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Antiamnesic and Antioxidant Effect of *Acacia catechu*-catechin in Normal, Aged and Scopolamine Challenged Cognitive Deficit Mice

[1]S.M. Biradar, [1]K.C. Tarak, [1]V.H. Kulkarni, [2]P.V. Habbu and [2]D.M. Smita

[1]Department of Pharmacology and Toxicology, Post Graduate Studies and Research Centre, SET's College of Pharmacy, Dharwad, 580002, Karnataka, India

[2]Department of Pharmacognosy, Post graduate Studies and Research Centre, SET's College of Pharmacy, Dharwad, 580002, Karnataka, India

Corresponding Author: K.C. Tarak, Department of Pharmacology and Toxicology, Post Graduate Studies and Research Centre, SET's College of Pharmacy, Dharwad, 580002, Karnataka, India Tel: 0836-2448540, +919620162373

ABSTRACT

In the present study *Acacia catechu*-Catechin (CTN) was evaluated for antiamnesic and antioxidant activity using various *in vivo* models. Scopolamine and natural aging were used to induce experimental amnesia in mice. The tested does of CTN (40, 20 and 10 mg kg^{-1}) significantly enhanced the learning capacity and retention of memory in Passive Shock Avoidance and Spatial Water cage exteroceptive behavioural models. Pre-treatment with CTN restored the increased levels of lipid peroxidation and reduced glutathione due to scopolamine and natural aging. A dose dependent CTN (40, 20 and 10 mg kg^{-1}) antioxidant activity of Thiobarbituric acid reactive substances (TBARS) and reduced glutathione (GSH) in whole brain was seen, which were comparable to Standard Piracetam (400 mg kg^{-1}). Hence, it is worthwhile to explore the potential of this *Acacia catechu*-Catechin in the management of Neurodegenerative disorders of the type Alzheimer's disease.

Key words: *Acacia catechu*-Catechin, passive shock avoidance, spatial water cage, antioxidant

INTRODUCTION

Neurodegenerative disorders such as Alzheimer's disease result in an impaired cognitive function and behavioural decline resulting in the development of severe dementia (Farbood *et al*., 2009). Based on current population projections, it has been estimated that by 2050 the number of individuals over 65 will increase to 1.1 million worldwide and as a consequence, the number of individuals with dementia will reach 37 million (Lokhart and Lestage, 2003). The drugs used in AD are cholinergic activators (Tacrine), CNS stimulants (Amphetamines), Glutamate (NMDA) antagonist (Mematine) and other cerebroactive agents (Piracetam) (Bhattacharya, 1999). But the problems associated with these drugs are cholinergic, serotonergic and dopaminergic side effects and habituation. All of these agents do not alter the natural course of the disease, but provides a partial improvement in memory and cognitive function (Shintani and Uchida, 1997). Since modern health system of medicine is yet to provide a vital aid, it is advantageous to look for new directions, which would attenuate the memory loss seen in elderly patients and minimizes the stress of different types in this advanced and fast forward world. At this juncture, the quest for a novel

cognitive enhancer arises and when it has to be virtually free from severe deleterious effects, one has to turn to nature and its remedies.

The disease preventive and health primitive approach of Ayurveda, has developed certain therapeutic measures to delay ageing and rejuvenating dynamics of the body organs. This is known as the 'Rasyana chikitsa' Rasayana drugs act inside the body by modulating the neuro-endocrino-immune systems. Various rasayana drugs are *Convolvulus pluricaulis, Centella asiatica, Bacopa monnieri, Acorus calamus, Celastrus paniculatus* (Joshi and Parle, 2006).

Acacia catechu (Linn. F.) Willd, belongs to the family Mimosaceae. Ethnobotanical investigations communicates that *Acacia catechu* has numerous advantages in leprsory, loose motions, blood clots, smoothened conditions of teeth gums, buccal cavity and mouth, stomatitis, inflammatory bowel disease (Khare, 2007). Catechin has been scientifically proven for its astringent, anti-diarrheal activity (Goyal *et al*., 2011), Hypoglycemic and Ocular-protective activity (Chigozie and Chidinma, 2012), prevention of atherosclerosis and stroke (Alipoor and Rad, 2012), antioxidant activity (Sabli *et al*., 2012; Gupta *et al*., 2008), antiplatelet activity (Gilani *et al*., 2006), antibacterial and antifungal activity (Chakraborty and Chakraborti, 2010) and also its protective effect on Colonic Aberrant Crypt Foci (Verghese *et al*., 2008). *Acacia catechu* envelops high amount of catechin, epicatechin, quercetin etc (Li *et al*., 2010). Catechin is also present in various other plant species like *Argania spinosa*, (Charrouf and Guillaume, 2007) and also in the *Etlingera* and *Zingiber* species belonging to the family Zingiberaceae (Sabli *et al*., 2012). Catechin (Haque *et al*., 2006) and quercetin (Tong-Un *et al*., 2010) is responsible for cognitive enhancement. Catechin also has promising antioxidant property which may be essential to shrink the AD due to oxidation (Naik *et al*., 2003). Similarly, catechin and epicatechin also display Mono Amino Oxidase inhibitory activity, which is acceptably used as a bite of the treatment of Parkinson's and Alzheimer's disease and hence may be an effective tool to inhibit neurodegeneration *in vitro* (Hou *et al*., 2005). Therefore, the hypothesis is that this drug can enhance the cognitive function in the brain in normal and aged animals.

MATERIALS AND METHODS

Time duration and year of the study: This current project was carried out for 8 months, during the month of June 2011 to February 2012.

Chemicals: *Acacia catechu*-Catechin (CTN) was obtained as a gift sample from Natural Remedies, Bangalore. Piracetam (Pira) was obtained as gift sample from Elite pharmaceuticals, Gujarat. Scopolamine (Sco) was obtained from Alkaloids Corporation of India as a gift sample. 5, 5'-dithiobis (2-nitro benzoic acid) (DTNB) was purchased from HiMedia, Mumbai, India. Thiobarbituric acid and Tri-chloro acetic acid were obtained from Spectrochem, Bangalore, India.

Animals: All the experiments were carried out with young 3 months old Swiss Albino Mice of 22-28 g and Aged 14 months old of 35-42 g after approval from the Institutional Animal Ethical Committee (Approval Number: SETCP/IAEC/2010-2011/454). Animals were kept in the animal house of S.E.T's College of Pharmacy, Dharwad, India, under controlled conditions of temperature (23±2°C), humidity (50±5%) and 12 h light-dark cycle. Animals were fed with rat diet pellet (obtained from Venkateshwara enterprises, Bangalore) and water *ad libitum*. All the animals were acclimatized for seven days before to start the experimental studies.

Preparation of doses: The selected doses of CTN 40, 20, 10 mg kg^{-1} b.wt. was administered orally (p.o) by dissolving in Distilled Water (DW) based on literature survey. Piracetam (400 mg kg^{-1}, b.wt.), standard drug was dissolved in distilled water and administered per orally (p.o). Amnesia was induced by Scopolamine (3 mg kg^{-1}, b.wt.) i.p., by dissolving it in distilled water.

Experimental design: In the present investigation the mice were divided into different groups for employing various interoceptive and exteroceptive behavioural memory models. Each group comprised of a minimum of six animals. Young Normal animals received Distilled Water (DW) in the dose of 10 mL kg^{-1} b.wt. orally. CTN (40, 20 and 10 mg kg^{-1}) was administered orally for 14 successive days to young and aged mice. After 90 min of the administration of the last dose on 14th day, amnesia was induced in young animals by injecting Sco (3mg kg^{-1}, i.p.) and in aged mice, naturally aging of mice was considered as amnesia. Young and aged mice were exposed to the training session after 30 min of scopolamine injection (only young mice) using Passive shock avoidance and Spatial water cage. After training trials, retention memory was recorded on 15th day. Piracetam (400 mg kg^{-1}, p.o.) was used as an established nootropic agent and was injected for 14 days to positive control groups.

Passive shock avoidance (step through) paradigm: The passive avoidance task was measured in an apparatus consisting of one light and one dark compartment. After treatment, each animal was placed in the light compartment and the time was measured of how long it took to move into the dark compartment (acquisition latency). A shock of 0.4 mA/2 sec was applied as soon as the animal stepped into the dark compartment. Immediately after that, the animal returned to its home cage and 24 h later, animals were again replaced into the light compartment in order to measure the time it took to move from the light side into the dark one (retention latency). Animals which did not enter dark compartment even after 180 sec were removed from the apparatus, 180 sec was considered as an upper cut-off time of retention (Espinola *et al*., 1997).

Spatial water cage: Spatial two-chambered cage was used with the dimension 16 inch length, 11 inch breadth and 5 inch height. A partition placed at a distance of 6 inches from one of the end of cage; divide the cage into a smaller and larger chamber. A water feeding bottle was kept in smaller chamber; the animals were water deprivation for 24 h. After 90 min of treatment on 15th day, the animals were placed in the larger chamber and allowed to explore the cage. Once the water deprived animal locate the bottle, it was allowed to drink the water for 30 sec, the time required to locate the water bottle was noted as 1st retention time. Immediately after 1st retention test before the animal being placed in home cage all the animals except group 1 were injected with Scopolamine (3 mg kg^{-1} i.p.). After 24 h later the animals were again placed in the larger chamber of two-chamber cage. The time required to locate the water bottle was noted as a day second reading (2nd retention test), but this time the water bottle was kept empty (Martinez *et al*., 1979; Schindler *et al*., 1994).

Determination of thio barbituric acid reactive substances (TBARS): The animals were sacrificed; whole brain was dissected out and homogenized in phosphate buffer pH 8, 10% w/v. The

homogenates were centrifuged at 15,375 xg at 4°C for 20 min using Remi C-24 high speed cooling centrifuge. The 2.0 mL of the tissue homogenate (supernatant) was added to 2 mL of freshly prepared 10% w/v trichloroacetic acid (TCA) and the mixture was allowed to stand in an ice bath for 15 min. After 15 min, the precipitate was separated by centrifugation and 2.0 mL of clear supernatant solution was mixed with 2 mL of freshly prepared 0.67% thiobarbituric acid (TBA). The resulting solution was heated in a boiling water bath for 10 min. It was then immediately cooled in an ice bath for 5 min. The colour developed was measured at 532 nm against reagent blank. The values were expressed in μM L^{-1} (Slater and Sawyer, 1971). Extinction co-efficient for TBARS: 1.56×10^5 M^{-1} cm^{-1} (Yousuf *et al.*, 2005).

Determination of reduced glutathione (GSH): The animals were sacrificed; whole brain was dissected out and homogenized in phosphate buffer pH 8, 10% w/v. The homogenates were centrifuged at 15,375 xg at 4°C for 20 min using Remi C-24 high speed cooling centrifuge. Equal volumes of tissue homogenate (supernatant) and 20% trichloroacetic acid were mixed. The precipitated fraction was centrifuged and to 0.25 mL of supernatant, 2 mL of 0.6 mM 5, 5'-dithiobis (2-nitro benzoic acid) reagent was added. The final volume was made up to 3 mL with phosphate buffer (0.2M, pH 8.0). The colour developed was read at 412 nm against reagent blank. The values were expressed in μM L^{-1} (Moron *et al.*, 1979). Extinction co-efficient for GSH: 13.6×10^3 M^{-1} cm^{-1} (Yousuf *et al.*, 2005).

Statistical analysis: The data were analyzed statistically using analysis of variance (ANOVA) followed by Tukey's post test. Values are expressed as Mean±Standard errors of mean (SEM). $p<0.05$ is considered as significant and $p<0.05$ were considered as non-significant. Statistical comparisons were performed by Tukey's post test using Graph Pad Prism version 5.0, USA.

RESULTS

Passive shock avoidance: The administration of Sco (3 mg kg^{-1}; i.p.) before training trials induced amnesia in mice using Passive Shock Avoidance (PSA) exteroceptive behavioural model. Naturally induced amnesic model in aged mice has also been studied. However, CTN alone produced significant improvement in PSA ($p<0.01$), as indicated in Table 1. Furthermore, Sco administered mice and aged mice significantly decreased the Step Through Latency (STL) compared to normal group of animals in PSA behavioural model. These observations suggested that Sco and aging had produced impairment in learning as well as memory. Also, Sco and aging induced memory deficits were successfully reversed by CTN 40 mg kg^{-1} ($p<0.001$), 20 mg kg^{-1} ($p<0.001$), 10 mg kg^{-1} ($p<0.01$) as indicated by increased STL as indicated in Table 2 and 3, respectively. Pre-treatment with Pira (400 mg kg^{-1}, p.o.) reversed Sco induced and aging induced memory deficits ($p<0.001$) as expected.

Table 1: Effect of *Acacia catechu*-catechin on step-through-latencies (STL) of normal young mice, on passive shock avoidance

Groups	Dose	14th day (sec)	15th day (sec)
Young normal	10 mL kg^{-1}, p.o.	53.67±2.77	70.33±3.38
Young+Pira	400 mg kg^{-1}, p.o.	56.17±3.00	157.50±4.48 $^{###}$
Young+CTN	40 mg kg^{-1}, p.o.	59.50±2.86	89.00±3.89$^{##}$

Values are Mean±SEM. $p<0.05$ is considered as significant, $^{###}p<0.001$, $^{##}p<0.01$: Significant values as compared to normal control

Table 2: Effect of *Acacia catechu*-catechin on step-through-latencies (STL) of Sco group on passive shock avoidance

Groups	Dose	14th day (sec)	15th day (sec)
Young normal	10 mL kg^{-1}, p.o.	53.67±2.77	70.33±3.38
Sco	3 mg kg^{-1}, p.o.	60.00±2.86	42.00±1.00 ###
Sco+Pira	400 mg kg^{-1}, p.o.	52.50±3.09	132.3±3.08***
Sco+CTN	40 mg kg^{-1}, p.o.	54.83±2.97	91.67±3.01***
Sco+CTN	20 mg kg^{-1}, p.o.	56.50±3.17	62.67±4.56**
Sco+CTN	10 mg kg^{-1}, p.o.	52.17±2.86	57.17±1.19*

Values are Mean±SEM, $p<0.05$ is considered as significant, ###$p<0.001$: Significant values as compared to normal control, ***$p<0.001$, **$p<0.01$, *$p<0.05$: Significant values as compared to Sco group

Table 3: Effect of *Acacia catechu*-catechin on step-through-latencies (STL) of aged group on passive shock avoidance

Groups	Dose	14th day (sec)	15th day (sec)
Young normal	10 mL kg^{-1}, p.o.	53.67±2.77	70.33±3.38
Aged mice	10 mL kg^{-1}, p.o.	46.17±2.94	51.50±2.11###
Aged+Pira	400 mg kg^{-1}, p.o.	55.67±0.80	130.8±1.99***
Aged+CTN	40 mg kg^{-1}, p.o.	53.67±2.53	103.7±3.15***
Aged+CTN	20 mg kg^{-1}, p.o.	52.33±3.16	66.50±2.11**
Aged+CTN	10 mg kg^{-1}, p.o.	50.83±0.65	64.00±2.70*

Values are Mean±SEM, $p<0.05$ is considered as significant, ###$p<0.001$: Significant values as compared to normal control and $^{\dagger\dagger\dagger}p<0.001$, $^{\dagger\dagger}p<0.01$, $^{\dagger}p<0.05$: Significant values as compared to aged group

Table 4: Effect of *Acacia catechu*-catechin on time required to find the water bottle in normal young mice on spatial water maze

Groups	Dose	Day 14 (sec)	Day 15 (sec)
Young normal	10 mL kg^{-1}, p.o.	101.2±6.42	33.83±3.09
Young+Pira	400 mg kg^{-1}, p.o.	103.3±2.01	19.50±5.63
Young+CTN	40 mg kg^{-1}, p.o.	106.5±6.93	21.83±1.25

Each group consists of 6 animals (n = 6), Values are Mean±SEM, $p<0.05$ is considered as significant, ###$p<0.001$, ##$p<0.01$ #$p<0.05$: Significant values as compared to normal control

Spatial water cage: The administration of Sco (3 mg kg^{-1}; i.p.) before training trials induced amnesia in mice using Spatial Water Maze (SWM) exteroceptive behavioural model. Naturally induced amnesic model in aged mice has also been studied. However, CTN alone produced non-significant improvement in SWM ($p>0.05$) as indicated in Table 4. Furthermore, Sco administered mice and aged mice significantly decreased the time to find the water bottle compared to normal group of animals in SWM behavioural model. These observations suggested that Sco and aging had produced impairment in learning as well as memory. Also, Sco and aging induced memory deficits were successfully reversed by CTN 40 mg kg^{-1} ($p<0.01$), 20mg kg^{-1} ($p<0.05$), 10 mg kg^{-1} ($p>0.05$) as indicated by increase in time required to find the bottle as indicated in Table 5 and 6, respectively. Pre-treatment with Piracetam (400 mg kg^{-1}; p.o.) reversed Sco and aging induced memory deficits ($p<0.001$) as expected.

Reduced glutathione (GSH): Young mice Pre treated with Pira ($p<0.001$) and CTN ($p<0.01$) were shown significant increased antioxidant activity of reduced glutathione when comparative to young normal control group, which were pre-treated with plane distilled water as indicated in Fig. 1. Administration of Sco (3 mg kg^{-1}; i.p.) and naturally aged induced amnesia decreased brain GSH

Table 5: Effect of *Acacia catechu*-catechin on time required to find the water bottle in Sco group on spatial water maze

Groups	Dose	Day 14 (sec)	Day 15 (sec)
Young normal	10 mL kg^{-1}, p.o.	101.2±6.42	33.83±3.09
Sco only	3 mg kg^{-1},p.o.	116.8±5.34	80.67±1.07###
Sco+Pira	400 mg kg^{-1}, p.o.	111.5±6.72	39.67±1.99***
Sco+CTN	40 mg kg^{-1}, p.o.	113.8±6.54	61.83±3.36**
Sco+CTN	20 mg kg^{-1}, p.o.	114.5±7.37	64.00±3.64*
Sco+CTN	10 mg kg^{-1}, p.o.	113.7±8.31	73.67±2.24

Values are Mean±SEM,. $p<0.05$ is considered as significant, ###$p<0.001$: Significant values as compared to normal control, ***$p<0.001$, **$p<0.01$, *$p<0.05$: Significant values as compared to Sco group

Table 6: Effect of *Acacia catechu*-catechin on time required to find the water bottle in aged mice on spatial water maze

Groups	Dose	Day 14 (sec)	Day 15 (sec)
Young normal	10 mL kg^{-1}, p.o.	101.2±6.42	33.83±3.09
Aged mice+DW	10 mL kg^{-1}, p.o.	106.8±2.28	78.50±4.93###
Aged+Pira	400 mg kg^{-1}, p.o.	105.2 ±1.10	17.83±1.07***
Aged+CTN	40 mg kg^{-1}, p.o.	109.3±9.41	61.33±1.56**
Aged+CTN	20 mg kg^{-1}, p.o.	111.5±6.27	63.50±2.98*
Aged+CTN	10 mg kg^{-1}, p.o.	110.7±9.24	74.83±1.49

Values are Mean±SEM, $p<0.05$ is considered as significant, ###$p<0.001$: Significant values as compared to normal control, †††$p<0.001$, ††$p<0.01$, †$p<0.05$: Significant values as compared to aged group

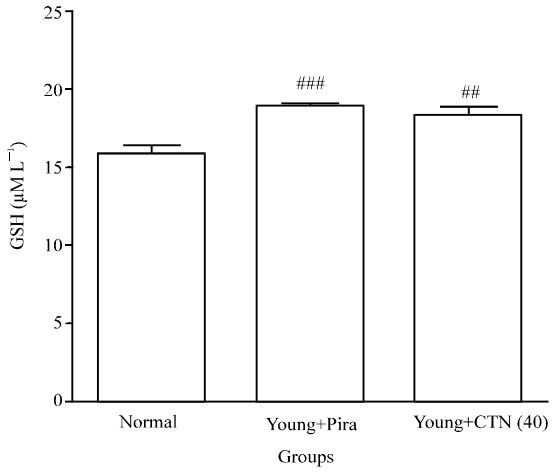

Fig. 1: Effect of *Acacia catechu*-catechin on whole brain GSH of normal young mice, Values are Mean±SEM, $p<0.05$ is considered as significant ###$p<0.001$, ##$p<0.01$, as compared to normal control

levels ($p<0.001$) which were considered as an increase in oxidation activity in brain when compared to control group of animals. The administration of CTN 40 mg kg^{-1} ($p<0.001$), 20 mg kg^{-1} ($p<0.01$) and 10 mg kg^{-1} ($p<0.05$) and Piracetam significantly($p<0.001$) reversed both, Sco induced and aging induced decrease in brain GSH levels as indicated in Fig. 2 and 3, respectively.

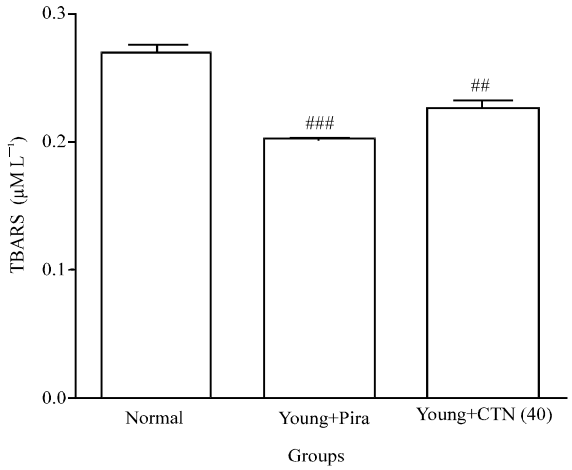

Fig. 2: Effect of *Acacia catechu*-catechin on whole brain GSH of Sco group, Values are Mean±SEM, p<0.05 is considered as significant, ###p<0.001, as compared to normal control, ***p<0.001, *p<0.05 compared to Sco group

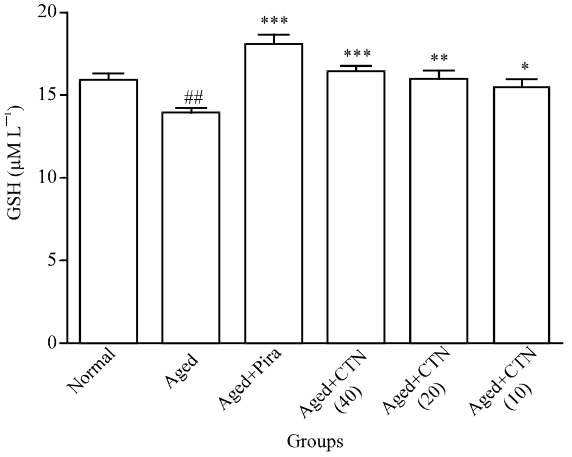

Fig. 3: Effect of *Acacia catechu*-catechin on whole brain GSH of aged mice, Values are Mean±SEM, p0.05 is considered as significant. ##p<0.01, as compared to normal control, ***p<0.001, **p<0.01, *p<0.05 compared to aged group

Thio barbituric acid reactive substances (TBARS): Young mice Pre treated with Pira (p<0.001) and CTN (p<0.01) were shown significant increased antioxidant activity of TABRS when comparative to young normal control group, which were pre-treated with plane distilled water as indicated in Fig. 4. Administration of Sco (3 mg kg^{-1}; i.p.) and naturally aged induced amnesia increased the brain TBARS levels (p<0.001) which were considered as an increase in oxidation activity in brain when compared to control group of animals. The administration of CTN 40 mg kg^{-1} (p<0.001), 20 mg kg^{-1} (p<0.001) and 10 mg kg^{-1} (p<0.01) and Piracetam significantly (p<0.001) reversed both, Sco induced and aging induced increase in brain TBARS levels as indicated in Fig. 5 and 6, respectively.

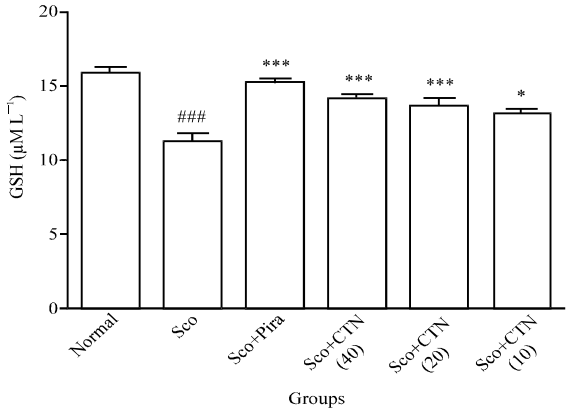

Fig. 4: Effect of *Acacia catechu*-catechin on whole brain TBARS of normal young mice, Values are Mean±SEM, $p<0.05$ is considered as significant. $^{###}p<0.001$, $^{##}p<0.01$ as compared to normal control

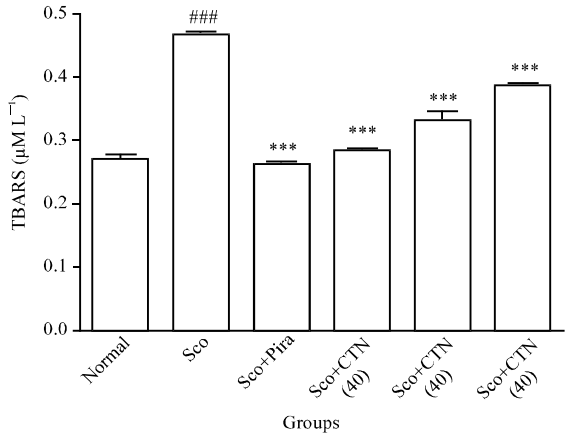

Fig. 5: Effect of *Acacia catechu*-catechin on whole brain TBARS of Sco group, Values are Mean±SEM, $p<0.05$ is considered as significant $^{###}p<0.001$, as compared to normal control, ***$p<0.001$, **$p<0.01$, *$p<0.05$ compared to Sco group

DISCUSSION

Alzheimer's disease is associated with cognitive dysfunction and decline in the memory. Despite the harshness and predominance of this disease, modern health system of medicine is yet to provide a vital aid. Therefore, we were prompted to utilize the potential of traditional herbs to tackle this disease. Two different exteroceptive behavioural models have been employed in this present study, Passive Shock Avoidance (PSA) and Spatial Water Maze (SWM). In PSA, the stimulus employed is shock, which prevents it from entering into the dark compartment. Whereas, in SWM, the stimulus employed is water deprivation, which in turn helps to locate the water bottle in the maze and indirectly improves the spatial memory. In this present study, pre-treatment with CTN for 14

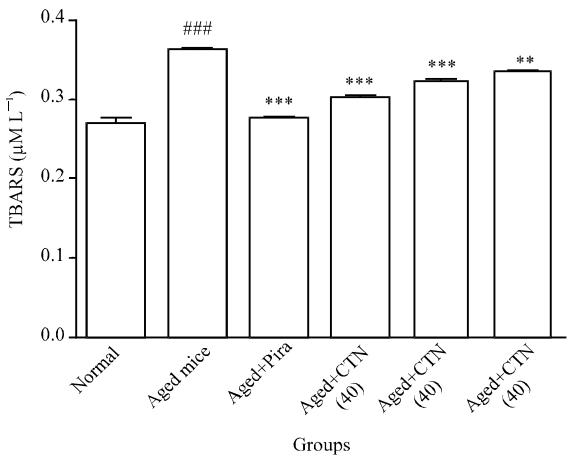

Fig. 6: Effect of *Acacia catechu*-catechin on whole brain TBARS of aged mice, Values are Mean±SEM, $p<0.05$ is considered as significant $^{###}p<0.001$, as compared to normal control, $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$ compared to aged group

days enhanced the memory deficits induced by Scopolamine and natural aging as indicated by increase in both, STL and time required to find the bottle in PSA and SWM, respectively.

The brain is particularly susceptible to oxidative attack by free radicals because of its high utilization of oxygen, its relatively low concentration of antioxidative enzymes and free radical scavengers (Shuter *et al*., 1990). Lipid peroxidation or TBARS is able to cause extensive damage and is known to play a major role in the deterioration of the brain and spinal cord that occurs after traumatic, excitotoxic or ischemic injury (Yoshikawa *et al*., 1994). It has been observed that there is an age-dependent depletion in intracellular GSH of many organisms including humans. Since the brain requires extensive ROS detoxification it is evident that a decrease in GSH content could increase oxidative damage making the brain more susceptible to neurological disorders such as AD. To counter this oxidative stress, the cell maintains a battery of detoxifying enzymes viz. CAT, SOD and GPx and small molecules such as GSH.

Scopolamine and natural aging induced animals significantly elevated the oxidative stress as indicated by the elevated levels of TBARS and reduced GSH levels in this current study. The administration of CTN for 14 successive days to young and aged mice not only reduced oxidative stress but also arrested the Scopolamine induced rise in oxidative disturbance as indicated by the depleted TBARS and elevated GSH levels. These findings suggest the possible neuroprotective role for *Acacia catechu*-Catechin. However, further investigation is warranted to explore the possible involvement of acetylcholinesterase, brain biogenic amines and pyramidal neurons responsible for antiamnesic activity of *Acacia catechu*-Catechin.

CONCLUSION

The results of the present study showed that the *Acacia catechu*-Catechin reverses the Sco and aging induced memory deficits, by increasing the STL and time required to find the bottle in PSA and SWM behavioural models respectively. Sco and natural aging elevates the level of TBARS and decreases the level of GSH. This is change in antioxidant enzyme levels induce cognitive

dysfunction. Due to the antioxidant characteristic of CTN, it reduces the TBARS and increases the GSH level in brain tissue which may delay the process of Neurodegeneration and natural aging.

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