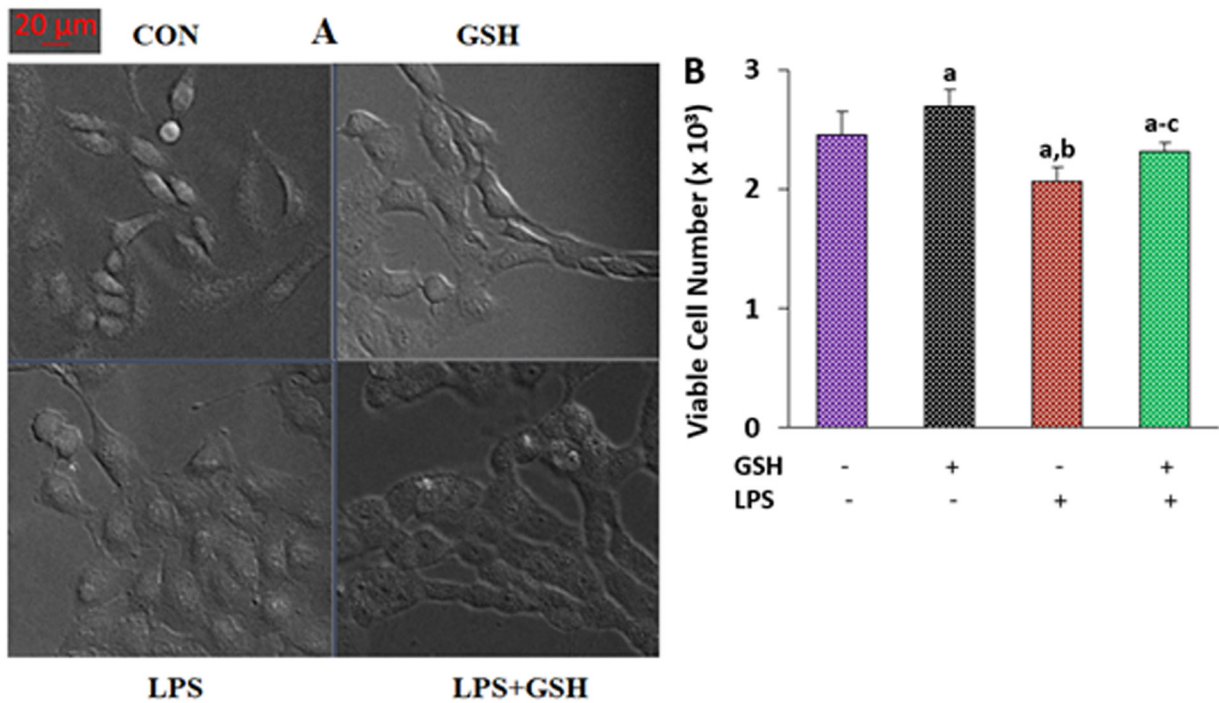


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Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A-Ion Channels (Na⁺- K⁺ Channels, Cl⁻ channels, Ca²⁺ channels, ADP-Ribose and metabolism of NAD⁺, Patch-Clamp applications)

B-Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C-Interaction Between Oxidative Stress and Ion Channels in Neuroscience

(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD⁺ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D-Gene and Oxidative Stress

(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

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Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

Effects of Coenzyme Q10, Ramipril, and Vinpocetine on the Regulation of Oxidative Stress and Cognition in Rats with Chronic Insomnia and REM Sleep Deprivation

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List of Abbreviations;

ACE, angiotensin converting enzyme; **ACh**, acetylcholine; **AChE**, acetylcholinesterase; **AD**, Alzheimer's disease; **CoQ10**, Coenzyme Q10; **CPCSEA**, Committee for the Purpose of Control and Supervision of Experiments on Animals; **Disodium EDTA**, ethylenediaminetetraacetic acid disodium salt; **DTNB**, 5,5'-dithiobis(2-nitrobenzoic acid); **EEG**, electroencephalography; **GSH**, glutathione; **MDA**, malondialdehyde; **MWM**, Morris water maze; **NREM**, nonrapid eye movement; **REM**, rapid eye movement; **REM S-DEP**, random eye movement sleep deprived; **Rpm**, rotations per minute; **S-DEP**, sleep deprived; **TCA**, trichloroacetic acid

Abstract

This study evaluated the impact of various drugs on cognitive function and oxidative stress in a chronic insomnia rat model induced by rapid eye movement (REM) sleep deprivation using modified multiple-platform method. Forty-eight albino rats were divided into eight

groups (n=6 per group): the control group; REM sleep-deprived groups, which were treated with water, corn oil, donepezil, vinpocetine, Coenzyme Q10 + corn oil, ramipril, and Coenzyme Q10 + corn oil + ramipril. Spatial learning and memory were assessed using the Morris water maze. On the 3rd and 4th days of the acquisition trials, the latency of Coenzyme Q10, ramipril and their combination was lower than that of REM sleep-deprived rats. In the probe trial, sleep-deprived rats spent less time in the target quadrant than REM controls. In contrast, vinpocetine, Coenzyme Q10 and the combination of ramipril + Coenzyme Q10 resulted in a greater percentage of time spent in the target quadrant than REM sleep-deprived rats. Biochemical analysis of hippocampal tissue revealed that, compared with REM sleep-deprived rats, those treated with donepezil, vinpocetine, ramipril, Coenzyme Q10, or their combination presented reduced malondialdehyde and acetylcholinesterase levels but increased reduced glutathione levels. In conclusion, these findings suggest that donepezil, vinpocetine, ramipril, Coenzyme Q10, and their combination effectively ameliorate the cognitive

deficits and oxidative stress induced by REM sleep deprivation.

Keywords: Acetylcholinesterase, cognition, oxidative stress, Morris water maze, reduced glutathione, sleep deprivation

Introduction

Sleep is a biologically acceptable form of routine rest. It is a form of inactivity, both physical and mental, that allows us to revitalize ourselves upon waking (Rasch et al., 2013). A normal and reversible state of reduced responsiveness to external stimuli and relative inactivity, accompanied by a loss of consciousness, can be a reasonable definition of sleep. The sleep cycle has been divided into two distinct stages: nonrapid eye movement sleep and rapid eye movement sleep (Le Bon, 2021). When electroencephalography (EEG) is used, both forms of sleep have distinct characteristics. The characterization and differentiation of rapid eye movement (REM) sleep from non-REM sleep and a state of wakefulness can be accomplished through defined behavioral and physiological attributions and involves brisk frequency cortical EEG, high-amplitude hippocampal EEG, altered thalamic center regulation and repressed skeletal muscle activity (Peever et al., 2016). Numerous animal studies have utilized behavioral models, such as the Morris water maze, to demonstrate memory deficits elicited by REM sleep deprivation (Vorhees et al., 2014). The underlying mechanisms of the impact of sleep deprivation on memory are unknown.

Oxidative stress occurs once the burden of prooxidants such as reactive oxygen species (ROS) exceeds the antioxidant systems of the body. According to the literature, this imbalance can be generated by an increase in the concentration of prooxidants, impaired antioxidant defense, or a combination of both conditions. This imbalance can lead to potential damage to lipids, proteins, and DNA, as described in aged conditions such as carcinogenesis and neurodegenerative diseases (Beckman and Ames, 1998; Sies, 2021). Sleep represents a state with increased antioxidant activity, which promotes brain protection against free radicals via a decrease in oxidant production (Davinelli et al., 2024). ROS and other oxidative stress markers can accumulate in brain tissue during wakefulness, and after a threshold is reached, these markers can act as sleep promoters (Yıldızhan and

Nazıroğlu 2019; Mir et al., 2025). Oxidative stress leads to alterations in cellular activity with an accumulation of oxidation products, including lipid peroxidation products. An increase in the level of malondialdehyde (MDA), which is a sensitive and specific marker of *in vivo* lipid peroxidation, has been reported in cerebrospinal fluid and the brain (Hameed et al., 2024).

Reimund's free radical flux theory attempts to propose a reasonable explanation. In theory, during sleep, there is an increase in the activity of endogenous antioxidant mechanisms and a decrease in ROS synthesis in the brain. Thus, sleep acts as an antioxidant facilitator (Reimund 1994). Inflammation-related conditions such as cardiovascular disease (Sateia, 2014), immune dysfunction (Thamaraiselvi et al., 2012; Zhao et al., 2014), and metabolic disorders (Sateia, 2014) are linked to a lack and poor quality of sleep. Since sleep deprivation has well-documented proinflammatory effects, these associations are more likely to be coincidental than causal (Draper and Hadley, 1990; Toth, 1996).

CoQ10 is a well-anticipated cofactor in the electron transport chain of the mitochondrial membrane and has a central role in the synthesis of adenosine triphosphate. Treatment with CoQ10 improves cognitive deficits by interfering with mitochondrial function (Baydas et al., 2003; Beal, 2004). It scavenges the ROS generated in the inner mitochondrial membrane. (Pala et al., 2018). CoQ10 deficiency has been identified in conditions where oxidative stress plays a significant role, such as neurodegenerative disorders, diabetes, and cardiovascular diseases (Dhanasekaran and Ren, 2005).

Ramipril is a potent angiotensin converting enzyme (ACE) inhibitor. It has been shown to increase memory by regulating the levels of angiotensin II in the brain, in turn inhibiting the activity of acetylcholinesterase and regulating the antioxidant system (Anderson et al., 2011; Nade et al., 2015). Vinpocetine is a derivative of vincamine, an alkaloid of a common periwinkle plant (*vinca minor*), which has been shown to exert a neuroprotective effect on the brain through its combined effects on cerebral circulation, brain metabolism and the rheological properties of the blood. Vinpocetine is a neuroprotective and memory-enhancing supplement (Shekarian et al., 2020). Donepezil is an acetylcholinesterase inhibitor that improves cognitive function by increasing acetylcholine levels and thereby enhancing neurotransmission (Guo et al., 2015). It also has

potent anti-inflammatory effects. It is used as a cognition enhancer (Kim et al., 2014). Ramipril and vinpocetine have been shown to improve the cognitive impairment induced by REM sleep deprivation, with studies demonstrating enhanced performance in memory tasks and increased time spent in target quadrants following sleep loss. Donepezil, although also associated with improved cognitive parameters in REM-deprived models, is known to cause insomnia and vividly disturb dreams because increased cholinergic activity affects REM sleep architecture. When used together, these agents may exert additive cognitive benefits, but donepezil's sleep-disrupting effects could counteract some restorative sleep processes influenced by ramipril and vinpocetine. Overall, the combination may enhance cognitive outcomes under REM deprivation but requires caution owing to donepezil's known insomnia-related adverse effects of donepezil (Amberkar et al., 2023; NeuroLaunch 2024).

All these drugs act via different mechanisms to improve cognition. It is known that ramipril modulates the renin-angiotensin system, which influences cerebrovascular health and may impact cognitive outcomes. ACE inhibitors such as ramipril lower Angiotensin II levels and affect Angiotensin I receptor-mediated pathways (Zhou et al., 2024). Vinpocetine acts primarily as a phosphodiesterase-1 inhibitor, increasing cAMP and cGMP, which support vasodilation, cerebral blood flow, synaptic plasticity, and neuroprotection. It has demonstrated antioxidant and anti-inflammatory effects and protects against long-term potentiation in animal models of Alzheimer's disease (Shekarian et al., 2023). It regulates microglial activation and exosome signalling, improving neuronal survival under ischemic conditions (Zang et al., 2021). CoQ10 functions as a mitochondrial electron carrier that is essential for ATP synthesis and acts as a potent lipid-soluble antioxidant to protect neurons from oxidative stress—key mechanisms in cognition (Pradhan et al., 2021). Donepezil is a well-established symptomatic treatment for Alzheimer's disease; it improves cognitive and daily functioning but does not halt disease progression.

The aim of this study was to evaluate the effects of CoQ10, ramipril and vinpocetine on cognition in chronic insomnia induced by REM sleep deprivation in rats and to compare them with those of donepezil.

Materials and Methods

Experimental Animals

Forty-eight 8- to 10-week-old adult albino Wistar rats weighing 150–200 grams were utilized in the present study. The animals were kept in polypropylene cages measuring 41 cm × 28 cm × 14 cm. The atmospheric room temperature ($25^{\circ}\text{C} \pm 3^{\circ}\text{C}$) and humidity (approximately $50 \pm 10\%$) with 12 hours of light and alternating 12-hour dark cycles were maintained. Standard animal feed (VRK Nutritional Solution, Pune, India) and water were provided *ad libitum*. The experiment was conducted after approval was obtained from the Institutional Animal Ethics Committee (Reg. No 94/1999/CPCSEA. IAEC/KMC/130/2019).

Table 1. Experimental Groups According to Dose, Route and Duration

	Groups	Duration
1	control	4 weeks
2	REM S-DEP	4 weeks
3	REM S-DEP + 2 ml corn oil po	4 weeks
4	REM S-DEP + donepezil 10 mg/kg po	4 weeks
5	REM S-DEP + vinpocetine (4 mg/kg) ip	4 weeks
6	REM S-DEP + CoQ10 (10 mg/kg) dissolved in 2 ml po corn oil	4 weeks
7	REM S-DEP + ramipril (10 mg/kg) po	4 weeks
8	REM S-DEP + CoQ10 + 2 ml corn oil po + ramipril (10 mg/kg) po	4 weeks

Experimental Groups

Donepezil (10 mg/kg), vinpocetine (4 mg/kg, ip), CoQ10 and ramipril (10 mg/kg) were dissolved in distilled water and used in this study (Table 1). Control, REM sleep-deprived animals were treated with water, corn oil, donepezil, vinpocetine, coenzyme Q10 + corn oil, ramipril, and coenzyme Q10 + corn oil + ramipril. Donepezil (10 mg/kg), vinpocetine (4 mg/kg), and CoQ10 (10 mg/kg) were dissolved in 2 ml of corn oil, and ramipril (10 mg/kg) was used. The dose of each drug, the administration route, and the duration of treatment were taken from previous studies (Nade et al., 2015; Shang et al., 2016; Shin et al., 2018; Park et al., 2020). Ramipril from Lupin Ltd., vinpocetine (Vivid Biotek Pvt Ltd.), donepezil from Intas Pharmaceuticals Ltd., and CoQ10 (Supplements) were purchased from a local pharmacy.

Sleep Deprivation Procedure

The setup used in this study was the modified version of the multiple platform technique (Nath et al., 1995). The modified multiple-platform model is an improved version that eliminates both isolation and restraint factors.

Setup of the modified multiple platform water tank: The apparatus consists of 16 circular platforms (6.5 cm in diameter, each horizontally and vertically spaced 6 cm apart and 9 cm above the floor) inside a large square tank. The platforms were connected to the bottom of the tank using metal rods. The large tank was filled with 24°C water up to 1 cm below the platform. The wire mesh lid used to cover the top of the cage held food and water, allowing free access to the rats. The animals were laid on the platform and were allowed to move freely. Male Wistar rats were housed on small platforms with water to induce sleep deprivation (van Hulzen and Coenen, 1981; Kumar et al., 2023).

The animals in the control group were placed over a platform with a diameter of 7.5 cm. The water in the cages was changed daily. REM sleep was disturbed for 18 hours per day from 3:00 pm to 9:00 am by allowing the animals to stay on the platform for 21 days. The rats were allowed to sleep normally for the remaining 6 hours. The drugs were administered for 1 month (Kumar et al., 2023).

Assessment of Spatial Learning and Memory

The experimental methodology was performed as described by Morris R (Vorhees et al., 2006). The apparatus has a circular tank (diameter of 150 cm and height of 45 cm) filled with water and maintained at 25°C. (Q1, Q2, Q3, and Q4) Four quadrants were divided in the tank, and a platform (10 cm²) was centered in quadrant Q4 of the pool, which was a target quadrant. A black and white cue card was placed near the maze, enabling the rats to establish a spatial map strategy. Throughout the training session, the platform location and additional maze cues were maintained.

Spatial Acquisition Trial

The training of the rats was performed for 4 consecutive days. A total of 4 trials were performed each day with an interval of 5 minutes, and each trial lasted for 120 seconds. The rats were released facing the wall of the maze from different positions around the perimeter of the tank (northeast Q1, northwest Q2, southeast and southwest Q4) and were required to locate the platform. The rats were

gently guided to the platform on the basis of their inability to locate it and were allowed to remain there for 20 seconds. The time to reach the platform and latency period were recorded.

Spatial Probe Trial

On the fifth day, each rat was subjected to a spatial probe trial in which no platform was positioned. Sixty seconds were given for the rats to locate the hidden platform. The latency to enter the Q4 target quadrant was recorded as the time and distance travelled.

Preparation of Tissue Homogenates

Upon completion of the dosing period and assessment of the learning task, cervical dislocation was performed under deep anaesthesia, and the rats were sacrificed. Immediately after the animal was sacrificed, the whole brain of each rat was isolated and weighed. They were placed in ice-cold phosphate-buffered saline (0.1 M, pH 7.4), and the whole brain was dissected and used for biochemical estimation.

MDA Estimation

MDA levels were quantified using the thiobarbituric acid reactive substances assay. The tissue supernatant (0.5 ml) was mixed with 3 ml of 10% trichloroacetic acid (TCA; 10 mg/100 ml distilled water) and allowed to stand at room temperature for 10 minutes. After centrifugation (2000 rpm, 15 min), the supernatant was reacted with 0.67% thiobarbituric acid (670 mg/100 ml of 0.05 N NaOH). The mixture was heated in a boiling water bath for 10 minutes and cooled, and the resulting pink chromogen was measured spectrophotometrically (Eppendorf AG 22331 Hamburg, Germany) at 532 nm (D'Souza et al., 2012).

Estimation of Reduced Glutathione

Ellman's protocol was used to calculate the level of reduced glutathione. Ellman's reagent (5,5'-dithiobis-(2-nitrobenzoic acid, DTNB) is reduced by the -SH groups in GSH to produce a yellow compound with a peak absorbance at 412 nm that can be measured with a spectrophotometer. Twenty microliters of whole blood/tissue supernatant were mixed with 1.81 ml of distilled water and 3 ml of PPT solution. The preparation was allowed to stand for 5 min and then filtered. Two sets of test tubes were labelled as blanks, and the test and reaction mixtures were prepared. Standard curve

preparation: GSH standards were prepared at concentrations of 0.33 ml, 0.67 ml, 1 ml, 1.33 ml, and 1.67 ml, made up to 2 ml with distilled water, and then treated with phosphate buffer containing 0.3 M Na₂HPO₄ (8 ml) and DTNB (1 ml) (Rahman et al., 2006).

AChE Assay

AChE activity was quantitatively measured via Ellman's method. Ellman's reagent (DTNB) reacts with

thiocholine to form a yellow compound with a 412 nm absorbance. To a cuvette containing 2.6 ml of phosphate buffer (0.1 M, pH 8) and 100 µl of DTNB, a 0.4 ml aliquot of the homogenate was added, the mixture was mixed thoroughly with bubbling air, and the absorbance was measured at 412 nm in a spectrophotometer. The basal readings were recorded when the absorbance reached a stable value. Twenty microliters of acetylthiocholine were added, and the change in absorbance was recorded for 10

Table 2. Bodyweight changes at baseline (g) and after 21 days of REM sleep deprivation. (N=6 and mean ± SEM).

Groups	Baseline Body Weight	Post REM S-DEP Body Weight
Control	213.00 ± 8.85	229.16 ± 10.03
S-DEP	212.66 ± 8.25	191.66 ± 3.57*
S-DEP + corn oil	214.67 ± 10.73	192.33 ± 7.52
S-DEP+ donepezil (10 mg/kg po)	197.50 ± 6.29	189.00 ± 7.17
S-DEP + vinpocetine (4 mg/kg ip)	238.83 ± 9.62	229.16 ± 7.85 ** ^a
S-DEP + CoQ10 (10 mg/kg po)	215.50 ± 9.10	205.06 ± 10.21 ^b
S-DEP + Ramipril (10 mg/kg po)	193.83 ± 9.45	246.50 ± 8.50
S-DEP + Ramipril + CoQ10 (10 mg/kg)	208.50 ± 8.38	207.16 ± 6.07

P values were calculated via one-way ANOVA followed by post hoc Tukey's test. **p* < 0.05 vs control; ***p* < 0.05 vs S-DEP; ^a*p* < 0.05 vs donepezil; ^b*p* < 0.05 vs vinpocetine.

Table 3. Effects of donepezil, vinpocetine, ramipril, and CoQ10 on latency in REM sleep-deprived rats during the acquisition trial.

GROUPS	Acquisition trials – latency (time required to reach hidden platform) in seconds. (Mean ± SD).			
	DAY 1	DAY 2	DAY 3	DAY 4
Control	50.97 ± 13.45	44.66 ± 12.12	22.95 ± 6.55	9.08 ± 0.53
S-DEP	61.66 ± 14.53	41.25 ± 13.99	30.21 ± 8.68	23.65 ± 3.15 *
S-DEP + 2 ml corn oil	49.81 ± 9.76	46.48 ± 10.93	28.01 ± 9.17	21.73 ± 3.11
S-DEP + donepezil (10 mg/kg po)	57.57 ± 11.88	52.91 ± 11.62	16.49 ± 4.96 ^a	11.93 ± 0.64
S-DEP + vinpocetine (4 mg/kg ip)	58.25 ± 11.90	52.35 ± 10.64	17.7 ± 8.30	13.33 ± 1.64
S-DEP + CoQ10 (10 mg/kg po)	52.91 ± 15.13	44.55 ± 15.73	17.4 ± 4.77 ^a	7.35 ± 1.16 ^a
S-DEP+Ramipril (10 mg/kg po)	55.20 ± 6.93	48.91 ± 9.17	14.31 ± 4.54 ^a	9.45 ± 1.12 ^a
S-DEP+Ramipril + CoQ10 (10 mg/kg)	57.5 ± 8.40	50.06 ± 5.96	18.8 ± 5.97	6.90 ± 1.96 ^a

One-way ANOVA followed by post hoc Tukey's test was used. **p* < 0.001 vs control; ^a*p* < 0.001 vs S-DEP.

minutes at intervals of 2 minutes. The change in the absorbance per minute was thus determined. (Ellman et al., 1961).

Histopathological Examination

The whole brain was dissected after the rats were sacrificed. The brain samples were sectioned and stained with cresyl violet for histopathological investigation. Initially, the tissue was blocked or embedded. The tissue was subsequently transferred from the final wax bath to a mould filled with molten paraffin wax. A microtome was used to cut thin 4-micron-thick tissue blocks. The tissue sections were floated in a 50°-52° water bath before being placed on microscopic slides. After passing through alcohol, the slides were immersed in distilled water for 15 min, stained for 25–30 min with 0.1% cresyl violet stain and allowed to cool at room temperature. The stained sections were again immersed in distilled water for 5 min and then subjected to an ascending gradient of alcohol for 2 min. Finally, the sections were dipped in xylene for clearing and mounted with DPX. Histopathological evaluation of the hippocampus was performed.

Statistical Analyses

One-way analysis of variance (ANOVA) followed by post hoc analysis with Tukey's test was used for data analysis. Student's paired t test was used to compare the results before and after treatment. The level of significance for any measure was set at $p < 0.05$ at a confidence level of 95%. The body weight change data are expressed as the means \pm standard errors, and the remaining data are expressed as the means \pm standard deviations (SDs).

Results

Effects on the Body Weights of the Animals

At baseline, there was no statistically significant difference in the weights of the animals between the groups. At the end of 21 days of REM sleep deprivation, there was a significant decrease ($p < 0.05$) in the body weights of sleep-deprived rats compared with those of the control group. Compared with those of the donepezil-treated group, the body weights of the rats treated with vinpocetine were significantly greater ($p < 0.05$). Compared with those in the vinpocetine treatment group, the body weights of the rats treated with coenzyme were significantly lower ($p < 0.05$) (Table 2).

Spatial Memory during Acquisition Trials Post-REM Sleep Deprivation

During the acquisition trials of day 1 and day 2, all the groups were comparable with respect to the time required to reach the hidden platform. On day 3, a significant decrease ($p < 0.001$) in latency was observed in rats treated with vinpocetine and CoQ10 compared with donepezil-treated rats. On day 4, an increase in latency was observed in sleep-deprived rats compared with control rats ($p < 0.001$). A statistically significant decrease ($p < 0.001$) in latency was observed in rats administered CoQ10, ramipril, or their combination compared with REM sleep-deprived rats (Table 3).

Probe Trial

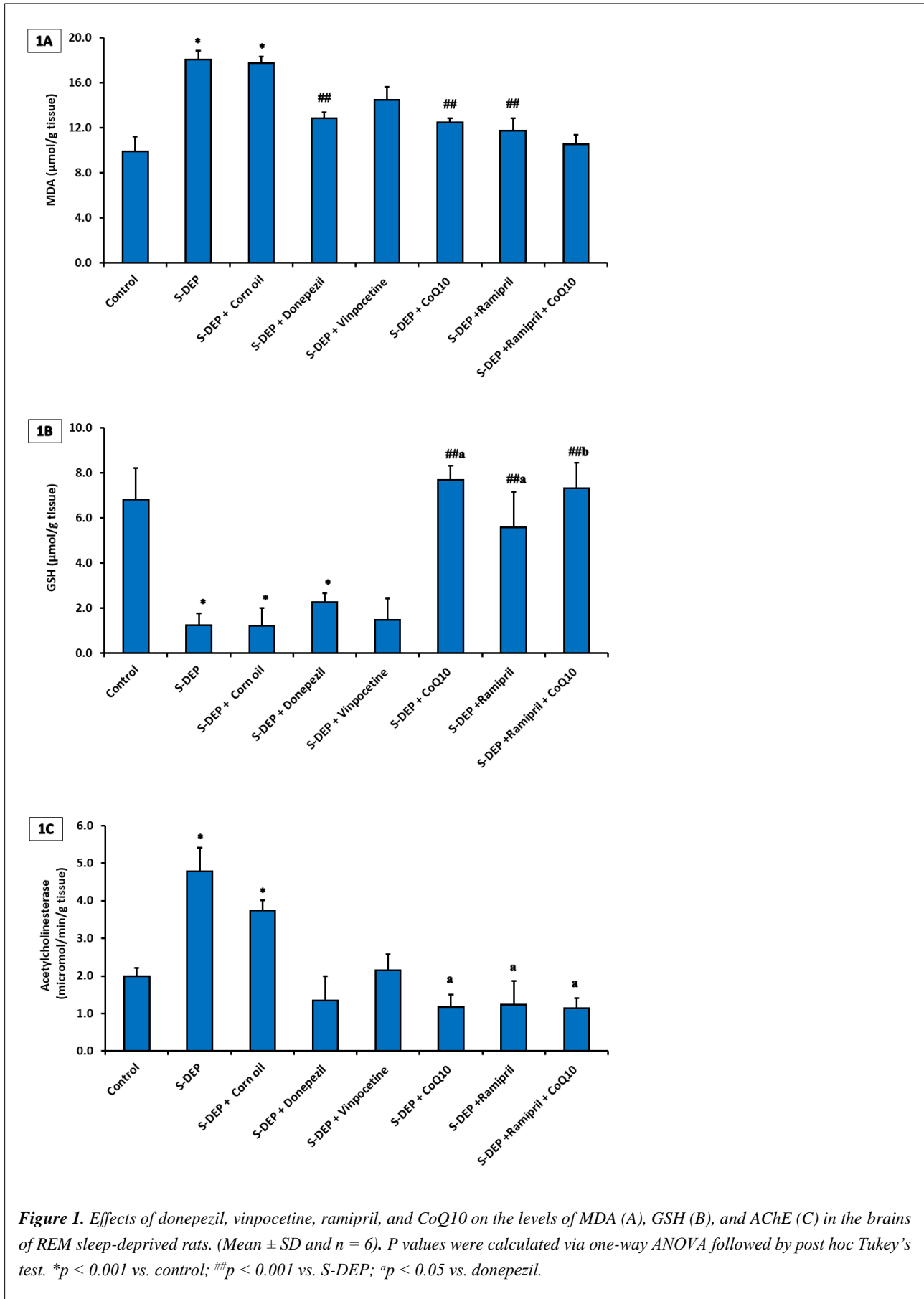
Percentage of Time Spent in the Target Zone

The percentage of time the sleep-deprived rats spent in the target zone during the probe trial was significantly lower ($p < 0.001$) than that of the control group. Compared with that of REM sleep-deprived rats, the percentage of time spent was significantly greater ($p < 0.001$) by the rats treated with vinpocetine, CoQ10, or the combination of ramipril and CoQ10. There was also an increase ($p < 0.05$) in the percentage of time spent when the combination of ramipril and CoQ10 was used compared with the donepezil treatment group ($p < 0.001$) (Table 4).

Table 4. Effects of donepezil, vinpocetine, ramipril, and CoQ10 on REM sleep-deprived rats during Probe Trials. (Mean \pm SD)

Groups	Time spent in target zone (%)
Control	40.90 \pm 9.27
S-DEP	12.36 \pm 3.60 *
S-DEP + 2 ml co	14.28 \pm 2.95
S-DEP + donepezil (10 mg/kg po)	31.76 \pm 7.15
S-DEP + vinpocetine (4 mg/kg ip)	37.73 \pm 6.01 **
S-DEP + CoQ10 (10 mg/kg po)	42.35 \pm 8.15 **
S-DEP + Ramipril (10 mg/kg po)	44.20 \pm 7.89 **
S-DEP + Ramipril + CoQ10 (10 mg/kg)	47.73 \pm 14.35 ** ^a

One-way ANOVA followed by post hoc Tukey's test was used. * $p < 0.001$ vs. control; ** $p < 0.001$ vs. S-DEP; ^a $p < 0.05$ vs donepezil.



Biochemical Analysis

MDA and GSH levels and AChE Activity in Brain Homogenates

A significant increase ($p < 0.001$) in brain MDA (Figure 1A) levels and AChE (Figure 1C) activity was observed in sleep-deprived rats compared with control rats, although GSH levels were decreased (Figure 1B). Compared with REM sleep-deprived rats, rats treated with standard donepezil and ramipril, CoQ10, or their combination presented significantly lower ($p < 0.001$) brain MDA levels and AChE activity, although GSH levels were greater in the treatment groups. A significant decrease ($p < 0.05$) in brain MDA levels and AChE activity was also observed when ramipril and CoQ10 were combined, although GSH levels were greater in the combined groups.

Histopathology

Group 1 (control), Group 2 (sleep deprivation), Group 3 (sleep deprivation + corn oil), Group 4 (donepezil), Group 5 (ramipril), Group 6 (ramipril + coenzyme Q10), Group 7 (coenzyme Q10) and Group 8 (vinpocetine) were used. [Magnification: 40x10 X].

In all three areas, the amygdala (Figure 2), hippocampal CA3 (Figure 3), and dentate gyrus (Figure 4) in the control group presented normal healthy cell bodies (green arrows in the figures). Distinct edges of the plasma membrane were observed, with a clear cytoplasm and nucleus. In group 2, several degenerating flame-shaped, pyknotic cell bodies of neurons were observed (red arrow in Fig.3). Compared with those in groups 2 and 3, there was an increase in the number of healthy neurons and a decrease in the number of flame-shaped degenerating

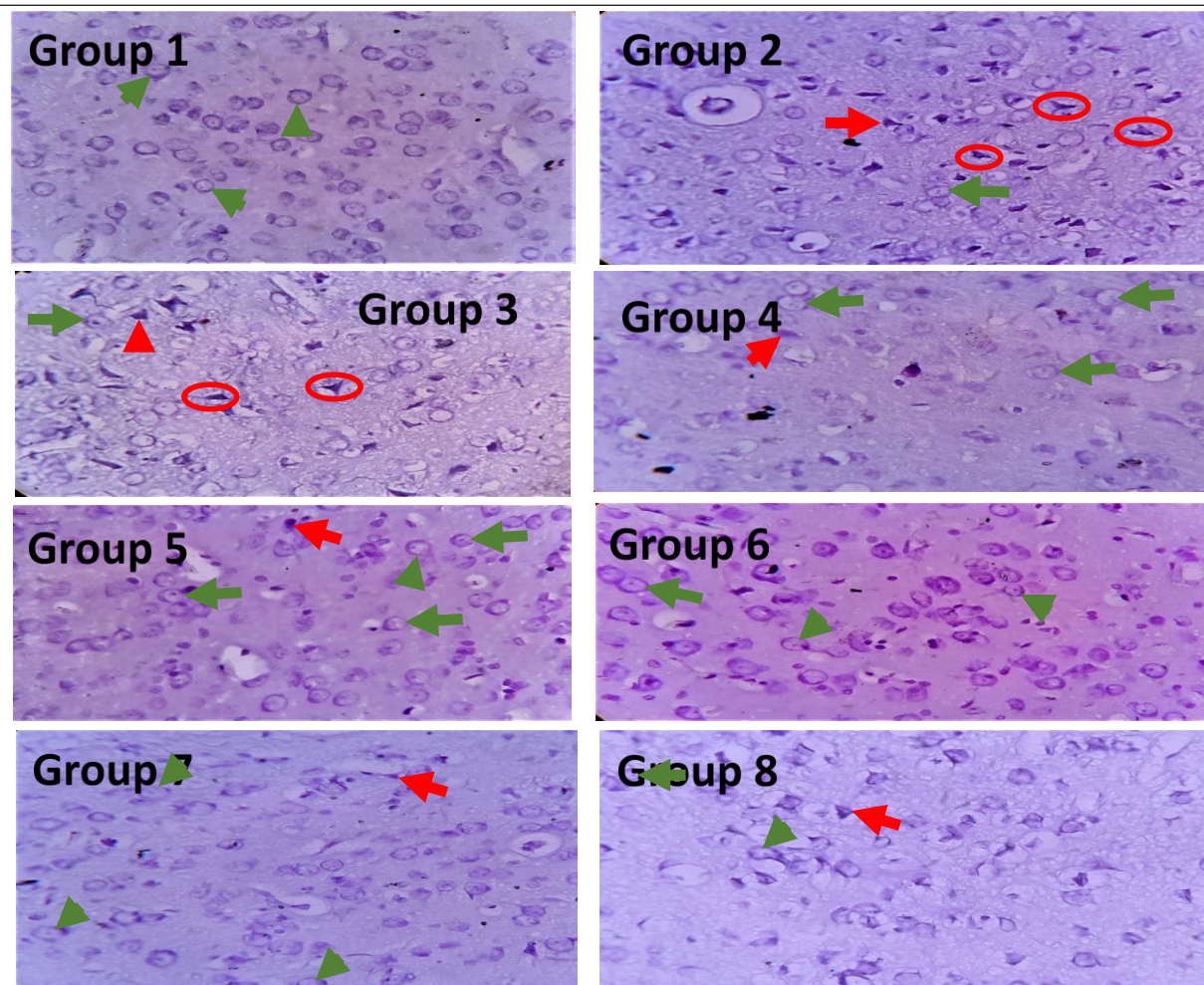


Figure 2. Histopathology of the amygdala (cresyl violet stain). Amygdaloid neurons

neuronal cell bodies in groups 4, 5, 7 and 8. Compared with those in groups 2 and 3, there was a substantial increase in the number of healthy neurons and very few or negligible numbers of flame-shaped degenerating neurons in group 6.

memory. Numerous studies have concluded that REM sleep is closely linked to cognition and that REM sleep deprivation has a significant effect on cognition. Reports from previous studies concluded that REM S-DEP using

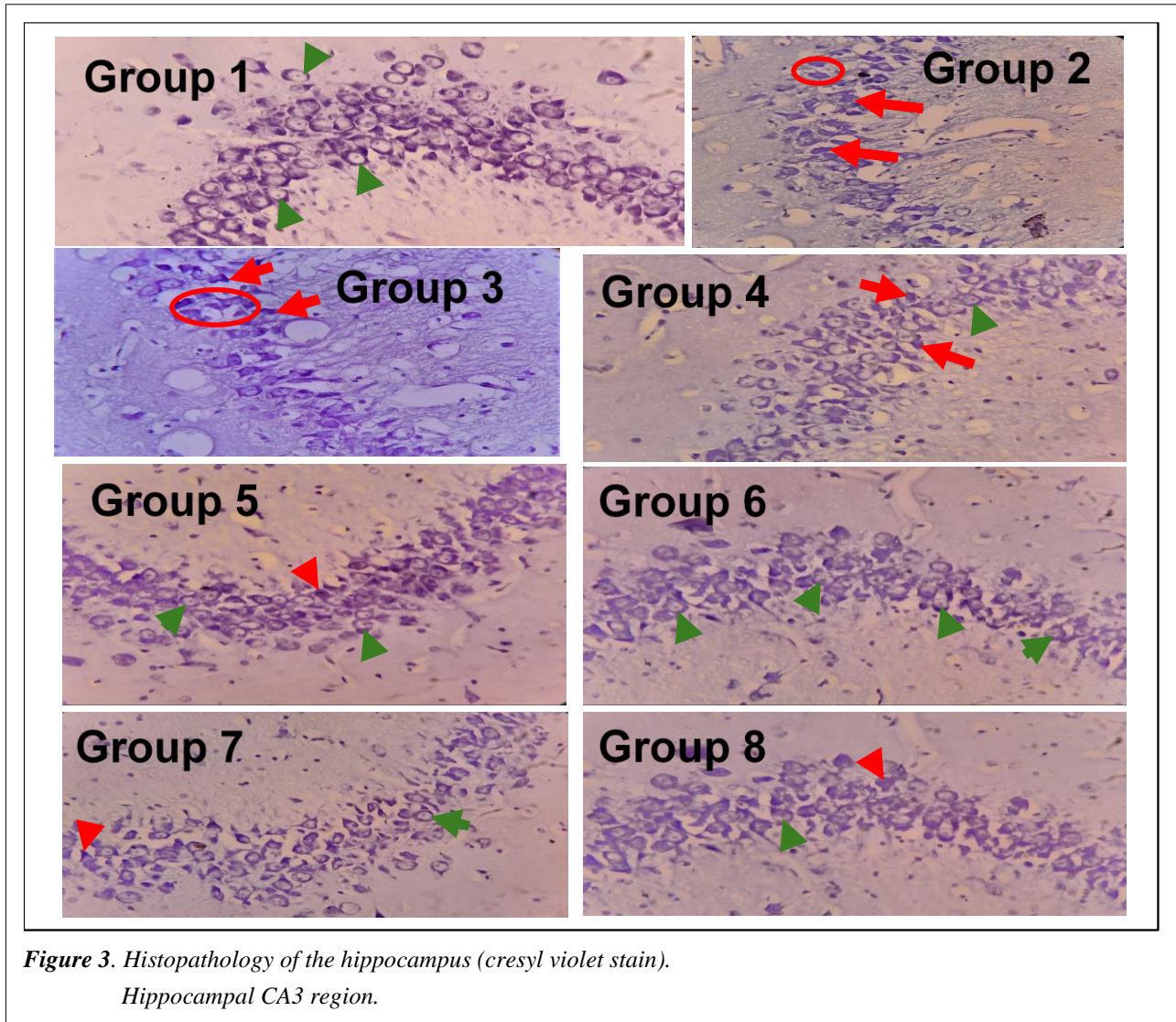


Figure 3. Histopathology of the hippocampus (cresyl violet stain). Hippocampal CA3 region.

Discussion

The current study assessed the effects of CoQ10, ramipril, vinpocetine and their combination in reducing the memory impairment caused by chronic REM sleep deprivation (18 hours/day) for 21 days of chronic dosing. The Morris water maze test was used to assess spatial learning and memory. Our model produced a marked decrease of 90% to 95% REM sleep. This finding was confirmed by Machado et al. (2004), who used electroencephalographic recording to monitor sleep deprivation. Our data showed that chronic REM S-DEP (21 days) was comparable in impairing spatial learning and

the flowerpot method for a period of 72 hours impaired their acquisition rate and further impaired their ability to trace the platform in retention trials via the MWM (Youngblood et al., 1997). Impairment in learning and memory using the modified MWM was also demonstrated by Ruskin et al., who reported a significant effect on spatial reference memory. The spatial working memory was intact (Ruskin et al., 2004).

The current study employs the modified multiple-platform model owing to several improvements over the other models of sleep deprivation. Sleep deprivation can be induced in animals without the need for electrophysiological monitoring of sleep characteristics (Alkadhi et al., 2013). However, confounding factors, such as stress and anxiety, may also impact these findings. Importantly, both sleep deprivation models had varying degrees of impact on both the REM and NREM sleep phases. In a study performed by Everson et al. (1989), rats subjected to total sleep deprivation via the disk apparatus presented a debilitated appearance, lesions on their tails and paws, and weight loss despite increased food intake. Weight changes in total sleep-deprived rats were attributed to increased energy expenditure because of chronic sleep deprivation. Very few studies, including that of Bhanot et

al. (1989), have shown that REM sleep deprivation increases the intake of carbohydrate-rich food and body weight gain in rats, but most studies have shown that the sleep deprivation method results in weight loss, including in the human population. The results of this study were in accordance with those of previous studies, as a significant decrease in the body weight of the rats after 21 days of chronic sleep deprivation was observed. (Chen et al., 2023)

Sleep appears to reduce metabolic demands. According to the current study, REM sleep loss causes an increase in MDA and a decrease in total GSH, which may indicate the production of free radicals. Nath et al. (1995) reported that depriving rats of REM sleep decreases membrane fluidity in the rat brain. An increase in hippocampal oxidative stress is reflected by decreased levels of glutathione and increased MDA levels. The

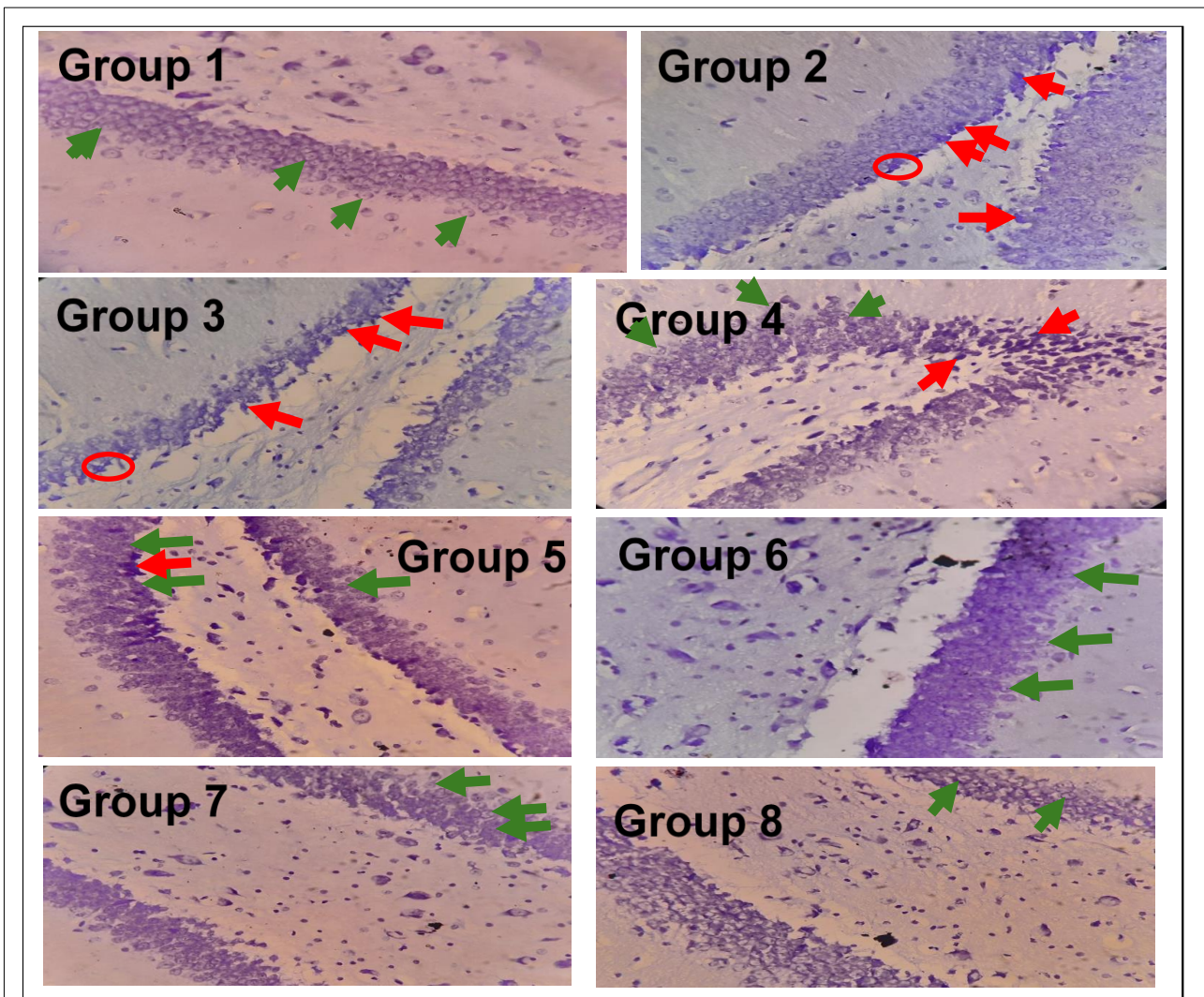


Figure 4. Histopathology of the dentate gyrus (cresyl violet stain).
Dentate gyrus

findings of the present study indicated that the impairment of learning function may be related to the oxidative damage observed in the hippocampus. These findings support previous reports that sleep deprivation induces hippocampal oxidative stress, which reflects neuronal excitability, molecular signalling, and cognitive functions (Silva et al., 2004; Karimfar et al., 2014; Bukareva et al., 2025).

In this study, treatment with ramipril, vinpocetine, and CoQ10 in combination with REM S-DEP for 21 days resulted in a reduction in the MDA level and an increase in the GSH level in the brain tissue of the rats compared with those in the sleep-deprived group. These results are in accordance with those of previous studies in which potential ACE inhibitors, such as ramipril, were shown to reduce oxidative stress. The peripheral administration of ACE inhibitors can infiltrate the blood–brain barrier in a dose–dependent manner and can mediate the effects of angiotensin II. The antioxidant effects of ramipril, an ACE inhibitor, can be attributed to its ability to block reactive oxygen species involved in angiotensin II signalling pathways (Nade et al., 2015). In AD, impairments in learning and memory are partly caused by changes associated with the cholinergic system. Cholinergic transmission involves the choline acetyl transferase enzyme, which is involved in ACh synthesis and is terminated mainly by acetylcholine hydrolysis via the acetylcholinesterase enzyme. It is believed that AChE activity could affect the underlying processes in Alzheimer's disease. Thus, in this study, the effects of ramipril, CoQ10, and their combination on AChE activity were evaluated, and the findings were correlated with their ability to improve cognition, which significantly inhibited AChE activity within the hippocampus of the rats. Compared with the test groups, the experimental groups presented a similar level of inhibition (Saavedra, 2012).

Early experiments with vinpocetine indicated its neuroprotective action against oxidative stress-mediated cell injury. Several studies have reported the effectiveness of vinpocetine on cognitive function. Gupta et al. (2015) reported that treatment with vinpocetine can reduce chronic cerebral hypoperfusion. Reactive oxygen species are known to cause ischemic injury and neurodegenerative disorders, and the results suggest that vinpocetine improves spatial memory by acting through an antioxidant mechanism, modulating cholinergic functions, and preventing neuronal cell damage. In this study, the effect

of vinpocetine, a potent antioxidant, was evaluated. The neuroprotective action of vinpocetine has been correlated with previous studies and has been shown to be partially correlated with improved memory impairment in rats.

For the prospective treatment and prevention of disorders such as AD, the comparable use of antioxidants has attracted considerable attention. The therapeutic benefits of CoQ10 have been observed in oxidative stress-mediated neurodegenerative disorders (Dumont et al., 2011). This study is comparable in determining the role of CoQ10 as an antioxidant. The ameliorative effect of CoQ10 may be due to its antioxidant properties, which subject affected brain cells to less oxidative stress, resulting in a reduced amount of brain damage and enhanced neuronal function and contributing to improved memory. In this study, CoQ10 was administered to the rats as a single dose and in combination with ramipril. The ameliorative effects of CoQ10 in treated and REM sleep-deprived rats were significant.

In conclusion, the results of the present study demonstrated that vinpocetine, ramipril, and CoQ10 in combination were able to reverse REM sleep deprivation-induced cognitive impairment, which was evident in the results of the behavioral, biochemical analyses and histopathological analyses. These findings were consistent with their antioxidant properties. These findings suggest that vinpocetine, ramipril, coenzyme Q10, and their combination effectively ameliorate the cognitive deficits and oxidative stress induced by REM sleep deprivation.

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Author Contributions

AMV and MKK designed the study. TS collected and organized the data. AMV and TS analysed and interpreted the data. TS and DT conducted the biochemical analysis with the help of RM. MRKG performed the histopathological analysis. TS wrote the initial draft of the article. AMV and MKK critically reviewed and approved the manuscript. All the authors critically reviewed and

approved the final draft and were responsible for the content and similarity index of the manuscript.

Conflict of Interest

Dr. Amberkar Mohanbabu Vittalrao and Dr. Meena Kumari K have applied for Design Patent through MAHE for the REM sleep deprivation model.

Availability of Data and Materials

The data of this study are available from the corresponding author upon request.

Compliance with Ethical Standards

The authors are committed to compliance with ethical standards.

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