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KEYNOTE (GREEN)

Selenium-containing compounds: a new hope for innovative treatments in Alzheimer's disease and Parkinson's disease

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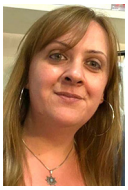
Neurodegenerative diseases are challenging to cure. To date, no cure has been found for Alzheimer's disease or Parkinson's disease, and current treatments are able only to slow the progression of the diseases and manage their symptoms. After an introduction to the complex biology of these diseases, we discuss the beneficial effect of selenium-containing agents, which show neuroprotective effects *in vitro* or *in vivo*. Indeed, selenium is an essential trace element that is being incorporated into innovative organoselenium compounds, which can improve outcomes in rodent or even primate models with neurological deficits. Herein, we critically discuss recent findings in the field of selenium-based applications in neurological disorders.

Jadwiga Handzlik is a full professor of medicinal chemistry and head of the Department of Technology and Biotechnology of Drugs at the Medical College of Jagiellonian University in Krakow, Poland. Her scientific expertise concerns the design and synthesis of G protein-coupled receptors and multi-drug resistance agents, with experience in pharmacological screening. Recently, her main interest has been ligands for serotonin receptors (5-HTRs) against neurodegenerative diseases. Her group identified the first-in-class highly potent Se-containing agents for 5-HT_6R and 5-$HT_{7/1A}$R among 1,3,5-triazine and arylpiperazine derivatives, respectively. Thanks to comprehensive screening through widespread internal and international collaborations, those 5-HT_6R Se-antagonists turned out to be a hope for innovative therapies for Alzheimer's disease.

Clemens Zwergel is currently an assistant professor at the Department of Drug Chemistry and Technologies of Sapienza University in Rome. After gaining his license to practise as a pharmacist from his country of origin (Germany), he moved to Exeter in the United Kingdom to complete a diploma in pharmaceutical sciences. Before moving to Italy, he was a Marie Curie fellow at the University of Lorraine in Metz, France, where he obtained his EuroPhD within the RedCat network. Since 2010, his main research interest has been in the design and synthesis of analogues of natural compounds, as well as modulators of epigenetic enzymes with potential applications in cancer and neurodegenerative, metabolic and infectious diseases.



Cecilia Battistelli is currently an associate professor at the Department of Molecular Medicine of Sapienza University in Rome. Among other areas, her research has involved the characterization of new molecular pathways and mechanisms involved in cancer onset and development, as well as neurodegenerative progression. In recent years, she has focused on dissecting the molecular-level effects of small molecules and artificial non-coding RNAs. In parallel, she is developing several studies to better decipher the role of extracellular vesicles, microRNAs and long non-coding RNAs in the metastasis of hepatocellular carcinoma.

Keywords: selenium; Alzheimer's disease; Parkinson's disease; neuroprotection; oxidative stress

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https://doi.org/10.1016/j.drudis.2024.104062

Introduction

Selenium and seleno-compounds have been largely studied in diseases with distinct aetiologies and development stages, such as cancer and neurodegenerative diseases.[(p1),(p2),(p3),(p4),(p5),(p6)] With regards to the latter group, considerable research efforts are ongoing, driven by the hope of obtaining therapeutics that are less toxic and more effective than current treatments. Selenium has been reported to exert diametral effects on the central nervous system (CNS), showing both toxic and protective properties.[(p7),(p8)] Thus, several groups have focused on different strategies to incorporate selenium into bioactive compounds and small molecules.[(p9)]

Over the past 40 years, evidence in the scientific literature has demonstrated that small selenium-containing compounds represent good candidates in drug discovery, particularly because of their ability to counteract cancer development and cellular oxidation.[(p10)] The design, synthesis and testing of bioactive molecules has grown exponentially, and the focus, at first limited to a few diseases, has been rapidly extended to a larger spectrum of pathologies.

Here, we provide a concise overview of the potential of selenium-containing compounds, which represent a growing field of investigation for treating neurodegenerative diseases. Specifically, we focus on two neurological disorders that represent an open question for both scientists and clinicians: Alzheimer's disease (AD) and Parkinson's disease (PD).

For AD, there has been interest in dissecting the molecular mechanisms involved in its onset to allow the development of new therapeutic strategies.[(p11)] The mechanisms responsible for the decline of cognitive abilities, cytotoxicity, inflammation and the oxidative stress induced by amyloid-β (Aβ) aggregates, all typical hallmarks of AD, have been extensively dissected to identify specific molecular targets for the design of highly selective small molecules. In this frame, some seleno-compounds, alone or in combination with other molecules, have demonstrated efficacy against stress oxidation and cytotoxicity, as well as against tau tangles and Aβ aggregate accumulation (Figure 1).[(p12)]

In the case of PD, selenium derivatives have been tested both *in vitro* and *in vivo* for their ability to reduce neurotoxicity, cellular oxidation in the brain and the typical symptoms of the disease. Hence, selenium derivatives could represent a good strategy for new therapies.[(p13)]

Within this keynote review, we critically discuss recent findings in the field of selenium-based applications in neurological disorders, hand in hand with their relative targets.

Alzheimer's disease

AD is one of the most prevalent neurodegenerative disorders worldwide, both in incidence and prevalence. It is characterised by cognitive decline due to the aberrant accumulation of toxic protein fragments: that is, Aβ plaques outside the neurons, and tau proteins within cells. Aβ plaques cause cell death because of negative interference with intercellular communication at the synapsis level, whereas tangles of tau interfere with the passage of nutrients and other compounds inside neuronal cells.

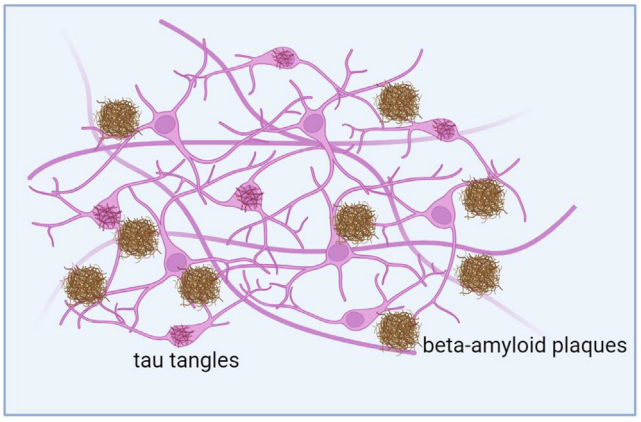

FIGURE 1

The accumulation of Aβ plaques in the extracellular compartment and of tau protein tangles within neuronal cells in AD.

There are two different forms of AD: late-onset (from 65 years of age) and early onset (30–65 years of age), which are also both classified into familial or sporadic forms.[(p14)] The familial form is caused by the inheritance of autosomal mutations in genes encoding proteins associated with Aβ aggregates, such as the *APP* gene.[(p15)] The protein product of *APP* is a precursor that physiologically requires cleavage by enzymes such as α-secretase, β-secretase (also known as BACE1) and γ-secretase.[(p16),(p17),(p18)] The accumulation of mutations in exons 16 and 17, close to the cleavage sites, causes protein misfolding that increases or changes the production rate of Aβ aggregates, inducing neurotoxicity associated with repercussions in inflammation, mitochondrial dysfunction, oxidative stress, cellular permeability, and the function of channels and receptors.[(p18)]

Another crucial molecular hallmark of AD is hyperphosphorylation of the tau protein, a microtubule-associated protein that is involved in the structure of dendrites and the formation of synapses. The activity of the tau protein is related to its post-translational modifications; indeed, its hyperphosphorylation seems to decrease its affinity to microtubules, causing neuronal death and dementia.[(p19),(p20)] In addition, the apolipoprotein E gene can be involved in the onset and development of AD. However, the molecular basis of this involvement has not yet been elucidated.[(p21)]

The sporadic form of AD is the most common and most well-studied one, and the main risk factors for the disease include environmental factors such as pesticides.[(p22)] There are also shreds of evidence indicating that epigenetic mechanisms and non-coding RNAs could be a potential cause of AD progression.[(p23)] Treatment of AD is currently based solely on the alleviation of cognitive symptoms. However, recent evidence has highlighted the potential of selenium derivatives for counteracting AD progression through their antioxidant activity.[(p12),(p24)]

According to the cholinergic hypothesis, an Alzheimer's brain is characterised by a very low concentration of the neurotransmitter acetylcholine (ACh), which is normally cleaved into acetate and choline in response to the activity of the enzyme acetylcholine esterase (AChE). This neurotransmitter is vital for

the function of synapses, and it affects brain function, muscle contraction, neuronal communication and memory. Concerning AD progression, the low level of ACh is associated with a propensity to formation of Aβ plaques, causing neuronal degeneration.[p25],[p26] Furthermore, the glutamate receptors [also known as *N*-methyl-D-aspartate (NMDA) receptors], which are essential for proper neuronal communication, are hyperactivated in AD, causing excitotoxicity that ends with cell death.[p27],[p28]

In terms of dissecting the mechanisms involved in the progression of AD, it has been proposed that neuroinflammation is related to the disease's development and contributes significantly to its severity. A constant high level of proinflammatory cytokines, such as interleukin-18 (IL-18), causes mitochondrial dysfunction and oxidative stress in the cells, and is also associated with tau protein hyperphosphorylation.[p29],[p30]

Moreover, it has been demonstrated that the presence of Aβ plaques in the extracellular matrix contributes to the generation of a cellular state characterised by high oxidative stress; this excess of reactive oxygen species (ROS) can be directly controlled by molecular mediators such as nuclear factor-κB (NF-κB) and transforming growth factor-β (TGFβ). ROS and nitrogen species contribute to the process of tau protein phosphorylation, and the oxidation of nucleic acids is the basis for the induction of cellular death.[p31],[p32]

Different studies have highlighted that in people with AD, there is a reduction in the levels of dopamine (DA), norepinephrine (NE) and serotonin [5-hydroxytryptamine (5-HT)] and their receptors, and the resulting interference in neuronal signal transmission is followed by symptoms such as depression, anxiety and memory-function impairment.[p33]

The mammalian target of rapamycin (mTOR) pathway is also affected in AD.[p34] mTOR is a serine/threonine protein kinase that is involved in the initiation of cellular signalling and is able to regulate protein translation and cellular growth. In AD, it seems that the mTOR pathway is hyperactivated, triggering high production of the tau protein, which contributes to cell death.[p35]

Last, but not least, the Notch pathway is involved in AD development; presenilin 1 (the core protein of the γ-secretase complex) can interact with APP, positively regulating its cleavage. It also helps Notch to release its intracellular domain, which translocates into the nucleus to modulate the expression of genes involved in cellular death (Figure 2).[p36]

Selenium compounds as Alzheimer's disease target agents

Potential selenium anti-Alzheimer's disease agents tested in vivo in animal models

The literature indicates that among the neurodegenerative diseases, the most intensive research with the highest chemical diversity of Se-compounds has been in AD. Among the selenium anti-AD agents described are chemical families of organoselenium compounds that, in addition to showing neuroprotective effects and influence on AD protein targets *in vitro*, have shown promising activity in *in vivo* animal models, which make them attractive for future therapies (Figure 3). Most data concern mouse models of AD, particularly the intracerebroventricular streptozotocin injection model (icv STZ), a well-established sporadic AD model. Both Se-endocyclic and Se-exocyclic chemical representatives have been confirmed as active in this model. According to the results of Klann and collaborators, the most widely investigated Se-endocyclic compound, ebselen (compound 1 in Figure 3a), was effective against peripheral oxidative stress in icv STZ models in the range of the commercial anti-AD drug donepezil.[p37]

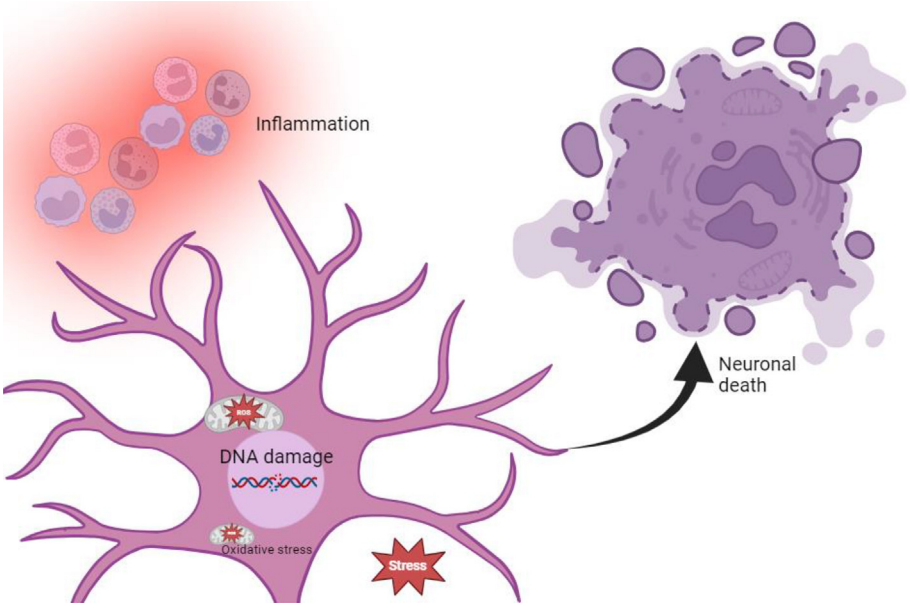

FIGURE 2
The contribution of oxidative stress (the production of ROS) to DNA damage, inflammation and the induction of cell death in neuronal cells.

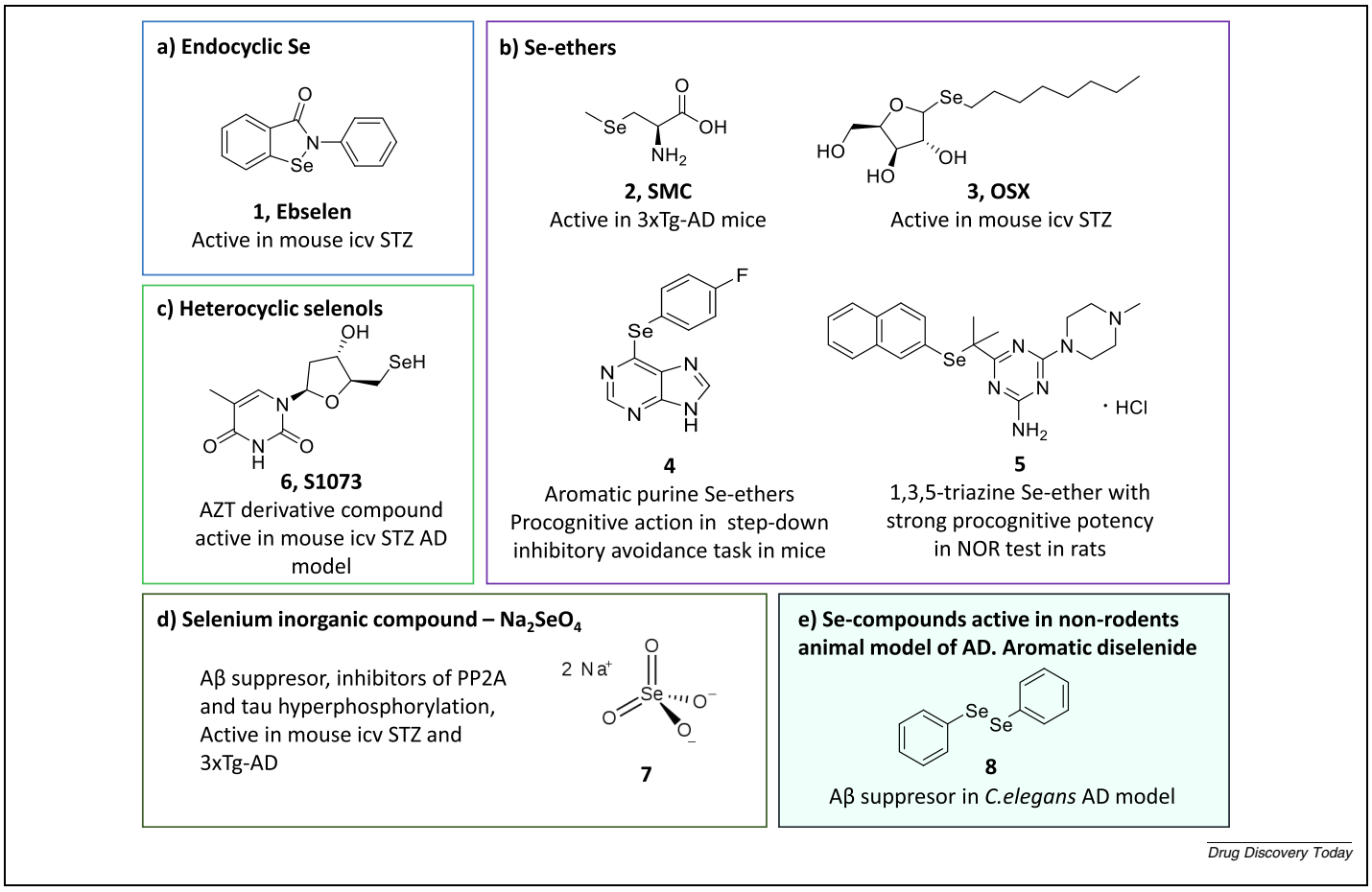

FIGURE 3

Se-compounds active in an animal model of AD or AD-associated impairments. **(a–d)** Compounds tested in rodent models *in vivo* (white background). **(e)** Compound tested in a nematode model (green background).

Interesting *in vivo* activities in rodents were also observed for various Se-ether compounds with either amphiphilic or hydrophobic properties, with or without aromatic fragments. The Se-cysteine derivative (SMC; compound 2 in Figure 3b) has been found to ameliorate neuropathology and cognitive deficits in a triple-transgenic mice model of AD (3xTg-AD mice).[p38] The amphiphilic octylseleno-xylofuranoside (OSX; compound 3 in Figure 3b) was confirmed to possess protective effects in the AD mouse icv STZ model, in addition to showing antioxidant and antidepressant-like activities through modulation of the monoaminergic system and synaptic plasticity pathways.[p39],[p40] In the group of purine aryl selenoethers, 6-((4-fluorophenyl)selanyl)-9H-purine (compound 4 in Figure 3b) inhibited AChE activity and improved non-spatial long-term memory, which was investigated using a step-down inhibitory avoidance task, and thus it is a promising agent for the treatment of AD.[p41],[p42] Our recent studies,[p43] found that β-naphthyl selenoether 1,3,5-triazine (compound 5 in Figure 3b) demonstrated a strong procognitive-like activity, as examined in rats using a novel recognition object (NOR) test. The compound was able to reverse the rodents' memory impairment after administration at doses lower than those of donepezil, and also led to anxiolytic-like activity in the elevated plus maze (EPM) test. The pharmacokinetics parameters *in vivo* confirmed blood–brain barrier (BBB) penetration, and the brain concentration of compound 5 was found to be desirable for therapeutic effects, combined with a favourable absorption, distribution, metabolism and excretion (ADME) and toxicity profile.[p43]

In addition to the selenoethers mentioned above and Se-endocycles (ebselen), the results of Thomé and colleagues confirmed that thymidine-derived selenol (S1073, compound 6 in Figure 3c) displayed neuroprotective effects in memory and learning impairment induced by icv STZ in the aforementioned model of AD in mice.[p44]

Although the extensive search for anti-AD Se-drugs has mainly focused on organoselenium compounds, few inorganic selenium compounds play a crucial role, such as sodium selenate (compound 7 in Figure 3d). Based on animal studies,[p45] supplementation of compound 7 resulted in a significant reduction of lipid peroxidation and protein carbonylation in the cerebral cortex and hippocampus of icv STZ rat models.[p46],[p47] Supplementation of compound 7 compensated for memory and motor deficits, and enhanced the stability of primary progressive aphasia-tau (PPA-tau), which is deeply associated with decreased tau phosphorylation.[p48],[p49] It also attenuated the inhibition of protein phosphatase 2A (PP2A) and tau hyperphosphorylation induced by traumatic brain injury,[p50] and it positively altered the phosphorylation status of key proteins involved in oxidative stress and protein degradation in a cellular model of AD, as well as resulting in a reduction of Aβ levels.[p51] The results of studies

comparing 3xTg-AD mice with wild-type mice indicated that compound 7 has a profound effect on the hippocampus of triple transgenic AD mice, altering six AD-associated proteins, and thus indicating it could be an effective therapeutic agent in the future.[p45] High-dose supplementation with compound 7 is well tolerated and can modulate CNS selenium concentrations, although individual variation in selenium metabolism must be considered to optimise the potential benefits in AD.[p52] However, recently it has been shown that compound 7 also exhibits neurotoxic effects in various mouse models.[p53],[p54]

Finally, diselenides cover a chemical space of great pharmacological interest that has been investigated in more comprehensive animal models, including rodents, as well as simpler organisms such as nematodes. Zamberlan and collaborators,[p55] used a transgenic *Caenorhabditis elegans* nematode AD model to analyse the effects of treatment with diphenyl diselenide [$(PhSe)_2$; compound 8 in Figure 3e] on Aβ peptide-induced toxicity. Chronic exposure to compound 8 attenuated oxidative stress induced by $A\beta_{1-42}$ to recover associative learning memory in *C. elegans*. This diselenide suppressed $A\beta_{1-42}$ expression, reducing the need for chaperone hsp-16.2 under $A\beta_{1-42}$-induced toxicity, thus displaying a pharmacologically promising ability for potential AD treatment protection against oxidative stress-induced toxicity. In the case of rodent models, the diselenide *p, p'*-methoxyldiphenyl diselenide [$(MeOPhSe)_2$] showed beneficial effects when tested against STZ-induced sporadic dementia of Alzheimer's type (SDAT) in rats. According to Pinton and colleagues,[p56],[p57] a 30-day supplementation with $(MeOPhSe)_2$ resulted in reverted STZ-induced memory impairment in rats, as confirmed with the Morris water maze and step-down passive avoidance cognitive tasks.

Potential selenium anti-Alzheimer's disease agents found in vitro in preclinical studies

An even greater variety of Se-compounds have shown promising results in primary *in vitro* screening (Figures 4–6). The majority of Se-compounds that have shown promise as potential therapies for CNS and neurodegenerative diseases are glutathione peroxidase (GPx) modulators or mimetics.[p58],[p59],[p60],[p61],[p62],[p63] GPx is an antioxidant enzyme that uses thiol as a cofactor to catalyse the reduction of hydroperoxides, and since its ability to protect haemoglobin from oxidative degradation was confirmed in the middle of the twentieth century, it has been one of the most well-studied selenoproteins. Subsequent studies have shown that GPx has an active site that contains selenium and that has a function in maintaining the redox equilibrium of cells. The identification of selenium compounds (selenocysteine) in GPx1 changed the long-held belief about the toxicity of Se-compounds and drew attention to the key function of selenium in antioxidant defence.[p64]

The beneficial cell-protective effect of GPx mimetics has broad therapeutic significance that is not specific only to neurodegenerative diseases; however, in this review, we focus only on those selenium GPx mimetics that produce neuroprotective effects that are specific to a neurodegenerative disease.

Most lines of evidence indicate that Se-compounds might function as antioxidants, inhibiting oxidative stress in several neurodegenerative diseases, including AD. They act as GPx mod-

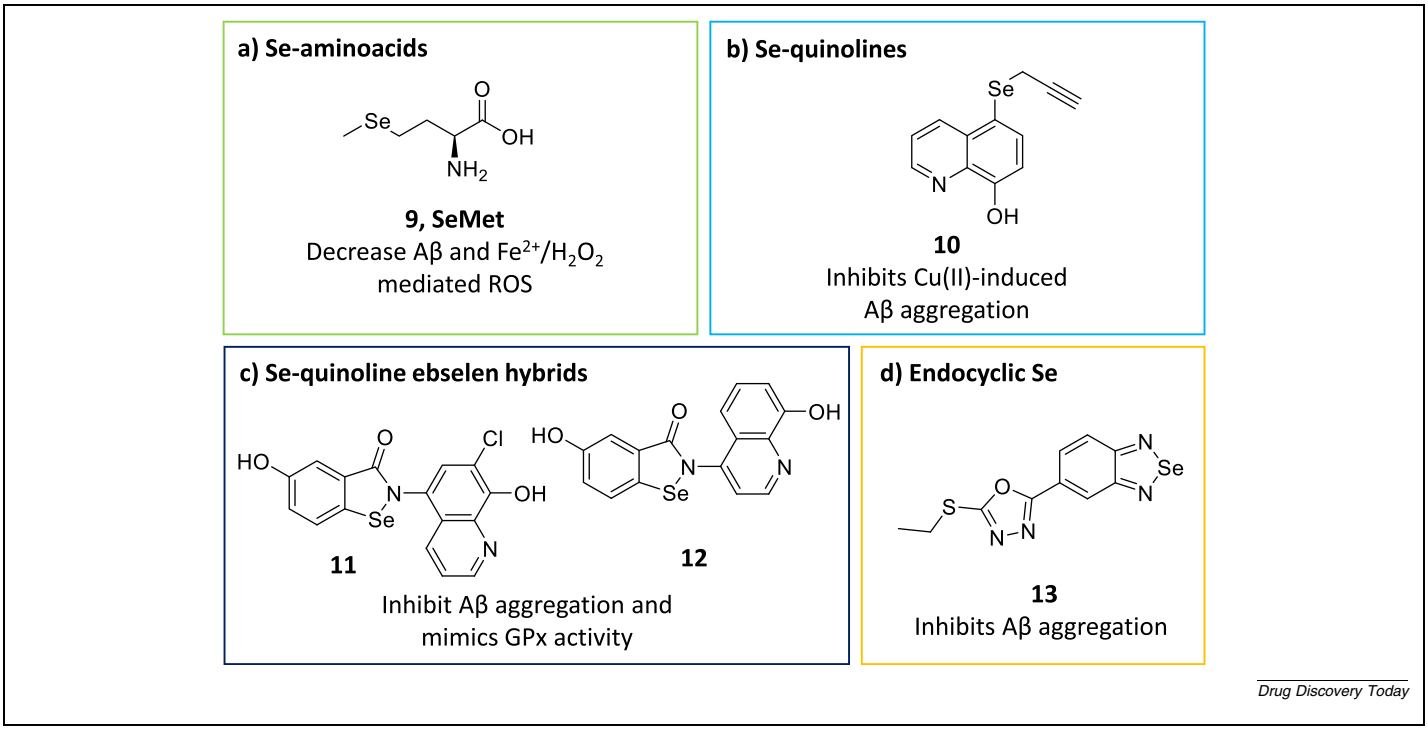

FIGURE 4

Selenium-containing Aβ aggregation inhibitors and GPx modulators: **(a)** Se-amino acids; **(b)** Se-quinolines; **(c)** Se-quinoline ebselen hybrids; **(d)** endocyclic Se-containing compound.

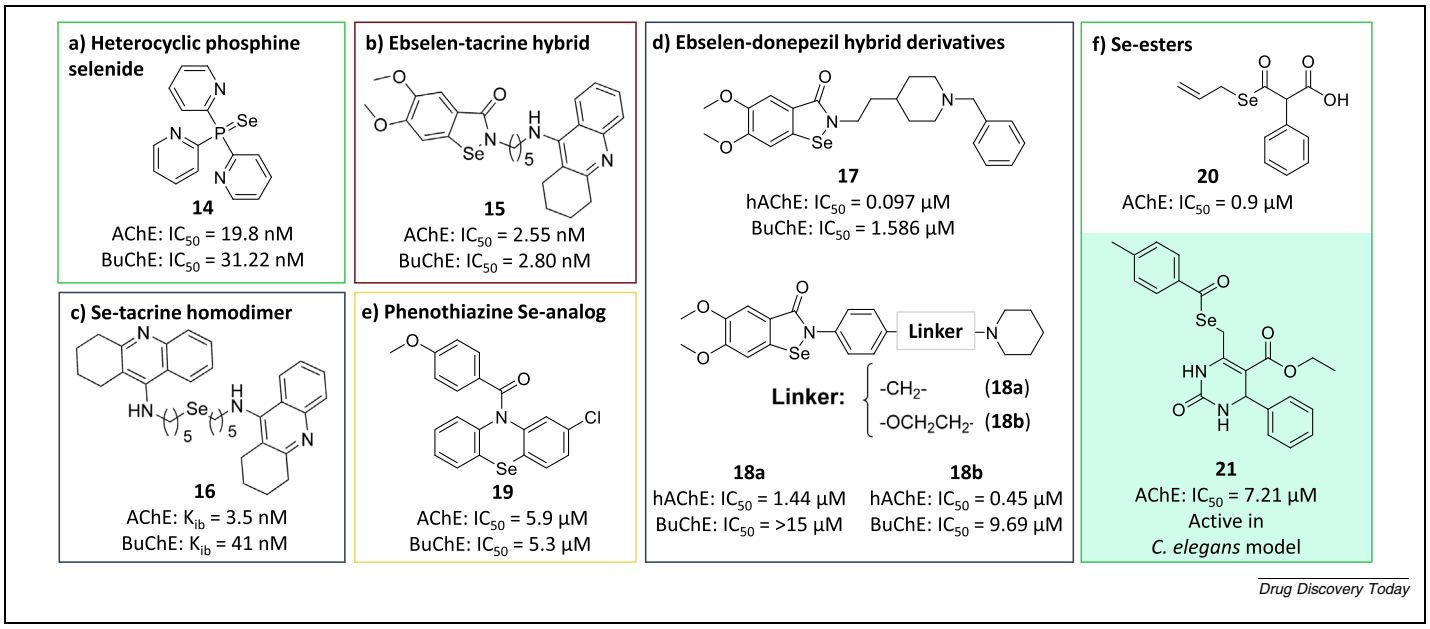

FIGURE 5

Cholinesterase inhibitors (ChEIs) with Se in the structure: **(a)** Heterocyclic phosphine selenide; **(b–d)** Se-hybrids of ChEIs; **(e)** Se-bioisosteric phenothiazines; and **(f)** Se-esters, the activities of which were confirmed in nematode models (green).

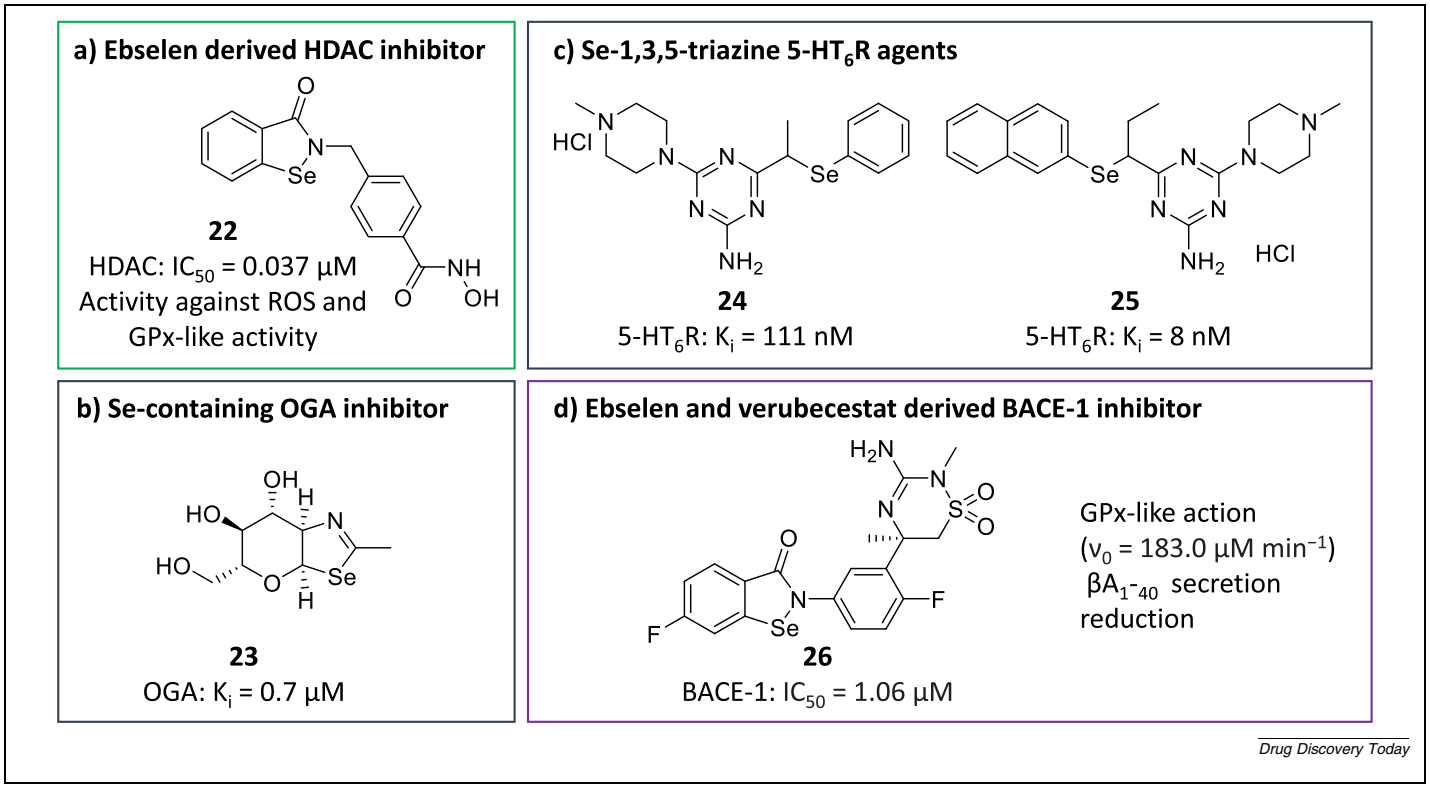

FIGURE 6

Miscellaneous targets ligands with Se in the structure: **(a)** Ebselen derived HDAC inhibitor; **(b)** Se-containing OGA inhibitor; **(c)** Se-1,3,5-triazine 5-HT_6-R agents; **(d)** Ebselen and verubecestat derived BACE1 inhibitor.

ulators and Aβ aggregation inhibitors, additionally having effects on AD proteins (mainly on cholinesterases, but also on various other AD targets). The importance of those targets for potential therapeutic success in AD has been increasingly emphasised.

Selenium compounds as Aβ aggregation inhibitors and GPx modulators

In terms of AD therapy, the simple and known structure of seleno-L-methionine (SeMet; compound 9 in Figure 4a) has

shown promising effects; it has been confirmed to decrease free radical generation induced by Fe^{2+}/H_2O_2 or $A\beta_{25–35}$ through the modulation of GPx.[p12] These neuroprotective effects have also been demonstrated for other chemical classes, that is, linear Se-ethers, selenols and Se-endocyclic compounds, and in some cases the effects were even more pronounced. Wang and collaborators,[p65] described a series of clioquinol-derived selenoethers, followed by hybrids of ebselen with 8-hydroxyquinolines,[p8],[p66] which exhibited inhibition of metal-induced Aβ aggregation, antioxidative properties, hydrogen peroxide scavenging and the prevention of copper redox cyclin, together with beneficial BBB penetration *in vitro*. The propynylselanyl derivative (compound 10 in Figure 4b) turned out to be the most promising in the first series, while compound 11,[p8] and compound 12,[p66] were the optimal structures out of the ebselen-containing hybrids (Figure 4c), with respect to different positions of quinoline-ebselen linkage. Compounds 10, 11 and 12 demonstrated an excellent ability to scavenge peroxide and to inhibit self- and metal-induced Aβ aggregation, as well as to disassemble pre-formed self- and metal-induced Aβ aggregates. They possessed GPx-like activity, enabling the modulation of metal-induced Aβ aggregation. Departing from the structure of ebselen, Kalsoom and colleagues,[p67] found a selenadiazole-based library of Se-endocyclic compounds that act against the fibrillization paradigm of Aβ. The most active members of this group (such as compound 13 in Figure 4d) completely inhibited Aβ fibrillization, stabilising Aβ at the monomeric stage.

Cholinesterase inhibitors

Various lines of evidence indicate several Se-derivatives that display the properties of AChE and/or butyrylcholinesterase (BuChE) inhibitors, with or without additional neuroprotective action. Gülçin and collaborators described tris(2-pyridyl) phosphine selenide (compound 14 in Figure 5a), which showed nanomolar activity for both AChE and BuChE.[p68] Furthermore, several groups have functionalised known cholinesterase inhibitors (ChEIs), such as tacrine or donepezil, via the introduction of Se, either in Se-ether or in an endocyclic form (Figure 5b–d). A series of tacrine–ebselen hybrids were designed by Mao and colleagues as possible anti-AD agents[p69]; among them, the tacrine linked with 5,6-dimethoxybenzo[d][1,2]selenazol-3(2H)-one by a C5-alkyl chain was the most potent AChE and BuChE inhibitor (with an IC_{50} of 2.55 and 2.80 nM, respectively). This compound (compound 15 in Figure 5b) also demonstrated similar hydrogen peroxide and peroxynitrite scavenging activity to ebselen, as shown in the horseradish peroxidase assay and peroxynitrite scavenging activity assay. In the group of tacrine-based homo- and heterodimers that incorporate an antioxidant tether,[p70] the best compounds were found to be potent and highly selective AChE inhibitors, with inhibition constants within the low nanomolar range, and they also showed good inhibitory activity towards Aβ self-aggregation (compound 16 in Figure 5c).

However, the bulky hydrophobic fused rings of tacrine as a hybrid component are somewhat less 'drug-like' than other chemotypes that fit within the pharmacophores of AChE/BuChE inhibitors. Therefore, efforts have been made to search for hybrids of ebselen with donepezil and their bioisosteres. Luo and collaborators,[p71] described a series of such hybrids, out of which the dimethoxy-substituted ebselen linked with benzylpiperidine via a C2 long linker turned out to be the most potent AChE inhibitor, and also acted on BuChE (with IC_{50} values of 0.042 μM and 1.586 μM, respectively); this compound (compound 17 in Figure 5d) was found to exert hydrogen peroxide/peroxynitrite scavenging and GPx-like activity without toxic effects in a rodent model. In subsequent studies,[p72] the authors changed the topology of the AChE pharmacophoric fragment to obtain piperidine-ended structures, and two molecules (compounds 18a and 18b in Figure 5d) were found to be the most active against AChE, with IC_{50} values of 0.76 and 0.46 μM, respectively. Compounds 18a and 18b were also good GPx mimics when compared with ebselen, with satisfying *in vitro* hydrogen peroxide scavenging activity.

Because the phenothiazine derivative 2-chloro-10H-pheno thiazin-10-yl-(4-methoxyphenyl) methanone was identified to be a highly potent, dual, non-selective ChEI (with IC_{50} values of 5.9 ± 0.6 μM for AChE and 5.3 ± 0.5 μM for BuChE), Tin and colleagues synthesised its Se-analogue as well. The phenoselenazine (compound 19 in Figure 5e), as well as its N10 unsubstituted analogues, exhibited multiple anti-AD abilities by inhibiting cholinesterase, reducing Aβ aggregation and displaying antioxidant properties.[p73]

Among exocyclic Se-compounds, some families of selenoesters have also been confirmed to be ChEIs, and thus could potentially have therapeutic applications in AD. Astrain-Redin and collaborators described 3-(allylselanyl)-3-oxo-2-phenylpropa noic acid (compound 20 in Figure 5f), which showed almost identical AChE inhibitory activity to galantamine, along with threefold higher *in vitro* BBB permeation.[p74] Similarly, Barbosa and colleagues,[p75] and Perreira and collaborators,[p76] have found a series of dihydropyrimidinone-derived selenoester AChEIs with good antioxidant activity associated with their excellent lipid peroxidation inhibition and good iron chelation activity. The best representatives (e.g., compound 21 in Figure 5f) showed AChEI activity that was superior to that of galantamine.

Selenium compounds that are active towards miscellaneous Alzheimer's disease targets in vitro (HDAC, OGA, 5-HT_6R and BACE1)

In addition to the aforementioned series of Se-compounds with confirmed activity on Aβ-fibrillation or cholinesterases, scientific reports have indicated that selected groups of Se-compounds show activity against other protein therapeutic targets related to the aetiology of AD. These other targets are attracting more and more attention in the search for innovative AD therapies that could more effectively improve patients' quality of life and inhibit the progression of this neurodegenerative disease.

In this context, Hu and colleagues described ebselen-based hybrid *N*-hydroxy-4-((3-oxobenzo[d][1,2]selenazol-2(3H)-yl)alkyl)-benzamide compounds that display histone deacetylase (HDAC)-inhibiting action, along with GPx-like and antioxidant activity, without exhibiting toxicity.[p77] HDAC6 in particular is implicated in AD memory-related dysfunction,[p78],[p79] and is therefore a favourable therapeutic target for the treatment of neurodegenerative diseases that feature memory disorders, such as AD.[p80] The results of *in vitro* assays on HDAC6 indicated that 14 out of the 16 hybrid compounds investigated exhibited

submicromolar HDAC inhibitory effects, but the methylene-linked compound 22 (Figure 6a) emerged as the most potent HDAC inhibitor (IC_{50} = 0.037 μM). Compound 22 also possesses a rapid hydrogen peroxide scavenging activity and GPx-like activity (v0 = 150. 0 μM min^{-1}), as well as good free oxygen radical absorbance capacity (value of ORAC: 2.2).

O-linked 2-acetamido-2-deoxy-β-D-glucopyranosyl (O-GlcNAc) residues play an important part in the signalling mechanism of the post-translational modification of both cytoplasmic and nuclear proteins; the dysregulation of O-GlcNAc modifications has been implicated in AD.[p81] Among others, O-GlcNAc metabolism is regulated by the enzyme O-GlcNAcase (OGA). Thus, molecules that are able to inhibit OGA might be useful in the potential treatment of AD. Based on the structure of the potent OGA inhibitor GlcNAc-thiazoline, Kim and colleagues,[p82] investigated its Se-analogue, GlcNAc-selenazoline (compound 23 in Figure 6b), using FDGlcNAc as the OGA substrate in the assay.[p83] The results indicated that compound 23 competitively inhibited OGA with a K_i of 0.7 μM. Although the activity of compound 23 was 70-fold less potent than that of its thiazoline analogue, this is still a significant submicromolar OGA-inhibiting action, which might translate into potential therapeutic effects against AD, and compound 23 could be a good starting point in the search for innovative AD therapies involving OGA inhibition.

Since the identification of the 5-HT_6 serotonin receptor subtype (5-HT_6R) in the 1990s, both agonists and antagonists of 5-HT_6R have been of great interest in the search for innovative drugs against AD and dementia disorders. This has strong scientific justification, because 5-HT_6R is located almost exclusively in the CNS, in the areas responsible for memory and cognitive functions. Moreover, numerous reports based on studies in animal models indicate that both agonists and antagonists of this receptor give recognitive, antidepressant and anxiolytic effects, which is promising for the treatment of neurodegenerative diseases, and AD in particular.

Our research team has focused on 1,3,5-triazine derivatives, a promising family of 5-HT_6R receptor ligands.[p43],[p84],[p85],[p86],[p87],[p88] In the initial phase, we attempted to develop Se-compounds with moderate activity by incorporating Se into the linker,[p43],[p86] and the phenylselene ether derivative of 1,3,5-triazine (compound 24 in Figure 6c) showed the highest affinity (K_i = 111 nM).[p86] Great benefits were brought by further pharmacomodulation, consisting of a replacement of the phenyl moiety with a β-naphthyl one and modifications in the linker branching, which resulted in the most active structures with 5-HT_6R affinity in the range of K_i = 8–14 nM, where the most potent antagonist was compound 25 (Figure 6c). Although its neuroprotective effects, when tested *in vitro*, turned out to be slightly less attractive than that of compound 5 (Figure 3a),[p43] its beneficial 5-HT_6R and ADMET profile *in vitro* promoted compound 25, together with compound 5, for extended pharmacological studies in the search for a new effective AD therapy based on the action on 5-HT_6R.

Finally, chemical compounds that are able to inhibit BACE1 and other transcription factors form another influential group of potential anti-AD agents. These compounds can provide neuroprotective effects by activating the Kelch-like ECH-associated protein 1 (KEAP1)–nuclear factor erythroid 2-related factor 2 (NRF2)–antioxidant response element (ARE) pathway and stimulating downstream antioxidant proteins [heme oxygenase-1(HO-1), NAD(P)H quinone dehydrogenase 1 (NQO1), thioredoxin reductase 1 (TrxR1), glutamate-cysteine ligase, catalytic subunit (GCLC) and glutamate-cysteine ligase, modifier subunit (GCLM)], with a favourable ADME and toxicity profile. Hence, Qu and colleagues described interesting ebselen-verubecestat hybrid compounds.[p89] In this group, the difluoro-derivative (compound 26 in Figure 6d) was found to be the most attractive, showing satisfying low-micromolar BACE1 inhibition, together with potent GPx-like properties. Compound 26 was able to reduce Aβ secretion in HEK APPswe 293 T cells, and it displayed neuroprotective antioxidative action against hydrogen peroxide or 6-hydroxydopamine (6-OHDA), as well as activating the KEAP1–NRF2–ARE pathway and stimulating antioxidant proteins downstream; however, compound 26 showed weak toxicity in a PC12 cell model.

Summing up, the search for Se-compounds with potential use in AD therapy is characterised by relatively high diversity, both in terms of structure and the explored protein targets. Although research has not yet advanced beyond the preclinical stage, promising results have been observed in animal models, indicating potent pharmacological effects. The early preclinical studies *in vitro* demonstrate interesting effects of Se-containing hybrids and bioisosteres of current anti-AD drugs, such as donepezil, which could provide neuroprotective effects as well as modulating cholinesterase. Furthermore, innovative research is being done on promising AD protein targets such as HDAC, OGA or 5-HT_6R, as well as other proteins involved in neuroprotection and inflammation. The search for innovative AD therapies with higher effectiveness than those currently available on the market has resulted in a wide range of novel Se-compounds, encompassing not only the popular ebselen-like and SeMet-derived compounds, but also various innovative selenoether, selenol or selenoendocyclic structures (e.g., selenazolines or triazine-containing Se-ethers) with promising preclinical data. However, one important point to consider is that most of the studies mentioned above have not evaluated the toxicity and safety profiles of the compounds studied, unless otherwise specified. This latter point should be, however, considered carefully in the further development of Se-containing AD agents.

Parkinson's disease

PD is a neurodegenerative, multisystem disorder that affects the CNS, the enteric nervous system (ENS), the gastrointestinal system and the immune system. It is clinically characterised by a progressive motor deficit, such as bradykinesia, instability, rigidity and tremor. These clinical features are caused by the death of DA-producing neurons that are present in the substantia nigra, and the substantial depletion of DA is associated with the formation of Lewy bodies.[p90] Dopaminergic neurons are particularly sensitive to oxidative stress, and thus to cell death.[p91]

Although PD is considered idiopathic, several mutated genes have been identified as molecular actors that actively induce its onset and development.

Synuclein alpha (*SNCA*) is one of the most studied genes in PD because it encodes α-synuclein, one of the major components of

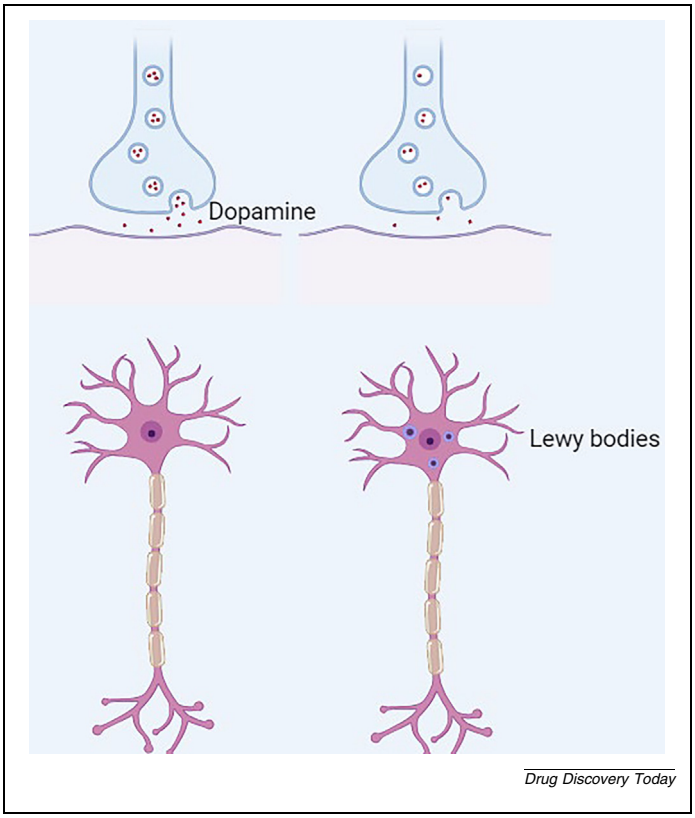

FIGURE 7
Reduction of DA extracellular release and formation of Lewy bodies inside neuronal soma in PD.

Lewy bodies. It physiologically works in the synaptic vesicles, suggesting a role in synaptic transmission. In pathological conditions, it can assume β-sheet secondary structures that can form aggregates and Lewy bodies (Figure 7). Post-translational modifications deeply influence the folding and function of this protein, so the landscape of expression and activity of the enzymes responsible for these modifications is also important.

Selenium depletion in the diet also seems to represent a risk of developing PD.[p91]

One of the main features of PD at a cellular level is oxidative stress; it occurs when the production of ROS competes with the antioxidant cellular activities, causing protein collapse, enzyme breakdown and, finally, cell death. NADPH oxidases (NOXs) are the major producers of ROS, but mitochondrial function also leads to ROS production.[p92]

Ferroptosis also seems to be involved in PD. Ferroptosis is a type of programmed cell death that is induced by iron and caused by the accumulation of peroxidised lipids.[p93],[p94]

Several studies have underlined that mitochondrial dysfunction is clearly involved in PD, above all in dopaminergic neuron degeneration and chronic ROS production. Moreover, mitochondrial dysfunction could also relate to mutation accumulation on specific genes such as Parkin (*PARK2*), PTEN induced kinase 1 (*PINK1*), leucine-rich repeat kinase 2 (*LRRK2*) and protein deglycase (*DJ1*).[p95]

To summarise, although the actual aetiology of PD is not well defined, some factors particularly contribute to this disease, including mitochondria dysfunction, ROS production and excitotoxicity due to high glutamatergic transmission.

In this scenario, selenium and selenoproteins have been defined as potent regulators that play a fundamental part as antioxidant molecules that can ameliorate the oxidative status in individuals with PD.[p96]

Selenium compounds as Parkinson's disease target agents

Potential selenium anti-Parkinson's disease agents tested in vivo in animal models

PD represents a neurodegenerative problem for which new therapeutic solutions using Se-compounds might be a promising strategy. In addition to their anti-AD action mentioned above, both diselenides and ebselen (compound 1 in Figure 3a) hold promise as potential PD therapies. Among the diselenides, $(PhSe)_2$ (compound 8 in Figure 3e) was tested in a model of PD induced by 6-OHDA in male Wistar rats, and showed a positive outcome.[p97] The findings of this study highlight that compound 8 has a neurorestorative effect against motor impairment induced by 6-OHDA in rats, influencing the behavioural impairment and restoring ipsilateral striatal TH levels. Compound 1, which has been widely described in AD (Figure 3a), has also been tested in animal models of PD. Moussaoui and colleagues[p98] evaluated the effects of compound 1 in the marmoset 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model. This is a widely used experimental model in PD research, because marmosets share neuroanatomical and physiological similarities with humans. When exposed to MPTP, these primates develop PD-like symptoms, providing a valuable model for studying the disease's pathophysiology and testing potential therapeutic interventions.[p99] The results showed that preventive treatment with compound 1 reduced MPTP neurotoxicity and Parkinsonian symptoms in marmosets without exhibiting neuro-toxic effects.

A SeMet derivative (compound 9 in Figure 4a) was tested successfully in AD animal models, so Chang and collaborators investigated the neuroprotective potential of plant-derived *N*-γ-(L-glutamyl)-L-selenomethionine (Glu-SeMet; compound 27 in Figure 8a) in a *C. elegans* model of PD.[p100] Compound 27 showed significant protective effects against 6-OHDA-induced dopaminergic neuron damage, improved behavioural outcomes and reduced intracellular ROS levels. Compared with approved PD drugs, compound 27 exhibited greater ameliorative effects, and it induced nuclear translocation of SKN-1 (the analogue of mammalian NRF2) as well as increasing mRNA levels of SKN-1, GST-4 and GCS-1 in the *C. elegans* PD model. These findings underline the potential therapeutic value of compound 27 in mitigating PD-related neurotoxicity and oxidative stress.

Among synthetic organoselenium compounds, selenoethers are the main group described in the literature as active in models of PD *in vivo* (Figure 8). Pinz and colleagues,[p101] described the most active representative of the quinoline phenylselenoether compounds, 8-chloro-4-(phenylselanyl)quinoline (4-PSQ; compound 28 in Figure 8b), which showed satisfactory acute anti-inflammatory and antinociceptive effects on mice,[p102] without toxic effects at high doses *in vivo* (25 and 50 mg/kg). Compound 28 was tested in two neurodegenerative disease models, one in which AD was induced by Aβ-peptide in Swiss mice,[p103] and another in which a PD-like phenotype was induced by rotenone

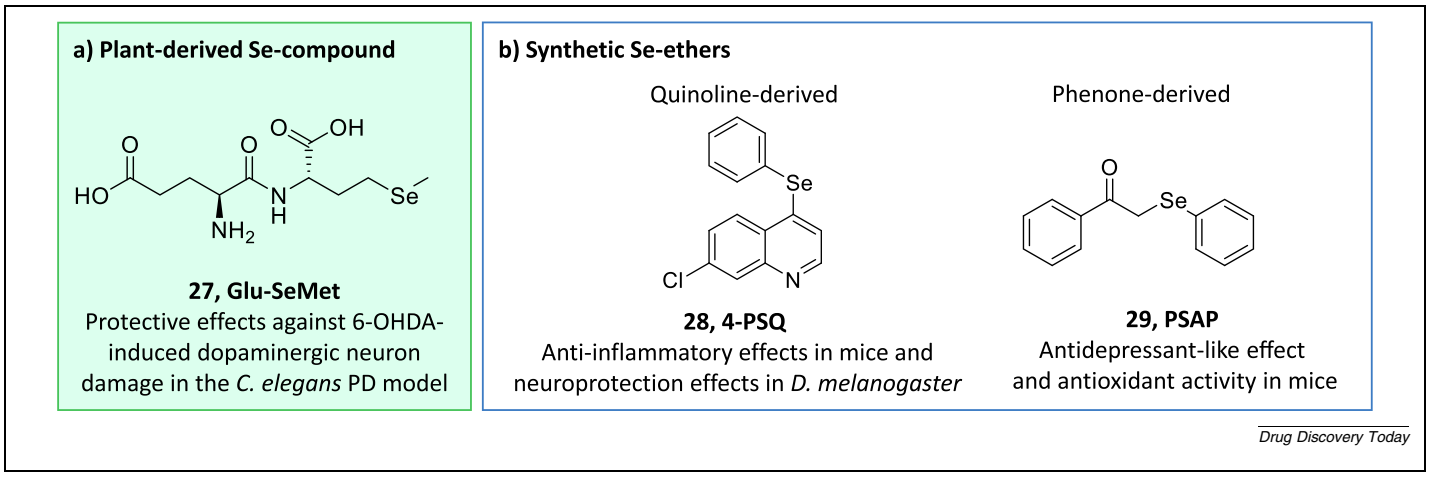

FIGURE 8

Se-compounds active in an animal model of PD: **(a)** nematode model (green background): **(b)** rodent model (white background).

(ROT) in *Drosophila melanogaster*.[p104] The results indicated that compound 28 exhibited protective effects against learning and memory impairment as well as anxiety in the mouse model. In the fruit flies (*D. melanogaster*), compound 28 demonstrated multiple positive effects, including the restoration of DA levels, improvement in ROT-induced mortality and locomotor deficits, reduction in oxidative damage, enhancement of antioxidant defences and an anticholinesterase action, additionally correlating with selenium levels in fly heads. Notably, compound 28 demonstrated a multi-target drug profile, as evidenced by its actions as an anticholinesterase and antioxidant, highlighting its pharmacological versatility in treating either AD or PD.

Another selenoether compound examined in PD in animals is the α-(phenylselanyl) acetophenone (PSAP; compound 29 in Figure 8b) described by Gerzson and colleagues.[p105] Compound 29 reduced immobility time and increased swimming time without altering climbing behaviour in reserpinized mice, which indicated an antidepressant-like effect.[p105] Moreover, compound 29 exhibited potent antioxidant activity in mouse brain homogenates, inhibiting lipid peroxidation induced by sodium nitroprusside (SNP). Furthermore, compound 29 displayed antioxidant properties by neutralising 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) free radicals, indicating its potential to prevent or reduce oxidative damage without showing any toxic effects in mice.

Potential selenium anti-PD-agents found in preclinical studies in vitro

Antioxidant/GPx mimetics. As in AD, antioxidants and GPx mimetics are pivotal in PD therapy owing to their role in combating oxidative stress, a prominent factor in disease progression. Their potential for mitigating oxidative damage offers avenues for neuroprotection and improved outcomes in individuals with PD.

Dominiak and colleagues investigated an organic selenium compound, selol (compound 30 in Figure 9a), for its effect on lipopolysaccharide (LPS)-mediated inflammation in the rat brain.[p106] When peripherally administrated, compound 30 demonstrated protective effects, significantly preventing LPS-evoked changes. Compound 30 effectively mitigated these effects by inhibiting oxidised glutathione accumulation and enhancing the activity and expression of key antioxidant enzymes, including GPx, glutathione reductase and TrxR1, suggesting its potential as a neuroprotective agent against neuroinflammation and oxidative stress in PD.

GPx mimetics can replicate the antioxidant actions of GPx. By mimicking GPx activity, these compounds have the potential to enhance cellular defence mechanisms, reducing the impact of oxidative damage on dopaminergic neurons. Among organoselenium compounds possessing GPx-like activity (Figure 9a), the simple cyclic seleninate ester compound 31 described by Back and collaborators exhibited a robust GPx-like activity.[p107] Further research involved the modification of compound 31 to increase its metabolic stability by introducing an aromatic moiety. However, the introduction of an aromatic ring decreased the water solubility of the compound, which was further resolved by introducing a novel hydroxymethyl derivative, compound 32, by McNeil and colleagues.[p108] Compound 32 showed moderate GPx-like activity.

The diselenides described by Pacuła and collaborators,[p109] and the ebselen derivatives described by Landgraf and colleagues,[p110] can be included in the GPx-mimetics group as well. Diselenide 33 (Figure 9b) showed the highest antioxidant capacity in the dithiothreitol (DTT) test, mimicking the GPx activity. By contrast, the ebselen derivatives (compounds 34 and 35 in Figure 9c) were tested with an oxidation test using NADPH. The compounds showed higher GPx activity than ebselen in the assay, which correlates with a higher reduction rate of cumene hydroperoxide. In 2019, Di Stefano and colleagues,[p111] tested a selenoether compound (SP6; compound 36 in Figure 9d) using SH-SY5Y human neuroblastoma cells differentiated towards a dopaminergic phenotype. SP6 demonstrated significant protective effects against the neurotoxic actions of 6-OHDA and hydrogen peroxide by reducing ROS levels and potentially increasing the antioxidant system in dopaminergic cells. The incorporation of selenium into SP6 suggested a mechanism involving the modulation of GPx activity.

MAO and SIRT inhibitors. Monoamine oxidase B (MAO-B) is gaining more attention as a target for PD treatment. Patients with PD have been shown to have increased MAO-B activity,

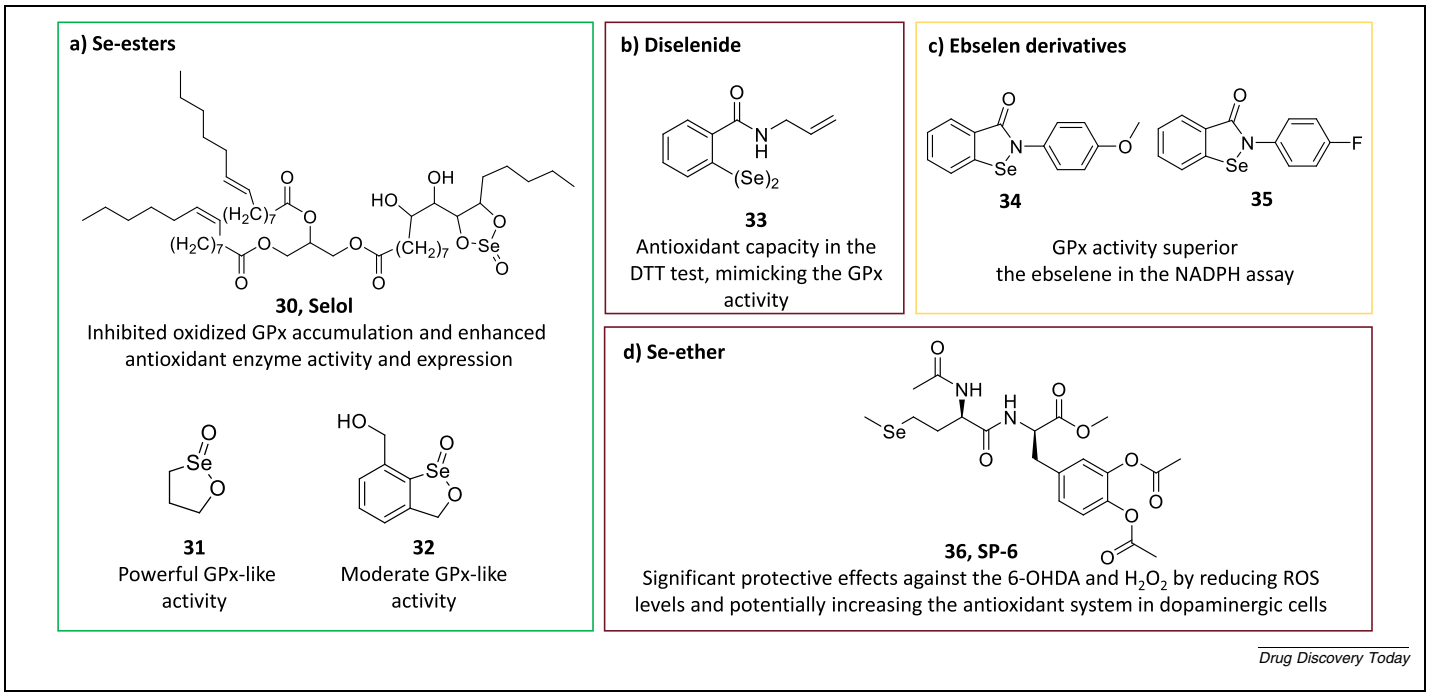

FIGURE 9

Se-compounds active in *in vitro* assays for PD: **(a)** Se-esters; **(b)** Diselenide; **(c)** Ebselen derivatives; **(d)** Se-ether.

which can lead to increased oxidative stress and neurodegeneration. Inhibitors of the MAO-B enzyme can help to preserve DA levels and potentially slow down the progression of PD.[p112] Some examples of organoselenium inhibitors of the MAO-B enzyme can be found in the literature. Sampaio and colleagues discovered a selective and reversible MAO-B inhibitor among the isoquinoline family: that is, 3-phenyl-4-(phenylseleno) isoquinoline (PSI; compound 37 in Figure 10a), possessing K_i = 7.07-μM.[p113] In the study, other derivatives of compound 37 were tested, but the non-substituted compound 37 demonstrated a higher inhibitory effect on MAO-B. This compound was also tested for its antidepressant-like action in the mouse-forced swimming test (FST), with a positive outcome.[p114] Bortolatto and collaborators found another MAO-B inhibitor among the diselenides, namely 2,2′-dithienyl diselenide (DTDS; compound 38 in Figure 10b).[p115] Whereas compound 37 acted selectively on the MAO-B enzyme, compound 38 showed activity towards both enzymes, with IC_{50} values of 44.56 μM and 33.28 μM for MAO-A and MAO-B, respectively.

Among the many targets that are potentially interesting for PD treatment, the sirtuin family, containing seven NAD^+-dependent deacetylases (SIRT1–7), has gained particular attention. This family coordinates cellular responses to various environmental stressors, with its deacetylase activity playing a crucial part in regulating protein function, DNA repair and gene expression, making sirtuins essential for cellular health and adaptation.[p116] SIRT1 and SIRT2, key members of the sirtuin family, are important regulators in the pathogenesis of PD. SIRT1, which has a crucial role in cellular stress response and metabolic regulation, not only influences neuroinflammation and mitochondrial function, but also shows potential for neuroprotective activity.[p117] At the same time, SIRT2, known for its role in maintaining protein homeostasis, has a crucial role in modulating α-synuclein aggregation, a hallmark of PD pathol-

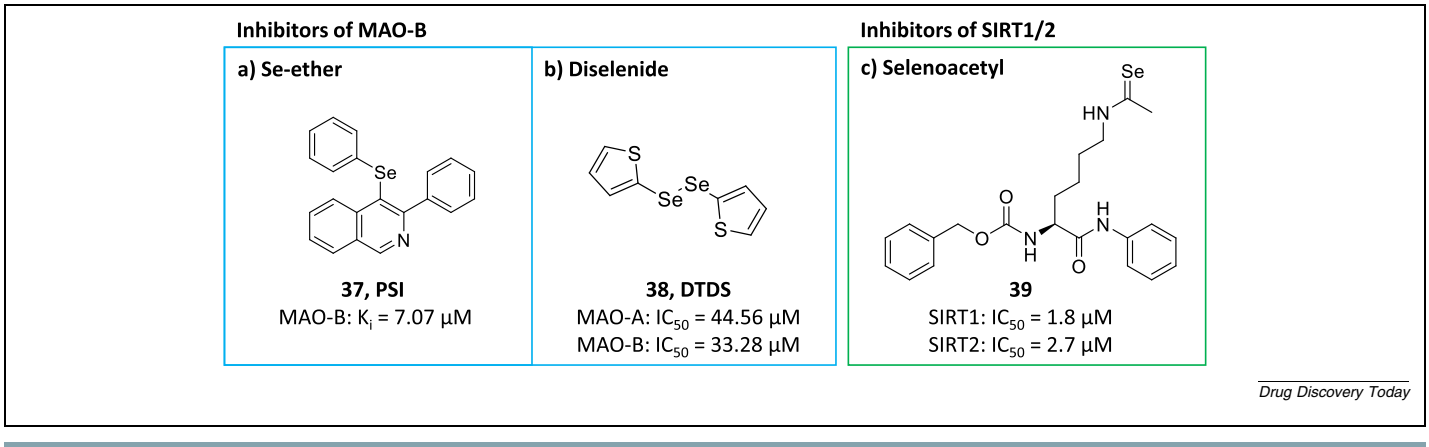

FIGURE 10

Se-compounds as inhibitors of MAO-B **(a, b)** and SIRT1/2 **(c)** enzymes.

ogy.[p118] The intricate involvement of these sirtuins in the mechanisms of PD could provide potential therapeutic avenues for targeted approaches to this complex neurodegenerative disease. In 2010, Huhtiniemi and collaborators developed a potent SIRT1/2 inhibitor (compound 39 in Figure 10c) that contains a selenium atom among the Nε-modified lysine group.[p119] In the study, Nε-selenoacetylated compounds demonstrated equivalent or enhanced inhibition of SIRT1 and SIRT2 when compared with Nε-thioacetylated compounds, and compound 39 emerged as the most potent SIRT2 inhibitor, with IC_{50} = 2.7 μM.

To sum up, recent lines of evidence indicate that several Se-compounds tested in various PD animal models might be promising for PD therapy. In addition to the widely investigated phenyl diselenides, ebselen, plant-derived compounds (compound 27) and synthetic selenoether compounds (including quinoline- and acetophenone-derived ones) have been confirmed to be beneficial against PD in animal models; however, this is mostly without considering the safety and toxicity of the Se-containing compounds.

Furthermore, the chemical space of Se-compounds has been explored and tested more expansively *in vitro*. Thus, cyclic Se-esters, Se-ethers, ebselen derivatives and aromatic or heterocyclic diselenides have been found to have non-PD-specific actions as GPx mimetics or MAO-B inhibitors, while more PD-specific SIRT1/2 inhibition has been described for a selenoacetyl representative. The results strongly justify an exploration of the Se-containing chemical space in search of innovative PD drugs, and they indicate the importance of expanding pharmacological screening using PD models, especially in light of the literature that provides a wide range of PD animal models used in preclinical studies.

Conclusions and perspective

Research into neurodegenerative diseases remains challenging: there is still no cure for AD or PD, although there are treatments available that can help to slow the progression of the diseases and manage the symptoms.[p12],[p13],[p120] It is well recorded in the literature that Se in its elemental form is neurotoxic, as reviewed by Vinceti and colleagues and Naderi and colleagues[p121],[p122]: for example, recently it was shown that sodium selenate exhibits neurotoxic effects in various mouse models.[p53],[p54] Indeed, it is increasingly accepted that high doses of inorganic or elemental Se exhibit toxic effects in the neurological system.[p52],[p123],[p124] However, small organic compounds containing Se often exhibit a more favourable safety profile when data are available.[p1],[p122],[p125]

Overall, toxicological studies regarding Se and its derivatives have produced mixed results, and Naderi and colleagues rightly state that very high and environmentally irrelevant doses of Se-containing compounds are often tested.[p122] Thus, the experimental design needs to be carefully considered in future investigations, because, as mentioned above, toxicology and safety studies have mostly been omitted to date. However, it is promising that when these data are available, a good safety profile can be observed in the cases of AD and PD.

In line with the mixed safety data available, as a precaution, the safe Se-uptake level has recently been lowered[p126]; however, further studies are likely to be required, because Se toxicity is context-dependent and needs deeper evaluation on a case by case basis.[p1],[p122],[p125],[p127] Thus, discretion should be used when considering the incorporation of Se in synthetic compounds, keeping in mind the potential pharmacological utility and safety. Medicinal chemists should proceed with caution every time selenium replaces an oxygen or sulfur atom in small organic compounds, and above all, they should perform safety and toxicity studies.

To summarize, as outlined above, researchers have developed numerous organoselenium compounds to improve the outcomes of patients with neurological deficits, and herein, we have summarised the most promising ones. In this context, the relatively richest library of potential Se-agents has been described for AD. The most advanced Se-compounds in preclinical studies have been confirmed to be active *in vivo* in AD mice models (such as the icv STZ, 3xTg-AD and (D-gal)-induced models).[p37],[p38],[p39],[p40],[p128] In addition to the most investigated Se-compounds (that is, the organic ebselen and the inorganic Na_2SeO_4), potent action has been confirmed for tetrahydrofuran selenol and selenoether compounds (Figure 3).[p41],[p42],[p43],[p44],[p128] It is worth underlining that *in vivo* procognitive-like actions have been confirmed in rodents for aromatic Se-ether derivatives such as compound 5 in the step-down inhibitory avoidance task and NOR tests,[p43] while the diselenide compound 8 was an active Aβ suppressor in a *C. elegans* AD model.[p55] The preliminary results of *in vitro* studies have demonstrated promising actions of some Se-compounds on protein targets closely associated with AD, in particular the inhibition of Aβ aggregation or AChE and BuChE.[p68],[p69],[p70],[p71],[p72],[p73]

Particularly noteworthy is the evidence of single Se-compounds acting on miscellaneous AD protein targets, that is, the enzymes HDAC, BACE1, OGA and 5-HT_6R, which are increasingly being emphasised in the search for new, more effective AD therapies.[p77],[p80],[p83] Thus, several Se-compounds could offer starting points for further pharmacomodulation and extended pharmacological screening, including the ebselen derivatives endocyclic N-hydroxybenzamide (against HDAC; compound 22),[p77] and aminothiadiazinyl (against BACE1; compound 26),[p89] as well as tetrahydropyrano-selenazole (against OGA; compound 23)[p82],[p83] and arylselenoether 1,3,5-triazine compounds (against 5-HT_6R; compounds 5 and 25)[p43],[p84],[p85],[p86],[p87],[p88] (Figure 6).

In the case of PD, there is a lower number and variety of potential new Se-agents than for AD. However, they seem to be at a somewhat more advanced stage than those for AD, because they have been investigated in a broader range of PD animal models, including primates.[p99] In addition to the chemical families mentioned in AD studies, acetophenone-derived phenylethers were found to be active in PD mice models: both 3-phenyl-4-(phenylselanyl)isoquinoline (compound 37) and 1,2-di(thiophen-2-yl)diselane (compound 38) turned out to be 'hit' selenoinhibitors of MAO-B, a principal but non-specific PD target.[p112],[p113],[p114],[p115] Furthermore, a selenoamide (compound 39) was found to be the only 'hit' inhibitor for PD-specific SIRT1/2 protein targets.[p119]

However, the Se-containing compounds with activity against specific neurodegenerative diseases are a minority compared with the number of Se-containing compounds that show 'uni-

versal' neuroprotective effects in various experimental models of neurodegeneration, such as GPx mimetics and antioxidants.

To sum up, research on the use of Se-containing compounds in neurodegenerative diseases is still of an initial nature, even in the case of the more extensively explored AD. The research so far has covered only a small number of possible therapeutic targets in AD, and the remaining ones, such as mTOR, cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase 3β (GSK3β), Rho-associated protein kinase 1 (ROCK1), ROCK2, microtubule affinity regulating kinase 4 (MARK4), 5-HT_7 serotonin receptors, and ferroptosis and necroptosis proteins, remain unexplored in terms of the possible action of Se-containing compounds. The potential protein targets and molecular mechanisms involved in the aetiology of PD remain even less well explored in terms of Se-containing agents.[(p29),(p30),(p35)]

Currently, the relatively large range of preclinical *in vitro* and *in vivo* tests described for a few chemical representatives of the Se-compounds is insufficient to find a regular structure–activity relationship that would clearly indicate the most favourable directions for further research. Despite the fact that a toxicity evaluation is often absent in most studies, we can still be optimistic as in the few cases when data are available a promising safety profile, along with neuroprotective effects accompanied by the desired pharmacological activity, and often also a satisfactory pharmacokinetic profile of the tested Se-compounds could be observed.

The encouraging preclinical data of several compounds nurture the hope that new therapies will be available in the future to effectively treat AD or PD, improving the lives of people with the disease. However, further research is needed to develop Se-containing agents in a clinical setting, with special consideration of their toxicity and safety profile. Numerous shreds of evidence from recent biological studies underline the potential of ebselen and ebselen-derived compounds, along with diselenides and Se-amino acids. In the years to come, we can expect a rapidly expanding knowledge and interest in the field of selenoethers, which give a safe and universal linker for non-selenium moieties that is desirable for appropriate pharmacological effects, as well as new (non-ebselen) Se-endocyclic compounds that are bioisosteric to current non-selenium AD or PD agents.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

The authors used standard web tools to conduct the literature research. More specifically, PubMed, Google Scholar, ChEMBL database and SciFinder were fed with the following keywords or a combination of these: Alzheimer's, Parkinson's, selenium, selenium-containing compounds and treatment. The results were checked manually to determine whether they fitted into the scope of the present review (selenium-containing small organic compounds in AD or PD).

CRediT authorship contribution statement

Patryk Pyka: Writing – original draft, Visualization, Funding acquisition. **Sabrina Garbo:** Writing – original draft, Visualization. **Rossella Fioravanti:** Resources, Formal analysis, Data curation. **Claus Jacob:** Resources, Formal analysis, Data curation. **Marius Hittinger:** Resources, Formal analysis, Data curation. **Jadwiga Handzlik:** Writing – review & editing, Funding acquisition, Conceptualization. **Clemens Zwergel:** Writing – review & editing, Funding acquisition, Conceptualization. **Cecilia Battistelli:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Data availability

No data was used for the research described in the article.

Acknowledgements

This work was supported by Sapienza SEED PNR 2021, Sapienza Progetti di Ricerca Medi to C.B. (RM12218166AEFC72) and by the National Science Centre, Poland, grant no. 2018/31/B/NZ7/02160 to J.H. C.Z. is thankful for the generous funding from FSE REACT-EU within the program PON 'Research and Innovation' 2014–2020, Action IV.6 'Contratti di ricerca su tematiche Green', as well as the funding from the Italian Ministry of Health Ricerca Finalizzata GR-2021-12374415, from the KOHR GmbH and from the Sapienza Ateneo Project funding scheme. Kohr Aerospace was not involved in the study design, collection, analysis, interpretation of data, the writing of this article or the decision to submit it for publication. A significant part of this paper was prepared by P.P. during his ERASMUS + program internship at Sapienza University, partly supported by Jagiellonian University statutory research project N42/DBS/000331. C.Z. and C.B. are grateful for the valuable critical discussions with Antonello Mai, Marco Tripodi and Sergio Valente. Finally, all of the authors would like to thank Manfred Fugger and Ken Rory for their helpful technical assistance. The article is dedicated to Thomas Zwergel, who passed away during its preparation. Though he may be gone for almost a year, his impact continues to be felt. All authors are forever grateful for the time they had together.

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