Available online on www.ajper.com

Asian Journal of Pharmaceutical Education and Research

Vol -3, Issue-1, April-June 2014

ISSN: 2278-7496

RESEARCH ARTICLE

EFFECT OF CURCUMIN IN CELECOXIB AND STREPTOZOTOCIN INDUCED EXPERIMENTAL DEMENTIA OF ALZHEIMER`S DISEASE IN MICE

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Article Received on 17 Feb 2014.

Revised on 22 Feb 2014,

Accepted on 03 Mar 2014

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Abstract:

To investigate the effect of Curcumin in Celecoxib and STZ induced experimental dementia of Alzheimer disease in mice. Celecoxib and STZ for administrations were used to induce experimental dementia. Curcumin (150 mg/kg, *p.o*) treatment started two days prior to Celecoxib or STZ administration followed by treatment of Celecoxib (100mg/kg, *p.o*) and STZ (3mg/kg, *i.c.v*). Cognitive behaviour was asses by using Morris water maze and elevated plus-maze was used for by measuring transfer latency (TL). On 9^{th} day animals were sacrificed and acetyl cholinesterase activity was measured to assess cholinergic activity of the brain, thiobarbituric acid reactive species (TBARS) levels, catalase activity, DPPH assay and reduced glutathione (GSH) levels were measured to asses the oxidative stress in brain. The present data demonstrate that curcumin improves memory in celecoxib or STZ induced dementia. From the present data it may be concluded improvement of memory by treatment of Curcumin is due to decrease the oxidative stress.

Keywords: Morris water maze, elevate plus maze, oxidative stress, acetyl-cholinesterase activity, TBARS, DPPH, GSH, Alzheimer`s disease.

INTRODUCTION:

Alzheimer's disease is named after Dr. Alois Alzheimer, a German doctor, (1907) he was noticed changes in the brain tissue of a woman who had died of an unusual mental illness. It is characterized by the presence of excessive amount of neuritic plaque containing amyloid β protein and abnormal tau protein filaments in the form of neurofibrillary tangle, loss of cholinergic cells, particularly in the basal forebrain is accompanied by loss of neurotransmitter acetylcholine[1]. There are two forms of the disease a genetics based early onset familial Alzheimer disease and a more prevalent age depandant form called Sporadic Alzheimer disease[2]. It is the most common cause of dementia, leading to deterioration in vital cognitive process such as memory, understanding, speech and its symptoms can also include unpleasant behavioral changes such as anxiety and dysphoria[3]. It is also known as dementia, characterized into four stages namely, Pre- dementia, early dementia, Moderate dementia, and advanced dementia. Dementia is characterized by a decline in cognitive faculties and occurrence of behavioral abnormalities, which interfere with an individual's activities of daily living. Dementing disorders usually affect elderly individuals but may occur in individuals younger than 65 years (early-onset dementia or EOD) . Inflammatory or immunologic paradigms are often viewed as a corollary of the amyloid cascade hypothesis. Certainly, brain amyloid deposition associates with local inflammatory and immunologic alterations. Inflammation is relevant to Alzheimer`s disease (AD) neurodegeneration [4]. The inflammatory/ immunologic hypotheses argue that although β amyloid protein may have direct neurotoxicity, at least some of its toxicity might actually be an indirect consequence of a β amyloid.

This oxidative damage can occur in virtually all types of neuronal macromolecules (e.g., lipids, carbohydrates, proteins and nucleic acids) [5]. The brain is especially vulnerable to damage from oxidative stress because of its high oxygen consumption rate, abundant lipid content and relative paucity of antioxidant enzymes compared to other organs. In neurons, oxidation can result in numerous problems, including upregulation of proinflammatory cytokines and irreversible DNA damage [6]. Oxidative stress is thought to be important early in AD progression because it is temporally linked to the development of plaques and NFTs .

Material and method:

Experimental Animal:

In the behavioral paradigm for Alzheimer study, Swiss albino mice of either sex, weighing about 20-30 g was used. They were housed in animal house facility of the institute, in polypropylene cages with husk bedding under standard condition of light and dark cycle. They were feed on standard chow diet and provided water *ad libitium.* Animal were acclimatized to laboratory condition five days prior to behavioral study. All the behavioral assessments were carried between 9.00 to 18.00 h in semi- sound proof laboratory. The experimental protocol was approved by the Institutional Animal Ethical Committee (IAEC) in accordance with the national guidelines on the use of Laboratory animals. All experiments for a given treatment were performed using age-matched animals in an attempt to avoid variability between experimental groups[7].

Reagent and Chemicals-

Streptozotocin (Sigma Aldrich ,USA), Celecoxib (Himedia laboratories, Pvt. ltd, Mumbai), Curcumin (Himedia laboratories, Pvt. ltd, Mumbai), CMC (carboxy methyl cellulose) (CDH Laboratory Reagent), Streptozotocin was freshly prepared by dissolving in ACSF (Artificial cerebro spinal fluid). Celecoxib was dissolved in carboxyl methyl cellulose (CMC) and curcumin was dissolved in distilled water. Ellman's reagent (Sigma Aldrich,USA), tricholoracetic Acid (CDH Laboratory Reagent), thiobarbituric Acid (Chemworth, India), DPPH (2,2-diphenyl, 1-picryl hydrazyl) (Sigma Aldrich, St Louis.USA), methanol (CDH Laboratory Reagent), anesthetic ether (CDH Laboratory Reagent), acetylthiocholine Iodide (Sigma Aldrich, St Louis.USA), di-sodium hydrogen phoshphate (CDH Laboratory Reagent), potasium dihydrogen phosphate (CDH Laboratory Reagent), sodium chloride (CDH Laboratory Reagent), potassium chloride (CDH Laboratory Reagent), dextrose (CDH Laboratory Reagent), hydrogen peroxide (CDH Laboratory Reagent).

Experimental Groups: Five groups of mice were employed in the present study and each group comprised of 6 mice.

GROUP I – (Normal control group), no treatment.

GROUP II- (Disease control group), mice were administered celecoxib (100 mg/kg, *p.o*) daily for 5 days and again for the next four consecutive days (day 1^{st} to day 4^{th}, 45 min before) during acquisition trials. On 5^{th} day, the animals were administered vehicle, before retrival trial.

GROUP III- (Disease control group), mice were administered streptozotocin (3 mg/kg, *ICV*) in two schedules i.e. on 1^{st} and 3^{rd} day.

GROUP IV- (Streptozotocin and curcumin treated group), mice were pretreated with Curcumin (150 mg/kg, *p.o*) two days before the administration of streptozotocin (3 mg/kg, *ICV*) and continue day before the retrival trial.

GROUP V- (Celecoxib and curcumin treated group), mice were pretreated with curcumin (150 mg/kg, *p.o*) two days before and continue till the retrieval trial after the administration of celecoxib.

Intracerebroventricular Administration of Streptozotocin-

Experimental dementia of Alzheimer`s disease (AD) in mice was induced by *i.c.v.* (intracerebroventricular) Streptozotocin. Mice were anesthetized with anesthetic ether and *i.c.v.* injection was made with a hypodermic needle of 0.4 mm external diameter attached to a 10µl hamiltion microliter syringe (Praveen chemicals, Mathura). The needle was covered with a polypropylene tube except for 3mm of the tip region so as to insert this portion of the needle perpendicular through the skull into the brain of mouse. The injection site was 1mm to right or left midpoint on the line drawn through to the anterior base of the ear. Injection were performed into the right or left ventricle randomly. Two doses of streptozotocin (3mg/kg) were administered by *i.c.v.* injection bilaterally. The second dose was administered 48 h after the first dose. Streptozotocin was dissolved in freshly prepared artificial cerebro spinal fluid (147mM NaCl, 2.9mM KCl, 1.6 mM$MgCl_2$, 1.7mM dextrose [8,9].

Behavioral Assessment:

Following validated behavioral models of rodents were used to assess the learning and memory.

Elevated plus Maze:

Utility of elevated plus maze in the assessment of learning and memory is well documented in literature [10]. The apparatus consists of two open arms (50×10 cm) and two closed arms (50×10×40 cm) extended from a central platform (10×10 cm). The maze is elevated to a height of 40 cm from the floor. The experiment was performed in two stages. On day 1st each mice was placed at the end of an open arm facing away from the centre. The time taken to enter any one of the closed arms was recorded as transfer latency (TL). All four legs inside the close arm are counted as an entry cut off time allotted for each mouse was 180 sec. Those animals which did not enter the closed arm within cut off time were excluded from the study. Retention testing was conducted 24 h after the after the first trial (day 2nd) and transfer latency was recorded in a similar manner as mentioned before Shortened transfer latency was considered as an index of improvement of memory [11].

Morris water maze (MWM)-

The Morris Water Maze is a circular pool filled with water. Rats or mice are trained to use extra-maze visual cues to locate an escape platform hidden just below the surface of the opaque water[12]. The hidden platform version of the Morris Water Maze is a test of spatial memory which is sensitive to hippocampal damage, while the visible platform version of the Morris Water Maze is a non-hippocampal task, which is disrupted by dorsal striatum lesions [13]. While both rats and mice can be tested in the Morris Water Maze, they may show different learning strategies [14]. There are also concerns that anxiety or fear may be induced in mice in the water maze, suggesting involvement of the amygdala as well as the hippocampus [15]. The MWM test was employed to assess the learning and memory of the animals. MWM is a swimming based model where the animal learns to escape on to a hidden platform. It consisted of a large circular pool (150 cm in diameter, 45 cm in height, filled to a depth of 30 cm with water maintained at 28±1°C). The water was made opaque with white colored non-toxic dye. The tank was divided into four equal quadrants with the help of two threads fixed at right angles to each other on the rim of the pool. A submerged platform (10 cm^2), painted in white, was placed inside the target quadrants of this pool, 1 cm below the surface of water. The position of platform was kept unaltered throughout the training session. Each animal was subjected to four consecutive training

trials on each day with intertribal gaps of 5 min. The mouse was gently placed in the water between quadrants, facing the wall of pool with the drop location changing for each trial, and allowed 120 s to locate submerged platform. The animal was allowed to stay on the platform for 20 s. If it failed to find the platform within 120 s, it was guided gently onto the platform and allowed to remain there for 20 s. Day 4 escape latency time (ELT) to locate the hidden platform in water maze was noted as an index of acquisition or learning. Each animal was subjected to four training trials each day for four consecutive days. The starting poison was changed with each exposure as mentioned below and the target quadrant (Q4) remained constant throughout the training period.

Day1 Q1 Q2 Q3 Q4

Day2 Q2 Q3 Q4 Q1

Day3 Q3 Q4 Q1 Q2

Day4 Q4 Q1 Q2 Q3

On the fifth day, the platform was removed and each mouse was allowed to explore the pool for 120 s. The mean time spent in all four quadrants was noted. The mean time spent by the animal in the target quadrant searching for the hidden platform was noted as an index of retrieval or memory. The experimenter always stood at the same position. Care was taken regarding the relative location of the water maze with respect to other objects in the laboratory so that prominent visual clues were not disturbed during the total duration of study. All of the trials were completed between 09:00 and 18:00 [9,10,12,16]

Collection of sample-

On the 9th day, after behavioural assessment animals were sacrificed by cervical dislocation, brains were removed. Each brain was separately put on ice and rinsed with ice cold saline. A (10% w/v) homogenate was prepared in 0.1 M phosphate buffer (pH-7.4). The homogenate were then used for biochemical estimation.

Biochemical Estimation-

Acetyl cholinesterase Estimation - AchE inhibitory activity was measured by method of Ellman *et al.,* 1961. The homogenates was centrifuged at 1000 rpm for 10 min at 40°C, The total acetyl cholinesterase activity in the aliquot of the homogenate was estimated. The aliquot was mixed with phosphate buffer (pH 7.0). To this, the substrate acetyl thiocholine iodide and dithiobisnitrobenzoic acid reagent were added. Acetyl thiocholine iodide was hydrolyzed to

thiocholine and acetate by AchE. Thiocholine reacted with DTNB reagent to produce a yellow colour. The rate of formation of thiocholine from acetylcholine iodide in the presence of tissue cholinesterase was measured using a spectrophotometer. The rate of colour development is the measure of the AchE activity. Change in absorbance per minute of the sample was read at 412 nm. The enzyme activity was expressed as the n moles of substrate hydrolyzed/min/mg of protein.

TBARS assay – This assay is used to determine the lipid peroxidation. Aliquots of 0.5 mL distilled water were added with 1mL of tricholoroacetic acid and were added with 0.5 mL of brain tissue homogenate. This is centrifuged at 3000 rpm for 10 min. To the 0.2 mL supernatant, 0.1 mL thiobarbituric acid was added. Total solution is placed in water bath at 80°C for 40 min and cooled at room temperature. Absorbance was read at 532 nm [17].

Estimation of GSH – Supernatant of homogenate was mixed with tricholoroacetic acid in 1:1 ratio. This is centrifuged at 1000 rpm for 10 min at 4°C.The supernatant obtains (0.5 ml) was mixed with 2 ml of 0.3 m disodium hydrogen phosphate. Then 0.25 ml of 0.001 m freshly prepared DTNB dissolved in 1% w/v sodium citrate was added and absorbance was noted spectrophotometrically at 412 nm [16,18].

Catalase Activity- Catalase activity was assessed by the method of luck, where in the breakdown of hydrogen peroxide is measured. In this method 3mL of H_2O_2 phosphate buffer was added to 0.05 mL of the supernatant of the tissue homogenate. The absorbance was recorded at 240 nm using spectrophotometer. The result was expressed as micromoles of H_2O_2 decomposed per min per protein [19].

DPPH Assay – In this measurement is made from the bleaching of purple coloured methanol solution of DPPH. To the 1000µL of diverse concentration of the sample 4mL of 0.004% methanolic solution of DPPH was added. After 30 min incubation absorbance was read at 517 nm. Inhibition of free radical by DPPH in % was calculated in the following way:

$[\% = (A_{blank} - A_{sample} / A_{blank}) \times 100]$

A_{blank}: Absorbance of control reaction.

$A_{sample:}$ Absorbance of test sample.

Values of inhibition were calculated [17].

STATISTICAL ANALYSIS –

The results are expressed as Mean ± SD. The behavioral and biochemical data were analysed using one-way analysis of variance (ANOVA) followed by Graphical Prism Software for multiple comparison. The p value < 0.05 was considered to be statistically significant.

Results-

Morris Water Maze Test-

Administration of celecoxib (100 mg/kg, *p.o*) for 9 days or streptozotocin (3mg/kg, *i.c.v*) for two days (1st day and 3rd day) significantly increase escape latency time as compare to control group and markedly reduced time spent in target quadrant (Q_4) in search of missing platform during retrival trial, reflecting impairment of learning and memory (figure 1, 2). Pretreatment of curcumin showed a significant (P<0.05) improvement in memory as by decreasing the escape latency time and increase the time spent in target quadrant (Q_4) compare to the disease control group, i.e. celecoxib (100 mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*) treated group.

Elevate Plus Maze Test-

Administration of celecoxib (100 mg/kg, *p.o*) for 9 days or streptozotocin (3mg/kg, *i.c.v*) for two days (1st day and 3rd day) significantly increase the transfer latency on 2nd day compared to control group (figure: 3). Pretreatment of curcumin in celecoxib (100 mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*) treated group showed a significantly decrease the transfer latency time as compare to disease control group, i.e. celecoxib (100 mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*) treated group.

Biochemical Parameters-

Estimation of AchE activity-

Administration of celecoxib (100mg/kg, *p.o*) for 9 days or streptozotocin (3mg/kg, *i.c.v*) for two days i.e. 1st day and 3rd day significantly, increased the brain AchE activity when compared with control . Curcumin treatment group significantly (P<0.05), decreases the AchE activity as compare to disease control group, i.e. celecoxib (100 mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*) treated group. Results are summarized in (Table 1).

Estimation of TBARS assay-

Administration of celecoxib (100mg/kg, *p.o*) for 9 days or streptozotocin (3mg/kg, *i.c.v*) for two days i.e. 1st day and 3rd day significantly, increased the brain TBARS level compared with control group, which reflects enhanced oxidative stress. Curcumin treated group significantly (P<0.05), decreased the brain TBARS level compare with disease control i.e. celecoxib (100

mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*) treated group. Results are summarized in (Table 2).

Estimation of GSH levels of brain-

Administration of celecoxib (100mg/kg, *p.o*) for 9 days or STZ (3mg/kg, *i.c.v*) for two days i.e. 1st day and 3rd day significantly, reduced the brain GSH levels, compared with control group of animals, which reflects enhanced oxidative stress. Curcumin treated group showed significantly (P<0.05), increase the brain GSH level compare with disease control i.e. celecoxib (100 mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*). Results are summarized in (Table 3).

Estimation of Catalase activity-Administration of celecoxib (100mg/kg, *p.o*) for 9 days or STZ (3mg/kg, *i.c.v*) for two days i.e. 1st day and 3rd day significantly, reduced the catalase levels, compared with control group. Curcumin treated group significantly (P<0.05), increase the catalse level compare with disease control i.e. celecoxib (100 mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*). Results are summarized in (Table 4).

Estimation of DPPH assay-Administration of celecoxib (100mg/kg, *p.o*) for 9 days or streptozotocin (3mg/kg, i.c.v) for two days i.e. 1st day and 3rd day significantly, reduced the inhibition of enzyme, compared with control group . Curcumin treated group significantly (P<0.05), increase the catalse level compare with disease control. Results are summarized in (Table 5).

Fig1: Morris water maze, Effect of curcumin on celecoxib or STZ induced incresase in day 4th Escape

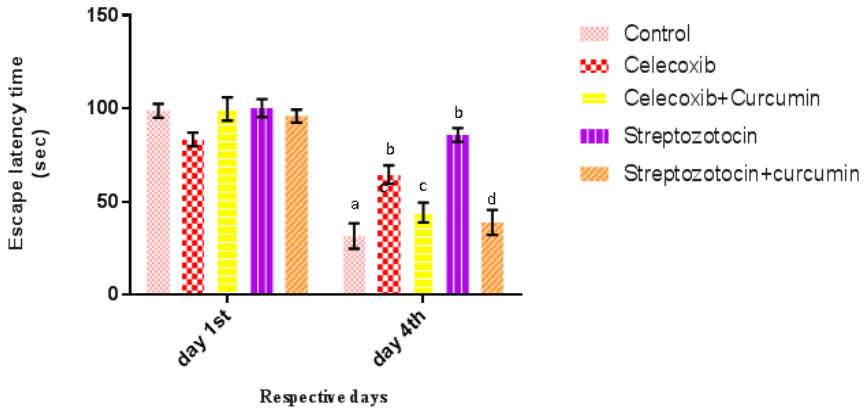

Fig:2. Effect of curcumin on celecoxib or streptozotocin induced decresae in time spent in target quadrant on 5th day.

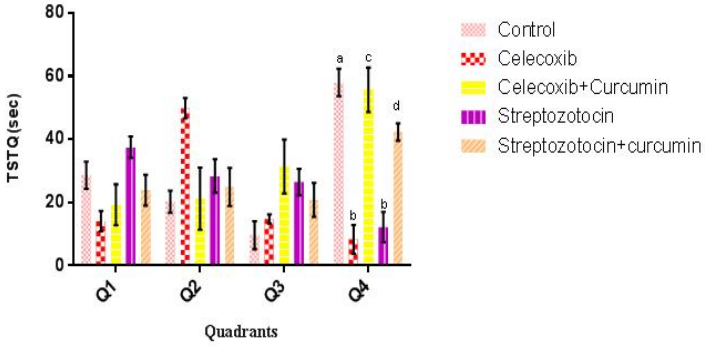

Fig:3. Elevate plus maze, Effect of curcumin on celecoxib or streptozotocin induced increase in transfer latency.

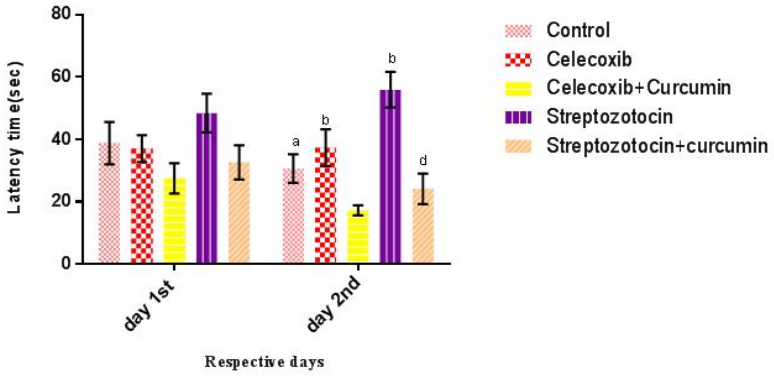

Table1 : Effect of curcumin on celecoxib or streptozocin induced increase in brain AchE activity.

Group	Treatment	AchE activity of brain (in micro moles of Ach hydrolysed/min/mg of protein)
I	Control	132±4.8
II	Cel	176±4.5[a]
III	Cel + Cur	158±4.4[b]
IV	STZ	198±4.7[a]
V	STZ + Cur	152±4.02[c]

Table 2: Effect of curcumin on celecoxib or STZ induced increase in TBARS levels.

Group	Treatment	TBARS in n M/mg of protein
I	Control	5.8±0.88
II	Cel	18.4±0.9[a]
III	Cel + Cur	10.6±0.5[b]
IV	STZ	26.4±0.68[a]
V	STZ + Cur	12.9±1.2[c]

Table 3: Effect of curcumin on celecoxib or streptozotocin induced decrease in brain GSH level.

Group	Treatment	GSH levels(n M/mg of protein)
I	Control	21±1.4
II	Cel	14.9±0.98 [a]
III	Cel + Cur	18.3±0.69[b]
IV	STZ	15.2±1.2[a]
V	STZ + Cur	19.2±0.99[c]

Table 4: Effect of curcumin on celecoxib or streptozotocin induced increase in brain H_2O_2 Scavanging activity.

Group	Treatment	H_2O_2 Scavenging activity (%)
I	Control	80
II	Cel	45[a]
III	Cel + Cur	72[b]
IV	STZ	33[a]
V	STZ + Cur	69[c]

Table 5: Effect of curcumin on celecoxib or STZ induced increase in DPPH activity.

Group	Treatment	Percentage of inhibition (%)
I	Control	65
II	Cel	21 [a]
III	Cel + Cur	58 [b]
IV	STZ	18[a]
V	STZ + Cur	50[c]

Discussion-

Loss of memory is associated with dementia of different types . Dementia is a syndrome of progressive nature marked by gross behavioral and personality disturbances. This syndrome occurs in Alzheimer`s disease, the main histological features of AD include extracellular deposition of Aβ plaques and intraneuronal neurofibrillary tangles, loss of cortical cholinergic neurons in AD probably accounts for memory impairment [20]. Results of the present study indicate that curcumin pretreatment group significantly improve the cognitive function, restored AchE enzyme activity, glutathion enzyme activity, catalase activity, TBARS and DPPH activity in celecoxib and STZ treated groups. Systemic administration of celecoxib and STZ caused impairment in the memory tasks observed in Morris water maze, elevate plus maze and locomotor activity paradigms. It has been reported that short-term treatment of celecoxib increases the amyloid beta-42 (Aβ42) segment in brain cells [21]. Amyloid beta-42 is mainly responsible for formation of insoluble aggregates [22]. Increase in Aβ are likely to result in a higher likelihood of oligomer formation, intermediate assemblies, such as soluble oligomers of Aβ [23] as well as, insoluble aggregates, possess toxic effects leading to programmed neuronal cell death (apoptosis) [24-26], while accumulation of insoluble fibrils of A β peptide, generate negligible neuronal loss [27]. Accumulation of β-amyloid may eventually lead to neuronal damage and dementia [28].

The *ICV* STZ model has been described as an appropriate animal model for AD (Lannert and Hoyer, 1998). Cerebral glucose and energy metabolism is associated with oxidative stress [29]. After *ICV* administration, the highest concentration of STZ (3mg/kg) reaches the fornix and periventricular white matter at the level of third ventricle, which show the greatest damage [30], and *ICV* STZ induced amnesia is independent of its hyperglycemic effect [31]. Although the

mechanism of action of STZ on memory impairment is not yet known, it probably involves the induction of oxidative stress, to which myelin is particularly vulnerable [32].

In elevate plus maze (EPM), test time elapsed (Transfer latency- TL) in entry in to enclosed arm from open arm is measure of memory function and TL get reduced after successive exposure of mice [19]. Curcumin pretreated group significantly increase the number of counts in 10 mins as compare to disease control group. The observation indicates that curcumin increases the CNS activity, because locomotor activity is influenced by most of the CNS drug in animals [33], which also indicates the learning ability. On the basis of present study increases number of counts indicates the improvement memory function.

Curcumin, it is a natural product of MMP inhibitor , it has been reported, that a low dose of curcumin significantly suppressed the inflammatory reactions, oxidative damage and plaque burden and decrease the amount of insoluble amyloid [34].

Administration of STZ(3mg/kg, *i.c.v*) for 2 days significantly decrease the memory, measured in term of decrease in time spent in target quadrant (TSTQ) and increase the escape latency time (ELT) in Morris water maze (MWM), increased the latency time (LT) in elevate plus maze (EPM) and decrease the number of counts in locomotor activity. Pre-treatment of curcumin (150mg/kg, *p.o*) for 15 days significantly, improve the memory measure in term of decrease the escape latency time (ELT) and increase the time spent in target quadrant (TSTQ) in Morris water maze (MWM) , decrease the transfer latency (LT) in elevate plus maze (EPM), increased the number of counts in locomotor activity.

In our study 9 days treatment of celecoxib (100mg/kg, *p.o*) significantly decrease the memory, measured in term of decrease in time spent in target quadrant (TSTQ) and increase the escape latency time (ELT) in Morris water maze (MWM), increased the latency time (LT) in elevate plus maze (EPM) and decrease the number of counts in locomotor activity. Pretreatment of curcumin (150mg/kg, *p.o*) for 15 days, significantly improve the memory by decreasing the escape latency time (ELT) and increasing the time spent in target quadrant (TSTQ) in Morris water maze (MWM) , decrease the transfer latency (LT) in elevate plus maze (EPM), increased the number of counts in locomotor activity. Treatment of celecoxib (100mg/kg, *p.o*) and streptozotocin (3mg/kg, *i.c.v*) significantly increase the oxidative stress (TBARS, GSH, Catalase activity, DPPH assay) and decrease the acetylcholine level. It may due to its antioxidant property.

In the present investigation, curcumin pretreatment significantly improve cognitive function and restored AchE enzyme activity, brain oxidative stress noted in term of decrease in TBARS

and increase in GSH levels, increases the catalase activity as compare to the disease control group. Oxidative stress is the cytotoxic consequence of oxy-redical and oxidant formation and the reaction with cellular constituents. Reactive oxidative species (ROS) are generated continuously in nervous system during normal metabolism and neuronal activity. The nervous system is particularly vulnerable to the deleterious effects of ROS, because the brain has a high consumption of oxygen, large amount of polyunsaturated fatty acids (PUFAs), high contents of free ions and low levels of antioxidants defense were compare to other organ [35]. It has been reported due to increase the memory and decrease the oxidative stress [32,36, 37, 38, 39, 40].

Conclusion-

On the basis of above discussion those following findings may be concluded:

1. Celecoxib (a selective COX – 2 inhibitor) induces experimental dementia closely related to dementia of Alzheimer's disease.
2. ICV administration of STZ at sub-diabetogenic dose produced significant impairment in acquisition as well as retrieval of memory.
3. Curcumin treatment may attenuate celecoxib (selective COX – 2 inhibitor) and STZ induced dementia, by virtue of their neuroprotective/ antioxidative/ decreased brain AChE activity. Curcumin may be of enormous use in dementia associated with various neurodegenerative disorders.

Acknowledgement

We are thankful to Shri Narayan Das Agrawal, honorable Vice Chancellor of GLA, University, Mathura and Dr. H.N Yadav Head, Department of Pharmacology, GLA, University, Mathura (India), for their constant encouragement and for providing us the research facilities.

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