UDC code: 546.62+504.054
DOI: https://doi.org/10.17816/MAJ64912

THE PHYSICOCHEMICAL PROPERTIES AND DISTRIBUTION OF ALUMINUM IN THE ENVIRONMENT, THE EFFECT ON LIVING ORGANISMS, THE REDUCTION OF ITS TOXIC EFFECT

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To cite this article: Kutai VE, Tsygankov VYu. The physicochemical properties and distribution of aluminum in the environment, the effect on living organisms, the reduction of its toxic effect. *Medical Academic Journal.* 2021;21(2):25–36. DOI: https://doi.org/10.17816/MAJ64912

Received: 07.04.2021 Revised: 16.05.2021 Accepted: 21.06.2021

The review examines the physicochemical properties, distribution in the environment, the effect on living organisms, including toxicity and ecotoxicity, ways of removing aluminum and its compounds from the human and animal organism. Analysis of scientific literature has shown that the widespread use of aluminum in nature, its use in the agricultural, food, cosmetic, aluminum, oil-producing industries, medicine, water treatment processes and other fields of activity leads to an increased intake of this element into the human body. The cumulative nature of the toxic effect of aluminum and its compounds leads to negative consequences for the respiratory, nervous, musculoskeletal systems, and mammary glands.

Keywords: aluminum toxicity; cognitive dysfunction; toxicokinetics and toxicodynamics of aluminum.

ФИЗИКО-ХИМИЧЕСКИЕ СВОЙСТВА И РАСПРОСТРАНЕНИЕ АЛЮМИНИЯ В ОКРУЖАЮЩЕЙ СРЕДЕ, ВЛИЯНИЕ НА ЖИВЫЕ ОРГАНИЗМЫ, СНИЖЕНИЕ ЕГО ТОКСИЧЕСКОГО ДЕЙСТВИЯ

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Как цитировать: Кутай В.Е., Цыганков В.Ю. Физико-химические свойства и распространение алюминия в окружающей среде, влияние на живые организмы, снижение его токсического действия // Медицинский академический журнал. 2021. Т. 21. № 2. С. 25–36. DOI: https://doi.org/10.17816/MAJ64912

Поступила: 07.04.2021 Одобрена: 16.05.2021 Принята: 21.06.2021

В обзоре рассмотрены физико-химические свойства, распределение в окружающей среде, влияние на живые организмы, в том числе токсичность и экотоксичность, способы выведения из организма человека и животных алюминия и его соединений. Анализ научной литературы показал, что широкое распространение алюминия в природе, его использование в сельскохозяйственной, пищевой, косметической, алюминиевой, нефтедобывающей промышленности, медицине, процессах водоподготовки и других отраслях деятельности вызывают повышенное поступление этого элемента в организм человека. Кумулятивный характер токсичного действия алюминия и его соединений приводит к негативным последствиям для дыхательной, нервной, опорно-двигательной систем, молочных желез.

Ключевые слова: токсичность алюминия; когнитивные дисфункции; токсикокинетика и токсикодинамика алюминия.

Background

Aluminum is one of the most widespread and most frequently used metals in human life and activities. It is found in water, the essential compound for the existence of living organisms. Aluminum is present in natural water and aluminum dishes. Its compounds are used in water purification, which contributes to the element's entry into drinking water. The content of this metal is 8% in the earth's crust and 0.6–7.0 μg/l in atmospheric air.

In medicine, aluminum compounds are used as adjuvants. They are included in vaccines and drugs, such as antacids and buffered aspirin. Aluminum oxide and hydroxide are present in many cosmetic products for skin and nails care, antiperspirants, and others. Various compounds of this element are found in food, including dietary supplements.

In this case, the toxicity of aluminum should be considered. It is one of the most common

neurotoxic elements that cause cognitive dysfunction at high concentrations, promote Alzheimer's disease [1], and are involved in immunological disease development [2]. Its toxicity has been confirmed by *in vitro* experiments, in animals, and the results of epidemiological studies [3]. However, the mechanisms underlying this indicator are understudied.

In this regard, **this review aims** to systematize knowledge about the physicochemical properties, toxicokinetics, and toxicodynamics of aluminum and aluminum-containing compounds for a new means of binding aluminum ions and then to remove them from the human and animal body.

Physicochemical properties of aluminum and its compounds

Aluminum was discovered and extracted from rocks in the 19th century. It quickly began to be used for many purposes because of its properties, such as low gravity, ductility, reflectivity, high tensile strength, corrosion resistance, easily workable shapes, and high electrical conductivity. This is how the "aluminum age" began [4].

Over time, natural rock weathering and volcanic activity processes led to aluminum redistribution in the environment through aerosols deposited in surface waters and on the ground.

Aluminum combines with oxygen, fluorine, silicon, sulfur, and other elements. It does not exist in its elemental state under natural conditions but is usually in the form of bauxites, silicates, and cryolite. Its compounds, such as alkyl halides, hydrides, bromides, chlorides, iodides, carbides, chlorates, nitrides, and phosphides, react actively with water. However, the metal, oxide, and hydroxide forms are mostly insoluble in water and organic solvents [5].

Research experience with aluminum compounds is extensive and depends on the specific physical and chemical form. Monomeric aluminum compounds are of the greatest interest,

Table 1 / Таблица 1

Physicochemical properties of aluminum and its compounds
Физико-химические свойства алюминия и его соединений

Property	Aluminum	Aluminum oxide	Aluminum hydroxide	Aluminum phosphate	Aluminum chloride
Chemical structure	Al	Al_2O_3	$Al(OH)_3$	$AlPO_4$	$Al(Cl)_3$
Physical state	Malleable, ductile metal; cubic crystal	Crystalline powder	Bulk amorphous powder	Refractory powder	White hexagonal hygroscopic plates
Color	Silver white	White	White	White	White
Molar mass, g/mol	26.98	101.94	78.01	121.95	133.34
Density at 20°C, g/cm^3	2.70	4.0	2.42	2.56	2.48
Melting point, °C	660	~2000	300	>1460	192.6
Boiling point, °C	2327	2980	Not available	Not available	182.7[1] (sublimation temperature)
Water solubility	Insoluble	Soluble at 4°C, 0.000098 g/100 cm^3; insoluble in hot water	Insoluble	Almost insoluble	Reacts violently with water to form hydrochloric acid and heat
Solubility in other solvents	Soluble in HCl, H_2SO_4, hot water, and alkalis	Very slightly soluble in acid, alkali	Soluble in alkaline or acid solutions	Almost insoluble in acetic acid; very slightly soluble in concentrated HCl and HNO_3 acids	Soluble in benzene, carbon tetrachloride, and chloroform
Steam pressure	1 mm Hg at 1284°C	1 mm Hg at 2158°C	Not available	Not available	1 mm Hg at 100°C

[1] at 752 mm Hg.

as their solubility in water is pH-dependent, and their gastrointestinal bioavailability is much higher than that of hydrated aluminum silicates. Table 1 presents the physicochemical properties of aluminum compounds.

Distribution of aluminum in the environment

Aluminum ranks first regarding metal content in the soil, second in metal use, and is the third most abundant element. The figure illustrates the main stages of working with aluminum and its application.

Aluminum is ubiquitous. Its levels in the environment vary greatly depending on location, industrialization, degree of pollution, and the place of sampling. So, its content in soil and rocks varies from 7 to more than 100 g/kg in different geographic and geological regions. In surface water, the concentration of aluminum is usually less than 0.1 mg/l. However, in water with a high humic acid or fulvic acid content, its soluble form increases due to the good solubility of oxide and salts. Exposure to acid rain is controlled by the buffering capacity, considering the metal content in the water. Geological factors include the nature of the primary rocks concerning essential minerals and acid-soluble toxic metals and the depth, structure, and mineral and organic content of the overlying soil.

Background levels of aluminum in the atmosphere range from 0.6 to 7.0 μg/L. Higher levels are registered in urban and industrial areas, especially in industrialized cities and heavily polluted regions [4, 7].

Many natural aluminosilicate minerals are formed as a result of geological hydrothermal

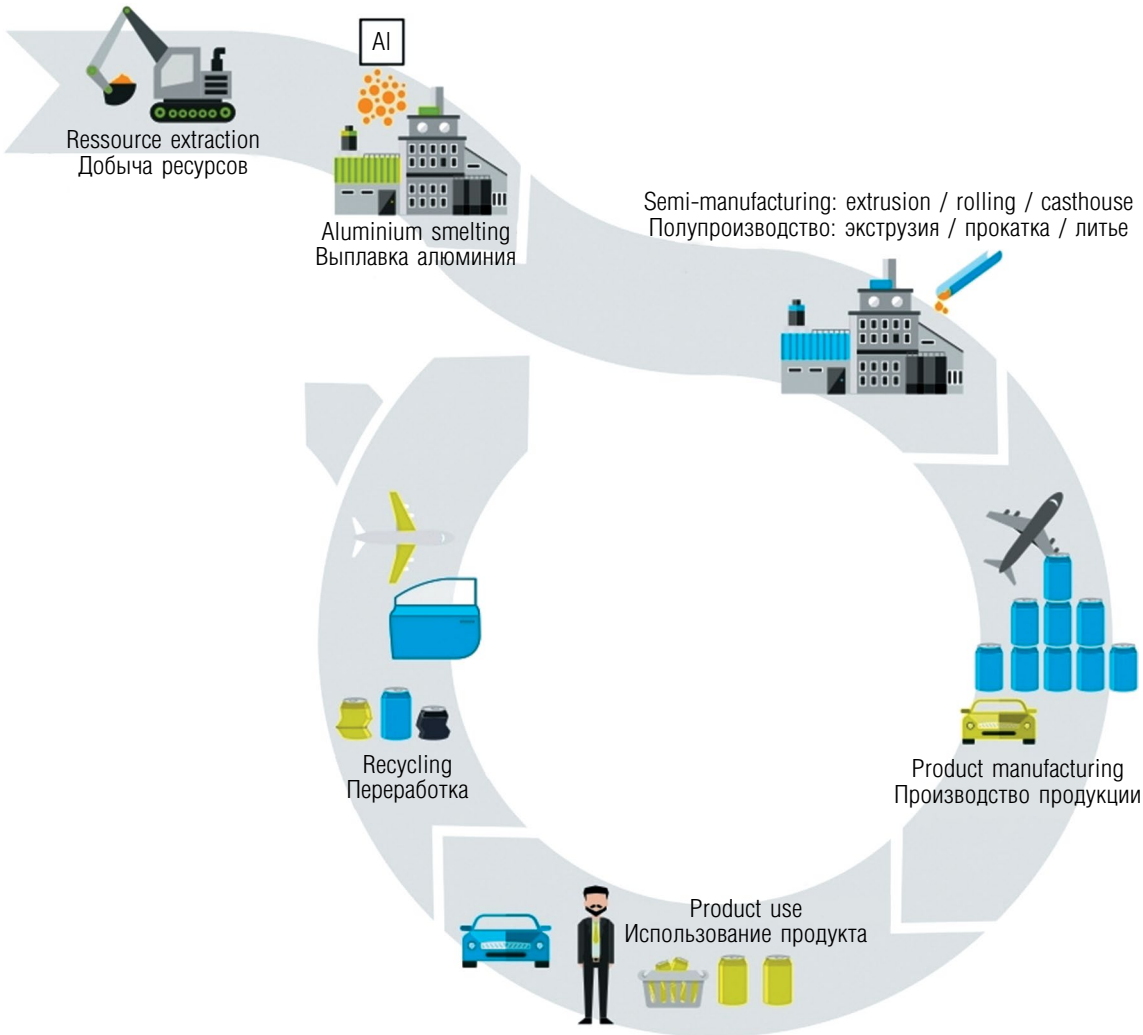

Figure. Life cycle of aluminum in the environment [6]

Рисунок. Жизненный цикл алюминия в окружающей среде [6]

processes. Similar solids can be generated from industrial activities, such as oil production [8].

In the automotive and aviation industries, aluminum is used in alloys with silicon carbide and graphite, which improve the mechanical and tribological properties of composite materials [9].

Aluminum phosphide ("rice tablet") is a component of pesticides that are inexpensive and widespread. They are used to protect grain from rodents and other household pests. Cases of mass agrochemical poisoning (accidental and intentional) resulting in death have occurred in Albania, Iran, Saudi Arabia, India, Iran, the Sub-Himalayan region, and Nepal. Self-poisoning by pesticides accounts for about 20%–25% of suicides in the Western Mediterranean, Africa, and Southeast Asia [10–16].

Aluminum hydroxide, aluminum phosphate, and alum represent the primary forms of aluminum widely used globally as adjuvants and enhance the body's immune response [17].

Alumina and aluminum hydroxide are found in cosmetic products, such as nail products, makeup remover, skincare products, and lipsticks. Aluminum hydroxide can also be found in oral hygiene and tanning products [18].

Aluminum oxide and hydroxide are used in cosmetic products, such as flatting agents, absorbents, abrasives, and antiperspirants [19].

Among the aluminum-containing medicinal drugs, antacids and aspirin are the most widespread and studied [20].

Aluminum is used for water purification. Although a small amount of it enters the water, aluminum is found in various food products that directly or indirectly affect the body. Various aluminum compounds, such as oxides, are used as preservatives, fillers, colorants, and emulsifiers, leading to their increased content in certain products. Aluminum-containing food additives are E523, E541, E554, E555, E556, E558, and E559. Aluminum is also present in infant formula [21–23].

Toxicokinetics and toxicodynamics of aluminum and its compounds

The bioavailability of aluminum depends on its combination with other elements and food components that can form complexes with aluminum, thereby increasing or inhibiting its absorption. When administered orally, the bioavailability of aluminum increases due to citrate and other carboxylic acids, acidic pH, uremia, and increasing doses of soluble forms of aluminum. In contrast, its bioavailability decreases with the administration of silicon-containing compounds [20]. Aluminum is poorly absorbed on oral and inhalation exposure. It has almost no absorption percutaneously. Approximately 0.1%–0.6% of ingested aluminum is usually absorbed. In aluminum hydroxide, absorption is about 0.1%, and excretion from intramuscular areas and the abdominal cavity is slow. However, it is completed in a few days if the doses are within physiological limits and do not mix with chloride and nitrate anions [24]. Aluminum hydroxide dissolves slowly in the stomach. It reacts with hydrochloric acid to form aluminum chloride and water to inhibit the action of pepsin by increasing the pH and adsorption. The kidneys excrete more than 95% of aluminum due to glomerular filtration, and less than 2% are excreted with bile.

The toxic effect of aluminum and its compounds is cumulative. Aluminum accumulates in the bones, liver, lungs, and brain, negatively affecting the respiratory, nervous, and musculoskeletal systems.

Many nervous system dysfunctions can be associated with aluminum neurotoxicity and its accumulation in the body [19, 25]. The earliest studies date back to 1980–1990. At that time, the onset of Alzheimer's disease was associated with aluminum neurotoxicity. However, today there is no consensus on the relationship between these two factors. Some studies report that aluminum deposits were initially detected in patients after the onset of Alzheimer's disease, whereas other researchers report Alzheimer's disease was induced by aluminum deposits [26].

Aluminum can cross the blood-brain barrier, inducing various cell damage and cell death.

Aluminum affects the membrane functions of the blood-brain barrier, increases the rate of transmembrane diffusion, selectively modifies the saturable transport systems without disrupting membrane integrity or changing central nervous system hemodynamics. Such changes in the access to the brain of nutrients, hormones, toxins, and drugs can cause central nervous system dysfunction [27].

The action of aluminum is associated with neurodegenerative diseases, such as autism, multiple sclerosis, epilepsy, and amyloid angiopathy.

In multiple sclerosis, increased aluminum concentrations in brain tissue have been registered [28]. In other studies, a relationship was revealed between the neurotoxicity of aluminum and epilepsy, where the hippocampus was the primary site of aluminum deposition; among other things, in their work, scientists mentioned Dravet syndrome [29]. Increased aluminum deposits in the brain were detected in the study of brain tissue with autistic disorder [30]. Aluminum is assumed to exhibit cytotoxicity, and it affects both neurons and neuronal cells. Its content correlates with inflammatory cells. Aluminum accumulations are both extracellular and intracellular. Aluminum neurotoxicity is associated with cerebral amyloid angiopathy [31]. In this case, intracellular aluminum accumulation and the connection with inflammatory cells and neuroglia cells were revealed.

The occupational exposure of aluminum industry workers is due to the inhalation of aluminum dust and the effect of aluminum nanoparticles on the central nervous system [26, 32]. This particle deposition begins in the alveoli and then enters the bloodstream and gains exposure through the nasal cavity to the olfactory neurons. Then, it is absorbed through the systemic circulation of the nasal cavity choroid. When particles are deposited in the lungs, fibrosis develops, and dermatitis develops when aluminum dust and alloys contact the skin. Aluminum industry workers also have high levels of aluminum in their urine and blood plasma.

Aluminum compounds accumulate in bone osteoblasts, the sites of calcium salt deposition, and therefore, the calcification process deteriorates, and osteomalacia develops. At the same time, hypercalcemia and hypercalciuria can occur in the body with an excess of aluminum content due to the calcium imbalance. The aluminum deposited in the bones prevents the normal process of calcium salt deposition and displaces it. Hypocalcemia results from hungry bone syndrome, which manifests as the chelating of aluminum deposited in the bones using deferoxamine. Also, its removal from the bones leads to the absorption by bone tissue of large amounts of excess calcium in the blood, resulting in hypocalcemia and a low concentration of parathyroid hormone in blood serum [33]. The half-life of aluminum in bone tissue is very long and can last for several years. Such processes are especially hazardous for children since they develop bone tissue. However, these processes are also typical for people of other age groups, who have problems with renal function, receive hemodialysis, perineal dialysis, or complete parenteral nutrition. Aluminum can bind to transferrin, which causes adverse consequences [25, 26]. In addition, it is reported that when aluminum is administered to rats at a dose of 200 mg/kg, the level of hemoglobin and leukocytes is significantly reduced, and the regulation of the acquired immune response is impaired [34, 35].

Aluminum can adversely affect the gastrointestinal tract. According to one study [36], inflammatory processes in the colon are caused by an increase in inflammatory cytokines. Aluminum-induced dysfunction of the epithelial barrier negatively affects the expression of proteins that support the intestine in performing its barrier function.

Aluminum affects estrogen, estrogen signaling and lowers the levels of other antiapoptotic molecules. In addition, aluminum affects the mitochondria and exhibits toxicity that can cause their dysfunction. In one experiment, aluminum hydrochloride increased reactive oxygen species, promoting oxidative stress in nerve cells. Researchers have identified the effect of aluminum hydrochloride on specific estrogen receptor proteins, namely ERα and ERβ. In particular, it lowered the level of ERβ and increased the level of ERα.

In contrast, ERβ has antioxidant and antiapoptotic properties, and an increase in ERα may weaken these functions. Aluminum hydrochloride reduced the induction of ERβ in both undifferentiated and neuronally differentiated neuroblastoma cells. Aluminum compounds influenced estrogen signaling in estrogen-sensitive breast cancer by increasing estrogen receptor alpha protein and others [37].

Acute toxicity and ecotoxicity of aluminum are presented in Tables 2 and 3. Chronic toxicity has been the most studied for aluminum chloride (Table 4).

Promising methods for removing aluminum from the human and animal body

One option for solving the toxic effects of aluminum on human health is using materials with metal-binding activity. The most promising of

Table 2 / Таблица 2

Acute aluminum toxicity
Острая токсичность алюминия

Component	LD_{50}*, oral	LD_{50}*, transcutaneous	LC_{50}**, inhalation
Aluminum	>5900 mg/kg (rat)	Not listed	Not listed
Aluminum oxide	No information available		
Aluminum hydroxide	>5000 mg/kg (rat)	Not listed	Not listed
Aluminum phosphate	>5 g/kg (mouse)	>4640 mg/kg (rabbit)	Not listed
Aluminum chloride	3470 mg/kg (rat)	>2 g/kg (rabbit)	Not listed

* LD_{50} — median lethal dose; ** LC_{50} — median lethal concentration.

Table 3 / Таблица 3

Aluminum ecotoxicity
Экотоксичность алюминия

Component	LC_{50}*, fish: *Ctenopharyngodon idella* (grass carp)	LC_{50}*, crustaceans: *Daphnia magna* (water flea)	LC_{50}*, fish: *Oncorhynchus mykiss* (rainbow trout)	LC_{50}*, fish: *Gambusia affinis* (topminnow)
Aluminum	260 μg/l/96 h	2.6 mg/l/24 h	120 μg/l/96 h; static	–
Aluminum chloride	–	LC_{50}: 3.9 mg/l 48 h LC_{50}: 27.3 mg/l 48 h	–	27.1 mg/l 97 h

* LC_{50} — median lethal concentration.

Table 4 / Таблица 4

Chronic toxicity of aluminum chloride (38)
Хроническая токсичность алюминия хлорида (38)

Route of administration/organism	Dose (lowest toxic dose)	Effects
Intracerebral/mouse	1000 μg/kg/5 days intermittently	Degenerative changes (brain and integument), changes in psychophysiological test results (behavioral)
Intraperitoneal/mouse	1000 μg/kg/5 days intermittently	It adversely affects the testes, epididymis, spermatic duct (reproductive system), and lipid metabolism as a mediator, including transport (biochemical)
Intraperitoneal/rat	415 mg/kg/21 days intermittently	Changes in the number of leukocytes (blood), changes in iron levels (nutritional value and general metabolism), inhibition, induction, or alterations of enzyme activity in the blood or tissues (biochemical)
Intraperitoneal/rat	6000 mg/kg/60 days intermittently	Degenerative changes (brain and integument), change in classical determination (behavioral), inhibition, induction, or changes in the activity of enzymes in the blood or tissues: oxidoreductase (biochemical)
Oral/rabbit	3808 mg/kg/16 weeks intermittently	It adversely affects the spermatogenesis, including genetic material, morphology, motility, and sperm count (reproductive system), changes in testicular weight (associated with chronic factors), inhibition, induction, or changes in enzyme activity in the blood or tissues (biochemical)
Oral/mouse	12600 mg/kg/18 weeks intermittently	Degenerative changes (brain and integument), inhibition, induction, or changes in the activity of enzymes in the blood or tissues, namely true cholinesterase (biochemical), inhibition, induction. or changes in the activity of enzymes in the blood or tissues, namely catalase (biochemical)

End of Table 4 / Окончание табл. 4

Route of administration/organism	Dose (lowest toxic dose)	Effects
Oral/rat	4500 mg/kg/45 days intermittently	Changes in psychophysiological test results (behavioral); induction, or changes in the activity of enzymes in the blood or tissues, namely true cholinesterase (biochemical)
Oral/rat	2380 mg/kg/70 days intermittently	Changes in testicular weight (associated with chronic factors), inhibition, induction, or changes in the activity of enzymes in the blood or tissues (biochemical)
Oral/rat	476 mg/kg/4 weeks intermittently	Degenerative changes (brain and integument), inhibition, induction, or changes in the activity of enzymes in the blood or tissues, namely true cholinesterase (biochemical), impaired liver function (liver)
Oral/rat	4200 mg/kg/6 weeks intermittently	Degenerative changes (brain and integument), inhibition, induction, or changes in the activity of enzymes in the blood or tissues, namely true cholinesterase (biochemical); inhibition, induction or changes in the activity of enzymes in the blood or tissues, namely oxidoreductase (biochemical)
Oral/rat	5600 mg/kg/16 weeks intermittently	Changes in psychophysiological test results (behavioral), weight loss or weight reduction (nutritional value and general metabolism), inhibition, induction, or alteration of enzyme activity in the blood or tissues (biochemical)
Oral/rat	2307 mg/kg/26 weeks intermittently	Changes in motor activity (specific analysis) (behavioral), changes in serum composition (bilirubin, cholesterol) (blood), inhibition, induction, or changes in the activity of enzymes in the blood or tissues, namely phosphatase (biochemical)

these are nonstarch polysaccharides. Their primary sources are terrestrial plants, algae, herbs, and some types of bacteria and fungi [39]. Different types of nonstarch polysaccharides have diverse biological properties and differ in the type of effects on human health. They can interact with heavy metals to form ion-coordination bonds by participating with carboxyl and hydroxyl groups of the uronic acid pyranose cycles of neighboring polymer chains is of greatest interest [40–42]. This property enables using polyuronides to prevent the absorption of toxic metals from the intestine into the blood and facilitates the excretion of metal ions deposited in the body [43].

Japanese scientists identified two aluminum-tolerant strains, Alt-OF2 and Alt-OF5, of *Schizoblastosporion* genus yeast that absorb aluminum. The use of these yeast strains to extract aluminum ions from processed food products has been proposed [44].

Studies in mice treated with aluminum chloride showed that treatment with isorhynchophylline resulted in decreased malondialdehyde levels, increased superoxide dismutase and catalase activity, increased glutathione levels and suppressed acetylcholinesterase activity in mouse brain tissue. The experiment demonstrated that isorhynchophylline reduced learning and memory impairments caused by aluminum salts in rodents [45].

In a rat experiment, the joint administration of silymarin with aluminum chloride corrected the neuronal damage in the rat hippocampus caused by aluminum chloride administration [46]. When other researchers administered D-(–)-quinic acid to animals, they registered a decrease in histopathological changes in animals with aluminum chloride-induced dementia, such as Alzheimer's disease [47].

In albino mice with aluminum chloride-induced cognitive impairment, the simultaneous administration of citicoline and magnesium sulfate induced a significant increase in the discrimination index in object recognition and the

delay time in the passive avoidance test. Thus, citicoline prevented memory impairment caused by aluminum chloride, and magnesium sulfate reversed the destructive effect of the latter on memory [48].

Conclusion

An analytical review was performed to study the mechanisms of action of aluminum and aluminum-containing compounds and the search for a new means of binding and excretion. Studying the physicochemical properties and the effects of aluminum and its compounds on humans and mammalian organisms enabled the development of promising methods for treating aluminum intoxication. According to the studies analyzed, the main organs and systems that are most susceptible to the influence of aluminum are the nervous (brain), respiratory (lungs), and musculoskeletal (bones) systems, and the liver and organs of the gastrointestinal tract. Due to the ubiquitous occurrence of aluminum in the environment, reducing its toxic effects remains relevant. Today, scientists are improving the existing therapeutic methods and exploring new ways to reduce aluminum concentrations in living organisms for the prevention and treatment of intoxication with this element.

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