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Corn Oil Supplementation Enhances Locomotor Performance and Mitochondrial Function in *Drosophila melanogaster*

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Abstract

Polyunsaturated fatty acids are vital for brain health, supporting cognitive development and helping to prevent neurodegenerative diseases. Since the body cannot produce them, they must be obtained through food. This study aimed to assess the effects of corn oil on the behavior and biochemical parameters of *Drosophila melanogaster*. The flies were fed a diet supplemented with different concentrations of corn oil from the larval stage until the fifth day of adulthood. A diet containing corn oil (37.8 mg/mL of linoleic acid) reduced mortality under starvation conditions and enhanced locomotor performance ($p < 0.01$). Biochemical analyses revealed increased levels of glutathione ($p < 0.001$), citrate synthase activity ($p < 0.05$), and mitochondrial phosphorylation ($p < 0.05$), indicating a potential boost in energy metabolism. Conversely, a decrease in acetylcholinesterase activity ($p < 0.05$) was observed, suggesting cholinergic modulation. These results demonstrate that corn oil supplementation supports neural health in this animal model, opening pathways for further research into non-pharmacological treatments for neurodegenerative diseases such as Alzheimer's disease.

Keywords: *Drosophila melanogaster*; corn oil; biochemical and behavioral parameters; functional food

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1. Introduction

In the last decade, much has been said about the benefits of polyunsaturated fatty acids (PUFAs) and their various indications, primarily in neurobiochemical processes. Studies have shown that omega-3 PUFAs, predominantly found in fish, nuts, seeds, and plant oils, can enhance neuronal and glial survival, reduce lipid peroxidation, and decrease protein oxidation in models of neural injury [1]. They serve as protectors against cognitive impairment, and they lower the risk of developing Alzheimer's disease (AD) [2]. However, the protective effects of omega-3 are typically associated with prolonged exposure and

high doses [3] and may not be evident in the short and medium term [4,5]. Among the PUFAs, docosahexaenoic acid (DHA) is vital to brain metabolism, and its supplementation demonstrates anti-inflammatory, antioxidant, neuroprotective, and non-apoptotic activity [6]. Additionally, low doses of omega-6, such as linoleic acid (LA), can shield the brain against inflammation through its oxidation products. When combined with eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), they may reduce migraine frequency; however, excessive intake can lead to the opposite effect, increasing blood coagulability and proinflammatory effects, as leukotrienes release lysosomal enzymes and generate free radicals [7,8].

As a nutritional source, consuming corn oil, which is rich in LA, is highly digestible and provides energy and has demonstrated significant biological effects, including antioxidant activity that helps protect cells from free radicals and prevents cardiovascular, inflammatory, and neurodegenerative diseases in animal models [9] such as *Drosophila melanogaster* that cannot convert LA to the longer chain fatty acids [10,11].

D. melanogaster is an insect with over a hundred years of history in scientific research, used as an alternative model in experimental studies of multicellular organisms [12]. This insect has high reproductive capacity, rapid development, a short lifespan, and conserved biological processes, making it an ideal model for toxicological assessment [13]. Additionally, the daily food consumption of a single *D. melanogaster* is approximately 1.5 µL, which represents 1.7 times its body mass [14]. Furthermore, females in the maturation stage of fertilized eggs consume more solid food than virgin females [15].

Using *D. melanogaster* as an experimental model to investigate the effects of corn oil ingestion provides an accessible, rapid, and relevant method to explore the mechanisms underlying its impact. This model is well known for its application in studying neurodegenerative diseases. Given that LA is typically associated with maintaining a healthy cellular function, this study aimed to address two key questions:

Can corn oil affect the behavioral parameters of *D. melanogaster*?

Can corn oil modulate the metabolism and biochemical parameters of the flies?

2. Materials and Methods

2.1. Fly Strain and Rearing

All the experiments in this study were conducted with wild-type (WT) w^{1118} (BDSC 3605) and *Canton Special* (BDSC 64349) flies obtained from the Bloomington Drosophila Stock Center (BDSC), Bloomington, IN, USA. The flies were maintained at 25 ± 1 °C on a standard diet comprising cornmeal (6.5% *m*/*v*), agar (CAS n. 9002-18-00) (1.0% *m*/*v*), yeast (6.5% *m*/*v*), and Nipagin (CAS n. 99-76-3) (3.0% *v*/*v*) [16–18].

The Amyloid Precursor Protein—β-amyloid peptide 42 (APP-β_{42}) expressing line was cultured at 29 ± 1 °C and was created by recombining the APP-β_{42} transgene under the control of the upstream activation sequence (UAS) UAS-APP-β_{42} with the glass multimer reporter Gal4 driver (GMR-Gal4) (BDSC 1104) on chromosome II, followed by crossing those flies with flies carrying UAS-APP-β_{42} (BDSC 33773) on chromosome II. All crosses were performed with transgenic lines using *Canton Special* as a background.

2.2. Phenotypic Analysis

The heads of fifty flies (GMR-Gal4; UAS-APP-β_{42} and *Canton Special*) were isolated through dissection in a 1 M sodium phosphate dibasic (CAS n. 10028-24-7) and sodium phosphate monobasic (CAS n. 10049-21-5) buffer (pH 7.0) and were fixed in 4% (*v*/*v*) paraformaldehyde at 25 ± 1 °C. This study calculated the arithmetic mean for each metric across all ommatidia detected in images obtained using a Zeiss Stemi 508 microscope (Jena, Germany) with Axiocam 208 software, based on the ommatidia metrics.

2.3. Validation of APP

To verify the effect of the supplementation diet in the mutant lines, fifty heads of *D. melanogaster* GMR-Gal4; UAS-APP-β_{42} and *Canton Special* were homogenized in a Congo Red (CR) buffer containing 10 mM of a sodium phosphate buffer (pH 7.4), 2.7 mM KCl (CAS n. 7447-40-7), 0.137 M NaCl (CAS n. 7647-14-5), 6.1 µM of Congo Red (CAS n. 573-58-0), and 10% ethanol [19]. The samples were incubated in a CR buffer for 24 h to detect fibril amyloid. The binding of fibril amyloid and Congo Red was determined spectrophotometrically at 541 nm using a Model Cary 50MPR Varian Spectrophotometer (Varian Ltd., Melbourne, Australia). The results were expressed as arbitrary absorbance units (A.A.U.)/mg protein.

2.4. Exposure to a Diet Supplemented with Corn Oil

For the treatment, different corn oil concentrations were assayed. Mutant (GMR-Gal4; UAS-APP-β_{42}) and WT (w^{1118} and *Canton Special*) strains (male and female) were maintained under two different experimental conditions for three hours after the eggs hatched and the larvae were fed (1) a standard diet and (2) a standard diet supplemented with corn oil (the main component being linoleic acid, at final concentrations of 18.9, 37.8 and 45.9 mg/mL).

After 5 days of supplementation, female thoraces (50 samples/microtubes) and heads (50 samples/microtubes) were dissected and homogenized with tungsten carbide beads (cat no 69997, Qiagen) in a solution (NaCl 0.9%, pH 7.0) (CAS n. 7647-14-5) containing a protease inhibitor cocktail diluted to 1:200 (CAS n. 66701-25-5). The homogenates were centrifuged at 10,000× *g* for 10 min at 4 °C. Afterward, the supernatant was collected and stored at -20°C until use.

2.5. Determination of the Pupal Volume of D. melanogaster

Five days after the WT (w^{1118}) larvae were fed different diets, metamorphosis in adults began. To evaluate the effect of dietary conditions on pupal development, this study calculated the volume and axial ratio (length/width) of 40 pupae [20].

2.6. Eclosion Assay

This study initiated the assay one day after most WT (w^{1118}) pupae had turned black and recorded the number of flies emerging from each vial every two hours until most flies in each culture vial had emerged [21].

2.7. Starvation Assay

After the WT (w^{1118}) larvae were fed various diets as described in Section 2.4, the pupae were transferred to test tubes containing agar (1% *m*/*v*). Following eclosion, the adult flies were moved every 24 h to new tubes filled only with agar, and the survival rate was recorded [22] over five days.

2.8. Survival Assay

The effect of corn oil supplementation on WT (w^{1118}) *D. melanogaster* lifespan was assessed using newly emerged flies. On the first day post-eclosion, the flies were transferred to different tubes (120 flies/vial and 5 vials/group) and were maintained either on a standard diet or a diet supplemented with corn oil. The vials were changed every two days to provide fresh food, ensure optimal physiological conditions, and avoid mortality due to other causes such as sticking to the moist food, mold, or bacterial growth [23]. Mortality was recorded in each vial for 15 days.

2.9. Climbing Assay

The locomotor behavior of the WT (w^{1118}) flies was monitored using a counter-current apparatus [24]. The flies (2, 5, 10, and 15 days old) were transferred to empty cylindrical tubes that are 15 cm tall. The tubes were then tapped to settle the flies at the bottom, and they were given 60 s to climb the 15 cm from the bottom of the vial. The experiment was conducted over five trials/replicates. Results were obtained using the phototaxis index $\sum(I \times Ni)/N$, where N represents the total number of flies tested, and Ni is the number of flies in each tube [25].

2.10. Reduced (GSH) Glutathione Levels

Fifty thoraces and heads of WT (w^{1118}) *D. melanogaster* were homogenized in a 100 mM sodium phosphate buffer (pH 7.4) containing 6 mM EDTA and 1 mg/mL OPT for 15 min [26]. Glutathione levels were assessed spectrophotometrically at 420 nm using a Model Cary 50MPR Varian Spectrophotometer (Varian Ltd., Melbourne, Australia).

2.11. Lactate Content

Fifty thoraces and heads of WT (w^{1118}) *D. melanogaster* (dissected and stored at −20 °C in protease inhibitor) were macerated and homogenized in a 0.1 M sodium phosphate (CAS n. 7601-54-9) buffer at pH 7.4. The homogenate was centrifuged at 10,000× *g* for 10 min at 4 °C, and the supernatant was collected. The lactate content was measured by the lactate oxidase method according to the manufacturer's instructions (Labtest, Brazil, cat. n. #138-1/50). Absorbance was monitored spectrophotometrically at 550 nm using a Model Cary 50MPR Varian Spectrophotometer (Varian Ltd., Melbourne, Australia). The lactate content was expressed as mg/dL of lactate per total protein amount in the sample.

2.12. Citrate Synthase (CS) Activity

Fifty thoraces and heads of WT (w^{1118}) *D. melanogaster* (dissected and stored at −20 °C in protease inhibitor) were homogenized in 200 mM Tris (pH 8.0) with 0.2% *v*/*v* Triton X-100 (CAS n. 9036-19-5) [27]. The homogenates were centrifuged at 9000× *g* for 30 min at 4 °C. The supernatant was collected, and the protein concentration was determined. Citrate synthase (CS) activity was assayed by adding 0.01 mg of protein to a final volume of 170 µL of a Tris buffer containing 10 mM Acetyl-CoA (CAS n. 32140-51-5), 1 mM 5′5′-Dithiobis-2-nitrobenzoic acid (DTNB) (CAS n. 69-78-3), and 10 mM oxaloacetate (CAS n. 328-42-7). The reduced coenzyme A (CoA-SH) formed by CS activity converts the DTNB into 2-nitro-5-thiobenzoic acid (TNB). CS activity was evaluated by the rate of TNB formation, measured spectrophotometrically at 412 nm according to Srere (1969) [28] using a Model Cary 50MPR Varian Spectrophotometer (Varian Ltd., Melbourne, Australia).

2.13. Oxygen Consumption

Respiration was assessed using isolated tissues from mutant (GMR-Gal4; UAS-APP-β_{42}) flies, with samples consisting of ten heads or three thoraces each, without chemical permeabilization. Tissues were placed in a 2.1 mL MiR05 respiration buffer (20 mM 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES) (CAS n. 7365-45-9), 10 mM KH_2PO_4, 110 mM sucrose, 20 mM taurine, 60 mM K-lactobionate, 0.5 mM ethyleneglycol-*bis*(β-aminoethyl)-N,N,N′,N′-tetraacetic acid (EGTA) (CAS n. 67-42-5), and 3 mM of $MgCl_2$, 1 g/L fatty acid-free BSA, pH 7.1) [29]. They were maintained at 600 rpm and 25 °C using a high-resolution Oxygraph (OROBOROS Oxygraph) along with the DataLab software package, version 5.0 (OROBOROS, Innsbruck, Austria) for data acquisition (at 2 sec time intervals) and analysis. Respiration rates were determined first without exogenous respiratory substrates (Routine state, R) and then in 4.95 mM pyruvate, 1.9 mM malate, and

2.38 mM succinate (LEAK state, L). For the phosphorylation state (state P), 1.9 mM of ADP was added to assess phosphorylating respiration. Subsequently, 1.9 mM rotenone was added to inhibit respiration at complex I. Finally, to inhibit mitochondrial respiration and evaluate residual oxygen consumption from non-mitochondrial oxidative reactions (ROX state), 1.9 mM cyanide (CN) was used and described below.

2.14. Acetylcholinesterase (AChE) Activity

Fifty thoraces and heads of WT (w^{1118}) *D. melanogaster* were homogenized in 100 mM of sodium phosphate buffer (containing protease inhibitor), pH 7.4, to disrupt the cells. Homogenates were centrifuged at 9000× *g* for 30 min at 4 °C [30]. The supernatant (0.01 mg of protein) was incubated with 100 mM of sodium phosphate buffer, pH 7.4, containing 150 mM of acetylthiocholine (CAS n. 1866-15-5) and 1 mM DTNB. AChE activity was determined spectrophotometrically using a Model Cary 50MPR Varian Spectrophotometer (Varian Ltd., Melbourne, Australia) according to the method of Ellman et al. (1961) [31]. The results were expressed as nmol conjugated formed/min/mg protein.

2.15. Protein Assay

The Bradford assay determined the protein concentration by using BSA (CAS n. 9048-46-8) as the standard [32]. This assay involves an interaction between the protein and the Coomassie Blue reagent (CAS n. 6104-59-2), with the reading performed at 596 nm.

2.16. Statistical Analysis

The data are presented as mean ± SEM. N represents the number of female flies per group used in each experiment. Statistical analysis was performed using GraphPad ©Prism version 8.0 software (San Diego, CA, USA). The statistical significance of the mean values for multiple comparisons was assessed in untreated and treated flies using *t*-tests and one-way ANOVA with Tukey's and Bonferroni's post-hoc tests. Results were considered significant when $p < 0.05$.

3. Results

3.1. Determination of Developmental Parameters of D. melanogaster

During *Drosophila melanogaster* development, the shape and size in the pupal stage are characterized by the axial ratio (AR, length/width) of the cuticle. No significant changes in pupal volume were observed (Figure 1A). Corn oil supplementation (49.5 mg/mL) in the semisolid diet significantly reduced the eclosion rate ($p < 0.001$; Figure 1B). Additionally, the flies subjected to the starvation assay after 5 days exhibited substantial mortality for animals fed during the larval instar with 18.9 mg/mL ($p < 0.0001$), 37.8 mg/mL ($p < 0.0001$), and 45.9 mg/mL ($p < 0.0001$) (Figure 1C).

3.2. Longevity and Climbing Activity

The ingestion of corn oil (45.9 mg/mL) significantly reduced the lifespan of flies after five days, with a survival rate of only approximately 4% compared to untreated control flies (Figure 2A and Figure S1). Flies fed corn oil at a concentration of 37.8 mg/mL for two days exhibited improved climbing ability. However, the diet supplemented with 18.9 mg/mL ($p < 0.01$) and 49.5 mg/mL ($p < 0.05$) of corn oil exhibited a progressive decline in climbing ability beginning after two days of feeding (Figures 2B and S2).

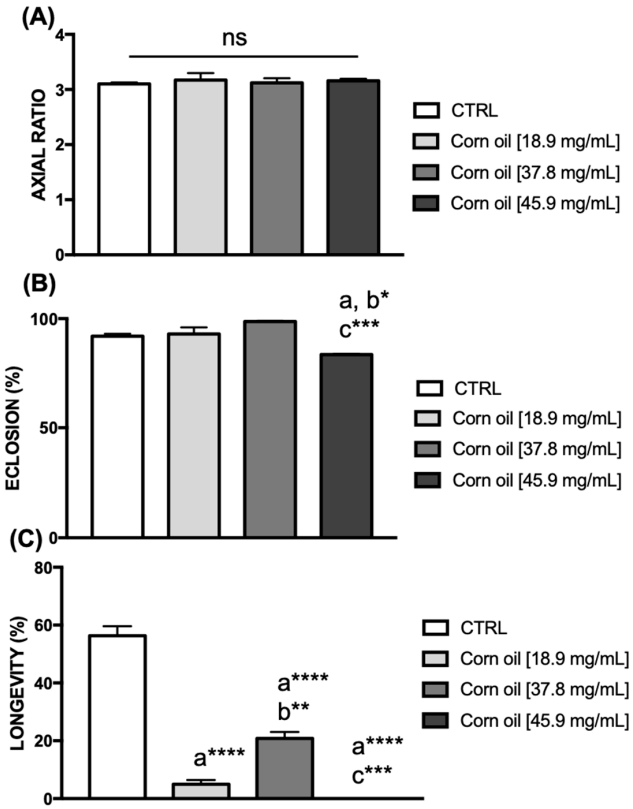

Figure 1. Quantification of pupal volume, eclosion percentage, and longevity during starvation in *D. melanogaster*. (**A**) The body shape of a pupa can be described by length (L)/width (W) n = 40. (**B**) Percentage of pupae eclosed n = 120. (**C**) Longevity during starvation in flies, n = 80. The values represent the mean ± SEM (One-Way ANOVA and nonparametric) of three experiments. The results were considered statistically significant when * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$: [a] vs. CTRL, [b] vs. Corn oil (18.9 mg/mL), [c] vs. Corn oil (37.8 mg/mL).

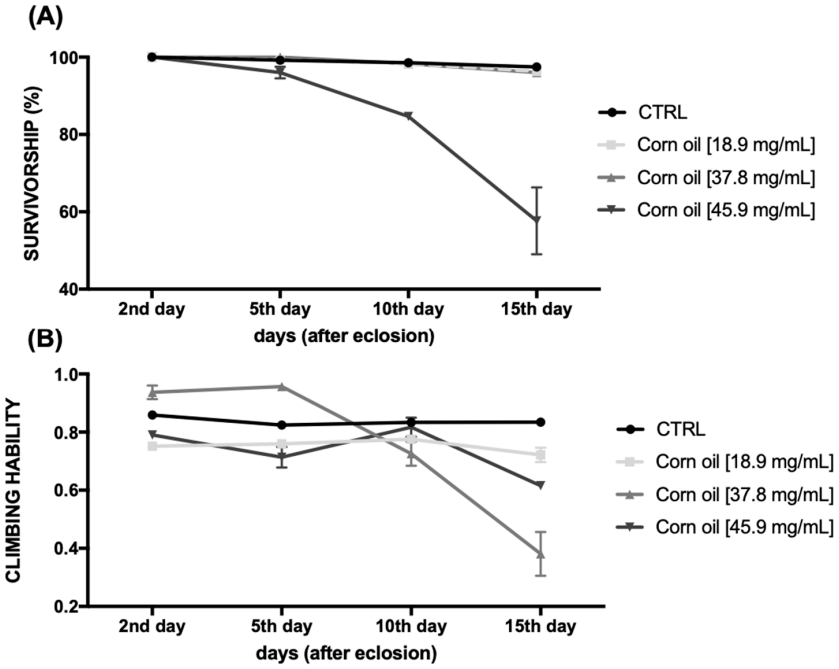

Figure 2. Behavioral parameters. (**A**) Longevity and (**B**) Climbing ability of *Drosophila melanogaster* (n = 120) submitted to a diet supplemented with corn oil and statistical analyses as Supplementary Materials (Figures S1 and S2). The values represent the mean ± SEM (One-Way ANOVA and nonparametric) of three experiments.

3.3. Glutathione Reduced Levels

Flies fed corn oil exhibited increased levels of reduced glutathione in their heads (Figure 3A) and muscles (Figure 3B) ($p < 0.001$).

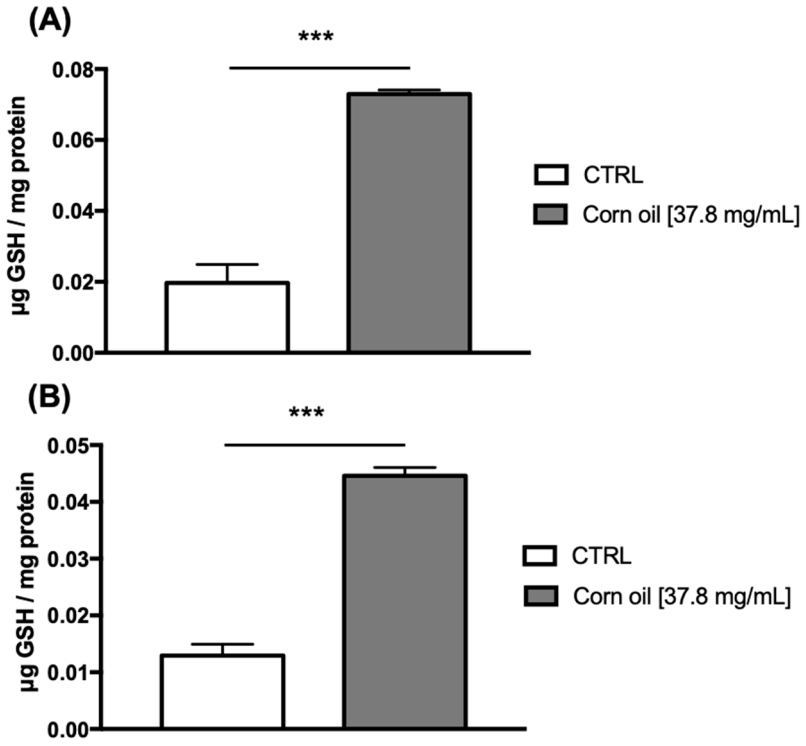

Figure 3. GSH concentration in (**A**) heads and (**B**) thoraces of *Drosophila melanogaster* fed on a diet supplemented with corn oil (n = 100). The values represent the mean ± SEM (unpaired *t* test) of three experiments. The results were considered statistically significant when *** $p < 0.001$.

3.4. Lactate

Lactate levels in the heads and thoraces remained unchanged in flies fed corn oil (Figure 4).

3.5. Mitochondrial Parameters

Flies fed corn oil exhibited increased CS activity in the head ($p < 0.01$) (Figure 5A) and thorax ($p < 0.05$) (Figure 5B). CS is a key enzyme of the Krebs Cycle and is commonly used as an indicator of mitochondrial content. Corn oil supplementation enhanced head tissue respiration in the Routine state (endogenous substrate, $p < 0.01$; Figure 6B) and in the LEAK state (with exogenous substrate, $p < 0.05$; Figure 6D). Additionally, the P2/P1 ratio analyses support oxidative phosphorylation facilitated by NAD^+-linked substrates (State P1) or succinate (State P2), showing a higher mitochondrial complex 2 relative to complex 1 in the heads ($p < 0.05$) (Figure 6F) and thoraces ($p < 0.01$) (Figure 6G) of flies fed corn oil. No significant changes were noted in State Rox (oxygen consumption unrelated to respiratory chain activity) (Figure 6H,I).

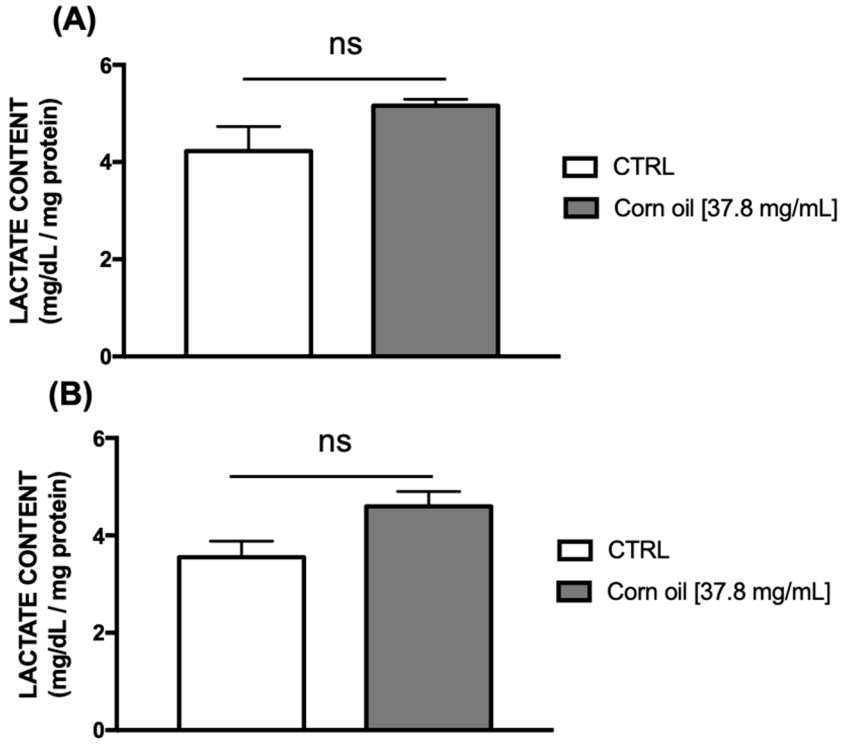

Figure 4. Lactate concentration in (**A**) heads and (**B**) thoraces of *Drosophila melanogaster* fed on a diet supplemented with corn oil (n = 100). The values represent the mean ± SEM (unpaired *t* test) of three experiments. The results were considered statistically significant when $p < 0.05$.

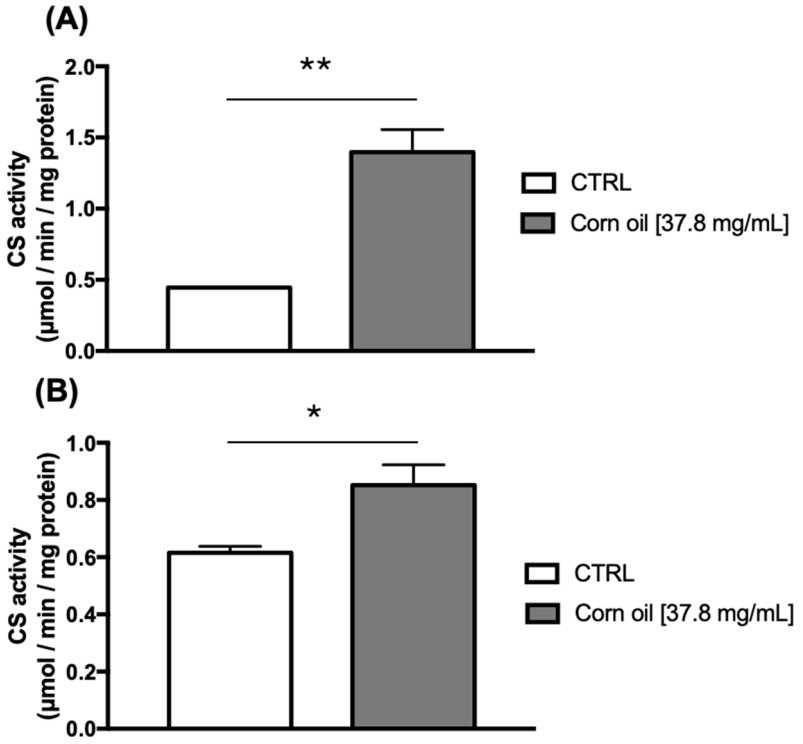

Figure 5. CS activity in (**A**) heads and (**B**) thoraces of *Drosophila melanogaster* fed on a diet supplemented with corn oil (n = 100). The values represent the mean ± SEM (unpaired *t* test) of three experiments. The results were considered statistically significant when * $p < 0.05$, ** $p < 0.01$.

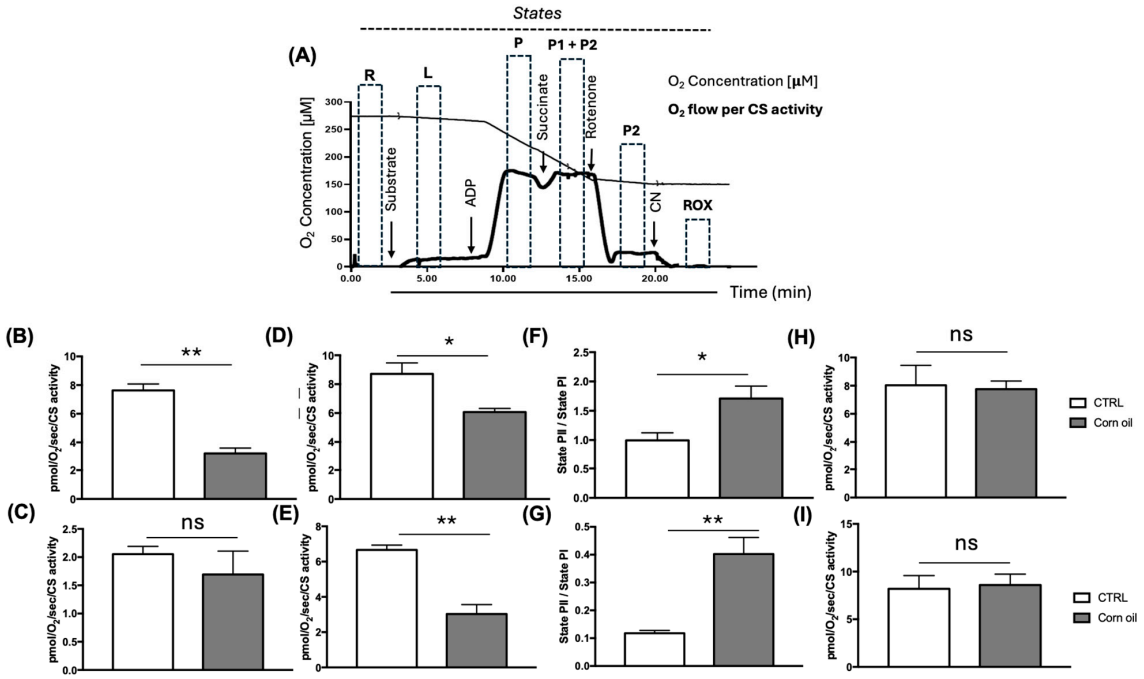

Figure 6. Mitochondrial respiratory parameters of heads and thoraces of *D. melanogaster* fed a standard diet or supplemented with corn oil. (**A**) Thoraces (3 per chamber) were placed into the oxygraph chamber filled with MIR05 solution, as described in Materials and Methods. Respiratory rates in *States* of Routine (R), NetRoutine (NetR), OXPHOS or coupled (P), coupled on complex I (P1), coupled on complex II (P2), and residual (ROX) of heads (**B**,**D**,**F**,**H**) and thoraces (**C**,**E**,**G**,**I**) of flies (n = 5). The values represent the mean ± SEM (unpaired *t* test) of three experiments. The results were considered statistically significant when * $p < 0.05$, ** $p < 0.01$.

3.6. Acetylcholinesterase Activity

The ingestion of corn oil resulted in a significant reduction in Acetylcholinesterase activity (AChE) in the heads ($p < 0.05$) (Figure 7A) and thoracic muscles ($p < 0.05$) (Figure 7B).

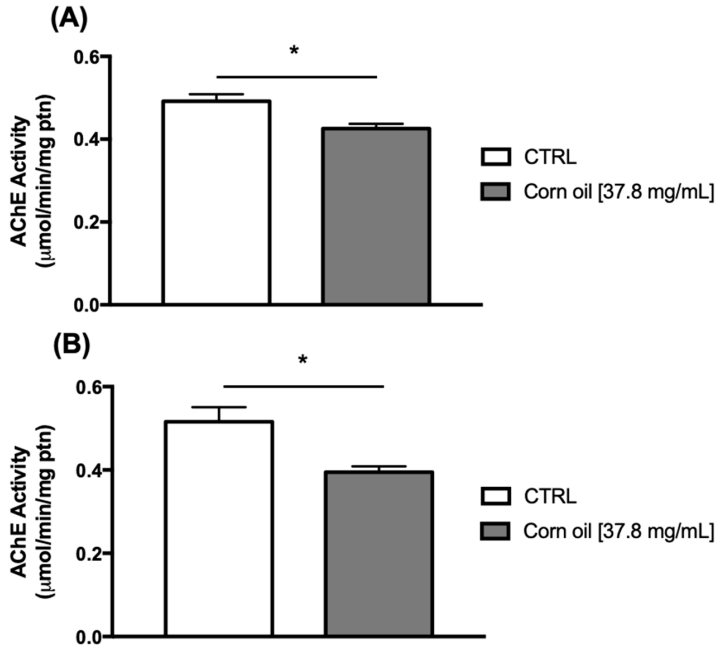

Figure 7. AChE activity in (**A**) heads and (**B**) thoraces of *Drosophila melanogaster* fed on a diet supplemented with corn oil (n = 100). The values represent the mean ± SEM (unpaired *t* test) of three experiments. The results were considered statistically significant when * $p < 0.05$.

3.7. Measurement of β_{42} Fragments in the Flies' Eyes

Initially, this study assessed the morphological changes in the eyes of mutant flies fed a diet supplemented with or without corn oil (Figure 8A). Subsequently, we examined changes in the eye area; however, these were not statistically significant (Figure 8B). Total amyloid content was evaluated using Congo Red to verify the amyloidogenic pathway from AD-like [19]. Flies expressing human APP and β_{42} fragments showed no significant changes in the detection of amyloid protein fragments (Figure 8C).

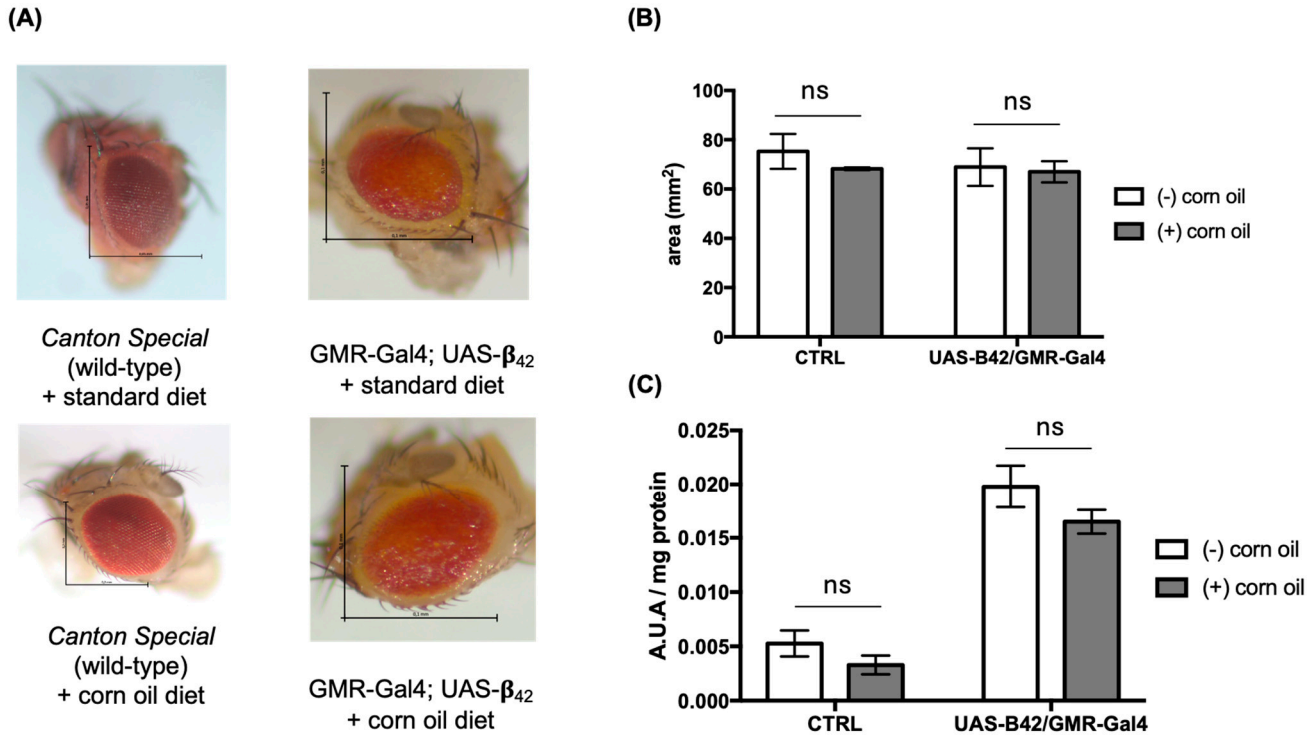

Figure 8. Expression of human β_{42} in the *Drosophila melanogaster* eye. (**A**) Phenotypic image, (**B**) area (**C**) amyloid aggregation in heads of *Drosophila melanogaster* fed on a diet supplemented with corn oil (n = 10). The values represent the mean ± SEM (Two-Way ANOVA, Bonferroni as post-hoc test) of three experiments. The results were considered statistically significant when $p < 0.05$.

4. Discussion

Corn oil is rich in linoleic acid (LA), which plays an essential role in neural development and the regulation of inflammation [33], lipid-lowering properties [34], anticarcinogenic properties, and body weight reduction [35], and it is found in the tissues of *Drosophila melanogaster* during ingestion [11]. However, excessive intake of LA leads to the formation of oxidized LA metabolites, impairments in mitochondrial function, and free radical production [36]. In this study, exposure to a diet containing corn oil did not result in changes in pupal volume when compared to studies by Alencar et al. (2023) [17] and Ramalho et al. (2024) [18], which demonstrated intoxication during the pupal stage, as indicated by reduced pupal development. However, the positive relationship between body size and fitness is not confined to insects; it has also been observed in vertebrates, including reptiles and mammals [37]. Furthermore, our results showed a significant decrease in the hatching rate of *D. melanogaster* only after the larvae ingested 45.9 mg/mL of corn oil, suggesting that lower doses do not impair development into adulthood. Additionally, the ingestion of vegetable oils with varying concentrations of PUFAs in a mouse model with Alzheimer's disease (AD) reduced cognitive impairment and offered benefits against oxidative stress, improved learning and memory parameters, and significantly affected neurogenesis [38].

Moreover, *D. melanogaster* fed LA exhibited inhibitory effects on the cytotoxicity of β_{42} fragments [36].

D. melanogaster has four developmental stages: egg, larva, pupa, and adult. In the larval stage, they feed continuously to accumulate nutrients and use them as an energy reserve in fat cells [39]. Food deprivation after 48 h demonstrated lower mortality in *D. melanogaster* fed with differing concentrations and ratios of protein and carbohydrates [40], modulating the lifespan as in *Caenorhabditis elegans* [41], turtle [42], and mice [43]. Our results show that larvae fed with 37.8 mg/mL of corn oil resulted in ~20% survival of flies living after five days of starvation, suggesting that the oil ingestion during the larval stage or instar promoted lipid storage and energy mobilization for the metabolism during fasting [44].

The locomotor activity in animals is linked to AChE activity. This enzyme plays a crucial role in regulating cholinergic neurotransmission and exists in two forms: soluble in the cytosol (neural tissue) and membrane-bound (muscle tissue) [45,46]. Dysfunction of this enzyme, such as high concentrations, is associated with neurodegenerative diseases like AD [45]. Our results show that supplementation with corn oil (37.8 mg/mL) for five days promoted greater longevity and improved climbing activity, similar to the effects observed in *D. melanogaster* supplemented with different PUFAs [29]. It also enhanced cholinergic transmission, either by increasing the synthesis and release of acetylcholine and has thus far proven to be the most effective in improving cognitive performance through dietary means [47].

The primary energy source is carbohydrates, which undergo oxidation to produce energy carriers and metabolic intermediates such as ATP, NADH, $FADH_2$, and pyruvate. When there is not enough oxygen to oxidize pyruvate, anaerobic glycolysis occurs, producing lactate, which also provides energy. This process happens in the muscles during physical activity. However, lactate is also present in the postprandial period and is preferable for supplying energy to the brain, heart, and skeletal muscle [48,49]. Astrocytes are highly glycolytic, involved in metabolic interactions for energy production and cellular homeostasis [48]. The buildup of lactate from Paraquat derivatives intoxication indicates neural and muscular degeneration [18]. Our results show that lactate levels did not significantly change during ingestion with corn oil, suggesting that using lactate as an energy substrate prevents its intracellular accumulation, optimizing neuronal function or serving as an energy source for the maturation of the flies between the early stages of development [50,51].

Our results demonstrate that corn oil supplementation did not compromise mitochondrial function, indicating that cellular energy metabolism was preserved. Furthermore, in flies fed corn oil, this study clearly demonstrated that CS activity was significantly increased compared to controls, and it influenced the respiratory states P2/P1, increasing mitochondrial respiratory and phosphorylation capacity through complex II, as demonstrated in hypertensive heart failure patients [52]. With regard to the mitochondrial generation of reactive oxygen species [53,54], flies fed corn oil exhibited an antioxidant status, protecting cellular macromolecules from both endogenous and exogenous reactive oxygen and nitrogen species, evidenced by enhanced GSH production rates, similar to the effect observed in studies with quercetin and vitamin C [55,56].

Beta-42 fragments are toxic peptides derived from amyloid precursor protein (APP), which are abundant in neurons and essential for synaptic function. The accumulation of these fragments in the brain is directly linked to the development and progression of neurodegenerative diseases, such as AD [6]. Our results did not show a significant change in beta-42 fragments in flies treated with corn oil compared to those that were untreated. Consistent with our previous observations, wild-type flies fed corn oil experienced a

decrease in AChE activity that contributes to the cholinergic system, which regulates acetylcholine in the synaptic cleft and calcium influx for muscle contraction [57]. This mechanism of action is similar to that of AChE inhibitor drugs, which are widely used in the treatment of neurodegenerative diseases, particularly in AD [58]. Here, our results suggest that corn oil intake may be related to both amyloid and cholinergic mechanisms involved in AD. Studies involving Alzheimer's disease models in rats and mice [59–61] have demonstrated that PUFA supplementation was associated with protection against oxidative stress and mitochondrial dysfunctions.

5. Conclusions

The ingestion of corn oil by *D. melanogaster* led to changes in behavioral parameters, including longevity and climbing ability. Furthermore, antioxidant and mitochondrial factors were assessed, as evidenced by an increase in GSH levels and improved phosphorylation by the substrate from complex II, with mitochondrial content represented by CS activity. This suggests potential modulation of mitochondrial and cholinergic pathways by corn oil, warranting further studies in vertebrate models.

6. Study Limitations

A key limitation of the present study is the exclusive use of female animals, which may restrict the generalizability of our findings to both sexes. Female animals were chosen for their high ingestion of LA supplemented in the diet. To address this, future studies should include male animals, as this would provide a more comprehensive understanding of LA ingestion and its neuroprotective effects.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app15137607/s1, Figure S1: Survivorship of D. melanogaster fed a diet supplemented with corn oil. The values represent the mean ± SEM (One-Way ANOVA and nonparametric) of three experiments. The results were considered statistically significant when * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$: a vs. CTRL, b vs. Corn oil (18.9 mg/mL), c vs. Corn oil (37.8 mg/mL). Figure S2. The climbing ability of D. melanogaster fed a diet supplemented with corn oil. The values represent the mean ± SEM (One-Way ANOVA and nonparametric) of three experiments. The results were considered statistically significant when * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$: a vs. CTRL, b vs. Corn oil (18.9 mg/mL), c vs. Corn oil (37.8 mg/mL).

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