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The Liver of Young and Old Female Rats Exhibits Heightened Susceptibility to Dichlorvos Exposure

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Exposure to industrial and agricultural environmental contaminants has been shown to produce deleterious effects on different organs of the human body. Dichlorvos [O, O-dimethyl O-(2,2-dichlorovinyl) phosphate, DDVP] is a major organophosphate pesticide used mostly in developing countries for domestic and agricultural insect control. The toxic effects of DDVP have been reported on many organs. However, its gender and age-dependent effects on the liver are yet to be documented. This study investigated the influence of gender and age on liver damage in male and female rats exposed to DDVP. Animals were divided into control and experimental groups with age

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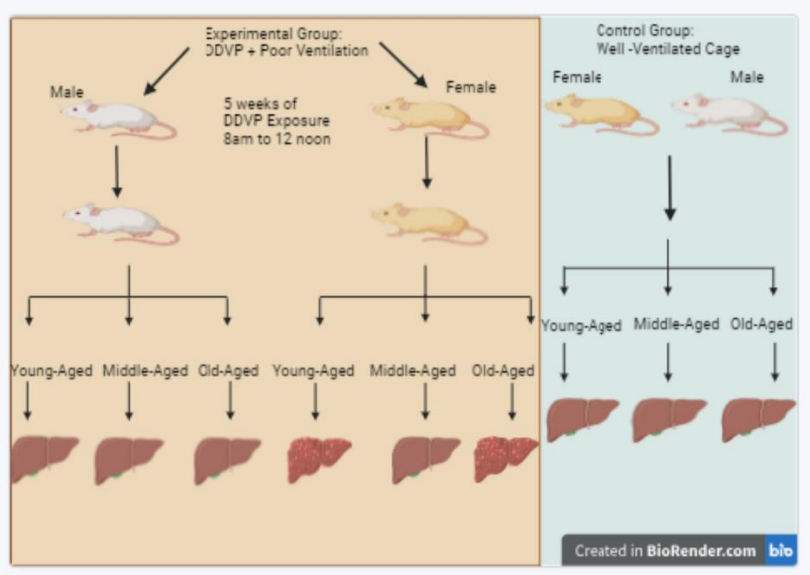
and gender classification. Using age, rats were classified into young, middle-aged, and old age groups. Rats in the experimental groups were exposed to DDVP from 8 am to 12 noon for five weeks. Rats were subsequently euthanized and liver tissues were harvested for biochemical assay. Glutamyl transferase (GGT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH), Albumin, and conjugated bilirubin were assayed using ELISA kits. Statistical analysis was done using two-way ANOVA, followed by Tukey post-Hoc test at significance level of $p<0.05$. Our study found that DDVP exposure caused liver damage in female rats only with significant elevation in liver enzymes such as ALP, ALT, AST, and LDH. However, the male rats showed more resistance to DDVP exposure. The liver damage observed in female rats was age-dependent, with young and old rats showing higher susceptibility compared to middle-aged female rats. Nutritional and pharmacological strategies are recommended to mitigate the effect of DDVP exposure, particularly in populations at higher risk of exposure.

Graphical Abstract



Keywords: DDVP; dichlorvos; liver enzymes; age; gender differences.

1. INTRODUCTION

Exposure to industrial and agricultural environmental contaminants has been shown to produce deleterious effects on different organs of the human body [1,2]. These contaminants reach the human body mainly through inhalation, ingestion, and oral absorption. Among these environmental contaminants are pesticides which could cause acute and/or chronic effects. Dichlorvos [O, O-dimethyl O-(2,2-dichlorovinyl) phosphate, DDVP] is a major organophosphate pesticide used mostly in developing countries for domestic and agricultural insect control [3]. In the last few years, the effects of DDVP on various organs have been documented. For example, Ezeji et al. [4] and Mishani et al. [5] reported the disruptive effects of DDVP on reproductive organs in mice. The scholars reported how DDPV decreased sperm quality, reduced testosterone levels, compromised testicular germ cells, and interfered activity of androgen receptors. Ige et al. [6] reported the negative effects of DDVP on hematological parameters such as platelet counts, hemoglobin concentration, red blood cell counts, and white blood cell counts. Furthermore, Quintino-Ottonicar et al [3] showed how DDVP disrupted the morphology and lipid metabolism of rat ventral prostate. The LD50 of DDVP in rats was determined to be 24mg/kg mg/kg i.p [7].

While the blood, lung, spleen, and kidney metabolize DDVP, the liver is the major site of detoxification of this pollutant [7], making it more susceptible to DDVP toxicity. Zhao et al. [8]

reported autoimmune hepatitis caused by chronic exposure to DDVP in a 49-year-old Chinese woman. In the animal study, Owoeye [9] reported histological changes in the liver of rats exposed to DDVP. Furthermore, Ben Salem et al. [10] noted that dichlorvos exerted its effect by inducing apoptosis through the mitochondrial pathway in liver tissue. In the nervous system, DDVP exerts its toxicity effect by inhibiting acetyl cholinesterase at cholinergic junction of the nervous system [10]. However, studies on DDVP toxicity effects have often not considered gender and age differences.

Several animal and human studies have reported gender and age differences in the responses of body organs to different exposures (Abad-Díez et al., [11], Ige et al., 2021a; Denise et al., 2023; Ayilara and Owoyele, 2023). Johnstone et al. [12] advocated gender-responsive interventions to address gender-specific challenges. We earlier reported age-related changes associated with DDVP exposure in Wistar rats, showing age-dependent effects on hematological parameters (Ige et al., 2021b). It is known that absorption, distribution, metabolism, and elimination of chemicals could change with age [13]. However, studies mostly focused on drugs, neglecting toxic environmental substances while assessing these toxicokinetic measures. Further insights showing the impact of gender and age on other systems could help to develop specific treatments to manage DDVP exposure in the general population. Therefore, this study aims to investigate the influence of gender and age on liver damage in animals exposed to DDVP.

2. MATERIALS AND METHODS

2.1 Animal Care and Management

Sixty healthy male and female Wistar rats were used in this study. They were kept in polyvinyl wire mesh cages, bedded with wood shavings in the animal house of the Department of Physiology, Ladoke Akintola University of Technology, Ogbomoso, Nigeria. They had free access to food and water, with frequent changes of dirty beddings, under standard laboratory conditions of 12h light and dark cycle. Animals were grouped into twelve major groups of five animals each.

2.2 Experimental Protocol

Sixty male and female Wistar rats with age differences were grouped into 12 major groups of five animals each.

Group A: Control middle-aged male (8 weeks old), not exposed to DDVP.

Group B: An experimental old female (12 weeks old) was exposed to DDVP.

Group C: Control middle-aged female (8 weeks), not exposed to DDVP.

Group D: Control old female (12 weeks), not control to DDVP.

Group E: An experimental young male (4 weeks) was exposed to DDVP.

Group F: Control young female (4 weeks), not exposed to DDVP.

Group G: Control young male (4 weeks), not exposed to DDVP.

Group H: Experimental young females (4 weeks) were exposed to DDVP.

Group I: Control old male (12 weeks), not exposed to DDVP.

Group J: Control middle-aged male (8 weeks), not exposed to DDVP.

Group K: Experimental old males (12 weeks) were exposed to DDVP.

Group L: Experimental middle-aged (8 weeks), were exposed to DDVP.

2.3 Dichlorvos Exposure

Rats in DDVP groups were exposed to DDVP from 8 am to 12 noon for five weeks. Dichlorvos was purchased from an agrochemical shop in Ogbomoso, Oyo state, Nigeria. Preparations and exposure of the animals to dichlorvos were according to the method reported by Edem *et al*., 2012. On each day of exposure, experimental groups in their respective cages were placed in a poorly ventilated compartment. Dichlorvos solution was prepared by mixing 100ml of dichlorvos with 100ml of distilled water. On each day of exposure, dichlorvos solution was freshly prepared.

2.3.1 Animal sacrifice and collection of organ/tissue

The animals were carefully euthanized twenty-four hours after the end of the experiments by

cervical dislocation; the abdomen was opened immediately by vertical incision. Blood samples were collected from the heart into lithium heparin tubes/bottles and plain tubes for liver function tests.

The liver was excised, rinsed in cold normal saline solution, and weighed. Liver tissue was accessed and then cut into two (for biochemical analysis and histological evaluation).

2.4 Biochemical Analysis Procedures

2.4.1 Sample collection

Liver tissues were homogenized in ice-cold phosphate buffer saline (0.01M, pH=7.4). The homogenates are then centrifuged for 5-10 min at 5000×g at 2-8℃ to get the supernatant. Glutamyltransferase (GGT), Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH), Albumin, and conjugated bilirubin were assessed using the commercially available assay kit. Glutathione, Superoxide dismutase, and malondialdehyde were assessed using the method described by Ellman [14] and Colado *et al.* (1997)**.**

2.5 Statistical Analysis

Statistical analysis was done with Graph pad 8.02.263 (GraphPad Software Inc., CA, U.S.A), using two-way ANOVA, followed by Tukey post-Hoc test at significance level of $p<0.05$.

3. RESULTS

3.1 Dichlorvos Exposure Increased Alkaline Phosphatase Levels in Young Female Rats

The effect of age and gender on alkaline phosphatase level was assessed in this study and data obtained were analyzed using two-way ANOVA. As shown in Fig. 1, There is no significant association between the gender and age of the rats exposed to dichlorvos and their alkaline phosphatase across the groups. However, the young-age female rodents showed a significant increase in their Alkaline phosphatase level compared to the control. In addition, between the young-age rats exposed to dichlorvos, there is a significant association between their gender and the level of alkaline phosphatase. This demonstrated the susceptibility of young female rats to a deranged level of ALP upon exposure to dichlorvos.

3.2 Dichlovors Increased ALT Levels in Female Rats

Fig. 2 shows that there is a significant association between gender irrespective of age and the level of ALT following exposure to dichlorvos in this study. This is demonstrated by the significant increase level of ALT across the female groups exposed to dichlorvos when compared to the male groups exposed to ALT. In addition, the young rats showed a gender dimorphic response in their level of ALT as shown by the significant increase in the level of ALT in the young female rats exposed to dichlorvos when compared to the young male rodents.

3.3 AST Level Increased in All the Female Rat Livers Exposed to Dichlorvos

Fig. 3 showed that there is a significant increase in the liver AST levels in the old-age, middle-aged, and young-age female rats exposed when compared to the male rats exposed to dichlorvos. The data also showed that young female rats are more susceptible to an increase in liver AST when compared to young male rats. This demonstrates that gender plays a more significant influence on the AST levels increment following dichlorvos exposure.

3.4 Dichlorvos Exposure Increased Lactate Dehydrogenase in Young Female Rat

Exposure of the rodents in this study to dichlorvos showed no significant increment across all age groups of experimental lactate dehydrogenase when compared to their respective controls except in the experimental young female rats when compared to the control. Evaluation of the effect of gender on lactate dehydrogenase following dichlorvos exposure in Fig. 4, showed that there is no significant increment in LDH levels when between old age male and old age female, middle age male and female. However, young age females showed a significant increment in LDH levels when compared to young age males.

3.5 Dichlorvos Increased Liver Glutamyl Transferase in Young Female Rats

The results obtained for the effect of age and gender on liver glutamyl transferase shown in Fig. 5, showed that there is no significant

increase in liver GGT across all male rats irrespective of their age. The same observation was recorded for old age females and middle-aged females except for the young age female rats. In addition in the young age rats, there is a significant increase in the liver GGT of the female young rats when compared to the male rats.

3.6 Effect of Age and Gender on Albumin Level on Rats Exposed to Dichlorvos

As shown in Fig. 6, there is no significant increase in Albumin levels of male and female rats across all age groups. However, the female rodents across all age groups showed a significant increase in their level of albumin when compared to their male counterparts exposed to dichlorvos except in the middle age groups where the increment is not statistically significant. In addition, the old age female and young age female rodents showed the most increment in their albumin level.

3.7 Conjugated Bilirubin Level Decrease in Young Female Rats Exposed to Dichlorvos

As shown in Fig. 7, there is a significant reduction in conjugated bilirubin levels of young female rodents exposed female rats when compared to its control. However, the young male rats showed an insignificant increase in their level of conjugated bilirubin. In addition, in the old age female rats showed an increase in their conjugated bilirubin level when compared to its control and old-age male rats, albeit statistically insignificant. While the male and female middle-aged rats showed a decrease in their conjugated bilirubin levels when compared to their controls, these observations are not statistically significant across all age groups and genders.

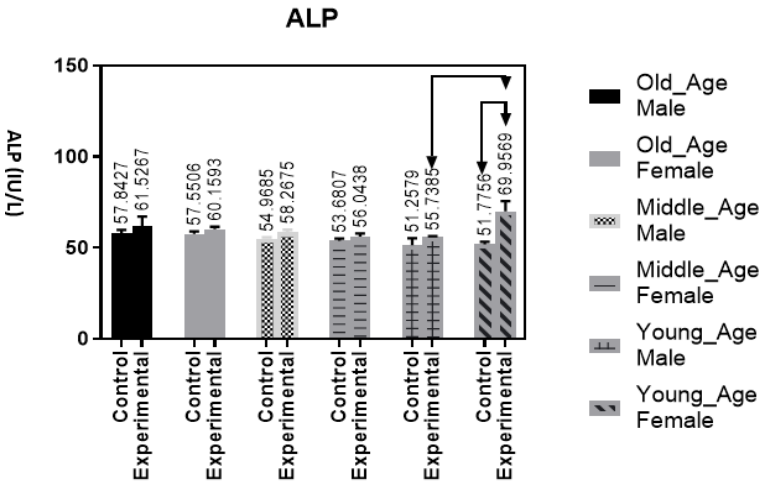


Fig. 1. Dichlovos exposure increased alkaline phosphatase levels in young female rats

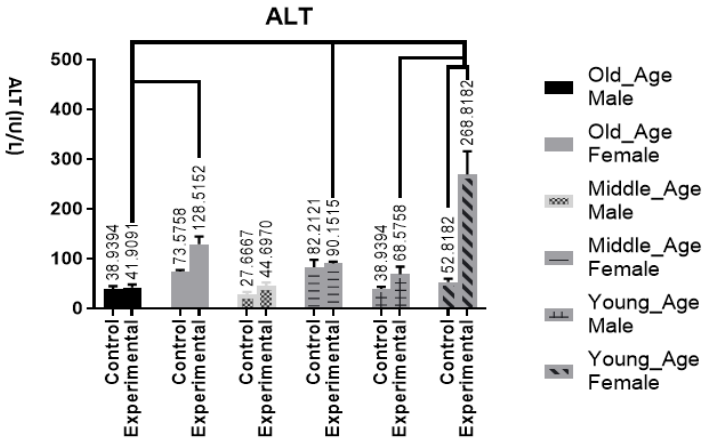


Fig. 2. Dichlovors increased ALT levels in female rats

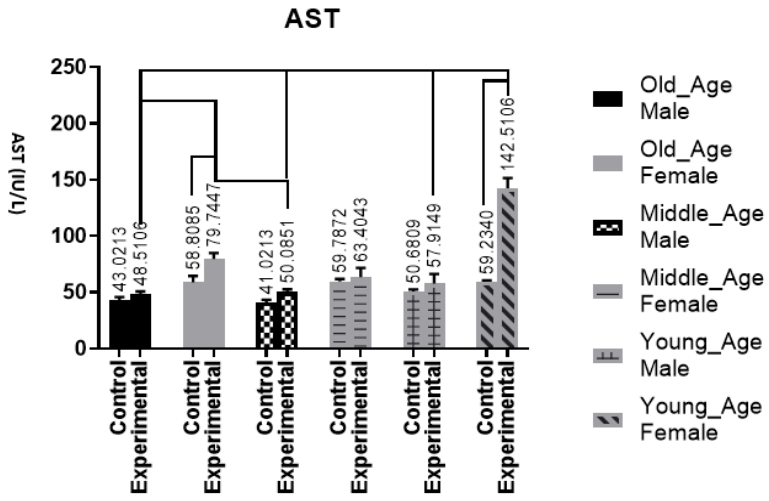


Fig. 3. AST Level increased in all the female rat livers exposed to dichlorvos

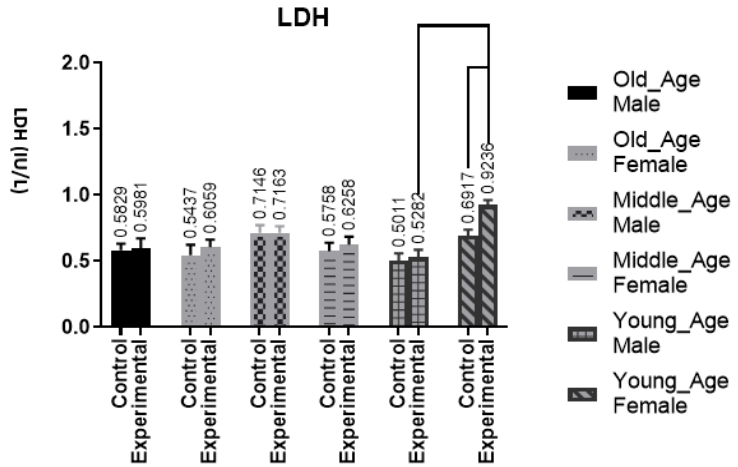


Fig. 4. Dichlorvos exposure increased lactate dehydrogenase in young female rat

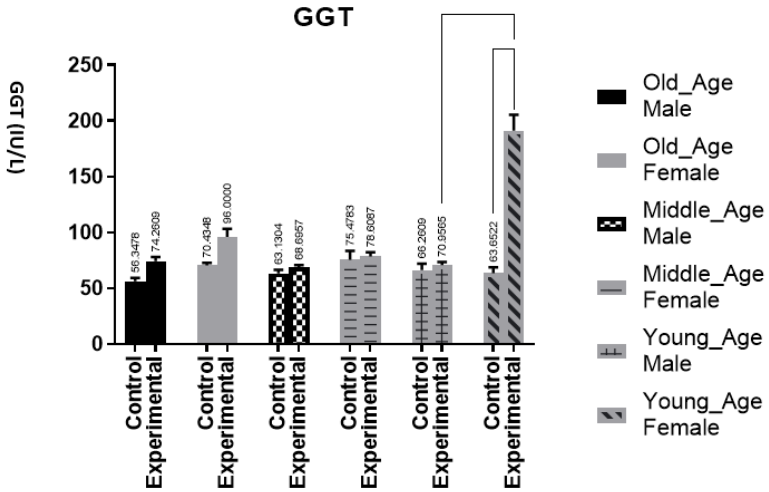


Fig. 5. Dichlorvos increased Liver glutamyl transferase in young female rats

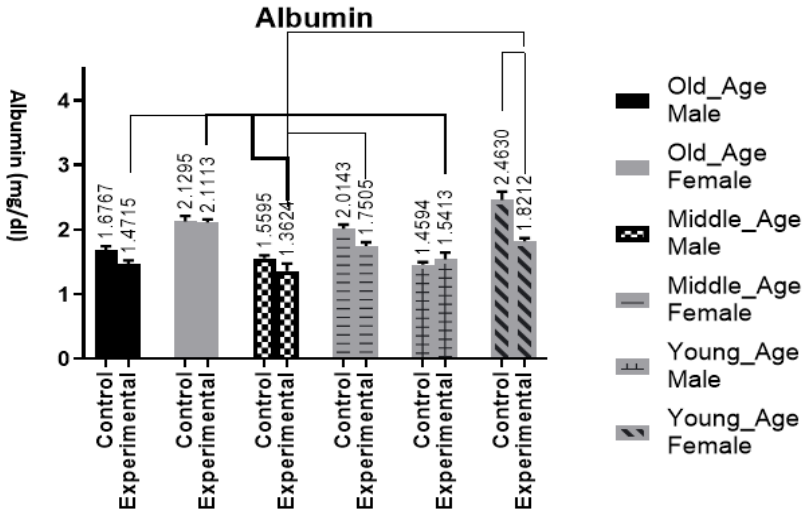


Fig. 6. Effect of Age and gender on Albumin level on rats exposed to dichlorvos

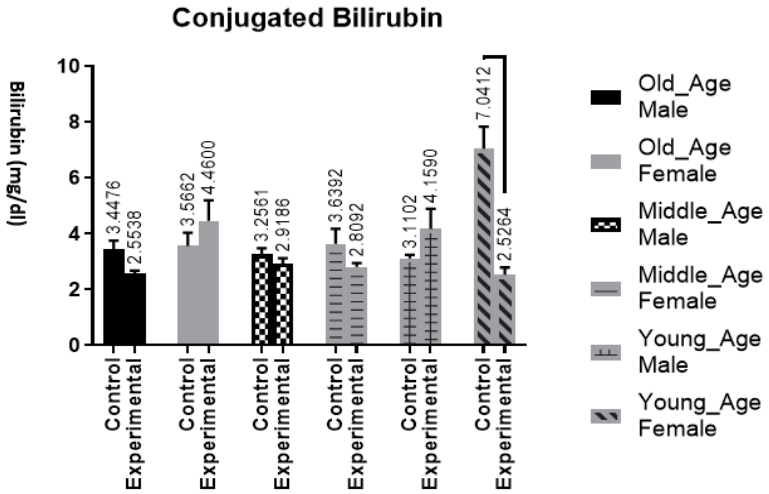


Fig. 7. Conjugated bilirubin level decrease in young female rats exposed to dichlorvos

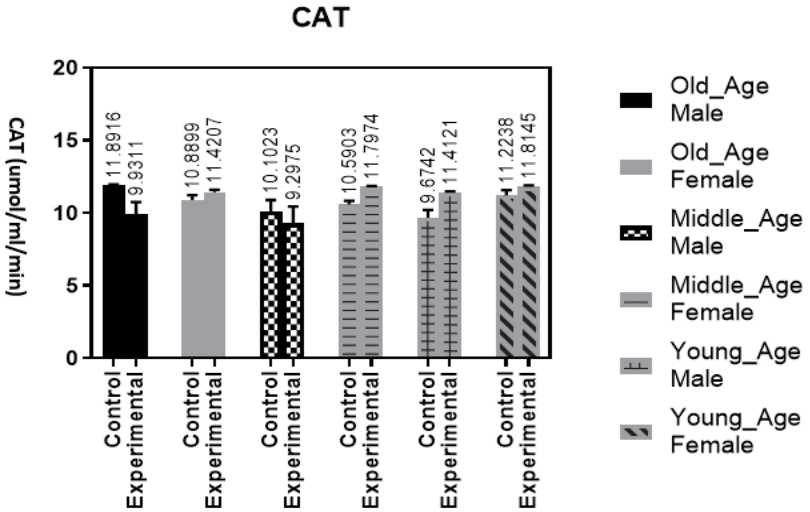


Fig. 8. Effects of gender and age on catalase level in dichlorvos-exposed rats

3.8 Effects of Gender and Age on Catalase Level in Dichlorvos Exposed Rats

The results obtained as shown in Fig. 8 showed that there is an insignificant decrease and increment in catalase levels across in male and female rats exposed to dichlorvos across all age groups. In addition, the female rodents showed an insignificant increase across all age groups when compared to the male who maintained an insignificant decrease in their level of catalase across all age groups. This showed that there is no association between age and catalase level in this study, however, the gender dimorphic difference is statistically insignificant.

3.9 Effect of Age and Gender on Malondialdehyde Level in Rats Exposed to Dichlorvos

As shown in Fig. 9, there is no significance in the level of malondialdehyde between the control and the dichlorvos experimental across all age and gender groups. In addition, the old age male, middle-aged female, and young age rats showed a reduction in their level of malondialdehyde. They showed that there is no significant difference in the level of MDA across all age groups albeit some insignificant increase in the level of MDA in the old age female and middle age male rats exposed to dichlorvos. While the old age females and middle-aged males showed a significant increase in their MDA level when compared to the young age males. This is not enough to conclude a significant association between dichlorvos exposure and MDA level in the rats.

3.10 Dichlorvos Decrease Glutathione Levels in Young Female Rats

Fig. 10 showed that exposure to dichlorvos caused a reduction in glutathione levels in old-age, male middle-aged, and young female rats, although this is insignificant in the old-age and middle-aged male rats, while it is significant in the young-age female rats. The middle-aged female and young age male rats showed an insignificant increase in their glutathione level when compared to their other rodents of the different age groups and genders across the groups. Therefore, across all age groups, an average decrease in glutathione level is observed, however, gender dimorphic differences were not observed for the glutathione level.

3.11 Effect of Age and Gender on Superoxide Dismutase Level Following Rats' Exposure to Dichlorvos

Fig. 11 showed an insignificant increase in the level of superoxide dismutase in male rodents exposed to dichlorvos when compared to their respective controls across all age groups, while, both old age females and young age females exposed to dichlorvos showed an insignificant decrease in their respective superoxide dismutase levels when compared to their control. Depicting the influence of gender difference on superoxide dismutase levels between old age males and young age females. However, the middle age male and female rats exposed to dichlorvos showed an increase in their SOD levels when compared to their controls.

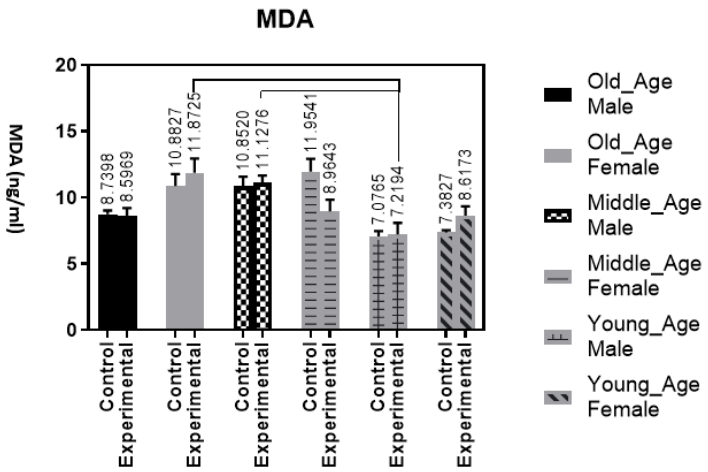


Fig. 9. Effect of age and gender on malondialdehyde level in rats exposed to dichlorvos

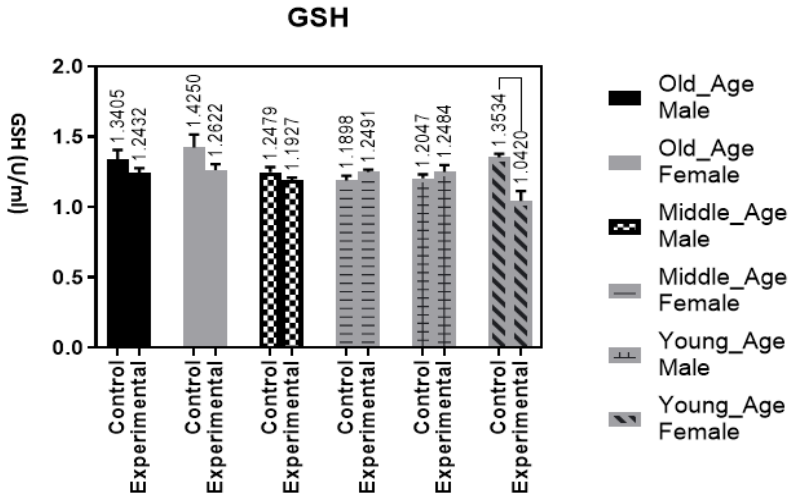


Fig. 10. Dichlorvos decrease glutathione level in young female rat

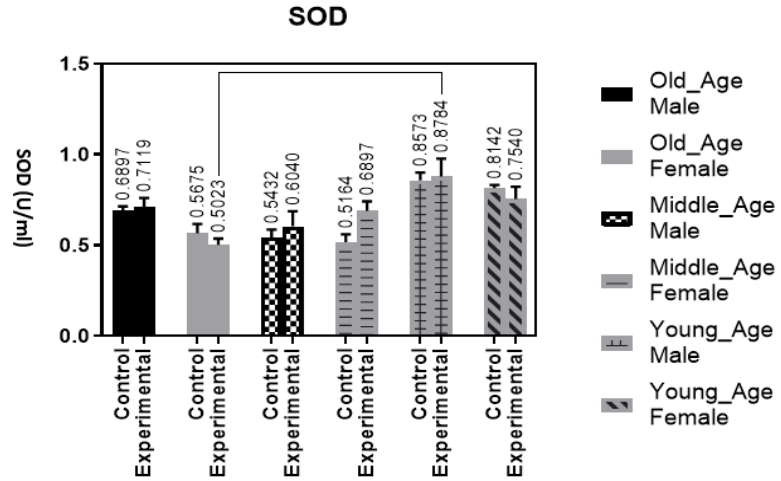


Fig. 11. Effect of age and gender on superoxide dismutase level following rats' exposure to dichlorvos

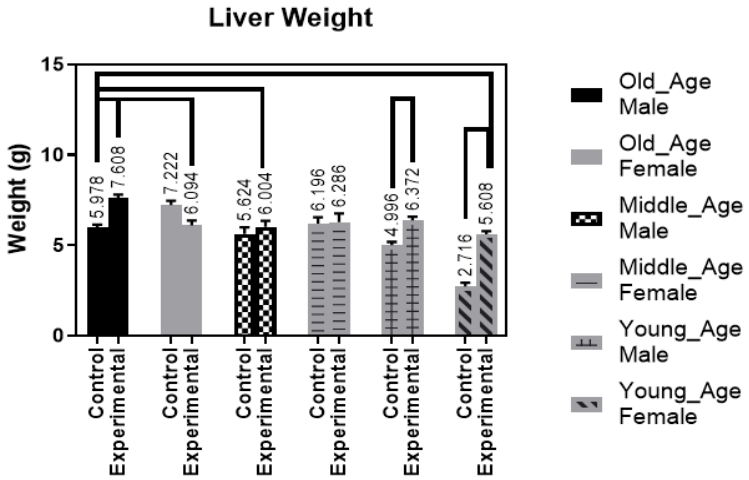


Fig. 12. Effect of age and gender on liver weight after dichlorvos exposure

3.12 Effect of Age and Gender on Liver Weight after Dichlorvos Exposure

Exposure to dichlorvos increased liver weight across all age groups regardless of gender although only Old-age males, middle-aged males and females, young-age males, and females showed a significant increase in liver weight while the old-age females showed an insignificant decrease in their liver weight in this study (Fig. 12). Also, only old-age male females showed a significant influence of gender on their liver weight when compared to other age groups with the old-age males showing a significant increase in liver weight when compared to the old-females with a decrease in their liver weight when compared to their control.

4. DISCUSSION

This study aims to investigate the age and gender effects of dichlorvos exposure in the livers of Wistar rats. The study found that young-age female rodents showed a significant increase in ALP, ALT, AST, GGT, and LDH indicating greater liver damage. Similarly, significant increases in levels of AST and ALT were observed in middle-aged and old-age female rats exposed to dichlorvos. The study also found that conjugated bilirubin levels decreased in young female rats. The assessment of oxidative markers in the liver revealed that female rats reported greater oxidative stress, mostly dominant in the young and old female rats. Additionally, the study observed a significant increase in the albumin level in old age females and young age female rodents. Male rat's livers, regardless of age, were not significantly impacted by dichlorvos exposure. However, dichlorvos exposure increased liver weight across all age groups regardless of gender.

Liver functionality has been assessed by measuring ALT, AST, GGT, and LDH levels. Elevations of these enzymes often denote liver damage and diseases such as hepatocellular disease [15]. In addition, the elevation of the individual enzymes indicates specific diseases. For example, the elevation of GGT is more specific for biliary disease [16] while decreased conjugated bilirubin could indicate drug toxicity [17].

The current study observed the livers of female mice were more susceptible to dichlorvos exposure compared to male rats. Interestingly, there was no observable liver damage in male rats regardless of age. There were similar studies that have found heightened susceptibility in the livers of female rodents. For example, Spruss et al. [18] reported female mice were more susceptible to nonalcoholic fatty liver disease compared to male mice. However, Du et al. [19] reported lower susceptibility of female mice to acetaminophen hepatotoxicity while Mohar et al. [20] also reported that female rodents are more resistant to liver damage. In human studies, however, Lekei et al. [21] reported higher acute pesticide poisoning in adolescent girls and women compared to men.

This study found susceptibility to DDVP poisoning to be age-dependent, with young and old mice more susceptible. In our previous study, we found a similar pattern in the effect of DDVP on hematological parameters with young and old rats reported to be more affected [22]. Other animal and human studies have acknowledged old age to be a risk factor for liver diseases. For example, Georgieva et al. [23] showed old age to be a risk factor for drug-induced injury in humans and recommended nutritional and pharmacological strategies for managing elderly liver diseases. Indeed, we previously reported the ethnopharmacological property of *Allium cepa* in ameliorating Cd-induced hepatic damage [22,23]. Furthermore, Cogger et al. [24] corroborated our findings by reporting the impaired liver regeneration seen in older people and animal models. Meng et al. [25] reported liver damage susceptibility among younger children compared to adults. This could be because the liver is still in its developmental stage, explaining the susceptibility observed in young female rats used in our study [26,27].

With the limitations in conducting liver disease research in humans due to ethical and high-cost issues, animal studies continue to be relevant in investigating possible mechanisms of liver damage by environmental pollutants. Although Spruss et al. (2012) has implicated increased acute phase PAI-1 in the liver of female rodents as the reason for female susceptibility to chemical insults, it is not yet clear why male rodents are more protected. In our future studies, we will elucidate molecular mechanisms underlying the protection of male rats against DDVP exposure. Pretreatment of male rats with estradiol could explain the cause of higher susceptibility in females found in our study. We will further investigate the possible reasons

middle-aged rats were resistant to liver damage induced by DDVP [28,29].

5. CONCLUSION

Our study showed that DDVP exposure caused liver damage in female rats only while the male rats showed more resistance. The liver damage observed in female rats was age-dependent, with young and old rats showing higher susceptibility. Nutritional and pharmacological strategies are recommended to mitigate the effect of DDVP exposure, particularly in populations at higher risk of exposure.

HIGHLIGHT

1. Gender and Age-Dependent Susceptibility: The study reveals that exposure to Dichlorvos (DDVP) led to liver damage primarily in female rats, with males showing greater resistance. This susceptibility was found to be age-dependent, with young and old female rats being more vulnerable.

2. Liver Enzyme Levels: DDVP exposure resulted in significant increases in liver enzyme levels such as ALT, AST, GGT, and LDH in female rats, particularly in young and old age groups. This indicates severe liver damage in female rats compared to males.

3. Biochemical Markers of Liver Damage: The study examined various biochemical markers of liver damage and found significant alterations in levels of alkaline phosphatase (ALP), ALT, AST, GGT, and LDH in female rats exposed to DDVP.

4. Oxidative Stress and Antioxidant Status: Evaluation of oxidative markers showed increased oxidative stress in female rats, especially in young and old age groups. This was reflected in decreased levels of antioxidants like glutathione and superoxide dismutase.

5. Liver Weight Increase: DDVP exposure led to an increase in liver weight across all age groups, indicating a physiological response to toxicity. However, this increase was more pronounced in male rats.

6. Age and Gender-Specific Responses: Young and old female rats exhibited the most significant alterations in liver parameters following DDVP exposure, highlighting age-specific susceptibility. Furthermore, gender-specific differences were observed in enzyme levels and oxidative stress markers.

7. Implications for Human Health: The findings suggest potential health risks associated with DDVP exposure, particularly for specific demographic groups such as young and elderly females. Nutritional and pharmacological strategies are recommended to mitigate these effects.

Overall, the study provides valuable insights into the gender and age-dependent effects of DDVP exposure on liver health in rats, emphasizing the importance of considering these factors in toxicological research and risk assessment.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

CONSENT

It is not applicable.

ETHICAL APPROVAL

The animal caring procedure was examined and approved by the ethical committee, Faculty of Basic Medical Sciences, LAUTECH, Ogbomoso, Oyo State Nigeria. Principles of laboratory animal care (NIH publication No. 8523, revised 1985) were also followed.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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