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Original Article

Effect of *Cocos nucifera* L. Water on Scopolamine-Induced Memory Impairment in the Wistar Rat

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ABSTRACT

Memory loss is an important Alzheimer's disease indicator (AD) linked with hippocampal damage. Scopolamine (SCO) antagonizes muscarinic acetylcholine receptor (mAChR) whose effect is similar to AD symptoms. *Cocos nucifera* L. (coconut) water is a crucial biological fluid containing nutritional components, and consumed for its health benefits. This study investigated the effect of *C. nucifera* water on memory impairment caused by SCO in rats. Thirty-two male Wistar rats were divided into four groups (n=8): control (normal saline); SCO (1 mg/kg/i.p.), *C. nucifera* water (0.4 mL/20 g) + SCO (1 mg/kg/i.p.), and donepezil (5 mg/kg/i.p.)+ SCO (1 mg/kg/i.p.). The levels of acetylcholinesterase (AChE), brain-derived neurotrophic factor (BDNF), interleukin-6 (IL-6), tumour necrosis factor (TNF-α), and cyclo-oxygenase-2 (Cox-2) were measured. Hippocampal histology was done. Utilizing GraphPad Prism for statistical analysis, pre-treatment with *C. nucifera* water and donepezil displayed higher ($p<0.01$) spontaneous alternation in the Y-maze, and decreased escape latency, increased entries and time spent in the target quadrant ($p<0.01$) of the Morris water maze compared to the SCO group. These pre-treatment also inhibited AChE activity ($p<0.001$), and reduced expressions of IL-6, TNF-α and Cox-2 ($p<0.001$). However, there were no marked differences ($p>0.05$) in BDNF across the groups. Histology of SCO-only group revealed degenerated neurons, whereas the pre-treated groups showed regenerated neurons with less necrotic cells. The administration of SCO to the rats resulted in some form of memory impairment, and *C. nucifera* water showed promise for reversing this deficits.

Keywords
Cocos nucifera Water, Scopolamine, Alzheimer's disease, Hippocampus

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INTRODUCTION

Memory impairment is the classical symptom displayed by Alzheimer's patients, typically affecting the hippocampus. Non-human creatures make poor navigational decisions without the hippocampus or appear completely lost (Lisman et al. 2017). Alzheimer's disease (AD) is a complicated infection that develops gradually over a long period, much like diabetes, cardiovascular disease, and other chronic disorders. Age, hereditary characteristics, climate, way of life, and metabolic diseases are among the variables that may change an individual's likelihood of contracting AD (Fernando et al. 2015). Clinical trials have tested many cholinergic medications for treating or improving AD symptoms. These treatments inhibit acetylcholinesterase and, thus, increase the availability of acetylcholine in the brain (Drever et al. 2007). As it turns out, acetylcholinesterase inhibitors (AChE), which temporarily improve acetylcholine's accessibility at cholinergic synapses, are the most well-known class of medications for AD (Lanctôt et al. 2009). However, AChE inhibitors are not free from side effects, with the most common being nausea and, in some cases, cardiac arrhythmia (Kho et al. 2021).

Donepezil is one of the currently used medications to treat AD. Being an AChE inhibitor, it increases the amount and

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duration of action of acetylcholine in the synaptic cleft by inhibiting the breakdown after its action on the post-synaptic neurons (Colovic et al. 2013). However, there have been reports of side effects with Donepezil, including irregular heartbeat, sleeplessness, vomiting, and cramping (Audira et al. 2020). Consequently, AD patients also undergo an elective treatment procedure.

Optional treatment methods have been considered, such as regular items, angiotensin-converting enzyme inhibitors (Jawaid et al. 2015), and diet (Sakata et al. 2006). Studies have linked the risk of AD to diet-modifiable conditions like type 2 diabetes, hypertension, and cardiovascular diseases; as a result, dietary approaches to AD prevention are attracting great attention (Fernando et al. 2015). Furthermore, these techniques are highly promising in preclinical models of scopolamine-initiated memory impairment.

Scopolamine (SCO) antagonizes muscarinic acetylcholine receptor (mAChR), presenting symptoms like learning and memory impairments, similarly observed in AD patients (Sherman et al. 2003). Therefore, SCO has been utilized to design trial models to investigate the restorative benefits of dementia drugs. Additionally, in the cortex and hippocampus, SCO is believed to increase the amount of AChE, and it has been used to investigate anti-dementia dietary interventions, such as aged foods (Weon et al. 2013), tonic drinks (Sakata et al. 2005), and organic foods (Jee et al. 2020).

One of humans' most economical yet important trees is *Cocos nucifera* L. (coconut) (Huang et al. 2013). Its fruit juice, more commonly called water, is one of the planet's most universal natural organic products. This fluid within a young coconut is a natural source of nutrients and bioactive compounds to promote growth and improve health by preventing oxidative stress, improving lipid profile, and having anti-inflammatory effects (Siti 2019). *C. nucifera* belongs to the family Arecaceae (Palmae), which contains approximately 217 genera and 2500 species. Present in the *C. nucifera* water are lipids, sugar, amino acids, sugar alcohol, natural acids, nitrogenous mixtures and catalysts, which, due to their unique synthetic properties, play various roles in plant and human frameworks. *C. nucifera* water has mitigated obesity-related and general inflammatory effects (Mohamad et al. 2017). Given the association between inflammation and neurodegenerative disorders (Stephenson et al. 2018) and the numerous medical benefits of coconut water, it is possible that it can be beneficial for memory impairment. A rat model of SCO-induced amnesia was utilized to investigate the efficacy of coconut water on memory impairments.

MATERIALS AND METHODS

The study utilized male Wistar rats weighing 120-150g from the Animal Facility of the Department of Physiology, Lead City University, Ibadan, Nigeria. They were kept in normal laboratory conditions with 12-hour light and dark cycles and had unlimited access to food and water. All of the measurements were taken daily between 10 am and 2 pm. Lead City University Animals Ethics Committee sanctioned the experimental protocol with the number, LCU/ERB/AN0208.

Drugs

Scopolamine (Cadila Healthcare PVT Ltd, India) and Donepezil (Alkem Laboratories Ltd, Mumbai, India) were obtained. Fresh tender West African tall green species of coconuts were obtained from the Ibode market in Ibadan. The plant was identified at the Forest Herbarium of Forest Research Institute of Nigeria (FRIN) Ibadan with the identification number FHI-113489. SCO and Donepezil were dissolved in deionized water to achieve the desired concentration.

Experimental Design

The animals (N = 32) were weight-matched into four groups of eight animals each: Group 1 were administered normal saline; group 2, SCO (1 mg/kg/i.p.); group 3, 0.4 mL/20 g/p.o. of coconut water (Effiong et al. 2010) via oral gavage, followed by 1 mg/kg/i.p. SCO, and. Group 4 received 5 mg/kg/i.p. Donepezil and 1 mg/kg/i.p. SCO. These procedures lasted for fourteen days.

Behavioural Studies

Y-maze Test: As described by Murray and Ridley (1997), learning ability was tested in a wooden Y-maze, which had three arms of equal size (60 cm long, 11.5 cm wide and 25 cm height). The Y-maze test was conducted on day 14 to evaluate spontaneous alternation. Before initial use, the marked arms, 'A', 'B', and 'C', were meticulously cleaned with 70% ethanol and then distilled water. Before the beginning of a testing session, a video camera was set up so that rats in the maze could be tracked accurately. The video camera was activated when the rat was gently placed in the starting arm (A) while moving far away from the maze. Each rat's spontaneous behaviour was observed for 10 min. The maze was cleaned with 70% ethanol after each session before placing the next rat in the maze. The process was repeated for every animal. An arm entry was reported to occur when all four paws of the rat crossed the central zone threshold, and the animal's snout was oriented toward the arm's end. A spontaneous alternation occurred when a mouse entered a different arm of the maze in each of the three consecutive arm entries. The percentage of spontaneous alternation was calculated using the formula below:

$$\text{Spontaneous alternation } \% = \frac{\#\ spontaneous\ alternations}{total\ number\ of\ arm\ entries\ -\ 2} \times 100$$

Morris Water Maze Test: The Morris water maze (MWM) was also used to evaluate learning and memory functions in the rat. The apparatus consists of a circular water pool (120 cm in diameter with a depth of 60 cm), which was divided into four equal quadrants (north, south, east, and west) with some external cues. The pool was filled with water, and non-toxic white was added to the water to make

it opaque. A circular platform (10 cm in diameter) was placed in the centre of the quadrant, 1 cm below the water surface. Testing began from day 7 to day 12. The first five days were acquisition training with an invisible platform. On the sixth day, a probe trial was conducted with no escape platform. During acquisition trial sessions (days 1–5), rats were placed individually in the water facing the pool wall and allowed to swim freely to find the hidden platform within 60 sec. They were gently guided to the platform if they could not find it and allowed to stay on it for 20 sec before being removed. The platform was stable throughout training, while the starting points were randomly selected. The mean escape latency time of the rat to find the hidden platform was recorded as an index of acquisition or learning. Each animal received four trials of 60 sec/per day. On the sixth day of the trial, the platform was removed from the pool for the probe test. Each animal also received four trials of 60 sec. The average time in and the frequency of entries to the target quadrant were recorded as an index of spatial memory (Gallagher et al. 2015).

Histological Studies

The animals were sacrificed on day 15 by cervical dislocation. Three randomly selected animals in each group were perfused with 4 % paraformaldehyde in 0.1M phosphate buffer. The removed brains were post-fixed in the 4 % paraformaldehyde for 24 h. Each processed tissue was embedded in paraffin wax, and serial sections were obtained using a rotary microtome at 4 µm. The sections on slides were stained following the haematoxylin and eosin technique. At ×400 magnification, the hippocampal lesions were examined under a microscope (Avwioro 2014).

Biochemical tests

Tissues Homogenization: The brains of the remaining five animals in each group were carefully separated to remove the hippocampus and then rinsed with cold isotonic saline. The hippocampus was homogenized in 0.1M phosphate buffer at pH 7.4 to obtain 10% w/v homogenate. The homogenates were centrifuged at 3000 rpm for 15 min, and aliquots of the supernatants obtained were used for biochemical assay.

AChE Estimation: AChE was quantified in the hippocampus using the Ellman method (Ellman et al., 1961). In this test, the Ellman's reagent, 5, 5'- dithiobis (2-nitrobenzoate), (DTNB), was used to assay for free thiol groups. The phosphate buffer (2.7 mL) and 0.1 mL of DTNB were added to the homogenate and allowed to stand for 5 min. Following the addition of 0.1 mL of newly made acetylthiocholine iodide (pH 8), the absorbance was read at 412 nm using spectrophotometer (model no. 745N).

BDNF, IL-6 and TNF-α Estimations: The supernatant obtained from the hippocampal homogenates was processed to detect the levels of BDNF, IL-6 and TNF-α using rat-specific ELISA kits (ElabScience, USA) that are commercially available with catalogue numbers E-EL-R1235, E-El-R0015 and E-EL-R2856 respectively. The double-antibody sandwich ELISA (DAS-ELISA) approach was used to determine our anticipated levels. At 450 nm wavelength, the optical density value was read from a spectrophotometer (model no. 745N) using an enzyme marker, and the predicted concentration was determined using a standard curve.

Statistical Analysis

One-way analysis of variance (ANOVA) (to compare means among the four groups) and Dunnett's posthoc test (to test the experimental group against negative control and positive control, respectively) were utilized for the statistical analysis of data. In addition, the significance level of $p<0.05$ was used, and the results were expressed as mean ± standard error of the mean. GraphPad Prism 5.04 software (GraphPad Software, Inc.) was used for data analysis and the preparation of the graphs.

RESULTS

Memory Impairment Induced by Scopolamine (SCO) in Y-Maze

In comparison to the control, the group that received SCO alone displayed significantly less ($p<0.05$) spontaneous alternation in the Y-maze (Fig. 1). The spontaneous alternation of the coconut water-treated group was higher ($p<0.01$) when compared with the SCO-injected memory-impaired group. The group treated with Donepezil also showed higher ($p<0.05$) spontaneous alternation when compared with the SCO-injected memory-impaired group. There was no significant difference ($p>0.05$) between the control group and the pre-treated groups (coconut water and Donepezil).

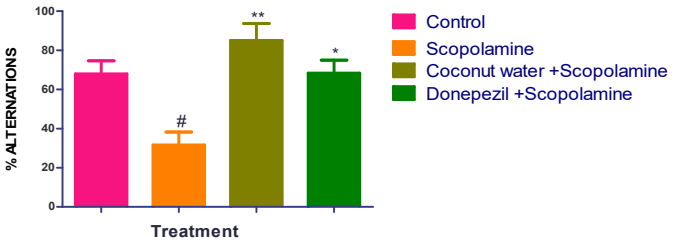

Fig. 1: Percentage spontaneous alternation in the Y-maze across various groups. Data presented as mean ± SEM (n = 5). *p < 0.05, **p < 0.01, compared to scopolamine only; #p < 0.05 compared to control.

Memory Impairment Induced by SCO in Morris-water Maze (MWM)

In the MWM, as shown in Figure 2a, the SCO-injected memory-impaired group showed significantly higher ($p<0.05$) escape latency than the control and the pre-treated groups on the last training day. However, coconut water and Donepezil significantly decreased ($p<0.01$) escape latency compared with the SCO-injected memory-impaired group on days 3, 4, and 5 of training. In addition, coconut water significantly decreased ($p<0.05$) escape latency on day three compared to the control group.

The number of entries to the target quadrant was significantly reduced ($p<0.05$) in the SCO-injected memory-impaired group when compared to the control group as shown in Figure 2b. However, the pre-treatment with coconut water and SCO showed a significant increase in the number of entries ($p<0.01$) when compared to the SCO-injected memory-impaired group but showed no statistical differences when compared with the control group ($p>0.05$).

The percentage of time spent in the target quadrant was significantly reduced ($p<0.05$) in the SCO-injected memory-impaired group compared to the control, as shown in Figure 2c. However, pre-treatment with coconut water caused a significant increase in the percentage of time spent in the target quadrant ($p<0.01$) when compared to the SCO-injected memory-impaired group but showed no differences when compared with the control group ($p>0.05$).

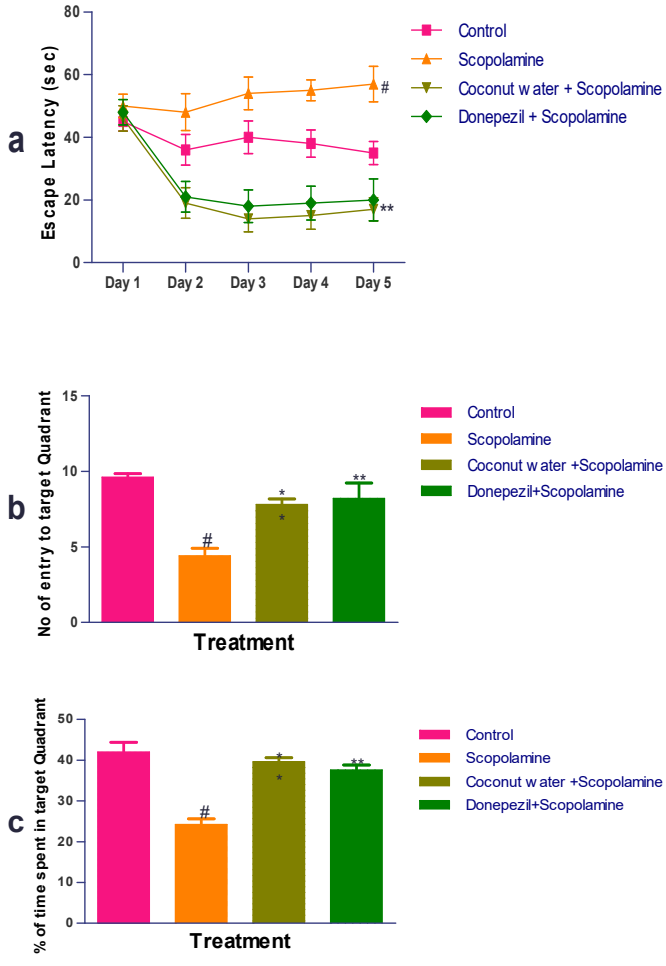

Fig. 2: a) Escape latency; b) Number of entries to target quadrant; c) Percentage time spent in target quadrant latency in Morris water maze. Data presented as mean ± SEM (n = 5). **p < 0.01, ***p < 0.001, compared to scopolamine only, #p < 0.05 compared to control

AchE Level in the Hippocampus of SCO-Induced Memory-Impaired Rats

The AChE activity was significantly increased ($p<0.001$) in the hippocampal tissues of the SCO-injected memory-impaired group, while pre-treatment with coconut water and Donepezil significantly decreased ($p<0.001$) SCO-induced hippocampal tissues AChE activity (Fig. 3). However, the AChE levels between the pre-treated and control groups were not significantly different ($p>0.05$).

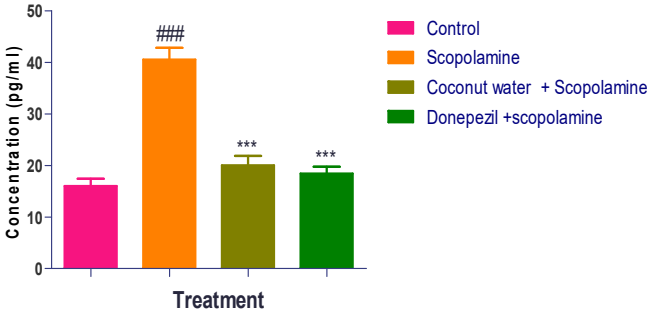

Fig. 3: Acetylcholinesterase levels across various groups. Data presented as mean ± SEM (n = 5). p < 0.001 compared to scopolamine-only group, #p < 0.05 compared control.

Pro-Inflammatory Cytokines Levels in the Hippocampus of SCO-Induced Memory-Impaired Rats

Interleukin-6 and TNF-α were markedly increased ($p<0.001$) in the hippocampal tissues of the SCO-injected memory-impaired group compared to the control, as shown in Figures 4a and 4b, respectively. These pre-treatment groups (coconut water and Donepezil) showed decreased IL-6 and TNF-α ($p<0.01$) and ($p<0.001$), respectively, when compared to the SCO-injected memory-impaired group (Figure 4a and 4b). However, there was no significant difference between the pre-treatment groups and the control ($p>0.05$).

Cox-2 and BDNF Levels in the Hippocampus of SCO-Induced Memory-Impaired Rats

Cox-2 level was significantly increased ($p<0.01$) in the hippocampus of the SCO-injected memory-impaired group when compared to the control, as shown in Figure 5a. In contrast, the pre-treated groups revealed significant reductions ($p<0.01$) compared to the SCO-injected memory-impaired group. However, there was no significant difference between the pre-treated groups and control ($p>0.05$).

In Figure 5b, there were no significant differences in the BDNF levels across the groups ($p>0.05$)

Hippocampal Histology of the SCO-Induced Memory-Impaired Rats

The CA3 region of the hippocampus has a well-layered arrangement of its strata as lacunosum-moleculare, radiatum, lucidum, pyramidal, and oriens. The histomorphology presentation of the CA3 region showed the presence of densely packed cells, a distinct central nucleus, and a well-stained cytoplasm in the control group

(Fig 6A). The SCO-injected memory-impaired group showed homogenous and pyknotic cells (Fig 6B). The coconut water pre-treated group and donepezil pre-treated group (Fig 6C and D) showed regenerating neurons characterized by few necrotic cells and mild vacuolations in the neuropil compared to the control and SCO-injected memory-impaired groups.

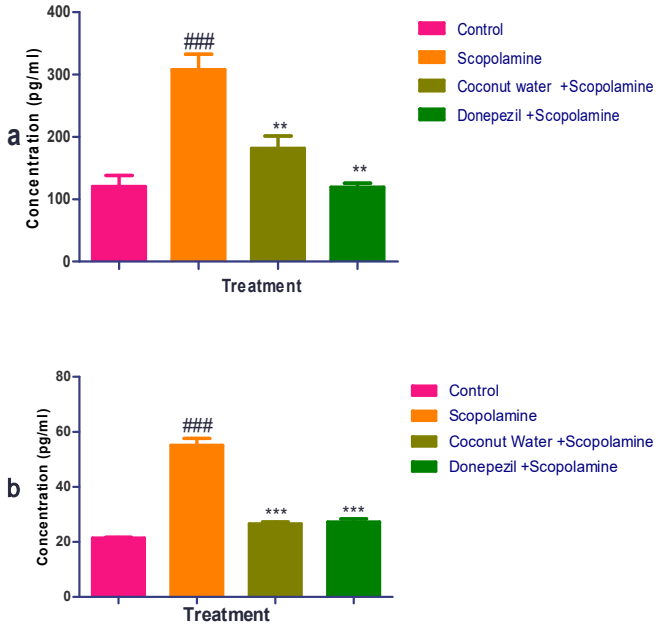

Fig. 4: Pro-inflammatory cytokines levels across groups: a) IL-6; and b) TNF-α. Data presented as mean ± SEM (n = 5). **p < 0.01, ***p < 0.001, compared to scopolamine-only group; #p < 0.05 compared to scopolamine-only group control.

DISCUSSION

The current study assessed the effect of coconut water on SCO-induced memory impairment in Wistar rats. The Y-maze test is an example of an unrestricted rotation or spatial working memory test. It evaluates short-term memory by allowing the animal to explore all three arms of the maze freely. A rat with a good working memory will remember the arms of the maze that it has previously visited and will exhibit a tendency to enter a less recently visited arm, resulting in an increase in rotation known as spontaneous alternation (Kraeuter et al. 2019). Our findings indicate that the administration of scopolamine significantly reduced spontaneous alternation, whereas coconut water pre-treatment significantly increased it to a greater degree than the standard treatment, Donepezil.

Scopolamine-treated rats showed cognitive impairment and memory deficit as indicated by increased escape latency time, lower number of entries to the target quadrant, and reduction in the percentage of time spent in the target quadrant in the MWM test, all of which were prevented by oral administration of coconut water and Donepezil. On the other hand, coconut water pre-treated rats showed significant improvement in acquisition trials, as evidenced by a reduction in the escape latency time compared to the SCO group.

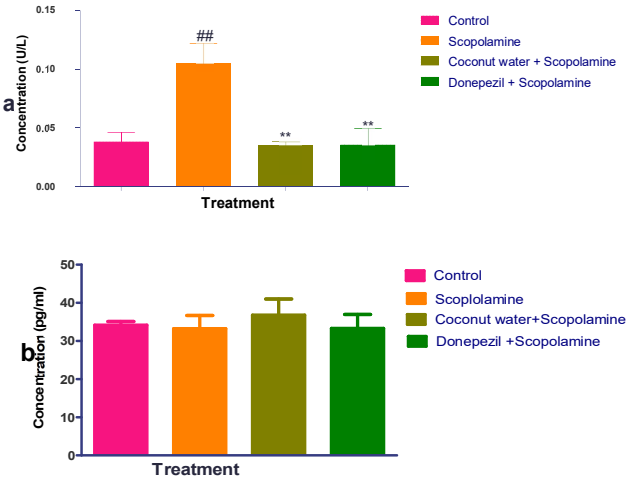

Fig. 5: Effects of coconut water on scopolamine-induced memory impairments: a) Cyclooxygenase (COX-2); and b) Brain-derived neurotrophic factor (BDNF). Data presented as mean ± SEM (n = 5). **p < 0.01 compared to scopolamine-only group; ##p < 0.01 compared to control

The cholinergic system is indispensable for learning and memory. It is unsurprising, therefore, that inhibition of

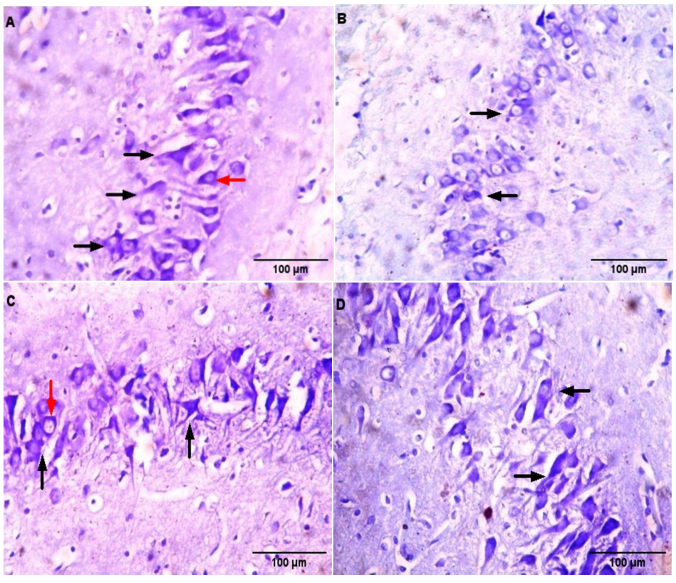

Fig. 6: A representative photomicrographs of sections of the hippocampus of the experimental animals showing the CA3 region. A, B, C, D are control, scopolamine only, Coconut water + Scopolamine, and donepezil + scopolamine groups, respectively (Haematoxylin and Eosin, × 400).

acetylcholinesterase has been identified as the mechanism of action of Donepezil in memory improvement (Andalib et al. 2019). Moreover, previous studies have shown the inhibitory effect of coconut water and oil on the enzyme acetylcholinesterase (Yong et al. 2009; Fernando et al. 2015). Coconut water contains many antioxidant phytochemicals (Lima et al. 2015, Nyayiru Kannaian et al. 2020), so its memory-enhancing effect is likely due to its anti-acetylcholinesterase activity. Cholinergic inhibition may underlie cognitive deficits in SCO-induced amnesia models (Hirokawa et al. 1996). Pre-treatment with coconut water decreased ACHE activity in our model to an extent comparable to that of Donepezil. Increased AChE is a hallmark of amnesia induced by SCO, and its decreased activity is a predictor of memory improvement (Smach et al. 2020). ACh is a fundamental neurotransmitter associated with learning and memory cycles; increasing ACh levels can enhance cognitive performance (Pepeu and Giovannini 2004). ACh is an example of a classical neurotransmitter because ACh hydrolysis by AChE terminates its synaptic activity (Ballard et al. 2005). In another vein, an excessive amount of AChE activity leads to chronic low levels of acetylcholine and thus results in cognitive deficits (Deak et al. 2016). Therefore, one therapeutic strategy for managing Alzheimer's disease is inhibiting the enzyme acetylcholinesterase activity.

Available scientific evidence suggests increased neuroinflammation and microglial activation are pinned to mental disorders (Jang et al. 2013). People with dementia have elevated brain levels of pro-inflammatory cytokines (Mitsuhashi et al. 2013). In response to dementia, pro-inflammatory cytokines activate microglia, contributing to synaptic disappointment (Park et al. 2010). SCO has been known to cause inflammation by increasing oxidative stress. As a result, there is the release of pro-inflammatory cytokines. Coconut water abrogates pro-inflammatory cytokines by preventing the iNOS protein expression (Lakshmanan et al. 2020). iNOS expression is regulated by NF-κB, activated by reactive oxygen species and is involved in the progression of inflammation (Mao et al. 2017). Usually, NF-κB is kept in the cytoplasm by the inhibitory action of IκBα. Once IκBα is phosphorylated, the inhibitory potentials are withdrawn, triggering the nuclear translocation of NF-κB. This phosphorylation is caused by the activation of reactive oxygen species (Kumar et al. 2018). Coconut water may have prevented these processes of phosphorylation. Donepezil likewise decreased the expression of an inflammatory gene by inhibiting NF-kB signalling (Hwang et al. 2010). In our study, coconut water significantly decreased levels of IL-6 and TNF-α. Based on the hypothesis that pro-inflammatory cytokines and inflammation cause SCO-induced memory impairment (Cheon et al. 2021), it is deduced that decreased levels of IL-6 and TNF-α may protect against the cognitive deficit and memory impairment caused by SCO.

Optimum physiological conditions require the formation of long-term potentiation in the dentate gyrus and hippocampus cells via neuronal cyclooxygenase-2 (COX-2) activity (Chen et al. 2002). When in excess, the neuronal COX-2 accelerates the memory deficit in aged mice (Andreasson et al. 2001). Prostaglandin production by COX-2 exacerbates neuronal damage by disrupting calcium homeostasis (Woodling et al. 2016). SCO also produces prostaglandin E2 and mRNA expression of COX-2 in the brain (Xian et al., 2015). Prostaglandin E2 induces inflammation (Tsuge et al. 2019). In addition, it may stimulate COX-2 (Madrigal-Martínez et al. 2019). Coconut water contains flavonoids with potent anti-inflammatory effects and, as a result, may inhibit the synthesis of prostaglandins (Kumar et al. 2013). Donepezil has also been shown to reduce the expression of COX-2 (Goschorska et al. 2018). In this study, coconut water and Donepezil inhibited COX-2 expression in the hippocampus tissues, with attendant protection against the SCO effect.

Brain-derived neurotrophic factor (BDNF) is inextricably linked to the segregation and survival of neurons. BDNF, in recent times, has evolved as a key regulator of the synaptogenesis and synaptic plasticity mechanisms that govern learning and memory. It enhances long-term potentiation, which is a neuronal correlate of learning and memory (Cunha et al. 2010). However, in this present study, there was no significant difference across the groups, indicating that the cognitive benefits of coconut water are probably not mediated by the BDNF pathway.

Neuroinflammation and neurodegeneration are the most prominent SCO-induced changes in the hippocampus. This study's histological findings support that SCO affects hippocampal neurons (Seifhosseini et al. 2011; Onasanwo et al. 2021) and induce neurotoxicity in the brain as indicated by the cellular clusters with pyknotic presentations and poorly stained cytoplasm in the CA3 region of the hippocampus. Consistent with the documented anti-inflammatory properties of coconut water, pre-treatment of rats with it reduced neuronal loss similar to that of Donepezil. The neuroprotection executed by coconut water may be due to its anti-inflammatory properties (Siti 2019), which underlie its therapeutic action in improving behavioural and cellular functions in SCO-treated rats.

Conclusion

Collectively, coconut water enhanced Y-maze performance and Morris water maze learning and prevented the alteration of biochemical marker levels associated with memory impairment. Coconut water may prevent memory loss in this SCO-induced amnesia model by inhibiting acetylcholinesterase and improving cholinergic transmission.

Grants and Financial Support

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Conflict of Interest

None declared.

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Authors' Contribution

Conceptualization and Data acquisition was done by BT; Data analysis was done by BH; Methodology was done by AO; Supervision was done by SA; Roles/Writing - original draft; Writing - review and editing was done by AS.

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