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Original Article

Phyllanthus emblica (Amloki) Modifies Cognitive Impairments in A Rat Model of Alzheimer's Disease Induced by Colchicine

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Abstract

Background: *There has been a consistent increase in the number of patients experiencing dementia, including dementia linked to Alzheimer's disease. The effective treatment of dementia remains an unfulfilled medical requirement. In this point of view, drug treatment for this purpose has become less favorable for their prolonged time requirement and wide range of adverse effects. So, this PE may be a suitable treatment option for addressing cognitive decline as well.* ***Objective:*** *To assess the effects of ethanolic extract of Phyllanthus emblica (EEPE) fruit on memory performance in colchicine induced memory impaired male Long-Evans rats.* ***Methods:*** *This experimental study was conducted at KM Fariduddin Animal Research Laboratory, Department of Physiology, BMU on 24 male Long-Evans rats (8±2 weeks; 225±75 gm). On the basis of treatments, all rats (6 rats/group) were grouped into normal control (NC), sham control (SC), colchicine control (ColC), pre-colchicine Phyllanthus emblica treatment (Pre PE Exp). A single dose of colchicine (15 µg) was administered intrahippocampally to induce memory impairment, and subsequent behavioral changes were monitored in the Morris water maze (MWM) test in all rats. The statistical analysis was conducted using one-way ANOVA, followed by the Bonferroni post hoc test, with p≤0.05 deemed statistically significant.* ***Results:*** *Colchicine showed significantly (p≤0.001) higher Escape latency (EL) in training and test phase as well as in acquisition phase and significantly (p≤0.001) lower Target crossing (TC) and Time spent in target (TT) in ColC rats in comparison to those SC rats. In contrast, significantly (p≤0.001) lower EL and significantly (p≤0.001) higher TC and TT were found in Pre PE Exp rats when compared to those of ColC rats. Strikingly, no statistically significant difference was observed in any memory performance between NC and Pre PE Exp rats.* ***Conclusion:*** *The current study demonstrated that Phyllanthus emblica (Amloki) effectively prevented colchicine induced impairments in both working and reference memory in male long-Evans rats. Furthermore, the dosage and duration regimen of Phyllanthus emblica (Amloki) was adequate to restore these concerning effects to normal levels.*

Key words: *Memory impairment, Colchicine, Hippocampus, Phyllanthus emblica (PE), Morris water maze.*

Introduction: Senile dementia, which is also called Alzheimer's disease (AD), is a disorder affecting the central nervous system, marked by a gradual onset and a slow, progressive disease course, commonly observed in the early stages of aging. The primary clinical symptoms observed in AD patients include notable reductions in memory and cognitive function, along with a progressive decline in self-care capabilities. One of the key features of dementia is memory impairment, which is presently observed in more than 55 million people worldwide[1]. Inadequate physical activity, a predominantly inactive lifestyle, or stressful living environments are all related to memory impairment.

The hippocampus, found in the deepest area of the temporal lobe cortex, is essential for the creation and conservation of memories. The suggested mechanisms for memory impairment include neurodegeneration in the hippocampus due to oxidative stress[2], an increase in Beta amyloid protein[3], neuroinflammation[4], and an increase in acetyl cholinesterase (AchE) activity in the hippocampus[5].

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These days, the treatment protocols for memory impairment involve a variety of drugs, including galantamine, rivastigmine, donepezil, and others[6]. However, a wide array of negative effects is associated with the regular consumption of these medications, which limits their effectiveness in managing memory impairment. In this regard, *Phyllanthus emblica* (PE) fruit extract may be a worthwhile alternative to explore.

Phyllanthus emblica (PE), often referred to as 'Amloki', is a crucial medicinal fruit with a diverse array of medicinal applications such as-hepatoprotective[7], antitussive[8], anti-pyretic and analgesic[9], antidiabetic[10], antimalignant[11], anti-malarial[12], anti-inflammatory[13], hypolipidemic[14], nephroprotective[15] as well as antimicrobial[16]. In terms of the effective dose and duration of this PE treatment for preventing memory impairment, the results varied across different animal models where in most of the studies PE was administered orally. However, PE showed no toxic effect even after 3 weeks oral administration of 1000 mg/kg in rat[17]. Consequently, this study was conducted to assess the impact of *Phyllanthus emblica* (PE) on memory performance prior to colchicine-induced dementia in male Long-Evans rats.

Materials and Methods:

Animals

All experiments were carried out using 24 healthy adult male Long-Evans rats weighing about 225±75 gm, age 8±2 weeks, collected from the central animal house of Bangladesh Medical University (BMU) Dhaka, Bangladesh. The rats were housed in 6 per animal cage and placed under standard environmental conditions (27 to 28°C) with a half day light and dark cycle. Standard laboratory food and water were administered properly. The protocol of the experiment was approved by the Institutional Review Board (Registration No: 4469) of that University and the study was conducted in the KM Farid Uddin animal laboratory of the Department of Physiology of Bangladesh Medical University (BMU), Dhaka, Bangladesh.

Extract preparation

In August 2023, fresh leaves of PE were collected from Hazigonj Upazilla, situated in the Chadpur district of Bangladesh. Identification was carried out by an expert taxonomist from the Bangladesh National Herbarium, Mirpur, Dhaka, Bangladesh and A voucher specimen (Accession number: DACB 90617) has been stored in the herbarium for future reference. According to Uddin et al. (2016), 5 kg fruits of PE was collected, washed and shade dried for 30 minutes. After removing the seeds, the fruits were dried for an additional 7 days with irregular sun drying. The dried fruits were ground into powder and stored in an airtight container for extraction. About 500 gm of powder (from 5kg) was soaked in 2.5 liters of 98% ethanol in room temperature (24 -27 o C) for 7 days with frequent shaking. The mixture was filtered through cotton and then Whatman (Grade no.1) filter paper, concentrated, and dried at 50°C by rotatory evaporator, then ethanolic extract stored at 4°C for later use.

Drugs and chemicals

Normal saline (Opso Saline Ltd, Bangladesh), gentamicin (Incepta Pharmaceuticals Ltd, Bangladesh), thiopental sodium (Gonosasthaya Pharmaceuticals Ltd), di-ethyl ether (MERCK, Germany) and Ethanol (MERCK, Germany) were purchased from local market. Colchicine was obtained from Incepta Pharmaceuticals Ltd, Bangladesh.

Study design

Rats were divided randomly into 4 groups as follows (6rats/group):

NC group: Healthy group (No stereotaxic surgery and PE treatment)

SC group: Intrahippocampal infusion of 1 µl normal saline by stereotaxic surgery and no PE.

ColC group: Single dose colchicine (15 µg in 1 µl normal saline) was infused in hippocampus by stereotaxic surgery without any PE treatment.

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Pre PE Exp group: Ethanolic extract of *Phyllanthus emblica* (EEPE) was administered intraperitoneally (i.p) at a dose of 700 mg/kg for 7 days, then hippocampal infusion of colchicine (15 µg in 1 µl normal saline) by stereotaxic surgery.

Intra Hippocampal colchicine infusion by stereotaxic surgery

In previous studies[18,19,20], colchicine was given to rats in the hippocampus using stereotaxic surgery. Before the surgery, the rats were fasted overnight but had water. On the surgery day, they were anesthetized using thiopental sodium (45 mg/kg, i.p) and placed in a stereotaxic apparatus. After scalp incision and retraction 15 µg of colchicine in 1 µl normal saline was injected into each hippocampus using a Hamilton micro syringe very slowly over 1 minute and then micro syringe was kept place for the next minute (60 seconds) before being slowly withdrawn. The coordinates for the infusion were: -3.6 mm anterior-posterior, ± 2 mm lateral-medial and -3.4 mm dorso-ventral relative to bregma. Control subjects received a vehicle injection. The scalp was subsequently closed with sutures. Immediately following the surgery, the rat was placed in a post-operative cotton bed for 2 days, with all aseptic precautions and care taken for feeding until it recovered from the surgical stress. Gentamycin (5 mg/kg, i.p) was administered post-operately to prevent sepsis.

Morris Water Maze (MWM) test

Apparatus

The MWM test is designed to evaluate reference and working memory by utilizing a large circular pool that is 150 cm in diameter and 50 cm high, filled with water21,22. To avoid providing visual cues, the pool's walls and platform are painted black, and it is located in a room that includes extra maze cues to help orient the rats. The pool was divided into four quadrants including eight starting points, north (N), south (S), east (E), west (W), north-east (NE), north-west (NW), south-east (SE) and south-west (SW), with a platform which is hidden and has a diameter of 15 cm and a height of 28 cm, is found in the center of the northeast quadrant, with its top 2 cm submerged beneath the water surface, thereby making it invisible from the pool's interior. Two testing methods assess memory abilities, and working plans for four rat groups are shown in figure 1.

Reference memory test

As depicted in figure 1 rat underwent 3-days swimming phase for 3 minutes without a platform to facilitate instrumental acclimatization and habituation phase of the reference memory. In the acquisition phase, they participated in four trials each day over six days, always starting from a different position but looking for a fixed platform in the NE quadrant. Each trial lasted 60 seconds, and a time of 50 seconds was allowed between trials for drying. The mean escape latency (the time taken to find the platform) was recorded using a stopwatch to judge their learning ability. About 24 hours after the final trial of acquisition phase on day 6 (which occurred on day 7), after removing the platform, a probe trial was done. Here, the rats were permitted to swim freely for duration of 60 seconds. The measured target crossings (TC) refer to the number of instances the rats crossed the quadrant of the MWM within this 60-second timeframe after the platform was removed. Additionally, the time spent in the target (TT) indicates the duration the rats remained in the quadrant from which the platform was removed during the same 60 seconds. These metrics were recorded to evaluate learning strength and retrieval.

Working memory test

Approximately 48 hours after the probe trial, a working memory assessment was performed using a method based on Sarihi et al. (2000). The 6-day acquisition phase of the reference memory test was regarded as the pre-training phase of the working memory. Following this, training and testing phase took place over 4 days, with 4 trials conducted each day. Each day, the platform's position was changed, yet remained consistent for the 4 trials carried out daily. Nonetheless, each rat was released from 4 separate starting points during the 4 daily trials, all of which were located at a distance from the platform's position. In the first trial each day, rats discovered the platform by chance, while later trials required them to remember the new location. The mean escape latency (EL) during the training and testing phases was recorded as previously mentioned to evaluate learning capability.

Statistical analysis

Results were presented as mean±SEM (Standard Error of Mean). Statistical analysis of the data was conducted through ANOVA, followed by the Bonferroni post hoc test in SPSS (version 25.0), considering $p \leq 0.05$ as statistically significant.

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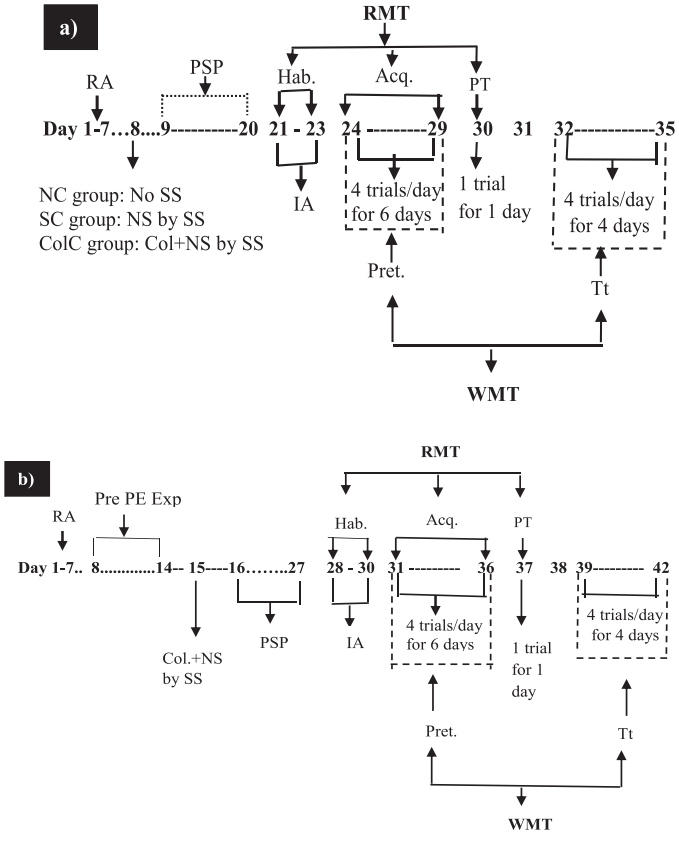

Figure 1: Experimental design for a) control rats (normal control; sham control; colchicine control) and b) experimental rats (Pre PE Exp) RMT: Reference Memory Test; WMT: Working Memory Test; RA=Room Acclimatization; PSP= Post-Surgical Period; Hab.=Habituation; Acq.=Acquisition; PT=Probe Trial; IA=Instrumental Acclimatization; Pret.= Pretraining; Tt=Training and Test; NS=Normal Saline; SS=Stereotaxic Surgery; Col.=Colchicine

Results

Effect of pretreatment of EEPE on reference memory

As indicated in Table I, ColC rats exhibited a significantly ($p \leq 0.001$) higher mean escape latency (EL) across all acquisition days when compared to SC rats. Nevertheless, EEPE enhanced the learning performance of our rats, as shown by statistically significant ($p \leq 0.001$) differences in mean EL between our ColC and experimental (Pre PE Exp) rats. Notably, the differences in this variable between Pre PE Exp and NC rats were statistically non-significant on the final acquisition day. These findings illustrate that colchicine impaired reference memory learning ability, which was nearly restored to normal levels by systemic PE.

In the study (Table II), ColC rats exhibited retrieval impairment, as demonstrated by significantly ($p \leq 0.001$) lower Target crossings (TC) and Time spent in target (TT) compared to SC rats. The Pretreatment with EEPE resulted in significantly ($p \leq 0.001$) higher TC and TT in Pre PE Exp rats relative to ColC rats. Furthermore, Statistical analysis indicated that the differences in these variables between NC and Pre PE Exp rats were not significant (Table II). This data suggests that the learning strength (retrieval) was adversely affected by colchicine and was nearly restored to normal levels by i.p EEPE.

Table I: Mean escape latency (EL, in seconds) in acquisition phase of Morris water maze test in different groups of rats

Mean EL of acquisition day	NC	SC	ColC	Pre PE Exp
1st	26.21±2.29	30.63±2.43	60.0±0.00***	43.04±2.06###/£££
2nd	22.58±0.99	25.42±0.62	58.88±0.53***	38.63±1.95###/£££
3rd	14.54±1.82	18.92±0.44	56.5±1.17***	36.00±1.91###/£££
4th	13.08±1.71	17.5±0.76	53.92±0.66***	30±0.97###/£££
5th	12.96±1.19	15.92±0.71	51.71±1.09***	25.42±1.64###/£££
6th	12.21±0.96	13.33±0.35	49.46±1.99***	16.92±1.16###

Each day represents mean ± SEM of 4 trials of 6 rats in that day. Values in parenthesis indicate ranges. Statistical analysis was done by ANOVA (among groups) followed by Bonferroni's post hoc test (between groups). *=SC vs ColC, # = ColC vs Pre PE Exp, £ = NC vs Pre PE Exp. In the interpretation of results, $p \leq 0.05$ was considered as significant. ***/###/£££ = $p \leq 0.001$, **/##/££= $p \leq 0.01$ */#/£= $p \leq 0.05$.

Table II: Target crossings (TC, in frequency/ minute) and time spent in target (TT, in seconds/minute) in probe trial of Morris water maze test in different groups of rats

Variables in probe trial day	Groups			
	NC	SC	ColC	Pre PE Exp
TC	8.00 ± 0.26	7.17 ± 0.27	1.66± 0.18***	7.00±0.37###
TT	18.16 ± 0.48	16.17 ± 0.61	5.83± 0.67***	17±0.37###

Each column symbolizes mean ± SEM for 6 rats. Values in parenthesis indicate ranges. Statistical analysis was done by ANOVA (among groups) followed by Bonferroni's post hoc test (between groups). * = SC vs ColC, # = ColC vs Pre PE Exp. In the interpretation of results, $p \leq 0.05$ was considered as significant. ***/### = $p \leq 0.001$.

Effect of pretreatment of EEPE on working memory

In Table III, it was demonstrated that ColC rats exhibited a significantly ($p \leq 0.001$) higher mean EL compared to SC rats across all trials on all test days. Nevertheless, EEPE enhanced the learning performance of our rats, as indicated by statistically

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significant differences in mean EL between our ColC and experimental Pre PE Exp ($p \leq 0.01$ in trial 1 and 2, $p \leq 0.001$ in trial 3 and 4) rats. Notably, the differences in this variable were statistically non-significant between NC and Pre PE Exp in trial 4 across all test days. These findings imply that colchicine caused a learning impairment in working memory, while our PE supplementation effectively mitigated this impairment to levels comparable to those of normal rats.

Table III: Mean escape latency (EL, in seconds) in training and test phase of Morris water maze test in different groups of rats

Mean EL in trial	Groups			
	NC	SC	ColC	Pre PE Exp
1	20.75±0.59	22.13±1.84	41.13±1.34***	31.63±1.83##/££
2	10.88±0.63	14.88±1.74	37.38±1.12***	25.38±2.13##/£££
3	8.38±0.52	9.88±1.09	32.75±1.19***	23±0.83###/£££
4	7.75±0.52	10.38±1.25	27.63±1.14***	12.88±1.29###

Trial 1 = mean ± SEM of 4 trial 1s of 6 rats in consecutive 4 days; Trial 2 = mean ± SEM of 4 trial 2s of 6 rats in consecutive 4 days; Trial 3 = mean ± SEM of 4 trial 3s of 6 rats in consecutive 4 days; Trial 4 = mean±SEM of 4 trial 4s of 6 rats in consecutive 4 days. Values in parenthesis indicate ranges. Statistical analysis was done by ANOVA (among groups) followed by Bonferroni's post hoc test (between groups). * = SC vs ColC, # = ColC vs Pre PE Exp, £ = NC vs Pre PE Exp. In the interpretation of results, $p \leq 0.05$ was considered as significant. **/##/££ = $p \leq 0.01$; ***/###/£££ = $p \leq 0.001$.

Discussion

Memory represents one of the most complex functions of the brain, crucial for the efficient functioning of any living being. Impairment of this memory can significantly obstruct an individual's cognitive capabilities, thereby affecting their personal conduct and social interactions. Neverthless, in clinical environments, patients experiencing spatial memory impairment often seek medical consultation following a diagnosis. It emphasizes the significance of studying the influence of any intervention after spatial memory impairment. Notably, there is a lack of experimental research on the role of PE fruit in preventing hippocampal damage induced memory impairment. This finding motivates us to investigate the potential effect of systemic EEPE administration in preventing colchicine-induced memory decline.

In this study, we used Morris water maze (MWM) test to examine the effects of Ethanolic extract of Phyllanthus emblica (EEPE) in spatial learning and memory on colchicine induced memory impaired rat model. Here, in the Working memory version, the platform's location was altered daily, forcing the animals to acquire and utilize new orientation cues within minutes during the testing session. Conversely, in the Reference memory task, the animals underwent training for 6 days to memorize a fixed platform position, with the consolidation of learned memories affecting the animal's final performance. Through the application of this memory test on the experimental model, the current study revealed that pretreatment with EEPE could enhance memory impairment.

In this research, we administered 15 µg colchicine/hippocampus to induce memory impairment through significant damage to hippocampal cells, as suggested by Nakagawa et al. (1987)[18]. The intra hippocampal colchicine may interact with microtubule binding protein (tubulin)[23], potentially leading to their depolymerization[24], which results in reduced cellular growth and differentiation[18] as well as damage to hippocampal cholinergic neurons[25,26]. Furthermore, intrahippocampal colchicine may lead to an increase in acetyl cholinesterase (AchE) activity[5], serving as indirect evidence of cholinergic neuronal damage, along with an increase in the development of beta amyloid protein (BAP) in the hippocampus[3]. In this study, both reference and working memory deficits were observed in the memory-impaired rats, as indicated by their diminished learning and retrieval capabilities compared to the normal and sham control groups of rats.

However, PE has shown improvements in both reference and working memory deficits, as demonstrated by enhanced learning capabilities, consolidation and retrieval skills in our experimental rats (Pretreated) when compared to memory-impaired rats. In our research, intraperitoneal PE may inhibit AchE activity, leading to an increase in acetylcholine (Ach) levels in the hippocampus, which in turn enhances learning and memory[27]. This systemic administration of PE may also prevent memory impairment by reducing the formation of Aβ plaques through the inhibition of APP breakdown by β and γ secretases[27]. Besides, PE treatment may inhibit the release of proinflammatory cytokines (TNF-α, IL-1β) in the hippocampus, thereby mitigating neuroinflammation and neuronal cell death[28].

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As a whole, experimental rats (Pre PE Exp) showed almost similar reference and working memory performances when compared to those of normal rats. From this finding, we proposed that our 7 days pretreatment of EEPE administration could prevent almost all the aspects of memory disability near to normal.

Conclusion

Phyllanthus emblica (Amloki) can prevent intrahippocampal colchicine induced cognitive dysfunction in male long-Evans rats.

Conflict of interest

None

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