The Journal of Anatomical Sciences
Email: journalofanatomicalsciences@gmail.com

J. Anat Sci 16(1)

Effects of Sesame Oil on the Liver of Adult Male Wistar Rat following Permethrin Exposure

[1]Adisa, Faridah Ololade, [2]Abdulkadir, Hawau Olaide, [1]Imam, Abubakar Lekan, [1]Jaji-Sulaimon, Rukayat, [1]*Omotoso, Gabriel Olaiya

[1]Department of Anatomy, [2]Department of Physiology, Faculty of Basic Medical Sciences, University of Ilorin, P.M.B. 1515, Ilorin, Nigeria.
***Corresponding Author**: Email: omotoso.go@unilorin.edu.ng
Tel: +234 703 050 5707

Abstract
The liver performs many vital functions to eliminate toxins and harmful substances from the body. Hepatotoxic agents can react with basic cellular components and consequently induce almost all types of liver lesions. This study aimed to investigate the possible hepatoprotective role of sesame oil against permethrin-induced hepatotoxicity in adult male Wistar rats from the histological and biochemical perspectives. In this study, forty adult male Wistar rats were used. They were grouped into four groups: the control group, the permethrin-treated group, which received feeds mixed with feed (1000 mg/kg permethrin), the sesame oil group, which received (5 ml/kg body wt), and the permethrin + sesame oil group. This treatment was done for 4 weeks, after which the rats were euthanized, the liver harvested, weighed, and either homogenized for biochemical studies or fixed in 10% formalin for histological analysis. The findings revealed notable microarchitectural changes in permethrin-treated animals, elevated liver enzymes, and depletion of oxidative markers. These changes were mitigated by sesame oil supplementation to a good extent. The study suggests that sesame oil supplementation has hepatoprotective effects against permethrin-induced hepatotoxicity.
Keywords: permethrin, sesame oil, hepatotoxicity, liver function, oxidative stress

INTRODUCTION

The use of insecticides is common in many homes to kill various kinds of insects. They are toxic substances that can affect human health when exposed to them. Pyrethroids are synthetic derivatives of natural pyrethrins from the plant *Chyrsanthemum cinerariaefoliun*[1]. Pyrethroid insecticides demonstrate a selective toxicity towards insects and are mainly used for mosquito eradication and pest control [2]. They are divided into type I and type II, depending on the structure of the compound, its action, and symptoms [3]. Type I pyrethroids can cause hyperexcitation, ataxia, and paralysis, while type II pyrethroids provoke hypersensitivity, salivation, and choreoathetosis[4,5]. Permethrin is a synthetic type I pyrethroid widely used in the textile industry, agriculture, and public health[6]. The main mechanism of permethrin action is through interference with sodium channels, receptor-ionophore complexes, and neurotransmitters[7]. Some studies have reported that permethrin increases the risk of toxicity, such as neurotoxicity, genotoxicity, fetotoxicity, cytotoxicity, and hepatotoxicity[7]. The generation of reactive oxygen species (ROS) and nitrogen species (RNS) is one of the possible mechanisms responsible for permethrin toxicity through oxidative stress injury, suppression of the antioxidant defense system, and damage to biomolecules such as lipids, proteins, and DNA[8]. The liver is the main site of permethrin metabolism and the major target of greater accumulation of metabolites[9]. These perturbations could alter the structure and function of the biological cell. In fact, a direct association between mitochondrial dysfunction and permethrin toxicity has been demonstrated[9]. Based on clinical and animal evidence *in vitro* and *in vivo*, inhibitory effects have been described for Ca^{2+} channels, ATPases, and complex activities[10, 11]. These mitochondrial alterations may be crucial in many aspects of permethrin hepatotoxicity.

Natural herbal products have been used in traditional medicine in the management of a variety of diseases, including liver pathology[12]. Sesame oil, which is an edible oil obtained from the seeds of the sesame plant *Sesamum spp*, consists mainly of acyl lipids (triacyglycerols) and fatty acids such as palmitic, stearic, oleic acid, and alpha linoleic acids, and is now recognized as a functional food due to its various health benefits. For instance, alpha linoleic acid is well known for its anti-inflammatory activities, which are believed to be mediated by its ability to interfere with arachidonic acid metabolism, thereby inhibiting the biosynthesis of pro-inflammatory prostaglandins[13].

The non-acyl component of sesame oil constitutes a much lesser fraction and is made up primarily of two major lignans, sesamin and sesamolin, along with small amounts of other phenolic compounds such as sesaminol, sesamolinol, pinoresinol, and lariciresinol, which are reportedly responsible for the antioxidant activity of sesame seed oil[14]. In addition to these bioactive compounds, sesame oil is also a rich source of total tocopherols and small amounts of tocopherols[15]. Various health-promoting effects, such as antioxidant, antihypertensive, antiproliferative, and hepatoprotective activities, have been associated with sesame seed oil, and these are thought to emanate from its bioactive chemical constituents, especially sesamin and sesamolin[16]. The present study explored the potential of sesame seed oil in protecting the liver architecture and chemistry against cytotoxicity occasioned by exposure of Wistar rats to permethrin.

MATERIALS AND METHODS

Animal use and care

The study was approved by the University Ethical Review Committee. A total of 40 adult male Wistar rats weighing between 148 and 200 g were used for this study. The study was conducted in the Animal House of the Department of Anatomy, College of Health Sciences, University of Ilorin, Nigeria. The animals were allowed to acclimatize for two weeks before the commencement of the study,

and they had access to feed and water under optimum conditions.

Treatment of animals

Rambo insect powder (Rambo® Gongoni Co. Ltd, Kano, Nigeria) containing 0.6% permethrin and 99.4% inert carriers was procured and used for this study. The rats were divided into four groups (A-D), each consisting of 10 rats. Group A received standard rat diet; Group B received standard rat diet mixed with permethrin insecticide (1000 mg/kg) [17-19]; Group C received 5 ml/kg of sesame seed oil[16] via an oral cannula, and Group D received both sesame seed oil (5 ml/kg) and permethrin insecticide (1000 mg/kg). Treatment was carried out for 28 days.

Termination of treatment

Following the completion of treatment, the rats were anesthetized using a ketamine injection. An incision was then made from the abdomen to the thorax, after which a butterfly needle was inserted into the apex of the heart, and transcardial perfusion with normal saline occurred for 2 minutes, after which a solution of 10% formalin was also passed through transcardial perfusion for 3 minutes. The liver was thereafter removed and placed in fixative. However, the liver tissues for biochemical studies were obtained from rats that were sacrificed by cervical dislocation to avoid any possible chemical interaction with the anesthetic agent.

Tissue processing for histological demonstration

The liver tissue was placed in a cassette and preserved in a solution of 10% formalin to prevent dehydration and decomposition before being subjected to routine processing, which included dehydration, clearing, infiltration, embedding, sectioning, and staining. The tissues were dehydrated by immersion in ascending grades of alcohol concentration (70% ethanol, 90% ethanol, and 100% ethanol). This was done to remove water and fixatives from the tissue. After dehydration, the tissues were cleared in two changes of xylene to replace the alcohol because it is miscible with both alcohol and paraffin wax. Tissues were infiltrated with melted paraffin wax at 60^{o}c using a thermo-regulated oven. The tissue was then placed in blocks, embedded in paraffin wax, and allowed to cool. Embedded tissues were sectioned at 5 µm to obtain tissue sections, using a microtome, and then stained with Hematoxylin and Eosin (H&E) stain.

Biochemical analysis

Liver tissues for biochemical studies were prepared using cold 30% sucrose. These were homogenized using a homogenizer, and the homogenates were emptied into a 5 ml plain specimen bottle, which was then centrifuged at 3000 revolutions per minute for 5 minutes. The supernatants were used for biochemical analysis of oxidative markers (superoxide dismutase, glutathione peroxidase, and malondialdehyde) and liver enzymes (alkaline phosphatase and alanine aminotransferase) using appropriate biochemical kits and according to manufacturers' guidelines.

Data analysis

The quantitative data obtained were subjected to statistical analysis, expressed as mean ± standard error of mean (mean ± SEM). Means were compared by analysis of variance (ANOVA). A p-value of ≤ 0.05 was considered statistically significant in all cases. The software package GraphPad Prism was used for the analysis and graphical representation of data.

RESULTS

Rats exposed to a permethrin diet had the lowest body weight gain, followed by rats that received co-administration of permethrin and sesame seed oil, compared to the other groups. Administration of sesame seed oil only led to an increase in body weight gain, though not as high as the control group (Table 1).

Table 1: Body and liver weight changes

GROUP	INITIAL WEIGHT (g)	FINAL WEIGHT (g)	WEIGHT DIFFERENCE (g)
Control	158±10.09	207.6±12.02	49.6±8.63
Permethrin	163±10.42	184±12.48	24.2±7.33
Sesame seed oil	169.6±8.84	199±13.51	41.4±8.74

Permethrin + sesame seed oil	165.8±11.61	188.8±13.88	27.0±8.77

Biochemical analysis

Changes in enzymatic markers of liver pathology

The activity of alkaline phosphatase (ALP) and alanine transaminase (ALT) was elevated in the liver of rats that received a permethrin diet only when compared with the Control. The level of ALP in rats treated with SSO only was higher than that of the Control but lower than that of the permethrin only group. Co-administration of permethrin and SSO led to a reduction in ALP, though higher than in rats that received SSO without exposure to permethrin (Figure 1). There were no significant changes in the liver levels of ALT in rats treated with SSO or a combination of permethrin and SSO compared with the Control, though the levels were lower than in the rats that consumed the permethrin diet only (Figure 1).

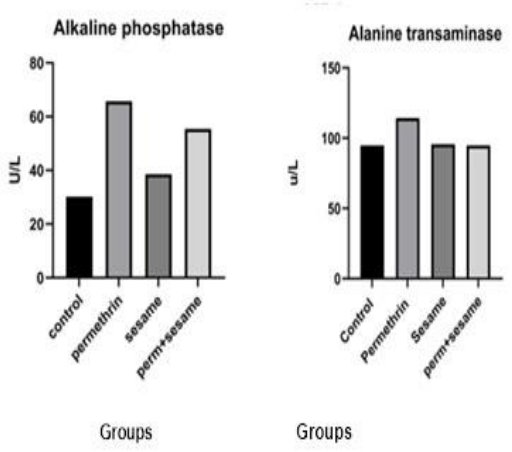

Figure 1: Increase in the levels of alkaline phosphatase and alanine transaminase in the liver of rats exposed to permethrin when compared with the Control and other groups.

Sesame seed oil improves oxidative stress markers and reduces lipid peroxidation.

Permethrin exposure led to depletion in the liver level of enzymatic oxidative markers-superoxide dismutase (SOD) and glutathione peroxidase (GPx), compared with the Control and other groups (Figure 2). The level of SOD in the liver of rats administered with sesame seed oil (SSO) was higher than that of the control, while rats that received both SSO and permethrin had an SOD level that was higher than the permethrin-only group. Rats that received SSO either singly or in combination with permethrin had the highest levels of GPx. The level of malondialdehyde, a marker for lipid peroxidation, was highest in the liver of permethrin-treated rats, while the level was lowest in SSO-treated rats compared with the Control and the rats that received a combination of permethrin and SSO (Figure 2).

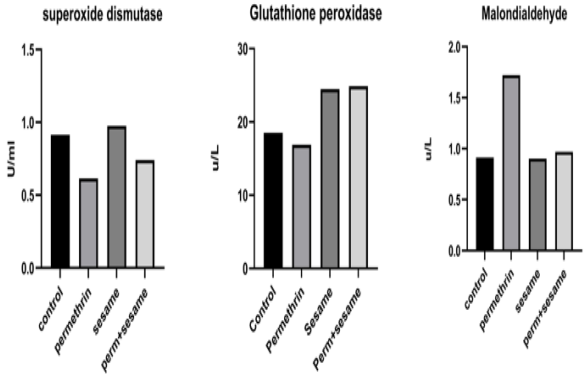

Figure 2: Reduction in the levels of superoxide dismutase, glutathione peroxidase, and an increase in malondialdehyde in the liver of rats exposed to permethrin when compared with the Control.

Histological observation

The cellular assortment and regions of the liver in control and sesame seed oil were normal, with large hepatocytes and deeply stained nuclei. The cellular assortment and regions of the liver in the group that received permethrin showed ruptured central vein and portal vein with intrusion of bile contents, inflamed sinusoids, and hepatocytes that appeared necrotic and inflamed. Intervention with sesame seed oil preserved the histoarchitecture of the liver following permethrin hepatotoxicity, as the

photomicrographs of this group present similar features to those of the control groups (Figure 3).

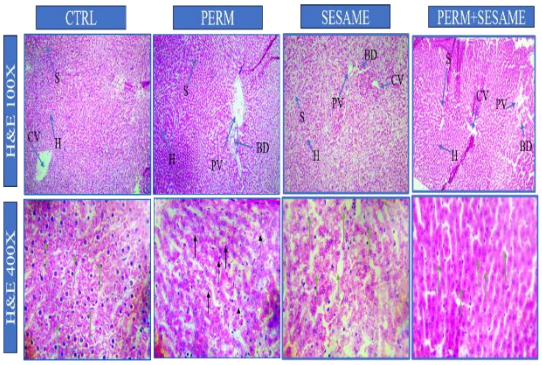

Figure 3: Photomicrographs of the liver of Wistar rats of Control (CON) and experimental groups treated with permethrin diet (PERM), sesame seed oil (SSO) and combination of permethrin diet and sesame seed oil (PERM+SSO), showing normal hepatocytes with deeply stained nucleus in the control and SSO groups (*blue arrows*), ruptured central vein, inflamed sinusoids (*blue arrows*) and necrotic and inflamed hepatocytes in PERM group (*red arrows*), and fairly preserved liver histoarchitecture in the PERM+SSO. Low (x100) and high (x400) magnification stained with H&E.

DISCUSSION

The results of this study showed significant differences in the body weights and biochemical markers in the Wistar rats exposed to permethrin, those co-treated with permethrin and sesame oil, and the control group. It was observed that permethrin caused weight loss in the rats due to its disruption of the nervous system, leading to increased metabolic rate and reduced food intake, potentially caused by hyperactivity, tremors, and altered feeding behavior, which are common signs of pyrethroid toxicity in animals. However, permethrin caused enlargement of the liver by disrupting lipid metabolism within the liver, leading to fat accumulation and hepatomegaly due to its effects on cellular processes like increased microsomal activity and altered gene expression, particularly at high doses or prolonged exposure[20].

Superoxide dismutase (SOD) is an enzyme that plays a critical role in the detoxification of superoxide radicals, which are a type of reactive oxygen species generated during oxidative stress[21].

Permethrin induces oxidative stress in the liver, as noted in this study. The elevated levels of reactive oxygen species can overwhelm the antioxidant defense system, thereby leading to a redox imbalance in the system. As a result, the activity of SOD may become impaired, leading to inadequate removal of superoxide radicals. This impairment can further contribute to cellular damage, inflammation, and ultimately, liver dysfunction. Moreover, the induction of toxic stress of permethrin can cause alterations in the expression levels of SOD. It is known that exposure to toxic substances can either upregulate or downregulate the expression of SOD depending on the severity of the oxidative stress and the cellular context. Sesame seed oil was revealed in this study to be a potent antioxidant and particularly against permethrin-induced hepatotoxicity. This suggests that sesame seed oil has a protective effect and can help maintain normal enzyme activity in the liver.

Glutathione peroxidase (GPx) is an important antioxidant enzyme that helps protect cells from oxidative stress by catalyzing the reduction of hydrogen peroxide and organic peroxides[22]. It utilizes glutathione, a powerful antioxidant, as a substrate to neutralize these harmful substances, thereby preventing cellular damage. GPx is a vital enzyme for protecting against oxidative stress, and its levels can serve as an indicator of liver health in the context of toxic exposure. The current study showed that permethrin decreased GPx levels, which may indicate that the ability of the liver to combat oxidative damage was compromised, and this would lead to increased vulnerability to cellular injury. The rats treated with sesame seed oil alone showed a noticeable

increase in glutathione peroxidase levels, suggesting also that sesame seed oil has a positive effect of boosting antioxidant levels in the rats, while the rats treated with both permethrin and sesame seed oil exhibited the highest levels of glutathione peroxidase, indicating that sesame seed oil mitigates the negative effects of permethrin and enhances antioxidant enzyme production. Monitoring GPx levels can provide insights into the oxidative stress status of the liver following permethrin exposure.

Malondialdehyde (MDA) is a key biomarker for lipid peroxidation and oxidative stress, making it a relevant focus when discussing the effects of permethrin on the liver. When permethrin is metabolized in the liver, it can lead to the generation of reactive oxygen species, which in turn can initiate lipid peroxidation. This process results in the breakdown of polyunsaturated fatty acids in cell membranes, leading to the formation of MDA[23]. Elevated levels of MDA in liver tissues indicate increased oxidative damage and stress. When the liver is exposed to permethrin, the accumulation of MDA can be a sign of compromised cellular integrity and function. The presence of MDA not only reflects the extent of oxidative damage but can also contribute to further cellular dysfunction by affecting signaling pathways and promoting inflammation. A very high level of MDA was observed in this study in the liver of rats exposed to permethrin. This significant increase suggests that permethrin exposure is linked to higher levels of lipid peroxidation, further emphasizing oxidative stress associated with permethrin toxicity. As noted earlier in other enzyme markers, the use of sesame seed oil remarkably reduced lipid peroxidation, as we observed a very low level of MDA in this group of rats. The levels of MDA in the control, rats treated with SSO only, and permethrin-exposed rats that received SSO intervention were around the same range. This observation highlights the potential benefits of sesame seed oil in reducing lipid peroxidation and oxidative stress induced by permethrin.

Alkaline phosphatase (ALP) is an enzyme found in various tissues throughout the body, with particularly high concentrations in the liver, bile ducts, and bones. It plays a crucial role in dephosphorylation, which is important for various biological processes, including bone mineralization and liver function[24]. When the liver is exposed to toxins such as permethrin, it can lead to cholestasis, which is a condition where bile flow is impaired. This impairment can result in an increase in ALP levels in the bloodstream. Elevated ALP levels often indicate liver dysfunction or biliary obstruction, as the enzyme is released into the circulation when bile ducts are damaged or blocked.

In the context of permethrin exposure, monitoring ALP levels can provide valuable information about liver health and the potential for cholestatic injury[25]. If ALP levels are elevated, it suggests that the liver is under stress, and there may be issues related to bile flow or liver cell integrity. ALP serves as an important marker for liver and biliary health, and its elevation in response to permethrin exposure can indicate liver dysfunction and cholestatic conditions. Elevated ALP levels, as observed in this experiment, indicate liver dysfunction or biliary obstruction due to permethrin exposure, reflecting cholestatic injury, which was mitigated by the administration of sesame seed oil.

Alanine aminotransferase (ALT) is an enzyme primarily found in the liver. It plays a key role in amino acid metabolism, specifically in the conversion of alanine and alpha-ketoglutarate to pyruvate and glutamate[26]. ALT is considered a marker for liver function because it is released into the bloodstream when liver cells are damaged. When the liver is exposed to toxins like permethrin, it can lead to hepatocellular injury, which results in elevated ALT levels in the blood. High ALT levels are often indicative of liver inflammation or damage, making it a crucial parameter in assessing liver function and health. Monitoring ALT levels can help determine the extent and progression of liver injury. In the current study, the control group

had the lowest levels of ALT, indicating the baseline level of the enzyme, while the rats that received permethrin alone had the highest level of the enzyme in the liver, which is a pointer towards hepatocellular injury. Only a slight difference existed among the remaining groups, yet lower than that of the permethrin-treated rats, suggesting that sesame seed oil has a notable effect in reducing the activity of ALT.

The cellular assortment and regions of the liver in control and sesame seed oil were normal, with large hepatocytes and deeply stained nuclei. The cellular assortment and regions of the liver in the group that received permethrin showed ruptured central vein and portal vein with intrusion of bile contents, inflamed sinusoids, and hepatocytes that appeared necrotic and inflamed. Intervention with sesame seed oil preserved the histoarchitecture of the liver following permethrin. Histopathological changes in the liver following the permethrin diet revealed varying degrees of abnormalities, disruptions, and degenerations, which potentially are detrimental to the normal functioning of the liver. Permethrin affects both the cellular components and the biliary system, hence the possibility of hepatocellular and cholestatic injury. Previous studies demonstrated that pyrethroids affect the energy coupling by mitochondria, where a dose-dependent inhibition of glutamate and succinate sustained state 3 respiration, a condition that causes disturbance in hepatic cell function and consequently hepatic histopathological changes[27].

Conclusion

Permethrin is hepatotoxic, predisposing the liver to both hepatocellular and cholestatic derangements. The use of sesame seed oil mitigates permethrin-induced oxidative stress, histochemical and morphological abnormalities, making sesame seed a promising substance to explore in the management of liver cytotoxicity.

REFERENCES

1. Omotoso G, Oloyede O, Lawal S, Gbadamosi I, Mutholib N, Abdulsalam F, *et al*. Permethrin exposure affects neurobehavior and cellular characterization in the rats' brains. Environmental Analysis, Health and Toxicology, 2020;35(4): e2020022.
2. Stoops CA, Qualls WA, Nguyen TT, Richards SL. A Review of Studies Evaluating Insecticide Barrier Treatments for Mosquito Control From 1944 to 2018. Environ Health Insights 2019;13: 1178630219859004. doi:10.1177/1178630219859004
3. Nasuti C, Cantalamessa F, Falcioni G, Gabbianelli R. Different effects of Type I and Type II pyrethroids on erythrocyte plasma membrane properties and enzymatic activity in rats. Toxicology. 2003;191(2-3):233-244.
4. Breckenridge CB, Holden L, Sturgess N, Weiner M, Sheets L, Sargent D, *et al*. Evidence for a separate mechanism of toxicity for the Type I and the Type II pyrethroid insecticides. NeuroToxicology 2009; 30: S17-S31
5. Ranatunga M, Kellar C, Pettigrove V. Toxicological impacts of synthetic pyrethroids on non-target aquatic organisms: A review. Environmental Advances 2023; 12: 100388. https://doi.org/10.1016/j.envadv.2023.100388.
6. Hodoșan C, Gîrd CE, Ghica MV, Dinu-Pîrvu C-E, Nistor L, Bărbuică IS, *et al*. Pyrethrins and Pyrethroids: A comprehensive review of naturally occurring compounds and their synthetic derivatives. Plants. 2023; 12(23):4022. https://doi.org/10.3390/plants12234022
7. Wang X, Martínez MA, Dai M, Chen D, Ares I, Romero A, *et al*. Permethrin-induced oxidative stress and toxicity and

metabolism. A review. Environmental Research 2016;149: 86–104.

8. Sule RO, Condon L, Gomes AV. A Common Feature of Pesticides: Oxidative Stress-The Role of Oxidative Stress in Pesticide-Induced Toxicity. Oxid Med Cell Longev. 2022;2022:5563759. doi:10.1155/2022/5563759
9. Aoiadni N, Chiab N, Jdidi H, Gargouri Bouzid R, El Feki A, Fetoui H, *et al*. The pyrethroid insecticide permethrin confers hepatotoxicity through DNA damage and mitochondria-associated apoptosis induction in rat: Palliative benefits of *Fumaria officinalis*. Journal of Biochemical and Molecular Toxicology, 2022;36(10): e23172. https://doi.org/10.1002/jbt.23172
10. Chedik L, Bruyere A, Le Vee M, Stieger B, Denizot C, Parmentier Y, *et al*. Inhibition of Human Drug Transporter Activities by the Pyrethroid Pesticides Allethrin and Tetramethrin. *PLoS One*. 2017;12(1):e0169480. doi:10.1371/journal.pone.0169480
11. Akbar SMD, Sharma HC, Jayalakshmi SK, Sreeramulu K. Effect of pyrethroids, permethrin and fenvalarate, on the oxidative stress of *Helicoverpa armigera*. World Journal of Science and Technology 2012, 2(1):01-05.
12. Ouassou H, Bouhrim M, Bencheikh N, Addi M, Hano C, Mekhfi H, *et al*. *In vitro* antioxidant properties, glucose-diffusion effects, α-amylase inhibitory activity, and antidiabetogenic effects of *C. Europaea* Extracts in experimental animals. Antioxidants (Basel). 2021;10(11):1747. doi:10.3390/antiox10111747
13. Fujimoto Y, Yonemura T, Sakuma S. Role of linoleic Acid hydroperoxide preformed by cyclooxygenase-1 or -2 on the regulation of prostaglandin formation from arachidonic Acid by the respective enzyme. J Clin Biochem Nutr. 2008;43(2):65-68.
14. Li M, Luo J, Nawaz MA, Stockmann R, Buckow R, Barrow C, *et al*. Phytochemistry, Bioaccessibility, and Bioactivities of Sesame Seeds: An Overview. Food Reviews International, 2023; 40(1), 309–335.
15. Rangkadilok N, Pholphana N, Mahidol C, Wongyai W, Saengsooksree K, Nookabkaew S, *et al*. Variation of sesamin, sesamolin and tocopherols in sesame (*Sesamum indicum* L.) seeds and oil products in Thailand. Food Chemistry. 2010; 122(3): 724-730.
16. Zubair HO, Awujoola MT, Meduna VO, Omoboye LT, Ayodeji AO, Omotoso GO: Sesame oil protects against permethrin-induced memory decline and oxidative stress in the hippocampus of Wistar rats. The Journal of Anatomical Sciences 2023;14(2): 63-70.
17. Omotoso GO, Onanuga IO, Ibrahim RB. Histological effects of permethrin insecticide on the testis of adult Wistar rats. Ibnosina Journal of Medicine and Biomedical Sciences, 2014;6(3):125-129.
18. Alabelewe MT, Odey NR, Sylvester JO, Kolo RM, Salaudeen BO, Gbadamosi IT, *et al. Moringa oleifera* oil modulates cerebellar neuroinflammation and oxidative stress associated with permethrin neurotoxicity. The Journal of Anatomical Sciences 2024;15(1):63-70.
19. Lewu FS, Omotoso AB, Sylvester JO, Odey NR, Alabelewe MT, Kolo RM, *et al*. Protective effects of Moringa oleifera oil on permethrin-induced toxicity in the prefrontal cortex of young male Wistar rats. Journal of Experimental and Clinical Anatomy 2024;21(2); 301-308.
20. Sun YJ, Liang YJ, Yang L, Long DX, Wang HP, Wu YJ. Long-term low-dose exposure of permethrin induces liver and kidney damage in rats. BMC Pharmacol Toxicol. 2022;23(1):46. doi:10.1186/s40360-022-00586-2

21. Zheng M, Liu Y, Zhang G, Yang Z, Xu W, Chen Q. The Applications and Mechanisms of Superoxide Dismutase in Medicine, Food, and Cosmetics. *Antioxidants (Basel)*. 2023;12(9):1675. doi:10.3390/antiox12091675
22. Pei J, Pan X, Wei G, Hua Y. Research progress of glutathione peroxidase family (GPX) in redoxidation. Front Pharmacol. 2023;14:1147414. doi:10.3389/fphar.2023.1147414
23. Ayala A, Muñoz MF, Argüelles S. Lipid peroxidation: production, metabolism, and signaling mechanisms of malondialdehyde and 4-hydroxy-2-nonenal. Oxid Med Cell Longev. 2014;2014:360438. doi:10.1155/2014/360438
24. Shaban SM, Jo SB, Hafez E, Cho JH, Kim D-H. A comprehensive overview on alkaline phosphatase targeting and reporting assays. Coordination Chemistry Reviews 2022; 465: 214567. https://doi.org/10.1016/j.ccr.2022.214567 .
25. Siddique A, Kowdley KV. Approach to a patient with elevated serum alkaline phosphatase. Clin Liver Dis. 2012;16(2):199-229.
26. Ellinger JJ, Lewis IA, Markley JL. Role of aminotransferases in glutamate metabolism of human erythrocytes. J Biomol NMR. 2011;49(3-4):221-229.
27. Gassner B, Wüthrich A, Scholtysik G, Solioz M. The pyrethroids permethrin and cyhalothrin are potent inhibitors of the mitochondrial complex I. J Pharmacol Exp Ther. 1997;281(2): 855-860.