Saudi Journal of Biological Sciences 28 (2021) 4232–4239

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Original article

Neuroprotective effects of ononin against the aluminium chloride-induced Alzheimer's disease in rats

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ARTICLE INFO

Article history:
Received 14 May 2021
Revised 7 June 2021
Accepted 10 June 2021
Available online 15 June 2021

Keywords:
Ononin
Neuroinflammation
Alzheimer's disease
Oxidative stress
PPAR-γ

ABSTRACT

Alzheimer's disease (AD) is a chronic neurodegenerative disease categorized by the deficiency in the cognition and memory. Approximately 50 million peoples has the AD, which is categorized by the deficiency in the cognition, memory and other kinds of cognitive dissention. The present exploration was designed to unveil the ameliorative properties of ononin against the aluminium chloride (AlCl3)-provoked AD in animals via the suppression of oxidative stress and neuroinflammation. AD was provoked to the Sprague Dawley rats through administering orally with 0.5 ml/100 g b.wt. of AlCl3 25 days and then supplemented with the 30 mg/kg of ononin orally for 25th day to 36th day. The behavioural changes were examined using open field and Morris Water Maze test. The acetylcholine esterase (AChE) activity was studied by standard method. The status of Aβ1-42, MDA, SOD, total antioxidant capacity (TAC) were quantified using respective assay kits. The interleukin(IL)-1β and TNF-α, BDNF, PPAR-γ, p38MAPK, and NF-κB/p65 status was quantified using respective assay kits. Brain histology was studied using microscope. The ononin treatment effectively modulated the AlCl3-triggered behavioural alterations in the AD animals. Ononin appreciably suppressed the AChE, Aβ1-42, and MDA and improved the SOD and TAC in the brain tissues of AD animals. The status of IL-1β, TNF-α, p38MAPK, and NF-κB were suppressed and the BDNF and PPAR-γ contents were elevated in the brain tissues of AD animals. The outcomes brain histology analysis proved the attenuate role of ononin. Our findings recommended that the ononin treatment could ameliorate the cognitive impairment, suppress the neuroinflammation and oxidative stress in the AD animals.

1. Introduction

Alzheimer's disease (AD) is an age associated chronic neurodegenerative disease categorized by the occurrence of intracellular amyloid accumulations and extracellular neurofibrillary tangles (Jack et al., 2018). The initial phase of AD is involved in a short term memory loss and progressive other disease signs like alterations in the mood and behavior, aggressions, confusions, avoiding of peoples and social connections, and long term memory loss (Livingston et al., 2020). AD affects the patients in a different way, as their experience in signs and progression of disease is diverse (Weller and Budson, 2018) because of the variations in the factors like age and genetics (Fan et al., 2020). The prime cause of mortality in AD patients is not typically because of these alterations in the brain tissues but because of their related difficulties like pneumonia, immobility, and malnutrition because of the trouble in food consumption (Scott et al., 2020).

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2021.06.031
1319-562X/

The oxidative stress, inflammation, and apoptosis are the mostly dysregulated cascades implicated in the AD progression. These factors are tightly connected to the numerous neurodegenerative ailments and reported to perform a ultimate deleterious roles (Gan and Johnson, 2014). Accordingly, the triggering of endogenous antioxidant regulators is a crucial approach in counteracting the AD associated difficulties (Skibinski et al., 2016). Among these factors, the hypothesis of participation of oxidative stress and inflammation in AD progression are gained much attention among the researchers. Inflammation is considered as one of the imperative reasons in the AD initiation and progression. Many studies recommended that the oxidative stress and inflammation can be managed via the utilization of natural supplements with the antioxidant and anti-inflammatory properties that could hinder or postpone the AD progression (Szczechowiak et al., 2019).

Reactive oxygen species (ROS) are the prime players during the activation of numerous downstream signaling molecules like MAPKs. Among these kinases, p38MAPKs has gained greater attention of researchers. p38MAPKs is retorting to various stress stimuli like inflammatory mediators and ROS. It was already highlighted that the p38MAPKs were convoluted in AD initiation and progression, hence, lessening of p38MAPK cascade could be a hopeful target to treat the AD (Lee and Kim, 2017). Furthermore, brain-derived neurotrophic factor (BDNF) is an imperative regulator of neurogenesis and maintaining the plasticity of synapsis (Oliveira et al., 2013). BDNF demonstrates the neuroprotective effects and reinstates the memory and cognitive deficiencies in the AD (Xu et al., 2015).

AD is categorized as the continuous loss of synaptic and neuronal functions that resulting to the weakening of cognition and memory. The accumulation of amyloid beta peptides (Aβ) in the neuronal cells and the development of intracellular neurofibrillary knots are regarded as the prime histopathological characteristics of AD (Armstrong, 2013). The pathological progression of AD is multifaceted. The neuroinflammation, oxidative stress, and amyloidogenesis was regarded as the chief pathogenic measures in AD (Cheignon et al., 2018). Furthermore, the numerous preceding investigations has pointed out that the enhanced nuclear factor-βB (NF-κB) status through the Aβ accumulation that was enormously expressed in the brain tissues of the AD patients. As well, the overexpression of Aβ elevates the acetylcholine (ACh) degradation that plays a prime function in the normal memory and cognition (Yan and Feng, 2004).

Numerous studies has disclosed that the heavy metals are tightly connected with the neurodegenerative ailments like AD (Hussien et al., 2018). Aluminium (Al) is one of the major heavy metals participated in the initiation and progression of neurodegenerative ailments, as it directly affects the numerous metabolic cascades in the nervous system. The utilization of aluminum chloride (AlCl3) is highly compounded because it found in various commercially manufactured products like toothpaste, foods, medicines, and in packaged drinking water (Cao et al., 2017). AD initiation was directly associated with the consumption of some metal toxicants like Al that was hosted to the body via and work-related exposure, food contaminants, drinking water contaminants, and foods prepared in the Al cookware (Exley and Vickers, 2014). Al could change the blood brain barrier (BBB) and eventually gathered in the brain (Mirza et al., 2017). Consequently, it is regarded as the risk factor of neurological ailments by Al brain intoxication (Inan-Eroglu and Ayaz, 2018). Additionally, Al could hinder the antioxidant enzyme activities, changing brain neurochemistry and results in the brain DNA injury (Liaquat et al., 2019). Experimentally it was proved that the long-term exposure to Al was directly affects the neurological signs that mimic the progressed neurodegeneration. Also the neurofilamental alterations in the hippocampus, spinal cord, and cerebral cortex, additionally biochemical alterations were noted in the Al-provoked AD in animals. Consequently, AlCl3-triggered AD in animals are suggested as the most extensively adapted animal model that mimics the human AD (Garcia et al., 2010).

The goal of exploring the drug therapy against AD is to avert the progression and expressively postponement of the onset of disease pathology. Ononin is a isoflavone glycoside extensively found in numerous plants like *Smilax scobinicaulis*, *Ononis angustissima*, and *Millettia nitida* (Li et al., 2014; Ko, 2014). It was already reported that the ononin was exhibited the potent anti-inflammatory (Dong et al., 2017), antiviral (Yu et al., 2019) and ameliorated the obesity-provoked metabolic injury through the inflammation inhibition (Hoo et al., 2010). Nevertheless, the therapeutic role of ononin against the AlCl3-triggered AD in not studied yet. Therefore, the current investigation was aimed to inspect the ameliorative actions of ononin against the AlCl3-provoked AD in rats through the suppression of oxidative stress and neuroinflammation.

2. Materials and methods

2.1. Chemicals

Ononin, AlCl3, NaCl, rivastigmine, and other chemicals were attained from the Sigma-Aldrich, USA. All the assay kits for biochemical investigations were acquired from the Mybiosource, USA, Biocompare, USA, and Thermofisher Scientific, USA, respectively.

2.2. Experimental animals

The Sprague Dawley rats weighing above 170–200 g were utilized in this current investigation and same was acquired from the institutional animal facility. All rats were caged in a clean confines beneath the well-organized cabin with 22–24 °C temperature and 12 h light/dark series. All animals were permitted to free access of water and food throughout the study.

2.3. Experimental design

All animals were alienated into four groups as group I-IV. Group I animals are control and administered with regular diet without any treatments. Group II animals are given with 175 mg/kg of AlCl3 orally for 25 days to provoke the AD and 0.9% of NaCl (5 ml/kg) from 25th day to 36th day. AlCl3 was suspended in distilled water and given orally at 0.5 ml/100 g b.wt. dosage. Group III animals were challenged with the AlCl3 as used in the group II for 25 days and supplemented with the 30 mg/kg of ononin orally for 25th day to 36th day. Group IV animals were challenged with the AlCl3 as same for group II for 25 days and administered with the 2.5 mg/kg of rivastigmine for 25th day to 36th day as a standard drug.

2.4. Open-field test

Open field test usually identifies the alterations in the investigative behavior and emotionality under the mild stress conditions (Cunha and Masur, 1978). The investigation was executed on the square wooden box with 80 × 80 × 40 cm dimensions with the red walls and white floor separated by the black lines with 16 identical squares at 4 × 4 cm size. Animals were located separately at box's center and the cautiously monitored for 3 min. The ambulation frequency measurements and the exploratory rearing numbers are utilized to allocate the alterations in the investigative capacity. While the inflection of emotionality was identified by

detecting the defecation (fecal pellet numbers) and frequency of grooming.

2.5. Morris water Maze (MWM) test

The learning and memory of the animals were examined by the MWM test. The black pool with 50 cm depth and 180 cm diameter was utilized for this examination. The pool was apparently separated into four quadrants as northeast as quadrant no.1, southeast as no.2, southwest as no.3, and northwest as no.4. The depth of water is 40 cm and an undetectable rounded platform with 10 cm diameter was located in 3rd quadrant. Platform was located 1 cm below the water and the skimmed milk was used to make water opaque. The three signals were fixed on the walls around the pool so that animals could use them to allot the routes to the platform. The video camera with the computerized tracking system was utilized to track the speed, duration, and path of the rats. The time spent in the target quadrant, time spent in the opposite quadrant, and the crossing numbers were carefully noted and tabulated.

2.6. Measurement of acetylcholine esterase (AChE) content

The content of AChE in the brain tissues of control and treated animals were studied by the method of Oikarinen et al. (1983). Hippocampus tissues from the treated animals were suspended in the 0.25 M of sucrose buffer and were sustained for 30 min. The samples were then centrifuged at 10000 rpm and the supernatant was utilized to examine the AChE content using spectrophotometric technique. Absorption was taken at 412 nm and outcomes were portrayed as ng/g tissue.

2.7. Quantification of Aβ1-42

The status of Aβ1-42 in the brain tissues of control and treated animals were investigated using the commercial assay kits as per the protocols suggested by manufacturer (Mybiosource, USA).

2.8. Detection of oxidative stress and antioxidant markers

The oxidative stress marker malondialdehyde (MDA) and antioxidants superoxide dismutase (SOD) activity and total antioxidant capacity (TAC) in the brain tissues of control and treated animals were quantified using respective assay kits as per the protocols suggested by manufacturer (Biocompare, USA).

2.9. Quantification of inflammatory markers

The interleukin(IL)-1β and tumor necrosis factor-α (TNF-α) in the brain tissues of control and treated animals were quantified using respective assay kits as per the manufacturer protocols (Mybiosource, USA).

2.10. Measurement of BDNF, PPAR-γ, p38MAPK, and NF-κB/p65 levels

The status of BDNF, PPAR-γ, p38MAPK) and NF-κB/p65 in the brain tissues of control and treated animals were quantified using respective assay kits as the manufacturer's protocols (Thermofisher Scientific, USA).

2.11. Histopathological study

The hippocampus portions from the control and treated animals were excised and spliced into small portions and then fixed in the Bouin's fixative solution for 24 h. Then the sections were paraffinized and sectioned at 4–6 μm thick. The sections were stained with hematoxylin and eosin and lastly photographed beneath the light microscope attached with the camera.

2.12. Statistical analysis

The biochemical outcomes were displayed mean ± SD of triplicates. Statistical variations between groups were studied via applying one-way ANOVA sequentially Tukey's post hoc assay. A p-value < 0.05 was regarded as significant.

3. Results

3.1. Effect of ononin on the AlCl3-activated behavioral changes in the AD rats by open field test

The behavioral alterations in the control and treated animals were detected using open field test and outcomes were depicted in the Fig. 1. AlCl3-provoked AD animals demonstrated the diminished ambulation frequency, rearing frequency and improved grooming frequency and defecation (increased fecal pellets) as compared with control. Besides, the supplementation of 30 mg/kg of ononin to the AlCl3-provoked AD rats exhibited the noticeable elevation in the ambulation and rearing frequencies, and suppressed the grooming frequency and defecation status (Fig. 1). The standard drug rivastigmine also appreciably reverted back the AlCl3-triggered behavioral alterations.

3.2. Effect of ononin on the AlCl3-activated behavioral changes in the AD rats by MWM test

The outcomes from the MWM test revealed that the memory and learning was notably disrupted in the AlCl3 provoked AD animals (Fig. 2). The learning ability of the AD animals were drastically affected as evidenced by the increased escape latency. The AlCl3 challenge effectively improved the escape latency and suppressed the memory of rats as evidenced by the reduction in the time spent in the target quadrant. These impairments were remarkably modulated by the ononin treatment. The administration of 30 mg/kg of ononin to the AlCl3 provoked AD animals demonstrated the suppressed escape latency and remarkably enhanced the time spent in the target quadrant (Fig. 2). The standard drug rivastigmine also notably modulated the AlCl3-triggered behavioral changes in the AD animals.

3.3. Effect of ononin on the AChE and Aβ1-42 contents in the brain tissues of AlCl3-activated AD animals

The brain contents of AChE and Aβ1-42 was drastically elevated in the AlCl3-triggered AD animals as compared with control. Fig. 3 demonstrated that the 30 mg/kg of ononin administered AD animals displayed the remarkable diminution in the AChE and Aβ1-42 contents in the brain tissues. The treatment with the standard drug rivastigmine was also appreciably suppressed the AChE and Aβ1-42 contents in the brain tissues of AD animals. The ononin and rivastigmine treatments demonstrated the analogous outcomes.

3.4. Effect of ononin on the AlCl3-activated oxidative stress and antioxidant markers in the AD animals

The status of oxidative stress marker MDA and antioxidants SOD and TAC in the brain tissues of control and treated animals were examined and the outcomes were depicted in the Fig. 4. The AlCl3-provoked AD rats exhibited the severe enhancement in

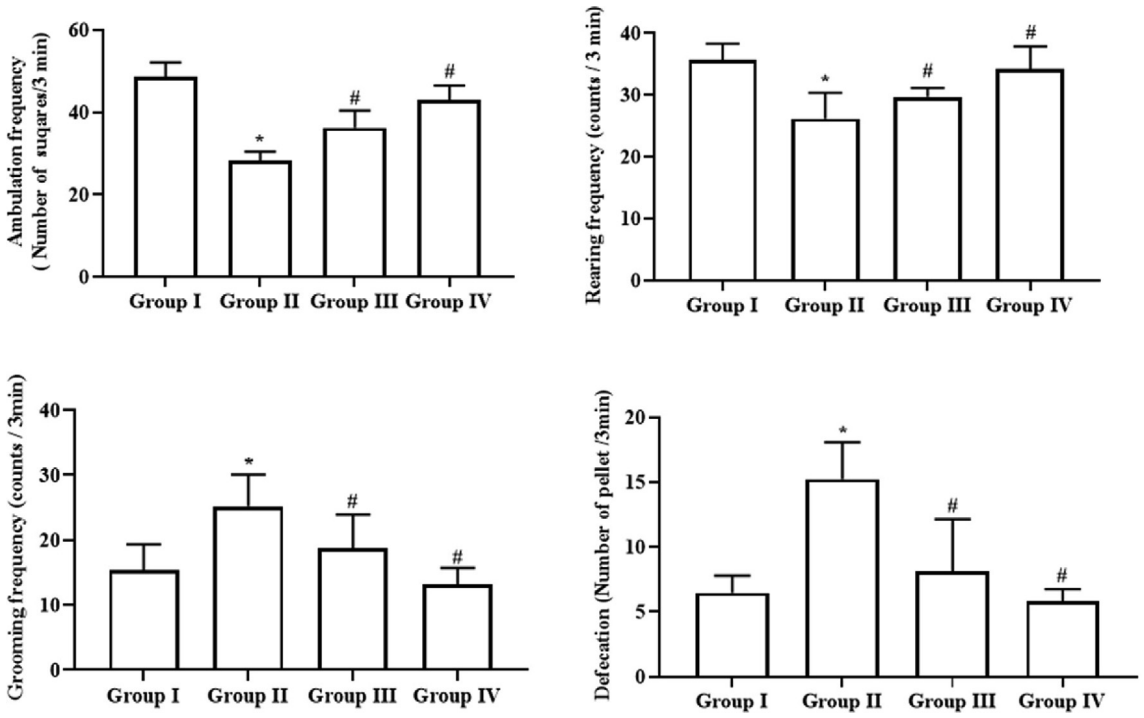

Fig. 1. Effect of ononin on the AlCl3-activated behavioral changes in the AD rats by open field test. Results were given as mean ± SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's post hoc assay. '*' $p < 0.05$ compared with control and '#' $p < 0.01$ compared with AlCl3-intoxicated group.

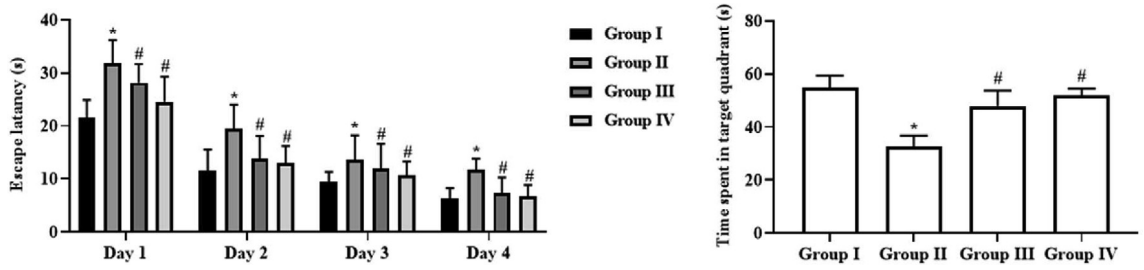

Fig. 2. Effect of ononin on the AlCl3-activated behavioral changes in the AD rats by MWM test, Results were given as mean ± SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's post hoc assay. '*' $p < 0.05$ compared with control and '#' $p < 0.01$ compared with AlCl3-intoxicated group.

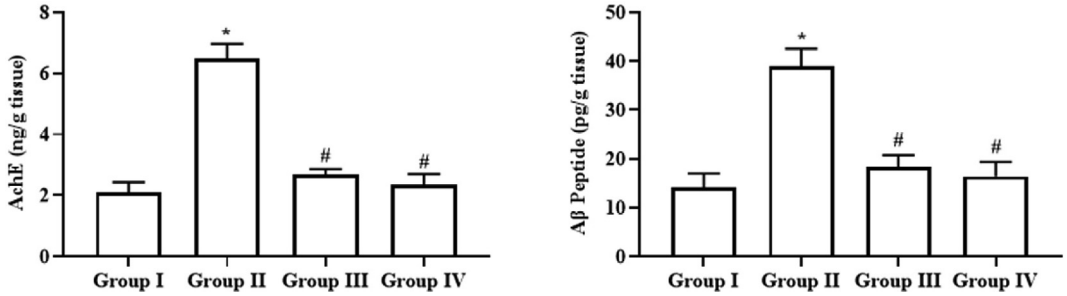

Fig. 3. Effect of ononin on the AChE and Aβ1-42 contents in the brain tissues of AlCl3-activated AD rats. Results were given as mean ± SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's post hoc assay. '*' $p < 0.05$ compared with control and '#' $p < 0.01$ compared with AlCl3-intoxicated group.

the MDA level and suppression in the SOD and TAC status compared with control. In contrast, the administration of 30 mg/kg of ononin to the AD animals demonstrated the appreciable suppression in the MDA status and improved the SOD and TAC status in the brain tissues (Fig. 4). Rivastigmine treatment also diminished the MDA level and enhanced the SOD and TAC contents as seen in the ononin treated AD animals.

3.5. Effect of ononin on the inflammatory markers in the brain tissues of AlCl3-activated AD animals

Fig. 5 demonstrated status of pro-inflammatory markers IL-1β and TNF-α in the brain tissues of control and treated animals. The IL-1β and TNF-α status was found enhanced in the brain tissues of AlCl3-challenged AD animals when compared with the

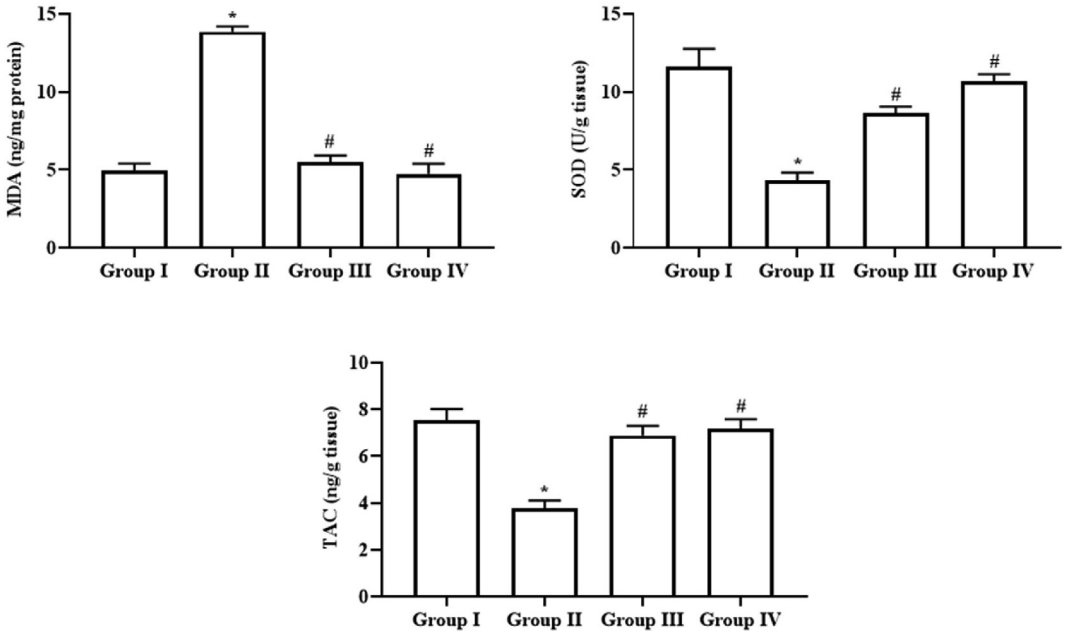

Fig. 4. Effect of ononin on the AlCl3-activated oxidative stress and antioxidant markers level in the AD rats, Results were given as mean ± SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's post hoc assay. '*' $p < 0.05$ compared with control and '#' $p < 0.01$ compared with AlCl3-intoxicated group.

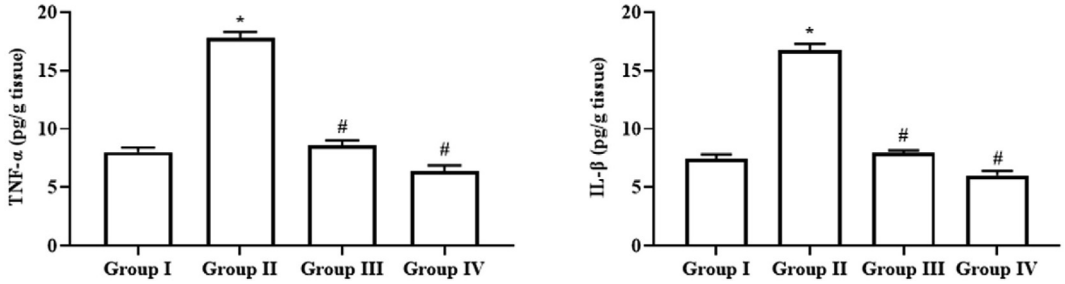

Fig. 5. Effect of ononin on the inflammatory markers in the brain tissues of AlCl3-activated AD rats. Results were given as mean ± SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's post hoc assay. '*' $p < 0.05$ compared with control and '#' $p < 0.01$ compared with AlCl3-intoxicated group.

control. Substantially, the 30 mg/kg of ononin supplemented AD animals exhibited the considerable suppression in the IL-1β and TNF-α contents in the brain tissues. Ononin effectively reverted back the IL-1β and TNF-α status and set to the near normal level, which is similar to the outcomes of rivastigmine treatment.

3.6. Effect of ononin on the BDNF, PPAR-γ, p38MAPK, and NF-κB/p65 levels in the brain tissues of AlCl3-activated AD rats

The levels of BDNF, PPAR-γ, p38MAPK, and NF-κB/p65 in the brain tissues of control and treated animals were detected and the outcomes were portrayed in the Fig. 6. AlCl3-challenged AD rats demonstrated the drastic elevation in the p38MAPK, and NF-κB/p65 and suppressed the BDNF and PPAR-γ status in the brain tissues. The ononin treatment effectively modulated the levels of these markers. Ononin administration suppressed the p38MAPK, and NF-κB/p65 levels and enhanced the BDNF and PPAR-γ contents in the brain tissues of AlCl3-provoked AD animals (Fig. 6). The same kind of outcomes were observed in the rivastigmine administered AD animals.

3.7. Effect of ononin on the brain histopathology of the AlCl3-activated AD rats

The hippocampus portions of the control animals demonstrated the typical structures like dentate gyrus and cornus ammonis (Fig. 7). Conversely, the AlCl3-triggered AD animals displayed the various degenerating cells within the dentate gyrus and cornus ammonis portions with occurrence of microglia cells and the areas of reduced cell density. The hippocampus of the rivestigmine administered animals demonstrated the almost normal hippocampus structures (Fig. 7). The 30 mg/kg of ononin administered animals also demonstrated the protective actions as evidenced by the reduced histological alterations and typical cellular structures, which is similar to the outcomes of rivastigmine treatment.

4. Discussion

Approximately 50 million peoples has the AD, which is categorized by the deficiency in the cognition, memory and other kinds of cognitive dissention and consequently leads to the death within 3–9 years after the diagnosis. AD is the age-associated dementia and illustrates a severe global health risk with a great impact on the peoples status and social burden (Querfurth and LaFerla, 2010). The sporadic memory deficiency is the predominant symptom of the initial phase of AD, moreover continues cognitive deficiency and changes in the behavioral and functional activities that was a major influence of individuals capacity to perform a daily tasks (Inouye et al., 2010). Although numerous executive activities like language, attention, judgment, and orientation are affected and that was a most predominant indicators of the AD and responsible for continuing memory loss (Anand et al., 2014).

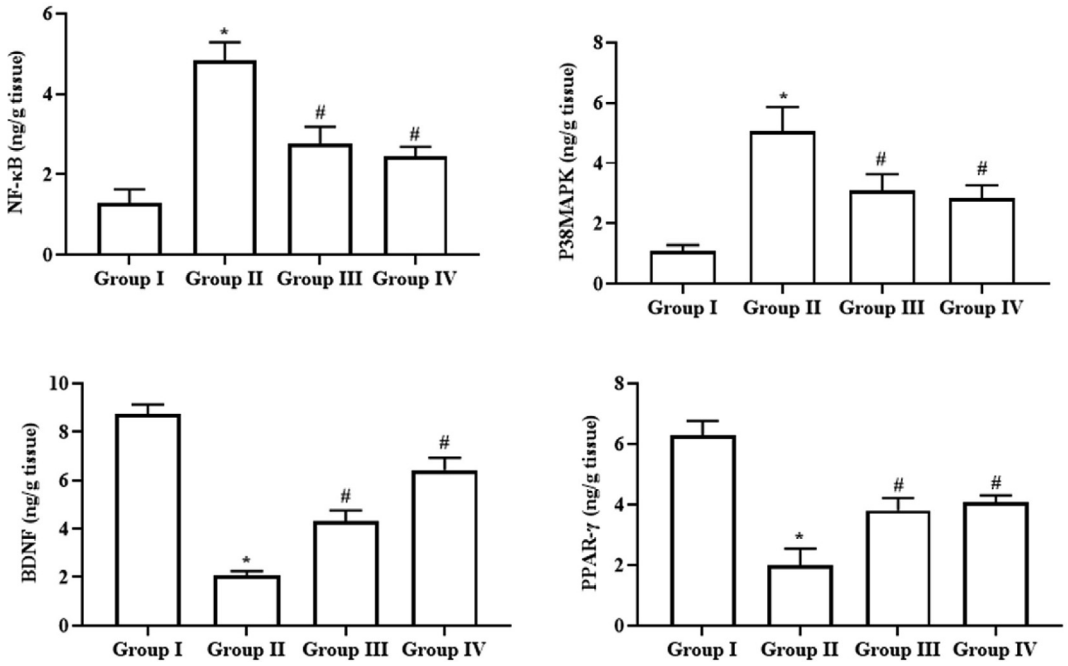

Fig. 6. Effect of ononin on the BDNF, PPAR-γ, p38MAPK, and NF-κB/p65 levels in the brain tissues of AlCl3-activated AD rats. Results were given as mean ± SD of three discrete experiments. Data are investigated using one-way ANOVA sequentially Tukey's post hoc assay. '*' $p < 0.05$ compared with control and '#' $p < 0.01$ compared with AlCl3-intoxicated group.

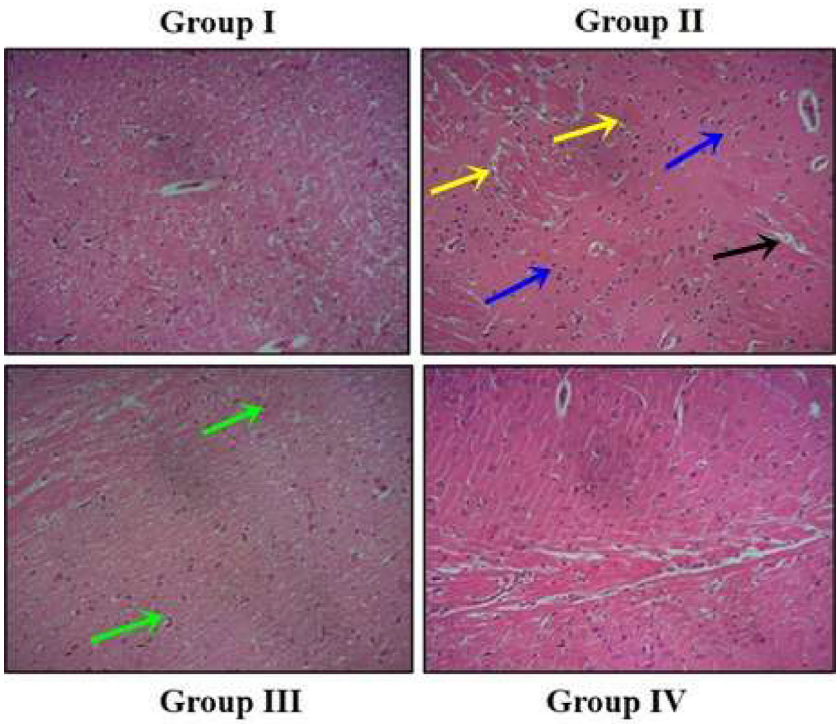

Fig. 7. Effect of ononin on the brain histopathology of the AlCl3-activated AD rats. Control animals exhibited the typical histological structures of hippocampus (Group I). The AlCl3-triggered AD animals demonstrated the diverse degenerating cells (blue arrows), inflammatory regions (yellow arrows), and reduced cell (black arrow) density (Group II). The hippocampus of the 30 mg/kg of ononin and 2.5 mg/kg of standard drug rivastigmine administered animals demonstrated the near normal hippocampus structures (green arrows) with reduced histological alterations (Group III & IV).

Furthermore, the exact root cause of AD is not understood yet. Numerous investigations disclosed that some risk factors like depression, aging, head injury, oxidative stress, neuroinflammation, and chronic exposure to the environmental metal toxicants are linked with the initiation and expansion of AD (Kinney et al., 2018; Jiang et al., 2016). Additionally, growing evidences unveiled that the metal toxicity like Al, cadmium, and lead are connected to the neurological ailments and Al is the most potent neurotoxicant (Huat et al., 2019). The brain is a potent target for Al toxicity and it could easily cross the BBB through its high affinity to the receptors

and eventually accumulates into the brain (Chiroma et al., 2019; Liaguat et al., 2019).

There are numerous potent elucidations for the cognitive deficiencies connected with the AD. The oxidative stress is one among them and strongly related with the AD. Al is well recognized to cross the BBB and gather in various regions of the brain and it could also trigger the free radicals production that could cause the brain injury particularly regions responsible for the memory and learning (Kumar et al., 2009; Saba et al., 2017). Oxidative stress facilitated neurotoxicity is a prime pathological event in the primary neurodegenerative process of AD (Kim et al., 2015; Qu et al., 2016).

Antioxidants is one of the hopeful factors to prevent the commencement and development of AD. Al intoxication triggers the drastic oxidative stress through elevating the pro-oxidant actions of iron in the brain and decreasing the antioxidant enzyme actions (Pratico et al., 2002). Living cells generates endogenous antioxidants that buffer the accumulated free radicals and offers fortification against oxidative damage. The most predominant endogenous antioxidants GSH and CAT. The condition of free radicals accumulated surpass the capacity of the cells to counteract them via antioxidants is called as the oxidative stress (Aguilar et al., 2016). The status of MDA are imperative biomarkers of the oxidative stress. MDA is accumulated via lipid peroxidation due to the ROS that causes injury and membrane degradation (Busch and Binder, 2017). Al hastens the LPO and triggers augmented free radical accumulation, thus causing oxidative stress that ultimately leads to the neurotoxicity (Kawahara and Kato-Negishi, 2011). The brain is highly susceptible to the oxidative stress resulted from augmented status of free radicals and suppressed the antioxidant status subsequently toxicity (Kumar and Gill, 2014).

Frequent AlCl3 exposure imperatively improved the MDA status and suppressed the antioxidants SOD, CAT, and TAC status in the various brain portions that was supported our findings from this investigation (Li et al., 2019). Ononin administered AD animals displayed the remarkable suppression in the MDA status and enhanced the SOD and TAC status in the brain tissues (Fig. 4). ACh is a cholinergic neurotransmitter with the imperative role in the neuronal signal transmission between neurons and it was tightly related to the upholding of learning memory in the brain. AChE is the enzyme that participated in the hydrolyzing of ACh to choline and acetate. The commencement of AD starts with the ACh absence and thus reducing the AChE activity that improves the ACh status has the positive influence on the cognitive function (Pohanka, 2011).

Cholinergic transmission primarily affects the cognition, learning, and memory. It is tightly connected to the short-term memory. The transmission impairment levels associates with the sternness of dementia (Amberla et al., 1993). Al is a strong cholinotoxin that could change the BBB to provoke alterations in the cholinergic transmission. This neurotoxic ability of Al remarkably enhances the AChE activity (Zatta et al., 2002). Al is a potent neurotoxin and its enhancement in the brain tissues is related with the cognitive deficiency and dementia. Furthermore, Al interrupts the cholinergic neurotransmission, where it improves the AChE activity and thereby elevate the breakdown of ACh in the brain. As the same, it was exhibited in our current investigation, where AlCl3-triggered animals notably improved the AChE content in the brain tissues. Captivatingly, the supplementation of 30 mg/kg of ononin to the AlCl3-provoked AD animals displayed the remarkable suppression in the AChE content (Fig. 3). This findings were coincides with the previous report mentioned by Lin et al. (2015).

Neuroinflammation is the vital player of the initiation and progression of neuronal ailments. It could leads to the memory and learning difficulties (Cheng et al., 2019). The neuroinflammation has the crucial role in the pathological progression of the neuronal ailments like AD. IL-1β and TNF-α are the predominant inflammatory mediators that participates in the dysfunction and regulate the inflammation in the cells and organs (Trovato Salinaro et al., 2018). NF-κB are the crucial players of the synaptic plasticity and neurogenesis in the brains the mirrored on the memory and learning. Besides, the connection between neurotoxicity and NF-κB was well reported, where the diminution of NF-κB suppressed the neurotoxicity (Shih et al., 2015). We found that the status of IL-1β, TNF-α, and NF-κB in the brain tissues of AlCl3-challenged AD animals were elevated (Fig. 6) drastically and the same was considerably suppressed by the ononin treatment.

5. Conclusion

The findings from this study suggested that the ononin administration could alleviate the cognitive impairment, suppress oxidative stress and neuroinflammation, and reinstate the brain histological architecture. Based on that, the ononin can be a talented supplement for the fortification against AD. However, the precise therapeutic role of ononin against the AD was not disclosed yet and hence additional studies were still needed in the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

The Author would like to extend their sincere appreciation to the Deanship of Scientific Research at King Saud University for its funding of this research through the Research Group Project No. RGP-300.

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