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Astaxanthin as Potential Antioxidant Agent Protects from Accumulation of Heavy-metals in Brain

Mohammed Said Moosa Al-Bulish [1,2], Changhu Xue [1], Mostafa I. Waly [2], Jie Xu [1], Yuming Wang [1], Qing-Juan Tang [1]

1 College of Food Science and Engineering, Ocean University of China, Qingdao City, Shandong Province, P.R.China

2 Food Science and Nutrition Department, College of Agricultural and Marine Sciences, Sultan Qaboos University, Oman.

Abstract: Humans are increasingly exposed to heavy-metals from food, water, medicine, vaccines, and cosmetics. The toxicity of heavy-metals in humans is briefly summarized, links the possible causal relationships between a high heavy-metals body burden and a number of neurological disorders including Alzheimer's, Parkinson and Autism disorders. This study aimed to assess the antioxidant properties of Astaxanthin (ASTA) to determine the effect of orally administered ASTA capability of restrict accumulation and toxicity of heavy-metals in brain of rats. It also, assess against Hydrogen peroxide induced oxidative stress and antioxidant potential properties of ASTA with comparing the affectivity of 5% and 10% of ASTA in increased glutathione-recycling enzymes (GPx oxidation). A significant change was observed as increased glutathione-recycling enzymes (GPx oxidation) of rats and showed a protective effect against accumulation of Aluminum(AL) in rat's brain tissues. The results of this in-vivo study demonstrated that ASTA 10% is more can affective in restriction of accumulation and toxicity of Al in rate brain and its contented can protects against oxidative-stress.

Keywords: Heavy-metal, Astaxanthin, toxicity, brain, antioxidant.

1. Introduction:

Long-term dialysis using fluids containing aluminum has been associated with encephalopathy (Alfrey et al., 1976)1, osteomalacia, Parkinson's disease and anemia (Elliott et al., 1978)2, due to aluminum toxicity. Dialysis dementia is characterized by speech disorders, myoclonus, coma and possibly death (McMillan et al., 1993)3. In experimental models of aluminum toxicity, encephalopathy, nerve cell degeneration, demyelination of the brain stem cells and impaired motor co-ordination are observed (Perl Dp et al, 1980)4. Cerebral accumulation of aluminum has also been reported in several other neuro-pathological disorders including Alzheimer's disease (Blaurock et al 2011)5, Down's syndrome (Crapper et al., 1973)6, amyotrophic lateral sclerosis (Gadjusek and Salazer, 1982)7; and the dementia of Parkinson's disease (Hirsch et al., 1991)8. Toxic levels of heavy-metals and low levels of essential minerals have been suggested to play a critical role in the pathogenesis of autism spectrum disorders (ASD). Few studies have explored the levels of heavy metals and essential minerals among children diagnosed with ASD in Arabian

Gulf countries (Al-Aayadhi et al 2005)9, Preliminary surveys have suggested that this region has a significant number of children with ASD; the rate has been shown to range from 29/10,000 in the United Arab Emirates (Eapen et al, 2007)10, to 1.4/10,000 in Oman (Al-Farsi et al 2011)11. The role of aluminum in these disorders is less clear, however high concentrations of aluminum are found in certain regions of the brains of patients with Alzheimer's disease (Crapper et al., 1976)12.

There is also an epidemiological association between aluminum in drinking water and the incidence of Alzheimer's disease (Martin et al., 1986)13. Histological analysis has also revealed high concentration of aluminum in the nuclei of neurons associated with neurofibrillary tangle in Alzheimer's disease, and senile plaques (Candy et al.,1986)14. Despite the ample clinical and experimental data, the mechanisms of aluminum toxicity remain largely unknown. *In vitro* and *in vivo* experimental studies have implicated the formation of reactive oxygen species in the potential neurotoxic effect of aluminum, particularly in Alzheimer's disease (Halliwell, 1992)15; (Evans, 1993)16 and (Zaman et al 1994)17 they showed that Al stimulates NADPH oxidation and takes part in the process of free radical formation. Experimental animal models and cell culture studies reveal that aluminum affects the expression of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase and glutathione (GSH) possibly leading to membrane fragility as a consequence (Julka and Gill, 1996)18; (Campbell et al., 1999)19.

Food, drinking water, air and medicines are considered to be sources of the aluminum load for humans. With the utilization of aluminum growing and bioavailability is increasing continuously. In 1950 this dietary aluminum load was thought to be approximately 1 mg per day, it is estimated to be 100 mg in 2050 (Exley et al 2013)20. Aluminum is excreted primarily via faces and urine, with skin, hair, nails, sebum, semen, and sweat also having been described as excretion routes (Exley et al 2013)20. Neurodegenerative effects due to increased concentrations of aluminum have been demonstrated in senile plaques in the brains of Alzheimer patients.

The property of aluminum to produce amyloid-beta and cause damage to neurons, as well as epidemiologic connections, have been indicative of a relationship between aluminum and Alzheimer's disease for decades. Current reviews cite respective, but sometimes contradictory, studies (Ohyagi et al 2013)21, to summarize the current state of knowledge (Bondy et al2014)22. Lipid oxidation, resulting from free radical–initiated reactions, is linked to the occurrence of degenerative pathological conditions in humans and other animals (Halliwell and Gutteridge 1989)23.

There by impacting on speed of signal transduction and effectiveness of neurotransmission (Cunnane et al., 2009)24. Consequently, neuronal membrane becomes more sensitive to oxidative injury if not properly counterbalanced by antioxidant defenses that sustain the optimal dose– response hermetic ratio (Calabrese et al., 2010)25. These data support the role of oxidative stress in aluminum induced cellular dysfunction and if this is indeed the case, antioxidants, such as astaxanthin, may be protective. The aim of the present study was to investigate the effect of administering high doses of aluminum on indices of

oxidative stress in the rat and their modulation by dietary astaxanthin and to demonstrate that it can restrict accumulation according to their effects as protects against oxidative stress.

2. MATERIALS AND METHODS

Chemicals and supplies:

All chemicals and supplies, unless otherwise specified, were purchased from Sigma Chemical Co (St Louis, MI, USA) and Changsha Huakang biotechnology development CO., LTD (HUNAN, CHINA).

Animals:

54 Male Sprague–Dawley rats, aged 3 months were used in this experiment. The rats were housed in individual polypropylene cages and were provided with standard laboratory chow diet (Oman Mills, Muscat, Oman) and normal tap water ad-libitum. Rats were kept under standard conditions (i.e. temperature 22 ± 2°C, relative humidity 60%) and a 12-hour light: dark cycle. The protocol used in this study was approved by the Animal Ethics committee at the Sultan Qaboos University and was conducted in accordance with international laws and policies (McPherson et al 1980)26. It has been divided in to two divisions. 24 rats in first division were randomly divided to 3 groups (n=8 rats/group) G1: untreated control rats and G2 group treated with astaxanthin 5%. The G3 group treated with astaxanthin 10%.

The 2nd division 30 rats were randomly divided in to 3 groups (n=10 rats/group) G1: control (C) group rats. G2: control group that received oral feeding $AlCl_3$ of 2 ml extract/kg BW 2 day in a week. G3: rats treated with $ALCL_3$+ ASTA 10% oral dose of 2 ml extract/kg BW two days a week.

Animals sacrifice and samples collection:

At the end of the 12 weeks' treatment, after an overnight fasting animals were anesthetized with a lethal dose of a cocktail containing ketamine (1 mg), xylazine (5 mg), and acepromazine (0.2 mg). For the 1st division the whole pancreas tissue from each rat was removed and used for: (I) Homogenization (~50 mg in 5 ml of 100 mm potassium phosphate buffer, pH 7.2) by a Glass-Teflon Homogenizer with an ice-cold jacket and centrifuged at a speed of 4,000 g for 20 minutes at 4°C. The resulting supernatant was used for biochemical antioxidant markers and protein content measurements.

The 2nd division sacrificed by decapitation under diethyl ether anesthesia and the brain was immediately homogenized in 5 mL of 100 mm potassium phosphate buffer (pH 7.2) with a Glass-Teflon homogenizer with an ice-cold jacket and centrifuged at 10,000 g at 4°C for 60 minutes. The resulting supernatant was used for biochemical measurements.

Biochemical measurements:

Protein content:

Protein content of pancreas tissue homogenates was assayed by the method of Lowry *et al.*, (1951) using bovine serum albumin as standard and protein content was expressed as mg/ml of sample.

Oxidative stress biomarkers assays:

The biochemical parameters (Glutathione peroxidase (GPx) were measured according to the manufacturer's instructions (Bio Vision Incorporated, Milpitas, CA USA) parameters were assayed in 96 wells plates and measured using Biochrom EZ Read 400 Micro plate Reader (Biochrom Ltd, England).

Heavy metal measurement in rat brain:

The Heavy metal concentrations ($\mu g\ g^{-1}$) of brain samples were determined using an Inductively coupled Plasma-Atomic Emission Spectroscopy ICP-AES) method. One gm of each sample was digested by analytical grades of 36% HNO_3 (50mL) and 30% H_2O_2 (50mL) at a temperature of 120°C for 2 h. Then the samples were cooled and filtered through Whatman Glass fiber filters 110mm in diameter. The standard solution of 1000 mg L^{-1} Plasma/free stock was used to calibrate the analysis. The intermediate and working standards were prepared by serial dilution immediately before use.

Statistical Analysis:

Statistical analysis was performed using GraphPad Prism (version 5.03; GraphPad Software Inc., San Diego, CA, USA). The results are expressed as Means ± Standard Error of Means (SEM). Comparisons of groups were performed using one-way analysis of variance, followed by Tukey's test. The Student's unpaired t-test was used for pair wise comparisons. The values at the level of $p<0.05$ were considered to be significantly different.

3. RESULTS:

The findings of this study revealed that oral administration of Astaxanthin has protective effect against the oxidative stress and it improves the antioxidant defense in the brain as it showed by marked increase in Al concentration in rat brain tissues and with treatment of rats Astaxanthin decreased the observed Al cellular insult and restricted AL accumulation in the brain. Moreover, the results are presented essential minerals concentration in rat brain tissues, as its shows improvement in the treated case rat with astaxanthin as will in pancreatic tissue as evidenced that 10% of astaxanthin has the significant increase in GSH comparing to 5%.

Oxidative status and the antioxidant potential of ASTA in Pancreatic tissues:

Administration of ASTA caused replenishment for the depleted glutathione in the group. By contrast, oxidative stress indices (glutathione peroxidase) were significantly increased in the treated group G2 and G3 compared to control group. Glutathione peroxidase is an important enzyme in cellular antioxidant defense systems, detoxifying peroxides and hydroperoxides. As a component of the glutathione cycle, it protects the liver from reactive oxygen metabolites.

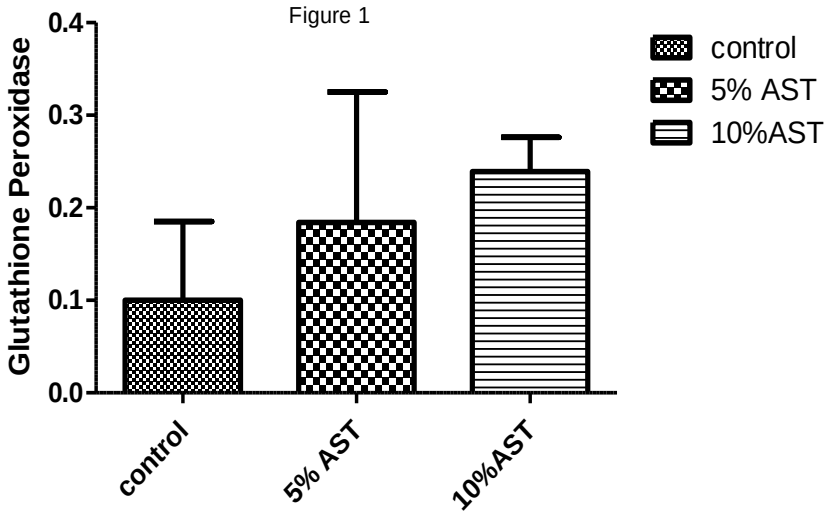

Figure 1: Oxidative status of 5% AST and 10%AST and the antioxidant potential of astaxanthin in Pancreatic, Glutathione peroxidase. *P*-value of less than 0.05 is considered significant.

The antioxidant potential properties from (figure1) of astaxanthin in pancreatic tissues of the rats showed significant results in concentration compering the 5% and 10% in treated group when compared also to non- treated group. Results showed that treated groups with ASTA 5% have significantly lowered glutathione peroxidase as compared to 10% treated rats. Oxidative stress plays a significant role in the pathogenesis and the complications of many diseases, and GSH as an intracellular antioxidant is crucial for the detoxification of ROS and lipid hydro-peroxides (Brenna et al, 2007)26. The observed depletion of GSH content in the tissues of rats and its normalization with Astaxanthin suggested its potent antioxidant properties and we hypothesized that ASTA as a functional food supplement decreases oxidative stress *in-vivo* due to both of improved antioxidant activities and decreased peroxidation processes. Another mechanism that was suggested is that ASTA via its antioxidant properties prevents the death of β pancreatic cells, allowing healing of partially destroyed cells as an oxidizing agent mellitus (Haghani et al, 2016) 27.

Comparison of levels of heavy metals and essential minerals in brain samples of cases with Astaxanthin and controls (Table 1):

This study examined and compared the levels of essential minerals and heavy metals among rat treated with Astaxanthin and those without. Biochemical analysis of heavy metal levels in brain revealed statistically significant differences for each of the metals analyzed ($p<0.001$), When compared to controls, rat had significantly higher levels of several essential minerals (copper, magnesium and zinc) in their brain samples (Table1).Where in groups non- treated with Astaxanthin, there were an increase in the level of heavy-metals in brain as compared to control group but the levels were less than the groups treated with Astaxanthin to $AlCl_3$ compared to case Rats (figure 2).

Table 1: Comparison of levels of heavy metals and essential minerals in brain samples of Cases with Astaxanthin and controls:

Element	Controls	Astaxanthin and Cases	Cases
Copper	0.1736	0.16841	**0.2055**
Manganese	0.1616	0.06307 a	**0.060 b**
Zinc	13.926	11.8858 a	**7.893 b**
Cadmium	14.5942	14.9787	**8.23625 a**
Cobalt	9.1400	6.5202	-
Chromium	0.2512	0.25318	**0.25325**
Molybdenum	0.1422	0.05298	**0.0480**
Lead	0.1836	0.11804	**0.1952 b**

The results are presented of heavy metals concentration in rat brain tissues a Compared to the control group. b Compared to the ASTA+Cases group. ($p < 0.0001$).

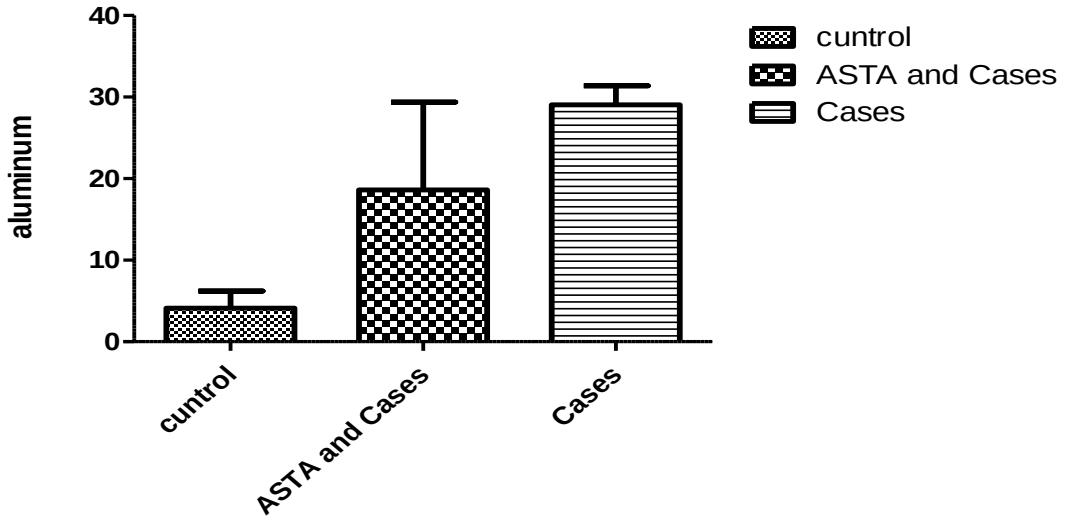

Figure 2: The results are presented as mean ± SD of aluminum concentration in rat brain tissues. Compared to the control group. ASTA+Cases group and Cases. ($P < 0.0001$).

Moreover, our results showed a significant reduction of AL levels in the brain as compared with control (figure2) and increase in same essential minerals witch will be helpful for brain. This can be explained the fact that once Aluminum (Al) is a trivalent cation, and has a high affinity for negatively charged groups it has been proposed that Al preferentially interacts with phosphate groups, such as nucleic acids and phosphorylated proteins. So, Al remarkably decreases DNA and RNA synthesis (Nicholis et all 1995)28; (Yumoto et al 2001)29 and inhibits embryonic cell proliferation and protein synthesis.

4. DISCUSSION:

Aluminum exposure enhanced the neuronal lipid perooxidative damage with concomitant alterations in the enzymatic antioxidant defense status (savory et al 2003)30 and (Johnson et al 2005)31. This having serious bearing on the functional and structural development of the central nervous system (Dua et al 2001)32. Similar data recorded a decrease in the antioxidants such as GSH (Wu et al 2003)33 in the brain of aluminum exposed rats and human (Flora et al 2003)34. Moreover, such results are consistent with the studies indicated that aluminum intake produced an oxidative stress-related change, contributed to its neurotoxicity (Gomez et al 2005)35. However, in rats a significant relationship between aluminum exposure and the presence of oxidative stress was established also (Gomez et al 2005)36. This could be caused by inflicting damage to membrane lipids, proteins and anti-oxidative enzyme defense system (Jyoti et al 2007)37. The increased aluminum concentration could deleteriously affect the neurons, leading to depletion of antioxidants and metal ions (kumar et al 2008)38. Alternatively, the decreased enzyme activities could be related to a reduced synthesis of the enzyme proteins as a result of higher intracellular concentrations of aluminum (Albendea et al 2007)39. DNA fragmentation and increase in the appearance of comets have also been reported in other studies as a consequence of aluminum exposure (Lima et al 2007)40. Aluminum is known to increase the levels of reactive oxygen species (Bondy et al 1996)41 and (Bondy et al 1998)42 which is known to cause damage to various macromolecules and also to DNA. By the results obtained in the present study we conclude that properties as significant neuron protection it decreasing level of Aluminum. It is a ubiquitous metal and has been implicated in the etiology of neurodegenerative disorders and cognitive dysfunction, where it exacerbates brain oxidative damage (Kumar et al 2009)43, causes neuronal inflammation and induces impairment in working memory, visual-perception, attention and semantic memory (Platt et al 2001)44. Aluminum also functionally alters the blood brain barrier and produces changes in the cholinergic and noradrenergic neurotransmission (yokel et al 2000)45. As oxidative damage is mediated by free radicals, it was necessary to investigate the status of endogenous antioxidant enzymes like catalase, superoxide dismutase and glutathione, which are the first line of defense against free radical damage under oxidative stress conditions. In the present study, rat's exposure to aluminum chloride increased aluminum concentrations in the brain of the rats. Increased concentrations of aluminum have also been observed in the brains of Alzheimer's disease patients who present declines in visual memory, attention concentration, frontal lobe function and vocabulary scores. The results presented here showed that Astaxanthin was able to reduced concentration of aluminum in the brain of rats. Therefore, the present study highlights that improved biochemical function in the treated rats, an effect that could be partially correlated with its anti-oxidant properties. However, further cellular studies are required to understand the effect of Astaxanthin on oxidative stress in different experimental systems.

Astaxanthin decreased the observed of AL mediated cellular insult and restricted AL accumulation in the brain moreover the essential minerals concentration in rat brain tissues its show improvement in the treated case rat with astaxanthin. ASTA supplementation can be suggested as a nutritional additive to human life, with other putative health benefits associated, especially against ROS/RNS-related and diseases (Barros et al 2011)46. The "neurohormesis" principle, supported by accurate physiological information from (preferably non-invasive) redox biomarkers may thus dictate pharmacological strategies to create specific formulations that could group all these relevant factors for the efficient treatment of neuronal diseases. Further studies are necessary to better identify the hallmarks of brain redox impairment at different stages of progressive neurodegenerative disease.

5. CONCLUSION:

This study strongly suggests beneficial effects of ASTA supplementation for immune competence, based on the redox balance in non-activated neutrophils (increased glutathione-recycling enzymes GPx) and neutrophils of rats. Moreover, ASTA better offered antioxidant. The bulk of data reinforces the hypothesis that habitual consumption of astaxanthin is strongly associated with human health, in particular with improvement of immune response, Neurotoxicity related and lower risks for vascular and infectious pathologies (Lara et al 2007)47.

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REFERENCES:

1- Alfrey AC, Le Gendre GR, Kaehny WD, (1976). The dialysis encephalopathy syndrome: possible aluminum intoxication. N. Engl.J. Med. 294: 184-187.

2- Elliott,H.L.,andA.I.McDougall.1978.Aluminum studies in dialysis encephalopathy. Proc. Eur. Dial. Transplant Assoc.15:157-163.

3- McMillan, W.H.;Hall,D.R.H.;Evans,P.H.;Day,A.M.1993.Twinningin beef cows: preliminary results from embryo transfer studies. Proceedings of the New Zealand Society of Animal Production 53: 263-266.

4- Perl DP, Brody AR. Alzheimer's disease: X-ray spectrometric evidence of aluminum accumulation in neurofibrillary tangle-bearing neurons. Science. 1980 Apr 18;208(4441):297–299.

5- Blaurock-Busch E, Amin OR, Rabah T (2011) Heavy metals and trace elements in hair and urine of a sample of Arab children with autistic spectrum disorder. Maedica (Buchar) 6 (4):247–257 381

6- Crapper DR, Krishnan SS, Dalton AJ (1973). Brain aluminum distribution in Alzheimer's disease and especially neurofibrillary degeneration. Science 180: 511-513.

7- Gadjusek CD, Salazar AM (1982). Amyotrophic Lateral Sclerosis and Parkinsonian Syndromes in high incidence among A Jape people of West New Guinea. Neurology. 32: 107-115.

8- Hirsch EC, Brandel JP, Galle P, Jvoy-Agid F, Agid Y (1991). Iron and aluminum increase in the substantial Ingra of patients with Parkinson's disease; an X-ray microanalysis. J. Neurochem. 56: 446- 451.

9- Al-Ayadhi LY (2005) Heavy metals and trace elements in hair samples of autistic children in central Saudi Arabia. Neurosis (Riyadh) 10(3):213–218.

10- Eapen V, Mabrouk AA, Zoubeidi T, Yunis F (2007) Prevalence of pervasive developmental disorders in preschool children in the UAE. J Trop Pediatric 53:202–205

11-Al-Farsi, Y.M., et al. (2011) Effect of high parity on occurrence of anemia in pregnancy: A cohort study. BMC Pregnancy and Childbirth, 11, 7-15. doi:10.1186/1471-2393-11-7

12- Crapper DR, Krishnan SS, Quittkat S (1976). Aluminium, neurofibrillary degeneration Alzheimer's disease. Brain 99(1): 67-80.

13- Martin, P.F., Martin, A., Osmania, A. (1986). A transient expression assay for tissue-specific gene expression of alcohol dehydrogenase in Drosophila. Dev. Biol. 117(): 574--580.

14- Candy JM, Klinowski J, Perry RH, et al. (1986). Aluminosilicates senile plaque formation in Alzheimer's disease. Lancet i: 354-357.

15- Halliwell B (1992). Reactive oxygen species the central nervous system. J. Neurochem. 59: 1609-1623.

16- Evans P (1993). Free radicals in brain metabolism and pathology. Br. Med. Bull. 49: 577-587.

17- Zaman GJ, Flens MJ, van Leusden MR, de Haas M, Mulder HS, Lankelma J, Pinedo HM, Scheper RJ, Baas F, Broxterman HJ, et al. (*1994*) The human multidrug resistance-associated protein MRP is a plasma membrane drug-efflux pump. *Proc Natl Acad Sci USA 91: 8822*–8826.

18 - Julka D, Gill KD, (1996). Altered calcium homeostasis: a possible Mechanism of aluminum-induced neurotoxicity. Biochem. Biophys. Acta 1315: 47-54.

19- Campbell A, Prasad KN, Bondy SC (1999). Aluminum-induced oxidative events in cell lines: glioma are more responsive than neuroblastoma. Free Radic. Biol. Med. 26(9-10): 1166-1671.

20- Exley C. Human exposure to aluminum. Environ Sci Process Impacts2013;15(10):1807–16.

21- Ohyagi Y, Miyoshi K. Aluminum and Alzheimer's disease: an update. JAlzheimers Dis Parkinsonism 2013; 3:118.

22- Bondy SC. Prolonged exposure to low levels of aluminum leads to changes associated with brain aging and neurodegeneration. Toxicology 2014;315.

23- Halliwell, B. & Gutteridge, J.M.C. (1989) Free Radicals in Biology and Medicine. Clarendon Press, Oxford, UK.

24- Cunnane SC, Plourde M, Pifferi F, Bégin M, Féart C, Barberger-Gateau P. Fish, docosahexaenoic acid and Alzheimer's disease. Prog Lipid Res 2009;48:239–56.

25- Calabrese V, Cornelius C, Dinkova-Kostova AT, Calabrese EJ, Mattson MP. Cellular stress responses, the hormesis paradigm, and vitagenes novel targets for therapeutic intervention in neurodegenerative disorders. Antitoxic Redox Signal 2010;13: 1763–811.

26- Brenna O, Qvigstad G, Brenna E, Waldum HL. Cytotoxicity of streptozotocin on neuroendocrine cells of the pancreas and the gut. Dig Dis Sci 2003; 48(5):906-910.

27 - Haghani K, Bakhtiyari S, Doost Mohammad pour J. Alterations in plasma glucose and cardiac antioxidant enzymes activity in streptozotocin-induced diabetic rats: Effects of *Trigonellafoenum-graecum*extract and swimming training. Can J Diabetes. 2016; doi: 10.1016/j. PMID: 26778682.

28- Nicholis, D.M., G.M. Spears, S. Asian and A.C.M. Miller, 1995. Brain mRNA from Infants of Aluminium-exposed Lactating Rabbits. Int. J. Biochem. Cell Biol., 27: 365-370.

29- Yumoto, S., H. Nagai and H. Matsuzaki, 2001. Aluminum incorporation into the brain of rat fetuses and suckling's. Brain Res Bull., 55: 229-234.

30- Savory J, Herman MM, Ghribi O (2003) Intracellular mechanisms underlying aluminum induced apoptosis in rabbit brain. J. Inorg. Biochem. 97: 151-154.

31- Johnson VJ, Kim SH, Sharma RP (2005) Aluminum-maltolate induces apoptosis and necrosis in neuro-2a cells: Potential role for p53. Toxically. Sci., 83: 329-339.

32- Dua R and Gill KD (2001) Aluminum phosphide exposure: Implications on rat brain lipid peroxidation and antioxidant defense system. Pharmacology Toxicol89:315–9

33 - Wu D, Cederbaum I (2003) Alcohol, Oxidative Stress, and Free Radical Damage. Alcohol Res. Health, 27: 277-284.

34- Flora SJS, Mehta A, Satsangi K, Kannan GM, Gupta M (2003) Aluminum induced oxidative stress in rat brain: response to combined administration of citric acid and HEDTA. Comp. Biochem. Physiol., Part C, 134:319–28.

35 - Gomez M, Esparza JL, Nogués MR, Giralt M, Cabré M, (2005) Proxidant activity of aluminum in the rat hippocampus: gene expression of antioxidant enzymes after melatonin administration. Free Radic. Biol. Med. 38: 104–111.

36 - Jyoti A, Sethi P, Sharma D (2007) Bacopa mon-niera prevents from aluminum neurotoxicity in the cerebral cortex of rat brain. J Ethnopharmacol 111(1):56–62

37 - Kumar P, Taha A, Sharma D, Kale RK, Baquer NZ (2008) Effect of dehydroepiandrosterone (DHEA) on monoamine oxidase activity, lipid peroxidation and lipofuscin accumulation in aging rat brain regions. Biogerontol. 4: 283–284.

38- Albendea CD, Trullen EMG, Broto LE, Miana-Mena FG, Plano SM, Gonzales MCR, Balların EM, Garcia JJ (2007) Melatonin reduces lipid and protein oxidative damage in synaptosomes due to aluminum. J. Trace Elem. Med. Biol 21:261–268

39 - Lima PDL, Leite DS, Vasconcellos MC, Cavalcanti BC, Santos RA, Costa-Lotufo LA, Pessoa C, Moraes MO, Burbano RR (2007) Genotoxic effects of aluminum chloride in cultured human lymphocytes treated in different phases of cell cycle. Food Chem Toxically 45:1154–1159

40 - Bondy SC, Kirstein S (1996) The promotion of iron-induced generation of reactive oxygen species in nerve tissue by aluminum. Mol.hem. Neuropathic 27:185–194

41 - Bondy SC, Liu D, Guo-Ross S (1998) Aluminum treatment induces nitric oxide synthase in the rat brain. Neurochem Int 33:51–54.

42 - Kumar A, Dogra S, Prakash A: Effect of carvedilol on behavioral, mitochondrial dysfunction, and oxidative damage against D-galactose induced senescence in mice.Naunyn Schmiedebergs Arch Pharmacology, 2009, 380, 431–441.

43 - Platt B, Fiddler G, Riedel G, Henderson Z: Aluminium toxicity in the rat brain: histochemical and immunocytochemical evidence. Brain Res Bull, 2001,55, 257–267.

44 - Yokel RA: The toxicology of aluminum in the brain: a review. Neurotoxicology, 2000, 21, 813–828.

45 - Barros, M.P.; Poppe, S.C.; Souza-Junior, T.P. Putative benefits of microalga astaxanthin on exercise and human health. *Braz. J. Pharm.* 2011, *21*, 283–289.

46 - J.J. Lara, M. Economic, A.M. Wallace, A. Rumley, G. Lowe, C. Slater, M. Caslake,N. Sattar, M.E. Lean, Benefits of salmon eating on traditional and novel vascular risk factors in young, non-obese healthy subjects, Atherosclerosis 193 (2007) 213–221.

الملخص : يتعرض البشر بشكل متزايد للمعادن الثقيلة من الغذاء والماء والدواء واللقاحات ومستحضرات التجميل. يتم ترسب سمية المعادن الثقيلة في البشر لفترة و التي ترتبط بعلاقات سببية محتملة بين عبء الجسم الثقيلة المعادن الثقيلة وعدد من الاضطرابات العصبية بما في ذلك مرض الزهايمر، باركنسون واضطرابات التوحد. هدفت هذه الدراسة إلى تقييم الخصائص المضادة للأكسدة لأستازانتين (أستا) لتحديد تأثير قدرة أستا التي تعطى عن طريق الفم لتقييم تراكم وسمية المعادن الثقيلة في دماغ الفئران. كما أنها تقيم ضد الإجهاد التأكسدي الناجم عن بيروكسيد الهيدروجين والخصائص المحتملة المضادة للأكسدة من أستا مع مقارنة التأثيرية من 5٪ و 10٪ من أستا في زيادة الانزيمات إعادة التدوير الجلوتاثيون (أكسدة غس). وقد لوحظ تغير كبير في زيادة الانزيمات الجلوتاثيون إعادة تدوير (غكس أكسدة) من الفئران وأظهرت تأثير وقائي ضد تراكم الألومنيوم (آل) في أنسجة المخ الفئران. وأظهرت نتائج هذه الدراسة في الجسم الحي أن أستا 10٪ يكون أكثر ارتباطا في تراكم وسمية الالمونيوم في الدماغ.