1 after treating animals with Permethrin for 45 days in comparison to the control group and other treatments. Meanwhile, treated groups (T2, T3, and T4) showed a significant decrease ($P<0.05$) in comparison to the first treated group T1 exposed to Permethrin. Simultaneously, results showed a significant increase in treated groups T2 and T3 in comparison to the control group. Results also indicated a non-significant increase in TNF-α concentration in the treated group T4 in comparison to the control group, and concurrently a non-significant decrease when comparing the treated group T3 with the fifth treated groupT4at the above probability level.

Table 3. Effect of Selenium and 6-Shogaol treatment on IL-6 and TNF-α levels in male white rats treated with Permethrin

Group	TNF-α	IL-6
C	21.00 ±1.34 d	15.53 ± 0.72 e
T1	94.1 ± 9.10 a	108.31 ± 4.78 a
T2	55.37 ±3.62 b	62.69 ± 3.98 b
T3	40.37 ± 2.79 c	42.10 ±3.03 c
T4	30.22 ± 2.38 cd	26.49 ± 1.17 d
L.S.D	11.6	7.80

Different letters indicate significant differences ($P < 0.05$).

4. Histological Changes of the Liver

The histological examination of sections taken from the liver of the control group (C) showed normal liver architecture, characterized by hepatocytes radially arranged in a hexagonal shape around the central vein (Figure 1).

In the first treatment (T1), which represented animals treated with Permethrin with an emphasis of 75 mg/kg for 45 days, severe adipose degeneration was observed where hepatocyte nuclei were peripherally located. This was accompanied by inflammatory cell infiltration, particularly macrophages, dilation of hepatic sinusoids, hyperplasia, and congestion of the bile duct in comparison to the control group (Figure 2).

Conversely, the treated group (T2), which was treated with Permethrin and Selenium for 45 days, showed normal radial arrangement of hepatocytes with inflammatory cell infiltration and Kupfer cell proliferation. Hepatocytes appeared normal with clear centrally located nuclei, except for the presence of adipose degeneration and bile duct hyperplasia (Figure 3).

In the treated group (T3), treated with Permethrin and Shogaol for another 45 days , a clear improvement in hepatocytes was observed. They appeared radially arranged around the central vein with inflammatory cell infiltration and Kupfer cell proliferation, except for mild adipose degeneration and mild bile duct hyperplasia (Figure 4).

In treatment (T4), administered Permethrin, Selenium, and Shogaol for 45 days, an improvement in tissue state was observed compared to the first treatment (T1). The normal radial arrangement of hepatocytes around the central vein appeared with mild adipose degeneration, dilation of hepatic sinusoids, and Kupfer cell proliferation, while the bile duct appeared normal (Figure 5).

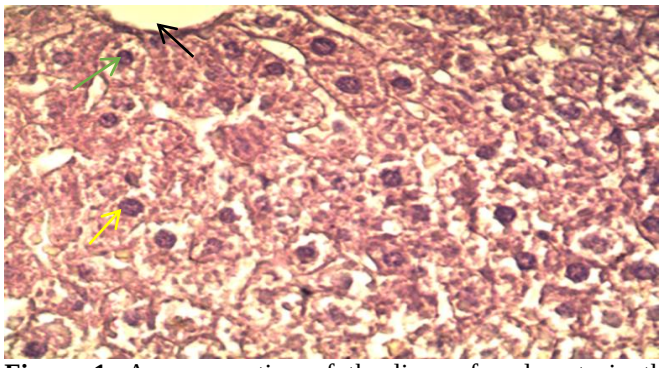

Figure 1. A cross-section of the liver of male rats in the control group (C), showing cell nuclei (yellow arrow), with hepatocytes radially arranged (green arrow) around the central vein (black arrow) (H& E40x).

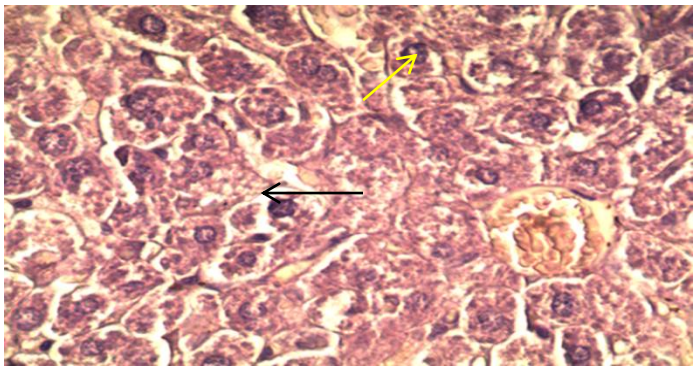

Figure 2. A cross-section of the liver of male rats in the first treated group (T1), showing peripherally located hepatocyte nuclei with adipose degeneration (black arrow), dilation of hepatic sinusoids, and hyperplasia with congestion of the bile duct (yellow arrow) (H & E40x).

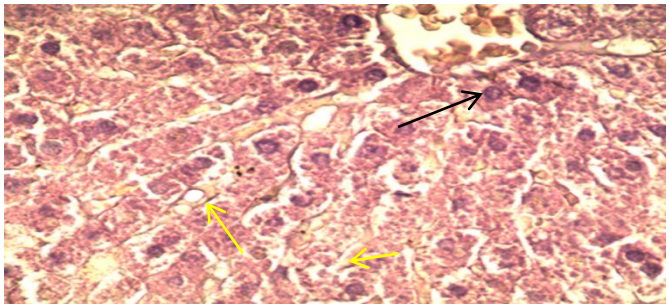

Figure 3. A cross-section of the liver of male rats in the group (T2), showing the normal radial arrangement of hepatocytes (black arrow), along with adipose degeneration and mild bile duct hyperplasia (yellow arrow) (H& E40x).

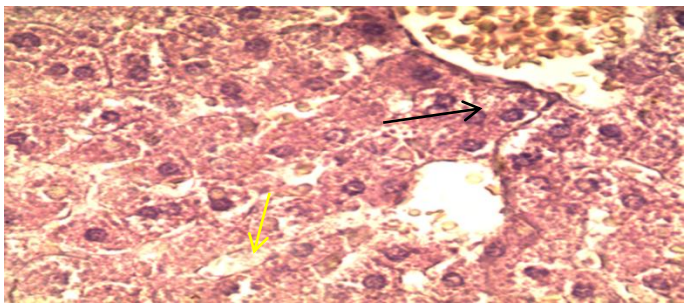

Figure 4 A cross-section of the liver of male rats in the group (T3), showing the normal radial arrangement of hepatocytes (black arrow), along with adipose degeneration and mild bile duct hyperplasia (yellow arrow) (H& E40x).

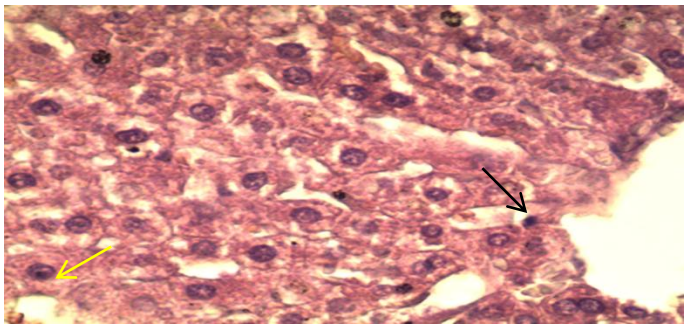

Figure 5. A cross-section of the liver of male rats in the group (T4), showing the normal radial arrangement of hepatocytes around the central vein (black arrow) with mild adipose degeneration (yellow arrow), while the bile duct appears normal (H & E40x).

Discussion

The Statistical analysis results in Table (1) showed a significant increase ($P < 0.05$) in the level of liver enzymes (AST, ALT, and ALP) in the T1 group after animals were treated with Permethrin. This may be attributed to liver dysfunction, which agrees with the findings of (13) . the liver is primarily responsible for synthesizing the above enzymes, direct damage to hepatocytes is likely to alter protein synthesis. These changes may reflect a loss of functional integrity of the hepatocyte membrane, revealing that Permethrin not only affects the liver at the functional level but also induces significant cellular stress that may lead to organ dysfunction (14). In fact, (15) reported that sub-chronic exposure to Permethrin induces physical changes in cell membranes, manifested as a decrease in membrane fluidity, disrupting liver function. According to (16), increased serum transaminase activity reflects cellular leakage resulting from the loss of functional integrity of the hepatocyte membrane. Consequently, enzymes normally present in the cytoplasm leak into blood circulation. This is evident in the first treatment with Permethrin, which led to elevated AST and ALT enzymes in the current study.

As highlighted by Bak et al. in their 2012 study, 6-Shogaol exhibits potent antioxidant properties. Their research revealed that the extract upregulates the gene expression of heme oxygenase 1 (HO-1) by activating the Nrf2/ARE gene pathway, a mechanism mediated through the activation of the p38 MAPK protein at the cellular level (17) . This molecular pathway is consistent with our study's physiological results, which demonstrated the extract's efficacy in shielding liver tissue from permethrin-induced toxicity. Additionally, it significantly reduced serum markers of liver damage, such as ALT and AST, while lowering malondialdehyde (MDA) levels.

In parallel, groups treated with selenium also presented a marked reduction in liver enzyme levels when compared to the T1 treatment group. These findings align with earlier research, including those by (18). According to (19), selenium's beneficial effects on liver enzymes stem from its capacity to mitigate oxidative stress. This is achieved by decreasing free radical production, thereby halting free radical chain reactions, as noted by (20). Moreover, selenium's liver-protective attributes may be tied to its regulatory role in antioxidant systems and its powerful free radical scavenging activity, as discussed by (21). Selenium is also believed to prevent lipid peroxidation in cell membranes and suppress inflammatory responses. These actions serve to safeguard liver cells from damage, prevent enzyme leakage, and stabilize liver enzyme levels, as supported by (22).

Exposure to the herbicide permethrin has been shown to adversely impact SOD and GPx enzyme activity while triggering an increase in MDA levels. This pattern signifies a disruption in oxidative balance. Elevated MDA levels are indicative of heightened lipid peroxidation, a process that compromises liver function and overall health. These observations corroborate prior studies linking pesticide exposure to oxidative stress. For instance, (23) reported a 75% rise in MDA levels in mice subjected to permethrin, suggesting enhanced reactive oxygen species (ROS) production, leading to the depletion of internal antioxidant reserves.

Elevated levels of reactive oxygen species can trigger a cascade of molecular and transcriptional processes. This leads to the production of pro-inflammatory cytokines by local microglia, along with infiltrating neutrophils, monocytes, and lymphocytes (24). While other brain cells are capable of producing cytokines, microglia serve as the principal source of TNF-α, as well as other cytokines like interleukin-1 and interleukin-6, particularly during neuroinflammation (25, 26). Our study revealed a significantly higher expression of TNF-α. As a pro-inflammatory cytokine, TNF-α plays a crucial role in various processes, such as neurogenesis, neurotransmission, cell proliferation, and neuronal excitability (27). In this context, our findings revealed that a high dose of permethrin led to an increase in TNF-α expression in rats. Due to its interaction with voltage-gated sodium channels, permethrin may directly activate microglial cells, resulting in an excessive buildup of intracellular sodium. This, in turn, causes cell depolarization and triggers the release of TNF-α (28). 6-Shogaol has been shown to have anti-inflammatory properties in several earlier studies. For example, 6-Shogaol was found to lower inflammatory markers in the buccal pouch carcinogenesis hamster model (29). Sohn et al. also noted that 6-Shogaol prevented HMC-1 cells from producing proinflammatory cytokines.

CONCLUSION

This study highlights the promising protective effects of Selenium and 6-Shogaol in countering Permethrin-induced toxicity. Their therapeutic potential primarily stems from robust antioxidant properties that neutralize free radicals and restore redox balance by reducing MDA levels and boosting the indigenous antioxidant enzymes' activity such as SOD and CAT. Additionally, both agents demonstrated notable anti-inflammatory and cytoprotective capabilities, alleviating liver tissue damage and underscoring their potential as natural bioactive supplements to combat environmental chemical hazards..

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N/A

Conflict of Interest
The authors declare no conflict of interest.

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