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Biochemical Foundations of Insecticide Resistance in Culex Mosquitoes from Minna, Nigeria: A Focus on Glutathione-S-Transferase and Protein Dynamics

Timileyin Joshua Oluwadepo [1, *], Ferdinand Ekeh [2], Nashima N. Tarnongu [3], Ayodeji Ibraheem [4], Bassey Jeremiah Usang [5], Joshua Tsado Vatsa [6] and Hassan Abdulsalam Adewuyi [6]

[1] *Department of Public Health, Texila American University, Guyana.*
[2] *Department of Sociology, University of Ibadan.*
[3] *Department of Community Medicine Primary Health Care, Bingham University.*
[4] *EHESP-Ecole des hautes etudes en santé publique.*
[5] *GEONALTECH LTD/GTE.*
[6] *Department of Biochemistry, Federal University of Technology Minna PMB 65 Niger State.*

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Abstract

The escalating challenge of insecticide resistance among mosquito populations presents a substantial obstacle to managing disease vectors across sub-Saharan Africa. This research delves into the biochemical foundations of this resistance in Culex mosquitoes collected from Minna, Nigeria, paying specific attention to shifts in protein levels and the activity of the detoxification enzyme glutathione-S-transferase (GST) after exposure to standard insecticides. Larvae gathered from the field were reared to adulthood and then subjected to standardized susceptibility tests using six different insecticides. We then used spectrophotometric techniques to compare the total protein concentration and GST enzyme activity between mosquitoes that survived the exposure (resistant) and those that died (susceptible). Our findings revealed that mosquitoes which survived insecticide exposure displayed a marked increase in GST activity, especially following contact with pyrethroid-based insecticides. Conversely, higher protein concentrations were consistently observed in the deceased mosquitoes, which may indicate that oxidative stress and associated protein damage are factors in their mortality. The pronounced rise in GST activity among the survivors strongly suggests that an enhanced capacity for detoxification is a critical mechanism enabling resistance in these Culex populations. This study underscores the value of biochemical markers in tracking resistance and offers crucial baseline information for guiding insecticide resistance management strategies in Nigeria. We recommend that ongoing surveillance of enzyme activity be incorporated into vector control initiatives to help design more effective interventions and prolong the usefulness of existing insecticides.

Keywords: Culex Mosquitoes; Insecticide Resistance; Glutathione-S-Transferase; Detoxification Enzymes; Metabolic Detoxification; Nigeria; Public Health Entomology

1. Introduction

Illnesses transmitted by mosquitoes continue to be some of the most urgent public health issues worldwide. In this context, Culex mosquitoes are significant vectors for pathogens causing lymphatic filariasis, West Nile virus, and various other arboviral diseases [1,2]. Within Nigeria, where such vector-borne illnesses are persistently common, Culex quinquefasciatus is notably widespread and medically important [3]. The primary strategy for controlling these mosquitoes has long relied on chemical insecticides. However, this dependence has led to the widespread emergence of resistance, significantly undermining the success of control programs [4].

*Corresponding author: Timileyin Joshua Oluwadepo

Insecticide resistance in mosquitoes can develop through several pathways. These include behavioral changes that help mosquitoes avoid contact with insecticides, genetic mutations at the target site of the insecticide, reduced penetration of the insecticide through the cuticle, and metabolic detoxification [5,6], where enzymes break down the toxin before it can cause harm. Among these, metabolic detoxification by enzyme systems such as cytochrome P450 monooxygenases, esterases, and glutathione-S-transferases (GSTs) is particularly crucial. These enzymes can neutralize or sequester insecticides, preventing them from reaching their intended targets [7]. Elevated GST activity, in particular, has been frequently linked to resistance against organochlorines and pyrethroids. These enzymes are also known to detoxify harmful by-products of lipid peroxidation caused by insecticide exposure and can even contribute to cross-resistance between different classes of insecticides [8]..

Protein metabolism offers another window into the physiological stress induced by insecticide exposure. Research indicates that resistant mosquitoes often preserve protein homeostasis through efficient detoxification processes. In contrast, susceptible or dead mosquitoes tend to show an accumulation of protein, which may be tied to oxidative damage and a breakdown in metabolic balance [9]. Despite the clear importance of these mechanisms, there is a scarcity of biochemical data connecting GST activity and protein profiles to resistance in Nigerian Culex populations, which are under constant insecticide pressure from both public health and agricultural practices [10].

This study was therefore designed to explore the biochemical basis of insecticide resistance in Culex mosquitoes from Minna, Nigeria. We quantified glutathione-S-transferase activity and protein concentrations in resistant and susceptible individuals following exposure to a range of insecticides. By correlating these enzymatic activities with survival outcomes, our work provides foundational insights into the resistance mechanisms at play, which can inform the development of more effective vector control and resistance management programs in the region.

2. Materials and Methods

2.1. Study Location and Mosquito Collection

The early life stages(larvae and pupae) of Culex mosquitoes were gathered from diverse breeding sites in Minna, Niger State, Nigeria, adhering to World Health Organization (WHO) standard procedures using collection dippers. Sampled locations included rice fields, drainage gutters, streams, temporary rain pools, dams, and water collected in discarded tires. The collected larvae were carefully transported in clearly labeled plastic containers, filled with water from their original habitat, to the insectary at the Department of Biochemistry, Federal University of Technology, Minna. Here, they were reared under controlled environmental conditions until they reached the adult stage. The resulting adult mosquitoes were sustained on a 10% sucrose solution and identified by genus and species using established morphological keys [1].

2.2. Insecticide Susceptibility Testing

Adult female mosquitoes,aged 3–5 days and not having taken a blood meal, were used for WHO susceptibility tube tests. We evaluated a total of six insecticides, representing four major chemical classes:

- Organochlorine: DDT (4%)
- Pyrethroids: Permethrin (0.75%) and Deltamethrin (0.05%)
- Organophosphates: Malathion (5%) and Pirimiphos-methyl (0.25%)
- Carbamate: Bendiocarb (0.1%)

For each bioassay, 25 mosquitoes were placed in a test tube, with four replicates conducted for every insecticide. A control group was exposed to untreated papers. The exposure period was one hour, during which knockdown was recorded at ten-minute intervals. Mosquitoes that survived this period were transferred to holding containers, provided with sucrose solution, and held for 24 hours before a final mortality count was taken. Individuals that died and those that survived were separated and stored for subsequent biochemical analysis.

2.3. Preparation of Mosquito Homogenates

For the biochemical assays,pools of 10 mosquitoes (either all dead or all alive) from each insecticide treatment group were homogenized together in a chilled glass homogenizer containing 1.0 ml of a 0.1 M phosphate buffer solution. The resulting homogenates were then centrifuged at a high speed and low temperature to separate solid debris. The clear supernatant (the liquid fraction) was carefully extracted and used for measuring both protein concentration and enzyme activity [3].

2.4. Protein Concentration Determination

The total protein content in the mosquito homogenates was measured using the well-established Lowry method,with bovine serum albumin serving as the protein standard. The absorbance of the samples was read at a specific wavelength, and protein concentrations were calculated and expressed in milligrams per milliliter (mg/ml).

2.5. Glutathione-S-Transferase (GST) Activity Assay

The activity of the GST enzyme was determined using 1-chloro-2,4-dinitrobenzene(CDNB) as the substrate. The assay procedure monitors the rate at which the enzyme conjugates CDNB with reduced glutathione (GSH), a reaction that produces a measurable change in absorbance. The reaction mixture included phosphate buffer, the CDNB substrate, reduced glutathione, and a sample of the mosquito homogenate to initiate the reaction. The change in absorbance was tracked for five minutes, and GST activity was calculated and reported in units of micromoles of CDNB conjugated per minute per milligram of protein (µmol/min/mg protein).

2.6. Statistical Analysis of Data

All data were processed and analyzed using SPSS statistical software.The results for protein concentration and GST activity are presented as the mean value plus or minus the standard error of the mean (SEM). To determine the statistical significance of the differences observed between the resistant (surviving) and susceptible (dead) mosquito groups, we employed Student's t-test and one-way analysis of variance (ANOVA). A probability value of less than 0.05 ($p < 0.05$) was considered statistically significant.

3. Results

3.1. Protein Levels in Resistant and Susceptible Mosquitoes

We measured and compared protein concentrations in both deceased(susceptible) and surviving (resistant) Culex mosquitoes after their exposure to the six insecticides. A consistent pattern emerged across all insecticide groups: the dead mosquitoes exhibited significantly higher protein concentrations than the survivors. The most pronounced difference was seen in mosquitoes exposed to DDT, where the protein level in dead individuals was nearly double that of the survivors. In contrast, the lowest protein concentrations overall were recorded in mosquitoes from the permethrin exposure group.

Table 1 Protein concentrations (mg/ml) in dead and surviving Culex mosquitoes after insecticide exposure

Insecticide	Dead (Susceptible) Mean ± SEM	Surviving (Resistant) Mean ± SEM
DDT (4%)	5.68 ± 0.15	3.12 ± 0.10
Permethrin (0.75%)	3.95 ± 0.09	2.41 ± 0.07
Deltamethrin (0.05%)	4.22 ± 0.11	2.88 ± 0.08
Malathion (5%)	4.87 ± 0.13	3.04 ± 0.09
Pirimiphos-methyl (0.25%)	4.75 ± 0.12	2.96 ± 0.10
Bendiocarb (0.1%)	4.12 ± 0.10	2.71 ± 0.08

Values represent the mean ± SEM. Protein levels were statistically significantly higher in dead mosquitoes for all insecticides ($p < 0.05$).

3.2. Glutathione-S-Transferase (GST) Activity

The analysis of GST activity revealed a striking and opposite trend.Mosquitoes that survived insecticide exposure demonstrated substantially higher GST activity compared to those that died. This elevation was most prominent in survivors of pyrethroid exposure (permethrin and deltamethrin), which showed the highest enzyme activity levels of all the groups. Survivors from organophosphate exposures also displayed significantly elevated GST activity compared to their deceased counterparts, though the levels were not as high as those induced by the pyrethroids.

Table 2 Glutathione-S-transferase (GST) activity in dead and surviving Culex mosquitoes after insecticide exposure

Insecticide	Dead (Susceptible) Mean ± SEM (µmol/min/mg protein)	Surviving (Resistant) Mean ± SEM (µmol/min/mg protein)
DDT (4%)	254.6 ± 8.3	498.4 ± 10.2
Permethrin (0.75%)	276.5 ± 9.1	713.3 ± 12.5
Deltamethrin (0.05%)	289.4 ± 9.5	728.0 ± 11.9
Malathion (5%)	268.3 ± 8.9	615.7 ± 12.1
Pirimiphos-methyl (0.25%)	261.9 ± 8.6	602.4 ± 11.5
Bendiocarb (0.1%)	247.7 ± 8.0	495.6 ± 10.4

Values represent the mean ± SEM. GST activity was statistically significantly higher in surviving mosquitoes for all insecticides ($p < 0.05$).

3.3. Interpretation of Key Findings

The collective results paint a clear biochemical picture.The elevated protein concentrations found in dead mosquitoes suggest that insecticide exposure inflicts significant physiological stress, potentially leading to oxidative damage and the accumulation of damaged proteins that disrupt cellular function. On the other hand, the survivors not only maintained lower protein levels possibly indicative of more efficient protein turnover and repair—but also possessed a greatly enhanced capacity for detoxification, as evidenced by their high GST activity. This robust enzymatic response, particularly to pyrethroids, appears to be a cornerstone of the resistance mechanism in these Culex populations from Minna.

4. Discussion

The evidence from this investigation strongly supports the conclusion that resistance to insecticides in Culex mosquitoes from Minna, Nigeria, is closely associated with increased activity of the glutathione-S-transferase (GST) enzyme and distinct changes in protein metabolism. The markedly higher GST activity in mosquitoes that survived exposure, especially to pyrethroid insecticides, indicates that an enhanced detoxification system is a fundamental adaptation driving resistance in this local population.

GSTs are versatile enzymes that facilitate the conjugation of glutathione a potent cellular antioxidant to a wide array of toxic compounds, including insecticides and the harmful oxidative by-products they generate [1]. Their documented role in conferring resistance to multiple insecticide classes is well-aligned with our findings[2,3]. The sharp rise in GST activity following pyrethroid exposure observed in our study is consistent with reports from other parts of Africa, where similar metabolic adaptations have been linked to pyrethroid resistance in both Culex and Anopheles mosquito species [4,5].

In the Nigerian context, while previous studies have hinted at metabolic resistance, our work provides quantitative, biochemical confirmation that GST upregulation is a key factor, particularly in response to the pyrethroids that are extensively used in public health initiatives like insecticide-treated nets [6]. The higher protein concentrations we observed in dead mosquitoes likely reflect a failure of their metabolic systems. Insecticide exposure can induce oxidative stress, leading to protein denaturation and aggregation; without sufficient detoxification capacity, this damage accumulates, ultimately leading to death. In contrast, resistant mosquitoes appear to manage this stress more effectively, maintaining protein homeostasis, possibly through a combination of efficient detoxification and robust protein repair or recycling mechanisms [7].

The patterns of resistance identified in Minna are not isolated. Similar biochemical mechanisms, including elevated GST activity, have been reported in Culex populations in Ghana, Tanzania, and Kenya, and are recognized as a global phenomenon [8]. This consistency underscores that metabolic resistance is a widespread and evolutionarily convergent response to intense insecticide selection pressure [9].

From a practical standpoint, the dominance of GST-mediated detoxification has critical implications for vector control. The continued and often exclusive reliance on pyrethroids is likely fueling this specific resistance pathway [10]. Furthermore, because GSTs can contribute to cross-resistance, their activity can diminish the effectiveness of other

insecticide classes, thereby shrinking the available toolkit for mosquito management [11]. To combat this, it is imperative to integrate biochemical monitoring, such as regular assays for GST activity, into existing surveillance programs. The data generated can then guide the implementation of scientifically sound resistance management strategies [12,13]. These should include rotating insecticides with distinct modes of action, using synergists like piperonyl butoxide (PBO) that can inhibit detoxification enzymes and restore susceptibility, and advocating for the development of novel insecticidal compounds that are less vulnerable to these metabolic breakdown processes [16].

We acknowledge that this study focused primarily on GST and protein profiles. A more comprehensive picture would require also assessing other key detoxification enzymes like cytochrome P450s and esterases, as well as investigating the molecular genetics underlying resistance (e.g., specific gene mutations) [17]. Future research in this direction, combined with longitudinal studies and field trials of synergist-based interventions, will be vital for strengthening Nigeria's overall approach to managing insecticide resistance.

5. Conclusion

This research demonstrates a clear biochemical distinction between insecticide-resistant and susceptible Culex mosquitoes from Minna, Nigeria. Resistance is strongly linked to a significant increase in glutathione-S-transferase (GST) activity, which provides a enhanced detoxification capability, particularly against pyrethroid insecticides. Conversely, susceptibility and mortality are associated with higher levels of protein accumulation, likely a consequence of unmet oxidative stress and cellular damage. These findings confirm that GST-mediated detoxification is a central mechanism driving insecticide resistance in this region and highlight the critical need to monitor these biochemical traits to inform and improve vector control strategies.

Recommendations

Based on the findings of this study, the following actions are recommended:

- Enhance Resistance Monitoring: Incorporate biochemical assays, specifically the measurement of GST activity, into routine mosquito resistance surveillance programs to provide an early warning of developing metabolic resistance.
- Implement Insecticide Rotation: Develop and enforce policies for the strategic rotation of insecticides used in public health, ensuring that different classes with distinct modes of action are used in sequence to reduce selection pressure for any single resistance mechanism.
- Adopt Synergist-Based Tools: Promote and deploy insecticide formulations that include synergists like piperonyl butoxide (PBO), which can inhibit detoxification enzymes and help overcome metabolic resistance, thereby restoring the efficacy of existing insecticides.
- Expand Research Scope: Future studies should be expanded to include molecular analyses (e.g., identifying specific GST gene polymorphisms and kdr mutations) to build a more complete genetic and biochemical understanding of resistance in Nigerian mosquito populations.
- Foster Integrated Pest Management (IPM): Encourage a cross-sectoral approach that regulates and rationalizes insecticide use in both agriculture and public health to minimize the overall selection pressure and slow the development of cross-resistance.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors affirm no competing financial interests or personal relationships that could influence this work.

Statement of ethical approval

This study involved the collection of mosquitolaevae from various aquatic habitats. This study did not involve the use of human participants, formal ethical approval and informed consent were not required. Access to public drainage system and pre-urban areas was conducted in accordance with local guidelines.

The study utilizes mosquito larva and adults. Rearing and morphological identification of adult mosquitoes are in standard entomological procedures and are not subjected to specific animal welfare regulations for invertebrates in Nigeria.

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Author's contributions

Authors TJO conceived the study. FE, TJO participated in the design and quality assessment of the study. Author NNT and TJO took part in the selection and extraction of the plant samples used. Author AI and TJO reconstituted the chemicals/reagents used, as well as carried out the experiment, with the assistance of the Laboratory Technologists. BJU, JTV and HAA carried out the statistical analysis and drafted the manuscript, with significant input from TJO. All authors proofread the manuscript and made inputs. All authors approved the final manuscript for publication.

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