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Neuroprotective Effects of *Cucumeropsis mannii* Seed Oil on Enzymatic Mechanisms Underlying Scopolamine-Induced Neurotoxicity in Albino Rat Brain

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ABSTRACT

A common method for simulating cognitive decline is scopolamine-induced neurotoxicity, which disrupts neurotransmitter systems and neuronal membrane function. Therapeutic interest in natural compounds with multi-target neuroprotective potential persists. Using standard biochemical techniques to assess scopolamine-induced neurotoxicity in albino rats, this study examined the impact of CMSO on key brain homogenate neurotransmitter-related enzymes, including acetylcholinesterase (AChE), monoamine oxidase (MAO), adenosine amino esterase, and sodium–potassium ATPase (Na^+/K^+-ATPase). Six groups were created from a total of thirty-six adult male albino rats: Groups II through VI received scopolamine to cause neurotoxicity, while Group I acted as the normal control. Group II received no treatment, whereas the treated groups received different doses of CMSO (2.5, 5.0, and 7.5 mg/kg) or donepezil as a conventional medication. The administration of scopolamine resulted in a significant increase in adenosine amino esterase activity ($p < 0.001$) and a significant decrease in AChE, MAO, and Na^+/K^+-ATPase activities compared with the control group. This implies an aberration of the membrane-mediated ion transport, purinergic, cholinergic, and monoaminergic systems. CMSO therapy significantly enhanced AChE, MAO, and Na+/K+-ATPase activities while inhibiting adenosine amino esterase activity ($p < 0.05– 0.001$), thereby normalizing these parameters in a dose-dependent manner, in contrast to the scopolamine group. At the highest recommended dosage (7.5 mg/kg), enzyme activity had returned to levels corresponding to those of the control and donepezil-treated groups ($p > 0.05$). The study's coordinated modulation of purinergic, cholinergic, monoaminergic, and ionic homeostasis pathways demonstrates therapeutic potential comparable to that of donepezil for the treatment of cognitive impairment.

Keywords: Acetylcholineesterase, Cognitive impairment, Neurodegeneration, Phytotherapy.

Introduction

The detrimental effects of neurotoxic substances, such as chemical, biological, or physical agents, on the central and peripheral nervous systems can cause neurotoxicity, a pathological disease that impairs both structure and function (Gouri and Bhalla, 2025; Was *et al*., 2022). Neurodegenerative illnesses like Alzheimer's and Parkinson's are exacerbated by neurotoxic chemicals, which can be internally or

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externally generated and impact the interaction between neurons, neurotransmitter balance, and enzyme activity (Ayeni *et al*., 2022; Nabi and Tabassum, 2022). Scopolamine, a muscarinic receptor antagonist, is one of the neurotoxic agents that has been extensively utilised in studies to cause cognitive impairment and memory loss, simulating the signs of neurodegenerative illnesses (Afzal *et al*., 2022). When formulating strategies for therapy, it is imperative to comprehend the biochemical alterations driven by scopolamine-induced neurotoxicity.

By disrupting muscarinic acetylcholine receptors, the non-selective muscarinic antagonist scopolamine predominantly disrupts cholinergic neurotransmission, resulting in cognitive impairments and neurochemical abnormalities (Johnson *et al*., 2022; Miravalles *et al*., 2025). It is frequently used in animal research to mimic the cognitive impairments associated with Alzheimer's disease (AD) (Vaidya *et al*., 2022). Several cellular enzyme mechanisms, among which are sodium-potassium ATPase (Na^+/K^+ ATPase) (Zhu *et al*., 2022), monoamine oxidase (MAO) (Buneeva and Medvedev, 2025), acetylcholinesterase (AChE) (Walczak-Nowicka and Herbet, 2021), and adenosine amino esterase (ADA) (Garcia-Gil *et al*., 2021), are essential for sustaining the functionality of neurons while minimizing neurological damage. The deregulation of these metabolic enzymes has been linked to neurodegeneration, oxidative stress, inflammation, and cognitive decline. They also control neurotransmitter levels, ion balance, and synaptic activity. The hydrolysis of cholinergic into choline and acetate by acetylcholinesterase (AChE) disrupts synaptic transmission at cholinergic synapses (Pawar *et al*., 2023). In models of Alzheimer's disease, heightened AChE activity exacerbates cholinergic impairment (Chen *et al*., 2022). Monoamines, including dopamine, serotonin, and norepinephrine, incur oxidative deamination when they are catalysed by monoamine oxidase (MAO). Neuropsychiatric and neurodegenerative disorders are influenced by altered MAO activity (Behl *et al*., 2021). The vital enzyme sodium-potassium ATPase, also known as Na^+/K^+-ATPase, maintains electrochemical gradients across the neuronal membrane, which are critical for the propagation of impulses and neuronal excitability (Huang *et al*., 2024). Cognitive impairments emerge when Na^+/K^+-ATPase is dysfunctional, as it disrupts neuronal signalling. As a neuromodulator involved in synaptic remodeling, neurological protection, and cognitive processes, adenosine amino esterase (ADA) plays an essential function in its metabolism (Garcia-Gil *et al*., 2021). Natural products have been at the center of recently published studies on their potential effectiveness in decreasing neurotoxicity.

Cucumeropsismannii (white melon) a cucurbitaceae family, is traditionally used in African ethnomedicine for its purported health benefits (Fajinmi *et al.*, 2022). Its common names in the three basic language in Nigeria which are Igbo, Yoruba and Hausa are Egunshi, Egusi and Agushi, respectively. Its seed oil contains bioactive compounds such as omega-3 and omega-6 fatty acids, antioxidants, and phytosterols (Omozuwa *et al*., 2024). The seeds are used in making soups because it has thickening properties and also it can be processed for its oil products and it can also be taken as an " in between" mealworm refreshment (Tibe *et al.*, 2024). It has an overall 44 % of oil, 10 % carbohydrate, 4 % ash, 3 % fibre and 30 % protein that are mainly essential amino acids (Anwar *et al*., 2025; Fajinmi *et al.*, 2022).

This study aims to evaluate the effects of acetylcholinesterase, monoamine oxidase, sodium-potassium ATPase, and adenosine amino esterase on scopolamine-induced neurotoxicity in albino rats. By investigating the enzymatic activity alterations in response to scopolamine, this research seeks to elucidate the biochemical mechanisms underlying cognitive impairments and explore potential therapeutic targets for neurodegenerative conditions.

Materials and Methods

Biological Materials

Animals

The Department of Biochemistry, Federal University Oye-Ekiti (FUOYE), Ekiti State, Nigeria, purchased

36 male albino rats weighing 150–200 g each from the Animal House of the Department of Biochemistry, Ekiti State University (EKSU), Ekiti State, Nigeria. The rats were housed in wooden cages in a well-ventilated animal house with uninterrupted access to clean water and conventional rodent chow, and they were acclimated for 14 days (12 hours of light/dark cycles at room temperature). All measures were conducted according to the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals (NIH Publications No. 8023, revised in 1996).

Cucumeropsis manni seed

Cucumeropsis manni seeds were bought from a local farmer in Ndingwuta Amachi-NdeborIzzi, Abakaliki L.G.A., Ebonyi State.

Chemicals and Reagents

Scopolamine hydrobromide and other analytical-grade reagents were obtained from Sigma-Aldrich (USA). CMSO was extracted using cold-press methods and stored at 4°C until use.

Figure 1: Fruits opened to reveal flesh and seeds of melon kernel.

Extraction of *Cucumeropsis Mannii* Seed Oil (CMSO)

The CMSO was extracted using the method of Oti and Eze-Ilochi, (2017) (JO and Olivia, 2017) with modifiations. The *C. mannii* seeds as shown in Figure 1 (opened fruit revealing flesh and seeds) and Figure

Figure 2: Picture of *Cucumeropsis mannii* seed

2 (washed and dried seeds) was dehauled manually followed by hand-picking to remove the shells. A manually operated milling machine was cleaned using steaming water and detergent. After washing with detergent and rinsing with distilled water, the seeds will be pulverized four times with an automatic grinder to get a powdery texture. The ground sample was extracted by squeezing it onto a smooth stainless surface that was moderately tilted to the horizontal. Warm water was incorporated in drips (about four drops) at scheduled intervals in order to accelerate the oil's dispersion because water aids in cell rupture. According to Agu *et al*. (2022), the water that bursts cells and expels hydrocolloids (mucilage and gum) will inevitably be stored aside. To generate a purer form of the oil that would be stored in a different clean bottle, the extract was allowed to remain undisturbed in a capped vial for five to seven days to sediment before being separated using the decantation technique.

Experimental Design

There were six groups of rats (n = 6 per group). Following pretreatment with concurrent administration of CMSO and donepezil by oral intubation once daily for fourteen days, scopolamine was given intraperitoneally (i.p.) to induce neurotoxicity. Table 1 describes the groups and the treatments administered. Prior to and following the animal treatment, the weight of each group's animals was recorded. **2.5 Enzyme Activity Assays.**

Table 1: The Groups and Their Respective Treatment

GROUP	DESIGNATION	TREATMENT DESCRIPTION
I	Negative Control	Received Regular diet only
II	Positive Control	Administered 1 ml Scopolamine
III	Standard Control	Received 1ml of scopolamine + 5 mg/kg bw donepezil
IV	Treatment Group 1	Administered 1ml of Scopolamine + 2.5 ml of CMSO
V	Treatment Group 1I	Administered 1ml of Scopolamine + 5.0 ml of CMSO
VI	Treatment Group 1II	Administered 1ml of Scopolamine + 7.5 ml of CMSO

Following treatment, rats were sacrificed, and brain tissues were homogenized. Enzymatic activities were measured using established spectrophotometric methods:

- **AChE activity:** Ellman's method (da Silva Lucas *et al*., 2025).
- **MAO activity:** Holt and Baker, 1972 (Mohammed and Khadrawy, 2022).
- **Na^+/K^+ ATPase activity:** Reinila *et al.* 1971 (Mourelle and Franco, 1991).
- **ADA activity:**Giusti, 1974 (Egba *et al*., 2022).

Statistical Analysis

Data were expressed as mean ± SEM. Statistical comparisons were made using one-way ANOVA followed by Tukey's post hoc test. Significance was accepted at $p < 0.05$.

Results

The impact of CMSO on AChE activity in scopolamine-induced neurotoxicity is depicted in Figure 3. In contrast to the control group, AChE activity was substantially decreased in the scopolamine-only (SPL) group ($p < 0.001$). Donepezil co-treatment significantly increased AChE activity compared with the SPL group ($p < 0.001$), bringing enzyme levels back to levels similar to those of the control group ($p > 0.05$). Rats treated with scopolamine showed a dose-dependent increase in AChE activity when given CMSO. At 2.5 mg/kg ($p < 0.05$ vs. SPL), a significant rise was observed, and highest at 5.0 mg/kg ($p < 0.01$ vs. SPL). Enzyme levels were not substantially altered relative to those of the donepezil-treated or control groups ($p > 0.05$); however, CMSO significantly elevated enzyme activity at 7.5 mg/kg compared with the SPL group ($p < 0.001$). In albino rats with scopolamine-induced neurotoxicity, Figure 4 shows how CMSO affects monoamine oxidase (MAO) activity. The SPL group had considerably lower MAO activity than the control group ($p < 0.001$). MAO activity was less than that in the control group ($p < 0.05$), but it was substantially greater in the donepezil-treated group than in the SPL group ($p < 0.01$). When rats were administered scopolamine, CMSO therapy led to a notable, dose-dependent rise in MAO activity. Compared with the SPL group, CMSO at 2.5 mg/kg significantly increased MAO activity ($p < 0.001$) and exceeded the level observed in the donepezil-treated group ($p < 0.05$). At 5.0 mg/kg, there was an additional substantial increase ($p < 0.001$ vs. SPL). At 7.5 mg/kg CMSO, the highest MAO activity was seen. This activity was substantially higher than that of the control and donepezil-treated groups ($p < 0.01$) and was significantly higher than that of the SPL group ($p < 0.001$).

The effect of CMSO on adenosine amino esterase activity in albino rats with scopolamine-induced neurotoxicity is shown in Figure 5. The SPL group had considerably higher enzyme activity than the control group ($p < 0.001$). Adenosine amino esterase activity was considerably lower in the donepezil-treated group compared to the SPL group ($p < 0.01$),

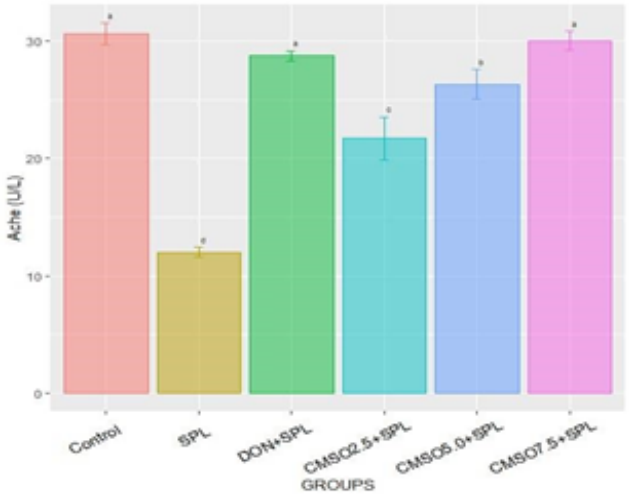

Figure 3: Treatment of CMSO on Acetylcholine esterase (AChE) activity in scopolamine induced neurotoxicity in albino rats

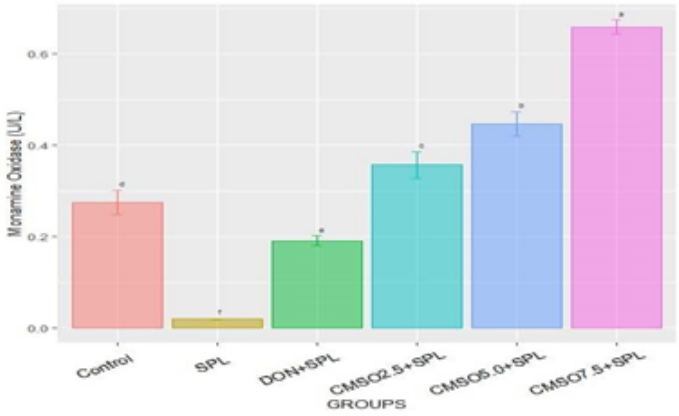

Figure 4: Treatment of CMSO on Monoamine oxidase (MAO) activity in scopolamine induced neurotoxicity in albino rats

but was still greater than control levels ($p < 0.05$). Rats treated with scopolamine showed a dose-dependent decrease in adenosine amino esterase activity when given CMSO. Compared with the SPL group, CMSO at 2.5 mg/kg significantly reduced enzyme activity ($p < 0.05$), with levels similar to those in the donepezil-treated group ($p > 0.05$). At 5.0 mg/kg, an additional substantial decrease was noted ($p < 0.01$ vs. SPL). In comparison with the SPL group, CMSO dramatically decreased enzyme activity at 7.5 mg/kg ($p < 0.001$), returning levels to values not significantly different from those of the control group ($p > 0.05$).

In scopolamine-induced neurotoxicity, Figure 6 demonstrates how CMSO alters sodium–potassium ATPase (Na^+/K^+-ATPase) activity. Na^+/K^+-ATPase activity was significantly decreased in the SPL group compared to the control group ($p < 0.001$). Compared with the SPL group, co-treatment with donepezil significantly increased enzyme activity ($p < 0.001$) and produced levels higher than those in the control group ($p < 0.01$). Rats treated with scopolamine exhibited a dose-dependent recovery of Na^+/K^+-ATPase activity after administering CMSO. Although values remained lower than those of the control group ($p < 0.05$), enzyme activity increased substantially at 2.5 mg/kg CMSO compared with the SPL group ($p < 0.05$). The rise was more noticeable at 5.0 mg/kg ($p < 0.01$ compared to SPL). Na^+/K^+-ATPase activity was significantly elevated at 7.5 mg/kg compared with the SPL group ($p < 0.001$), and enzyme levels were similar to those of the control group ($p > 0.05$).

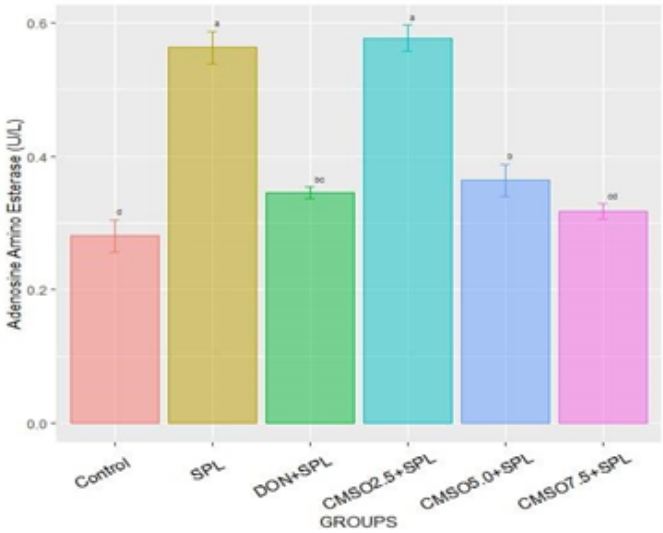

Figure 5: Treatment of CMSO on Adenosine amino esterase (AAE) activity in scopolamine induced neurotoxicity in albino rats

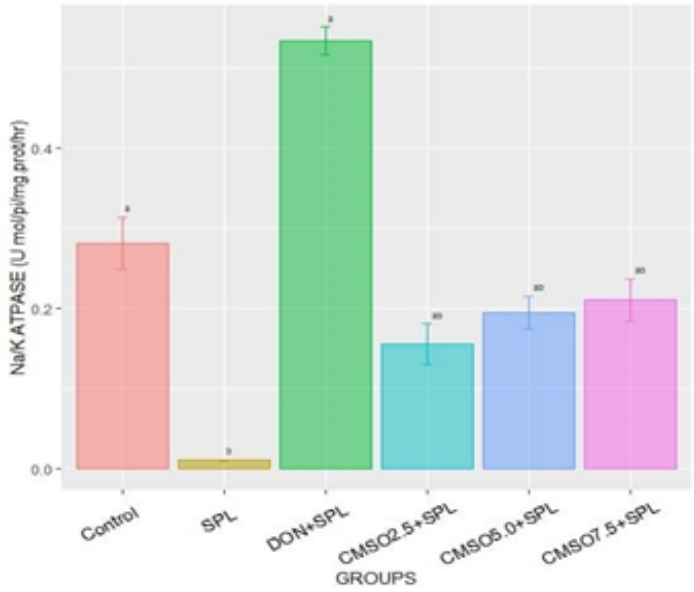

Figure 6: Treatment of CMSO on Sodium potassium ATPase activity in scopolamine induced neurotoxicity in albino rats.

Discussion

At cholinergic synapses, AChE reduces neurotransmission by breaking down acetylcholine (ACh) into acetate and choline. When scopolamine was administered, AChE activity in the brain decreased significantly compared with the control group, consistent with its role as a muscarinic receptor antagonist (Park *et al.*, 2024; Vaidya *et al*., 2022). Lower AChE activity means more acetylcholine remains in the synapse. Scopolamine does not directly block AChE, but it disrupts normal cholinergic signalling and affects memory and learning by blocking muscarinic receptors (Venkatesan, 2022). Donepezil, unlike CMSO, raised AChE activity in a dose-dependent way, suggesting a neuroprotective effect (de Cassia Ribeiro, 2021). This inhibition of AChE supports the idea that improving cholinergic function can enhance memory, as with standard AChE inhibitors used to treat dementia. These findings suggest that CMSO helps restore the cholinergic balance disrupted by scopolamine. Scopolamine-induced neurotoxic rats had significantly reduced MAO activity compared to the control group. The mitochondrial enzyme MAO (A and B isoforms) disintegrates serotonin, norepinephrine, and dopamine, while MAO-B degrades dopamine and phenylethylamine (Buneeva and Medvedev, 2025). Scopolamine interferes with cholinergic signalling, which causes neurotransmitter imbalance, oxidative stress, and mitochondrial malfunction. The scopolamine-induced decrease in MAO activity was considerably reduced by CMSO therapy (Oh *et al*., 2023). By maintaining neurotransmitter levels, reducing oxidative stress, and improving behavioral outcomes, the decrease in MAO activity suggests a modulatory influence on monoaminergic neurotransmission, potentially enhancing neuroprotection (Ostadkarampour and Putnins, 2021).

Na^+/K^+-ATPase, the membrane-bound enzyme that pumps 3 Na^+ out and 2 K^+ in per ATP hydrolysed, is crucial for maintaining the resting membrane potential and neuronal excitability. It needs ATP, which is heavily reliant on mitochondrial energy metabolism (Fedosova *et al*., 2022). According to Baracaldo-Santamaría *et al.* (2023), scopolamine alone significantly reduced Na^+/K^+-ATPase activity compared to control cortex activity, indicating impaired ionic homeostasis and increased neuronal vulnerability to excitotoxic damage. Scopolamine induces oxidative stress, mitochondrial dysfunction, and lipid peroxidation, which damage membrane proteins and reduce ATP availability. Na^+/K^+-ATPase activity was markedly elevated by CMSO treatment in a dose-dependent manner. This recovery suggests enhanced energy metabolism, stabilised membrane potential, and enhanced synaptic function. Increased activity of this enzyme suggests that CMSO counteracts scopolamine's inhibitory effects by supporting neuromembrane integrity and neuronal energy balance.

Additionally, the brains of the scopolamine-induced neurotoxic rats had much higher ADA activity than the cortex of the control group (Babatunde *et al*., 2024). An imbalance may cause neuroinflammation, excitotoxicity, and the irreversible deamination of adenosine to inosine since ADA is involved in purine metabolism and affects adenosinergic neurotransmission. Compared

with the scopolamine group, CMSO injection significantly reduced ADA activity. According to this research, CMSO may reduce neuroinflammation, which is known to contribute to cognitive decline and neuronal death in neurodegenerative diseases, and help control purinergic signalling (Chandran and Binninger, 2023; Teleanu *et al*., 2022). Scopolamine's documented neurotoxic effects are supported by the enzyme alterations it causes.

In neurodegenerative diseases, memory problems are linked to disruptions in cholinergic systems, whereas mood issues are associated with changes in monoaminergic systems, as evidenced by elevated AChE and MAO activity (Asim *et al.*, 2025). Lower Na+/K+-ATPase activity may reflect reduced nerve cell activity and energy use (Zhang *et al*., 2022). Lower ADA activity suggests changes in immune regulation and purinergic signalling.

Conclusion

This study shows that *Cucumeropsis mannii* seed oil helps reduce scopolamine-induced changes in important brain enzymes linked to neurotoxicity. Neurons control MAO to prevent too much breakdown of monoamines, which helps maintain mood, thinking, and reward signals. Na^+/K^+-ATPase, a membrane enzyme, repairs damage from oxidative stress, supports cognitive function, and boosts energy for active transport. The way CMSO affects ADA may help control neuroinflammation and support neurotrophic effects. More research is needed to identify the active components and understand the molecular mechanisms involved.

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