Role of micronutrients in Alzheimer's disease: Review of available evidence

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Abstract

Alzheimer’s disease (AD) is one of the most common age-related neurodegenerative disorders that have been studied for more than 100 years. Although an increased level of amyloid precursor protein is considered a key contributor to the development of AD, the exact pathogenic mechanism remains known. Multiple factors are related to AD, such as genetic factors, aging, lifestyle, and nutrients. Both epidemiological and clinical evidence has shown that the levels of micronutrients, such as copper, zinc, and iron, are closely related to the development of AD. In this review, we summarize the roles of eight micronutrients, including copper, zinc, iron, selenium, silicon, manganese, arsenic, and vitamin D in AD based on recently published studies.

Key Words: Alzheimer’s disease; Iron; Micronutrient; Zinc

Core Tip: Significant advances have been made in characterizing the relationship between Alzheimer’s disease (AD) and micronutrients copper, zinc, iron, selenium, silicon, manganese, and arsenic. This study provides a new perspective and direction for future scientific research, development of new drugs, and routine preventive measures against AD.
INTRODUCTION

Alzheimer’s disease (AD) is a common age-related neurodegenerative disease[1,2]. Owing to progressive population aging, the incidence of AD will continue to increase[3,4]. In China, an estimated 14% of the general population over the age of 65 years and approximately 30% general population over the age of 85 years were affected by AD. In China, the estimated annual cost of medical care for AD approaches one hundred billion RMB, as the conventional diagnosis of AD is based on expensive investigations such as magnetic resonance imaging, positron emission tomography, and analysis of cerebrospinal fluid[5].

Individuals with AD typically suffer from loss of learning ability and memory, impaired judgment and reasoning[6,7], and loss of analytical ability[8], which can seriously affect their quality of life. This imposes a heavy economic and psychosocial burden on the affected families and the society. Clinical treatment of AD is typically challenging[9]. Currently, clinical research on AD in China and overseas is only at the stage of exploration, while the basic research on AD is still at the stage of hypotheses or theories. Studies have shown that AD is closely related to the dynamic changes in body micronutrients, such as decrease in iron and zinc content, and increase in copper content[10-12]. This article reviews the evidence from contemporary research conducted across the world on the link between AD and micronutrients.

This article is primarily based on a literature search conducted in the NCBI database for studies investigating the link between AD and micronutrients published in the last five years.

AD AND MICRONUTRIENTS

AD and copper

Copper is a ubiquitous element. Red meat, nuts, and vegetables are rich sources of copper. Copper is one of the most abundant transition metals in the human body. It is involved in collagen synthesis, antioxidant defense, skin pigmentation, neurotransmitter synthesis, and iron homeostasis[13]. Thus, it plays an important role in human physiology.

Copper is closely related to AD[14,15]. The most common neuropathic lesions in AD are plaques of neurofibrillary tangle, amyloid, and soluble oligomers with large amounts of copper at their core. Patients with AD were shown to have significantly higher levels of copper in their brain tissue than the general population, which promotes the formation of neurofibrillary tangle, amyloid, and other proteins[16-18].

Copper promotes the neurofibrillary tangle of hyperphosphorylation Tau, which aggravates homeostatic disorders; in addition, copper promotes oxidative stress, which has been observed in the brain tissue of many patients with AD[19]. Rosmarinic acid is a commonly used anti-AD drug. Rosmarinic acid has been shown to reduce copper-induced neurotoxicity due to its antioxidant effect in vitro and in vivo, by preventing the binding of amyloid protein with copper[20]. The properties of copper-bound amyloid proteins have been employed for auxiliary positron emission tomography in the diagnosis of AD in mouse models[21].

Detection of copper is useful in the diagnosis and prevention of AD[22,23]. In addition, long-term exposure to copper is associated with cognitive decline and microglia degeneration[24]. TDMQ20 was shown to reduce the copper content in the cerebral cortex of mice[25], and ameliorate oxidative stress in the cerebral cortex of mice, further attenuating the neurotoxicity of amyloid[26]. High affinity metal ion chelating agents such as chitosan can be an effective treatment for AD. The therapeutic effect of chitosan is related to its ability to absorb copper ions[27].

AD and zinc

Zinc is one of the essential micronutrients in the body and the second most abundant micronutrient in the central nervous system[28,29]. Zinc is involved in growth and development, wound healing, immune regulation, catalytic reactions, and substance synthesis. Zinc also regulates excitatory and inhibitory neurotransmitters in brain tissue[30,31]. As the zinc content in the body decreases with age, abnormal zinc metabolism may serve as a therapeutic target for AD. In particular, zinc and selenium or iron and zinc have been concomitantly used to treat AD[32,33].

Studies have shown that zinc release increases with age, especially in female rats, and that zinc deficiency leads to neuronal death; this phenomenon is related to the involvement of zinc in the...
recognition of neuronal receptors and ligands, which is one of the main risk factors for AD and its associated brain neuropathology[34]. On the contrary, zinc supplementation was shown to improve cognitive deficit and rescue the decline in key molecular targets of synaptic plasticity and insulin signaling in the hippocampus of rats with sporadic AD[35]. Oxidative stress plays a key role in neurodegeneration and impaired cognitive function. Diet rich in antioxidants is a novel strategy for prevention of AD. Compared with healthy individuals, patients with AD showed significantly lower serum levels of Se, Cu, and Zn[36].

Studies have shown that the disorder of zinc dynamic equilibrium can cause abnormal synthesis and increased deposition of amyloid protein in brain tissue, and increase the degree of neuronal damage. The underlying mechanism involves binding of zinc to histidine residues of brain tissue-amyloid protein leading to the formation of amorphous aggregates of amyloid protein, which then leads to the formation of age spots[37]. The combination of zinc and copper was shown to accelerate the formation of amorphous aggregates of amyloid protein[38], and the high saturation magnetization of zinc ferrite was found to improve the formation of amorphous aggregates of amyloid protein[39].

An increasing body of evidence has shown that the basal level of extracellular zinc in hippocampus is typically in the low nanomolar range, and that the increase in zinc content aggravates the neurotoxicity of amyloid protein[40]. Zinc was shown to increase the expression of amyloid precursor protein in a mouse model of AD, which in turn increased amyloid synthesis.

Pathological dynamic equilibrium of copper, iron, and zinc promotes the deposition of amyloid proteins in brain tissue and affects structural changes in Tau Proteins. S100B is one of the most abundant proteins in the brain[41], which is involved in the regulation of amyloid deposition and zinc homeostasis. Use of zinc chelating agents can improve amyloid deposition levels by interfering with S100B[42]. Klotho protein is a zinc-rich protein which has neuroprotective, anti-inflammatory, anti-oxidant, and promyelination effects. Increasing serum Klotho protein can play a role in neuroprotection, anti-inflammation, and anti-oxidation[43]. Evidence suggests that AD is associated with increased levels of Tau, which is related to the presence of multiple zinc binding sites in the Tau protein. Low zinc levels stimulate Tau, leading to increased neurofibrillary tangle in the neurons[44]. The antioxidant zinc carboxylate inhibits the activity of acetylcholine esterase (ACHE) and butyrylcholinesterase and plays an anticholinesterase role, which indicates the benefit of zinc carboxylate in the treatment of AD[45]. Zinc homeostasis is involved in the pathogenesis of AD. Zinc can significantly increase the activity of carnosine, which is beneficial in the treatment of AD[46].

Zinc deficiency can lead to a decrease in learning ability and memory in AD. Zinc supplementation (3 mg/kg) was shown to improve learning and memory in a mouse model of AD, which may be related to the decrease in inflammatory activity in NLRP3[47]. Zinc can promote the aggregation of SFPQ in cultured neurons by regulating the nuclear SFPQ protein, which is an important marker of AD[48].

**AD and iron**

Iron is one of the essential trace metal elements which is widely distributed in the human body. Iron is involved in material transportation, growth and development, cell differentiation, gene expression, and lipid peroxidation. Abnormal heme content and deranged iron homeostasis are more common in AD [49].

Accumulation of iron in the brain is a common phenomenon in many neurodegenerative disorders. Postmortem studies have documented markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[50]. Inadequate iron intake during pregnancy may cause iron deficiency in fetal brain tissue, increasing the risk of neurological defects. With the increase in age, accumulation of iron in brain tissue can also occur because of brain tissue-amyloid protein deposition and plaque, which in turn promotes further iron deposition[51].

A growing body of evidence suggests that iron dysregulation in brain neurons plays a key role in AD [52]. Studies have documented high iron concentrations in deep gray matter structures of brain tissue in patients with AD[53]. Iron deposition promotes increased Tau levels in brain tissue and neurofibrillary Tangle Tau formation[10,54]. Iron also accelerates the deposition of amyloid proteins in brain tissue[55]. Increased concentration of iron-rich pollutants in the air predisposes people to AD[56].

Studies have shown that-amyloid precursor protein can be hydrolyzed to-amyloid, which is dependent on iron transporter transmembrane transport[57]. CISD2 gene encodes CDGSF FT-DOMAIN Protein 2, and up-regulation of CDGSF FT-DOMAIN PROTEIN 2 can improve mitochondrial structure and synaptic function, which plays a neuroprotective role[58].

Research has shown that oxidative stress promotes iron deposition in brain tissue, which plays an important role in the development of AD. In a study, scanning electron microscope and transmission electron microscope were used to examine specific iron-rich areas in the hippocampus of anatomical specimens of brain tissue from patients with AD. The authors found a significant increase in both Tau and amyloid proteins in brain tissue, which suggests that the effect of oxidative stress on AD is related to the oxidation of iron[59].

Endothelial cells in brain tissue can promote the formation of new blood vessels in the environment of embryonic development, and they rely on specific metabolic pathways to achieve different cellular functions. Pilin-1, a transmembrane protein of endothelial cells, regulates mitochondrial function and iron homeostasis, thus affecting the development of AD[60]. Use of iron chelating agents such as desfer-
Ferrioxamine mesylate (desferrioxamine) was shown to reduce the iron content in brain tissue in animal models of AD. This effect was related to the ease with which desferrioxamine crosses the blood brain barrier[61].

Multi-functional nanoparticles w20xd4-spions may contribute to the diagnosis and treatment of AD. This is related to the ability of multi-functional nanoparticles w20xd4-spions to readily cross the blood-brain barrier and enhance microglia phagocytosis[62]. Iron oxide nanoparticles have been used in clinical studies to improve AD, owing to their ability to cross the blood-brain barrier[63]. Iron deposition is a pathway that regulates cell death, initiated by glutathione and lipid peroxidation signals [64].

Ferroptosis, a recently discovered form of cell death caused by accumulation of byproducts of lipid peroxidation, is also involved in the pathogenesis of AD. Excess iron was shown to exacerbate oxidative damage and cognitive deficit in a mouse model of AD. Use of specific iron deposition inhibitors was shown to alleviate the degree of neuronal death and memory damage in mice, especially in the hippocampus[65]. Brain iron metabolism disorder is one of the main characteristics of AD. Hemagglutinin neutralizes heme toxicity, maintains iron homeostasis, enhances antioxidant capacity by breaking down metabolites, biliverdin and carbon monoxide, and alleviates iron-mediated lipid peroxidation, which improves hippocampal volume, metabolism, and cognitive function in patients with AD[66].

AD and selenium

Selenium is one of the most common micronutrients in the body. It is involved in biological oxidation, cell differentiation, protein synthesis, and gene transcription. In particular, selenium inhibits ACHE and butyrylcholinesterase, which has a positive effect on the treatment of AD[67]. Selenium is a central component of many antioxidant enzymes (glutathione peroxidase) that regulate redox levels in the body and have a positive effect on the immune system[68].

Selenium deficiency is believed to be involved in the causation of AD. Selenium deficiency impairs immunity and leads to overproduction of oxidized products and amyloid-beta protein. Selenium can interact with metals by using selenomethionine and improve the body’s antioxidant capacity’[69]. Chondroitin sulfate selenium has been shown to improve spatial learning and memory impairment in mice with AD, reduce the degree of synaptic edema of hippocampal neurons, and protect the integrity of mitochondria. The underlying mechanism involved activation of the P38 mitogen activated protein kinase signaling pathway by chondroitin sulfate selenium[70].

Glutathione peroxidase 1 is a major antioxidant enzyme that has a protective effect against memory impairment induced by-amyloid in mice with AD; this phenomenon is related to the activation of Erk signal pathway by glutathione peroxidase-1[71]. Memory impairment is the most well-known symptom of AD. The combination of nano-selenium (0.4 mg/kg) and stem cells increased the levels of brain-derived neurotrophic factor and reduced amyloid deposition in an Alzheimer mouse model; these results suggest that the combination of selenium and stem cells can reduce neurotoxicity in mice with AD[72].

Clinical studies have shown that AD is associated with cognitive decline. Higher blood selenium levels in older people were shown to be associated with higher cognitive scores; a general linear model was observed between blood selenium concentrations and cognitive function. It is suggested that selenium ameliorates the decrease of cognitive ability[73,74]. Selenium is essential for brain health. In a study of 984 men and 1032 women conducted between 2011 and 2014, selenium was found to be associated with cognitive function. The study involved assessment of whole blood selenium concentrations; there was no correlation between blood selenium concentration and sex. The results indicated that adequate selenium was positively associated with cognitive ability in the elderly[75].

Alzheimer’s and silicon

Silicon is one of the most common micronutrients in the body. It is divided into amorphous silicon and crystalline silicon, which exists in the form of silicate or silicon dioxide. Silicon is involved in collagen synthesis, immune system regulation, bone mineralization, and Tau phosphorylation[76]. Silicon was shown to lower the risk of AD[77].

Recent studies have shown the health benefits of silicon in humans. Soluble silicic acid is a useful form of silicon in the human body. The absorption, distribution, and metabolic characteristics of soluble silicic acid in human body are closely related to human health. The unique cross-linking ability of soluble silicic acid and its antagonism to toxic aluminum may protect against AD[78].

Studies have shown an increase in the incidence of degenerative diseases in Western countries. Diet has a positive effect on AD. Beer, which is rich in silicon and hops, plays an important role in preventing brain disorders. This is primarily related to the ability of beer to regulate inflammation, oxidation, and cholinesterase activity[79]. Nerve growth factor (NGF) plays an important role in reducing the number of cholinergic neurons in AD. Studies have demonstrated the neuroprotective effect of NGF on rat pheochromocytoma PCL2 cells by using biodegradable porous silicon oxide carriers[80].
**AD and manganese**

Manganese is one of the essential micronutrients in the body. It is involved in oxidation-reduction, lipid synthesis, and protein degradation, which are mostly related to the alkylation of manganese. Various aromatic, heterocyclic aromatic, and aliphatic secondary amines, such as indole and resveratrol-derived amines, can be obtained by alkylation reaction[81]. Most studies have found that AD can occur with decreased or normal levels of manganese[82].

With rapid industrialization and the increasing environmental pollution, excessive intake of heavy metal manganese will have a neurotoxic effect and promote neurodegeneration. Astrocyte is the main stable cell type in the central nervous system. Excessive intake of manganese can affect the structure and function of astrocytes, as well as the synthesis and degradation of glutamate. Effective control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD[83]. Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, zinc, and other micronutrients, and thus induce AD[84].

Studies have shown the role of manganese in the diagnosis of AD. Manganese enhanced magnetic resonance imaging can be used to assess the level of pathological Tau accumulation[85]. Treatment with Manganese chelating agents may play a role in neurodegenerative diseases such as AD, providing a new strategy for the clinical treatment of AD[86].

AD is associated with a decline in learning and memory. Use of naringin reduces amyloid accumulation, a manganese-induced form of AD in rats. It is suggested that naringin has a neuroprotective effect, which is closely related to the anti-oxidant, anti-inflammatory and anti-amyloid degeneration effect of naringin[87]. Manganese-rich nanocapsules were shown to improve cognitive ability in animal models with AD, which is related to the decrease of Tau protein in animal brain tissue[88].

**AD and arsenic**

Arsenic is an essential micronutrient of the body. It is widely found in nature in the form of Ash, black, and yellow arsenic. Arsenic is highly toxic, but in small amounts it is beneficial. Arsenic participates in biotransformation, protein synthesis, and material metabolism.

Sodium arsenite (1–10 mol/L) was shown to increase Tau phosphorylation and promote the formation of neurofibrils in human neuroblastoma SH-SY5Y cells, which are used to study AD. This effect was related to the activation of Erk Pathway by sodium arsenite[89].

Animal studies have shown that arsenic in drinking water can cause abnormal circadian rhythm and movement behavior in mice with AD, as well as accumulation of amyloid proteins in the frontal cortex and hippocampus. This was found to be related to arsenic-induced lipid peroxidation in mice[90]. Sodium arsenite was shown to cause behavioral disorders and memory change in male rats with AD, which was alleviated by gallic acid (100 mg/kg); this indicated the neuroprotective effect of gallic acid[91].

In a clinical study, arsenic levels were measured in the nails and hair of 40 individuals with AD using inductively coupled plasma mass spectrometry. Arsenic levels in AD were higher than those in controls. This implies that individuals with AD often have elevated levels of arsenic[92].

**Alzheimer’s and vitamin D**

Vitamin D is an antioxidant hormone. There is a close linkage between vitamin D, human microbiome, and the immune system. Vitamin D can regulate innate and adaptive immune responses[93].

Vitamin D enhances the immune function and may delay aging; thus, it may play a role in the treatment of AD[94].

The key findings of the aforementioned micronutrients related to AD are summarized in Table 1.

**CONCLUSION**

AD is the most common type of dementia with an elusive etiology. An increasing number of studies have explored the effects of micronutrients on the pathogenesis and development of AD[95]. Abnormal copper homeostasis plays an essential role in the development of many neurodegenerative diseases, including AD[14]. Zinc status affects the progression of AD, as evidenced by cognitive decline observed under conditions of zinc deficiency[32]. Excessive iron contributes to the deposition of β-amyloid and the formation of neurofibrillary tangles in AD, as well as other neurodegenerative diseases[96]. Selenium may have a protective role against the development of AD[97]. Silicon may lower the risk of AD by protecting against accumulation of toxic substances in the brain[98]. Manganese is critical for neurodevelopment but has also been implicated in the pathophysiology of several neurological diseases, including AD[99]. Chronic manganese exposure increases the risk of amyloid plaques and the development of AD[100]. Increased level of arsenic was shown to be associated with brain damage and neurobehavioral changes, which may exacerbate AD symptoms[90]. Vitamin D and its receptors are fundamentally involved in neurodegenerative mechanisms and vitamin D deficiency is recognized as a risk factor for AD[101]. Collectively, these findings suggest that aberrant homeostasis of these micronutrients is a key contributor to AD progression.
### Table 1 Roles of different micronutrients in Alzheimer's disease

| Micronutrient | Key findings related to AD |
|---------------|---------------------------|
| **Copper**    |                           |
|               | Plaques of neurofibrillary tangle, amyloid, and soluble oligomers have large amounts of copper at their core[^18] |
|               | AD patients have significantly higher levels of copper in brain tissues[^19-21] |
|               | Copper promotes neurofibrillary tangle of hyperphosphorylation Tau and oxidative stress[^22] |
|               | Copper is useful marker for the diagnostic and prevention of AD[^27] |
| **Zinc**      |                           |
|               | Zinc and selenium or iron and zinc have been concomitantly used to treat AD[^35,36] |
|               | Combination of zinc and copper accelerates the formation of amorphous aggregates of amyloid protein[^40] |
|               | High saturation magnetization of zinc ferrite improves the formation of amorphous aggregates of amyloid protein[^41] |
|               | Zinc increases the expression of amyloid precursor protein in a mouse model of AD[^43] |
|               | Zinc deficiency leads to a decrease in the learning ability and memory of AD mice[^51] |
| **Iron**      |                           |
|               | Markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[^55] |
|               | Iron dysregulation in brain neurons plays a key role in AD[^57] |
|               | Iron deposition increases Tau levels in brain tissue and promotes neurofibrillary Tangle Tau formation[^10,59] |
|               | Iron accelerates the deposition of amyloid proteins in brain tissues[^60] |
|               | Iron oxide nanoparticles have been used in clinical studies to improve AD[^68] |
| **Selenium**  |                           |
|               | Chondroitin sulfate selenium improves spatial learning and memory impairment in mice with AD[^75] |
|               | The combination of nano-selenium and stem cells increases the levels of brain-derived neurotrophic factor and reduces amyloid deposition in AD mice[^77] |
|               | Selenium ameliorates the decrease of cognitive ability[^78,79] |
| **Silicon**   | Silicon may lower the risk of AD[^82] |
|               | The unique cross-linking ability of soluble silicic acid and its antagonism to toxic aluminum may protect against AD[^83] |
| **Manganese** | Excessive intake of manganese can affect the structure and function of astrocytes, as well as the synthesis and degradation of glutamate. Effective control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD[^88] |
|               | Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, and zinc, and thus induce AD[^89] |
|               | Manganese-rich nanocapsules improve cognitive ability in animal models with AD[^93] |
| **Arsenic**   | Sodium arsenite increases Tau phosphorylation and promotes the formation of neurofibrils in human neuroblastoma cells[^94] |
|               | Presence of arsenic in drinking water induces accumulation of amyloid proteins in the frontal cortex and hippocampus of AD mice[^95] |
|               | Sodium arsenite causes behavioral disorders and memory change in male AD rats[^96] |
|               | The levels of arsenic in the nails and hair of AD patients were higher than that in healthy controls[^97] |
| **Vitamin D** | Vitamin D regulates innate and adaptive immune responses, which may play a role in the development of AD[^98] |
|               | Vitamin D enhances the immune function and may delay aging; thus, it may be used in AD treatment[^99] |

AD: Alzheimer’s disease.

Some limitations of this review warrant mention. First, this is a narrative review, which lacks predetermined research question or specific search strategy. Future studies with a systemic design and a specified protocol are required for a more in-depth characterization of the roles of these micronutrients in AD. Secondly, the animals studies included in this review only used rodent AD models. The results from other animal AD models should be taken into account in future analysis.

In conclusion, this review summarizes the recent findings on the relationships between AD and micronutrients, which may provide a new perspective and direction for future scientific research, development of new drugs, and preventive measures against AD. Although significant advances have been made in characterizing the relationships between AD and these micronutrients, further studies are required to provide more robust evidence.
REFERENCES

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FOOTNOTES

1 Lauretti E, Dincer O, Praticò D. Glycogen synthase kinase-3 signaling in Alzheimer's disease. Biochim Biophys Acta Mol Cell Res 2020; 1867:118664 [PMID: 32906534 DOI: 10.1016/j.bbamcr.2020.118664]
2 Zetterberg H, Bendlin BB. Biomarkers for Alzheimer's disease-preparing for a new era of disease-modifying therapies. Mol Psychiatry 2021; 26: 296-308 [PMID: 32251378 DOI: 10.1038/s41386-020-0721-9]
3 Hadjichrysanthou C, Evans S, Bajaj S, Siakallis LC, McRae-McKee K, de Wolf F, Anderson RM; Alzheimer's Disease Neuroimaging Initiative. The dynamics of biomarkers across the clinical spectrum of Alzheimer's disease. Alzheimers Res Ther 2020; 12: 74 [PMID: 32534594 DOI: 10.1186/s13195-020-00636-z]
4 Memon AA, Coleman JJ, Amara AW. Effects of exercise on sleep in neurodegenerative disease. Neurobiol Dis 2020; 140: 104859 [PMID: 32243913 DOI: 10.1016/j.nbd.2020.104859]
5 Rossini PM, Di Iorio R, Vecchio F, Anfossi M, Babiloni C, Bozzali M, Bruni AC, Cappa SF, Escudero J, Fraga FJ, Giannakopoulos P, Guntekin B, Logroscino G, Marra C, Miraglia F, Panza F, Tecchio F, Pascual-Leone A, Dubois B. Early diagnosis of Alzheimer's disease: the role of biomarkers including advanced EEG signal analysis. Report from the IFCN-sponsored panel of experts. Clin Neurophysiol 2020; 131: 1287-1310 [PMID: 32302946 DOI: 10.1016/j.clinph.2020.03.003]
6 Hierro-Bujalance C, Infante-Garcia C, Del Marco A, Herrera M, Carranza-Naval MJ, Suarez J, Alves-Martinez P, Lubian-Lopez S, Garcia-Alloza M. Empagliflozin reduces vascular damage and cognitive impairment in a mixed murine model of Alzheimer's disease and type 2 diabetes. Alzheimers Res Ther 2020; 12: 40 [PMID: 32264944 DOI: 10.1186/s13195-020-00607-4]
7 Cui W, Sun C, Ma Y, Wang S, Wang X, Zhang Y. Neuroprotective effect of tormentic acid against memory impairment and neuroinflammation in an Alzheimer's disease mouse model. Mol Med Rep 2020; 22: 739-750 [PMID: 32468017 DOI: 10.3892/mmr.2020.11154]
8 Kumar A, Sidhu J, Goyal A, Tsao JW. Alzheimer Disease. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright© 2021, StatPearls Publishing LLC., 2021
9 Quazi Z, Carter MM, Wei A, Li X. Management of cognitive decline in Alzheimer's disease using a non-pharmacological intervention program: A case report. Medicine (Baltimore) 2020; 99: e20128 [PMID: 32481282 DOI: 10.1097/MD.00000000000020128]
10 Spotorno N, Acosta-Calbunero J, Stromrud E, Lampinen B, Strandberg OT, van Westen D, Hansson O. Relationship between cortical iron and tau aggregation in Alzheimer's disease. Brain 2020; 143: 1341-1349 [PMID: 32330946 DOI: 10.1093/brain/awaa089]
11 Casati M, Boccardi V, Ferri E, Bertagnoli L, Bastiani P, Ciccone S, Mansi M, Scamosci M, Rossi PD, Meccoci P, Arosio B. Vitamin E and Alzheimer's disease: the mediating role of cellular aging. Aging Clin Exp Res 2020; 32: 459-464 [PMID: 31054115 DOI: 10.1007/s40520-019-01209-3]
12 Solovyev N. Selenoprotein P and its potential role in Alzheimer's disease. Hormones (Athens) 2020; 19: 73-79 [PMID: 31250406 DOI: 10.1007/s42000-019-00112-w]
13 Gromadzka G, Tarnacka B, Flaga A, Adamczyk A. Copper Dyshomeostasis in Neurodegenerative Diseases-Therapeutic Implications. Int J Mol Sci 2020; 21 [PMID: 32912628 DOI: 10.3390/ijms21239259]
14 Coelho FC, Squitti R, Ventriglia M, Cerchiaro G, Daher JP, Rocha JG, Rongioletti MCA, Moonen AC. Agricultural Use of Copper and Its Link to Alzheimer's Disease. Biomolecules 2020; 10 [PMID: 32545484 DOI: 10.3390/biomin0060897]
Patel R, Aschner M. Commonalities between Copper Neurotoxicity and Alzheimer's Disease. *Toxics* 2021; 9 [PMID: 33430181 DOI: 10.3390/toxics9010004]

Moynier F, Borgne ML, Lahoud E, Mahan B, Mouton-Liger F, Hugon J, Paquet C. Copper and zinc isotopic excursions in the human brain affected by Alzheimer's disease. *Alzheimers Dement (Amst)* 2020; 12: e12112 [PMID: 33102682 DOI: 10.1002/dad2.12112]

Ding S, Xu Y, Liu Q, Gu H, Zha A, Shi G. Interface engineering of microelectrodes toward ultrasensitive monitoring of β-amyloid peptides in cerebrospinal fluid in Alzheimer's disease. *Analyst* 2020; 145: 2331-2338 [PMID: 32030388 DOI: 10.1039/c9an02285g]

Isaey NK, Stelmashaok EV, Gennrich EE. Role of zinc and copper ions in the pathogenetic mechanisms of traumatic brain injury and Alzheimer's disease. *Rev Neurosci* 2020; 31: 233-243 [PMID: 31747384 DOI: 10.1515/revenuro-2019-0052]

Zubčič K, Hof PR, Šimić G, Jazviničák Jembrek M. The Role of Copper in Tau-Related Pathology in Alzheimer's Disease. *Front Mol Neurosci* 2020; 13: 572308 [PMID: 33071757 DOI: 10.3389/fnmol.2020.572308]

Kola A, Hecel A, Lampomi S, Valensin D. Novel Perspective on Alzheimer's Disease Treatment: Rosmarinic Acid Molecular Interplay with Copper(II) and Amyloid β. *Life* (Basel) 2020; 10 [PMID: 32698429 DOI: 10.3390/life10070118]

Cho HJ, Huyhn TT, Rogers BE, Mirica LM. Design of a multivalent bifunctional chelator for diagnostic 64Cu PET imaging in Alzheimer's disease. *Proc Natl Acad Sci U S A* 2020; 117: 30926-30933 [PMID: 33234563 DOI: 10.1073/pnas.2014591117]

Niu Y, Ding T, Liu J, Zhang G, Tong L, Cheng X, Yang Y, Chen Z, Tang B. Fluorescence switch of gold nanoclusters stabilized with bovine serum albumin for efficient and sensitive detection of cysteine and copper ion in mice with Alzheimer's disease. *Talanta* 2021; 223: 121745 [PMID: 32892826 DOI: 10.1016/j.talanta.2021.121745]

Sasanian N, Bernson D, Horvath I, Wittung-Stafshede P, Eshjörner EK. Redox-Dependent Copper Ion Modulation of Amyloid-β (1-42) Aggregation In Vitro. *Biomolecules* 2020; 10 [PMID: 32570820 DOI: 10.3390/biom10060924]

Lim SL, Rodríguez-Ortiz CJ, Hsu HW, Wu J, Zemkehr J, Kilian J, Vidal J, Ayata P, Kitazawa M. Chronic copper exposure directs microglia towards degenerative expression signatures in wild-type and J20 mouse model of Alzheimer's disease. *J Trace Elem Med Biol* 2020; 62: 126578 [PMID: 32599538 DOI: 10.1016/j.jtemb.2020.126578]

Zhao J, Shi Q, Tian H, Li Y, Liu Y, Xu Z, Robert A, Liu Q, Meunier B. TDMQ20, a Specific Copper Chelator, Reduces Memory Impairments in Alzheimer's Disease Mouse Models. *ACS Chem Neurosci* 2021; 12: 140-149 [PMID: 33322892 DOI: 10.1021/acschemneuro.0c00621]

Heo Y, Kim K, Kim J, Jang J, Park CB. Near-Infrared-Active Copper Bismuth Oxide Electrodes for Targeted Dissociation of Alzheimer's βAmyloid Aggregates. *ACS Appl Mater Interfaces* 2020; 12: 23667-23676 [PMID: 32664368 DOI: 10.1021/acsami.0c02349]

Malhi CRA, Taketa TB, Rocha-Neto JBM, Almeida WP, Beppu MM. Copper Ion Uptake by Chitosan in the Presence of Amyloid-β and Histidine. *Appl Biochem Biotechnol* 2020; 199: 949-965 [PMID: 31630339 DOI: 10.1007/s12010-019-03126-2]

Xie Z, Wu H, Zhao J. Multifunctional roles of zinc in Alzheimer's disease. *Neurotoxicology* 2020; 80: 112-123 [PMID: 32717200 DOI: 10.1016/j.neurotox.2020.07.003]

Khalighinejad P, Parrott D, Sherry AD. Imaging Tissue Physiology In Vivo by Use of Metal Ion-Responsive MRI Contrast Agents. *Pharmaceuticals (Basel)* 2020; 13 [PMID: 32987721 DOI: 10.3390/ph13100322]

Narayanan SE, Rehuman NA, Harilal S, Vincent A, Rajamma RG, Behl T, Uddin MS, Ashraf GM, Mathew B. Molecular mechanism of zinc neurotoxicity in Alzheimer's disease. *Environ Sci Pollut Res Int* 2020; 27: 43542-43552 [PMID: 32969132 DOI: 10.1007/s11356-020-10477-w]

Lippi SLP, Kakalec PA, Smith ML, Flinn JM. Wheel-Running Behavior Is Negatively Impacted by Zinc Administration in a Novel Dual Transgenic Mouse Model of AD. *Front Neurosci* 2020; 14: 854 [PMID: 33292260 DOI: 10.3389/fnins.2020.008544]

Farhood Y, Sarkaki A, Mahdavinia M, Ghadiri A, Teimoori A, Seif D, Dehghani MA, Navabi SP. Protective Effects of Co-administration of Zinc and Selenium Against Streptozotocin-Induced Alzheimer's Disease: Behavioral, Mitochondrial Oxidative Stress, and GPR39 Expression Alterations in Rats. *Neurotox Res* 2020; 58: 398-407 [PMID: 32504391 DOI: 10.1007/s13149-020-02226-9]

Rao SS, Lago L., Gonzalez de Vega R, Bray L, Hare DJ, Classes D, Doble PA, Adlard PA. Characterising the spatial and temporal brain metal profile in a mouse model of tauopathy. *Metallomics* 2020; 12: 301-313 [PMID: 31904058 DOI: 10.1039/c9mt00267g]

Datki Z, Galik-Olah Z, Janosi-Mozes E, Szegedi V, Kalman J, Hunya AG, Fulop L, Tamano H, Takeda A, Adlard PA, Bush AI. Alzheimer risk factors age and female sex induce cortical Aβ aggregation by raising extracellular zinc. *Mol Psychiatry* 2020; 25: 2728-2741 [PMID: 32518388 DOI: 10.1038/s41380-020-0800-y]

Baltaci SB, Unal O, Gülbahce-Mutlu E, Gunus H, Pehlivanoglu S, Yardimci A, Mogulkoc R, Baltaci AK. The Role of Zinc Status on Spatial Memory, Hippocampal Sensitive Plasticity, and Insulin Signaling in icv-STZ-Induced Sporadic Alzheimer's-Like Disease in Rats. *Biol Trace Elem Res* 2021 [PMID: 34727320 DOI: 10.1007/s12011-021-02999-2]

Socha K, Klimiuk K, Naliwajko SK, Soroczynska J, Puścion-Jakubik A, Markiewicz-Zukowska R, Kochanowicz J. Dietary Habits, Selenium, Copper, Zinc and Total Antioxidant Status in Serum in Relation to Cognitive Functions of Patients with Alzheimer's Disease. *Nutrients* 2021; 13 [PMID: 33498452 DOI: 10.3390/nu13020287]

Radko SP, Khmeleva SA, Kaluzhny DZ, Kechko OI, Kiseleva YY, Kozin SA, Mitkevich VA, Makarov AA. The English (H68R) Mutation of the Alzheimer's Disease Amyloid-β Peptide Modulates Its Zinc-Induced Aggregation. *Biomolecules* 2020; 10 [PMID: 32630528 DOI: 10.3390/biom10060961]

Boopathi S, Din Quc Huy P, Gonzalez W, Theodorakis PE, Li MS. Zinc binding promotes greater hydrophobicity in Alzheimer's Aβ42 peptide than copper binding: Molecular dynamics and solvation thermodynamics studies. *Proteins* 2020; 88: 1285-1302 [PMID: 32419254 DOI: 10.1002/pro2.25901]

Antonoglou O, Giannoussi M, Mourdikoudis S, Dendrinos-Samara C. Magnetic nanoemulsions as candidates for...
Alzheimer's disease dual imaging theranostics. *NanoTechnology* 2020; 31: 465702 [PMID: 32750688 DOI: 10.1088/1361-6524/abac35]

Sato Y, Takiguchi M, Tamano H, Takeda A. Extracellular Zn²⁺-Dependent Amyloid-β Neurotoxicity in Alzheimer's Disease Pathogenesis. *Biochimie* 2021; 199: 53-61 [PMID: 32281074 DOI: 10.1016/j.biochi.2021-02-02131-w]

Ahmadi S, Wu B, Song R, Zhus S, Simpson A, Wilson DJ, Kraetz HB. Exploring the interactions of iron and zinc with the microtubule binding repeats R1 and R4. *J Inorg Biochem* 2020; 205: 110987 [PMID: 31927402 DOI: 10.1016/j.jinorgbio.2019.110987]

Cristóvão JS, Figueira AJ, Carapeto AP, Rodrigues MS, Cardoso I, Gomes CM. The S100B Alarmin Is a Dual-Function Chaperone Suppressing Amyloid-β Oligomerization through Combined Zinc Chelation and Inhibition of Protein Aggregation. *ACS Chem Neurosci* 2020; 11: 2753-2760 [PMID: 32709672 DOI: 10.1021/acscchemneuro.0c00392]

Chen CD, Rudy MA, Zeldich E, Abraham CR. A method to specifically activate the Klotho promoter by using zinc finger proteins constructed from modular building blocks and from naturally engineered Egr1 transcription factor backbone. *FASEB J* 2020; 34: 7234-7246 [PMID: 32479878 DOI: 10.1096/fj.202000171R]

Singh V, Xu L, Boyko S, Surewicz K, Surewicz WK. Zinc promotes liquid-liquid phase separation of tau protein. *J Biol Chem* 2020; 295: 5850-5856 [PMID: 32295852 DOI: 10.1074/jbc.AC12.013166]

Zafar R, Zubair M, Ali S, Shahid K, Waseem W, Naureen H, Haider A, Jan MS, Ullah F, Sirajuddin M, Sadiq A. Zinc metal carboxylates as potential anti-Alzheimer's disease candidate: *in vitro* anticholinesterase, antioxidant and molecular docking studies. *J Biomat Sci Dyn* 2021; 39: 1044-1054 [PMID: 32013770 DOI: 10.1080/07391102.2020.1724569]

Moulahoum H, Ghobaranzamani F, Timur S, Zihnioglu F. Zinc enhances carcinosin inhibitory effect against structural and functional age-related protein alterations in an albumin glycoxidation model. *Biometals* 2020; 33: 353-364 [PMID: 32997290 DOI: 10.1007/s10534-020-02054-0]

Rivers-Auty J, Tapia VS, White CS, Daniels MJ, Drinkall S, Kennedy PT, Spence HG, Yu S, Green JP, Hoyle C, Cook J, Bradley A, Mathers AE, Peters R, Tzeng TC, Gordon MJ, Beatjie JJ, Brough D, Lawrence CB. Zinc Status Alters Alzheimer's Disease Progression through NLRP3-Dependent Inflammation. *J Neurosci* 2021; 41: 3025-3038 [PMID: 33532706 DOI: 10.1523/JNEUROSCI.1980-20.2020]

Huang J, Ringuet M, Whitten AE, Cariou S, Lim YW, Badhan R, Anggono V, Lee M. Structural basis of the zinc-induced cytoplasmic aggregation of the RNA-binding protein SFPQ. *Nucleic Acids Res* 2020; 48: 3356-3365 [PMID: 32034402 DOI: 10.1093/nar/gkaa076]

Ashraf A, Ashton NJ, Chatterjee P,Goovee K, Shen K, Frippe JM, Ames D, Rowe C, Masters CL, Villemagne V, Hye A, Martins RN, So PW, ABL. Plasma transferrin and hemopexin are associated with altered AIJ uptake and cognitive decline in Alzheimer's disease pathology. *Alzheimer's Res Ther* 2020; 12: 72 [PMID: 32517787 DOI: 10.1186/s13195-020-00634-1]

van der Weerd L, Lefering A, Webb EA, Egli R, Bossoni L. Effects of Alzheimer's disease and formalin fixation on the different mineralised-iron forms in the human brain. *Sci Rep* 2020; 10: 16440 [PMID: 33020534 DOI: 10.1038/s41598-020-73324-5]

Ashraf A, So PW. Spotlight on Ferroptosis: Iron-Dependent Cell Death in Alzheimer's Disease. *Front Aging Neurosci* 2020; 12: 196 [PMID: 32760266 DOI: 10.3389/fnagi.2020.00196]

Bulk M, Abdelmoula WM, Geut H, Wiarda W, Ronen I, Dijkstra J, van der Weerd L. Quantitative MRI and laser ablation-inductively coupled plasma-mass spectrometry imaging of iron in the frontal cortex of healthy controls and Alzheimer's disease patients. *NeuroImage* 2020; 215: 116808 [PMID: 32289451 DOI: 10.1016/j.neuroimage.2020.116808]

Damulina A, Pirpamer L, Soellradl M, Sackl M, Tinauer C, Hofer E, Gesierich B, Duering M, Ropele S, Jaenicke R, Pfeuffer B, Hecht MS, Gasser T. Sorcinin is upregulated in sporadic Alzheimer's disease brain and associated with Aβ pathology. *J Inorg Biochem* 2020; 199: 619-626 [PMID: 32602825 DOI: 10.1016/j.jinorgbio.2020.192541]

Ashraf A, Jeandriens J, Parkes HG, So PW. Iron dyshomeostasis, lipid peroxidation and perturbed expression of cystine/glutamate antiporter in Parkes-Hog's disease: Evidence of ferroptosis. *Redox Biol* 2020; 32: 101494 [PMID: 32199332 DOI: 10.1016/j.redox.2020.101494]

Cloggsw PM, Wiste HJ, Senjem ML, Gunter JL, Weigand SD, Schwarz CG, Arani A, Therneau TM, Lowe VJ, Knopman DS, Botha H, Graff-Radford J, Jones DT, Kantarci K, Vemuri P, Boeve BF, Mielke MM, Petersen RC, Jack CR Jr. Associations of quantitative susceptibility mapping with Alzheimer's disease clinical and imaging markers. *NeuroImage* 2021; 224: 117433 [PMID: 33035667 DOI: 10.1016/j.neuroimage.2021.117433]

Calderon-Garcidueñas L, Herrera-Soto A, Jury N, Maher BA, González-Maciel A, Reynoso-Robles R, Ruiz-Rudolph P, van Zundert B, Varela-Nallar L. Reduced repressive epigenetic marks, increased DNA damage and Alzheimer's disease hallmark in the brains of humans and mice exposed to particulate urban air pollution. *Environ Res* 2020; 183: 109226 [PMID: 32045727 DOI: 10.1016/j.envres.2020.109226]

Tsatsanis A, Wong BX, Gunn AP, Aytoun S, Bush AI, Devos D, Duce JA. Amyloidogenic processing of Alzheimer's disease β-amyloid precursor protein induces cellular iron retention. *Mol Psychiatry* 2020; 25: 1958-1966 [PMID: 32445469 DOI: 10.1038/s41386-020-0762-0]

Nobili A, Krashia P, D'Amelio M. Cis/2: a promising new target in Amlzheimer's disease. *J Pathol* 2020; 251: 113-116 [PMID: 32207855 DOI: 10.1002/path.5436]

Madsen SJ, DiGiacomo PS, Zeng Y, Goubren M, Chen Y, Rutt BK, Born D, Vogel H, Sinclair R, Zeineh MM. Correlative Microscopy to Localize and Characterize Iron Deposition in Alzheimer's Disease. *J Alzheimer's Dis Rep* 2020; 4: 525-536 [PMID: 33532700 DOI: 10.3233/ADR-200234]

Bosseboeuf E, Raimonci C. Signalling, Metabolic Pathways and Iron Homeostasis in Endothelial Cells in Health, Atherosclerosis and Alzheimer's Disease. *Cells* 2020; 9 [PMID: 32191833 DOI: 10.3390/cells9092055]

Farr AC, Xiong MP. Challenges and Opportunities of Deferoxamine Delivery for Treatment of Alzheimer's Disease, Parkinson's Disease, and Intracerebral Hemorrhage. *Mol Pharm* 2021; 18: 593-609 [PMID: 32926630 DOI: 10.1021/acs.molpharmaceut.0c00474]

Liu XG, Zhang L, Lu S, Liu DQ, Zhang LX, Yu XL, Liu RT. Multifunctional Superparamagnetic Iron Oxide
Nanoparticles Conjugated with Aβ-Oligomer-Specific scFv Antibody and Class A Scavenger Receptor Activator Show Early Diagnostic Potentials for Alzheimer's Disease. Int J Nanomedicine 2020; 15: 4919-4932 [PMID: 32764925 DOI: 10.2147/IJN.S240935]

63

Lou S, Ma C, Zha MQ, Ju WN, Yang Y, Wang X. Application of Iron Oxide Nanoparticles in the Diagnosis and Treatment of Neurodegenerative Diseases With Emphasis on Alzheimer's Disease. Front Cell Neurosci 2020; 14: 21 [PMID: 32184709 DOI: 10.3389/fncel.2020.00021]

64

Aytos S, Porthury S, Kalininowski P, Agarwal P, Doui O, Schneider JA, Morris MC, Bush AI. Regional brain iron associated with deterioration in Alzheimer's disease: A large cohort study and theoretical significance. Alzheimers Dement 2021; 17: 1244-1256 [PMID: 33491917 DOI: 10.1002/alz.12282]

65

Bao WD, Pang P, Zhou XT, Hu F, Xiong W, Chen K, Wang J, Wang F, Xie D, Hu YZ, Han ZT, Zhang HH, Wang WX, Nelson PT, Chen JG, Lu Y, Man HY, Liu D, Zhu LQ. Loss of ferropoitin induces memory impairment by promoting ferropoitin in Alzheimer's disease. Cell Death Differ 2021; 28: 1548-1562 [PMID: 33398092 DOI: 10.1038/s41418-020-00685-9]

66

Ashraf AA, Dani M, So PW. Low Cerebrospinal Fluid Levels of Hemopexin Are Associated With Increased Alzheimer's Disease, Hippocampal Hypometabolism, and Cognitive Decline. Front Mol Biosci 2020; 7: 596979 [PMID: 33392254 DOI: 10.3389/fmolb.2020.590979]

67

Gülçin İ, Trofinov B, Kaya R, Taslimi P, Sobenina L, Schmidt E, Petrova O, Malyshova S, Gusarova N, Farzaliyev V, Sujayev A, Alwasel S, Supuran CT. Synthesis of nitrogen, phosphorus, selenium and sulfur-containing heterocyclic compounds - Determination of their carbonic anhydrase, acetylcholinesterase, butyrylcholinesterase and α-glycosidase inhibition properties. Bioorg Chem 2020; 103: 104171 [PMID: 32891857 DOI: 10.1016/j.bioorg.2020.104171]

68

Sharma G, Shin EJ, Sharma N, Nah SY, Mai HN, Nguyen BT, Jeong JH, Lei XG, Kim HC. Glutathione peroxidase-1 and neuremodulation: Novel potentials of an old enzyme. Food Chem Toxicol 2021; 148: 111945 [PMID: 33359022 DOI: 10.1016/j.fct.2021.111945]

69

Vicente-Zurdo D, Romero-Sánchez I, Rosales-Conrado N, Leon-González ME, Madrid Y. Ability of selenium species to inhibit metal-induced Aβ aggregation involved in the development of Alzheimer's disease. Anal Bioanal Chem 2020; 412: 6485-6497 [PMID: 32322953 DOI: 10.1002/1616-0026(2020)412:11.<fsk.>10442-1</fsk.>

70

JI D, Wu X, Li D, Liu P, Zhang S, Gao D, Gao F, Zhang M, Xiao Y. Protective effects of chondroitin sulphate nanoselenium on a mouse model of Alzheimer's disease. Int J Biol Macromol 2020; 154: 233-245 [PMID: 32171837 DOI: 10.1016/j.ijbiomac.2020.03.079]

71

Shin EJ, Chung YH, Sharma N, Nguyen BT, Lee SH, Kang SW, Nah SY, Mi B, Nabeeshima T, Jeong JH, Kim HC. Glutathione Peroxidase-1 Knockout Facilitates Memory Impaired by β-amyloid (1-42) in Mice via Inhibition of PKC β-II-Mediated ERK Signaling; Application with Glutathione Peroxidase-1 Gene-Encoded Adenovirus Vector. Neurochem Res 2020; 45: 2991-3002 [PMID: 33064252 DOI: 10.1007/s11064-020-03147-3]

72

Gholamigervand B, Shahidi S, Afshar S, Gholipour P, Samzadeh-Kermami A, Amiri K, Majidi M, Abbasalipourkabir R, Arabestani MR, Soleimani Asl S. Synergistic effects of adipose-derived mesenchymal stem cells and selenium nanoparticles on streptozotocin-induced memory impairment in the rat. Life Sci 2021; 277: 112946 [PMID: 33607156 DOI: 10.1016/j.lfs.2021.112946]

73

Yan X, Liu X, Sun X, Qin S, Wu M, Qin L, Wang Y, Li Z, Zhong X, Wei X. A cross-sectional study of blood selenium concentration and cognitive function in elderly Americans: National Health and Nutrition Examination Survey 2011-2014. Ann Hum Biol 2020; 47: 610-619 [PMID: 33050724 DOI: 10.1080/03014460.2020.1836253]

74

Lima M, Pestana C. Changes in Peripheral Blood Biomarkers with Aging and Neurodegenerative Disorders. Curr Aging Sci 2021; 14: 112-117 [PMID: 33504320 DOI: 10.2174/1874609814666210127090100]

75

R Cardoso B, Hare DJ, Macpherson H. Sex-dependent association between selenium status and cognitive performance in older adults. Eur J Nutr 2021; 60: 1153-1159 [PMID: 32918622 DOI: 10.1007/s00394-020-02384-0]

76

Lu Q, Chen C, Xiong Y, Li G, Zhang X, Zhang Y, Wang D, Zha Z, Li X, Qing G, Sun T, Liang X. High-Efficiency Phosphopeptide and Glycopeptide Simultaneous Enrichment by Hydrogen Bond-based Bifunctional Smart Polymer. Anal Chem 2020; 92: 6269-6277 [PMID: 33223396 DOI: 10.1021/acs.analchem.9b02643]

77

Tedesco E, Benetti F, Pezzani R. In vitro evaluation of different organic matrices used to modulate silicon bioavailability. FASEB J 2023; 34: 12229-12238 [PMID: 32681588 DOI: 10.1096/fj.202000601R]

78

Shu WQ, Luo JH, Zhang JJ. [The relationship between soluble silicate acid in drinking water and food and human health]. Zhonghua Yu Yi Xue Za Zhi 2020; 54: 702-707 [PMID: 3242290 DOI: 10.3760/cma.j.cn121120-20030318-00378]

79

Sánchez-Muniz FJ, Macho-González A, Garcimartín A, Santos-López JA, Benedí J, Bastida S, González-Muñoz MJ. The Nutritional Components of Beef and Its Relationship with Neurodegeneration and Alzheimer's Disease. Nutrients 2019; 11 [PMID: 31295866 DOI: 10.3390/nut11071558]

80

Zilony-Hanin N, Rosenberg M, Richman M, Yeluda R, Schori H, Motiei M, Rahimipour S, Grosisman A, Segal E, Shefi O. Neuroprotective Effect of Nerve Growth Factor Loaded in Porous Silicon Nanostructures in an Alzheimer's Disease Model and Potential Delivery to the Brain. Small 2019; 15: e1904203 [PMID: 31482695 DOI: 10.1002/smll.201904203]

81

Wei D, Yang P, Yu C, Zhao F, Wang Y, Peng Z. N-Alkylation of Amines with Alcohols Catalyzed by Manganese(II) Chloride or 2020; 2254-2263 [PMID: 33049595 DOI: 10.1021/acs.orglett.0c02407]

82

Cilliers K. Trace element alterations in Alzheimer's disease: A review. Clin Anat 2021; 34: 766-773 [PMID: 33580904 DOI: 10.1002/ca.23727]

83

Li B, Xia M, Zorec R, Papura V, Verhrakatosky A. Astrocytes in heavy metal neurotoxicity and neurodegeneration. Brain Res 2021; 1752: 147234 [PMID: 33414125 DOI: 10.1016/j.brainres.2020.147234]

84

Kawahara M, Kato-Negishi M, Tanaka KJ. Neurotoxins in the Pathogenesis of Prion Diseases. Int J Mol Sci 2021; 22 [PMID: 33525334 DOI: 10.3390/ijms20231267]

85

Koren SA, Hamm MJ, Cloyd R, Fontaine SN, Chishti E, Lanzillotta C, Rodriguez-Rivera J, Ingram A, Bell M, Galvis-Escobar SM, Zulía N, Di Domenico F, Duong D, Seyfried NT, Powell D, Vandsburger M, Frolinger T, Hartz AMS, Koren J 3rd, Axten JM, Laping NJ, Abisambra JB. Broad Kinase Inhibition Mitigates Early Neuronal Dysfunction in Tauopathy. WJCC
Int J Mol Sci 2021; 22 [PMID: 33530349] DOI: 10.3390/ijms22031186

86 Martins AC Jr, Gubert P, Villas Boas GR, Meirelles Paes M, Santamarina A, Lee E, Tinkov AA, Bowman AB, Aschner M. Manganese-induced neurodegenerative diseases and possible therapeutic approaches. Expert Rev Neurother 2020; 20: 1109-1121 [PMID: 32799578] DOI: 10.1080/14737175.2020.1807330

87 Kaur G, Prakash A. Involvement of the nitric oxide signaling in modulation of naringin against intranasal manganese and intracerebroventricular β-amyloid induced neurotoxicity in rats. J Nutr Biochem 2020; 76: 108255 [PMID: 31759198] DOI: 10.1016/j.jnutbio.2019.108255

88 Cai X, Zhang K, Xie X, Zhu X, Feng J, Jin Z, Zhang H, Tian M, Chen H. Self-assembly hollow manganese Prussian white nanocapsules attenuate Tau-related neuropathology and cognitive decline. Biomaterials 2020; 231: 119678 [PMID: 31864019] DOI: 10.1016/j.biomaterials.2019.119678

89 Wisessaoowapak C, Visitsomthachat D, Watcharavivat P, Satayavivad J. Prolonged arsenic exposure increases tau phosphorylation in differentiated SH-SY5Y cells: The contribution of GSK3 and ERK1/2. Environ Toxicol Pharmacol 2021; 84: 103626 [PMID: 33621689] DOI: 10.1016/j.etap.2021.103626

90 Niño SA, Morales-Martínez A, Chi-Ahumada E, Carrizales L, Salgado-Delgado R, Pérez-Severiano F, Díaz-Cintra S, Jiménez-Capdeville ME, Zarazúa S. Arsenic Exposure Contributes to the Bioenergetic Damage in an Alzheimer's Disease Model. ACS Chem Neurosci 2019; 10: 323-336 [PMID: 30141907] DOI: 10.1021/acschemneuro.8b00278

91 Samad N, Jabeen S, Imran I, Zulfiquar I, Bilal K. Protective effect of gallic acid against arsenic-induced anxiety-depression-like behaviors and memory impairment in male rats. Metab Brain Dis 2019; 34: 1091-1102 [PMID: 31119507] DOI: 10.1007/s11011-019-00432-1

92 Koseoglu E, Kutuk B, Nalbantoglu OU, Koseoglu R, Kendirci M. Arsenic and selenium measurements in nail and hair show important relationships to Alzheimer's disease in the elderly. J Trace Elem Med Biol 2021; 64: 126684 [PMID: 32865443] DOI: 10.1016/j.jtemb.2020.126684

93 Murdaca G, Greco M, Negrini S, Casciaro M, Gangemi S. The Role of Skin and Gut Microbiome and Epigenetic Modifications in Skin-Autoimmune Disorders. Curr Mol Med 2021; 21: 283-290 [PMID: 32787761] DOI: 10.2174/1566524020666200812222324

94 Murdaca G, Biancheri S, Tonacci A, Nencioni A, Monacelli F, Gangemi S. Vitamin D and Folate as Predictors of MMSE in Alzheimer's Disease: A Machine Learning Analysis. Diagnostics (Basel) 2021; 11 [PMID: 34073931] DOI: 10.3390/diagnostics11060940

95 Fernández-Sanz P, Ruiz-Gabarre D, García-Escudero V. Modulating Effect of Diet on Alzheimer's Disease. Diseases 2019; 7 [PMID: 30691140] DOI: 10.3390/diseases7010012

96 Liu J, Fan YG, Yang ZS, Wang ZY, Guo C. Iron and Alzheimer's Disease: From Pathogenesis to Therapeutic Implications. Front Neurosci 2018; 12: 632 [PMID: 30250423] DOI: 10.3389/fnins.2018.00632

97 Zhang ZH, Song GL. Roles of Selenoproteins in Brain Function and the Potential Mechanism of Selenium in Alzheimer's Disease. Front Neurosci 2021; 15: 646518 [PMID: 33762907] DOI: 10.3389/fnins.2021.646518

98 Grochowski C, Blicharska E, Bogucki J, Proch J, Mierzwinska A, Baj J, Podkowińska A, Flieger J, Teresiński G, Maciejewski R, Niedzielski P, Rzymski P. Increased Aluminum Content in Certain Brain Structures is Correlated with Higher Silicon Concentration in Alcoholic Use Disorder. Molecules 2019; 24 [PMID: 31058813] DOI: 10.3390/molecules24091721

99 Pfalzer AC, Bowman AB. Relationships Between Essential Manganese Biology and Manganese Toxicity in Neurological Disease. Curr Environ Health Rep 2017; 4: 223-228 [PMID: 28417441] DOI: 10.1007/s40572-017-0136-1

100 Martins AC Jr, Morello P, Jjome OM, Venkataramani V, Harrison LF, Lee E, Bowman AB, Aschner M. New Insights on the Role of Manganese in Alzheimer's Disease and Parkinson's Disease. Int J Environ Res Public Health 2019; 16 [PMID: 31546716] DOI: 10.3390/ijerph16193546

101 Dursun E, Gezen-Ak D. Vitamin D basis of Alzheimer's disease: from genetics to biomarkers. Hormones (Athens) 2019; 18: 7-15 [PMID: 30484096] DOI: 10.1007/s42000-018-0086-5
