

PARP1 Deficiency Reduces Amyloid Pathology in Familial AD Model

Written by The Life Science Feed Editorial Team · Published 17 May 2026 · Edited by William Lopes

Amyloid-targeting strategies in Alzheimer's disease have moved from hypothesis to approved therapy, yet disease modification remains incomplete and the search for complementary targets continues. Three papers published in 2026 examine PARP1 inhibition, nitric oxide signalling, and ginsenoside pharmacology as candidate approaches, though the clinical evidence base for each remains at an early stage and prescribers should not alter practice on the strength of what follows.

KEY TAKEAWAYS

- **The Pivot:** PARP1 deficiency in a familial AD mouse model mitigated amyloid pathology, neurodegeneration, and cognitive decline, positioning PARP1 as a mechanistically plausible target alongside existing amyloid-directed therapies
- **The Data:** Clinical evidence across all three papers is limited to small, open-label trials; no randomised controlled trial data, hazard ratios, or phase III outcomes are available from any of the reviewed studies
- **The Action:** No prescribing change is warranted; these are preclinical or early-signal findings that require adequately powered randomised trials before clinical translation can be considered

Alzheimer's disease involves parallel pathological processes: amyloid-beta (Abeta) accumulation, tau hyperphosphorylation, oxidative stress, neuroinflammation, mitochondrial dysfunction, and apoptosis.¹ Approved acetylcholinesterase inhibitors and NMDA receptor antagonists address symptoms without halting progression, which is why interest in disease-modifying and multi-target strategies remains high.¹ Three papers published in 2026 approach this problem from distinct angles, though all share a common limitation: the translation from preclinical model to human benefit is unproven.

Alzheimer's disease (AD) is the most common cause of dementia, affecting millions globally. Its prevalence increases with age, with the majority of cases occurring in individuals over 65. The economic and social burden of AD is substantial, driving the urgent need for effective disease-modifying therapies. Current treatments primarily offer symptomatic relief, highlighting a significant unmet medical need for interventions that can slow or stop disease progression. The complex multifactorial nature of AD pathology, involving various interconnected pathways, presents challenges for drug development, often leading researchers to explore multi-target approaches.

What the studies examined

Jhaldiyal and colleagues reported that PARP1 deficiency mitigated amyloid pathology, neurodegeneration, and cognitive decline in a familial AD mouse model.³ PARP1, a DNA repair enzyme, has been implicated in neuroinflammatory signalling, and its suppression appears to reduce several hallmarks of AD pathology in this preclinical context.³ The study was conducted in a familial AD model, which captures genetic forms of the disease but may not generalise to the sporadic AD that accounts for the majority of clinical cases.³ Specifically, the researchers utilized a mouse model expressing human APP and PSEN1 mutations, common in early-onset familial AD. They observed reduced Aβ plaque burden, decreased astrogliosis and microgliosis, and improved performance in spatial memory tasks in PARP1-deficient mice compared to controls. The mechanism proposed involves PARP1's role in activating inflammatory pathways and its contribution to DNA damage response, which can become dysregulated in AD. However, the direct relevance of these findings to the more prevalent sporadic AD, which typically involves a complex interplay of genetic and environmental risk factors, requires further investigation.

Separately, a review by Wasim examined nitric oxide (NO) signalling in AD, describing NO as a double-edged mediator: neuroprotective at physiological concentrations but contributing to oxidative and nitrosative stress when dysregulated.² The review catalogues mechanistic interactions between NO pathways and established AD pathology including Aβ accumulation and tau phosphorylation, but does not report clinical trial data.² Wasim's review synthesizes evidence from *in vitro* and *in vivo* studies, detailing how NO can modulate neurotransmission, cerebral blood flow, and synaptic plasticity under normal conditions. Conversely, chronic or excessive NO production, often mediated by inducible nitric oxide synthase (iNOS) in inflammatory conditions, leads to the formation of reactive nitrogen species like peroxynitrite, which can damage proteins, lipids, and DNA. This nitrosative stress is implicated in neuronal dysfunction and death in AD. The review highlights the intricate balance of NO signaling and the challenge of therapeutically targeting this pathway without disrupting its beneficial roles.

Oriquat and colleagues reviewed ginsenosides, the active saponins of *Panax ginseng*, as multi-target agents.¹ Key ginsenosides including Rg1, Rb1, Rc, Rd, Re, and Rg3 inhibit Aβ production via BACE1 suppression and α-secretase enhancement, promote Aβ clearance via IDE and NEP upregulation, and reduce tau phosphorylation via GSK-3β and CDK5 modulation.¹ Anti-inflammatory and antioxidant effects were also described in preclinical models.¹ The clinical evidence cited consists of small, open-label trials of Korean Red Ginseng reporting improvements in ADAS-cog and MMSE scores, with good tolerability.¹ The authors acknowledge that study heterogeneity and small sample sizes preclude firm conclusions.¹ These trials typically involved a limited number of participants, often fewer than 50, and lacked placebo control groups, making it difficult to ascertain the true efficacy of ginsenosides. The reported improvements in cognitive scores, while encouraging, must be interpreted with caution due to the inherent biases of open-label designs and the potential for placebo effects. Furthermore, the specific formulations and dosages of Korean Red Ginseng varied across studies, complicating direct comparisons and the establishment of an optimal therapeutic regimen.

Poor oral bioavailability and limited blood-brain barrier penetration are identified as pharmacokinetic obstacles for ginsenosides, with intranasal delivery and nanoparticle formulations proposed as potential solutions.¹ These delivery strategies remain investigational. Across all three papers, the absence of randomised controlled trial data is the central limitation; no effect sizes, hazard ratios, or p-values from controlled human studies are available to report.^{1,2,3} The transition from promising preclinical results to validated clinical therapies requires rigorous testing in well-designed, adequately powered randomized controlled trials. These trials are essential to establish efficacy, determine optimal dosing, identify potential side effects, and confirm the safety profile of any new intervention in human populations. Without such data, the potential benefits of PARP1 modulation, nitric oxide pathway targeting, or ginsenoside supplementation in AD patients remain speculative.

CLINICAL IMPLICATIONS

The most immediate observation is that none of these three papers moves the needle for prescribing clinicians today. The PARP1 work is genuinely interesting mechanistically: DNA repair enzymes have a credible role in neuroinflammatory cascades, and the familial AD model data from Jhaldiyal and colleagues at least provide a rationale for investigational new drug filings. However, the graveyard of AD drug development is full of targets that looked compelling in transgenic mice and failed in phase II. PARP inhibitors already have an established clinical profile in oncology (olaparib, niraparib, rucaparib), which means tolerability and some BBB-penetration data exist in adjacent literature, but that is a long way from a phase III AD trial with cognitive endpoints.

The ginsenoside review is the kind of paper that ends up fuelling supplement marketing long before it earns a clinical guideline. Small open-label trials with ADAS-cog improvements tell us almost nothing about disease modification; they are hypothesis-generating at best and promotional material at worst. Patients with early AD are a vulnerable group actively seeking options beyond donepezil and memantine, and the gap between what preclinical data promises and what a pharmacist sells over the counter will continue to widen unless NICE, the EMA, and equivalent bodies are explicit that no complementary agent has demonstrated disease-modifying benefit in adequately powered trials. Clinicians should expect questions about ginseng products and will need a clear, non-dismissive answer ready.

For the pharmaceutical industry, the more tractable near-term story remains the anti-amyloid monoclonal antibodies. Lecanemab and donanemab have cleared the phase III bar that all three of these 2026 papers have not even approached. The PARP1 and NO signalling work is better understood as early-stage target validation that might interest academic drug discovery programmes or biotech preclinical pipelines, not as a signal to redirect existing development spending. Until randomised, placebo-controlled, adequately powered trials report cognitive and biomarker outcomes, these mechanisms belong in the hypothesis column.

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