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Research Article

Ameliorative Treatment with Ellagic Acid in Scopolamine Induced Alzheimer's Type Memory and Cognitive Dysfunctions in Rats

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Abstract

Objective: To determine neuroprotective effects of Ellagic acid (EA) as a preventive herbal drug to impede cholinergic dysfunctions and oxidative stress in Alzheimer's disease (AD) in scopolamine induced Alzheimer's type dementia in rats.

Methodology: Alzheimer's type dementia was induced by intraperitoneal injection of scopolamine (0.7 mg/kg, i.p.) to rats for period of 7 days. EA (25 mg/kg or 50 mg/kg, p.o.) or Donepezil (0.5 mg/kg, p.o.) alone was treated for 6 days and then scopolamine (0.7 mg/kg, i.p.) was administered together with EA or Donepezil for another 7 days. Memory-related behavioral parameters were evaluated using the elevated plus maze (EPM) once a day for 2 consecutive days and Morris water maze (MWM) once a day for 5 consecutive days. At the end of protocol schedule i.e day 14, biochemical parameters were estimated. AChE, MDA, GSH, catalase and SOD to evaluate the neuroprotective action of EA via AChE inhibition and antioxidant activity.

Result: Scopolamine treatment increased the transfer latency in EPM, escape latency time and shortened time spent in the target quadrant in MWM; these effects were reversed by EA. Scopolamine-mediated changes in malondialdehyde (MDA) and AChE activity were significantly attenuated by EA in rats. Recovery of antioxidant capacities, including reduced glutathione (GSH) content, and the activities of SOD and catalase was also evident in EA treated rats.

Conclusion: The present findings sufficiently encourage that EA has a preventive properties. Although EA was found to be less effective than Donepezil, but few modification in pharmaceutical properties it can be an efficient phytochemical for Alzheimer type dementia. The EA can be used to prevent cholinergic dysfunctions and oxidative stress associated with Alzheimer type dementia.

Keywords: Neuroinflammation; Oxidative stress; Acetylcholinesterase; Polyphenols

Introduction

Alzheimer's disease (AD) is a severe neurodegenerative disorder that gradually results in loss of memory and impairment of cognitive functions in the elderly [1,2].

Many naturally occurring compounds have been proposed as potential therapies to slow or prevent the progression of AD, mostly by acting as antioxidants [3-5], but also with some direct anti-amyloid actions [6-8]. Recent studies have suggested the positive effects of dietary antioxidants as an aid in potentially reducing somatic cell and neuronal damage by free radicals [3,9,10]. The beneficial health effects of plant-derived products have been largely attributed to polyphenolic compounds, as well as vitamins, minerals and dietary fibers [3,4,11].

Ellagic acid (EA), a non flavonoid polyphenol, plays an essential role in explaining the pharmacological properties of fruits, food and beverages which exhibit this phyto-constituent [12-14]. EA has been well proven to contain anti-oxidant [15-17], anti-inflammatory [18,19], anti-proliferative [20-22], antidiabetic [23,24] and cardioprotective [25,26] properties.

Neuroprotection can be a property of EA as it prevents both neuro-oxidation and neuroinflammation [27-30]. Moreover, in *in-vitro* studies it was observed that EA inhibits β-secretase (BACE1), thus inhibiting Aβ-fibrillation and decrease AChE activity [31-33]. Recent studies suggested that glucose metabolism is affected during AD [34]. The EA stimulated GLUT4 translocation primary factor responsible for insulin induced glucose uptake and maintain glucose homeostasis [35,36]. The EA also shows modulation of monoaminergic system (serotonergic and noradrenergic systems) and GABAnergic system [37,38]. Cognitive impairment in AD patients correlates with disturbance in various neurotransmitters, as the ratio of excitatory-inhibitory neurotransmitter level disturbs, cytotoxic damage to neurons and glia occurs and norepinephrine and

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serotonin levels declined [39-43]. Further, Gamma-amino butyric acid (GABA) increases the formation of soluble receptor for advanced glycation end products (RAGE) and decreases the levels of full-length RAGE, lowering the Aβ uptake and inflammatory mediated reactions [44,45].

Scopolamine, an anti-muscarinic agent, competitively antagonizes the effect of acetylcholine on the muscarinic receptors by occupying postsynaptic receptor sites with high affinity and increases AChE activity in the cortex and hippocampus [46-50]. Scopolamine diminish cerebral blood flow due to cholinergic hypofunction [51,52]. Scopolamine additionally triggers ROS, inducing free radical injury and an increase in a scopolamine-treated group brain MDA levels and deterioration in antioxidant status [53-55]. Scopolamine induces neuro-inflammation by promoting high level of oxidative stress and pro inflammatory cytokines in the hippocampus [56-58]. Scopolamine is proven to increase levels of APP and Tau. Administration of scopolamine led to marked histopathological alterations in the cerebral cortex, including neuronal degeneration [59,60]. Scopolamine administration has been used both in healthy human volunteers and in animals as a model of dementia to determine the effectiveness of potential new therapeutic agents for Alzheimer's disease [61-66] (Figure 1).

Donepezil is a well established drug for clinical treatment and scopolamine induced Alzheimer type dementia. Donepezil, a reversible inhibitor of AChE, is neuroprotective due to not only activation of cholinergic transmission but also by reducing the amount of the toxic form of amyloid β fibrils [67-71]. Donepezil ameliorated the scopolamine induced memory impairment by reducing AChE activity and oxidative stress and restoring cerebral circulation [72-74]. With this background, EA might show neuroprotection via inhibiting neuronal dysfunctions. This research was an attempt to investigate the neuroprotective effect of EA, potential of doses for the prevention of Alzheimer's disease.

Material and Method

Chemicals

EA was purchased from Yucca Interprises, Mumbai, India and suspended in saline solution. Scopolamine hydrochloride was purchased from Sigma–Aldrich, St, Louis, MO, USA. Donepezil was obtained from Ranbaxy Pvt. Limited, Mumbai, India and both scopolamine and doenpezil were dissolved in saline solution. All reagents used in this study were of analytical grade and high purity.

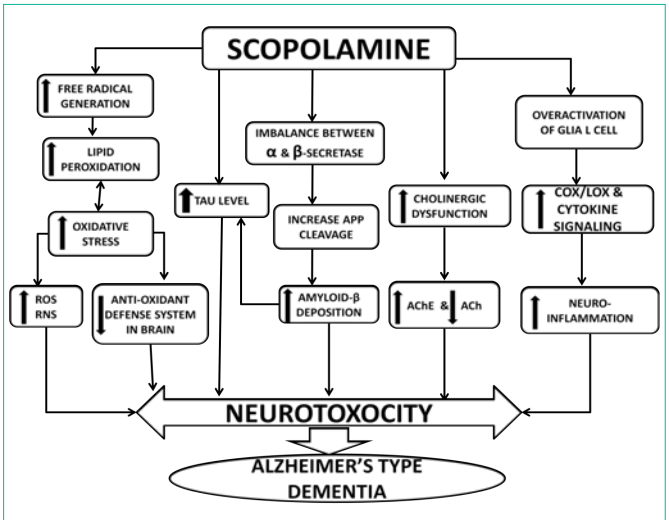

Figure 1: Scopolamine induced experimental model of Alzheimer's type dementia.

Animals

Male Wistar rats (weighing 220-250 g, aged 8-10 months) obtained from the Animal House of the Institute were employed in the studies. The animals were kept in polyacrylic cages with wire mesh top and soft bedding. They were kept under standard husbandry conditions of 12h reverse light cycle with food and water *ad libitum*, maintained at temperature 22±2°C. The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India (RITS/IAEC/2013/01/01). Animals were acclimatized to laboratory conditions prior to experimentation.

Drug administration

EA was administered by oral (p.o.) route in dose of 25 mg/kg and 50 mg/kg. Scopolamine was administered by intraperitoneal (i.p.) route in dose of 0.7 mg/kg. Donepezil was administered in dose of 0.5 mg/kg, p.o.

Six groups (each group consist six rats) were employed in the present study. (i) Group1-Normal Control (ii) Group2-Scopolamine Control (0.7mg/kg,i.p.) (iii) Group3-EA Perse (50mg/kg, p.o.) 25mg/kg, p.o. + Scopolamine (0.7mg/kg, i.p.) (vi) Group6-EA 50mg/kg, p.o. + Scopolamine (0.7mg/kg, i.p.). After a 5-day habituation period, rats were given EA (25 or 50 mg/kg, p.o.) and Donepezil (0.5 mg/kg, p.o.) for total of 13 days. EA or Donepezil alone was treated for 6 days and then scopolamine (0.7 mg/kg, i.p.) was administered together with EA for another 7 days. Rats underwent locomotor activity (LMA) for 2 days i.e. 6th day and 13th day, MWM test for 5 days i.e. 7th day to 11th day. The day after completion of Morris water maze (MWM), the elevated plus maze (EPM) was conducted for 2 days i.e. 12th to 13th day. The day after EPM, the rats were sacrificed and biochemical parameters were estimated (Figure 2).

Elevated plus maze

Elevated plus maze (EPM) served as the behavioral model (where in the stimulus existed outside the body) to evaluate learning and memory in rats. It consists of two opened arms (50cm*10cm) and two covered arms (50cm*40cm*10cm). The arms were extended from central platform (10cm*10cm), and the maze was kept elevated to a height of 50cm from the floor. The EPM was conducted for 2 days i.e. 12th to 13th day of protocol schedule. Each animal was kept at the end of an open arm, facing away from the central platform on 12th day. Transfer Latency (TL), which was taken as the time taken by the animal to move into any one of the covered arms with all its four legs, recorded on 12th day i.e. acquisition trial [75]. If the rat did not enter into one of the covered arms within 120s then it was gently pushed into one of the two covered arms and the TL was assigned as 120s. The rats were allowed to explore the maze for 10s and then were returned to its home cage. TL was again examined 24hr after the first trial on 13th day of protocol schedule i.e. retention latency.

Spatial navigation task in Morris water maze

Morris water maze employed in the present study was a model to evaluate spatial learning and memory. Escape from water itself acts as motivation and eliminates the use of other motivational stimuli such as food and water deprivation. Water provides uniform environment and eliminates interference due to olfactory clues [76]. Animals were trained to swim to a platform in a circular pool (180cm diameter*60cm) located in a sound attenuated dark test room. The pool was filled with water (28±2^{O}C) to a depth of 40cm. A movable circular platform, 9cm in diameter and mounted on a column, was placed in the pool 2 cm below the water level for escape latency time (ELT), while during time spent in the target quadrant (TSTQ) the platform was removed. Four equally spaced locations around the edge of the pool (N, S, E, and W) were used to divide the pool into 4 quadrants and one of them is used as start point, which was same during all trials. The pool was filled with opaque water to prevent visibility of the platform in the pool. The escape platform was placed in the middle of one of the random quadrants of the pool and kept in the same position throughout the experiments. Animals received a training session consisting of day 7 to 10 and ELT was recorded. ELT defined as the time taken by the animal to locate the hidden platform. ELT was noted as an index of learning. Each animal was subjected to single trial for four consecutive days (starting form 7th day of EA administration to 10th day), during which they were allowed to escape on the hidden platform and to remain there for 20 s. If the rats failed to find the platform within 120 s, it was guided gently onto the platform and allowed to remain there for 20 s.

On fifth day (i.e., 11th day of EA administration) the platform was removed. Rats were placed in water maze and allowed to explore the maze for 120 s. Time spent in three quadrants, that is, Q1, Q2 and Q3 was recorded and TSTQ in search of the missing platform provided as an index of retrieval. Care was taken not to disturb the relative location of water maze with respect to other objects in the laboratory.

Assessment of locomotor activity

Gross behavioral activity was assessed by digital actophotometer on 6th day and 13th day of protocol schedule to rule out any interference in locomotor activity by drugs which may affect the process of learning and memory, in before and after of MWM task. Each animal was observed over a period of 5 min in a square (30 cm) closed arena equipped with infrared light-sensitive photocells and values expressed as counts per 5 min [77]. The beams in the actophotometer, cut by the animal, were taken as measure of movements. The apparatus was placed in a darkened, sound-attenuated and ventilated testing room.

Preparation of brain homogenate

On 14th day of protocol schedule, Animals were sacrificed by decapitation, brains removed and rinsed with ice cold isotonic saline solution. Brain tissue samples were then homogenized with 10 times (w/v) ice cold 0.1M phosphate buffer (pH 7.4). The homogenate was centrifuged at 10,000 x g for 15min, supernatant was separated and aliquots were used for biochemical estimations [77].

Protein estimation

The protein content was measured by using Agappe protein estimation kit (Biuret method).

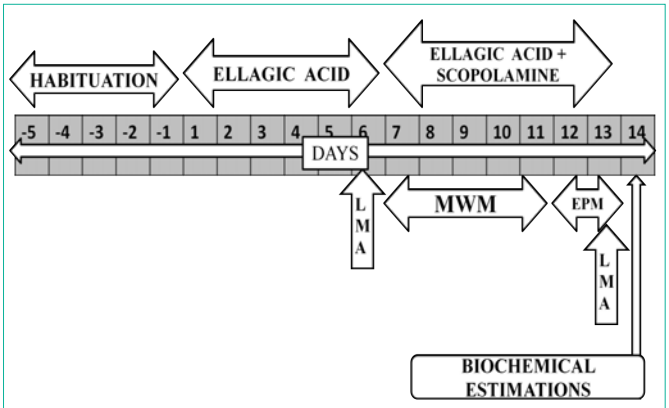

Figure 2: Protocol schedule to determine the neuroprotective effect of Ellagic Acid in scopolamine induced Alzheimer' type memory and cognitive dysfunctions.

Estimation of Acetylcholinesterase levels

The quantitative measurement of AChE activity in brain was performed according to the method described by Ellman et al. (1961) [78]. The enzymatic activity in the supernatant was expressed as nmol per mg protein.

Estimation of malondialdehyde

The quantitative measurement of MDA– end product of lipid peroxidation-in brain homogenate was performed according to the method of Wills (1966) [79]. The concentration of MDA was expressed as nmol per mg protein.

Estimation of reduced glutathione

GSH in brain was estimated according to the method described by Ellman et al. (1959) [80]. The concentration of glutathione in the supernatant expressed as µmol per mg protein.

Estimation of superoxide dismutase activity

SOD activity was measured according to the method described by Misra and Frodvich (1972) [81]. The activity of SOD was expressed as % activity.

Estimation of Catalase activity

Catalase activity was measured by the method of Aebi (1974) [82]. The activity of catalase was expressed as % activity.

Statistical analysis

All the results and data were expressed as mean ± standard deviation. Data was analyzed using two way ANOVA followed by post hoc test Bonferroni and one way ANOVA followed by post hoc test Tukey's multi-comparison test. $P<0.05$ was considered as statistically significant.

Results

Effect of Ellagic acid on rats in elevated plus maze

On 12th day of protocol schedule, acquisition latency was recorded. Retention was observed as transfer latency (TL) on 13th day to evaluate learning and memory in rats using EPM. On 12th and 13th day Scopolamine administered rats showed remarkable increase ($p<0.001$) (113±9.3 and 106.5±11.1 sec) in TL, when compared to normal (64±4.2 and 36.833±6.7 sec) and EA *perse* rats (63.333±10.3

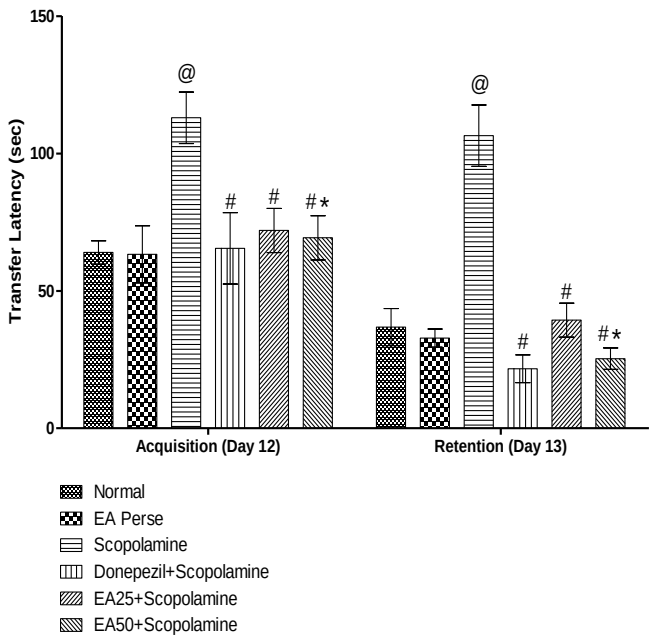

Figure 3: Effect of Ellagic acid on Transfer latency of rats using Elevated Plus Maze.
Values were mean ± SD, @ p<0.05 as compared to Normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine

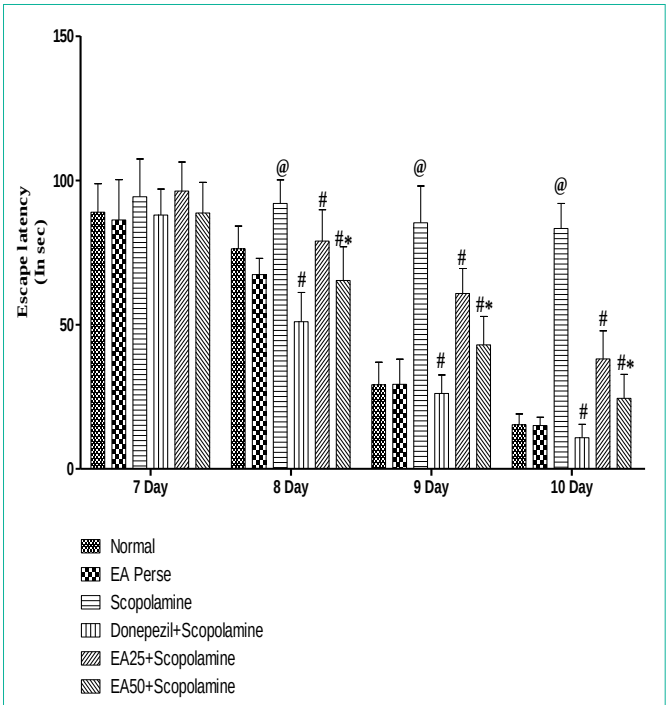

Figure 4: Effect of Ellagic acid on Escape latency time of rats on 7th day to 10th day using Morris Water Maze.
Values were mean ± SD, @ p<0.05 as compared to Normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine

and 32.833±3.3 sec). During experiment, EA *perse* administration did not reveal any change (p>0.05), when compared to normal rats in TL. Donepezil, a well established standard drug for AD considerably decrease (p<0.001) (65.5±13.0 and 21.666±5.0 sec) TL, when compared to Scopolamine administered rats and reversed the memory impairment induced by Scopolamine. Administration of EA at the dose of 25 mg/kg, *p.o.* exhibit notable decrease (p<0.001) (72.00±8.0 and 39.333±6.1 sec) in TL, when compared to Scopolamine treated rats. EA (50 mg/kg, *p.o.*) administration also decrease (p<0.001) (69.333±8.0 and 25.333±3.8 sec) TL, when compared to Scopolamine administered rats and there were significant variation (p<0.05) was found in between doses of EA 25 & 50 mg/kg, *p.o.* indicating improved retention memory. Donepezil administered rats did not reveal any change (p>0.05) in TL, when compared to EA (25 or 50 mg/kg, *p.o.*) administered rats (Figure 3).

Effect of Ellagic acid on rats in spatial navigation task using Morris water maze

On 7th to 10th day of 14 day protocol schedule, escape latency time (ELT) was observed. On 7th day, there were no significant changes (p>0.05) observed in Scopolamine (94.33±13.1 sec) treated rats, when compared to normal (89±9.8 sec) and EA *perse* treated (86.33±13.9 sec) rats. EA *perse* administration did not show any significant change (p>0.05) when compared to normal rats. Moreover, Donepezil treated rats did not show any considerable changes (p>0.05) (88±9.0 sec), when compared to Scopolamine and EA (25 or 50 mg/kg, *p.o.*) administered rats. In the treatment groups, administration of EA did not confirm notable changes (p>0.05) (96.33±10.0; 88.66±10.6 sec) in ELT at 25 and 50 mg/kg, *p.o.* when compared to Scopolamine treated rats. There were no changes (p>0.05) found in ELT between treatment doses of EA 25 & 50 mg/kg, *p.o.*

Comparison data of 8th day, 9th day and 10th day ELT in MWM, showed that Scopolamine administered rats manifest remarkable increase (p<0.05, p<0.001 and p<0.001) (92±8.1, 85.33±12.7 and 83.33±8.6 sec) in ELT, when compared to normal (76.33±7.8, 29.16±7.8 and 15.33±3.7 sec) and EA *perse* (67.33±5.6, 29.33±8.7 and 15±2.8 sec) rats. EA *perse* administration did not show any significant difference (p>0.05), when compared to normal rats during ELT. Donepezil administered rats significantly decreased (p<0.001, p<0.001 and p<0.001) (51±10.1, 26.16±6.4 and 10.83±4.6 sec) ELT when compared to Scopolamine administered rats. EA at 25 mg/kg, *p.o.* proved remarkable decreased (p>0.05, p<0.001 and p<0.001) (79±10.8, 60.83±8.6 and 38.16±9.7 sec) in the ELT, when compared to Scopolamine administered rats. EA at the dose 50 mg/kg, *p.o.* significantly decreased (65.33±11.7, 43±9.8 and 24.5±8.3 sec) the ELT, when compared to Scopolamine (p<0.001, p<0.001 and p<0.001) and EA 25 mg/kg, *p.o.* treated rats (p<0.05, p<0.01 and p<0.05), indicating remarkable improvement in learning. Donepezil administered rats more significantly decreased ELT when compared to EA 25 mg/kg, *p.o.* (p<0.001, p<0.001 and p<0.001) and 50 mg/kg, *p.o.* administered rats (p<0.005, p<0.001 and p<0.005) (Figure 4).

On 11th day of protocol schedule TSTQ was performed. Time spent in target quadrant (TSTQ) in search of missing platform provided as an index of retrieval. Scopolamine treated rats showed remarkable decrease (p<0.001) (7.667±3.0 sec) in TSTQ when compared to normal (45.17±8.0 sec) and EA *perse* treated (43.83±6.2 sec) rats. In *perse* group of EA, there were no changes (p>0.05) during TSTQ when compared to normal group. Further, Donepezil administered rats improved (p<0.001) (46.17±5.3 sec) memory when compared

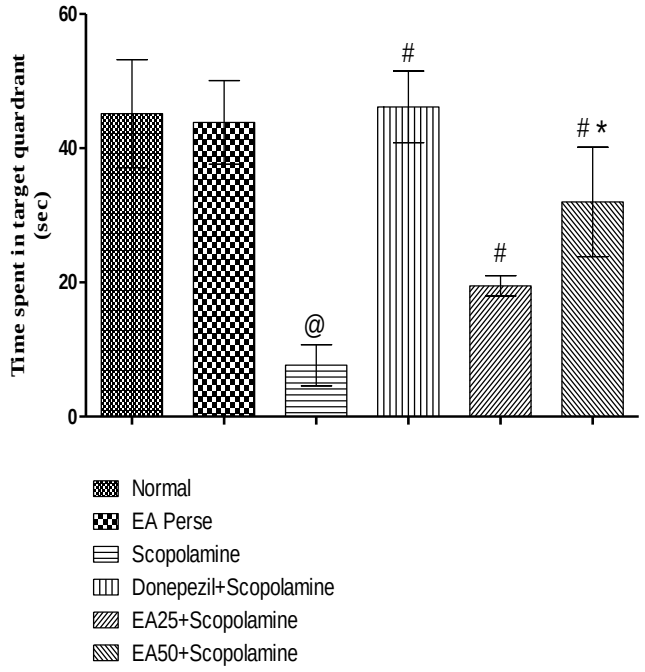

Figure 5: Effect of Ellagic acid on time spent in target quadrant of rats using Morris Water Maze.
Values were mean ± SD, @ p<0.05 as compared to Normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine.

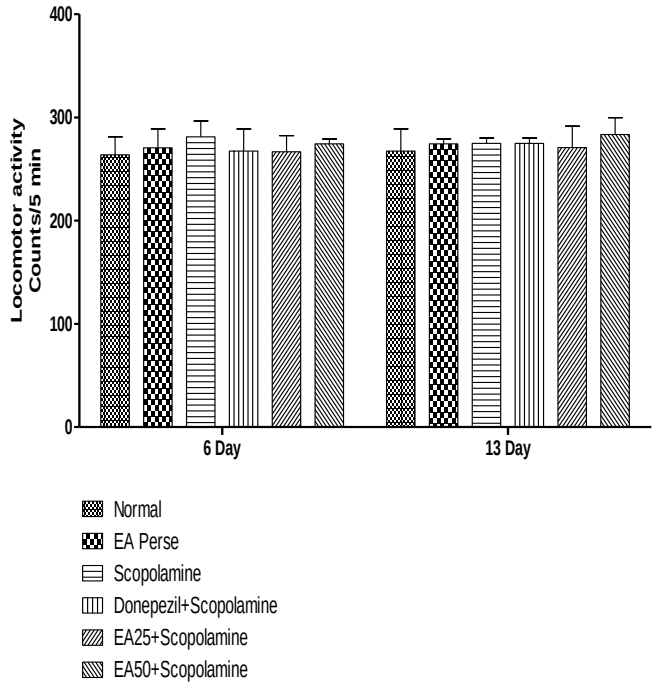

Figure 6: Effect of Ellagic acid on locomotor activity of rats using actophotometer.
Values were mean ± SD

to Scopolamine treated rats. EA (25 mg/kg, *p.o.*) administration showed remarkable increase (p<0.05) (19.50±1.517 sec) in TSTQ when compared to Scopolamine treated rats. EA (50 mg/kg, *p.o.*) administration indicated improvement (p<0.001) (32.00±8.1 sec) in memory function when compared with Scopolamine administered rats. Moreover, markedly difference (p<0.05) was also observed in between treatment doses of EA. Donepezil administered rats showed more significant improved memory when compared to EA 25 mg/kg, *p.o.* (p<0.01) and 50 mg/kg, *p.o.* administered rats (p<0.05) (Figure 5).

Effect of Ellagic acid on rats in locomotor activity

On 6th day and 13th day of protocol schedule, locomotor activity was observed to rule out any interference in locomotion by treatment drug. Scopolamine employed rats did not reveal any significant changes (p>0.05) (281.333±15.3 and 274.833±5.3) in locomotor activity when compared to normal (263.833±17.4 and 274.5±21.3) and EA *perse* (270.666±18.2 and 274.5±4.7) rats. EA *perse* administration also did not show any considerable change (p>0.05) in locomotor activity at 50 mg/kg, *p.o.* when compared to normal rats. Donepezil treated also showed insignificant changes (p>0.05) (267.5±21.3 and 274.833±5.3) when compared to Scopolamine and EA (25 or 50 mg/kg, p.o.) treated rats. EA 25 mg/kg, *p.o.* (266.833±15.4 and 270.833±20.6) and 50 mg/kg, *p.o.* (274.5±4.764 and 283.5±16.208) administration did not showed any notable changes (p>0.05) in locomotor activity of rats when compared to Scopolamine treated rats, indicating there were no effect on locomotor activity (Figure 6).

Effect of Ellagic acid on acetylcholinesterase levels

Prolongation of availability of acetylcholine has been used to enhancing cholinergic function. This prolongation may be achieved by inhibiting AChE. Scopolamine administered rats significantly increased (p<0.001) (415.0±19.6) the AChE level when compared to normal (136.8±4.9) and EA *perse* (137.2±4.1) rats. EA *perse* administration did not show any appreciable changes (p>0.05) in AChE level at the dose of 50 mg/kg, *p.o.* when compared to normal rats. Donepezil treated rats appreciably decreased (p<0.001) (231.0±7.6) the AChE level in contrast to Scopolamine administered rats. EA (25 mg/kg, *p.o.*) showed remarkably diminished (p<0.001) the AChE level (360.8±15.9) when compared to Scopolamine rats. Administration of EA (50 mg/kg, *p.o.*) significantly reduced (p<0.001) (311.7±17.6) the AChE level when compared to Scopolamine administered rats. Moreover, there were expressive distinction (p<0.001) was present in between treatment doses of EA. In Donepezil administered rats, AChE level was more significantly decreased when compared to EA 25 mg/kg, *p.o.* (p<0.01) and 50 mg/kg, *p.o.* administered rats (p<0.01) (Figure 7).

Effect of Ellagic acid on malondialdehyde levels

MDA is an indicator of lipid peroxidation. Scopolamine administration increased (p<0.001) (42.50±3.0) the MDA level when compared to normal (19.88±0.9) and EA *perse* (19.15±1.8) rats. Further, EA *perse* administration did not show any considerable changes (p>0.05) in MDA levels when compared to normal rats. Donepezil appreciably decreased (p<0.001) (23.12±0.5) the MDA level when compared to Scopolamine administered rats. EA (25 mg/kg, *p.o.*) administration showed remarkably decrease (p<0.001) (33.57±3.3) in MDA level when compared to Scopolamine administered rats. EA administered rats at the dose of 50 mg/kg, *p.o* significantly decreased (27.97±2.0) in MDA level when compared to Scopolamine (p<0.001) and EA 25 mg/kg, *p.o.* treated rats (p<0.05).

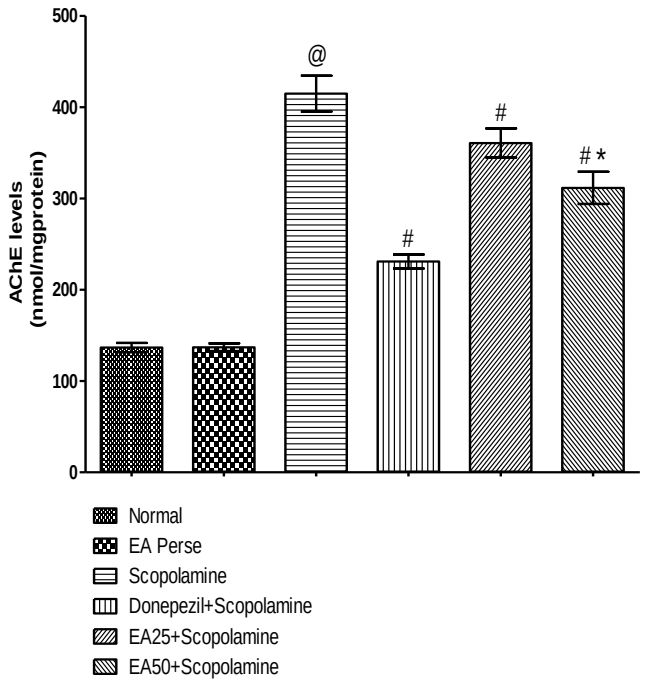

Figure 7: Effect of Ellagic acid on Acetylcholinesterase levels.
Values were mean ± SD, @ p<0.05 as compared to Normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine

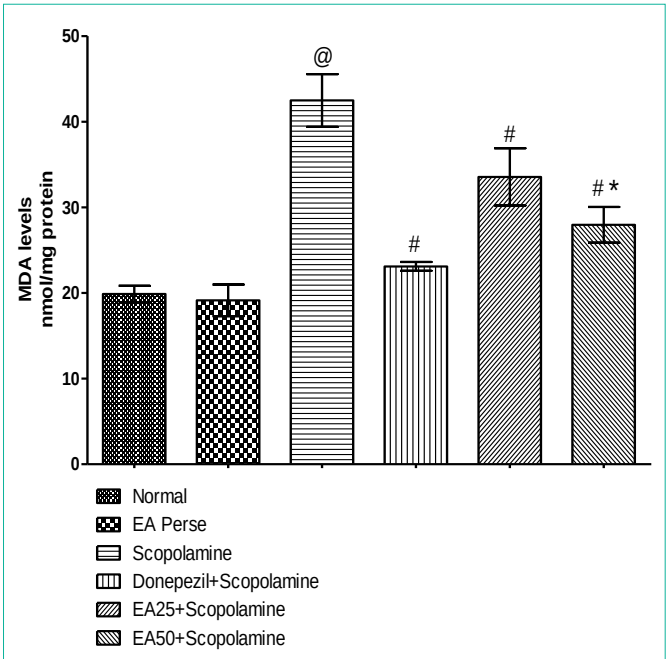

Figure 8: Effect of Ellagic acid on Malondialdehyde levels.
Values were mean ± SD, @ p<0.05 as compared to normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine

In Donepezil administered rats, MDA level was more significantly decreased when compared to EA 25 mg/kg, *p.o.* (p<0.01) and 50 mg/kg, *p.o.* administered rats (p<0.05) (Figure 8).

Effect of Ellagic acid on reduced glutathione levels

Reduced GSH is a marker of cellular antioxidant and provide protection against oxidative stress. Scopolamine governed rats remarkably decreased (p<0.001) (2.067±0.4) the GSH level when compared to normal (9.833±0.7) and EA *perse* treated (9.733±0.7) rats. EA *perse* administration did not show any considerable changes (p>0.05) in GSH levels in contrast to normal rats. Donepezil significantly increase (p<0.001) (7.767±0.3) the GSH levels when compared to Scopolamine treated rats. EA (25 mg/kg, *p.o.*) administration exhibited remarkable increase (p<0.001) (5.250±0.5) in GSH level when compared to Scopolamine treated rats. EA (50 mg/kg, *p.o.*) showed significantly increase (p<0.001) (6.317±0.3) in GSH level when compared to Scopolamine treated rats. Moreover, in between treatment doses of EA, there were significance difference (p<0.05) was present. In Donepezil administered rats, GSH level was more significantly increased when compared to EA 25 mg/kg, *p.o.* (p<0.01) and 50 mg/kg, *p.o.* administered rats (p<0.05) (Figure 9).

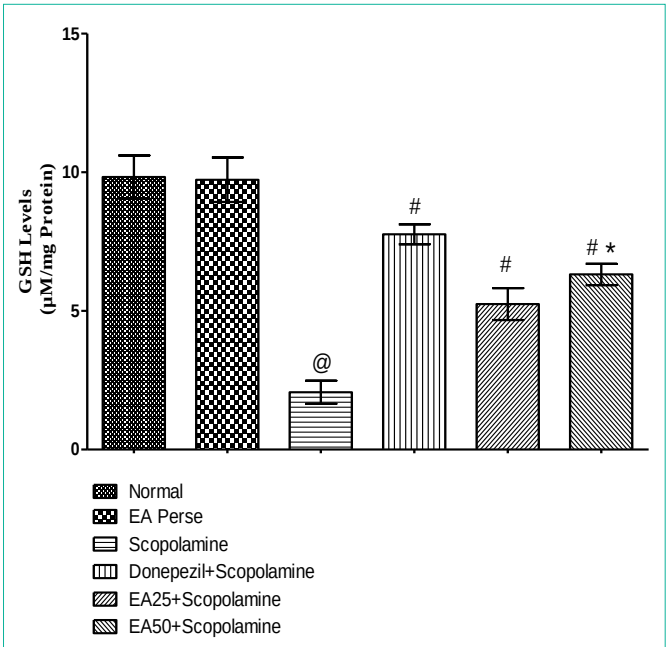

Figure 9: Effect of Ellagic acid on reduced Glutathione levels.
Values were mean ± SD, @ p<0.05 as compared to Normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine

Effect of Ellagic acid on superoxide dismutase activity

SOD is an antioxidant enzyme, which plays a key role in detoxifying superoxide anions. Scopolamine administered rats significantly decreased (p<0.001) (27.33±3.3) the SOD levels in brain homogenate when compared to normal (100.0±0.0) and EA *perse* (95.83±2.6) rats. EA *perse* administration did not reveal any considerable change (p>0.05) in SOD activity when compared to normal rats. Donepezil expressively increase (p<0.001) (82.00±3.9) SOD activity when compared to Scopolamine treated rats. In treatment group, EA (25 mg/kg, *p.o.*) administration showed remarkable increase (p<0.001) (59.17±8.0) in SOD activity when compared to Scopolamine treated rats. EA (50 mg/kg, *p.o.*) administration showed significantly increase (p<0.001) (71.33±4.0) in SOD activity when compared to Scopolamine treated rats and there were remarkably disparity (p<0.001) was found

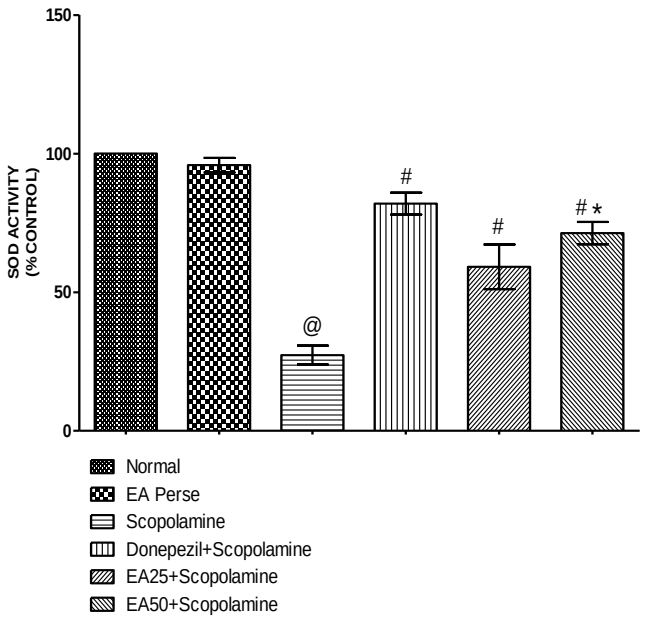

Figure 10: Effect of Ellagic acid on Superoxide dismutase activity.
Values were mean ± SD, @ p<0.05 as compared to Normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine

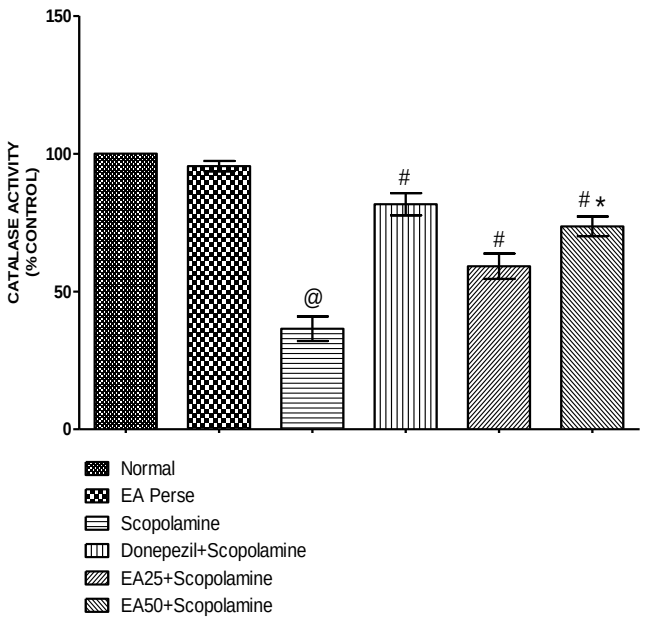

Figure 11: Effect of Ellagic acid on catalase activity.
Values were mean ± SD, @ p<0.05 as compared to normal & EA perse, # p<0.05 as compared to Scopolamine, * p<0.05 as compared to EA 25 + Scopolamine

in between EA treated groups. In Donepezil administered rats, SOD activity was more significantly increased when compared to EA 25 mg/kg, *p.o.* (p<0.01) and 50 mg/kg, *p.o.* administered rats (p<0.05) (Figure 10).

Effect of Ellagic acid on catalase activity

Catalase is also an antioxidant enzyme which has capability to detoxify oxidative free radicals. Scopolamine treated rats manifested remarkable decrease (p<0.001) (36.50±4.4) in catalase activity in brain homogenate when compared to normal (100.0±0.0) and EA *perse* treated (95.50±1.8) rats. EA *perse* administration did not show any considerable changes (p>0.05) in catalase activity when compared to normal rats. Donepezil significantly increase (p<0.001) (81.67±4.0) in catalase activity when compared to Scopolamine treated (36.50±4.4) rats. EA (25 mg/kg, *p.o.*) remarkably increased (p<0.001) (59.17±4.5) the catalase activity when compared to Scopolamine treated rats. EA (50 mg/kg, *p.o.*) administration exhibited significantly increase (p<0.001) (73.67±3.5) in catalase activity when compared to Scopolamine and EA 25 mg/kg, *p.o.* treated rats. In Donepezil administered rats, catalase activity was more significantly increased when compared to EA 25 mg/kg, *p.o.* (p<0.01) and 50 mg/kg, *p.o.* administered rats (p<0.05) (Figure 11).

Discussion

Clinically AD is characterized by an insidious degradation of memory, associated with functional decline and neurobehavioral disturbances [83]. Despite the availability of various treatment strategies, the severity and prevalence of this disease are not yet under control. Therefore, alternative and complementary medicines including herbal supplements, phytochemicals and extracts are being utilized in the management of AD [84-87]. The current hypothesis about the mechanisms by which neurons come into necrotic or apoptotic processes has led to believe that the therapeutic use of natural antioxidants may be beneficial in aging and neurodegenerative disorders [88,89].

In the present study, the effect of improving memory deficit of EA was evaluated using scopolamine induced Alzheimer's type dementia in rats.

Scopolamine induced Alzheimer's type dementia model has been widely used to provide a pharmacological model of memory dysfunction for screening potential cognition enhancing agents [47,55]. The cognitive-enhancing activity of EA on scopolamine induced memory impairments in rats was investigated by using behavioral and biochemical parameters.

During elevated plus maze, decrease in retention latency indicated improvement of memory and vice versa [90]. In EPM, it was shown that long term injected scopolamine also drastically increase in TL, demonstrating that the central cholinergic neuronal system plays an important role in learning acquisition. EA dose-dependently decreased TL prolongation induced by scopolamine. These results suggested that the neuroprotective effect of EA on scopolamine-induced memory impairment may be related to mediation of the cholinergic nervous system.

In order to confirm the effects of EA, MWM was used to test spatial learning in rats, where scopolamine treated rats were taking more time to reach at the hidden platform which shows memory impairments in this spatial task. EA treated rats impressively reduced the escape latency prolonged by scopolamine. Moreover, EA exhibited appreciable improvement of cognitive performance as indicated by significant decrease in ELT. It is important to notice that MWM test investigating spatial learning and memory has been used in detecting changes of the central cholinergic system [91,92]. If the

animals spent more time in target quadrant where the platform had previously been placed during the training session, this would indicate that the animals learned from prior experience with the MWM test, showing the spatial memory improvement. Scopolamine treated rats decreased TSTQ, on the other side EA treated rats expressively increased the TSTQ. Both the test doses viz., 25 mg/kg, *p.o.* and 50mg/kg, *p.o.* significantly attenuated these behavioral changes in rats with scopolamine induced memory and cognitive impairment.

Along with EPM and MWM, Locomotor activity also was investigated using actophotometer to determine any modulation in locomotor activity by treatment drugs which may affect locomotion in EPM and MWM. However no significant difference in locomotor activity was observed in any of the animal groups. These results suggest that there was not any sedative effect or interference in EPM and MWM locomotion. Therefore, transfer latency in EPM, escape latency and TSTQ in MWM were purely result of improved memory. Therefore, EA can repair the long-term memory in scopolamine-induced memory impairments.

To investigate the effect of EA on cholinergic function, that governs vital aspects of memory and other cognitive functions, brain acetylcholinesterase activity was measured in the present study. The hippocampus, amygdala and cortical regions of the brain are mainly involved in cholinergic transmission to monitor learning and memory processing and seem to be more prone to oxidative damage [93].

In this study, scopolamine was found to significantly elevate AChE activity, an enzyme responsible for degradation of Ach, which is in tune with earlier reports [58]. This increase in AChE activity was significantly restored dose dependently by EA. These observations suggest the modulation of cholinergic neurotransmission and/or prevention of cholinergic neuronal loss.

Recently, many studies have reported that memory impairments is associated to oxidative damage in the scopolamine-induced dementia in rats [55].

Lipid peroxidation is an important indicator of neurodegeneration of brain. Unlike other body membranes, neuronal membranes contain a very high percentage of long chain polyunsaturated fatty acids because they are used to construct complex structures needed for high rates of signal transfer. ROS are generated continuously in nervous tissues during normal metabolism and neuronal activity. The brain is subjected to free radical induced lipid peroxidation because it uses one-third of the inspired oxygen [94,95]. Lipids and proteins, the major structural and functional components of the cell membrane, are the target of oxidative modification by free radicals in neurodegenerative disorders [96]. Extensive evidence exists on lipid peroxidation and protein oxidation leading to loss of membrane integrity, an important factor in acceleration of aging and age-related neurodegenerative disorders. Oxidative stress has been implicated in the pathogenesis of AD in humans [97,98].

In the present study, scopolamine-injection in rats significantly induced peroxidation of lipids and proteins, and reduced antioxidant defense indicating increased oxidative stress. MDA is an end product of lipid peroxidation and is a measure of free radical generation and scopolamine injected rats showed extensive lipid peroxidation as evidenced by increase in MDA levels. In order to evaluate the effect of EA on lipid peroxidation in brain, MDA level was assessed. MDA level was remarkably increased by scopolamine and EA dose-dependently reduced MDA level, indicating the reduced peroxidation of lipids.

Lipid peroxidation may enhance due to depletion of GSH content in the brain, which is often considered as the first line of defense of the cell by this endogenous antioxidant against oxidative stress [96,99]. Evidence has been presented that the neuronal defense against H_2O_2, which is the most toxic molecule to the brain, is mediated primarily by the glutathione system [100,101]. GSH is a tri-peptide, an endogenous antioxidant found in all animal cells in variable amounts and is a very accurate indicator of oxidative stress [102]. Consistent with previous studies, in present study, scopolamine treatment significantly decreased the GSH levels. Further, co-administration of EA markedly improved GSH levels.

The most important antioxidant enzymes are SOD and catalase. SOD plays a key role in detoxifying superoxide anions, which otherwise damages the cell membranes and macromolecules. Scopolamine administration showed a significant reduction in enzymatic activity of SOD and catalase. On the other side, Catalase has the capability to detoxify H_2O_2 radicals. Release of H_2O_2 promotes the formation of numerous other oxidant species that greatly contributes for oxidative stress leading to the pathogenesis of AD [103]. Scopolamine treatment was found to be decreased SOD and catalase activities. Treatment of rats with EA significantly preserved the activities of SOD and catalase.

The results of the present study suggest that chronic administration of EA *perse* did not have any significant effect on cognitive performance in normal animals. But, EA treatment groups at the dose of 25 & 50 mg/kg, *p.o.* showed marked improvement in cognitive tasks when compared to scopolamine treated rats suggesting the significant role of ACh in long lasting administrated scopolamine mediated cognitive dysfunction. Reports also support that ACh is involved in memory acquisition and retention [104,105]. Moreover, scopolamine injection drastically impaired memory retention, resembling Alzheimer's dementia [50,55]. The same has been reported to be attenuated by pretreatment with herbal supplements and extracts, and phytochemicals [85,86].

The presented data in this study also suggests that EA possesses potent antioxidant activity by scavenging ROS and exerting a neuroprotective effect against oxidative damage induced by scopolamine. Predominant role of AChE inhibition, antioxidant activity reveal an important contributory factor to the beneficial effects of EA against dementia. Higher dose of Ellagic acid i.e. 50 mg/kg, *p.o.* was found more neuroprotective in all behavioral and biochemical evaluations. At lastly, the neuroprotective effects of EA might result from the regulation of AChE and the anti-oxidative defense system. These results suggest that EA can be used as a preventive herbal drug to impede cholinergic dysfunctions and oxidative stress in AD.

Conclusion

It was concluded that administration of scopolamine could cause Alzheimer's type dementia via increase AChE levels and oxidative stress. Scopolamine mediated Alzheimer's type dementia is mainly associated with cognitive and memory impairments in behavioral models. On the basis of this study, the major bio-markers

of Alzheimer's disease like amyloid beta, inflammatory cytokines and histopathological changes can be further evaluated according to current protocol schedule to confirm and justify the strong evidence of Ellagic acid in long term injected scopolamine mediated dementia. Ellagic acid diminished the acetylcholinesterase level and improves the anti-oxidant defense system. Further, Ellagic acid downturned the cognitive impairments induced by scopolamine. Like Donepezil, Ellagic acid reversed the scopolamine induced Alzheimer's type dementia in rats.

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