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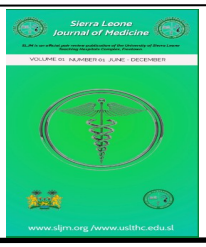

Impact of Red Acalypha (Acalypha Wilkesiana) Extract on Weight, Oxidative Stress, Memory, and Hippocampal Structure in Sprague-Dawley Rats

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ABSTRACT

Background: The therapeutic potential of medicinal plants in neurological health has gained attention. Acalypha wilkesiana, or Red Acalypha, has traditionally been used for anti-inflammatory, antimicrobial, and wound-healing properties. The hippocampus, a key brain region for memory, learning, and spatial navigation, is vulnerable to damage, making it a focus for studying natural compounds' effects on cognitive health. Damage to the hippocampus can impair cognitive abilities, emphasizing the need for interventions to prevent neurodegeneration.

Methods: This study assessed Acalypha's effects on hippocampal health in rats. Four groups of seven rats each were used. The control group received distilled water, while the other groups were given Acalypha extracts at doses of 100 mg/kg, 200 mg/kg, or 400 mg/kg orally for 28 days after a 14-day acclimatization. The study measured body weight, spatial memory using the Morris water maze, oxidative stress markers (superoxide dismutase [SOD], glutathione [GSH], catalase [CAT], malondialdehyde [MDA]), and hippocampal histology.

Results: Relative to the control, Acalypha treatment significantly ($p < 0.05$) improved multiple parameters, including mitigating weight loss, enhancing spatial memory performance in the Morris water maze test, and reducing oxidative stress markers such as SOD, GSH, CAT, and MDA in a dose-dependent manner. Additionally, it provided neuroprotection to the hippocampus, as evidenced by a reduction in vacuolation compared to the control group.

Conclusions: Acalypha demonstrated notable neuroprotective effects, improving memory and reducing oxidative stress. This suggests its potential as a therapeutic agent for preserving hippocampal health and enhancing cognitive function, particularly against neurodegenerative conditions.

Key words: Acalypha Wilkesiana, Hippocampus, Medicinal Plants, Neuroprotection, Oxidative Stress, Spatial Memory.

1. INTRODUCTION

The use of medicinal plants in traditional medicine has attracted significant attention for their potential therapeutic benefits for neurological health. One such plant is Acalypha wilkesiana (Acalypha), also known as Red Acalypha. Traditionally, Acalypha has been used in various cultural settings for its anti-inflammatory, antimicrobial, and wound-healing properties[1].

Acalypha contains several bioactive phytochemicals, including flavonoids, tannins, alkaloids, saponins, phenolic compounds, and terpenoids, which contribute to its medicinal properties. These compounds exhibit antioxidant, anti-inflammatory, antimicrobial, and neuroprotective effects through mechanisms such as free radical scavenging, modulation of inflammatory pathways, microbial inhibition, and immune system enhancement. Flavonoids and phenolics reduce oxidative stress, tannins and alkaloids exhibit antimicrobial activity, while saponins and terpenoids modulate inflammation and immune function [2,3].

Recent studies have also suggested that this plant may contain bioactive compounds that can affect the central nervous system (CNS), potentially influencing cognitive functions such as learning and memory[4].

The hippocampus is a key brain structure involved in memory, learning, and spatial navigation[5]. Due to its role in synaptic plasticity, the hippocampus is highly susceptible to damage, making it an important target for studies exploring the effects of natural compounds on cognitive health[6]. Any changes in the structural or functional integrity of the hippocampus can significantly affect overall cognitive function[7]. Emerging research suggests that plant-derived compounds, particularly those with antioxidant and anti-inflammatory properties, may have neuroprotective effects that could help protect against hippocampal damage[8, 9].

There is growing interest in understanding the effects of herbal extracts on the CNS, particularly their impact on neurogenesis and protection against oxidative damage—a major factor in hippocampal degeneration[10]. Oxidative stress plays a crucial role in hippocampal dysfunction and is thought to be a key contributor to neurodegenerative diseases and memory impairment[11]. Extracts from Acalypha have shown significant antioxidant effects in vitro, suggesting their potential as neuroprotective agents against oxidative stress in the hippocampus[12]. While previous studies have explored its antioxidant and anti-inflammatory potential, the investigation of its effects on hippocampal morphology represents a novel aspect of research[2]. Given the limited studies on the potential effects of Acalypha on the CNS, this study aims to evaluate the impact of the crude aqueous extract of Red Acalypha on hippocampal structure and memory function in Sprague-Dawley rats. Using a rodent model provides an effective way to investigate the plant's influence on cognitive processes, allowing us to better understand its effects on hippocampal integrity and associated behaviors[13]. This research seeks to determine whether Acalypha extract can protect or impair hippocampal structure and spatial memory, thereby providing insights into its potential application for managing neurological disorders.

2. MATERIALS AND METHODS

2.1 Collection and Identification of Plant Material

The leaves of Red Acalypha were collected from the Bowen University Botanical Garden, Iwo, Osun State, Nigeria. The plant material was identified and authenticated by the Department of Plant Biology, Bowen University. Following collection, the leaves were thoroughly washed with distilled water to remove impurities and subsequently air-dried in the laboratory under controlled conditions to preserve their phytochemical constituents.

2.2 Preparation of the Aqueous Leave Extract

The air-dried leaves were initially crushed using a mortar and pestle and subsequently ground into a fine powder using a Silver Crest high-power blender. A total of 500 g of the powdered material was dissolved in 2 L of distilled water and allowed to macerate for 24 hours with occasional stirring to facilitate extraction. The mixture was filtered using Whatman No. 1 filter paper, and the filtrate was concentrated using a water bath at 40°C for five days. The resulting crude slurry was then placed in an oven at 40°C for two additional days to ensure complete drying[14].

2.3 Experimental Animals

The animals were housed in the Animal House of the College of Health Sciences, Bowen University, in well-ventilated cages under hygienic conditions. They were maintained under a 12-hour light/dark cycle, with free access to water and commercial feed. Prior to the start of the experiment, the animals were acclimatized for a period of two weeks. Body weights were recorded before the commencement of treatment and weekly thereafter until the completion of the study. All experimental procedures were approved by the Research Ethics Committee of the College of Health Sciences, Bowen University, with the approval number BUI/4C/23.

2.4 Experimental Design

The rats were randomly divided into four groups, each consisting of seven animals. Group A (control) received feed and distilled water only, while Group B (low dose) received 100 mg/kg of Acalypha extract, Group C (medium dose) received 200 mg/kg of Acalypha extract, and Group D (high dose) received 400 mg/kg of Acalypha extract[15]. The treatments were administered orally once daily for four weeks using a ball-end cannula. Body weights of the animals were measured and recorded weekly throughout the experimental period.

At the conclusion of the administration period, a behavioral assessment of spatial memory using the Morris water maze test was performed. Subsequently, a subset of the rats was euthanized by cervical dislocation to maintain the biochemical integrity of their brains. The hippocampi were meticulously dissected from the rats, weighed, and homogenized in chilled 0.1 M phosphate buffer (pH 7.4). The resulting homogenates were centrifuged at 3000 rpm for 15 minutes to collect the supernatant, which was subsequently used for biochemical analysis, including superoxide dismutase (SOD), glutathione (GSH), catalase (CAT), and malondialdehyde (MDA) measurements. The remaining rats were anesthetized with ketamine, and their hippocampi were collected and fixed in 4% paraformaldehyde for subsequent histological analysis using hematoxylin and eosin staining.

2.5 Morris Water Maze Test

The Morris Water Maze (MWM) test was conducted to evaluate the cognitive abilities of rats, following a standard protocol. A circular pool filled with opaque, milk-colored water was used, with a platform positioned within. During the acquisition phase (days 1–3), rats were trained to locate a visible platform. On day 4, the platform was submerged to assess spatial memory by measuring the time taken to find the hidden platform. To minimize stress during the test and ensure reliable cognitive outcomes, several measures were implemented. First, the animals were handled and habituated to the testing environment before the experiment to reduce anxiety. Water temperature was maintained at a comfortable level (around 22–25°C) to prevent thermal stress. The pool area was kept quiet, with minimal external disturbances, to avoid unnecessary agitation[16].

2.6 Evaluation of SOD Activity

The activity of SOD in inhibiting the auto-oxidation of adrenaline was evaluated following the method of Sun and Zigman (1978). This assay relies on the increase in absorbance at 480 nm, which reflects the self-oxidation of adrenaline. The reference cuvette contained 2.95 mL of buffer, 0.03 mL of the epinephrine substrate, and 0.02 mL of distilled water. Enzyme activity was quantified by monitoring the change in absorbance at 480 nm over a five-minute period[17].

2.7 Evaluation of GSH Level

The concentration of GSH was determined using the method described by Sedlak and Lindsay (1968). Ellman's reagent, consisting of 19.8 mg of 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB), was dis-

Table 1: Effect of Acalypha Extract on Body Weight and Spatial Memory. Data are Presented as Mean ± S.E.M. with Statistical Significance Determined at p < 0.05 (*)

Groups	Body Weight Change (%)	Escape Latency (s)
Control	28.1 ± 2.5	48.18 ± 0.71
Low Dose Acalypha	*20.8 ± 3.1	*32.10 ± 1.28
Medium Dose Acalypha	*16.5 ± 2.2	*26.11 ± 0.35
High Dose Acalypha	*14.2 ± 1.0	*21.29 ± 1.23

solved in 1.0 mL of 0.1% sodium nitrate and mixed with 3.0 mL of phosphate buffer (0.2 M, pH 8.0). The absorbance of the resulting solution was measured at 412 nm using spectrophotometry[18].

2.8 Evaluation of CAT Activity

Catalase activity was determined following the method outlined by Aebi (1984). This involved monitoring the decomposition of H_2O_2 by catalase, which was quantified by measuring the reduction in absorbance at 240 nm. The reaction mixture consisted of phosphate buffer (50 mM, pH 7.0) and H_2O_2 as the substrate. The decrease in absorbance, corresponding to the breakdown of H_2O_2, was recorded over a two-minute period using a SpectraMax plate reader, with readings taken at 10-second intervals. The rate of decrease in absorbance is directly proportional to the enzymatic activity of catalase[19].

2.9 Evaluation of MDA Level

The levels of MDA, a marker of lipid peroxidation, were quantified in the hippocampal homogenate supernatant using a modified version of the procedure described by Saraiva et al. (2018). This spectrophotometric method involves reacting MDA with thiobarbituric acid (TBA) to form a pink chromogen, which can be detected at an absorbance of 532 nm. The hippocampal tissue was first homogenized in a cold phosphate buffer, and the homogenate was centrifuged to obtain the supernatant. The MDA levels were then measured to assess the extent of oxidative stress-induced lipid peroxidation in the hippocampal tissue[20].

2.10 Histological Study

The euthanasia of the rodents was conducted via intraperitoneal injection of ketamine at a dosage of 10 mg/kg body weight. Subsequently, a thoracotomy was performed to expose the heart, and intracardiac perfusion was carried out using 0.9% normal saline followed by 4% paraformaldehyde to achieve complete tissue fixation. The hippocampi were then excised and post-fixed in 10% phosphate-buffered formalin until further use. After fixation, the tissues were rinsed three times with 0.25 M sucrose, each for five minutes. The specimens were subsequently processed for sectioning, mounted on slides, and stained with H and E to assess hippocampal morphology. Finally, the stained slides were examined under a light microscope at ×400 magnification to evaluate structural changes in the hippocampus[21].

2.11 Statistical Analysis

Using the GraphPad software version 9.5, the data collected from each group were combined and subjected to one-way ANOVA statistical analysis. Tukey's post hoc test for multiple comparisons was used to compare the group means obtained after each treatment with control measurements. Data results were presented as mean ± standard error of mean, with significance defined as P < 0.05.

Data Availability Statement

The data that support the findings of this study are openly available in Zenodo at https://doi.org/10.5281/zenodo.14210722

3. RESULT

3.1 Aqueous Acalypha Extract Reduced Body Weight and Improved Spatial Memory in Sprague-Dawley Rats

Compared to the control group, all Acalypha-treated groups exhibited a significant decrease ($p < 0.05$) in percentage body weight change. Among the treated groups, weight loss was found to be dose-dependent, with higher doses of Acalypha extract leading to greater weight reduction. Additionally, the control group took the longest time to locate the escape platform. All Acalypha-treated groups demonstrated significantly shorter escape latencies ($p < 0.05$) compared to the control group. The data also revealed a progressive reduction in escape latency across all Acalypha-treated groups over the course of the experiment (Table 1).

3.2 Aqueous Acalypha Extract Improved Hippocampal Antioxidant Status in Sprague-Dawley Rats

Compared to the control group, the Acalypha-treated groups showed a statistically significant increase ($p < 0.05$) in the levels of antioxidant markers, including SOD, GSH, and CAT. Conversely, the level of MDA was significantly reduced ($p < 0.05$) in all Acalypha-treated groups relative to the control (Table 2).

3.2 Aqueous Acalypha Extract Preserves Hippocampal Histoarchitecture in Sprague-Dawley Rats

The histological evaluation using H and E staining revealed a normal histological structure in the control and low-dose Acalypha groups (Fig. 1A and B), with only minor nuclear shrinkage and moderate vacuolation in the pyramidal cell layer. The medium and high-dose Acalypha groups (Fig. 1C and D) exhibited regenerating nuclei and a typical appearance of pyramidal cells, with no detectable signs of neurodegeneration.

4. DISCUSSION

This study aims to investigate the effects of aqueous Acalypha leaf extract on the hippocampus using a Sprague-Dawley rat model. The findings indicate that Acalypha extract exerts significant neuroprotective effects on the hippocampal structure and function, suggesting potential cognitive benefits, especially in relation to learning and memory.

The findings of the present study demonstrate that Acalypha extract significantly reduced body weight in rats, which aligns with the results reported by Ibrahim et al. (2020)[14]. This reduction in body weight may be linked to the inhibition of lipid accumulation, possibly through the regulation of adipocyte differentiation, involving decreased expression of peroxisome proliferator-activated

Table 2: Effect of Acalypha Extract on Hippocampal Oxidant and Antioxidant Parameters. Data are Presented as Mean ± S.E.M. with Statistical Significance Determined at p < 0.05 (*)

Group	SOD (µmol/ml)	GSH (µmol/ml)	CAT (µmol/ml)	MDA (µmol/ml)
Control	184.23 ±3.8	119.18 ±1.6	215.42 ±3.6	428.66 ±3.3
Low Dose Acalypha	*212.87 ±2.4	*131.55 ±0.4	*239.82 ±2.5	*369.88 ±2.7
Medium Dose Acalypha	*219.34 ±1.7	*136.67 ±1.3	*257.96 ±1.2	*348.41 ±1.6
High Dose Acalypha	*227.38 ±3.6	*141.48 ±0.7	*283.52 ±4.7	*326.28 ±3.4

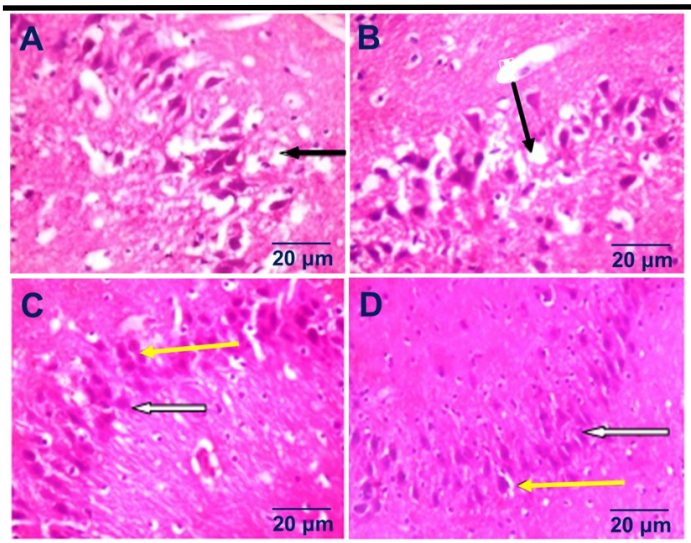

Figure 1: H and E Stain for Histological Assessment. A: Control, B: Low-Dose Acalypha, C: Medium-Dose Acalypha, D: High-Dose Acalypha (Black Arrow: Vacuolation; Yellow Arrow: Regenerating Nuclei; White Arrow: Normal Pyramidal Cells).

receptor-gamma (PPARγ) and CCAAT/enhancer-binding protein alpha (CEBP/α), as suggested by Idowu et al. (2021)[22]. PPARγ and CEBP/α are key transcription factors that regulate adipogenesis, and their downregulation has been associated with reduced fat accumulation and enhanced lipolysis[23].

Additionally, bioactive compounds such as flavonoids and polyphenols in Acalypha may contribute to weight reduction by enhancing mitochondrial function, increasing fatty acid oxidation, and modulating insulin sensitivity[2]. Studies have also indicated that plant extracts rich in saponins and alkaloids can suppress appetite by influencing leptin and ghrelin levels, leading to decreased caloric intake and improved metabolic balance[24].

Memory deficits are characteristic disorders commonly associated with hippocampal degeneration[25]. In this study, rats treated with Acalypha extract demonstrated improved spatial memory in a dose-dependent manner. To our knowledge, this is the first report on the memory-enhancing effects of Acalypha. Acalypha may enhance hippocampal function by modulating NMDA receptor activity, promoting synaptic plasticity, and reducing oxidative stress. NMDA receptors play a crucial role in learning and memory by facilitating long-term potentiation (LTP), a key mechanism for synaptic strengthening[26,27]. The extract's bioactive compounds, such as flavonoids and polyphenols, may enhance NMDAR-mediated signaling, increasing synaptic protein expression while mitigating oxidative damage[27]. Additionally, by balancing excitatory neurotransmission and preventing excitotoxicity, Acalypha could offer neuroprotection and cognitive benefits, making it a potential therapeutic candidate for neurodegenerative diseases like Alzheimer's and Parkinson's[28].

A key indicator of cellular health is the reduction in MDA levels, a secondary byproduct of lipid peroxidation[29], along with increased activity of key antioxidants such as SOD, CAT, and GSH[30]. The observed enhancement in antioxidant capacity in this study may be attributed to the free-radical scavenging ability of Acalypha, which is linked to its phytochemical constituents, including flavonoids and tannins—potent antioxidants known for their protective effects[31, 32].

Histological analysis revealed preserved hippocampal pyramidal neurons in Acalypha-exposed rats, along with noticeable maintenance of normal histoarchitecture. These neuroprotective features may be attributed to the influence of flavonoids on neurochemical signaling pathways within the hippocampus[33, 34]. A recent study by Kingsley et al. (2023) highlights the neuroprotective effects of Acalypha which are attributed to its rich phytochemical composition, including flavonoids, alkaloids, tannins, and polyphenols. These compounds enhance antioxidant defenses by upregulating Nrf2, reducing oxidative stress, and preventing neuronal damage, thereby supporting hippocampal structure and function[35]. The aqueous extract significantly increased the activities of antioxidant enzymes such as SOD, CAT, and GSH, while reducing MDA levels, indicating protection against lipid peroxidation. Moreover, Acalypha improved spatial memory, potentially through mechanisms involving enhanced synaptic plasticity and NMDA receptor activation. These results suggest that the plant holds therapeutic potential for preserving cognitive function and preventing hippocampal degeneration.

4.1 Conclusion

In conclusion, Acalypha extract exhibits significant neuroprotective effects by enhancing antioxidant defenses, reducing oxidative stress, and supporting hippocampal structure and function. Its ability to improve spatial memory and boost antioxidant enzyme activities suggests a promising therapeutic potential for preserving cognitive function and preventing hippocampal degeneration. Future studies should explore its application in neurodegenerative disease models and human trials to validate its efficacy and clinical relevance.

Limitation of the Study

This study has some limitations, including a small sample size and a short duration, which may limit the generalizability and long-term understanding of Acalypha effects. While neuroprotection and reduced oxidative stress were observed, the precise molecular mechanisms remain unclear. Future research should explore chronic exposure effects, broader cognitive assessments, and specific signaling pathways to better understand its therapeutic potential.

Conflict of Interest

The authors declare that they have no financial or personal relationship(s) which may have inappropriately influenced them in writing this paper.

Contributor Roles Taxonomy (CRediT) Statement

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