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INVESTIGACIÓN

Alzheimer's disease and its association with dietary aluminum: a review

Enfermedad de Alzheimer y su relación con el aluminio consumido a través de los alimentos: una revisión

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Abstract

Context: Alzheimer is a neurodegenerative disease that not only occurs in the adult population. Some cases have also occurred in younger people. This has led to research relating to the ingestion of aluminum (considered a precursor to this disease) including its sources, which in many cases comes from food consumption.

Objective: To conduct a literature review to provide an overview of Alzheimer's disease and its relationship to dietary aluminum.

Methodology: A literature review was carried out using the Scopus databases Science Direct, SpringerLink, Scielo, ResearchGate, Web of Science, and Google Scholar. In addition, information was obtained from websites.

Results: Studies were found which associated aluminum intake in various forms with the onset of Alzheimer's disease. Other studies demonstrated the presence of aluminum residue in various prepared foods through direct or indirect migration from utensils, water, or additives used in their preparation.

Conclusions: It was identified that some foods can be a high source of aluminum intake due to leaching, direct absorption from the soil, or through the addition of this element via additives or colorants. This has raised awareness because of the link between this metal and Alzheimer's disease.

Keywords: contaminated food, dementia, health, heavy metal, migration, water.

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Resumen

Contexto: El Alzheimer es una enfermedad neurodegenerativa que no solo se presenta en población adulta, sino que algunos casos también se han presentado en personas de menor edad. Esto ha llevado a que se realicen investigaciones relacionando la ingesta de aluminio (el cual es considerado un precursor de esta enfermedad) y su fuente de ingesta, que en muchos casos es provenientes del consumo de alimentos.
Objetivo: Establecer mediante una revisión literaria una visión general de la enfermedad de Alzheimer y su relación con el aluminio consumido a través de la ingesta de alimentos.
Metodología: Se realizó una revisión de literatura, usando como herramientas las bases de datos Scopus, Science Direct, SpringerLink, Scielo, ResearchGate, Web of Science e Google schoolar. Además, se contó con información proveniente de sitios web.
Resultados: Se encontraron investigaciones donde se asocia la ingesta de aluminio en diferentes formas con la aparición de Alzheimer. Asimismo, se hallaron estudios en los cuales se demostraron la presencia de residuos de aluminio en distintos alimentos preparados, por la migración directa o indirecta de utensilios, agua o aditivos utilizados en su preparación.
Conclusiones: Se pudo identificar que algunos alimentos pueden ser una alta fuente de ingesta de aluminio debida a la lixiviación, a la absorción directa del suelo o por la adición de este elemento a través de aditivos o colorantes. Esto ha generado conciencia debido a la relación existente entre este metal y la enfermedad de Alzheimer.

Palabras clave: alimentos contaminados, demencia, salud, metal pesado, migración, agua.

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INTRODUCTION

Dementia is a disease which is a common and progressive neurological disorder primarily associated with older people (Kjaergaard *et al.*, 2021). The prevalence and reporting of this disease varies according to the region of the world; countries with the best health care systems typically report a higher number of people suffering from this disease. According to data reported by the World Health Organization (WHO) in 2019, the highest registration of people with dementia occurred in the Pacific region (20.1 million reported cases), followed by Europe (14.1 million), the Americas (10.3 million), South-East Asia (6.5 million), the Eastern Mediterranean (2.3 million), and Africa (1.9 million) (WHO, 2021). The low registration of dementia cases in Africa may be associated with the poor healthcare systems in the majority of African countries. Currently, few countries give the necessary priority to dementia patients to access diagnostic and post-diagnostic services. This, coupled with low education, low socio-economic status, depression, social isolation, physical inactivity, smoking, hypertension, obesity, and diabetes, results in the under-recording of dementia cases (Mukadam *et al.*, 2019).

Alzheimer's is considered the most common neurodegenerative disease. Its main characteristics are gradual memory loss and impairment of cognitive functions, including attention span, language, and visuospatial skills (Ballard *et al.*, 2016; Martinez *et al.*, 2019). According to the American Alzheimer's Association (2023), between 2000 and 2017, the number of reported deaths from Alzheimer's disease (AD) compared to the number of deaths from stroke, heart disease, and prostate cancer increased by 145 %. In 2019, AD was the sixth leading cause of death in the United States and the fifth leading cause of death among Americans aged 65 and older, according to official death certificates. However, between 2020 and 2021, it was the seventh leading cause of death due to deaths from SARS-CoV-2. Currently, approximately 6.7 million people have AD; this number may increase to 7.2 million in the United States by 2025, while it is expected that there will be 115 million people with AD worldwide by the year 2050.

AD is not a disease that only affects older individuals, as there have been cases where this disease begins in individuals with an average age of 50 years. In these cases, it is unknown whether there was a genetic predisposition. Studies which included cases of this type have found that the affected subjects have been exposed occupationally (Exley *et al.*, 2014; Mirza *et al.*, 2016) or environmentally (Exley and Esiri, 2006) to high levels of aluminum for prolonged periods. These results have allowed researchers to identify the link between exposure to this element with the onset of AD (Exley, 2017).

Aluminum is one of the most abundant chemical elements in nature, being a metal with proinflammatory, pathological, and genotoxic characteristics which is especially harmful to the homeostatic performance of brain cells, particularly as concerns normal genetic and cytoplasmic functioning. This metal migrates to humans through the consumption of water, contaminated food, and/or processed foods that contain alumimum which is frequently used in packaging and preservatives and/or colorants, the latter being the most bioavailable form absorbed by the intestine. The consumption of food contaminated with aluminum can gradually lead to memory loss. It should be noted that the maximum tolerable level of aluminum exposure is 1 mg aluminum/kg body weight/week (Crisponi *et al.*, 2013; Bondy, 2016; Matías-Cervantes *et* *al.*, 2018).

Considering the relationship between aluminum and AD, studies have been developed such as those conducted by Matias-Cervantes *et al.* (2018), Mera *et al.* (2016), Arcila and Peralta (2016) and Ekong *et al.* (2017), evidencing that treated water could be contaminated with aluminum, this being one of the main routes of intake. This has led to new research on the use of vegetable coagulants obtained from seeds (moringa, jatropha curcas, nirmali), peels, rinds, and skins (banana, watermelon, beans, cassava, papaya, okra), fruit waste, and other natural sources to reduce the use of traditional aluminum-based coagulants (alum, sodium aluminate, aluminum chloride, polyaluminum chloride, polyaluminum chlorosulfate, and polyaluminum sulfate) due to their associated health hazards (Teh *et al.*, 2016; Owodunni & Ismail, 2021). Therefore, the purpose of this research was to conduct a literature review to provide an overview of Alzheimer's disease and its relationship to dietary aluminum.

METHODOLOGY

This article is based on a literature review exploring the relationship between aluminum from food or the food industry and AD, which was conducted by searching for publications available in the databases Scopus, Science Direct, SpringerLink, Scielo, ResearchGate, Web of Science, and Google scholar. In addition, information was obtained from websites. The books, articles, and other research sources consulted for this review were all published between 2003 and 2023. For the above, keywords and boolean operators were used (Table 1).

Table 1. Terms and Boolean operators used for literary review

KEYWORDS	BOOLEAN OPERATORS
"Alzheimer's disease", "Alzheimer", "Alzheimer's" "Alzheimer's diseases", "Alzheimer disease", "Alzheimer's disease"	OR
"Aluminum", "Migration of aluminum", "exposure to aluminum", "aluminum ingestion", "aluminum in additives", "aluminum in water", "aluminum in plants", "Aluminum foil", "aluminum lixiviation"	AND/OR
"Food", "Food packaging", "food packaging materials"	AND/OR

Sources: Authors

Background

Research on AD began when Dr. Alois Alzheimer discovered histological alterations in the brain of a 51-year-old woman in the late 1880s. In 1906, Dr. Alzheimer, during a lecture in Tubingen (Germany), presented his first observations on the symptoms and pathology of this disease (Hippius and Neundörfer, 2003; Lopera, 2004). In 1907, Dr. Alzheimer formally established the existence of a new disease, which was initially considered a strange form of presenile dementia characterized by behavioral disorders, depression, psychotic symptoms, and cognitive impairment. At the time, these symptoms were considered strange because the main origin of dementia was believed to be the "hardening of the arteries". In 1910, Emil Kraepelin assigned the name .Alzheimer's disease"to this pathology, a disease which was a significant burden for patients, their caregivers, and the community at large (Hippius & Neundörfer, 2003). Subsequent advances in neuropathology allowed AD to be considered a type of presenile dementia distinct from senile dementia. This hypothesis prevailed until the 1960s, and for the next 20 years, AD remained the dominant and prototypical form of dementia, centered on prominent memory disturbances. However, the term dementia has gradually fallen out of use when referring to major neurocognitive disorder and the heterogeneity of the syndrome at the phenotypic and molecular levels has once again been recognized (Assal, 2019).

Diagnosis of Alzheimer's disease

A definitive diagnosis of AD should include multiple types of progressive cognitive impairments leading to dementia with post-mortem neuropathologic confirmation, as well as a clinical history of memory impairment. Recently, the importance of the use of biomarkers that aid in the in vivo diagnosis of AD has been accepted. Among these markers, one can find the main cerebrospinal fluid (CSF) biomarkers of AD, namely are amyloid-beta (Aβ42), which shows the cortical deposition of amyloid, total tau (t-tau), which reflects the intensity of neurodegeneration, and phosphorylated tau (p-tau), which correlates with pathological neurofibrillary changes. Magnetic resonance imaging (MRI) and fluorodeoxyglucose (FDG) positron emission tomography (PET) techniques have also been implemented to discard intracranial causes (meningioma, subdural hematoma) and have been complemented by the notion that the demonstration of regional atrophy in the medial temporal region can provide positive diagnostic information (Scheltens *et al.*, 2016).

MRI remains the modality of choice for the assessment of cerebral vascular changes, such as white matter hyperintensities, lacunae, and microbleeds, which have gained increasing attention because these are frequent secondary effects in antiamyloid trials. Meanwhile, FDG PET estimates the density and distribution of aggregated tau neurofibrillary tangles in cognitively impaired adults being evaluated for AD. Precise interpretation of FDG with PET in patients with dementia is not based on the presence or absence of a single region of hypometabolism, but should take into account the pattern of hypometabolism throughout the cortex (Scheltens *et al.*, 2016; Barthel, 2020). However, further standardization is required to have universal clinical use of biomarkers (McKhann *et al.*, 2011; Barthel, 2020). Likewise, although age is one of the primary factors associated with AD, there is a wealth of research which currently points to neurodegeneration, inflammation, atrophy, and other elements of concern as chronic circumstances that may favor the manifestation of dementia as well as the development of lesions in the structures of the medial temporal lobe, hippocampus, and entorhinal cortex. These lesions are characteristic of the anatomopathological alterations typical of AD due to Aβ protein plaques outside neurons and Tau protein neurofibrillary tangles inside neurons, physiological characteristics of a patient which usher the progression of the disease (Stephan *et al.*, 2012).

General information on aluminum

Aluminum is the third most abundant chemical element in the earth's crust, making up 7.5 % of its composition. Despite its prevalence, it has no biological function in human or animal organisms. However, its low density and ability to self-passivate cause it to be widely used in industries (Stephan *et al.*, 2012; Stahl *et al.*, 2017). According to the European Aluminum Foil Association, aluminum has been used commercially for more than a century.

Due to its abundant availability and characteristics, since the late 19th century, it has increasingly shaped the modern lifestyle and has become necessary for space exploration, electricity transmission, the construction of modern buildings, and the manufacturing of aircrafts, automobiles, vessels, and currently, high-quality packaging of various types for the food industry, to which it is especially suited given its low cost and high levels of conductivity which enable effective temperature regulation (Casaburi *et al.*, 2019).

Therefore, the production of primary aluminum has increased significantly in recent years, reaching a worldwide production level of 68,461 thousand metric tons in 2022, with China being the largest producer at 40,430 thousand metric tons (International-Aluminum, 2023). However, alloying additives and recycled aluminum, which are excluded from the processing of primary aluminum, are used in the production of secondary aluminum, a process which can be repeated almost indefinitely, which cuts costs and multiplies environmental benefits. Aluminum figures are thus expected to increase considerably due to advances in aluminum alloy metallurgy (Brough & Jouhara, 2020).

Sources and behavior of aluminum in food

The migration of aluminum into food impacts the health of consumers, bringing as consequences neurological diseases involving inflammatory neural degeneration, behavioral deterioration, and cognitive impairment (Barthel, 2020). In addition, its accumulation in the central nervous system (CNS) over time can lead to irreversible brain cell damage and functional decline resulting in cognitive, memory, and behavioral deficits. Consequently, researchers have analyzed the aluminum content of the temporal lobe neocortex, finding a range of 1.9 - 16.8 ug aluminum/gm tissue in autopsies performed on patients whose cause of death was AD (McLachlan *et al.*, 2018).

One of the causes of aluminum accumulation in the human body is the consumption of foods which contain this element, either from primary or secondary sources. Primary aluminum in food is generated by the natural migration of aluminum from the earth's crust (where this element is present) to food. This phenomenon occurs primarily in plants. Plants absorb nutrients from the soil that are used for nutrition, development, and growth. Aluminum can be found in fresh vegetables, with values between 2 and 10 mg/kg, depending on the type of soil (alkaline or acidic) where it is harvested, the concentration of aluminum present in the soil, the water used for irrigation, and the type of vegetable, leafy vegetables having the highest values, followed by bulb, stem, flower, pod, root, and tuber vegetables. In fruits, on the other hand, concentrations are lower (mean value of aluminum 1.3 mg/kg) (Liang *et al.*, 2019; Daouk *et al.*, 2020).

Estimates suggest that 40-50 % of cultivable soils worldwide are acidic (pH <5.0). Here, aluminum is present in a cationic form (being highly soluble) which allows plants to easily obtain a higher concentration (Rahman *et al.*, 2018). However, cereal plants are among the plants with the lowest aluminum accumulation. Levels of aluminum in cereal plants are also highly variable between countries or even regions of the same country, as shown in Table 2, which outlines the presence of this metal not only in grains but also in other parts of plants (leaves and shoots) and cereal-based products.

Soil geochemistry not only affects plants and plant products through aluminum migration but also alters water quality. This contamination causes water quality to decrease to levels prejudicial to biota in waterways affected by the easy discharge of aluminum due to the high solubility of this contaminant in more acidic conditions such as those in acidic soil and rain (acid rain) (Hu *et al.*, 2017; Toivonen *et al.*, 2020). Therefore, the above-mentioned phenomena may be factors in the increased levels of aluminum in some plants, as is the case of tea plants (Camellia sinensis) which are produced in acid soils with a pH range of 3.5 - 5.6 (De Silva *et al.*, 2016; Hu *et al.*, 2017). Research has reported aluminum concentrations in tea leaves between 1836.77 and 487.57 mg/kg (Peng *et al.*, 2018; de Silva *et al.*, 2016; Li *et al.*, 2015), which has generated research to address the management and control of aluminum levels in soils and crops. Reducing these levels could help counteract the concentrations present in water systems.

Besides coming from areas with acidic rocks and soils, this metal can also be found in nature, in lake water, either as untreated water or as water treated with Al salts or with electrocoagulation/electroflotation. The latter is a recognized decontamination method for water treatment

Table 2. Aluminum concentration (mg/kg) in some grains, parts of plants, or cereal products

Reference	**Plant, food, or product**	**Aluminum concentrations (mg/Kg)**	**Country**
Chen *et al.* (2008)	Rice, soybean, and corn leaves	< 500	China
	Rice sprouts	< 200	
Bratakos *et al.* (2012)	Cereals and cereal products	7.10	Greece
Chen *et al.* (2017)	Wheat	18.6	China
	Wheat	11	
	Soybeans	8.8	
Liang *et al.* (2019)	Corn	6.2	China
	Millet	2.7	
	Rice	2.1	
	Soybeans	89	
	Rye	50	
	Rice	30	
Squadrone *et al.* (2021)	Oats	28	Italy
	Triticale	21	
	Barley	20	
	Wheat	17	
	Corn	2.9	

in which aluminum electrodes can be used wherever the release of aluminum metal molecules may occur to decontaminate the water containing dyes (Garcia *et al.*, 2016). Moreover, these electrodes are used to remove heavy metals such as chromium present in water (Villabona-Ortíz *et al.*, 2021). Salts are also inappropriately used as coagulants in drinking water treatment to reduce organic matter, color, turbidity, and microorganism levels. In this way, aluminum is transported via the liquid until it reaches residences where it is sometimes consumed directly from the tap. This water could contain a higher aluminum content after purification with aluminum salts since this compound increases the percentage of dissolved polyaluminum species (Al Zubaidy *et al.*, 2011; D'Haese *et al.*, 2019).

This can cause a risk to human health, especially when aluminum is present in high concentrations ($\geq$ 0.1 mg/L aluminum) as it becomes a catalyst for AD and dementia (FAO/WHO, 2007; Matías-Cervantes *et al.*, 2018). Similarly, water treatment affects the aquatic ecosystem by generating contamination with non-essential oligoelements, mainly aluminum, which is transferred through the trophic chain to crustaceans and especially fish. The latter has been held to be amongst the most susceptible aquatic organisms to the accumulation of metals. Consequently, these marine species become vectors of metal contamination for humans which can cause health risks when levels of toxic elements are very high (Trevizani *et al.*, 2019; Dos Santos *et al.*, 2023). Therefore, research has focused on finding natural alternatives to reduce the use of aluminum salts as flocculants in drinking water purification (Ekong *et al.*, 2017; Chao *et al.*, 2020).

Another way in which humans can be exposed to aluminum is through the ingestion of aluminum through food contaminated during processing, packaging, and/or storage. This is secondary source of aluminum associated with the lixiviation of this element from kitchen equipment and utensils (pots, cutlery, trays, knives, frying pans, grills, etc.) that are manufactured with the material. Aluminum is widely used in the industry for the production of these utensils mainly because it is an easily obtainable material with good malleability, thermal conductivity, ease of clean up, and durability (Odularu *et al.*, 2013; Stahl *et al.*, 2018). Despite these industrial benefits, aluminum can easily leach into food due to factors such as the type of aluminum utensils used, exposure time, cooking temperature, salinity, pH, fat content, and food composition in general (Al Zubaidy *et al.*, 2011; Bassioni *et al.*, 2012). Another secondary factor of aluminum exposure is the use of aluminum foil in food preparation and culinary practices. Aluminum foil has been widely used to wrap heat-sensitive foods (mainly seafood and meat products) before cooking, which can generate a high concentration of aluminum in the product after heating.

Table 3 shows studies that have evaluated the leaching of aluminum from aluminum foil into various foods. It shows that the amount of leaching can increase depending on the characteristics of the food, pH, whether it is marinated (wines, citric acid, tomato juice, apple cider vinegar), acidity, or whether it contains spices or additives. Here, acidic solutions and spices, along with increased temperature and cooking time, contributed to increased leaching of the aluminum exposure area. Weidenhamer *et al.* (2016) studied the release of aluminum from cookware materials in 10 developing countries (Bangladesh, Guatemala, India, Indonesia, Ivory Coast, Kenya, Nepal, Philippines, Tanzania, and Vietnam), finding that there was an average aluminum exposure for all cookware studied of 125 mg per serving, six times higher than the provisional tolerable weekly intake for a 70-kg adult (20 mg/day). These authors made preliminary evaluations of three possible methods to reduce metal leaching in the cookware tested (boiling or near-boiling water, addition of curcumin, and fluoropolymer coating), where the fluoropolymer coating reduced up to 98 % of the aluminum level in the final extraction.

Table 3. Leaching of aluminum from food through food preparation and storage.

References	Material	Conditions	Food	Aluminum concentration (mg/kg)
Mol and Ulusoy (2020)	Wrapped in aluminum foil thickness of 12 µm. Opaque part (inner part) was in contact with the product.	Baking on the grill or griddle (200 °C for 20 min). No salt, spices, oil or metal equipment were used during preparation.	Sea bass (Dicentrarchus labrax Linnaeu)	3.8 (Baked with skin/shell) 4.9 (Baked without skin/shell)
			Mussels (Mytilus galloprovincialis Lamarck)	289 (Baked with skin/shell) 252 (Baked without skin/shell)
			Shrimps (Parapenaeus longirostris Lucas)	45.7 (Baked with skin/shell) 58.9 (Baked without skin/shell)
Fermo *et al* (2020)	Wrapped in aluminum foil thickness of 20 µm	Baking in oven (180 °C for 1 h) Seasoning and not seasoning	Chicken	40 (Seasoning)
			Beef	40 (Seasoning)
			Fish	42 (Not seasoning)
Ejovwokoghene and Philipa (2020)	Wrapped in aluminum foil	Oven drying	Barbeque catfish	0,007
Inan-Eroglu *et al.* (2019)	Wrapped in aluminum foil	Baking in oven (150 °C for 40 min and at 200 °C for 20 min) marinated	Salmon	1,228 (150 °C for 40 min)
			Haddoc	0,999 (150 °C for 40 min)
Dordevic *et al.* (2019)	Degree of aluminum leakage from aluminum foil	Baking in oven (220 °C for 40 min) marinated and not marinated	Atlantic salmon	41,86
			Mackerel Scomber,	49,34
			Duck breasts,	117,26
			Cheese Hermelín,	4,46
			Tomato,	7,78
			Paprika,	1,32
			Carlsbad dumplings,	1,88
			Pork roast,	15,87
			Pork neck,	4,91
			Chicken breasts,	5,25
			Chicken thighs	3,6
Hafez *et al.* (2018)	Aluminum cup, aluminum foil cup and silicon cup	Baking in oven (180 °C for 25 min) storage for 20 days	Orange cake	15,47
			Milk cake	12,02
			Control cake	9,02
Ertl, and Goessler (2018)	Wrapped in aluminum foil	Baking in oven (180 °C for 45 min)	Beef	0,27
			Fishfilet	0,18
			Onion	0,51
			Pork	0,28
			Poulard	0,083

			Potato without peel	0,30
			Potato with peel	1,1
Jabeen *et al.* (2016).	Wrapped in aluminum foil	Different food solutions	Chicken	209.52 (yogurt + lemon Juice)
			Beef	292.25 (tomato juice + citric acid + salt)
Al Juhaiman (2015)	Wrapped in aluminum foil thickness of 40 µm	Baking in oven (180 °C for 20, 40, 60 min and 160 °C, 180 °C, 220 °C for 60 minutes) with additives	Chicken	59.20 (60 min.) 154.04 (220 °C)
			Cow stakes	85.34 (60 min.) 111.51(220 °C)
			Fish	132.01 (60 min.) 91.23(220 °C)

Likewise, trays or containers can be found in the market, which are made of aluminum sheets with thicknesses greater than those used to make paper; these are mainly designed for solid and/or semi-solid products. Therefore, this material has attracted much interest in the industry as it is an excellent barrier against gases, light, moisture, odors, flavors, and micro-organisms and has properties of impermeability, resistance to freezing, inertness, especially perfect dead fold characteristics, and recyclability (Sarkar & Aparna, 2020). However, it can pose risks to human health due to the migration that occurs when the material comes into contact with food and is exposed to heat. This can lead to corrosion and erosion of the container, allowing aluminum to leach into the food and then follow the digestive and circulatory tract, and finally, it is stored in the tissues, including the brain; similar process happens with aluminum containers, traces of this metal are extracted from the walls of the container, it passes to the liquid phase and followed by the product, presenting itself in low pH sauces and fruit juices (Bejarano & Suárez, 2015; Deng *et al.*, 2021).

Aluminum can also be found as a secondary source of food additives. These are substances that are intentionally added to food for a technological purpose in the manufacture, preparation, processing, treatment, packaging, wrapping, transport, or preservation of the food, so the use of Al-containing additives can affect the total concentration in the final product (Yokel, 2016; FAO/WHO, 2021). In the additives market, aluminum can be found as an ingredient in several of these compounds, such as sodium aluminum sulfate (sodium aluminum duplex sulfate, E521, INS 521), potassium aluminum sulfate (potassium alum, E522, INS 522), ammonium aluminum sulfate (ammonium alum, E523, INS 523), potassium aluminum sulfate (potassium alum, E522, INS 522), ammonium aluminum sulfate (ammonium alum, E523, INS 523), sodium aluminum phosphate (aluminum salt and phosphoric acid salt, E541i, INS 541i), sodium aluminosilicate (sodium aluminum silicate, E554, INS 554), calcium aluminum silicate (E556, INS 556), and aluminum silicate (E559, INS 559). These additives are technically used in processed products and water as synthetic stabilizers, coagulants, and leavening agents to control the rate of CO2 gas generation, emulsifiers, and acidity regulators (Ogimoto *et al.*, 2016; FAO/WHO, 2021). Among the above-mentioned additives are included fermenting agents, demolding agents, anti-caking agents, and protectants such as aluminum and sodium silicate in cake mixes and dry products, gelatins, wheat flour, and wheat-based foods (including fried dough sticks, fried dough cakes, steamed bread, noodles, cakes, and pastries, etc.). These are the foods with the highest levels of aluminum and potassium dodecahydrate due to the use of aluminum and potassium sulfate dodecahydrate, fried dough cakes, steamed bread, noodles, cakes, and pastries, etc.) are the foods with the highest levels of aluminum due to the use of aluminum potassium sulfate dodecahydrate (alum) in the preparation of these types of products (Ning *et al.*, 2016; Wang *et al.*, 2022). Due to the health risks posed by aluminum, some countries, such as China, have conducted several studies (Guo *et al.*, 2015; Chen *et al.*, 2017; Ding *et al.*, 2021) on the use of additives containing this metal to provide scientific information to the government so that it can better control the limits of aluminum residues in food additives.

In the food industry, aluminum is also used as a colorant (E173), known as Çl pigment metal", which presents a silver-gray hue or tiny sheets used to decorate bakery and confectionery products (Silva *et al.*, 2022). It is also used in the extraction process of some colorants such as carmine (carminic acid E120), which is obtained naturally from cochineal when it is subjected to a heat treatment and pH 5 in combination with aluminum, citric acid, and calcium salts (Gebhardt *et al.*, 2020). This colorant is commonly used in the production of meat products (smoked fish, crustacean paste, fish paste, pre-cooked crustaceans), dairy products (yogurts, ice creams, fresh flavored cheeses, cured cheeses, edible cheese rinds), among others (candies, sweets, candies, chewing gum, desserts, cakes, pastries, candies, jams, vitamins, pharmaceutical tablets, and medicinal capsules), due to the tonality (purple to red) that it imparts in the product mainly used (Silva *et al.*, 2021). Another colorant extensively used to improve the appearance of soft drinks, dairy products, candies, and confectionery, are anthocyanins (E163) which can be obtained from vegetables and edible fruits, such as blueberries, strawberries, raspberries, blackberries, currants, and grapes. In this colorant can be found aluminum particles product of the extraction of this compound (Gebhardt *et al.*, 2020; Silva *et al.*, 2022). Also, aluminum in the form of aluminum oxide is used to improve the technological properties of titanium dioxide or "CI white pigment 6", a colorant that is used in confectionery products, decorations, dairy products and analogs, surimi and similar products, salmon substitutes, seasonings, condiments, mustard, sauces, broths, soups, among others (Ropers *et al.*, 2017; Silva *et al.*, 2022).

In general, the use of aluminum-containing additives is gaining increasing significance due to the technological benefits they offer in terms of their visual impact on food. Sometimes these additives enhance the food's color, making it much more attractive than its natural hue. Additionally, some additives like sodium aluminum silicate, calcium aluminum silicate, and aluminum silicate, serve as anti-caking agents in dry powdered products and generate greater solubility at the time of preparation (FAO/WHO, 2021). Sodium aluminum phosphate is also used to emulsify and improve product quality, melt cheese, thicken juices and sauces, and for pickling vegetables, and is found in fruit confectionery, meat binders, dough reinforcers, stabilizers, buffers, neutralizers, texturizers, and curing agents (Ogimoto *et al.*, 2016). Likewise, the additives aluminum sodium sulfate, aluminum potassium sulfate, and aluminum ammonium sulfate are used to regulate acidity in order to reduce the growth of organisms both in water and in foods, mainly of vegetable origin, resulting in them being used as preservatives. Therefore, these additives function in ways that both appeal to consumers and, at the same time, lead to better results for the industry due to the profitability of these foods on the market. Thus, in some countries, attempts to ban the use of additives which contain aluminum have not been successful, which has led to the regulation of the use of each additive based on the concentration of aluminum it contains. This includes stipulations that products must be labeled with the type of additive used according to the specifications established by the Codex alimentarium (Ropers *et al.*, 2017; FAO/WHO, 2021).

Adverse effects of aluminum on human health

According to WHO, the tolerable daily intake (TDI) of aluminum for humans should be 1 mg/kg body weight/day (FAO/WHO, 2007). Exposure at these levels is not a problem since the human body can excrete small amounts of this metal very efficiently. Unfortunately, a large part of the population is exposed to and ingests more than their bodies can excrete. As a result, the effects that this metal can produce on tissue function can be significant, starting with the reduction of human brain cell growth, proportional to the amount of concentrated aluminum (Diamond, 2008; Bassioni *et al.*, 2012). The above has spurred a surge in research on the relationship between the accumulation of aluminum in the human body and the risk of multiple neurological pathologies. Some studies, cited in Table 4, were carried out to determine the levels of aluminum present in patients diagnosed with neurological pathologies such as autism spectrum disorder, the precise origins of which are unknown. Mold *et al.* (2018) performed the first study which examined the aluminum content in the brain tissue of people diagnosed with autism. The results showed a high presence of aluminum in the extracellular and intracellular tissue, suggesting that aluminum may be related to the etiology of this disorder. Likewise, aluminum has been associated with breast cancer due to the accumulation of traces from the use of cosmetic products such as deodorants that may contain aluminum salts. In the cases studied, women and the elderly were found to be the most susceptible to the accumulation of metals in their bodies as a result of the use of some medications, environmental exposure, water intake, and foods with high concentrations of additives such as those mentioned in this study. Therefore, it is important to give consumers the information necessary to make informed decisions about the type of products consumed and the type of utensils used for their preparation. This is especially important for pregnant women, since this metal may from an early age, and research has even established that aluminum may be related to congenital malformations of the central nervous system (Troisi *et al.*, 2019).

Also in the studies mentioned in Table 4, AD is one of the most studied pathologies because of the relationship aluminum has with the neurotoxin associated with the disorder. The research indicates that the abnormal aluminum concentrations found in elderly patients, as well as in young patients with AD, can cause an excess of inflammatory activity in the brain, which is a factor that accelerates the rate of brain aging, in turn inevitably increasing the incidence of age-related neurological diseases (Bondy, 2016).

According to Exley (2017), AD is considered an acute response to chronic aluminum intoxication, with aluminum acting as a catalyst in the early onset of the disease because of the way the brain responds to this aluminum load. This metal is accumulated in the body in the frontal cortex and hippocampal regions of the brain, generating neurotoxic activities in the central nervous system which lead to decreased enzymatic activities, increased oxidative stress, and aggregation of proteins such as beta-amyloid (Aβ), all of which contribute to the generation of senile plaques where a series of processes can lead to neurodegeneration and cell death (Kabir *et al.*, 2020).

Research on aluminum from cookware and aluminum foil

One of the sources of aluminum contamination in food is cooking equipment such as pots and pans, among others, which, when subjected to high temperatures (>100 ºC), undergo a leaching process, causing the food to absorb traces of aluminum which are subsequently ingested by the consumer. In 2010, Luján studied the aluminum ingestion that occurs when boiling water and cooking food in pots made with aluminum. The results found that aluminum was present in the water and food (vegetable soup) after 30 minutes of heating at concentrations of 220 μg/L for the water and 400 µg/L for the soup. In another study, Cisneros *et al.* (2019) found a range between 2.33 and 5.12 mg/kg of aluminum in rice cooked in 6 containers from different brands, which exceeds the limits set out in European regulations of 1 mg/kg.

Another source of contamination by this element is aluminum foil, which is widely used to wrap food for cooking or reheating, either in the oven or using pots or pans. To address this concern, Ertl and Goessler (2018) evaluated the aluminum content in foods that were coated with aluminum foil and baked at 5 min at 180 °C. Notably, the results revealed a 12-fold increase of aluminum in cow (from 0.021 to 0.27 mg/kg), a 5-fold increase in onion (from 0.088 to 0.51 mg/kg), and a 4-fold increase in pork (from 0.055 to 0.28 mg/kg), after the baking process. These findings provide clear evidence of the metal leaching into the food after being subjected to a thermal process. In this same research, it was found that high temperatures are not the only cause of aluminum leaching into foods. After 3 days of refrigeration at 7 ºC, foods such as salmon, ham, lemon, and orange increased their aluminum content 16 times (from 0.13 to 2.2 mg/kg), 32 times (from 0.11 to 3.6 mg/kg), 163 times (from 0.032 to 5.2 mg/kg), and 200 times (from 0.034 to 6.9 mg/kg) respectively.

Likewise, Ejovwokoghenea and Philipa (2020) investigated the risk of aluminum consumption through the ingestion of barbecued catfish that was wrapped in aluminum foil for protection during cooking. These researchers found that the fish went from 0.039 mg/kg (raw) to 0.047 mg/kg after the cooking process, which indicated the rate of leaching of 18.65 % aluminum into the fish. However, consuming this food in small quantities, prepared as described here, does not pose a danger, as the aluminum content remains below the amount allowed by the norms (1 mg/kg).

Table 4. Research on the relationship between aluminum and human health risks

Reference	Purpose	Population	Results
Bocca *et al.* (2015)	Determination of neurotoxic metals in cases of Amyotrophic Lateral Sclerosis (ALS).	34 ALS patients (62 ± 10 years old) and 30 controls (65 ± 11 years old).	The results indicated that, Aluminum concentrations were higher in blood (p = 0.045) in ALS subjects with respect to controls (8.04 μg/L vs. 6.68 μg/L).
Virk *et al.* (2015)	occupational exposure to aluminum and risk of AD.	1056 individuals from 3 retrospective case-control studies.	Occupational aluminum exposure was not associated with AD (odds ratio, 1.00; 95 % confidence interval, 0.59 to 1.68).
Zioła- Frankowska *et al.* 2015	Evaluate the aluminum concentrations between the femoral head and neck, and whether these concentrations may pose a risk to human health.	96 patients operated on for total hip replacement (THR), not diagnosed with dementia-related diseases, nor with AD and renal disease.	The highest aluminum concentrations in the femoral neck were found in patients aged 41 - 50 years (4,443 μg/g), and in the femoral head at ages 51 - 60 years (2,478 μg/g), some cases aluminum concentrations in older patients were higher than in the younger group
Wang *et al.* (2016)	Meta-analysis to investigate whether chronic aluminum exposure is associated with an increased risk of AD.	10567 individuals from 8 cohort and case-control studies.	Chronic exposure to aluminum was found to be associated with AD with a probability of more than 71 % (OR: 1.71, 95 % confidence interval (CI), 1.35-2.18).

Linhart *et al.* (2017)	Breast cancer risk associated with the use of cosmetic products containing aluminum salts in the armpits.	460 women, 210 were breast cancer cases and 250 were healthy controls.	Median (interquartile) aluminum concentrations were significantly higher ($p = 0.001$) in cases than in controls (5.8, 2.3–12.9 versus 3.8, 2.5–5.8 nmol/g). In ten breast cancer patients, aluminum concentrations over 60 nmol/g up to 367 nmol/g dry weight (15-115 nmol/g wet weight) were observed.
Choi *et al*. (2018)	Association between serum aluminum level and amnestic mild cognitive impairment (aMCI) or AD.	136 patients with aMCI and 191 patients with AD.	Blood aluminum levels were 11.09 μg/L (95 % CI: 10.20, 12.06) in the aMIC group and 11.16μg/L (95 % CI: 10.04, 12.39) in AD patients, indicating that blood aluminum level was positively associated with the risk of aMIC and AD.
McLachlan *et al.* (2018)	Aluminum content of the temporal lobe neocortex in the brains of human neurological and neurodegenerative disease ever undertaken.	511 high quality human brain samples from 18 diverse neurological and neurodegenerative disorders, including 2 groups of age-matched controls.	There is a statistically significant trend for aluminum to be increased only in AD to a mean of ∼8.08-fold over these controls (N=186; range 1.9-16.8 ug aluminum/gm tissue); Down's syndrome (DS) to a mean of ∼4.53-fold over age and gender-matched controls (N=24; 2.0-7.1 ug aluminum/gm tissue) and dialysis dementia syndrome (DDS) to a mean of ∼3.69-fold over age and gender-matched controls (N=27; range 1.2-6.2 ug aluminum/gm tissue).

Mold *et al*. (2018)	Measured aluminum in brain tissue in autism and identified the location of aluminum in these tissues.	5 individuals with Autism Diagnostic Interview-Revised ASD, 4 males and 1 female, aged 15–50 years old.	The aluminum content of all tissues ranged from 0.01 (the limit of quantitation) to 22.11 μg/g dry wt, with a mean for each lobe of 3.82(5.42), 2.30(2.00), 2.79(4.05), 3.82(5.17) and 8.74 (11.59) μg/g dry weight.
Bichu *et al*. (2019)	Association between use of aluminum utensils for cooking and occurrence of Chronic Aluminum Toxicity (CAT) in Patients on Maintenance Hemodialysis (MHD).	31 patients on MHD for more than one year were included, 10 cases and 21 controls.	The relative risk of having CAT in Patients on Maintenance Hemodialysis (MHD) because of use of aluminum utensils compared to not using was 28.46 (1.81 to 445.3) and the odd's ratio estimated was 120 (5.45 to 2642).
Troisi *et al*. (2019)	Between specific congenital defects and maternal exposure to heavy metals.	111 patients with a diagnosis of fetal anomalies and 90 were control.	Serum aluminum concentration was significantly higher in mothers with a fetus affected by a congenital CNS defect (0.14 ± 4.72) compared to serum samples from mothers with a normally-developed fetus (-5.03 ± 1.27).
Wen *et al.* (2019)	Associations between the multiple metals in plasma and the risk of ischemic stroke.	2554 participants: 1277 newly diagnosed IS patients and 1277 control subjects.	Positive associations with ischemic stroke risk were observed for aluminum, where a concentration of 10.49 (95 % CI: 7.38, 14.90) was found in the single-metal model and 4.23 (95 % CI: 2.63, 6.79; p -trend <0.001) with the multi-metal model.

Adani *et al.* (2020)	Environmental risk factors in the etiology of early onset dementia (EOD), taking into account its different clinical types.	112 participants (58 patients with EOD and 54 controls)	Aluminum exposure was associated with an increased risk of frontotemporal dementia (FTD) (OR 4.1, 95 % CI 0.5-34.5), but not for AD. Thus, most of the investigated cases presented positive associations between EOD and occupational exposure to aluminum, pesticides, and other chemicals (dyes, paints or thinners.

On the other hand, the presence of aluminum can also be caused by migration from the food packaging. Iscuissati *et al.* (2021) evaluated the migration of aluminum to coffee prepared by a high-pressure machine with metal seals (Nespresso® Essenza Mini machine). It was found that using the machines to prepare the beverages contributes to increase the aluminum content by approximately 13 % (459 μg/L) compared to a conventional filtration coffee preparation process (408 μg/L). Concerns are also expressed about the reuse of ground coffee, since the increase in aluminum content is approximately 3.5 times higher in this after its preparation, and therefore this recycling strategy should be discarded.

For this reason, Stahl *et al.* (2018) investigated human exposure to aluminum and food contact materials. The study found regional differences that led to variations in the global consumption of aluminum. For the adult population, the average exposure to this metal was between 0.2 and 1.5 mg/kg body weight/week. On the other hand, children and adolescents, who have a lower body weight, were found to have a higher aluminum concentration (between 0.7 and 2.3 mg/kg body weight/week). These results show values between 14 and 105 mg of aluminum/week for an adult weighing 70 kg while the values for a child weighing 30 kg were 21 to 69 mg aluminum/week. These values indicate that a portion of the human population can consume enough aluminum through their usual diet to reach the tolerable weekly intake.

Between 2015 and 2016, Takanashi *et al.* (2018) conducted a survey in Japan on the aluminum content in flour-based products and confectionery with baking powder. Aluminum was found in 33.33 % of the evaluated products (corresponding to 41 out of 123 samples), at levels between 0.01 (limit of quantification) and 0.40 mg/g. The presence of this metal in confectionery products was reduced compared to previous studies. However, the presence of aluminum was high in Japanese confectionery and flour-based foods. Consuming one serving of 4 of the 41 samples analyzed would result in an aluminum intake that exceeds the recommended levels for young children, whose average weight was 16 kg.

To study the toxic risk of aluminum intake, Hardisson *et al.* (2017) collected and compared data on the concentrations of this metal across various types of foods, aiming to estimate the total dietary intake. The most predominant analytical techniques for aluminum determination were inductively coupled plasma atomic mass spectrometry and atomic emission spectroscopy (ICP-OES and ICP-AES). The highest aluminum levels were found in vegetables (16.8 mg/kg), fish and shellfish (11.9 mg/kg), and roots and tubers (9.60 mg/kg). Among the foods that contributed most to the tolerable weekly intake of this metal were fruits (18.2 % for adults and 29.4 % for children) and vegetables (32.5 % for adults and children). As a result, it could be concluded that the dietary intake of aluminum may pose a health risk due to the accumulation of this metal in the brain caused by long-term intake.

Plant extracts to fight Alzheimer's disease

Considering the need of reducing the effects generated by aluminum on the nervous system, researchers have been driven to explore the potential of the Moringa oleifera plant. Ekong *et al.* (2017) studied the neuroprotective effects of moringa leaf extract on aluminum-induced temporal cortical degeneration in rats and concluded that it protects against aluminum-induced neurotoxicity of the temporal cortex of rats.

Previous research has confirmed that yerba mate (*Ilex paraguariensis*) has an antioxidant potential that could help reduce the risk of developing neurodegenerative diseases, such as AD; antioxidants can mitigate the oxidative stress that causes and/or contributes to the development or progression of AD. Bortoli *et al.* (2018) evaluated the potential of *I. paraguariensis* in the etiology of AD using *Caenorhabditis elegans* strains. The study explored the concentration of aluminum and antioxidants in the plant's leaf extract. It was determined that the metal content impacts the Acetylcholinesterase (AChE) activity. Consequently, acute and chronic exposure to both the element and leaf extract of *I. paraguariensis* demonstrated notable similarity to wild-type worms. In addition, it was observed that the results in both transgenic strains exposed long-term to leaf extract and aluminum concentrations showed an increase in AChE activity.

Similarly, Elufioye *et al.* (2019) found that extracts from the leaves of *Macrosphyra longistyla* have high antioxidant and anticholinesterase activities. According to the results found, extracts from this plant can potentially be used in the treatment of neurodegenerative diseases such as AD. Similarly, Oboh *et al.* (2021) found that extracts from the leaves of *Heinsia crinita* and *Pterocarpus soyauxii*, owing to their anticholinesterase, antioxidant and metal chelating properties, can reduce the presence of aluminum in the body. Researches have shown that the use of extracts from natural sources (mainly plants like the aforementioned) can be an alternative against AD, due to the multiple benefits they offer.

CONCLUSIONS

The results of the research in this area provide important information to consider that AD is a degenerative disease and may be related to the accumulation of aluminum in the brain. This metal is accumulated in the human body mainly through the ingestion of foods contaminated with aluminum; being a heavy metal, it is often found in the soil and is therefore easily present in fruits and vegetables, as well as in water. In addition, the use of containers or kitchen utensils made of aluminum becomes a source of contamination of products since the migration process of this metal is accelerated when exposed to heat in contact with food. In the last few years, the population has become increasingly aware of the health risks caused by the ingestion and accumulation of this metal in the human organism. The concern generated by the consumption of aluminum through food matrices and its consequences on the health of consumers has led researchers, industry, and consumers to develop and use alternatives for kitchen utensils, packaging, food additives, and water treatment with materials that do not contain this metal, with the purpose of mitigating the risks of aluminum consumption and its relationship with AD.

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