Improvement of Learning and Memory of Mice by Plumbagin

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Received: July 7, 2016 | Revised: August 16, 2016 | Accepted: Oct. 17, 2016

Published online: November 02, 2016

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Abstract: Roots of Plumbago zeylanica have been reported to improve learning and memory of mice, but the effect of plumbagin on learning and memory of mice and the possible mechanisms for its effect on memory have not been explored till date. So the present study was designed to evaluate the effect of plumbagin on learning and memory of Swiss young male albino mice. Plumbagin (4, 8, 16 mg/kg, p.o.) and physostigmine (0.1 mg/kg, i.p.) per se were administered for 15 successive days to separate groups of mice. Behavioral parameters of learning and memory were recorded using Morris water maze. Acetylcholinesterase activity was estimated in brain of mice. Effect of plumbagin on scopolamine (0.4 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.)-induced amnesia was also investigated. Locomotor activities of mice were also recorded. Plumbagin (8 and 16 mg/kg) and physostigmine significantly improved learning and memory of mice, as indicated by decrease in escape latency during training and increase in time spent in target quadrant of Morris water maze during retrieval. The drugs did not show any significant effect on locomotor activities of mice. Memory improving activity of plumbagin (16 mg/kg) was equivalent to physostigmine. Plumbagin significantly reversed scopolamine- and diazepam- induced amnesia in mice. Plumbagin and physostigmine also significantly reduced brain acetylcholinesterase activity of mice. In conclusion, plumbagin significantly improved memory of mice possibly through inhibition of brain acetylcholinesterase activity and through involvement of GABA-benzodiazepine pathway. Thus, plumbagin may be explored further for management of cognitive dysfunction.

Keywords: Acetylcholinesterase, Learning, Memory, Morris water maze, Plumbagin
1. INTRODUCTION

Learning is acquisition of new knowledge and skills, whereas memory is retention and retrievals of facts composed of experiences (Kumar et al., 2012). Alzheimer’s disease is a progressive neurodegenerative disorder characterized by the gradual onset of dementia. It is characterized by gradually progressive decline in cognitive function, with deficits especially in memory retrieval (Kalaria et al., 2008). The primary cause of Alzheimer’s disease appears to be reduction in cholinergic activity. Acetylcholinesterase enzyme (AChE) plays a key role in the regulation of the cholinergic system and hence, inhibition of AChE is a most promising target for the treatment of Alzheimer’s disease (Lu et al., 2010). A number of cholinesterase inhibitors like donepezil, rivastigmine, tacrine and rivastigmine etc. are in practice for the treatment of various cognitive disorders (Ellis, 2005). However, the adverse effects associated with anti-cholinesterase drugs (rivastigmine, galantamine, donepezil) include anorexia, nausea, vomiting, diarrhoea, and insomnia (Kavirajan and Schneider, 2007). Physostigmine, a cholinesterase inhibitor, improved memory of Alzheimer’s disease patients (Mohs et al., 1985). But this drug has a short half-life and requires complex forms of administration (Filho and Birks, 2001). So there is a need to discover new drugs with better efficacy and having less adverse effects. Plants have been used since ancient times in traditional medicinal systems for the treatment of memory dysfunction. Bacopa monniera, commonly called as Brahmi, has been proven to be clinically effective in treatment of cognitive disorders (Pase et al., 2012). The bioactive compounds isolated from plants such as galantamine (Raskind et al., 2000), huperzine alpha (Zhang et al., 2002), etc. have been reported to be effective for treatment of cognitive deficits in patients of dementia.

Plumbagin, an active constituent of Plumbago zeylanica roots, has been reported to possess various pharmacological activities such as antioxidant (Kumar et al., 2013), neuroprotective (Son et al., 2010), antiparkinsonian (Choi et al., 2012), anti-inflammatory (Lou et al., 2010) and antidepressant (Dhingra and Bansal, 2015). Plumbago zeylanica roots have been reported to improve learning and memory of mice (Mittal et al., 2010), but the effect of plumbagin on learning and memory of mice has not been explored till date. Therefore, the present study was designed to investigate the effect of plumbagin on learning and memory of mice by employing behavioral models.

2. MATERIALS AND METHODS

2.1 Experimental animals
Swiss male albino mice, weighing around 25-30 g, were purchased from Disease Free Small Animal House, Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar (Haryana, India). Female mice were not included in the study because estrogens (female sex hormones) have been found to have memory improving effect (Harburger et al., 2007), so we excluded female mice and used only male mice. Animals were housed separately in groups of 6 - 7 per cage (Polycarbonate cage size: 29×22×14 cm) under proper laboratory conditions with alternating light and dark cycle of 12 h each. The animals had free access to food and water, except food was withdrawn 2 h before and 2 h after drug administration. The animals were acclimatized for at least five days before behavioral experiments which were carried out between 09:00 and 17:00 h. The experimental protocol was approved by Institutional Animals Ethics Committee (IAEC) and animal care was taken as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Environment and Forests, Government of India.

2.2 Drugs and chemicals

Plumbagin (Sigma-Aldrich, St. Louis, USA); physostigmine (Hi-Media Laboratories, Mumbai); Carboxy methyl cellulose (CDH- Central Drug House, New Delhi); Scopolamine hydrobromide (Sigma-Aldrich, St. Louis, USA); Acetylcholine iodide; 5, 5'-dithiobis-2- nitrobenzoic acid (Hi-Media laboratories Pvt. Ltd., Mumbai); Acetyl thiocholine iodide (Hi-Media laboratories Pvt. Ltd., Mumbai) were used in the present study.

2.3 Selection of doses

Doses of various drugs were selected on the basis of literature, i.e. 4, 8 and 16 mg/kg for plumbagin (Sivakumar et al., 2005), 0.4 mg/kg for scopolamine (Dhingra et al., 2004), 0.1 mg/kg for physostigmine (Sharma and Kulkarni, 1992).

2.4 Vehicle

Plumbagin was dissolved in 1% w/v carboxy methyl cellulose (CMC) solution. Scopolamine hydrobromide was dissolved in normal saline.

2.5 Laboratory model employed for evaluation of effect of plumbagin on learning and memory of mice

2.5.1 Morris water maze
The procedure and parameters for testing learning and memory of mice using Morris water maze were followed as reported earlier (Domange et al., 2013; Morris, 1984; Park and Singh, 2007). Briefly, Morris water maze for mice consisted of a circular pool (60 cm in diameter, 25 cm in height) filled to a depth of 20 cm with water maintained at 25° C. The water was made opaque with non-toxic white colored dye (Pidilite Ltd., Maharashtra, India). Two threads were fixed at right angle to each other on rim of the pool to divide the tank into four equal quadrants. Four quadrants were designated as Q1, Q2, Q3 and Q4. A submerged platform (with top surface 6 cm × 6 cm and painted in white) was placed inside the target quadrants (Q4 in present study) of this pool 1 cm below surface of water. The position of platform was kept at the same place throughout the training session. Each animal was subjected to four consecutive trials each day with a gap of 5 min for four consecutive days (starting from 11th day of drug administration to 14th day), during which they were allowed to escape on to the hidden platform and to remain there for 20 sec. During the training session, the mouse was gently placed in one of the quadrants, facing the wall of pool with drop location changing for each trial, and allowed 120 sec to locate submerged platform. If the mouse failed to find the platform within 120 s, it was guided gently on to the platform and allowed to remain there for 20 s. Escape latency (EL) is the time taken by the animal to move from the starting quadrant to find the hidden platform in the target quadrant. From 11th day to 14th day of training session, EL was recorded for each animal. Each animal was subjected to training trials for four consecutive days, the starting position was changed with each exposure as mentioned below and target quadrant (Q4 in the present study) remained constant throughout the training period.

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Q 1</th>
<th>Q 2</th>
<th>Q 3</th>
<th>Q 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 2</td>
<td>Q 2</td>
<td>Q 3</td>
<td>Q 4</td>
<td>Q 1</td>
</tr>
<tr>
<td>Day 3</td>
<td>Q 3</td>
<td>Q 4</td>
<td>Q 1</td>
<td>Q 2</td>
</tr>
<tr>
<td>Day 4</td>
<td>Q 4</td>
<td>Q 1</td>
<td>Q 2</td>
<td>Q 3</td>
</tr>
</tbody>
</table>

On the fifth day (i.e. 15th day of drug administration), platform was removed and mouse was placed in any of the three quadrants except Q4 and allowed to explore the target quadrant for 300 sec. The mean time spent in the target quadrant in search of the missing platform was noted as index of retrieval or memory. The observer always stood at the same position. Care was
taken not to disturb the relative location of water maze with respect to other objects in the laboratory.

### 2.5.2 Measurement of locomotor activity

Locomotor activities of control and drug-treated animals were measured for a period of 5 min using photoactometer (INCO, Ambala, India) (Dhingra et al., 2012).

### 2.6 Biochemical estimation

#### 2.6.1 Collection of brain sample

After recordings behavioral parameters on 15th day using Morris water maze, the animals were sacrificed on 16th day by cervical dislocation. Whole brain was carefully removed from the animals. For preparation of brain homogenate, the fresh whole brain was weighed first and then homogenized in 10 volumes of 0.1 M phosphate buffer (pH 8) using a glass homogenizer. The homogenate was centrifuged at 3000 rpm for 10 min at 4°C using refrigerated centrifuge (Remi, Mumbai). The resultant cloudy supernatant liquid was used for the estimation of brain acetyl cholinesterase activity.

#### 2.6.2 Estimation of brain acetylcholinesterase activity

Brain acetyl cholinesterase activity was estimated by the method as reported earlier (Ellman et al., 1961). 0.4 ml of brain homogenate was added into a test tube containing 2.6 ml of phosphate buffer. 5,5-dithiobis-2-nitrobenzoic acid reagent (0.1 ml) was added to the above mixture and absorbance was noted at 412 nm. Then 0.02 ml of acetylcholine iodide solution was added and again absorbance was noted 15 min thereafter. Change in absorbance per minute was calculated. The following formula was used to calculate rate of hydrolysis of substrate:

\[
R = \frac{\text{Change in absorbance/min} \times 5.74 \times 10^{-4}}{C_0}
\]

\[R=\text{Rate of hydrolysis of acetylcholine iodide/ min/ mg tissue}\]

\[C_0=\text{weight of tissue homogenate in mg/ml.}\]

### 2.7 Experimental protocol

#### 2.7.1 Groups for Morris water maze

Groups 1 to 5 (n = 7 each): CMC(1%w/v), plumbagin (4, 8 and 16 mg/kg, p.o.) and physostigmine (0.1 mg/kg i.p.), respectively were administered for 15 successive days. Escape latency (EL) was recorded 120 min after drug
administration from 11th day to 14th day. On 15th day, time spent in target quadrant (TSTQ) was noted 120 min after the drug administration. In case of animals administered with physostigmine, EL and TSTQ was noted after 30 min of drug administration.

Groups 6 and 7 (n = 6 each): CMC (1% w/v) and plumbagin (16mg/kg, p.o.) respectively were administered for 15 successive days. EL was recorded 120 min after drug administration from 11th day to 14th day. On 15th day, scopolamine (0.4 mg/kg) was injected 30 min after oral administration of plumbagin (16mg/kg) and TSTQ was noted 45 min after injection of scopolamine.

Groups 8 and 9 (n = 7 each): CMC (1% w/v) and plumbagin (16mg/kg, p.o.) respectively were administered for 15 successive days. EL was recorded 120 min after drug administration from 11th day to 14th day. On 15th day, diazepam (1 mg/kg, i.p.) was injected 30 min after oral administration of plumbagin (16 mg/kg) and TSTQ was noted 45 min after injection of diazepam.

2.7.2 Groups for locomotor activity
Groups 10 to 14 (n=6 each group): CMC (1%w/v), plumbagin (4, 8 and 16 mg/kg, p.o.) and physostigmine (0.1 mg/kg, i.p.), respectively were administered for 15 successive days. Locomotor activity was measured on 15th day using actophotometer (INCO, Ambala).

2.7.3 Groups for biochemical estimation
Brain acetylcholinesterase activity was measured 24 hour after behavior testing on animals of groups 1 to 5.

2.8 STATISTICAL ANALYSIS
All the results are expressed as Mean ± S.E.M. Data were analyzed by analysis of variance (ANOVA) followed by Tukey’s post hoc test in Graph Pad Instat version 3.05. p<0.05 was considered as significant

3. RESULTS
3.1 Effect of plumbagin and other drugs employed on escape latency (EL) and time spent in target quadrant (TSTQ) of mice using Morris water maze
Decrease of EL and increase of TSTQ by mice in Morris water maze indicates improvement of learning and memory and vice versa. Physostigmine (0.1mg/kg, i.p.) and highest dose (16 mg/kg, p.o.) of plumbagin per se administered for 15 successive days significantly decreased EL of mice from 11th to 14th day and
Table 1: Effect of plumbagin and physostigmine on escape latency (EL) of mice using Morris Water Maze.

<table>
<thead>
<tr>
<th>Treatment for 15 days</th>
<th>Dose (Kg⁻¹)</th>
<th>Escape latency (sec) Day-11</th>
<th>Escape latency (sec) Day-12</th>
<th>Escape latency (sec) Day-13</th>
<th>Escape latency (sec) Day-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (vehicle)</td>
<td>10ml</td>
<td>95.32 ± 1.35</td>
<td>94.00 ± 1.53</td>
<td>92.68 ± 1.36</td>
<td>90.62 ± 5.45</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>0.1mg</td>
<td>51.96 ± 5.58ᵃ</td>
<td>48.67 ± 1.42ᵃ</td>
<td>55.39 ± 1.82ᵃ</td>
<td>42.07 ± 1.45ᵃ</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>4 mg</td>
<td>94.53 ±1.81ⁿˢ</td>
<td>89.07 ± 2.37ⁿˢ</td>
<td>78.96 ± 1.88ⁿˢ</td>
<td>68.75 ± 1.44ⁿˢ</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>8 mg</td>
<td>85.82 ± 1.00ⁿˢ</td>
<td>81.00 ± 0.512ⁿˢ</td>
<td>53.39 ± 1.51ⁿˢ</td>
<td>42.14 ± 1.46ⁿˢ</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>16 mg</td>
<td>51.94 ± 2.13ᵃ</td>
<td>57.90 ± 1.99ᵃ</td>
<td>57.87 ± 2.04ᵃ</td>
<td>57.31 ± 1.31ᵃ</td>
</tr>
</tbody>
</table>

n=7 each group. Values are expressed as Mean ± SEM. Data was analyzed by one-way ANOVA followed by Tukey's Post-hoc test.

F (4, 30) = 58.946; p<0.0001 (Day 11)
F (4, 30) = 125.53; p<0.0001 (Day 12)
F (4, 30) = 99.395; p<0.0001 (Day 13)
F (4, 30) = 55.057; p<0.0001 (Day 14)

ᵃ = p< 0.001; as compared to control group; ns =non-significant

Table 2: Effect of plumbagin and other drugs employed on time spent in target quadrant (TSTQ) of Morris Water Maze.

<table>
<thead>
<tr>
<th>Treatment for 15 days</th>
<th>No. of animals (n)</th>
<th>Dose (kg)</th>
<th>Time spent (sec) in target quadrant (15th day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (vehicle)</td>
<td>7</td>
<td>10 ml</td>
<td>38.42 ± 2.88</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>7</td>
<td>0.1 mg</td>
<td>158.71±3.35ᵇ</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>7</td>
<td>4 mg</td>
<td>41.14±4.06ⁿˢ</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>7</td>
<td>8 mg</td>
<td>47.00 ± 4.32ᵃ</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>7</td>
<td>16 mg</td>
<td>127.00±4.80ᵇ</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>6</td>
<td>0.4 mg</td>
<td>28.14±5.18ᵇ</td>
</tr>
<tr>
<td>Diazepam</td>
<td>7</td>
<td>1 mg</td>
<td>29.57±3.26ᵃ</td>
</tr>
<tr>
<td>Plumbagin+ scopolamine</td>
<td>6</td>
<td>16 mg+0.4 mg</td>
<td>71.85 ± 2.91ᶜ</td>
</tr>
<tr>
<td>Plumbagin+ diazepam</td>
<td>7</td>
<td>16 mg + 1 mg</td>
<td>65.14±2.61ᵈ</td>
</tr>
</tbody>
</table>

Values are expressed as Mean ± SEM. Data was analyzed by one-way ANOVA followed by Tukey’s Post-hoc test.

F (8, 54) = 1016.7; p<0.0001

ᵃ= p<0.01; b = p<0.001 as compared to control; c = p<0.001 as compared to scopolamine; d = p<0.001 as compared to diazepam; ns = non-significant
increased TSTQ by mice on 15\textsuperscript{th} day as compared to the control, thus showed significant improvement of learning and memory. The lowest dose (4 mg/kg, \textit{p.o.}) and middle dose (8 mg/kg, \textit{p.o.}) of plumbagin significantly decreased EL on 13\textsuperscript{th} and 14\textsuperscript{th} days; and did not significantly affect EL on 11\textsuperscript{th} and 12\textsuperscript{th} days. Middle dose (8 mg/kg, \textit{p.o.}) of plumbagin also significantly increased TSTQ as compared to vehicle treated control. Scopolamine (0.4 mg/kg \textit{i.p.}) and diazepam (1 mg/kg, \textit{i.p.}) \textit{per se} administered on 15\textsuperscript{th} day significantly decreased TSTQ by mice, indicating their amnesic effects. Plumbagin (16 mg/kg, \textit{p.o.}) significantly reversed scopolamine-and diazepam-induced amnesia as compared to respective scopolamine and diazepam treated groups (Tables 1 and 2).

### 3.2 Effect of plumbagin and physostigmine on brain AChE activity of mice

**Table 3:** Effect of plumbagin and physostigmine on brain AChE activity of mice.

<table>
<thead>
<tr>
<th>Treatment for 15 days</th>
<th>Dose (kg\textsuperscript{-1})</th>
<th>Acetylcholinesterase activity (mol/l per min × 10\textsuperscript{-6}/g of tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (1% w/v CMC)</td>
<td>10 ml</td>
<td>0.057 ± 0.005</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>0.1 mg</td>
<td>0.0185 ± 0.002\textsuperscript{a}</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>4 mg</td>
<td>0.043 ± 0.005\textsuperscript{a}</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>8 mg</td>
<td>0.025 ± 0.001\textsuperscript{a}</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>16 mg</td>
<td>0.022 ± 0.003\textsuperscript{a}</td>
</tr>
</tbody>
</table>

\(n=6\) each group. Values are expressed as Mean ± SEM. Data was analyzed by one-way ANOVA followed by Tukey’s Post-hoc test.

\(F (4, 25) =21.211; p<0.0001\)

\(a= p<0.01\) as compared to control;

**Table 4:** Effect of plumbagin and physostigmine on locomotor activity of mice.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose (kg\textsuperscript{-1})</th>
<th>Locomotor activity counts / 5 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>10ml</td>
<td>430.5 ± 8.59</td>
</tr>
<tr>
<td>Physostigmine</td>
<td>0.1mg</td>
<td>415.83 ± 10.29</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>4 mg</td>
<td>429 ± 9.67</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>8 mg</td>
<td>442 ± 20.67</td>
</tr>
<tr>
<td>Plumbagin</td>
<td>16 mg</td>
<td>418 ± 12.50</td>
</tr>
</tbody>
</table>

\(n=6\) each group. Values are expressed as Mean ± SEM. Data was analyzed by one-way ANOVA followed by Tukey’s Post-hoc test.

\(F (4, 25) =0.6522; p=0.6307\)
Administration of plumbagin (8 and 16 mg/kg) and physostigmine per se for 15 consecutive days produced a significant decrease in brain AChE activity as compared to control group. The lowest dose of plumbagin (4 mg/kg) did not produce significantly decrease in AChE activity as compared to control group (Table 3).

3.3 Effect of plumbagin and physostigmine on locomotor activity of mice.

Plumbagin (4, 8 and 16 mg/kg) and physostigmine per se administered for 15 consecutive days did not significant affect locomotor activity of mice as compared to vehicle treated control (Table 4).

4. DISCUSSION

In the present study, plumbagin (16mg/kg) administered for 15 successive days significantly improved learning and memory of mice. Memory improving effect of plumbagin was comparable to physostigmine, a well known anticholinesterase nootropic drug. Morris water maze was employed as a behavioral model for evaluation of learning and memory. Plumbagin significantly decreased EL during training and it significantly increased TSTQ during retrieval, indicating improvement of learning and memory. It did not show any significant change on locomotor activities of mice as compared to the vehicle treated control, so this compound did not produce any motor effects. Thus, memory enhancing effect of plumbagin is specific and not false positive. Out of the three doses (4, 8 and 16 mg/kg, p.o.) of plumbagin, highest dose (16 mg/kg) produced better (p<0.001) memory enhancing effect in mice as compared to middle dose of (8 mg/kg) (p <0.05), whereas lowest dose (4 mg/kg) did not show significant memory improving effect. Hence, the highest dose (16 mg/kg) of plumbagin was employed for elucidating its probable mechanisms of memory improving activity.

In the present study, scopolamine and diazepam significantly impaired memory of mice. Memory impairment effect of scopolamine and diazepam has been reported in the literature (Parle & Dhingra, 2003). Plumbagin (16 mg/kg, p.o.) administered for 15 successive days significantly reversed scopolamine- and diazepam- induced amnesia in mice. Benzodiazepines produce amnesia in laboratory animals by activation of benzodiazepine receptors and GABAergic system (Singh et al., 1998). Flumazenil (benzodiazepine-receptor antagonist) and beta-carbolines (benzodiazepine inverse agonist) have been reported to reverse benzodiazepine-induced amnesia (Jensen et al., 1987). Reversal of scopolamine- and diazepam-induced amnesia by plumbagin indicated the possible facilitation of cholinergic transmission and
Acetylcholine is considered as the most important neurotransmitter involved in the regulation of cognitive functions (Hasselmo, 2006). Selective loss of cholinergic neurons and/or decreased synthesis of acetylcholine were reported to be a characteristic feature of dementia of Alzheimer’s disease type (Watanabe et al., 2009).

Drugs that reduce cholinergic function such as muscarinic receptor antagonist, scopolamine cause profound memory impairments in animals and humans (Deutsch and Rocklin, 1967). In the present study, scopolamine significantly impaired memory of mice. Plumbagin (16 mg/kg, p.o.) administered for 15 successive days significantly reversed scopolamine-induced amnesia in mice. Reversal of scopolamine-induced amnesia by plumbagin indicated the possible facilitation of cholinergic transmission. Plumbagin (16 mg/kg) also significantly reduced brain AChE activity in mice as compared to the control. This suggests that the memory enhancing effect of plumbagin might be due to inhibition of AChE, leading to increase in brain acetylcholine levels. Acetylcholine is considered to be the most important neurotransmitter involved in the regulation of cognitive functions. Cognitive dysfunction has been shown to be associated with impaired cholinergic transmission and the facilitation of central cholinergic transmission resulting in improved memory. The degeneration and dysfunction of cortical cholinergic neurons is closely associated with cognitive deficits of Alzheimer’s disease (Bartus et al., 1982; Coyle et al., 1983; Watanabe et al., 2009). Thus, the drugs which enhance cholinergic function can be used for treatment of dementia closely related to Alzheimer’s disease. Physostigmine (0.1 mg/kg, i.p.) injected for 15 successive days significantly improved memory of mice. The memory enhancing effect of physostigmine is in line with the earlier studies (Bekker et al., 2007). The memory improving effect of plumbagin was comparable to physostigmine.

5. CONCLUSION

Plumbagin administered for 15 successive days significantly improved learning and memory of mice probably through inhibition of brain acetylcholinesterase activity and through involvement of GABA-benzodiazepine pathway. Further studies may be carried out to explore the other possible mechanisms for nootropic activity of plumbagin and its usefulness in the management of cognitive disorders.
REFERENCES


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Parshad, S


