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Effects of Antimalarial Drugs on the Motor and Behavioral Programs in *Drosophila melanogaster*

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ABSTRACT

Anti-malarial drugs have been used for the control and prevention of malarial in several developing countries including Uganda. However, these drugs have been shown to cause neurological damage in laboratory animals thus there is need to study the safety of newly developed Artemisinin-Based Combination Therapies (ACT's) in Uganda. The objective of the study was to assess motor and behavioral effects of selected anti-malarial drugs in *Drosophila melanogaster*. Anti-malarial drugs (Fansidar, Chloroquine, Artesunate, Mefloquine and Quinine) were fed on starved *Drosophila melanogaster* wild type flies on filter paper for a period of 60 minutes. The grooming-aggression, feeding and locomotion assay were performed in triplicate and One way ANOVA was performed. Artesunate showed the highest aggressive and grooming behavior (P=0.021). Generally female flies fed faster (P = 0.000) than male flies and the Artesunate group (P = 0.001). The mean performance index for locomotion was shown to be highest in female *Drosophila* flies in the study 011. Artesunate. Mefloquine showed the lowest mean performance index of 0.31 in male Drosophila flies. In between group comparisons showed there was a strong significant (P =0.000) in the male flies compared to the females (P = 0.584). Anti-malarial drugs especially Artesunate had significant effects on feeding, grooming, aggression and locomotion behaviour in drosophila melanogaster through its interaction with specific neurotransmitters and neurons in the brain that are responsible for expression of behaviour. Mefloquine reduced the locomotion activity of these flies. Although Artesunate has shown increased effect on behavior in flies, the molecular mechanism of these effects should be studied in depth using the available genetic tools in *Drosophila*.

Keywords: Drosophila melanogaster, Anti-malarial drugs, Behavior, Feeding, Aggression

INTRODUCTION

Malaria is a febrile mosquito-borne infection classically characterized by periodic chills, rigors, and high fevers followed by profuse sweating. It is caused by one of the four species of the malarial parasite *Plasmodium* (i.e. *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodiumovale*, *Plasmodium malariae* and *Plasmodium knowleesi* with *P. falciparum* being the commonest cause of Malaria in Africa [1, 2]. In 2013, malaria caused an estimated 584,000 deaths globally. There were an estimated 249 million cases of malaria in 2022, and the estimated number of malaria deaths stood at 608,000 globally. African Region was home to 94% and 95% of the malaria cases and deaths, respectively. Children under 5 years of age are the most vulnerable group affected by malaria; in 2022, they accounted for nearly 80% of all malaria deaths in the African Region [2, 3, 4]. In Uganda, the situation with malaria reflects that of other countries in Sub-Saharan Africa facing a high burden of the disease. Malaria is endemic in over 95% of the country and in the remaining highland areas, transmission is unstable and epidemic-prone [5, 6]. Malaria is the leading cause of morbidity and mortality in Uganda, accounting for 30–50% of outpatient visits and 15–20% of hospital admissions [7]. Malaria, if not treated with immediate effect, is likely to cause organ damage, progress to the central nervous system, and may have a lasting effect on cognition, behavior, and performance in children, or even result in death. It is becoming clear that many episodes of malaria may have a long-term neurological impact that significantly affects a child's development and later life [8, 9]. It is because of malaria that various anti-malarial drugs have come into existence, with quinine being the first anti-malarial drug, a drug discovered from the bark of a cinchona tree. This discovery paved the way for the discovery of many other synthetic antimalarial drugs, these include quinoline anti-malarial drugs like chloroquine, mefloquine, and primaquine [10, 11].

Artemisinin Combination Therapies (ACTs) which were later discovered in 1970s from a Chinese herb, *Artemisinin annua* are now considered the safest and most effective anti-malarial drugs recommended by WHO as first-line treatment for uncomplicated malaria [12, 13]. However, a study reported hearing impairments as a neurological effect in humans caused by artemisinin-based combination therapy and injury to parts of the brain involved in hearing and balance in rodents [14]. Central nervous system toxicity and a risk of permanent neuronal degeneration within specific regions within the brain including the brainstem has also been associated with number of historical quinoline anti-malarial drugs [15]. This has been attributed to their long half-life in the body [16], high lipophilicity [17], and their ability to cross the blood-brain barrier and cause lesions in the brain [18, 19]. Despite the documented evidence of CNS side effects caused by some of the anti-malarial drugs, they are still on the market and are still being recommended for use in the prophylaxis and treatment of malaria infections in Africa and many other parts of the world. In Uganda, where drug safety is rarely monitored, younger children are at greater risk of getting malaria and may receive anti-malarial drugs three or more times a year [20]. Therefore, this study aims to evaluate the effects of anti-malarial drugs on the neurons controlling the motor and behavior programs in the brain of *Drosophila melanogaster*, since the brain of the adult fly is quite remarkable consisting of more than 100,000 neurons that form discreet circuits and neuropil that mediate complex behaviors, including circadian rhythms, sleep, learning and memory, courtship, feeding, aggression, grooming, and flight navigation. Significantly, the response of flies to many drugs that act within the CNS is similar to the effects observed in the mammalian system [21, 22, 23, 24, 25]. It has been estimated that nearly 75% of disease-related genes in humans have functional orthologs in the fly [26]. Moreover, *Drosophila melanogaster* is a cheap animal model, easy to maintain and genetic manipulation techniques can easily be applied to it [27].

METHODOLOGY

Area of study

This research took place in the Institute of Biomedical Research Laboratory of Kampala International University, located in Ishaka, Bushenyi District.

Study Design

The study design was experimental with control positive (P), control negative (N) and the experimental group (D).

Fly Strain

The wild white strain of *Drosophila melanogaster* was used for the study, 12-hour light and 12-hour dark cycle at room temperature before the experiment

Chemicals and reagents

Agar, yeast, wheat flour, blue color, apple juice media, water, glucose, nipagin, propionic acid, ethanol, and ether

Preparation of fly food

Ingredients were dissolved in 1 liter of water and boiled extensively on a hotplate until all ingredients were dissolved. Propionic acid (a mold inhibitor) was added. The media was poured into 175 mL bottles, and it was allowed to solidify. A large drop of live baker's yeast was added to the surface of the medium in each bottle. Each of the bottles was plugged with cotton wool.

Drugs

Sulfadoxine-pyrimethamine, Artesunate, Mefloquine, Quinine and Chloroquine.

Equipment

Digital camera, Brush, Petri dishes, microscope, plastic transparent vials, funnel, volumetric flasks, measuring cylinders, incubator, refrigerator, micropipettes, test tubes, stop cloak, chromatographic paper, cotton wool, graduated tubes (30cm) long, thermometer, and dark chamber.

Fly Preparation for Experiments.

Flies from the culture bottles were transferred to empty bottles 12 hours before the experiment. A cotton plug that was estimated to be of the same size as the bottleneck was soaked with ether. The bottle containing the flies was gently tapped on the table so that the flies fell to the bottom and the cotton plug was quickly replaced by a plug with ether. The cotton plug was removed soon after all the flies had been anesthetized using a microscope the flies were sorted according to sex, (male and female). Five flies of the same sex were placed in a vial using a brush with soft bristles to avoid injuring the flies.

Analysis of the effect of drugs

Vials containing female flies were labeled F and those containing males were labeled M. Foreach experimental setup, a group of 4 vials each containing 2 vials with male flies and two vials with female flies was made for each of the 3 experimental setups, i.e. the control positive (P), control negative(N), and the experimental group(D). The flies were starved for about 12 to 16hours.

Drug Administration

Fragments of Whatmann chromatographic filter paper of 2.5cm length and 1cm width were made and kept in a dry environment. A stock solution of 5% glucose was prepared and kept in the refrigerator. The drug to be tested was dissolved in a 5% glucose solution. A serial dilution to make concentrations of the dmg that was equivalent to the dose taken by a human being was made. Using a filter paper, a specific calculated amount of drug was dispensed onto the filter paper ensuring that it was adequately wetted. The starved flies were introduced into a vial containing the drug on filter paper. The flies were allowed to feed on the drug for 60 minutes.

Assays

i. Climbing Assay

The flies were aspirated and introduced into a graduated tube (pipette) about 30 cm long. The tube was tapped on the table so that all the flies fell to the bottom. The number of flies that were at the uppermost (U), middle-upper (M), and lower region (L) were recorded in one minute as by (Baiton*et al*., 2002). The procedure was then repeated 3 times for consistent results. The performance index was calculated.

Performance index= (U-L)/T

Where U = number of flies at the uppermost region

L= number of flies in the lower region

T =total number of flies

ii. Feeding assay

Already sorted female and male flies were transferred to empty vials after feeding on the drug for 30 minutes. The flies were then left without food for about 3 hours and then put m transparent vials containing food. The assay occurred with minimum noise and disturbance. A 30-minute gap was allowed before commencing the experiment. A feeding event was scored when a fly touched the food surface while performing a bobbing motion as described by Wong *et al*., 2009. This experiment was performed for 90 minutes and the number of flies feeding was recorded every 5 minutes.

For statistical analysis and comparisons, feeding data was expressed as a proportion by the experimental group = sum of scored feeding events divided by the total number of feeding opportunities.

Feeding opportunities = number of flies per vial x number of flies m a group x number of observations.

Feeding data = feeding event/ feeding opportunities.

iii. Aggression assay

Preparation of dark chambers for aggression study similar to those used by Hoffman *et al.*[28], i.e. 50mm Petri dishes top and bottom separated by a 20mm high spacer (50mm diameter and20mm height) was done. The bottom of the chamber was filled with 2% agar to moisturize the chamber. A food patch 5mm in diameter and 6 mm high was positioned at the center containing a mixture of 2% minced agar, apple juice, syrup, and yeast suspension as described by Reif *et al* [29]. Six males that had been given the drug and 3 females not exposed to the drug were introduced into the Petri dish containing the food patch. The Petri dish was put in the dark chamber and the camera was switched on and focused on the food patch. The experiment went on for about 1 hour recording every activity.

Behavior scoring

Only male-male interactions were classified as either aggressive or non-aggressive as defined by Hoffman [28]. Encounters that contained boxing, head butting, lunging, wrestling, tussling, charging, and chasing behaviors [28, 30, 31, 32, 33] were also classified as aggressive. The experiment was allowed to go on for about 30 minutes with control positive and control negative going through the same procedure.

Data entry and analysis

Statistical package for Social Sciences software (SPSS) was used for calculating the mean and standard deviation (SD), and one-way analysis of variance (ANOVA) with p-value < 0.05 was used to determine the level of significance. Tables and graphs were also used to present the data.

Ethical considerations

The research project was approved, by the examination committee of the School of Pharmacy. The *Drosophila melanogaster*, the animal model that was used for this study could not transmit diseases and was manipulated in a close environment to avoid the introduction of new variants into nature.

Limitations

The researcher was not able to open the brain of the fly to identify which part of the brain was affected by the anti-malarial drugs. The researcher was also not able to genetically modify the fly to identify how the various neurotransmitter pathways were affected by the anti-malarial drug.

RESULTS

Aggression and Grooming

Table 1: Aggression and grooming in *Drosophila* flies

Drugs	HA	LA	HNA	LNA	Grooming
	Mean ± SD				
Fansidar	38 ± 21.65	16.33 ± 3.21	23.33 ± 7.51	19.00 ± 8.00	53.33 ± 18.01
Artesunate	63 ± 20.30	25.33 ± 7.51	35.33 ± 15.01	18.33 ± 1.15	66.67 ± 24.44
Quinine	14.33 ± 8.33	11.33 ± 6.51	10.00 ± 2.65	13.00 ± 6.56	40.67 ± 11.02
Mefloquine	14.67 ± 9.29	9.67 ± 4.16	12.00 ± 3.61	8.67 ± 0.58	36.67 ± 17.01
Chloroquine	33 ± 4.58	14.67 ± 1.15	15.00 ± 4.36	11.00 ± 1.73	34.67 ± 13.32
Control	21.67 ± 7.64	14.67 ± 2.08	26.33 ± 6.51	11.33 ± 1.53	52.67 ± 31.01
Total	30.78 ± 20.80	15.33 ± 6.48	20.33 ± 11.25	13.56 ± 5.38	47.44 ± 20.60

KEY: HA= high aggressive; LA= low aggression; HNA = High non-aggressive; LNA = low non-aggressive.

F (5, 12) showed that there was no significant relationship (P =0.408) between grooming and drugs. Behavior highly aggressive behavior (P = 0.07); low aggressive behavior (P = 0.021); high non-aggressive behavior (P = 0.013) was found to be significant. There was no relationship in the low non aggressive group (P = 0.68).

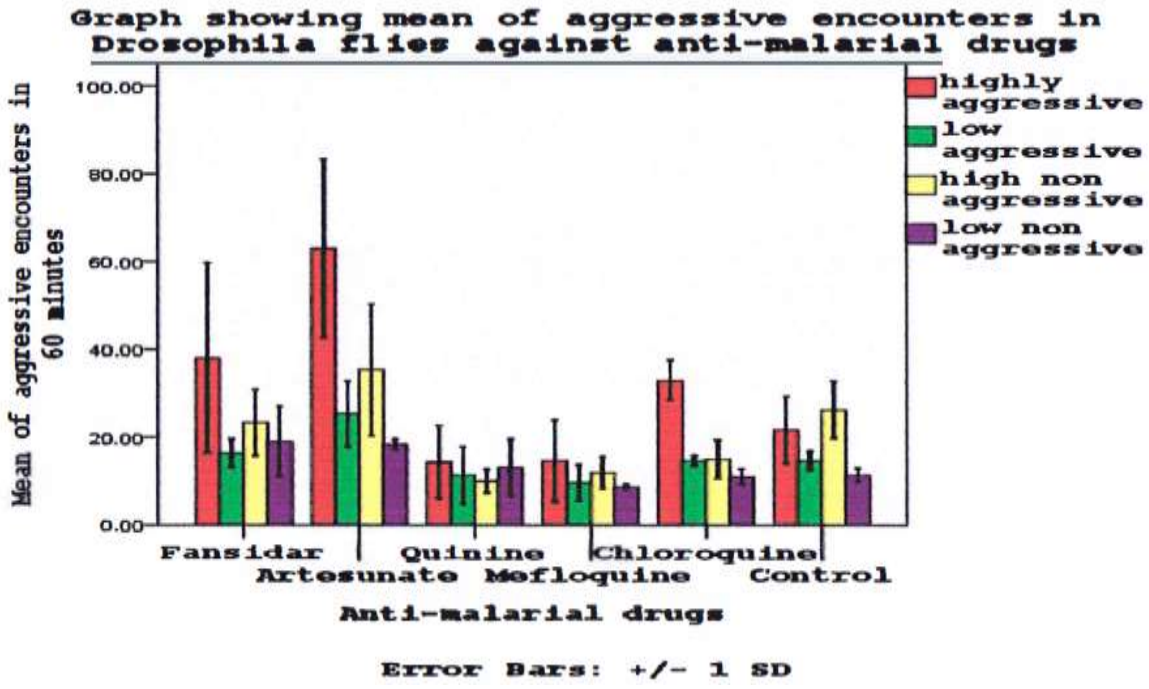

Figure 1: Showing aggressive behavior in *Drosophila* flies

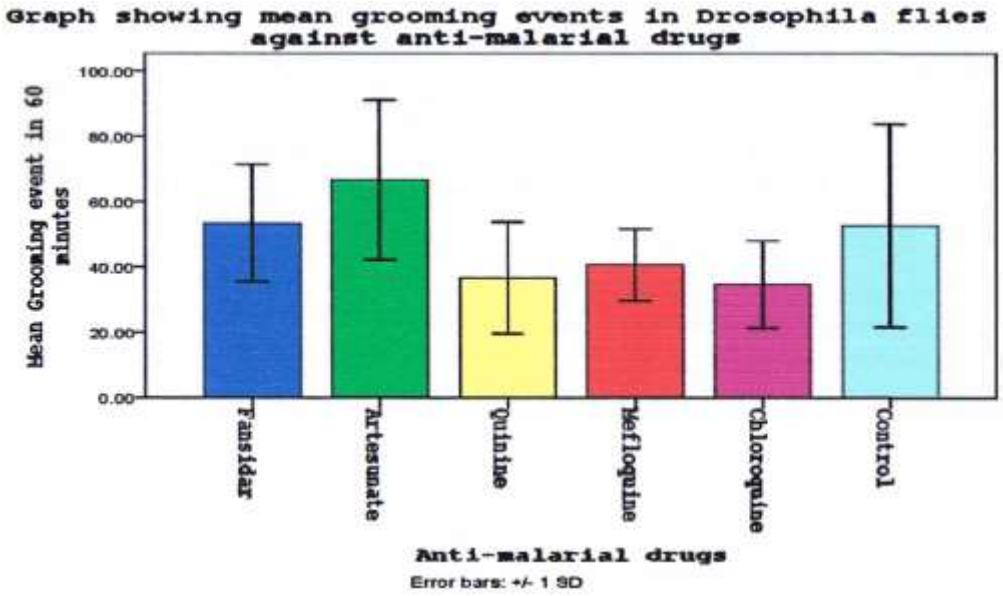

Figure 2: Showing mean grooming events in Drosophila flies

Feeding behavior in Drosophila flies

Table 2: Showing feeding behavior in Drosophila flies

Drug	Male	Control Male	Female	Control Female	Time/min
	Mean ±SD				
Fansidar	0.69 ± 1.02	0.82 ± 0.88	1.93 ± 1.49	1.86 ± 1.34	47.72 ± 25.99
Artesunate	0.68 ± 0.81	0.87 ± 0.88	2.91 ± 1.56	2.64 ± 1.15	46.07 ± 26.78
Quinine	0.59 ± 0.79	0.66 ± 0.76	2.13 ± 1.48	2.38 ± 3.91	47.50 ± 26.18
Mefloquine	0.85 ± 0.94	0.73 ± 1.01	1.67 ± 1.21	1.79 ± 1.38	47.50 ± 26.18
Chloroquine	0.96 ± 1.39	0.67 ± 0.96	1.78 ± 1.73	1.50 ± 1.31	47.50 ± 26.18
Total	0.75 ± 1.01	0.75 ± 0.90	2.09 ± 1.56	2.04 ± 2.12	47.25 ± 26.08

KEY: SD= Standard deviation

F-test results showed that there is a relationship (P = 0.000) between the drugs on the feeding behavior of Drosophila flies in the study. In between group comparisons showed there was a strong significant (P = 0.000) in the female flies compared to the males (P = 0.32) under F (1,4) especially in the group feeding (P = 0.001) on artesunate.

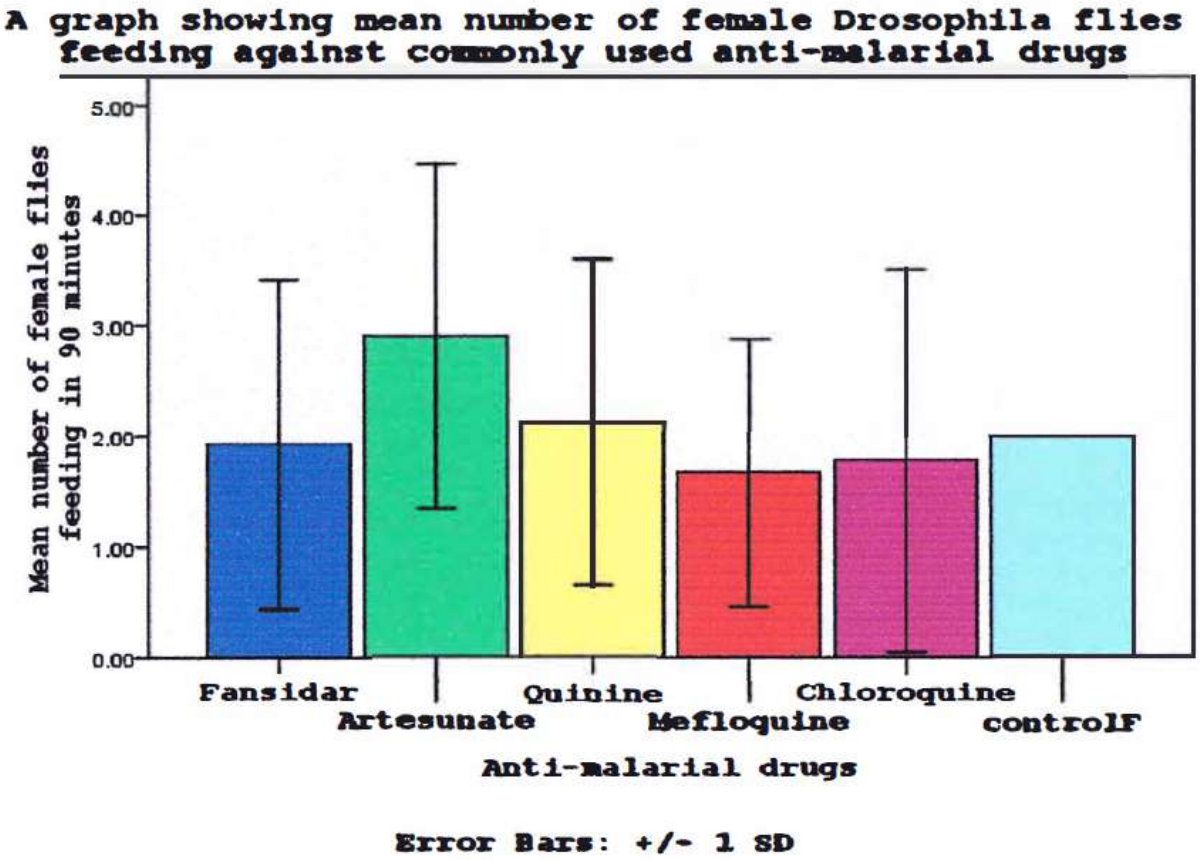

Figure 3 Showing feeding behavior in female *Drosophila* flies on antimalarial drugs

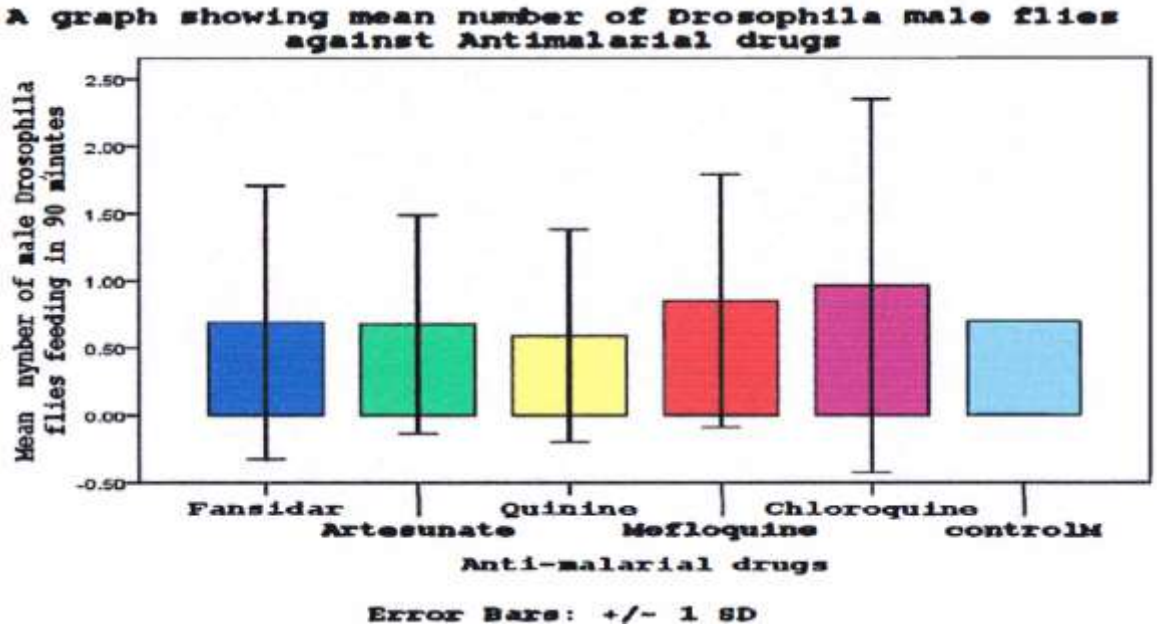

Figure 4 Showing feeding behavior in male *Drosophila* flies on anti-malarial drugs

Mean performance index

The mean perfom1ance index for locomotion was shown to be highest 1.0 ± 0.00 in female *Drosophila* flies in the study on Artesunate. Mefloquine showed the lowest mean performance index of 0.31 ± 0.23, 0.82 ± 0.31 in male Drosophila flies.

Table 3 Showing mean performance index in Drosophila flies

Drug	Mean ± SD performance index	
	Male	Female
Fansidar	0.87 ± 0.20	0.73 ± 0.40
Artesunate	0.82 ± 0.19	1.0 ± 0.00
Quinine	0.87 ± 0.17	0.82 ± 0.34
Mefloquine	0.31 ± 0.23	0.82 ± 0.31
Chloroquine	0.76 ± 0.24	0.84 ± 0.28

KEY: SD= Standard deviation

F-test results showed that there is a relationship (P = 0.000) between the drugs and the flies understudy. In between group comparisons showed there was a strong significant (P = 0.000) in the male flies compared to the females (P = 0.584) under F (1,5) in mefloquine.

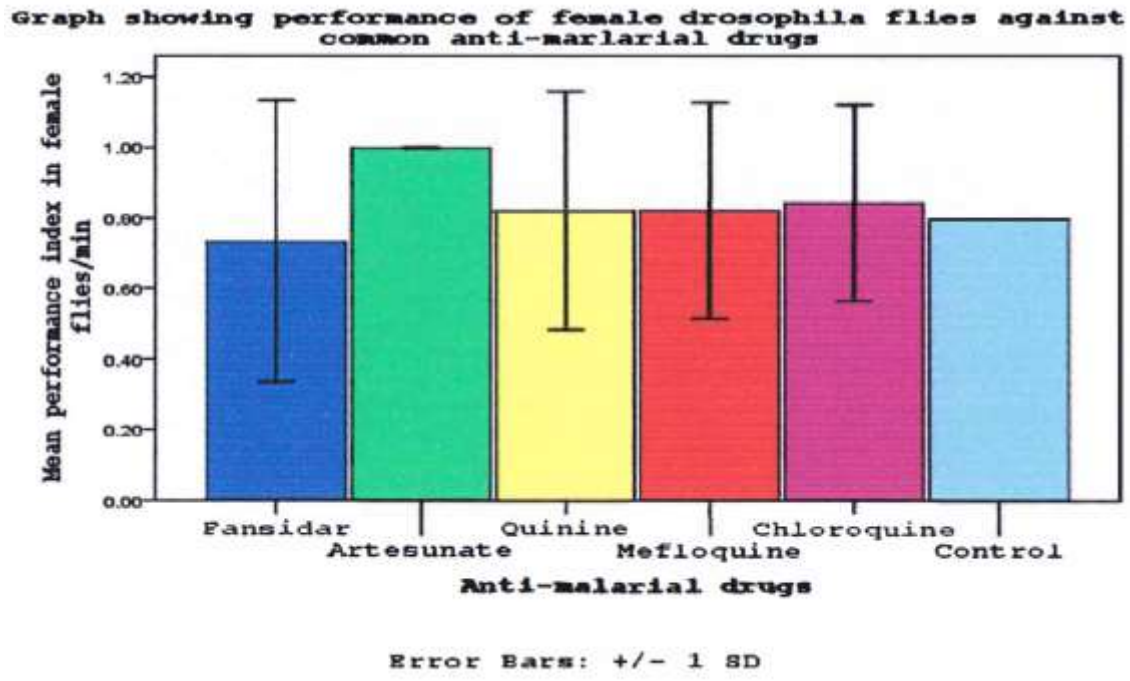

Figure 5 Showing performance of female *Drosophila* flies against common anti-malarial drugs

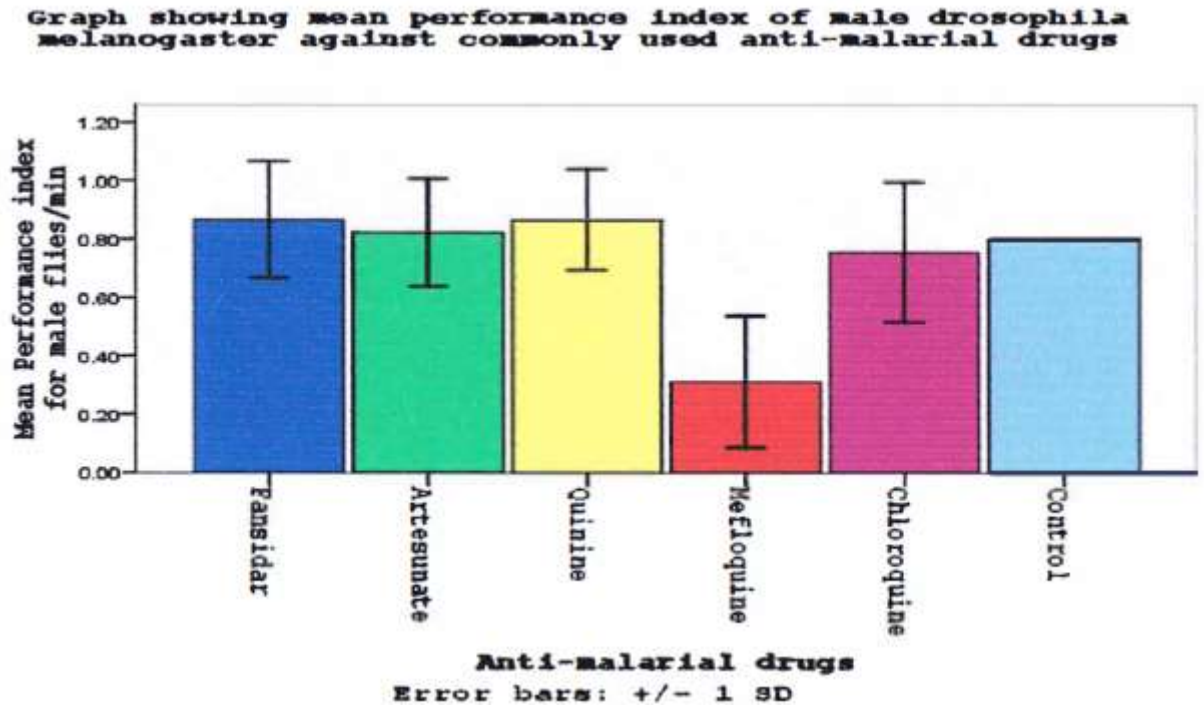

Figure 6 Showing the mean performance index of male *Drosophila melanogaster* flies against commonly used anti-malarial drugs.

DISCUSSION

The study showed that *Drosophila melanogaster* flies feeding on Artesunate showed the highest aggressive behavior and grooming ($P < 0.05$), especially in the male flies as shown in Table 1and Figures *1* & 2**.** There are multiple excitatory neurotransmitters and neuroactive peptides that play a role in aggression in *Drosophila melanogaster* and previously octopamine, dopamine and a region in the *Drosophila* brain called the mushroom bodies, all profoundly influence the expression of aggressive behavior [34]. Pharmacological stimulation of octopamine has been shown to enhance male aggression [35]. Aggressive behavior is widely present throughout the animal kingdom and is crucial to ensure survival and reproduction [36]. Aggressive actions serve to acquire territory, food, or mates and in defense against predators or rivals; while in some species these behaviors are involved in establishing a social hierarchy. Aggression is a complex behavior, influenced by a broad range of genetic and environmental factors [37]. Grooming behavior has been shown to be controlled by neural mechanisms which may be in response to emotional states, depression and anxiety [38, 39]. Artesunate probably interacts with the gene optomotor-blind (OMB) which has been shown to play a crucial role in Drosophila behavior including grooming (Pflugfelder & Heisenberg, 1995). Artesunate further showed the fastest feeding ($F(1,4)$, $P = 0.001$) than all other groups as shown in Table 2and Figures 3 & 4**.** Inferential analysis showed that females fed more ($P < 0.05$) compared to males. Hug neurons undertake the role of integrating gustatory sensory as well as internal pharyngeal chemosensory signals with higher brain functions and feeding behavior [40]. These further modulate hug neurons function within a neural circuit that modulates taste-mediated feeding behavior [41]. These would probably be working in synergy with enhanced expression of the GR6a sucrose receptor gene since glucose was used as a food composite [42]. The mean performance index for locomotion was shown to be high in both male and female *Drosophila melanogaster* flies in the study, especially in the Artesunate feeding group. Mefloquine showed the lowest mean performance index of 0.31 ± 0.23, 0.82 ± 0.31 in both male and female Drosophila flies as shown in Table 3and Figures 5 & 6**.** In between group comparisons showed there was a strong significance ($P = 0.000$) in the male flies compared to the females ($P = 0.584$) under $F(1,5)$ in mefloquine while this was reversed in females. This was probably due to the inhibition of excitatory neurotransmitters (acetylcholine) thus leading to a reduced performance index [43].

CONCLUSION

Anti-malarial drugs especially Artesunate had significant effects on feeding, grooming, aggression, and locomotion behavior in drosophila melanogaster through their interaction with specific neurotransmitters and neurons in the brain that are responsible for the expression of behavior. Mefloquine reduced the locomotion activity of these flies.

Recommendations

Drugs with the least effects in animal models should be the preferred treatment in the clinic. Since studies in laboratory animals show that ACTs cause brain damage, and Artesunate has shown an increased effect on behavior in flies, the molecular mechanism of these effects should be studied in depth using the available genetic tools in *Drosophila*. Once there is a better understanding of the action mechanism, then action can be taken about the use of these drugs in humans.

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