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# Screening Antimalarial Drugs for Modulation of Aggressive Behaviour in *Drosophila melanogaster*

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## ABSTRACT

Aggressive behavior is crucial to survival and reproduction in organisms and this can be affected by environmental factors. Antimalarials are commonly used in medical practice, and it's possible that they would interact with modulators of aggression to influence behavior since some have been shown to cause neuro-damage. This study evaluated common antimalarial drugs for the modulation of aggressive behavior in *Drosophila melanogaster* model. *Drosophila melanogaster* specie (W118) was used in this study. Flies were divided into male and female and experiments were conducted on adult, middle, and juvenile age groups. Flies were exposed to chloroquine (0.0025 mg/ml), quinine (0.000135 mg/ml), Fansidar (0.0025 mg/ml), Artesunate (0.0003 mg/ml), and Artemether lumefantrine (0.0003 mg/ml). These were later on exposed to neurotransmitter modulators i.e. octopamine (stimulatory-clonidine (1 mg/ml); inhibitory-promethazine (0.00025 mg/ml), dopamine (stimulatory-L-dopa (0.001 mg/ml); inhibitor-haloperidol (0.0001 mg/ml), serotonin (stimulatory-fluoxetine (0.0002 mg/ml), inhibitory-cyproheptadine (0.00004 mg/ml). Data was recorded in triplicate and analyzed in MS Excel. Information was presented in mean± SEM and significance at 95% was considered. The study showed that Artesunate had the highest effects of aggression in male *Drosophila melanogaster* flies while Quinine and Chloroquine were associated with low effects and Artemether lumefantrine was associated with low levels of aggression in female flies. These observations would have been due to their interaction with neurotransmitter release which is essential for aggressive behavior. Fansidar and Artemether-lumefantrine acted synergistic to octopaminergic stimulation in both males and females respectively. Artesunate antagonized actions of promethazine by leading to increased aggression, especially in male flies. Fansidar and Artemether-lumefantrine acted synergistically to dopaminergic stimulation while Artesunate antagonized dopaminergic inhibition, showing that it plays a crucial role in aggression. Serotonin leads to decreased aggression and Fansidar showed antagonist activity in males while in females this was in Artemether Lumefantrine. Artesunate showed strong inhibitory activity on serotonin release, thus leading to increased aggression. In the age groups, aggression by Artesunate was highest in adult male and female flies and this raises major pharmaceutical concerns. In the juveniles, Fansidar and Artesunate showed significant aggression, thus showing implications in neural development.

The molecular mechanism of actions of Artesunate and Fansidar on modulation of neurotransmitter release needs to be investigated further to gain clear insight.

**Keywords:** Aggressive behavior, Drosophila melanogaster, Antimalarial drugs, Neurotransmitters, Pharmacology

## INTRODUCTION

Aggressive behavior, a fundamental aspect of animal behavior, plays a crucial role in ensuring survival and reproduction [1]. It is widely observed throughout the animal kingdom and is employed for various purposes, such as acquiring territory, food, or mates, and defending against predators [2]. In humans, two distinct subtypes of aggression have been identified: the controlled instrumental subtype and the reactive impulsive subtype [3]. Reactive aggression is considered more impulsive and is typically associated with anger, while instrumental aggression is regarded as more purposeful and goal-oriented. The expression of aggressive behavior is modulated by a broad range of genetic, biological, and environmental factors [4, 5]. Many of these factors, such as neurotransmitters, hormones, pheromones, sex, and individual anatomical differences, have been studied in various species. However, the pathways through which these factors modulate aggressive behavior are largely unknown [6]. Understanding the relationship between biological signals and aggression is of particular interest, as it may provide insights into the contribution of these signals to aggressive behavior in humans. Biological signaling

molecules, such as serotonin, dopamine, β-alanine, gamma-aminobutyric acid (GABA), monoamine oxidase, and noradrenaline, have been implicated in the regulation of aggressive behavior [7]. Specifically, serotonin hypofunction has been suggested as a biochemical trait that predisposes individuals to impulsive aggression, with dopamine hyperfunction contributing in an additive manner to the serotonergic deficit [8]. Disruption of the serotonergic system is a highly significant feature in predisposing aggression [9]. Generally, low serotonin (5-HT) levels are associated with higher levels of impulsivity and aggressiveness [10], and manipulations that lower 5-HT signals tend to increase impulsivity and aggression [11]. The role of dopamine in aggression has been elucidated through animal experiments. Animals can be conditioned to increase dopamine secretion in anticipation of aggressive interactions [12], suggesting a connection with instrumental aggression. Antagonists of both the D1 and D2 receptors have been found to reduce aggression in male mice [13]. In addition to biological factors, drugs are also known to influence aggressive behavior and mood. Various types of drugs, such as stimulants (e.g., cocaine and amphetamine), depressants (e.g., alcohol and barbiturates), opiates (e.g., morphine and codeine), hallucinogens/psychedelics (e.g., lysergic acid diethylamide (LSD) and mescaline), and marijuana, can alter human behavior or mood [14] While these drugs may produce short-term effects, some drugs can also lead to long-term behavioral changes due to prolonged use. The study of aggressive behavior and its modulation by various factors is essential for understanding the complex interplay between genes, biological signals, neural circuits, and the environment that influence the development and expression of aggressive behavior [6]. Drosophila melanogaster, the fruit fly, has emerged as a powerful model organism for studying the neurobiology of aggression [15]. Despite its evolutionary divergence from humans, Drosophila shares a significant number of conserved homologous genes and functional orthologs with humans, making it a suitable model for investigating complex behaviors [15, 16]. The use of Drosophila melanogaster as a model organism offers several advantages, including its well-established genetic manipulation techniques, behavioral richness, and cost-effectiveness [17]. By leveraging the genetic tools and resources available for Drosophila, researchers can gain insights into the molecular mechanisms underlying aggressive behavior and its modulation by various factors, including antimalarial drugs.

## METHODOLOGY

### Area of study

The 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).

### Materials

- **Fly starch.**

The wild (W1118) white strain Drosophila melanogaster was used for the study 12-hour dark cycle at room temperature prior to the experiment.

- **Chemicals and reagents**

Reagents included; Agar, yeast, wheat flour, apple juice media, water, glucose, nipagin, propionic acid, ethanol and ether. Chemicals included; Levodopa, haloperidol, clonidine, promethazine, fluoxetine and cyproheptadine.

- **Preparation of fly food**

Ingredients as shown above were dissolved in 1 liter of water and boiled extensively on a hot plate until all ingredients were dissolved. Propionic acid (a mold inhibitor) was added. The media was paired into 175ml 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**

Chloroquine, Quinine, Fansidar, Artesunate and Artemether /Lumefantrine.

- **Equipment**

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

### Methods

- **Fly preparation for the experiment**

Virgin flies raised in the lab in culture bottles were transferred to empty bottles 12 hours before the experiment. A cotton plug 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 such 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 flies were anesthetized. Using a microscope the flies were sorted according to sex, (male and female). Flies of the same sex were placed in a vial using a brush with soft bristles to avoid injuring the flies. Vials containing female flies were labeled F and those containing males were

labeled M. For each experimental setup, a group of 8 vials each containing four vials with male flies and four vials with female flies were 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 15 hours [18].

**Drug administration**

A serial dilution to make a concentration of the drug that is equivalent to the dose taken by human beings was made. Using a filter properly, a specific calculated amount of the drug was dispensed onto the filter paper ensuring that it is 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 30-45 minutes. Flies were observed directly using a camera, dish and computer for phenotypic aggression parameters in the first five days following treatment; at age 21-25 days and age 40-45 days in both sexes. The parameters to be scored included; retreat, approach, wing threat, lunge, shove, thrust with a wing threat, head butt, fencing, chasing, holding, tussling, and boxing [19] where;

- Retreat refers to walking, flying, or running away
- Approach refers to turning or walking toward the opponent
- Wing threat refers to raising one or both wings to a 45-90° angle toward the opponent (<1 min)
- Lunge refers to rearing up on hind legs and collapsing on the opponent
- Shove means thrusting torso towards the opponent with both legs extended without recoil
- Thrust with a wing means to thrust and lift one or both wings to a 45-90° angle (<1 min)
- Head butt means to thrust the torso toward the opponent and strike the opponent with the head; usually followed by recoiling of the torso
- Fencing is to extend the leg and contact the opponent in a normal standing posture
- Chasing means to run after the opponent
- Holding is to grasp the opponent with forelegs and try to immobilize
-To tussle is to tumble over each other sometimes leaving the food surface and
-Boxing is to rear up on hind legs and strike the opponent with forelegs.

The above parameters were categorized into three groups as follows;

1. High aggression (Boxing, Tussling, Head butt, Lunge and Shove).
2. Medium aggression (Holding, Wing threat and Thrust with a wing).
3. Low aggression (Approaching, Chasing, Retreat and Fencing).

**Pharmacological treatments**

Using a new set of flies, stimulation and inhibition of neurotransmitters serotonin, Octopamine and Dopamine was done [15].

- **Serotonin (5HT)**

a. Flies were fed with 0.0002mg/ml of fluoxetine in Sucrose solution. This treatment produces high levels of serotonin (5HT+).

b. Flies were also fed with 0.00004mg/ml Cyproheptadine in sucrose solution. This treatment produces low levels of serotonin (5HT).

- **Dopamine**

a. Flies were fed with 0.001 mg/ml L-DOPA in sucrose solution. This treatment produces high levels of dopamine (DA+).

b. Flies were also fed with 0.0001 mg/ml Haloperidol in sucrose solution. This treatment produces low levels of dopamine (DA-)

- **Octopamine**

a. Flies were fed with 0.001 µg/ml Clonidine in sucrose solution. This treatment produces high levels of octopamine.

b. Flies were also fed with 0.00025mg/ml Promethazine in sucrose solution. This treatment produces low levels of octopamine.

After 30-45 minutes, the flies were observed directly using a dish, camera and computer for phenotypic aggression parameters following treatment as shown above. Parameters were scored using tabulation.

**Anti-malarial interference with Neurotransmitter pathways**

A new set of flies was given an antimalarial drug first as described in the first experiment above for 30 -45 minutes. They were then allowed one hour for drug absorption to take place.

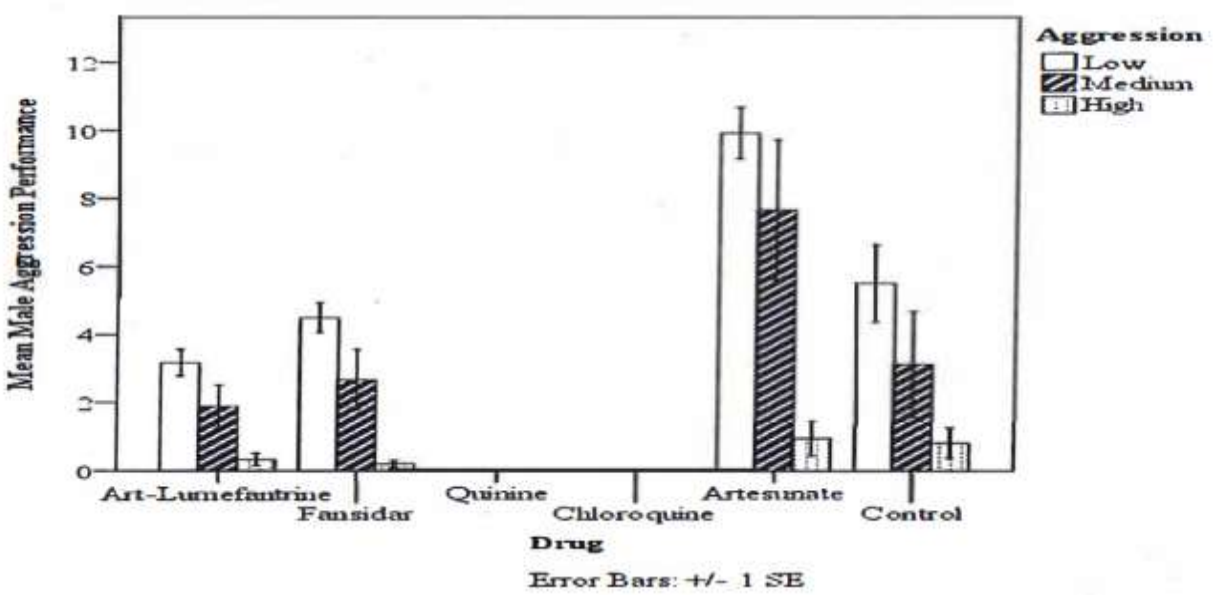
The same flies were then stimulated and inhibited for dopamine, Octopamine and serotonin as described in the second experiment above.The interference of the antimalarial drugs with the dopaminergic, octopaminergic and serotonergic pathways was observed using the same aggression parameters as above and the mechanisms of modulation of the neurotransmitter pathways by these drugs was later discussed in the following chapters.

## RESULTS

### Behavioral changes in flies treated with antimalarials

The study showed that Artesunate had the highest effects of aggression in male *Drosophila melanogaster* flies while Quinine and Chloroquine were associated with low effects.

**Figure 1: Showing behavior changes in male flies treated with antimalarial**




Artesunate and Artemether Lumefantrine are associated with high aggression in femaleDrosophila melanogaster while moderate aggression was shown by Fansidar group.

**Figure 2: showing behavior changes in female flies treated with antimalarials**

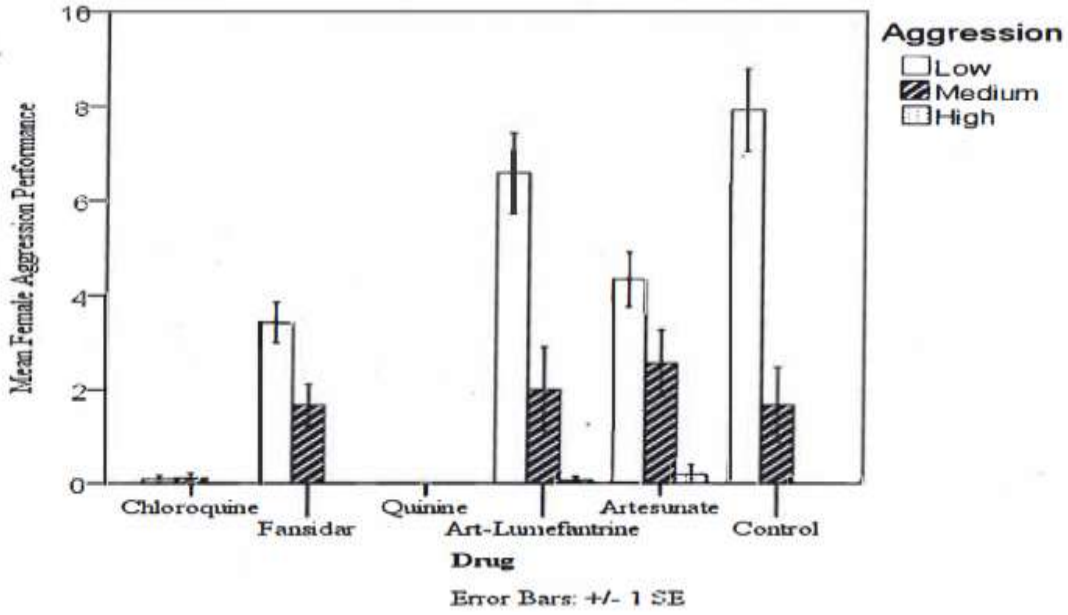



**Table 1: Showing group comparisons for behavioral changes in flies treated with antimalarials**

| Drugs | Mean ± SEM Aggression performance | |
|---|---|---|
| | Male | Female |
| Art-Lumefantrine | 1.67±0.5 | 2.72±0.42 |
| Fansidar | 2.25±0.5 | 1.56±0.42 |
| Quinine | 0.00±0.5* | 0.00±0.42* |
| Chloroquine | 0.00±0.5* | 0.06±0.42* |
| Artesunate | 5.61±0.5* | 2.17±0.42 |
| Control | 2.94±0.5 | 3.06±0.42 |

**KEY:** *$P < 0.05$

The study showed an aggression performance of 1.67±0.5 and 2. 72±0.42 in both males andfemales on Art-Lumef. Artesunate aggression was high in males than females at 5.61±0.5 and2.17±0.42 and significant differences *($P < 0.05$)* were seen in both Art-Lumef and Artesunate respectively as shown in **Table 1.**

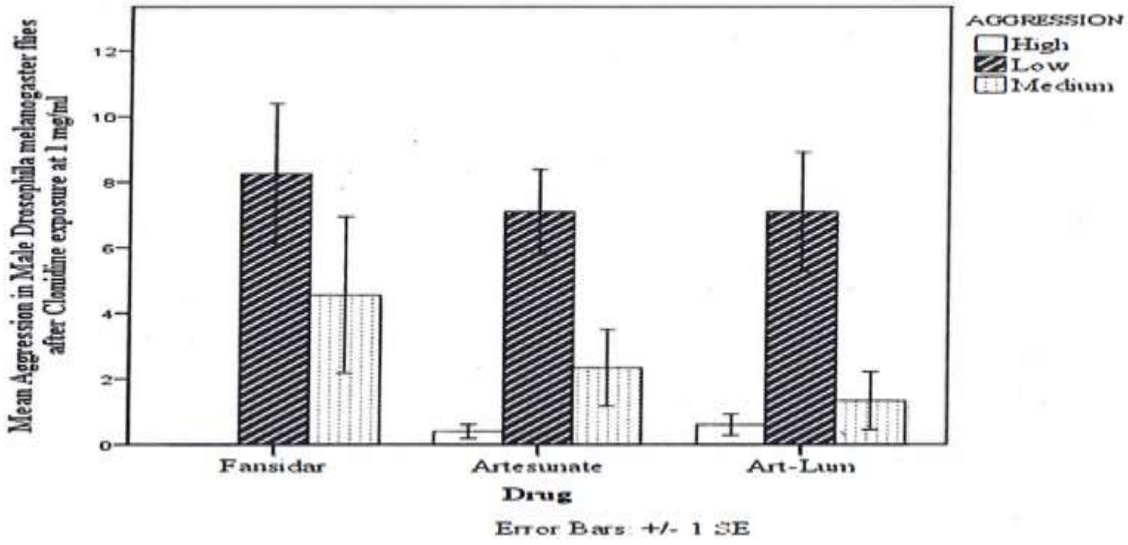
**Activities of antimalarials on mediators of aggression**

**A. FOR OCTOPAMINE**

**Action of Clonidine treatment**

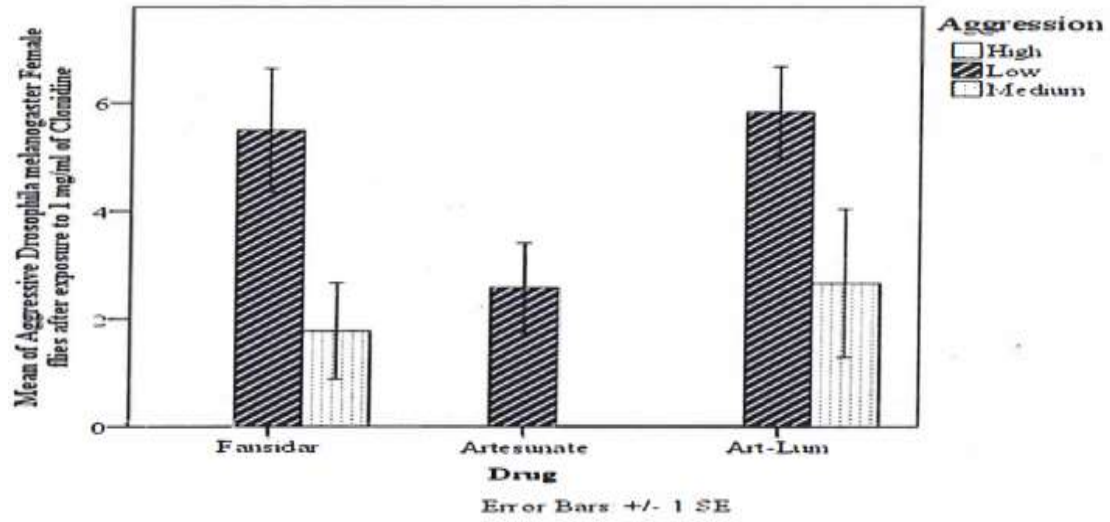
Artemether-lumefantrine and Artesunate showed high aggression behavior in male *drosophila melanogaster* while medium aggression was found to be highest in Fansidar group.

**Figure 3: showing action of Clonidine following antimalarial treatment in male Drosophila flies**




Artemether lumefantrine showed the highest aggression in female *Drosophila melanogaster* whileFansidar showed moderate aggression.

**Figure 4: showing action of Clonidine following antimalarial treatment in female Drosophila flies**




**Action of promethazine treatment**

Artesunate showed the highest aggression in male Drosophila melanogaster while Fansidar and Artemether lumefantrine showed no aggression at all.

**Figure 5: Showing action of Promethazine following antimalarial treatment in male Drosophila flies**

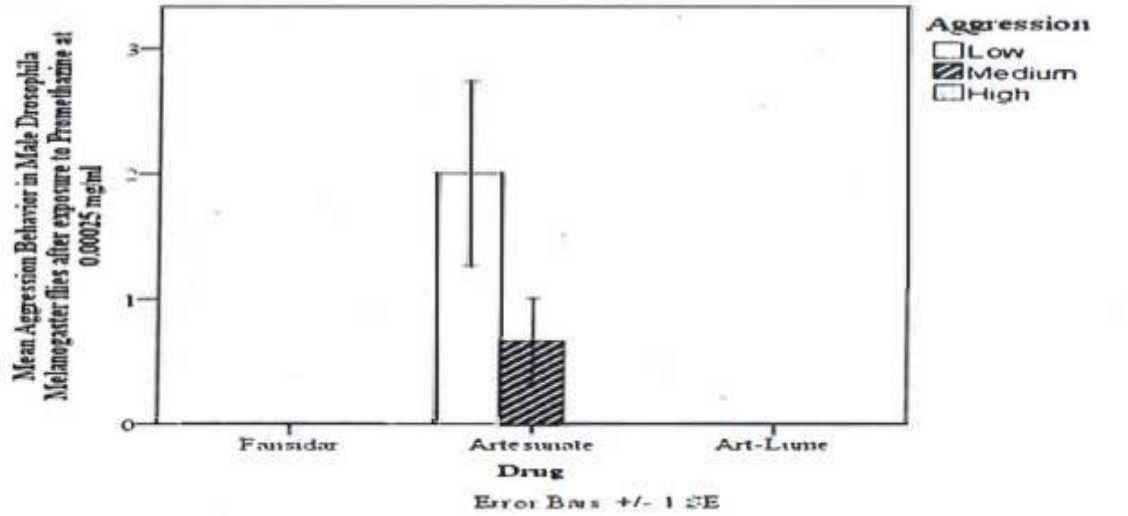
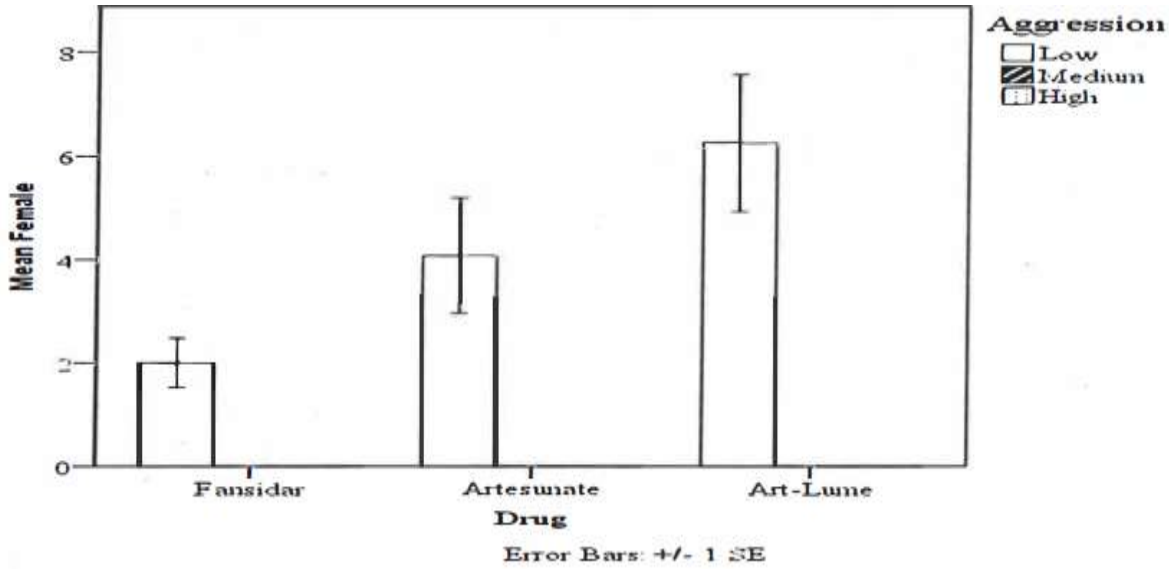



**Figure 6: Showing action of Promethazine following antimalarial treatment in female Drosophila flies**

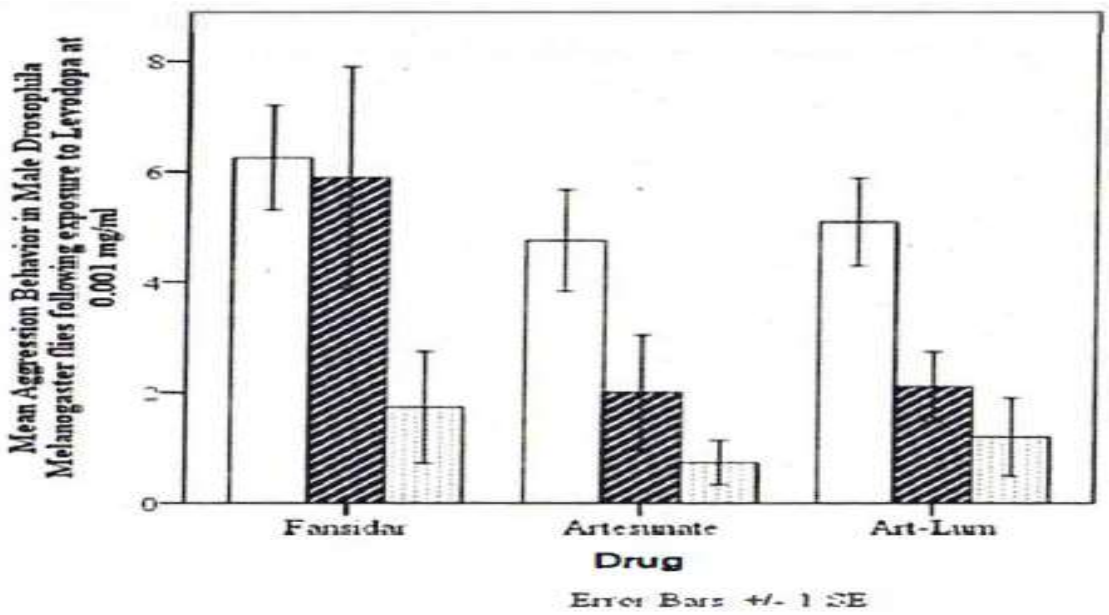



**B. FOR DOPAMINE**

**Action of L-DOPA treatment**

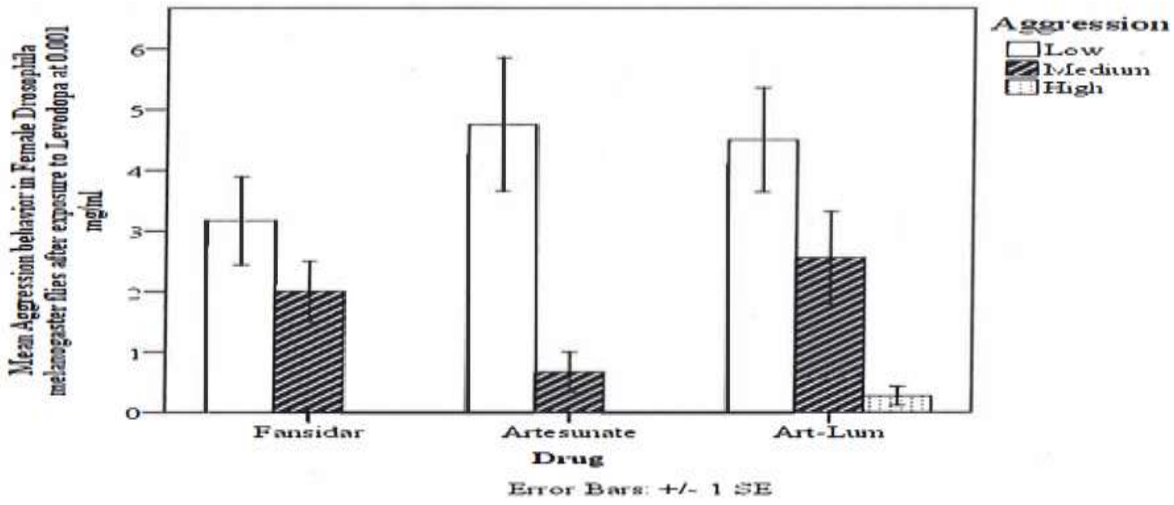
Fansidar showed the highest aggression in male *Drosophila melanogaster* while Artesunate and Artemether lumefantrine showed moderate aggression.

**Figure 7: Showing action of Dopamine following antimalarial treatment in male Drosophila flies**




Artemether Lumefantrine showed high aggression in female *Drosophila melanogaster* while aggression was found to be moderate in Fansidar group.

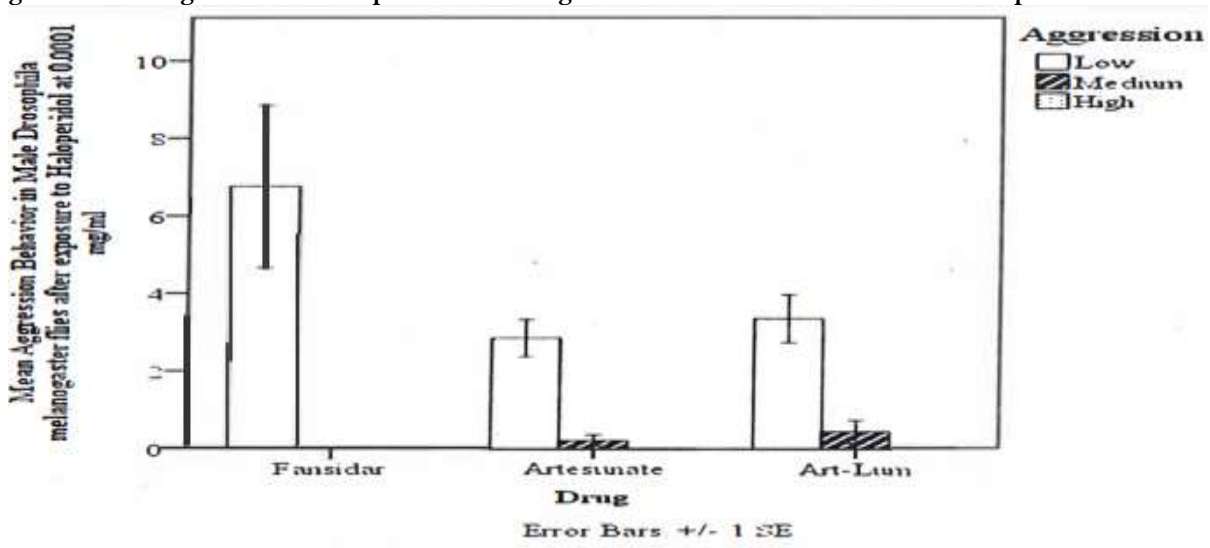
**Figure 8: Showing action of Dopamine following antimalarial treatment on female Drosophila flies**




**Action of Haloperidol treatment**

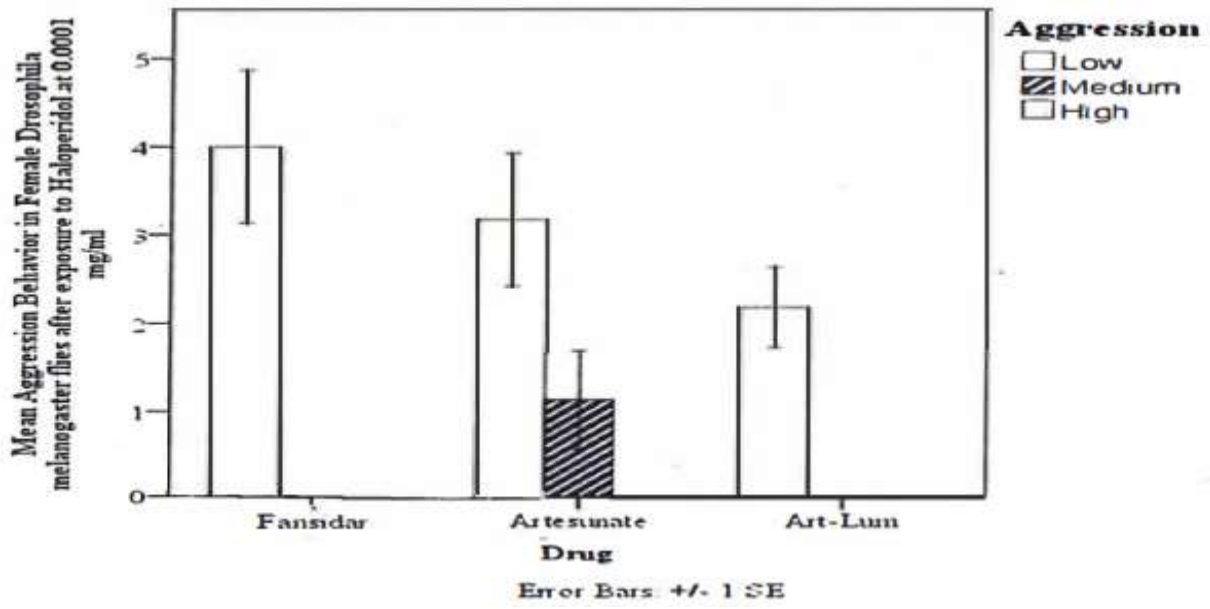
Medium aggression was found to be highest in the Artemether Lumefantrine group in male *Drosophila melanogaster* while Artesunate showed moderate aggression.

**Figure 9: Showing action of Haloperidol following antimalarial treatment in male Drosophila flies**




Artesunate showed medium aggression in female *Drosophila melanogaster* while low aggression was found to be highest in Fansidar group.

**Figure 10: Showing action of Haloperidol following antimalarial treatment in female Drosophila flies**

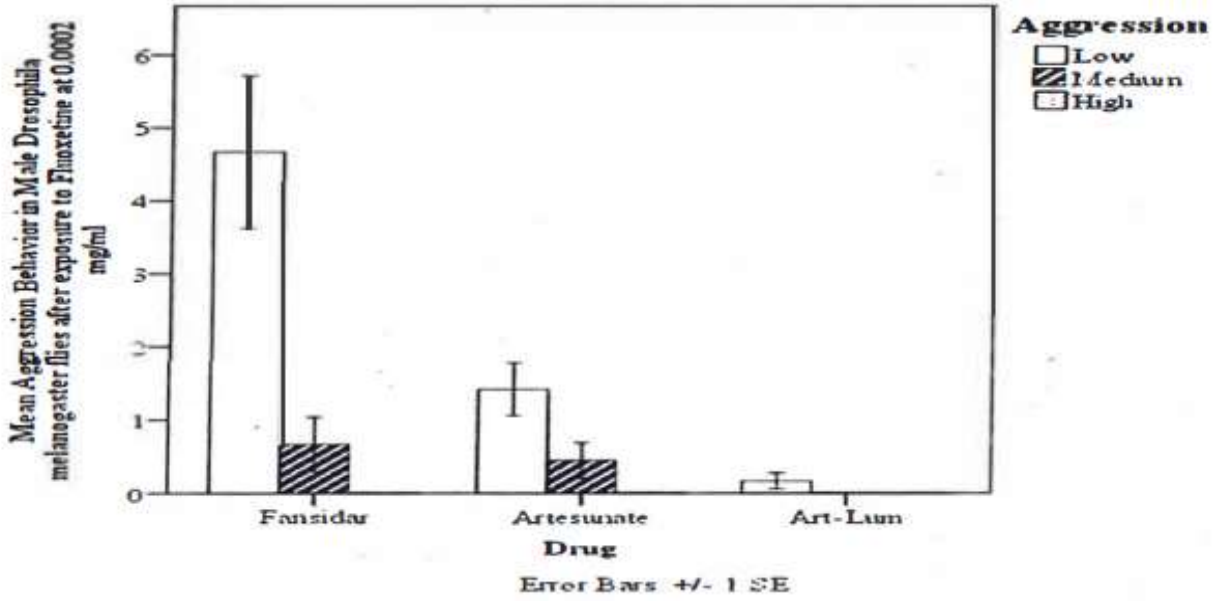



**C. FOR SEROTONIN**

**Action of Fluoxetine treatment**

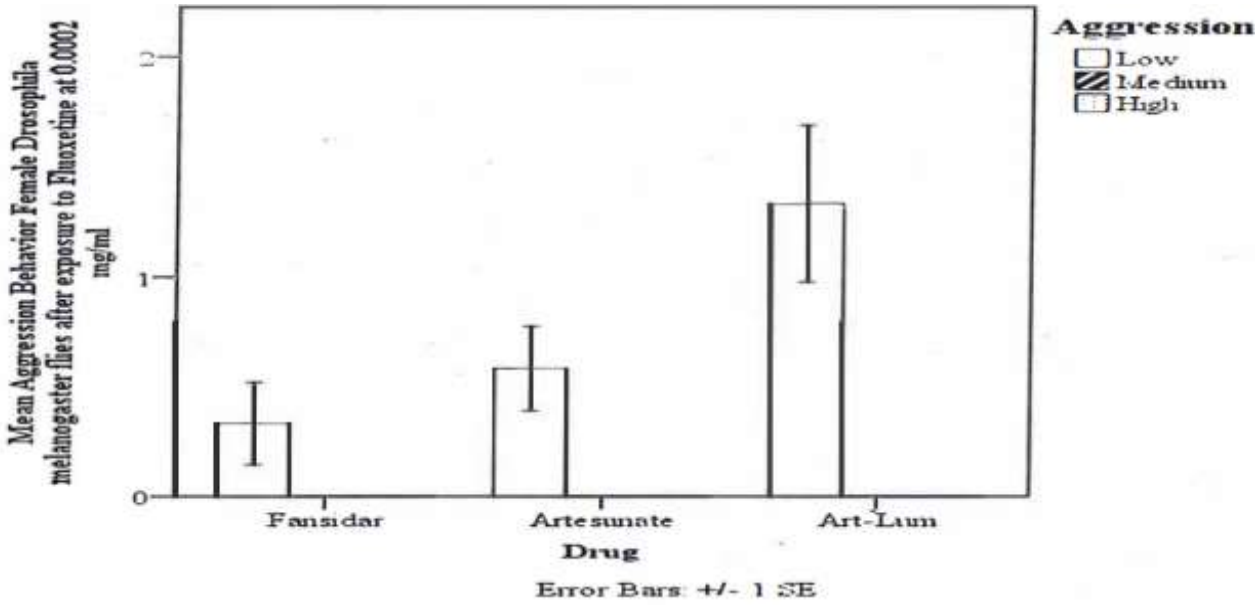
Fansidar showed the highest aggression in male *Drosophila melanogaster* while moderate aggression was shown by Artesunate.

**Figure 11: Showing the action of Fluoxetine following antimalarial treatment in male Drosophila Flies**




Artemether Lumefantrine showed the highest aggression in female *Drosophila melanogaster* moderate aggression was shown by Artesunate.

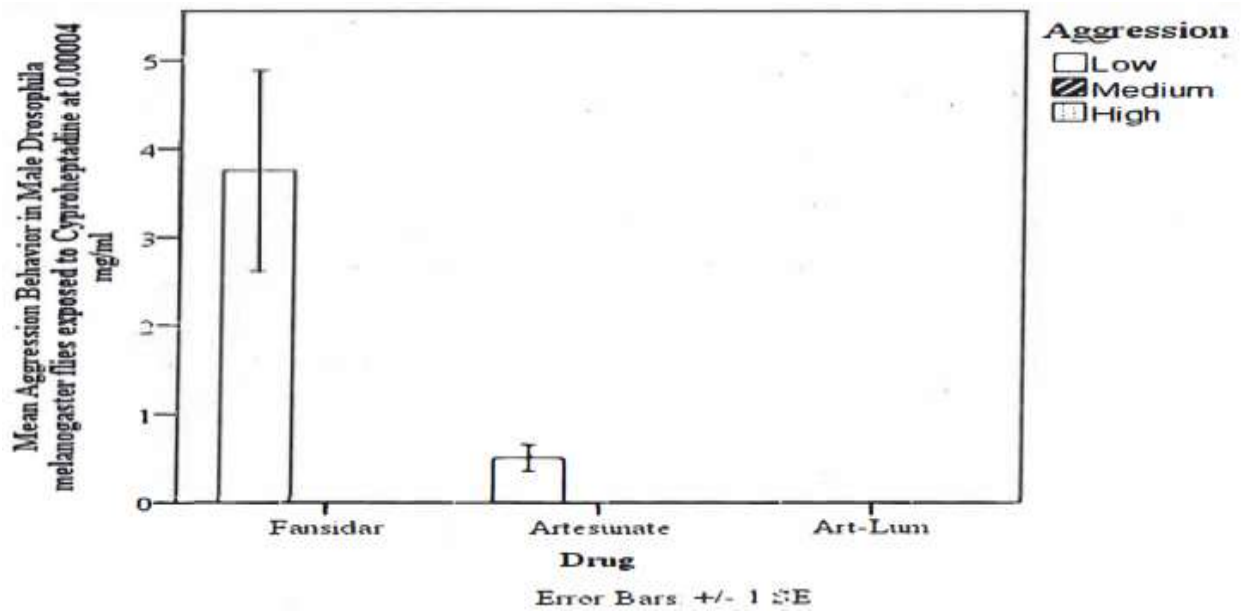
**Figure 12: Showing action of Fluoxetine following antimalarial treatment in female Drosophila flies**



**Action of Cyproheptadine treatment**

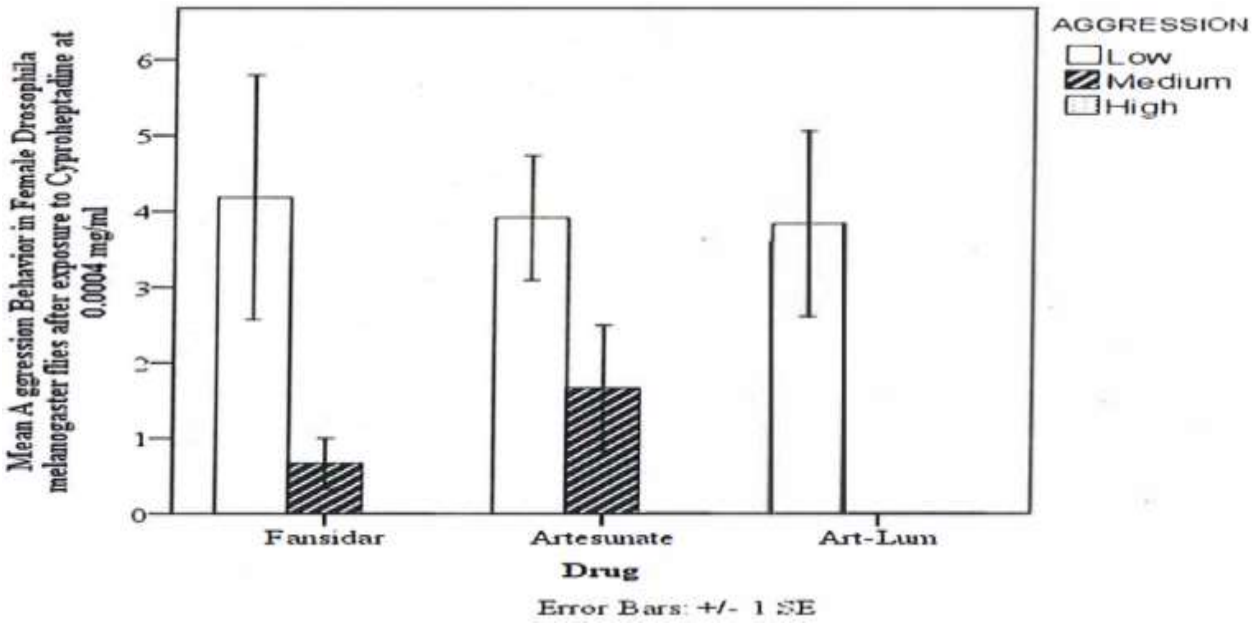
Fansidar showed the highest aggression in male *Drosophila melanogaster*.

**Figure 13: Showing action of Cyproheptadine following antimalarial treatment in male Drosophila flies**




Artesunate showed the highest medium aggression in female *Drosophila melanogaster* while low aggression was found to be highest in Fansidar group.

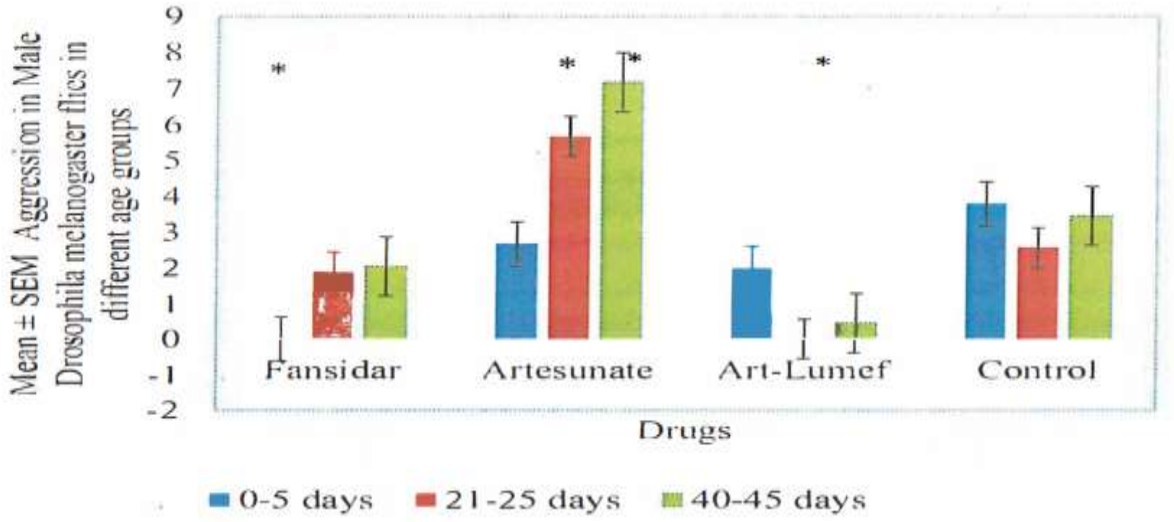
**Figure 14: Showing action of Cyproheptadine following antimalarial treatment on female Drosophila flies**




**Relationship Between Age and Antimalarial Drug-Induced Aggressive Behavior**

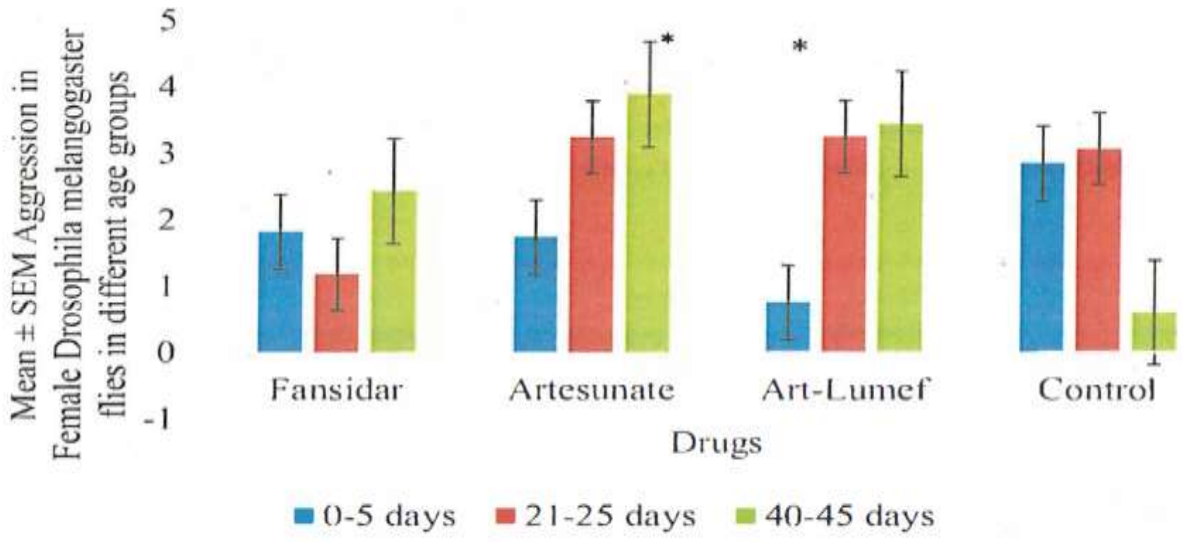
Artesunate showed the highest aggression across all age groups in male *Drosophila melanogaster* with the highest effects amongst 40 -45 days, while Fansidar showed moderate aggression in both 21-25 and 40-45 days.

**Figure 15: Showing the effect of the drug on age in male Drosophila flies**




Artesunate showed the highest aggression for the age group 40-45 days old female *Drosophila melanogaster*. Aggression for the age group 21-25 in Artesunate equals that in Artemether Lumefantrine and aggression for the age group 0-5 in Fansidar equals that in Artesunate.

**Figure 16: Showing the effect of the drug on age in female Drosophila flies**




**KEY:** * Drug comparisons against the control ($P < 0.05$).

**Table 2: Showing group comparisons on the effect of drugs on age in Drosophila flies**

| Drugs | Male | Female | Male | Female | Male | Female |
|---|---|---|---|---|---|---|
| | Mean ± SEM | | | | | |
| | 0-5 days | | 21-25days | | 40-45days | |
| Fansidar | 0.00±0.61* | 1.83± 0.56 | 1.89±0.55 | 1.19±0.54 | 2.03±0.82 | 2.44±0.79 |
| Artesunate | 2.67±0.61 | 1.75±0.56 | 5.67±0.55* | 3.25±0.54 | 7.17±0.82* | 3.89±0.79* |
| Art-Lumef | 2.00±0.61 | 0.75±0.56* | 0.00±0.55* | 3.25±0.54 | 0.44±0.82 | 3.44±0.79 |
| Control | 3.78±0.61 | 2.86±0.56 | 2.56±0.55 | 3.08±0.54 | 3.44±0.82 | 0.61±0.79 |

**KEY:** *In group comparisons against the control $P < 0.05$. Art-Lumef= Artemether Lumefantrine.

The group comparisons showed significant effects for Fansidar 0-5 days in male *Drosophila*, Artesunate 21-25 in male *Drosophila* and 40-45 days in both male and female *Drosophila* and Artemether lumefantrine 0-5 and 21-25 days in female and male *Drosophila* respectively as shown in **Table 2.**

## DISCUSSION

### Aggression in flies treated with antimalarials

The study revealed that Artesunate exhibited the highest aggression effects in male Drosophila melanogaster flies, while Quinine and Chloroquine showed comparatively lower effects. Artesunate, known for its sedative properties and reduced movement synchronization, likely modulates behavior through the involvement of brain regions like the cerebral cortex and cerebellum [20]. Artesunate's aggression-enhancing effects may stem from increased activity of various neurotransmitters such as serotonin, GABA, glutamate, opioids, cholecystokinin, substance P, norepinephrine, dopamine, and acetylcholine, all crucial in aggression modulation [21]. Notably, aggression in humans, influenced by cognitive brain centers, shapes an individual's social interactions [22], with previous experiences shaping behavior [23]. Additionally, female Drosophila melanogaster flies exhibited distinct aggression levels compared to males. Specifically, Artemether-lumefantrine showed low aggression levels, Artesunate displayed moderate effects, and Quinine exhibited minimal aggression. Notably, female flies demonstrated heightened aggression (Table 1). Given Artemether-lumefantrine's widespread use in malaria management and its perceived safety profile [24], re-evaluating its neurological effects is imperative due to its observed behavioral impacts in this study. Further analysis revealed significant effects ($P < 0.05$) of Quinine and Chloroquine in both male and female flies, while Artesunate's effects were significant only in males. Quinine and Chloroquine's toxicological effects on myocardial tissue, mediated by epinephrine suppression, have been documented [25].

### Activities of antimalarials on mediators of aggression

### FOR OCTOPAMINE

In this study, Fansidar exhibited the highest aggression in male *Drosophila melanogaster*, while Artesunate and Artemether-lumefantrine displayed moderate aggression levels. Octopamine, functioning as a neuromodulator, neurotransmitter, and neuro-hormone in insect nervous systems, plays a pivotal role in various behaviors, including sensory inputs, arousal, and rhythmic behaviors [27]. Clonidine's role in neurological behavior has been documented [26], with its stimulation of octopaminergic receptors indicating its involvement in vertebrate alpha-adrenoreceptor activation [28]. Although Sulfadoxine-Pyrimethamine usage is recommended in humans, concerns about its neurological effects persist [29]. Artemether-lumefantrine demonstrated the highest aggression in female *Drosophila melanogaster*, while Fansidar showed moderate aggression, underscoring gender differences in interactions with octopaminergic receptors. Regarding promethazine treatment, Artesunate exhibited the highest aggression in male *Drosophila melanogaster*, whereas Fansidar and Artemether-lumefantrine showed no aggression. Promethazine, known to decrease aggression in humans, raises concerns due to reported abuse [30, 31]. Artesunate's role in aggression modulation appears enhanced, possibly due to reduced promethazine activity following antimalarial exposure. Conversely, Artemether-lumefantrine displayed the highest aggression in female Drosophila melanogaster, with Artesunate showing moderate aggression, emphasizing drug significance in females.

**FOR DOPAMINE**

**Action of L-DOPA treatment**

Fansidar exhibited the highest aggression in male Drosophila melanogaster, while Artesunate and Artemether lumefantrine displayed moderate aggression. The dopamine D2 receptor (D2) has been implicated in aggressive behavior, highlighting its role in offensive behavior [32]. Abnormal behavior is associated with increased activation of the dopaminergic system, likely responsible for the observed high aggression [33]. Fansidar may enhance dopamine release, contributing to its effect in males. Additionally, Artemether Lumefantrine showed high aggression in female Drosophila melanogaster, while aggression was moderate in the Fansidar group. Regarding Haloperidol treatment, it helps calm situations of aggression, indicating its role in human psychosis [34]. Medium aggression was highest in the Artemether Lumefantrine group in male Drosophila melanogaster, while Artesunate showed moderate aggression, suggesting antagonistic actions to haloperidol. Although haloperidol usage in combination with promethazine is recommended for psychiatric behavior management [35], the modulatory effects of Artesunate, as demonstrated in this study, should be carefully considered. Artesunate was associated with medium aggression in female Drosophila melanogaster, while low aggression was highest in the Fansidar group.

**FOR SEROTONIN (SHT)**

**Action of Fluoxetine treatment**

Fansidar demonstrated the highest aggression in male Drosophila melanogaster, with Artesunate showing moderate aggression. Fluoxetine has been linked to decreased aggression in humans [36], possibly through increased serotonin production. In fish and dogs, fluoxetine has been effective in treating aggression [37, 38]. Fansidar may inhibit serotonin activity, particularly in males. Artemether Lumefantrine displayed the highest aggression in female Drosophila melanogaster, while Artesunate showed moderate aggression. Serotonin (5-HT) remains a key determinant in aggression, with other molecules acting indirectly through 5-HT signaling [39].

Regarding Cyproheptadine treatment, Fansidar exhibited the highest aggression in male Drosophila melanogaster, suggesting its role in serotonin antagonism. Cyproheptadine, a serotonin antagonist, is used to control CNS effects associated with aggression [40, 41]. It is recommended for serotonin medication overdose reversal [42]. Conversely, Artesunate displayed medium aggression in female Drosophila melanogaster, while low aggression was highest in the Fansidar group. These findings underscore the potential interference of antimalarials with neurological behavior through various modulatory pathways involved in aggression [39].

**Effect of Drugs on Age**

Artesunate exhibited the highest aggression in male Drosophila melanogaster across all age groups, with the most pronounced effects observed in the 40–45-day range, while Fansidar showed moderate aggression in both the 21-25- and 40-45-day groups. A recent study in young children found no significant CNS effects of Artesunate, consistent with our findings [43]. However, the heightened aggression observed in our study highlights the need for further investigation into the drug's effects in adults. Artesunate also induced the highest aggression in female Drosophila melanogaster aged 40-45 days. Aging is associated with cognitive decline in humans, potentially leading to increased aggression in older populations [44]. Statistical analysis revealed significant effects for Fansidar in the 0–5-day male Drosophila group, Artesunate in the 21–25-day male Drosophila group, and in both male and female Drosophila aged 40-45 days, as well as for Artemether Lumefantrine in the 0-5- and 21-25-day groups for female and male Drosophila, respectively. These findings emphasize the importance of assessing and controlling the use of these pharmaceutical agents, especially in older populations where increased aggression episodes may occur.

**CONCLUSION**

Antimalarial drugs, particularly Artesunate, demonstrated significant effects on aggressive behavior in Drosophila by interacting with specific neurotransmitters and neurons responsible for aggression, while Chloroquine and Quinine reduced aggressive tendencies. Understanding the molecular mechanisms behind these effects using genetic tools in Drosophila is crucial, especially considering the potential brain damage associated with ACTs and Artesunate's impact on aggression. Additionally, Clonidine and Levodopa increased aggression, Fluoxetine reduced it post-antimalarial treatment, and Promethazine, Haloperidol, and Cyproheptadine generally decreased aggression.

**Recommendations**

Considering the demonstrated impact of antimalarials on neurological behavior across different age groups and sexes, it's imperative to reassess their usage, especially in patients with neurological complications. Moreover, there's a pressing need to elucidate the specific pathways through which these drugs exert their effects, facilitating a deeper understanding of their interactions at the cellular level.

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