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Nootropic Activity of Ethanolic Extract of *Zingiber officinale* and *Centella asiatica* on Stress Induced Rats

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ABSTRACT: Nootropics, natural or synthetic substances that boost brain function and cognitive abilities, were investigated in this study. Specifically, the effects of *Zingiber officinale* and *Centella asiatica* extracts were compared to the standard nootropic piracetam. Both plant extracts demonstrated nootropic activity and contained phytochemicals like flavonoids, tannins, and saponins that protect the brain from oxidative damage. Sterols such as stigmasterol inhibiting acetyl CoA esterase activity were also present. Tests were conducted on rats given the extracts or piracetam daily for 7 to 21 days. High and low doses were used. Nootropic effects were measured using elevated plus maze and Morris water maze tests compared to controls. The results were promising: At higher doses, the extracts significantly reduced latency time to 21 ± 0.33 seconds compared to 33.33 ± 0.12 seconds for piracetam and 54 ± 0.08 seconds for controls. This suggests the plant extracts have considerable nootropic potential when administered at higher doses.

KEYWORDS: Nootropics, Elevated plus maze, Morris water maze, *Zingiber officinale*, *Centella asiatica*

INTRODUCTION

Though nootropics have gained popularity to boost mental functions, more research is needed to evaluate their potential benefits, especially for conditions like Alzheimer's [1]. Commonly used natural nootropics are thought to enhance brain function by altering neurotransmitters. Nootropics may work by dilating blood vessels in the brain, improving blood flow and the delivery of nutrients, chemicals, and oxygen [2]. Some act as modulators of acetylcholine or glutamate receptors, enhancing neurotransmitter activity and long-term potentiation between neurons. Plants have long been a source of medicines. Active compounds are isolated from plant parts like leaves, stems, roots and rhizomes [3,4]. However, many plants remain unexplored for their pharmaceutical potential. This study aimed to demonstrate the nootropic effects of *Zingiber officinale* and *Centella asiatica* individually and in combination. Elevated plus maze and Morris water maze apparatuses were used.

MATERIALS AND METHODS

A. Materials

Rhizomes of Zingiber officinale and leaves of Centella asiatica were procured from the surrounding areas of Kakinada and Surampalem, Andhra Pradesh India and were validated by Dr. T. Raghuram, Taxonomist, Maharani College, Peddapuram.

B. Methodology

Preparation of ethanolic extract of *Zingiber officinale*: Freshly harvested ginger rhizomes were cleaned to remove dirt. They were then sliced and dried in the shade for a period of time. The dried rhizomes were coarsely ground into a powder. The powdered ginger was weighed and mixed with ethanol for several days. The mixture was then repeatedly filtered under heat for about 3 hours. The extract solution was concentrated through evaporation of the ethanol solvent. The remaining product was dried and stored in a desiccators [5].

Preparation of ethanolic extract of *Centella asiatica*: Freshly harvested leaves of Centella asiatica were cleaned to remove dirt. They were then dried in the shade for several weeks. The dried leaves were coarsely ground into a powder. The powdered Centella asiatica leaves were weighed and mixed with ethanol for several days. The mixture was then repeatedly filtered under heat for about 3 hours. The extract solution was concentrated through evaporation of the ethanol solvent. The remaining product was dried and stored in a desiccators [6].

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Experimental animals: Both male and female albino rats weighing 100 to 180 grams were used in this study. The animals were cared for and used in accordance with the standard procedures approved by the Institutional Animal Care and Use Committee [7].

Elevated pluz maze: The elevated plus maze apparatus consists of a wooden cross-shaped platform elevated about 60 cm above the floor. There are two closed arms measuring 50 cm by 10 cm opposite two open arms measuring 50 cm by 10 cm by 30 cm, with a center area where the arms meet [8].

Transfer latency determination using elevated plus maze test: The research included four groups of rats in the elevated plus maze experiment. Rats were individually placed at the end of an open arm facing away from the central platform. The time each rat took to move from the end of the open arm to one of the closed arms (transfer latency) was recorded. The plant extracts were administered for nine days before the experiment. The experiment was conducted over repeated trials and the average of three tests was calculated and reported. The four groups of rats were as follows: the control group received no treatment, the low dose group received 100 mg/kg body weight of the ethanol plant extract, the high dose group received 200 mg/kg body weight of the ethanol plant extract, and the standard group received piracetam [9,10].

Stress induction: The rats were subjected to mild chronic stress. They were placed in a basin about 60 cm high and 45 cm in diameter. The basin was filled with around 40 cm of water kept at room temperature between 22 - 28 ^{0} C. The rats were forced to swim in the water to induce stress. Additionally, the rats were placed on a rostrum surrounded by 2 cm of water overnight without food and water. This was done on alternate days after the rats had 3 hours access to restricted food and 2 hours access to an empty water bottle [11,12].

Morris water maze: The apparatus consists of a large bowl of clean water that serves as a pool for the rats to be suspended. Other requirements for this procedure included a non-toxic paint/powder, a thermometer, cotton towel, an elevation (placed in the bowel with colored water) and a timer. The basin was filled with water, made opaque in appearance using powdered milk or non-toxic paint and maintained at the right temperature. A platform is positioned in the middle of the basin that is slightly above the water during pre-training phase but later covered with opaque water during the actual trial phase.The rats were placed inside the pooland are forced to swim and figure out the location of the platform on their own using external/extra-maze cues. The rats learn about the position of the platform and the time spent in locating it decreases as it becomes more acquainted with the mission. This makes Morris water maze one of the benchmarks to study behavioral neurophysiology [13,14].

RESULTS

Elevated pluz maze: Transfer latency, the time in seconds for the rats to move from an open arm to a closed arm, is an important factor in the elevated plus maze test. This reflects the rat's natural tendency to move to the more enclosed and secure closed arm compartment. Before administering the plant extracts, all the rats were trained to move to the closed arm when placed in an open arm. The test, standard and control groups underwent the same training. The training continued until all the rats learned to make the transition to the closed arm, using an irritating stimulus when needed. A shorter transfer latency indicates better nootropic effects of a test substance. The rats treated with *Zingiber officinale* and *Centella asiatica* extracts showed lower transfer latencies than the vehicle-treated control rats and the standard group, in a dose-dependent manner. The transfer latency after 7 days of treatment revealed the effects of the plant extracts on improving the rats' learning ability [15]. A significant reduction in retention latency reflects enhancement of memory or cognitive function. The results are shown in Table 1 and Figure 1

Table 1. The Nootropic Effects of Ethanol Extracts on Transfer Latency in Normal Rats Using the Elevated Plus Maze Test

Sl. No.	***Treatment***	***Transfer latency (in seconds)****		
		Day 0	***Day 7***	***Day 14***
01	Vehicle	73.0 ± 0.57	72.1 ± 0.46	72.1 ± 0.46
02	Piracetam (100mg/kg)	41.0 ± 0.24	38.0 ± 0.33	33.3 ± 0.12
03	Ethanolic extract of *Zingiber officinale* and *Centella asiatica (100mg/kg)*	40.0 ± 0.20	32.0 ± 0.13	25.0 ± 0.33
04	Ethanolic extract of *Zingiber officinale* and *Centella asiatica (200mg/kg)*	38.0 ± 0.57	30.0 ± 0.20	21.0 ± 0.33

**n=3, mean ± standard deviation*

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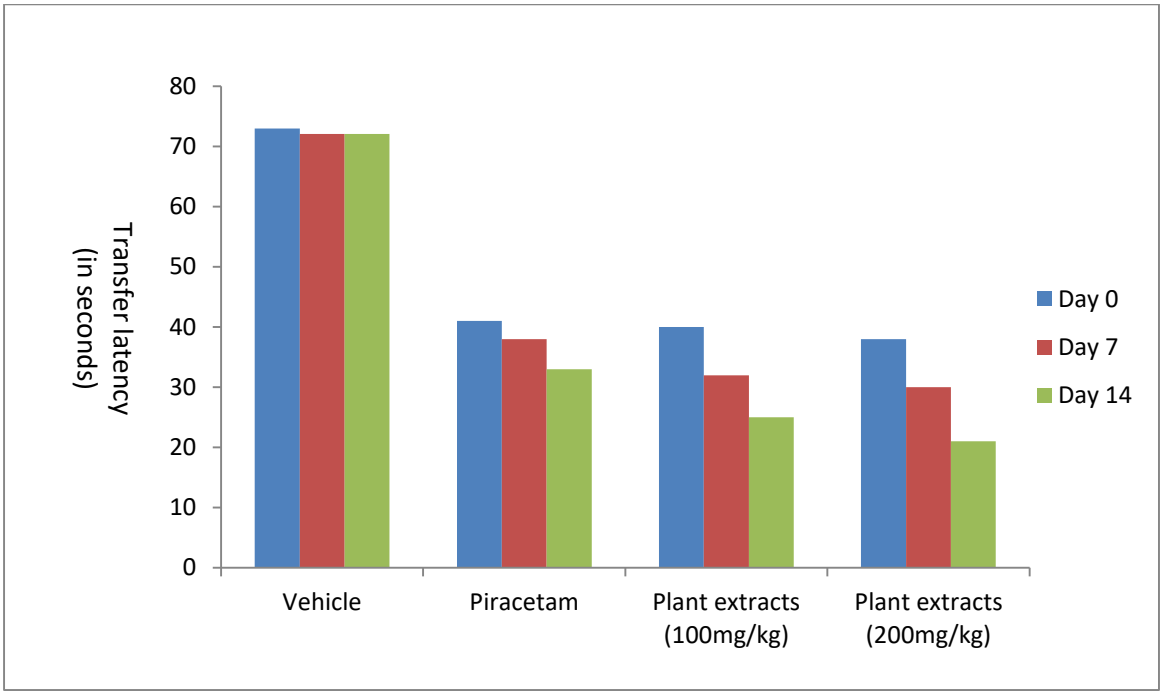

Figure 1. Effect of ethanolic extracts on transfer latency on normal rats using elevated plus maze (piracetam was used as standard drug).

The elevated plus maze experiment was repeated on stressed rats. These rats were subjected to stress by forced swim prior to the maze experiment to increase their stress levels. This was done to determine the effect of stress on the learning and memory retention capacity on the rats [16]. The result shown below was obtained. The results are shown in Table 2 and Figure 2.

Table 2. The Nootropic Effects of Ethanol Extracts on Transfer Latency in stress induced rats using the Elevated Plus Maze Test

Sl. No.	***Treatment***	***Transfer latency (in seconds)****		
		Day 0	***Day 7***	***Day 14***
01	Vehicle	76.4 ± 0.20	76.3 ± 0.52	76.1 ± 0.44
02	Piracetam (100mg/kg)	48.2 ± 0.82	43.4 ± 0.33	35.2 ± 0.52
03	Ethanolic extract of *Zingiber officinale* and *Centella asiatica (100mg/kg)*	43.1 ± 0.33	38.0 ± 0.16	30.0 ± 0.06
04	Ethanolic extract of *Zingiber officinale* and *Centella asiatica (200mg/kg)*	32.2 ± 0.54	29.0 ± 0.57	25.0 ± 0.57

**n=3, mean ± standard deviation*

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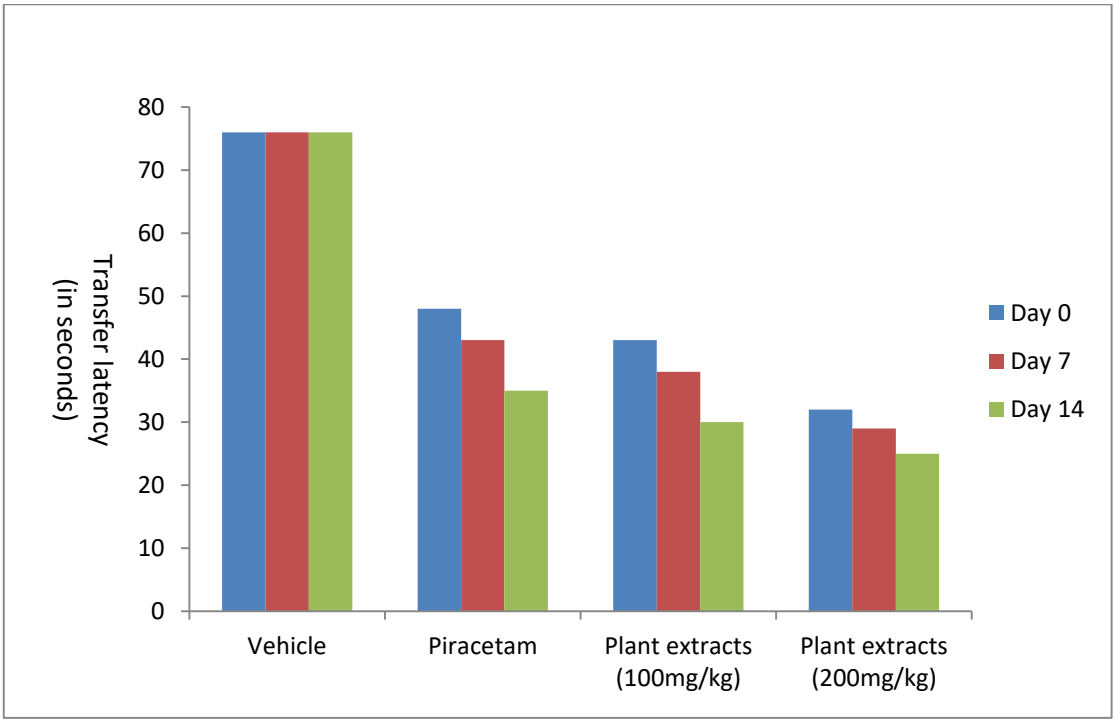

Figure 2. Effect of ethanolic extracts on transfer latency on stress induced ats using elevated plus maze (piracetam was used as standard drug).

Morris water maze: The Morris water maze test was used to study spatial memory, learning, and behavioral neurophysiology in rats. The maze consists of a pool of water with no visual cues. In the test, the rat is placed in the water and must swim to locate an elevated platform that acts as a resting place. Testing is done over a single day to avoid any confounding factors like hormone level changes in female rats. Reference memory can be tested in probe trials where the platform is removed. Rats that learned the platform location will spend more time searching around that area. Working memory can be assessed by placing the platform at a new location each day [17]. The rats must figure out the new location on the first trial each day and remember it over subsequent trials. The data showed that rats treated with *Zingiber officinale* and *Centella asiatica* extracts had a decrease in escape latency time -indicating improved working memory - in a dose-dependent manner compared to vehicle-treated controls. Probe trials also suggested an enhancement in reference memory in the drug-treated rats. The results are shown in Table 3.

Table 3. The Nootropic Effects of Ethanol Extracts on escape latency of rats using the Morris water maze Test

Sl. No.	***Treatment***	***Transfer latency (in seconds)****			
		Day 0	***Day 7***	***Day 14***	***Day 21***
01	Vehicle	22.3 ± 0.14	21.1 ± 0.03	21.0 ± 0.39	21.0 ± 0.16
02	Piracetam (100mg/kg)	9.3 ± 0.28	9.1 ± 0.16	7.3 ± 0.05	5.4 ± 0.39
03	Ethanolic extract of *Zingiber officinale* and *Centella asiatica (100mg/kg)*	6.3 ± 0.33	6.0 ± 0.19	5.0 ± 0.24	4.6 ± 0.41
04	Ethanolic extract of *Zingiber officinale* and *Centella asiatica (200mg/kg)*	5.5 ± 0.05	3.6 ± 0.14	3.3 ± 0.07	2.3 ± 0.94

**n=3, mean ± standard deviation*

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DISCUSSION

The results demonstrated that both *Zingiber officinale* and *Centella asiatica* possess nootropic activity. The ethanol extracts of both plants were administered at two doses: a high dose of 200 mg/kg and a low dose of 100 mg/kg. In the elevated plus maze test, both doses showed greater improvements compared to the standard and control groups. There was a significant decrease in transfer latency times in the extract-treated groups compared to controls, in a dose-dependent manner. The higher dose of 200 mg/kg showed a greater effect than the lower dose, indicating a potentiation of learning and memory retention in the rats. In the Morris water maze test, escape latency times were significantly reduced compared to vehicle-treated controls, suggesting improvements in spatial memory and learning. Overall, the results demonstrate that the plant extracts have effects on learning and memory in the experimental rats, showcasing their potential as nootropics [18]. However, further studies are needed to evaluate other pharmacological parameters like potential side effects, effects on specific organs, and determination of optimal doses. This will ensure the safety and efficacy of using these plant extracts as nootropic supplements.

CONCLUSION

In conclusion, the results provide promising evidence that *Zingiber officinale* and *Centella asiatica* have nootropic properties. However, more research is needed to establish their safety and efficacy profiles, determine optimal dosing, and evaluate potential effects on vital organs before they can be recommended as nootropic supplements. With proper follow-up studies, these plant extracts may represent viable natural alternatives to synthetic nootropics.

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