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Antihyperglycemic Effects of Artocarpus Heterophyllus Leaf Extracts in Drosophila Melanogaster

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ABSTRACT

Background: Diabetes mellitus (DM) is a metabolic syndrome and a major cause of global mortality rate and concern to health sector. Exploring therapeutic properties of natural plant has attracted array of interests in managing this challenge. This study, therefore, aimed to explore the antihyperglycemic effects of leaf extracts from *Artocarpus heterophyllus* (*A. heterophyllus*) in high sucrose diet-treated *Drosophila melanogaster* (*D. melanogaster*). **Methods:** Flies were divided into two groups of 50 flies (both sexes), i.e., i. Survival tests: with high sucrose diet; aqueous extract of *A. heterophyllus* (AEAH); ethanolic extract of *A. heterophyllus* (EEAH); and ii. Treatment groups: with AEAH, EEAH, and 30% sucrose diet. **Results:** The results showed that there was a significant (P<0.05) increase in mortality rate, glucose and oxidative biomarkers such as H_2O_2, nitrite with a significant (P<0.05) decrease in locomotion (negative geotaxis), glutathione peroxidase (GPx), catalase (CAT), and superoxide dismutase (SOD) activities, as well as total thiol and GSH levels among the high-sucrose diet-treated group compared to normal flies. However, Treatment with AEAH and EEAH resulted in a significant reduction (P<0.05) in mortality rates, glucose levels, and oxidative biomarkers. Additionally, there was a notable increase (P<0.05) in locomotion, as well as in the activities of GPx, CAT, and SOD. This was accompanied by a rise in total thiol and GSH levels when compared to normal flies. **Conclusion:** Extracts of *A. heterophyllus* caused a reduction in mortality and enhanced locomotion in *D. melanogaster* possibly by amelioration of antioxidant imbalance and hyperglycemia.

Introduction

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia due to impaired insulin secretion, activity, or both (Bai *et al.*, 2018, Skyler, 2004). This persistent high blood sugar disrupts glucose homeostasis, contributing to obesity and other metabolic

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diseases (Chukwunonso Obi *et al.*, 2016, Khan and Sievenpiper, 2016). It also affects lipid and protein metabolism, often leading to complications such as peripheral neuropathy, retinopathy, and coronary heart diseases (Omoboyowa *et al.*, 2018, Omoboyowa *et al.*, 2021).

Studies have indicated that chronic hyperglycemia promotes glucose autoxidation and protein glycosylation, resulting in oxidative damage through excessive reactive oxygen species (ROS) production and depletion of antioxidant defences (González *et al.*, 2023, Papachristoforou *et al.*, 2020). Oxidative stress has been identified as a key factor in the pathogenic effects of diabetes (Giacco and Brownlee, 2010, Matschke *et al.*, 2019). While the precise mechanisms behind the long-term complications of diabetes remain unclear, evidence suggests that oxidative stress plays a significant role in hyperglycemia and its related complications (Forbes *et al.*, 2008, Negre-Salvayre *et al.*, 2009). Consequently, regulating ROS generation is critical in managing diabetes and preventing its complications.

Drosophila is an established valuable model to study numerous human diseases (Grotewiel *et al.*, 2005). Diabetic *D. melanogaster* model has been reported as an ideal experimental paradigm for investigating DM (Bai *et al.*, 2018). Glucose-metabolizing genes, in particular, are largely conserved across humans and D. melanogaster (Graham and Pick, 2017). Due to the improved tolerance of chemicals from organic sources by the human body, the World Health Organization (WHO) has consistently endorsed research on utilizing molecules from natural sources for the management of chronic illnesses such as DM (Tahraoui *et al.*, 2007, Tilburt and Kaptchuk, 2008).

Artocarpus heterophyllus (*A. heterophyllus*), commonly known as Jackfruit, belongs to the *Moraceae* family and is a species of tree indigenous to the Western Ghats of India and Indonesia. Additionally, it can be found in various regions, including several Pacific Islands, Florida, Brazil, Southeast Asia, central and eastern Africa (Shanmugapriya *et al.*, 2011). A report highlights that this medicinal plant is a rich source of carbohydrates, minerals, carboxylic acids, dietary fiber, flavonoids, and vitamins such as thiamine and ascorbic acid (Wei *et al.*, 2005). In Africa, traditional medicine has long utilized different species of *Artocarpus* in treating various health conditions, including skin diseases, diarrhea, dysentery, stomach aches, ulcers, and inflammation (Adisa *et al.*, 2004). *A. heterophyllous* has been reported to possess antibacterial, anti-diabetic, anti-inflammatory, antioxidant, and anti-helmintic properties (Soeksmanto *et al.*, 2007). Majority of these studies have linked different properties of *A. heterophyllous* extracts to their high flavonoid contents using different models (Omar *et al.*, 2011). However, anti-diabetic efficacy of solvent extracts of *A. heterophyllus* leaves in high sucrose diet-induced hyperglycaemic *D. melanogaster* model has not been investigated. Therefore, this study investigated antihyperglycemic effects of leaf extracts from *A. heterophyllus* in high sucrose diet-treated *D. melanogaster* by assessing longevity, glucose levels, oxidative biomarkers, and locomotor activities.

Materials and Methods

Materials

Chemicals such as sucrose, ethanol, dipotassium hydrogen trihydrate, potassium dihydrogen phosphate, hydrogen peroxide, dithiobis (2 nitro benzoic acids), and sorbitol were procured from Sigma-Aldrich, Inc. (Saint Louis, MO, USA). All other reagents used in this study were of analytical grades and were prepared in all-glass apparatus with distilled water. Wild-type of *D. Melanogaster* flies (Harwich strain) were obtained from *Drosophila* research laboratory of the Department of Biochemistry, College of Medicine, University of Ibadan, Oyo State, Nigeria.

Collection and authentication of plant sample

The leaves of *A. heterophyllus* were bought from Adadia community Market in Uruan Local Government, Akwa Ibom State, Nigeria. A voucher specimen was deposited and authenticated by a taxonomist (Specimen No.: 2019800) at the herbarium of the Department of Plant Science and

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Biotechnology, Ekiti State University, Ado-Ekiti, Nigeria.

Preparation of plant extracts

The plant leaves were rinsed and air dried to a constant weight for 14 days, and then powdered using an automated laboratory blender. The sample was weighed (150 g) and soaked in 1 litter of distilled water for 24 h with a continuous agitation. The sample was then concentrated using a rotary evaporator set to 40 °C after being filtered using filter paper and stored at 4 °C before use. Similarly, leaf powder (150 g) was extracted into 1 litter of 95% ethanol by maceration for 72 h. The extract was also filtered using Whatman No 1 filter paper and the filtrate was concentrated, lyophilized and thereafter preserved for further use. For the preparation of the solution to be added to the fly diet, the resulting powder was reconstituted in water.

Fruit flies treatment

All flies were maintained at a constant temperature of 23±2 °C and relative humidity with a 12-hour light/dark clock cycle in vials containing corn meal. Young flies that were 2 to 3 days old were collected under mild ice anesthesia and placed into vials. The flies, 50 of each sex per vial, were transferred to new vials containing fresh food every three days to maintain consistent food quality. The flies were flipped into new vials (50 flies in each (both sexes)) containing fresh feed every three days to ensure feed quality consistency.

Experimental design and procedure

The experimental study was divided into two groups as follows; (i) Survival test with 30 and 60% sucrose-based diet; 0.1-1.0 mg/kg AEAH; and 0.1-1.0 mg/kg EEAH, and (ii) Treatment groups with 0.1 mg/kg AEAH, 0.1 mg/kg EEAH, and 30% sucrose diet.

Treatment with sucrose in wild-flies

Treatment with sucrose for the induction of hyperglycemia-like effects in wild-flies was performed according to the method of Tennessen *et al*. with modifications. Briefly, sucrose (30% and 60% w/v) was incorporated into the regular fly diet (Tennessen *et al.*, 2014). All other ingredients of the standard fly diet (1% w/v brewer's yeast, 2% sucrose, 1% w/v powdered milk, 1% w/v agar, and 0.08% w/v nipagin) were kept constant. The glucose levels of flies homogenates were monitored according to the method of Palanker Musselman *et al.* (Palanker Musselman *et al.*, 2011).

Survival/ longevity study

Survival rate of flies in 30 and 60% sucrose-treated diet and treatments with optimal doses of AEAH and EEAH were monitored using the method described by Abolaji *et al*. (Abolaji *et al.*, 2019). Mortality was observed in flies each day for the period of exposure (28 days). The survival rate was calculated and presented as percentage of living flies after each treatment as reported by Abolaji *et al*. (Abolaji *et al.*, 2019).

Treatment groupings of wild-type flies

Five vials of 50 flies (n=50; both sexes) each were collected and divided into two groups of survival test and treatment groups are shown in **Table 1.**

Measurement of locomotor performance (Negative geotaxis activity)

The locomotor activities of flies were determined using negative geotaxis method as previously described by Adedara *et al.* (Adedara *et al.*, 2016). Ten flies (both genders, five each) were immobilized under mild ice anesthesia and placed separately in labelled vertical glass columns (15 cm x 1.5 cm). After recovering from ice exposure for 20 minutes, the flies were gently tapped to the bottom of the column. The number of flies that climbed up to the 6 cm mark within 6 seconds was recorded, along with the number that remained below the mark after this time. The scores (%) were expressed as the percentage of mean total (ΔT) of flies at the top to total number (T) of flies as shown below. This procedure was repeated three times with a 1-minut interval.

Locomotor activity (%) = ΔT/T x 100

Where; ΔT represents mean total of flies at the top; while T is total number of flies.

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Table 1. Grouping

1. Survival tests
i. <u>with high sucrose diet only</u>:
Group 1: Normal wild-type flies;
Group 2: Wild-type flies treated with 30% Sucrose;
Group 3: Wild-type flies treated with 60% Sucrose.
ii. With AEAH:
Group 1: Normal wild-type flies;
Group 2: Wild-type flies treated with 0.1 mg/kg AEAH;
Group 3: Wild-type flies treated with 0.5 mg/kg AEAH;
Group 4: Wild-type flies treated with 1 mg/kg AEAH.
iii. With EEAH:
Group 1: Normal wild-type flies;
Group 2: Wild-type flies treated with 0.1 mg/kg EEAH;
Group 3: Wild-type flies treated with 0.5 mg/kg EEAH;
Group 4: Wild-type flies treated with 1 mg/kg EEAH.
2. Treatment groups:
Group 1: Normal wild-type flies;
Group 2: Wild-type flies + 30% sucrose;
Group 3: Wild-type flies treated with 0.1 mg/kg AEAH + 30% sucrose;
Group 4: Wild-type flies treated with 0.1 mg/kg EEAH + 30% sucrose.

***AEAH**: Aqueous extract of A. heterophyllus; **EEAH**: Ethanolic extract of A. heterophyllus; Note: All the experiments lasted for twenty-eight days (28 days).*

Preparation of flies tissues for biochemical assays

Flies homogenization: After anaesthesia, flies were collected, weighed, and homogenized in 0.1 M phosphate buffer (pH 7.4, 1:10 w/v). The homogenate was centrifuged at 4000 rpm (using Mikro 220R centrifuge) at 40 °C for 10 min. The supernatant was then separated into labelled Eppendorf tubes while the pellet was discarded. The sample was kept in the refrigerator for biochemical assays.

Biochemical analyses: Biochemical parameters, such as total thiol, were measured using the method of Ellman (Ellman *et al.*, 1961), reduced glutathione levels by the method of Jollow *et al.* (Jollow *et al.*, 1974), glutathione-S-transferase (GST) activity by the method of Habig and Jakoby (Habig and Jakoby, 1981), catalase (CAT) activity by the method of Claiborne (Claiborne, 1985), and hydrogen peroxide level using the method described by Wolff (Wolff, 1994). Nitric oxide (NO) level was determined as previously reported by Moncada *et al*. (Moncada, 1992) and glucose level was determined according to the method of Palanker Musselman *et al*. (Palanker Musselman *et al.*, 2011).

Data analyses

Data analyses were performed using one-way ANOVA, followed by Tukey's test for post-hoc analysis and graphical representation of results was performed using GraphPad Prism 8.5 version (GraphPad Software, San Diego, CA, USA). All values were expressed as mean±SE (n=6). Statistical differences were considered at P-value< 0.05 (Zar, 1984).

Results

Survival test

Effects of 30% and 60% sucrose-treated diets on survival/longevity in D. melanogaster: **Figure 1** represents the effects of 30% and 60% sucrose-treated diets on survival/longevity of *D. melanogaster*. As shown in the result, 60% sucrose-treated flies revealed a significantly (P<0.05) high mortality rate before 28 days of the experimental study compared to the 30% sucrose treated group and normal control.

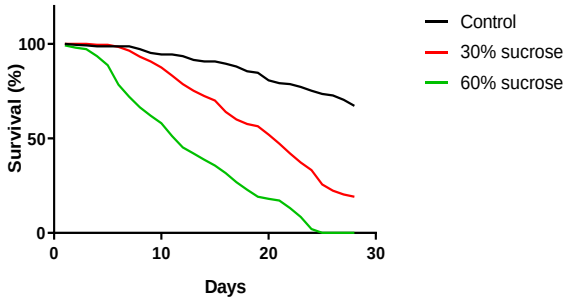

Figure 1. Effect of 30% and 60% sucrose treatments on the survival and longevity in *Drosophila melanogaster*.

Effects of 30% and 60% sucrose-treated diets on glucose levels, oxidative stress, and antioxidant parameters in D. melanogaster: **Figure 2** (a-g) represents the effects of 30% and 60% sucrose-treated diets on glucose levels, oxidative stress markers (such as H_2O_2 and nitrite levels), and

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antioxidant parameters (total thiol, GSH, GST and CAT) in *D. melanogaster*. As indicated in the results, 30% and 60% sucrose treated groups showed a significant (P<0.05) increase in glucose (**Figure 3a**) and oxidative biomarkers such as H_2O_2 (**Figure 2b**) and nitrite (**Figure 2c**) levels with a significant decrease (P<0.05) in the levels of total thiol (**Figure 2d**) and GSH (**Figure 2e**), and activities of GST (**Figure 2f**) and CAT (**Figure 2g**) compared to the control flies. Similarly, a significant (P<0.05) difference was found only in glucose, H_2O_2, and GSH levels of the 30% sucrose treated flies compared to 60% sucrose treated flies. However, no significant (P>0.05) difference was indicated in the levels of nitrite and total thiol as well as GST and CAT activities in 30% sucrose treated compared to 60% sucrose treated flies

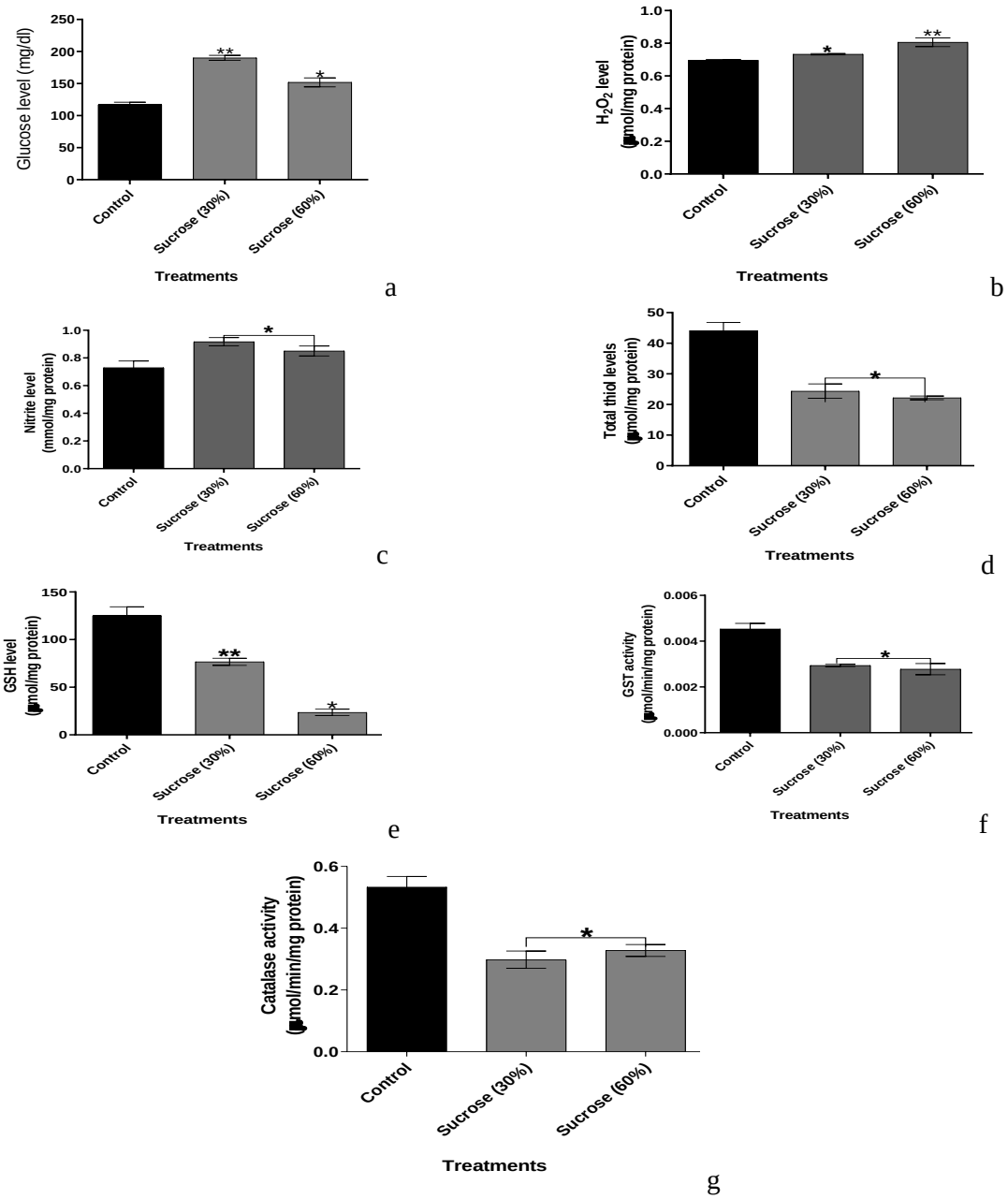

Figure 2. (a-g): Effect of 30% and 60% sucrose treatments on glucose levels, xidative stress biomarkers, and antioxidant parameters in *Drosophila melanogaster*. Values are expressed as mean ± SE (n=50). * *and* ** indicate a significant (P<0.05) difference vs. control.

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Effects of 30% and 60% sucrose-treated diets on locomotor (climbing) activity in D. melanogaster: **Figure 3** represents the effects of 30% and 60% sucrose-treated diets on locomotor (climbing) activities of *D. melanogaster*. There was a significant ($p<0.05$) decrease in the climbing activity of 60% sucrose-treated flies compared to 30% sucrose-treated group and control flies.

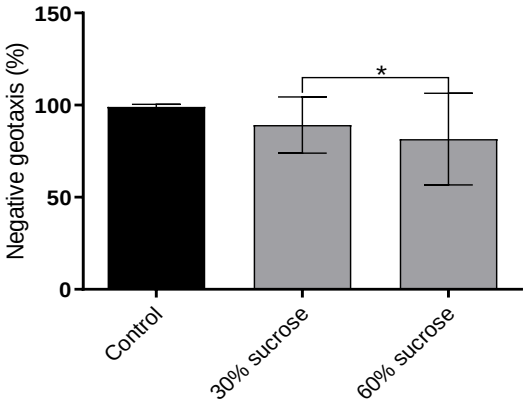

Figure 3. Effect of 30% and 60% sucrose treatments on locomotor (climbing) activity in *Drosophila elanogaster*. Values are expressed as mean±SE (n=50). *indicates a significant ($P<0.05$) difference vs. control.

Treatments

Effects of aqueous and ethanolic extracts of A. heterophyllus on survival of D. melanogaster: **Figure 4** represents the effects of (a) AEAH-treated (b) EEAH-treated diets on survival of *D. melanogaster*. As indicated in the result (**Figure 4a**), the survival of flies in the presence of the AEAH was in a concentration-dependent manner. However, the survival rate significantly increased ($P<0.05$) among groups treated with 0.1–1.0 mg/kg AEAH compared to the control group. Similarly, as revealed in **Figure 4b**, the survival and longevity rate of flies treated with different doses (0.1, 0.5, and 1.0 mg/kg) of EEAH were favourable compared to basal diet. However, 0.1–1.0 mg/kg AEAH-treated flies revealed a significant ($P<0.05$) decrease moderately in flies survival compared to the control flies.

Effects of aqueous and ethanolic extracts of A. heterophyllus on oxidative stress and antioxidant parameters in D. melanogaster: **Figure 5** (a-f) represents the effect of AEAH-treated diet on oxidative stress markers (H_2O_2 and nitrite) and antioxidant parameters of *Drosophila melanogaster*.

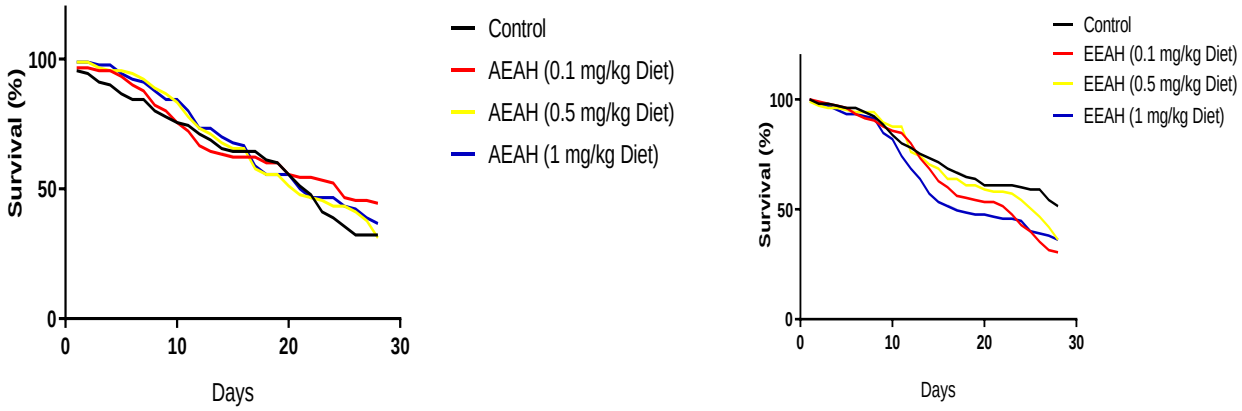

Figure 4 (a and b). Effects of (a) aqueous extract and (b) ethanolic extracts of *A. heterophyllus* on *Drosophila melanogaster* survival (longevity).

There was a significant ($P<0.05$) increase in the levels of H_2O_2 produced among AEAH-treated flies (**Figure 5a**) with a significant ($P<0.05$) decrease in the levels of nitrite produced (Fig. 5b) in the highest doses (0.5 and 1.0 mg/kg) compared to the control flies. However, no significant ($P>0.05$) difference was observed in the total thiol levels except for 0.5 mg/kg AEAH-treated group (**Figure 5c**). Also, a similar effect was noticeable in GSH levels except for 0.5 mg/kg AEAH-treated

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group where a significant (P<0.05) increase was noticeable in GSH level compared to normal flies (**Figure 5d**). However, a significant (P<0.05) decrease was observed in GST (**Figure 5e**) and CAT (**Figure 5f**) activities among 0.1 and 0.5 mg/kg AEAH-treated groups. There was a significant (P<0.05) increase among 1.0 mg/kg AEAH-treated groups compared to normal flies.

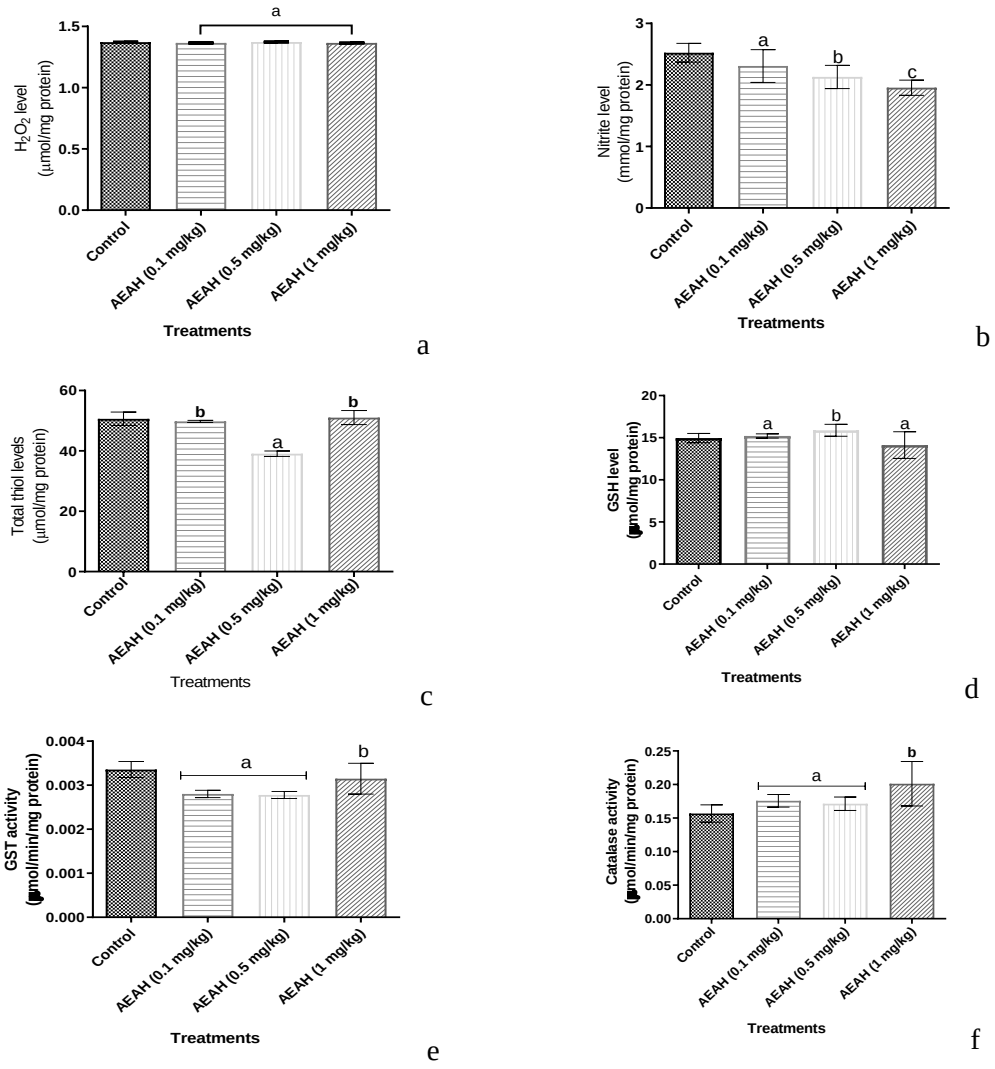

Figure 5 (a-f). Effect of the aqueous extract of *A. heterophyllus* on oxidative stress biomarkers and antioxidant parameters of *Drosophila melanogaster*.
Values are expressed as mean±SE (n=50). Alphabets (a and b) indicate a significant (P<0.05) difference *vs.* control.

Effect of ethanolic extract of A. heterophyllus on oxidative stress and antioxidant parameters in D. melanogaster: **Figure 6** (a-f) represents the effects of EEAH on oxidative stress markers and antioxidant parameters of *D. melanogaster*. There was no significant (P>0.05) difference in the levels of H_2O_2 produced among different doses of EEAH-treated flies compared to control (**Figure 6a**). However, a significant (P<0.05) decrease was observed in nitrite levels of 0.1 and 0.5 mg/kg EEAH-treated flies with a significant increase (P<0.05) in 1.0 mg/kg EEAH-treated group compared to control flies (**Figure 6b**). Also, a significant (P<0.05) increase was observed in total thiol level of 0.1 mg/kg EEAH-treated flies, while no significant (P>0.05) difference was noticeable

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among 0.5 and 1.0 mg/kg EEAH-treated flies compared to normal flies (**Figure 6c**). Similarly, a significant (P<0.05) increase was observed in GSH level of 0.5 mg/kg EEAH-treated flies with no significant (P>0.05) difference among 0.1 and 1.0 mg/kg EEAH-treated flies (**Figure 6d**). Furthermore, dose-independent effects were noticeable in activities of GST (**Figure 6e**) and CAT (**Figure 6f**) among EEAH-treated flies. However, 0.5 and 0.1 mg/kg EEAH caused a significant (P<0.05) increase in GST and CAT activities compared to normal flies.

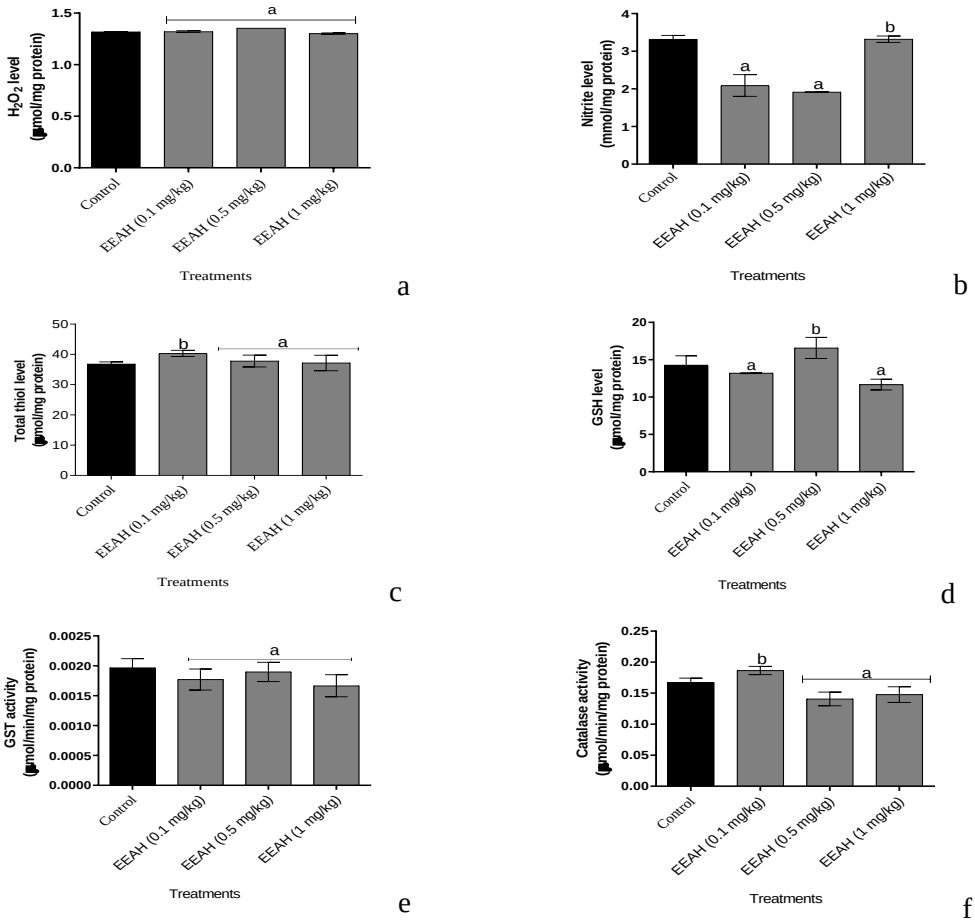

Figure 6 (a-f). Effect of the ethanolic extract of *A. heterophyllus* on oxidative stress biomarkers and antioxidant parameters of *Drosophila melanogaster*.
Values are expressed as mean±SE (n=50). Alphabets (a and b) indicate significant (P< 0.05) difference *vs*. control.

Effect of aqueous and ethanolic extracts of A. heterophyllus on locomotor (climbing) activity of D. melanogaster: **Figure 7** shows the effect of (a) different doses of AEAH-treated and (b) EEAH-treated diets on locomotor (climbing) activity of *D. melanogaster*. There was no significant (P>0.05) difference in locomotor activities of different doses of AEAH-treated flies compared to the control. Similarly, as shown in **Figure 7b**, there was no significant (P>0.05) difference in locomotor activities of the different doses of EEAH-treated flies compared to the control.

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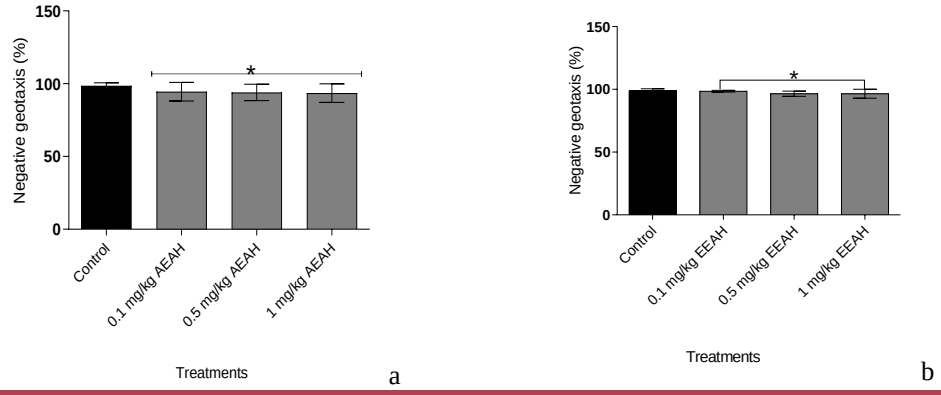

Figure 7. Effect of the (a) aqueous and (b) of ethanolic extract *A. heterophyllus* on locomotor activity of *Drosophila melanogaster*.
Values are expressed as means±SE (n=50). *Indicates a significant (P< 0.05) difference *vs*. control.

Effect of aqueous and ethanolic extracts of A. heterophyllus on high sucrose diet treated D. melanogaster: **Figure 8** (a-g) presents AEAH and EEAH effects on high sucrose diet-induced hyperglycemia in *D. melanogaster*. There was a significant (P<0.05) increase in glucose level of sucrose-treated group compared to the control flies (**Figure 8a**). However, treatment with 0.1 mg/kg AEAH and EEAH caused a significant (P<0.05) decrease in glucose concentrations compared to sucrose-induced hyperglycemic flies and normal flies in the control group. Also, a significant (P<0.05) decrease was seen in oxidative stress makers such as H_2O_2 and nitrite levels of sucrose-induced hyperglycaemic flies treated with 0.1 mg/kg AEAH and EEAH compared to untreated sucrose-induced hyperglycaemic flies and normal control (**Figure 8b** and **c**). Similarly, a significant (P<0.05) increase was observed in total thiol and GSH levels (**Figure 8d** and **e**) as well as GST and CAT activities of sucrose-induced hyperglycaemic flies treated with 0.1 mg/kg AEAH and EEAH compared to untreated sucrose-induced hyperglycaemic flies and normal control (**Figure 8f** and **g**). This observation was compared between the extracts; however, there was no significant (P>0.05) difference in the effects of 0.1 mg/kg AEAH and 0.1 mg/kg EEAH on sucrose-induced hyperglycaemic flies.

Discussion

Recent studies have indicated that medicinal plants have long served as a vital resource for managing various metabolic disorders in humans (Grover *et al.*, 2002). Their therapeutic potential arises from a rich array of phytonutrients, including flavonoids, phenolics, and saponins (Saleem *et al.*, 2022). *A. heterophyllus* is a medicinal plant with reported anti-diabetic activities (Adediwura and Kio, 2009, Gobinath *et al.*, 2022). *D. melanogaster* is often used in studying various biological processes, including aging and longevity as well as nutritional intervention studies, as it exhibits many similarities with mammalian species. Therefore, the current investigation aimed to explore the antihyperglycemic effects of both aqueous and ethanolic extracts of this plant on a high sucrose diet-induced hyperglycemic model using *Drosophila melanogaster*.

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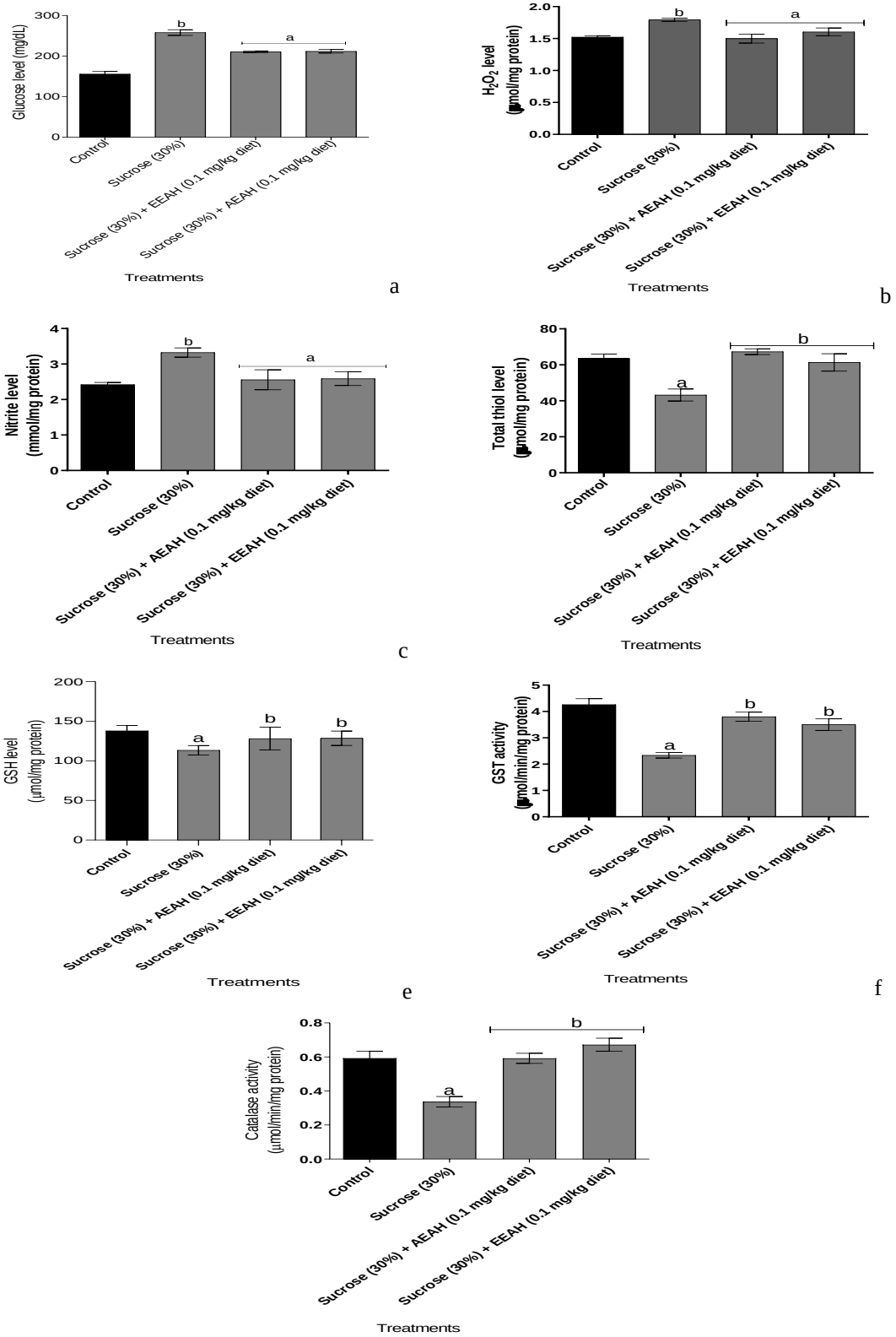

Figure 8 (a-g). Effects of the aqueous and ethanolic extracts of *A. heterophyllus* on high-sucrose diet-induced hyperglycemia in *Drosophila melanogaster*. Values are expressed as mean±SE (n=50). Alphabets (a, b & c) indicate a significant (P< 0.05) difference vs. control.

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According to a recent report, standardized diets are essential for the survival, longevity, and reproductive activity of *D. melanogaster* (Eickelberg *et al.*, 2022). However, in the current study (**Figure 1**), flies treated with a high sucrose diet (HSD) exhibited an increased mortality rate, accompanied by high glucose levels and markers of oxidative stress (H_2O_2 and nitrite levels) (**Figure 2a**, **b**, and **c**), with a concomitant depletion of cellular antioxidant systems (**Figure 2d**, **e**, **f**, and **g)**. These findings signal hyperglycemic phenotype traits induced by high sucrose diet exposure in flies, which could possibly have resulted from insulin signalling dysregulation (Morris *et al.*, 2012, Palanker Musselman *et al.*, 2011). However, this uncontrollable condition possibly resulted into cellular stress and toxicity, affecting survival and longevity of flies, an observation that is consistent with the report of Bhagwat *et al.* (Bhagwat *et al.*, 2008).

HSD-exposed flies demonstrated a locomotion deficit, as evidenced by negative geotaxis assays (**Figure 3**). Reports have indicated that negative geotaxis reflects a combination of behavioural, neurological, and reproductive changes in *D. melanogaster* (Lushchak *et al.*, 2011). Similarly, a reduction in locomotor activity according to Omale *et al.* could possibly reflect an impairment that parallels insulin-resistant in diabetes, where peripheral neuropathy leads to loss of coordination and reflexes (Omale *et al.*, 2020, Usai *et al.*, 2022). However, our observation following the treatment with diet-based extracts indicated that different doses of AEAH and EEAH fractions (**Figures 4-8**) are capable of simultaneously enhancing lifespan, mobility and reversing HSD-induced cellular redox imbalance and toxicity in *D. melanogaster (Mohammed et al., 2017)*. This finding supports the claims that medicinal plants play an important role in the management of several metabolic-related syndromes, as they are reservoir of compounds capable of mitigating the damaging effects of ROS (Biworo *et al.*, 2015, Omale *et al.*, 2020). Experimented extracts also showed a degree of safety similar to previous reports by Ogbonnia *et al.* and Ogunbolude *et al.* (Ogbonnia *et al.*, 2008, Ogunbolude *et al.*, 2009).

This study indicated the possible toxic doses of the extracts of *Artocarpus heterophyllus* (Jackfruit) leaf and as well as their ameliorating potentials in high sucrose-induced diabetic phenotype in *Drosophila melanogaster*. However, the study did not identify or characterize the specific bioactive compounds responsible for the observed antihyperglycemic and antioxidant effects. Also, it did not examine the possible effect using human subject and no clinical trials were conducted.

Conclusion

Based on the findings of this study, HSDs diets caused diabetic phenotypic reactions in *D. melanogaster* that possibly corroborate insulin signalling derangement and a redox imbalance state. However, the aqueous and ethanolic extracts of *A. heterophyllus* leaves showed significant reductions in glucose levels, neurological improvements, and cellular protection, which are crucial for managing metabolic-related syndromes in *D. melanogaster*. Similarly, results of this study further highlight the value of *D. melanogaster* and high sucrose diets as effective instruments for researching metabolic diseases and possible treatments. Overall, it could be inferred that AEAH and EEAH possess antidiabetic potential.

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Authors' contribution

Olowoyo OF, Afolabi OB, and Otorunlagbo AO carried out the analyses, data collection, data analysis, and manuscript writing. Oloyede OI, Abolaji AO, Adewale OB, Afolabi OB, and Omotoso BA conceptualized the study, designed research methods and approved the study. All authors read and approved the manuscript final draft and submission.

Conflicts of interest

The authors confirm that they have no conflicts

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of interest concerning the study described in this manuscript.

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