Original Article

Learning and memory enhancing activity of *Ficus carica* (Fig): An experimental study in rats

Abstract

Objective: The study aimed to assess the learning and memory enhancing activity of the ethanolic fruit extract of *Ficus carica* in rats using elevated plus maze (EPM), Hebb-William maze (HWM) and Morris water maze (MWM). **Materials and Methods:** Wistar rats (100-150 g) of either sex, were divided into 5 groups (n = 6). Group I (control) animals received vehicle, Group II (scopolamine control) animals received scopolamine (0.4 mg/kg i.p), Groups III and IV animals received ethanolic fruit extract of *F. carica* (200 mg/kg and 400 mg/kg p.o) and Group V animals received piracetam (400 mg/kg i.p) for 27 days. The rats of Groups III-V were injected with a single dose of scopolamine (0.4 mg/kg i.p) on 19th and 27th day. Assessment of transfer latency (TL), time taken to reach reward chamber (TRC) and swim latency (SL) was done on 19th and 27th day using EPM, HWM and MWM, respectively. The data was analyzed by one-way Analysis of Variance followed by Dunnett's test. $P \leq 0.05$ was considered to be significant. **Results:** Ethanolic fruit extract of *F. carica* decreased TL, TRC and SL in comparison to scopolamine treated rats. **Conclusion:** The fruit of *F. carica* enhanced learning and memory activity.

Key words:
Elevated plus maze, Hebb-William maze, learning, memory, Morris water maze, piracetam, scopolamine

Introduction

Learning is defined as the acquisition of information and skills and subsequent retention of that information is called memory.[1] Memory is one of the complex functions of the brain. It ultimately involves multiple neuronal pathways and neurotransmitters.[2] Learning and memory can be conceived as both psychological process, as well as a change in synaptic neural connectivity.[1] Loss of memory and disturbed cognitive functions are major concerns in people afflicted with neurological diseases world-wide.

Memory is the natural counter part of learning. Poor memory, low retention and slow recall are common problems in today's stressful and competitive world. Age, stress, emotions are conditions that leads to cognitive disorders.[3] Cognitive deficits have long been recognized as severe and consistent neurological disorders associated with numerous psychiatric and neuro-degenerative states such as senile dementia, multi-infract dementia, Parkinson's disease, Huntington's chorea etc[1] and Alzheimer's disease, amnesia, delirium, depression, schizophrenia etc. are the results of impairments in learning and memory.[2]

The Indian system of medicine is replete with medicinal plants claimed to promote learning, memory and intelligence. Plants like *Bacopa monnerie*, *Azadirachta indica*, *Withania somnifera*, as well as *Ocimum sanctum*, have been investigated for their effect on cognitive functions.[4] The fruit of *Ficus carica* Linn., family *Moraceae*, is commonly known as fig. *F. carica* is a potential herbal drug and traditionally used as mild laxative, diuretic, expectorant, aphrodisiac, anti-pyretic, purgative, in the treatment of diabetes, leucoderma and ringworms, inflammation and paralysis and for checking hemorrhage etc.[5] *Ficus* species contain flavonoids, glycosides, alkaloids,

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phenolic acids (gallic acid and ellagic acid), steroids, saponins, furanocoumarins (psoralen, bergapten) tannins, triterpinoids (oleanolic acid, ursolic acid, α-hydroxy ursolic acid, protocatechuic acid, maslinic acid) and vitamin C. The enzymatic constituents present are ascorbate oxidase, ascorbate peroxidase, catalase and peroxidase.[6]

Extensive literature search revealed that *F. carica* fruit possess learning and memory enhancing activity,[7] but failed to get the scientific, documentary evidence. It is also an ingredient in Janamghutti, a drop of which is given to newborn babies, traditionally, for about 40 days, all over India. Hence, present study is taken up to investigate and validate learning and memory enhancing activity of *F. carica* in young rats.

Materials and Methods

Plant material

Standardized ethanolic extract of *F. carica* fruit, procured from Green Chem Herbal extract and formulations, Bangalore, India was used for the study (Voucher specimen number for *F. carica* FCE/RD/01). The plant extract was suspended in distilled water (200 mg/ml) and administered orally to rats.

Chemicals and drugs

Scopolamine was procured from Zydus Health Care, Bangalore. Piracetam was procured from Micro Labs Limited, Bangalore.

Experimental animals

Inbred, young Wistar rats, 4-8 weeks old, weighing 100-150 g, were used in the study. The animals were maintained under standard laboratory conditions of room temperature of 24°C ± 5°C; relative humidity 45-55% and natural day and night cycle. The animals had free access to standard rat pellet (Pranav Agro Industry, Bangalore), with water supplied *ad libitum*. All the protocols and the experiments were conducted in compliance to ethical principles and guidelines provided by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Permission was taken from the animal ethics committee of Visveswarapura Institute of Pharmaceutical Sciences, Bangalore (Registration no 152/99/CPCSEA) before starting the animal experiments.

Experimental protocol

Wistar albino rats were divided into 5 groups of six rats each for each of the three models (elevated plus maze [EPM], Hebb-William maze [HWM] and Morris water maze [MWM]). Group I (control) animals received distilled water. Group II (scopolamine control) animals, received scopolamine 0.4 mg/kg i.p.[8] Groups III and IV animals, received ethanolic fruit extract of *F. carica*, 200 and 400 mg/kg p.o.[9] respectively for 27 days. Group V animals, received piracetam 400 mg/kg i.p.[7] for 27 days. Doses of *F. carica,* scopolamine and piracetam were selected based on the earlier study.[8,9] The rats of Groups III-V were subjected to training session on 16th, 17th and 18th day. On 19th day, single dose of scopolamine was administered to all the animals' except group one animals, 30 min after the respective treatment. Transfer latency (TL) using EPM, time taken to reach reward chamber (TRC) in HWM and swim latency (SL) using MWM was assessed 45 min thereafter respectively. The respective treatments continued for 1 week and on 27th day, scopolamine was administered to all the animals' except group one animal's, 30 min after the respective treatment. TL, TRC and SL was assessed 45 min thereafter respectively EPM served as the exteroceptive behavioral model to evaluate memory in rats. In this model, the change in the latency to go from open arm to closed arm is an indicator of learning and memory. The EPM consist of two open arms and two closed arms (50 cm × 10 cm × 40 cm) with an open roof arranged so that the two arms are opposite to each other. The maze is elevated to a height of 50 cm. On the 1st day each rat was placed at the end of an open arm, facing away from the central platform. TL is the time taken by the animal to move from the open arm into any one of the enclosed arms with all its four paws. TL was recorded on the 1st day for each animal. The rat was allowed to explore the maze for another 2 min and then returned to its home cage. Retention of this learned-task (memory) was examined 24 h after the 1st day trial. The animals, after 15 days of drug(s) treatment underwent the training on 16th, 17th and 18th day. The retention of memory was examined again on 19th and 27th day of the treatment, 45 min after the scopolamine injection. Significant reduction in TL value indicate improvement in memory.[8,10]

HWM is an incentive-based exteroceptive behavioral model useful for measuring spatial working memory of rats. In this model, changes in time taken by the animal to reach reward chamber from start box (TRC) was taken as learning and memory enhancing activity. The HWM, also called as rectangular maze, consists of completely enclosed rectangular box with an entry and reward chamber appended at opposite ends. The box is partitioned with wooden slots into blind passages leaving just one twisting corridor leading from the entry to the reward chamber. The rat was placed in the animal chamber or start box and the door was opened to facilitate the entry of the animal into the next chamber. The door of the start box was closed immediately after the animal moves into the next chamber to prevent back-entry. The time taken by the animal to reach the reward chamber from the start box was recorded on the 1st day (training session) for each animal. Each animal is allowed to explore the maze for 3 min with all the doors opened before returning to its home cage. TRC was recorded on the 1st day (training session) for each animal. Retention of this learned task (memory) was examined 24 h after the 1st day trial. The animals, after 15 days of drug(s) treatment underwent the training on 16th, 17th and 18th day. The retention of memory was examined again on 19th and 27th day of the treatment, 45 min after the scopolamine injection. Significant reduction in TRC value indicate improvement in memory.[8,10]

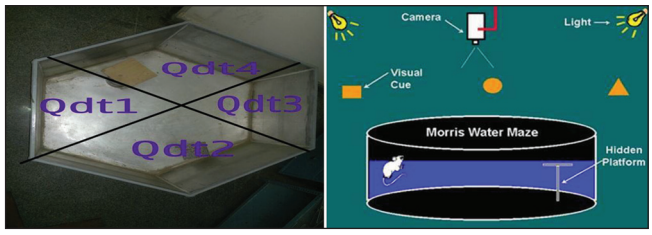
MWM is used to assess the spatial memory in young rats and is based on the principle that, "the rat learns to find an escape

platform hidden under water when allowed in the water tank". The water maze consists of a circular/hexagonal pool (150 cm diameter and 30 cm height) filled with water to a depth of 20 cm. A circular/square escape platform (6 cm diameter and 12 cm high) is located in 1 quadrant 2 cm below the water level. The water, at about 25°C, was made opaque using titanium dioxide suspension during the experiment. Initially, the rats were trained on 3 consecutive days, with 4 consecutive trials per day with an inter-trial interval of 6-10 min. Each trial was started from one of four assigned polar positions with a different sequence each day. The latency to find the platform was measured as the time of placement of the rat in the water to the time it finds the platform.[11] If the animal fails to find the platform in any trial within 3 min it is placed on it for 10 s. During the drug treatment period of 27 days, the animals were trained once daily on MWM on day 16, 17 and 18. Assessment of learning and retention of memory was done 45 min after the scopolamine injection on day 19 and 27.

Statistical analysis

All the values are expressed as mean ± standard error of the mean. The data was analyzed by one-way Analysis of Variance, followed by Dunnett's test $P \leq 0.05$ was considered as significant.

Photograph of elevated plus maze



Photograph of Morris Water maze

Photograph of Hebb-William maze

Results

Effect of *F. carica* on TL using EPM

As it has shown in Table 1, scopolamine increases the time taken by rat to reach the closed arms on a final evaluation (27th day) compared with the control groups, (i.e. induces amnesia). *F. carica* decreased TL significantly ($P < 0.01$) on the day 27th which was comparable with Piracetam (400 mg/kg).

Effect of *F. carica* on time TRC using HWM

As shown in Table 2, scopolamine increases the TRC on the final evaluation (27th day) compared to control groups, (i.e. induces amnesia). *F. carica* pretreatment decreased TRC significantly ($P < 0.01$) on the day 27th which was comparable with Piracetam (400 mg/kg).

Effect of *F. carica* on SL using MWM

As shown in Figure 1, scopolamine increases SL on the final evaluation (27th day) compared to control groups, (i.e. induces amnesia). *F. carica* pretreatment decreased SL significantly ($P < 0.01$) on the day 27th which was comparable with Piracetam (400 mg/kg).

Discussion

Learning is the process of acquiring knowledge and memory is the retention of the acquired knowledge, which can be retrieved as and when, required.[12] The present study was undertaken to evaluate learning and memory enhancing activity of *F. carica* in amnesic rats. The study was designed to investigate the effect of ethanolic fruit extract of *F. carica* on TL, TRC and SL.

In our study we found that *F. carica* reduced TL, time TRC and SL in scopolamine induced amnesic rats using EPM, HWM, MWM respectively. This can be interpreted as learning and memory enhancing activity of *F. carica*, which may be due to its antioxidant[6] and immunostimulant activity.[13] Antioxidant properties of *F. carica* was attributed to flavonoids and also to non-enzymatic phenolic compounds like, gallic acid and ellagic acid.[6] Several studies have shown that flavonoids

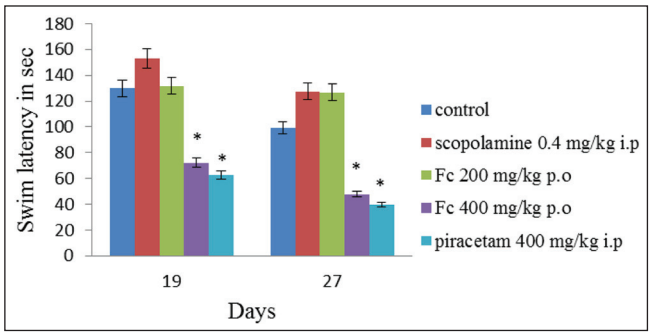


Figure 1: Effect of ethanolic fruit extract of *Ficus carica* on swim latency in rats using Morris-Water maze values are expressed as mean ± standard error of mean, $n = 6$. *$P < 0.05$ v/s scopolamine, one-way Analysis of Variance followed by Dunnett's test

Table 1: Effect of ethanolic fruit extract of *Ficus carica* on TL in rats using EPM

Treatment	TL on 16th day (s)	TL on 17th day (s)	TL on 19th day (s)	TL on 27th day (s)
Control	56.17±5.199	53.83±4.277	19.150±0.8918	17.988±0.42
Scopolamine 0.4 mg/kg i.p	65.50±8.401	63.67±2.940	35.66±2.963	39±2.633
Fc 200 mg/kg p.o	55.89±5.580	52.33±4.477	37±4.274	22.5±4.185
Fc 400 mg/kg p.o	48.64±8.291	27.17±4.012*	5.362±0.597*	3.942±0.4098*
Piracetam 400 mg/kg i.p	38.36±10.72*	25.50±4.13*	4.378±0.47*	2.838±0.11*

Values are expressed as mean ± SEM; *n* – 6; **P*<0.05 versus scopolamine; one way Analysis of Variance followed by Dunnett's test; TL – Transfer latency; SEM – Standard error of mean; EPM – Elevated plus maze

Table 2: Effect of ethanolic fruit extract of *Ficus carica* on TRC in rats using HWM

Treatment	TRC on 16th day (s)	TRC on 17th day (s)	TRC on 19th day (s)	TRC on 27th day (s)
Control	131.66±12.34	101.83±7.842	62.33±6.09	28.33±4.01
Scopolamine 0.4 mg/kg i.p	142.16±11.731	123.6±9.58	117.33±8.35	110.83±9.43
Fc 200 mg/kg p.o	126.16±5.036	119.5±4.349	112.33±3.97	107.5±4.031
Fc 400 mg/kg p.o	83.5±12.225*	55.66±7.03*	33.83±4.64*	13.5±2.37*
Piracetam 400 mg/kg i.p	68.83±4.07*	47.166±4.31*	20.66±3.52*	10±1.15*

Values are expressed as mean ± SEM; *n* – 6; **P*<0.05 versus scopolamine; one way Analysis of Variance followed by Dunnett's test; TRC – Time taken to reach reward chamber; SEM – Standard error of mean; HWM – Hebb-William maze

and other fruit and vegetable-derived phytochemicals have a beneficial effect on learning and memory. Previous reports have established a role for flavonoids in preventing dementia in humans.[14] It's reported, that Immunosuppressant drugs have produced a cognitive impairment, histopathologically associated with degeneration of hippocampal neurons. Since alteration of immune function affects learning and memory, it was hypothesized that immunostimulant drugs improves learning and memory.[15] Earlier studies[6,13] have reported antioxidant and immunostimulant activity of *F. carica*, justifying the results in present study.

As could be observed from Tables 1 and 2, Figure 1 the TL, TRC and SL is reduced significantly, in each group of animals (control, scopolamine control, *Ficus* treated and piracetam treated) on 19th day when compared to 16th day, which is the 1st day of training. Parle *et al*., 2006, have reported that regular rehearsal help consolidation of long-term memory.[16] The training for 3 consecutive days and memory enhancement due to drug(s) is thus reflected in the drop of TL, TRC and SL values in *F. carica* and piracetam treated animals from 16th day to 19th and to 27th day [Tables 1 and 2, Figure 1].

Conclusion

F. carica or fruit of fig improves learning and memory. This may be attributed to antioxidant and immunostimulant activity, which is due to, flavonoids present in it.

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