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REVIEW

The Role of Gut Microbiota in the Neuroprotective Effects of Selenium in Alzheimer's Disease

Anatoly V. Skalny[1,2] · **Michael Aschner**[3] · **Abel Santamaria**[4,5] · **Tommaso Filippini**[6,7] · **Viktor A. Gritsenko**[8] · **Yousef Tizabi**[9] · **Feng Zhang**[10] · **Xiong Guo**[10] · **Joao B. T. Rocha**[11] · **Alexey A. Tinkov**[1,2]

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Abstract

The objective of the present review was to provide a timely update on the molecular mechanisms underlying the beneficial role of Se in Alzheimer's disease pathogenesis, and discuss the potential role of gut microbiota modulation in this neuroprotective effect. The existing data demonstrate that selenoproteins P, M, S, R, as well as glutathione peroxidases and thioredoxin reductases are involved in regulation of Aβ formation and aggregation, tau phosphorylation and neurofibrillary tangles formation, as well as mitigate the neurotoxic effects of Aβ and phospho-tau. Correspondingly, supplementation with various forms of Se in cellular and animal models of AD was shown to reduce Aβ formation, tau phosphorylation, reverse the decline in brain antioxidant levels, inhibit neuronal oxidative stress and proinflammatory cytokine production, improve synaptic plasticity and neurogenesis, altogether resulting in improved cognitive functions. In addition, most recent findings demonstrate that these neuroprotective effects are associated with Se-induced modulation of gut microbiota. In animal models of AD, Se supplementation was shown to improve gut microbiota biodiversity with a trend to increased relative abundance of *Lactobacillus*, *Bifidobacterium*, and *Desulfivibrio*, while reducing that of *Lachnospiracea*_NK4A136, *Rikenella*, and *Helicobacter*. Moreover, the relative abundance of Se-affected taxa was significantly associated with Aβ accumulation, tau phosphorylation, neuronal oxidative stress, and neuroinflammation, indicative of the potential role of gut microbiota to mediate the neuroprotective effects of Se in AD. Hypothetically, modulation of gut microbiota along with Se supplementation may improve the efficiency of the latter in AD, although further detailed laboratory and clinical studies are required.

Keywords Selenium · Gut microbiota · Neuroprotection · Amyloid beta · Tau protein

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✉ Alexey A. Tinkov
tinkov.a.a@gmail.com

[1] Laboratory of Ecobiomonitoring and Quality Control, Yaroslavl State University, Sovetskaya Str. 14, Yaroslavl 150000, Russia

[2] Laboratory of Molecular Dietetics, IM Sechenov First Moscow State Medical University (Sechenov University), Bolshaya Pirogovskaya St., 2-4, Moscow 119146, Russia

[3] Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY 10461, USA

[4] Facultad de Ciencias, Universidad Nacional Autónoma de México, 04510 Mexico City, Mexico

[5] Laboratorio de Nanotecnología y Nanomedicina, Departamento de Atención a la Salud, Universidad Autónoma Metropolitana-Xochimilco, 04960 Mexico City, Mexico

[6] Environmental, Genetic and Nutritional Epidemiology Research Center (CREAGEN), Department of Biomedical, Metabolic and Neural Sciences, Medical School, University of Modena and Reggio Emilia, Modena, Italy

[7] School of Public Health, University of California Berkeley, Berkeley, CA, USA

[8] Institute of Cellular and Intracellular Symbiosis, Russian Academy of Sciences, Orenburg 460000, Russia

[9] Department of Pharmacology, Howard University College of Medicine, Washington, DC 20059, USA

[10] Key Laboratory of Trace Elements and Endemic Diseases, Health Science Center, School of Public Health, National Health and Family Planning Commission, Xi'an Jiaotong University, Xi'an 710061, China

[11] Departamento de Bioquímica E Biologia Molecular, CCNE, Universidade Federal de Santa Maria, Santa Maria, RS, Brazil

Abbreviations

AChE	Acetylcholinesterase
AD	Alzheimer's disease
AINX	Internexin
AMPK	AMP-activated protein kinase
APP	Amyloid β precursor protein
ARE	Antioxidant responsive element
ASC	Adaptor protein
Aβ	Amyloid β
BACE1	β Secretase
BBB	Blood-brain barrier
BDNF	Brain-derived neurotrophic factor
ChAT	Choline acetyltransferase
CN37	2′,3′-Cyclic-nucleotide-3′-phosphodiesterase
CREB	CAMP response element-binding protein
CTFβ	C-terminal fragment β
D-gal	D-galactose
ERK	Extracellular signal-regulated kinases
GFAP	Glial fibrillary acidic protein
GM	Gut microbiota
GPX	Glutathione peroxidase
GSK3β	Glycogen synthase kinase 3β
HO-1	Heme oxygenase 1
IGF1	Insulin-like growth factor type 1
IL-6	Interleukin 6
InsR	Insulin receptor
Irs1	Insulin receptor substrate-1
JNK	C-Jun N-terminal kinase
Keap1	Kelch-like ECH-associated protein 1
LPS	Lipopolysaccharide
mAChR	Muscarinic acetylcholine receptors
MAPIA	Microtubule-associated protein 1A
MAPK	Mitogen-activated protein kinase
MsrB1	Methionine sulfoxide reductase B1
mTOR	Mammalian target of rapamycin
NFL	Neurofilament light polypeptide
NF-κB	Nuclear factor kappa B
NLRP3	NLR family pyrin domain containing 3
NMDA	*N*-Methyl-d-aspartate
Nrf2	Nuclear factor erythroid-2-related factor 2
PI3K	Phosphoinositide 3 kinase
PKC	Protein kinase C
PP2A	Protein phosphatase 2A
PRX1	Peroxiredoxin-1
PS1	Presenilin-1
PSD-95	Postsynaptic density protein 95
pTau	Phosphorylated Tau
ROS	Reactive oxygen species
sAPPβ	Soluble amyloid precursor protein β
SCFAs	Short-chain fatty acids
SeCNPs	Se-chondroitin sulfate nanoparticles
SeCQDs	Se-doped carbon quantum dots
SELENOK	Selenoprotein K
SELENOM	Selenoprotein M
SELENOO	Selenoprotein O
SELENOP	Selenoprotein P
SELENOR	Selenoprotein R
SELENOS	Selenoprotein S
SeMet	Selenomethionine
SeNPs	Selenium nanoparticles
SIRT1	Sirtuin 1
STZ	Streptozotocin
TNFα	Tumor necrosis factor α
TrkB	Tropomyosin receptor kinase B
TRPM2	Transient receptor potential cation channel subfamily M member 2
TRPV1	Transient receptor potential cation channel subfamily V member 1
TXNRD	Thioredoxin reductase
UCHL-1	Ubiquitin carboxyl-terminal hydrolase isozyme L1
WDR1	WD repeat-containing protein 1

Introduction

Selenium (Se) is an essential metalloid involved in a variety of metabolic pathways in multiple tissues and organs, including the brain [1]. Specifically, Se is required for appropriate brain development and functioning [2]. The role of Se in brain physiology is mainly mediated by the biological functions of various selenoproteins. In addition to maintenance of redox homeostasis by antioxidant selenoproteins like glutathione peroxidase (GPX) and thioredoxin reductase (TXNRD) [3], certain selenoproteins modulate neurotransmission [4]. In contrast, overexposure to Se may result in neurotoxic effects [5]. Therefore, dysregulation of Se metabolism in the brain may be associated with a wide spectrum of brain diseases, including Alzheimer's disease (AD) [6].

Existing epidemiological studies indicate that AD is associated with a significant decrease in circulating [7], as well as brain [8] Se levels. Several studies showed that Se supplementation may improve cognitive functions [9], although the results of the previous meta-analysis did not reveal any significant impact of Se supplementation on cognitive decline [10]. Moreover, excessive inorganic Se exposure [11] as well as increasing serum and cerebrospinal fluid selenoprotein P (SELENOP) [12] may promote transition from a mild cognitive decline to AD. Moreover, the relationship between serum SELENOP levels and neurodegenerative diseases was observed only at lower range, while cerebrospinal fluid SELENOP differentially correlated with the risk of AD, amyotrophic lateral sclerosis, and mild cognitive impairment [13]. Finally, SELENOP levels were shown to be increased in prediabetes and type 2 diabetes mellitus [14, 15], both being associated with Alzheimer's disease

[16]. In turn, laboratory evidence demonstrated that Se may be involved in AD pathogenesis through the modulation of amyloidogenesis and Aβ aggregation, tau phosphorylation and fibrillation, along with its subsequent neurotoxicity and neuroinflammation, although further investigation of the role of Se in AD is required [17]. Hence, Se may act as a double-edge sword most likely dependent on its concentration in the body in general, and in the brain, in particular.

Gut microbiota (GM) was shown to play a significant role in modulation of Se bioavailability [18] and selenoprotein metabolism [19]. In addition, existing data demonstrate that alterations in Se supply may significantly impact GM. Thus, Se deficiency may significantly reduce GM biodiversity [20], while Se supplementation may promote beneficial microbiota growth [21]. Moreover, GM disruption due to Se deficiency may play an important role in various diseases including cancer and cardiovascular diseases [22].

A recent study by Ramírez-Acosta et al. [23] demonstrated that Se administration may affect brain selenoprotein expression and GM composition as well as brain metabolomics, including pathways involved in glyoxylate, dicarboxylate, and amino acid metabolism [23]. This has led to the suggestion that the neuroprotective effects of Se compounds are mediated via modulation of the gut-brain axis [24], although the existing data on the contribution of gut microbiota to the neuroprotective effects of Se species in AD are scarce. Therefore, the objective of the present review was to provide an update on the molecular mechanisms underlying beneficial role of Se in AD. We have focused on various Se compounds and AD pathogenesis and discuss the potential role of GM contribution to Se neuroprotective effects.

A Brief Review of Selenoproteins in Alzheimer's Disease

Existing data demonstrate that selenoproteins, and specifically SELENOP, may be involved in AD pathogenesis [25]. SELENOP was shown to regulate synaptic Zn^{2+} levels and Zn-dependent tau phosphorylation through upregulation of antioxidant selenoprotein expression, while SELENOP1 knockout resulted in impaired Zn^{2+} release from intracellular stores [26]. Correspondingly, improvement of learning and memory deficits in 3xTg-AD mouse model of AD by hippocampal delivery of His-rich motif of SELENOP also improved Zn homeostasis by upregulation of MT3 and ZnT3 expression and activation of brain-derived neurotrophic factor (BDNF)- and Src-mediated tropomyosin receptor kinase B (TrkB) signaling altogether contributing to reduced Aβ and phosphorylated Tau (pTau) aggregation [27]. Histidine-rich domain of SELENOP was also shown to bind $Cu^{+/2+}$ cations thus decreasing Cu-induced Aβ aggregation with subsequent reactive oxygen species (ROS) overproduction and cell death [28]. This domain was also responsible for inhibition of Cu-induced tau fibrillation, ROS production, as well as improvement of synapse formation and mitochondrial functioning in neurons [29]. Finally, the role of SELENOP in regulation of Aβ generation is indirectly supported by the observation of co-localization of Aβ and SELENOP in human cortex [30]. It is also suggested that direct interaction between His-rich motif of SELENOP and the C-terminus tubulin alpha 1a may also possess protective effect against tau fibrilization [31]. As stated earlier, SELENOP was also found to be colocalized with GFAP in a model of a cognitive decline in intraventricular lipopolysaccharide (LPS)-injected mice [32], indicative of the potential role of SELENOP not only in amyloid and tau metabolism, but also in neuroinflammation. At the same time, SELENOP was considered the potentially neurotoxic species in humans due to its positive correlation with biomarkers of neurodegeneration [33].

Several studies demonstrated protective effects of antioxidant selenoenzymes GPX and TXRND in amyloidogenesis. GPX1 expression was shown to be down-regulated following Aβ intracerebroventricular injection in mice, whereas introduction of an adenoviral vector encoded with the GPX1 gene attenuated memory loss and cholinergic dysregulation through the activation of M1 muscarinic acetylcholine receptors (mAChR)-dependent cAMP response element-binding protein (CREB)/BDNF signaling [34]. The key role of GPX1 in anti-amyloidogenic effects of Se treatment may also be mediated by upregulation of protein kinase C (PKC) βII-mediated extracellular signal-regulated kinases (ERK) signaling, ultimately resulting in prevention of Aβ1-42-induced memory loss [35].

Overexpression of GPX4 significantly reduced toxicity of Aβ25-35 and Aβ1-40 in primary cortical neurons [36]. In addition, GPX4 was shown to possess protective effects against amyloid-β induced ferroptosis in SH-SY5Y cells [37], and in amyloid β precursor protein (APP) and presenilin-1 (PS1) mutated APP/PS1 mice [38], supporting the role of GPX4 disruption in ferroptosis [39].

The role of TXNRD in Aβ toxicity was demonstrated in *C. elegans*. Specifically, in addition, inactivation of TXNRD1 was observed in retinas of mice overexpressing Aβ [40]. Moreover, TXNRD activity was also found to be reduced in patients with both AD and vascular dementia, in comparison to healthy subjects [41].

Although most studies demonstrate the role of SELENOP and antioxidant selenoproteins GPX and TXNRD in AD, a number of observations revealed the interference of other selenoproteins with AD pathogenesis. Selenoprotein M (SELENOM) gene was also found to be down-regulated in human mutant presenilin-2 (N141I) transgenic mice [42], indicative of the potential role of this selenoprotein in AD. SELENOM overexpression was shown to activate ERK, but not c-Jun N-terminal kinase (JNK) or p38 mitogen-activated protein kinase (MAPK) signaling, subsequently resulting in downregulation of α and γ-secretase, as well as reduction of tau phosphorylation [43]. In addition, Se-induced SELENOM expression may be responsible for inhibition of Aβ aggregation [44, 45]. Correspondingly, Sec-to-Cys mutant SELENOM, as well as His-rich domain of SELENOP, were shown to coordinate Zn^{2+} and Cd^{2+} cations, suppressing Aβ42 fibrillization with subsequent reduction of Zn^{2+-}Aβ42-induced ROS overproduction and cytotoxicity [46]. At the same time, SELENOM knockout was shown to result in obesity without cognitive deficits in rodents [47].

Selenoprotein S (SELENOS) was found to be essential for interaction for APP-derived C99 fragment p97(VCP), an essential component of endoplasmic reticulum-associated protein degradation complex, and the subsequent inhibition of amyloidogenesis [48]. In addition, restriction of SELENOS expression upon endoplasmic reticulum stress was found to contribute to tau hyperphosphorylation, while this effect was reversed by Se supplementation and SELENOS overexpression [49].

Selenoprotein R (SELENOR), also known as methionine sulfoxide reductase B1 (MsrB1), interacts directly with Aβ42, affecting its aggregation likely through the reduction of oxidized methionine that is involved in Aβ oligomerization [50]. Moreover, SELENOR was shown to interact with clusterin, a molecular chaperone that binds misfolded proteins, as well as Aβ, resulting in reduced ROS production in N2aSW cells, a cellular model of AD [44, 45].

Finally, it is suspected that upregulation of selenoprotein O (SELENOO) expression in cellular (N2aSW cells) and animal (3xTg-AD mice) models of AD, is responsible for selenomethionine (SeMet)-induced improvement of mitochondrial division and dynamics, mitochondrial potential, bioenergetics, and inhibition of apoptosis [51].

Taken together, the majority of these experimental findings demonstrate that some selenoproteins are involved in the regulation of Aβ formation and aggregation, tau phosphorylation and neurofibrillary tangles formation, as well as mitigating the toxic effects of Aβ and phosphor-tau in neuronal cells. These effects are believed to be mediated through the inhibition of oxidative stress, neuroinflammation, and signaling pathways dysregulation. Thus, it is posited that modulation of selenoprotein expression may underlie most effects of Se supplementation in AD, although other mechanisms may also be involved.

Molecular Effects of Se Supplementation in AD Models

Dietary Se deficiency was associated with increased Aβ plaque deposition in Tg2576 transgenic mice [52]. These findings generally corroborate the results of earlier studies demonstrating reduced brain Se content in patients with AD [8]. Therefore, several studies aimed to investigate the neuroprotective effects of various Se-containing compounds supplementation in AD. At the same time, the effects of Se-met, Se(VI) and Se(IV) can be mediated by the upregulation of different selenoproteins [53]. Given certain contradictions in the epidemiological studies on the association between various Se species levels and AD [54, 55], as well as recent results from laboratory studies demonstrating different molecular mechanisms of various Se compounds in AD [56], we will briefly discuss the protective mechanisms of various Se compounds separately, in order to underline the potential similarities and differences in their molecular mechanisms (Fig. 1).

Selenomethionine (SeMet)

In vitro studies demonstrate that SeMet treatment significantly reduced Aβ production. Specifically, in neuron-2a/AβPPswe (N2aSW) cells SeMet significantly reduced Aβ production through downregulation of β secretase (BACE1) as well as increasing autophagosome-lysosome fusion and Aβ autophagic degradation as evidenced by Aβ and LC3 colocalization [57–59]. Correspondingly, SeMet treatment significantly decreased Pb-induced APP mRNA and protein expression, Aβ formation, and proapoptotic increased in Bax levels in SH-SY5Y and PC12 [60]. In addition, SeMet was shown to ameliorate Aβ neurotoxicity. Earlier studies demonstrated that SeMet pretreatment ameliorates ROS overproduction and cell death in primary rat hippocampal neurons exposed to Fe^{2+}/H_2O_2 or Aβ through the upregulation of GPX activity [61]. Moreover, SeMet promoted proliferation and neuronal differentiation in the neural stem cells derived from 3xTg-AD mice hippocampus. It was suggested that this effect was due to activation of β-catenin and cyclin-D signaling through phosphoinositide 3 kinase (PI3K)-Akt-glycogen synthase kinase 3β (GSK3β)-Wnt pathway [62].

Anti-amyloidogenic effects of SeMet were also confirmed in animal studies. Specifically, SeMet administration significantly reduced hippocampal and cortical Aβ formation and accumulation. This was achieved through up-regulation of hippocampal GPX and TXNRD and downregulation of APP and BACE1 [63].

In addition, animal studies demonstrate that SeMet treatment can reduce tau phosphorylation. Specifically, cognitive improvement and improved synaptic plasticity in 3 × Tg-AD mice following SeMet treatment was associated with reduction of total and phosphorylated tau levels due to downregulation of GSK3β and upregulation of PP2A expression and activity, as well as prevention of glial activation [64]. In olfactory bulb of 3 × Tg-AD mice, SeMet reduced the activity of cyclin-dependent kinase 5 (CDK5), which is

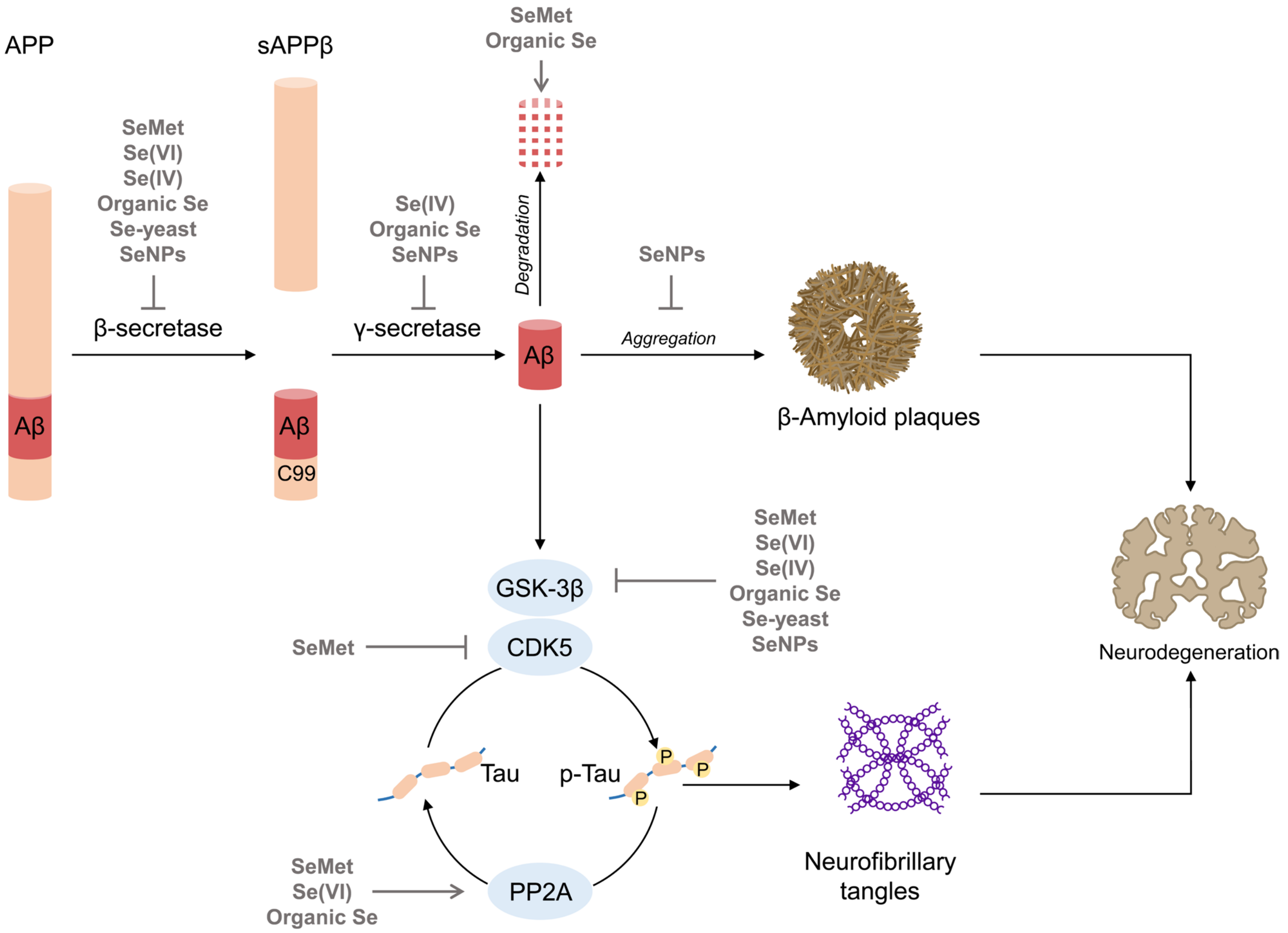

Fig. 1 The molecular mechanisms underlying neuroprotective effects of various Se species in laboratory AD models

also involved in tau phosphorylation [65, 66]. In addition to reduction of tau hyperphosphorylation, SeMet promoted tau clearance both in 3xTg-AD mice and primary 3xTg neurons through autophagy initiation and enhanced autophagic flux via modulation of AMP-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) signaling pathway [57–59].

SeMet improved cognitive function and synaptic plasticity in 3 × Tg-AD mice, and these effects were related to inhibition of extra-synaptic and stimulation of synaptic *N*-methyl-d-aspartate (NMDA) receptors, thus regulating Ca^{2+} flux that may be mediated by up-regulation of selenoprotein K (SELENOK) expression [67]. Moreover, transcriptomic analysis demonstrated upregulation of genes involved in neural regeneration (*Fabp7*, *Evt5* and *Gal*), cognitive function (*Areg*), and antioxidant and antiapoptotic defense (*Adcyap1* and *Scg2*), along with downregulation of genes involved in apoptosis and inflammatory response (*Lrg1*, *Scgb3a1*, *Pglyrp1*) following SeMet treatment in a 3 × Tg-AD mouse model [68]. Another study demonstrated that both in cellular (N2aSW) and animal (3xTg-AD) models of AD, the neuroprotective effect of SeMet supplementation may be mediated through promotion of mitochondrial fusion and dynamics involving upregulation of *Nrf1* and *Mfn2* and downregulation of *OPA1* and *Drp1*. Furthermore, at least partially due to Se-induced SELENOO expression, there were improvements of mitochondrial potential, bioenergetics, and apoptosis inhibition [51].

Selenate (Se(VI))

In 3 × Tg-AD mice, sodium selenate (Se(VI)) treatment was shown to improve hippocampal synapse growth and glucose uptake while reducing hippocampal Aβ1–42 accumulation through downregulation of APP, BACE1, soluble amyloid precursor protein β (sAPPβ), and C-terminal fragment β (CTFβ) protein expression, as well as decreasing tau phosphorylation. It was proposed that Se(VI)-induced activation of protein phosphatase 2A (PP2A) may result not only in inhibition of GSK-3β, but also in an increase in β-catenin levels with the subsequent activation of Wnt/β-catenin signaling, ultimately resulting in repression of BACE1 transcription, as well as transactivation of c-myc, survivin, and TXNRD2 genes [69]. Yet, another study demonstrated that Se(VI) treatment affects tau phosphorylation at Ser202 and Ser396/Thr404, and its total levels, along with inhibition of astrogliosis, rather than Aβ deposition [70]. As demonstrated in THY-Tau22 mice, Se(VI)-induced activation of PP2A was shown to be mediated by prevention of its catalytic subunit PP2Ac demethylation which results in its inactivation [71].

In a mouse APP/PS1 model of AD, Se(VI) treatment significantly modulated the expression of genes involved in neuronal development, neurite growth, tau folding, and insulin/insulin-like growth factor type 1 (IGF1)-related pathway. Se(VI)-induced changes in the latter were characterized by increased cortical insulin receptor substrate-1 (*Irs1*) and insulin receptor (*InsR*), as well as hippocampal *Irs1* mRNA expression, along with down-regulated *Srsf3* expression in brain cortex and hippocampus, being indicative of improved central insulin sensitivity [72].

Proteomic analysis demonstrated that Se(VI) treatment significantly reversed alterations in protein expression in 3xTg-AD mice through positive regulation of metabolic, antioxidant, and structural proteins, as well as signaling molecules and proteasomal degradation proteins, including alpha internexin (AINX), WD repeat-containing protein 1 (WDR1), microtubule-associated protein 1A (MAPIA), 2′,3′-cyclic-nucleotide-3′-phosphodiesterase (CN37), and peroxiredoxin-1 (PRX1) [73]. In turn, proteomic analysis of brain cortex of 3xTg-AD mice revealed that Se(VI) supplementation reversed the effects of AD on structural and synaptic proteins, metabolic and Ca^{2+} regulating proteins, signaling and stress related proteins, as well as transporters. In addition, Se(VI) had a stimulatory effect on protein expressions of MAP1A, CN37, AINX, ubiquitin carboxyl-terminal hydrolase isozyme L1 (UCHL-1), neurofilament light polypeptide (NFL), and peroxiredoxin-6 (PRX6) [74].

Additionally, Se(VI) was shown to improve brain ionome in 3 × Tg-AD mice by preventing an increase in Fe, Ca, Co, Zn, Cu, As, Cd, and Hg levels, while maintaining brain Mn content and brain GPX and TRXND activities [75].

Selenite (Se(IV))

Sodium selenite (Se(IV) was shown to reduce Aβ40, Aβ42, and sAPPβ production and subsequent cell death in SH-SY5Y cells and primary cultured rat cortical neurons through the inhibition of β-secretase and γ-secretase activity [76]. Inhibitory effect of Se(IV) on γ-secretase activity was shown to be mediated by ERK-induced phosphorylation of nicastrin and presenilin 1, the components of γ-secretase complex [77]. In PC12 cells, Se(IV) not only downregulated Aβ1-40 accumulation upon Aβ25-35 treatment, but also significantly decreased tau phosphorylation through the inhibition of GSK-3β [78]. Thus, an inhibitory effect of Se(IV) on tumor necrosis factor α (TNFα)-induced tau phosphorylation was shown to be mediated by reduced phosphorylation of GSK-3β and Akt [79].

In a rat model of AD, induced by intracerebroventricular injection of streptozotocin, Se(IV) prevented learning and memory defects and reduced hippocampal and cortical oxidative stress, while improving choline acetyltransferase (ChAT) activity [80]. Similarly, in intraventricular LPS-injected mice, Se(IV) improved cognitive function, which was associated with the upregulation of selenoprotein expression, improvement of blood–brain barrier (BBB) integrity, reduction of proinflammatory cytokine production, downregulation of nuclear factor kappa B (NF-κB) signaling, M1 macrophage polarization, as well as glial activation [32]. Finally, in scopolamine-exposed aged rats, selenite supplementation significantly reduced transient receptor potential cation channel subfamily M member 2 (TRPM2) and subfamily V member 1 (TRPV1) in hippocampal neurons through the modulation of oxidative stress, resulting in reduced intracellular and mitochondrial Ca^{2+} accumulation and decreased apoptosis [81].

Organic Se Compounds

Treatment with ebselen, a lipid-soluble organoselenium GPX mimic, significantly improved spatial memory and learning, along with synaptic plasticity in 3 × Tg-AD mice. Ebselen, decreased Aβ formation through downregulation of APP and β-secretase expression, and reduced tau phosphorylation at Thr231, Ser396, and Ser404 residues via modulation of GSK 3β and PP2A activities [82]. Ebselen was more efficacious than SeMet in restoring acetylcholinesterase (AChE) and protecting SH-SY5Y cells the from okadaic acid and Aβ toxicities [83]. It is also notable that ebselen derivatives efficiently reduced LPS-induced production of NO and TNFα in glia, and improved survival of SH-SY5Y cells following exposure to microglia-activated medium [84]. Correspondingly, neurotoxicity of Aβ1-42 in rodent hippocampal neurons in culture was attenuated by diphenyl diselenide and ebselen [85]. Treatment with another lipid-soluble organoselenium compound, Selol, significantly reduced neuroinflammation characterized by up-regulated cortical TNFα and interleukin 6 (IL-6) mRNA and protein expression and ameliorated inhibition of BDNF mRNA expression in LPS-injected mice. Ebselen also promoted the expression of antioxidant selenoproteins such as GPX1 and TRXND [86].

Se-methylselenocysteine treatment significantly reduced brain oxidative stress by prevention of Cu, Fe, and Zn overaccumulation, decreased Aβ formation through down-regulation of APP and BACE1 expression, and prevented tau phosphorylation with subsequent neurofibrillary tangle formation via up-regulation of protein phosphatase 2A (PP2A), that may be at least partially mediated by the inhibitory effect of MEK (MAPK)/ERK signaling [87]. Proteomic analysis demonstrated that Se-methylselenocysteine treatment ameliorated down-regulation of proteins involved in energy and amino acid metabolism, synaptic structure and functioning, and redox homeostasis [88].

It is important to note that Ebselen does not contribute to the synthesis of selenoproteins, because the Se is not released from its organic moiety. In contrast, methyl-selenocysteine can be metabolized to HSe^- and be incorporated in selenoproteins [53].

Neuroprotective effects of certain other Se-containing compounds were also associated with downregulation of Aβ production and aggregation. Specifically, reduction of Aβ accumulation in APP/PS1 mice was associated with reduced oxidative DNA and RNA damage in brain cortex of APP/PS1 mice following organoselenium supplementation [89]. Similarly, selenepezil (which has a structure similar to donepezil, but also has a Se bound to one C and to one N forming a region similar to ebselen) treatment was shown to attenuate Aβ25 – 35 induced cognitive decline in rats through up-regulation of brain antioxidant system that may be mediated by activation of Kelch-like ECH-associated protein 1 (Keap1) – Nuclear factor erythroid-2-related factor 2 (Nrf2) – antioxidant responsive element (ARE) pathway [90]. Octylseleno-xylofuranoside also provided neuroprotection in intracerebroventricular streptozotocin (STZ)-injected model of AD by reducing oxidative stress, as well as down-regulation of APP, β and γ-secretases mRNA expression [91]. Diphenyl diselenide treatment was shown to improve learning and memory in transgenic *Caenorhabditis elegans* AD model by reducing Aβ1-42 gene and protein expression. This was associated with downregulation of hsp-16.2, and increased peripheral AChE activity which resulted in paralysis in worms [92].

A few studies have demonstrated beneficial effects of organoselenium compounds on cholinergic signaling in animal models of AD. Specifically, protective effects of selenothymidine pretreatment in STZ-induced AD model may be mediated by inhibition of AChE activity and reduction of oxidative stress [93]. Similar effects in this model were observed for p,p'-methoxyl-diphenyl diselenide [94]. Improvement of cholinergic signaling in STZ-induced AD model by Se-containing purine derivative (6-((4-fluorophenyl) selanyl)-9H-purine) was shown to be associated with prevention of AChE activation, and upregulation of choline acetyltransferase and Na + /K + -ATPase activity [95].

Se-Enriched Yeast

The Se-enriched yeast preparations usually has as main organoselenium compound the amino acid selenomethionine, but in addition to SeMet, more than 10 chemical forms (either as diselenidees or selenide-sulfide) are also found [96, 97]. Administration of Se-enriched yeast to 3 × Tg-AD mice resulted in a significant improvement of cognitive function and synaptic protein postsynaptic density protein 95 (PSD-95), Synapsin1, and Synaptophysin levels. In addition to reduction of brain oxidative stress and tau phosphorylation through the inhibition of GSK-3β, these effects were associated with prevention of astrocyte and microglia activation as evidenced by reduced glial fibrillary acidic protein (GFAP) and CD45 expression [57–59]. In addition, Se-enriched yeast treatment significantly reduced cortical and hippocampal Aβ accumulation in 3 × Tg-AD mice through downregulation of APP and BACE1 protein expression and restoration of the autophagic flux by modulating AMPK/Akt/mTOR/p70S6K signaling [98]. It is noteworthy that despite stronger accumulation of Se following SeMet treatment, Se-yeast administration resulted in a more profound decrease in hippocampal APP and Aβ levels. This was suspected to be due to the presence of various nutrients, including vitamins in Se-yeast [63].

Selenium Nanoparticles (SeNPs)

An accumulating body of evidence demonstrate that Se-based nanoparticles possess neuroprotective effect in AD models, although the underlying mechanisms appear to vary significantly among various SeNP forms [99].

Administration of sodium selenosulphate-based SeNPs in STZ-induced AD model ameliorated learning and memory dysfunction, hippocampal oxidative stress, as well as Aβ accumulation [100]. Moreover, sodium selenosulphate-based SeNPs were shown to improve the efficiency of adipose-derived mesenchymal stem cell transplantation in STZ-induced AD model by promoting stem cell survival and proliferation, ultimately resulting in reduced Aβ accumulation and upregulation of BDNF [101].

Several nanoparticle composites were constructed to evaluate the neuroprotective effects of Se and phenolic antioxidants. Specifically, SeNPs significantly increased the protective effects of resveratrol against Cu^{2+}-induced Aβ42 aggregation, ROS overproduction and subsequent cell death [102, 103]. Reduction of Aβ accumulation and tau hyperphosphorylation by resveratrol-SeNPs in $AlCl_3$-induced AD model was also associated with upregulation of sirtuin 1 (SIRT1) and inhibition of miRNA-134 expression. These resulted in inhibition of STAT3 signaling, lower neuroinflammation, and improvement of neurite outgrowth [104]. Mesoporous nano-selenium delivery system based on the borneol target, β-cyclodextrin nanovalves with loaded resveratrol, capable of passing through BBB, significantly reduced ROS generation, and Ab aggregation as well as tau phosphorylation, ultimately resulting in improved memory in APP/PS1 mice [105]. Correspondingly, SeNPs also potentiated rutin-induced upregulation of Nrf2 and heme oxygenase 1 (HO-1) expression in PC12 cells, also reducing H2O2-induced apoptosis and cytotoxicity [106]. The ability to reduce Aβ aggregation was also demonstrated for several other SeNPs, including epigallocatechin-3-gallate (EGCG)-stabilized SeNPs, coated with Tet-1 peptide [107], chlorogenic acid bound to SeNPs [102, 103], and curcumin-containing poly-lactide-co-glycolide polymer encapsulated with SeNPs [108].

The ability to reduce AD-type pathology was also demonstrated for selenium-chondroitin sulfate nanoparticles (SeCNPs). Specifically, reduced Aβ aggregation and tau phosphorylation, following treatment with SeCNPs, was associated with attenuation of actin cytoskeleton instability in okadaic acid-exposed SH-SY5Y cells [109]. Administration of SeCNPs to $AlCl_3$/D-galactose exposed mice significantly reduced tau phosphorylation through downregulation of GSK-3β, and inhibition of oxidative stress. Moreover, ERK1/2, p38 MAPK, and NF-κB pathways were inhibited, resulting in downregulation of TNF-α, IL-6 and IL-1β expression [110]. Noteworthy, significant antiinflammatory effect was demonstrated for biogenic SeNPs. Specifically, SeNPs from *Lactobacillus casei* (ATCC 393), significantly reduced toxic effects of Aβ25-35 treatment in PC12 cells by reducing ROS overproduction and apoptosis, inhibiting IL-1β and IL-18 secretion and promoting anti-inflammatory IL-10 secretion, at least partially through Akt/CREB/BDNF signaling [111, 112].

Various SeNPs were shown to inhibit metal-induced amyloidogenesis. Specifically, SeNPs stabilized with chitosan prevented Aβ42 aggregation induced by divalent metals, including Fe, Cu, and Zn [113], or by amino acid enantiomers [114]. Similar protective effects against Zn^{2+}-induced intracellular Aβ40 aggregation was observed for chiral penicillamine-modified SeNPs [115].

Moreover, selenium-containing clioquinol derivatives inhibited Cu^{2+}-induced Aβ aggregation and promoted Aβ fibril disaggregation [116]. Similarly, large amino acid mimicking Se-doped carbon quantum dots (SeCQDs) prevented Aβ aggregation and fibril formation by direct binding to Aβ in an AD model generated by direct Aβ40 injection into the hippocampus [117]. SeCQD had similar effects in vitro and in another in vivo model where improvements in learning and memory were also observed [118].

Dual-functional SeNPs containing two proteins LPFFD and TGN significantly inhibited Aβ fibrillation and neurotoxicity in PC12 cells. This was achieved by combination of effects on hydrophobic and electrostatic interactions, as well as decreasing Aβ-induced ROS generation [119].

Thus, despite high heterogenicity of various SeNPs, they all show beneficial effects in animal models of AD albeit by different mechanisms or combination of them. These include direct interaction with Aβ, and reducing its aggregation, interfering with amyloidogenesis and tau phosphorylation, or possessing antioxidant and anti-inflammatory properties. However, it is yet questionable whether similar effects may be observed in humans.

The Role of Gut Microbiota Modulation in Neuroprotective Effects of Se in AD

It is now well-established that GM plays a critical role in brain physiology and pathology through the gut-brain axis [120–122]. Se-induced modulations of GM may contribute to its influence in neurological diseases [24]. Herein, we address Se-GM-AD connection vis-à-vis the molecular mechanisms responsible for the neuroprotective effects of Se in experimental in vivo models of AD (Table 1).

In a rat AlC13/D-gal-induced model of AD, treatment with SeNPs-enriched *L. casei* (ATCC 393) significantly increased GM α-diversity and the relative abundance of Firmicutes and Actinobacteria, while decreasing that of *Chloroflexi*, *Verrucomicrobia* and *Proteobacteria.* Moreover, Firmicutes-to-Bacteroidetes ratio was reduced following SeNPs treatment [111, 112]. In addition to significant alteration of GM at the genus level and intestinal barrier dysfunction, AD was shown to be associated with reduced cecal short-chain fatty acids (SCFA). However, SeNPs supplementation significantly increased both total SCFAs, and the levels of acetate, isovalerate, and valerate. The abundance of particular bacterial taxa was shown to be significantly associated with Aβ accumulation, neurotransmitter dysregulation, and brain inflammation, all being reversed by Se treatment [111, 112]. In addition, SeMet ameliorated a decrease in GM α-diversity along with improvements in cognitive functions as well as restoration of cholinergic neurotransmission in a model of D-galactose-induced cognitive dysfunction [123]. Notably, at the genus level, SeMet abrogated D-gal-induced increase in *Staphylococcus* and reduction of *Clostridium* IV, *Clostridium* XIVa, and *Desulfovibrio* abundances, whereas the abundance of *Akkermansia*, *Dorea*, *Acetatifactor*, *Atopostipes*, *Enteractinococcus*, and *Paenalcaligenes* was increased [123]. Significant correlations between GM taxa and metabolic parameters, including hippocampal H_2O_2 level and cholinergic dysfunction, demonstrate that improvement of GM may at least partially mediate the neuroprotective effects of SeMet [123]. Neuroprotective, antioxidant, anti-inflammatory, and anti-amyloidogenic effect of resveratrol-loaded selenium/chitosan nano-flowers in AlC13/D-gal-exposed mice additionally fed high-fat diet was associated with improvement of GM α-diversity, amelioration of AD-induced decrease in Bacteroidetes relative abundance, and an increase in Firmicutes population [124]. At the genus level, AlC13/D-gal/HFD-induced reduction in *Desulfovibrio*,

Table 1 A summary of neuroprotective effects of Se associated with improvement of gut microbiota in in vivo models of AD-type pathology

Animals	Design	Effects on gut microbiota, Se vs Model group	Effects on brain and other tissues, Se vs Model group	Reference
C57BL/6 mice	Model i.p. injection of D-galactose (150 mg/kg b.w.) and oral gavage of AlCl$_3$ (20 mg/kg b.w.) daily for 8 weeks Se treatment L. casei ATCC 393-SeNPs diet (the final Se content of 0.3 mg/kg) for 13 weeks	↑α-diversity, Firmicutes, Actinobacteria ↓ *Chloroflexi*, *Verrucomicrobia Proteobacteria,* Firmicutes-to-Bacteroidetes ratio ↑cecal total SCFAs, acetate, isovalerate, and valerate	↓AD-induced cognitive impairment ↑ DA, 5-HT (serum and brain), GABA, T-SOD, GPx, TrxR (serum, brain, ileum) ↓MDA (serum, brain, ileum) Brain ↓Aβ aggregation, p-tau, apoptosis, IL-1β, IL-18, microglia activation ↑p-Akt, CREB, BDNF, IL-4, IL-10 Ileum ↑ZO-1, Occludin, Claudin 1	[111, 112]
Kuming mice	Model s.c. injections of D-galactose (100 mg/kg b.w.) for 8 weeks Se treatment i.g. gavage SeMet 30 μg daily for 8 weeks	↑Shannon index ↓Simpson index ↓ *Staphylococcus* ↑ *Clostridium* IV, *Clostridium* XIVa, *Desulfovibrio*, *Akkermansia, Dorea, Acetatifactor, Atopostipes, Enteractinococcus, Paenalcaligenes*	↓D-galactose-induced cognitive impairment Hippocampus ↑Ach, ChAT, SEPP ↓AChE, MAO, H$_2$O$_2$, AGEs,	[123]
ICR mice	Model i.p. injection of D-galactose (120 mg/kg b.w.) and oral gavage of AlCl$_3$ (50 mg/kg b.w.) with high-fat diet Se treatment Oral administration of resveratrol-loaded selenium nanoparticles/chitosan nanoparticles (60 mg/kg b.w.)	↑ α-diversity ↑ Bacteroidetes, *Desulfovibrio*, *Candidatus_Saccharimonas*, *Roseburia*, *Lachnospiraceae*_UCG-006, *Alloprevotella, Ruminococcus* ↓ Firmicutes, *Anaerotruncus*, *Rikenella*, *Enterococcus, Colidextribacter*	↓HFD + AlCl3 + D-gal-induced cognitive dysfunction, adiposity ↓Aβ, MDA, IBA1 +, GFAP, IL-6, IL-1β, TNFα, neuronal loss (Brain) ↑SOD, GPX, CAT (Brain) ↓TC, TG, LPS, insulin resistance (Serum) ↑ claudin-1 and ZO-1 (Intestine)	[124]
ICR mice	Model i.p. injection of D-galactose (60 mg/kg b.w.) and oral gavage of AlCl$_3$ (35 mg/kg b.w.) Se treatment Resveratrol-selenium- blood – brain barrier transport peptide (TGN peptide) nanocomposites (50 mg/kg b.w.) by oral gavage for 16 weeks	↑ α-diversity index ↓ *Alistipes*, *Helicobacter*, *Lachnospiraceae_*NK4A136_group, *Rikenella*, *Odoribacter* ↑ *Lachnoclostridium*, *Faecalibaculum*	↓Memory Impairments and cerebral atrophy Brain ↑ GABA, Ach, NE ↓ Aβ, MDA, Glu, ERK, JNK, Akt, p38 MAPK, NF-κB, IBA1 +, GFAP, COX2, iNOS Brain and serum ↑ SOD, GPX, CAT, IL-10 ↓ IL-1β, IL-6, TNFα	[125]
APP/PS1 mice	Model Transgenic Se treatment SeNPs decorated with chitosan and blood brain barrier targeting peptide (Tg-CS/DMY@SeNPs, 250 ng Se/g) 50 mg/kg b.w. by oral gavage for 16 weeks	↓ Allobaculum ↑ Desulfovibrio, Enterorhabdus, Bifidobacterium, Candidatus_saccharimonas, Colidextribacter, Streptococcus, Gordonibacter	Brain ↓ Aβ, IL-1β, IL-6, TNFα, IL-18, p-IκB/IκB, nuclear translocation NF-κB ↑ Nissl bodies, IL-10 Intestine ↑ Claudin 1 ↓ ACS, NLRP3, Casp1	[126]

Table 1 (continued)

Animals	Design	Effects on gut microbiota, Se vs Model group	Effects on brain and other tissues, Se vs Model group	Reference
APP/PS1 mice	Model Transgenic Se treatment Flowerlike selenium nanocluster containing brain-targeting peptide (TGN peptide) and chlorogenic acid (TGN-CGA@SeNCs) administered orally at a dose of 80 mg/kg b.w. daily for 16 weeks	↑ microbial richness and diversity ↓ Desulfobacterota, Actinobacteriota, Desulfivibrio, Dubosiella, Enterorhabdus, Erysipelatoclostridium ↑ *Bacteroidetes,* Verrucomicrobiota, Akkermansia, Turicibacter, Colidextribacter, Romboutsia, Ruminococcus, Alloprevotella, Alistipes,	↓ cognitive impairment and Aβ Brain ↓ Aβ, IL-1β, IL-6, IL-18, TNFα, p-IκB/IκB, nuclear translocation NF-κB, GFAP, IBA1 +, tau ↑ GLUT1, GLUT3, p-AMPK, p-Akt, p-GSK-3β	[127, 128]
APP/PS1 mice	Model Transgenic Se treatment Intragastric administration of 100 mg/kg selenium-containing α-D-1,6-glucan for two months	↑ α-diversity (Shannon, Chao1, ACE index) ↓ Firmicutes-to-Bacteroidota ↑ Akkermansia muciniphila Intestine ↑ acetic acid, propionic acid, isobutyric acid	↓ cognitive dysfunction, neuronal loss Brain ↓ PS1, Aβ40, Aβ42, GFAP, IBA1 +, NLRP3, Caspase 1, ASC, IL-1β ↑ SYN, PSD95 Serum ↓ LPS, MDA	[129]
ICR mice	Model i.p. injection of 300 µg/kg BW/day LPS from days 21 to 28 Se treatment Oral administration of 30 mg/kg b.w. selenopeptide Val-Pro-Arg-Lys-Leu-SeMet daily for 28 days	↑ *Lactobacillus, norank_f_Muribaculaceae*	Brain ↓ MCP-1, TNFα, IL-1β, MDA ↑ IL-10, SOD, CAT	[130]
ICR mice	Model i.p. injection with 300 µg/kg b.w. LPS daily from 21 to 28 days Se treatment Se-peptides Se-P1 (VPRKL(Se)M) and Se-P2 (RYNA(Se)MNDYT) from Se-enriched *Cordyceps militaris* were administered orally at a dose of 10–30 mg/kg b.w for 28 days	↑ Richness (Chao index), diversity (Shannon index) ↑ *Lactobacillus, Alistipes,* Firmicutes-to-Bacteroidetes *ratio* ↓ *Akkermansia, Bacteroides*	↓LPS-induced learning and memory dysfunction Brain and colon ↓ LPS, MCP-1, TNFα, IL-1β, MDA ↑ IL-10, SOD, CAT ↓ Intestinal mucosa damage, inflammation	[130]

↑—increase; ↓—decrease; 5-HT – 5-hydroxytryptamine; ACh – acetylcholine; AChE – acetylcholinesterase; AGEs – advanced glycation end products; Akt – serine/threonine kinase (protein kinase B); Aβ – amyloid β; BDNF – brain-derived neurotrophic factor; Casp1 – caspase 1; CAT – catalase; ChAT – choline acetyltransferase; COX2 – cyclooxygenase-2; CREB – cAMP response element-binding protein; DA – dopamine; ERK – extracellular signal-regulated kinase; GABA – γ-Aminobutyric acid; GFAP – glial fibrillary acidic protein; Glu – glutamate; GLUT1 – glucose transporter 1; GPX – glutathione peroxidase; IBA1 +– ionized calcium-binding adaptor molecule 1 (Iba1)-positive cell; IL-1β – interleukin 1β; iNOS – inducible nitric oxide synthase; IκB – inhibitor of nuclear factor kappa B; JNK – c-Jun N-terminal kinase; LPS – lipopolysaccharide; MAO – monoamine oxidases; MDA – malondialdehyde; NE – norepinephrine; NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells; NLRP3 – NLR family pyrin domain containing 3; p38 MAPK – p38 mitogen-activated protein kinases; GSK-3β – glycogen synthase kinase-3 beta; PSD95 – postsynaptic density protein 95; SEPP – selenoprotein P; SOD – superoxide dismutase; SYN – synaptophysin; TC – total cholesterol; TG – triglyceride; TNFα – tumor necrosis factor α; TrxR – thioredoxin reductase; ZO-1 – zonula occludens-1

Candidatus_Saccharimonas, *Roseburia*, *Lachnospiraceae_*UCG-006, *Alloprevotella* and *Ruminococcus* populations, along with an increase in *Anaerotruncus*, *Rikenella*, *Enterococcus* and *Colidextribacter* abundance, all of which were reversed by SeNPs administration [124]. Moreover, the abundance of *Entercoccus*, *Colidextribacter*, and *Rikenella* positively correlated with brain oxidative stress, liver triglyceride and total cholesterol content, as well as brain proinflammatory cytokine (IL-6, IL-1β, and TNF-α) production, while populations of *Candidatus_Saccharimonas*, *Ruminococcus*, and *Alloprevotella* were inversely associated with these parameters [124]. Finally, it has been demonstrated that improvement in cognitive functions in a $AlCl_3$/D-gal-induced model of AD by resveratrol-Se-peptide nanocomposites (RSeNC) was associated with a recovery in brain γ-aminobutyric acidacetylcholine, acetylcholine, and norepinephrine levels, and a reduction in glutamate production. These effects, along with reduction of oxidative stress and mitigation of neuroinflammation via down-regulation of ERK, JNK, Akt, p38 MAPK, and NF-κB signaling, were associated with GM modulation. Specifically, treatment with RSeNC ameliorated $AlCl_3$/D-gal-induced alterations in GM, resulting in a decrease in relative abundance of *Alistipes*, *Helicobacter*, *Lachnospiraceae*_NK4A136_group, *Rikenella*, and *Odoribacter*, and an increase in *Desulfovibrio*, *Candidatus_Saccharimonas*, Ruminococcaceae_UCG-014, *Lachnoclostridium*, *Enterorhabdus*, and *Faecalibaculum* populations. The role of GM modulation in neuroprotective effects of Se was supported by the positive correlations of the abundance of *Helicobacter*, *Lachnospiraceae*_NK4A136_group, *Rikenella*, *Odoribacter*, and *Alistipes* with neuroinflammation and brain oxidative stress [125]. Taken together, these findings demonstrate that in an AlCl3/D-gal-induced model of AD in laboratory rodents, modulation of GM may contribute to the effects of Se on Aβ accumulation, neurotransmitter metabolism, neuronal oxidative stress, as well as neuroinflammation.

The potential association of Se-induced changes in GM with neuroprotective effects of Se compounds was also observed in other AD models. Specifically, an increase in the relative abundance of *Bifidobacterium*, *Dubosiella*, *Desulfovibrio*, and *Gordonibacter*, as well as Bateroidetes-to-Firmicutes ratio, following treatment with dihydromyricetin-coated SeNPs decorated with chitosan and blood brain barrier targeting peptide, was associated with downregulation of NLR family pyrin domain containing 3 (NLRP3) inflammasome protein expression and neuroinflammation in APP/PS1 mouse model of AD [126]. Correspondingly, administration of brain-targeting peptide (TGN peptide) and chlorogenic acid-containing flowerlike Se nanocluster to APP/PS1 mice resulted in a significant increase in the relative abundance of *Akkermansia*, *Alistipes*, *Alloprevotella*, *Colidextribacter*, *Romboutsia*, *Ruminococcus*, *Turicibacter*, that were significantly associated with brain glucose transporters and antioxidant enzyme activity, while correlating inversely with brain proinflammatory cytokine levels [127, 128]. Se-containing α-D-1,6-glucan administration also significantly reduced cognitive dysfunction in APP/PS1 mice through the prevention of neuronal damage, improvement of synaptic plasticity, reduction of brain Aβ accumulation [129]. These effects were associated with downregulation of APP and presenilin 1 expression, inhibition of astrocyte and microglia activation, and inhibition of NLRP3 inflammasome activation due to decreased NLRP3, Caspase 1, adaptor protein (ASC), and IL-1β expression [129]. Along with these improvements, Se-containing α-D-1,6-glucan also reversed the gut dysbiosis, and caused an increase in SCFAs, acetic, propionic, and isobutyric acids production [129], indicative of the role of gut-brain axis modulation in protective effects of Se in AD through microbial metabolites, as well as regulation of neuroinflammation.

In view of the role of neuroinflammation in AD pathogenesis [131], the impact of Se on GM and neuronal health was investigated in animal models of inflammation-induced cognitive decline. Specifically, in LPS-injected mice, supplementation with selenopeptide Val-Pro-Arg-Lys-Leu-SeMet significantly ameliorated neuroinflammation and brain oxidative stress. This was associated with changes in histidine, lysine, and purine metabolism as well as increases in *Lactobacillus* and reductions in *Lachnospiracea* relative abundance [132]. Correspondingly, Se-rich proteins obtained from Se-enriched *Cordyceps militaris* were shown to protect against LPS-induced oxidative stress and inflammation both in intestine and brain through downregulation of proinflammatory cytokine production and enhancement of anti-inflammatory cytokine levels and antioxidant enzyme activity [130]. Se administration also increased the relative abundance of *Lactobacillus* and *Alistipes*, while decreasing that of *Akkermansia* and *Bacteroides*, that may contribute to neuroprotective effects of Se against LPS-induced cognitive dysfunction [130]. Furthermore, in a murine model of irritable bowel syndrome, induced by chronic unpredictable mild stress, administration of Se-enriched *Bifidobacterium longum* significantly reduced intestinal wall permeability and proinflammatory cytokine production, improved GM biodiversity, and restored the abundance of *Lactobacillus*, *Desulfovibrio*, *Akkermansia*. These effects were associated with upregulation of hippocampal serotonin, γ-aminobutyric acid, neuropeptide Y, and BDNF expression, and reductions in depression and anxiety-like behaviors [133]. Taken together, in the models of inflammation-induced cognitive decline, Se not only improved the cognitive function but also ameliorated GM dysbiosis. For example, by increasing the abundance of *Lactobacillus*, Se reduced neuroinflammation and oxidative stress and restored cognitive functions.

In view of previous indications of the role of brain hypoxia in AD [134], as well as hypoxia-inducible factor 1α (HIF-1α)-mediated protective effect of gut microbiota modulation in AD [135], it is notable that Se supplementation possesses protective effects against cerebral ischemia, at least partially through reversal of stroke-induced gut dysbiosis and a decrease in gut bacteria-derived trimethylamine N-oxide production [136]. SeMet was also shown to reduce neuronal damage, impaired mitochondrial dynamics, apoptosis, and neuroinflammation, at least partially through modulation of GM metabolome in pigs exposed to ammonia [127, 128], that is also known to be associated with AD progression [137]. Finally, in mice exposed to a chemical cocktail containing various heavy metals (As, Hg, Cd), and pharmaceuticals such as diclofenac, and flumequine, showing significant brain metabolic impairments [138], Se supplementation significantly improved brain metabolomics, at least partially through GM modulation as evidenced by significant associations between the relative abundance of bacterial taxa in gut and particular brain metabolites [138]. Although this study was not performed in AD model, previous studies demonstrating the association between heavy metal exposure and AD [139] allow to extrapolate these data on AD.

Conclusions and Perspectives

Taken together, existing data demonstrate that Se provides protective effects in in vitro and in vivo experimental models of AD through reduction of Aβ and phosphorylated tau accumulation, whereas the protective role of selenium against AD in humans is still debatable and may depend on the selenium levels and chemical speciation. In laboratory studies, the neuroprotective effect of selenium may be mediated by inhibiting the enzymes involved in amyloidogenesis (e.g., β- and γ-secretases) or tau phosphorylation (e.g., GSK-3β), or enhancing Aβ clearance. On the other hand, certain selenoproteins and SeNPs may interact directly with Aβ. In addition, Se may mitigate the neurotoxicity of Aβ and phospho-tau by several other mechanisms including reduction of oxidative stress and neuroinflammation, inhibition of neuronal apoptosis, and facilitation of neurogenesis and synaptic plasticity. More recent studies demonstrate that Se-induced modulation of GM is significantly associated with its neuroprotective effects. This contention is supported by in vitro and in vivo experimental models AD, but there are still no data on clinical or epidemiological studies with patients. Despite certain contradictions, the findings show that Se supplementation significantly increases the relative abundance of beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Desulfivibrio*, while reducing that of the potentially harmful ones such as *Lachnospiracea*_NK4A136, *Rikenella*, and *Helicobacter*. Modulation of the abundance of these taxa, as well as other gut bacteria, correlated significantly with Aβ accumulation, tau phosphorylation, neuronal oxidative stress, and neuroinflammation (Fig. 2). However, this issue requires further investigation in experimental models involving germ-free mice or methods of fecal microbiota translocation and antibiotic treatment to evaluate which of the specific effects of Se in AD models are directly dependent on its effects on gut microbiota or other effects of Se (for instance, promotion of selenoprotein synthesis, antioxidant effects, etc.). Another line of research worthy of pursuit is whether changes in gut microbiota may at least partially mediate the neurotoxic effects of Se overload. Finally, it is proposed that modulation of gut microbiota along with Se supplementation may improve the latter's efficacy in AD prevention and/or treatment, although further detailed laboratory and clinical studies are required.

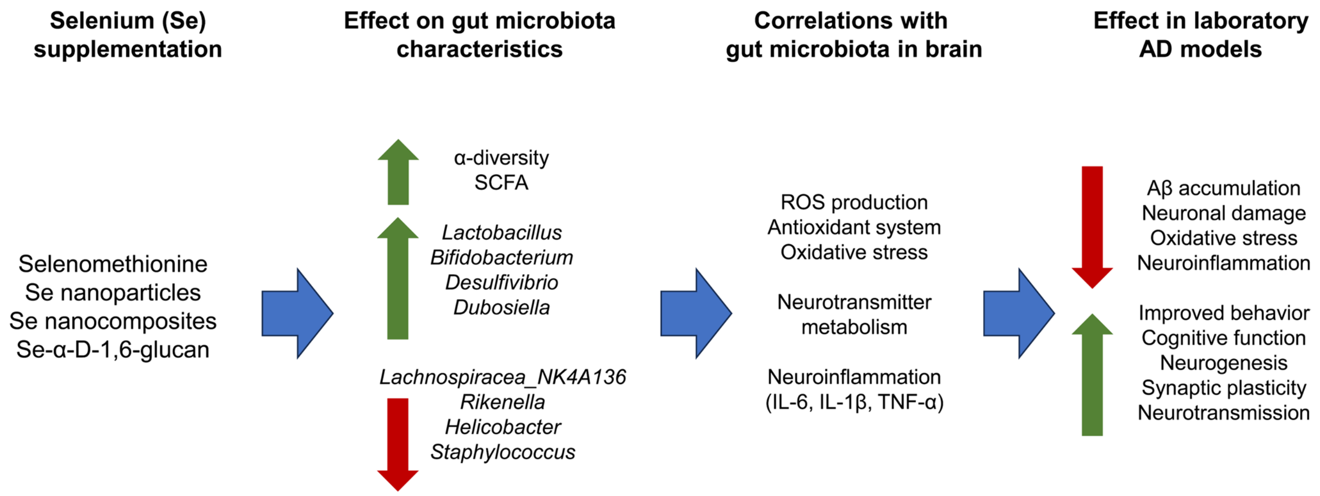

Fig. 2 A simplified scheme of the role of GM modulation in mediating neuroprotective effects of Se in laboratory AD models

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Data Availability No datasets were generated during this review study.

Declarations

Ethics Approval This is a review study. The Yaroslavl State University Ethics Committee has confirmed that no ethical approval is required.

Competing Interests The authors declare no competing interests.

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