# Protective Effect of *Boswellia carteri* on Aluminium Chloride-Induced Alzheimer's Disease in Male Albino Rat

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## ABSTRACT

Alzheimer's disease (AD) is one of the most common dementia causes. *Boswellia carteri* is used for its memory enhancing effects. The present experimental study investigates the effects of *B. carteri*on aluminium chloride ($AlCl_3$)-induced AD in adult male albino rats. Forty adult male Albino rats were randomly divided into five groups (8 rats each). Rats of the first group were served as controls; rats of the second group *B. carteri* group were supplemented orally with *B. carteri* aquatic extract (500 mg /kg b.w./day) for 8 weeks; rats of the third group $AlCl_3$ group (AD model) were treated orally with $AlCl_3$ (100 mg/ kg b.w./day) for 8 weeks; rats of the forth group (*B. carteri* + $AlCl_3$) received 500 mg/ kg b.w./day and $AlCl_3$ (100 mg/ kg b.w./day) orally for 8 weeks; rats of the fifth group (rivastigmine + $AlCl_3$) received orally rivastigmine (0.3 mg/kg.w./day) and $AlCl_3$ (100 mg/kg b.w./day) for 8 weeks. After eight weeks, the behavioral test (maze learning test) was done for rats to assess learning and memory, acetylcholinesterase (AchE), some neurotransmitter levels [dopamine (DA), norepinephrine (NE), gamma amino butyric acid (GABA)] and oxidative stress markers as [reduced glutathione (GSH), oxidase glutathione (GSSG), superoxide dismutase (SOD) and lipid peroxidation (LPO)] were measured in cortex and hippocampus homogenate, and histopathological studies were made for the hippocampus area. Aluminum exposure significantly decreased the learning and memory in the maze learning test. Significant increase of cortex and hippocampus homogenate levels of AchE and LPO but significant decrease in NE, DA and GABA, GSH, GSSG and SOD were observed in rats subjected to $AlCl_3$. Histopathological examination of hippocampus sections showed severe changes including increase of degenerated cells and structural damage in $AlCl_3$ treated rats. Treatment of rats with *B. carteri* or rivastigmine leads to improvement of rat's memory and learning, neurotransmitters and oxidative stress markers and pronounced attenuation on the hippocampus and cortex damage caused by $AlCl_3$. This study suggests that chronic oral intake of *B. carteri* have neuroprotective effect and improve the learning and memory in AD rat's models and these effects may be due to its antioxidant properties.

**Key Words:** Alzheimer's Disease, Aluminium Chloride, Boswellia Carteri, Maze Learning Test, Acetylcholinesterase, Neurotransmitters, Oxidative Stress Markers, Rats.

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## INTRODUCTION

The world's population is rapidly aging which is considered as a multi-factorial process and causes several changes from cellular to organism levels. Nowadays, the primary focus has been on the use of higher cognitive ability such as working memory, long-term memory, mental images or reinforcing learning, judgment and reasoning in cognitive neuroscience [1]. Alzheimer's disease (AD) is neurodegenerative disease that results in complete need for care after diagnosis. It is a main reason of dementia in people aged above 60 years [2]. Alzheimer's disease (AD) is the most common form of chronic diseases among the elderly [3]. It can be difficult to differentiate between the different types of dementia using laboratory tests only, as not all of the causes of dementia can be identified [4]. AD has become a major medical, social and financial burden. AD results from multifactorial processes including environmental exposure, genetic risk factors, cerebrovascular risk

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factors, oxidative stress, infectious agents, age and sex [5]. Many of neurotransmitters are disturbed in AD as the cholinergic, adrenergic, glutamatergic, serotonergic, GABAergic and dopaminergic neurotransmitters [6].

The human organisms are constantly and inevitably exposed to aluminium (Al). Al increases as a result of continued acidification of industrialized society environment and it causes harmful effects on various organs. Al is the highly neurotoxic element and its exposure is proposed to be included in AD development where it produce clinical and pathological features similar to AD. There is no curative treatment for AD and current pharmacological treatments only gives temporarily symptomatic relief in some patients [7].

Many studies have shown that herbal medicine has the ability to provide effective treatment of neurodegenerative diseases as AD where natural compounds have antioxidant properties and very low side effects. For about 3000 years, *Boswellia* tree (frankincense) resin was an important trade material in North Africa and Arabian Peninsula. In Arabic language, frankincense is also known as "al-luban", which means "white" or "cream" and is a basis of the other name, olibanum [8]. Frankincense contains 6-30% gums (polysaccharides), 60-85% resins (terpenes), and 5-9% essential oil [9]. It had been reported that frankincense from many species of *Boswellia* genus improves memory in both normal brain [10, 11] and affected memory cases [12, 13].

Relatively few studies have examined the effect of *B. carteri* on AD. This study aimed to examine the protective actions of chronic oral intake of *B. carteri* on AD rat's model.

## MATERIALS AND METHODS

### Animals

Forty adult male Albino Wistar rats weighting 170-210 g were used in the study. The rats were obtained from the Experimental Animal Unit of Faculty of Pharmacy, King Abdulaziz University, Jeddah, Saudi Arabia. The animals were housed 8 rats per cage and maintained under controlled laboratory status of 12 h light: dark cycle, 65% humidity and temperature of 20±1 °C. Rats were acclimatized to laboratory status for one week before beginning of experiments. Rats fed *ad libitum* on commercial chow and freely access tap water. All experimental steps were approved and made according to the ethical roles of Animal Care and Use Committee of King Abdulaziz University (1161439).

### Chemicals

$AlCl_3$ (Techno Pharmchem, Haryana, India) was supplied as white powder. Rivastigmine, Exelon, 1.5 mg was purchased from Novartis Company (Basel, Switzerland). Sodium chloride (NaCl) and sodium hydroxide (NaOH) were obtained from Panreac (Barcelona, Spain). Potassium dihydrogen phosphate ($KH_2PO_4$), potassium chloride (KCl), disodium phosphate ($Na_2HPO_4$), and formaldehyde were obtained from Riedel-dehaen (Sleeze, Germany).

### Olibanum (B. carteri)

*B. carteri* was obtained from a local market in Jeddah, Saudi Arabia. *B. carteri* was imported from Somalia. It was purchased in closed packages.

### Preparation of Olibanum Extraction

A volume of 50 ml of boiling-hot distilled water was poured on 5 g of the resin in a beaker. The mixture was allowed to stand for 30 min before it was filtered with a filter paper. The infusion was always freshly prepared so as to prevent growth of fungi [14].

### Experimental Design

The experimental rats were sorted into five experimental groups, 8 rats each. Groups were: **Group 1 (control group):** Rats were orally supplemented with 0.9 ml of saline solution (0.9% NaCl, vehicle) daily for eight weeks. **Group 2 (*B. carteri* group)**: rats were orally supplemented with *B. carteri* aquatic extract at a dose 0.9 ml that contains 500 mg/ kg b.w./day for eight weeks [15]. **Group 3 ($AlCl_3$ group):** rats were given 0.9 ml that contains 100 mg/ kg b.w./day of $AlCl_3$ orally daily for eight weeks [16]. **Group 4 (*B. carteri* + $AlCl_3$ group)**: rats were orally supplemented with *B. carteri* aquatic extract at the same dose taken to group 2 and $AlCl_3$ after 1 hour at the same dose given to group 3 daily for eight weeks. **Group 5 (Rivastigmine+ $AlCl_3$ group)**: rats were orally supplemented with rivastigmine at the dose 0.9 ml that contains 0.3 mg/ kg b.w./ day [17] and $AlCl_3$ after 1 hour at the same dose given to group 3 daily for eight weeks.

### Behavior Study (Maze learning test)

Maze learning test is a reliable method of studying trial and error learning. The base measure of the maze was 100 x 60 cm (L x W), and the walls were 20 cm high. The entire maze was made of wood with a glass cover over the maze to prevent escape of rats and to allow easy observation**.** Rats were deprived of food 23 hours before the initiation of the experiments. Rats were given their daily amount of food as a reward at the end of the maze. The hungry rats were given one trial per day for five consecutive days. The following measurements were recorded: the elapsed time to reach the food (minutes) and the number of errors (passage in blind alleys) as previously described [18].

### Tissue preparation

After the behavioral test, the rats were euthanized by decapitation according to the rules of King Abdulaziz University. After dissection, their brains were removed and washed with saline and divided into two halves. One fixed in 10% formalin for histopathological studies. The hippocampus and cortex of the other half was dissected out. Then, hippocampus and cortex tissues were immediately frozen in -80 °C for preparation of tissues homogenate. For biochemical studies the frozen hippocampus and cortex were homogenized separately, and centrifuged for 15 min at 3000 revolutions per minute (rpm) at 4 °C. After that, supernatant was separated, and aliquot was stored in Eppendorf tube at -80 °C for the biochemical assay.

### Biochemical assay

ELISA kits for the measurement of hippocampus and cortex tissues homogenate for Acetylcholinesterase (AchE) (Cat. # MBS038896), Norepinephrine (NE) (Catalog # MBS269993), Dopamine (DA) (Catalog Number # MBS7214676) and Gamma-aminobutyric acid (GABA) (Catalog Number # MBS740443), Superoxide Dismutase (SOD) (Catalog # MBS266897), Lipid Peroxide (LPO) (Catalog # MBS2515688) while, Fluorometric Assay kits were used to measure reduced glutathione (GSH) and oxidase glutathione (GSSG) (Catalog Number # MBS841503). All the kits were purchased from My BioSource (San Diego, USA).

### Histopathological studies

After fixation of brain tissues in formalin saline (10%) for 24 hours, brain tissues were subjected to serial dilution of alcohol for dehydration. Brain tissues were immersed in paraffin, cut into 3 µm thick sections and stained in haematoxylin and eosine (H and E) to be examined by light microscope**.**

### Statistical analysis

The statistical analysis was made by Statistical Package for Social Science (SPSS program, version 25) (SPSS Inc., Chicago, IL, USA). Values were expressed as mean +/- standard error. The difference between different experimental groups was made using One Way ANOVA (Tukey test). *P*-value <0.05 was recognized as significant value.

## RESULTS

### Behavior study (Maze learning test)

At the 1st day, duration of elapsed time in the maze was significantly increased in $AlCl_3$ group versus control (P <0.05). Compared with $AlCl_3$ group, duration of elapsed time in the maze was significantly decreased in rivastigmine + $AlCl_3$ group (P <0.05), while in *B. carteri* + $AlCl_3$ group was significantly increased. At the 2nd, 3rd, 4th and 5th days, duration of elapsed time in the maze was significantly prolonged in $AlCl_3$ group compared with control, *B. carteri* + $AlCl_3$, and rivastigmine + $AlCl_3$ groups (P <0.05) (Figure 1).

At the 1st, 2nd, 3rd, 4th, and 5th days, number of error in the maze was significantly decreased in control, *B. carteri* + $AlCl_3$ and rivastigmine + $AlCl_3$ groups versus $AlCl_3$ group (P <0.05) (Figure 2).

### Acetylcholinesterase and Some Neurotransmitter levels in cortex and hippocampus homogenate

Levels of AchE in the cortex and hippocampus homogenate was significantly increased in $AlCl_3$ group versus control group (*P*<0.05). Cortex and hippocampus AchE levels were significantly decreased in *B. carteri* + $AlCl_3$ and rivastigmine +$AlCl_3$ groups versus $AlCl_3$ treated group (*P*<0.05). Compared with control, the levels of DA, NE and GABA in the cortex and hippocampus homogenate was markedly decreased in $AlCl_3$ treated group (*P*<0.05). Cortex and hippocampus DA, NE and GABA levels in rats treated with $AlCl_3$ were significantly decreased compared with *B. carteri* + $AlCl_3$ and rivastigmine + $AlCl_3$ groups (*P*<0.05) (Table 1).

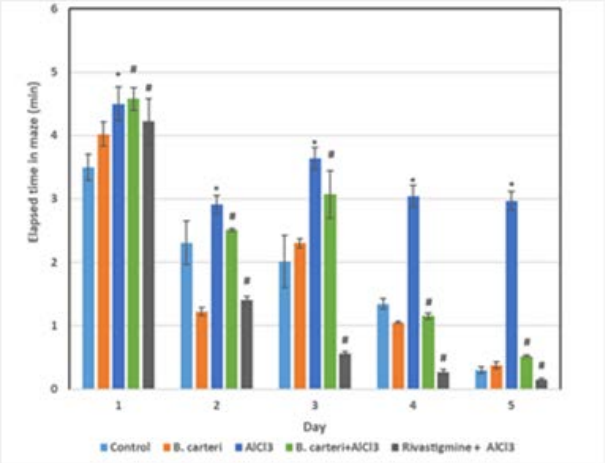


**Fig. 1. Protective effects of *Boswellia carteri* and rivastigmine on the time taken to find the food in the learning maze by Alzheimer's disease-induced in rats.**

Values were expressed as mean±SE

*P<0.05 compared with control #P<0. 05 compared with AlCl3

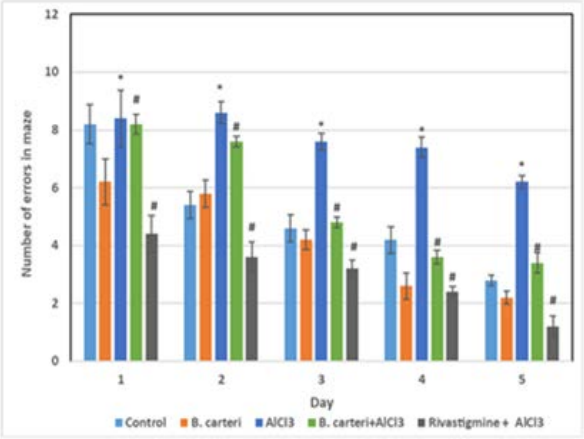


**Fig. 2. Protective effects of *Boswellia carteri* and rivastigmine on the number of errors in the learning maze by Alzheimer's disease-induced in rats.**

Values were expressed as mean±SE.

*P<0.05 compared with control #P<0. 05 compared with AlCl3

**Table 1. Protective effects of *Boswellia carteri* and rivastigmine on cortex and hippocampus homogenate levels of acetylcholinesterase and some neurotransmitters content in Alzheimer's disease-induced rats**

| Groups / Parameters | | Control | *B. Carteri* | $AlCl_3$ | *B. Carteri*+ $AlCl_3$ | Rivastigmine + $AlCl_3$ |
|---|---|---|---|---|---|---|
| AchE (U/mg) | Cortex | 0.65±0.0821 | 0.675±0.0567 | 1.3567±0.0761[a] | 0.6317±0.0956[b] | 0.7283±0.0624[b] |
| | Hip | 1.79±0.1099 | 1.675±0.0567 | 2.6883±0.1272[a] | 1.915±0.0591[b] | 2.025±0.0615[b] |
| DA (pg/mg) | Cortex | 3.625±0.2869 | 3.5783±0.1827 | 0.4817±0.1311[a] | 2.845±0.181[b] | 3.455±0.2067[b] |
| | Hip | 4.2±0.4227 | 4.7833±0.3724 | 0.8083±0.1087[a] | 3.1467±0.1925[b] | 4.0667±0.249[b] |
| NE (pg/mg) | Cortex | 4.5867±0.3553 | 4.5833±0.338 | 1.0267±0.3371[a] | 3.425±0.1954[b] | 5.8333±0.3566[b] |
| | Hip | 5±0.4017 | 4.6167±0.3364 | 1.7483±0.2893[a] | 4.4017±0.2259[b] | 6.7033±0.2939[b] |
| GABA (µmol/mg) | Cortex | 0.2767±0.0113 | 0.2918±0.0279 | 0.0738±0.0144[a] | 0.3052±0.021[b] | 0.465±0.0184[b] |
| | Hip | 0.4383±0.0402 | 0.4433±0.035 | 0.0985±0.0142[a] | 0.38±0.0257[b] | 0.7067±0.0226[b] |

Values were expressed as means ±S.E of eight animals. P<0.05 (significant)
a = Significant difference comparing to the normal control group.
b = Significant difference comparing to $AlCl_3$ group.

### Oxidative stress markers levels in cortex and hippocampus homogenate

The levels of GSH, GSSG and SOD were significantly decreased, while LPO was significantly increased in the cortex and hippocampus homogenate of $AlCl_3$ group versus control ($P$<0.05). $AlCl_3$ treated rats with *B. carteri*, and rivastigmine led to significant increase in cortex and hippocampus GSH, GSSG, SOD levels and significant decrease in LPO in *B. carteri* + $AlCl_3$ and rivastigmine +$AlCl_3$ groups compared with $AlCl_3$ group ($P$<0.05) (Table 2).

### Histopathological results

The hippocampus sections in Cornu Ammonis (CA1) were formed of three layers: polymorphic (POL), pyramidal (PYR), and molecular (MOL). Also, the dentate gyrus (DG) was formed of three layers: molecular (MOL), granular (GRA), and polymorphic (POL). The hippocampus sections in CA1 of control, *B. carteri* extract-treated rats showed normal pyramidal cells with rounded vesicular nuclei. Furthermore, the hippocampus sections in DG of control, *B. carteri* extract treated rats revealed normal granular cells with vesicular nuclei and increase in the thickness of the granular layer in *B. carteri* extract treated group. After eight weeks of $AlCl_3$ treatment, the treated rats revealed an abnormal morphology in CA1 and DG of hippocampus characterized by degenerated shrunken cells with darkly stained nuclei. In rats treated with *B. carteri* + $AlCl_3$, rivastigmine + $AlCl_3$, hippocampus sections in CA1 and DG showed reduced degenerated cells. In addition, the hippocampus cells in CA1 and DG showed minimal changes compared with cells structure of $AlCl_3$ only treated rats (Figure 3).



**Table 2. Protective effects of *Boswelliacarteri* and rivastigmine on cortex and hippocampus homogenate levels of oxidative parameters in Alzheimer's disease-induced rats**

| Groups / Parameters | | Control | *B. Carteri* | $AlCl_3$ | *B. Carteri*+ $AlCl_3$ | Rivastigmine + $AlCl_3$ |
|---|---|---|---|---|---|---|
| GSH (µmol/mg) | Cortex | 4.255±0.3425 | 4.59±0.1627 | 0.8783±0.1126[a] | 2.9067±0.2153[b] | 4.2833±0.3722[b] |
| | Hip | 4.42±0.4694 | 4.1167±0.3331 | 0.7167±0.1126[a] | 3.0033±0.2966[b] | 5.725±0.2722[b] |
| GSSG (µmol/mg) | Cortex | 4.635±0.3059 | 4.905±0.3641 | 1.0417±0.1551[a] | 3.0083±0.1287[a,b] | 4.9717±0.404[b] |
| | Hip | 4.99±0.2762 | 4.555±0.3133 | 1.2867±0.1991[a] | 3.0833±0.0995[a,b] | 5.455±0.2796[b] |
| SOD (µmol/mg) | Cortex | 85.8333±7.0067 | 91.8333±6.3293 | 20.45±2.7835[a] | 55.0833±3.7426[a,b] | 91±5.2409[b] |
| | Hip | 86±6.4057 | 92.4167±7.9185 | 16.2333±2.3638[a] | 49.9±1.6488[a,b] | 79±6.2794[b] |
| LPO (µmol/mg) | Cortex | 0.735±0.0703 | 0.9383±0.0961 | 9.2±0.0394[a] | 2.7467±0.0365[b] | 0.2483±0.0904[b] |
| | Hip | 1.0917±0.0703 | 3.3167±0.0961 | 36±0.0394[a] | 9.645±0.0365[a,b] | 0.7383±0.0904[b] |

Values were expressed as means ±S.E of eight animals. P<0.05 (significant)
a = Significant difference comparing to the normal control group.
b = Significant difference comparing to $AlCl_3$ group

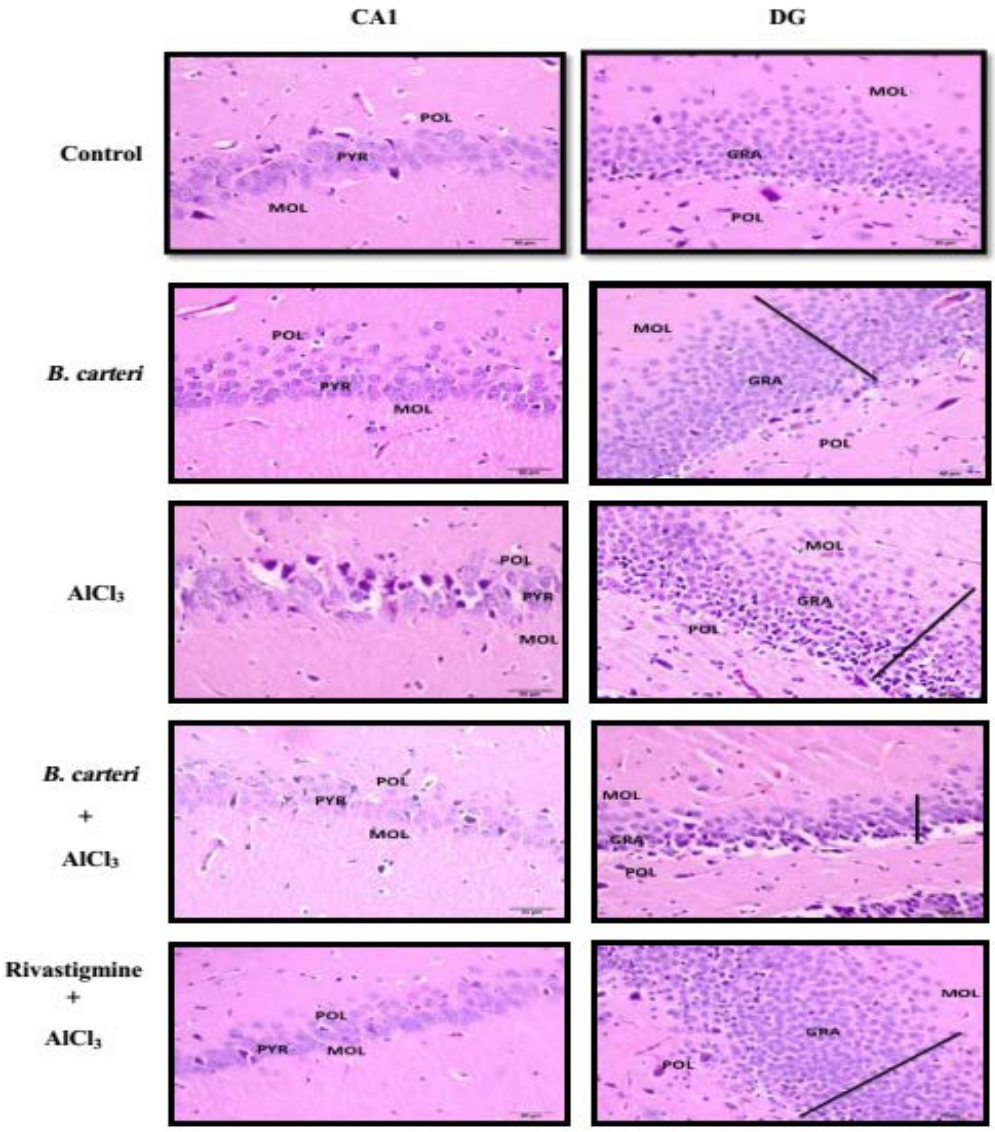


**Fig. 3. H&E staining (magnification 400×). The pyramidal cells in CA1 have large vesicular nuclei in control, *B. carteri*-treated groups and rivastigmine treated group but in Al group have irregular forms. The granular cells in DG have vesicular nuclei in control, *B. carteri*-treated groups and rivastigmine treated group but in Al group have irregular forms. Also, an increase was observed in the thickness of the granular layer in *B. carteri*-treated groups and rivastigmine treated group. Treatment by *B. carteri* improved morphological changes induced by $AlCl_3$**

## DISCUSSION

The results of this study revealed that intake of $AlCl_3$ (100 mg/ kg b.w. orally daily) for eight weeks to rats (AD model) leads to impairment of the learning and memory abilities compared with normal rats that manifested by increase in elapse time and increase in the number of error in the maze learning test to get the food. These results indicated that $AlCl_3$ exposure resulted in impairment of locomotor activity and exploratory behavior (maze learning test) of the rats and decrease in spatial memory. These results agreed with the previous study which reported that Al exposure had a neurodegeneration effect that leads to learning deficits. Rats injected intraperitoneal with $AlCl_3$ for 60 days (100 mg/ kg b.w.) showed a decrease in the memory in the Morris water task (MWT) and passive avoidance test that assess spatial memory [19]. Ach is responsible to short-term memory. In Al exposed animals, Al can induce disorder in cholinergic neurotransmission leading to memory alterations [20]. Results of this study revealed that, compared with $AlCl_3$-treated rats, the learning and memory abilities were significantly improved in AD rats group treated with *B. carteri* (500 mg/ kg b.w., orally) daily for 8 weeks as showed by decrease in elapse time, and decrease in the number of errors in the maze.

Therapeutic effect of *B. carteri* on AD rat model caused by streptozotocin (STZ) injection intracerebroventricular (i.c.v) has been studied previously [21] which clarified that STZ increased stimulations numbers needed for initiation of short-term memory and decreased step-through latency (STL) on tested day. Furthermore, oral administration of *B. carteri* aqueous extract (50 mg/kg) for 21 days didn't change learning measurements, but its injection for 42 days significantly enhanced STL, decreased STL number into dark compartment and decreased stay time in dark compartment. Also, Zaker *et al*. [22] found that acute administration of the aqueous extract of *B. carteri* (100 and 300 mg/kg b.w.) orally 30 minutes before the test didn't change learning, but chronic administration of 50 mg/kg b.w. for 21 days improved memory retrieval. Beheshti and Karimi [23] studied the effect of *B. carteri* on memory in rats treated with lipopolysaccharide (LPS) that disturbed memory retrieval by significantly decreasing STL and increasing tumor necrosis factor alpha (TNF-α) levels in the hippocampus versus control. Intake of hydro-alcoholic extracts of *B. carteri* (50 mg/kg b.w.) orally prior to LPS improved memory retrieval and reduced hippocampal TNF-α level than control group. Yassin *et al*. [14] revealed that intake of aqueous infusions of *B. serrata* (90 mg/kg/ b.w. daily for 2 weeks) to rats caused a reduction in the duration taken by rats to reach food in T-maze test; in other words, it corrected the cognitive functions and memory in rats. Hosseini *et al*. [12] showed that chronic intake of 100 and 500 mg/ kg *B. serrata* in hypothyroid male rats inhibits deterioration of learning and memory. The action of frankincense on memory is due to structural changes in brain neuronal circuits [24].

Rivastigmine is used as standardized drug for treatment of AD. The rivastigmine efficacy in dementia treatment has been examined in moderate-to-severe AD patients lived in long-term care facilities [25]. Treatment of AD rats with rivastigmine as a protective or therapeutic agent led to significant decrease in error numbers in the maze versus AD-induced groups of rats [14].

It is reported that Ach has essential activity in learning and memory neurons. Cognitive dysfunction was closely related to the decrease of the activity of cholinergic transmitters. AchE is a hydrolase enzyme that plays a key role in cholinergic transmission by catalyzing Ach hydrolysis [26]. The results of the present work showed that oral intake of $AlCl_3$ for 8 weeks in AD rat model produced a significant increase in AchE activities of the cerebral cortex and hippocampus homogenate accompanied with a significant decrease in DA, NE and GABA contents in comparison with control group. AchE enzyme has received marked attention in Al neurotoxicity studies [27]. Such results of increase of AchE activities were coincided with the findings of others [14, 28]. Also, Kaizer *et al*. [29] and Zhang *et al*. [30] demonstrated an increase in AchE activity in different mice and rats' brain regions after treatment with Al. It has been demonstrated that the increase in AchE activity after Al exposure was due to allosteric action between Al and peripheral anionic location of enzyme molecule resulting in modification of secondary structure and enzyme activity [31].

Imbalance in brain biopterins may lead to a disturbance of various neurotransmitters as DA and NE [32]. However, the decrease of monoamines level may be due to alterations in the dopaminergic system [33], or might be due to decreased synthesis resulting from Al damage of the ileal mucosa and reduction in ilea absorption, where a decrease in tryptophan absorption would decrease serotonin synthesis, and a decrease in L-tyrosine absorption may decrease DA, NE and epinephrine (E) production [34]. Moreover, the marked changes of brain neurotransmitters levels (DA and NE) in $AlCI_3$ rats may be due to enhanced formation of $O_2$- and $H_2O_2$ in the hippocampus that leads to neurodegenerative diseases and Lewy bodies' accumulation [35]. Furthermore, the increased iron species concentration among Al rats groups enhance DA oxidation forming DA quinones that react with cysteine residues of functional proteins as GSH suppressing their activities and detoxification actions [36].

Regarding inhibitory neurotransmitters, $AlCl_3$ induced reduction in cerebral cortex and hippocampus GABA contents, observed herein, is similar to that described previously [37] who demonstrated that $AlCl_3$ selectively modulates GABA receptors function leading to widespread changes in inhibitory circuits that contribute to neuropathology [38]. The significant decline in GABA level may be due to its increased destruction via enzymatic action and selective loss of GABAergic neurons due to exposure to $AlCl_3$ [39]. Generally, disturbance in amino acids neurotransmitters leads to direct or indirect $AlCl_3$ effects on protein metabolism and interfere with GABA formation and destruction via a reactions known as GABA shunt. Both GABA and glutamate may have some common ways of metabolism including astrocyte where they are up taken and changed to glutamine, which is then returned back to the presynaptic vesicles. In the excitatory neurons it is changed to glutamate while in the inhibitory neurons it is changed to GABA with glutamate as intermediate substance [28]. Meanwhile, Shuchanga *et al*. [40] reported that Al-exposed rats had a lower glutamate levels and higher GABA level.

The results of this study showed that oral intake of *B. carteri* (500 mg/kg b.w., orally) every day for 8 weeks leads to a marked decrease in AchE contents of

hippocampus and cerebral cortex homogenate accompanied with a significant increase in DA, NE and GABA contents in comparison with control group. Yassin *et al*. [14] reported that *B. serrata* infusion extract leads to significant improvement in animals with AD and increase the brain Ach levels and also significantly decrease brain AchE levels in dose dependent manner. Boswellic acids, as the major components of *B. serrata* are reported to have anticholinesterase activity [41]. It has been demonstrated that 11-keto-beta-boswellic acid and 11alpha-hydroxy-beta-boswellic acid extracted from *B. serrate* exert inhibitory activity on AchE. The suppressive effect of these compounds on AchE appears to be associated with the presence of either free hydroxyl group or keto group at C-11 and the presence of free hydroxyl group at C-3 in the ursane skeleton [42]. Inhibiting neuronal AchE activity would increase Ach level and improve cognitive function [43].

In view of our results, it has been demonstrated that the treatment of AD- rats with rivastigmine produces marked decline in AchE activity of cortex and hippocampus homogenate and increase in DA, NE and GABA levels. These results are in agreement with others who demonstrated that rivastigmine intake increases levels of Ach and inhibits AchE activity in the brain [14]. Rivastigmine is a carbamate derivative pseudo-irreversible cholinesterase inhibitor that suppressed both BuchE1 and AchE. Rivastigmine is destructed by synapse rather than by hepatic cytochrome enzymes [44]. The glutamatergic system is changed after AchE inhibition after rivastigmine [45]. Therefore, the mechanism by which rivastigmine could improve the cognition of these rats is related to its potential to increase Ach and decrease AchE activity as shown in the present study.

In this study, exposure of rats to $AlCl_3$ leads to significant decrease in the cortex and hippocampus homogenates of antioxidant enzymes as GSH, GSSG and SOD and significant increase in oxidative stress as LPO levels. Several studies revealed that GSH decrease is important in oxidative stress production. Decrease of GSH enhances signaling processes, leading to central excitabilities and neuronal death [46]. Deloncle *et al*. [47] reported that $AlCl_3$ neurotoxicity due to increase in LPO and blood–brain barrier damage. SOD catalyzes the rapid removal of superoxide radicals generating hydrogen peroxide ($H_2O_2$), which is eliminated by catalase (CAT) [48]. The observed decrease in antioxidant enzymes activity after $AlCl_3$ administration versus control groups is in accordance with those reported by others [49]. Mahdy *et al*. [50] reported that $AlCl_3$ AD-induced rats showed significant increases in serum levels of NO and MDA and marked decreases in total antioxidant capacity (TAC) and SOD activities. Abd-Elhady *et al*. [51] reported that after Al toxicity, GSH synthesis was declined due to glutathione synthetase decrease. Oxidative stress with the subsequent production of reactive oxygen species (ROS) was postulated as one of the mechanisms of Al toxicity [52]. Free radicals cause protein and DNA injury, inflammation that lead to cellular apoptosis. Moreover, Al disturbs the antioxidant mechanism of eliminating free radicals from inside the cell [53].

In this study, treatment of AD rats with *B. carteri* daily for 8 weeks leads to significant increase in cortex and hippocampus homogenates of GSH, GSSG and SOD and significant decrease in LPO levels. The antioxidant activity of *B. serrata* (45 or 90 mg/kg b.w.) in the cerebrovascular system has been revealed [54]. *B. serrate* has potent antioxidant actions as shown by previous studies [55]. Forouzanfar *et al*. [56] reported that after cerebral ischemia, *B. serrata* extracts intake decrease MDA, and also increase GSH and SOD in cerebral cortex that suggests its antioxidant properties. Previous studies reported that boswellic acid has strong antioxidant activity [57]. The possibility of boswellic acid being an antioxidant and memory enhancer makes this agent an ideal neuroprotective agent. This finding is in agreement with others that high antioxidant agents increase learning and memory capacities of rats [58].

Treatment of AD rats with rivastigmine as a protective or therapeutic agent led to an improvement in the oxidative stress status, as represented in this study by a significant increase in the cortex and hippocampus homogenates of GSH, GSSG and SOD and significant decrease in LPO levels. Rivastigmine act via glutameric mechanism, decreasing oxidative stress and restoring antioxidant defense [59].

Neuropathological examination of brain tissue sections of AD- rats showed neuronal degeneration and edema. Abnormal morphology in CA1 and DG of hippocampus characterized by degenerated shrunken cells with darkly stained nuclei. However, Al leads to hippocampus morphologically changes due to damage of neurons and gliosis, and this may affect various enzymes responsible for synthesis and destruction of the neurotransmitters [60]. Moreover, Al can pass the blood brain barrier, accumulate in brain and hippocampus, and produce neurotoxin damage [19].

In AD rats treated with *B. carteri*, or rivastigmine, hippocampus sections in CA1 and DG showed reduced degenerated cells. In addition, the hippocampus cells in CA1 and DG showed slight changes versus cells structure of rats treated with $AlCl_3$ alone. The hippocampus sections of CA1 in control, *B. carteri* extract and *B. carteri* + $AlCl_3$ treated rats revealed normal pyramidal cells with vesicular nuclei. Furthermore, the hippocampus sections of DG in control, *B. carteri* extract and *B. carteri*

+ $AlCl_3$ treated rats revealed normal granular cells with vesicular nuclei. Also, there was an increase in the thickness of the granular layer in *B. carteri* extract and (*B. carteri* + $AlCl_3$) treated groups.

Long-term oral intake of *B. serrata* in aged Wistar rat (100 mg/ kg/ day for 8 weeks) showed neuroprotective activity and increases CA1 pyramidal cells of hippocampus dendritic arbors [61]. Hosseini-Sharifabad *et al*. [62] reported that chronic administration with *B. serrata* (100 mg/ kg / day for 8 weeks) enhanced dendritic complexity in DG cells compared with control rats. Hippocampal granule cells of *B. serrata*- treated aged rats showed larger arbors, increased numerical branching density, more dendritic segments, and more dendritic spines versus controls. Karima *et al*. [24] revealed that boswellic acids increase neurite growth, branching and tubulin polymerization dynamics. Increase effect of boswellic acid on microtubule polymerization kinetics may be responsible for increasing axonal growth and branching. It prevents destruction of integrity of microtubule protein [63] due to neurodegeneration caused by aging [64]. *Boswellia* resin has many active substances in addition to boswellic acids. Incensole acetate, another substance of *Boswellia* resin also decrease hippocampal neuro-degeneration via its anti-inflammatory actions on brain [65]. Meanwhile, further studies need to know the biological mechanism by which *Boswellia*-induced neuritic enhancement.

In consistence with our histopathological results in *B. carteri* + $AlCl_3$ treated group, therapeutic and protective actions of *B. serrata* on $AlCl_3$ -induced AD in rats, have been found [11]. Chronic intake of methanolic extract of *B. serrate* had anti-inflammatory effects against neuro-inflammation manifested in $AlCl_3$ (AD rats model) [66]. It is probable that boswellic acids of frankincense might prevent starting of neuro-inflammation. Antioxidants prevent oxidative stress as they remove metal ions involved in neuronal plaque formation. Furthermore, in post-oxidative stress scenarios, antioxidant therapy hunts down free radicals and ROS and thus prevent neuronal degeneration [53].

Photomicrograph of brain of AD rats treated with rivastigmine revealed no histopathological alterations in the hippocampus. Coleman *et al*. [67] showed that rivastigmine treatment in a primary cell culture model preserve neuron, and preserve neuronal morphology and synaptic markers that are essential for normal neuronal action. Moreover, Bihaqi *et al*. [68] demonstrated normal histological appearance of the brain cells treated with rivastigmine tartrate. These authors stated that rivastigmine could reverse the histopathological alterations of the brain caused by Al.

## CONCLUSION

From the result of this study we can conclude that *B. carteri* has a neuroprotective effect on rats with AD, prevents LPO rising, increases GSH, GSSG and SOD levels and improve memory and learning in the AD rat model. They also increase neurotransmitter formation in the brain as DA, NE and GABA and decreased AchE enzyme activity that destruct Ach which is excitatory neurotransmitter in the brain. They could ameliorate the neurodegenerative characteristics of AD. These results represented satisfactory therapeutic approaches for intervention against the progressive neurological damage associated with AD, with special reference to oxidative insults. Further clinical trials on humans are required to determine the efficacy of *B. carteri*, or one or more of its constituents, on neurodegenerative disorders.

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