

Protective Effect of Epigallocatechin-3-Gallate (EGCG) the Major Tea Polyphenolic, Against Intracerebroventricularly Colchicine Induced Oxidative Damage Production in Brain and Cognitive Dysfunction in Mice

Ananya Bagchi*

Department of Agriculture and Food Engineering, Indian Institute of Technology, Kharagpur, India

Abstract

Alzheimer's disease is a neuro degeneration which generates memory impairment in human. Administration of colchicine centrally in brain is well known to generate cognitive impairment and memory dysfunction in central nervous system which produces Alzheimer's disease. In this present experimental study, evaluation of the therapeutic effects of EGCG against the colchicine generated cognitive impairment and oxidative dysfunction in Alzheimer's disease induced rat model is executed. Colchicine was given intra-cerebroventricularly which results a memory loss in Morris water maze and produced marked oxidative stress induced damage. It also caused a profound increment in acetyl cholinesterase enzyme inhibitory activity. Treatment with EGCG was given every day orally for a course of 25 days prior to colchicine application in rat model. Treatment with EGCG caused significant improvement in the cognitive function and reduced oxidative damage in rat model. This study demonstrates the therapeutic effect of EGCG against colchicine produced cognitive and oxidative injury generated in Alzheimer's disease model.

Keywords: EGCG; Acetylcholinesterase; Alzheimer's disease; Oxidative damage; Colchicin

Introduction

Epigallocatechin-3-gallate (EGCG) is the major polyphenol found in tea (*Camellia sinensis*) and in Carob flour which can be derived from the ground pods of the carob plant or *Ceratonia siliqua* [1]. EGCG is a polyphenol which has powerful antioxidant property and can prevent many diseases like atherosclerosis, cancer and neurodegenerative diseases [2]. After consumption of tea, catechins are subjected to many pathways of methylation, glucuronidation and sulfation. It has been found that orally administered EGCG (10 mg/kg) could inhibit Acetylcholinesterase enzyme activity, glutathione peroxidase activity and oxygen free radical content concentration in streptozotocin-model of Alzheimers [3-5]. In mutant PS2 AD mice, EGCG (3 mg/kg indrinking water) enhanced memory formation and alpha-secretase activity, and suppressed gamma-secretase activity [6] found that EGCG administration, i.p (20 mg/kg) and p.o. (50 mg/kg in drinking water), affected tau profile and showed effect on cognitive function improvement to transgenic mice [6]. Besides, EGCG (5-10 μ M) exhibits good iron-chelating property and degrades both immature and full length cellular holo-Amyloid peptide [7,8]. EGCG (1.5 and 3 mg/kg in drinking water) also inhibited lipopolysaccharide generated memory dysfunction and cell mediated apoptosis via non-amyloidogenic proteolysis pathway which prevents beta-site APP cleaving enzyme (BACE-1) activity, APP expression and A β -levels [9]. In the model of Alzheimer's disease, EGCG (1, 10 and 100 μ M) inhibits astrocytes activation and inflammation generation factors which include TNF- α , IL-1 α , macrophage colony-stimulating factor, soluble intracellular adhesion molecule-1, COX-2, IL-6, inducible nitric oxide synthase (iNOS) [5,10,11]. In this present study our aim is to evaluate the effect of EGCG on acetylcholinesterase inhibitory activity and the activities of free radical scavengers like superoxide dismutase, catalase in Alzheimer's disease mice model. Also the behavioural changes of Alzheimer's disease mice model upon EGCG administration are studied.

Materials and Methods

Animals

70 healthy, adult male albino rats (Charles-Foster strain) weighing

200-250 g (6-8 weeks of age) were used in this experimental study. Animals were housed individually in polypropylene animal cages with food pellet and water *ad libitum*. The animal room was temperature was maintained at 25°C with a 12 h light dark cycle (light 7 am to 7 pm). According to the regulations set by institutional animal ethical committee, all adequate measures were taken to minimize the pain and discomfort in the rats. The standard protocol which was used was approved by the Institutional Animal Ethics Committee (SR group of Institutions Jhansi India) No. SRGI/COP/SAEC/AM-IITKGP/16/01.

Preparation of experimental rat model of alzheimer's disease by colchicine

7.5 μ g of colchicine (Sigma Chemical Co., St. Louis, MO, USA) dissolved in 2.5 μ L artificial CSF was injected slowly for 5 minutes in the lateral ventricle of rat. The lateral ventricle of both sides of the brain of each rats was approached stereotaxically [12] (AP-0.6 mm from bregma, L \pm 1.5 mm and V+2.8 mm below cortical surface) through a steel cannula (0.45mm diameter) connected to a Hamilton syringe in anesthetized rats (Nathiopentone, 50 mg/kg bodywt. i.p [13]).

Drugs and treatment schedule

Colchicine and EGCG were purchased from (Sigma Chemical Co., St. Louis, MO, USA) and standard solutions were made freshly at the beginning stage of each experiment. Colchicine was prepared in artificial cerebrospinal fluid in a manner that a 15 mg dose should be given in a 5 mL injection volume for intracerebroventricular

*Corresponding author: Ananya Bagchi, Department of Agriculture and Food Engineering, Indian Institute of Technology, Kharagpur, India, Tel: +919836277421; E-mail: bagchiananya13@gmail.com

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administration of the compound. For oral administration, EGCG treatment was given with drinking water in a dose of 0.5 mL/100 g of body weight. Animals were divided and placed into groups consisting of ten animals in each: Group 1 consists sham-operated animals (received vehicle for EGCG); Group 2, ACSF (5 mL i.c.v.) þ vehicle for EGCG; Group 3, colchicine-treated group (15 mg/5 mL i.c.v.) þ vehicle for EGCG; Group 4, EGCG (40 mg/kg, p.o.) þ ACSF (5 mL i.c.v.); Group 5, EGCG (80 mg/kg, p.o.) þ ACSF (5 mL i.c.v.); Group 6, EGCG (40 mg/kg, p.o.) þ colchicine (15mg/5 mL i.c.v.); and Group 7, EGCG (80 mg/kg, p.o.) þ colchicine (15 mg/5 mL i.c.v.)

Behavioural assessment

Assessment of cognitive performance of the mice was done by elevated plus maze paradigm. Each rat was adjusted to the laboratory environmental condition and with the elevated maze one hour earlier to the start of the experiment. Training was carried out on the day 13 after administration of colchicine. Rats were colonized one by one at one end of the open arm facing away from the central square. The time latency by an animal to go from an open arm to the closed arm was calculated and noted as the initial transfer latency (ITL). Animals were acquiesced to travel the maze for the next 20 s after the ITL was recorded and then they were brought back to their home cage. Retention of memory was studied by placing the animals in an open arm on day 14 and day 21 of ITL, which was calculated as the first retention transfer latency (1st RTL) and second retention transfer latency (2nd RTL).

Assessment of cognitive performance: spatial navigation task

The spatial navigation task was done by using the Morris water maze [13]. Animals were trained to swim to a visible platform in a circular pool fixed in a test room. The pool was filled up with water (28°C) to a height of 40 cm. A revolving circular platform (9 cm in diameter) situated on a column was kept in the pool 2 cm above the water level during the addition phase. A similar platform was kept in the pool 2 cm below the water level for memory retention experimentation. The water was made non transparent by adding a nontoxic dye. Four equally spaced locations around the edge of the pool (N, S, E and W) were denoted as starting points and thus the pool were divided into four equal parts.

(a) Maze acquisition phase (training). Animals were treated with a training session consisting of four trials on day 13. A trial was started by releasing the animal into the maze which is facing towards the wall of the pool. The time taken by an animal to find the escape platform was noted (cut off time, 90 s). The time taken by each rat to reach the platform was noted as the initial acquisition latency (IAL). At the end of each trial, the animal was kept in their home cage. A constant 5 min interval was fixed between subsequent trials.

(b) Maze retention phase: Following 24 h (day 14) and 8 days (day 21) after IAL, animals was freed randomly at one of the edges of the wall facing the pool and testing was done for retention of response. The time latency taken to find the covert platform on day 14 and day 21 following central administration of colchicine was noted and denoted as first retention latency (1st RL) and second retention latency (2nd RL), respectively.

Biochemical tests

Biochemical tests were done after 24 h of the behavioural test. The animals were sacrificed and the brains were removed, treated with ice-cold isotonic saline, and the brains were homogenized with ice-cold 0.1 mmol/L phosphate buffer (pH 7.4). The homogenates (10% wt/vol)

were then centrifuged at 10,000 g for 15 min and the supernatants were used for the different biochemical analysis.

Measurement of lipid peroxidation

The lipid peroxidation in the brain was analysed quantitatively by the method as given by Wills [26]. The amount of malondialdehyde (MDA) was estimated by reaction with thiobarbituric acid at 532 nm of wavelength using a Perkin Elmer (Waltham, MA, USA) spectrophotometer. The values were calculated using the fixed value of molar extinction coefficient of the chromophore [1.56-10⁵ (mol/L)cm⁻¹].

Estimation of reduced glutathione

It was measured according to the method proposed by Ellmans [9]. In this procedure 1 mL of supernatant of the brain sample was precipitated with 1 mL of 4% sulfosalicylic acid and the digestion was made for 1 h in the cold at 48°C. The samples were then centrifuged at 1,200 g for 15 min at 48°C. To the 1 mL of the supernatant gained 2.7 mL of phosphate buffer (0.1 mmol/L, pH 8) and 0.2 mL of 5,5'-dithio-bis(2-nitrobenzoic acid) were added. The yellow colour generated was measured at 412 nm using the Perkin Elmer Lambda 20 spectrophotometer. Results were calculated using the molar extinction coefficient of the chromophore.

Estimation of nitrite

The accumulation of nitrite in the supernatant, an indicator of the production of nitric oxide, was determined by a colorimetric assay with Greiss reagent [0.1% N-(1-naphth-1-yl)ethylenediaminedihydrochloride, 1% sulfanilamide and 5% phosphoric acid] according to the procedure of Green et al. Equal volumes of the supernatant and Greiss reagent were mixed and incubated for 10 min at room temperature in the dark. The absorbance was measured at 540 nm using the Perkin Elmer Lambda 20 spectrophotometer. The concentration of nitrite in the supernatant was determined from a standard curve.

Superoxide dismutase activity

Superoxide dismutase (SOD) activity was assayed by the method of Kono. The assay system consists of 0.1 mM EDTA, 50 mM sodium carbonate, and 96 mM nitro blue tetrazolium. In the cuvette, 2 mL of the above mixture, 0.05 mL of hydroxylamine, and 0.05 mL of the supernatant were mixed, and autooxidation of hydroxylamine was measured for 2 min at 30 s intervals by measuring absorbance at 560 nm using the Perkin Elmer Lambda 20 spectrophotometer.

Catalase activity

Catalase activity was measured by the method of Luck, 30 where the breakdown of H₂O₂ is measured. In brief, the assay mixture consists of 3 mL of H₂O₂ phosphate buffer and 0.05 mL of the supernatant of the tissue homogenate. The change in absorbance was recorded for 2 min at 30 s intervals at 240 nm using the Perkin Elmer Lambda 20 spectrophotometer. The results were expressed as mmol of H₂O₂ decomposed/minute/mg of protein.

Glutathione S-transferase activity

The activity of glutathione S-transferase (GST) was analysed by the method of Habig and Jakoby. The assay mixture constitutes 2.7 mL of phosphate buffer, 0.1 mL of GSH, 0.1 mL of 1-chloro-2,4-dinitrobenzene as a substrate, and 0.1 mL of supernatant. The increase in the absorbance was noted at 340 nm for 5 min at 1 min intervals by using the Perkin Elmer Lambda 20 spectrophotometer. The results

were represented as nmol of 1-chloro-2, 4-dinitrobenzene conjugated/ minute/mg of protein.

Acetylcholinesterase activity

Acetylcholinesterase (AChE) enzyme is an enzyme for loss of cholinergic neurons in the forebrain. The AChE activity was measured by the method of Kumar et al. [14]. The assay mixture contains 0.05 mL of supernatant, 3 mL of sodium phosphate buffer (pH 8), 0.1 mL of acetylthiocholine iodide and 0.1 mL of 5,5'-dithio-bis(2-nitrobenzoic acid) (Ellman re-agent). The change in the absorbance was measured and recorded upto 2 min at 30 s intervals at 412 nm wavelength using the Perkin Elmer Lambda 20 spectrophotometer. Results were expressed as mmol of acetylthiocholine iodide hydrolyzed/ minute/mg of protein.

Protein estimation

The protein was measured by the biuret protein estimation method using bovine serum albumin as a standard.

Statistical Analysis

Datas are represented as mean-SEM values. The behavioural analysis data were analysed by a repeated-measurement and two-way analysis of variance. The biochemical estimations were separately analysed by one-way analysis of variance. Comparisons between groups were done using Tukey's test taking $P < 0.05$ level of significance.

Results

Effect of EGCG on memory performance determination in the elevated plus maze paradigm in colchicine-injected rats

In our experiment the average ITL on day 13 for each rat was stable and no such significant variation could be seen. All the mice entered into the closed arm within 90 s. It was found that sham-operated, ACSF-injected and EGCG (40 and 80 mg/kg) treated rats entered the closed arm more quickly and the average retention transfer latencies (1st RTL and 2nd RTL) to enter the closed arm on days 14 and 21 were relatively quicker to the respective ITL values on day 15 of each group. On the contrary colchicine-injected rats acted poorly throughout the whole experiment and had not showed any alteration in the average retention transfer latencies on days 16 and 22 relative to the pertaining latency on day 15. Consistent administration of EGCG (40 and 80 mg/kg) at the beginning prior to colchicine injection significantly lowered mean retention latencies on days 16 and 22 following colchicine injection ($P < 0.05$ vs. i.c.v. colchicine group) (Table 1).

The IAL values on day 13 and mean retention latencies on days 14 (1st RL) and 21 (2nd RL) after Colchicine administration were determined in the Morris water maze test. Data are represented as mean \pm SEM values. Two-way analysis of variance was done followed by Tukey's test for multiple comparisons. Mean transfer latencies of EGCG (40 and 80 mg/kg, p.o.)-treated in colchicine-injected (i.c.v.) groups were significantly lower from that of only EGCG treated groups on days 14 and 21 ($P < 0.05$) (Table 1).

Effect of EGCG on the spatial navigation task in colchicine-injected rats

It is observed that Sham-operated, ACSF-injected, and EGCG (40 and 80 mg/kg, p.o.)-injected groups of rats quickly learned to reach at the platform in the Morris water maze on day 13. Although colchicine-injected rats proved to be an initial rise in elude latency but it deteriorating with continuing training throughout the asserting of a

spatial navigation task on day 13. A notable difference in the average IAL of the colchicine-injected mice group compared to the ACSF-injected group on day 13, expressing colchicine-induced ruination in performance of the spatial navigation task ($P < 0.05$). On the contrary EGCG (40 and 80 mg/kg, p.o.) treatment significantly decreased the IAL to reach the platform in comparison to the colchicine treated rats on day 13 (Table 2). Following training, mean retention latencies (1st and 2nd RL) to desertion to the hidden platform was significantly lowered in sham-operated and ACSF-injected rats on days 14 and 21, in comparison to the IAL on day13 following colchicine injection. Conversely the performance of colchicine injected rats showed increased mean retention latencies on days 14 and 21 in comparison to the IAL on day 13 of the ACSF-injected group. The results show that colchicine induced memory impairment. Though chronic EGCG treatment (40 and 80 mg/kg, p.o.) prior to the colchicine injection partially reversed 1st and 2nd RL values compared to colchicine injected rats on days 14 and 21, respectively, after colchicine injection (Table 2).

Data are expressed as average in terms of SEM values. CAT, catalase (in mmol of H_2O_2 decomposed/minute/mg of protein); GSH, reduced glutathione synthase (in nmol/mg of protein); MDA, malondialdehyde (in nmol of MDA/mg of protein); GST, glutathione S transferase (in nmol of 1-chloro-2,4-dinitrobenzene conjugation/minute/mg of protein);SOD, superoxide dismutase (in units/mg of protein) and Nitrite level is in mmol/mg of protein. Analysis of repeated measurements were done by one-way analysis of variances with Tukey's test for multiple comparisons

Effect of EGCG on brain lipid peroxidation, nitrite and GSH levels and GST, SOD and catalase activities in colchicine-injected rats

Administration of ACSF Intracerebroventricularly did not affect profoundly on brain lipid peroxidation, nitrite concentration and GSH, GST, SOD, and catalase levels significantly in comparison to sham-operated rats. Colchicine administration centrally significantly elevated lipid peroxidation and the nitrite concentration and lowered reduced GSH, GST, SOD, and catalase levels in comparison to ACSF-injected

Treatment (mg)	ITL	1 st RL	2 nd RL
sham	70.05-3.25	30.25-4.25	25.0-4.08
ACSF	72.68-3.5	20.25-3.4	18.3-2.52
EGCG (40)	80.5-1.25	75.25-3.25	78.55-3.25
EGCG (80)	62.35-2.25	20.35-2.5	20.55-4.5
EGCG (40) _p col	65.25-1.25	52.55-3.5	45.26-3.5
EGCG (80) _p col	62.55-3.6	32.2-2.5	28.65-3.8

Table 1: Effect of EGCG (40 and 80 mg=kg, p.o.) on Memory Performance in the elevated plus maze paradigm in intracerebroventricular colchicine-injected rats. Mean transfer latency (seconds, s)

EGCG IN COLCHICINE-INDUCED TOXICITY			
Treatment (mg=kg)	Mean latency (seconds)		
	ITL	1 st RL	2 nd RL
sham	47.5 \pm 2.39	13.25 \pm 2.5	11.5 \pm 2.26
ACSF	53.33 \pm 2.6	13.5 \pm 2.5	11.2 \pm 2.49
COL	77.0 \pm 3.5 ^a	75.0 \pm 3.58 ^a	65.5 \pm 3.65 ^a
EGCG (40)	56.25 \pm 2.51	17.2 \pm 2.65	15.2 \pm 2.7
EGCG (80)	52.5 \pm 2.5	14.5 \pm 2.5	12.5 \pm 2.4
EGCG (40) _p col	62.6 \pm 2.87 ^b	45.0 \pm 2.58 ^b	35.76 \pm 1.8 ^b
EGCG (80) _p col	58.66 \pm 2.45 ^{bc}	32.0 \pm 2.5 ^{bc}	25.5 \pm 2.1 ^{bc}

Table 2: Effect of EGCG (40 and 80 mg=kg, p.o.) on the spatial navigation task in intracerebroventricular colchicine-injected rats.

rats. However, chronic EGCG (40 and 80 mg/kg, p.o.) administration significantly attenuated the rise in lipid peroxidation and nitrite Concentration and depletion of GSH (Table 3) and restored the levels of GST SOD and catalase (Table 3). However, treatment with EGCG (40 and 80 mg/kg, p.o.) did not produce any significant effect on these parameters compared to ACSF-injected rats.

Effect of EGCG on brain AChE levels in colchicine-injected rats

Administration of ACSF intra-cerebroventricularly did not show any significant effect on brain AChE levels in comparison to sham-operated rats. On the contrary central colchicine administration significantly enhanced AChE activity in comparison to the ACSF-injected rats. However chronic oral treatment with EGCG (dosage 40 mg/kg, 80 mg/kg) significantly lowered AChE activity as compared to colchicine treated animals.

Discussion

Alzheimer's disease (AD) is a neurodegenerative disorder. Early symptoms of AD are often mistakenly thought to be 'age-related' disease or consequences of stress [14]. As the disease advances other symptoms like confusion, irritability and aggression, mood swings, language problem, and long-term memory loss etc. happens [14,15]. Though the actual cause of the disease is still not known different competing hypotheses are proposed. The oldest hypothesis is the cholinergic hypothesis [16]. The present study is mainly executed on the cholinergic hypothesis that states the depletion in availability of acetylcholine which is one of the main neurotransmitter responsible for transmitting neuron signal in brain. The reduction is due to the hyperactivity of acetyl cholinesterase (AChE) which is an enzyme found in brain breaks acetylcholine into choline and acetate, [16]. In this present study intra cerebroventricularly administered colchicine caused significant memory deterioration which can be turned back by chronic EGCG treatment. In the Morris water maze test the asset was done by identification for the visual platform as a non-spatial version, which helps to measure the reference memory, and the retrieval was done by searching for the same hidden platform in the target quadrant, which indicates the spatial memory. Earlier experimental reports suggest that intra-cerebroventricular colchicine administration originates more production of free radical formation and that causes oxidative stress leads to cognitive impairment [17]. In this present study, chronic administration of EGCG helps to scavenge colchicine-induced reactive oxygen free radical damage. In the present study EGCG has significant effect in colchicine produced oxidative damages. EGCG significantly lowered the rise in lipid peroxidation and nitrite levels and decreased the exhaustion of GSH levels and SOD, catalase, and GST activities, which proves its formidable antioxidant-like effect. EGCG has been effective to block the lipid peroxidation caused by H₂O₂ [18]. Glutathione (GSH) which is an endogenous antioxidant usually found in its reduced

form within the cells. It has been seen that glutathione reacts with the oxygen free radicals and inhibit the generation of hydroxyl free radical [18]. The decrease of GSH concentration level and GST biochemical activity in colchicine-treated rats prove that there was an increased accumulation of free radicals and that activity of the glutathione system was suppressed the oxidative stress. EGCG administration can be effective to restore the depleted GSH level and GST activity. This may give an explanation of the fact that EGCG pre-treatment and post-treatment in colchicine-treated rats produce a noteworthy increase in the catalase and SOD activities in cells. Colchicine also causes an increase in generation of analytical nitric oxide synthase which causes an increase in nitric oxide levels, which acts as a forerunner for the peroxynitrite free radical [19]. Over production of nitric oxide level is neurotoxic to cholinergic neuronal cells [20]. This depicts that how intracerebroventricularly administered colchicine causes a significant rise in the nitrite levels in the brain and how EGCG treatment was capable to decline the nitrite levels. Thus, the overfed beneficial effect of EGCG might be due to its inhibitory effect on the nitric oxide synthase enzyme or skiving nitric oxide free radicals [20]. The concentrations of various neurotransmitters like dopamine, acetylcholine, and noradrenaline alter drastically during AD (Figure 1).

Cholinergic system has an important process for storage and healing of memory and its annihilation causes cerebral deficit [21]. Intra-cerebroventricular administration of colchicine promotes necrosis of cerebellar granule cells, olfactory bulb neurons, and forebrain cholinergic neurons [22]. Colchicine also responsible for the cholinotoxicity, which is responsible for reduced acetylcholine transferase activity [23]. These proclamation elaborates administration of colchicin centrally causes oxidative stress, which results cognitive impairment. This explains that administration of colchicine centrally causes cognitive dysfunction and oxidative stress and inhibited acetylcholine turnover. The mechanisms

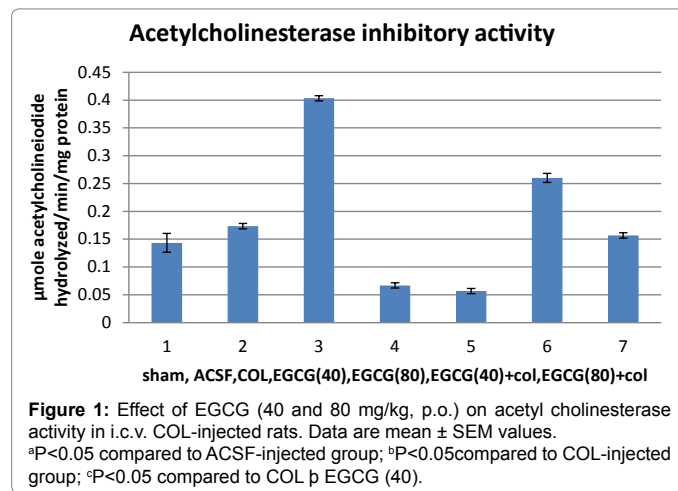


Figure 1: Effect of EGCG (40 and 80 mg/kg, p.o.) on acetyl cholinesterase activity in i.c.v. COL-injected rats. Data are mean ± SEM values. ^aP<0.05 compared to ACSF-injected group; ^bP<0.05 compared to COL-injected group; ^cP<0.05 compared to COL p EGCG (40).

Treatment (mg=kg)	Percentage of control					
	MDA	Nitrite	GSH	CAT	SOD	GST
SHAM	100 ± 5.2	100 ± 4.5	100 ± 5.6	100 ± 3.9	100 ± 7.8	100 ± 6.3
ACSF	109.0 ± 6.7	106.74 ± 3.9	100.54 ± 3.5	93.86 ± 3.5	96.87 ± 5.4	105.72 ± 3.2
COL	295.45 ± 13.1 ^a	285.74 ± 9.4 ^a	24.48 ± 5.2 ^a	20.87 ± 4.8 ^a	19.35 ± 5.5 ^a	26.5 ± 5.8 ^a
EGCG (40)	110.3 ± 8.5	113.3 ± 5.6	85.86 ± 6.4	87.52 ± 4.7	99.15 ± 3.7	95.85 ± 4.8
EGCG (80)	112.7 ± 6.08	115.67 ± 4.5	90.27 ± 5.4	93.2 ± 3.8	99.57 ± 4.6	99.18 ± 5.4
EGCG (40)+COL	198.25 ± 11.8 ^b	201.15 ± 8 ^b	52.25 ± 4.8 ^b	42.85 ± 5.2 ^b	34.95 ± 5.1 ^b	38.85 ± 6.4 ^b
EGCG (80)+COL	165.92 ± 14.3 ^{bc}	163.08 ± 7.6 ^{bc}	73.1 ± 3.5 ^{bc}	64.98 ± 4.9 ^{bc}	59.72 ± 5.3 ^{bc}	65.56 ± 6.2 ^{bc}

Table 3: Effect of EGCG on brain lipid peroxidation, nitrite, and GSH levels and GST, SOD and catalase activities in colchicine treated rats.

by which colchicine creates the depletion of the cholinergic neurons are reduction of fast axoplasmic flow and direct toxicological effects to the cholinergic neurons [24].

Chronic EGCG administration reduces the amplitude of AChE concentration after intra-cerebroventricular administration of colchicine which proves its importance in inhibition of AD pathologic process. It has been observed that AChE hyperactivity increase in rat brain cells by several free oxygen radical generation [25]. In our present experiment, colchicine induced a drastic increase in AChE activity that probably the reason for causation of cognitive deficits. The present experimental study depicts that the free radical scavenging and antioxidant properties of EGCG surely have a significant role against the reduction of AChE which is involved in the cholinergic system in cognitive dysfunction [26-30].

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