GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(REVIEW ARTICLE)

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Tea (*Camellia sinensis*) leaves accumulate higher levels of Aluminum: Potential Health Risk- Alzheimer's disease (AD): An updated review of evidence

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GSC Advanced Research and Reviews, 2024, 20(01), 313–337

Publication history: Received on 09 June 2024; revised on 17 July 2024; accepted on 19 July 2024

Article DOI: https://doi.org/10.30574/gscarr.2024.20.1.0264

Abstract

This review paper of literature highlights the role of accumulation of aluminum in tea leaves and its toxic effects on human health. Tea is the most consumed beverage in the world after water and contains heavy metals and trace elements that may cause potential negative effects on health. Tea is known to be a metal accumulator. However, drinking even a very high dietary amount of black tea or green tea would be unlikely to cause these adverse effects in humans. Thus, for the majority of heavy tea drinkers around the world, tea is likely to be the largest single source of aluminum intake. Addition of milk to tea can decrease or completely inhibit tea antioxidant properties. According to the literature survey, it is well known that the tea plant accumulates aluminum in its leaves to a greater extent than most other edible plants, and would be a potentially important source of dietary aluminum. Aluminum can be transferred into tea infusions through brewing tea, then enter the human body via tea drinking, thereby causing potential harm to human health. On the basis of literature survey, even though some epidemiological reports were contradictory, there was mounting scientific evidence suggesting a relationship between the neurotoxicity of aluminum and the pathogenesis of Alzheimer's disease. In particular, the link between aluminum and Alzheimer's disease has been the subject of scientific debate for several decades. The literature survey confirmed that aluminum hypothesis has been the subject of much debate and criticism for several decades. Evidence from human clinical trials suggested that moderate (1–6 cups/day) rather than excessive consumption of tea could bring diverse health benefits. The relationship between tea consumption and dementia has not been well established yet and other studies reported no significant association. The cause of Alzheimer's disease and any association with aluminum is still unknown. There have been conflicting findings in the scientific literature.

Keywords: Aluminum; Alzheimer's disease; Black tea; *Camellia sinensis*; dementia; Epigallo-catechin gallate; Lemon juice; Neurotoxicity; Tea infusions

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1. Introduction

Chai or Tea (*Camellia sinensis* (L.) O. Kuntze is the second most popularly consumed beverage worldwide after water [1-2-130]. Tea is one of the most common drinks, all over the world and is produced from the leaves of *Camellia sinensis* [1-2]. Among all the beverages, about 98% of people prefer drinking the tea for the first choice. 75% (approx. 2.5 millions) of the desiccated tea produced annually are processed into black tea [1-5-150]. Tea is one of the most popular alcohol-free and caffeinated beverages in the world [1-2]. It is made from new tea leaves and then brewed with boiling drinking water to get a tea infusion [1-2-10-25]. In India, tea is much more than just a drink, it is an emotion [1-2]. India is the second largest producer and consumer of tea in the world with 80% of tea is consumed in India accounting for 27% of the world tea production [2]. The tea industry has an important and special place in the Indian economy [2]. Tea is an aromatic beverage made by adding dried and crushed leaves and leaf buds of *the Camelia Sinensis* plant in boiling water [1-2-130]. Tea is the Indian primary beverage, with almost 80% of total households in the country consuming tea [2]. The Indian tea industry is controlled by the Tea Board of India [2]. The Indian tea market size reached 1.2 Million Tons in 2022 [2]. Looking forward, the market expected to reach 1.5 Million Tons by 2028, exhibiting a growth rate (CAGR) of 4.5% during 2023-2028, according to IMARC Group's latest report [2].

Assam state is the largest tea growing region in India and is home to India's indigenous, wild-growing tea plant variety, *Camillia sinensis Assamica* [2]. Indian tea is very famous throughout the world and known for famous Assam tea, Darjeeling tea, Niligiri tea, Kodagu or Coorg tea, Chikkamagalore organic tea, Baba Budan hills tea, Kangra tea, Sikkim tea, and Mannar tea [2]. Several Indian states have greatly contributed to the Indian tea production and raising its economy [2]. Indian teas especially from Assam, Darjeeling, Coorg, Chikamagalur, Baba Budan hills, Nilgiris (Trinitea) are valued for their characteristic aroma and taste [2]. The plant *Camellia sinensis* variety: *Assamica* or *sinensis* is the source of different teas (black, green, white, yellow, and oolong) consumed worldwide, which are classified by the oxidation degree of their bioactive compounds [2-25]. Thus, teas are classified according to their processing, where the main variation occurs in the degree of oxidation that modifies chemical and sensory characteristics (aroma, color and flavor) [1-2-5-20]. Green tea and black tea are processed differently during manufacturing from *Camellia sinensis*, variety: *Assamica* or *sinensis*. Teas became more than simply pleasing and cultural hot drinks [2-10-100].

Different varieties of tea, including black, green, oolong, white, and yellow tea are all derived from *Camellia sinensis*, but climatic differences and processing methods account for differences in the composition and degree of anti-oxidative behavior[1-10-130]. Tea is the most popular hot beverage in India, consumed both at home and outside [2]. Indian tea culture has very rich history and tea is served in every street of India by Chai Wallah as Cutting [2]. The Indian tea industry has grown to own many global tea brands, and has evolved to be one of the most technologically equipped tea industries in the world [2-20]. India has always been a major market in tea production [2]. Generally, these consumable tea products can be classified as green (non-fermented), white (slightly fermented), yellow (mild fermented), oolong (half fermented), black (fully fermented), and dark (post-fermented) tea based on their processing technologies blended or unblended [1-2-20]. Among these, black and green teas are the two most consumed tea products worldwide, which accounting for about 80% and 27% global tea consumption, respectively [2]. Black tea is typically made from the *Camellia sinensis assamica* variety that originated from the Assam districts of India [2]. This darker type of tea is made by using leaves that are fully oxidized before they are processed and dried [1-10]. The flavor profile for black tea can range anywhere from slightly sweet nutty notes to smoky and malty[2-10]. It is typically stronger and bolder in flavors than green tea varieties [1-89-130]. The production of tea in Turkey began in the early years of the Republic along the Eastern Black Sea Region and most of the tea plantations are centered in Rize, Turkey [1-20-155].

Epigallo-catechin gallate (**EGCG**) is an important biochemical marker of Assam state, and Northeast Indian tea as it contributes 50% of total catechins [2-100]. Good quality organic tea is rich in melatonin content, if consumed in the right quantity can have major positive effects on the body [2]. Tea trees are mainly grown in some Asian and African countries, such as India, China, Sri Lanka, Nepal, Kenya, Turkey, Iran and Zimbabwe, etc[1-25-100]. Because tea contains tea polyphenols (catechins), amino acids, tannic acid, and other antioxidants [1-89-130]. Drinking tea is considered beneficial to human health, including the prevention of many diseases since it has been proven to prevent high blood pressure, and obesity [2-130].

To make black tea, the leaves are air-dried (withered) before they are bruised through rolling and cutting to activate the endogenous enzyme polyphenol oxidase [1-92-140]. This starts the fermentation process, which largely consists of oxidation of the polyphenols present in the tea leaves [1-89-150]. When the quality is judged optimal, fermentation is arrested by drying [2-100]. In contrast, green tea is not (or only very lightly) fermented, but the leaves are treated by steaming or pan firing to inactivate the polyphenol oxidase, thus avoiding oxidation [2-100]. If the firing is carried out immediately after the leaves are plucked, the result is 'white' tea, if the leaves are withered (and therefore, lightly

fermented) before firing, the result is 'yellow' tea. Oolong tea (also called 'red' tea) is an intermediate type of tea, produced employing a shorter fermentation time than for black tea [1-2-80-150].

Tea is a rich source of caffeine, polyphenols, antioxidants, and minerals, including manganese, calcium, and potassium [1-89-140]. Its moderate consumption helps provide instant relaxation, minimize the damage caused by free radicals in the body, boost the immune system, reduce inflammation, facilitate weight management, and lower cholesterol levels in the blood [1-89-130].Teas have prevailed for their laxative, hypoglycemic, antioxidant, anti-inflammatory, neuroprotective, anti-carcinogenic, anti-obesity, cardiovascular and liver protection properties, especially when consumed through functional foods or food supplements in a limited quantity [1-89-130]. However, consumption of large amounts of black or green tea may cause nutritional health problems because of the strong binding activities of tea polyphenols and the caffeine content [1-89-140]. However, drinking even a very high dietary amount of black tea or green tea would be unlikely to cause these adverse effects in humans [1-89-150]. Addition of milk to tea can decrease or completely inhibit tea antioxidant properties [1-89-150].

The quality of tea is important for the development of the tea industry, tea farmers' income, and the health of tea drinkers [1-89-150]. In particular, heavy metals in tea are important indicators in the process of tea quality evaluation, as they can be transferred into tea infusions through the process of brewing tea, then enter the human body by means of tea consumption, and thus pose potential risks to human health [1-89-150]. Thus, the chemical components in tea, particularly heavy metals, have received great interest because they are related to human health [1-89-150]. Tea (*Camellia sinensis*) is one of a few plants accumulating aluminum (Al), making tea a major source of dietary aluminum intake [1-89-150]. On the other hand, tea plants have been demonstrated to be aluminum accumulators due to the acidic soils where tea plants are grown [1-150]. Excessive intake of aluminum can be harmful for human health, particularly for kidney [1-89-150]. Kidney insufficiency results in an increase in aluminum concentrations in the kidneys of the dialysis patients [1-89-150]. Aluminum (Al) is clearly a powerful neurotoxicant, and also has a potential for skeletal and haematopoietic toxicity, especially in patients on dialysis due to chronic renal failure [1-89-150]. In dialysis patients, tissue accumulation of aluminum to levels high enough to cause toxicity is mainly due to a combination of high exposure and these patients' lack of kidney function, which is the main excretion route for aluminum [1-89-150]. The tea plants contain a higher concentration of aluminum (Al) than many other plants and would be a potentially important source of dietary aluminum[1-2-150]. Even though some epidemiological reports were contradictory, there was a mounting scientific evidence suggesting a relationship between the neurotoxicity of aluminum and the pathogenesis of Alzheimer's disease[1-89-150].

According to the literature survey, the most controversial issue is whether aluminum exposure is causally related to Alzheimer's disease (AD), and although considerable evidence exists for such a relation, it is still open to debate whether the relation is causal [1-89-150]. Although aluminum content of tea has been determined in various teas from many countries, there is no detailed researches investigating aluminum content in the teas produced in different countries[1-89-150]. One of the study conducted in Turkey confirmed that the aluminum content of tea increased with the increment of the duration of infusion ($p < 0.05$). In order to reduce the occurrence of aluminum content in the tea infusion, it is necessary to keep the infusion time short [1-89-150].

This literature review paper highlights about aluminum toxicity to human health particularly by the consumption tea. In the following section, accumulation of aluminum in tea leaves, and relation with Alzheimer's disease has been discussed.

2. Tea leaves: Aluminum accumulation: Alzheimer's disease (AD)

It is well known that the tea plant accumulates aluminum in its leaves to a greater extent than most other edible plants [1-95]. Aluminum is essential for tea root growth by maintaining DNA integrity in meristems [1-95]. Culturally, tea prefers soils with pH values ranging from 4.5 to 5.5 in well-watered tropical environments[1-97-148]. Further since the daily allowable intake (DA Aluminum) of aluminum is 6–14 mg/day for teens and adults, as set by Joint FAO/WHO Expert Committee on Food Additives[1-95]. Information already exists on aluminum concentrations in tea leaves from different origins, such as China, India, Japan, Sri Lanka, Turkey, Iran and Vietnam, and Hawaii[1-95]. Much research has been done in the analysis of aluminum concentrations in tea products because of the underlying correlation between dietary aluminum intake and potential toxicities, for example, Alzheimer's disease, osteodystrophy, and kidney failure[1-95-155]. Aluminum concentrations found in commercial tea products ranged from 123 to 3260 μg/g [1-95]. Aluminum can be transferred into tea infusions through brewing tea, then enter the human body via tea drinking, thereby causing potential harm to human health [1-95-155]. In addition, aluminum is present in food, such as fruits, vegetables, and cereal products, and is used in various processed foods as a common food additive[1-95]. The typical concentrations of aluminum found in the "young" tea leaves ranged from 250 to 660 μg/g (dry weight), and higher levels

of aluminum in "old" tea leaves ranged from 4300 to 10,400 µg/g (dry weight) [1-95]. The hypothesis that aluminum is an environmental contributor to the pathogenesis of Alzheimer's disease, termed the "aluminum hypothesis", was proposed in the 1960s based on various neurotoxicological, analytical, and epidemiological findings [1-95-155]. In spite of these findings, the aluminum hypothesis has been the subject of much debate and criticism for several decades[1-95-150]. An association between aluminum poisoning and memory disorder in humans was first reported in 1921[1-95-150]. As a component of dialysis solutions or aluminum -containing pharmacological compounds, aluminum is known to cause various dialysis-related disorders, including osteomalacia (aluminum bone disease), microcytic anemia, β2-microglobulin-associated amyloidosis, and dialysis encephalopathy in hemodialysis patients[1-95-150]. The aluminum (Al) can cause health problems to human being at overdose[1-97-148]. The black tea is among the most common beverages in the world but may contain higher amount of aluminum[1-95-150]. The relationship between tea consumption and dementia has not been well established yet [1-95-150]. Although most studies in healthy aging showed that tea was protective against dementia, some studies reported no significant association [1-95-150]. The credibility of these findings is easily compromised by the cross-sectional designs, insufficient follow-up periods, small sample sizes or different reference groups [1-95-150]. A recent cohort study reported that tea consumption was associated with lower risks of dementia, VD, post stroke dementia and stroke[1-95-150]. Evidence from human clinical trials suggested that moderate (1–6 cups/day) rather than excessive consumption of tea could bring diverse health benefits[1-95-150]. Another study concluded that, tea consumption was shown to be associated with a lower risk of dementia in the total participants [1-95-150]. As a potentially modifiable lifestyle factor, tea consumption could play a pivotal role in the primary prevention for dementia [1-95-150]. This study would offer a relatively simple and low-cost solution to the interventions of age-related cognitive decline or dementia[1-95-150].

Tea is a widely consumed beverage around the world and it contains various kinds of biomolecules such as polyphenols [1-95]. Tea intake has been found to be associated with the prevention of various diseases, such as stroke, cardiovascular diseases and neurodegenerative diseases[1-95-150]. Recently, accumulating epidemiological studies and systemic reviews have suggested that tea intake can suppress brain aging and ameliorate cognitive dysfunction[1-95-150]. A population-based study has found that green tea can mitigate the pathological changes of Alzheimer's disease [1-95-150]. Alzheimer's disease mouse models showed that the main component of black tea could inhibit the deposits of amyloid in the brain and reduce Aβ pathology[1-95-150]. Mechanistic studies revealed that tea biomolecules (e.g., epigallocatechin gallate [EGCG], the predominant polyphenol in green tea) could invoke extensive cellular pathways of antioxidants and activities of neurorescue, which might prevent memory deficits [1-95-150]. Also, tea biomolecules were found to have anti-inflammatory properties, thereby halting the progression of cognitive decline[1-95-150]. Tea was reported to play a neuroprotective role in the cognitive decline not only resulting from aging, but also from ischemia-reperfusion [1-95-150]. Previous studies suggested that tea had positive impacts (e.g., vasodilative functions) on cerebral blood vessels[1-95-150].

3. Tea Infusions and Aluminum toxicity

Literature survey confirmed that tea is one of the very few plants that accumulate aluminum [1-95]. In fact, most plants are quite sensitive to aluminum toxicity, which is a large problem in agriculture [1-95]. Aluminum toxicity is probably the major factor limiting crop productivity on acid soils, which occupy about 30% of the world's ice free land area [1-100]. In contrast, aluminum stimulates the growth of tea plants, possibly through improvement of the absorption and utilisation of phosphorus and perhaps other essential elements [1-130]. Old tea leaves may contain up to 2 to /3% aluminum (dry weight), but the leaves are usually harvested long before they reach such levels [1-145]. When plucked for human consumption, aluminum concentrations are typically about 300 to/1500 µg g^{-1}[1-95].

Aluminum (Al) concentrations in black, green, and white tea with different infusion times and teapot materials were evaluated in one of the study[1-95]. Commercially available tea samples were brewed in 5 different teapots, consisting of aluminum, copper, glass, steel, and porcelain materials for 5, 10, and 15 min[1-95]. Aluminum concentrations in tea samples were determined by high-performance liquid chromatography with a fluorescence detector [1-95-155]. Aluminum concentrations in tea samples were in the range of 38.46±5.08–844.75±10.86 µg/L [1-95]. Both teapot type ($p \leq 0.001$) significantly influenced aluminum concentrations in tea samples[1-95]. The interaction between tea type, teapot material, and infusion time was statistically significant ($p \leq 0.001$) [1-95]. The hazard ratio was less than 1 for black and white tea infusions except for one sample whereas it was greater than 1 for green tea [1-95]. These data suggest that green tea consumption might be a potential risk factor for aluminum exposure[1-95].

The average total daily dietary intake of aluminum in most countries is a few milligrams per day[1-95]. Recently published values for adults include 3.1 mg per day in the Netherlands, 3.4 mg per day in the UK, 3.5 mg per day in Japan, and 7 to/ 9 mg per day in the US [1-95-155]. Because typical levels of aluminum in tea infusions are 1 to /6 mg l^{-1} [1-95]. Tea is a major source of dietary aluminum exposure, and heavy tea drinking may more than double an individual's

intake of aluminum [1-95-130]. Furthermore, aluminum is generally very poorly absorbed in the gastrointestinal tract; roughly in the order of 0.1% of the dietary intake is absorbed, depending on the chemical form (species) of aluminum [1-95-140]. Thus, if the species of aluminum present in tea are more bio-available than the species present in other dietary items, tea could make a larger contribution to human uptake of aluminum than indicated from the total concentration present[1-95-130-155].

It is well documented that in tea infusions as prepared for human consumption, the total concentration of aluminum rarely falls outside the range 1 to/ 6 mg $l.^{-1}$[1-95-155]. Thus, for the majority of heavy tea drinkers around the world, tea is likely to be the largest single source of aluminum intake [1-95-120]. The most important exceptions are individuals regularly consuming aluminum containing antacids, and individuals with a diet rich in aluminum-containing food additives [1-95-150]. On the basis of literature survey, all four studies investigating urinary excretion in human volunteers reported that tea consumption considerably increased aluminum excretion relative to water consumption, indicating measurable absorption of aluminum from drinking tea infusions [1-95-140]. However, two of the studies must be interpreted with caution because the concentrations of aluminum in urine are very high relative to the presently accepted normal values of about 3 to 10 mg aluminum l^{-1}[1-95-110]. One of the studies reporting acceptably low aluminum concentrations indicated that the increased aluminum excretion when drinking tea could be at least partly explained by increased urinary volume[1-95-110]. One study of aluminum in blood reported no differences when drinking tea or water[1-95-110]. Therefore, drinking tea leads to measurable, but moderate increases in urinary aluminum excretion, and that the aluminum present in tea is not much more bio-available than that from other dietary sources [1-95-150]. Furthermore, aluminum is very poorly absorbed (in the order of 0.1%) in the gastrointestinal tract, a dietary source of aluminum with high bioavailability could greatly increase the uptake of aluminum, even if the total concentration of aluminum in this source is not particularly high [1-95-130]. Hence, one could expect that the actual speciation of ingested aluminum would be of minor importance for bioavailability, since in the acid environment of the stomach, low-solubility aluminum compounds would largely pass into solution and a complete re-speciation of aluminum could be expected to take place[1-95-115]. All three major studies, investigating the speciation of aluminum in tea infusions before and after stomach condition treatment clearly indicated a shift to lower-molecular-mass species under stomach conditions [1-95-130]. When shifting from stomach to intestinal conditions (pH 6.3 to /6.5), a new dramatic re-speciation took place, either to high-molecular-weight soluble species or to insoluble species. It is perfectly conceivable, however, that certain species of aluminum could be stable enough to pass the gastrointestinal tract unchanged [1-95-130]. For certain organic complexes of aluminum, differences in lipophilicity, hydrophilicity and hydrolytical stability are associated with remarkable differences in the biological effects [1-95-130]. An especially interesting compound is aluminum maltolate , which is very stable to hydrolysis and seems to be an unusually potent neurotoxin[1-95-140]. Maltol has been identified in green tea, and tea could also contain other organic aluminum complexes with properties similar to those of aluminum maltolate, stable enough to pass through the stomach and accumulate in brain and bone [1-95-136].

Another study also shown that the total concentrations of Al, Mn, Cu, Pb, and Cd in tea leaves in China maybe influenced by the soil conditions, tea variety, harvest season, and leaf maturity [1-95-113]. The levels of these elements in commodity tea could be managed by consideration of the tea variety, plucking time, and the maturity at harvest, particularly in soils or plantations that carry higher concentrations of aluminum and Mn [1-95-134]. Furthermore, individuals are not at risk of consuming dangerous doses of single metal of adverse health effects through tea consumption based on the values of HQ, and potential adverse health effects were not likely to happen in the examination of commercially available teas [1-95-120]. Various studies have shown that tea has numerous beneficial effects on health [1-95-110]. However, some risk chemicals in tea products may bring a health threat to tea drinkers, such as polycyclic aromatic hydrocarbons (PAHs), new pollutant—perchlorate , pesticides , and some risk elements like aluminum (Al), cadmium (Cd), manganese (Mn), lead (Pb), and copper (Cu) [1-95-150].

Tea is known to be a metal accumulator [1-95]. The quantities of heavy metals and trace elements in the tea leaves can vary depending on the content and the type of soil in which the tea is grown, the type of tea, the season in which the tea is produced, the maturity of the tea leaves, the duration and kind of the brewing, as well as the teapot type [1-95-130]. Aluminum (Al) is one of the metals contaminating tea [6, 8]. The presence of aluminum in the soil structure is essential for the development of the tea plant [1-95-130]. However, this leads to the natural accumulation of aluminum in tea plants [1-95]. It has been previously reported that aluminum accumulation may lead to Alzheimer's disease, Parkinson's disease, dialysis encephalopathy, multiple sclerosis, autism spectrum disorder, and toxicity [1-95-155]. herefore, it is crucial to investigate whether tea consumption causes exposure to toxic levels of aluminum as tea is a widely consumed beverage in most cultures[1-95-130]. In this manner, some studies have been carried out to determine aluminum in a variety of tea types and to evaluated its potential adverse effects on health [1-95-150]. In addition, aluminum and some other trace elements were analyzed in tea infusions brewed in stainless steel, ceramic, porcelain, plastic teapots, and

some local teapots made of clay, regardless of the infusion time [1-95-130]. The effect of infusion time from 15 to 30, 45, and 60 min on aluminum release was also evaluated in some studies[1-95-140].

When discussing possible negative health effects of tea related to its aluminum content, it is important to realize that tea is a rich source of antioxidants, so it may potentially have positive effects on human health [1-95-140]. There is a rapidly growing body of scientific evidence indicating that tea consumption may protect against cardiovascular diseases and several types of cancer [1-95-140]. In addition, tea may have a positive effect on the intestinal microflora, and protect against kidney stones, bacterial infections and dental cavities[1-95-130]. Epidemiological studies have shown that tea consumption reduces the risk of coronary heart disease and stroke [1-95-130]. Besides, tea polyphenols are known to have an anti-carcinogenic effect against the skin, liver, lung, gastrointestinal system, pancreas, and bile cancers [1-95-120]. In addition to phenolic compounds, tea contains minerals and trace elements[1-95-140]. However, due to the processes carried out during production, tea is exposed to toxic chemical contaminants such as polycyclic aromatic hydrocarbons, pesticides, per-chlorate, and heavy metals [1-95-138].

According to literature survey, calcium stress causes severe growth inhibition and metabolic disorders in tea plants, whereas an appropriate dose of aluminum facilitates root growth and promotes the accumulation of valuable metabolites [1-95-120]. The status of the aluminum supply clearly protected against negative changes in root growth and the accumulation of leaf metabolites in tea plants in response to calcium stress [1-95-130]. However, the ability of aluminum to alleviate the inhibitory effects of calcium stress on plant growth was limited, which was only reflected in the improvement of root tip number and the accumulation of some secondary metabolites [1-95-130]. Overall, comprehensive analysis of the effects of calcium-aluminum interactions on tea plant growth and quality can provide a theoretical basis for improving calcium-aluminum nutrient management in tea plantations[1-95-130].

4. Aluminium

Aluminum is the most abundant metal, making up 8% of the earth's crust[1-95-145]. Because of this, soil contains aluminum, and it also enters water sources through natural processes like rocks wearing away [1-95]. This means many of food, particularly fruit, vegetables and seafood, contain aluminum due to it being in the soil and water where food is grown or lives [1-95-140]. The air we breathe also contains natural traces of aluminum, from the eruption of volcanoes and weathering processes [1-95-140]. Human activities such as mining, industrial processes and waste water treatment can also release aluminum into environment [1-95-120]. Acid rain, caused by industrial pollutants dissolving in rain water, has worsened this effect as aluminum can dissolve more easily in acidic conditions and enter water sources [1-95-140]. Some food additives contain aluminum and cooking with certain aluminum utensils may further increase the levels of aluminum found in food [1-95-130]. Emissions from various human activities like burning coal, car exhaust fumes and mining has also contributed to higher levels of aluminum in the air[1-95-140]. Lead, cadmium, mercury, and arsenic are known toxic metals [1-95-109]. Aluminum is used in construction, manufacturing, fuel additives and medications, cosmetics, and personal care products [1-95-107]. Aluminum gets into our food from the soil in which it is grown, and also from additives such as anti-caking, antifoaming, emulsifying, firming, and leavening ingredients [1-95-110]. The drinking water also contains some aluminum, and the chemical purification process called flocculation (a process by which fine particulates are caused to clump together) can increase the level [1-95-130].

Aluminum (Al) is abundantly distributed in environment, and compounds containing aluminum have been used in manufacturing (e.g., clays, glasses, and alum) for centuries [1-95-130]. Despite its abundance, aluminum was first isolated as an element in 1827, and its use as being a silvery metal began only after 1886 [1-95]. Aluminum is a new metal in this contex t[1-95-140]. Because of its beneficial characteristics such as a lightweight, nonmagnetic, malleable, and ductile element, aluminum has a widespread and important use in industrial applications and consumer products [1-95-140]. Aluminum is also used in cooking utensils and in pharmacological agents including antacids and antiperspirants from which the element enters the human body [1-95-120]. Aluminum is reported to influence more than 200 biologically important reactions and to cause various adverse effects on the mammalian central nervous system (CNS) [1-95-130]. Consequently, aluminum causes apoptotic death of neurons and glial cells[1-95-140].

Furthermore, preparing meals using aluminum cookware or eat foods packaged in aluminum wraps from which a small amount of metal is also leached into the food[1-95-120]. Use of an aluminum hydroxide-based antacid, it could add several additional grams of aluminum to daily intake[1-95-130]. Almost all of the aluminum that has been ingested leaves human bodies in feces and perspiration, but a small fraction accumulates in human internal organs, including brains [1-95-150]. Other sources of aluminum include anti-perspirants, cosmetics and vaccines[1-95-140]. Some vaccines contain small, safe amounts of aluminum, as it helps to trigger the immune system's response to the vaccine, which in turn boosts the level of immunity of the person [1-95-150]. This may sound like a lot but even though it is everywhere, the levels of aluminum most of are exposed to everyday are considered safe [1-95-130]. A healthy

individual normally carries between 30-50 mg of aluminum in their body [1-95-140]. Aluminum has no biological function in human bodies since it is everywhere, and very high levels of aluminum can also be harmful[1-95-140]. Human bodies have evolved efficient ways to get rid of aluminum and keep safe [1-95]. Only a very tiny 0.1% of aluminum from human food and drink is absorbed by the gut and enters the bloodstream [1-95-140]. In healthy individuals, this is swiftly and efficiently removed by the kidneys and leaves the body in urine[1-95-140].

Aluminum is the third most abundant element in the earth's crust and the most abundant metal [1-95-140]. It is used in many applications, including food preservation, cans, cookware, automobiles, and vaccine adjuvants [1-95]. In mammals, specific functions of aluminum are obscure because of its toxicity to living organisms due to its strong reactivity with carbon and oxygen [1-95-130]. The kidney quickly eliminates aluminum from food and environmental sources in humans [1-95-140]. However, aluminum salts in vaccine adjuvants are biologically active and accumulate in the nervous system[1-95-155]. Aluminum has been associated with Alzheimer's disease and other diseases[1-95-150]. It was found to accumulate with Aβ peptide in the brains of individuals with dialysis-associated encephalopathy [1-95-140]. Surprisingly, their symptoms disappeared soon after its removal from the dialysis solution[1-95-150]. A recent meta-analysis found that chronic aluminum exposure increased the incidence of Alzheimer's disease by almost 70%[1-95-148]. Furthermore, an association between numbers of Alzheimer's disease patients and their exposure to aluminum-adjuvanted vaccines was identified with increased levels of aluminum found in their hair, blood, and urine[1-95-130]. Aluminum hydroxide injections cause long-term memory loss, anxiety, and neurodegeneration in the spinal cord and motor cortex in mice [1-95-120]. Oxidative stress and mitochondrial dysfunction may also be responsible for neurological damage[1-95-150]. However, several studies do not account for confounding factors such as genetic backgrounds that may predispose an individual to aluminum-induced neurological dysfunction[1-95-130]. Aluminum-induced neurotoxicity is likely due to a combination of genetic and environmental[1-95-120].

Whilst being environmentally abundant, aluminum is not essential for life[1-95-140]. On the contrary, aluminum is a widely recognized neurotoxin that inhibits more than 200 biologically important functions and causes various adverse effects in plants, animals, and humans [1-95-140]. The relationship between aluminum exposure and neurodegenerative diseases, including dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia in the Kii Peninsula and Guam, and Alzheimer's disease (AD) has been suggested [1-95-140]. In particular, the link between aluminum and Alzheimer's disease has been the subject of scientific debate for several decades [1-95-155]. However, the complex characteristics of aluminum bioavailability make it difficult to evaluate its toxicity[1-95-140]. Therefore, the relationship remains to be established[1-95-140]. Mounting evidence has suggested that significance of oligomerization of β-amyloid protein and neurotoxicity in the molecular mechanism of Alzheimer's disease pathogenesis[1-95-155]. Aluminum may play crucial roles as a cross-linker in β-amyloid oligomerization [1-95-130].

On the basis of literature survey [1-95-140], the aluminum content in the tea plant is influenced by various environmental factors such as soil conditions, climate, altitude and precipitation [1-95-130]. In addition, anthropogenic factors such as air and soil pollution caused by industrial activities and urbanisation, horticultural practices (including the application of organic and inorganic fertilizers, the use of pesticides and soil conditioners) and the quality of water used for irrigation can affect the content of these elements [1-95-140]. Nevertheless, the greatest variations in the total content of fluorine and aluminum, which mainly accumulate in tea leaves, are associated with the age of the leaves, genetic varieties of the plant, the plucking method (mechanical or manual), and the duration of the wilting period[1-95-130]. Both fluorine and aluminum leach out during infusion, with fluorine mainly occurring in the form of fluoride ions (F^-) and aluminum in different species (abbreviated as Al) such as Al-citrate, Al-oxalate, Al-polyphenol and Al-fluoride complexes [1-95-140]. Comparing results from different studies is difficult because the leaching efficiency of fluoride and aluminum depends on the method of infusion preparation (e.g., the amount of tea in relation to water, infusion time and temperature) [1-95-130]. In general, the F^- concentration in infusions of tea available in Europe typically ranges between 0.31 and 8.9 mg/L[1-95-135]. The aluminum concentration is higher, and can reach up to 20 mg/L [13,20–23]. Comparable concentrations are also reported in sparse studies investigating both F^- and aluminum concentrations in infusions [1-95]. Thus, the consumption of tea infusions may significantly contribute to the daily intake of both elements[1-95-140]. It has been known for almost a century that fluoride ions have a beneficial effect against dental caries [1-95-130]. A higher fluoride intake for a prolonged period of time can also affect various tissues and organs of the human body before the most obvious signs of fluoride poisoning appear, i.e., the development of dental fluorosis in children and skeletal fluorosis in children and adults [1-95-140]. In contrast, aluminum ions do not play a physiological role in metabolic processes, but can be toxic in high amounts, which is why EFSA set its tolerable weekly intake (TWI) at 1 mg/kg bw[1-95]. On the other hand, there is no clear consensus on the risks of aluminum associated with tea consumption [1-95-145]. The increased toxicity of fluoride in the form of aluminum-fluoride complexes, which can form in infusions and mimic the chemical structure of a phosphate and impair the activity of phosphoryl transfer enzymes, is also a concern [1-95]. According to one of the study, the price of loose tea is significantly lower than that of filter tea [1-

95-124]. Hence, loose tea should be the first choice for a consumer due to its lower fluoride and aluminum concentration, lower price and reduced packaging material [1-95-140]. Tea is often consumed chronically and a larger consumption (1 L) of tea with F– and aluminum concentrations, could pose a potential health risk [1-95-130].

5. Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder that impairs mental ability and interrupts cognitive function [97-148]. Heavy metal exposure like aluminum chloride is associated with neurotoxicity linked to neuro-inflammation, oxidative stress, accumulation of amyloid plaques, phosphorylation of tau proteins associated with AD like symptoms [1- 97-148]. The hallmark diagnosis of Alzheimer's disease features includes formation of senile plaques and neurofibrillary tangles [1-97-148]. Alzheimer's disease is the most common form of dementia, a serious brain disorder that impacts daily living through memory loss and cognitive changes [1- 97-148]. Alzheimer's disease is also age related neurodegenerative disorders caused by progressive loss of structure or function of neurons, resulting in neuronal cell death [97-148]. Alzheimer's patients have an **acetylcholine** deficiency [1- 97-148]. Stressful conditions, free radical scavenging and oxidation are often associated with loss of memory and cognitive functions, which may lead to threats of schizophrenia and Alzheimer's disease [97-148]. Alzheimer's disease is characterized by the profound memory loss affecting daily routine life [1- 97-148]. Memory impairment (short memory loss) is the hallmark symptom of Alzheimer's disease[97-148]. Alzheimer's is the most common form of dementia [1- 97-148]. Alzheimer's disease is a neurodegenerative pathology, is the most common form of mixed dementia [97-148]. Mixed dementia is a condition in which Alzheimer's disease and vascular dementia occur together [97-148].

Alzheimer's disease is a brain disorder named after German physician Aloes Alzheimer, who first described it in 1906[97-148]. In 1906, Alois Alzheimer, a psychiatrist and neuroanatomist, reported “a peculiar severe disease process of the cerebral cortex” to a gathering of psychiatrists in Tübingen, Germany [97-148]. The case was a 50-year-old woman who suffered from memory loss, delusions, hallucinations, aggression and confusion – all of which worsened until her untimely death five years later [97-148]. In the autopsy, Alzheimer noticed distinctive plaques on her brain [97-148]. These plaques – clumps of amyloid-beta protein are still considered to be the cause of Alzheimer’s disease[97-148]. However, this theory has two major problems. First, it does not explain why many subjects (even old people) have plaques in their brains in the absence of any neurological symptoms, such as memory loss[97-148]. Second, clinical trials for drugs that reduce these plaques have been unsuccessful – with one recent exception, but more of that later [97-148]. When amyloid-beta protein accumulates in the form of plaques (insoluble clumps), the original soluble form of the protein, which performs important functions in the brain, is consumed and lost [97-148]. Some studies have shown that reduced levels of soluble amyloid-beta – called amyloid-beta 42 – have led to patients having worse clinical outcomes [97-148].

Dementia is a leading cause of mental and physical disability [97-148]. On the basis of literature survey, the cause and progression of Alzheimer's disease are not well understood [97-148]. Research indicates that the Alzheimer's disease is associated with **plaques** and **tangles** in the brain[97-148]. Dementia is composed of Alzheimer’s disease (AD), which may contribute to 60–70% of cases, vascular dementia (VD), which may contribute to 25% of cases, and other forms of dementia [97-148]. The development of dementia is associated with genetic and environmental factors. Among the environmental factors, diet is a potentially modifiable lifestyle factor for preventing dementia[97-148]. Dementia is an important public health concern [97-148]. Currently, with around 55 million cases worldwide and an incidence of more than 10 million new cases per annum[97-148]. Dementia has become a major cause of disability, dependency as well as mortality among older people, and has posed substantial burden on patients, their careers, families as well as the society [97-148].

As people age, it is normal to have occasional memory problems, such as forgetting the name of a person that recently met [97-148]. However, Alzheimer's is more than occasional memory loss[97-148]. It is a disease that causes brain cells to malfunction and ultimately die [97-148]. When this happens, an individual may forget the name of a longtime friend or what roads to take to return to a home they have lived in for decades [97-148]. **Alzheimer's disease has no survivors** [1- 97-148]. It destroys brain cells and causes memory changes, erratic behaviors and loss of body functions [97-148]. It slowly and painfully takes away a person's identity, ability to connect with others, think, eat, talk, walk and find his or her way home[97-148]. According to literature survey, Alzheimer's can strike people in their 30s, 40s and even 50s [97-148]. This is called younger-onset Alzheimer's (also referred to as early onset) [97-148]. It is estimated that there are more than 5 million people living with Alzheimer’s disease in the United States [1-97-148]. This includes the over 5 million people age 65 and older and 200,000 people younger than age 65 with younger-onset Alzheimer’s disease [97-148]. During the 1960s and 1970s, aluminum emerged as a possible suspect in Alzheimer’s[1- 97-148]. This suspicion led to concern about exposure to aluminum through everyday sources such as pots and pans, beverage cans, antacids and antiperspirants[1- 97-148]. Since then, studies have failed to confirm any role for aluminum in

causing Alzheimer's [1-97-148]. Experts today focus on other areas of research, and few believe that everyday sources of aluminum pose threat to human life[1- 97-148].

Although aluminum (Al) is highly neurotoxic when it is experimentally administered in animals [1-97-148]. Aluminum can cause fatal encephalopathies in humans in whom it cannot be properly excreted due to renal failure or whose brain was in direct contact with aluminum -based cements used in neurosurgery [1-97-148]. The involvement of this metal in the etiology and pathogenesis of Alzheimer's disease (AD) has only circumstantially been supported [1-97-148]. Nevertheless, this has been a long-standing, controversial and appealing neuropathological hypothesis [1-97-148]. Alzheimer's disease (AD) is a progressive neurodegenerative cerebral disorder [97-148]. Alzheimer's disease is the major cause of dementia and accounts for 60–70% of cases of progressive cognitive deterioration in the elderly [97-148]. Histopathologically, Alzheimer's disease is characterized by deposition of amyloid β-peptide (Aβ) and neurofibrillary degeneration of neurons in the brain [97-148]. Although the pathogenesis of Alzheimer's disease is still unclear, concordance studies on identical versus non-identical twin pairs indicated that the etiology of Alzheimer's disease is multi-factorial with both environmental and genetic susceptibility factors[1-97-148].

Aluminum (Al) is a known neurotoxin and aluminum exposure is considered to be a risk factor for the pathogenesis of Alzheimer's disease[1-97-148]. *In vivo* laboratory evidence has demonstrated that aluminum administration increases Aβ production, promotes its aggregation and inhibits its degradation in the brains of experimental animals, consistent with the process of Alzheimer's disease[1-97-148]. Aluminum -induced accumulation of Aβ has also been confirmed by *in vitro* studies with cultured neurons of rat cerebral cortex[1-97-148]. Recently, the association between aluminum and Alzheimer's disease has been reinforced by the postmortem examination of the aluminum content in Alzheimer's disease-affected brains that revealed an excessive load of aluminum in patient's brain after chronic exposure to aluminum[1-97-148]. Aluminum is neurotoxic and is found in brain tissue in extracellular milieu associated with neuropathology including senile plaques and neurofibrillary tangles in Alzheimer's disease [1-97-148]. While there is no longer any debate as to the presence of aluminum in human brain tissue, there remains the question of how much aluminum in brain tissue is too much [1-97-148]. A number of recent studies have provided data on aluminum content in brain tissue in Alzheimer's disease, multiple sclerosis and autism [1-97-148]. One of the study reported that the data for these control tissues were compared with data (measured using identical procedures) for sporadic Alzheimer's disease, autism spectrum disorder and multiple sclerosis[1-97-148]. Detailed statistical analyses showed that aluminum was significantly increased in each of these disease groups compared to control tissues[1`-97-148]. Therefore, this study confirmed previous conclusions that the aluminum content of brain tissue in Alzheimer's disease, autism spectrum disorder and multiple sclerosis is significantly elevated [1-97-148]. Further research is required to understand the role played by high levels of aluminum in the etiology of human neurodegenerative and neurodevelopmental disease[1-97-148].

Aluminum and its compounds have long been extensively used in industry, water purification, medications, food additives, Aluminum-adjuvanted vaccines and many other products [1-97-148]. Aluminum pollution of water and soil is also increasing due to acid rain that solubilizes aluminum and enhances aluminum uptake into plants, animals, and humans[1-97-148]. Thus, human body is readily exposed to a significant amount of aluminum and may be at risk of Alzheimer's disease due to chronic aluminum exposure[1-97-148]. However, the associations between chronic exposure to aluminum and Alzheimer's disease in previous epidemiological studies are not consistent, possibly due to differences in study populations, levels of aluminum exposure and study designs [1-97-148]. Some studies found a significant association between chronic aluminum exposure and an increased risk of Alzheimer's disease, while other studies failed to demonstrate the association [1-97-148].

Current medications do not cure Alzheimer's, but three treatments — Aducanumab (Aduhelm®), Donanemab (Kisunla™) and Lecanemab (Leqembi®) — are aimed at changing the underlying biology and, therefore, progression of the disease [97-148]. These therapies demonstrated that removing beta-amyloid, one of the hallmarks of Alzheimer's disease, from the brain reduces cognitive and functional decline in people living with early Alzheimer's[97-148]. Other drugs may help lessen symptoms, such as memory loss and confusion, for a limited time [1-97-148]. An early Alzheimer's diagnosis provides patient with a better chance of benefiting from treatment [97-148].

Dementia is a syndrome associated with progressive impairments in memory and learning ability, memory loss, confusion, cognitive skills, disorientation, recent memory loss, and mood changes, forgetfulness, behavior, insomnia, anxiety, depression, disruptive behavior, and hallucinations, activities of daily living, and quality of life [97-148]. The loss of memory is considered to be the result of a shortage of the nerve transmitter acetylcholine[1-97-148]. Several studies have found evidence that Alzheimer's disease is a disease that is caused by the decreased metabolic activity in the brain [97-148]. It is possible to increase the level of this transmitter in the brain by inhibiting the activity of the enzyme acetylcholinesterase, which splits or breaks down the transmitter substance [97-148]. Several studies have

revealed that natural antioxidants, such as vitamin E, vitamin C, and beta-carotene, may help in scavenging free radicals generated during the initiation and progression of this disease [97-148]. Drugs that inhibit the breakdown of the messenger or transmitter acetylcholine delay the development of the disease [97-148]. Memory is the ability of an individual to record sensory stimuli, events, information, etc., retain them over a short or long period of time, and recall the same at a later date when needed [97-148]. Learning is the process of acquiring knowledge about the world and memory could be considered as the retention of the acquired knowledge, which can be recalled as and when needed [97-148]. Dementia is a mental disorder characterized by loss of intellectual ability, which invariably involves impairment of memory and also other higher mental functions [97-148]. The most common cause of dementia is Alzheimer's disease, which is a progressive neurodegenerative disorder associated with loss of neurons in distinct brain areas [97-148]. Furthermore, etiology of neurodegenerative disorders is linked to genetic defect that is 10–15% of total cases [1-97-148]. In Alzheimer's disease, loss of neurons appears in sub-cortical structure, cortex and hippocampus[97-148]. Various compounds have been identified by phytochemical studies such as alkaloids, sterols, triterpenes, polyphenols, tannins, flavonoids and lignins that have pharmacological activities including anti-cholinesterase and anti-amyloidogenic[97-148].

There are numerous types of dementia, among which vascular dementia is the second most common cause after Alzheimer's disease[97-148]. Vascular dementia often coexists with other forms of dementia especially Alzheimer's disease[1-97-148]. Other common forms of dementia include Parkinson's disease, dementia with Lewy bodies, frontotemporal dementia, Huntington's disease, and alcohol related dementia[97-148]. Alzheimer's disease is also associated with functional decline, and behavioral disturbances leading to the cause of disability[97-148]. The incidence and prevalence of Alzheimer's disease rose with increasing age, especially for those over the age of 65 years [97-148]. Therefore, there is a significant clinical challenge to treat patients suffering from Alzheimer's disease[97-148]. **Acetylcholinesterase inhibitors** are usually prescribed to treat Alzheimer's disease [97-148]. These drugs help in enhancing cognitive functions such as memory and thoughts [97-148]. The **tau and amyloid hypothesis** has led to focus on tau and amyloid as treatment targets[97-148]. The current therapeutic goals are to decrease amyloid levels and prevent amyloid toxicity/aggregation and tau aggregation/phosphorylation in Alzheimer's disease patients [97-148].

Alzheimer's disease (AD) is a disorder that causes degeneration of the cells in the brain and it is the main cause of dementia, which is characterized by a decline in thinking and independence in personal daily activities [1-97-148]. Alzheimer's disease (AD) is considered a multifactorial disease: two main hypotheses were proposed as a cause for Alzheimer's disease (AD), cholinergic and amyloid hypotheses[1-97-148]. Additionally, several risk factors such as increasing age, genetic factors, head injuries, vascular diseases, infections, and environmental factors play a role in the disease[1-97-148]. Currently, there are only two classes of approved drugs to treat Alzheimer's disease (AD), including inhibitors to cholinesterase enzyme and antagonists to N-methyl d-aspartate (NMDA), which are effective only in treating the symptoms of Alzheimer's disease (AD), but do not cure or prevent the disease. Nowadays, research is focusing on understanding Alzheimer's disease (AD) pathology by targeting several mechanisms, such as abnormal tau protein metabolism, β amyloid, inflammatory response, and cholinergic and free radical damage, aiming to develop successful treatments that are capable of stopping or modifying the course of Alzheimer's disease (AD) [1-97-148]. Several criteria have been proposed for a more accurate diagnosis of Alzheimer's disease (AD), including clinical biomarkers, bodily fluids, and imaging studies[1-97-148].

Despite that, the treatment of Alzheimer's disease (AD) remains symptomatic, without alteration in the disease's prognosis[1-97-148]. Inhibitors to cholinesterase enzyme such as galantamine, donepezil, and rivastigmine, and NMDA antagonists such as memantine, improve memory and alertness but do not prevent progression[1-97-148]. Several studies have shown that modification in lifestyle habits like diet and exercise can improve brain health and reduce Alzheimer's disease (AD) without medical intervention and is considered as a first-line intervention for all Alzheimer's disease (AD) patients[97-148]. Recently, the research is focusing on targeting the pathological features of Alzheimer's disease (AD) such as Aβ and p-tau[1-97-148]. Designing a potent, selective, and effective drug is urgently needed to treat patients with Alzheimer's disease (AD) and those at risk for developing the disease[97-148].

6. Aluminum and Alzheimer's disease

On the basis of literature survey, it was concluded that aluminum is not considered necessary in our diets, but it is known to affect many processes in human bodies, especially when present in a high concentration[1-97-148]. Among other things, aluminum can interfere with the expression of genes, the synthesis of chemical messengers that cells use to communicate with one another called neurotransmitters, inflammatory responses, and other processes[1-97-148]. In mice designed to accumulate one of the hallmarks of Alzheimer's (the tau protein), aluminum was shown to increase the clumping and accumulation of tau and neurological dysfunction[1-97-148]. Additional animal research suggests

aluminum might also affect amyloid production and degradation (the other hallmark of Alzheimer's) [1-97-148]. The relevance to humans of these aluminum effects in animal models has been debated without a definitive conclusion[1-97-148]. However, suspicion regarding a link between aluminum and Alzheimer's first emerged in 1965 when scientists used an aluminum-containing chemical in their research[1-97-148]. Injection of this chemical, aluminum phosphate, seemed to trigger cognitive changes and also neurofibrillary tangle formation in animal studies [1-97-148]. These tangles were determined to be similar but not identical to the tangles found in the brains of people with Alzheimer's[1-97-148]. Some years later, in 1973, brain tissue collected from deceased persons known to have Alzheimer's were found to have high aluminum levels [1-97-148]. Although this evidence was circumstantial, it led researchers to ask whether aluminum exposure might cause or even increase the progression of Alzheimer's changes in the brain[1-97-148].

When large-scale studies attempted to link aluminum exposure with Alzheimer's, results were mixed[1-97-148]. One study concluded that exposure to more than 100 micrograms/liter of aluminum in drinking water or occupational exposure increased Alzheimer's risk by 71 percent[1-97-148]. Another large study, a meta-analysis (a study of studies), strongly identified late-life depression and type 2 diabetes as evidence-based risk factors for Alzheimer's but also noted "suggestive evidence" for five additional risk factors: aluminum exposure, herpes viral infections, low-frequency electromagnetic fields, educational level, and exposure to non-steroidal anti-inflammatory drugs (NSAIDs) [1-97-148]. Aluminum's likelihood of importance as a risk factor was less supported than other factors such as physical activity, depression, and type 2 diabetes[1-97-148]. Another very large analysis of previous aluminum studies chosen for their high quality and credibility concluded that "there is little evidence that exposure to aluminum increases the risk for Alzheimer's." [1-97-148]. A persuasive editorial in 2014 reviewed the history of the "Aluminum Hypothesis," which states aluminum exposure increases Alzheimer's risk[1-97-148]. The author pointed out that studies have not agreed in their results, some demonstrating concerning results but many finding no reason for concern[1-97-148]. The author also noted that animal studies have not supported the link between aluminum exposure and typical Alzheimer's pathology and that inconsistent results were reported in studies of works with high occupational aluminum exposure, finding both positive and negative results [1-97-148]. One of the most convincing of these studies, a careful investigation of miners from northern Ontario exposed to aluminum given as a protection against silicotic lung disease (a disease caused by breathing in tiny bits of silica over many years), then examined thoroughly for toxic effects, found no statistically significant neurological or cognitive differences between exposed and unexposed miners[1-97-148]. Despite the inconsistent findings that have led many researchers to abandon the aluminum hypothesis, a few researchers remain convinced that aluminum increases Alzheimer's risk[1-97-148]. It would be fair to say, however, that this does not represent current mainstream thinking about Alzheimer's [1-97-148]. If aluminum is a risk factor, it appears to be one of less importance than many others[1-97-148].

It has been suggested that there is a relationship between chronic routine exposure to aluminum and increased risk of a number of neurodegenerative disorders including Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), and Alzheimer's disease -type dementia in Parkinson patients [1-97-148]. In most of the studies reviewed here, the routes of aluminum exposure were through intragastric, oral, intracisternal, intraventricular, or intracerebral modes of administration and are effectively bypassed the blood-brain barrier (BBB) [1-97-148]. Oral studies are very good because they mimic human aluminum exposure risk, but because only a limited amount of aluminum is absorbed, it is necessary to have a much longer exposure periods for aluminum to accumulate in neurons to toxic amounts[1-97-148]. Alzheimer's disease has a long prodromal phase, with pathologic changes often preceding the onset of clinical symptoms by more than a decade [1-97-148]. High aluminum absorption may someday be recognized as a risk factor for Alzheimer's disease[1-97-148]. Humans usually are exposed to aluminum neurotoxicity either through the skin or through food additives[1-97-148]. For this reason, it is crucial to do more research on the bio-availability of this metal and its effectiveness in crossing the gastrointestinal and the blood brain barriers, which could show prime cellular changes in the pathogenesis of Alzheimer's disease[1-97-148].

Over the years, a handful of drugs have been approved to be used in the fight against Alzheimer's disease but unfortunately none of these drugs have proven to be solid-treatments[1-97-148]. Alzheimer's disease is one of the most prominent diseases observed in the elderly population[1-97-148]. Aluminum is abundantly present on the earth's crust and hence becomes easily accessible to man[1-97-148]. This makes it an obvious choice in the preparation of numerous substances, packaging, etc[1-97-148]. Such wide usage of the metal can pave an easy access to the body, leading to toxicities. Aluminum toxicity has been linked to oxidative stress which has an established relation with neurodegeneration and mitochondrial damage[1-97-148]. Scientists have not yet conclusively discovered whether aluminum causes Alzheimer's disease [1-97-148]. Historical research suggests this metal may be a factor[1-97-148]. However, some modern researchers disagree[1-97-148]. Despite most of the initial evidence being undermined, the study that found high levels of aluminum in the brains of people who had died with Alzheimer's has been reinforced by more recent research[1-97-148]. This research has shown higher aluminum levels in the brain and the fluids that bathe the brain in people with Alzheimer's when compared to healthy individuals[1-97-148].

When someone has Alzheimer's disease, their brain cells become damaged and do not function normally [1-97-148]. This loss of function affects many biological systems work, including the blood-brain barrier [1-97-148]. A damaged blood brain barrier allows things to enter human brain tissue that would not normally get through, like aluminum particles [1-97-148]. Research also showed that human brain's waste disposal system does not function properly in Alzheimer's disease, which means that if aluminum does get through, it might not be removed as efficiently[1-97-148]. This is why most scientists think that aluminum build-up in the brain is more likely to be a consequence of Alzheimer's disease rather than a cause [1-97-148]. Scientists have also found aluminum in the same areas of the brain where amyloid plaques, a hallmark feature of Alzheimer's disease, are found[1-97-148]. One of the research study showed a high concentration of aluminum in these plaques, has led some to suggest that it could have a role to play in the formation of these plaques in the first place [1-97-148]. This is just a theory, and studies to date have failed to confirm it[1-97-148]. Because, the kidneys remove aluminum, people with low kidney function can have a higher level of aluminum in their body[1-97-148]. Studying these patients has given researchers an opportunity to see if these higher levels of aluminum affect their brain health[1-97-148]. Research into these patients with kidney failure and others that have a higher exposure to aluminum than the normal population, has found no link between this higher aluminum exposure and an increased risk of Alzheimer's disease[1-97-148].

Every day, people absorb aluminum into their bodies from the environment, air, and food[1-97-148]. While a small amount of this metal reaches their brain tissues, the typical levels of aluminum in a person's body are generally not harmful[1-97-148]. People with Alzheimer's disease tend to have higher levels of aluminum in their brains[1-97-148]. However, scientists do not yet know whether this is a cause of the condition or an effect [1-97-148]. Researchers are continuing to investigate if aluminum causes Alzheimer's disease [1-97-148]. **Post-mortem examinations** of humans with Alzheimer's disease sufferers showed that many have **higher amounts of aluminum** than normal in their brains[1-97-148]. Aluminum is not normally found in healthy brain tissue and researchers do not know how or why the metal accumulates in the brain [1-97-148]. It is still unclear if the presence of aluminum causes or affects the progression of Alzheimer's disease [97-148]. It is known that aluminum is toxic to nerves in animals, and likely has a similar effect on human nerve cells and brain tissue[1-97-148]. Early research into aluminum exposure and Alzheimer's disease in animal models suggested that the two could be linked. Injection of aluminum salts into the brains of test animals triggered changes similar to the ones found in human sufferers[1-97-148]. Therefore, the cause of Alzheimer's disease and any association with aluminum is still unknown[1-97-148]. There have been conflicting findings[1-97-148].

There is growing evidence for a link between aluminum and Alzheimer's disease, and between other metals and Alzheimer's disease[1-97-148]. Nevertheless, because the precise mechanism of Alzheimer's disease pathogenesis remains unknown, and this issue is controversial [1-97-148]. However, it is widely accepted that aluminum is a recognized neurotoxin, and that it could cause cognitive deficiency and dementia when it enters the brain and may have various adverse effects on central nervous system (CNS) [1-97-148]. In general, the absorption of metals by the gastrointestinal tract is widely variable and is influenced by various factors including an individual difference, age, pH, stomach contents [1-97-148]. Recent studies using mass spectrometry of aluminum have demonstrated that small, but a considerable amount of aluminum crosses the blood brain barrier, enters into the brain, and accumulates in a semi-permanent manner[1- 97-148]. Therefore, aluminum can cause severe health problems in particular populations, including infants, elderly people, and patients with impaired renal functions, and unnecessary exposure to aluminum should be avoided for such patients [1-97-148]. In 1989, a joint FAO/WHO Expert Committee on Food Additives (JECFA) recommended a provisional tolerable weekly intake (PTWI) of 7.0 mg/kg body weight aluminum[1-97-148]. However, this was changed in 2007 to 1.0 mg/kg body weight because of potential effects on the reproductive system and the developing nervous system [1-97-148]. The characteristics of aluminum neurotoxity are complex, and further research is needed especially in relation to bioavailability, cellular effects, metabolism, and metal-metal interactions[97-148].

The brain is a highly compartmentalized organ exceptionally susceptible to accumulation of metabolic errors [97-148]. Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of the elderly and is characterized by regional specificity of neural aberrations associated with higher cognitive functions [97-148]. Aluminum (Al) is the most abundant neurotoxic metal on earth, widely bioavailable to humans and repeatedly shown to accumulate in Alzheimer's disease (AD) -susceptible neuronal foci [97-148]. In spite of this, the role of aluminum in Alzheimer's disease (AD) has been heavily disputed based on the following claims: 1) bioavailable aluminum cannot enter the brain in sufficient amounts to cause damage, 2) excess aluminum is efficiently excreted from the body, and 3) aluminum accumulation in neurons is a consequence rather than a cause of neuronal loss [1-97-148]. Research, however, reveals that: 1) very small amounts of aluminum are needed to produce neurotoxicity and this criterion is satisfied through dietary aluminum intake, 2) aluminum sequesters different transport mechanisms to actively traverse brain barriers, 3) incremental acquisition of small amounts of aluminum over a lifetime favors its selective accumulation in brain tissues, and 4) since 1911, experimental evidence has repeatedly demonstrated that chronic aluminum intoxication reproduces neuropathological hallmarks of Alzheimer's disease[1-97-148]. Misconceptions about aluminum bioavailability may

have misled scientists regarding the significance of aluminum in the pathogenesis of Alzheimer's disease (AD) [1-97-148]. The hypothesis that aluminum significantly contributes to Alzheimer's disease is built upon very solid **experimental evidence and should not be dismissed**[1-97-148]. Immediate steps should be taken to lessen human exposure to aluminum, which may be the single most aggravating and avoidable factor related to Alzheimer's disease (AD) [1-97-148].

Aluminum is a ubiquitously abundant nonessential element[97-148]. Aluminum has been associated with neurodegenerative diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis, and dialysis encephalopathy [97-148]. Many continue to regard aluminum as controversial although increasing evidence supports the implications of aluminum in the pathogenesis of Alzheimer's disease[1-97-148]. Aluminum causes the accumulation of **tau protein and Ab protein** in the brain of experimental animals[1-97-148]. Aluminum induces neuronal apoptosis in vivo and in vitro, either by endoplasmic stress from the unfolded protein response, by mitochondrial dysfunction, or a combination of them[1-97-148]. Some, people who are exposed chronically to aluminum, either from through water and/or food, have not shown any Alzheimer's disease pathology, apparently because their gastrointestinal barrier is more effective [1-97-148]. Aluminum is not a member of the human metallome [1-97-148]. However, its omnipresence in human tissue and especially the brain cannot be without consequence[1-97-148]. It is only inimical to life, there is no homeostasis, and it is always a burden to life's processes[1-97-148]. Every atom of aluminum in human brain tissue must be accommodated as aluminum as Al^{3+} (aq), is highly biologically reactive. Life is robust and some aluminum in human brain tissue is tolerated without overt effects[1-97-148].

Looking at all the evidence in field of Alzheimer's research, there is not enough high-quality evidence to conclude that everyday aluminum exposure in a healthy individual causes Alzheimer's disease[1-97-148]. It is possible that larger, more sophisticated studies may one day find a link, but for now we can be reasonably confident that exposure to aluminum does not seem to be an important risk factor for the disease[1-97-148]. Alzheimer's disease is one of the most common neurodegenerative diseases[1-97-148]. The patients have to undergo a lot of difficulties and required constant monitoring as they may harm themselves without even knowing [1-97-148]. Heavy metals like aluminum may play a major in the pathogenesis of the disease[1-97-148]. As promising antioxidants are on paper, only few positive results have been achieved in the treatment of Alzheimer's disease, but we must understand that with a wider range of methodologies with constant efforts may still have a chance to get better results [97-148]. Thus, with wider range of extensive studies may discover the treatment of Alzheimer's Disease at the earliest[1-97-148].

7. Chemical Analysis of Aluminium in tea

At present, the methods that can be used to detect the content of aluminum in tea mainly include inductively Coupled plasma - Optical emission spectrometry (ICP-OES), Graphite furnace atomic absorption spectrometry (GFAAS), Flame atomic absorption spectrometry (FAAS), and Tungsten coil atomic emission spectrometry (WCAES) [1-97-148-155]. These methods are also commonly used in laboratories and can meet the daily detection work [1-97-148-155].

ICP-OES is a powerful, versatile, and advanced analytical technique with excellent detection properties [152-155]. Due to its extraordinary features, it has been widely employed for the analysis of a wide variety of chemical elements in the past few years with great success[1-97-148-155]. It offers the least detection time, lower detection limits, broader linear dynamic range, and greater matrix tolerability as well as negligible chemical interferences[1-97-148-155]. Beyond this, it can handle multiple varieties of samples including aqueous, inorganic, organic liquids, and solids as well [152-155]. It comprises complex instrumental makeup which enables it to detect up to 2 to 70 elements simultaneously with great accuracy[1-97-148-155]. Recent reports evidenced that this hyphenated technique has been employed in several analytical determinations including food analysis, agricultural investigations, geological studies, drug/metabolite analysis, and environmental and forensic sciences [152-155].

Inductively coupled plasma optical emission spectroscopy (ICP-OES), sometimes referred to as ICP-atomic emission spectroscopy, is the technique of choice for many applications that require analyzing a sample for its elemental content[152-155]. Typical samples include those in the environmental, metallurgical, geological, petrochemical, pharmaceutical, materials, and food safety arenas[1-97-148-155]. It can be applied to varying sample types such as aqueous and organic liquids and solids. Some of these sample types need specific sample preparation techniques or the use of specific accessories to allow the sample to be introduced into the ICP-OES instrument[152-155]. The advantages of using ICP-OES over other elemental analysis techniques such as inductively coupled plasma mass spectrometry (ICP-MS) or atomic absorption spectrometry (AAS) include its wide linear dynamic range, high matrix tolerance, and the enhanced speed of analysis that can be achieved [152-155].

The chrome azurol S method is also the most widely used spectrophotometric method in the determination of aluminum content in food[1-97-148]. The principle of this method is that under certain pH conditions, aluminum ions and chrome azurol S solution can react to form a blue-green chelate, and the converted absorbance value is the aluminum content[1-97-148-155].

Spectrophotometry is the most commonly used method for the detection of aluminum in tea, but the accuracy is not enough [1-97-148-155]. The great advantage of aluminum nuclear magnetic resonance spectroscopy for the determination of aluminum in tea is that the detection limit can be very low[1-97-148-155]. Compared with the sample size of 2 ~ 3 cm^3 needed for ICP-OES analysis[1-97-148-155]. This method only needs a sample of 0.5 cm^3 at most[1-97-148-155]. Using FAAS can save costs, but the sensitivity is not as high as GFAAS[1-97-148-155]. GFAAS has high efficiency and long detection time. WCAES has low power requirements and a very fast heating speed[1-97-148-155]. Although it has low accuracy, it can be made portable and suitable for on-site use[1-97-148-155]. ICP-MS has very fast sample detection speed, less interference than spectroscopy, high accuracy, and high instrument operating costs[1-97-148-155]. Therefore, in the actual detection work, it is necessary to select efficient, reasonable and accurate detection methods according to the actual situation[1-97-148-155]. **Following are the few detection methods for aluminum in tea samples** [1-97-148-155].

1) In one of the method described by Yang et al., (2022) [1], the samples of tea leaves were further cleaned with damp paper towels to remove visible dust, placed in a forced-draft oven at 55 ^oC for 12 h[1]. Then ground with a Wiley mill to pass 2 mm[1]. Further a 0.50 g sample was dry-ashed in a porcelain crucible for 4–6 h at 500^0 C in a muffle furnace, cooled, dissolved in 1 mol/L HNO_3, evaporated to dryness[1]. Further ashed again for 1 h[1]. The resulting residue was dissolved in 25 mL of 1 mol/L HCl[1]. All prepared samples (dried leaf, powdered tea, and infusion) were then analyzed for total aluminum by inductively-coupled plasma optical emission spectrometry (ICP-OES) [1, 93-155], using a wavelength of 396.152 nm according to the AOAC Official Method 953.01[1]. The laboratory's contemporary ability to accurately perform total aluminum analyses on previously ashed samples was confirmed with the relative standard deviation <1%[93-155].

Calculation of Target Hazard Quotient (THQ) and Estimated Daily Intake (EDI) of aluminum

According to the method of Yang et al., (2022) [1], the EDI was calculated with Equation (1), while the THQ was calculated with Equation (2). A THQ value being <1 indicates no significant risk of aluminum contamination to human health, whereas a THQ value being >1 indicates potential adverse effects to human health[1, 93-155].

$$EDI = \frac{(C \times EF \times ED \times FIR)}{(W_{AB} \times TA \times 1000)} \quad \text{Equation- No-1}$$

$$THQ = \frac{EDI}{RfD} \quad \text{Equation-N0-2}$$

where C is aluminum concentration in tea (_g/g); FIR is average consumption of tea (8 g/person/day); ED is exposure period (70 years); EF is exposure frequency (365 d/year); TA is duration of exposure (EF x ED); and W_{AB} is average adult body weight (60 kg). According to the U.S. Environmental Protection Agency (USEPA), the RfD (Reference Dose) value of aluminum is 1.0 µg/g/day[1, 93-155].

2) In one of the recent study reported by Öztürk et al. (**2024)** [68], black, green, and white tea samples were purchased from a local supermarket [68]. Tea samples (5 g each) were weighed for each infusion[68]. Five teapots of aluminum, copper, glass, steel, and porcelain were used [68]. Tea infusions were prepared by brewing in water at 100 °C[68]. For this purpose, 100 mL of ultra-pure water was added to five teapots and boiled[68]. Afterward, 5 g of tea samples (black, green, and white) were added and left to brew separately for 5, 10, and 15 min for each tea type[68]. Analyses were performed in three replicates[68]. Analysis of aluminum in tea samples was achieved by an HPLC-FD method previously described by Shibukawa et al [68]. The mobile phase was prepared with 10 mM Bis–Tris, 0.3 mM HQS, 7.0 mM TBABr, 70 mM NaCl, and 25% acetonitrile (v/v) [68-155]. A sample preparation solution was prepared using twice the amounts of the reactants [68]. The extracts obtained by mixing the tea infusions and sample preparation solutions (1:1 v/v) were placed in vials after filtering through a 0.45 µm membrane filter[68]. HPLC-FD conditions were set as follows: excitation wavelength 366 nm, emission wavelength 510 nm, column temperature 25°C, flow rate 1 mL/min, and

injection volume 20 µL[68]. Under optimized conditions, the method was linear in the range of 10–1000 µg/L with a calibration equation of y=2923.1x+226212 (r=0.9983) [68-155].

According to the study reported by Öztürk et al. (**2024),** estimated daily intake (EDI) of metals was calculated according to Equation. 1[68] using the amount of metal in the food, the amount consumed, and the individual's body weight [68]. For this calculation, body weight and daily tea consumption were accepted as 70 kg and 10 g, respectively[68].

$EDI = \frac{C_{metal} \times W_{food}}{BW}$ ---------- (mg/kg BW/day)---------Equation-1

BW (mg/kg BW/), C_{metal} = Concentration of heavy metal (mg/kg), W_{food}=Daily average consumption (g), BW=Body weight (kg) [68]. The hazard quotient (HQ), which was calculated according to Equation. (2), is the metal ratio in the food consumed to the reference oral dose (RfD) of the metal with EDI[68]. The United Nations Food and Agriculture Cover (FAO)—World Health Organization (WHO) on Joint Food Additives Expert Committee (JECFA) has accepted a tolerable daily aluminum intake of 1 mg/kg per body weight. If the HQ value is less than 1 (HQ≤1), the consumption of relevant food is considered safe[68].

$HQ = \frac{(2)\ EDI(mg/kg/day)}{RfD(mg/kg/day)}$ ---------- Equation-2

Tea is among the most consumed beverages today and has the potential for health-promoting effects, but it may also be a source of some contaminating agents[68]. In this study, aluminum concentrations of white, green, and black tea samples brewed in aluminum, copper, glass, steel, and porcelain teapots for three infusion times were determined[68]. The concentration of aluminum in green tea was the highest. Results showed that green tea could cause a significant amount of aluminum exposure[68]. Necessary precautions should be taken to prevent and minimize aluminum exposure from tea[68]. Determining the type of tea, preferring a tea containing less aluminum, determining the type of teapot that will cause less aluminum contamination, and infusion time should be considered in reducing the aluminum exposure[68-155].

3) In one of the method reported by Rao (1994) [93-155] fresh tea leaves (10 samples) from Ooty (South India) and commercial tea powders (6 brands, 10 samples each) were collected and aluminum contents were estimated by dry ash method for fresh tea leaves and wet ashing method for tea infusions using Inductively Coupled Plasma Spectrometer (ICPS) [93-155]. Different tea infusions were prepared in a borosilicate glass beaker and the pH of the infusions were measured using pH meter [93].

- 1000 ml of water was boiled for 5 min and then 2 g of commercial tea powder was added and again boiled for 5 min. This tea infusion was taken for the estimation of aluminum (pH N 4.5) [93].
- Two grams of commercial tea powder samples were added to 1000 ml of water and boiled for 10 min; this infusion was taken for aluminum estimation (pH u 4.5) [93-155].
- Two grams of commercial tea powder samples were added to 1000 ml of water and boiled for 10 min; to this infusion 75 ml milk was added and boiled for 2 min; the tea was taken for aluminum estimation (pH N 6.5) [93-155].
- Tea infusions were prepared in low quality utensils (LQU) (Al-Pb alloy) by boiling 2 g of tea powder in 1000 ml of water for 5 min. These infusions were tested for aluminum (pH 4.5). Similarly, tea infusions were prepared in high quality utensils (HQU) (Al-Mn alloy) and used for aluminum estimation (pH = 4.5) [93-155].
- 50 tea samples were randomly bought from roadside tea shops and tested for aluminum contents (pH = 6.5) [93].
- Commercial tea powders were repeatedly boiled for 1 - 3 times and the infusions were used for aluminum estimation (pH '- 4.5) [93-155].

The above tea samples were filtered and the filtrates were digested with I N HNO_3, and aluminum contents were estimated by Inductively Coupled Plasma Spectrometer (ICPS) [93-155]. The organic and inorganic complexation of aluminum was studied by passing the tea infusions, one set with lemon and the other with milk, through molecular weight cut-off filter membranes for 5,000, 10,000 and 20,000 molecular weights filtration [93-155].

The infusions were tested for aluminum concentrations and the per cent organic and inorganic complexes were calculated [93]. Further, the inorganic speciation of aluminum in tea infusions was studied using potentiometric titration curves for aluminum in water and aluminum in tea infusion and mole fraction of aluminum species were computed [93].

To predict the presence of soluble forms of aluminum in stomach and intestine, different prepared infusions namely tea infusions with lemon and without lemon and tea infusion with milk were passed through 0.45 pm millipore filter and then passed through Dowex SOX column[93-155]. Monomeric and polymeric inorganic species were retained by the column, while organic complexes of aluminum were eluted [93]. Further, tea infusions were incubated at pH 3.0 (stomach pH) and pH 8.0 (intenstine pH) for 2 h at 37 ^{o}C and passed through the Dowex SOX column[93-155]. By altering the pH of Dowex SOX column to 2.0, bound inorganic aluminum complexes were eluted[93]. Both inorganic and organic filtrates were acid digested (I N HNO_3,) and aluminum content was estimated by ICPS [93]. Alum complexation with tea components like theoflavin, tannic acid and nicotinic acid was studied using potentiometric titration curves and stability constant values (log Ks) were calculated[93]. The data on aluminum were subjected to thc STUDENT 't' test and p-values were computed[93-155].

This study indicated that aluminum exists in inorganic forms as A13+, Al(OH):, AI(OH)'+ and also as organic complexes with theoflavin and tannic acid in tea infusions[93]. This is because tea infusions have lower pH values (≤ 4.5) and favor the formation of absorbable aluminum species[93]. **Addition of lemon juice** (pH 3.5) enhances the soluble form of aluminum because of the presence of citric and acetic acids[93]. These acids were found to enhance the soluble form of aluminum[93]. However, addition of milk to tea infusions enhanced the pH (6.5) nearer to neutral pH thus reducing the formation of soluble aluminum forms[93].

Longer boiling time and the addition of lemon juice caused a higher mineral content in tea infusions [93-94]. Among the macro-elements tested, calcium content increased the most after the addition of lemon juice (2-3) times higher in black and green teas, 3.5-4 times higher in white teas) [93]. However, potassium extraction decreased by about 10% after the addition of lemon juice [93-94]. The aluminum content, which is associated with human neurodegenerative diseases, increased from 19 to 50% in black teas, from 56 to 200% in white teas and from 27 to 41% in green teas [93-94]. Addition of **lemon juice** influences the pH of teas, which plays an important role in mineral mobility and the ability to solubilise in water [93-94].

It can be concluded that the mineral content in tea infusions depends on the tea type, time of boiling and addition of lemon juice [93-155]. Both the two latter factors, in most cases, caused a higher mineral content in tea infusions (the highest for calcium) but with one exception – phosphorus extraction decreased after the addition of lemon juice[93-94]. Among the macro-elements tested, the calcium content increased the most after the addition of lemon juice (2-3 times higher in black and green teas, 3.5-4 times higher in white teas[93]. However, potassium extraction decreased by about 10% after the addition of lemon juice[93-94]. he aluminum content, which is associated with human neurodegenerative diseases, increased from 19 to 50% in black teas, from 56 to 200% in white teas and from 27 to 41% in green teas[93]. Generally, the mineral concentration in black, white and green teas was of the order of (in descending sequence) K>Ca>P>Mg>Al [93-155]. The content of aluminum in teas should be examined, and its concentration should be taken into account during tea consumption, especially among young children, for which the aluminum intake can exceed the provisional tolerable weekly intake [93-155].

4) According to the method adopted by Ozdemir et al., (2022) [149] black tea leaves (*Camellia sinensis*) were collected three times during three harvest seasons (May, July and August) from three factories located in Giresun, Trabzon and Rize in **Turkey**[149]. Furthermore, about 5 g of tea plant powder was put in tared nicel containers and dried at 105 °C up to constant weight[149-155]. The dry matter was calculated by considering the loss of weight. For the preparation of tea infusions, 5 g black tea samples and 200 mL of hot deionised water (approximately 96 ºC) were put in the cleaned glass teapot[149]. After different brewing times (15, 30, 45 and 60 min), the infusions were filtered with Nylon to remove big particles and leaves[149]. The so-called blank water followed the same procedure without tea leaves[149]. The total aluminum was investigated for both tea infusions and tea plants [149]. Briefy, 1 g of the black tea samples were digested with 16 mL HNO_3 (65% AR nitric acid) and 4 mL $HClO_4$ (70% perchloric acid) at 200 °C in a 100-mL volumetric flask. ICP-OES standard of Al was purchase from Merck (Darmstadt, Germany) [149]. 1 $mg.ml^{-1}$ of stock solution was used and the standard solutions were prepared by diluting the stock solution in 5% (v/v) HNO_3 immediately before use[149].

The aluminum contents of tea leaves and transferred during the preparation of infusions of teas from Giresun, Trabzon and Rize were analyzed [149]. The average aluminum contents of teas in Rize, Trabzon and Giresun were ordered between 8894 mg/kg and 14,058.03 mg/kg; 8177.75 mg/kg and 11,226.51 mg/kg; 8809.94 mg/kg and

15,657.72 mg/kg, respectively. Results of the analyses showed that the samples of Trabzon contain a statistically lower amount of aluminum comparing to the other cities ($p \leq 0.05$) [149]. When comparing to the previous studies, the results of the aluminum content detected in the present study were found higher. In this case, **Turkish people** who have high tea consumption habits may have health problems[149]. This study showed that the aluminum content of tea increased with the increment of the duration of infusion (($p \leq 0.05$) [149]. In order to reduce the occurrence of aluminum content in the tea infusion, it is necessary to keep the infusion time short [149-155].

5) This method is adopted by Street et al. (2007) [151]. According to this method, a total of 29 tea samples of different origin imported to the Czech Republic were collected and analyzed [151]. For the determination of the accumulation of total aluminum in tea leaves, aliquots (0.5 g) of the dried and powdered biomass were heated in 50 ml quartz–glass beakers up to 500° C for 16 h on a hot plate and in a muffle furnace, with a stepwise increase of the ashing temperature [151-155]. The ash was then heated for 5– 10 min at 100°C in 3 ml of Aqua Regia and than transferred quantitatively to test tubes and filled up to 20 ml with deionised water. Tea infusions were prepared, to test the solubility of the aluminum, after (i) 5 min, (ii) 60 min, and (iii) 24 h, as follows: 1 g of tea was carefully weighed out into standardized glass beakers) [151]. Boiled distilled water (50 ml) was poured into the glass beakers, after which they were covered with watch glasses [151]. After the given time, the extracted solution (tea infusion) was filtered through filter paper (blue label) into test tubes, and immediately measured [151]. When the influence of tea additives was tested, 5.5 g of sugar and/or 0.5 ml commercial lemon juice was added to 50 ml of filtered tea infusion and carefully stirred) [151]. For the extraction of mobile forms of aluminum in soils, the following procedures were applied: (i) exchangeable forms: 0.5 M KCl (adjusted to pH 5.8) in ratio 1:10 w/v, shaking for 24 h, (ii) weakly organically bound forms: 0.3 M $CuCl_2$ solution in ratio 1:10 w/v, shaking for 2 h, (iii) total organically bound forms: 0.05 M $Na_4P_2O_7$ solution in ratio 1:20 w/v, shaking for 24 h [151]. Extracts were separated from suspension by centrifugation (20 min, 13,500 rpm), and, when necessary, further purified by filtration) [151]. Content of weakly organically bound aluminum was calculated as the difference between aluminum amount extracted by $CuCl_2$ and by KCl) [151]. Content of strongly organically bound aluminum was calculated as the difference between aluminum amount extracted by $Na_4P_2O_7$ and by $CuCl_2$ [151]. The content of aluminum in the plant digests, tea infusions, and soil extracts were determined by inductively coupled plasma optical emission spectrometry with axial plasma configuration (ICP-AES – Varian Vista Pro, Australia, equipped with auto sampler SPS-5), at spectral line k = 308.2 nm [151-155].

The results of this study concluded that tea plantations have a high aluminum pool and a low pH in their soil, which would be considered too acidic for normal agricultural practices [151-155]. Organic substances, especially humic acids, should be added to the soil, which would partly immobilize aluminum, as they have a high aluminum-binding capacity) [151]. This action should reduce aluminum accumulation in tea plants) [151]. More research needs to be done regarding aluminum uptake from soil to plants) [151-155]. The total content of aluminum in tea leaves differs according to the type of tea (green or black) and is probably influenced by many other factors, e.g., soil properties. The addition of sugar and lemon juice changed the pH of the tea infusions [151-155]. The addition of lemon juice lowered the pH of the infusion and caused the green tea, which originally had a higher pH than black tea, to have a lower pH than the black [151]. This suggests that the buffering capacity of green tea is low compared to that of black tea [151-155].

A number of studies have reported the total concentration of aluminum in tea infusions) [1-151-155]. The total metal components in tea plants depend on many factors, primarily the age of the tea leaves, but also the soil conditions, rainfall, altitude, genetic make up of the plant, etc) [1-151]. This affects the metal concentration in an infusion) [1-151]. The preparation method (infusion time, temperature, tea–water ratio) also has a large influence) [151-155]. Despite the variation in infusion conditions, the reported aluminum concentrations in tea infusions are remarkably consistent) [1-151-155]. With few exceptions, the aluminum values are in the range of 1–6 mg l^{-1}) [151]. Tea is a major dietary source of aluminum , and tea drinking can more than double an individual's intake of aluminum [1-151]. It is suggested that aluminum in tea infusions is fully or partly bound with relatively large organic molecules, which may be polyphenolic compounds [1-151]. Tea polyphenols have a high affinity for metals and also for biological macromolecules, such as alkaloids, carbohydrates and proteins) [1-151]. One of the study found that the pH of readily available tea (commercial products) to be lower than that of the infusions, and stated it was probably due to the presence of citric acid and other products generally added for the preservation of commercial drinks) [1-151]. Citric acid is known to markedly enhance aluminum absorption) [1-151]. Tea contains a large number of compounds that are able to complex aluminum) [1-151]. It has often been assumed that the polyphenols, which make up 40% of the dry matter present in tea, are the most important aluminum -complexing compounds in tea due to the many phenolic hydroxyl groups that provide a large number of potential complexation sites) [1-151]. Infusions of green and black tea differ chemically, mainly within the polyphenolic fraction) [1-151-155]. The difference results from the oxidation of simple polyphenols to more complexed and condensed ones [151-155]. A large fraction of black tea polyphenols has not been chemically identified, and these compounds are often referred to as thearubigens [1-151].

6) This method of estimation of aluminum in tea samples is adopted by Rohilla et al., (2021) [95]. Black Tea of different companies and different brands were bought from a local market store that is being consumed by more than 1 million peoples. Total eleven types of tea bought were in different packages of different weight ranging 100 gm and 250 gm. Prior to analysis to avoid any contamination of previously present heavy metals, all glassware and plastic ware were soaked in 2% HNO_3 solution for 24 h and boiled for 1 h and washed 3 times with 2% HNO_3 solution[95]. Samples were prepared in the same manner in which the tea brew (Chai) is made in India. *i.e* boiling the tea leaves in water rigorously for 2-3 times, so that the experimental brew become same as the real composition that people take in tea brew [95]. Tea packets were opened just before making the tea brew [95-155]. Tea brew were prepared by boiling 500 mg of tea leaves from each packet in 50 ml of 5% HNO_3 solution, taken in platinum coated stain less steel vessel for five minutes on induction cooking plate operating at 1000 W power, the solution reduced to 15 ml [95]. HNO_3 used was of AR grade and water was distilled deionised Millipore water [95]. The reduced solution is then directly filtered into 15 ml vials of high density polyethylene (HDPE) with the help of funnels of same HDPE material and Filter paper (Watman No. 42) [95]. Solution is then diluted in 2% HNO_3 in the ratio of ten is to one and analyzed in Perkin Elmer NexIon-300x Inductively Coupled Plasma Mass Spectrometer (ICP-MS) [95-155].

8. Conclusion

On the basis of literature survey, it is confirmed that a range of plant species has evolved mechanisms that enable them to grow on acid soils, where toxic concentrations of Al^{3+} can limit plant growth. Organic acids play a central role in these aluminum tolerance mechanisms. Being environmentally abundant, aluminum is not essential for life and no enzymatic reaction requires aluminum. Some plants detoxify aluminum in the rhizosphere by releasing organic acids that chelate aluminum. There are approximately 25 plant families with members that accumulate aluminum at concentrations exceeding 1000 mg kg^{-1} in their leaves. Among them, tea plants (*Camellia sinensis* L.) are among the most important. Old leaves of tea may contain up to 30 mg of aluminum per gram dry weight. Tea plants not only tolerate high aluminum but also their growth is strongly enhanced by aluminum supply. Aluminum (Al) is the most ubiquitous metal in the Earth's crust. Even though its toxicity is well-documented, the role of aluminum in the pathogenesis of several neurological diseases remains debatable in the scientific literature. According to literature survey, the relationship between aluminum exposure and neurodegenerative diseases, including dialysis encephalopathy, amyotrophic lateral sclerosis and Parkinsonism dementia in the Kii Peninsula and Guam, Gulf War syndrome, and Alzheimer's disease (AD) has been suggested.

In recent years, concerns regarding the effects of aluminum pollution on human health have gained significant attention. Aluminum is a naturally occurring element and is the third most abundant metal in the Earth's crust. Its widespread use in industries such as construction, transportation, packaging, and electronics has resulted in the release of aluminum compounds into the air, water, and soil. Additionally, aluminum based products like cookware, beverage cans, and antacids contribute to its exposure in our daily lives. Moreover, aluminum exposure has been associated with respiratory issues, such as lung fibrosis and reduced lung function. Individuals working in aluminum-related industries or residing near manufacturing facilities may be particularly vulnerable to inhalation of aluminum particles or fumes. On the basis of literature survey, prolonged exposure to higher levels of aluminum has also been associated with bone disorders, kidney damage, hormonal imbalances, cancers and Alzheimer's disease (AD).

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] **Yang H**, Chen Y, Shido JM, Hamasaki RT, Iwaoka WT, Nakamoto ST, Wang H, Li QX. Potential Health Risk of Aluminum in Four *Camellia sinensis* Cultivars and Its Content as a Function of Leaf Position. Int. J. Environ. Res. Public Health. **2022**; 19: 11952.

[2] **Malabadi RB,** Kolkar KP, Acharya M, Chalannavar RK. **Tea (*Camellia sinensis*)**: Phytochemistry and Health Benefits- Tea Cup that Cheers has Tears. International Journal of Innovation Scientific Research and Review. 2022; 4(4): **2**620-2633.

[3] Peng CY, Zhu XH, et al., Aluminum and Heavy Metal Accumulation in Tea Leaves: An Interplay of Environmental and Plant Factors and an Assessment of Exposure Risks to Consumers. Journal of Food Science. 2018; Vol. 00, Nr. 00,

[4] Hu HY, Wu BS et al., Tea consumption and risk of incident dementia: A prospective cohort study of 377 592 UK Biobank participants. Translational Psychiatry. 2022; 12:171.

[5] Cornelis MC, van Dam RM. Habitual coffee and tea consumption and cardiometabolic biomarkers in the UK Biobank: The role of beverage types and genetic variation. J Nutr. 2020;150:2772–88.

[6] Zhang Y, Yang H, Li S, Li WD, Wang Y. Consumption of coffee and tea and risk of developing stroke, dementia, and poststroke dementia: A cohort study in the UK Biobank. PLoS Med. 2021;18:e1003830

[7] Eskelinen MH, Ngandu T, Tuomilehto J, Soininen H, Kivipelto M. Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. J Alzheimer's Dis: JAD. 2009;16:85–91.

[8] Shirai Y, Kuriki K, Otsuka R, Kato Y, Nishita Y, Tange C, et al. Green tea an d coffee intake and risk of cognitive decline in older adults: the National Institute for Longevity Sciences, Longitudinal Study of Aging. Public Health Nutr. 2020;23:1049–57.

[9] Eskelinen MH, Kivipelto M. Caffeine as a protective factor in dementia and Alzheimer's disease. J Alzheimer's Dis: JAD. 2010;20(Suppl 1):S167–74.

[10] Shen W, Xiao Y, Ying X, Li S, Zhai Y, Shang X, et al. Tea consumption and cognitive impairment: A cross-sectional study among Chinese elderly. PloS one. 2015;10: e0137781.

[11] Ma YH, Wu JH, Xu W, Shen XN, Wang HF, Hou XH, et al. Associations of green tea consumption and cerebrospinal fluid biomarkers of Alzheimer's Disease pathology in cognitively intact older adults: The CABLE study. J Alzheimer's Dis: JAD. 2020;77:411–21.

[12] Pervin M, Unno K, Ohishi T, Tanabe H, Miyoshi N, Nakamura Y. Beneficial effects of green tea catechins on neurodegenerative diseases. Molecules (Basel, Switzerland). 2018;23:1297.

[13] Kakutani S, Watanabe H, Murayama N. Green tea intake and risks for dementia, Alzheimer's disease, mild cognitive impairment, and cognitive Impairment: A Systematic Review. Nutrients. 2019;11:1165.

[14] Lavretsky H. Lifestyle medicine for prevention of cognitive decline: Focus on green tea. Am J Geriatr Psychiatry: Off J Am Assoc Geriatr Psychiatry. 2016;24:890–2.

[15] Tomata Y, Sugiyama K, Kaiho Y, Honkura K, Watanabe T, Zhang S, et al. Green Tea Consumption and the Risk of Incident Dementia in Elderly Japanese: The Ohsaki Cohort 2006 Study. Am J Geriatr Psychiatry: Off J Am Assoc Geriatr Psychiatry. 2016;24:881–9.

[16] Arendash GW, Schleif W, Rezai-Zadeh K, Jackson EK, Zacharia LC, Cracchiolo JR, et al. Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain beta-amyloid production. Neuroscience. 2006;142:941–52.

[17] Ran LS, Liu WH, Fang YY, Xu SB, Li J, Luo X, et al. Alcohol, coffee and tea intake and the risk of cognitive deficits: a dose-response meta-analysis. Epidemiol Psychiatr Sci. 2021;30:e13.

[18] Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S. Green tea effects on cognition, mood and human brain function: A systematic review. Phytomedicine: Int J. Phytother Phytopharmacol. 2017;34:26–37.

[19] Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol. 2018;14:653–66.

[20] Bell IR. Diet and nutrition in Alzheimer's disease and other dementias of late life. Explor (N. Y, NY). 2005;1:299–301.

[21] Ros E. Can specific nutrients, foods, or dietary patterns modulate cognitive function in (older) adults? Latest evidence from randomized controlled trials. Current opinion in clinical nutrition and metabolic care. 2021;24:511–20.

[22] Bonfiglio R, Scimeca M, Mauriello A. The impact of aluminum exposure on human health. Arch Toxicol. **2023***;* **97**: 2997–2998.

[23] **Bryliński Ł,** Kostelecka K, Woliński F, Duda P, Góra J, Granat M, Flieger J, Teresiński G, Buszewicz G, Sitarz R, Baj J. Aluminium in the Human Brain: Routes of Penetration, Toxicity, and Resulting Complications. Int J. Mol Sci. **2023**; 13;24(8):7228.

[24] Rezaee E, Mirlohi M, Fallah A, Babashahi M. A Systematic Review on Exposure to Toxic and Essential Elements through Black Tea Consumption in Iran: Could It be a Major Risk for Human Health. Int J. Prev Med. 2014;5:1351-9.

[25] Sun L, Zhang M, Liu X, Mao Q, Shi C, Kochian LV, Liao H. Aluminium is essential for root growth and development of tea plants (*Camellia sinensis*). J. Integr. Plant Biol. **2020**; 62: 984–997.

[26] Street R, Drabek O, Szakova J, Mladkova L. Total content and speciation of aluminum in tea leaves and tea infusions. Food Chem**. 2007**; 104: 1662–1669.

[27] Kandimalla R, Vallamkondu J, Corgiat EB, Gill KD. Understanding aspects of aluminum exposure in Alzheimer's disease development. Brain Pathol. **2016**; 26: 139–154.

[28] Klotz K, Weistenhöfer W, Neff F, Hartwig A, van Thriel C, Drexler H. The health effects of aluminum exposure. Dtsch. Ärzteblatt Int. **2017**; 114: 653–659.

[29] Tietz T, Lenzner A, Kolbaum AE, Zellmer S, Riebeling C, Gürtler R, Jung C, Kappenstein O, Tentschert J, Giulbudagian M. et al. Aggregated aluminium exposure: Risk assessment for the general population. Arch. Toxicol. **2019**; 93: 3503–3521.

[30] Carr HP, Lombi E, Küpper H, Mcgrath SP, Wong MH. Accumulation and distribution of aluminum and other elements in tea (*Camellia sinensis*) leaves. Agronomie. 2003; 23: 705–710.

[31] Flaten TP. Aluminum in tea-concentrations, speciation and bioavailability. Coordin. Chem. Rev. 2002; 2: 385–395.

[32] Yokel RA, Florence RL. Aluminum bioavailability from tea infusion. Food Chem. Toxicol. 2008; 46: 3659–3663.

[33] Wong MH, Zhang ZQ, Wong JWC, Lan CY. Trace metal contents (Al, Cu and Zn) of tea: Tea and soil from 2 tea plantations, and tea products from different provinces of China. Environmental Geochemistry and Health. 1998; 20(2): 87–94.

[34] Li L, Fu QL, Achal V, Liu Y. A comparison of the potential health risk of aluminum and heavy metals in tea leaves and tea infusion of commercially available green tea in Jiangxi, China. Environmental Monitoring and Assessment. 2015; 187(5), 228.

[35] Cao H, Qiao L, Zhang H, Chen J. Exposure and risk assessment for aluminium and heavy metals in Puerh tea. Science of the Total Environment. 2010; 408(14): 2777–2784.

[36] Zhang J, Yang R et al., Accumulation of Heavy Metals in Tea Leaves and Potential Health Risk Assessment: A Case Study from Puan County, Guizhou Province, China. Int. J. Environ. Res. Public Health. 2018;15: 133.

[37] Flaten TP. Aluminium in tea/concentrations, speciation and bioavailability. Coordination Chemistry Reviews. 2002; 228: 385-/395.

[38] Schwalfenberg G et al., The Benefits and Risks of Consuming Brewed Tea: Beware of Toxic Element Contamination. Hindawi Publishing Corporation. Journal of Toxicology . 2013; Volume 2013, Article ID 370460, 8 pages http://dx.doi.org/10.1155/2013/370460

[39] Ozdemir Z, Zannou O, Koca I. Assessment of the aluminum contents of black tea and black tea infusions. Discover Food. 2022; 2:13

[40] Han Q, Mihara S, Fujino T. Multi-element detection in green, black, oolong, and Pu-erh teas by ICP-MS. Biochem Physiol. 2014;3:132.

[41] Wong MH, Fung KF, Carr HP. Aluminum and fluoride contents of tea, with emphasis on brick tea and their health implications. Toxicol Lett. 2003;31(137):111–20.

[42] Olivier J, Symington EA, Jonker CZ, Rampedi IT. et al. Comparison of the mineral composition of leaves and infusions of traditional and herbal teas. South Afr. J. Sci. 2012;108(1–2):1–7.

[43] Mossion A, Potin-Gautier M, Delerue S, et al. Effect of water composition on aluminium, calcium and organic carbon extraction in tea infusions. Food Chem. 2008;106:1467–75.

[44] Kroppl M, Zeiner M, Cindric IJ, Stingeder G. Differences in aluminum content of various tea powders (black, green, herbal, fruit) and tea infusions. Eur Chem Bull. 2012;1:382–6.

[45] Kralj B, Križaj I, Bukovec P, et al. Speciation of aluminum in tea infusions by use of SEC and FPLC with ICP–OES and ES–MS–MS detection. Anal Bioanaly Chem. 2005;383(3):467–75.

[46] Ansari F, Norbaksh R, Daneshmandirani K. Determination of heavy metals in Iranian and imported black tea. Iran. J. Environ. Health. Sci. Eng. 2007; 4:4: 243-248.

[47] Mehra A, Baker CL. Leaching and bioavailability of aluminum, copper and manganese from tea (*Camellia sinensis*). Food Chem. 2007;100:1456–63.

[48] Shekoohiyan S, Ghoochani M, Mohagheghian A, et al. Determination of lead, cadmium and arsenic in infusion tea cultivated in north of Iran. J. Enviro Health Sci Eng. 2012;9:1–37.

[49] Shen FM, Chen HW. Element composition of tea leaves and tea infusions and its impact on health. Bull Environ Contam Toxicol. 2008;80(3):300–4.

[50] Nookabkaew S, Rangkadilok N, Satayavivad J. Determination of trace elements in herbal tea products and their infusions consumed in Thailand. J. Agric Food Chem. 2006;54(18):6939–44.

[51] Bonfiglio R, Scimeca M, Mauriello A. The impact of aluminum exposure on human health. Archives of Toxicology. 2023; 97:2997–2998.

[52] Fung KF, Zhang ZQ, Wong JWC, et al. Aluminium and fluoride concentrations of three tea varieties growing at Lantau Island, Hong Kong. Environ Geochem Health. 2003;25:219–32.

[53] Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. J Toxicol Environ Health B Crit Rev.2007;10(suppl 1):1-269.

[54] Rogers MA, Simon DG. A preliminary study of dietary aluminum intake and risk of Alzheimer's disease. Age Ageing. 1999;28(2):205–9.

[55] Gani A, Prasad K, Ahmad M, Gani A. Time-dependent extraction kinetics of infused components of different Indian black tea types usingUV spectroscopy. Cogent Food Agric. 2016;2:1.

[56] Yadav GU, Joshi BS, Patwardhan AW, Singh G. Swelling and infusion of tea in tea bags. J. Food Sci Technol. 2017;54(8):2474–84.

[57] **Zhang H,** Song Y, Fan Z, Ruan J, Hu J, Zhang Q. Aluminum Supplementation Mediates the Changes in Tea Plant Growth and Metabolism in Response to Calcium Stress. Int. J. Mol. Sci. **2024**; 25: 530. https://doi.org/10.3390/ijms25010530.

[58] Hajiboland R, Bahrami Rad S, Barceló J, Poschenrieder C. Mechanisms of Aluminum-Induced Growth Stimulation in Tea (Camellia sinensis). J. Plant Nutr. Soil Sci. 2013; 176: 616–625.

[59] Liu Y, Tao J, Cao J, Zeng Y, Li X, Ma J, Huang Z, Jiang M, Sun L. The Beneficial Effects of Aluminum on the Plant Growth in Camellia Japonica. J. Soil Sci. Plant Nutr. 2020; 20: 1799–1809.

[60] Morita A, Yanagisawa O, Takatsu S, Maeda S, Hiradate S. Mechanism for the Detoxification of Aluminum in Roots of Tea Plant (*Camellia sinensis* (L.) Kuntze). Phytochemistry. 2008; 69: 147–153.

[61] Mukhopadyay M, Bantawa P, Das A, Sarkar B, Bera B, Ghosh P, Mondal TK. Changes of Growth, Photosynthesis and Alteration of Leaf Antioxidative Defence System of Tea [*Camellia sinensis* (L.) O. Kuntze] Seedlings under Aluminum Stress. Biometals. 2012; 25: 1141–1154.

[62] Unno K, Nakamura Y. Green tea suppresses brain aging. Molecules (Basel, Switzerland). 2021;26:4897.

[63] Singh NA, Mandal AK, Khan ZA. Potential neuroprotective properties of epigallocatechin-3-gallate (EGCG). Nutr J. 2016;15:60.

[64] Ran LS, Liu WH, Fang YY, Xu SB, Li J, Luo X, et al. Alcohol, coffee and tea intake and the risk of cognitive deficits: a dose-response meta-analysis. Epidemiol Psychiatr Sci. 2021;30:e13.

[65] Mancini E, Beglinger C, Drewe J, Zanchi D, Lang UE, Borgwardt S. Green tea effects on cognition, mood and human brain function: A systematic review. Phytomedicine: Int J. Phytother Phytopharmacol. 2017;34:26–37.

[66] Shen W, Xiao Y, Ying X, Li S, Zhai Y, Shang X, et al. Tea consumption and cognitive impairment: A cross-sectional study among Chinese elderly. PloS one. 2015;10: e013778.

[67] Ma YH, Wu JH, Xu W, Shen XN, Wang HF, Hou XH, et al. Associations of green tea consumption and cerebrospinal fluid biomarkers of Alzheimer's Disease pathology in cognitively intact older adults: The CABLE study. J Alzheimer's Dis: JAD. 2020;77:411–21.

[68] **Öztürk E**, Yıldırım S, Akyol A. Determination of aluminium concentrations in black, green, and white tea samples: efects of diferent infusion times and teapot species on aluminium release. European Food Research and Technology. **2024**; https://doi.org/10.1007/s00217-024-04532-w

[69] Nayak P. Aluminum: impacts and disease. Environ Res. 2002; 89(2):101–115.

[70] Fung K, Carr H, Poon B, Wong MH. A comparison of aluminum levels in tea products from Hong Kong markets and in varieties of tea plants from Hong Kong and India. Chemosphere. 2009; 75(7):955–962.

[71] Cao H, Qiao L, Zhang H, Chen J. Exposure and risk assessment for aluminum and heavy metals in Puerh tea. Sci Total Environ. 2010; 408(14):2777–2784.

[72] Zhang J, Yang R, Chen R, Peng Y, Wen X, Gao L. Accumulation of heavy metals in tea leaves and potential health risk assessment: a case study from Puan County, Guizhou Province, China. Int J Environ Res Public Health. 2018; 15(1):133

[73] Moghaddam MA, Mahvi AH, Asgari AR, Yonesian M, Jahed GH, Nazmara SH. Determination of aluminum and zinc in Iranian consumed tea. Environ Monit Assess. 2008; 144(1–3):23–30.

[74] Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol. 2018;14:653–66.

[75] Karak T, Bhagat RM. Trace elements in tea leaves, made tea and tea infusion: a review. Food Res Int. 2010; 43(9):2234–2252.

[76] Olivier J, Symington EA, Jonker CZ, Rampedi IT, van Eeden TS. Comparison of the mineral composition of leaves and infusions of traditional and herbal teas. S Afr J Sci. 2012; 108(1/2):97– 103.

[77] Peng CY et al., Aluminum and heavy metal accumulation in tea leaves: An interplay of environmental and plant factors and an assessment of exposure risks to consumers. J Food Sci. 2018; 83(4):1165–1172

[78] de Oliveira LM et al., Metal concentrations in traditional and herbal teas and their potential risks to human health. Sci Total Environ. 2018; 633:649–657.

[79] Saletnik B et al., Effect of infusion time and addition of lemon juice on the mobility of selected macro-elements and aluminium during aqueous extraction of quality brands of leaf tea. J Elem. 2018; 23(2):611–624.

[80] Street R, Drabek O, Szakova J, Mladkova L. Total content and speciation of aluminum in tea leaves and tea infusions. Food Chem. 2007; 104(4):1662–1669.

[81] Mehra A, Baker CL. Leaching and bioavailability of aluminum, copper and manganese from tea (Camellia sinensis). Food Chem. 2007; 100(4):1456–1463.

[82] Öztürk E, Yıldırım S, Akyol A. Determination of aluminum concentrations of parenteral nutrition solutions by HPLC. Eur J Clin Nutr. 2020; 75(3):567–569.

[83] **Peng A** et al., Aluminum and fluoride stresses altered organic acid and secondary metabolism in tea (Camellia sinensis) plants: Influences on plant tolerance, tea quality and safety. Int J. Mol Sci. **2023**; 24(5):4640.

[84] Bolle F, Brian W, Petit D, Boutakhrit K, Feraille G, Van Loco J. Tea brewed in traditional metallic teapots as a signifcant source of lead, nickel and other chemical elements. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2011; 28(9):1287– 1293.

[85] Li L, Fu QL, Achal V, Liu Y. A comparison of the potential health risk of aluminum and heavy metals in tea leaves and tea infusion of commercially available green tea in Jiangxi, China. Environ Monit Assess. 2015; 187(5):228.

[86] Mathuranath PS, George A, Ranjith N, Justus S, Kumar MS, Menon R, et al. Incidence of Alzheimer's disease in India: A 10 years follow-up study. Neurol. India. 2012;60(6):625–630.

[87] LIczbiński P, Bukowska B. Tea and coffee polyphenols and their biological properties based on the latest in vitro investigations. Ind Crops Prod. 2022; 175:114265

[88] Fernández-Cáceres PL, Martín MJ, Pablos F, González AG. Differentiation of tea (Camellia sinensis) varieties and their geographical origin according to their metal content. J Agric Food Chem. 2001; 49(10):4775–4779.

[89] Khan N, Mukhtar H. Tea polyphenols for health promotion. Life Sci. 2007; 81(7):519–533

[90] **Pavlovi˘c A**, Tav˘car G, Ponikvar-Svet M. Fluoride and Aluminium in Tea (*Camellia sinensis* L.)—Tea Quality Indicators and Risk Factors for Consumers. Molecules. **2023**; 28: 6396.

[91] **Ozdemir Z**, Zannou O, Koca I. Assessment of the Aluminium Contents of Black Tea and Black Tea Infusions. Discov. Food. **2022**: 2, 13.

[92] Rajwanshi P, Singh V, Gupta MK, Kumari V, Shrivastav R, Ramanamurthy M, Dass S. Studies on aluminum leaching from cookware in tea and coffee and estimation of aluminium content in toothpaste, baking powder and paan masala. Sci Total Environ. 1997; 30;193(3):243-9.

[93] **RAO KSJ.** Aluminum content in tea leaves and in differently prepared tea infusions. Die Nahrung. 1994; 38: 5: 533 - 537.

[94] Saletnik B, Zaguła G, Grabek-Lejko D, Kasprzyk I, Bajcar M, Czernicka M, Puchalski Cz. Effect of infusion time and addition of lemon juice on the mobility of selected macroelements and aluminium during aqueous extraction of quality brands of leaf tea. J. Elem. 2018; 23(2): 611-624.

[95] **Rohilla**, V, Kathait GS, Biswas D, Thapliyal P, Ruhela B. Estimation of Heavy Metals in Some Indian Black Tea Leaves by Inductively Coupled Plasma Mass Spectrometer (ICP-MS) and Associated Health Risks. Indian Journal of Agricultural Research. **2021**; 55(2): 181-186.

[96] Indian Tea Industry Analysis Report 2023-2028 | LinkedIn.

[97] **Malabadi RB**, Kolkar KA, Meti NT, Chalannavar RK. Recent updates on the role of herbal medicine for Alzheimer's disease (Dementia). Int. J. Curr. Res. Biosci. Plant Biol. **2021**; 8(1): 14-45.

[98] Kandimalla R, Vallamkondu J et al., Understanding Aspects of Aluminum Exposure in Alzheimer's Disease Development. Brain Pathology. 2016; 26: 139–154.

[99] Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020; 25: 5789.

[100] Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020; 8;25(24):5789.

[101] Alzheimer's & Memory Loss Myths | Alzheimer's Association.

[102] Kawahara M, Kato-Negishi M. Link between Aluminum and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminum and Amyloid Cascade Hypotheses. Int J. Alzheimers Dis. 2011; 8:276393.

[103] Tomljenovic L. Aluminum and Alzheimer's disease: After a century of controversy, is there a plausible link? J Alzheimers Dis. 2011;23(4):567-98.

[104] Ellison JM. Aluminum and Alzheimer's: Is There a Connection? | BrightFocus Foundation.

[105] CCOHS: Alzheimer's Disease and Aluminum Exposure.

[106] Exley C. The toxicity of aluminum in humans. Morphologie. 2016; 100: 51–55.

[107] Aluminium and Alzheimer's: An unproven link - Alzheimer's Research UK (alzheimersresearchuk.org).

[108] House E, Esiri M, Forster G, Ince PG, Exley C. Aluminum, iron and copper in human brain tissues donated to the medical research council's cognitive function and ageing study. Metallomics. 2012; 4: 56–65.

[109] **Exley C**, Clarkson E. Aluminum in human brain tissue from donors without neurodegenerative disease: A comparison with Alzheimer's disease, multiple sclerosis and autism. Scientific Reports. **2020**; 10:7770 | https://doi.org/10.1038/s41598-020-64734-6

[110] Exley C, House E. Aluminum in the human brain. Monat. Chem. – Chem. Monthly. 2011; 142: 357–363.

[111] Bondy SC. Low levels of aluminum can lead to behavioural and morphological changes associated with Alzheimer's disease and age-related neurodegeneration. Neurotoxicology. 2016; 15: 222–229.

[112] Stahl T, Falk S, Taschan H, Boschek B, Brunn H. Evaluation of human exposure to aluminum from food and food contact materials. Eur. Food Res. Technol. 2018; 244: 2077–2084.

[113] Bondy SC. The neurotoxicity of environmental aluminum is still an issue. Neurotoxicology. 2010; 31: 575–81.

[114] Exley C. What is the risk of aluminum as a neurotoxin? Expert Rev. Neurother. 2014; 14: 589–591.

[115] Exley C, Mold MJ. Aluminum in human brain tissue: How much is too much? J. Biol. Inorg. Chem. 2019; https://doi.org/10.1007/ s00775-019-01710-0.

[116] Mirza A, King A, Troakes C, Exley C. Aluminum in brain tissue in familial Alzheimer's disease. J. Trace Elem. Med. Biol. 2017; 40: 30–36.

[117] Polizzi S. et al. Neurotoxic effects of aluminum among foundry workers and Alzheimer's disease. Neurotoxicology. 2002; 23: 761–774.

[118] **Zeb** Z, Sharif A, Akhtar B, Shahnaz. 3-Acetyl coumarin alleviate neuroinflammatory responses and oxidative stress in aluminum chloride-induced Alzheimer's disease rat model. Inflammopharmacology. **2024** Apr;32(2):1371-1386.

[119] **Exley C**, Clarkson E. Aluminum in human brain tissue from donors without neurodegenerative disease: A comparison with Alzheimer's disease, multiple sclerosis and autism. Sci Rep*.* **2020***;* 10: 7770.

[120] Yiannopoulou KG, Papageorgiou SG. Current and future treatments in Alzheimer disease: An update. J. Cent. Nerv. Syst. Dis. 2020; 12.

[121] Yaari R, Fleisher AS, Tariot PN. Updates to diagnostic guidelines for Alzheimer's disease. Prim. Care Companion Cns Disord. 2011; 13: 11f01262.

[122] **Livingston G**, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, Brayne C, Burns A, Cohen-Mansfield J, Cooper C., et al. Dementia prevention, intervention, and care: **2020** report of the Lancet Commission. Lancet. 2020; 396: 413–446.

[123] Neugroschl J, Wang S. Alzheimer's disease: Diagnosis and treatment across the spectrum of disease severity. Mt. Sinai J. Med. N. Y. 2011; 78:596–612

[124] Schachter AS, Davis KL. Alzheimer's disease. Dialogues Clin. Neurosci. 2000; 2: 91–100.

[125] Brion JP. Neurofibrillary tangles and Alzheimer's disease. Eur. Neurol. 1998; 40: 130–140.

[126] Ricciarelli R, Fedele E. The amyloid cascade hypothesis in Alzheimer's disease: It's time to change our mind. Curr. Neuropharmacol. 2017; 15: 926–935.

[127] Tcw J, Goate AM. Genetics of beta-Amyloid precursor protein in Alzheimer's disease. Cold Spring Harb. Perspect. Med. 2017; 7: a024539.

[128] Paroni G, Bisceglia P, Seripa D. Understanding the amyloid hypothesis in Alzheimer's disease. J. Alzheimer's Dis. Jad. 2019; 68: 493–510.

[129] Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM. Alzheimer's disease: Targeting the Cholinergic System. Curr. Neuropharmacol. 2016; 14: 101–115.

[130] Monczor M. Diagnosis and treatment of Alzheimer's disease. Curr. Med. Chem. Cent. Nerv. Syst. Agents. 2005; 5: 5–13.

[131] Overk CR, Masliah E. Pathogenesis of synaptic degeneration in Alzheimer's disease and Lewy body disease. Biochem Pharm. 2014; 88:508–516.

[132] Metaxas A, Kempf SJ. Neurofibrillary tangles in Alzheimer's disease: Elucidation of the molecular mechanism by immunohistochemistry and tau protein phospho-proteomics. Neural Regen. Res. 2016; 11: 1579–1581.

[133] Singh SK, Srivastav S, Yadav AK, Srikrishna S, Perry G. Overview of Alzheimer's disease and some therapeutic approaches targeting a beta by using several synthetic and herbal compounds. Oxidative Med. Cell. Longev. 2016; 7361613.

[134] Spires-Jones TL, Hyman B. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron. 2014; 82: 756–771.

[135] Kawahara M. Effects of aluminum on the nervous system and its possible link with neurodegenerative diseases. J. Alzheimer's Dis. 2005; 8: 171–182; discussion 209–215.

[136] Kumar V, Bal A, Gill KD. Aluminum-induced oxidative DNA damage recognition and cell-cycle disruption in different regions of rat brain. Toxicology. 2009; 264:137–144.

[137] Zhidan W. *et al*. Aluminum content in *Camellia sinensis* (L.) O.Kuntze cultivars with delayed leaf-plucking. *Acta Tea Sinica.* 2016; 57(1): 13-17.

[138] Yanqin Q. *et al*. Determination and leaching at brewing of aluminum, iron and manganese in white tea. *Acta Tea Sinica*. 2018; 59(4): 211-214.

[139] Koch KR. *et al*. Determination of aluminum levels in tea and coffee by inductively coupled plasma optical emission spectrometry and graphite furnace atomic absorption spectrometry. *Analyst.* 1989; 114(8): 911-913.

[140] **Islam F**, Shohag S, Akhter S, Islam MR, Sultana S, Mitra S, Chandran D, Khandaker MU, Ashraf GM, Idris AM, Emran TB and Cavalu S. Exposure of metal toxicity in Alzheimer's disease: An extensive review. Front. Pharmacol. **2022**; 13:903099.

[141] Yokel RA. The toxicology of aluminum in the brain: A review. Neurotoxicology.2000;21(5):813–828.

[142] Yuan CY, Hsu GS, Lee YJ. Aluminum alters NMDA receptor 1A and 2A/B expression on neonatal hippocampal neurons in rats. J Biomed Sci. 2011;18(1):1–9.

[143] Yuan CY, Lee YJ, Hsu GSW. Aluminum overload increases oxidative stress in four functional brain areas of neonatal rats. J Biomed Sci. 2012;19(1):1–9.

[144] Mathuranath PS, George A, Ranjith N, Justus S, Kumar MS, Menon R, et al. Incidence of Alzheimer's disease in India: A 10 years follow-up study. Neurol. India.2012;60(6):625–630.

[145] Krewski D, Yokel RA, Nieboer E, Borchelt D, Cohen J, Harry J. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. J Toxicol Environ Health B Crit Rev.2007;10(suppl 1):1-269.

[146] **Choudhury R**, Ashtekar H, Khot1 KB, Malngiang M, Vijay Kumar M, Mandal S, Das B. Aluminum toxicity induced Alzheimer's Disease and its potential treatment using antioxidants - A review. Braz. J. Pharm. Sci. **2023**;59: e21587.

[147] Aguilar F, Autrup H, Barlow S, Castle L, Crebelli R, Dekant W, et al. Scientific opinion of the panel on food additives, flavourings, processing aids and food contact materials on a request from european commission on safety of aluminum from dietary intake. EFSA J. 2008;754:1-122.

[148] Kawahara M, Midori Kato-Negishi. Link between Aluminum and the Pathogenesis of Alzheimer's Disease: The Integration of the Aluminum and Amyloid Cascade Hypotheses Masahiro. SAGE-Hindawi Access to Research International Journal of Alzheimer's Disease. 2011; Article ID 276393, 17 pages. doi:10.4061/2011/276393.

[149] Ozdemir Z, Zannou O, Koc I. Assessment of the aluminum contents of black tea and black tea infusions. Discover Food. 2022; 2:13 | https://doi.org/10.1007/s44187-022-00014.

[150] Ghoochani M, Shekoohiyan S, Yunesian M, Nazmara S, Mahvi AH. Determination of aluminum and zinc in infusion tea cultivated in north of Iran. J Environ Health Sci Eng. 2015; 31;13:49.

[151] Street R, Drabek O. et al., Total content and speciation of aluminum in tea leaves and tea infusions. Food Chemistry. 2007; 104: 1662–1669.

[152] Khan SR, Sharma B, Chawla P.A. *et al.* Inductively Coupled Plasma Optical Emission Spectrometry (ICP-OES): A Powerful Analytical Technique for Elemental Analysis. Food Anal. Methods. 2022; 15: 666–688.

[153] Liu HL, Meng Q et al., Inductively coupled plasma mass spectrometry (ICP-MS) and inductively coupled plasma optical emission spectrometer (ICP-OES)-based discrimination for the authentication of tea. Food Control. 2021; 123: 107735.

[154] Froes RES, Borges Neto W, Beinner MA. *et al.* Determination of Inorganic Elements in Teas Using Inductively Coupled Plasma Optical Emission Spectrometry and Classification with Exploratory Analysis. Food Anal. Methods. 2014; 7: 540–546

[155] Kilic S, Soylak M. Determination of trace element contaminants in herbal teas using ICP-MS by different sample preparation method. J Food Sci Technol. 2020 ;57(3):927-933.