Veterinary Journal of Kastamonu University Review
2023 Volume 2 (Issue 1) Pages 52-64

Aluminum and toxicity

Sedat GÖKMEN[1,a,*], Burcu GÜL[2,b]

[1]Kastamonu University, Faculty of Veterinary Medicine, Department of Pharmacology and Toxicology, Kastamonu, Türkiye; [2]Fırat University, Faculty of Health Sciences, Department of Nursing, Elazığ, Türkiye.
[a]ORCID: https://orcid.org/0000-0002-4793-3030; [b]ORCID: https://orcid.org/0000-0002-9122-8953

*Corresponding author: sgokmen@kastamonu.edu.tr
Received 09.05.2023 - Accepted 20.06.2023 - Published 30.06.2023

Abstract: Aluminum (Al) is the third most prevalent element on earth after oxygen and silicon. Al compounds are used in the production of many different products including pots, pans, paints, varnishes, lubricants, cosmetics, vaccinations, pharmaceuticals, and nano-carrier systems, in the field of veterinary medicine and industry. The toxicity in animals can occur through various routes, including ingestion (food, drinking water), inhalation (air, pharmaceutical, agrochemical), and injection (pharmaceutical, vaccine). Acute poisoning in animals is rare and usually occurs following exposure. Numerous pathological effects have been associated with Al accumulation in mammalian tissues. The accumulation in tissues can Al accumulation in mammalian tissues causes various pathological disorders affecting nervous, immune, skeletal, reproductive system, lungs and breast health. The toxic effects of Al cause oxidative stress, immunological changes, genotoxicity, proinflammatory, peptide denaturation or transformation, enzymatic dysfunction, metabolic dysregulation, amyloidogenesis, membrane disruption, iron dyshomeostasis, apoptosis, necrosis and dysplasia. Al is neurotoxic, increases the permeability of the blood brain barrier and inhibits many important enzymes in the brain. This study aimed to reveal the toxicity of Al, its mechanism of action and its relationship with conditions such as vaccines, cancer, etc. in animals.
Keywords: Aluminum, effects, toxicity, veterinary medicine.

Alüminyum ve toksisite

Özet: Alüminyum (Al), oksijen ve silikondan sonra yeryüzünde en yaygın bulunan üçüncü elementtir. Al bileşikleri, veteriner hekimlik ve sanayi alanında tencere, tava, boya, vernik, yağlayıcı, kozmetik, aşı, ilaç ve nano-taşıyıcı sistemler gibi birçok farklı ürünün üretiminde kullanılmaktadır. Hayvanlarda toksisite, yutma (gıda, içme suyu), soluma (hava, farmasötik, zirai ilaç) ve enjeksiyon (ilaç, aşı) dahil olmak üzere çeşitli yollarla meydana gelebilir. Hayvanlarda akut zehirlenme nadirdir ve genellikle kronik maruziyetin bir sonucu olarak ortaya çıkar. Çok sayıda patolojik etki, memeli dokularında Al birikimi ile ilişkilendirilmiştir. Dokulardaki birikimi sinir, bağışıklık, iskelet, üreme sistemi, akciğer ve meme sağlığını etkileyen çeşitli patolojik bozukluklara neden olur. Al'ın toksik etkileri oksidatif strese, immünolojik değişikliklere, genotoksisiteye, proinflamatuar etkiye, peptit denatürasyonuna veya transformasyonuna, enzimatik işlev bozukluğuna, metabolik düzensizliğe, amiloidogenez, membran bozulmasına, demir dishomeostazına, apoptoz, nekroz ve displaziye neden olur. Al nörotoksiktir, kan beyin bariyerinin geçirgenliğini bozar ve beyindeki birçok önemli enzimi inhibe eder. Bu çalışmanın amacı hayvanlarda Al'un toksisitesi, etki mekanizması ve aşı, kanser vb. durumlarla ilişkisini ortaya koymaktır.
Anahtar kelimeler: Alüminyum, etkiler, zehirlilik, veteriner hekimlik.

Introduction

Aluminum (Al) is widespread in the environment, constituting approximately 8% of the earth's crust. After oxygen and silicon, it is the third most prevalent element (Gupta et al., 2013; Herndon, 2015), and it was first identified in 1827 (Liu et al., 2008). Al is a soft, nonmagnetic, ductile, and silvery-white metal (Soni et al., 2001).

Al metal is derived primarily from bauxite, which contains Al (Gupta, 2012a). Natural processes or anthropogenic sources both release it into the environment (Bjerregaard et al., 2015). Al occurs naturally in the trivalent state (Al^{3+}) as silicates, oxides, and hydroxides. Al does not exist in the environment as a pure metal because of its high reactivity; instead, it combines with other elements, for example, sodium and fluorine, and forms combinations with organic substances (Gupta, 2012a). The substances in question are Al chloride, Al hydroxide, Al nitrate, Al sulfate, Al potassium, Al phosphate, Al ammonium sulfate, and Al silicate (Igbokwe et al., 2019).

In environments contaminated by industrial waste, both animals and humans may be exposed to high levels of Al. Several chemical compounds containing Al are widely used in a wide range of products and processes. The compounds are used in pharmaceuticals (drugs, buffered aspirin antacids, astringents), vaccines, fumigants, and pesticides, in addition to paints and varnishes, cosmetics, detergents, water treatment and purification, tanning leather, waterproofing clothes and concretes, industrial filtration, and measuring radiation exposure (Gupta, 2012a; Igbokwe et al., 2019).

While Al rarely has toxicological consequences in animals when exposed acutely, it can cause a number of problems when exposed subacutely or chronically. Toxicosis induced by Al accumulation in mammalian tissues has been linked to numerous pathological effects. According to reports, poisoning from Al accumulation in mammalian tissues can cause a variety of pathological disorders that affect the nervous system, immune system, skeleton system, lungs, mammary health, and reproductive system.

Al primarily accumulates in the nervous tissues and brain. It is believed to play a significant role in the emergence of neurodegenerative diseases (such as Parkinson's disease) in humans. It is also associated with encephalopathy and amyotrophic lateral sclerosis. In Simmental calves, Frank et al. (1992) reported multifocal polioencephalomyelomalacia correlated with high Al levels (Frank et al. 1992). Many domestic and wildlife species, in addition to fish, have shown adverse effects from high Al levels. Al has also been involved in the etiology of grass tetany, and a clinical description such as grass tetany was reported. Because Al quickly passes the placental and the blood-brain barrier, developmental toxicity and

neurotoxicity appear to be of special concern when it comes to Al toxicity. Al phosphide, a common insecticide, has been found in cases of cow poisoning, which is of interest from a toxicological perspective. In cases like these, the majority of the hazardous effects arise from phosphine (PH_3) gas, which is produced from phosphide in the gastrointestinal system (Igbokwe et al., 2019; Gupta, 2012a).

Toxicokinetic: Al toxicity in animals can occur through various routes, including ingestion (food and drinking water), inhalation (air, pharmaceuticals, and agrochemicals), and injection (pharmaceuticals and vaccines). The toxicity of Al depends on various factors, such as the age and health of the animal, the dose and duration of exposure, and the route of exposure (Gupta, 2012a, b). Al is absorbed after oral or inhalation exposure, while little or none is absorbed after dermal exposure. Al's bioavailability depends on its chemical form and particle size. After oral exposure, Al is primarily absorbed in the jejunum and duodenum. Al may be dissolved from insoluble species such as $Al(OH)_3$ by the gastric's acidic pH, facilitating absorption. It is well established that consuming $Al(OH)_3$ with citrus juices or certain common organic components of the diet (citrate, lactate and succinate, etc.) may significantly enhance Al absorption. Al is probably mostly taken in by passive diffusion through paracellular routes. Al could be taken up by mucous cells, which may prevent it from getting into the body. Free Al ions are found in very small amounts because they combine with numerous compounds in the body, amino acids, nucleotides, carbohydrates, and macromolecules. So, the toxicokinetic and toxicodynamic of Al can be different based on what these complexes are made of. Between 80 and 90% of the Al in the blood is linked to proteins in the plasma. There is evidence that Al binds mostly to transferrin and only a little bit to albumin. After dogs get Al through an IV, the average $t_{1/2}$ of Al in their plasma is about 4.5 h. Al circulates to all organs, with the largest concentration in bone. Post-inhalation lung concentrations are the largest. The lungs contain 25% of Al and the skeleton 50%. Al accumulates in bone after long-term oral exposure and is slowly released. Al accumulates in the tissues of the brain, liver, kidneys, and hematological system. In the lungs, Al levels rise with aging. Al accumulates in the nucleus, lysosomes, and chromatin of the cell. Al levels in the brain are generally lower than in many other tissues. Al is known to cross the blood-brain barrier and get into the brain through transferrin receptor-mediated endocytosis. Al can infiltrate the brain via the olfactory tract, nasal epithelium, and axonal transport following inhalation. It's worth noting that the cells that accumulate the most Al are long-lived postmitotic cells like neurons. Increases in Al concentrations in the brain of rabbits of four to tenfold and ten to twentyfold are associated with neurotoxicity and mortality, respectively. An energy-dependent process actively removes Al from the brain. However, it has

been reported that with the increase in iron load in the body, the accumulation of Al in the tissues decreases, and the accumulation of Ca or Mg deficiency in the brain and tissues may increase. Aluminum is predominantly eliminated in the urine, with only trace amounts in the bile. Renal Al elimination depends on the Al complex. Renal Al elimination depends on the Al complex. Al in a low-molecular-weight compound can be filtered and expelled by the renal glomeruli, but not in a high-molecular weight complex. Animal studies show that Al levels in urine can rise 14-fold after a single exposure. Al is mostly eliminated in urine in the first 24 hours after exposure. This could be because of the high Al concentrations, which likely created unfilterable Al complexes, lowering the plasma filterable Al percentage. Aluminum only excretes a small amount in the milk due to the restricted GI tract absorption of Al. Unabsorbed Al is excreted in the feces following oral consumption (Gupta, 2012a).

Mechanism of the toxicity: Aluminum alters the vast majority of physical and cellular processes. Al's toxicity may be due to its interaction with the plasma membrane, apoplastic, and symplastic targets. Neurotoxic effects, such as neuronal atrophy are the most serious complications of Al toxicity (Jaishankar et al., 2014). Al's toxicity results primarily from its pro-oxidant activity, which causes oxidative stress, free radical attack, and lipid oxidation. Al ions interact with oxygen-containing amino acids, side chains, and the protein backbone to convert protein polypeptides to secondary structures, denaturing or altering their conformation or structure, as seen in β-amyloid. Al binds to nucleotide phosphate groups, affecting energy metabolism. Hepatocytes exposed to Al have decreased ATP synthesis, glycolysis, tricarboxylic acid cycle activity, and lipid oxidation. These metabolic disturbances may cause Al-exposed animals to lose weight and produce fewer eggs. Also, exposure to Al can disrupt iron homeostasis resulting in iron excess. Excess iron from Al has been proven to promote the peroxidation of lipids, damage to DNA, and reactive oxygen species-induced apoptosis (Igbokwe et al., 2019).

Aluminum toxicity is believed to primarily affect the skeletal and central nervous system. Although it is known that Al causes neurotoxicity, the mechanismremains unclear. Al mostly accumulates in the cortex, hippocampus, and amygdala, which are also parts of the brain rich in glutamatergic neurons and transferrin receptors. When Al enters the brain, it displaces and regulates the metabolism of physiological cations such as Mg, Ca, and Fe. According to research (Gupta, 2012a), the amounts of tissue and cytoplasmic calcium can influence Al neurotoxicity. Al disrupts neurotransmitter release and changes neurotransmitter systems by substituting calcium in the synaptic region.

Acute and chronic toxicity: Acute Al poisoning is rare in animals. However, a high acute dose or repeated exposure over an extended period can result in severe toxicological effects. The toxicity depends on its chemical form, exposure route, and animal species (Table 1). Female rabbits were lethally affected by a single oral exposure to 540 mg/kg of Al lactate. Al has been found to be lethal to mice in subchronic and chronic investigations, but not to rats or dogs. Dermatitis, nasal discharges, loss of pigmentation on the nose pad, and aggressive and violent behavior are all signs of intoxication in dogs. The toxic effects depend on which organ is affected. These effects may be caused in part by the accumulation of Al and the substitution of calcium, magnesium, and iron. The main target organs are the myocardium, bones and CNS. Aluminum deposits can cause changes in the bone by interfering with heme synthesis and causing anemia, in the heart by causing myocardial infarction, and in the brain by causing neurotoxicity and memory loss. Al can also lead to problems with the liver and kidneys and osteoarthritis (Gupta, 2012a).

Table 1. Al toxicity in pregnancy, lactation and neonates (Gomez et al., 1991; Golub et al., 1992; Reinke et al., 2003; Gupta, 2012a).

Form	Species	Toute	Toxic effect
Al-lactate	Rabbit	Injection	Embryotoxicity and neurotoxicity
Al-chloride	Rat	Injection	Al plasma levels increased 30-fold ↑, Al milk/plasma ratio 6.6, growth retardation, Brain and nuclear fraction (brain cell nuclei) of rat fetus and cub ↑
Al-lactate	Mice	Oral	Growth retardation in cub, Impaired negative geotaxis and decreased forelimb or rear limb grip strength
Al-hydroxide	Rat	Oral	Organogenesis, skeletal abnormalities↑

Animal studies have shown that oral administration of Al compounds causes neurotoxicity (Abu-Taweel et al., 2012; Dey & Singh, 2022). Al toxicity in vulnerable animals, such as rabbit and cat, is characterized by gradual neurological impairment leading to death from status epilepticus. Neurofibrillary tangles are the most prominent early pathologic change in large neurons, proximal axons, and dendrites of neurons in many brain regions. This is associated with synaptic loss and dendritic tree atrophy. There is evidence to show that following exposure to Al, more severe problems emerge in the brain. Not all species demonstrate this Al reaction. For example, rats do not develop neurofibrillary tangles or encephalopathy, and monkeys develop neurofibrillary tangles only after receiving an Al infusion for more than a year. Frequently observed are impairments in cognitive and motor function as well as behavioral abnormalities (Liu et al., 2008).

Maternal mice exposed to doses of 184-250 mg/ kg/ day Al lactate during pregnancy and lactation showed prominent indications of neurotoxicity, such as paralysis, ataxia, splaying and dragging of the hind limbs (Golub et el., 1987; 1992). In other studies, rats given 12 mg/ kg/ day of Al fluoride in drinking water and a base diet for 45-52 weeks observed higher Al levels and also histological changes in the brain (Varner et al., 1993; 1998). There is some evidence that prenatal exposure to neurotoxic chemicals results in delayed development of the nervous system and modest neurobehavioral dysfunction without physical deformity. Al crosses the placental barrier and accumulates in embryonic tissues, causing embryonic/ fetal toxicity, birth defects, developmental and neurobehavioral toxicity. It is significant to note that the creation of the extremely toxic gas phosphine (PH_3), rather than Al, is the primary cause of the acute toxicity linked to the consumption of Al phosphide. There have been cases when cows have perished after consuming grains that have been fumigated with Al phosphide. Chronic exposure to Al causes an increase in Al levels in bones, which can lead to bone abnormalities such as decreased bone formation and demineralization, or even osteoarthritis. Dogs and pigs exposed to Al show osteomalacia. Al can induce pulmonary fibrosis when inhaled chronically. In addition, prolonged exposure to Al can result in hepatic and renal failure as well as endocrine disruption (Gupta, 2012a). Additionally, it has been reported to influence the IL-6 levels in rats administered ammonium chloride (Gul et al., 2022).

Al is very toxic to fish when solubilized under acidic or alkaline circumstances, which helps explain fish population crashes linked with freshwater acidification. Waterborne Al poisoning targets the gill since internal organ accumulation is slow. Toxic mechanisms include cationic Al species (particularly Al^{3+}) impairing gill ionoregulation and/ or respiratory dysfunction due to precipitation of $Al(OH)_3$ or polymerization of Al hydroxides on the gill surface during water alkalinization. The latter produces gill inflammation, histopathologies, and profuse mucus at pH 5-6. These toxic pathways decrease cardiovascular and aerobic swimming performance, malnutrition, growth, spontaneous activity, and reproduction. Episodic exposure to severe [Al] and low pH may limit many fish species, while chronic low-level exposure can increase resistance. Even 2-day exposure to moderately increased Al in freshwater impairs seawater tolerance in migratory salmonids like salmon smolts (Wilson, 2011).

Placental toxicity: Al crosses the membrane of the placenta and accumulates in the tissues of the fetus at amounts that are detrimental to fetal development. Al crosses the blood-brain barrier, penetrates the placental passage, and reaches the maternal milk. According to studies conducted on mice and rabbits, placenta has 4-5 times more Al than embryonic or maternal tissues (Yokel and McNamara, 1985; Cranmer et al., 1986). Importantly, the

accumulation of Al in the placentas of mice and rabbits does not preclude its accumulation in fetal tissues (Gupta; 2012a, b). During gestation, mice exposed to Al lactate (83 mg/ kg/ day) observed an increase in cleft palate, dorsal hypokyphosis, and delayed parietal ossification (Patermain et al., 1988). Studies have shown that Al retards the skeletal development of pups. Major fetal abnormalities include digit, wavy rib, missing rib, absence of xiphoid, and poor ossification, especially in the cranial bones, the lower part of the spine, and the long bones of the limb (Paternain et al., 1988; Bernuzzi et al., 1989). High rates of skeletal defects and poor ossification in fetuses whose mothers were given Al chloride show that Al has a negative effect on bone formation in fetuses. This is because Al binds to phosphate, lowering the amount of phosphate that can be used to make bones. Due to a problem with how blood clots, a lack of phosphate can also cause abdominal bleeding in the fetus. Also, neurotoxicity and neurobehavioral changes have been found in the pup of rat, mice, and rabbits that were given Al at amounts that did not adversely affect the mothers. Al citrate and Al nitrate, two other types of Al, can also have the same effects on growth. Growing embryos are generally more sensitive to Al toxicity than adults (Gupta, 2012b).

Numerous animal investigations have demonstrated that Al can pass through the placenta and accumulate in fetal tissue, particularly the bones (Table 1). A majority of studies focus on the effects of prenatal exposure to Al on postnatal development and pup behavior. Common results involved reduced birth weight, a slower rate of weight gain during lactation, abnormal skeletal development, impairment of neurological functions, increase in stillbirth and perinatal mortality rates. Additionally, Al has been detected in the milk of mothers exposed to Al for an extended period of time (Reinke et al., 2003). During gestation, administration of subcutaneous Al lactate to rabbit decreases litter size. Even at lower dosages (2.7 mg/ kg), stillbirth and postnatal mortality rates in the pup were marginally increased. During the period of lactation, young animals gained less weight (Yokel, 1984; 1985).

The harmful effects of Al on young rats through Al transfer during lactation (Yumoto et al., 2001). Oral administration of Al salts via drinking water, food or gavage has been shown to cause embryo/fetal damage in rats and mice.

Diagnosis: Aluminum poisoning can be identified by looking at the history of exposure, the symptoms, and the amount of Al. It can be measured in tissue, blood, urine, feces, and hair with an atomic absorption spectrometer or an inductively coupled plasma spectrometer. The only measurement of urine can indicate whether a person has recently been exposed to excessive levels of Al. High concentrations in the lung are typically indicative of inhalation exposure, whereas elevated concentrations in the bone, liver, and spleen indicate sequestration.

When Al phosphide poisoning is suspected, liver and kidney tests for Al and stomach/rumen content test for phosphine are performed in the diagnostic setting. Aluminum concentrations in cattle and sheep 6-11 ppm (in the liver) and 4-5 ppm (in the kidney) are considered toxic. Aluminum levels of ≥1.2 ppm in the canine liver are regarded as elevated. Dietary Al levels exceeding 1 200 ppm are considered toxic to cattle and sheep. There is insufficient data to establish a correlation between Al exposure levels and blood or urine levels (Gupta, 2012a).

Treatment: For acute Al toxicity, there is no particular treatment present. So, the treatment contains symptomatic and supportive therapies (Gupta, 2012a). Prevention and treatment of Al toxicity may involve decreasing ingestion and intestinal absorption, increasing renal extraction and tissue accumulation, and administering antioxidants and chelating agents (Igbokwe et al., 2019). Given activated charcoal can be beneficial. For chronic exposure, chelation therapy with deferoxamine or 3-hydroxypyridine-4-ones is highly efficacious (Gupta, 2012a). Deferoxamine, a crystalline base chelating drug, is used in the treatment of Al intoxication. The primary use of deferoxamine is as an iron-chelating medication to treat iron overload. But because iron and Al share some chemical properties, it can also effectively remove too much Al from the body. Malic acid, selenium, melatonin, boric acid, and vitamin C can be used to treat Al toxicity. Plants and extracts of ginger, grape seed, wheat grass powder, black tea, and fenugreek seed may be used to ameliorate the toxicosis caused by Al exposure. Moreover, chenodeoxycholic acid reduced the neurotoxicity of Al by increasing insulin sensitivity (Igbokwe et al., 2019), and propolis prevented the genetic and hepatic damage caused by Al poisoning (Turkez et el., 2010). As a chelating agent and antioxidant, chlorogenic acid was advantageous against the toxicity of Al (Cheng et al., 2019).

Relationship with cancer: Recent studies suggest that Al may play a role in two disorders affecting the mammary gland (breast cancer and cyst) (Ogoshi et al., 1994; Darbre, 2016; Gorgogietas et al., 2018). Al levels in the breast tissues of breast cancer patients were higher than in blood serum. Cancer patients had higher Al levels in nipple aspirates than healthy controls and breast cyst liquid had higher Al levels than milk or serum (Darbre et al., 2011; 2013a, b; Darbre, 2016). Al levels in breast cancer patients' nipple aspirates were correlated with biomarkers of inflammation and oxidative stress in the breast (Darbre et al., 2013b). Carcinogenesis is a possible result of the buildup in breast tissue, which may affect the biological features of breast epithelial cells. (Pineau et al., 2014). According to current findings, Al can cause DNA damage in human breast epithelial cells, leading to cell growth. As a result of working as a metalloestogen, Al may increase the risk of breast cancer. In the presence of Al, the migratory and invasive properties of estrogen-responsive MCF-7 human breast cancer

cells were improved. Long-term Al exposure boosted the motility and matrix metalloproteinase production of estrogen-unresponsive human breast cancer cells in culture (MDA-MB-231) (Darbre et al., 2013a, b; Bakir & Darbre, 2015; Darbre, 2016).

Relationship with vaccine: Some adjuvants, such as Al compounds, enhance the development of aggregates, which are easier to phagocytose. Vaccines containing different levels of Al salts are used in both humans and animals (Spickler & Routh, 2003). Several commercial vaccinations use Al components (Table 2).

Table 2. Some types of vaccines used in veterinary medicine (Lindblad, 2004; Jensen-Jarolim, 2015; Burakova et al., 2018).

Viral vaccines	**Bacterial vaccines**	**Experimental antiparasitic vaccines**
Avian infectious bronchitis virus	*Bacteriodes nosodus*	*Cooperia punctata*
Canine hepatitis virus	*Bordetella bronchispetica*	*Nematospiroides dubius*
Foot-and-mouth Disease	*Cl. botulinum, Cl. chauvoei, Cl. chauvoei, Cl. perfringens, Cl. septicum, Cl. sordellii*	*Onchocerca lienalis*
Newcastle Disease Virus	*Leptospira interrogans*	*Trichinella spiralis*
Bovine herpes virus 1 (IBRV)	*Pasteurella multocida*	
Parainfluenza virus type 3 (PI3V)	*Haemophilus somnus*	

Al salt causes high-titer IgG antibodies with long-term the immune system, ease of formulation, and safety. Early tests with potassium Al showed that the depot effect of the adjuvant increased the immune response in rabbit. Many therapeutic trials have used Al compounds with other adjuvants to boost Th1 cell-mediated responses and improve their efficiency against viral infections (Burakova et al., 2018). Al adjuvants increase the T helper 2 (Th2) immunological response by secreting IL-4. This produces IgG, IgE, and eosinophil, making these adjuvants ideal candidates for antibacterial and antiparasitic vaccines.

Vaccines containing Al may cause significant granulomas in sheep. Granulomas are frequently linked to storage adjuvants, and their resolution can take weeks or months. At the end of the 1980s, there was a worrying increase in the incidence of vaccine-associated sarcomas in cats. Currently, available data places the incidence of these sarcomas between 1 and 10 per 10,000 vaccinated cats. These vaccine-associated sarcomas form at the site of immunization, contain residual Al adjuvant, and have inflammatory features. They have been associated with rabies, feline leukemia, and additional vaccines. Al adjuvants can cause inflammation and cats should avoid them. Nevertheless, this recommendation is contentious.

Relationship with antacids: Aluminum- containing antacids include Al salts; Al hydroxide, Al magnesium silicate, Al phosphate, and Al chloride. Al-based mineral antacids

have the effect of increasing the pH of the stomach. But the salts can cause constipation. So, it's common practice to combine these active ingredients. Patients with kidney disease can use Al hydroxide to stop their bodies from absorbing as much phosphate because Al creates phosphate complexes in the intestine (Boothe, 2001; Segev et al., 2008; Papich; 2018).

Relationship with nanomedicine: Aluminum-oxide nanoparticles (Al-NPs) are among the most important nano-metals, with extensive applications in a variety of disciplines, including veterinary, medicine, food, agriculture, industry, engineering, and others. The using of Al-NPs results in their enormous release into the environment, which may have negative effects on animal and human health. The extensive application of Al-NPs in a variety of applications has adverse effects on animal and human health (Elkhadrawey et al., 2021). It has been reported that Al-NPs were rapidly absorbed and systemically distributed to many organs (kidney and liver) (Krause et al., 2020). It accumulated most in the kidneys, blood, liver, and brain. This showed that size is a barrier to the absorption of Al-oxide in rats (Balasubramanyam et al., 2009). Al-NPs may induce liver damage, kidney damage, neurological damage, oxidative stress, DNA damage, an inflammatory response, and apoptotic effects upon cellular accumulation. Some toxic effects are seen in Table 3 (Elkhadrawey et al., 2021).

Table 3. Studies on the toxic effects of Al nanoparticles.

Toxic effect	Species	Route	Effects
Hepatotoxicity	Rat	Injection	TP↓, TL↓, ALT↑ and AST↑ in serum, hepatic histopathological alterations
Hepatotoxicity	Rat	Oral	increase ALP, AST, ALT, LDH, GGT and bilirubin in plasma, histopathological changes
Hepatotoxicity	Mice	Oral	increase ALT and AST activities in serum, hepatic histopathological changes
Nephrotoxicity	Rat	Injection	increase urea and creatinine in serum, renal histopathological changes
Nephrotoxicity	Rat	Oral	increase urea, BUN and creatinine in plasma, renal histopathological changes; increase aggregation
Neurotoxicity	Mice	Injection	ROS↑, brain energy homeostasis disruption, ippocampus-dependent memory impairment, neuropathology induction
Neurotoxicity	Rat	Injection	Al accumulation, oxidative stress↑, hippocampus of acetylcholinesterase ↓
Neurotoxicity	Mice	Nasal drip	impaired spatial learning and memory, oxidative stress, pathological changes in the ultra-structure of mitochondria, mitochondrial dysfunction
Oxidative damage	Fish	Oral	Liver SOD↓, CAT↓, and GST↑
Oxidative damage	Mice	Oral	LPO↑ and GSH↓ in brain, liver, kidney and spleen
Genotoxicity	Mice	Oral	DNA damage↑ in brain, spleen, testis, liver, and kidney
Genotoxicity	Rat	Oral	DNA damage in testicular cells↑
Apoptotic effect	Rat	Oral	p53 level↑, PGC1α↓ and mTFA↓ in liver; Leyding cells caspase-3↑
Inflammatory	Mice	Nasal drip	TNF-α↑, IL-1β↑, and IL-6↑ in serum, spleen and thymus
Inflammatory	Rat	Oral	IFN-γ↑, TNF-α↑, IL-1β↑ and IL-6↑ in hippocampus

AST; Aspartate aminotransferase, ALT; Alanine aminotransferase, ALP; Alkaline phosphatase, GGT; Gamma glutamyltransferase, LDH; Lactate Dehydrogenase, BUN; Blood urea nitrogen, ROS; Reactive oxygen species, SOD; Superoxide Dismutase, CAT; Catalase, GST; Glutathione-S-Transferase, LPO; Lipid peroxidation, GSH; Glutathione, TNF-α; Tumor Necrosis Factor Alpha, IL; Interleukin, IFN; Interferon

Conclusion

There is no exact treatment for Al toxicity. In case of toxicity or overdose of Al, the effect of the cellular mechanism will be revealed by further studies. Perhaps it will be beneficial to develop and put into use new therapeutic agents and phytotherapeutic products to treat poisoning.

Financial Support

This research received no grant from any funding agency/sector.

Ethical Statement

This study does not present any ethical concerns.

Conflict of Interest

The authors declared that there is no conflict of interest.

References

Abu-Taweel, G.M., Ajarem, J.S., & Ahmad, M. (2012). Neurobehavioral toxic effects of perinatal oral exposure to aluminum on the developmental motor reflexes, learning, memory and brain neurotransmitters of mice offspring. *Pharmacology Biochemistry and Behavior, 101*(1), 49-56. https://doi:10.1016/j.pbb.2011.11.003

Bakir, A., & Darbre, P.D. (2015). Effect of aluminium on migration of oestrogen unresponsive MDA-MB-231 human breast cancer cells in culture. *Journal of Inorganic Biochemistry, 152,* 180-185. https://doi: 10.1016/j.jinorgbio.2015.09.001

Balasubramanyam, A., Sailaja, N., Mahboob, M., Rahman, M.F., Hussain, S.M., & Grover, P. (2009). In vivo genotoxicity assessment of aluminium oxide nanomaterials in rat peripheral blood cells using the comet assay and micronucleus test. *Mutagenesis, 24*(3), 245-251. https://doi: 10.1093/mutage/gep003

Bernuzzi, V., Desor, D., & Lehr, P.R. (1989). Developmental alternations in offspring of female rats orally intoxicated by aluminum chloride or lactate during gestation. *Teratology, 40*(1), 21-27. https://doi:10.1002/tera.1420400104

Bjerregaard, P., Christian, B.I., & Andersen, O.A. (2015). Ecotoxicology of metals-sources, transport, and effects on the ecosystem. In: G.F. Nordberg, & M. Nordberg (Ed.), *Handbook on the toxicology of metals* (4th ed., pp. 425-459), Academic Press.

Boothe, D.M. (2001). The analgesic, antipyretic, anti-inflammatory drugs. In: R. Adams. (Ed.), *Veterinary pharmacology and therapeutics* (8th ed., pp. 433-451). Iowa State University Press.

Burakova, Y., Madera, R., McVey, S., Schlup, J. R., & Shi, J. (2018). Adjuvants for animal vaccines. *Viral Immunology, 31*(1), 11-22. https://doi:10.1089/vim.2017.0049

Cheng, D., Zhang, X., Tang, J., Kong, Y., Wang, X., & Wang, S. (2019). Chlorogenic acid protects against aluminum toxicity via MAPK/Akt signaling pathway in murine RAW264.7 macrophages. *Journal of Inorganic Biochemistry, 190*, 113-120. https://doi: 10.1016/j.jinorgbio.2018.11.001

Cranmer, J.M., Wilkins, J.D., & Cannon, D.J. (1986). Fetal-placentalmaternal uptake of aluminum in mice following gestational exposure: effect of dose and route of administration. *Neurotoxicology*, 7, 601-608.

Darbre, P.D. (2016). Aluminium and the human breast. *Morphologie, 100*, 65-74. https://doi: 10.1016/j.morpho.2016.02.001

Darbre, P.D., Bakir, A., & Iskakova, E. (2013a). Effect of aluminium on migratory and invasive properties of MCF-7 human breast cancer cells in culture. *Journal of Inorganic Biochemistry, 128*, 245-249. https://doi: 10.1016/j.jinorgbio.2013.07.004

Darbre, P.D., Mannello, F., & Exley, C. (2013b). Aluminium and breast cancer: sources of exposure, tissue measurmenets and mechanisms of toxicological actions of breast of breast biology. *Journal of Inorganic Biochemistry, 128*, 257-261. https://doi: 10.1016/j.jinorgbio.2013.07.005

Darbre, P.D., Pugazhendhi, D., & Mannello, F. (2011). Aluminium and human breast diseases. *Journal of Inorganic Biochemistry, 105*(11), 1484-1488. https://doi: 10.1016/j.jinorgbio.2011.07.017

Dey, M. & Singh, R.K. (2022). Chronic oral exposure of aluminum chloride in rat modulates molecular and functional neurotoxic markers relevant to Alzheimer's disease. *Toxicology Mechanisms and Methods, 32*(8), 616-627. https://doi:10.1080/15376516.2022.2058898

Elkhadrawey, B, El-Bialy, B., Shimaa, A.Z., Nermeen, E.B., & Hesham, E. (2021). Potential toxic effects of aluminum nanoparticles: An overview. *Journal of Current Veterinary Research, 3*(2), 94-106. https://doi: 10.21608/JCVR.2021.199440

Frank, A.A., Hedstrom, O.R., Braselton, W.E., Huckfeldt, R.E., & Snyder, S.P. (1992). Multifocal polioencephalomyelomalacia in Simmental calves with elevated tissue aluminum and decreased tissue copper and manganese. *Journal of Veterinary Diagnostic Investigation, 4*, 353-355. https://doi:10.1177/104063879200400326

Golub, M.S., Gershwin, M.E., & Donald, J.M. (1987). Maternal and developmental toxicity of chronic aluminum exposure in mice. *Fundamental and Applied Toxicology, 8*, 346-357. https://doi:10.1016/0272-0590(87)90084-4

Golub, M.S., Keen, C.L., & Gershwin, M.E. (1992). Neurodevelopmental effect of aluminum in mice: fostering studies. *Neurotoxicology and Teratology, 14*(3), 177-182. https://doi:10.1016/0892-0362(92)90013-z

Gomez, M., Domingo, J.L., & Llobet, J.M. (1991). Developmental toxicity evaluation of oral aluminum in rats: influence of citrate. *Neurotoxicology and Teratology, 13*(3), 323-328. https://doi:10.1016/0892-0362(91)90078-b

Gorgogietas, V.A., Tsialtas, I., Sotiriou, N., Laschou, V.C., Karra, A.G., Leonidas, D.D., Chrousos, G.P., Protopapa, E., & Psarra, A.G. (2018). Potential interference of aluminum chlorohydrate with estrogen receptor signaling in breast cancer cells. *Journal of Molecular Biochemistry, 7*(1), 1-13.

Gul, B., Yerebasan, U., Korkak, F.A., Yuce, H., Baykalir, Y., Parlak Ak, T., Gul, H.F. (2022). The effect of aloe vera on interleukin-6 levels in rats given aluminium chloride. International Asian Congress On Contemporary Sciences-VII. December 9-11, 414, Olongapo City, Philippines.

Gupta, N., Gaurav, S.S., & Kumar, A. (2013). Molecular basis of aluminium toxicity in plants: a review. *American Journal of Plant Sciences, 4*(12), 21-37. https://doi: 10.4236/ajps.2013.412A3004

Gupta, R. C. (2012a). Aluminum. In: R. C. Gupta. (Ed.), *Veterinary Toxocology Basic and Clinical Principle* (2nd ed., pp. 493-498). Academic Press.

Gupta, R.C. (2012b). Placental toxicity. In: R.C. Gupta. (Ed.), *Veterinary Toxocology Basic and Clinical Principle* (2nd ed., pp. 319-336). Academic Press.

Herndon, J.M. (2015). Aluminum poisoning of humanity and Earth's biota by clandestine geoengineering activity: implications for India. *Current Science, 108*(12), 2173-2177.

Igbokwe, I.O., Igwenagu, E., & Igbokwe, N.A. (2019). Aluminium toxicosis: a review of toxic actions and effects. *Interdisciplinary Toxicology, 12*(2), 45-70. https://doi:10.2478/intox-2019-0007.

Jaishankar, M., Tseten, T., Anbalagan, N., Mathew, B.B., & Beeregowda, K.N. (2014). Toxicity, mechanism and health effects of some heavy metals. *Interdisciplinary Toxicology, 7*(2), 60-72. https://doi:10.2478/intox-2014-0009

Jensen-Jarolim, E. (2015). Aluminium in allergies and allergen immunotherapy. *World Allergy Organization Journal, 8*(1), 1-7. https://doi:10.1186/s40413-015-0060-5

Krause, B.C., Kriegel, F.L., Rosenkranz, D., Dreiack, N., Tentschert, J., Jungnickel, H., Jalili, P., Fessard, V., Laux, P., & Luch, A. (2020). Aluminum and aluminum oxide nanomaterials uptake after oral exposure-a comparative study. *Scientific Reports, 10*(1), 1-10. https://doi: 10.1038/s41598-020-59710-z

Lindblad, E.B. (2004) Aluminium compounds for use in vaccines. *Immunology Cell Biology, 82*(5), 497-505. https://doi:10.1111/j.0818-9641.2004.01286.x

Liu, J, Robert, A., & Waalkes, M.P. (2008). Toxic effect of metal. In: C.D. Klaassen. (Ed.), *Casarett and Doull's toxicology the basic science of poisons* (8th ed., pp. 931-980). McGraw-Hill.

Ogoshi, K., Yanagi, S., Moriyama, T., & Arachi, H. (1994). Accumulation of aluminum in cancers of the liver, stomach, duodenum and mammary glands of rats. *Journal of trace elements and electrolytes in health and disease, 8*(1), 27-31.

Papich, G.P. (2018). Drugs for Treating Gastrointestinal Diseases. In: J.E. Riviere & M.G. Papich (Ed.), *Veterinary Pharmacology and Therapeutics* (10th ed., pp.1245-1277). Wiley.

Patermain, J.L., Domingo, J.L., & Llobet, J.M. (1988). Embryotoxic and teratogenic effects of aluminum nitrate in rats upon oral administration. *Teratology, 38*, 253-257. https://doi:10.1002/tera.1420380309

Pineau, A., Fauconneau, B., Sappino, A.P., Deloncle, R., & Guillard, O. (2014). If exposure to aluminium in antiperspirants presents health risk, its content should be reduced. *Journal of Trace Elements in Medicine and Biology, 28*(2), 147-150. https://doi: 10.1016/j.jtemb.2013.12.002

Reinke, C.M., Breitkreutz, J., & Leuenberger, H. (2003). Aluminum in over the-counter drugs: risks outweigh benefits. *Drug Safety, 26*, 1011-1025. https://doi:10.2165/00002018-200326140-00003

Segev, G., Bandt, C., Francey, T., & Cowgill, L.D. (2008). Aluminum toxicity following administration of aluminum-based phosphate binders in 2 dogs with renal failure. *Journal of Veterinary Internal Medicine, 22*, 1432-1435. https://doi:10.1111/j.1939-1676.2008.0206.x

Soni, M.G., White, S.M., Flamm, W.G., & Burdock, G.A. (2001). Safety evaluation of dietary aluminum. *Regulatory Toxicology and Pharmacology, 33*(1), 66-79. https://doi:10.1006/rtph.2000.1441

Spickler, A.R., & Roth, J.A. (2003). Adjuvants in veterinary vaccines: modes of action and adverse effects. *Journal of Veterinary Internal Medicine, 17*(3), 273-281. https://doi:10.1111/j.1939-1676.2003.tb02448.x. PMID: 12774966

Turkez, H., Yousef, M.I., & Geyikoglu, F. (2010). Propolis prevents aluminium-induced genetic and hepatic damages in rat liver. *Food and Chemical Toxicology, 48*(10), 2741-2746. https://doi: 10.1016/j.fct.2010.06.049.

Varner, J.A., Huie, C., & Horvath, W. (1993). Chronic AlF3 administration. II. Selected histological observations. *Neuroscience Research Communications, 13*, 99-104.

Varner, J.A., Jensen, K.F., & Horvath, W. (1998). Chronic administration of aluminum fluoride or sodium fluoride to rats in drinking water: alterations in neuronal and cerebrovascular integrity. *Brain Research, 784*, 284-298. https://doi: 10.1016/s0006-8993(97)01336-x

Wilson, R.W. (2011). Aluminum. In: C.M. Wood, A.P. Farrell, & C.J. Brauner (Ed.), *Fish Physiology* (1 st ed., pp. 67-123). Academic Press.

Yokel, R.A. (1984). Toxicity of aluminum exposure during lactation to the maternal and suckling rabbit. *Toxicology and Applied Pharmacology, 75*(1), 35-43. https://doi:10.1016/0041-008x(84)90073-5

Yokel, R.A. (1985). Toxicity of gestational aluminum exposure to the maternal rabbit and offspring. *Toxicology and Applied Pharmacology, 79*(1), 121-133. https://doi:10.1016/0041-008x(85)90374-6. PMID: 404939

Yumoto, S., Nagai, H., Matsuzaki, H., Matsumura, H., Tada, W., Nagatsuma, E., & Kobayashi, K. (2001). Aluminium incorporation into the brain of rat fetuses and sucklings. *Brain Research Bulletin, 55*(2), 229-234. https://doi:10.1016/s0361-9230(01)00509-3