IJBPAS, November, 2023, 12(11): 4984-4997

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

MOLECULAR FACETS OF ALUMINIUM PROMPTED NEURO-DEGENERATION AND THE FUTURE OF HERBAL REMEDIES

RATNA B[1*], RAJENDRA SANDUR V[2] AND DAS K[2]

1: Krupanidhi College of Pharmacy, 12/1, Chikka Bellandur, Carmelaram, VarthurHobli, Off Sarjapur Rd, Bengaluru, Karnataka-35, India

2: Mallige College of Pharmacy, Department of Pharmacognosy and Phytochemistry, 71, Silvepura, Chikkabanavara, Post, Bengaluru, Karnataka-90, India

[*]**Corresponding Author: Ratna B: E Mail: ratnababuraj2@gmail.com**

Received 19th Sept. 2022; Revised 16th Oct. 2022; Accepted 21st Feb. 2023; Available online 1st Nov. 2023

https://doi.org/10.31032/IJBPAS/2023/12.11.7533

ABSTRACT

Neurodegenerative disorders are one of the greatest threats to humankind as they inflict on millions of people globally ensuing debility dementia and neurobehavioral derangement. Aging, oxidative stress, excitotoxicity, neuroinflammation, exposure to neurotoxicants and heavy metals etc. are some of the principal elements contributing to neurotoxicity. Antioxidants play a promising role in curbing free radical-mediated induced by oxidative stress and neurotoxins. Herbal medicines and phytocompounds being the powerhouse of antioxidants are propitious in treating neurodegeneration with added perquisites as they're nearly devoid of side effects. By embracing methods like drug discovery, combinatorial chemistry, through other modern means, these phytocompounds may be effectively developed into potential drug moieties that would aid in handling these complex diseases in a better manner. The molecular face aluminum-mediated neurotoxicity combined with a bunch of selected herbs and a few potential phytocompounds and their protective role in aluminium-mediated neurotoxicity have been mentioned in this article.

Keywords: Aluminium, Neurodegeneration, Phytocompounds, oxidative stress, neurotoxicity

INTRODUCTION

In the present world, millions of people are suffering from various neurodegenerative disorders, and are mainly prevalent in geriatric category causing debility that negatively impacts the quality of life. The main culprits behind these disorders are ageing, neurotoxicants, heavy metals and oxidative stress. Aluminium (Al) is an airborne industrial released intoxicant and is an obnoxious besotted metal present in copious amounts in the environment. The average exposure to aluminium is around 10–20 mg /day which enters the system through environmental pollutants, food, aluminium cookware, drinking water **[1]** deodorants, cosmetics medicines **[2]** OTC drugs **[3]** sewage treatments **[4]** techniques such as waterproofing clothes, industrial filtration, hemodialysis, leather industry, fire extinguishers and flame retardants, anticorrosives, certain food additives, vaccines which contains aluminum in adjuvant etc. and exerts oxidative stress-induced damage. Aluminium induces serious neurological, hematopoietic, skeletal, respiratory, immunologic system toxicity and autoimmunity **[5]**, long-term brain inflammation and associated neurological complications **[6]**. It is a mutagenic, teratogenic, carcinogenic, genotoxic agent and a pro-oxidant and induces bone disease, osteomalacia, microcytic anemia, renal failure, neurodegeneration, encephalopathy, AD, autism **[7]** etc. Aluminium weakens the antioxidant status of brain as it elevates reactive oxygen species, deranges neurotransmitter levels, and leads to neuroinflammation, neurodegeneration, protein aggregation, and accumulation and neuronal apoptosis **[8]**. It activates the inflammasome and induces the release of cytokines, interleukins and other mediators of inflammation resulting in lipid peroxidation **[9]**. In this review, a systematic examination of literature that depicts the oxidative stress inducer role of aluminum and its role in excitotoxicity and neurotoxicity, and the role of herbal plants and phytocompounds as neuroprotectants in combating aluminium-induced neuro-degeneration is being discussed. Obstacles faced while carrying out this review was due to different physical and chemical forms of aluminium being used for the studies, different routes of administration different doses and duration of exposure to aluminium opted for the studies, and the damage it caused to different organ systems which involve different processes and various mechanisms through which different herbs

and phytocompounds work in ameliorating aluminium induced toxicity.

Aluminium entering the mammalian system deposits in tissues such as the brain, bone, liver and kidney **[10]** and its elimination half-life from the human brain is around seven years. The brain is mainly susceptible to free radical-induced oxidative damage induced by aluminium due to its lipid composition, calcium and glutamate levels, auto-oxidation of neurotransmitters, and modest antioxidant defense. Aluminium is a neurotoxicant and excitotoxic and the main miscreant behind Alzheimer's disease **[11]** causing neural tube defects, and other neurodegenerative complications **[12]**. Aluminium interacts with water and generates superoxide which depletes mitochondrial Fe and promotes the generation of oxygen radicals that accounts for oxidative damage and apoptosis **[13]**. The safe amount of aluminium exposure is still a question. The tolerable weekly intake set by the European Food Safety Authority (EFSA) of 1 mg aluminum/kg body weight can be reached through dietary exposure alone whereas infants and patients with renal disorders can tolerate a very low level as there are chances for fatal systemic aluminium intoxication. The present review compiles recent studies on the role of aluminium in oxidative stress-induced damage in the living system, homeostatic alterations in the brain, the noxious effect of aluminium on the nervous system, oxidative stress, excitotoxicity and the neuroprotectant role of herbal plants in aluminium induced neurotoxicity.

SOURCE OF INFORMATION:

The information about the current article has been collected from PubMed, science direct, Medline, and various other databases including scientific traditional literature.

Aluminium and excitotoxicity:

Excitotoxicity is a complex process that results in the degeneration of dendrites causing neurodegeneration, and neuronal death resulting in conditions like Alzheimer's disease, cerebral ischemia brain trauma, Huntington's disease, and ALS. Excitotoxicity is triggered by the overactivation of glutamate receptors, resulting in Na^+ and Ca^{2+} influx across through the plasma membrane **[14]**. The rise in cytoplasmic Ca^{2+} levels in response to glutamate receptor activation can induce Ca^{2+} uptake into the mitochondria which in excess generates reactive oxygen species, oxidative stress, and inhibition of adenosine triphosphate (ATP) production. By activating proteases and oxidative stress, Ca^{2+} acts as a

key mediator of excitotoxic cell death **[15]** by activating cyclooxygenases and lipoxygenases and disrupts mitochondrial metabolism, inducing membrane lipid peroxidation which in turn renders neurons susceptible to excitotoxicity **[16]**.

Many signaling mechanisms can protect neurons against excitotoxicity such as those activated by neurotrophic factors such as brain-derived neurotrophic factor (BDNF). CREB appears to be the primary transcription factor involved in the transcriptional regulation of genes that are required for neuronal survival, and the inhibition of CREB signaling by the extra synaptic NMDAR likely contributes to excitotoxicity **[17, 18]**. Among the pro-survival genes that are upregulated by CREB, BDNF has been extensively characterized, and it is critical to NMDAR/CREB-mediated neuronal survival signaling **[19]**. Specific sub-populations of the NMDAR mediate neuronal death and neuronal survival. Extra synaptic NMDAR has been shown to inhibit CREB-mediated BDNF gene expression.

Excitotoxicity plays a vital role in the neurotoxic action of aluminum. Prolonged inflammation and excitotoxicity triggered by immune mediators like cytokine and glutamate receptors are responsible for most of the metal's toxicity **[20]**. Aluminium apro-oxidant entering the mitochondria of cells interrupts energy metabolism causing energy deficit, alters the glutaminergic pathway, interferes with calcium homeostasis, increases levels of reactive oxygen and nitrogen species and lipid peroxidation products like 4HNE, lowers the levels of SOD, catalase, GSH, impairs glutamate transporters, causes microglial activation **[21]** mitochondrial dysfunction and induce oxidative stress-induced damage in tissues and all above to contribute to excitotoxicity. The generation of superoxide triggers apoptosis of astrocytes excitotoxicity-mediated neuronal death through the generation of peroxynitrite **[22]**. The excitotoxicity component rather than inflammation is the main culprit for actual damage to neurons and their processes **[23]**.

Aluminium, inflammatory markers and homeostatic alterations in the brain:

Membrane lipids attacked by reactive nitrogen and oxygen species result in highly destructive lipid peroxidation products, 4-hydroxynonenal (4-HNE), and acrolein which intensifies the responsiveness to excitotoxicity. The nicotinic receptors which are responsible for toning down brain inflammation are inactivated by aluminium and on the other side activate cholinergic neurotransmission resulting in brain

inflammation. The microglia and astrocytes form the main components of the brain's innate immune system maintains homeostasis and secretes basal levels of neurotrophic substances to maintain connectivity and the integrity of the circuit. Any external stimuli provoke the microglia whereby it assumes a reparative or neurorestorative phenotype and as a protective mechanism, releases a number of anti-inflammatory and trophic factors for neuronal survival. It may also release pro-inflammatory cytokines, cytotoxic factors, and toxins responsible for the neuro-destructive phenotype. Neurodegenerative conditions exhibit activated microglia/microgliosis which releases glutamate and the cells exhibit disease pathology **[24**. The release of glutamate from dying astrocytes is accountable for neurotoxicity and excitotoxicity and this serves as the main pathological mechanism for neuronal damage.

Aluminum elevates the levels of pro-inflammatory cytokines and this rise in levels of TNF-alpha triggers the release of glutamate from microglia. In the immature and developing brain, immune excitotoxicity might lead to a number of neurodevelopmental conditions, such as autism spectrum disorders and seizures. In the mature, and aging brain, these mechanisms can lead to progressive neurodegeneration, as seen with Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis **[25]**. Microglia play a crucial role in defense mechanisms after trauma, injury, tumor formation, and infections in the central nervous system and can pave the way for an autoimmune inflammatory reaction in the brain. Astrocytes direct metabolic activities like potassium homeostasis, lactate supply, pH regulation neurotransmitter uptake, and turnover. Neurons reckon the metabolic coupling with astrocytes to combat oxidative stress. In the nervous system, a superlative glial–neuronal interaction is entailed in gene expression regulation at transcriptional and translational levels **[26]**. Chaotic and dysregulated microglial activation is a pivotal factor that accords to several neurodegenerative diseases.

Immunohistochemical studies indicates the expression of CD32+ (FcγIIa) in the microglial cells of the hippocampus and also near the site of injection of aluminum which depicts the phagocytic role of microglia aluminum-induced excitotoxicity in the brain.

Aluminium exposure also elevates MDA levels in both blood and brain tissue homogenates. The active tion of microglial

cells during aluminium-induced neurodegeneration is substantiated in the study using an anti-CD68 antibody as a marker for cells of the macrophage lineage. The outcome of the study reveals a shoot-up in CD68 positive cell count in high-dose NaF and $AlCl_3$ group when compared with the control group **[25]**. The induction of oxidative stress by aluminium corresponds to activation of glial astrocytic cells, microglial cells and B-cells **[27]**.

Aluminium-induced oxidative stress:

Pro-oxidant action of aluminium promotes degenerative changes in biological tissues as it attenuates the ability of iron salts to promote reactive oxygen species (ROS). Lipid peroxidation triggered by iron leads to a build-up of reactive oxygen species and super-oxides. Superoxides are neutralized by Al^{3+} resulting in AlO_2 which increases oxidative damage. Through these peroxidative changes along with a fall in antioxidant status, aluminium impairs mitochondrial bioenergetics and causes a gradual accumulation of oxidatively modified cellular proteins **[28]**. Aluminium complexes with superoxide anion forming aluminium superoxide anion, which is a more potent oxidant than superoxide anion on its own and promotes the formation of hydrogen peroxide and hydroxyl radicals that contribute to an oxidizing environment. The brain exhibits a high affinity to aluminium, but has relatively low free-radical scavenging enzymes, levels of endogenous antioxidants, and possess membranes rich in oxidant-sensitive polyunsaturated fatty acids. All the above added to a high level of oxygen metabolism makes the brain prone to free-radical-induced damage **[29, 30]**.

Aluminium alters glutamate levels at the same time exerts its toxic effects also by altering cholinergic transmission, which is ultimately reflected in neurobehavioral deficits **[31]**. Cholinergic dysfunction is the main culprit behind cognitive deficits following intracerebral aluminium intoxication. AChE causes acetylcholine inhibition and interacts with Abeta to promote the deposition of amyloid plaques in the brain. Nitric oxide involved in $AlCl_3$-induced neurotoxicity, leads to temporal and spatial spreading of damage to the selectively vulnerable brain structures with impairment of cognitive functions and cholinergic transmission **[32]**.

Aluminum-induced Neurodegenerative Disease: Protective role of herbs:

Many scientific studies confirm the neuroprotective role of various herbs such as Guduchi (*Tinospora cordifolia* (Willd). Miers) *Elettaria cardamomum*, *Centella*

asiatica, *Glycyrrhiza glabra*, *Coptis chinensis*, *Curcuma longa, Celastrus paniculatus, Allium cepa , Moringa olifera*, *Terminalia bellerica*, *Coriandrum sativum, Bacopa monnieri*, *Salvia officinalis, Gingko biloba, Withania somnifera,* and many other species, etc. Following are a few herbs and compounds that have been proven for their neuroprotective role in aluminium-induced neurotoxicity.

Cardamom oil from *Elettaria cardamomum* of family Zingiberaceae consisting of 1,8 cineole as a major constituent proved effective against *in vitro* inhibition of AChE, improved cognition, showed anti-anxiety and anti-inflammatory action in $AlCl_3$-induced neurodegeneration. It also inhibited acetylcholinesterase activity,amyloid β expression in the hippocampus and cortex, and improved antioxidant status and brain levels of BDNF **[33]**.

Centella asiatica (L.) Urban (Apiaceae) with Asiatic acid (AA) being its major component showed a protective effect in the $AlCl_3$-induced rat model of Alzheimer's disease. It lowered aluminium levels, acetylcholinesterase activity, expressions of the amyloid precursor protein, amyloid $beta_{1-42}$, beta and gamma secretases, glial fibrillary acidic protein, ionized calcium-binding adaptor molecule 1, interleukins, TNF-α, nuclear factor- k beta and COX-2. The results are indicative of the neuroprotective action of Asiatic acid **[34]**.

The neuroprotective role of Ononin in AlCl3-induced Alzheimer's showed that ononin lowered AChE, Aβ1-42, and MDA and improved the SOD and TAC in the brain tissues of AD animals. The status of IL-1β, TNF-α, p38MAPK, and NF-κB were suppressed and the BDNF and PPAR-γ contents were elevated in animal brains. Ononin could ameliorate cognitive impairment, and suppress neuroinflammation and oxidative stress in animals **[35]**.

Glycyrrhizic acid, a phytocompound present in *Glycyrrhiza glabra* or liquorice (Fabaceae) effectively inhibited $AlCl_3$-induced memory deficit and activation of TLR4 signaling pathway including the downstream activation of NF-jB, mediated through their antioxidant and anti-inflammatory effect **[36]**.

Celastrus paniculatus (Celastraceae) effectively corrected the deranged neurobehavioral parameters, regulated AChE levels, and reduced lipid peroxidation and SOD levels, improved the number of viable and healthy neurons and cortical histology proving its antidementic effect **[37]**. Supplementation of *Allium cepa* (Liliaceae)

hydroethanolic extract in aluminium-exposed animals ameliorated muscle coordination and memory deficits as well as reduced oxidative stress, and corrected abnormal AChE levels, and aluminium deposition in the brain **[38]**.

Nigella oil isolated from *Nigella sativa* (NS) (Ranunculaceae) rich in thymoquinone (42.3–56.1%), p-cymene (33–38%) improved the neurobehavioral parameters, cognition, memory and lowered anxiety in $AlCL_3$ treated rats and ameliorated indices of psycho-cognitive functions and augmented Ki-67 expression in $AlCl_3$ treated rats **[39]**.

Withania somnifera (Solanaceae) or Ashwagandha ameliorates cognition and is a powerful neuroprotectant. Ashwagandha extract (200 mg/kg, orally) prevented the increase in AchE activity induced by $AlCl_3$ and prevented the increase in MDA, NO, free radicals and TNF-αlevels **[40]**.

A study employing naringin and hesperidin isolated from citrus fruits (Rutaceae) on behavioral impairments caused by aluminum showed that hesperidin reversed aluminium-induced memory loss and toxicity and preserved the normal histoarchitecture of hippocampus and cortex in rat brain through attenuation of AChE activity and amyloidogenic pathway **[41]**.

Syringic acid a phytocompound, when studied for its neuroprotective action in AlCl3, stimulated AD showed improved memory and learning impairments, augmented short-term memory loss, lowered acetylcholinesterase (AChE), and inflammatory protein expression in the brain. The NF-ƙB, IL-1β, IL-6, and TNF-α expressions were assuaged via the syringic acid supplementation to AD rats confirming the protective effect of syringic acid in$AlCl_3$-stimulated AD **[42]**.

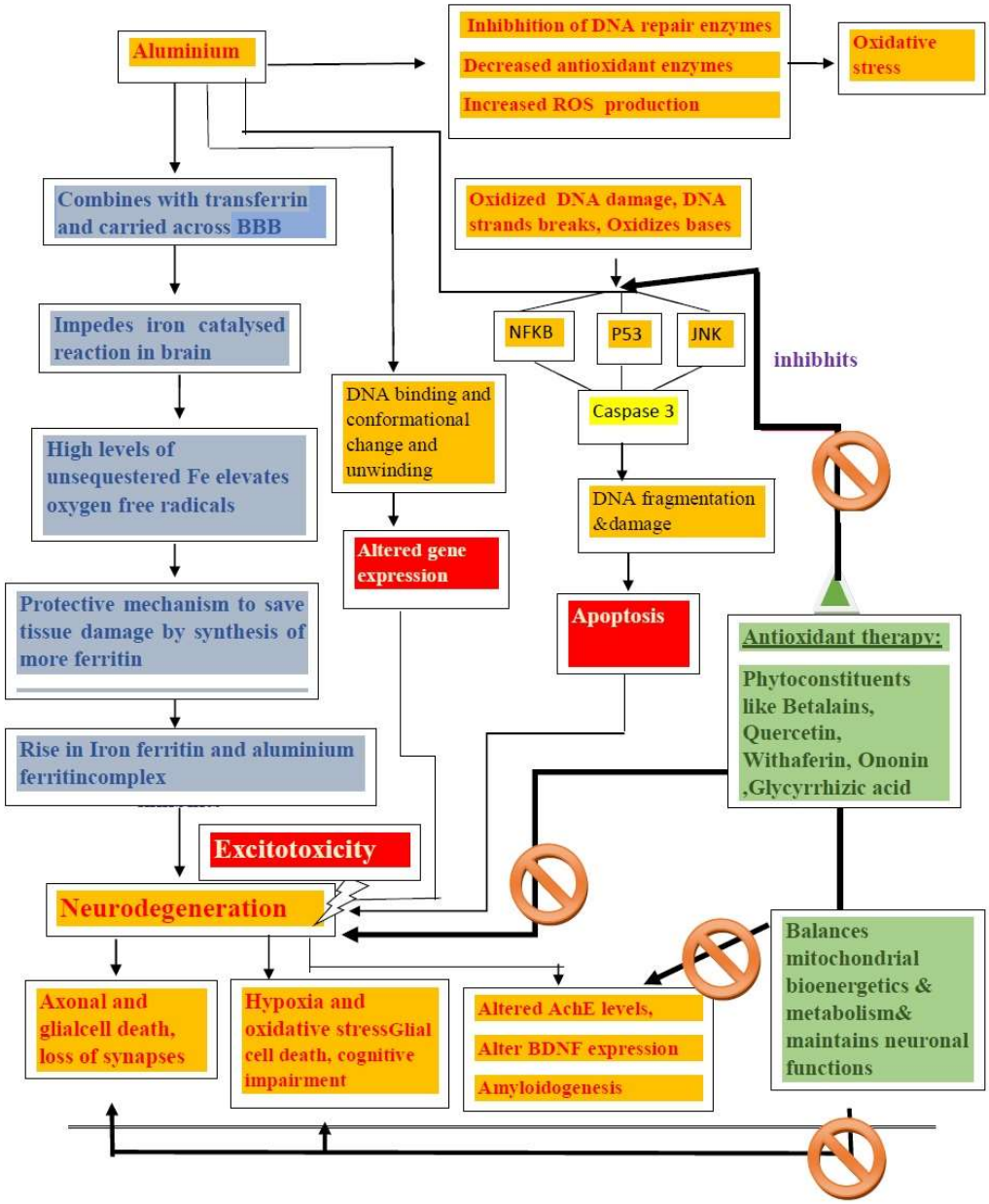

Figure 1: Mechanism of action of aluminium induced neurotoxicity

DISCUSSION:

Herbal plants are miraculous store houses of phytocompounds and are contemplated as an incredible source of curative drugs with minimal side effects which may be developed into promising novel therapeutic agents. The current review emphasizes various mechanisms involved in aluminium-induced neurotoxicity and it highlights the role of some Indian plants and the few phytoconstituents against $AlCl_3$-induced neurotoxicity. It also includes the possible course of action by which these herbs and Phytocompounds help to combat

the damage induced by aluminum on the brain and how far they can be made of use for their therapeutic potential. Progressive and futuristic literature encompassing study evidence are assessed, and the most admissible findings are tracked down in the work, which focuses on future researchers and the scientific community as a whole.

CONCLUSION

The medical industry is surfacing enormous defiance as a clearcut solution and cure for neurodegenerative disorders. The currently available treatments optionaresky-high in terms of cost at the same time are speculative and not very efficacious. Traditional medical practitioners, and systems of medicine like Ayurveda, Siddha etc. are regaining their importance these days as these treatments are completely plant-based or derived from natural sources which makes them free from side effects, without any compromise on the therapeutic efficacy. Though the herbal preparations and medicaments were prescribed from quite many centuries without much clinical trials and studies performed on them, the wonders they bring forthurged the researchers to investigate them in detail unveiling the prototype and mechanism of action of these astounding powerhouses of healing. Through drug development, these marvelous phytocompounds could be made useful for treating neurodegenerative disorders and other complex diseases.

REFERENCE:

[1] Krupińska I. Aluminium drinking water treatment residuals and their toxic impact on human health. Molecules. 2020; 25 (3): 641.

[2] Klotz K, Weistenhöfer W, Neff F, Hartwig, Thriel AC, Drexler H. The health effects of aluminum exposure. Dtsch. Arztebl. Int.2017;114 (39): 653.

[3] Basri, H, Don NNM, Kasmuri N, Hamzah NS, Azizan FA *et al.* Aluminium recovery from water treatment sludge under different dosage of sulphuric acid. J. Phys Conf. Ser. 2019; 1349 012005

[4] Tomljenovic L, Shaw CA. Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations. Lupus. 2012; 21(2): 223-230.

[5] McLachlan, CDR, Berkum VMFA, Swaab DF, Fliers E, Mirmiran M, Van Gool WA, Haaren VFE. Aluminum, a role in degenerative brain disease associated with neurofibrillary degeneration. Brain Research.1986;70:339.

[6] Lipman JJ, Colowick SP, Lawrence PL, Abumrad NN. Aluminum induced encephalopathy in the rat. Life Sci.1988; 42: 863.

[7] Exley C, Clarkson E. Aluminium in human brain tissue from donors without neurodegenerative disease, a comparison with Alzheimer's disease, multiple sclerosis and autism. Sci. Rep. 2020;10 (1): 1–7.

[8] Sumathi T, Shobana C, Kumari, BR & Nandhini DN. Protective Role of Cynodondactylon in Ameliorating the aluminium-induced Neurotoxicity in Rat Brain Regions. Biological Trace Element Research. 2011;144: 843–853.

[9] Willhite CC, Ball GL & McLellan CJ. Total allowable concentrations of monomeric inorganic aluminum and hydrated aluminum silicates in drinking water. Critical Reviews in Toxicology. 2012; 42: 358-442.

[10] Iglesias SS, Soto Otero RJ, Iglesias González MC, Barciela Alonso, Bermejo-Barrera P, Méndez-Alvarez E. Analysis of brain regional distribution of aluminium in rats via oral and intraperitoneal administration. Journal of Trace Element Medical Biology. 2007;21(1):31-34.

[11] Kawahara M, Kato-Negishi M. Link between aluminum and the pathogenesis of Alzheimer's disease, the integration of the aluminum and amyloid cascade hypotheses. J. Alzheimer's Dis.2011; 276393:1-17.

[12] Altamirano RMDJ, Navarro PF, Chiñas SE, Iturribarria HFDM, Cruz MR., Cruz, P.H., *et al*. The relationship of aluminium and silver to neural tube defects; a case control. Iran. J. Pediatr. 2021; 22 (3): 369-374.

[13] Kharoubi TO, Taeır OA, Hella lN, Benyettou I, Aoues A. Aluminium-induced acute neurotoxicity in rats, Treatment with aqueous extract of ArthrophytueutschesArzteblatt.2017 ; 114 (39): 653-659.

[14] Blaylock RL. Excitotoxicity, a possible central mechanism in fluoride neurotoxicity. Fluoride 2004; 37(4):301–314.

[15] Blaylock RLA. Possible central mechanism in Autism Spectrum Disorders. Immunoexcitotoxicity. Altered Therapeutic Health and Medicine. 2009; 15: 60-67.

[16] Excitotoxicity M.P. Mattson. Review in Stress, Physiology., Biochemistry., and Pathology.2019;304.

[17] Hardingham GE, Fukunaga Y and Bading H. Extrasynaptic NMDARs oppose synaptic NMDARs by triggering CREB shut-off and cell death pathways. Nature neuroscience.2002; 5(5): 405-414.

[18] Lai TW, Zhang SB, Wang YTC. Excitotoxicity and stroke, Identifying novel targets for neuroprotection. The CREB-miR-9 Negative Feedback Minicircuitry Coordinates the Migration and Proliferation of Glioma Cells. Progress in Neurobiology.2014; 115:157-188.

[19] Hansen HH, Briem T, Dzietko M, Sifringer M, Voss A, Rzeski W *et al*. Mechanisms leading to disseminated apoptosis following NMDA receptor blockade in the developing rat brain. Neurobiology of Disease. 2004;16: 440 – 453.

[20] Harry GJ, Kraft AD. Neuroinflammation and microglia, considerations and approaches for neurotoxicity assessment. Expert. Opin. Drug. Metab. Toxicol.2008;4 (10):1265-1277.

[21] Mander P, Brown GG. Activation of microglial NADPH oxidase is synergistic with glial iNOS expression in inducing neuronal death, a dual-key mechanism of inflammatory neurodegeneration. J. Neuroinflammation.2005; 2(20):1-15.

[22] Brown GC, Neher J.J. Inflammatory neurodegeneration and mechanisms of microglial killing of neurons. Molecular Neurobiology. 2010; 41 (2-3): 242-247.

[23] Nam DT, Arseneault M, Murthy V, Ramassamy C. Potential role of acrolein in neurodegeneration and in Alzheimer's disease. Curr. Mol. Pharmacol.2010; 3 (2): 66-78.

[24] Dantzer R, Kelley KW. Twenty years of research on cytokine induced sickness behavior. Brain. Behav. Immun. 2007; 21(2): 153-160.

[25] Nesic KJ, Shoenfeld Y, Spector NH. Aluminum Excytotoxicity and Neuro AutotoImmunity, The Role of the Brain Expression of CD32+ (FcγRIIa)., ICAM-1+ and CD3ε in

Aging. Current Aging Science. 2012; 5 (3).

[26] May D, Tress O, Seifert G, Willecke K. Connexin 47 protein phosphorylation and stability in oligodendrocytes depend on expression of Connexin43 protein in astrocytes., Journal of Neurosciences. 2013; 33:7985–7996.

[27] Akinrinade ID, Memudu AE, Ogundele OM. Fluoride and aluminium disturb neuronal morphology., transport functions., cholinesterase., lysosomal and cell cycle activities. Pathophysiology, the Official Journal of the International Society for Pathophysiology. 2015; 22(2):105-115.

[28] Stevanovic´a ID, Jovanovic´ MD, ColiM,Jelenkovic´ A, Bokonjic ´D, Ninkovic ´M. Nitric oxide synthase inhibitors protect cholinergic neurons against AlCl3 excitotoxicity in the rat brain. Brain Res. Bull. 2010; 81: 641–646.

[29] Kumar V, & Gill KD. Aluminium neurotoxicity, neurobehavioural and oxidative aspects. Arch. Toxicol.2009; 83(11): 965–978.

[30] Farhat SM, Mahboob A, Iqbal G & Ahmed T. Aluminum-Induced Cholinergic Deficits in Different Brain Parts and Its Implications on Sociability and Cognitive Functions in Mouse. Biol Trace Elem Research. 2016; 1-7.

[31] Exley C. The pro-oxidant activity of aluminium. Free Radic Biol Med.2004; 36: 380–387.

[32] Ivana S, Marina J, Ankica J. Effect of L-Name on AlCl3 induced toxicity in rat brain. Acta veterrinaria. 2009; 59(2-3):133-146.

[33] Rather MA, Thenmozhi AJ, Manivasagam T. Neuroprotective role of Asiatic acid in aluminium chloride induced rat model of Alzheimer's disease. Front Biosci (Schol Ed). 2018; 10(2): 262-275.

[34] Chen X, Zhang M, Ahmed M., *et al*.. (2021). Neuroprotective effects of ononin against the aluminium chloride-induced Alzheimer's disease in rats. Saudi J. Biol. Sci. 28(8), 4232-4239

[35] McLachlan DRC, Bergeron C, Alexandrov PN, Walsh WJ, Pogue AI, Percy M, Lukiw EWJ. Aluminum in Neurological and

Neurodegenerative Disease.Mol. Neurobiol.2019; 56(2):1531–1538.

[36] Khare CP. Indian Medicinal Plants, An illustrated dictionary. New Delhi, Springer India Pvt. Ltd. 2007: 134–135.

[37] Chakrabarty M, Bhat P, Kumari S, D'Souza A, Bairy KL, Chaturvedi A. Cortico-hippocampal salvage in chronic aluminium induced neurodegeneration by *Celastrus paniculatus* seed oil, Neurobehavioural biochemical histological study. J Pharmacol. Pharmacother. 2012; 3(2), 161–171

[38] [38] Singh T, Goel RK. Neuroprotective effect of *Allium cepa* L. in aluminium chloride induced neurotoxicity. Neurotoxicology. 2015; 49,1-7.

[39] Azeez ATO, Aminu I, Abdussalam B, Samson C, Musawwir AA, Asma'u SM. Nigella sativa oil attenuates aluminum-induced behavioral changes., oxidative stress and cortico-hippocampal neuronal degeneration in rats.JAAPS. 2020; 8 (1): 23-33.

[40] Elhadidy ME, Sawi HG, Meguid NA, Khadrawy YA. Protective effect of ashwagandha (*Withaniasomnifera*) against neurotoxicity induced by aluminum chloride in rats.Asian Pac. J. Trop. Biomed.. 2018; 8(1): 59-66.

[41] Thenmozhi, A.J ., Raja, T., Raja,W., Manivasagam,T., Janakiraman,U., Essa, MM. (2017). Hesperidin ameliorates cognitive dysfunction., oxidative stress and apoptosis against aluminium chloride induced rat model of Alzheimer's disease. NutrNeurosci, 20(6),360-368

[42] Zhao Y., Dang, M., Zhang, W., Lei , Y., Ramesh, T., Veeraraghavan, V.P., Hou, X. (2020). Neuroprotective effects of Syringic acid against aluminium chloride induced oxidative stress mediated neuroinflammation in rat model of Alzheimer's disease. Journal of Functional Foods,71, 1-8.