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QUERCETIN-SUPPLEMENTED DIET MODULATES ALUMINIUM CHLORIDE-INDUCED NEUROTOXICITY IN FRUIT FLIES

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ABSTRACT

Purpose: Neurotoxicity refers to the potential of a chemical substance, biological or physical agents to induce structural or functional defects in nerve tissue of the brain or peripheral nervous system. This study examined the therapeutic effect of dietary inclusion of Quercetin on Aluminium chloride-induced neurotoxicity in wild-type Fruit flies (*Drosophila melanogaster*).
Design/ Methodology/ approach: Flies were fed with diet supplements with AlCl3 (40mM) and Quercetin (0.1 and 1.0%) and counted daily throughout their life span. Flies were also raised on a diet supplemented with AlCl3 (40mM) and Quercetin (0.1 and 1.0%) for seven days. Flies were subsequently homogenized, and the activity of Acetylcholinesterase (AChE), Butyrylcholinesterase (BChE), Monoamine Oxidase (MAO), Catalase, and Glutathione-S-transferase (GST) were assayed.
Findings: Regarding the number of days required to reach 50% mortality, dietary inclusions of AlCl3 (40mM) reduced the life span of *D.melanogaster* more significantly than control flies. Also, Quercetin's 0.1 and 1.0% dietary inclusions significantly reduced AChE, BChE, and Monoamine Oxidase activity compared to the control.
Research Limitation/ Implications: The study focus on the dietary inclusion of Quercetin on Aluminium chloride-induced neurotoxicity in wild-type Fruit flies.
Practical Implication: There was a significant increase in the catalytic activities of GST and catalase in flies fed diet supplemented with 0.1 and 1.0% of Quercetin. However, dietary inclusion of both 0.1 and 1.0% of Quercetin seems tolerable as there was a less significant reduction in life span with a substantial effect on AChE, BChE, MAO activities, and its antioxidant activities compared to control flies.
Originality/ Value: The outcome of this research established that dietary inclusion of 40mM AlCl3 reduced the life span of *D.melanogaster. In contrast,* dietary inclusion of 0.1 and 1.0% of Quercetin produced some adaptive responses associated with reduction of neurotoxicity and elevated activities of some antioxidant enzymes.

Keywords*: aluminium chloride. fruit flies. neurotoxicity. monoamine oxidase .quercetin*

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INTRODUCTION

The genetic and biochemical basis of most neurodegenerative diseases is yet unknown. However, they are associated with environmental factors. Aluminium is one of the most wide metals on earth that induces neurotoxicity. Aluminium is the most abundant metal on earth and a well-known environmental neurotoxin. In past years, excessive Aluminium loading was proposed to be to some human neurodegenerative disorders like Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS)/Parkinsonism-dementia of Guam (Savory, Herman, & Ghribi, 2006).

Toxicity caused by Aluminium leads to several effects such as inhibition of the DNA's system of repair and causing the change in its structure stability (Karlik, Eichhorn, Lewis, & Crapper, 1980; Lankoff, Banasik, Duma, Ochniak, Lisowska, Kuszewski, Gozdz, & Wojcik, 2006), reducing the activity of PP2A (Walton, 2007), affecting the activity of antioxidant enzymes, disrupting the balance of cellular metal like that of iron(Fe) (Middaugh, Hamel, Jean-Baptiste, Beriault, Chenier & Appanna 2005; Ward, Zhang & Crichton, 2001), raising the level of reactive oxygen species (ROS) (Khanna & Nehru, 2007; Kumar, Bal, & Gill, 2009) and inducing apoptosis by altering NF-ϰB, p53, JNK pathway (Savory et al., 1999; Savory et al., 2006). Nevertheless, the core mechanism of Al toxicity remains unclear. In particular, it is unknown whether iron accumulation or ROS mediates Al toxicity, or they are just the consequence of cell-damaging damage.

The pharmacological and biological potential of quercetin (a biflavonoid) in the treatment of metabolic and neuro-inflammatory disorders has been well documented. It is a predominant dietary flavonoid found in many sources such as fruits (mainly citrus), green leafy vegetables as well as many seeds, buckwheat, nuts, flowers, barks, broccoli, olive oil, apples, onions, green tea, red grapes, red wine, dark cherries, and berries including blueberries and cranberries. The highest concentration of flavonols has been found abundantly in vegetables such as onions and broccoli, fruits like apples, cherries, and berries, and drinks such as tea and red wine (David et al., 2016).The fruit fly *Drosophila melanogaster* is receiving intense interest as an emerging model to study human neurodegenerative diseases at the molecular level. Herein, we employed the *Drosophila* model to examine the Al-induced-neurotoxicity and subsequent treatment with quercetin at varying concentrations.

Model organisms have been widely explored to understand signalling cascades in metabolic disease pathogenesis and vital biological process. *Drosophila melanogaster* is a fundamental model organism that has been harnessed in biomedical and biological sciences to have an in-depth understanding of physiological processes (Bilen & Bonini, 2005).

One of the technical advantages of Drosophila is their relatively easy culture process at an affordable cost under laboratory conditions. Comparative transcriptomics and proteomics data estimated that 75% of mutated human genes in diseases are highly conserved in *Drosophila*. There is a close similarity between the Human and *Drosophila* physiological processes, genetic components and conserved evolutionary regions. The fascinating characteristics of Drosophila are its smaller size and genome as these attributes help facilitate both high-level genetic studies.

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2. MATERIALS AND METHODS

2.1 MATERIALS

2.1.1 *D. melanogaster* Stock Culture

Wild type *D. melanogaster* (Oregon strain) stock culture was obtained from the Drosophila research laboratory, Functional Food and Nutraceutical Unit, Department of Biochemistry, Federal University of Technology Akure, Nigeria. The flies were bred on a standard diet consisting of cornmeal medium containing 1% w/v brewer's yeast and 0.08% v/w nipagin at constant temperature and humidity (25 ± 1oC; 60% relative humidity respectively) under 12 h dark/light cycle conditions. *D. melanogaster* strain remained unchanged throughout the experiment.

2.1.2 Reagents

Chemical reagents such as acetylthiocholine iodide, sulphanilamide, reduced glutathione, n-n-diethyl-para-phenylenediamine (DEPPD), ferrous sulphate, semicarbazide were procured from Sigma Aldrich Co. (St Louis, Missouri, USA). Trichloroacetic acid (TCA) and sodium acetate were sourced from Sigma Aldrich, Chemie GmbH (Steinheim, Germany), hydrogen peroxide, methanol, acetic acid, hydrochloric acid, aluminium chloride were sourced from BDH Chemicals Ltd., (Poole, England). Ascorbic acid and starch were products of Merck (Darmstadt, Germany). Except stated otherwise, all other chemicals and reagents were of analytical grades and the water was glass distilled.

2.2 METHODS

2.2.1 Experimental Design

Flies (both gender, 3-5 days old) were divided into 6 groups with 40 flies per vial. Group I was placed on a normal diet while group II-VI were fed with a normal diet comprising of Aluminium chloride, the sample (0.1 and 1.0%) and Aluminium chloride plus the sample (0.1 and 1.0%) as outlined below;

Groups Treatment
I Basal Diet
II Basal Diet + 40 mM Aluminium chloride
III Basal Diet + 0.1% Quercetin
IV Basal Diet + 1.0% Quercetin
V Basal Diet + Aluminium chloride + 0.1% Quercetin
VI Basal Diet + Aluminium chloride + 1.0% Quercetin

The concentration of the sample selection criteria was based on the previous survival study showing that the selected concentrations induced no significant mortality in the flies. The treatment regimen involves the exposure of breeded flies for seven days, and the fruit fly vials were kept at room temperature. All experiments were repeated and recorded at least three times, forming triplicates (n=6).

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2.2.2 Lethality Response

Both the control and treated flies were monitored daily for mortality and morbidity incidence throughout their life-cycle. The total number of dead files determines the survival rate. Meanwhile, the survivors were transferred to a freshly prepared diet every 7 days. The data were statically analyzed and plotted as cumulative mortality and percentage of live flies after the treatment period.

2.2.3 Preparation of Tissue Homogenate

The flies were anaesthetized in ice and homogenized in 0.1M phosphate buffer, pH 7.4, using a Teflon homogenizer. The resulting homogenates were centrifuged at 10,000 X g, 4°C for 10 minutes in a Kenxin refrigerated centrifuge Model KX3400C (KENXIN Intl. Co., Hong Kong). Numerous biochemical assays were carried out using the separated supernatant in the labelled Eppendorf tubes.

2.3 Biochemical Assays

2.3.1 Acetylcholinesterase (AChE) Activity Assay

Acetylcholinesterase activity was assayed according to the protocol described by Ellman *et al.,* (1959). The reaction mixture was made up of 50 µL of distilled water, 50 µL of 0.1M potassium phosphate buffer (pH 7.4), 30 µL of 10 mM 5,5-dithiol-bis(2-nitrobenzoic) acid (DTNB), 15 µL of tissue homogenate, and 30 µL of 8 mM acetylthiocholine. Thereafter, the reaction was monitored for 5 minutes at 412 nm in a spectrophotometer. The AChE level was estimated and the unit was reported as mmolAcSch/h/mg protein.

2.3.2 Determination of Catalase (CAT) Activity

Catalase enzyme activity homogenate samples were determined according to the method of Sinha *et al*., (1972). In brief, 0.05ml of each tissue homogenate sample was reacted with 0.1ml 2 M H2O2 in the presence of 0.25 ml 0.01M phosphate buffer (pH 7.0). The chemical reaction was halted by the addition of 0.4 ml dichromate acetic acid. The spectrophotometer measures the absorbance of the reaction mixture at a wavelength of 620nm. The calibration curve was determined by reacting 0.4mol of 2 M H2O2 with 2 ml dichromate acetic acid under the influence of 1.0ml 0.01M sodium phosphate buffer (pH 7.0). The catalase activity was thereafter calculated and expressed as µmol H2O2 consumed/mg protein.

2.3.3 Determination of Glutathione-S-Transferase Activity

The biochemical assay for the Glutathione-S-Transferase activity assay was based on the protocol of Habig *et al* (1981) with only slight modification. It involves the pre-incubation of reaction mixture containing 0.1 ml 0.25M phosphate buffer (pH 6.5), 25 mM 1- chloro-2,4-dinitrobenzene (CDNB) and 0.7 ml 0f distilled water for 5mins at 37C. The reaction mechanism was initiated by the addition of 0.02ml of the tissue homogenate and 0.01 ml 25 mM glutathione as substrate. The absorbance was read after 5minutes at 340nm in a spectrophotometer. The blank represents a reaction mixture without enzyme Reaction mixture without enzyme was used as a blank. The activity of GST was calculated and expressed as µmol/min/mg protein.

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2.3.4 Butyrylcholinesterase (BChE) Activity Assay

Butyrylcholinesterase activity was assayed according to the method described by Ellman *et al.,* (1959). The reaction mixture was made up of 50 µL of distilled water, 50 µL of 0.1M potassium phosphate buffer (pH 7.4), 30 µL of 10 mM 5,5-dithiol-bis(2-nitrobenzoic) acid (DTNB), 15 µL of tissue homogenate, and 30 µL of 8 mM butyrylthiocholine. Thereafter, the reaction was monitored for 5 minutes at 412 nm in a spectrophotometer. The BChE activity was thereafter calculated and expressed as mmolAcSch/h/mg protein.

2.3.5 Monoamine Oxidase (MAO) Activity Assay

The MAO activity was measured according to a previously reported method (Green and Haughton, 1961) with slight modifications. Notably, the reaction mixture comprises 0.025 M phosphate buffer (pH 7.0), 0.0125 M semicarbazide, 10 mM benzylamine, 100 µl of brain tissue homogenate. After 30 min incubation, acetic acid was added and incubated for 3 min in a boiling water bath. The homogenate was subjected to centrifugation. The resulting supernatant (1 ml) was reacted with an equal volume of 2, 4-Dinitrophenylhydrazine, and 1.25 ml of benzene was introduced gently into the reacting mixture after a 10 min incubating period at room temperature. After separating the aqueous layer, the benzene layer was mixed with an equal volume of 0.1 N NaOH. The resulting alkaline layer was decanted and incubated at 80 °C for 10 min. The spectrophotometer effectively measured the observed orange-yellow colour at 450 nm.

Data Analysis

The results of replicate readings were pooled and expressed as mean ± standard deviation (S.D). One-way Analysis of Variance (ANOVA) was employed to analyze the results followed by Turkey's post hoc test, with levels of significance accepted at $p<0.05$, $p<0.01$ and $p<0.001$. All statistical analysis was carried out using the software Graph pad PRISM (V.5.0).

3. RESULTS

Figure 1 illustrates the neuromodulatory effect of Quercetin on the life cycle of *D. melanogaster*. Administration of dietary inclusion of AlCl3 in a dose-dependent manner reduced the life span of *Drosophila melanogaster* significantly compared to the control and Quercetin-included diet and by the number of days required to reach LD50. The preliminary study is to estimate the therapeutic potential of Quercetin to attenuate aluminium induced neurotoxicity; toxicity with a strong association to neurodegenerative diseases.

Figures 2 and Figure 3 show the inhibitory activity and therapeutic applications of dietary inclusions of Quercetin on the Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE) activity in *D. melanogaster*. This outcome suggested a significant increase in acetylcholinesterase and butyrylcholinesterase activity in flies fed with a diet of aluminium inclusion shows when compared with the reference group. There is a significant decrease though when different concentrations of Quercetin was included with the diet containing AlCl3 compared with the control, showing that specific concentrations of Quercetin will possibly lower neurotoxicity event.

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Furthermore, Figure 4 shows the inhibitory effect of Quercetin on the activity of monoamine oxidase. It is observed that there is a significant difference in the monoamine oxidase activity of flies induced with AlCl3 and of flies treated with Quercetin, denoting that quercetin is a possible anti-neurotoxic agent. Figures 5 and 6 show that there is a low level of glutathione-S-transferase activity in flies induced with AlCl3 meaning that there is low antioxidant activity. Flies treated with Quercetin on the other hand show a significantly high level of antioxidant activity.

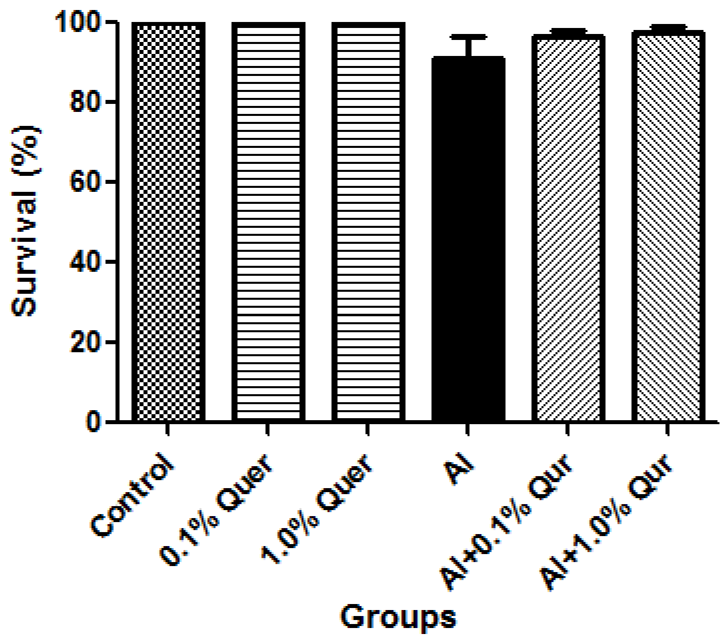

Figure 1: Day 5 Survival Rate (%) of *D. melanogaster* Fed Diet Supplemented with $AlCl_3$ and Quercetin
Bars represent mean ± SD

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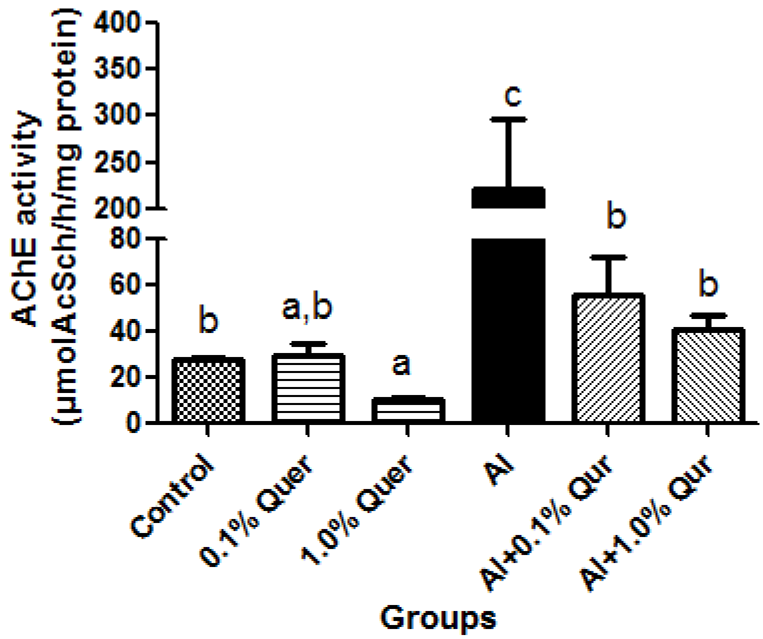

Figure 2: Effect of Dietary Inclusions of Quercetin on the Acetycholinesterase activity in *D. melanogaster*
Values represent mean ± SD

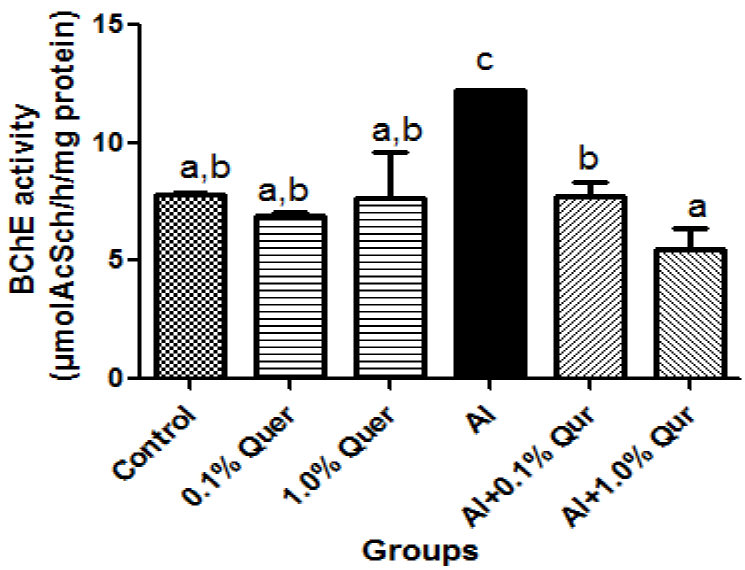

Figure 3: Effect of Dietary Inclusions of Quercetin on the Butyrylcholinesterase activity in *D. melanogaster* .Values represent mean ± SD

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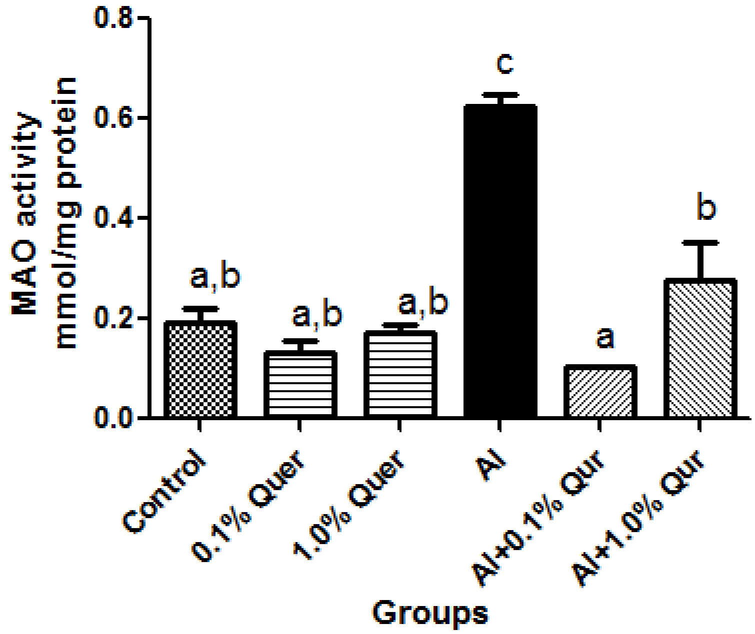

Figure 4: Effect of Dietary Inclusions of Quercetin on the Monoamine Oxidase activity in *D. melanogaster* Values represent mean ± SD

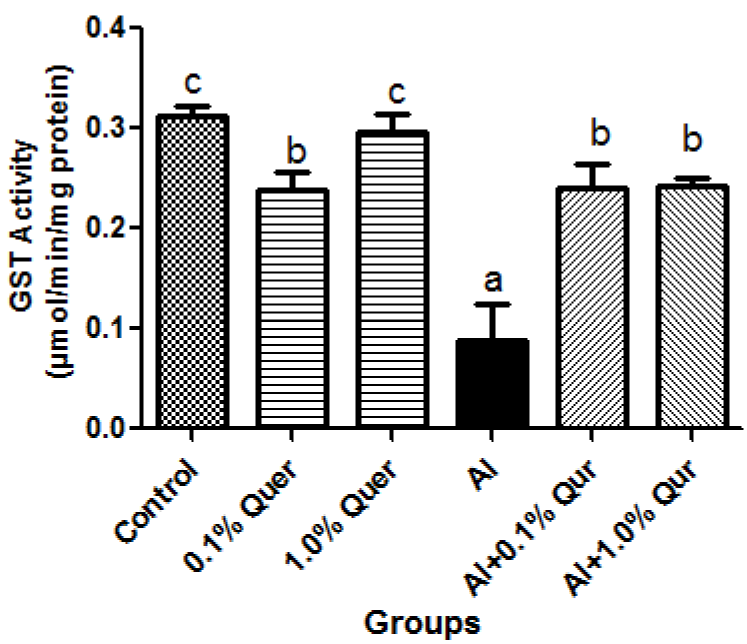

Figure 5: Effect of Dietary Inclusions of Quercetin on the Glutathione-S-Transferase activity in *D. melanogaster* Values represent mean ± SD

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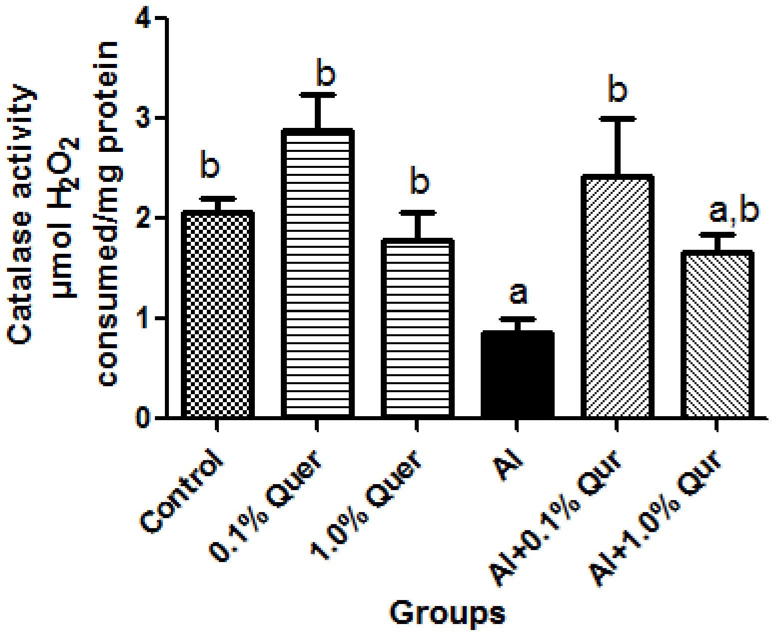

Figure 6: Effect of Dietary Inclusions of Quercetin on the Catalase activity in *D. melanogaster*
Values represent mean ± SD

4. DISCUSSION

Biochemical and physiological processes such as the development and maintenance of the central nervous system have been linked to the regulatory effect of Aluminium. However, excessive exposure to aluminium has been strongly associated with neurological disorders characterized by psychological and neurological abnormalities. Quercetin has been reported as the most commonly used bioflavonoid for treating metabolic deregulations and inflammatory diseases (Savory et al., 2006).

Quercetin has been widely studied for its biological activity, including anti-viral, anti-cancer, anti-diabetes, and anti-neuromodulatory effects. It is majorly found in the leaves and skins of plants such as onions, broccoli, curly kale, grape, apple, cherries, green tea, red wine, berry, citrus fruits, and kale (David et al., 2016).

The finding from this study shows the neuroprotective ability of Quercetin against aluminium-induced neurotoxicity in *D. melanogaster*. Genetic factors such as chromosome number, which is closely related to humans, are one of the prominent features that make Drosophila suitable as a model for toxicological and safety assessment of medicinal plants/plants derived products. Therefore, this research validates the use of *D. melanogaster* as a model organism for identifying safe and effective biologically active compounds from plants. From the multistep hypothesis, the results revealed that dietary inclusions of 40mM of aluminium chloride increase the AChE and

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BChE activities, leading to neurotoxicity. One of the risk factors in the pathogenesis of vascular dementia is cholinergic dysfunction. The cholinergic system is an essential therapeutic biomarker in the treatment of neurological disorders. Based on the literature, there is an increased level of brain acetylcholinesterase and butyrylcholinesterase in dementia which catalysis rapid breakdown of ACh and BCh neurotransmitters, thus disrupting the cholinergic system (Klafki *et al*., 2006). This is consistent with previous observations with an increase in the AChE and BChE activities in *Drosophila melanogaster* following dietary exposure to aluminium, which could lead to a reduction in cholinergic neurotransmission efficiency due to a decrease in acetylcholine and butyrylcholine levels in the synaptic cleft. (Adedara, Abolaji, Rocha, & Farombi, 2016).

Overproduction of ROS overwhelming antioxidant defence mechanism leads to oxidative stress, which causes cellular damage. (Valko, Leibfritz, Moncol, Cronin, Mazur & Telser, 2007). Antioxidant enzymes including Catalase, Superoxide Dismutase, and Glutathione-S-transferase act as primary protectors of cellular macromolecules against the invasion of free radical species (Rand, 2010). In this study, dietary inclusion of AlCl3 caused a significant increase in the activities of Catalase. Catalase is one of the enzymes that function as the first defensive line against tissue pro-oxidative injury (Abolaji, Kamdem, Lugokenski, Nascimento, Waczuk, Farombi, Loreto, & Rocha, 2014).

Catalase works closely with superoxide dismutase to prevent free radical damage to tissues, while superoxide dismutase facilitates the conversion of superoxide radicals to hydrogen peroxide, catalase converts hydrogen peroxide into water and molecular oxygen. Also, dietary inclusion of Aluminium chloride and Quercetin showed a decrease in catalase activity. In contrast, there is a significant increase in Quercetin's dietary inclusion. This means that Quercetin can be an efficient tool against oxidative stress caused by aluminium, which leads to a decrease in the antioxidant level.

5. CONCLUSION

The result showed that dietary inclusion of AlCl3 induced neurotoxicity in *Drosophila melanogaster* is due to the changes in the antioxidant enzymes status. These observations could be attributed to an increase in the AChE, BChE, Catalase, Glutathione-S-transferase and Monoamine Oxidase activities in the induced flies. However, the ameliorative effect of Quercetin, due to its antioxidant properties, in the induced flies was also observed. This study, therefore, suggests that consumption of Quercetin in feed could modulate the neurotoxicity in flies.

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