RESEARCH ARTICLE

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PERTURBATION OF BRAIN NEUROTRANSMITTERS BY ALUMINUM IN MALE RATS AND THE POTENTIAL ROLE OF SAGE

ABSTRACT:
The present study was designed to investigate the risk of aluminum (Al) exposure on brain neurotransmitters in rats and further to elucidate the potential role of three forms of *Salvia officinalis* (sage) in alleviating such disturbances. The animals were assigned in eight groups (6 rats each) as follows: normal control; AlCl₃ (100 mg/kg BW); three sage (water extract, ethanolic extract and oil) groups and other three groups given AlCl₃ in addition to sage in one of the mentioned forms respectively. Rats were administered their respective doses daily for 90 days (6 days a week) except sage oil which was given every other day. The results of the present study exhibited a significant increase in most of the excitatory amino acid neurotransmitters (glutamic acid, glutamine, aspartic acid, serine, glycine, and histidine) contents of the cerebral cortex and hippocampus in Al intoxicated rats with the exception of asparagine which showed a significant decrease compared to the normal control. On the other hand, the inhibitory neurotransmitters; gamma- amino butyric acid (GABA) and taurine indicated a significant reduction and elevation respectively by Al intoxication. Regarding cerebral monoamines, significant declines in serotonin and dopamine concomitant to a significant elevation in of noradrenalin were shown in the same brain regions following Al exposure. Moreover, the results showed also, that the different sage forms, by their antioxidant activity could be able to antagonize Al induced cerebral perturbation of neurotransmitters and consequently can be used as a neuroprotectants by regulating neurotransmission and related functions of the brain in Al intoxication.

KEY WORDS:
Aluminum neurotoxicity, Alzheimer's disease, *Salvia officinalis*, neurotransmitters, Monoamines

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INTRODUCTION:
Aluminum (Al) is a highly neurotoxic element and has been suggested to play a role in degeneration of nerve cells in the brain of human and experimental animals (Yumoto et al., 2001). Neurotoxicity of Al is known to result in impairment of learning memory and cognitive functions both from clinical observations and from animal experiments (Ashall and Goate, 1994). Aluminum has been implicated in human neurodegenerative diseases and it has been linked etiologically and epidemiologically to several neurological conditions including Alzheimer’s disease (Solfirizzi et al., 2006; Santibanez et al., 2007). Various investigations have suggested that Alzheimer’s disease is more common in areas where Al content of water supplies is the highest (Christen, 2000). Indeed, the brain is a target of Al toxicity which can alter bloodbrain barrier (BBB) mediating Al transport to the brain and gets deposited in the cortex and hippocampus by altering the physiological ligands present at these barriers in states (Yokel, 2000). Aluminum also forms stable complexes with aspartic and glutamic acids, which cross the blood brain barrier, and then are deposited in the brain (Deloncle et al., 1999). As a consequence, glutamic acid is not sufficiently available to form glutamine, thereby, ammonia is accumulated in the brain and exerts toxic effects leading to neuronal death and may affect each and every neurotransmitter system (El-Rahman, 2003). Al is known to interfere with cholinergic (Amador et al., 2001), glutamatergic (Platt et al., 1994) and gamma-aminobutyric acid neurotransmission (Cordeiro et al., 2003). In the mammalian brain, Al affects the synthesis, storage and transport of central...
neurotransmitter systems such as dopamine, serotonin, adrenal in, gamma amino butyric acid (GABA) and glutamate (Palmer and DeKosky, 1993).

The molecular mechanisms behind Al neurotoxicity are not clear and many hypotheses have been suggested. These hypotheses include exacerbation of oxidative stress (Kaneko et al., 2007), disruption of calcium homeostasis (Kaur and Gill, 2005) and impairment of intracellular signal transduction pathways (Shafer and Mundy, 1995). In the central nervous system, neurotransmission is coupled to learning and memory, therefore changes in the neurotransmission would certainly affect the behavioural responses (Bhalla et al., 2010).

The metabolism of neurotransmitters is altered in response to Al exposure; these alterations seem to be brain region specific and dependent on homeostasis of ion and energy conduction and on protein expression. In point of fact, neurotransmitters balance is a multifaceted process that may involve contributions from other cells rather than from presynaptic cells alone. In the presence of Al, the uptake of neurotransmitters was found to be below control levels, with some exceptions (Goncalves and Silva, 2007).

The most notorious alterations were the substantial reductions in the concentrations of serotonin in the cortex. Glutamic acid is present in the cerebrospinal fluid (CSF) at the highest concentration compared to the other amino acids. Serine, glycine, asparagine, taurine and histidine were found at higher concentrations in human AD than normal CSF (D’Aniello et al., 2005).

Numerous herbal extracts, containing several active constituents and often more than one plant species, have been suggested to treat CNS-related disorders. Amongst these, Salvia species (S. officinalis L. and S. lavandulaefolia) are prominent for their reputed beneficial effects on memory disorders, depression and cerebral ischaemia and used relevant to the treatment of Alzheimer’s disease (Perry and Pickering, 2005; Akhondzadeh and Abbasi, 2006); these have centered on the activity of the essential (volatile) oil (Perry et al., 2002; Savelev et al., 2003). Salvia officinalis extracts especially the oil inharne neurotransmitters functions and it is thought to be important to improve memory (Perry et al., 2003; Eidi et al., 2006) due to certain constituents (Coleta et al., 2008). Some studies have confirmed these findings and showed decreases also in anxiety within few hours of taking dried sage leaf supplements (300 to 600 mg) (Kennedy et al., 2005). It has been thought that certain criteria are necessary for molecules to pass through the blood brain barrier (BBB) to reach the CNS. The most recent studies, however, have shown that even molecules that do not meet these requirements are capable of passing through the BBB possibly through several receptors present on the BBB and also because some areas on the brain have greater permeability (Gomes et al., 2009).

Therefore, the main goal of the present study was to investigate the risk of alterations in the neurotransmitter contents of the brain in rats exposed to Al toxicity and its reflection on the function of the brain. The study was extended to exhibit the beneficial effects of various sage extracts in preventing or modulating such risk.

**MATERIAL AND METHODS:**

**Chemicals:**

Aluminum Chloride (AlCl3) was obtained from agent of Sigma Chemicals (St. Louis, MO, USA). Salvia officinalis (sage) oil was obtained from NATURE’S ALCHEMY distributed by LOTUS BRANDS, USA. Dried leaves of sage, for preparations of sage tea (water extract and ethanolic extract) were purchased from a local herb market. The taxonomic identity of the plant was confirmed by the botanists of the Department of Botany, Faculty of Science, Mansoura University, Mansoura, Egypt. All other chemicals were purchased locally and were of analytical reagent grade.

**Sage extract preparations:**

**Sage water extract (sage tea):**

Sage water extract was routinely prepared by pouring 150 ml boiling water onto 2 g of dried leaves and allowing it to steep for 5 min. (Lima et al., 2005).

**Sage ethanolic extract:**

Sage ethanolic extract was prepared according to the method described by Eidi et al. (2006). Dried grounded leaves of Salvia officinalis (60 g) were subjected to extraction with 300 ml of ethanol (80%) in a glass container for 72 h. The extract was decanted and filtered through Whatman No 1 filter paper into a clean flask. This same procedure was repeated a further two times. The solvent was evaporated using a rotary evaporator, and then the flask was weighed to determine dried weight of extract. The supernatant was reconstituted using 53% ethanol and assayed using serial dilutions and the dose was calculated according to the human dose (Ghosh, 1971).

**Sage oil:**

Diluted 1:2 in sunflower oil according to Perry et al. (2002).

**Experimental animals:**

This study was carried out on adult male albino rats weighing 130 ± 10g, supplied by The Urology & Nephrology Center; Mansoura University, Mansoura, Egypt. The rats were maintained under controlled temperature (25
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They were fed standard commercial rodent pellet diet and water ad libitum. The animals were weighed at the beginning of the experiment, then once a week and finally before sacrificing them.

**Experimental Protocol:**

After one week of acclimatization, the rats were divided into 8 groups consisting of 6 animals each. All treatments were continued for 90 days as follows:

1. Normal control (no treatment).
2. Sage water extract (given instead of drinking water) according to Lima et al. (2005).
3. Sage ethanolic extract (given orally by stomach tube as 0.1 ml/kg BW) (Akhondzadeh et al., 2003).
4. Sage oil group (given orally by stomach tube as 100 μl/kg BW) every other day (Perry et al., 2002).
5. Aluminum (Al) group (mixed with diet as 100mg AlCl3/ kg BW) (Bilkei, 1993).
6. Al + sage water extract group (given as in groups 2&5, respectively).
7. Al + sage ethanolic extract group (given as in groups 3&5, respectively).
8. Al + sage oil group (given as in groups 4&6, respectively).

**Sample preparation:**

At the end of the experimental period, overnight-fasted animals were decapitated. The brain was then gently removed; the cerebral cortex and hippocampus were separated on an ice-chilled glass plate as described elsewhere (Nayak and Chatterjee, 2001a). The tissue samples were quickly frozen on dry ice, weighed, and stored at -80°C until biochemical assay. Cortex and hippocampus were chosen for the present study because aluminum affects more severely the cortex and hippocampus regions than any other area of the central nervous system (Uran et al., 1997) also, these brain regions are known to be particularly susceptible in Alzheimer’s disease, and have an important role in learning and memory functions (Bihaqi et al., 2009).

**Biochemical analysis:**

Free amino acids and monoamines neurotransmitters were detected by HPLC using the precolumn PTC derivatization technique according to the methods of Heinrikson and Meredith (1984) and Pagel et al. (2000), respectively. Briefly, the samples were weighed and homogenized in 1/16 weight/volume of 75% aqueous HPLC grade methanol. The homogenate was spun at 4000 r.p.m. for 10 min and the supernatant was divided into two halves; the first was dried using vacuum (70 millipore) at room temperature for amino acids determination, whereas the second half was used for monoamines determination.

**Statistical Analysis:**

Data were presented as means ± standard error (SE). The statistical analysis was performed with one-way analysis of variance (ANOVA) using SPSS (version 17) software package for Windows followed by Dunken test. A p-value of less than 0.05 was considered statistically significant (Snedecor and Cochran, 1982).

**RESULTS:**

**Cortex and Hippocampus Neurotransmitters Content:**

As observed in tables 1a&b, the estimated amino acids neurotransmitters contents of cortex and hippocampus (glutamic acid, glutamine, aspartic acid, serine, glycine, taurine and histidine) were significantly increased in Al intoxicated rats while asparagine and gamma-aminobutyric acid (GABA) showed significant decreases compared to those of normal control rats.

Concerning rats treated with sage only, hippocampus glutamic acid and glutamine contents of animals administered sage oil and ethanolic extract, as well as histidine content of rats treated with sage oil group were significantly decreased respectively compared to those of normal rats.

Comparing to Al intoxicated group, the levels of cortex glutamic acid, glutamine, aspartic acid, taurine and histidine contents were significantly reduced in the groups administered all sage forms with Al except cortex serine and glycine contents of Al + sage water extract group which decreased insignificantly in comparison with Al intoxicated in group. In contrast, coadministration of sage different forms significantly revised the decline in cortex and hippocampus GABA and asparagine contents to significant increases except cortex asparagine of Al + sage water extract group which exhibited an insignificant increase indicating very little modulating effect.

On the other hand, except cortex glutamine which exhibited significant increase, there were marked improvement in all amino acid neurotransmitters contents of cortex and hippocampus of the groups administered sage in concomitant with Al specially in Al + sage oil group compared to that of normal control where insignificant changes were recorded in cortex and hippocampus glutamic acid and glycine, cortex taurine and histidine of Al + sage oil groups as well as in hippocampus glutamine and in cortex and hippocampus aspartic acid, and cortex serine, hippocampus taurine and histidine of Al + sage ethanolic extract and Al + sage oil groups. These results referring to complete return to the normal levels and were more pronounced in
case of sage oil followed by sage ethanolic extract with very little effect of sage waterextract. Concerning asparagine, marked improvement was seen in Al + sage ethanolic extract and Al + sage oil groups, where insignificant decreases were found comparing to that of the control group, while in Al + sage water extract group a significant reduction was still, presented in both cortex and hippocampus regions. In addition, significant decreases in cortex and hippocampus GABA contents were, still, observed in Al + sage water extract and Al + sage ethanolic extract groups but Al + sage oil group exhibited insignificant decrease compared to the level of the normal control rats.

Table 1a. Cortex and Hippocampus (Hip) Free Amino Acid Neurotransmitter Contents (μ mol/g fresh tissue) in Different Animal Groups

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Group</th>
<th>Cortex</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td></td>
<td>Sage water extract</td>
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<tr>
<td></td>
<td>Sage ethanolic extract</td>
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<tr>
<td></td>
<td>Sage oil</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Aluminum (Al)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Al + Sage water extract</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Al + Sage ethanolic extract</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Al + Sage oil</td>
<td></td>
<td></td>
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<tr>
<td>Glutamic acid</td>
<td>Control</td>
<td>8.36</td>
<td>±0.14</td>
</tr>
<tr>
<td></td>
<td>Sage water extract</td>
<td>9.24</td>
<td>±0.13</td>
</tr>
<tr>
<td></td>
<td>Sage ethanolic extract</td>
<td>9.21</td>
<td>±0.09</td>
</tr>
<tr>
<td></td>
<td>Sage oil</td>
<td>8.85</td>
<td>±0.14</td>
</tr>
<tr>
<td></td>
<td>Aluminum (Al)</td>
<td>15.18</td>
<td>±0.22</td>
</tr>
<tr>
<td></td>
<td>Al + Sage water extract</td>
<td>12.35</td>
<td>±0.13</td>
</tr>
<tr>
<td></td>
<td>Al + Sage ethanolic extract</td>
<td></td>
<td>±0.07</td>
</tr>
<tr>
<td></td>
<td>Al + Sage oil</td>
<td>11.18</td>
<td>±0.16</td>
</tr>
</tbody>
</table>

Values were expressed as means ±S.E of six animals. P<0.05 (significant)

Table 1b. Cortex and Hippocampus (Hip) Free Amino Acid neurotransmitter Contents (μ mol/g fresh tissue) in Different Animal Groups

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Group</th>
<th>Cortex</th>
<th>Hippocampus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Mean</td>
<td>SD</td>
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<tr>
<td></td>
<td>Sage water extract</td>
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<tr>
<td></td>
<td>Sage ethanolic extract</td>
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<td></td>
<td>Sage oil</td>
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<tr>
<td></td>
<td>Aluminum (Al)</td>
<td></td>
<td></td>
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<td></td>
<td>Al + Sage water extract</td>
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<tr>
<td></td>
<td>Al + Sage ethanolic extract</td>
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<td></td>
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<tr>
<td></td>
<td>Al + Sage oil</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamine</td>
<td>Control</td>
<td>2.05</td>
<td>±0.03</td>
</tr>
<tr>
<td></td>
<td>Sage water extract</td>
<td>1.98</td>
<td>±0.02</td>
</tr>
<tr>
<td></td>
<td>Sage ethanolic extract</td>
<td>1.94</td>
<td>±0.01</td>
</tr>
<tr>
<td></td>
<td>Sage oil</td>
<td>2.06</td>
<td>±0.02</td>
</tr>
<tr>
<td></td>
<td>Aluminum (Al)</td>
<td>3.64</td>
<td>±0.06</td>
</tr>
<tr>
<td></td>
<td>Al + Sage water extract</td>
<td>3.41</td>
<td>±0.02</td>
</tr>
<tr>
<td></td>
<td>Al + Sage ethanolic extract</td>
<td></td>
<td>±0.06</td>
</tr>
<tr>
<td></td>
<td>Al + Sage oil</td>
<td>2.18</td>
<td>±0.06</td>
</tr>
</tbody>
</table>

Values were expressed as means ±S.E of six animals. P<0.05 (significant)

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Administration of sage different forms, to Al intoxicated animals exhibited a complete recovery (non-significant changes) in cortex and hippocampus serotonin contents, compared to the normal control animals except in case of cortex of Al + sage water extract. Concerning cortex dopamine content of Al + sage water extract and Al + sage ethanolic groups still exhibited significant decreases, but (Al + sage oil) showed a complete recovery (non-significant decrease) compared to the normal control levels. On the other hand, hippocampus dopamine content was significantly decreased in Al + sage water extract and Al + sage oil groups, while it was non-significantly decreased in case of Al + sage ethanolic group. Cortex and hippocampus noradrenalin contents were, still, higher significantly in all groups of Al treated with sage different forms except cortex of Al + sage oil group which exhibited non-significant elevation compared to the normal control animals.

### DISCUSSION:

The results of the present study demonstrated that the exposure to Al produced a significant increase in glutamic acid, glutamine, aspartic acid, serine, glycine, taurine and histidine contents of the cerebral cortex and hippocampus accompanied with a decrease in GABA and asparagine contents in comparison with the control group. Such results indicate an obvious elevation in the excitatory amino acids and the inhibitoryamino acid taurine; a result which coincides with the findings of Struys-Ponsar et al. (2000) and Fattoretti et al. (2004). However, the elevated glutamate and glutamine levels are, also in agreement with the results obtained by Zielke et al. (1993), Bondy et al. (1998), and Matyia (2000); the formers claimed this increase to Al induced increase in glutamine-synthetase activity through increasing its mRNA and decreased glutaminase activity. Additionally, one of the contributory factors for the increase in glutamate level may be Al induced inhibition of glutamate transport by the synaptic vesicles (Wong et al., 1981) or inhibition of its release (Provan and Yokel, 1992). The complexity of compartmentation of glutamate metabolism within nerve terminals is not fully understood. Yet, it is plausible to assume that the reported inhibition by Al of glutamate dehydrogenase (Zatta et al., 2000) and aspartate transaminase could cause the compromise of the synaptic function. However, high glutamate triggers neuronal death (excitotoxicity). Excitotoxicity is associated with acute and chronic neurodegenerative diseases (Tanaka, 2005). Also, Al forms stable complexes with aspartic and glutamic acids, which cross the blood brain barrier, and deposite in the brain...
Aluminum accumulation in brain can alter neuronal signal transduction pathways associated with glutamate receptors, possibly through impairment of the glutamate pathway in brain (Canales et al., 2001) and interact with glutamate metabolism in astrocytes (Struys-Ponsar et al., 2000). Astrocytes, actively take up excitatory neurotransmitters terminating their transmitter action in the synaptic cleft and thereby protecting neurons from excitatory amino-acid-induced damage.

Alternatively, the responsibility of Al in raising the CNS cell load of oxidative stress and glutamate, may contribute, as aggregating factors, to the development of the neurodegenerative events described previously by Nayak and Chatterjee (2001 b) who showed Al induced alterations in the enzymes of the glutamate-GABA system. This effect counteracts one of the mechanisms of Al neurotoxicity. On the other hand, glutamate receptors are putative sites of action in Al neurotoxicity (Platt et al., 1994). Oxidative stress resulted from Al exposure elevates CNS glutamate levels by stimulating the activity of N-methyl-D-aspartate (NMDA) receptors and the prooxidant effects of Al alters the physical properties of membrane interfering with the functioning of voltage-activated ion channels and alters the secretion of neurotransmitters (Donald et al., 1989). As an interrelationship between glutamate and oxidative stress the elevated glutamate release can lower intracellular GSH levels (Kowluru et al., 2001). GSH depletion has been found to occur during apoptosis-mediated glutamate neurotoxicity (Almeida et al., 1998).

Regarding asparagine (the metabolite of aspartic acid), it apparently does not act as a neurotransmitter, but it can contribute to the biosynthesis of the excitatory neurotransmitter aspartate. The decrease in asparagine, herein, may explain the elevations of other excitatory neurotransmitters, especially aspartic acid and glutamine. Asparagine is also critically involved in protein synthesis (McGilvery and Goldstein, 1983) and posttranslational modification of proteins to form glycoproteins, and it is through this Nglycosylation that asparagine residues are involved in functional control of neural cell adhesion molecules (Milev et al., 1995).

Regarding serine, glycine and histidine, the mammalian brain contains high levels of serine. Surprisingly high concentrations of D-serine in astroglial cells contribute to cerebellar development and neuronal survival (Mitoma et al., 1998). Serine is metabolized in the body to glycine (Yudkoff, 1999). It has been found that two amino acids; glycine and aspartic acid, competitively inhibit serine formation, as do the aspartic acid metabolites, asparagines and oxaloacetic acid (Tsai et al., 1998). High levels of serine are associated with seizures and Huntington’s disease (Bonilla et al., 1988). Glycine is a neurotransmitter only in vertebrate animals. The glycine receptor is primarily found in the ventral spinal cord (Snell and Fell, 1990). For histidine, it is an essential amino acid, which is the precursor of histamine. This amine has an important role in brain functions, such as drinking and feeding behavior, self-stimulating, motor activity, analgesia, sleep, and neuroendocrine regulation (Green, 1987). It is considered as another precursor of glutamate, thus its rise contribute to its elevation.

Respecting inhibitory neurotransmitters, Al induced reduction in cerebral cortex and hippocampus GABA contents, observed herein, is similar to that described by Trombley (1998) who demonstrated that Al selectively causes decreases GABAergic neuron function leading to widespread changes in inhibitory circuits that contribute to neuropathology (Nayak and Chatterjee, 2003).

The significant decrease in GABA level may be attributed to its increased catabolism through enzymatic activity. Also, selective loss of cholinergic, and GABAergic neurons were demonstrated in response to exposure to Al (Goncalves and Silva, 2007).

Generally, disturbance in amino acids neurotransmitters could be attributed to direct or indirect effect of Al on protein metabolism and interaction with GABA biosynthesis and degradation through a series of reactions known as GABA shunt. It is well known that both GABA and glutamate may share some common routes of metabolism involving astrocyte where they are taken up and converted to glutamine, which is then transported back into the presynaptic vesicles. In the excitatory nerve it is converted to glutamate while in the inhibitory nerve converted to GABA with glutamate as intermediate (Struys-Ponsar et al., 2000).

Regarding taurine, another less potent inhibitory amino acid, is found in brain tissue more than anywhere else in the body. Taurine binds to GABA receptor, thereby stimulating that receptor, increasing GABA-like activity (Pearl et al., 2005). It has antioxidant properties and serves as a nerve cell membrane stabilizer, preventing excessive or erratic electrical activity in the brain. Therefore, the elevated level of taurine, may occur as a compensatory mechanism for the excessive consumption of the antioxidant system by Al intoxication. Thus, taurine could maintain the structural integrity of the membrane and regulate calcium binding and transport. Extracellular taurine inhibits glutamate-induced Ca2+ accumulation (prevent Ca2+ influx with no effect on efflux) (Zhang et al., 2010) thus protects the neurons from apoptosis. On the other side, sage
preparations (water, ethanolic extract and oil), in the present study, modulated to large extent the disturbances occurred in the amino acids neurotransmitters owing to Al intoxication. Such results are in harmony with the findings showing that sage extracts enhanced the receptor sensitivity for endogenous GABA, which is the wanted effect in the treatment of epilepsy (Salah and Jager, 2005) and enhance neurotransmitters functions (Perry et al., 2003; Eidi et al., 2006). The water extract showed little effect, whereas the ethanolic extract showed more activity and oil was the most effective in the present study.

Flavonoids, in sage, are known to bind to the GABAA-benzodiazepine site (Kahnberg et al., 2002). However, Salvia species are widely used for their anxiolytic and sedative properties via diverse number of constituents e.g., caffeic esters, cinnamic acid, citric acid, l-carnosic acid, miltirone, linalool, as well as monoterpenoids and terpineol which act as CNS depressants at GABA chloride channel and/or at glutamate binding sites (Buchbauer et al., 1993; Maklad et al., 1999; Brum et al., 2001) Further, the constituent, linalool has been shown to competitively antagonize glutamate binding to receptors (Brum et al., 2001). The decrease in glutamate could, in turn, be related to the increases in GABA or asparagine observed following sage administration where glutamine is an important GABA precursor (Peng et al., 1993) and contributes to the biosynthesis of asparagine. Thus all forms of sage showed beneficial effects and have modulating actions on neurotransmitters metabolism, specially the oil.

The data of the present study, showed a significant decrease in serotonin, dopamine in contrast to significant elevated levels of noradrenaline in both the cortex and hippocampus due to exposure of rats to Al. Similar observations were also reported by Ravi et al. (2000) and Kumar (2002) who showed region specific variations in the levels of serotonin with the lowest being in cortex.

Decreased release of serotonin suggested deactivation of the serotoninergic system. In fact, treatment of depression targets the serotonin reuptake transporter (SERT). By inhibiting SERT, serotonin is allowed to act for a longer time in the synapse, which is the wanted effect in treatment of depression (Salah and Jager, 2005). Alternatively, Al has been suggested to exert an inhibitory effect on 5-HT system due to the withdrawal of cholinergic input resulting in decreased levels of 5-HT in different regions (Kumar, 2002). Another important outcome of the presence of Al at the synapse could be the reduction of effective concentrations of neurotransmitters with biological activity, due to its binding to neurotransmitter molecules. It is plausible that Al may interfere with catecholaminergic, 5-hydroxytryptaminergic and glutamatergic neurotransmissions. However, the primary function of serotonin neurons is to facilitate gross motor output in toxic modes. Serotonin system acts to inhibit sensory information processing and to co-ordinate autonomic and neuroendocrine functions within the demand of ongoing motor outputs (Bhalla et al., 2010). Neurons, particularly those of the serotonergic group within the upper brain stem, have an important role in the neurofibrillary tangles in Alzheimer’s disease. Thus, increased brain Al levels have been related to impaired visuomotor coordination, poor long-term memory and intellectual impairment (Bowdler et al., 1979) suggesting neurochemical imbalance.

Regarding, Al inhibition of dopamine, seen herein may be explained partly by the effect of Al on the sensitivity status of 5-HT2C receptors in rats. The reactivity of 5-HT2C receptor may be a compensation for damage to the central dopaminergic system reflecting on the dopamine level (Brus et al., 1997). Also, the potential implications of Al in the etiopathogenesis of neurological disorders were attributed, at least in part, to the inhibitory effect of Al on the activity of dopamine-beta-hydroxylase (Milanese et al., 2001). Interestingly, he suppression of dopaminergic transmission in CNS might play an important role in Al- induced neurotoxicity (Zheng and Liang, 1998). However, inhibition of dihydropteridine reductase activity causes phenylalanine accumulation, which in turn, produces seizures, progressive cerebral and basal ganglia dysfunction resulting in rigidity, chorea, spasms and muscle hypotonia. Moreover, Al can interact with the catalytic center of tyrosine hydroxylase. Also, Al forms stable complexes with catecholamines and 5-hydroxytryptamine (Goncalves and Silva, 2007). Serotonin and dopamine are closely related neurotransmitter in the central nervous system proving that an increased extracellular level of serotonin in the striatum led to an increased dopamine level and vice versa (Yadid et al., 1994).

Concerning the elevation in cerebral noradrenaline (NE) shown in rats exposed to Al, in the present study, it may be a consequence to the stress, caused by the metal, causing the activation of its synthetic pathway, particularly the step which involves the conversion of dopamine to NE via hydroxylation (George and Siegel, 1999) and explain the decreased level of dopamine. Also, the disturbed protein metabolism and enzymes responsible for noradrenaline degradation and the amine release or uptake may be other reasons for the elevated NE levels in Al intoxicated rats. Generally, during stressful conditions, changes in monoamines are well associated with transient behavioral
aberrations in memory, learning and other mood disorders (Yadid et al., 1994). Actually, imbalance in brain biotoperins may cause a deficit of various neurotransmitters, including serotonin, dopamine and noradrenalin.

On the other side, sage coadministration to Al exposed animals, in the present study, was able to replenish the decreased levels of serotonin and dopamine and reduced the elevated noradrenalin in both the cerebral cortex and hippocampus regions. It was suggested that sage administration improved the neurotransmission by modulating the neurotransmitter metabolic enzymes pathways transport, secretion and uptake (Savelev et al., 2003; Coleta et al., 2008). Such effects may be achieved by sage constituents of potent antioxidative and antiinflammatory properties. The most effective antioxidant constituents were a diverse group of polyphenols (rosmarinic acid being the most representative) (Havsteen, 2002) that possess several modulatory effects. Thus, sage could ameliorate AI-induced imbalance in the brain neurotransmitters by its ability to counteracting the Al–induced oxidative and toxic assault, probably by quenching the free radicals, thereby protecting neurons from damage.

CONCLUSION:
The present study validates that chronic exposure to Al causes severe perturbation in the brain neurotransmitters and consequently neurotransmission that coupled to cognitive dysfunction as learning, memory and related behaviour. The results also revealed that sage curtailed or even greatly ameliorated most of Al-induced neurotransmission perturbations and highlighted the importance of sage antioxidant properties in counteracting aluminum damaging effect on the neural aspects. No fixed pattern of protection was seen specific for the different preparations of sage, so, we can’t recommend certain form.

The overall beneficial effects of sage different preparations against Al disturbances may be attributed, mainly, to their high ability to scavenger ROS and augment the repair of the antioxidant system, thus it has been suggested that sage has shown promise in the treatment of many neurodegenerative diseases including Alzheimer’s disease. Further molecular studies to elucidate the mechanisms underlying the protective effects of sage and its active components are needed.

REFERENCES:


النواقل العصبية المنبعثة قد أظهر أختها وهو التأثير ازداد في كل من قشرة المخ وانتشار في الجهاز العصبي المخيف. أما عن النواقل إزاحة الأمين فقد أظهر السيروتونين والدوبامين نفسي محظوة مما زاد النواوراداتينن ارتفاعاً محظياً. كما اشارت النتائج إلى أن مستخلصات نبات الميرامية بصورة مختلفة يمكن أن يكون لها دور فعالاً في تقليل الجلادات في مستوى النواقل العصبية المذكورة والتي نتجت عن التعرض للألومنيوم وما يعكس عن حي في الظروف والسلوكية المرتبطة بها وقد يعزى ذلك الى تأثيراتها المقاومة للنكس والمحبة للجهاز المضاد للأكسدة.

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صمم هذا البحث لمعرفة مخاطر العرض للألومنيوم على النواقل العصبية بمجرد الجردون وكذلك لتوضيح دورنظام صورن عصب الميرامية (المستخلص الفعال والمستخلص الكحول و الزيت) في تقليل اختلالات النواقل العصبية الناتجة عن ذلك. استخدم في هذه الدراسة ذكور الجردان البالغة حيث قسمت إلى ثمانية مجموعات ضم كل منها ستة جردان وكانت المجموعات كما يلي: المجموعة المبتعدة الفر معاملة بألومينيوم ثلاثة مجموعات عولجت كل منها واحد صور الميرامية بالإضافة لثلاث مجموعات أخرى تعرضت للألومنيوم وعولمت بحص صور الميرامية وقد استمرت المعاملة لمدة تسعون يوماً سنين أيام أسبوعية عدا ربت الميرامية الذي أعطي يوماً بعد يوم نفس المدة. أظهرت نتائج هذا البحث زيادة معنوية في جميع النواقل العصبية المفردة وهي (حمض الجلوتاميك والجلوتامين حمض السترات والسيروتين:الجليسين والهسبتين) في القشرة والحصين على الإسبارجين وكان ذلك في المجموعة التي تعرضت للألومنيوم لمدة تسعون يوما. وفقاً للثاني الآخر فإن...