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Salvia verticillata Improved Cognitive Deficits in a Chronic Cerebral Hypoperfusion Rat Model

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ABSTRACT

CCH, resulting from multiple cerebrovascular diseases, has been considered the primary cause of cognitive impairment in recent years. In this process, oxidative stress plays a critical role and damages hippocampal neurons. Research has shown that *Salvia verticillata* has a significant antioxidant and free radical-scavenging activity due to its polyphenolic compounds. Therefore, the present study aimed to evaluate the effect of *Salvia verticillata* on a rat model of chronic cerebral hypoperfusion. A total of 24 rats were subjected to Salvia verticillata or vehicle orally from one week before 2VO surgery for 14 days. Cerebral hypoperfusion was induced by the bilateral occlusion of the common carotid arteries (2VO, n = 12 and sham, n = 12). The cognition of rats was evaluated 1 week after surgery in the MWM. In the MWM test, 2VO rats showed longer escape latency time and swimming distance and spent a shorter time in the target quadrant ($p < 0.05$). Moreover, we observed that *Salvia verticillata* treatment significantly reduced escape latency time, shortened the swimming distance, and increased target quadrant time ($p > 0.05$). Our results indicated that Salvia verticillata treatment significantly improved cognitive deficits in cerebral ischemic rats, probably by reducing oxidative stress damage.

Keywords

Salvia verticillata, Rat, Hypoperfusion, Dementia

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Abbreviations

CCH: Chronic Cerebral Hypoperfusion
VD: Vascular Dementia
CBF: Cerebral Blood Flow
BCAO: Bilateral Common Carotid Arteries Occlusion
MWM: Morris Water Maze
2VO: Two-Vessel Occlusion
ROS: Reactive Oxygen Species
ANOVA: Analysis of variance

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Introduction

VD is the second most common form of dementia characterized by progressive mental decline and generally caused by hypoxia-ischemia or hemorrhage brain lesions [1-4]. It has been proposed that cerebrovascular diseases eventually reduce CBF. CCH is the outcome of CBF regulation and is identified as a prominent risk factor contributing to degenerative processes leading to dementia [1, 5-7]. The cerebral blood vessels deliver oxygen and nutrients, which are essential for cellular and neuronal metabolism, to the brain. The anaerobic metabolic capacity of neurons is limited, and adequate CBF is crucial for neuronal function and survival [8, 9]. CCH damages neurons in brain areas, especially the CA1 region of the hippocampus, leading to oxidative stress and inflammation. Studies showed that the mammalian hippocampus is highly involved in spatial learning and episodic memory, and is very sensitive to ischemia and hypoxia [10, 11].

Permanent BCAO in rats significantly reduces cerebral blood flow (hypoperfusion). It is one of the most commonly used CCH animal models for studying neuronal degeneration and memory disturbance, resembling those found in human subjects with vascular dementia [5, 12]. The BCAO surgery is relatively easy to perform and the ligation of both common carotid arteries with sutures takes approximately 10 minutes. Consequently, the use of CCH rat models is beneficial as a preclinical approach for investigating complex questions directly in human research [1, 7, 13].

Numerous studies demonstrated that free radicals play a pivotal role in CCH by causing oxidative damage, brain energy insufficiency, and cell apoptosis [7, 8, 14, 15]. ROS are metabolites produced during oxidative stress and cellular metabolism. Oxidative stress is an imbalance between ROS production and removal due to the uncontrolled production of ROS, decreased antioxidant defenses, or a combination of both [7, 8, 16]. The important role of oxidative stress in the pathogenesis of some neurological disorders, such as epilepsy and depression, has been demonstrated [17]. Augmented ROS values lead to oxidative damage (pathologic effects) to biomolecules, including nucleic acid, proteins, lipids, carbohydrates, or any other essential molecules [7, 8, 18, 19]. Protective mechanisms that neutralize the ROS and maintain free radicals in the physiologic range include an array of systemic enzymes and non-enzyme antioxidant defenses [20]. It has been established that reducing ROS, such as superoxide anion radical, hydroxyl radical, and hydrogen peroxide, by antioxidant therapy can moderate the symptoms of cerebral hypoperfusion and its related disease. Oxygen free radicals and resulting lipid peroxidation are critical to cerebrovascular dysfunction in a variety of conditions that result in CCH. Therefore, antioxidant therapy may be useful for managing cerebrovascular disorders, such as VD [7, 8]. Many antioxidants are reported to reduce ROS-mediated reactions and protect neurons from ischemia-reperfusion-induced neural loss in the animal models of cerebral ischemia [21].

Nowadays, many herbal or chemical medications are available for treating various neurological disorders. *Salvia L.* is the major genera of the family Lamiaceae, which includes large species distributed throughout the world. The main distribution regions of these species are Asia (Iran, Turkey, and Afghanistan), Europe, America, and Africa [22]. Members of this genus have been of extensive research interest due to their diverse medicinal properties [22-24]. It has been reported that many *Salvia* plants are used for treating various diseases, including bronchitis, cancer, hepatitis, other hepatic diseases, cardiovascular diseases, Alzheimer's disease, as well as mental and nervous conditions [24]. In addition, several studies have demonstrated that the *Salvia* genus is a valuable source of powerful antioxidants [25-27]. Phytochemical analysis of different *Salvia* species indicated that these plants contain diterpenoids, sesquiterpenoids, flavonoid glycosides, anthocyanins, and polyphenols [28, 29]. The species Salvia verticillata has shown high antioxidant activity in vitro. This plant is considered an antioxidant and acetylcholinesterase inhibitor [25-27]. *Salvia verticillata* contains a variety of diterpenoids, essential oils, and polyphenols, that may have the potential for being used in cognitive deficits [26]. Some researchers reported *Salvia verticillata* as a natural source of free radical scavengers [27, 30].

Therefore, this study was designed to investigate the effects of the alcoholic extract of *Salvia verticillata* on CCH in rats induced by permanent ligation of the common carotid arteries. We analyzed the effect of *Salvia verticillata* on learning and memory deficits using MWM.

Result

The mean latency to reach the underwater platform (time of escape latency) is shown in Figure 1. In all groups, the escape latencies decreased gradually during the 7 days of training in the MWM test. The saline-treated 2VO group consistently took longer latency to find the platform position than the drug-treated 2VO and sham-operated groups ($p < 0.05$). Two-way ANOVA revealed significant differences between groups. It showed that administration of *Salvia verticillata* decreased the escape latency of 2VO rats ($p < 0.05$).

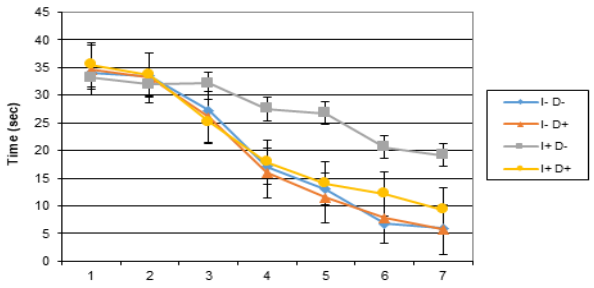

Figure 1.
Effects of *Salvia verticillata* on learning and memory impairment in 2VO rats. Morris water maze tests were performed on the day 7 to 14 post-surgery. Escape latency from the start point to locate the hidden platform.

Figure 2 shows that treatment with *Salvia verticillata* shortened the swimming distance compared to 2VO rats. The results were significantly different between saline-treated 2VO and other groups ($p < 0.05$), while no significant difference was observed between the drug-treated and sham groups ($p > 0.05$). In order to determine whether the animals' swimming ability contributed to swimming distance or platform location latency, swimming speed was also assessed (Figure 3). There was no significant difference in total speed between groups ($p > 0.05$).

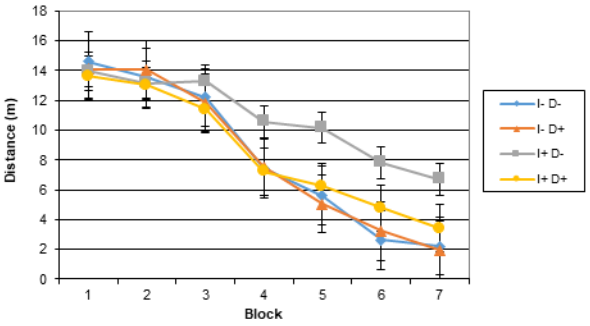

Figure 2.
Swimming distance of each group in the MWM test. Data are expressed as mean ± SD, n=6 for each group. 2VO: permanent bilateral common carotid artery ligation (2-vessel occlusion); HP: hypoperfusion, D: drug; SD: standard deviation.

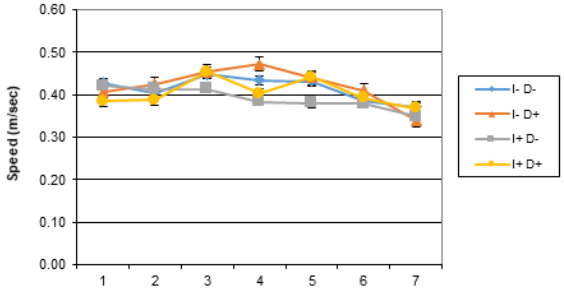

Figure 3.
Average swimming velocity in the MWM test. Data are expressed as mean ± SD, n=6 for each group. 2VO: permanent bilateral common carotid artery ligation (2-vessel occlusion); HP: hypoperfusion, D: drug; SD: standard deviation.

The results of spatial probe trials between groups are presented in Figure 4. It is shown that the 2VO model rats significantly spent less time in the N-E quarter (location of platform), compared to the sham groups ($p < 0.05$). After treatment with *Salvia verticillate*, the rats significantly spent more time in the target quadrant ($p < 0.05$).

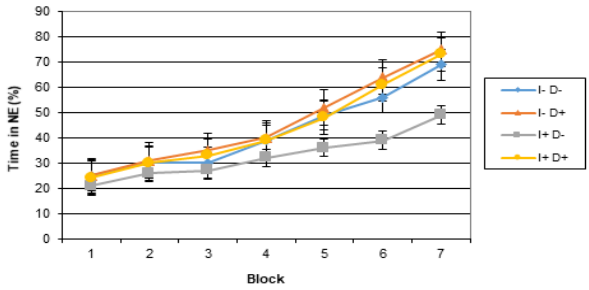

Figure 4.
Percent of time spent in target quadrant in 60 s probe trials (without platform). Data are expressed as mean ± SD, n = 6 for each group. 2VO: permanent bilateral common carotid artery ligation (2-vessel occlusion); HP: hypoperfusion, D: drug; SD: standard deviation.

Discussion

In this study, we demonstrated that administration of *Salvia verticillata* for 14 days markedly improved cognitive function using the MWM in a rat model of the 2VO method. Hypoperfused rats treated with vehicle alone showed significant cognitive deficits in the behavioral test.

In this research, we utilized the 2VO rat model to explore how *Salvia verticillata* affects cognitive impairment induced by decreased cerebral blood flow (hypoperfusion). In behavioral tests, 2VO rats exhibited a significant decline in spatial learning and memory abilities compared to the sham group as evaluated by the MWM test. This finding was consistent with previous studies on 2VO models [31, 32]. The 2VO model is capable of inducing a prolonged decrease in cerebral blood flow, which leads to neuronal damage and a decline in cognitive function [4, 5]. Euler *et al.* observed that the 2VO method resulted in the death of CA1 neurons in the hippocampus region and severe destruction of memory and learning in rats [33]. Therefore, this model is suitable for studying the learning and memory deficits in human dementia with the decline of cerebral circulation and drug effects on the disorder [34, 35].

Many behavioral tests have been designed to in-

vestigate brain lesions. One of the greatest common tests used to evaluate the memory and spatial learning function of cerebral hypoperfused rats is MWM. This test is similar to the non-verbal tests of cognitive function, which are sensitive in diagnosing aging disorders and dementia in the clinical environment [36]. Also, the reduction of non-cognitive functions such as sensorimotor, motor, and visual abilities of demented rats are not related to their performance in the MWM [36]. The probe trial distinguishes between different strategies used by demented rats to find the proper location of the hidden platform [36]. This test is a more accurate and reliable method for measuring memory accuracy [36]. In this type of learning test, considerable evidence has been compiled in support of 2VO-induced impairment [4]. Studies conducted previously have demonstrated that induced cerebral hypoperfusion in rats can adversely affect spatial learning and memory function [4]. In our MWM task, we observed that 2VO rats covered longer swimming distances, displayed longer escape latencies, and spent more time in the target quadrant. These results show that spatial learning and memory impairment were more pronounced in them than those in the sham rats. This finding is consistent with prior findings that indicated cerebral ischemia leads to an increase in the time required to locate the hidden platform and a decrease in the time spent swimming in the target quadrant [4, 37]. This result suggests that Salvia verticillata ameliorates cognitive deficits in 2VO rats.

Furthermore, the average swimming speed of rats during behavioral testing was not different between groups, indicating that swimming motivation and ability were similar between all animals. We concluded that the observed differences in the rats' spatial learning retention were not a result of sensorimotor impairment. Another study demonstrated that the swimming speed of rats did not change in the 2VO models [38].

Another factor discussed after the two-vessel method is the time to conduct behavioral tests after surgery. According to the literature, three phases can be defined for the two-vessel method. Acute phase that starts immediately after obstruction and will last for a maximum of 2-3 days. In this phase, the cerebral blood flow drops significantly and remains at the lowest level, which creates hypoxic-ischemic conditions and starts the electrophysiological activities of the nervous tissue damage [4]. Three days after 2VO surgery, the chronic hypoperfusion phase is started and continues for about 8-12 weeks. This phase closely resembles the conditions of decreased cerebral blood flow in elderly people with mental disorders. In the final phase, cerebral blood flow returns to baseline, and cerebral hypoperfusion and metabolism return to their original state [4].

Research has revealed that the chronic phase of 2VO is significant in the gradual decline of learning ability, but it is essential to consider the damage inflicted during the acute phase as well. With longer times after closing the vessels, cognitive disorders usually become more pronounced [4]. Ohta *et al.* showed that 10 days after vascular ligation, the behavior tests were significantly different between the two groups of 2VO and sham [39]. In another study, 2VO rats had more errors in finding the platform from day seven post-surgery [37]. Moreover, errors in behavioral tests have been reported from 3 days post-surgery in 2VO rats [5]. Therefore, in our study, behavioral tests were started on the 8th day after surgery, and the difference in the rats' learning was determined by test analysis.

There is a consensus that excessive generation of ROS leads to severe damage to cellular lipids, proteins, and DNA. Studies have shown that the brain is highly susceptible to ROS injury due to its dependency on aerobic metabolism, high contents of polyunsaturated lipids in cellular membranes, and low antioxidant defenses. Free radicals can cause degeneration and death of neurons [19]. In the 2VO model, hypoperfusion affects the cerebrum and hippocampus. The involvement of the sensorimotor cortex and hippocampus in memory and learning processes is unquestionable [40].

In the present study, it was found that the learning process in 2VO rats was progressively impaired in the MWM test. This result was confirmed in previous reports. Long-term administration of *Salvia verticillata* ameliorates the memory deficit of 2VO rats. Based on the laboratory studies,

the antioxidant properties of *Salvia verticillata* are significantly higher than other *Salvia* species [41]. The amount of phenolic content and antioxidant properties of the *Salvia verticillata* plant have been measured by different laboratory methods. Tosun et al. showed that the *Salvia verticillata* plant contained the highest amount of phenolic substances in comparison with seven other species of *Salvia* [41]. In a study by Matkowski *et al*., the high antioxidant power of *Salvia verticillata* in comparison with other species of this family has been emphasized [30]. In another research, the ethyl acetate extract of the leaf and stem of this plant had the highest antioxidant activity than other parts. Phenol is very important in scavenging free radicals due to its hydroxyl groups. Consequently, the phenolic content of the plant will probably have a direct relationship with its antioxidant properties [41]. This group allows phenol to remove the hydrogen end more easily to activate free radicals and destroy the antioxidant activation chain. The antioxidant capacity of these extracts is mostly related to their phenolic hydroxyl groups through various ways, such as preventing the formation of free radicals, catalyzing the temporary binding of metal ions, changing the state of peroxides, preventing the continuous accumulation of hydrogen, and scavenging free radicals [41]. As mentioned, the plants of the Lamiaceae family, especially *Salvia verticillata*, have a rich polyphenolic content. In summary, this study demonstrated that *Salvia verticillata* significantly improved cognitive deficits induced by CCH in rats. This effect is likely related to the antioxidant action of the medicine.

Materials and Methods

Animals

The Ferdowsi University of Mashhad's Institutional Animal Use and Care Committee approved this study, which was conducted in Mashhad, Iran.

Twenty-four male white rats aged 12 weeks (180-250 gr) were housed at 22°C ± 2°C room temperature and 60%±5% humidity, with a 12/12 h light/darkness schedule. The rats were provided with ad libitum access to commercial standard laboratory chow and tap water. They were housed in groups of three per cage and were utilized in compliance with regulations governing the examination of experimental animal administration.

The animals were chosen randomly and divided into two groups: 2VO (n = 12) and sham (n = 12). Rats in the 2VO groups underwent bilateral occlusion of carotid arteries through the procedures previously described by Pappas et al [37]. In brief, the rats were administered general anesthesia using isoflurane, following which a midline incision in the cervical region was made to carefully separate the bilateral carotid arteries from the vagus nerve and vein. The arteries were then tightly ligated using a 5-0 type silk suture. The same operation was conducted on the sham group, but without occluding the arteries. The procedure was carried out on a heating blanket, and the animal was kept warm until it regained consciousness. The rats were then randomly divided into four groups: a saline-treated 2VO group (n = 6), a drug-treated 2VO group (n = 6), a drug-treated sham group (n = 6), and a saline-treated sham group (n = 6). All animals were allowed a week of recovery.

Drugs and Administration

The plant *Salvia verticillata* L. was collected from Chalus, Mazandaran province, Iran, and was identified by the Department of Pharmacology, Faculty of Medical Sciences, Shahid Beheshti University, Tehran (6652-THE). The leaves were separated from the stem, dried in laboratory air, and kept in closed containers away from light until use. The dry leaves of the plant were completely powdered and 1000 grams of this powder were soaked in 4000 ml of methanol and placed in the laboratory environment for one night. The extract was evaporated at 40°C and under low pressure to obtain a syrupy extract weighing 264 grams. The methanolic extract was dispersed in 2000 ml of water and extracted with ethanol solvent. The extraction solvent was filtered and evaporated, and 27.5 grams of dry powder was obtained from the alcoholic extract [42]. One gram of *Salvia verticillata* was dissolved in 32 ml of distilled water prior to administration. Seven days before surgery until 7 days after surgery, drug-treated groups (2VO and sham) were treated with prepared *Salvia verticillata* (2 cc/250 gr body weight/d) orally using a stomach tube. Rats in the non-treated groups (2VO and sham) received only normal saline solution orally in a volume similar to *Salvia verticillata* at the same time. All rats were allowed one week to recover from the surgery and then a series of behavior tests were performed for 7 consecutive days.

Morris Water Maze Test

The learning and working spatial memory ability of rats was assessed using the MWM one week after 2VO surgery. In this model, each rat has to make four sequential performances to find a hidden platform in each trial. The MWM consisted of a circular tank (142 × 80 cm, height × diameter). It was filled with water at approximately 20°C ± 2°C to a height of a bit more than half mixed with innoxious ink. A transparent black metal platform (diameter 10 cm) was located at the center of the northeast quadrant at a constant position (target quadrant) and 1.5 cm below the surface of the water. There were many extra-maze visual cues (e.g., experimenter, window, computer, and rack) on the walls of the testing room to aid navigation. The maze was divided into four quadrants; north (N), south (S), west (W), and east (E). At each trial, animals were carefully placed into the water facing the wall of the tank in one of the four preplanned starting points (south, east, north, and west) that was selected randomly by computer. During the MWM task, the rat was given a time limit of 60 seconds to locate the platform by swimming. In case the rat was unable to find the platform during this time, the examiner gently placed it on the platform, and the escape latency time was recorded as 60 seconds. All rats were permitted to rest on the platform for 15 seconds irrespective of whether they found it or not. Each rat received four trials per day for 7 consecutive days, with a 30-second intertrial interval. Latency, the time required for each rat to find the platform, was recorded. Spatial learning was measured for each rat by averaging the latencies (seconds) across the four trials

per day. After the end of the learning trial on day 7, the platform was removed, and rats were subjected to the probe trial to evaluate the accuracy of the spatial memory. Following the completion of the MWM task, the rats were allowed to swim freely for 60 seconds, and the time spent in the quadrant where the platform was previously located was recorded. The rats' swimming activity and patterns were captured by a video camera, which was linked to a computer for further analysis. For each trial, various parameters, such as the escape latency time, path length, swimming speed, and the time spent in the target quadrant, were measured. The entire experiment, including the recovery period, took 21 days.

Statistical analysis

All data were presented as mean or median ± S.D. The main treatment effect on the escape latency, path length, and swim speed in the MWM was analyzed by repeated measures ANOVA followed by a turkey-Kramer post-hoc test for multiple comparisons between the two groups. Group differences in probe trials were analyzed using one-way ANOVA, followed by Duncan's multiple-range test. One-sample t-test was used to analyze performance in probe trials. $p < 0.05$ was considered statistically significant for all tests.

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No funding was received for conducting this study.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

Authors' Contributions

Conceptualization: Amir Afkhami goli, Hossein Kazemi Mehrjerdi; Methodology: [All Authors]; Formal analysis and investigation: [Amir Afkhami Goli]; Writing - original draft preparation: [All Authors]; Writing - review and editing: [Hossein Kazemi Mehrjerdi]; Funding acquisition: [Self-funding]; Supervision: [Hossein Kazemi Mehrjerdi, Amir Afkhami Goli]. All authors checked and approved the final version of the manuscript for publication in the present journal

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Competing Interests

The authors declare no conflict of interest.

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