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Research Article

ResArgin™, a conjugate of resveratrol and arginine, prevents memory impairment and oxidative stress in the Alzheimer's disease rat model intoxicated with aluminum chloride

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Abstract

Background: Effective drugs for the prevention and treatment of Alzheimer's disease (AD) remain scarce. Antioxidant compounds are increasingly being explored for their anti-Alzheimer's potential. This has led to the inclusion of up to three compounds in the 2023 Alzheimer's drug development pipeline for phase 3 trials targeting oxidative stress. This study presents the antioxidant effects of ResArgin™ (a conjugate of resveratrol and the amino acid arginine) and its protective effects against memory loss in a rat model of AD induced by $AlCl_3$. **Method:** Female rats were given $AlCl_3$ (50mg/kg bw) by oral gavage, except for the normal control group. One hour later, they were given distilled water for the positive control, 300 and 500 mg/kg b.w ResArgin™ for the test groups, or 1 mg/kg b.w Donepezil (reference 1) or 100mg/kg for vitamin E (reference 2) by daily gavage for 42 days. Neurobehavioral tests (Elevated Plus Maze and Morris Water Maze) were performed. Subsequently, the rats were sacrificed and the levels of MDA and GSH in rat brains were measured. The activity of antioxidant enzymes (SOD, CAT, GPx) and the level of reduced glutathione (GSH) were assessed in the rat brain. Histological sections of the regions of the hippocampus were made. **Results:** ResArgin™ (300mg/kgbw and 500 mg/kgbw) treatments preserved the learning profile and reduced latency time to reach the target quadrant in the MWM. ResArgin™ at 500mg/kg b.w (RSA500) significantly reduced ($p < 0.05$) the latency time to reach the target quadrant from 5.0 ± 1.01 seconds at week 2 to 2.3 ± 0.4 seconds at week 6. They protected the different areas of the brain (CA1, 3, and DG) from alterations induced by $AlCl_3$ and prevented oxidative stress in the brain. **Conclusion**: ResArgin™ prevents memory disorders, memory loss, altered hippocampus areas, and oxidative stress induced by $AlCl_3$ in rats.

Keywords: ResArgin™, oxidative stress, memory loss, Alzheimer's Disease, hippocampus, prevention

1. INTRODUCTION

Alzheimer's disease (AD) is the most common form of neurodegeneration, manifesting as memory loss, cognitive decline, brain shrinkage, creation of extracellular senile plaques, and intracellular neurofibrillary tangles[1]. Oxidative stress has been shown to play a crucial role not only in the early stages of Alzheimer's disease prior to cytopathology, but also in the induction and activation of various cellular signaling pathways that contribute to the formation of lesions caused by toxic substances, thereby promoting the development of AD[2]. In aluminum chloride-induced rat models of Alzheimer's disease, oxidative stress has been shown to accelerate the neuropathology of Alzheimer's disease by promoting increased phosphorylation of tau, an accumulation of insoluble beta-amyloid peptide (Aβ), its deposition, and dysfunction of cholinergic enzymes (AchE and BuchE)[3]. The challenge of current research is to find compounds capable of preventing and treating AD, especially as drugs are scarce against it[4]. In this light, antioxidant compounds are increasingly being explored for their anti-Alzheimer's potential. This explains why up to

three compounds (hydralazine hydrochloride, omega-3, and icosapentethyl) are registered in the Alzheimer's drug development pipeline for 2023 phase 3 trials targeting oxidative stress[5]. Additionally, the Keap1-Nrf2 pathway has been established as a therapeutic target for AD[6,7]. Several studies have revealed the neuroprotective effect of resveratrol thanks to its antioxidant effects[8]. However, its physicochemical and pharmacokinetic properties have shown their limitations[9]. In addition, its multiple biological effects (anti-obesity, anti-cancer, anti-diabetes, anti-ageing) show that it deserves to be promoted as a hit compound[8]. Recently, data reported significant improvements in microvascular function when 90 mg of resveratrol was consumed in the form of ResArgin™ (a conjugate of resveratrol and arginine), thus showing that ResArgin™ is a lead that can have more biological effects than its hit (resveratrol)[10]. This study presents the antioxidant effects of ResArgin™ and its protective effects against memory loss in a rat model of AD induced by Aluminium chloride.

2. MATERIALS AND METHOD

2.1. Drugs and chemicals

Drugs: ResArgin™ (a conjugate of resveratrol and the amino acid arginine) was obtained from Gateway Health Alliance Fairfield, California (Figure 1). Donepezil was purchased from the pharmacy (Yaoundé, Cameroon). ***Chemicals:*** All the chemicals used were of analytical grade and were purchased from Sigma Aldrich St Louis Mo, USA.

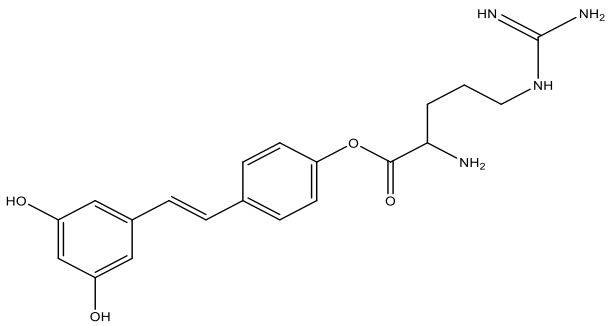

Figure 1: Chemical structure of ResArgin™

2.2. Experimental animals

Thirty-six adult female Wistar rats weighing 230-250g were obtained from the animal house of the Laboratory of Nutrition and Nutritional Biochemistry of the University of Yaoundé 1, Cameroon. They were housed in clean cages and maintained under standard conditions (room temperature with dark/light cycle 12/12 h). The rats were fed with a standard diet and had free access to potable water. They were acclimatized for seven days.

2.2.1. Ethical approval

Animals were treated following the guidelines of the ethical committee of the University of Yaoundé 1 and the Guide for the Care and Use of Laboratory Animals (8th edition).

2.2.2. Animal Experimentation

Testing the antioxidant potential and neuroprotective effect of ResArgin™ against aluminum chloride-induced neurotoxicity in rats

2.2.3. Treatments

The animals were randomly divided into six groups- a normal control (NC) (receiving distilled water only), a positive control (PC) (aluminum chloride at 50mg/kg bodyweight and distilled water), test group1 (50mg/kg bw $AlCl_3$ and ResArgin ™ at 300mg/kgbw), test group 2 (50mg/kgbw $AlCl_3$ and ResArgin™ at 500mg/kgbw), Reference 1 (50mg/kg bw $AlCl_3$ and Donepezil at 1 mg/kgbw) and Reference 2 (50mg/kg bw $AlCl_3$ and Vitamin E at 100mg/kg bw). After one hour, ResArgin ™ and reference drugs were administered to their corresponding groups, and the experimental period lasted for 42 days[11].

Table 1: Treatment summary

Groups	Treatments
NC	distilled water
PC	50mg/kg bw $AlCl_3$ + distilled water
Test 1 RSA300	50mg/kg bw $AlCl_3$ + 300mg/kg:bw ResArgin™
Test 2 RSA 500	50mg/kg bw $AlCl_3$ + 500mg/kg:bw ResArgin™
Reference 1 DNPZ (AD)	50mg/kg bw $AlCl_3$ + 1 mg /kg bw Donepezil
Reference 2 Vit E (Antioxidant)	50mg/kg bw $AlCl_3$ + 100mg /kgbw Vitamin E

RSA: resargin™; DNPZ: Donepezil; Vit E: vitamin E

2.2.4. Cognitive test

2.2.4.1. Elevated plus-maze (EPM) test

This study was carried out according to the protocol described by Walf and Frye[12]. The elevated plus-maze (EPM) is the most effective apparatus for the screening of anti-anxiety drugs. The elevated plus maze produced a novel environment that helped induce anxiety in animals because of the open nature of the arms and the elevation from the floor[13]. Rats present in the EPM prefer exploring the enclosed arms. Anxiety is marked by immobility and defecation. The parameters noted were time spent in open/closed arms, number of entries in the open/closed arms, number of rearing, weight of fecal body, and number of grooming. The percentages of time spent and the number of entries in each type of arm were calculated for each animal. After the test, the rectal temperature of each animal was measured using a medical thermometer.

2.2.4.2. Morris Water Maze test

The Morris water maze (MWM) test provides an accurate and reproducible measure of spatial memory

and is a highly sensitive tool for assessing hippocampal damage[14]. In the present study, the MWM test was performed in a black circular tank (diameter 120 cm × height 50 cm), half-filled with water in a lighted room. An 8-cm-diameter black drainage platform (colored to match the apparatus to make it invisible) was placed in a fixed position (south quadrant of the apparatus), submerged 1.0 cm below the water surface. The test included a 5-day acquisition and retention phase on day 6. Acquisition phase: Three trials were performed daily, with a 15-minute break between trials. At the end of each trial, the animals were properly cleaned and returned to their home cages. The principle of the MWM was that when the rats escaped from the water by climbing onto the platform, they learned the spatial location of the platform from any starting position in the pool. Retention phase: During this phase, to assess spatial memorization, the platform was removed, and each rat was released into the water in one of the fixed targets facing the target quadrant and had 60 seconds to swim and find the platform. A video recording system was used, and a camera was placed above the pool and connected to a computer. The videos were analyzed using Any-maze 7.3 software. The latency time to reach the exact position of the platform, the time spent in the target quadrant, and the number of entries in the target quadrant of the platform were recorded.

2.3. Animal sacrifice

2.3.1. Brain and blood tissue collection

At the end of the experiment period, animals were sacrificed by cervical decapitation after 12 hours of fasting. Blood samples were collected from the trunk in tubes containing EDTA and centrifuged at 1500 g at 4 °C for 15 min to obtain plasma.

2.3.2. Histopathological examination

One of the cerebral hemispheres of each rat was fixed in 10% formaldehyde, embedded in paraffin, cut (5 µm sections in the coronal plane), and processed for hematoxylin-eosin staining using standard procedures.

2.3.3. Preparation homogenate brain

The brains were rapidly removed, weighed, and thoroughly washed with isotonic saline. Brains were homogenized in 10 volumes of ice-cold (4 °C) medium containing 50 mM Tris (hydroxymethyl) aminomethane-HCl (Tris-HCl) buffer, pH 7.4, with 300 mM sucrose. Then, the homogenate was centrifuged (1000 g for 10 min). The resulting supernatant was immediately stored at -20 °C and used for biochemical analyses.

2.3.4. Oxidative stress markers

a) Malondialdehyde

The protocol was adopted with slight modifications as previously described[15]. Carbonyl compounds such as malondialdehyde react with thiobarbituric acid (TBA) to give pink chromophores absorbing at 530 nm. One hundred micro-liters of homogenate or 0.9%NaCl (blank), 250µL of trichloroacetic acid (TCA) 20% and 400µL of TBA 0.67% were added to the glass screw-top tubes (blank and test) and sealed. The mixture was heated in a water bath at 100^0C for 15 min and then cooled in a cold-water bath for 30 min. The tubes were left open to allow the gases formed during the reaction to escape. They were then centrifuged at 1500 rpm for 5 min, and the absorbance of the supernatant was read at 532 nm against the blank. The concentration of MDA was expressed in µM/g of brain.

b) Reduced Glutathione

The method was based on the measurement of thiol groups by monitoring the concentration of yellow-colored TNB (5-thio-2-nitrobenzoic acid), formed by reduction of DTNB (5,5-dithiobis (2-nitrobenzoic acid). One hundred (100) µL of homogenate and 900µL of Ellman's reagent were respectively introduced into blank and test tubes. After homogenization, the mixture was incubated at room temperature for 30 minutes. Optical densities were read at 420 nm against the blank containing 900µL of reagent solution and 100 µL of NaCl (0.9%), incubated under the same conditions. The concentration of reduced GSH in the brain tissues was expressed as µM/g of the brain[16].

c) Catalase Activity (EC 1.11.1.6)

Catalase present in the homogenate reduces hydrogen peroxide (H_2O_2) to water (H_2O) and oxygen (O_2). H_2O_2, not reduced by catalase, binds to potassium dichromate to form a blue-green precipitate of unstable perchloric acid. This is then decomposed by heat to form a green complex that absorbs at a wavelength of 570 nm. Catalase activity was proportional to optical density and was determined using a calibration curve. The activity was expressed as mmol H_20_2 consumed/min/mg protein/g brain[17].

d) Superoxide dismutase activity (EC 1.15.1.1)

The method described by Misra and Fridovich[18] was adopted. The method was based on the fact that SOD present in a sample inhibits the oxidation of adrenaline to adrenochrome. An aliquot of 0.2 mL of brain homogenate was introduced into 2.5 mL carbonate buffer (pH 10.2) to equilibrate the spectrophotometer. The reaction was then started by adding 0.3 mL of freshly prepared adrenaline to the mixture. After homogenization by inversion, the final mixture was read at 480 nm every 30 s for 150 s to follow the increase in absorbance. SOD activity was reported as units per g of brain.

e) Glutathione peroxidase (GPx) (EC 1.11.1.9) activity assay

GPx catalyses the reaction of hydroperoxides with reduced glutathione to form glutathione disulfide (GSSG) and the reduction product of hydroperoxide. The GPx activity of the sample was monitored at the rate of the decrease in reduced glutathione using H_2O_2 as a substrate according to the method of Flohe and Gunzler[19]. To 50 µL of the sample, 100 µL of reduced glutathione (0.1 mM) and 200 µL of H_2O_2 (0.1 mM) were added. The samples were then pre-incubated at 25 °C in a water bath for 5 min. One millimeter of trichloroacetic acid (20%) was added to the samples. The tubes were

further cooled on ice and centrifuged at 1000 g for 10 min. To 400 µL of supernatant fraction, 2.2 mL of phosphate buffer (50 mM; pH 7.0) and 320 µL of Ellman's reagent (DTNB: 5,5-dithiobis-2-nitrobenzoic acid) were added. The absorbance was read at 412 nm after 5 min of reaction. One enzyme unit of GPx activity was defined as 1 µmol of glutathione oxidized per minute at 25 °C.

2.6. Statistical analysis

GraphPad Prism 10.2.2 software was used for statistical analysis. The normality test was confirmed by the Shapiro-Wilk test, and a one-way analysis of variance (ANOVA) with Tukey's test was performed for comparison between groups. Results are expressed as mean value ± SD (n = 6). $P < 0.05$ was considered significant.

3. Results

3.1. ResArgin™ preserves learning patterns and protects spatial memory in rats given Aluminium Chloride (Morris Water Maze Test)

3.1.1. ResArgin™ preserves learning patterns

Figures 2 and 3 below show the progression in the escape latency for each trial at the second and sixth weeks, respectively. Figure 2 shows no difference in the average latency between all groups during week 2 in the Morris Water Maze test. During the sixth week (figure 3) of the Morris Water Maze, the average latency time in the positive control group increased compared to the normal control group. ResArgin™ 500 restored memory function, as evidenced by a reduced average latency time compared to the positive control group.

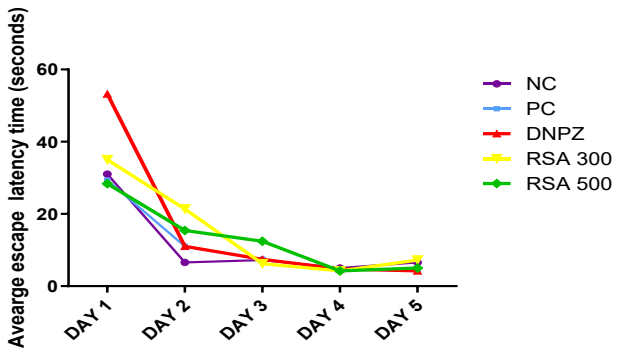

Figure 2: Action of ResArgin™ on the escape latency time into the target quadrant, week 2

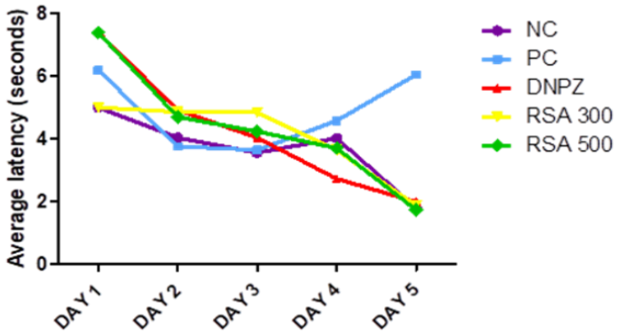

Figure 3: Action of ResArgin™ on escape latency into the target quadrant, week 6

3.1.2. ResArgin™ protects spatial memory

Table 2 shows the latency to reach the target quadrant, respectively, during the second and sixth weeks of the experiment (day-6).

Table 2: the latency time to reach the target quadrant, respectively, during the second and sixth weeks of the experiment (day-6)

Treatment groups	latency time into the target Second week of the experiment (s)	latency time into the target Sixth week of the experiment (s)
Normal control	6.6 ± 0.78[a]	2.6 ± 0.23[a]
Positive control	4.7 ±1.1[a]	5.4±0.67[b]
RSA 300	7.2 ± 1.3[a]	4.2 ± 1.3[b]
RSA 500	5 ± 1.01[a]	2.3± 0.4[a]
DONEPEZIL	4.7 ± 0.92[a]	1.9 ± 0.3[a]

The numbers assigned to different letters (a,b) are significantly different (P<0.05); RSA: resargin™

No significant difference was observed among all groups of the experiment with regard to the latency time to reach the target quadrant during the test day (day 6) of the second week. A significant difference ($P < 0.05$) in the latency time to reach the target quadrant was noted between NC and PC on test day (day 6), the sixth week of experimentation. Administration of ResArgin™ reduced this latency time. This reduction ($P<0.05$) was more pronounced at the dose of 500mg/kg b.w.

3.2. Anxiolytic action of ResArgin™

Figure 4 shows the time spent on the open arm, and Figure 5 shows the time spent on the closed arm during the second and sixth weeks of the experiment.

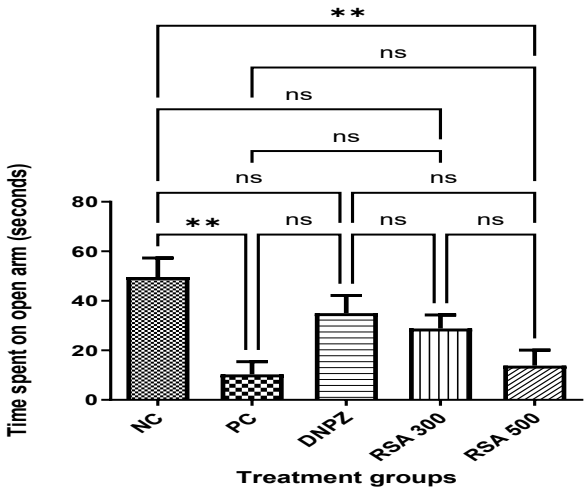

Figure 4: Time spent on the open arm

RSA: resargin™; DNPZ: Donepezil; NC: Normal control; PC: Positive control

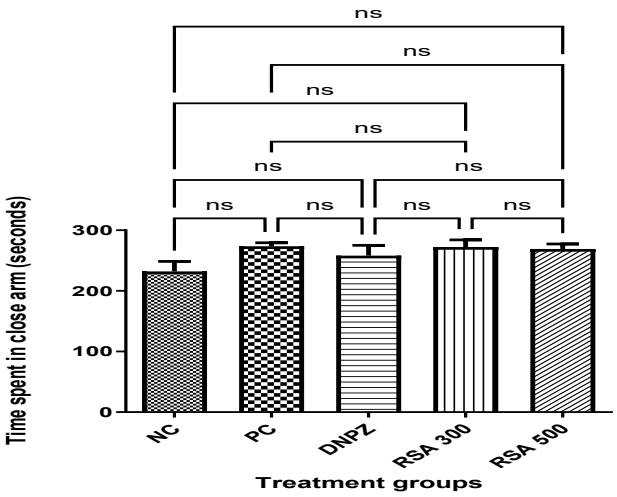

Figure 5: Time spent on closed arm

RSA: Resargin™; DNPZ: Donepezil; NC: Normal control; PC: Positive control

The results showed a significant decrease (P<0.01) in the time spent in the open arms of the PC group compared to the NC group. However, after administration of RSA300 and RSA500, a non-significant increase was obtained in these groups compared to the PC groups. On the other hand, the analysis of the time spent in the closed arms showed no significant difference between the different groups.

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3.3. Protective action of ResArgin™ on the hippocampal microarchitecture

Figure 6 shows the hippocampal microarchitecture (CA1,3 and DG)

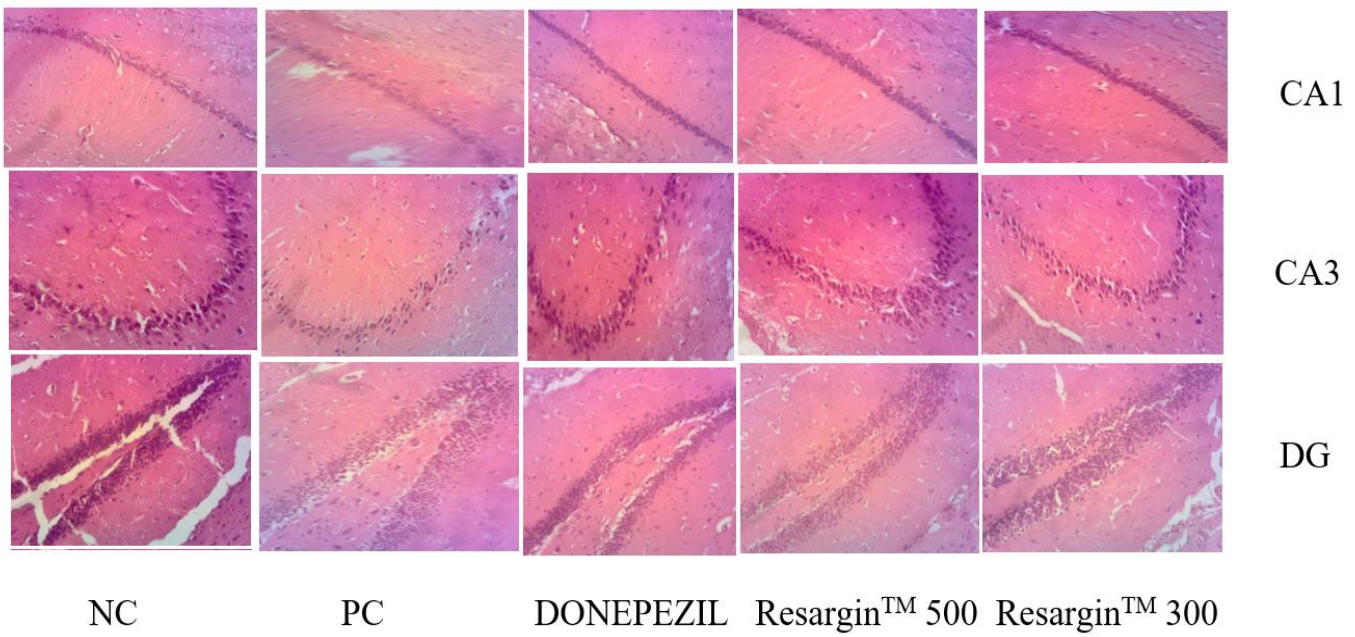

Figure 6: Protective action of ResArgin™ on hippocampal microarchitecture

In the normal control group, brain histology showed normal architecture of the different areas of the hippocampus (CA1, 3, and DG), while in the positive control group treated with aluminum, rat brain histology showed the presence of apoptosis, suggesting neurotoxicity induced by aluminum chloride. In the groups treated with ResArgin™, brain histology showed normal histology, demonstrating protection against aluminum chloride neurotoxicity compared to the positive control group.

3.4. ResArgin™ boosts brain antioxidant status

Table 3 shows the Effect of ResArgin™ on cerebral antioxidant status in female rats.

Table 3: ResArgin™ boosts brain antioxidant status

Treatment groups	SOD (U/mg protein/g of brain)	Catalase (mmol H_2O_2 consumed/ min/mg protein/g brain)	Glutathione (U/mg protein of brain)	MDA (µM/g of brain)
Normal control	1.48 ± 0.06[a]	4.2±0.1[a]	0.41 ± 0.02[a]	5.19 ± 0.84[a]
Positive control	1.08±0.08[b]	1.6±0.1[b]	0.18 ± 0.01[b]	9.23 ± 1.31[b]
RSA 300	1.249 ± 0.03[a]	3.6± 0.2[b]	0.30 ±0.01[a]	2.75 ±0.4[a]
RSA 500	1.36± 0.04[a]	4.40± 0.42[a]	0.31 ± 0.01[a]	4.59±0.42[ab]
Vitamin E 100	1.74 ± 0.02	2.35± 0.12	0.17±0.03	11.36 ±0.84

RSA: ResArgin™. The values are expressed as mean plus or minus standard error on the mean. Values with different values in the same column are significantly different.

In rat brain homogenate, statistical analysis shows a significant decrease in catalase, SOD, and glutathione peroxidase (GPx) activity in the positive control group compared to the normal control group. There was a significant difference in rat brain catalase, SOD, and GPx in the ResArgin™ 500-treated group compared to the positive control group, as shown in Table 3. ResArgin™ significantly increased the levels of catalase, SOD, and GPx.

Statistical analysis shows a significant ($p<0.05$) increase in the level of MDA between the positive control group and the normal control group, and a significant decrease in MDA level with the ResArgin™ treated group compared to the positive control group.

4. DISCUSSION

The search for effective treatments against AD remains a significant challenge today[1]. Antioxidant compounds represent a rapidly growing therapeutic option for this disease[20,21]. The present study was carried out to evaluate the preventive effect of ResArgin™ on oxidative stress and behavioral changes in aluminum-induced neurodegeneration in rats as a model of AD. Once in the brain, aluminum starts to compete with and replace calcium, magnesium, zinc, and phosphorus in a variety of enzymes and proteins. As a result, it sets in motion a series of biochemical cascades involved in abnormal processes, which culminate, optionally, together with pathological and clinical symptoms known as Alzheimer's disease. Research shows that aluminum chloride exposure in humans and animals results in behavioral changes and intellectual impairment[3].

The elevated plus maze test and the Morris water maze (MWM) tests were used to evaluate learning and memory[14]. In the MWM test, the learning profile in the PC was different from that of the NC in the sixth week of the test, which reflects an alteration of the memorization process by aluminum chloride. However, the treatment maintains the NC's learning profiles. Moreover, the PC group showed a significant ($p<0.05$) increase in escape latency compared to the normal control. This indicates an impairment in memory. Treatment with ResArgin™ at different doses significantly decreased the escape latency in the sixth week, indicating memory retention (Figures 2 and 3). The EPM result shows a significant ($p<0.01$) reduction in the time spent in the open arm in the PC compared to the NC. However, this time increased in the treated groups. This result shows that ResArgin™ may reduce anxiety levels in rats. The hippocampus was selected for histological cuts because it plays a more specific role in memory formation and learning[22]. Treatment with aluminum chloride led to histological changes in the positive control group compared to the normal control group. ResArgin™ 500-treated groups showed no hemorrhage or apoptosis in rat brains, indicating a neuroprotective effect (Figure 6).

The cognitive decline that occurs from neurodegeneration is mainly caused by oxidative stress in the brain[23]. Long-term exposure to aluminum chloride in female rats causes oxidative stress and changes in brain antioxidant enzymes[24]. This study demonstrates that chronic aluminum exposure induces cognitive impairment and alters brain markers in female rats, suggesting a model for studying AD pathology. However, limitations exist; first, the exclusive use of female rats limits generalizability to male rats. Future studies should include both species. Secondly, the exclusive use of aluminum chloride for the induction of AD may not fully replicate the complex pathology of AD. Results should be interpreted cautiously and considered alongside other findings from other AD models. Aluminum induces neurotoxicity and, consequently, neurodegeneration. The results of the present study showed a significant decrease in catalase and SOD activities, with an increase in lipid peroxidation shown by elevated malondialdehyde levels in the positive control group compared to the negative control group. This indicated that a state of oxidative stress was induced, leading to the formation of free radicals in the brains of rats[24]. Brain tissue is more susceptible to oxidative stress due to its greater oxygen consumption rate, high content of peroxidizable fatty acids, less regenerative capability, and low amounts of antioxidants.

Treatment with ResArgin™ 500 significantly elevated the levels of defensive antioxidant enzymes and decreased lipid peroxidation (Table 3). This indicates a

restoration in oxidative stress balance in rat brains. SOD is a vital antioxidant that detoxifies reactive oxygen species and acts as a cofactor for antioxidants like catalase and glutathione peroxidase[25]. This ability to restore the antioxidant system could be due to the presence of the amino acid arginine in addition to the hydroxyl groups found in ResArgin™. It has two amino groups in its structure; these are all electron-donating groups, which would scavenge the free radicals produced by donating their electrons[26,27].

The efficacy of ResArginTM to prevent oxidative stress and memory loss could be explained by the enzymatic release of resveratrol and arginine from ResArgin™ increasing plasma arginine level and consequently its bioavailability, usually limited to less than 24 hours[28]. The increased bioavailability of arginine certainly sustains and prolongs its neuroprotective effects, probably via slow digestion/absorption processes. The longer/relatively permanent supply of arginine via digestion/absorption of ResArginTM may decrease acute inflammatory reaction[29], contribute to the production of neuropeptide vasopressin, reducing neuronal death and improving functional recovery[30,31].

5. CONCLUSION

ResArgin™ prevents memory loss, memory disorders, altered hippocampus areas, and oxidative stress induced by aluminum chloride in rats.

Competing Interests: The authors have declared no competing interests.

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Author Contributions: OJ and AKGB conceived, designed, and supervised the study. ANI and DTRN conducted cognitive experiments. AN, AABD and AKGB performed biochemical analyses, analyzed results, and drafted the manuscript. The final version of the manuscript was read and approved by all the authors.

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