Oxidative stress-induced damage was shown to be one of the important mechanisms to indicate that aluminum has an association with the etiology of Alzheimer's disease (Kumar et al., 2009). Increased generation of reactive oxygen species (ROS) and lipid peroxidation has been found to be involved in the pathogenesis of many diseases of known and unknown etiology and in the toxic actions of many compounds (Andallu and Varadacharyulu, 2003). Aluminium is a non-redox active metal which is capable of increasing the cellular oxidative milieu by potentiating the pro-oxidant properties of transition metals such as iron and copper (Bjertness et al., 1996). An unusual aspect of the biochemistry of this non-redox active metal is its pro-oxidant activity, which might be explained by the formation of an Al superoxide semi-reduced radical ion (AlO$_2^{2-}$) (Exley, 2005). It has been shown that chronic aluminium exposure is involved in the impairment of mitochondrial electron transport chain (ETC) and increased production of ROS (Kumar et al., 2008). The formation of excessive ROS and reactive nitrogen species (RNS) can lead to oxidative injury. Reactive oxygen species (ROS) interact with all biological macromolecules, including lipids, proteins, nucleic acids, and carbohydrates. The resulting stress increases neuronal death, which contributes to the neuropathology associated with several diseases (Baydas et al., 2003).

Gene expression changes in the forebrain occur during normal and pathological aging. Altered gene expression is thought to contribute to the balance between normal aging and age-related memory disorders, including Alzheimer's disease (AD) (Berchtold et al., 2008). Synaptic dysfunction in AD is apparent before synapse and neuron loss and caused likely by accumulation of β-amyloid (Aβ) peptides (Selkoe, 2002). The cellular mechanisms underlying synaptic and memory dysfunction caused by altered activity-dependent gene transcription in AD are largely unknown. Understanding the molecular pathways regulating gene expression profiles in memory disorders may allow the identification of new signaling pathways for drug discovery (Altar et al., 2009). Several PCR techniques are used to determine the changes in the gene expression, in which the most accurate one is Real-time-PCR (RT-PCR). It is became the
most popular method of quantitating steady-state mRNA levels (Bustin, 2000). It is most often used for two reasons: either as a primary investigative tool to determine gene expression or as a secondary tool to validate the results of DNA microarrays. Because of the precision and sensitivity of real-time RT-PCR, even subtle changes in gene expression can be detected. Thus real-time PCR can be used to assess RNA levels with great sensitivity and precision.

There are several genes play main role in occurrence the AD diseases. The generation of amyloid β-peptide (Aβ) is widely held to play an early and critical role in the pathogenesis of Alzheimer’s disease (Hardy and Selkoe, 2002). Aβ is generated from the large precursor protein amyloid precursor protein (APP) by the sequential action of two proteases, β and γ-secretase. β-secretase has been identified as β-site APP-cleaving enzyme 1 (BACE1) which, together with its homolog BACE2, forms a novel subfamily of transmembrane aspartic proteases within the pepsin family (Vassar and Citron, 2000).

The formation of Alzheimer’s Aβ peptide is initiated when the amyloid precursor protein (APP) is cleaved by the enzyme β-secretase (BACE1); inhibition of this cleavage has been proposed as a means of treating Alzheimer’s disease.

Cyclooxygenase (COX-2) is continuously expressed within a distinct population of neurons in the brain (Breder et al., 1995), which is a common attribute in enzymes involved in physiological functions of the central nervous system such as memory, sensory integration, and autonomic regulation (Kaufmann et al., 1997). On the other hand, in various neuropathological conditions accompanied by inflammatory reaction, such as stroke (Tomimoto et al., 2000) and amyotrophic lateral sclerosis (ALS) (Yasojima et al., 2001), COX-2 up-regulation is thought to mediate neuronal damage presumably by producing excessive amounts of harmful prostanoids and free radicals. In AD brains, it has been reported that the expression of COX-2 mRNA and protein was elevated (Yasojima et al., 1999). However, it is not yet completely delineated how and in what type of cells COX-2 is increased in the AD brain.

Aluminum-induced depletion of antioxidants such as glutathione (GSH), glutathione peroxidase (GSH-Px), glutathione S-transferase (GST) and catalase (CAT) (Mahieu et al., 2005). Antioxidants thus play key roles in the protection against damage caused by reactive oxygen species (Baynes, 1991). Many plant extracts and plant products have been shown to have significant antioxidant activity (Anjali and Manoj, 1995), which may be an important property of medicinal plants associated with the treatment of several diseases including neurodegenerative diseases. Thus, herbal plants are considered useful means to prevent and/or ameliorate certain disorders, such as Alzheimer’s disease. Among these herbal resources, the plant Jasonia montana and Jasonia candi-
J. montanta and J. candicans occur in the Mediterranean and surrounding areas (Merxmuller et al., 1977), including the Sinai Peninsula (Tackholm, 1974). The herb has a strong aromatic odor and is used in traditional medicine for diarrhea, stomach ache, and chest diseases (Tackholm, 1969). A literature survey indicated that some mono- and sesquiterpenes (Ahmed and Jakupovic, 1990; Ahmed, 1991), flavonoids (Ahmed et al., 1989) and essential oils (Hammerschmidt et al., 1993) have been reported from the plant.

Rivastigmine is a carbamate derivative pseudo-irreversible cholinesterase inhibitor which can both inhibit acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). This drug is licensed for use in the UK for the symptomatic treatment of mild-to-moderately severe AD due to its inhibitory action on AChE activity (Foye et al., 1995). Rivastigmine has been reported to protect mice against cognitive impairment caused by oxygen deficit, improve learning in rats, and antagonize scopolamine induced impairment of cognitive function in rats (Desai and Grossberg, 2001; Howes et al., 2003). It has been demonstrated that Rivastigmine supplementation increased the concentration of acetylcholine and inhibited acetylcholine esterase activity (Liang and Tang, 2004).

The present study was designed to investigate the potential role of J. montanta and J. candicans total extracts against AlCl₃-induced oxidative stress and gene expression alteration of AD-related enzymes characterizing Alzheimer's disease in male rats.

**MATERIALS AND METHODS**

**Chemicals**

- Aluminium Chloride (AlCl₃): was purchased from Sigma. Its M.W. 133.34.
- Rivastigmine: Exelon 1.5 mg, was purchased from Novartis Co.

**Medicinal plants**

Fresh aerial parts of J. montana and J. candicans were collected from the Sinai Peninsula. Authentication of the plant was carried out by Prof. Dr. Samir M. Othman, Department of Pharmacognosy, Faculty of Pharmacy, October 6th University, October 6th City, Egypt.

**Preparation of medicinal plant extracts**

According to López et al. (2008), plant material was air-dried in the dark at room temperature. The dried-powder (180 meshes) was successively extracted 3-times with 200 ml dichloromethane, ethyl acetate, methanol, and water after maceration at 4°C for 24h. The dichloromethane, ethyl acetate, and methanol extracts were dried under reduced pressure at 30°C in a rotary evaporator and the aqueous extracts were lyophilized. The dry extracts were stored in glass vials at -40°C until tested and analyzed.

**Experimental animals**

Male aged Sprague Dawley rats (14-16 months) weighing 250-300 g were
obtained from the Animal House Colony of the National Research Centre, Cairo, Egypt and acclimated in a specific pathogen free barrier area at 25±1°C. Rats were kept constantly at a 12h light/dark cycle. They were individually housed with ad libitum access to standard balanced diet. Animals received human care in compliance with the guidelines of the Ethical Committee of Medical Research of National Research Centre, Egypt.

**Experimental Design**

Rats were randomly assigned into seven groups, ten rats each. The first group served as normal control. The second group was provided with AlCl₃ in drinking water in a dose of 0.3% for forty five days (Erazi et al., 2010), and served as Al intoxicated group. The third and fourth groups rats were given AlCl₃ in drinking water daily for forty five days then they were orally treated with 150 mg/kg b. wt./day of *J. montanta* and *J. candicans* extract, respectively, for another forty five days (Hussein, 2008). The fifth group rats were given AlCl₃ in drinking water daily for forty five days then they were orally treated with Rivastigmine in a dose of 0.3 mg/kg b. wt. (Carageorgious et al., 2008) as a reference drug daily for another forty five days. Rats in the sixth and seventh groups were administered orally with *Jasonia montanta* and *Janosia candicans* extracts, respectively, for forty five days.

At the end of experimental period, fasting blood samples were collected from retro-orbital venous plexus under anesthesia, in heparinezed tubes, and then centrifuged at 3000 rpm for 15 min. Plasma was separated and stored at -20°C until analysis.

After blood collection, brains were rapidly dissected, thoroughly washed with isotonic saline, and dried. Each brain was mid-saggitally divided into two portions. The first portion was stored in liquid nitrogen for gene expression analysis. While the second portion was weighed and homogenized immediately to give 10% (w/v) homogenate in ice-cold medium containing 50 mM tris HCl and 300 mM sucrose. The homogenate was centrifuged under cooling at 3000 rpm for 10 min. The supernatant (10%) was used for biochemical analyses.

**Biochemical analyses**

Quantitative estimation of total protein level in the brain homogenate was carried out according to the method of Lowry et al. (1951). Brain malondialdehyde (MDA) level was estimated by colorimetric method described by Ohkawa et al. (1979). Quantitative estimation of brain nitric oxide (BNO) level was assayed according to the method of Berkels et al. (2004) and brain total antioxidant capacity (TAC) level was colorimetrically determined according to the method of Koracevic et al. (2001).

**Gene expression analysis**

**Extraction of total RNA**

Brain tissues of rats within each group were used to extract total RNA us-
ing TRIzol® Reagent (cat#15596-026, Invitrogen, Germany). Total RNA was treated with 1 U of RQ1 RNase-free DNase (Invitrogen, Germany) to digest DNA residues, re-suspended in DEPC-treated water and photospectrometrically quantified at A260. Purity of total RNA was assessed by the 260/280 nm ratio (between 1.8 and 2.1). Additionally, integrity was assured with ethidium bromide-stain analysis of 28S and 18S bands by formaldehyde-containing agarose gel electrophoresis. Aliquots were used immediately for reverse transcription (RT), otherwise stored at -80°C.

**Synthesis of the cDNA using reverse transcription (RT) reaction**

The complete Poly(A)⁺ RNA isolated from rat brain tissues was reverse transcribed into cDNA in a total volume of 20 µl using RevertAid™ First Strand cDNA Synthesis Kit (MBI Fermentas, Germany). An amount of total RNA (5µg) was used with a reaction mixture, termed as master mix (MM). The MM consisted of 50 mM MgCl₂, 5 x reverse transcription (RT) buffer (50 mM KCl; 10 mM Tris-HCl; pH 8.3), 10 mM of each dNTP, 50 µM oligo-dT primer, 20 U ribonuclease inhibitor (50 kDa recombinant enzyme to inhibit RNase activity) and 50 U M-MuLV reverse transcriptase. The mixture of each sample was centrifuged for 30 sec at 1000 g and transferred to the thermocycler (Biometra GmbH, Göttingen, Germany). The RT reaction was carried out at 25°C for 10 min, followed by 1 h at 42°C, and finished with a denaturation step at 99°C for 5 min. Afterwards the reaction tubes containing RT preparations were flash-cooled in an ice chamber until being used for DNA amplification through Real Time polymerase chain reaction (RT-PCR).

**Quantitative real time-polymerase chain reaction (qRT-PCR)**

An iQ5-BIO-RAD Cycler (Cepheid, USA) was used to determine the quail cDNA copy number. PCR reactions were set up in 25 µL reaction mixtures containing 12.5 µL 1× SYBR® Premix Ex TaqTM (TaKaRa, Biotech. Co. Ltd.), 0.5 µL 0.2 µM sense primer, 0.5 µL 0.2 µM antisense primer, 6.5 µL distilled water, and 5 µL of cDNA template.

The reaction program consisted of three steps. The first step was at 95°C for 3 min. The second step consisted of 40 cycles in which each cycle was divided into three sub-steps: (a) at 95°C for 15 sec; (b) at 55°C for 30 sec; and (c) at 72°C for 30 sec. The third step consisted of 71 cycles which started at 60°C and then increased about 0.5°C every 10 sec up to 95°C. At the end of each sqRT-PCR a melting curve analysis was performed at 95°C to check for the quality of the used primers. Each experiment included a distilled water control.

The quantitative values of qRT-PCR of Amyloid precursor protein (APP; forward 5’-ACT GGC TGA AGA AAG TGA CAA T-3’; reverse 5’-AGA GGT GGT TCG AGT TCC TAC A-3’; Stein
and Johnson, 2002); β-site APP cleaving enzyme 1: \(BACE1\) (forward 5'-GCG CTT GCC ATG TGC AC-3'; reverse 5'-TGC CGT AAC AAA CGG ACC TT- 3'; Luo et al., 2003); β-site APP cleaving enzyme 2: \(BACE2\) (BACE2 forward 5'-AAA TTT CTG GGC CCT TTT CC-3', Reverse 5'-GGG CTC ATT CAG AGC CTG TG-3', Luo et al., 2003); and cyclooxygenase: \(COX-2\) (F: 5′- TGA TCG AAG ACT ACG TGC AAC A -3′, R: 5′- GCG GAT GCC AGT GAT AGA GTG -3′, Oyama et al., 2005) genes were normalized on the bases of β-actin (β-actin-F: 5′- CCC AGA GCA AGA GTA TC -3′, B-actin-R: 5′- AGA GCA TAG CCC TCG TAG AT -3′) expression.

At the end of each qRT-PCR a melting curve analysis was performed at 95°C to check the quality of the used primers.

**Calculation of gene expression**

First the amplification efficiency (Ef) was calculated from the slope of the standard curve using the following formulae (Bio-Rad 2006):

\[ Ef = 10^{\frac{1}{slope}} \]

Efficiency (%) = (Ef – 1) x 100

The relative quantification of the target to the reference was determined by using the \(AC_T\) method if E for the target (GH, IGF-1) and the reference primers (β-Actin) are the same (Bio-Rad 2006):

\[ \text{Ratio}_{\text{reference/target gene}} = \frac{E_T^{C_{\text{reference}}}}{C_T^{\text{target}}} \]

The amplification efficiency (E) for APP, BACE1, BACE2 and COX-2 were 1.996 (%E= 99.66), 2.00 (%E=100.08), 1.993 (%E=99.52) and 1.988 (%E=89.84) respectively. Whereas, the PCR conditions indicated that the slopes of APP, BACE1, BACE2 and COX-2 were -3.33, -3.32, -3.34 and -3.35, respectively.

Further, to ensure that the PCR efficiency (E = 10-1/s - 1) was similar between the sample and the standard which was close to 2, we analyzed whether the addition of RT products to the reaction mixture for the standard curve which was prepared for purified RNA affected the PCR efficiency.

**Statistical Analysis**

All results were expressed as Mean±S.E of the mean. Data were analyzed by one way analysis of variance (ANOVA) using the Statistical Package for the Social Sciences (SPSS) program, version 11 followed by least significant difference (LSD) to compare significance between groups (Armitage and Berry, 1987). Difference was considered significant when P < 0.05.

**RESULTS AND DISCUSSION**

**Biochemical study**

The data in Table (1) represents the effect of \(J. candicans\) and \(J. montana\) extracts on brain oxidant/antioxidant status in male rats received AlCl3 in drinking water. Administration of \(J. candicans\) and
*J. montana* extracts showed significant decrease in brain malondialdehyde (MDA) and brain nitric oxide (BNO) levels except *J. montana* extract which showed insignificant decrease in brain nitric oxide level in comparison with the negative control group. Moreover, they showed insignificant increase in brain total antioxidant capacity (TAC) as compared to the negative control group. On the other hand, the untreated AD induced rats showed significant increase in brain MDA and BNO levels associated with significant decrease in brain TAC in comparison with the negative control group. While, treatment of AD induced rats with *J. candidans* or *J. montana* extracts or rivastigmine produced significant decrease in brain MDA and BNO levels accompanied with significant increase in brain TAC when compared with the untreated AD induced group. Noteworthy, the treatment of AD induced rats with *J. candidans* or *J. montana* extracts caused insignificant change in brain MDA, BNO and TAC levels as compared with the AD induced rats treated with rivastigmine.

In neurodegenerative disorders involving oxidative stress, such as Alzheimer’s disease, stroke and Parkinson’s disease, BNO increases cell damage through the formation of highly reactive peroxynitrite (Guix et al., 2005). Dorheim et al. (1994) reported that the elevated level of BNO may result from the activation of nitric oxide synthase (NOS) which was also elevated in the brain of patients with AD, indicating that BNO may play a role in neuronal cell injury in this disease. One of the possible mechanisms by which Al could induce BNO elevation in brain tissue may be related to Al-induced nitric oxide synthase (NOS) activity with consequent increase in BNO products in rat brain tissue and microglial cells (Bondy et al., 1998). Guix et al. (2005) demonstrated that cerebellar levels of inducible NOS (iNOS), not neuronal NOS (nNOS) protein in rats were significantly elevated following both short-term and extended Al dosing.

Some reports suggest that Al-induced AD could interface with signal transduction pathways associated with NMDA receptors (Platt et al., 1995). In this pathway, activation of NMDA receptors leads to increased intracellular calcium in the postsynaptic neuron, which, in turn, binds to calmodulin and triggers the activation of the NOS enzyme opening a gate for the electron flux into the active center of the NOS in brain tissue (Canales et al., 2001). It has been demonstrated that all three isoforms of NOS (nNOS, eNOS, and iNOS) are aberrantly expressed during Al intoxication. This gives rise to the elevated levels of BNO that are apparently involved in neurodegeneration by different mechanisms, including oxidative stress and activation of intracellular signaling mechanisms (Lüth et al., 2001).

The preliminary studies conducted by this work revealed the non-toxic nature of *J. montana* and *J. candidans* on normal rats. This result is greatly supported by that of Hussein (2008). The current results revealed that brain MDA level was sig-
significantly lower in the groups of Alzheimer's disease group treated with *J. montana* and *J. candicans* extracts compared to Alzheimer's disease group. The above result suggests that both *J. montana* and *J. candicans* extracts may exert antioxidant activities and protect the tissues from lipid peroxidation (Hussein, 2008). It is most likely that the potential effect of *J. montana* and *J. candicans* extract in reducing the lipid product represented by MDA level is a consequence of the modulatory influence of these extracts on the biotransformation enzymes of detoxification. High content of flavonoids and phenolic compounds has been demonstrated in *J. montana* extract (Hussein and Abdel-Gawad, 2010) as well as in *J. candicans* one (Hammerschmidt et al., 1993) which may be responsible for free radical scavenging activity. The phenolic compounds such as quercetin and kaempferol which are present in high concentration in each of *J. montana* (Soliman et al., 2009) and *J. candicans* (Hammerschmidt et al., 1993) have been found to exhibit antilipid peroxidative effect (Dasgupta and De, 2007; Liu et al., 2008) due to their ability to inhibit H$_2$O$_2$-induced lipid peroxidation (Ammar et al., 2009). Flavonoids are able to inhibit lipid peroxidation on the mitochondrial membrane, thus these compounds possess good antilipidperoxidative activity (Sugihara et al., 1999) which indicates the pharmacological potential of flavonoids against pathological processes related to oxidative stress (Andarwulan et al., 2010).

The ability of each of *J. montana* and *J. candicans* total extracts to reduce brain nitric oxide (BNO) level in Alzheimer's disease-induced rats in the present study could be attributed to the efficacy of flavones content in these extracts to interfere with expression of the inducible nitric oxide synthase (iNOS). Therefore, they were considered as a powerful inhibitor for BNO production without BNO scavenging activity (Cerqueira et al., 2008). Hussein and Abdel-Gawad (2010) study greatly supported our results in this concern as they stated that BNO level is significantly depleted after *J. montana* treatment in rats-induced cholestasis. The high content of flavonoids and phenolic compounds in *J. montana* extract (Hussein and Abdel-Gawad, 2010) and *J. Candicans* (Hammerschmidt et al., 1993) may contribut in this effect.

The effect of *J. montana* and *J. candicans* total extracts on the total antioxidant capacity in the brain revealed that these extracts could significantly increase brain total antioxidant capacity in the Alzheimer's disease-treated rats. It has been found that *Jasonia* species can either increase the biosynthesis of glutathione or reduce the oxidative stress leading to less degeneration of glutathione or has both effects (Hussein, 2008). Also, this species has been demonstrated to improve the activities of the antioxidant enzymes (superoxide dismutase (SOD) and catalase (CAT)) attributed to the reduction of reactive oxygen free radicals. Moreover, Jasonia species could increase the activities of glutathione peroxidase (Gpx) and
The role of *J. montanta* and *J. candicans* against Alzheimer’s disease

Glutathione-s-transferase (GST) in the various tissues of rats (Hussein, 2008). Furthermore, Hussein and Abdel-Gawad, (2010) reported that Jassonia species extract effectively normalize the impaired antioxidant status in rats. The phenolic constituents sharing flavonoids in enhancing the total antioxidant capacity in Alzheimer’s disease- treated rats. These compounds exhibit both antioxidant activity and antiradical capacity (Liu et al., 2008; Esmaeili et al., 2010), which are responsible for the increased total antioxidant capacity (Robaszkiewicz et al., 2007).

**Expression of APP, BACE1, BACE2 and COX-2 genes**

The present results revealed a significant decrease of gene expression levels of *APP, BACE1, BACE2* and *COX-2* genes in untreated male rats (negative control) compared with those treated with AlCl₃ (Figs 1-4). The same trend was showed in rats supplemented with *J. montana* and *J. candicans*. Whereas, the expression of *APP, BACE1, BACE2* and *COX-2* genes showed low levels in *J. montana* and *J. candicans* groups compared with those treated with AlCl₃ (Figs 1-4).

In contrary, the expression levels of *APP, BACE1, BACE2* and *COX-2* genes in rats treated with AlCl₃ (0.3 g/L for 4 months) were significantly higher than those found in untreated rats or in rats supplemented with *J. montana* or *J. candicans* (150 mg/kg b.w.) alone (Figs 1-4).

The results showed also that *J. montana* and *J. candicans* were able significantly to reduce the expression level of AD related-genes in rat groups treated with AlCl₃ plus *J. montana* or treated with AlCl₃ plus *J. candicans* (Figs 1-4).

The formation of Alzheimer’s Aβ peptide is initiated when the amyloid precursor protein (APP) is cleaved by the *BACE1* and *BACE2* enzymes (Vassar and Citron, 2000). In AD brains, it has been also reported that the expression of *COX-2* mRNA and protein was elevated (Yasojima et al., 1999).

The current results revealed a significant increase of gene expression levels of *APP, BACE1, BACE2* and *COX-2* enzymes in rats treated with AlCl₃ induced AD disease compared with those in untreated rats or in rats supplemented with *J. montana* or *J. candicans*. In contrary, the expression levels of *APP, BACE1, BACE2* and *COX-2* genes in rats treated with AlCl₃ plus *J. montana* or *J. candicans* were significantly lower than those found in rats treated with AlCl₃ alone.

In agreement with our results, Hardy and Selkoe (2002) reported that the generation of amyloid β-peptide (Aβ) is widely held to play an early and critical role in the pathogenesis of Alzheimer’s disease. Aβ is generated from the large precursor protein amyloid precursor protein (APP) by the sequential action of two proteases, β and γ-secretase. β-secretase has been identified as β-site APP-cleaving enzyme 1 (BACE1) which, together with
its homolog BACE2, forms a novel subfamily of transmembrane aspartic proteases within the pepsin family (Vassar and Citron, 2000). The formation of Alzheimer’s Aβ peptide is initiated when the amyloid precursor protein (APP) is cleaved by the enzyme β-secretase (BACE1); inhibition of this cleavage has been proposed as a means of treating Alzheimer’s disease.

Remarkably, COX-2 is continuously expressed within a distinct population of neurons in the brain (Breder et al., 1995), which is an attribute common in enzymes involved in physiological functions of the central nervous system such as memory, sensory integration, and autonomic regulation and may suggest this role for COX-2 (Kaufmann et al., 1997). On the other hand, in various neuropathological conditions accompanied by inflammatory reaction, such as stroke (Iadecola et al., 1999; Tomimoto et al., 2000) and amyotrophic lateral sclerosis (ALS) (Yasojima et al., 2001), COX-2 upregulation is thought to mediate neuronal damage presumably by producing excessive amounts of harmful prostanoids and free radicals. In AD brains, it has been reported that the expression of COX-2 mRNA and protein was elevated (Yasojima et al., 1999). However, it is not yet completely delineated how and in what type of cells COX-2 is increased in the AD brain.

In the current study the results revealed that the expression levels of APP, BACE1, BACE2 and COX-2 genes in the brain samples collected from rats supplemented with J. montana plus AlCl3 were significantly lower (p ≤ 0.01) than those observed in rats treated with AlCl3 alone. Furthermore, the expression levels of APP and BACE2 genes in the brain samples collected from rats supplemented with J. candidans plus AlCl3 were significantly lower (p ≤ 0.01) than those observed in rats treated with AlCl3 alone. However, these levels of expression of BACE1 and COX-2 genes in the brain samples collected from rats supplemented with J. candidans plus AlCl3 were not significantly lower (P> 0.05) than those observed in rats treated with AlCl3 alone.

The expression levels of all genes tested except BACE1 gene in the brain samples collected from rats supplemented with rivastigmine were significantly lower (P< 0.01) than those observed in rats treated with AlCl3 alone.

Jasonia species occurs in the Mediterranean and surrounding areas (Merxmuller et al., 1977), including the Sinai Peninsula (Tackholm, 1974). The herb has a strong aromatic odor and is used in traditional medicine for diarrhea, stomach-ache, and chest diseases. A literature survey indicated that some mono- and sesquiterpenes (Ahmed and Jakupovic, 1990; Ahmed, 1991), flavonoids (Ahmed et al., 1989), and essential oils (Hammerschmidt et al., 1993) have been reported from the plant. The different extracts of the plant were also screened for hypoglycemic and antidiabetic activities (AL-Howiriny et al., 2005). Hussein (2008) reported that the
extract of this plant exerted rapid protective effects against lipid peroxidation by scavenging of free radicals. Thus, this plant showed a powerful antioxidant activity. Moreover, four sesquiterpenes isolated from Jasonia glutinosa D.C. (Asteraceae), namely lucinone, glutinone, 5-epikutdtriol and kutdtriol, have been evaluated for their in vitro anti-inflammatory activity in cellular systems generating cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) metabolites (Benito et al., 2002). López et al. (2008) have demonstrated the antioxidant and antifungal activities of these plants. Therefore, the antioxidant activity of these herb used in the present study may contribute to the reduction of the oxidative activity of AlCl₃ induced AD. Whereas, J. montana and J. candicans down-regulated the AD-related genes and reduced the oxidation status (MDA and BNO levels) as well as increased the antioxidant capacity (TAC level).

In conclusion, Administration of J. candicans and J. montana extracts showed decrease in brain MAD, BNO and expression level of APP, BACE1, BACE2 and COX-2 genes and increase in brain TAC in comparison with control group. The results suggest that the antioxidant activity of J. montana and J. candicans may be main reasons to reduce the oxidative activity of AlCl₃ induced AD.

SUMMARY

Alzheimer’s disease (AD) is an irreversible, progressive brain disorder that occurs gradually and results in memory loss, unusual behaviour, personality changes and a decline in thinking abilities. In this disease, the capacity to memorize is seriously reduced because of compromised neuronal transmission. Jasonia species are reported to possess a variety of activities, including antioxidant effects. Thus, the anti-Alzheimer and antioxidant effects of Jasonia montanta and Jasonia candicans extracts were evaluated via brain malondialdehyde (MDA), brain nitric oxide (BNO) and total antioxidant capacity (TAC) assays as well as quantitative real time-polymerase chain reaction (qRT-PCR) for amyloid precursor protein (APP), β-site APP cleaving enzyme 1(BACE1), β-site APP cleaving enzyme 2 (BACE2) and cyclooxygenase (COX-2). Seventy male rats were allocated in several groups. Untreated control rats and those treated with J. montana and J. candicans were supplemented with 0.3% of AlCl₃ drinking for forty five days to induce Alzheimer’s disease (AD). Afterwards, two groups of them were given orally for further forty five days 150 mg/kg b.wt./day of J. montanta or J. candicans extract. Another group was given 0.3 mg/kg b.wt. of Rivastigmine for further forty five days. The results revealed that administration of J. candicans and J. montana extracts showed decrease in brain MAD, BNO and expression level of APP, BACE1, BACE2 and COX-2 mRNAs and increase in brain TAC in comparison with control group. Moreover, treatment of AD induced rats with J. can-
dicans or J. montana extracts or rivastigmine produced significant decrease in brain MDA, BNO and expression level of APP, BACE1, BACE2 and COX-2 mRNAs accompanied with significant increase in brain TAC when compared with the untreated AD induced group. However, AD induced rats showed increase in brain MDA, BNO and expression level of APP, BACE1, BACE2 and COX-2 mRNAs associated with decrease in brain TAC in comparison with the control group. The results suggest that the antioxidant activity of J. montana and J. candidans may be main reasons to reduce the oxidative activity of AlCl$_3$ induced AD.

**ACKNOWLEDGEMENTS**

The authors also thanks everyone assistance in this study (430/028-17). We are grateful to deanship of scientific research for financial support to conduct this research.

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Table (1): Effect of *J. candidans* and *J. montana* extracts on brain oxidant/antioxidant status in male rats received AlCl₃ in drinking water. Data are represented as Mean ± SE of 10 rats/group.

<table>
<thead>
<tr>
<th>Groups</th>
<th>MDA</th>
<th>BNO</th>
<th>TAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(nmol/mg protein)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.6 ± 0.3</td>
<td>24.5 ± 0.97</td>
<td>14.2 ± 1.3</td>
</tr>
<tr>
<td><em>J. candidans</em></td>
<td>4.1 ± 0.5a</td>
<td>20.7 ± 0.8a</td>
<td>15.2 ± 0.8</td>
</tr>
<tr>
<td><em>J. montana</em></td>
<td>4.5 ± 0.3a</td>
<td>24.0 ± 0.6a</td>
<td>14.3 ± 0.2a</td>
</tr>
<tr>
<td>AlCl₃</td>
<td>8.6 ± 0.5a</td>
<td>35.9 ± 1.0a</td>
<td>7.5 ± 0.5a</td>
</tr>
<tr>
<td>AlCl₃ + <em>J. candidans</em></td>
<td>6.2 ± 0.3b</td>
<td>24.9 ± 1.0b</td>
<td>13.7 ± 0.4b</td>
</tr>
<tr>
<td>AlCl₃ + <em>J. montana</em></td>
<td>6.9 ± 0.3b</td>
<td>25.4 ± 0.6b</td>
<td>13.0 ± 0.9b</td>
</tr>
<tr>
<td>AlCl₃ + Rivastigmine</td>
<td>6.2 ± 0.3b</td>
<td>25.0 ± 0.7b</td>
<td>13.5 ± 0.6b</td>
</tr>
</tbody>
</table>

a: Significant at P< 0.05 in comparison with the negative control group; b: Significant at P< 0.05 in comparison with the untreated AD induced group.

Fig. (1): Semi-quantitative Real Time-PCR analysis of amyloid precursor protein (APP)-mRNAs in brain tissues collected from male rats (n=10) supplemented with *J. montana* and *J. candidans* extracts with or without AlCl₃. Means with different letters, within tissue, differ significantly (P ≤ 0.05).
Fig. (2): Semi-quantitative Real Time-PCR analysis of β-site APP cleaving enzyme 1 (BACE1)-mRNAs in brain tissues collected from male rats (n=10) supplemented with *J. montana* and *J. candidans* extracts with or without AlCl3. Means with different letters, within tissue, differ significantly (P ≤ 0.05).

Fig. (3): Semi-quantitative Real Time-PCR analysis of β-site APP cleaving enzyme 2 (BACE2)-mRNAs in brain tissues collected from male rats (n=10) supplemented with *J. montana* and *J. candidans* extracts with or without AlCl3. Means with different letters, within tissue, differ significantly (P ≤ 0.05).
Fig. (4): Semi-quantitative Real Time-PCR analysis of Cyclooxygenase (COX-2)-mRNAs in brain tissues collected from male rats (n=10) supplemented with *J. montana* and *J. candicans* extracts with or without AlCl₃. Means with different letters, within tissue, differ significantly (P ≤ 0.05).