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Effect Of Rhodiola Rosea Root On Spatial Learning Memory, Brain Antioxidant Enzymes Activity Against Morris Water Maze Model In Mice

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ABSTRACT

Alzheimer's disease (AD) is the commenest form of dementia amongst aging adult population. The Morris Water Maze (MWM) was designed to assess hippocampal-dependent learning, such as spatial memory acquisition and long-term spatial memory. This study was aimed to evaluate Nootropic potential of *Rhodiola rosea* (*R. rosea),*methanoilcextract of *R. rosea*effect was assessed on Spatial learning memory, Brain antioxidant enzymes activity against Morris water maze model in miceat a dose of 300 and 500 mg/kg. The transfer latency (TL) and estimation of brain oxidative stress markers GSH,LPO, SOD and CAT.The mice treated with R.rosea (300 and 500 mg/) extracts shows Learning and memory are linked with Escape Latency (EL) and Probe Trail (PT), Decline of 14th to 21stth day and augmentation of PT by mice on 7th to 21st day in comparison to the control.The mice administered with R.rosea 300 and 500 significantly elevated the CAT, SOD and GSH levels. However, distinctly reduced the concentration of LPO. Up on treatment with Piracetam considerably enhanced the level of CAT, SOD and GSH as well as markedly lessened the level of LPO with respect to the disease control. Form the results of this experimental work, can be concluded that R.rosea is a potential natural nootropics and therefore, its popularity is increasing its usage as supplement.

Key words:*R. rosea*,MWM,GSH, LPO, SOD and transfer latency.

INTRODUCTION

Cognitive degradation, memory loss, behavioural and functional abnormalities, and functional impairment are all key features of Alzheimer's disease (AD), which is the commonest type of age-related dementia. Alzheimer's disease (AD) is characterised by anovertime decline in hippocampal-dependent activities such as thinking and remembering, as well as behavioural and functional abnormalities and functional impairment. [1-2]. The etiopathogenesis of Alzheimer's disease is complex. The relevance of oxidative stress and cholinergic dysfunction in the start and course of the disease has been hypothesized [3-4].

Richard G. Morris, a neuroscientist, created the Morris Water Maze (MWM) in 1981 to assess hippocampal-dependent learning, such as spatial memory acquisition and long-term spatial memory[5].

Life expectancy has greater than before as a result of developments in science and technology, as well as enhanced healthcare services. Unfortunately, it comes at the cost of an increased incidence of age-related disorders like Alzheimer's disease.

Nootropic medications are herbs that act on the brain (GkNootropic = acts on the mind) and their extracted phytoconstituents are known as smart medications. [6]. "Nootropics" are substances that improve cognitive abilities. Learning and reminiscenceability can be regarded as both a psychological and a synaptic-neural connection shift. Cognitive deficiencies have long been recognized as serious and recurring neurological illnesses linked to a variety of mental and neurodegenerative conditions. [7]

In the family Crassulacea, there are over 200 species belonging to the Rhodiola genus, almost 20 of which are utilised as ethno-medicines in Asia [8], including Rhodiola rosea, Rhodiolaalterna, Rhodiolabrevipetiolata, Rhodiolacrenulatia, Rhodiolakirilowia, Rhodiolaquadrifida, Rhodiolasachalinens, Rhodiolaalterna. Rhodiola rosea plants are found predominantly in the Himalayan stretch, including China, Tibet, and Mongolia, although they are also grown commercially in Europe and North America. Supplements of Rhodiola rosea are available in the form of pills and juice on the market. [9-10] The terms "golden root" or "roseroot" are commonly used to describe this plant. According to the literature, Rhodiola rosea has various pharmacological effects. It has been reported to have adaptogenic (anti-stress), hepatoprotective, immune-modulatory, as well as antiviral, anti-inflammatory, and antibacterial activities [8-11]. There are several different types of polyphenols and flavonoids, as well as proanthocyanidines and tyrosol and cinnamyl alcohol found in R. rosea. There are also glycosides and organic acids, essential oils, sugars, lipids, and alcohols, as well as proteins. [11]. Rosavin, cinnamyl alcohol, salidroside, and tyrosol are among the polyphenols found in R. rosea plants, and they are the primary active constituents of the plants [10-11]. This investigation's goal was to investigate the effects of a methanolic extract of Rosa rosea on spatial learning, memory, and antioxidant enzyme activity in the brains of mice using the Morris Water Maze model as an anootropic activity in the Morris Water Maze model.

MATERIALS AND METHODS

Collection of plant material:

Dried roots of R.rosea (Golden root) family Crassulaceae were procured from local vendor, Seremban,negerisembilan,Malaysia. Roots are authenticated by Dr. Long chiau Ming, Associated Professor, Deputy Dean faculty of Pharmacy, Quest international university Perak.(QUIP-RR/02/2019).

PHOTOCHEMICAL EVALUATION

The phytoconstituents present in R. rosea extracts were determined using a variety of chemical tests performed on the extracts.12]

EXPERIMENTAL ANIMALS

Adult Wistar rats of either sex weighing 150–180 g and Swiss Albino mice weighing 20–25 g were procured from Sanzyme Lab Pvt. Nutrition was bought from the National Institute of Animal Nutrition and Physiology, Hyderabad. The animals were housed in standard laboratory conditions at 25°C with a 12-hour light/dark cycle and unlimited (ad libitum) availability of chow and water. The study was commenced after the approval by the institutional ethics committee. (IAEC/1447/PO/Re/S/11/34/A)

Morris water maze (MWM) test

Healthy Swiss albino mice(20-25gm) of any sex were divided into five groups. Each group comprising of six animals as per the details below:

Group I: Control group, administered with vehicleonly

Group II: Morris water maze test (MWM)

Group III – MWM + R. rosea300 mg/kg, p.o.

Group IV – MWM + R. rosea500 mg/kg, p.o. respectively.

Group V-MWM+piracetam 100mg/kg .p.o

Group III and IV animals were treated with R. rosea extract for 28 days, with all groups of animals excluding the control group being administered the extract 45 minutes prior to the acquisition trials in order to induce each mouse to perform the water maze task.

On the zero (0^{th}), seventh (7th), fourteenth (14th), and twenty-eighth (28th) days, animals were tested in a spatial version of the Morris water maze. The setup had a circular water tank in the middle (180 cm in diameter and 60 cm high). A platform (12.5 cm in diameter, 38 cm high) was placed inside the tank and filled with 28 ±2°C water.On either side of the tank was a large room with a number of brightly coloured cues that pointed outside of the mazeThose visible from the pool and used by the animals for spatial orientation. Throughout the study, the cues' positions were maintained in the same manner. The water maze task was completed for a total of 0, 7, 14, and 28 consecutive days following the completion of the post-intervention. The animals were subjected to everyday training trials for the first four days of a five-day training period. During each trial, which lasted ninety (90) seconds, there was an atrial pause of aboutthirty (30) seconds between trials. For each trial, each animal was placed into the water at one of four different initial positions, the order of which was determined by a random number generator. When conducting tests, animals were retained into the tank at a fixed point in the same direction as the wall, with their heads facing the wall. It was necessary for the animal to swim till it reached the platform that was plunged underneath the surface of the water. Following its ascent of the platform, the animal was allowed to stay there for a total of twenty (20) seconds prior to the start of the next trial. The position of the escape platform in relation to the distal cues was maintained at all times. The animal was positioned on the escape platform gently and allowed to stay there for the same amount of time if it did not reach the platform within the maximum permissible time of ninety (90) seconds. It was determined how long it took for the data to reach the platform (latency in seconds). A probe trial was conducted in order to determine the extent to which memory consolidation had occurred. The animal was placed in the pool in the same manner as in the training trial, with the exception that the hidden platform was removed from the pool for the probe trial. On the 28th day of the study, the transfer latency (TL) to reach the platform was measured. This was done using spatial reference memory. [13-16]

Biochemical Study

Following the afore mentioned procedures, on 29th day the mice from all of the different experimental groups were sacrificed under anaesthesia. The entire brain was removed from the skull, and then the cerebellum was removed from the rest of the brain. Later, the remaining brain portion (that is, the brain portion that did not contain the cerebellum) was bathed with an ice-cold solution of 0.9 percent sodium chloride, and then each hemisphere was parted. Using one of the two hemispheres, a 10 percent brain homogenate was prepared by homogenising the hemisphere in an ice-cold 30 mM phosphate buffer (pH 7.6) in a homogenizer at room temperature. The homogenates were centrifuged at 3000 RPM for 30 minutes at 4 degrees Celsius to obtain homogenates that were free of any type of cell debris, and the supernatant from the centrifuged homogenates was used for the estimation of GSH, LPO, SOD, and CAT levels. [17-20]

Estimation of catalase activity

To homogenise the separated brain tissue in a 1:10 (w/v) ratio, a 50 mM, pH 7.4 potassium phosphate buffer solution was utilised. The homogenate was spun for 20 minutes at 4°C and 10000 rpm in a cooling centrifuge. The 50 mL supernatant was added to a cuvette containing 2.95 mL of hydrogen peroxide (19 mM/L) generated in the phosphate buffer. The activity of the CAT enzyme was determined on the basis of breakdown of hydrogen peroxide by the CAT enzyme resulting in a decrease in absorbance. The 240 nm wavelength was captured selected at a rate of 1 nm per minute for three minutes.

The following formulas were used to determine CAT activity: [CAT activity 14 (DA/min - assay volume)/assay volume] (0.081 - homogenate volume - mg of protein) [17].

Estimation of superoxide dismutase activity

100 microliters of the resulting cytosolic supernatant were added to Tris HCl buffer (pH 8.5), and the amount of the buffer was increased to 3 mL with the addition of more buffer. 25 mL of 24 mM pyrogallol solution was added to it, and absorbance at 420 nm was measured every 1 minute for 3 minutes. In this study, the antioxidant enzyme SOD was examined on the basis of the notion that SOD has an inhibitory effect on the auto-oxidation of pyrogallol. The amount of enzyme required to cause 50% inhibition of pyrogallol auto-oxidation in 3 mL of assay mixture is described as 1 unit of SOD. This amount of enzyme is calculated as [Unit of SOD per mL of sample 14 (DA e DB) 100/ (DA 50)], where DA is the absorbance variance in 1 minute in the control sample and DB is the absorbance variance in 1 minute in the test sample. The data was reported in terms of SOD units per milligrams of protein. [18-19].

Estimation of lipid peroxide activity

0.5 mL of 30% trichloroacetic acid (TCA) and 0.8 percent thiobarbituricacid (TBA) reagents were transferred to tubes containing 1 mL of the suspension medium obtained from the 10% tissue homogenate. Tubes were wrapped in aluminium foil and placed in a shaking water bath at 800C for 30 minutes, followed by 30 minutes in ice-cold water, and lastly 15 minutes centrifuged at 3000 rpm. The absorbance of the centrifuge supernatant at 540 nm at room temperature was determined using a UV-spectrophotometer in comparison to a suitable blank. The amount of malondialdehyde (MDA), a byproduct of lipid peroxidation that forms a chromogenic adduct with two molecules of TBA, was

determined using a standard curve generated with various amounts (0.1, 0.2, 0.3, 0.4, 0.5, and 0.6 mL) of the standard reagent 1,1,3,3-tetraethoxy propane (4 mg/mL) [nmol of MDA/mg .156] [19].

Glutathione levels

Concentrations of glutathione p recipitated 1 mL of a 10% supernatant with 1 mL of a 4% sulphosalicylic acid. After at least one hour at 4°C, the samples were centrifuged at 1200 rpm for 15 minutes at 4°C. The assay mixture consisted of 0.1 ml supernatant, 2.7 ml phosphate buffer (0.1 M, pH 7.4), and 0.2 ml DTNB (5, 5, dithiobis2nitro benzoic acid) Ellman's reagent in a total volume of 3 ml. The developed yellow colour was instantly measured at 412 nm and expressed as grams of protein per milligrams of protein. The GSH concentrations in the samples were determined using a standard curve developed with known GSH concentrations and are statedas ng/mg protein. [20]

STATISTICAL ANALYSIS

SPSS 17.0 was used to analyse the data.was used to analyse the data. Descriptive statistics were employed to show the data in terms of mean SEM using ANOVA, and then by a post hoc Tukey's Multiple Comparison Test. Graph PadPrism software was used to examine the data (version 8.4.2 V; San Diego, CA) (version 8.4.2 V; San Diego, CA). When the P value is provided as mean score data expressed in terms of mean S.E.M, n = 6. (ANOVA) followed by Tukey Multiple Comparison Test, aP<0.001 against the normal group, bP<0.01, cP<0.001 vs the control group

RESULTS AND DISCUSSION

Presence of Alakloids, Glycosides, Phytosteroids, Flavonoids, Terpinoids, Vitamins, and Tannins has been revealed in R. rosea extract, which is evident from the preliminary phytochemical analysis.

Morris water maze in mice

Learning and memory are linked to Escape Latency (EL) and Probe Trail (PT), with a decline in EL from 14 to 21 days and an increase in PT from 7 to 21 days in mice compared to the control group, demonstrating priceless learning and memory enhancement. R.rosea extracts performed exceptionally well on EL and PT tests. When compared to MWM, extracts considerably lowered (P0.001) EL and dramatically increased PT (Table and graph). Memory and learning are aided by EL and the addition of PT by mice in MWM. When mice were fed R.rosea extracts for 28 days, the EL of the mice was dramatically reduced, as illustrated in (figure1-4)

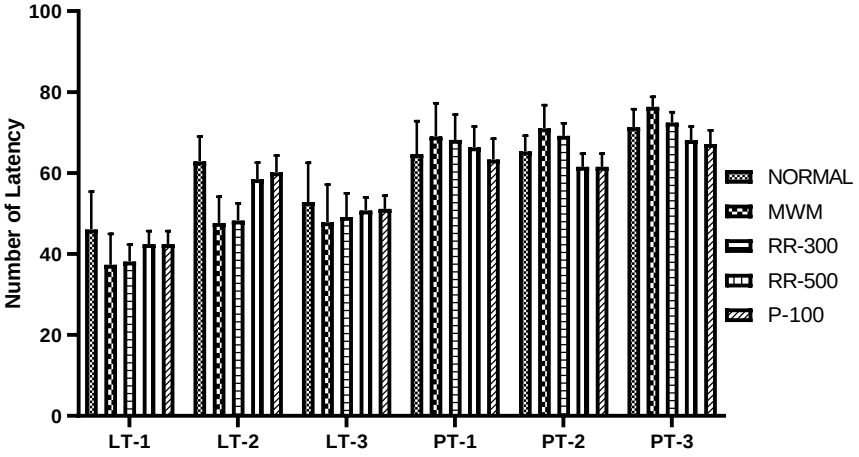

Figure 1: Effects of R.roseaextracts on Escape Latency (EL) and Probe Trail (PT) in Morris water maize on 0-day

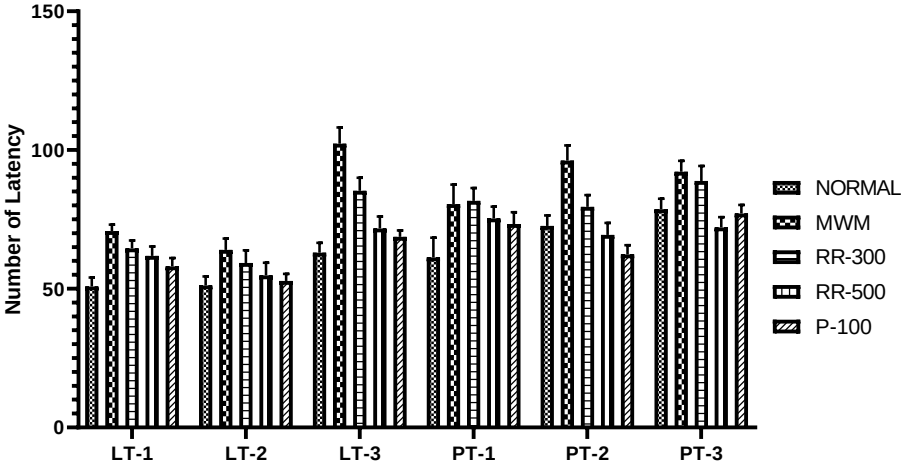

Figure 2: Effects of R.roseaextracts on EscapeLatency (EL) and Probe Trail (PT) in Morris water maize on 7-day

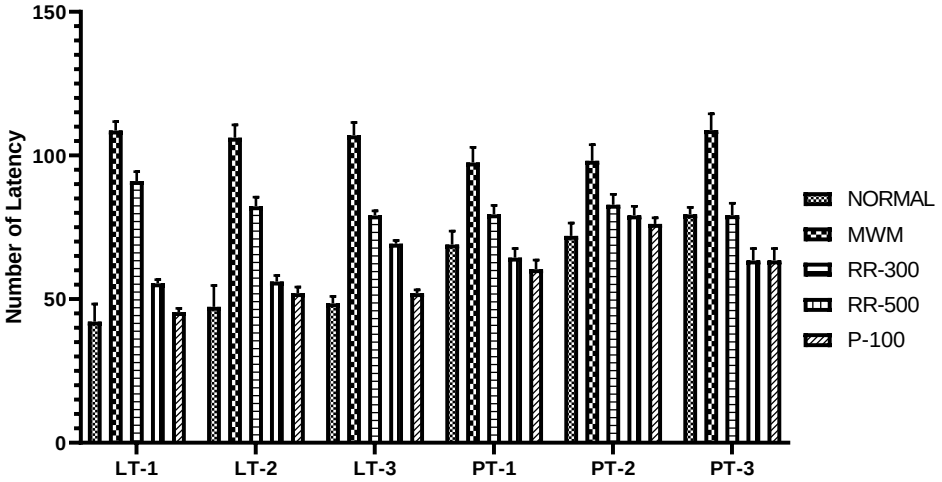

Figure3: Effects of R.roseaextracts on Latency (EL) and Probe Trail (PT) in Morris water maize on 14thday

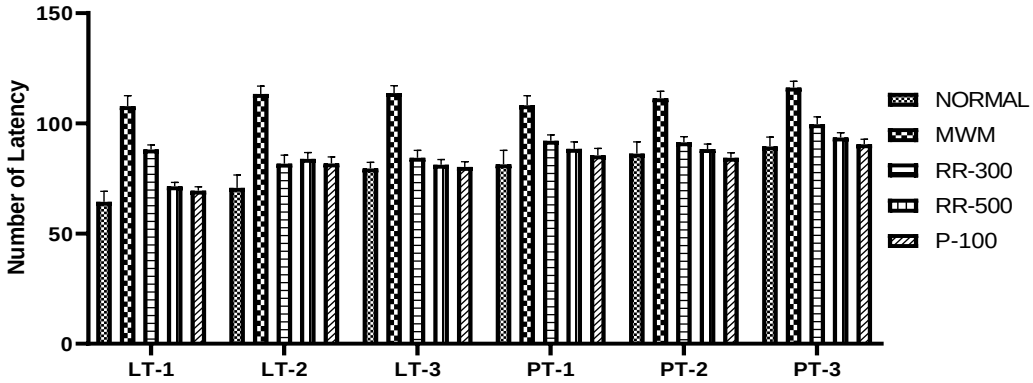

Figure4: Effects of R.roseaextracts on Latency (EL) and Probe Trail (PT) in Morris water maize on 21stday

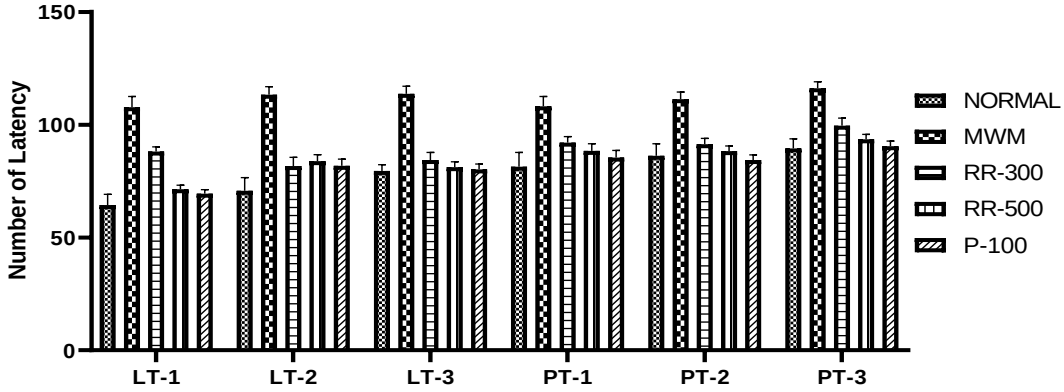

Figure4: Effects of R.roseaextracts on Latency (EL) and Probe Trail (PT) in Morris water maize on 28thday

MWM caused changes in antioxidant enzyme activity in mouse brain tissue homogenates, as reported in (table 1 and figure: A-D). R.rosea (300 and 500 mg/kg b.w.) considerably ($P < 0.05$, $P < 0.01$) raised the levels of CAT, SOD, and GSH, but significantly ($P < 0.01$) decreased the concentration of LPO. In comparison to the illness control, Piracetam treatment significantly ($P < 0.05$, $P < 0.01$)boosted the levels of CAT, SOD, and GSH, as well as significantly ($P < 0.05$, $P < 0.01$) lowered the level of LPO.

Table1: Effect of R. roseaextract on antioxidant activity in Morris water maize

Groups	LPO	SOD	Catalase	GSH
Normal	109 ± 0.41	321.4± 5.55	1.85 ±0.41	79.71± 9.31
MWM	333.9 ± 0.11	129.0 ± 4.41	0.73± 0.21	22.4± 2.52
R. rosea300mg/kg	181.8 ± 0.138	182.1 ± 3.431*	1.61± 0.41*	58.5 ± 2.5*
R. rosea500mg/kg	121.1± 0.431	246.1 ± 4.53***	1.71± 0.21***	66.08 ± 5.43***
Piracetam 100	107.1± 0.431	273.1 ± 4.03***	1.81± 0.11***	70.18 ± 5.13***

Differences were considered significant whenever the P value are reported as mean ± Score data expressed in terms of mean ± S.E.M, n=6. (ANOVA) followed by Tukey Multiple Comparison Test,[a]P<0.001 vs Normal group, [b]P<0.01, [c]P<0.001 vs group

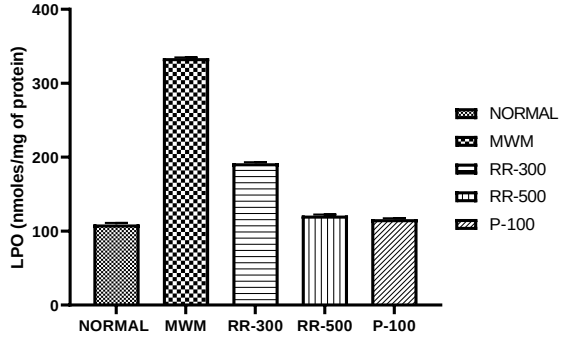

Figure A:Effect of R.rosea on LPO

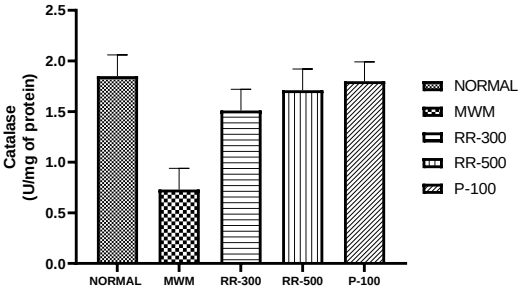

Figure B:Effect of R.rosea on Catalase

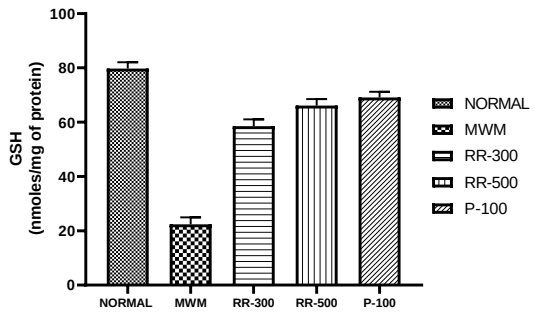

Figure A:Effect of R.rosea on GSH

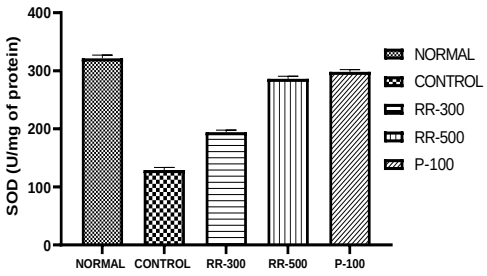

Figure A:Effect of R.rosea on SOD

The effects of R.rosea extracts on learning and memory abilities in a rat model of Alzheimer's disease were investigated in this study. The Morris water maze test was performed to investigate the changes in the mice's learning and memory abilities. [21]

In order to distinguish between spatial (the veiled platform) and non-spatial (the detectible platform), the MWM relies on a series of simple trials [22, 23]. The MWM testing setting also reduces odour trail interference [25]. Consequently, the test is extensively used in studies on the neurobiology and neuropharmacology of spatial learning and memory. MWM.is a reliable rat modes for neurocognitive illnesses like Alzheimer's disease.[26-27]

The levels of LPO (a lipid peroxidation marker) increased while the levels of GSH, SOD, and CAT dropped (an endogenous anti-oxidant enzymes). Superoxide is predominantly produced during oxygen metabolism and, if left unchecked, can cause a wide range of cell injury [28]. SOD is a metalloenzyme that shields cells from the destructive effects of oxygen. It catalyzes the radical dismutation of superoxide (O_2) into molecular oxygen (O_2) or hydrogen peroxide (H_2O_2) [29]. Hydrogen peroxide is also toxic, but at a lower concentration than CAT, and is degraded by different enzymes. CAT is a haem-based enzyme that shields the cell from oxidative damage caused by reactive oxygen species (ROS) [30]. It catalyzes the conversion of H_2O_2 to H_2O and O2, hence defending cells against H2O2 toxicity [731]. According to one study, per minute, a single CAT molecule may convert approximately 5 million H_2O_2 to H2O and O_2[32].The oxidation of lipids, or lipid peroxidation, is now thought to be a very important step in the development of a wide range of diseases in people of all ages [33]. There are many different types of reactive oxygen species (ROS) that can cause lipid peroxidation, such as hydroxyl radicals, hydrogen peroxide, and more [34]. If you have a lot of free radicals in your body, they can damage your cells by taking electrons from the fat on your cell membranes This process is kept going by a chain reaction of free radicals. It usually affects polyunsaturated fatty acids (PUFAs), which causes a chain reaction that keeps on going [35]. In fact, lipid peroxidation is a self-propagating chain reaction, which means that even small amounts can cause major tissue damage [36]. It's very bad for cells and tissues to have membrane lipids break down, as well as the end products of these lipid peroxidation events.The effects of R.rosea roots on brain antioxidant indicators and learning, particularly the acquisiti on of spatial memory and long term spatial memory were

investigatedThe current study discovered that using R.Rosea increases brain antioxidant enzymes while l owering LPO, spatial memory, and long-term spatial memory levels.[37].

Piracetam works by affecting the NMDA glutamate receptors, which are crucial in learning and memory. Piracetam, a GABA derivative, has a significant impact on cognitive performance. In the case of a chronic neurological impairment, many neural system adjustments occur that may not be present in the case of an acute neurological deficit. In the case of chronic deficiencies, it's crucial to assess the drug's long-term efficacy to rule out the possibility of tolerance or the production of a long-term effect.

CONCLUSION

Increasingly, consumers prefer natural nootropics since they are more convenient and less expensive.Currently, there is a huge global push to explore medicinal plants for boosting cognitive function and owing to its lessadverse effects.R. rosea has gained popularity as a medicinal herb and has been used in Chinese medicine for its adaptogenic properties.This research study was aimed at investigating the nootropic effect of R. rosea extracts. Besides, the extracts were evaluated for potential phytoconstituent effective against plays animportant role in cognitive function, many neural system accommodationstake place in the chronic neurological deficitsituation which may not be present in theacute deficiteffects of the extracts may be ascribed to the presence of various phytoconstituent including alcohol derivatives, flavonoids, and phenolic compounds,polyphenol includes Rosavin,cinnamyl alcohol, salidroside and tyrosol major components, a variety of glycosides and the essential oils.

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CONFLICT OF INTEREST

We have no conflict of interest to declare.

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