Original Article

Neuroprotective effect of 1, 3-β-glucan-curcumin mixing (Bioglucur) on Alzheimer Disease Induced in Mice by Aluminium Toxicity

Nesrine Ouda Amari[1], Noureddine Djebli[1,*], Le Mai Huong[2], Tran Thi Hong Ha[2], Nguyen Dinh Luyen[2], Vu Thi Bich[3,4]

[1]Laboratory of Pharmacognosy and Api Phytotherapy, University of Mostaganem, Mostaganem, ALGERIA.
[2]Institute of Natural Products Chemistry (INPC), Vietnam Academy of Science and Technology (VAST), Hoang Quoc Viet, Caugiay, Hanoi, VIETNAM.
[3]Institute of Theoretical and Applied Research, Duy Tan University, Hanoi, VIETNAM.
[4]Institute of Physics (IOP), Vietnam Academy of Science and technology (VAST), Dao Tan, Ba Dinh, Hanoi, VIETNAM.

ABSTRACT

Aim: The aim of this study was to evaluate the neuroprotective effect of oral administration of acomplex of curcumin with 1,3-β-glucan extracted from Vietnamese mushrooms named *Bioglucur* to increase drug delivery efficiency and biological effectin Alzheimer's model mice. **Materials and Methods:** Alzheimer's disease was induced in mice and treated in parallel by *Bioglucur.* **Results:** Results obtained show that the *Bioglucur* improves impart mental concentration and memory and decrease anxiety thus the storage capacity is improved during the Morris test and even neurons improvement in the histological study in treated mice. **Conclusion:** The mixture preparation of curcumin and 1,3-β-glucans from Vietnamese medicinal mushrooms increase the bioavibility of curcumin and helps recover neurons in mice Alzheimer's model.

Key words: Alzheimer's disease, Medicinal Mushroom, Curcumin, *Bioglucur*, Mice.

INTRODUCTION

Alzheimer disease (AD) is a devastating, progressive and irreversible neurodegenerative disorder, which is clinically characterized by the deterioration of memory, disorientation, increased confusion and other psychological as well as physical manifestations.[1] The appearance of extracellular amyloid-beta (Aβ) deposits in senile plaques and the development of intracellular neuro fibrillary tangles, reactive microgliosis and astrogliosis are the primary histopathological characteristics of AD.[2] Alzheimer's disease (AD), the main cause of dementia, is a major public health issue.[3] The risk's factors of Alzheimer's are multiples and poorly inderstand.[4] About 70% of the risk is believed to be genetic with many genes usually involved[5] vascular cardiopathy, environmental like Aluminium toxicity is recognized as a risk factor for neurogical disorders.[6] The toxicological effects include encephalopathy with presence of two abnormal proteins in the Alzheimer's brain. Despite the considerable research advances made and promising data obtained recently with aducanumab.[7] No real effective treatment has been identified up to date. Therefore, combination of innovative treatments, engaging not only one target but several ones, is currently mandatory to hope to treat this complex neurodegenerative disorder.

Medicinal plant extracts combined withmedicinal mushroom have a wide range of medicinal actions and through out history, have been used to treat many different types of diseases, including their neuroprotective degenerative disorders actions. Recent reports have suggested therapeutic potential of curcumin in the

Submission Date: 06-05-2020;
Revision Date: 14-07-2020;
Accepted Date: 23-09-2020

DOI: 10.5530/ijper.54.4.204

Correspondence:
Prof. Noureddine Djebli,
Laboratory of Pharmacognosy and Api Phytotherapy, University of Mostaganem, Avenue Hamadou Hossine, Mostaganem, ALGERIA.
Phone no: +213-45-365321
Email id: noureddine.djebli27@gmail.com

www.ijper.org

pathophysiology of AD, because of its antioxidant, anti-inflammatory and anti-amyloid effects.[8,9] Curcumin is an active natural polyphenol component of *Curcuma longa*.[10,11] It has been recently demonstrated that curcumin may inhibit protein aggregation, such as amyloid-β (Aβ) protein, which is related to several neurological pathologies, such as Alzheimer's disease (AD).[12] Never the less, no clinical studies have shown the efficacy of oral curcumin in treating AD. However, curcumin has only limited clinical applications due to the aqueous insolubility characteristic that reduces its biological availability. On the other hand, the mixture of 1,3-β-glucan and curcumin has potential as it increases solubility of hydrophobic substances such as curcumin.[13] *Hericium erinaceus* was reported to have activities related to nerve and brain health.[14] It is a member of the Herinaceae family, a culinary and medicinal mushroom. Both the mycelium and fruiting bodies of *Hericium erinaceus* have been shown to have therapeutic potential for brain and nerve health.[15] The bioactive metabolites of *Hericium erinaceus* can be high molecular weight compounds, such as polysaccharides and low molecular weight compounds, such as polypetides and terpenoids including erinacines and hericenones which were considered as nerve growth factors of the mushroom.[16,17] 1,3-β-glucan polysaccharides naturally found in cereal grains, bran and cell walls of certain fungi, especially mushrooms.[13] The aim of this study was to evaluate the neuroprotective effect of acomplex of curcumin with 1,3-β-glucan extracted from Vietnamese mushrooms named *Bioglucur,* administered orally to increase drug delivery efficiency and biological effectin Alzheimer's model mice.

MATERIALS AND METHODS

Plant materials

The mixture was prepared and friendly given by theInstitute of Natural Products Chemistry *(INPC)* Ha Noi, Vietnam. 1,3-β-glucan (Glu) used in this project was extracted from Lion's mane mushroom (*Hericium erinaceus*). *Hericium erinaceus* and *Curcuma longa* were collected in Vietnam and authenticated by (INPC). Curcumin was extracted from Vietnamese turmeric. The mixture was named *Bioglucur* and a voucher specimen (N^0. Fr.Le Mai.19/08/2016) is deposited in herbarium of (INPC).

Bioglucur preparation

In the first step of the method, 10 m.L of 1 m.g/m.L solution of curcumin in ethanol (99.8%) was dropped into 10 m.L solution of 20 m.g 1,3-β-glucan in deionized water. The mixture then had been stirred at room temperature for 48 h. Then, solvent was evaporated by a rotary evaporator. Next, product was centrifuged at 400 rpm to eliminate free curcumin. The mixture that contains 1,3-β-glucan and curcumin was then dried by Freeze Dry System (Labconco). The preparation was kept in obscurity and ambient temperature until use.[13]

The morphology size of *Bioglucur* were characterized by field emission scanning electron microscope (FESEM), followed by dynamic light scattering (DLS) imaging.

FTIR spectra were recorded on an IRAffinity-1S (SHIMADZU) in the 4000-400 cm^{-1} range with 32 scans in using the KBr pellet technique. Spectral resolution was 4 cm^{-1}.

Acute toxicity study

Acute toxicity study was assessed in mice by using an acute oral toxic class method of Organization of Economic Co-operation and Development (OECD)[18] guidelines.

Animals

Fourty healthy adult female mice weighing 33±5g were obtained from Algerian Pasteur Institute. Animals were kept in polyacrylic cages and maintained under standard housing conditions (room temperature at 25±5°C with 12:12 light: dark cycles) and water *ad libitum*. Food was provided by dry pellets. Animals were divided into four groups of ten mice each: control group (Control) was given only tap water, Alzheimer's model group (Alz) was given $AlCl_3$ (10mg/kg/day) orally with 0.1ml and D-galactose solution with concentration of (120mg/kg) intraperitoneally daily for 90 days.[19] Alzheimer's treated group (Alz T1): was given $AlCl_3$ (10mg/kg) orally with a D−galactose (120mg/kg/day) intraperitoneally for 90 days and treated in parallel by aqueous extract of Bioglucur (0.3ml) 200mg/kg/day orally starting from Forty-fifth day.

Alzheimer's treated group (Alz T2): Was given $AlCl_3$ (10mg/kg/day) orally with a D−galactose (120mg/kg/day) intraperitoneally for 90 days and treated in parallel by aqueous extract of Bioglucur (0.3ml) 250mg/kg/day orally starting from Forty-fifth day.

Behavioral and memory tests

Behavioral tests were carried out to determine motor, anxiety and depressive behavior. The open field and elevated plus maze (EPM) were done in 20 min divided into four phases of 5 min, while the forced swimming test was done in one phase of 5 min. Tests of memories were done in 5 days where each phase lasted 5 min. 5 mice from each experimental group were used for the tests at the rate of one test per day and each mouse was tested individually.

Locomotor activity

The locomotor activity test was performed to measure the motor functions of mice that tend to explore an enclosed space. The apparatus contains a platform divided into 16 equal squares. Each mouse was placed individually in the center of this platform and allowed to move freely during 5 min of exploration.[20] The number of squares visited was recorded for each mouse during a time of 5 min.

Test of Curiosity

Exploratory behaviour of mice in a novel environment was measured by using hole-board test.[21] The equipment consists of a wooden box (40 cm×40 cm×25 cm) with 16 equidistant holes 3 cm on the floor. The center of each hole was located 10 cm closest from the wall of the box. The box was placed 15 cm above the earth and divided into squares (10 cm×10 cm) with a waterproof marker. Each animal was placed singly in the center of the board and the number of head dipping into the hole was recorded over a 5-min exploration period on the board. Head dipping was counted only when both eyes disappeared into the hole.

Forced swimming test

The forced swimming test is frequently used to examine depressive behavior.[22] It consists of keeping the mouse in a warm bath of 21°C and a height of 16 cm so that the mouse does not touch the bottom and does not use its lower limbs to stand on the surface. The mouse will first struggle to escape and then becomes immobile, just keeping its nose above the water level, when it loses hope of escaping. The mice were observed for 5 min and the immobility time was recorded.

Anxiety test

The light/dark transition test is based on the innate aversion of rodents to brightly illuminated areas and on the spontaneous exploratory behaviour of rodents in response to mild stressors, that is, novel environment and light. The test apparatus consists of a small dark safe compartment (one third) and a large illuminated aversive compartment (two thirds).[23]

Anxiety test

The elevated plus maze (EPM), is an apparatus composed of two arms-a protected dark and enclosed environment and an unprotected brightly lit, open and elevated environment linked by a central platform allowing free access to both arms. The test is based on the natural anxiety related behavior of rodents to remain in shadow, close to walls and to avoid heights.[24] Mice were placed individually in the center of the maze which it is elevated 50 cm above the floor level, facing one of the open arms. The time spent in the open arms was recorded for 5 min. Increased activity in the open arms was indicative of less anxiety.[25]

Morris water maze test

The Morris water maze is the most common test used to evaluate cognitive functions related to memory and learning. The main component of the water maze set up should be a round pool, about 6 feet in diameter and about 3 feet deep. The water should be within one degree of 26°C. The animal may swim around the edge of the pool looking for a way out. Eventually, the animal will learn to search for the platform and climb up.

The test consists of two parts

Animals are placed in a pool of water where they must swim to platform (spatial working memory).

Animals are placed in a pool of water that is colored opaque with powdered non-fat milk, where they must swim to a hidden escape platform (spatial memory reference). Because they are in opaque water, the animals cannot see the platform and cannot rely on scent to find the escape route.[26]

Histological Study

At the end of exposure, animals were food deprived for 24 h. Mice were anesthised with chloral hydrate at dose 3% intraperitonealy and decapitated. The brains of mice were removed right after sacrifices, then quickly impressed in 10% neutral buffered formaldehyde for 24 hr, serial coronal paraffin sections of 4µm thickness were cut with a Leica microtome (M530, Allemagne) Serial sections were stained with Haematoxylin-Eosin (H&E) 1% and prepared for histopathological examination.[27]

Statistical Analysis

The experimental results were reported as means with SEM. Statistical analysis was performed using SPSS software. Analysis of variance (ANOVA) and LSD test were used to compare the experimental groups with the controls. The statistical significance of differences between groups was assessed with an analysis of variance followed by the student *t*-test (Control and Alz, Alz and Alz T1, Alz T2). *P* values less than 0.05 were considered as statistically significant.

RESULTS

Fourier Transform Infrared (FTIR) spectral analysis

The FTIR spectra of curcumin- Cur, *1,3-β-glucan*- Glu and 1,3-β-glucan-curcumin mixing - *Bioglucur* in solide in the 400-4000 cm^{-1} range are shown in Figure 1.

The results showed that curcuminoids extracted from Vietnamese turmeric had most of the characteristic peaksof curcumin. Their characteristic vibrational frequencies are almost the same. This confirms that the chemical structure of curcuminoid obtained from turmeric is comparable to that of commercial curcumin.[28] For 1,3-β-glucan-curcumin mixing, the characteristic feature peaks include characteristic peaks of both Curcumin and 1,3-β-Glucan. There are some factors proving that the complex has been formed. That is the shift in peak positions such as the peak of aromatic C= C at 1600 cm^{-1} and that of the carbonyl C =O peaks at 1628 cm^{-1} or the υ(C=O), δ(CCC) and δ(CC=O) at 1508 cm^{-1}, but FTIR spectra have shown almost the same in the case of curcumin and mixture (Table 1).

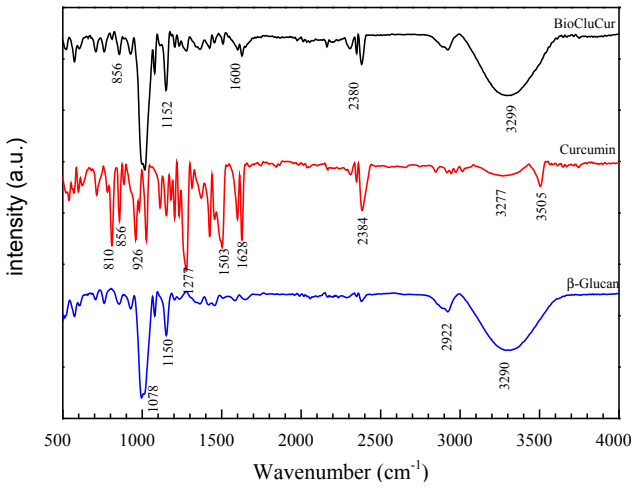

Figure 1: FTIR spectra of Curcumin, total-β-Glucan and *Bioglucur*.

FTIR results show in Figure 1 that the characteristic peaks of the *Bioglucur* mixing compared with curcumin do not change (within the permitted level of measurement errors). Therefore, we can conclude that the *Bioglucur* maintain the structure and properties of curcumin, increasing the practical value of the product when used regularly.

Effect of *Bioglucur* on acute toxicity studies

The acute toxicity tests with doses of 300, 500 and 2000mg/kg of the aqueous solution of *Bioglucur* caused no death in the mice. No lethal effects were noted throughout the short and long-term observation period. No toxicity signs were observed in the animals throughout the 14 days study period. Therefore, the extract may be safe at these doses and the oral LD_{50} considered was greater than 2000mg/kg in mice

Behavioral test

Test of locomotor activity

The results obtained show hyperactivity in Alzheimer's model mice compared to the control group. Nosignificant differences in locomotor activity were observed in Alzheimer's treated groups with two doses (200 and 250mg/kg) of *Bioglucur* and Alzheimer's model mice. Moreover, in the last phase of test, the locomotor activity was gradually decreased during the experimental period in all groups (Figure 2).

Table 1: Characteristic vibrational frequencies (cm^{-1}) và assignements of curcumin, β-Glucan and *Bioglucur* obtained by FTIR spectra.

Curcumin	β-1,3-Glucan	Bioglucur	Assignements
3505			(Phenolic O-H stret.), -OH vibrations of intermolecular-bonded OH group
3277	3290	3299	ν(OH)
	2922	2922	ν(C-H)
2384		2380	
1628		1628	ν (C=C), ν (C=O)
1599		1600	ν (C=C) aromatic ring
1508		1508	ν (C=O), υ(C=O), δ(CCC) and δ(CC=O)
1454		1454	$\delta(CH_3)$
1423		1423	$\delta(CH_3)$
1277		1279	δ (C-O-C), enol C-O
1204	1204	1206	δ (C=C-H)
1152	1150	1152	δ (C-O-C)
	1078	1078	The presence of starch
	926	928	Starch is associated

Test of Curiosity

The results obtained during this test showed that mice treated with the extract of *Bioglucur*at a dose of (200mg/kg) were very curious during the first phase of experimentation, the results are closer to that of the control group, this curiosity is decreased gradually during the following phases (Figure 3). Alzheimer's mice models were less exploratory than the other groups during the last phase.

Test of Anxiety

The results obtained during the test of anxiety showed that all experimental groups spend more time in the dark compartment than in the light one (Figure 4). We note that the group of Alzheimer's model treated with a dose *Bioglucur* (200mg/kg) spends much more time in the dark during the fourth phase compared to other groups. A significant differences between the control group, Alzheimer's model group and Alzheimer's treated with (200 and 250mg/kg) (P<0.05) were observed.

Test of anxiety

In this test, it was observed that the control group, Alzheimer's treated groups with (200mg/kg) and (250mg/kg) spend more time in hallway arm protected throughout the experiment compared with Alzheimer's group (Figure 5).

The Forced swimming Test (Persolt Test)

During the forced swim test (Figure 6) a significant differences (P<0.05) in the time were recorded in the Alzheimer's treated with *Bioglucur* (200mg/kg) and (250mg/kg) immobility was much longer than mice model Alzheimer's and control groups.

Memory Test - Arm radial maze - Spatial Working memory

In the spatial working memory test it shows that the number of repeated passages in control mice is witness higher unlike Alzheimer's and Alzheimer's treated groups (200mg/kg) and (250mg/kg) during the first four days of learning group. But during the fifth day

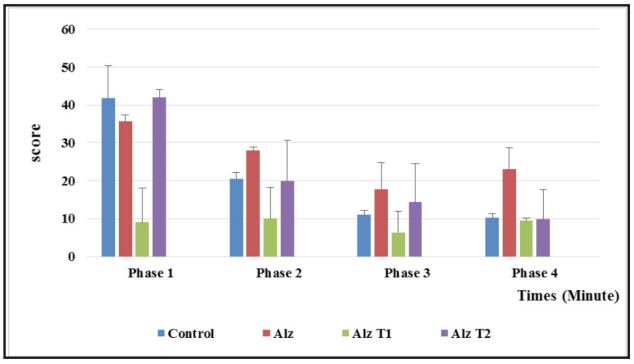

Figure 2: Locomotor activity in Alzheimer model mice poisoned by $AlCl_3$ (10 mg/kg) orally with D–galactose (120 mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250 mg/kg) compared to control mice for 90 days, significant difference (P < 0.05).

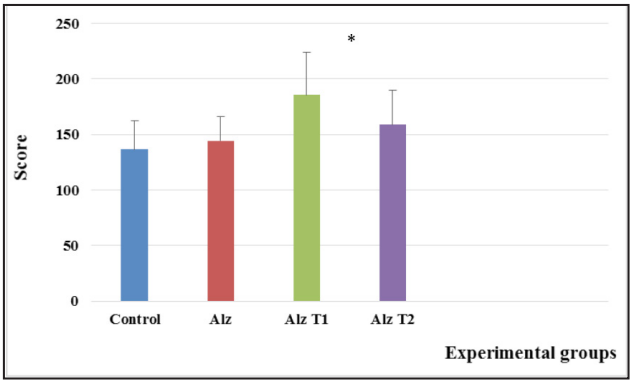

Figure 4: Test of anxiety (The light/dark transition test (LDT) in Alzheimer model mice poisoned by $AlCl_3$ (10 mg/kg) orally with D–galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference (P < 0.05).

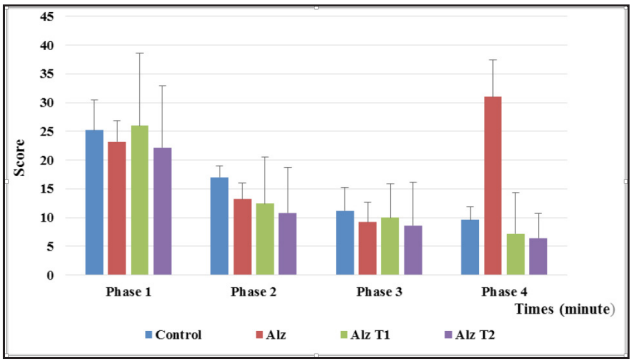

Figure 3: Test of curiosity in Alzheimer model mice poisoned by $AlCl_3$ (10 mg/kg) orally with D–galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference (P < 0.05).

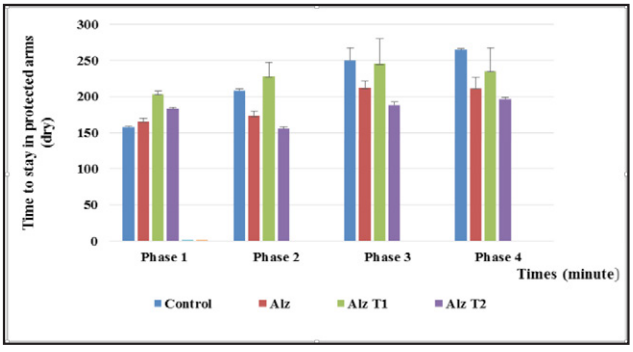

Figure 5: Test of anxiety (The elevated plus maze (EPM)) Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D– galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference (P < 0.05).

(memory test), we have noticed that the number of repeated corridors is much greater in the Alzheimer's model group compared to other groups. Significant difference ($P<0.05$) between Alzheimer's treated group (200mg/kg) and control group at the second and third day, highly significant ($P<0.01$) with Alzheimer's treated group (250mg/kg) at the fourth day (Figure 7.1 and 7.2).

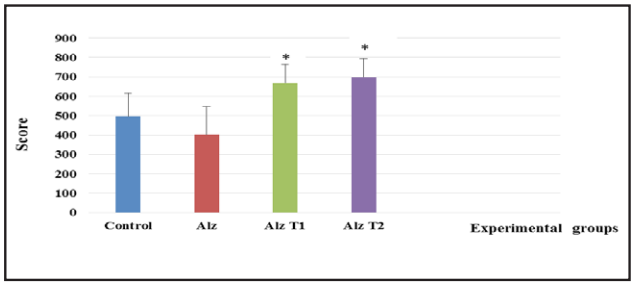

Figure 6: Test Porsolt in Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D–galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference ($P < 0.05$).

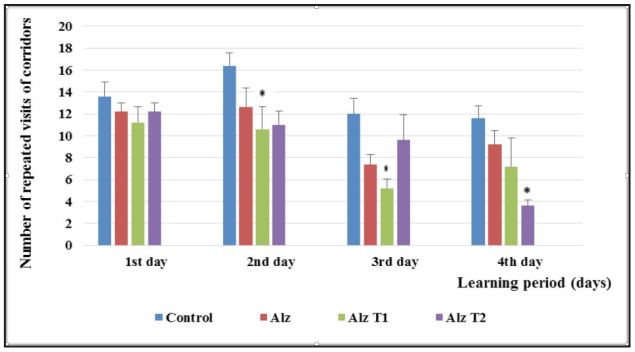

Figure 7.1: The results of the first four tests of spatial memory of work in Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D– galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference ($P< 0.05$).

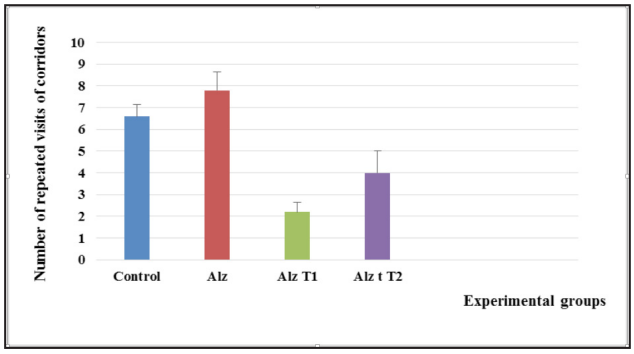

Figure 7.2: The results of the fifth test (5th day) of spatial memory of work in Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D-galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference ($P< 0.05$).

Morris water maze

Spatial Working memory (MST)

The results of the test of spatial working memory show that control group and Alzheimer's treated group (200mg/kg) take much longer to detect the visible platform as compared to Alzheimer's treated (250mg/kg) in the fourth days of learning. On the fifth day, the visible platform was detected quickly by Alzheimer's treated group, on the other hand, it was noticed that the mouse model Alzheimer's take a long period to detect the platform relative to the others groups (Figure 8.1 and 8.2).

Spatial reference memory (MSR)

During the spatial reference memory (MSR) the journey to the invisible platform is significantly higher in Alzheimer's model group from the second trial until the end of the experiment (Figure 9.1 and 9.2). However, we note that the journey to the invisible platform is

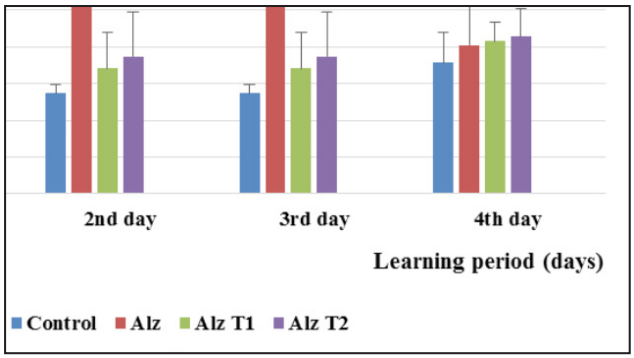

Figure 8.1: The results of the first four tests of Morris water maze test (MST) in Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D-galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference ($P< 0.05$).

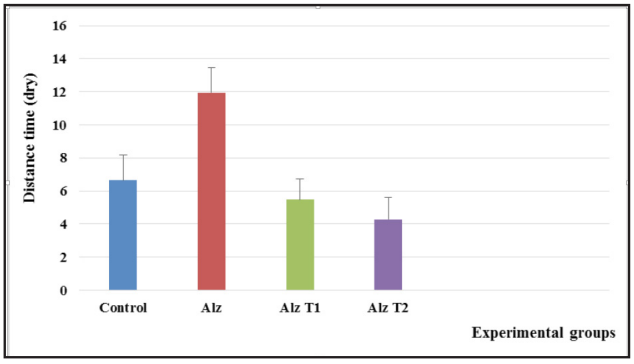

Figure 8.2: The results of the fifth test (5th day) of Morris water maze test (MST) in Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D-galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference ($P< 0.05$).

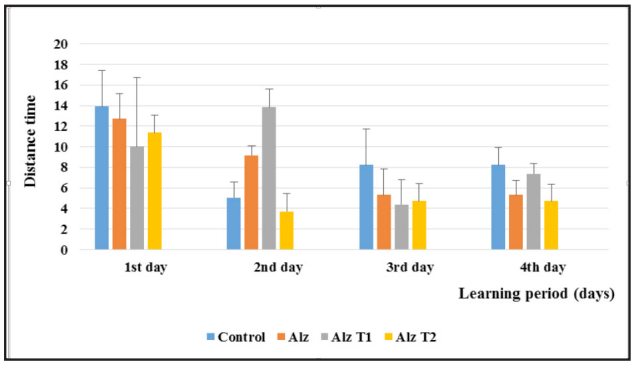

Figure 9.1: The results of the first four tests of Morris water maze test (MSR) in Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D– galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference (*P*< 0.05).

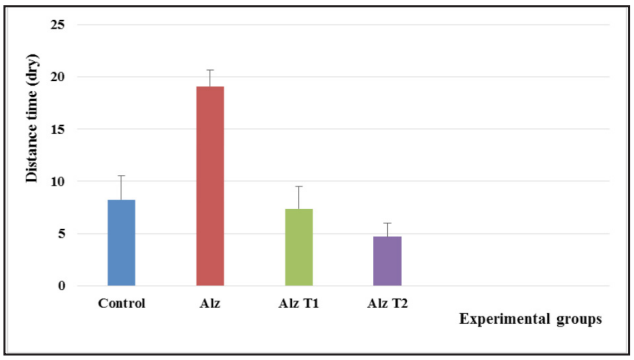

Figure 9.2: The results of the fifth test (5th day) of Morris water maze test (MSR) in Alzheimer model mice poisoned by $AlCl_3$ (10mg/kg) orally with D-galactose (120mg/kg) intraperitoneally and mice Alzheimer model treated by *Bioglucur* (200 and 250mg/kg) compared to control mice for 90 days, significant difference (*P*< 0.05).

significantly reduced in all experimental groups compared with Alzheimer's group. Highly significant difference ($P<0.01$).

Histological Studies

Histological study in the mid brainshows typical neuropathological changes Alzheimer's model group. In the control group, the neurons were full and arranged tightly, the nuclei were light stained. By comparison in the Alzheimer's model group mice, the cytoplasmof neuron were shrunken, vacuolation, the nuclei were side moved and dark stained (condensed chromatin, cellular alteration and neurons loss) were observed in mid brain region, similar results were obtained by Somova and *al.* 1997.[29] However co-administration of *Bioglucur* showed a good level of protection with no signs of adverse effects of Al intoxication in the mid brain (Figure 10).

(Control) Control group, (Alz) Alzheimer's model group, (Alz T1) Treated Alzheimer's model group (200mg/kg), (Alz T2) Treated Alzheimer's model group (250mg/kg). (G×400). Histopathological changes in the mid brain of mice: Control section showing normal histoarchitecture. (Alz): degeneration of neurons with cytoplasmic and nuclear vacuolations, dark small neurons. (Alz T1): Alzheimer treated mice by (200mg/kg), showed moderate neuroprotective effect of *Bioglucur*. (Alz T2): Alzheimer treated mice by (250mg/kg) of *Bioglucur*, showed improvement in histoarchitecure of neurons.

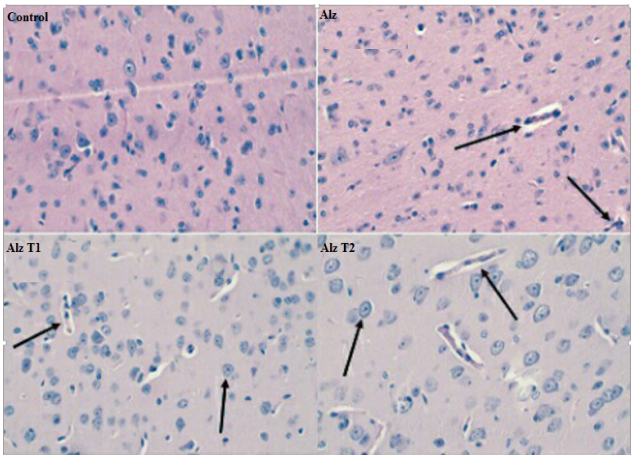

Figure 10: Microscopic study of mid brain performed by staining (H&E) in mice.

DISCUSSION

Alzheimer (AD) is a progressive neurodegenerative disease that deteriorates gradually over time.[30] Aluminum accumulation has been insinuated to be a contributing agent to AD, where elevated aluminum concentrations in AD patient brains have been observed.[31] It is said to enter the brain via transferrin like high affinity receptors and accumulate in the brain specifically in the hippocampus, the center for learning and memory.[31,32] Aluminum has been reported to be a potent neurotoxicant, capable of inducing and accelerating brain oxidative damage, neuron death, cholinergic degradation, Aβ deposition, memory and learning deficits.[32-36]

In the present study, the effects of aluminium exposure were investigated to describe the associated behavioral and brain modifications. The hyperactivity observed in our results could be the result of stress conditions. These results are consistent with the work of Golub *et al.*[37] and Kumar *et al.*[38]

The test results of curiosity, which measures the exploratory behavior shown by mice reveal that poisoned mice and Alzheimer mice model are less exploratory than the control and treated mice. It has been shown that changes in head-dipping behavior

may reflect the anxiogenic and / or the anxiolytic state of animals.[26] We noticed that Al exposed mice spent less time in dark than light, this suggest the anxiety of intoxicated animals, these results are in agreement with the work of Rebai and Djebli,[39] Douichene *et al.*[40] Alzheimer's model mice treated with a dose of *Bioglucur* (200mg/kg) spent less time in dark than light compared to no treated group, these results confirm the protective effect of the dual effect of 1,3-β-glucan and curcumin product (*Bioglucur*).

In our study, results obtained when testing at elevated cross maze show that Alzheimer's model mice prefer staying in the unprotected arm. Similarly, the control and treated groups with *Bioglucur* prefer protected, results are not consistent with the work of Rebai and Djebli.[39]

Forced swimming test is a common behavioural test for assessing depression in which animals have given up the hop of escape and depression remains controversial (Figure 5)[41] treatment with *Bioglucur* has an antidepressant activity reduce the time during which the animals remain immobile, similar result was obtained by other studies.[22,42] Morever, in the forced swim test, it was observed that the time recorded in the Alzheimer's treated with *Bioglucur* (200mg/kg) and (250mg/kg) of the immobility is much larger than mice model Alzheimer's and control groups which have recorded a short time. These results are in agreement with several studies.[41,43] This physical immobility is thought to be an indication of behavioral despair.

The spatial working memory test shows that the number of repeated passages in control mice and treated groups with two doses of *Bioglucur* are witness higher unlike Alzheimer's and Alzheimer's treated groups (200mg/kg) and (250mg/kg) during the first four days of learning group. But during the fifth day (memory test), we see that the number of repeated corridors is much greater in the Alzheimer's model group compared to other groups. These results translate into a deficit of spatial working memoryin procedural learning that is caused by an accumulation of Aluminium in the brain, this result is consistent with the work of Santucci *et al.*[44]

In both versions of the test of the morris water maze, spatial working memory and reference it was noted that the intoxicated Alzheimer's model mice takes longer to find platform compared to control and treated groups, these results are consistentwith the work of Luo *et al.*[45] the intoxicated mice shows a deficit of spatial learning and the ability to store.

In conclusion, the neuroprotective effect was improved in this study. In mice with neurodegenerative disease, Bioglucur improves both memory and cognitive function it has anti− dementia activity in a mouse model of Alzheimer's disease. It combats depression and anxiety and may help in Alzheimer's: it prevents the loss of spatial short− term memory. Lai *et al.* (2013),[46] found that the aqueous extract of *H. erinaceus* contained neuroactive compounds which induced NGF-synthesis and promoted neurite outgrowth in NG108-15 cells. The extract also enhanced the neurite outgrowth stimulation activity of NGF when applied in combination. The aqueous preparation of *H. erinaceus* had neurotrophic but not neuroprotective activities.[46] The *Bioglucur* from Vietnamese medicinal mushrooms helps recover neurons in mice Alzheimer's model.

Histological study shows that *Bioglucur* protect neurons from amyloid beta-induced neurotoxicity causes by aluminum. We notice improvement in brain tissues of treated mice compared to alzheimer's model mice, the mechanism of action of this new drug still unknown. Several researches are now in procceding between our laboratory and INPC to determine synergistic mechanism of action of curcumin and *Hericium erinaceus* as well as others biological activities.

ACKNOWLEDGEMENT

This research is funded by Algerian ministry of higher education and scientific research and VAST Grant No. NVCC 07.02, 20-20.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

mg: Milli gram; **mL:** Milliliter; **h:** Hours; **rpm:** Revolutionsper minute; **FESEM:** Fieldemission scanning electron microscope; **DLS:**dynamic light scattering; **FTIR:** Fourier Transform InfraRed; **g:** Grams; **Alz:** Alzheimer's model groups; **Alz T1:** Alzheimer's treated group 1; **Kg:** Kilogram; **EPM:** elevated plus maze; **MSR:** Spatial reference memory; **H&E:** hematoxylin and eosin.

REFERENCES

1. Jadoopat R. Review of Alzheimer's disease treatment and potential future therapies. Annu Rev Chang Healthc. 2018;2(1).
2. Heneka MT, O'Banion MK. Inflammatory processes in Alzheimer's disease. J Neuroimmunol. 2007;184(1-2):69-91.
3. Ando T, Xuan W, Xu T, Dai T, *et al.* Comparison of therapeutic effects between pulsed and continuous wave 810-nm wavelength laser irradiation for traumatic brain injury in mice. PLoS One. 2011;6(10):e26212.

4. Burns A, Iliffe S. Alzheimer's disease. BMJ. 2009;338:b158. Doi:10.1136/bmj.b158. PMID 19196745.
5. Ballard C, Gauthier S, Corbett A, Brayne C, *et al*. Alzheimer's disease. Lancet. 2011;377:1019-3.
6. Short AI, Winney RJ, Robson JS. Reversible microcytic hypochronicanaemia in dialysis patients due to aluminium intoxication. Proc Eur Dial Transplant Assoc. 1980;17:226-33.
7. BuddHaeberlein S, O'Gorman J, Chiao P, Bussiere T, *et al*. Clinical development of Aducanumab, an anti-abeta human monoclonal antibody being investigated for the treatment of early Alzheimer's disease. J PrevAlzheimers Dis. 2017;4(4):255-63.
8. Yang F, Lim GP, Begum AN, Ubeda OJ, *et al*. Curcumin inhibits formation of amyloid beta oligomers and fibrils, binds plaques and reduces amyloid *in vivo*. J Biol Chem. 2005;280(7):5892-901.
9. Balasubramanian K. Molecular orbital basis for yellow curry spice curcumin's prevention of Alzheimer's disease. J Agric Food Chem. 2006;54(10):3512-20.
10. Aggarwal BB, Harikumar KB. Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. Int J Biochem Cell Biol. 2009;41(1):40-59.
11. Alsamydai A, Jaber N. Pharmacological aspects of curcumin: Review article. Int J Pharmacogn. 2018;5(6):313-26.
12. Zhang C, Browne A, Child D, Tanzi RE. Curcumin decreases amyloid-β peptide levels by attenuating the maturation of amyloid-β precursor protein. J Biol Chem. 2010;285(37):28472-80.
13. Le MH, Do HD, Thi HHT, Le Vu Dung LV, *et al*. The dual effect of curcumin nanoparticles encapsulated by 1-3/1-6 β-glucan from medicinal mushrooms *Hericium erinaceus* and *Ganoderma lucidum.* Adv Nat Sci: Nanodci Nanotechnol. 2016;7(4):1-8.
14. He X, Wang X, Fang J, *et al*. Structures, biological activities and industrial applications of the polysaccharides from *Hericium erinaceus* (Lion's Mane) mushroom: A review. Int J BiolMacromol. 2017;97:228-37.
15. Cheng JH, Tsai CL, Lien YY, *et al*. High molecular weight of polysaccharides from *Hericium erinaceus* against amyloid beta-induced neurotoxicity. BMC Complement Altern Med. 2016;16(1):170.
16. Thongbai B, Rapior S, Hyde KD, *et al. Hericium erinaceus*, an amazing medicinal mushroom. Mycol Progress. 2015;14(10):91.
17. Wang K, Bao L, Qi Q, *et al*. Erinacerins C-L, isoindolin-1-ones with alpha-glucosidase inhibitory activity from cultures of the medicinal mushroom *Hericium erinaceus*. J Nat Prod. 2015;78(1):146-54.
18. OECD/OCDE. OECD Guidelines for the testing of chemicals, revised draft guidelines, Acute Oral Toxicity Acute Toxic class methods Revised Document October. 2000;423.
19. Yang DS, Kumar A, Stavrides P, Peterhoff CM, Pawlik M, Levy E, *et al*. Neutronal apoptosis and autophagy cross talk in aging PS/APP mice, a model of Alzheimer's disease. Am J Pathol. 2008;173(3):665-81.
20. Sáenz JCB, Villagra OR, Trias JF. Factor analysis of forced swimming test, sucrose preference test and open field test on enriched, social and isolated reared rats. Behav Brain Res. 2006;169(1):57-65.
21. Takeda H, Tsuji M, Matsumiya T. Changes in head− dipping behavior in the hole−board test reflect the anxiogenic and/ or anxiolytic state in mice. Eur J Pharmacol. 1998;350(1):21-9.
22. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice: A primary screening test for antidepressants. Arch Int Pharmacodyn Ther. 1977;229(2):327-36.
23. Bourin M, Hascoet M. The mouse light/dark box test. Eur J Pharmacol. 2003;463(1):55-65.
24. Albrechet-Souza L, Oliveira AR, DeLuca MC, *et al*. A comparative study with two types of elevated plus maze (transparent vs. opaque walls) on the anxiolytic effects of midazolam, one-trial tolerance and fear-induced analgesia. Prog Neuropsychopharmacol Biol Psychiatry. 2005;29(4):571-9.
25. Hogg S. A review of the validity and variability of the elevated plus-maze as an animal model of anxiety. Pharmacol Biochem Behav. 1996;54(1):21-30.
26. Morris R. Developments of a water-maze procedure for studying spatial learning in the rat. J Neurosci Methods. 1984;11(1):47-60.
27. Mahdy KA, Farrag ARH. Amelioration of aluminum toxicity with black seed supplement on rats. Toxicol Environ Chem. 2009;91(3):567-76.
28. Pawar HA, Gavasane AJ, Choudhary PD. A Novel and Simple Approach for Extraction and Isolation of Curcuminoids from Turmeric Rhizomes. Nat Prod Chem Res. 2018;6(300):2.
29. Somova LL, Missankov A, Khan MS. Chronic aluminum intoxication in rats: dose−dependent morphological changes Methods Find. Exp Clin Pharmacol. 1997;19(9):599-604.
30. Pavlik VN, Doody RS, Massman PJ, Chan W. Influence of premorbid IQ and education on progression of Alzheimer's disease. Dement Geriatr Cogn Disord. 2006;22(4):367-77.
31. Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, *et al*. Aluminum and silica in drinking water and the risk of Alzheimer's disease or cognitive decline: Findings from 15-year follow-up of the PAQUID cohort. Am J Epidemiol. 2009;169(4):489-96.
32. Roskams AJ, Connor JR. Aluminum access to the brain: A role for transferrin and its receptor. Proc Natl AcadSci USA. 1990;87(22):9024-7.
33. Kaur A, Gill KD. Possible peripheral markers for chronic aluminium toxicity in Wistarrats. ToxicolInd Health. 2006;22(1);39-46.
34. Platt B, Fiddler G, Riedel G, Henderson Z. Aluminium toxicity in the rat brain: Histochemical and immunocytochemical evidence. Brain Res Bull. 2001;55(2):257-67.
35. Germano C, Kinsella G. Working memory and learning in early Alzheimer's disease. Neuropsychol Rev. 2005;15(1):17-8.
36. Miu AC, Benga O. Aluminum and Alzheimer's disease: A new look. J Alzheimers Dis. 2006;10(2-3):179-201.
37. Golub MS, Keen CL, Gershwin ME. Neurodevelopemental effect of Aluminium in mice: Forstering studies. Neurotoxicolteratol. 1992;14:177-82.
38. Kumar A, Dogra S, Prakash A. Protective effct of curcumin (*Curcuma longa*) against aluminium toxicity: Possible behavioral and biochemical alteration in rats. Behavioral Brain Research. 2009;205(2):384-90.
39. Rebai O, Djebli N. Chronic exposure to Aluminum Chloride in Mice: Exploratory Behaviors and Spatial Learning. Advances in Biological Research. 2008;2(1-2):26-33.
40. Douichene S, Djebli N, Zerrouki K. Neuroprotective effect of Curcumin with afixator of absorption against both Aluminium neurotoxicity and Alzheimer's disease (experimental studies in mice). Journal of Pharmaceutical Sciences and Research. 2012;3(10):3837-41.
41. Gardier AM, Bourin M. Appropriate use of « Knockout » mice as models of depression or models of testing the efficacy of antidepressants. Psychopharmacology. 2001;153(3):393-4.
42. Borsini F, Meli A. Is the forced swimming test a suitable model for revealing antidepressant activity. Psychopharmacology. 1988;94(2):147-60.
43. Sahin G, Varol I, Temizer A. Determination of aluminium levels in the kidney, liver and brain of mice treated with aluminumhydroxide. Biol Trace Elem Res. 1994;41(1-2):129-35.
44. Santucci D, Rankin J, Laviola G, Aloa L. Section of Behavioral pathophysiology, Lab. Di Fisiopathologia di Organoedisistima, Institute superior di Sanita, Vial Regina Elena 299, 1−00161, Roma, Italy b institute of cell, Animal and population Biology, King's buildings, west mains road, Edinburgh EH9 3 JT, UKcinstituto di Neurobiologia, NR. Vial Carlo Marx. 2003;15:1-00155.
45. Luo Y, Nie J, Gong QH, Lu YF, *et al*. Protective effects of icarin against learning and memory deficits induced by aluminum in rats. Clin Exp Pharmacol Physiol. 2007;34(8):792-5.
46. Lai PL, Naidu M, Sabaratnam V, Wong KH, *et al*. Neurotrophic properties of the Lion's mane medicinal mushroom, *Hericium erinaceus* (Higher Basidiomycetes) from Malaysia. Int J Med Mushrooms. 2013;15(6):539-54.

Cite this article: Amari NO, Djebli N, Huong LM, Hong Ha TT, Luyen GD, Bich VT. Neuroprotective effect of 1, 3-β-glucan-curcumin mixing (Bioglucur) on Alzheimer Disease Induced in Mice by Aluminium Toxicity. Indian J of Pharmaceutical Education and Research. 2020;54(4):1089-97.