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Aluminium Choride Induced Neurotoxicity in Experimental Rats - a Review

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ABSTRACT

Introduction: aluminium is a nonferrous metal which is consumed daily by people knowingly or unknowingly from various sources like the air, food, drinking water and medicines. The debate on the issue that aluminium (Al) could be a contributing factor for some neurological diseases have intrigued several researchers to focus their study on effect of Al on the nervous system. The neurotoxicity of Al is well reported but the optimal neurotoxic dose of it is still not clear. This review article compiles different dosages of Aluminium choride (AlCl3) that has induced neurotoxicity in experimental rat models, as AlCl3 is predominanty used in antiperspirants, medicines and cosmetic materials. It is mainly focused upon two routes of administration of AlCl3 i.e oral & intra-peritoneal. The neurotoxic effect of Al leading to various disorders like Alzheimer's disease, dementia and toxic effect in cerebellum, were observed by various authors in experimental rats. We have tabulated different dosages of AlCl3 that has induced neurotoxicity and is effect on different parameters which would be helpful for researchers in conducting experiments in this area. The lethal dose of aluminium chloride (LD 50) is reported as 3630±400mg/kg/body weight by oral route in rats. From numerous studies on rats it is evident that the highest dose of Al given to rats was 1900mg/kgbw by oral route and 150mg/kgbw by intra-peritoneal route.

Keywords: Aluminium chloride; Dosage; Neurotoxicity; Alzheimer's disease; Ddementia.

Introduction

As the proportion of aged population is increasing in recent years the prevalence of neurological diseases has become a matter of concern for worldwide health system. Among environmental risk factors for neurological diseases aluminium (Al) is much discussed, though the contribution of it for the same is controversial. It is an extensively used metal since good olden days, for both household as well as industrial purposes. Al is a non-ferrous metallic element available on earth's crust most abundantly. It is the main component of bauxite rock and present in other aluminium salts, as cryolites and silicates which is used widely[1]. The usage of Al has increased in industrial applications due its qualities like lightweight, nonmagnetic, pliable, and ductile nature[2]. The production of Al for industrial activities and its use in manufacturing, exploration, smelting, mining and polishing cause anthropogenic release of great amount of Al to the environment, both aquatic & terrestrial. The powder of Al is used in production of paints, explosives, propellants as well as fuel additives. Apart from these, Al oxides are used as food additives, ceramic containers, catalysts, fibres which are heat and glass resistant, alloys, artificial gems etc. Al hydroxide is utilized in medicines like antacids and in vaccines. The Al components are used in some baking powder, colouring agents, fillers and preservatives. The natural Al minerals such as zeolite and bentonite are important for water purification, refining sugar, brewing and in paper industries. Due to its abundance in the environment, animals and humans get exposed to Al very easily by oral and respiratory roots[3]. Because of such easy absorption into the system, Al exerts its toxic effects through different pathways (Figure 1)[4].

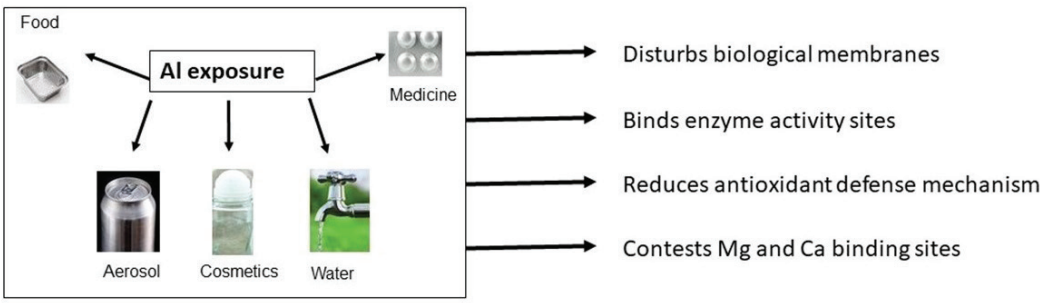

Figure 1. Exposure to Al and its toxicological impacts[4].

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Effect of Al on the body system: Chronic exposure of this metal leads to changes in skeletal, nervous, hematopoietic and respiratory systems though the effect of it depends on the amount of metal or its alloy used in the study on humans or animals[5-8].

Although only a small portion of aluminium is absorbed by gastrointestinal tract, Testolin *et al*. opine that the oral intake has the greatest toxicological implications[9]. The authors opine that absorption of Al is higher in proximal part of intestine when compared to stomach. According to them absorption of Al in the GIT appears to take pace in two steps, in which first step is uptake of Al by mucosal cells that will be released into the blood slowly in the second step. The mechanisms involved in absorption process of Al in the gastrointestinal tract have been proposed by diffusion as well as carrier and vesicular mediated transport process in cells of the intestine. According to WHO (World Health Organization) tolerable weekly dose of Al for 70 kg adult is 20 mg/kg/day[10]. When the investigation was done on cook wares made from scrap metals, it was observed that the mean exposure estimate for Al was 125mg per serving (250ml) in Al cookware which is about six times more than the WHO suggested tolerable weekly intake[11]. Also an average tea consumption can also transfer up to 50% of one's daily Al intake[5].

It has shown various negative effects, such as neurotoxicity in the form of memory loss & behavioural changes, loss of weight and even death in extreme cases[12].

The association between Al exposure and neurotoxicity is well established as depicted in Figure 2.

On this context various researchers have attempted to study the neurotoxic effect of Al using different animal models and dosages of Al compounds. In this review article we have compiled different dosages of AlCl3 that has induced neurotoxicity in Wistar rats. Though there are studies on different combinations of Al we have reviewed the dosage of AlCl3 as it is predominantly used in antiperspirants, medicines and cosmetic materials from where it can be easily absorbed into the system. Additionally, AlCl3 can be easily procured from the lab for study purpose.

A thorough literature was performed using different databases like PUBMED, SCOPUS and EBSCO to compile the effect of different dosages of AlCl3 on various parameters in rat brain.

Though there are number of factors that can induce neurotoxicity, the abundance of aluminium in air and eatables suggest it to be a trigger factor for neurotoxicity. Compilation of different dosages of AlCl3 that has induced neurotoxicity can benefit the researchers for their studies on the compounds that can ameliorate the toxic effect of Al (Table 1, 2 & 3).

Conclusion

In this review article we have compiled a range of doses of AlCl3 that has induced neurtoxicity. Accordingy, the highest dose of Al given orally to rat was 1900mg/kg/body weight with 56 days to induce neurotoxicity. The highest number of days of Al administration by oral gavage was 90 days[38, 39] and by mixing in drinking water was 180 days[42]. The LD50 for AlCl3 in rats is reported as 3630±400mg/kg/body weight[44].

Sanchez-Iglesias *et al*. found that aluminum accumulation in brain was comparatively more in rats administered with AlCl3 intraperitoneally than oral consumption[45]. This suggests that the distribution of Al in brain depends upon the route of administration also. From this it can be elucidated that intraperitoneal administration of AlCl3 is more effective to induce neurotoxicity in rats, than oral route and also it takes less duration as well as quantity of AlCl3.

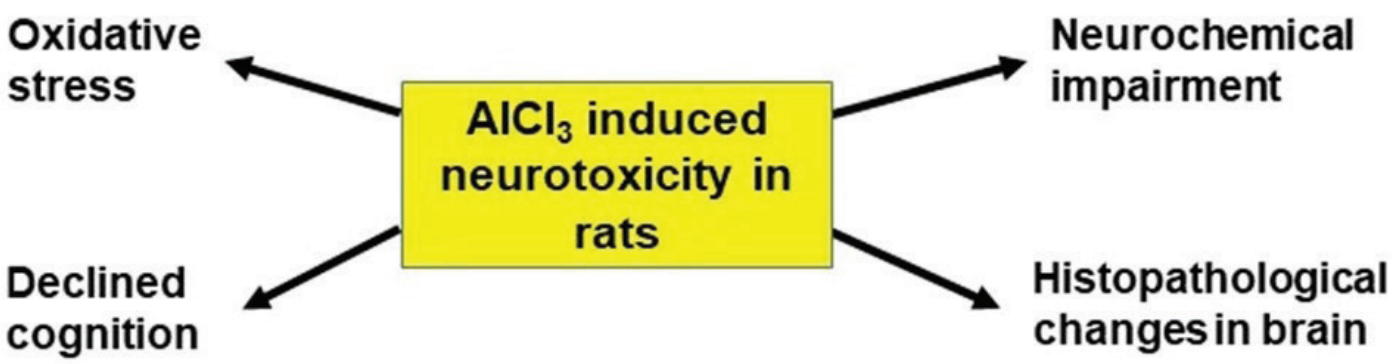

Figure 1. Acute aluminium chloride neurotoxicity revisited13

Table 1. Reports of neurotoxicity in experimental rats, induced by per oral administration of different dosages of AlCl3.

Author	Dosage (mg/kg bw/day)	Time (days)	Biochemical study result	Cognition test result	Histological Observation (IHC and H&E)
Khalil *et al*, 2020[14]	100	60	MDA↑ TAO ↓ MMP-2↑ MMP-9↑	Modified elevated plus maze, Y-maze task, Novel object recognition test showed reduction in memory power	Perivascular haemorrhage; astrocyte infiltrations, degenerated neurons in CA3 & CA4 regions of hippocampus; Purkinje cell necrosis in cerebellum
Bindhu *et al*, 2019[15]	100	42	CAT↓; GSH ↓ SOD ↓; MDA↑ AChE↑	Elevated plus Maze & rotarod test showed cognitive impairment	NFT seen in hippocampus
Chiroma *et al*, 2019[16]	200	70	----------	T-maze spontaneous alternation, modified elevated plus maze and novel object recognition test showed cognitive impairment	Pyramidal neurons in CA1 of hippocampus were degenerated
Hammoud *et al*, 2019[17]	100	42	----------	----------	Focal gliosis and haemorrhage in cerebrum
Kumar *et al*, 2019[18]	100	60	----------	Passive avoidance test displayed disability to learn or retain memory	Neurodegenerative alteration observed in CA3 and CA1 areas of hippocampus
Al-Balawi *et al*, 2018[19]	20	30	AChE↑ DOP & NE-unchanged	----------	----------
Rather *et al*, 2018[20]	100	42	AChE↑; iNOS↑ NFkB↑; TNF-α↑ IL-1β↑; IL-6↑ IL-4↑; IL-2↑ Iba-1↑; COX-2↑ APP↑; Aβ1–42↑ β-secretases ↑ γ -secretases↑	Morris water maze test & passive avoidance test displayed memory and learning impairment	----------
Nallagouni *et al*, 2017[21]	100	56	----------	----------	Neuronal damage in both the parts of brain
Said and Rabo, 2017[22]	84	28	TAS↓ MDA↑ TNF-α↑ AChE↑ Casp-3↑ BDNF↓ GFAP↓ Serotonin↓	----------	Lower the GFAP activity in the striatum; Meningeal vessels congestion were noted. pyknotic neurons in cerebral cortex and pyramidal cells of the hippocampus
Prema *et al*,2016[23]	100	42	AChE↑; APP↑ Aβ1–42↑ β-secretases ↑ γ-secretases↑ pAkt ↓; pGSK-3β↓	Passive avoidance test showed memory impairment.	----------
Ghoneim *et al*, 201524	17	28	BDNF↓ GFAP↑ Ki67↓ TrkB↓	----------	Shrunken small pyramidal cells and some cell loss in CA3 and CA1 regions of hippocampus; An increase in the number of GFAP immuno-reactive astrocytes and the glial fibres

John *et al*, 201525	175	60	Nitrite↑; MDA↑ AChE↓; Catalase↓; GSH↓ TNF-α↑	Morris water maze test displayed memory impairment	----------
Nampoothiri *et al*, 201526	175	60	Nitrite↑; MDA↑ AChE↓; Catalase↓ GSH↓; TNF-α↑	Morris water maze test displayed memory impairment	----------
Lin *et al*, 201527	100	42	Aβ1–42↑ AChE↑ Al↑	Morris water maze test exhibited earning & memory impairment	Shrunken and pyknotic nuclei in the neurons of CA1 & dentate gyrus of cerebrum
Sood *et al*, 201528	100	42	ATP levels↓ ATP synthesis↓ ATP hydrolysis↑ MDA↑ NADH dehydrogenase↓; Succinic dehydrogenase↓; cytochrome oxidase↓; ROS↑	----------	----------
Buraimoh *et al*, 201429	40	28	----------	----------	Purkinje cell loss
Kamel and Mostafa, 201330	320 mg/kg/ liter	56	----------	----------	Increased GFAP; astrocytes present in the polymorphic as well as molecular layers were extended their immunoreactivity into the pyramidal cell layer; Number of pyramidal cells in CA1 region decreased
Zaky, 201331	25	30	MDA↑; AST↓ GST↓; Catalase↓ GSH↓; Aβ↓ NF-kB↑; IL-6↑ TNF-α ↑; iNOS↑	----------	----------
Buraimoh *et al*, 201232	475, 950, 1425, 1900	56	----------	----------	Extensive neuronal vacuolization suggesting neurodegeneration
Kumar *et al*, 201133	100	42	Nitrite↑; MDA↑ Catalase↓; GSH↓ SOD ↓; GST↓ AChE↑	Memory deficit by Water Maze test	----------
Bihaqi *et al*, 200934	50	90	Na-K ATPase↓ AChE↑ M1 receptor↑ ChAT ↑; NGF-TrkA↑ Cdk5↑	----------	----------
Sethi *et al*, 200835	50 mg/kg/ liter	180	SOD ↓ GST↓ GPx ↓ Na-K ATPase↓ PKC	Morris water maze and open field test displayed spatial learning & memory deficit	----------

Table 2. reports of neurotoxicity in experimental rats, induced by different dosages of AlCl3 that has been administered by intraperitoneal method.

Author	Dosage (mg/kg bw/ day)	Time (days)	Biochemical Study Result	Cognition Test Result	Histological Observation (IHC & H&E)
Yin *et al*, 2020[36]	100	42	CAT↓; GSH ↓ SOD ↓; MDA↑ Na-K ATPase ↑ LDH↑; NO↑ ACH↑; IL-1β↑ IL -6↑; TNF-α ↑	Eight arm radial maze and elevated plus maze showed decline memory status	Neurodegeneration in hippocampus
Zhao *et al*, 2020[37]	100	60	NF-ƙB↑; IL-1β↑ IL-6↑; TNF-α ↑ CAT↓; GSH ↓ SOD ↓; MDA↑ Na-K ATPase ↑ LDH↑; NO↑ AChE↑	Morris water maze, Y-maze, elevated plus maze and open field test demonstrated reduced memory & locomotor activity, short term memory loss	Neuronal shrinkage and vacuolar spacing around the neurons of hippocampus
Alghamdi *et al*, 2018[38]	40ml/kg/day	45	GSH ↓ MDA↑	Novel object recognition test showed impairment of the working memory	Neuronal degeneration with electron dense cytoplasm and dilated rER with ribosome depletion
Al-Otaibi *et al*, 2018[39]	7	14	MDA↑; AChE↑ GSH ↓; SOD ↓ GR↓; protein carbonyl↓	----------	Abundant small dark neurons without nucleus and apoptotic neurons
Zghari *et al*, 2018[40]	0.125, 0.25, 0.5, 1	56	----------	Force Swimming Test, Open Field, Morris Water Maze, Elevated Plus Maze, Y-maze and Object Recognition Test displayed enhanced anxiety & depression along with cognitive disorders	----------
Thenmozhi *et al*, 2017[41]	100	60	AChE↑ APP↑ β amyloid↑ β & Y secretases↑	Reduced locomotor activity by open field test; Learning & memory deficit by Morris water maze test	Distorted neurons with disrupted cell membrane both in hippocampus and cerebral cortex
Sumathi *et al*, 2015[42]	4.2	28	CAT↓; GSH ↓ SOD↓; GPx ↓ GR↓; Na-K ATPase↓ Ca2+ ATPase↓ Mg2+ ATPase↓; ALT↑; AST↑; MDA↑	----------	Diffused gliosis along with pericellular oedema in cerebral cortex; Disruption in Purkinje cell layer of cerebellum
Khan *et al*, 2013[43]	10	25	Nitrite↑ AChE↑ Catalase↓ GSH↓ GST↓	Morris water maze test showed declined memory	----------

Abbreviations:
Aβ= amyloid beta-protein
ACHE = Acetylcholinesterase,
ALT - Alanine Transaminase;
APP-amyloid precursor protein, b amyloid (Ab1–42), b and c secretases
APP=amyloid precursor protein,
AST - Aspartate Transaminase
BDNF=brain derived neurotrophic factor
CAT=Catalase; GSH= reduced glutathione;
Cdk5=cycline dependent kinase5
ChAT =choline acetyl transferase
COX-2=cyclooxygenase-2
DOP= Dopamine,
EEC=electroencephalogram
GFAP=glial fibrillary acidic protein,
GPx= glutathione peroxidase.
GR- Glutathione reductase
GST= Glutathione–s-transferase
Iba-1=ionized calcium binding adaptor molecule 1,
IL-1β=interleukin-1β,
IL-6= interleukin-6,
IL-4=interleukins – 4
IL-2=interleukins – 2
iNOS =inducible nitric oxide synthase,
LDH= lactate dehydrogenase,
M1 receptor =muscarinic receptor 1,
MDA= malondialdehyde;
NFkB=nuclear factor- k beta
NO= nitric oxide,
NGF-TrkA =Nerve Growth Factor-Tyrosine kinase A receptor
SOD= superoxide dismutase,
TAS = Total antioxidant status,
TNF-α = tumor necrosis factor α.
TBARS= tissue preparation for biochemical estimation reactive substance and antioxidants
Trk =tyrosine kinase

References

1. Bauer A-S, Tacker M, Uysal-Unalan I, Cruz RMS, Varzakas T, Krauter V. Recyclability and Redesign Challenges in Multilayer Flexible Food Packaging—A Review. Foods. 2021;10(11):2702.
2. Kawahara M, Kato-Negishi M. Link between aluminum and the pathogenesis of Alzheimer's disease: the integration of the aluminum and amyloid cascade hypotheses. Int J Alzheimers Dis 2011; 8:276393.
3. Domingo JL, Gomez M, Sanchez DJ, Llobet JM, Corbella J. Effect of various dietary constituents on gastrointestinal absorption of aluminum from drinking water and diet. Res Commun Chem Pathol Pharmacol. 1993; 79(3): 377–80.
4. Mailloux RJ, Lemire J, Appanna VD. Hepatic response to aluminum toxicity: dyslipidemia and liver diseases. Exp Cell Res. 2011 Oct 1;317(16):2231-8.
5. Yokel R A. Aluminum. In: Cabello A (ed) Encyclopedia of human nutrition, 2013; 1(3) 57-63.
6. Afifi A. Renal osteodystrophy in developing countries. Artif Organs. 2002;26(9):767-9.
7. Chen J, Wang M, Run D, She J. Early chronic aluminium exposure impairs long-term potentaion and depression to the rat dentate gyrus in vivo. Neuroscience. 2002;112(4):879-87.
8. Campbell A. The potential role of aluminium in Alzheimers disease. Nephrol Dial Transplant. 2002;17(2):17-20. Liaquat L, Sadir S, Batool Z, Tabassum S, Shahzad S, Afzal A, Haider S. Acute aluminum chloride toxicity revisited: study on DNA damage and histopathological, biochemical and neurochemical alterations in rat brain. Life Sci 2019; 217: 202–11.
9. Testolin G, Erba D, Ciappellano D, Bermano G. Influence of organic acids on aluminum absorption and storage in rat tissues. Food Additives Contaminants.1996;13(1):21–7.
10. Weidenhamer JD, Fitzpatrick MP, Biro AM, Kobunski PA, Hudson MR, Corbin RW *et al*. Metal exposures from aluminum cookware: an unrecognized public health risk in developing countries. Sci Total Environ 2017; 579:805–13
11. Plieth C, Sattelmacher B, Hansen U P, Knight M R. Low-pH mediated in cytosolic calcium are inhibited by aluminium: a potential mechansm for aluminium toxicity. Plant J. 1999;18(6): 643-50.
12. Bekhedda H, Menadi N, Demmouche A, Ghani A, Mai H. Histological study of the effects of aluminum chloride exposure on the brain of wistar rats female. Journal of Drug Delivery and Therapeutics. 2020;10, 3-s:37-42.
13. Liaquat L, Sadir S, Batool Z, Tabassum S, Shahzad S, Afzal A, Haider S. Acute aluminum chloride toxicity revisited: study on DNA damage and histopathological, biochemical and neurochemical alterations in rat brain. Life Sci 2019; 217: 202–11.
14. Khalil HMA, Salama HH, Al-Mokaddem A, Aljuaydi SH, Edris AE. Edible dairy formula fortified with coconut oil for neuroprotection against aluminium chloride-induced Alzheimer's disease in rats. Journal of Functional Foods. 2020;75 (104296):1-14.
15. Bindhu KM, Vijayalakshmi A. Neuroprotective Effect of Carica papaya Leaf Extract against Aluminium Toxicity: An Experimental Study on Cognitive Dysfunction and Biochemical Alterations in Rats. Indian Journal of Pharmaceutical Education and Research, 2019;53(3s):s392-s398.
16. Chiroma SM, Baharuldin MTH, Taib CNM, *et al*. Protective effect of Centella asiatica against D-galactose and aluminium chloride induced rats: Behavioral and ultrastructural approaches. Biomedicine & Pharmacotherapy, 2019;109:853–64.
17. Hammoud GM, Shalaby RA. Experimental evaluation of protective action of resveratrol against aluminum- induced toxicity in male rats. International Journal of Advanced Research in Biological Sciences, 2019; 6(1):11-24.
18. Kumar P, Bairy K L, Nayak V, Reddy S K, Kiran A and Ballal A. Amelioration of Aluminium Chloride (AlCl3) Induced Neurotoxicity by Combination of Rivastigmine and Memantine with Artesunate in Albino Wistar Rats. Biomedical & Pharmacology Journal. 2019; 12(2):703-11.
19. Al-Balawi A A, Yousri M A, Ashwag A, Shareefa AA, Mustafa AZ *et al*. Modulation of the neurotoxicity induced by aluminium choride in rats using Beetroots and Broccoli extracts JPRI, 2018; 25(3): 1-18.
20. Rather MA, Thenmozhi AJ, Manivasagam T, Bharathi MD, Essa MM, Guillemin GJ. Neuroprotective role of Asiatic acid in aluminium chloride induced rat model of Alzheimer's disease. Frontiers In Bioscience. 2018; 10:262-75.
21. Nallagouni R and Reddy KP. Aluminum and Fluoride impacts cortex, hippocampus and dentate gyrus structure in rats: protective role of resveratrol C S. International Journal of Applied Biology and Pharmaceutical Technology. 2017; 8(1):89-97.
22. Said MM and Rabo MM. Neuroprotective effects of eugenol against aluminium-induced toxicity in the rat brain. Arh Hig Rada Toksikol. 2017;68:27-37.
23. Prema A, Thenmozhi A J, Manivasagam T, Essa M M, Akbar M D, Akbar M. Fenugreek Seed Powder Nullified Aluminium Chloride Induced Memory Loss, Biochemical Changes, AβBurden and Apoptosis via Regulating Akt/GSK3βSignaling Pathway. Plos one, 2016;1-19.
24. Ghoneim FM, Khalaf HA, Elsamanoudy AZ *et al*. Protective effect of chronic caffeine intake on gene expression of brain derived neurotrophic factor signaling and the immunoreactivity of glial fibrillary acidic protein and Ki-67 in Alzheimer's disease. Int J Clin Exp Pathol 2015;8(7):7710-28.
25. John J, Nampoothiri M, Kumar N, Mudgal J, Nampurath GK, Chamallamudi MR. Sesamol, a lipid lowering agent, ameliorates aluminium chloride induced behavioral and biochemical alterations in rats. Pharmacognosy Magazine. 2015;42(11):327-36.
26. Nampoothiri M, John J, Kumar N, Mudgal J, Nampurath GK, Chamallamudi MR. Modulatory Role of Simvastatin against Aluminium Chloride-Induced Behavioural and Biochemical Changes in Rats. Behavioural Neurology 2015;2015:1-9.
27. Lin WT, Chen RC, Lu WW, Liu SH, Yang FY. Protective effects of low-intensity pulsed ultrasound on aluminum induced cerebral damage in Alzheimer's disease rat model. Sci Rep. 2015; 5: 9671.
28. Sood PK, Verma S, Nahar U, Nehru B. Neuroprotective Role of Lazaroids Against Aluminium Chloride Poisoning. Neurochem Res. 2015; 40:1699–708.
29. Buraimoh AA, Ojo S, Tayo I. Effects of Aluminium Chloride on the Histology of Cerebellum of Wistar Rats. Pharmacology & Toxicology Research. 2014;1(1):1-4.
30. Kamel ES and Mostafa N. Effect of aluminum chloride on the hippocampus of adult rats and the possible protective role of Nigella sativa: a histological and immunohistochemical study. The Egyptian Journal of Histology. 2013; 36:505-13.
31. Zaky A, Mohammad B, Moftah M, Kandeel KM and Bassiouny AR. Apurinic/apyrimidinic endonuclease 1 is a key modulator of aluminum-induced neuroinflammation. BMC Neuroscience 2013;14:26.
32. Buraimoh AA, Ojo S A, Hambolu JO, Adebisi S. Effects of Aluminium Chloride Exposure on the Histology of the Cerebral Cortex of Adult Wistar Rats. Journal of Biology and Life Science, 2012; 3(1):87-113.
33. Kumar A, Prakash A, Dogra S. Neuroprotective effect of carvedilol against aluminium induced toxicity: possible behavioral and biochemical alterations in rats. Pharmacological Reports. 2011; 63:915-23.
34. Bihaqi SW, Sharma M, Singh AP, Tiwari M. Neuroprotective role of Convolvulus pluricaulis on aluminium induced neurotoxicity in rat brain. Journal of Ethnopharmacology, 2009;124(3):409-15.
35. Sethi P, Jyoti A, Singh R, Hussain E, Sharma D. Aluminium-induced electrophysiological, biochemical and cognitive modifications in the hippocampus of aging rats. Neuro Toxicology. 2008; 29(6):1069-79.
36. Yin S, Ran Q, Yang J, Zhao Y, Li C. Nootropic effect of neferine on aluminium chloride induced Alzheimer's disease in experimental models. J Biochem Mol Toxicol. 2020; 34(2): e22429.
37. Zhao Y, Dang M, Zhang W *et al*. Neuroprotective effects of Syringic acid against aluminium chloride induced oxidative stress mediated neuroinflammation in rat model of Alzheimer's

disease. Journal of Functional Foods. 2020; 71:104009.
38. Alghamdi BSA. Possible prophylactic anti-excitotoxic and anti-oxidant effects of virgin coconut oil on aluminium chloride-induced Alzheimer's in rat models. Journal of Integrative Neuroscience. 2018; 17:593–607.
39. Al-Otaibi SS, Arafah MM, Sharma B, Alhomida AS, Siddiqi NJ. Synergistic Effect of Quercetin and α-Lipoic Acid on Aluminium Chloride Induced Neurotoxicity in Rats. Journal of Toxicology. 2018; 2018:1-8.
40. Zghari O, Rezqaoui A, Ouakki A, Lamtai M, Chaibat J, Mesfioui A *et al*. Effect of Chronic Aluminum Administration on Affective and Cognitive Behavior in Male and Female Rats. Journal of Behavioral and Brain Science. 2018; 8:179-96.
41. Thenmozhi AJ, Raja TRW, Manivasagam T, Janakiraman U & Essa MM. Hesperidin ameliorates cognitive dysfunction, oxidative stress and apoptosis against aluminium chloride induced rat model of Alzheimer's disease, Nutritional Neuroscience, 2017; 20(6):360-8.
42. Sumathi T, Shobana C, Thangarajeswari M, Usha R. Protective effect of L-Theanine against aluminium induced neurotoxicity in cerebral cortex, hippocampus and cerebellum of rat brain – histopathological, and biochemical approach. Drug Chem Toxicol. 2015; 38(1): 22–31.
43. Khan KA, Kumar N, Nayak PG, Nampoothiri M, Shenoy RR, Krishnadas N *et al*. Impact of caffeic acid on aluminium chloride-induced dementia in rats. Journal of Pharmacy and Pharmacology. 2013; 65: 1745–52.
44. Kumar S. Acute toxicity of aluminium chloride, acephate, and their coexposure in male Wistar rat. International Journal of Toxicology, 2001; 20(4):219-223. doi: 10.1080/109158101750408046
45. Sancez-Iglesias S, Soto-Otero R, Iglesias-Gonzales J, Barciela-Alonso MC, Bermejo-Barrera P, Mendez-Alvarez E. Analysis of brain regional distribution of aluminium in rats via oral and intraperitoneal administration. Journal of Trace Elements in Medicine and Biology. 2007;21(1):31-34. doi: 10.1016/j.jtemb.2007.09.010.

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