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Ethanol extract of *Thaumatococcus Danielli* leaves mitigates Scopolamine-induced Behavioural and morphological changes in the Prefrontal cortex of Wistar rats

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ABSTRACT

The antioxidant potential of ethanol extract of *Thaumatococcus danielli* (T. danielli) leaves has been reported severally, however, there is a dearth of scientific information on its effect on scopolamine-induced changes in the rat prefrontal cortex. This study assessed the neuroprotective potential of ethanolic extract of *Thaumatococcus danielli* leaves on scopolamine induced neurotoxicity in rats. Eighty (80) adult Wistar rats weighing 180-200g were randomly divided into eight groups of 10 rats each. Group A was administered distilled water orally (10 ml/kg) and intraperitoneally (2ml /kg), groups B and C were administered T. danielli alone at 100 and 200 mg/respectively, while rats in group D received donepezil at 5mg/kg. Rats in group E received intraperitoneal (i.p) injection of scopolamine at 16 mg/kg, while groups F and G were administered scopolamine with *T. danielli* respectively. Rats in group H received scopolamine and donepezil. Scopolamine was administered daily for three days while T. danielli and donepezil was administered for 42 days At the end of treatment, rats were exposed to behavioural paradigms (Open field box and elevated plus maze). Twenty-four hours after the last behavioural test rats were euthanised and their brains removed a prefrontal cortex was sectioned and processed for general histology. Results showed that scopolamine was associated with decrease in weight, reduction in feed intake, anxiety-related behaviours and prefrontal cortex neurotoxicity. While the administration of ethanol extract of *Thaumatococcus danielli* leaves was associated with reversal of weight loss, increased feed intake anxiolysis and reversal of scopolamine induced neurotoxicity. In conclusion, this study shows that *T. danielli* has the ability to ameliorate scopolamine induced changes. However more studies are required to ascertain its suitability in humans.

KEYWORDS: **Amnesia; Cognition; Dementia; Herbal Extracts, Saponins, Flavonoids**

1. Introduction

Memory is one of the most essential roles of the brain, it is essential for survival because it is required by organisms to record their experiences and use this information to adapt their responses to the environment [1, 2]. Loss of memory and cognitive impairment are the major features of Alzheimer's disease (AD) [2, 3]. Acetylcholine has been reported to be efficient in the neocortex of individuals with Alzheimer's disease. The presence of acetylcholine within the neocortex has

also been shown to ameliorate learning deficits and restore memory [4, 5]. Decreased cholinergic firing in the brain, rise in oxidative stress, hypercholesterolemia, and neuroinflammatory reactions have been demonstrated to play crucial aetiological roles in the memory decline associated with dementias [6-8]. The central cholinergic system is involved in cognitive functions and plays an important role in learning and memory adaptations in both humans and rodents [9].

Alzheimer's disease, a progressive, irreversible neurodegenerative disorder first identified and reported by Alois Alzheimer in the early 1900s [10, 11], occurs gradually and results in cognitive impairment, unusual behaviour, personality changes, and ultimately death [10]. Alzheimer's disease is the most common form of adult-onset dementia [11]. Several experimental models have been used to examine drug response in dementia research [13]. Scopolamine-induced cognitive deficit model has also been shown to have predictive and construct validity with dementia in humans has also been used in numerous studies to identify and characterize therapeutic targets for AD [13, 14]. Scopolamine-induced amnesia is generally considered an excellent behavioural model to study dementia-related disorders including AD, the suitability of scopolamine as a pharmacological model in the study of the cellular and molecular changes as they relate to AD has been shown to have predictive and construct validity [13, 14].

The current pharmacotherapy for AD involves the use of acetylcholinesterase (donepezil, rivastigmine, and galantamine) and NMDA glutamate (memantine) inhibitors. While both classes of drugs provide mainly symptomatic relief their use has been associated with treatment failures and several side effect [15, 16]. This has necessitated the search for compounds like *Thaumatococcus danielli* with reported antioxidant potential which can also mitigate oxidative stress and possibly protect against the development of structural defects that have also been reported in AD [17].

Thaumatococcus danielli has been used in folkloric medicine in the management of a number of ailments. The leave sap of *T. danielli* is used in traditional medicine as antidote against venoms, stings, and bites. Leave and root sap are used as sedative and for treating psychiatric disorders [17,18]. There have also been reports that T. danielli leaves has been used as laxatives and also in the treatment of diabetes mellitus, and lung diseases [17-19]. Phytochemical studies carried out on T. danielli demonstrated high contents of terpenoids, flavonoids, alkaloids, and tannins [20, 21]. In-vitro studies have also shown that flavonoids have anti-inflammatory, anti-allergic [22], antimicrobial [17, 18], anticancer [19 20], and hypolipidemic effects [22, 23]. Furthermore, terpenoids and flavonoids have been reported to have potent antioxidant, hypolipidemic, and organ protective activity [22]. Presently, only a few studies have examined the neuroprotective potential of the plant. Therefore, the present study was designed to evaluate the neuroprotective potential of ethanolic extract of *Thaumatococcus danielli* leaves on scopolamine induced changes in rat prefrontal cortex.

2. Materials and Methodology

2.1 Chemicals and Drugs

Scopolamine 500 mg was obtained from Milpitas, CA, USA. Donepezil drugs 100 mg tablets was gotten from Akol Pharmacy Ogbomoso, Oyo state, Nigeria. Distilled water was obtained from Sumther Pharmacy, Starlite, Ogbomoso, Oyo state, Nigeria. Standard diet was obtained from the feed mill, Ogbomoso, Oyo state, Nigeria.

2.2 Animals

Healthy Wistar rats used in this study were obtained from the Empire Breeders, Osogbo, Osun State Nigeria. Rats were housed in wooden cages measuring 20 x 10 x 12 inches in quarters kept at room temperature with a 12hour light dark cycle. Rats were allowed free access to food and water. Research ethical approval was obtained and all procedures were conducted in accordance with the approved protocols of the Faculty of Basic Medical Sciences, Ladoke Akintola University of Technology with and within the provisions for animal care and use prescribed in the scientific procedures on living animals, European Council Directive (EU2010/63).

2.3 Preparation of Plant Material

Thaumatococcus danielli was collected from Foursquare camp Lagos-Ibadan express way Ogun state Nigeria. The extraction of *Thaumatococcus danielli* was carried out at the Food Science and Engineering (FSE) department, Ladoke Akintola University of Technology, Ogbomoso Nigeria. The air-dried *Thaumatococcus danielli* was pulverized using a grinding machine, the weight of the powdered form of the pulverized *Thaumatococcus danielli* was 2.6 kg and this pulverized *Thaumatococcus danielli* was soaked for 72 hours in 30 L of ethanol, for the proper mixing of the 3 kg sample of *Thaumatococcus danielli* with 30 L of ethanol, it was then put inside a big bowl with constant stirring for the 72hours. The mixture was then filtered using a Whatman filter. The filtrate in the round bottom flask was put on a heating mantle (Barnstead/ electrothermal) at 45ºC for 4 days for proper concentration. The concentrate formed was taken to an oven at 50ºC for 1 hour the final residue of about 500 g was a dark green mass which was stored at room temperature of 25ºC as previously described [24]

2.4 Determination of The Lethal Dose (LD_{50})

Acute toxicity test was carried out according to the modified Lorke method (1983). A total of 13 rats were used; in the initial

phase, animals were assigned randomly into 3 groups of 3 rats each. Animals in each group were administered intraperitoneal injection of extract at 1, 10 and 100 mg/kg body weight following which they were observed for signs of toxicity and death in the first 24 hours. In the second phase, another set of 4 rats were randomly assigned into four groups of 1 rat each and administered the extract intraperitoneally at 160, 320, 500, and 640 mg/kg based on the result of the first phase. The LD_{50} was then calculated to be 565.7 mg/kg body weight

2.5 Diet

All animals were fed commercially available standard rodent chow (29% protein, 11% fat,58% carbohydrate) from weaning until the commencement of the study. At the beginning of the experimental period, animals were either fed standard chow (29% protein, 11% fat, 58% carbohydrate) or *T. danielli* incorporated into the standard diet at 100 and 200 mg/kg of food and administered *ad libitum* for four weeks following previously described protocols [25].

2.6 Experimental Methods

Eighty (80) adult rats weighing 140—160 g each were randomly assigned into eight groups of ten (n=10) animals each. Group A served as normal control and received distilled water orally at 10 ml/kg and intraperitoneally (i.p) at 2ml/kg, rats in group B and C received ethanol extract of T. danielli at 100 and 200 mg/kg by oral gavage while animals in group D received donepezil orally at 5 mg/kg of donepezil [26]. Animals in group E were administered scopolamine i.p at 16 ml/kg daily for three days [27], rats in groups F and G received scopolamine daily for 3 days and were also administered T. danielli at 100 or 200 mg/kg, while rats in group H were administered scopolamine with donepezil. Donepezil and T. danielli were administered daily for 42 days. At the end of the experimental period, animals were exposed to behavioural paradigm (open field test, elevated plus maze, Y-maze and catalepsy bar test). Twenty-four hours after the last behavioural tests, animals were sacrificed by cervical dislocation and the brain was removed and fixed in 10% neutral buffered formalin. The prefrontal cortex was processed for paraffin embedding, cut at 5 µm and stained for histological study.

2.7 Determination of Feed intake and Body weight

Feed intake and body weight were assessed respectively using a Mettler Toledo weighing balance (Type BD6000, Greifensee, Switzerland) following previously described protocols [28]. Relative change in feed intake and body weight was calculated for individual rats using the equation shown below.

$$\frac{\text{Final body weight} - \text{Initial body weight}}{\text{Initial body weight}}\ g$$

$$\frac{\text{Feed intake on day 42} - \text{Feed intake on day 1}}{\text{Feed intake on day 1}}\ g$$

2.8 Behavioural Testing

2.8.1 Open field Behaviours

Open-field responses in rats illustrate arousal, inhibitory, and inspective exploration behaviours, as well as anxiety behaviours. Stereotypic behaviours, have also been exemplified by this paradigm. These behaviours typically signifies a rodent's capacity for exploration [29]. Ten minutes of behaviours in an open field, including grooming, rearing, and horizontal movement were observed and recorded in the open field apparatus. The open-field paradigm consists of a square enclosure with a rigid floor, measuring 36 x 36 x 26 cm. The wood was painted white, and the floor was segmented by permanent blue markings into 16 equal squares. Each rat was positioned near the centre of the field as previously described [30, 31]. Total horizontal locomotion (number of floor units traversed by all paws), rearing frequency (number of instances the rat stood on its hind legs, either with its forelimbs against the walls of the observation cage or freely in the air), and grooming frequency (number of body-cleaning actions involving paws, licking of the body and pubis with the mouth [32].

2.8.2 Catalepsy Bar test

Catalepsy bar tests are widely used to measure the failure to correct an imposed posture resulting from muscular rigidity. The bar test was set to a height of 12 cm, and rats were gently positioned, placing their forelimbs on the bar and their hind limbs on the floor of the apparatus. The time taken for the rat to move both paws from the bar is monitored using a stopwatch. The time recorded for the rat to correct this posture is an index of the intensity of catalepsy. A cataleptic rat will continue to hold onto the bar for a prolonged period while a normal rat will change its position within seconds [33].

2.8.4 Anxiety related behaviours

Anxiety-related behaviours was measured as time spent in the open arm of the elevated plus maze (EPM). The EPM is a plus

shaped behavioural paradigm that has two open arms measuring 25×5×5 cm lying across from one another and perpendicular to two closed arms measuring 25×5× 6 cm. The open arms have no side walls unlike the closed arms that have 2 high walls. At the beginning of the exposure animals are placed in the central platform in such a way that they face the closed arm, behaviours are then recorded for 5 minutes. The criterion for arm visit was considered only when the animal decisively moved all its four limbs into an arm as previously described [28, 31].

2.9 Tissue Histology

Rat brains were dissected, sectioned and fixed in neutral-buffered formol-saline. The prefrontal cortex was processed for paraffin-embedding, cut at 5 µm and stained with haematoxylin and eosin and cresyl fast violet for general histological analysis.

2.10 Photomicrography

Histologically processed sections of the prefrontal cortex were examined microscopically using a Sellon Olympus trinocular microscope (XSZ-107E, China) with a digital camera (Canon Powershot 2500). Photomicrographs were captured at ×400 magnification. Histopathological changes were assessed by a pathologist who was blinded to the groupings.

2.11 Statistical Analysis

Data was analysed using GraphPad prism software Soft-ware 9.0.0 using One-way analysis of variance (ANOVA). Tukey HSD test was used for intra and inter group comparisons. Results were expressed as mean ± S.E.M. and $p < 0.05$ was taken as the level of significant difference from control.

3. Results

3.1 Effect of *Thaumatococcus Danielli* on body weight and feed intake

Figure 1 (A-D) shows the effect of *Thaumatococcus danielli* on weekly body weight (Figure 1A), relative change in body weight (Figure 1B), weekly feed intake (Figure 1C) and relative change in feed intake (Figure 1D). Result of weekly body weight revealed gradual increase in weekly body weight in all treatment groups across the 4 weeks of treatment however, weight of animals administered T. danielli alone at 100 mg/kg, Donepezil and T. danielli combined with scopolamine lagged behind other treatment groups. Result of relative change in body weight (Figure 1B) revealed a significant decrease in body weight with T. Danielli (TH) at 100 and 200, and SCOP/TH at 100 and 200 compared to control and scopolamine control respectively. Result of weekly feed intake (Figure 1C) revealed no significant difference in feed intake in any group across the treatment period, however, result of relative change in feed intake (Figure 1D) revealed a significant decrease in feed intake with SCOP/TH100 and SCOPTH200 compared to control. While compared to SCOP control there was a significant decrease in feed intake with TH200.

3.2 Effect of *Thaumatococcus Danielli* on open field behaviours and catalepsy bar test score

Figure 2 (A-D) shows the effect of *Thaumatococcus danielli* on Line crossing (Figure 2A), rearing (Figure 2B), self-grooming (Figure 2C) behaviours in the Open field arena, and catalepsy score (Figure 2D) measured using the bar test. Line crossing (Figure 2A) decreased significantly with TH100, Donepezil, SCOP/TH100, SCOP/TH200 and SCOP/DONEP and increased with SCOP compared to control. Compared to scopolamine control, line crossing decreased with SCOP/TH100, SCOP/TH200, and SCOP/DONEP. Result of rearing activity (Figure 2B) showed a significant increase with TH100 and a decrease with SCOP/TH200 and SCOP/DONEP compared to control. Compared to SCOP control, rearing activity decreased with TH100, Donepezil, SCOP/TH200, SCOP/DONEP, while an increase in rearing was observed with SCOP/TH100.

Result of self-grooming behaviour (Figure 2C) showed a significant increase with TH200, SCOP/TH200 and SCOP/DONEP and a decrease with SCOP/TH200 compared to control. Compared to SCOP control, self-grooming increased with SCOP/TH100, SCOP/DONEP, while a decrease in self-grooming was observed with SCOP/TH200. Catalepsy score (Figure 2D) decreased significantly with TH100, TH200, SCOP, SCOP/ TH200 and SCOP/DONEP, and increased with DONEP and SCOP/TH100 compared to control. Compared to SCOP control, catalepsy score increased with SCOP/TH100 SCOP/TH200 and SCOP/DONEP.

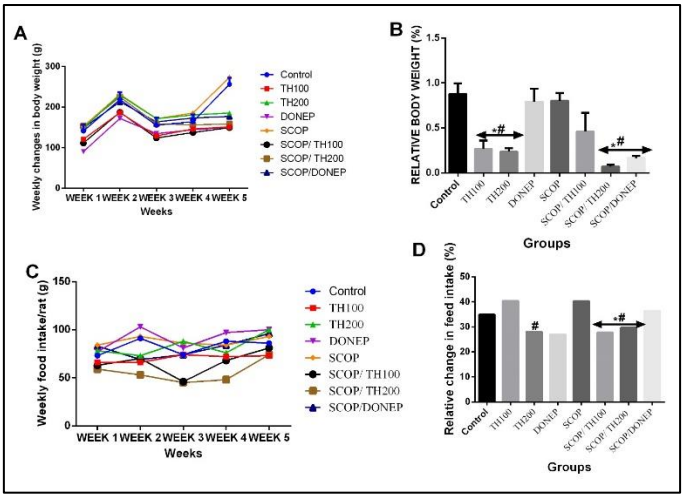

Figure 1(A-D): Effect of T. Danielli on weekly body weight (A), percentage change in body weight (B), relative feed intake (C), and percentage change in feed intake (D). Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05

significant difference from SCOP. TH: Thaumatococcus danielli, scop: Scopolamine, DONEP: Donepezil.

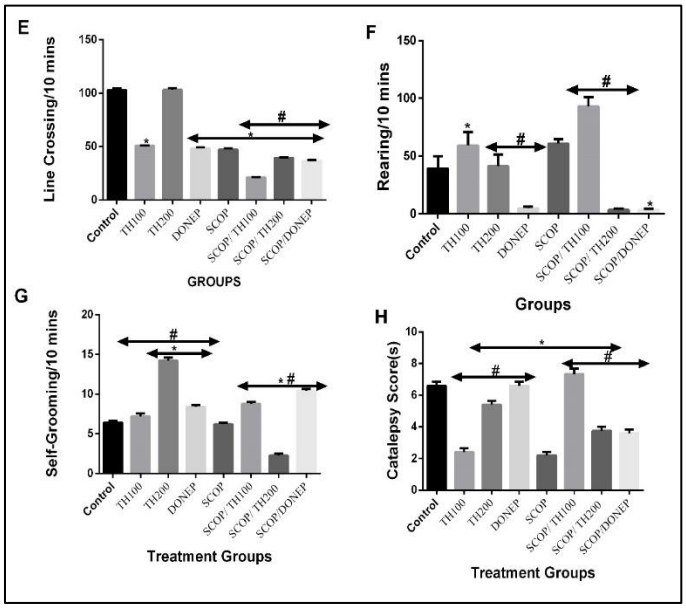

Figure 2(A-D): Effect of T. Danielli on line crossing(1E), rearing (1F), self-grooming (1G) and Catalepsy bar test (1H). Each bar represents Mean ± S.E.M, **p*< 0.05 vs. control, #P < 0.05 significant difference from SCOP. TH: Thaumatococcus danielli, scop: Scopolamine, DONEP: Donepezil.

3.3 Effect of *Thaumatococcus Danielli* on anxiety-related behaviours and spatial working memory

Figure 3A and 3B show the effect of *Thaumatococcus danielli* on open arm (Figure 3A) and closed arm (Figure 3B). Result of open arm time (Figure 3A) increased with TH100 and SCOP/TH100 and decreased with SCOP, compared to control. Compared to scopolamine, open arm time increased with SCOP/TH100, SCOP/TH200 and SCOP/DONEP. Result of time spent in the closed arm (Figure 3B) revealed a significant increase with SCOP and a decrease with SCOP/TH100 compared to control. Compared to Scopolamine, closed arm time, decreased with SCOP/TH100, SCOP/TH200 and SCOP/DONEP.

3.6 Effect of Thaumatococcus danielli on prefrontal cortex histomorphology

Plate 1(A-H) shows photomicrographs of representative haematoxylin and eosin-stained sections of the rat prefrontal cortex. Examination revealed distinct layers of the prefrontal cortex of rats in the control group (Plate 1A), groups administered T. danielli (Plate 1B and 1C) and the donepezil alone group (Plate 1D) characteristic outer granular layer with numerous pyramidal cells, granule cell and glial neurons were observed. However, in the group administered scopolamine (Plate 1E) numerous pyknotic cell with pale staining neurons and degenerating pyramidal cell were seen scattered throughout the neuropil. In groups administered scopolamine with T. danielli (Plate 1F and 1G) or donepezil varied degrees of reversal of scopolamine induced neurodegeneration was observed.

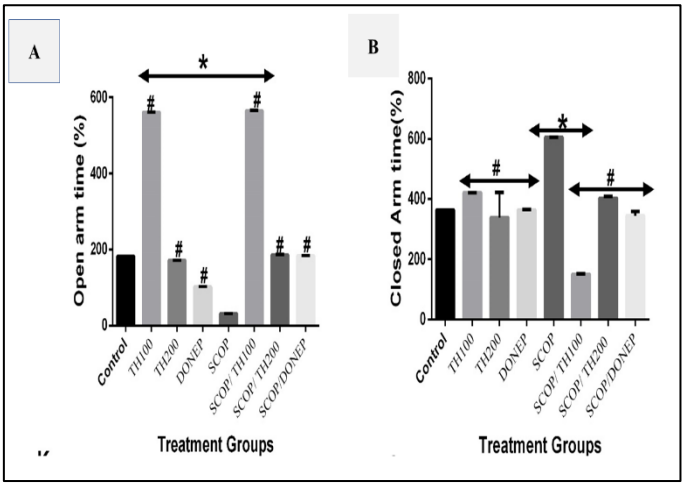

Figure 3: Effect of Quercetin on locomotor activity. Each bar represents Mean ± S.E.M, *p<0.05 significant difference from control. #p<0.05 significant difference from MSG. Number of rats per treatment group =10. MSG: Monosodium glutamate Q: Quercetin.

Plate 2 (A-H) are representative Cresyl Fast Violet-stained slides of the rat prefrontal cortex Examination of the slides revealed the characteristic layered arrangement of the prefrontal cortex with neurons with normal staining nuclei, the Nissl substance was also well preserved in the control group (Plate 2A), groups administered T. danielli (Plate 2B and 2C) and the donepezil alone group (Plate 2D). Degenerating neurons with chromatolytic nuclei and loss of Nissl substance was observed in the scopolamine group (Plate 2E), while protection against neuronal injury was observed in the groups treated with T. danielli (Plate 2F, Plate 2G). in the Scopolamine/donepezil group (Plate 2H) sparse staining of the Nissl substance was observed.

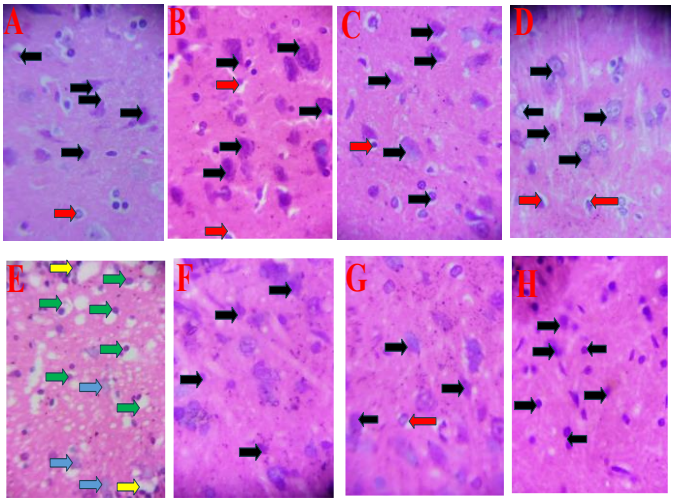

Plate 1 (A-H): Representative photomicrograph of haematoxylin and eosin-stained sections revealed distinct layers of rat prefrontal cortex

with presence of numerous pyramidal cell (PC)=black arrow, blood vessel=red arrow, granular cells (GC)=yellow arrow and Neuroglia (NC)=blue arrow. Mg. X400

Effect of Thaumatococcus danielli on prefrontal cortex histomorphometry (Haematoxylin & Eosin)

Figure 4 shows the number of cells per μm^2 in the haematoxylin and eosin-stained sections of the rat prefrontal cortex. There was a significant decrease in number of cells in the prefrontal cortex with SCOP compared to control. Compared to SCOP number of cell increased significantly with SCOP/TH100, SCOP/TH200 and SCOP/DONEP.

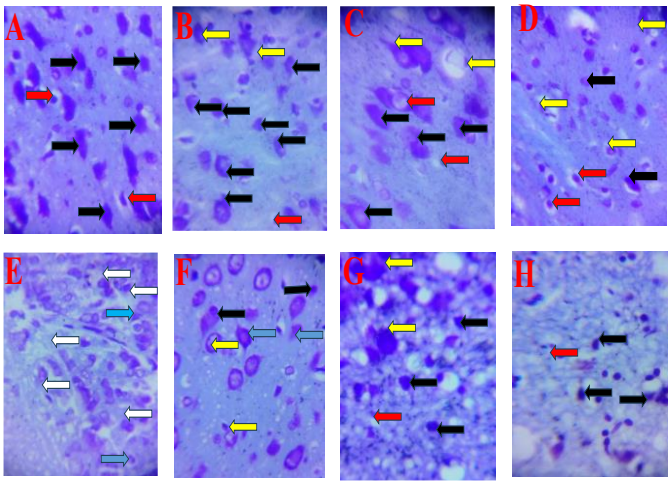

Plate 2 (A-H): Representative photomicrograph of cresyl fast violet-stained sections revealed characteristic layered arrangement of the rat prefrontal cortex with well-delineated numerous pyramidal cell (PC)=black arrow, blood vessel=red arrow, granular cells (GC)=yellow arrow, Neuroglia (NC)=blue arrow and Chromatolytic cell=white arrow. Mg. X400

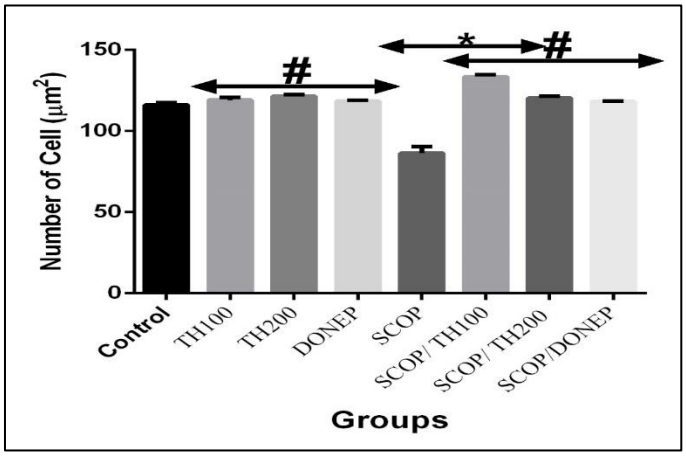

Figure 4: Effect of T. Danielli on Prefrontal cortex histomorphometric analysis (Haematoxylin and Eosin-stained slides). Each bar represents Mean ± S.E.M, *p< 0.05 vs. control, #P < 0.05 significant difference from SCOP. TH: Thaumatococcus danielli, scop: Scopolamine, DONEP: Donepezil.

4. Discussion

This study examined the neuroprotective effect of T. danielli leaves on scopolamine induced changes in the rat prefrontal cortex. The results revealed that administration of scopolamine was associated with changes in body weight, feed intake, open field behaviours, anxiety-related behaviour and prefrontal cortex neurotoxicity. The administration of ethanol extract of T. danielli was associated with a reversal of scopolamine induced changes.

In this study, weekly body weight and percentage change in weight increased in the control group and decreased in the groups administered scopolamine. The effects on body weight observed with scopolamine in this study are consistent with the results of several other studies that had also associated the administration of scopolamine with significant weight loss [17, 34, 35]. On the other hand, treatment with *Thaumatococcus danielli* mitigated scopolamine-induced weight loss. In the groups administered *T. danielli* alone and the T. danielli treated groups a significant decrease in body weight and feed intake was observed corroborating the results of the study by Ajayi et al [18]. The reduction on body weight and feed intake observed has been previously attributed to the presence of saponins which are phytochemical constituents of T. danielli [18], The binding of saponins to cholesterol moieties in the gut has been associated delayed gastric emptying and early satiety, the reduction of cholesterol synthesis and eventually the reduction in body weight [21]. Administration of T. danielli to health rats was associated with no change in weight consistent with the reports of some other studies [18, 19]. This would suggest that *T. danielli'* mitigates disease induced alterations in body weight without altering body weight in health y subjects [19].

The administration of scopolamine in this study was associated with a significant reduction in feed intake while treatment with *T. danielli* reversed scopolamine-induced changes in feed intake. In groups administered *T. danielli* alone, no significant difference in feed intake was observed, supporting earlier observations that *T. danielli*'s effect was to restore normalcy supporting a few studies that had also reported that *T. danielli* did not increase energy consumption [18, 36]. In the scopolamine treated groups, *T. danielli* reversed scopolamine-induced reduction in feed intake, consistent with the results of other studies that had observed *T. danielli*'s ability to reverse feed intake in a disease model [35]. The effects of *T. danielli*' on body weight and feed intake can also be attributed to its ability to influence central processes that regulate energy homeostasis [37]. The weight loss observed can also be attributed to reduction in feed intake, since there are reports of a positive relationship existing between feed consumption and weight change [19].

Neurobehavioural paradigms are non-invasive models that are employed for the assessment of normal central nervous system function or to investigate the effects of drug and/or drug candidates on the functioning of the central nervous system in health or disease [38]. In this study the effects of T. danielli on was also examined on scopolamine induced changes in behaviour and brain morphology. There have been reports suggesting that scopolamine, has potential for neurotoxicity [27, 39, 40]. In this study, it was observed that the administration of scopolamine was associated with central excitation and increased anxiety, corroborating a number of studies [34]. Scopolamine administration was also associated with morphological evidence of neuronal injury. Overall, the administration of scopolamine has a neurotoxic effect. However, reports from a few other studies [18] have shown no significant effect of scopolamine on locomotor activity and motor coordination; However, an increase in ambulatory behavior was observed during the assessment of rats' behavior in their home cages. Scopolamine readily crosses the blood-brain barrier and it is believed that inhibition of muscarinic receptors in the central nervous system causes a cholinergic deficit that impairs memory and possibly locomotor activity [41]. The administration of T*haumatococcus danielli* was associated with decreased horizontal locomotion, rearing and self-grooming, , while at both concentrations of *T. danielli*, an anxiolytic effect was observed. *T. danielli*'*s* ability to reverse brain injury has also been reported [19].

Morphometric analysis also revealed that T*haumatococcus danielli* had the ability to increase neuronal cell count Studies examining the mechanisms responsible for *T. danielli*'s impact on the brain have also listed its ability to rescue apoptotic pathways and increase neurogenesis as potential mechanisms of action [19].

Conclusion

In conclusion the result of this study shows the ability of ethanol extract of *Thaumatococcus danielli* leaves to ameliorate scopolamine induced changes in body weight, feed intake, neurobehaviour and prefrontal cortex histomorphology. However more studies are required to examine its efficacy in humans.

Funding.

None

Availability of data and materials

Data are available from the corresponding author on request.

Declarations Ethics approval

Ethical approval for the research was granted by the ethical committee of the faculty of Basic Medical Sciences with Identification code (ERCFBMSLAUTECH:078/11/2024)

Competing interests

None

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