









REVIEW PAPER

# The role of glutathione peroxidase enzymes in Alzheimer's disease

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## ABSTRACT

**Introduction and aim.** Alzheimer's disease (AD) is a neurodegenerative disorder that affects mainly the elderly. Among the variety of factors contributing to the pathogenesis of AD, oxidative stress has emerged as a key factor in the initiation and progression of the disease. Glutathione peroxidases (GPxs) are enzymes that are known to play a critical role in maintaining cellular redox balance. To this end, the present narrative review aims to explore the role of GPx enzymes in AD and discuss their contribution to oxidative stress pathways and AD pathogenesis.

**Literature search.** PubMed, Scopus, and Google Scholar were searched for relevant literature. No specific inclusion and exclusion criteria were used due to the narrative nature of the review.

**Analysis of the literature.** Available records suggest a strong association between oxidative stress and the pathological features of AD, including amyloid- $\beta$  aggregation, tau hyperphosphorylation, and neuroinflammation. The enzyme isoforms GPx1, GPx3, and GPx4 have been implicated in AD pathogenesis.

**Conclusions.** GPx enzymes play an important protective role in AD. Despite promising preclinical evidence, more translational research is required to clarify the therapeutic and biomarker potential of GPxs in AD.

**Keywords.** Alzheimer's disease, glutathione peroxidase, neurodegeneration, oxidative stress

## Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide, which can significantly affect a patient's cognitive abilities.<sup>1</sup> Despite the numerous studies undertaken, the underlying mechanisms that contribute to the pathogenesis and progression of AD have not been fully understood and, moreover, no definitive therapeutic strategy has yet been discovered.<sup>2,3</sup> The disease is characterized as a neuroinflammatory disease and oxidative stress is known to play a critical role in the initiation and progression of different inflammatory diseases.<sup>4</sup> Indeed, studies have shown that oxidative stress is a significant factor in the pathophysiology of AD.<sup>5,6</sup>

Glutathione peroxidases (GPx) are enzymes that are known to play a key role in protecting the organism from oxidative stress by reducing ROS.<sup>7</sup> The activation of these enzymes is known to be a protection factor against many diseases induced by oxidation and cell senescence.<sup>8</sup> GPx catalyze the reduction of hydrogen peroxide ( $H_2O_2$ ) and organic hydroperoxides in water ( $H_2O$ ) and corresponding alcohols, using reduced glutathione (GSH) as an electron donor.<sup>7</sup>

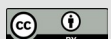
## Aim

This narrative review was undertaken to explore the role of GPx enzymes in the pathogenesis and progression of

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AD, their participation in the oxidative stress mechanisms that contribute to neurodegeneration, and their potential as therapeutic targets for the prevention or treatment of AD.

### Literature search

The databases PubMed, Scopus, and Google Scholar were searched to retrieve available literature on the role of GPxs in Alzheimer's disease dating from inception until December 2024. Keywords 'Glutathione peroxidase\*', 'GPx', 'Alzheimer', 'Oxidative stress', and "Dementia" were used in combination with Boolean operators. Due to the narrative nature of the review, there were no specific inclusion and exclusion criteria. Overall, original research, reviews, and meta-analyses from peer-reviewed journals with relevant information, including, written in English, were included in the synthesis of the present narrative review. No formal risk of bias assessment or quantitative synthesis was performed due to the narrative design of the review.

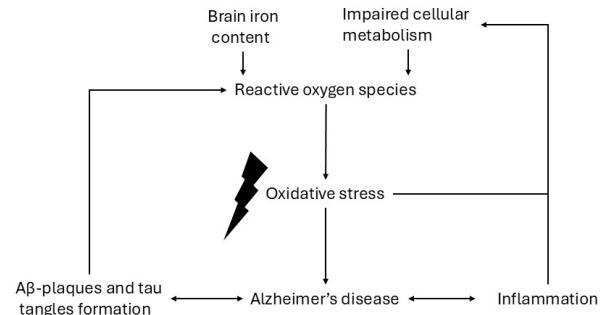
### Analysis of the literature

#### *The role of oxidative stress in AD*

Oxidative stress is increasingly recognized as a central factor in the pathophysiology of AD. Specifically, studies suggest a bidirectional relationship between oxidative stress and AD; oxidative stress can promote the formation of A $\beta$ -plaques by upregulating  $\beta$ - and  $\gamma$ -secretase activity, and also leads to tau tangle formation by activating inflammation-associated kinases, whereas in established Alzheimer's disease, amyloid and tau pathology themselves drive reactive oxygen species production, thus increasing oxidative stress.<sup>9</sup> Specifically, ROS exacerbate A $\beta$  aggregation and tau phosphorylation, perpetuating a vicious cycle that accelerates neurodegeneration.<sup>10,11</sup> It is also worth mentioning that oxidative stress is closely linked to impaired autophagy and hence can worsen neuronal vulnerability in AD.<sup>12</sup> Simultaneously, in AD, age and accumulation of A $\beta$ -plaques and tau tangles induce excessive ROS production, including superoxide, hydrogen peroxide and hydroxyl radicals.<sup>13</sup> This leads to harm in neurons, glial cells, and the integrity of the blood-brain barrier (BBB). The brain's susceptibility to oxidative damage arises from its high metabolic demands. Furthermore, the high iron content catalyzes ROS generation, coupled with relatively weak endogenous antioxidant defenses.<sup>14</sup> This results in mitochondrial dysfunction, activation of pro-inflammatory pathways, and cellular apoptosis. At the same time, activated microglia have been found to produce reactive oxygen species in Alzheimer's disease, increasing oxidative stress.<sup>15</sup> Overall, this leads to a vicious cycle that accelerates neurodegeneration.

Advanced glycation end products (AGEs), which accumulate in A $\beta$  plaques, also promote oxidative dam-

age, directly and indirectly contributing to neuronal death.<sup>16</sup> Figure 1 summarizes the pathways through which oxidative stress promotes the pathogenesis and progression of AD.



**Fig. 1.** Oxidative stress and the pathophysiology of Alzheimer's disease

#### *GPx and neurodegeneration*

GPx1 (cytosolic GPx) is the most widely expressed isoform of GPx and is predominantly localized in the cytosol and mitochondria of various tissues, where it plays a critical role in the detoxification of hydrogen peroxide.<sup>17</sup> Extensive studies in experimental models have shown that the absence of GPx1 significantly increases the vulnerability of cells to oxidative stress.<sup>18</sup> GPx1 knockout models show an increased susceptibility to cellular damage induced by hydrogen peroxide and exacerbate neurotoxic effects, particularly under conditions of elevated oxidative burden, as seen in neurodegenerative diseases such as Alzheimer's.<sup>19</sup> Furthermore, GPx1 is involved in modulating redox-sensitive signaling pathways, including those involving NF- $\kappa$ B, ERK1/2, and PKC $\beta$ II, which are critical in the regulation of neuronal excitability, inflammatory responses and cell survival.<sup>20</sup> It is still highly debated whether or not GPx1 plays a direct or secondary role in the development of AD. However, a study carried out in Brazil by Cardoso et al. suggested that the Pro198Leu genetic variation in the GPx1 gene was equally common in AD patients and healthy controls, suggesting that it does not increase the risk of AD, although AD patients with the Pro/Pro genotype had lower selenium levels compared to controls and, in turn, decreased antioxidant potential, suggesting that it affects the function of antioxidant enzymes in AD.<sup>21</sup> These findings highlight the need for further research on this genetic polymorphism in AD.

GPx2 (gastrointestinal GPx) is expressed primarily in the gastrointestinal epithelium, where it plays a crucial role in protecting epithelial cells from oxidative stress induced by dietary factors and gut microorganisms.<sup>22</sup> GPx2 works by catalyzing the reduction of hydrogen peroxide and other ROS to water, thus maintaining redox balance in the intestine and reducing inflammation and tissue damage.<sup>23</sup> Although its direct

involvement in Alzheimer's disease has not been established, it can hypothesize that since its function can lead to systemic oxidative stress, it may indirectly influence neuroinflammatory processes.<sup>24</sup> It is worth mentioning that the gut microbiome has been found to affect the presentation of Alzheimer's disease, further verifying the role of GPx2 in the pathogenesis.<sup>25,26</sup>

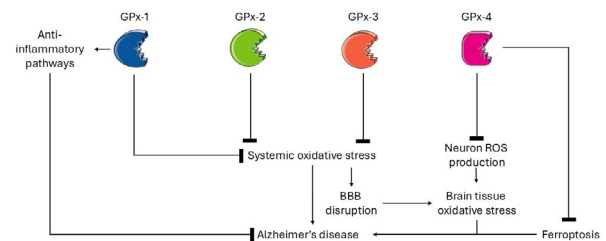
GPx3 (plasma GPx) is a secreted enzyme found primarily in extracellular fluids such as plasma, where it plays a crucial role in the defense of systemic antioxidant defense.<sup>27</sup> Studies have found a positive association between downregulation of GPx3 and the pathogenesis of Alzheimer's disease.<sup>28,29</sup> Specifically, peripheral oxidative stress and systemic inflammation can contribute to disruption of the blood-brain barrier (BBB), allowing peripheral oxidative damage to exacerbate neuronal damage, as seen in Alzheimer's disease.<sup>30</sup> Therefore, GPx3's antioxidant function in mitigating peripheral oxidative stress may be critical in protecting the CNS and maintaining brain health.

Among the GPx isoforms, GPx4 (phospholipid hydroperoxide GPx) is unique due to its ability to directly reduce lipid hydroperoxides in cellular membranes, lipoproteins, and organelles, which is essential for maintaining cellular integrity, particularly in tissues with high oxidative activity, such as the brain.<sup>31</sup> Moreover, the neurons of the hypothalamus, hippocampus, and the cerebellum have been found to contain GPx4 which is synthesized endogenously in the brain.<sup>32</sup> GPx4 was found to have a critical role in counteracting cellular deterioration and protecting against brain injury. Another important role for GPx4 is its participation in the regulation of ATP production during oxidative stress. As one may gather, this is of great importance due to the potential damage that can occur to mitochondria caused by oxidative stress. AD is an example of a condition related to mitochondrial problems. Furthermore, studies have proven that a deficiency in selenium could expose cells to ferroptosis and therefore make them more vulnerable all due to reduced GPx4 activity. Therefore, it is of great importance to highlight that selenium levels of selenium must be maintained to ensure GPx4 protective effects on neurons.<sup>33</sup>

The role is also critical in preventing ferroptosis, an iron-dependent form of programmed cell death driven by lipid peroxidation, which is implicated in neurodegenerative diseases.<sup>34</sup> Indeed, a study by Khan et al. suggested that ferroptosis plays a critical role in the progression of Alzheimer's disease.<sup>35</sup> Conditional knockout models of GPx4 exhibit severe neuronal loss, particularly in the hippocampus, a critical brain region for memory and learning, and is accompanied by increased lipid peroxidation and astrogliosis, both of which are features of Alzheimer's pathology.<sup>36,37</sup> The dysregulation of GPx4

and the resulting increase in lipid peroxidation, ferroptosis, and neuroinflammation are key factors in the progression of AD.<sup>36</sup>

Figure 2 summarizes the role of GPx enzymes in preventing AD.



**Fig. 2.** GPx and the prevention of Alzheimer's disease (BBB – blood-brain barrier, ROS – reactive oxygen species)

### Clinical uses of GPx in AD

Given the central role of oxidative stress in AD and the potential of GPx enzymes to mitigate this damage, these enzymes represent highly attractive therapeutic targets for the treatment of AD. Strategies aimed at enhancing GPx activity could help restore redox balance and prevent neuronal damage. Potential approaches include the development of small molecule activators of GPx enzymes, gene therapy to increase GPx expression, or the use of dietary antioxidants to support the GPx system. Small-molecule activators, such as ebselen, mimic the activity of GPx enzymes and have demonstrated their efficacy in reducing oxidative stress and inflammation in preclinical models.<sup>38</sup> Gleichzeitig, advances in gene-editing technologies, particularly CRISPR-Cas9, offer the potential to up-regulate GPx4 expression in affected brain regions, allowing targeted neuroprotection.<sup>39</sup> Supplementation with diet selenium also plays a significant role, since selenium serves as an essential cofactor for GPx activity. Supplementing selenium has shown potential to improve GPx function, demonstrating neuroprotective effects in clinical trials and mitigating oxidative damage.<sup>40-42</sup> In addition, combination therapies that integrate GPx-targeted interventions with other AD treatments, such as A $\beta$  aggregation inhibitors or tau modulating drugs, may provide synergistic benefits by addressing multiple aspects of the disease pathology, while the combined approach could offer enhanced neuroprotection, slowing neuronal damage, and preserving brain function.<sup>11,43,44</sup> It is also worth mentioning that certain natural plant products that upregulate GPx4, including senegenin, berberin and tannic acid have already been shown to exhibit neuroprotective effects in vitro and on mice, indicating them as possible ways of enhancing GPx4 activity for prevention of AD.<sup>45-47</sup> Nevertheless, no clinical trials were retrieved in the literature search that shows effects of GPx upregulation through pharmacological intervention in AD patients. Overall, there is currently no robust clinical evi-

dence that direct GPx-targeting therapies can modify AD outcomes in humans though preclinical data suggest GPx modulation may affect AD-relevant oxidative pathways.

GPx and ROS levels could also serve as an early indicator, with their use as biomarkers, of oxidative imbalance, having a vital role in the early detection and prevention of idiopathic and genetical AD. That is, the flavoprotein apoptosis-inducing factor, mitochondrial-associated 2 (AIFM2), also known as ferroptosis suppressor protein 1 (FSP1), has gained attention for its role in mitigating ferroptosis through suppression of lipid peroxidation suppression.<sup>48</sup> AIFM2 complements the function of GPx enzymes, particularly GPx4, by maintaining redox balance through reduction of ubiquinone to ubiquinol, a key antioxidant. Meanwhile, GPx3, which shares functional similarities with GPx1, but is unique in its sensitivity to selenium levels, offers a promising avenue as a biomarker of selenium status.<sup>49</sup> This characteristic makes it a valuable biological marker for assessing selenium content in the body, which is crucial for optimal GPx enzyme function. Given the correlation between selenium deficiency and impaired antioxidant defenses, monitoring GPx3 activity could provide information on systemic redox imbalances that precede AD onset.<sup>50</sup> However, it is worth mentioning that plasma GPx3 primarily reveals systemic oxidative status and is a practical state marker for epidemiologic or intervention studies, but directly reflect neuronal GPx activity, due to the difference in GPx levels between the central nervous system and serum, induced by the blood–brain barrier. On the contrary, GPx levels measured in cerebrospinal fluid, mainly those of GPx4, better reflect neuronal oxidative status and can be better used as diagnostic and theragnostic biomarkers, but with the acquisition of CSF samples, limiting the practicality of routine diagnostic.

#### *Future perspectives*

The role of GPx enzymes in AD is a promising area of research, with compelling evidence suggesting that these enzymes play a vital role in protecting against oxidative stress and neuronal damage. By reducing ROS, GPx enzymes help maintain cell redox balance and prevent the harmful effects of oxidative damage, which is central to the pathophysiology of AD. Although much remains to be understood about the precise mechanisms by which GPx enzymes contribute to AD progression, their potential as therapeutic targets deserves further investigation. Major gaps include varying clinical findings and the lack of interventional studies and clinical trials directly investing GPx in AD. The majority of findings originate from preclinical cell and animal models, which demonstrate credibility, but one cannot assume with certainty that translation directly to humans is plausible. Future research focusing on modulation of GPx activity could

provide new avenues for the prevention and treatment of Alzheimer's disease, offering hope to patients and families affected by this devastating disease.

The functional complexity of the GPx family and the varying roles of different isoforms in different tissues and cell types complicate the development of targeted therapies. There is a need for a multimodal approach combining redox regulation, neuroinflammation control, and BBB permeability strategies.<sup>51,52</sup> More research is needed to determine the most effective strategies for modulating GPx activity and optimizing the therapeutic potential of these enzymes.

#### **Conclusion**

Overall, in spite of the promising data, further studies and trials are needed to validate the reliability and consistency of GPx levels as biomarkers and therapeutic targets and identifying confounding factors.

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##### *Author contributions*

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##### *Conflicts of interest*

None to declare.

##### *Data availability*

Not applicable.

##### *Ethics approval*

Not applicable.

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