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Role of Curcumin in Protection of Chemobrain via Suppression of Oxidative Stress and Inflammatory Mediators in Swiss Mice

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ABSTRACT

Background: Cyclophosphamide (CP) is a cancer chemotherapeutic agent which shows a cognitive impairment i.e. termed as chemobrain or chemofog. Cyclophosphamide induced cognitive impairement (CICI) is mainly due to generation of reactive oxygen species (ROS) at the cellular level. Curcumin is a natural compound present in the Indian diet as turmeric. Traditionally it is used as analgesic and anti-inflammatory agent. Various pharmacological activities are proven such as antioxidant, anti-cancer and antiapoptotic properties.

Objective: In the present study, the neuroprotective effect of curcumin against cyclophosphamide induced cognitive impairment was evaluated on neurobehavioral, neuropathological and biochemical alteration in the adult Swiss mice. Additionally the inflammatory mediators as well as neurotransmitter level were estimated.

Methods: Animals were equally divided into five groups of 5 rats in each. Cyclophosphamide were injected intraperitoneally to the animals at dose of 50 mg/kg/week i.p. for 7 days and curcumin at a dose of 200 and 400 mg/kg for 21 days. After 21 days, cognitive dysfunction and motor coordination was assessed behaviorally based on pharmacological models such as passive avoidance test and Rota rod test. After behavioral assessment all the animals were sacrificed for anti-oxidant assay and histopathological studies. Inflammatory mediator Il-6 and neurotransmitter dopamine level were also evaluated in brain homogenate.

Results: Data showed that CP significantly elevated brain AChE activity in the brain. A decrease in the total antioxidant capacity and a reduction in the CAT, SOD, and GSH activity occurred in the brains of the rats exposed to CP. CP treated rats showed a significant impairment in long-term- memory and motor coordination. These results were supported by histopathological observations of the brain. Results revealed that the administration of curcumin ameliorated behavioral and histopathological changes induced by CP. Inflammatory mediators were also reduced along with the restoration of dopamine level in the animals treated with curcumin.

Conclusion: This study suggests that co-administration of curcumin with cyclophosphamide may be a useful adjunct therapeutic approach to overcome cyclophosphamide induced cognitive impairment.

INTRODUCTION

Cyclophosphamide (CP) is an alkylating agent indicated for cancer chemotherapy as well as immunosuppressive agent. Apart from its therapeutic success its assocated with various adverse event which includes nephrotoxicity, hepatotoxicity, urotoxicity, cardiotoxicity, immunotoxicity, mutagenicity, genotoxicity, carcinogenicity, teratogenicity and neuronal toxicity [1].

Cognitive impairments are a common adverse event for cancer patients treated with cyclophosphamide as chemotherapeutic agents. Approximately 50% of cancer survivors are suffering with a common issue i.e. chemobrain or chemofog which is characterized as reduced attention, learning, memory and information processing speed and mental slowness [2].

Acrolein is a metabolite of cyclophosphamide causes lipid peroxidation and generates reactive oxygen species (ROS). The over production of ROS interacts with normal cells of brain and cause cellular dysfunction [3].

Antioxidant compounds are well established to protect the tissues from the toxicity induced oxidative impairment. Curcumin (3-methyl-1-phenyl-2-pyrazolin-5-one), is a hydrophobic polyphenol obtained from rhizome of the plant curcuma longa (Turmeric). As the curcumin is able to cross the blood-brain barrier (BBB) therefore it is a promising agent for prophylaxis of neurodegenerative diseases. Curcumin is also having protective action against aluminium (Al), arsenic (As), lead (Pb) and Cadmium (Cd) induced neurotoxicity [4].

On the basis of antioxidant and anti-inflammatory property of curcumin, this study was aimed to investigate the possible protective effect of curcumin on cyclophosphamide induced cognitive impairments in mice.

Experimental Animals

Swiss albino mice, each weighing between 20 to 25 grams, of both genders, were obtained from the animal house of BBDNIIT Lucknow after receiving approval from the Institutional Animal Ethical Committee (IAEC approval number BBD/IAEC/81/02/2020). During the study, the animals were kept in an air-conditioned environment with a temperature maintained at 25 ± 2°C, a relative humidity of 55 ± 10%, and a 12-hour light/dark cycle. Additionally, the animals had free access to fresh water and food both before the start of the experiments and throughout the duration of the study. The animals were also given one week to acclimate prior to the start of the experiments.

Grouping and Treatments of Animal for Pharmacological Study

Design of experiments: The animals were randomly divided into five groups comprise of five animals in each. Curcumin and donepezil were suspended in 1% Corboxy methyl cellulose solution (CMC) and administered by oral gavage for the period of 21 days.

Group 1 (Normal control): Vehicle (1% CMC suspension) 10ml/kg p.o once a day for 21 days.

Group 2 (Disease control): Cyclophosphamide (50 mg/kg/week i.p.) once daily for three weeks

Group 3 (Standard): Cyclophosphamide (50 mg/kg/week i.p.) for three weeks +

Donepezil (3mg/kg OD, for 3 weeks p.o)

Group 4 (Test1): Cyclophosphamide (50 mg/kg/week i.p. for 3 weeks) + Curcumin suspension (100mg/kg body wt. OD, for three weeks)

Group 5 (Test 2): Cyclophosphamide (50 mg/kg/week i.p. for 3 weeks) + Curcumin suspension (200mg/kg body wt. OD, for 3 weeks.

Behavioral Tests

Passive Avoidance Test

A light and dark apparatus was used in this study to assess the long term memory in mice. Instrument was having two compartment one is light and second is dark compartments (22×21×22cm) which is connected by small entryway. Light compartment was illuminated with a 40W lamp from the height of 30cm from the floor. Dark compartment was having electrical grid on the floor (0.5mA, 75V, 50Hz) which can be triggered when the animals enter into the dark compartment. A training session was there to all groups of animals to habituate with the instrument. During training session each mouse was kept in light compartment and provide 1 min for habituation. The entry gate between the two compartments was opened and shut periodically as an when animals entered the dark compartment and electrical current was provided for 0.2 sec. At the execution day, every animal was again placed in the light compartment, 24h after the training session. The entry into the dark compartment was recorded in the two sessions. [5].

Rotarod Test

Motor coordination test was conducted by using Rotarod apparatus. The apparatus consists of separate sections where animals were kept individually there is an automatic cutoff plate where the rodent can fall without damage. All animals were trained on the rotarod device prior to final execution study. Three separate preliminaries were incorporated into the animal trail on day 1, with some- where around one hour of rest between preliminaries, under a quickening convention beginning at 20 rpm and achieving 40 rpm in 5 min and the dormancy to fall was recorded [6].

Euthanasia and Sample Collection:

At end of the 21 days of last dosing, animals were subjected to behavioral testing in passive avoidance test and rota rod test respectively. After completion of behavior test animals were anaesthetized. Prior to cervical dislocation of animals were administered with intraperitoneal injections of ketamine (90 mg/kg B.W.) and xylazine (5 mg/kg B.W.). Brain samples were quickly extracted, rinsed in ice-cold saline, homogenized, and used to determine biochemical parameters. The brain homogenates were centrifuged at 14000 rpm for 20 minutes at 4°C (REMI C-24), and the supernatants were collected to measure MDA, GSH contents, antioxidant enzyme activities (CAT and SOD), and AChE activity using the UV/VIS spectrophotometer (Shimadzu). Brian tissue samples were also dissected for cytokine estimation and histopathology [7] [8].

Estimation of MDA

Malondialdehyde (MDA) in brain tissues was quantified. After adding 300 µl of 30% trichloroacetic acid (TCA), 150 µl of 5N HCl, and 300 µl of 2% w/v 2-thiobarbituric acid (TBA) to 500 µl of tissue homogenate in phosphate buffer (pH 7.4), the mixture was heated for 15 minutes at 90 ◦C. The mixture was centrifuged for 10 minutes at 12,000g. A pink-colored supernatant was obtained, and its wavelength, 532 nm, was determined spectrophotometrically. Using 1, 1, 3, 3-tetraethoxypropane as a standard, the MDA concentration was calculated and reported as nmol/mg protein **[9]**.

GSH Concentration Determination

After mixing the 500 µl brain homogenate with an equal volume of 10% trichloroacetic acid (TCA), the mixture was centrifuged (using a Remi cold centrifuge) at 2000×g for 10 minutes at 4°C.The supernatant was utilized to estimate GSH. Add 0.4 ml of double-distilled water, 0.5 ml of DTNB (0.2 percent in 0.1 M sodium phosphate buffer, pH 8.4), and 2 ml of phosphate buffer (pH 8.4) to 0.1 ml of processed tissue sample and the mixture was shake vigorously on vortex. Within fifteen minutes, the absorbance was read at 412 nm. Glutathione was used as a standard to assess GSH concentration, which was expressed as µg/mg protein **[10].**

Estimation of Catalase

For the assessment of catalase level in tissues, 500µl of tissue homogenate was subjected to 1950µl of 50mM phosphate buffer of pH neutral and 1000µl of H_2O_2 30mM.At 240 nm, the absorbance was measured three times at intervals of 15 seconds. The absorbance at 0 to 30 seconds was subtracted to determine the real absorbance. Utilizing the millimolar extinction coefficient of H_2O_2 i.e., 0.071 mmol cm-1, the result was calculated. The activity was measured in terms of µmol of H_2O_2 broken down per min per mg of protein **[11]**.

Measurement of AChE Activity

500 µl of the brain homogenate will be mixed with 1% Triton X-100 (1% w/v in 0.03M sodium phosphate buffer, pH-7) and centrifuged for 60 minutes at 100,000xg at 4°C in an ultracentrifuge. The supernatant will be collected and stored at 4°C to estimate acetylcholinesterase using Ellman's method. The UV visible spectrophotometer will measure the kinetic profile of the enzyme activity at 412 nm at 15-second intervals. One unit of acetylcholinesterase activity will be defined as the number of micromoles of acetylthiocholine iodide hydrolyzed per minute per milligram of protein. The specific activity of acetylcholinesterase is expressed in µmoles/min/mg protein **[12]**.

Measurement of Pro-Inflammatory or Anti-Inflammatory Cytokines

Procedure for IL6 Measurement:

The sample was incubated at 37°C for 2 hours. After incubation, the liquid was removed without rinsing, and 100 µL of Biotin-antibody (1x) was added to each well. The plate was sealed and incubated for 1 hour at 37°C. If the Biotin-antibody appeared hazy, it was allowed to reach room temperature and gently mixed. The contents were aspirated, and the wells were washed three times using 200 µL of Wash Buffer, letting it stand for 2 minutes each time. Excess Wash Buffer was removed, and the plate was pressed onto absorbent towels. Then, 100 µL of HRP-avidin (1x) was added, sealed, and incubated at 37°C for 1 hour. After five additional washes, 90 µL of TMB Substrate was added and incubated in the dark for 15-30 minutes at 37°C. Stop Solution (50 µL) was added, and the plate was gently tapped to ensure proper mixing. Optical density was measured at 450 nm, with wavelength corrections at 540/570 nm to adjust for any optical imperfections **[13].**

Procedure for TNF-α Measurement:

Tests were performed, followed by instructions in the manual to prepare all reagents, samples, and standards. Then dispensed 100 microliters of standard or sample into each well. Allowed to incubate for 2.5 hours at room temperature or overnight at 4°C. Dispensed 100 microliters of the biotin antibody solution into each well. Allowed to incubate for 1 hour at room temperature. Dispensed 100 microliters of the prepared Streptavidin solution into each well. Allowed to incubate for 45 minutes at room temperature. Dispensed 100 microliters of TMB One-Step Substrate Reagent into each well. Allowed to incubate for 30 minutes at room temperature. Dispensed 50 microliters of Stop

Solution into each well. Measured the absorbance at a wavelength of 450 nm without delay **[14]**.

Procedure for DOPAMINE Measurement

To 0.2 mL of the aqueous phase, 0.05 mL of 0.4M HCl and 0.1 mL of an EDTA/Sodium acetate buffer (pH 6.9) were added. Subsequently, 0.1 mL of an iodine solution (0.1 M in ethanol) was introduced for oxidation. The reaction was halted after 2 minutes by adding 0.1 mL of Na2SO3 solution. After 1.5 minutes, 0.1 mL of acetic acid was incorporated. The mixture was then heated to 100°C for 6 minutes. Once the sample returned to room temperature, the excitation and emission spectra were recorded using a spectrofluorometer, with readings taken between 330nm **[15] [16]**.

Histopathological Examination

A hematoxylin and eosin stain were used for histopathological studies. Fixed tissues sample with 10% formaldehyde were dehydrated and finally embedded in paraffin wax. After that, paraffin sections of the brain were sectioned at 5µm thickness using a microtome, stained with hematoxylin and eosin stain and examined under light microscope at amplification of 100X.

Statistical Analysis

For the analysis of study data Graph Pad Prism version 5 was used. All the observed data were expressed as Mean±SEM. The data were analysed by an analysis of variance, one-way ANOVA followed by Tukey Post Test

1. RESULTS

Behavioral Tests

Passive Avoidance Test

As shown in Fig. (**1**), initial latency to enter in the dark compartment was reduced in disease control group as compared with Normal control animals. While the administration of Curcumin 200mg/kg significantly reverts this alteration in behavior.

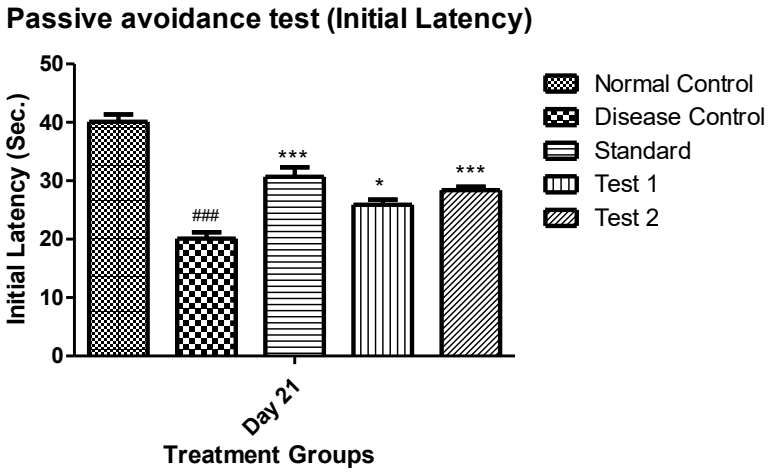

Fig.1: Effects of Test1 and Test 2 on initial latency in CYP induced memory impairment in mice on Day 21

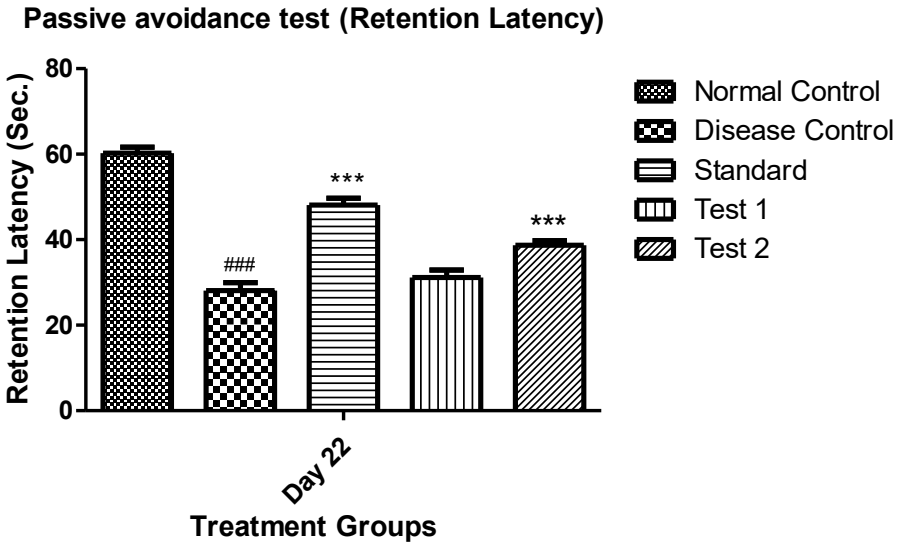

Fig.2: Effects of Test1 and Test 2 on retention latency in CYP induced memory impairment in mice on Day 22

Motor Coordination Test

As shown in Fig. **2** administration of cyclophosphamide significantly reduced the falling in activity when compared with the control group of animals ($^{###}p<0.001$). Groups treated with curcumin at both the doses 100 and 200mg/kg expanded the dormancy to fall. Curcumin at 200mg dose showed maximum effect on motor coordination (**p<0.01)

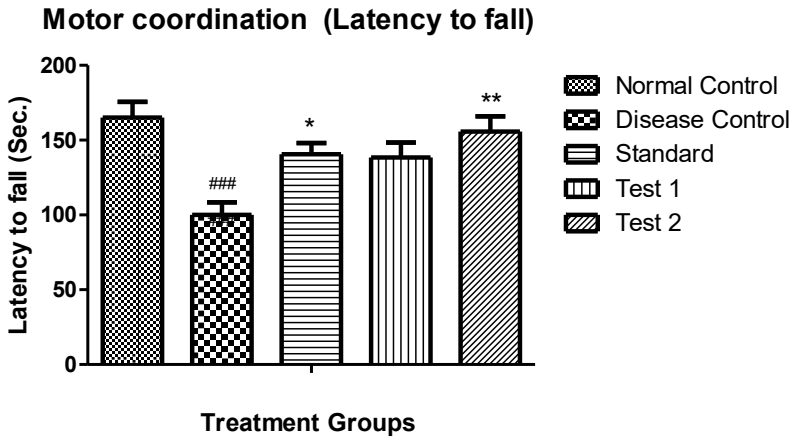

Fig. 3 Effects of Test1 and Test 2 CYP induced motor coordination impairment in mice.

Biochemical Measurements

Table 2. Effect of Curcumin on Cyclophosphamide-induced Oxidative Imbalance in the Brain

Groups	Catalase (U/min/mg protein	MDA (nmol/mg protein)	GSH (nmol/mg protein)	SOD (U/mg protein)
Normal Control	3.74 ± 0.10	2.54 ± 0.65	8.36 ± 0.59	1.62 ± 0.04
Diseased Control	0.99 ± 0.17	6.17 ± 0.54	3.26 ± 0.65	0.89 ± 0.02
Standard	2.01 ± 0.25 **	3.03 ± 0.35 **	7.32 ± 0.68 **	1.11 ± 0.03 **
Test-1	1.18 ± 0.19	5.92 ± 0.54	5.66 ± 0.86	0.75 ± 0.04 *
Test-2	1.79 ± 0.15 *	4.11 ± 0.23 *	7.04 ± 0.94 *	1.09 ± 0.03 **

Result expressed as Mean ± SEM (N = 5). *p<0.05, **p<0.01, ***p<0.001 when compared with the disease control group.

AChE Activity

Effects of Cyclophosphamide on AChE Activity in the brain Homogenates

In the control group, AChE activity was 0.69 µmol AcSCh/h/mg proteins however in the animals treated with cyclophosphamide indicated increased AChE significantly as compared with vehicle-treated control group. Continuous curcumin treatment restored the AChE activity.

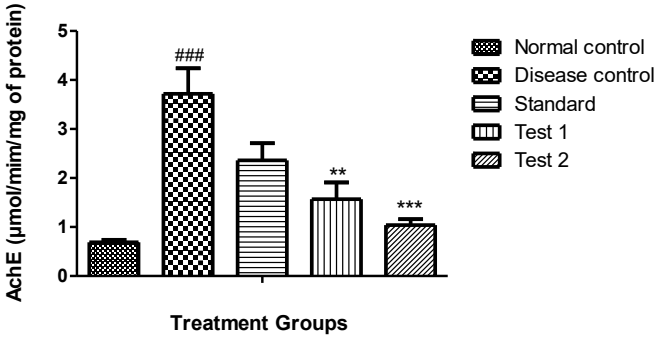

Fig. 4 Impact of curcumin treatment (100 & 200mg/kg, p.o.) on Acetylcholinesterase activity.

N=5, The results are expressed as mean ± SEM. ###(p<0.001) compared to the Normal control group, and **p<0.01, ***(p<0.001) compared to the Disease control group.

TNF-α Measurement

The CP treated Disease control group exhibited a significant increase in **TNF-α** levels (###p<0.001) compared to the normal control group. This enhancment was significantly prevented by Cyclophosphamide (100 & 200mg/kg) (***p<0.001) and by the donepezil group (**p<0.01) compared to the CP treated group.

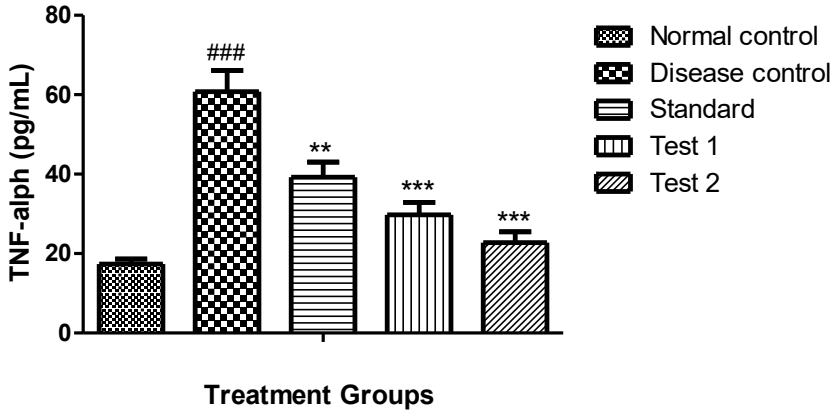

Fig.5: Impact of curcumin treatment (100 & 200mg/kg, p.o.) on TNF-α. N=5, The results are expressed as mean ± SEM. ###(p<0.001) compared to the Normal control group, and **p<0.01, ***(p<0.001) compared to the Disease control group.

Dopamine Level:

Animals treated with cyclophosphamide exhibited a significant decrease in the concentration of dopamine in brain homogenate levels (###p<0.001) compared to the control group. There was an increment dopamine levels of animals treated with curcumin 100mg/kg (**p<0.01) and 200mg/kg (***p<0.001).

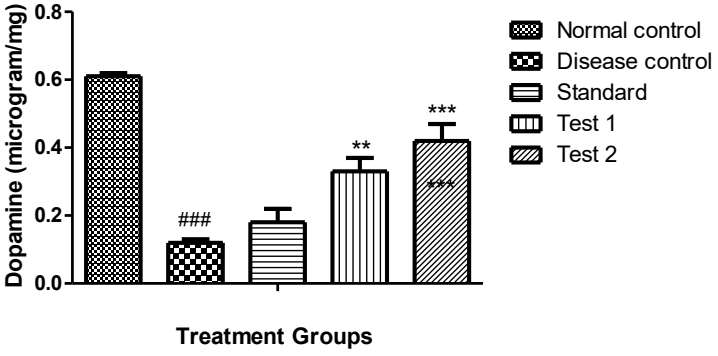

Fig. 6 Impact of curcumin treatment (100 & 200mg/kg, p.o.) on dopamice level. N=5, The results are expressed as mean ± SEM. ###(p<0.001) compared to the Normal control group, and **p<0.01, ***p<0.001 compared to the Disease control group.

IL-6 Measurement

Animals treated with cyclophosphamide exhibited a significant increase in IL-6 levels (###p<0.001) compared to the control group. This increase in IL-6 levels was reduced in the brains of rat treated with curcumin 200mg/kg (***p<0.001) and those treated with Donepezil 5 mg/kg (***p<0.001). When compared to the disease control group.

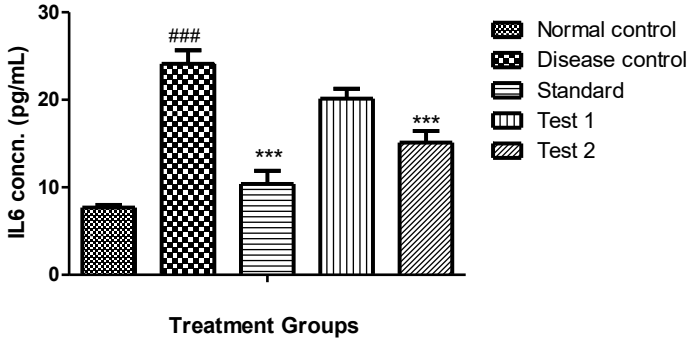

Fig. 7 Impact of curcumin treatment (100 & 200mg/kg, p.o.) on IL-6 level. N=5, The results are expressed as mean ± SEM. ###(p<0.001) compared to the Normal control group, and ***p<0.001 compared to the Disease control group.

Histopathological Study

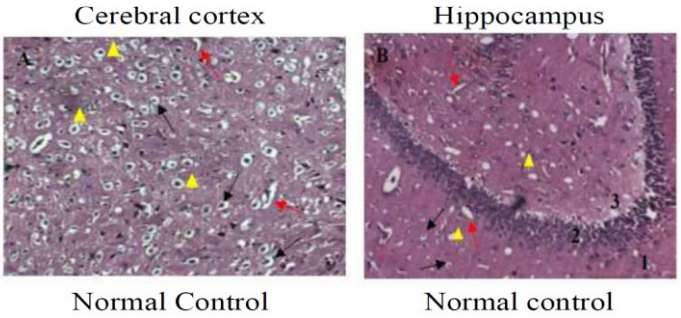

Fig. 8: Staining of the Cerebral Cortex and Hippocampusparts of Brain Tissues with H & E (X 100) for the Control Group of Animals.

Cerebral cortex: Displayed a normal histological structure with granule cells (yellow triangle), glial cells (black arrow), and blood vessels (red arrow).

Hippocampus: Exhibited a normal structural morphology granule cells (yellow triangle), glial cells (black arrow) & blood vessels (red arrow).

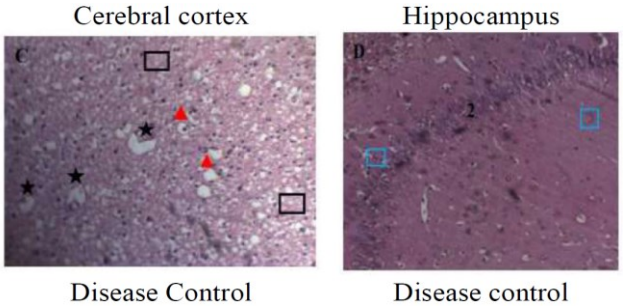

Fig. 9: Staining of the cerebral cortex and Hippocampus parts of brain tissues with H & E (x 100) of the animals treated with cyclophosphamide.

Cerebral Cortex: Neuronal degeneration characterized by pyknotic nuclei (red triangle), pericellular edema (black star), and plaque formation (black square).

Hippocampus: Disordered granular layer with many apoptotic cells (blue square).

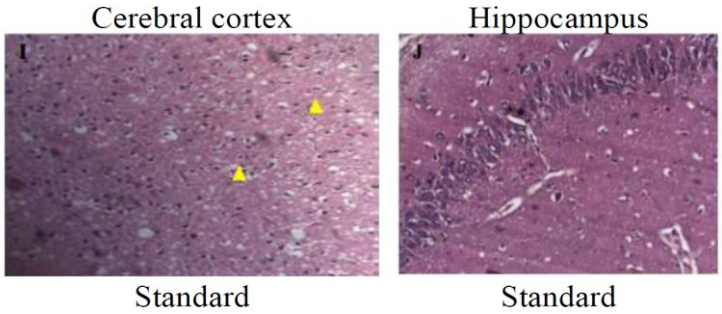

Fig. 10: Staining of the cerebral cortex and Hippocampus parts of brain tissues with H & E (x 100) of the animals treated with standard drug treated group: Normal histological structure in both the cerebral cortex and hippocampal zones.

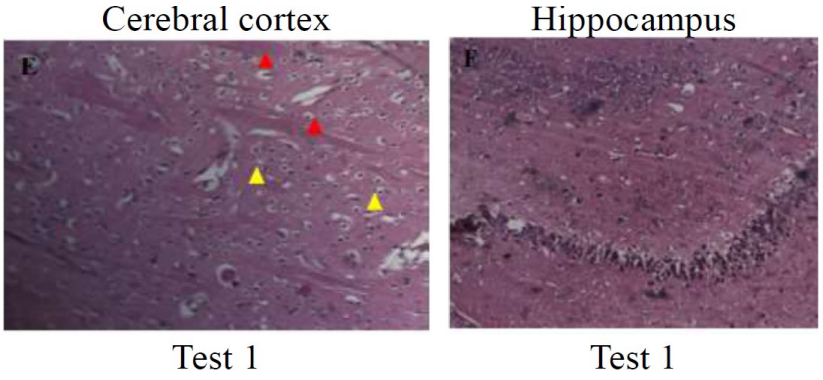

Fig. 11: Staining of the cerebral cortex and Hippocampus parts of brain tissues with H & E (x 100) of the animals treated with curcumin daily dose of 100mg/Kg

Cerebral Cortex: Exhibited mild nuclear pyknosis (red triangle) and slight pericellular edema in some neurons. Additionally, it showed a normal histological structure of granule cells (yellow triangle).

Hippocampus: Hippocampal zones appeared more organized, with moderate edema and apoptotic cell

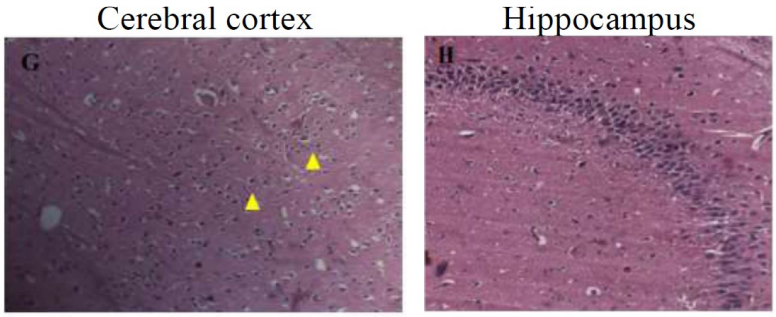

Fig. 12 : Staining of the cerebral cortex and Hippocampus parts of brain tissues with H & E (x 100) of the animals treated with curcumin daily dose of 100mg/Kg

Significant number of glial cells were still present in curcumin 200mg/kg treated animals, exhibited well-organized cerebral cortex and hippocampal zones.

DISCUSSION

This study was completed to evaluate the impact of curcumin treatment on cyclophosphamide induced brain oxidative status and AChE action. The observation of present examinations is similar as the published studies that the cyclophosphamide can disrupts the memory and learning. The increase in the concentration of AChE in the brain homogenate exhibited in this investigation demonstrates a decrease of cholinergic neural connections of the cyclophosphamide. Memory weakness and motor coordination in cyclophosphamide treated animals can be explained on the theory of suppression of the cholinergic framework by cyclophosphamide [17].

Oxidative stress is a major component of cyclophosphamide induced neurotoxicity. In the hippocampus, it causes impairment to mitochondria and causes mitochondrial death, bringing about the production of excess reactive oxygen species [18]. Cellular oxidative stress impairs the antioxidant resistance mechanism and results in neuronal death. Cell toxicity is being generated due to overproduction of ROS. [19]. By considering the theory of ROS and its relation of cyclophosphamide the present study was planned to overcome the imbalance of ROS with the co-administration of a natural anti-oxidant and anti-inflammatory agent curcumin. Curcumin is a well-known traditional remedy for inflammation as well as a neuroprotective agent. Furthermore, in the present study investigation proves that the curcumin enhanced the cholinergic system, shielded the neurons from oxidative stress and improved long term cognitive impairments in Swiss mice [20].

Lipid peroxidation was assessed in this study by estimating MDA level in the brain homogenate. MDA is one of the most prominent and reliable measure for lipid peroxidation. In the present study, curcumin improved cyclophosphamide induced elevation of MDA level, which proves that the curcumin treatment is able to restore the oxidative stress **[21]**.

Glutathione is a crucial intracellular free radical scavenger within the brain and a key component of the internal OS defense system. It functions as a substrate for detoxification enzymes such as GPx and interacts with OFR & organic peroxides. In this study, treatment with CP led to a reduction in brain glutathione activity compared to the normal control group animals. In contrast, treatment with donepezil (5mg/kg) & curcumin at doses of 100 and 200mg/kg resulted in increased glutathione activity compared to the CP treatment group **[22]**.

Catalase is an essential antioxidant enzyme present in almost all oxygen-exposed organisms, including animals, plants, and bacteria. It is crucial for protecting cells from oxidative damage by catalyzing the breakdown of H_2O_2, a ROS, into water & oxygen. In this study, treatment with CP led to a decrease in brain catalase activity compared to the Normal control group animals. However, administering donepezil (5mg/kg) and curcumin at doses of 100 and 200mg/kg led to elevated catalase activity relative to the CP treated group **[23]**.

The present research revealed that curcumin effectively mitigates oxidative stress in animals with CP induced cognitive impairments. It accomplishes this by reducing markers of ROS production. Additionally, curcumin boosts the production of antioxidant enzymes like GSH & CAT. The results obtained suggest that curcumin significantly influences the reduction of OS related CICI. Its mechanisms may include enhancing antioxidant enzyme function such as catalase. Curcumin may help to delay the onset and course of CICI by controlling OS **[24]**.

OS & the antioxidant system are crucial in the development of pathological neurological changes. Antioxidants are vital for maintaining health as they help protect the body from harmful substances. These agents combat the damaging effects of oxidation, which can compromise cellular integrity. Cells are subjected to damage or oxidation due to attacks by free radicals, which are extremely reactive molecules toward other cells because they have an unpaired electron in their outer shell. When a free radical interacts with a cell, it can cause oxidation and damage. One of the first things that contributes to memory loss is OS. Lipid peroxidation seems an important aspect of oxidative stress and is necessary to keep the balance of OS. In addition, compared to the CP treatment group, curcumin treatment resulted in lower levels of IL-6 and AChE. The NT ACh is broken down by the enzyme AChE into choline and acetate. An essential cytokine, IL-6 affects inflammation, immune responses, and the control of numerous physiological functions **[25]**.

The histopathological examination showed that animals exposed to CP displayed several brain abnormalities, such as pyknotic nuclei, pericellular edema, plaque formation, and a disorganized granular layer with numerous apoptotic cells **[26]**.

Whereas, rats administered with curcumin at doses of 100 and 200mg/kg showed fewer pathological changes. The group treated with 100mg/kg of curcumin displayed mild nuclear pyknosis and slight pericellular edema in some neurons, along with a normal histological structure of granule cells. The hippocampal zones were more organized, showing moderate edema and apoptotic cells, but a significant number of glial cells remained. Animals treated with 200mg/kg of curcumin exhibited a well-organized cerebral cortex and hippocampal regions. It showed a normal histological structure of granule cells **[27]**

Dopamine (DA), is an important neurotransmitter which is derived from L-tyrosine, is converted to L-Dopa by the enzymatic reaction in dopaminergic neurons. Once DA is synthesized, it is stored in synaptic vesicles. Cyclophosphamide administration decreases the dopamine by the inhibition of muscarinic autoreceptors. Activation of these autoreceptor reduces the release of dopamine. Both D1 and D2 receptors are involved in learning and memory processes. Insufficient and excessive amounts of dopamine is responsible for memory impairment. In this study animals administered with curcumin 200mg/kg significantly restores the level of dopamine **[28]**.

Overall, it is well determined from the present outcome of this study that curcumin is an excellent neuroprotective potential against CP induced memory impairments in Swiss albino mice. Cyclophosphamide administration caused motor incoordination, learning and memory impairments, as well as AChE and oxidative stress in the hippocampus. Co-administration of curcumin provided an ameliorative effect on rodents by expanding motor activity, memory capacity, and AChE action

and decreasing the generation of ROS.

CONCLUSION

It can be concluded by this study that curcumin can be therapeutically beneficial to overcome the toxic effect of cyclophosphamide by improving the brain antioxidant status and normalizing brain neurotransmitter level.

Financial Support and Sponsorship

Nil

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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