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EXPLORING THE THERAPEUTIC POTENTIAL OF TOMATO VARIETIES IN ALZHEIMER'S DISEASE: A FOCUS ON RADICAL SCAVENGING ABILITIES AND ACETYLCHOLINESTERASE INHIBITION.

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Abstract

Alzheimer's disease presents a significant global health challenge, with limited effective treatments available. Natural compounds, particularly those found in fruits and vegetables, have garnered attention for their potential therapeutic benefits in Alzheimer's disease. In this study, investigation was carried out on the antioxidant and neuroprotective properties of three tomato varieties *Trichosanthes cucumerina* (Snake tomato), *Solanum lycopersicum Linn* (Hausa variety), and *Solanum lycopersicum Linn* (Yoruba variety) in an Alzheimer's disease model induced by aluminum chloride using *Drosophila melanogaster*. Through *in vivo* and *in vitro* analysis, the radical scavenging abilities and acetylcholinesterase inhibition of each tomato variety was assessed. Findings reveal that Snake tomato exhibits potent radical scavenging abilities and significant AChE inhibition, suggesting its therapeutic potential in mitigating Alzheimer's disease pathology. Additionally, the antioxidant properties of Snake tomato correlated with its phenolic and flavonoid contents, highlighting its neuroprotective effects. While *Solanum lycopersicum Linn* (Hausa and Yoruba varieties) also demonstrated antioxidant properties, Snake tomato emerged as the most promising candidate for Alzheimer's disease management. These results show the importance of exploring natural compounds as alternative therapeutic approaches for Alzheimer's disease and warrant further investigation into the mechanisms underlying the therapeutic effects of tomato varieties.

Introduction

Fruits and vegetables are renowned for their natural antioxidant properties, offering protection against harmful free radicals and reducing the risk of chronic diseases like cardiovascular disease, cancer, and diabetes (Griffiths *et al.*, 2016; Zhang *et al.*, 2015). Antioxidants found in these foods, such as carotenoids, flavonoids, lycopene, and β-carotene, play crucial roles in these health benefits (Lu *et al.*, 2021; Robaszkiewicz *et al.*, 2010). One such beneficial fruit is the Snake tomato (*Trichosanthes cucumerina*), a variety predominantly found in southwestern Nigeria. This plant, a member of the Cucurbitaceae family, serves as an alternative to the Solanaceous tomato due to its appealing taste, aroma, and longer shelf life (Adebooye, 2008). With its rich nutritional profile, including high levels of flavonoids,

carotenoids, phenolic acids, and essential minerals, Snake tomato offers pharmacological and therapeutic benefits (Bamidele and Fasogbon, 2017; Devi, 2017). Despite the popularity of the regular Solanaceous tomato, its production in the Southwest of Nigeria falls short of consumption demands, often necessitating imports from the Northern region (Adebooye, 2008). Snake tomato, with its year-round cultivation potential, presents a viable solution to meet the growing demand and supplement the existing tomato supply.

The antioxidative properties of *Trichosanthes cucumerina* have been confirmed through the screening of its phenolic and flavonoid contents, indicating its potential to neutralize free radicals and combat oxidative stress (Badejo *et al.*, 2016). These antioxidant activities correlate with the plant's total phenolic and flavonoid contents, further highlighting its health-promoting potential (Badejo *et al.*, 2016).

Drosophila melanogaster, commonly known as the fruit fly, has been a focal model organism in biological research due to its adaptability to various food sources and its utility in studying organismal biology (Pandey and Nichols, 2011). Researchers have extensively investigated the optimal rearing conditions for Drosophila, focusing on developmental stages such as larvae and adults (Adedeji, 2017). Behavioral assays in Drosophila have expanded our understanding of larval and adult behaviors, providing valuable insights into neurodegenerative diseases and aging (Jeibmann and Paulus, 2009).

Neurodegenerative diseases encompass a broad spectrum of debilitating conditions characterized by the progressive degeneration and dysfunction of neurons in the central nervous system (Kormas and Moutzouri, 2023). These disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS), pose significant challenges to both individuals and healthcare systems worldwide (Choonara *et al.*, 2009).

Among neurodegenerative diseases, Alzheimer's disease stands out as one of the most prevalent and devastating, affecting millions of individuals globally (Singh *et al.*, 2019). Alzheimer's disease is characterized by the accumulation of abnormal protein aggregates, such as beta-amyloid plaques and tau tangles, in the brain, leading to cognitive decline, memory loss, and ultimately, severe impairment in daily functioning (Breijyeh and Karaman, 2020).

While conventional treatments for Alzheimer's disease focus on symptom management and disease progression slowing, there is a growing interest in exploring natural compounds and dietary interventions as potential therapeutic strategies (Sagud *et al.*, 2021). Natural treatments offer the advantage of being generally well-tolerated with fewer adverse effects compared to synthetic drugs.

Tomatoes, a staple in many diets worldwide, have garnered attention for their potential neuroprotective effects due to their rich antioxidant content. Studies have suggested that certain compounds present in tomatoes, such as lycopene, may possess anti-inflammatory and antioxidant properties that could mitigate neurodegenerative processes (Saini *et al.*, 2020).

In this context, exploring the therapeutic potential of different tomato varieties in Alzheimer's disease holds promise. By investigating the radical scavenging abilities and acetylcholinesterase (AChE) activity inhibition of various tomatoes in an Alzheimer's disease model. This study aimed to assess and compare the radical scavenging abilities of three tomato varieties *Trichosanthes cucumerina* (Snake tomato),

Solanum lycopersicum Linn (Hausa variety), and *Solanum lycopersicum Linn* (Yoruba variety) and their potential to inhibit acetylcholinesterase (AChE) activity in a *Drosophila melanogaster* model of Alzheimer's disease induced by aluminum chloride.

Materials and Method

Materials

Reagents/Chemicals: Preservative (nipagin), agar, aluminium chloride, 70% ethanol, distilled water, sulphonilamide, ortho-phosphoric acid, N-naphthylethylenediaminedihydro-chloride (NEDD), acetyl-thiocholine(substrate), 5,5-dithio- bis (2-nitro-benzoic) acid (DTNB), Sodium dihydrogen/disodium hydrogen phosphate. All reagents were gotten from the general analytical laboratory of the Department of Biochemistry, Adekunle Ajasin University, Akungba Akoko, Ondo State, Nigeria.

Sample collection.

Trichosanthes cucumerina (Snake tomato) were sourced from neighbourhood garden at Ikare – Akoko. Latitude = 7.5248°N and Longitude = 5.7669°E, Ondo State, Nigeria while *Solanum lycopersicum Linn* (Hausa variety) and *Solanum lycopersicum Linn* (Yoruba variety) were sourced from Market in Akungba Akoko Latitude = 7.4740°N and Longitude = 5.7379°E Ondo State, Nigeria. The three fruit samples alongside their whole plant were identified and authenticated in Plant Science and Biotechnology Departmental Herbarium (PSBH) Unit, Adekunle Ajasin University, Akungba Akoko, Ondo State, Nigeria with the specimen designated as PSBH – 262 for *Trichosanthes cucumerina*, PSBH – 263 for *Solanum lycopersicum Linn* (Hausa variety) and PSBH – 264 for *Solanum lycopersicum Linn* (Yoruba variety) were all deposited at the herbarium.

Preparation of Tomatoes

The pod of the ripe *Trichosanthes cucumerina* were split open using a knife. The seed separated from the pulp. The tomatoes were then packed into a well sterilized bowl, and blended using a dry, sterilized blender. The juice was poured into a clean, dry bowl.

The *Solanum lycopersicum Linn* (varieties) were processed using the same procedure. The tomatoes were well washed with running water and blended with a dry sterilized blender. The juice were poured into clean dry bowls respectively (Islam *et al.*, 2020)

Concentration of Samples

The three varieties of tomatoes were dried with a freeze dryer at -23°C for three days. After which the dried samples were scraped from the freeze-drying trays and packed into clean, moisture free bowls and covered with air-tight lids.

Flies Treatment

The flies were allowed to acclimatize for two weeks and then grouped as follows:

Table 1 Animal Grouping

Groups	Vial Labels	Interpretation
1	Norm Cntrl	Nornal Control (Basal diet)
2	Neg Cntrl	Basa diet + $AlCl_3$
3	Trt 0.1% ST	Basal diet+0.005g of Snake tomat o
	Trt 0.1% HT	Basal diet+0.005g of Hausa tomato
	Trt0.1% YT	Basal diet+0.005g of Yoruba tomato
4	Trt 1% ST	Basal diet+0.05g of snake tomato
	Trt 1% HT	Basal diet+0.05g of Hausa tomato
	Trt1% YT	Basal diet+0.05g of Yoruba tomato

5	IND+TRT 0.1%ST	Basal diet+AlCl +0.005g of Snake tomato
	IND+TRT 0.1%HT	Basal diet+AlCl+0.005g of Hausa tomato
	IND+TRT 0.1%YT	Basal diet+AlCl+0.005g of Yoruba tomato
6	IND+TRT 1%ST	Basal diet+AlCl +0.05g of Snake tomato
	IND+TRT 1%ST	Basal diet+AlCl +0.05g of Snake tomato
	IND+TRT 1%ST	Basal diet+AlCl +0.005g of Snake tomato

Feed Preparation

The working slab, cooking pot, stirrer, spoons and glass jars into which the flies will be transferred were sterilized using 70% ethanol and allowed to dry up before use. 700ml of distilled water was boiled for 10 minutes on the gas cooker. 5g of yeast was measured and poured into the boiling water and stirred for a few minutes. 7.9g of agar was added into the mixture and stirred continuously. 52g of corn meal, mixed with 150ml of distilled water to form a paste, was added to the mixture, and stirred continuously. After this, the cooker was switched off and 2ml of ethanol was used to dissolve 1g of nipagin (methyl paraben), which was poured into the feed and stirred.

Fly Transfer for New Emergence

The flies were transferred every 5 days in order to prevent overpopulation and contamination and also to breed new flies. The following method was used for the transfer of the flies from old jars to new jars. A funnel was placed on the new jar, while the old jar was gently tapped on a soft padded surface (towel) so that the flies fell to the bottom of the jar. The cotton plug on the jar mouth was quickly removed and then placed on the inverted funnel and slightly banged on the padded surface. This ensures the flies were transferred into a new feed.

Fly Transfer for Treatment

After having labelled the vial bottles as stated in table (2.1) above. Flies were counted in twenties into each vial bottles. A paper tape was placed at the narrow mouth of the funnel, thus, a medium sized hole was made on the tape, through which the flies can pass. The narrow mouth was placed into vial bottles containing the treatments with feed, a jar containing newly emerged flies were placed on the wide opening of the funnel. The flies were counted through an upward movement into the vial bottles.

The vial bottles were labelled according to the table above, the tomato samples were weighed accordingly i.e 0.005g for 0.1% in 5g of feed, and 0.05g for 1% sample in 5g of feed. Then stirred to mix with the hot feed

Preparation of Tissues

Ice cold phosphate buffer 0.1M phosphate buffer, pH 7.4 was pipetted into respective eppendorf tubes and homogenized till all part of the Drosophila were crushed. The homogenates were centrifuged at 3000rpm for 10 minutes. The supernatant was separated from the debris using a micropipette into the second group of labeled eppendorf tubes. The neurotoxic tissues were then stored in the freezer for further analysis.

Determination of Total Protein

2500ul of Bradford reagent was added to 50ul of sample in test tubes, while a blank of 2500ul reagent and 50ul distilled water. The mixture was incubated at room temperature for 30 minutes. The samples were read at 595 nm using a spectrophotometer.

Assessment of Nitric Oxide Level

50 µ L of tissues were pipetted into the test tube, 2.5ml of Griess reagent was added and the mixture was incubated at 37^0C for 2 hours in the water bath. The absorbance was read at 550nm.

Assessment of Acetylcholine Esterase (Ache) Inhibition Assay

Inhibition of AChE was assessed by a colorimetric method by Ellman *et al.,* (1961), with a slight modification (Ellman *et al.*, 1961).

AChE activity was determined in a reaction mixture containing 200µL of a solution of AChE (0.415 U/mL in 0.1 M phosphate buffer, pH 8.0), 60µ L of a solution of 5,5-dithio- bis (2-nitro-benzoic) acid (DTNB; 3.3 mM in 0.1 M phosphate buffered solution, pH 7.0, containing $NaHCO_3$ 6 mM), extract (0 – 75µ L) and 180µ L phosphate buffer, pH 7.4. After incubation for 20 min at 25 ° C, acetylthiocholine iodide (60 µ L of 8mM water solution) was added as the substrate, and AChE activity was determined by UV spectrophotometry from the absorbance changes at 412 nm for 5 min at 25 °C.

Results and Discussions

Oxidative stress, coupled with inflammatory processes, is increasingly recognized as a pivotal factor in cognitive impairment, neurodegeneration, and psychiatric disorders (Wadhwa *et al.*, 2018). In Alzheimer's disease (AD), oxidative stress plays a crucial role in the aggregation and toxicity of beta-amyloid proteins, contributing to neuronal damage and cognitive decline (Chakrabarti *et al.*, 2013). Excessive production of reactive nitrogen species leads to nitrosative stress, further exacerbating cellular damage and promoting the progression of AD pathology. Antioxidants play a vital role in mitigating oxidative stress by preventing, inhibiting, or repairing cellular damage. However, AD is characterized by high levels of oxidative stress and compromised antioxidant defenses, potentially exacerbating beta-amyloid aggregation and neurotoxicity (Zhao and Zhao, 2013). Understanding the interplay between oxidative stress, beta-amyloid pathology, and antioxidant defenses is essential for developing effective therapeutic strategies to combat AD and related neurodegenerative diseases.

The investigation explored the potential of various tomato varieties in mitigating nitric oxide (NO) radicals, crucial for understanding their antioxidant capacities. NO, a ubiquitous signaling molecule, plays diverse roles in cellular and organ functions, yet its accumulation can lead to nitrosative stress, exacerbating cellular damage. Our findings, depicted in Figures 1-3, underscore the efficacy of *Trichosanthes cucumerina*, *Solanum lycopersicum Linn* (Hausa variety), and *Solanum lycopersicum Linn* (Yoruba variety) in reducing NO levels in fruit fly models.

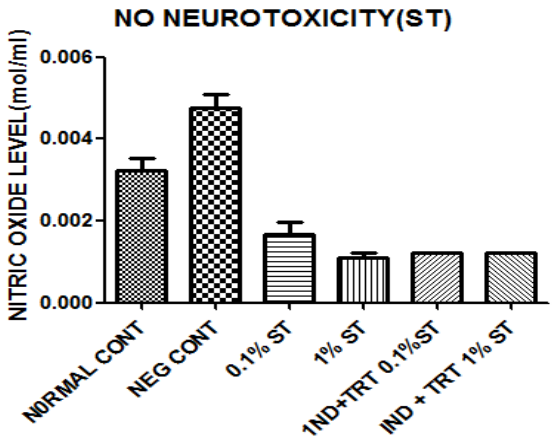

Figure 1: The nitric oxide level in fruit flies treated with *Trichosanthes cucumerina.*

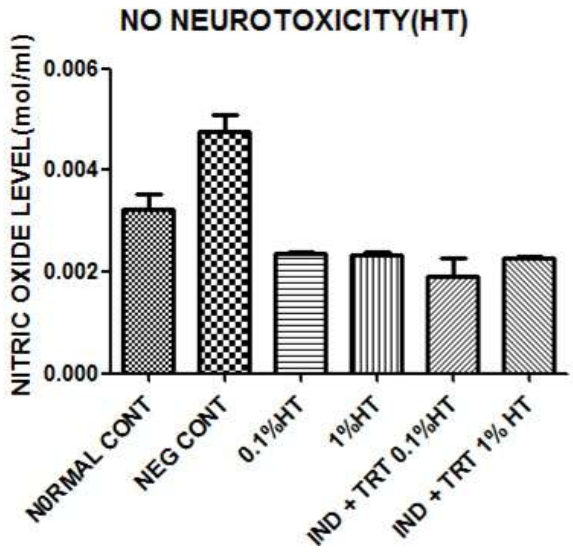

Figure 2: The nitric oxide level in fruit flies treated with *Solanum lycopersicum Linn* (Hausa variety).

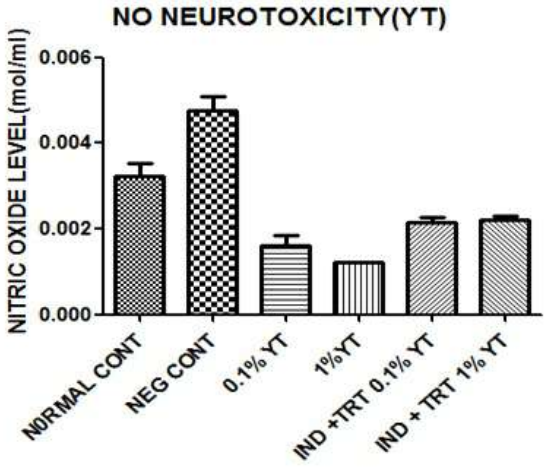

Figure 3: The nitric oxide level in fruit flies treated with *Solanum lycopersicum Linn* (Yoruba variety).

Figure 1 demonstrates a remarkable reduction in NO levels following pretreatment with *Trichosanthes cucumerina*, particularly notable at 0.1% concentration, showcasing its potent NO scavenging capabilities. Similarly, Figure 2 portrays *Solanum lycopersicum Linn* (Hausa variety) moderate NO reduction, with 0.1% concentration displaying superior scavenging ability compared to 1% administration. Moreover, Figure 3 illustrates the significant reduction in NO radicals post-treatment with *Solanum lycopersicum Linn* (Yoruba variety), highlighting their promising NO scavenging properties.

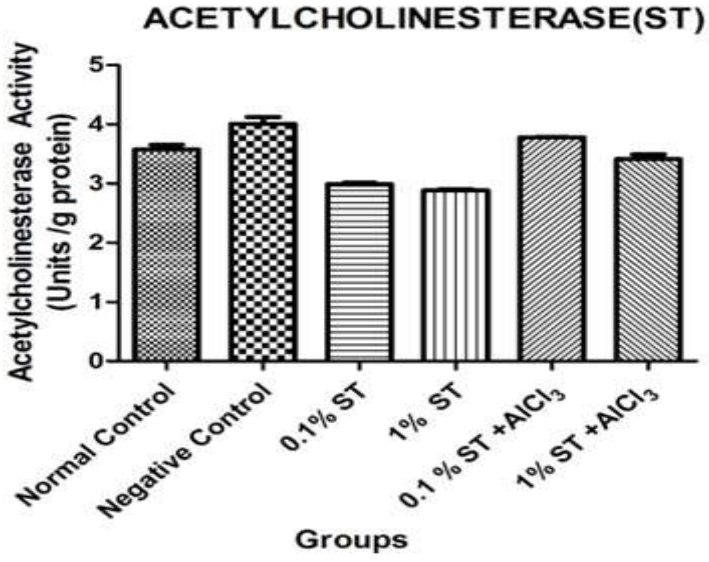

Figure 4: Acetylcholine esterase (AChE) inhibitory ability of *Trichosanthes cucumerina*

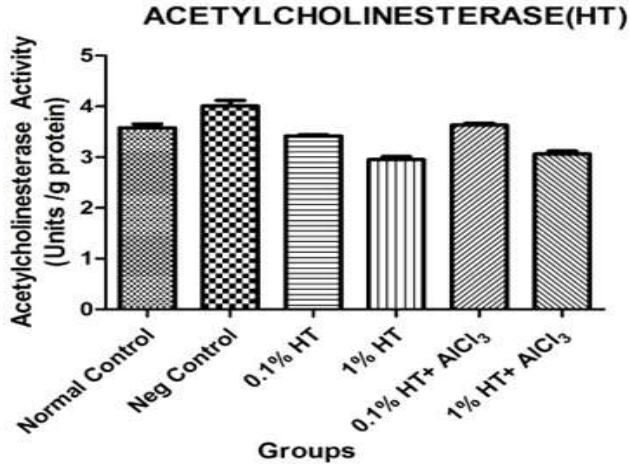

Figure 5: Acetylcholineesterase (AChE) inhibitory ability of *Solanum lycopersicum Linn* (Hausa variety).

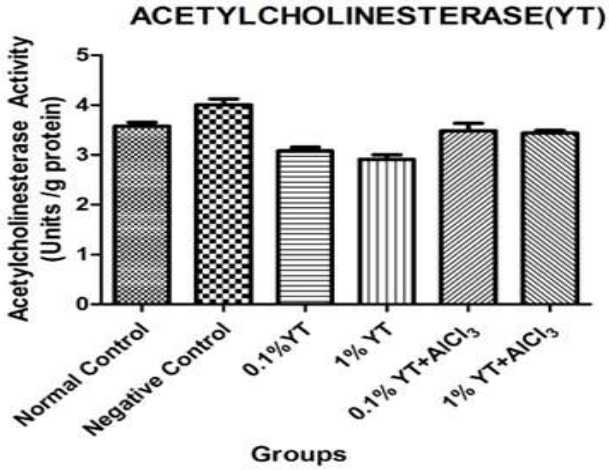

Figure 6: Inhibitory ability of *Solanum lycopersicum Linn* (Yoruba variety) on AChE.

Further analysis, depicted in Figures 4-6, elucidates the effectiveness of tomato varieties in scavenging NO radicals induced by aluminum chloride toxicity. Notably, *Trichosanthes cucumerina* exhibited significant NO scavenging activity, surpassing the efficacy of other tomato varieties (Figure 4). Additionally, *Solanum lycopersicum Linn* (Hausa variety) demonstrated dose-dependent scavenging ability (Figure 5), while *Solanum lycopersicum Linn* (Yoruba variety) exhibited promising scavenging properties at both 0.1% and 1% concentrations (Figure 6). The observed differences in NO scavenging efficacy among tomato varieties could be attributed to variations in their antioxidant composition, including carotenoids, vitamins, and phenolic compounds.

The therapeutic potential of three tomato varieties in managing Alzheimer's disease (AD) by assessing their ability to inhibit acetylcholinesterase (AChE) in an aluminum chloride-induced AD model in *Drosophila melanogaster* was also investigated. AChE inhibition is a promising therapeutic strategy due to its role in cholinergic deficit, a consistent early feature of AD. this investigation, depicted in Figure 4, revealed comparable AChE inhibitory activity of *Trichosanthes cucumerina* across 0.1% and 1% pretreatment concentrations compared to the positive control. Similarly, *Solanum lycopersicum Linn* (Hausa variety) exhibited significant AChE inhibition at 1% concentration, as depicted in Figure 3.5, with marginal activity observed at 0.1% concentration. Conversely, *Solanum lycopersicum Linn* (Yoruba variety) demonstrated moderate AChE inhibitory activity at both concentrations, as shown in Figure 6.

Interestingly, *Trichosanthes cucumerina* exhibited dose-dependent AChE inhibitory activity, with significant inhibition observed at 1% post-treatment concentration (Figure 4). Furthermore, *Solanum lycopersicum Linn* (Hausa variety) displayed dose-dependent activity, with better inhibition observed at 1% concentration (Figure 5), while *Solanum lycopersicum Linn* (Yoruba variety) exhibited consistent inhibition at both concentrations (Figure 6). These findings shows the diverse AChE inhibitory profiles of the tomato varieties, with *Trichosanthes cucumerina* and *Solanum lycopersicum Linn* (Hausa variety) showing promising potential in mitigating AD pathology.

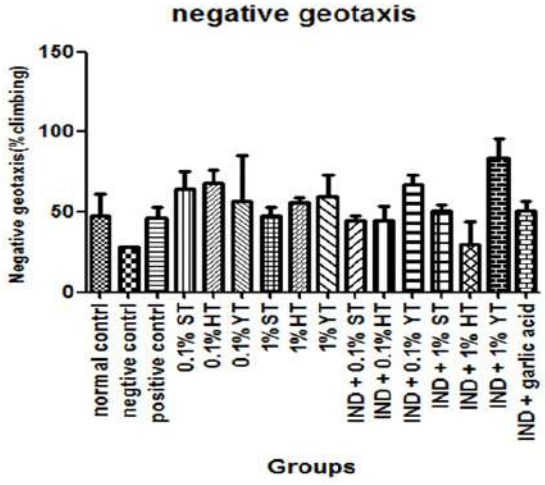

Figure 7 Negative geostaxis response in *Drosophila melanogaster*

A graph showing the behavioural response of Drosophila melanogaster to three different varieties of tomato (Snake tomato, Hausa tomato and Yoruba tomato) after being exposed to iron sulphate. The flies were fed with 0.1 mM gallic acid (GA). Locomotion assay were recorded at the indicated time.

Figure 7 illustrates the locomotor activity of flies post-treatment, with significant reductions observed in the negative control group, indicative of impaired motor function associated with AD. However, flies pre-treated with *Trichosanthes cucumerina* and *Solanum lycopersicum Linn* (Hausa variety) displayed preserved locomotor activity, suggesting potential neuroprotective effects. Notably, flies post-treated with *Solanum lycopersicum Linn* (Yoruba variety) exhibited enhanced climbing activity compared to the negative control, highlighting their possible therapeutic benefits.

The observed variations in AChE inhibitory activity among tomato varieties may be attributed to differences in their antioxidant compositions, including carotenoids and phenolic compounds. Lycopene, a major carotenoid in tomatoes, has been shown to possess potent antioxidative properties, emphasizing the potential role of these compounds in combating oxidative stress associated with AD (Saini *et a*l., 2020).

Conclusion

Overall, this study contributes to understanding the antioxidant properties of tomato varieties and highlights their potential therapeutic applications in neurodegenerative disorders. In conclusion, the study highlights the therapeutic potential of *Trichosanthes cucumerina*, *Solanum lycopersicum Linn* (Hausa variety), and *Solanum lycopersicum Linn* (Yoruba variety) in mitigating AD pathology through AChE inhibition and neuroprotective effects. Further research elucidating the underlying mechanisms and clinical implications of these findings is warranted to harness the full therapeutic potential of these natural compounds in AD management.

Recommendation

Despite being cultivated in Nigeria, particularly in the Southwestern region, *Trichosanthes cucumerina* remains relatively unknown in terms of its health benefits. While tomatoes from the Solanum family are widely consumed in Nigeria and other parts of the world, there is a lack of awareness about the potential health benefits of *Trichosanthes cucumerina*. Encouraging the consumption of *Trichosanthes cucumerina* is important due to its numerous health benefits, including its neuroprotective and antioxidant properties.

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