International Journal of Health Sciences
Available online at www.sciencescholar.us
E-ISSN: 2550-696X
Int. J. of Health Sci.
DOI: 10.53730

How to Cite:
Alenezi, A. A., Sattar, M. A. A. A., & Ibrahim, I. M. (2025). Effect of allopurinol and other xanthine oxidase inhibitors on oxidative stress in Alzheimer's disease: A systematic review and meta-analysis (2015–2025). *International Journal of Health Sciences*, *9*(S1), 355–377.
https://doi.org/10.53730/ijhs.v9nS1.12655

Effect of allopurinol and other xanthine oxidase inhibitors on oxidative stress in Alzheimer's disease: A systematic review and meta-analysis (2015–2025)

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***Abstract*---Background:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and neuropathology. Accumulating evidence implicates oxidative stress in AD pathogenesis. Xanthine oxidase (XO) is a major enzymatic source of reactive oxygen species in purine metabolism. XO inhibitors (e.g., allopurinol, febuxostat, topiroxostat) reduce XO-derived radicals and may thus ameliorate oxidative damage in the brain. We aimed to systematically review preclinical and clinical studies from 2015–2025 examining whether XO inhibition reduces oxidative stress markers, improves cognitive outcomes, or lowers dementia risk in AD. **Methods:** We searched PubMed, Scopus, Web of Science, and Google

Submitted: 27 April 2025, Revised: 18 June 2025, Accepted: 09 July 2025

Scholar (2015–2025) using keywords combining “Alzheimer OR dementia” with “xanthine oxidase OR allopurinol OR febuxostat OR topiroxostat” and “oxidative stress OR cognitive OR dementia incidence”. Inclusion criteria were English-language studies on AD or related dementia assessing XO inhibitor effects on oxidative stress biomarkers, cognitive performance, or dementia incidence. We included both preclinical (animal *in vitro* experiments and in vivo models) and clinical (observational or interventional) studies. Screening, data extraction, and bias assessments (SYRCLE for animal studies, Newcastle–Ottawa Scale for observational studies, Cochrane tools for trials) were performed by two independent reviewers (blinded as XX and YY). A PRISMA flow diagram was constructed to map study selection. For outcomes reported in ≥3 studies, we conducted meta-analyses using random-effects models to compute pooled effect sizes (risk ratios for incidence, standardized mean differences for continuous outcomes). Heterogeneity was quantified with I^2 and Cochran’s Q ($p < 0.1$ indicating significant heterogeneity). Publication bias was evaluated via funnel plots when ≥10 studies were available. **Results:** Out of 312 records identified, 27 studies met inclusion criteria (15 preclinical and 12 clinical). Preclinical studies consistently showed that XO inhibition reduces oxidative stress and protects against cognitive or neuropathological changes. For example, allopurinol treatment in a streptozotocin-induced AD mouse model improved memory (Morris water maze and passive avoidance performance) and attenuated neuronal oxidative damage and inflammation. Similarly, in chronic stress paradigms (which accelerate AD-like pathology), febuxostat prevented stress-induced cerebrovascular dysfunction, normalized brain free radical levels, and preserved working memory in mice. Meta-analysis of 5 animal studies showed a large overall effect of XO inhibitors in lowering markers of oxidative injury (standardized mean difference = –2.3, 95% CI –2.9 to –1.7) with minimal heterogeneity (I^2 = 18%). Clinical studies yielded mixed but generally promising findings. No completed randomized trials in AD were found; however, 8 observational studies (total N > 1.5 million) examined dementia outcomes in patients receiving XO inhibitors. Pooled analysis of four case–control studies indicated that allopurinol use was less frequent among dementia cases than controls (odds ratio [OR] = 0.91, 95% CI 0.87–0.95), consistent with a modest protective association. A 2023 population-based study likewise reported that allopurinol use was associated with a 23% lower risk of developing AD and related neurodegenerative diseases over 5 years. In contrast, an updated meta-analysis including longitudinal cohort data found long-term allopurinol exposure in gout patients slightly increased dementia risk (RR ~2.3), although this finding had potential confounding and zero heterogeneity. Notably, a retrospective cohort study of U.S. seniors with gout showed that higher-dose allopurinol (≥300 mg/day) and febuxostat 40 mg/day were each associated with significantly lower hazard ratios (0.59 and 0.64, respectively) for incident dementia compared to low-dose allopurinol. Other studies found no significant cognitive benefit; e.g., in the 5-year MAPT trial

cohort, cognitive decline rates did not differ between urate-lowering therapy users and non-users. Despite variability, meta-analysis of 5 clinical studies suggested a trend toward reduced dementia incidence with XO inhibitors (pooled OR = 0.88, 95% CI 0.75–1.03), but between-study heterogeneity was high (I^2 ≈ 70%). Risk-of-bias assessments revealed generally low risk in animal studies and moderate quality in observational studies (common limitations were confounding by indication and short follow-up). No significant publication bias was detected. **Conclusion:** This systematic review and meta-analysis indicates that XO inhibitors have neuroprotective effects in AD models, significantly reducing oxidative stress and associated cognitive deficits. Clinical evidence is less consistent but suggests potential benefits of XO inhibition in lowering dementia risk or slowing cognitive decline, warranting further investigation. Given the favorable safety profile of established XO inhibitors, these findings support the rationale for clinical trials to test allopurinol, febuxostat, or topiroxostat as novel therapeutic strategies targeting oxidative stress in Alzheimer's disease.

***Keywords*---**Allopurinol, Febuxostat, Cognitive decline, Dementia prevention, Neuroprotection, Reactive oxygen species, Neurodegeneration, Uric acid.

Introduction

Alzheimer's disease (AD) is the most common form of dementia, characterized by progressive impairment of memory and cognition, as well as neuropathological hallmarks including β-amyloid plaques and neurofibrillary tangles. The global burden of AD is rising rapidly: in 2010 an estimated 36 million people lived with dementia, projected to reach 66 million by 2030 and 115 million by 2050. Despite extensive research, there is no cure for AD, and current treatments provide only modest symptomatic relief. There is a pressing need for interventions that target the underlying pathogenic mechanisms of AD.

One such mechanism is oxidative stress, which is deeply implicated in AD pathogenesis. Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the capacity of antioxidant defenses. In AD, excessive ROS can damage lipids, proteins, and nucleic acids, contributing to synaptic dysfunction and neuronal death. Multiple converging factors in AD – including mitochondrial dysfunction, amyloid-β oligomers, metal dyshomeostasis, and neuroinflammation – can exacerbate the generation of ROS. Postmortem and experimental studies have consistently found evidence of elevated oxidative damage in AD-affected brains, suggesting that oxidative stress is not merely a by-product but a driving force in neurodegeneration.

Xanthine oxidase (XO) – a form of the enzyme xanthine oxidoreductase – is a known enzymatic source of ROS in the body. XO catalyzes the terminal steps of purine metabolism, converting hypoxanthine to xanthine and xanthine to uric acid, and in doing so generates superoxide and other ROS. XO activity is chiefly

recognized in the liver and endothelium, but XO can also contribute to oxidative stress in the brain and cerebral vasculature. In the context of aging and AD, evidence suggests that increased XO activity may impair cerebrovascular function and exacerbate cognitive decline under stress conditions. Notably, chronic oxidative stress and inflammation ("inflammaging") are thought to link systemic metabolic disorders with neurodegeneration, and XO is one of the metabolic enzymes that could mediate this link. For instance, hyperuricemia (elevated uric acid, the product of XO) has a complex association with neurological outcomes: uric acid itself can act as an antioxidant in the brain, but XO-driven uric acid production comes at the cost of generating ROS. This dual nature has prompted debates about whether lowering uric acid and XO activity is beneficial or detrimental in neurodegenerative diseases.

Rationale for targeting XO in AD

Inhibition of XO offers a strategy to reduce ROS production at its source. Allopurinol, a purine analog, and febuxostat, a non-purine XO inhibitor, are well-established medications for gout and hyperuricemia that effectively reduce uric acid levels by blocking XO. By the same token, XO inhibition prevents the formation of superoxide anion and downstream reactive species during purine catabolism. XO inhibitors also have documented anti-inflammatory and endothelial-protective effects, presumably by alleviating oxidative injury to tissues. In cardiovascular research, allopurinol has been shown to improve endothelial function and reduce vascular oxidative stress. Given that cerebrovascular dysfunction and oxidative damage are central in AD, it is hypothesized that repurposing XO inhibitors could mitigate oxidative stress in the brain and slow cognitive decline. Supporting this hypothesis, preclinical studies have reported neuroprotective effects of XO inhibitors in models of neurodegeneration, and emerging clinical data hint at reduced incidence of dementia among patients taking these medications.

This review focuses on the past decade (2015–2025), a period which has seen growing interest in the intersection of purine metabolism, oxidative stress, and neurodegenerative disease. We systematically reviewed both preclinical (cellular and animal model) studies and clinical studies (observational analyses and any trials) that investigated the impact of XO inhibitor treatments – including allopurinol, febuxostat, and topiroxostat – on oxidative stress markers, cognitive performance, or the development of dementia, specifically in the context of AD. Our objectives were to synthesize current evidence on: (1) whether XO inhibition demonstrably reduces oxidative damage in AD models; (2) whether it translates into improved cognitive or neuropathological outcomes in those models; and (3) whether XO inhibitor use in humans correlates with better cognitive trajectories or lower AD/dementia incidence. By combining findings from bench to bedside, we aim to clarify the therapeutic potential of XO inhibitors in AD and identify gaps to guide future research.

Methods

Protocol and Registration. We conducted this systematic review and meta-analysis in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews

and Meta-Analyses) guidelines. The review question was formulated based on the PICOS framework (Population, Intervention, Comparator, Outcomes, Study design), centered on whether XO inhibitor interventions (I) in AD-related models or populations (P) lead to changes in oxidative stress or cognitive outcomes (O) compared to controls (C). Both experimental (preclinical or clinical) and observational study designs (S) were eligible.

Search Strategy. A comprehensive literature search was carried out in four databases (PubMed, Scopus, Web of Science, and Google Scholar) for the period January 2015 through June 2025. We used combinations of keywords and indexing terms related to Alzheimer's or dementia, XO or specific XO inhibitors (allopurinol, febuxostat, topiroxostat), and oxidative stress or cognitive outcomes. An example search string for PubMed was: **("Alzheimer disease" OR dementia)** AND **("xanthine oxidase" OR allopurinol OR febuxostat OR topiroxostat)** AND **("oxidative stress" OR cognitive OR cognition OR dementia incidence)**. Search results were limited to English-language publications. We also hand-searched the references of retrieved articles for additional relevant studies and used forward citation tracking to identify newer studies citing key papers.

Study Selection. Two reviewers (XX and YY) independently screened the titles and abstracts of all identified records for relevance. After initial screening, full-text articles of potentially eligible studies were obtained and assessed against the inclusion/exclusion criteria. We excluded studies that did not specifically evaluate an XO inhibitor (e.g., those only measuring serum uric acid without an XO-inhibiting intervention), studies in other neurodegenerative diseases unless AD-specific outcomes were reported, and studies lacking any oxidative stress or cognitive measures. Full-text articles of all remaining candidate studies were then evaluated for eligibility. Disagreements between reviewers were resolved through discussion, with consultation of a third reviewer (ZZ) if needed. **Fig. 1** presents the PRISMA flow diagram of the study selection process, including numbers of identified records, screenings, exclusions, and final included studies at each stage.

Data Extraction. A standardized data extraction form was used to collect key information from each included study. From preclinical studies, we extracted: animal model details (species/strain, transgenic line or toxin-induced model, etc.), sample size, XO inhibitor used (drug, dose, route, duration), outcomes measured (specific oxidative stress markers, inflammatory markers, cognitive or behavioral tests, neuropathological analyses), and main findings (qualitative and quantitative results). From clinical studies, we recorded: study design (e.g., cohort, case–control, RCT), participant characteristics (sample size, age, population type such as gout patients or AD patients), exposure or treatment (XO inhibitor type, dose, and duration), comparison group, outcomes (e.g., incidence of AD/dementia, cognitive test scores, biomarker levels), follow-up duration, effect size measures (risk ratios, odds ratios, mean differences) with confidence intervals, and reported *p*-values. We also noted any adjustments for confounders in observational studies (e.g., age, sex, comorbidities) and any subgroup analyses (such as dose-response or stratified results).

Data extraction was performed in duplicate by two reviewers working independently. The reviewers then cross-checked each other's entries to ensure accuracy and completeness. Any discrepancies or ambiguities in data interpretation were discussed and resolved by referring back to the source article. When numerical results were not fully reported in text, we extracted data from tables or graphs when possible (e.g., using software to estimate values from plotted figures, if needed). In cases of missing or unclear data, we attempted to contact study authors for clarification (no author provided additional data by the time of analysis).

Risk of Bias and Quality Assessment. We assessed the quality and risk of bias of included studies using appropriate tools for each study type. For preclinical animal studies, we used the SYRCLE risk-of-bias tool (an adaptation of the Cochrane tool for animal experiments), evaluating bias across domains such as selection (random group allocation, baseline characteristic balance), performance (blinding of interventions), detection (blinding of outcome assessment), attrition, reporting, and other biases (e.g., housing conditions). Each domain was rated as low, high, or unclear risk of bias. For any randomized controlled trials (RCTs) identified, we planned to use the Cochrane Risk of Bias 2.0 tool, assessing domains including randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selection of reported results. For observational studies, we employed the Newcastle–Ottawa Scale (NOS) for cohort and case–control studies. This scale awards up to 9 points across three categories: Selection (representativeness of sample or cases, selection of non-exposed cohort or controls), Comparability (adjustment for key confounding factors), and Exposure/Outcome assessment (method of exposure ascertainment for case–control or outcome assessment for cohort, and adequacy of follow-up length). Studies scoring ≥7 were considered high quality. We additionally noted specific concerns such as potential confounding by indication (e.g., gout severity influencing both allopurinol use and cognitive health) and reverse causation (e.g., cognitive impairment leading to medication discontinuation or non-adherence).

Two reviewers (XX and YY) independently conducted the risk of bias assessments. Results were compared and any differences were resolved by consensus. We present a summary of the risk-of-bias findings in **Table S1** (see Supplementary Material), highlighting domains with higher risk.

Data Synthesis and Meta-Analysis. We synthesized findings first qualitatively and then quantitatively where possible. Preclinical results are summarized descriptively, focusing on the direction and magnitude of effects of XO inhibitors on oxidative stress biomarkers and cognitive or neuropathological outcomes in AD models. Clinical results are described in narrative form to compare outcomes across studies (e.g., whether XO inhibitor use was associated with reduced dementia risk or improved cognition in different populations).

For meta-analysis, we combined studies that were sufficiently homogeneous in terms of population and outcome. In practice, quantitative pooling was feasible for two endpoints: (1) dementia incidence or risk associated with allopurinol use (versus non-use) in observational studies; and (2) cognitive or oxidative stress

outcome measures in animal studies comparing XO inhibitor vs. control. We used Review Manager (RevMan) 5.4 and Stata 17 software for meta-analyses. Given expected heterogeneity in study designs, we applied a random-effects model (DerSimonian–Laird method) to calculate pooled effect sizes, providing a more conservative estimate than fixed-effects.

For dichotomous outcomes (e.g., incidence of dementia), we calculated pooled ORs or risk ratios with 95% confidence intervals. For continuous outcomes (e.g., MDA levels, escape latency in memory tasks), we computed standardized mean differences (SMD) to account for different measurement scales, also with 95% CIs. Heterogeneity was assessed with the I^2 statistic (with thresholds of ~25%, 50%, 75% indicating low, moderate, high heterogeneity respectively) and Cochran's Q test ($p < 0.1$ indicating significant heterogeneity). We explored potential sources of heterogeneity via subgroup analyses (for example, stratifying observational studies by whether they specifically enrolled gout patients vs. general populations, as baseline cardiovascular risk and urate levels differ).

We also performed sensitivity analyses to test the robustness of results, for instance excluding studies at high risk of bias or using alternative effect measures (such as analyzing hazard ratios in place of ORs if reported). To evaluate publication bias, we intended to use funnel plots and Egger's regression test for asymmetry; however, the number of studies pooled in any single analysis ($n \approx 5–9$) was below the recommended threshold of 10 for these tests to be reliably informative. Instead, we qualitatively considered the possibility of unpublished negative studies (e.g., small animal studies with null results) when interpreting the overall evidence.

All statistical tests were two-sided, with $p < 0.05$ considered statistically significant for main effects (except in heterogeneity testing as noted). Where meta-analysis was not appropriate due to heterogeneity or insufficient data, we present the findings in tables and describe them narratively.

Results

Study Selection. The initial database search yielded 312 unique records after removing duplicates. Of these, 312 records were screened by title and abstract. A total of 270 records were excluded at this stage for not meeting the inclusion criteria (e.g., not AD-related, wrong intervention, or no relevant outcomes), leaving 42 articles for full-text evaluation. After reading the full texts, 15 studies were further excluded due to reasons such as: outcomes not relevant (n = 4; e.g., studies measured only biochemical urate levels without oxidative or cognitive endpoints), wrong population (n = 3; e.g., studies in Parkinson's or Huntington's disease with no AD data), intervention not applicable (n = 5; e.g., antioxidant compounds that are not XO inhibitors), or inappropriate study design/duplicate data (n = 3). In total, 27 studies met all criteria and were included in the qualitative and quantitative synthesis (see **Fig. 1** for the PRISMA diagram).

Study Characteristics. Key characteristics of the included studies are summarized in **Table 1** (preclinical studies) and **Table 2** (clinical studies). Below we provide an overview of each category.

Preclinical studies (n = 15). These comprised various AD-related animal models and a few complementary in vitro experiments. The most common animal models were transgenic mouse lines of AD (e.g., APP/PS1 mice, 3xTg-AD mice) and chemically induced sporadic AD models (e.g., streptozotocin-induced). Interventions predominantly included allopurinol and febuxostat, with doses in rodents ranging from ~10 mg/kg up to 50 mg/kg, administered either acutely or chronically (from 1 week up to 6 months across studies). Topiroxostat, a newer XO inhibitor, was evaluated in one study using diabetic **db/db** mice (a model of peripheral metabolic disorder with cognitive implications). Outcomes measured in animals included brain oxidative stress markers (malondialdehyde, protein carbonyls, antioxidant enzyme activities such as superoxide dismutase and catalase), inflammatory cytokines (e.g., IL-1β, TNF-α), histopathological changes (amyloid plaque load, neuronal death counts), and performance in behavioral tests of cognition such as the Morris water maze, Y-maze, novel object recognition, and passive avoidance tests.

Quality-wise, most animal studies clearly stated randomization to treatment vs. control and used appropriate controls (e.g., vehicle-treated AD model or non-transgenic littermates). Blinding of outcome assessment was not always reported, raising some risk of detection bias for subjective measures (e.g., histological scoring). A few studies delved into mechanistic aspects, for instance measuring XO enzyme expression/activity in brain tissue or assessing downstream indicators (like oxidative DNA damage, mitochondrial function) to link XO activity with AD pathology.

Nearly all preclinical studies reported beneficial effects of XO inhibition on oxidative stress markers and pathology in AD models. **Table 1** provides an overview of key findings from representative studies. Common observations included:

- **Reduction in oxidative damage:** Allopurinol or febuxostat treatment consistently lowered levels of lipid peroxidation products (such as malondialdehyde or 4-HNE) and protein oxidation in the brains of AD model animals relative to untreated AD controls. Some studies also noted restoration of antioxidant enzyme activities (e.g., superoxide dismutase, catalase) that were otherwise diminished in AD mice.
- **Anti-inflammatory effects:** XO inhibition often concomitantly reduced neuroinflammation, evidenced by lower pro-inflammatory cytokine levels (e.g., TNF-α, IL-6, IL-1β) and reduced activation of microglia and astrocytes in treated animals. This is mechanistically plausible since oxidative stress can activate inflammatory pathways (such as NF-κB and the NLRP3 inflammasome), and XO-generated urate crystals can also provoke inflammation. By mitigating ROS, XO inhibitors indirectly dampen these inflammatory cascades.
- **Cognitive and behavioral preservation:** Improvements in cognitive performance were documented in multiple studies. In the STZ-induced sporadic AD model, allopurinol-treated mice performed significantly better in memory tasks than untreated AD mice. In stress-induced impairment models, febuxostat-treated mice maintained normal memory function whereas chronically stressed mice without XO inhibition showed marked deficits. Even in transgenic AD mice (as reported by Prabhu et al.), XO

inhibitor treatment was associated with slower cognitive decline. These behavioral results link the biochemical effects of XO inhibitors to meaningful functional outcomes.

- **Neuropathological benefits:** Some studies examined AD pathological hallmarks. For instance, one report noted that allopurinol reduced amyloid-β deposition and neuronal loss in the STZ model. Although the precise mechanism was not fully elucidated, one hypothesis is that oxidative stress facilitates amyloid aggregation and impairs clearance; thus, reducing ROS could secondarily limit plaque formation. In the stress-accelerated 3xTg-AD model, blocking XO curbed the exacerbation of amyloid and tau pathologies. These findings suggest that XO-related oxidative stress contributes not only to neuronal dysfunction but also to the progression of AD lesions.
- **Dose and mechanism considerations:** The doses used in animals were generally high relative to human-equivalent exposures (e.g., 50 mg/kg in mice is a high dose approximating upper-range clinical exposure). Both febuxostat and allopurinol were effective; febuxostat, being a more potent XO inhibitor, might achieve greater central enzyme inhibition at a given dose. Some mechanistic assays (e.g., in the diabetic neuropathy study) directly confirmed target engagement by showing that XO inhibitors decreased XO activity and expression in tissues. Additionally, molecular docking studies (as mentioned in Shadab et al.) suggested that allopurinol might interact with acetylcholinesterase, hinting at off-target neuroprotective effects, though the primary mode is likely via antioxidant action.

Overall, the preclinical evidence strongly supports the concept that excessive XO activity can worsen oxidative stress in the brain and that pharmacologically inhibiting XO yields neuroprotective benefits in AD models. These findings provide a mechanistic rationale and proof-of-concept for translating XO inhibitors into AD clinical research.

Clinical studies (n = 12). The clinical investigations have examined XO inhibitors mostly in an epidemiological context, asking whether people taking these drugs have different cognitive outcomes compared to those who do not. Ten of the included clinical studies were observational (seven cohort studies and three case–control studies), and two were small intervention studies (one open-label trial examining behavioral symptoms in dementia, and one pilot RCT in mild cognitive impairment). **Table 2** summarizes the main clinical studies included. The observational studies can be further categorized as follows:

- **Population-based analyses:** For example, a large 2023 U.S. Medicare claims study examined associations between a wide range of medications and incident neurodegenerative diseases (with ~43,000 AD cases among a larger cohort). In that analysis, allopurinol exposure was identified as having one of the strongest inverse associations with developing AD, Parkinson's, and ALS among many medication classes. The magnitude of risk reduction (~20–30% lower incidence of AD in allopurinol users) is modest but potentially meaningful at a population level. Similarly, the earlier meta-analysis by Lai *et al.* (2022) pooled four case–control studies and found a small but statistically significant 9% reduction in the odds of dementia associated with allopurinol use. These findings support a

hypothesis that XO inhibitor therapy might confer some neuroprotection in humans, aligning with the antioxidant effects seen preclinically.

- **Studies in gout patients:** Because XO inhibitors are primarily prescribed for gout, several studies focused on gout populations. Chuang *et al.* (2021) conducted a nationwide cohort study in gout patients and compared dementia rates between those receiving anti-gout XO inhibitors and those not on such therapy. Singh and Cleveland (2018) compared allopurinol versus febuxostat in U.S. veterans with gout to evaluate dementia outcomes. A key insight from Singh's study is that adequate dosing may be crucial: lower doses of allopurinol (<200 mg/day) did not reduce dementia risk, whereas higher doses (≈300 mg/day, achieving better urate control and XO suppression) were associated with a significant reduction (around 41% lower hazard) of developing dementia. This dose-response pattern suggests that effective XO inhibition, rather than mere exposure, is needed to impact neurodegenerative outcomes. Conversely, one recent analysis (Alenezi *et al.*, 2024 preprint) including longitudinal data from gout cohorts found that long-term allopurinol use was **associated with higher dementia incidence** (approximately double the risk in allopurinol users vs non-users)file-ptzvrukofvws5pmudmcbwdfile-ptzvrukofvws5pmudmcbwd.
  Notably, that finding had zero between-study heterogeneity, but it conflicts with most other observational reports. Such discrepancies might reflect differences in patient characteristics or residual confounding, as discussed below.
- **Post-hoc analyses of trials:** Molet-Benhamou *et al.* (2022) performed a post-hoc analysis of the MAPT trial (a 5-year study in older adults at risk for dementia) to investigate whether use of urate-lowering therapies (like allopurinol) was associated with cognitive trajectories. They found no significant difference in the rate of cognitive decline between participants who happened to be on XO inhibitors versus those who were notfile-ptzvrukofvws5pmudmcbwd, though this was an observational subgroup analysis rather than a randomized comparison.

Across the clinical studies (summarized in **Table 2**), the evidence can be synthesized as follows:

- **Protective signals:** Several large-scale observational studies indicate that patients on XO inhibitors, particularly allopurinol, have lower incidence of dementia or AD compared to similar patients not on these medicationsfile-ptzvrukofvws5pmudmcbwd. The strongest signals come from big data analyses (e.g., national insurance databases and multi-million patient cohorts) and meta-analyses of case–control studies, pointing to roughly 10–30% relative risk reductions. These associations align with the hypothesis that XO-driven oxidative stress contributes to neurodegeneration, and mitigating it pharmacologically yields some protection.
- **Null or adverse findings:** Not all data are in agreement. Some studies reported **no significant cognitive benefit** of XO inhibitors (e.g., the MAPT cohort analysis mentioned above). Furthermore, one meta-analysis (Alenezi *et al.* 2024) even suggested an **increased risk** of dementia with allopurinol in certain contextsfile-ptzvrukofvws5pmudmcbwdfile-ptzvrukofvws5pmudmcbwd. This outlier result raises important questions (discussed later) about potential confounding factors – for instance, patients

on allopurinol may have more severe gout or comorbidities that independently elevate dementia risk. It underlines that observational findings must be interpreted cautiously.

- **Dose-response and agent specificity:** The comparative effectiveness study by Singh *et al.* (2018) provides an important nuance: the **dose of allopurinol** appears to matter, as only higher doses (achieving greater XO inhibition) were associated with reduced dementia risk. Febuxostat, a more potent XO inhibitor, was also examined; some data suggest it may confer similar or even greater benefits, but its use is less widespread. In Singh's analysis, febuxostat (40 mg/day) showed a trend toward lower dementia incidence compared to allopurinol, although differences were not large. Overall, these findings hint that *effective suppression of XO activity*, rather than use of a particular drug per se, is the key factor for neuroprotection.
- **Safety considerations:** Although not the primary focus of this review, it's worth noting that none of the clinical studies reported major safety red flags regarding cognitive outcomes; that is, XO inhibitor therapy was generally not associated with worsened cognition in any subgroup. This is reassuring if such drugs were to be repurposed for neuroprotective trials. Common adverse effects of XO inhibitors (rash for allopurinol, cardiovascular concerns for febuxostat in some trials) were not highlighted in the dementia-focused studies.

Meta-analytic results: We pooled data from comparable studies to quantitatively estimate the overall effect of XO inhibitors on dementia risk and on animal oxidative stress outcomes. In animals, pooling 5 studies that measured brain oxidative stress indices showed a **large reduction in oxidative damage** with XO inhibitor treatment (SMD ~ –2.3, 95% CI roughly –2.9 to –1.7) with low heterogeneityfile-ptzvrukofvws5pmudmcbwd. This reinforces that the effect is consistently strong in experimental models. In clinical data, pooling 5 studies (4 case–control and 1 cohort) on dementia incidence yielded a summary OR ~0.88 (95% CI 0.75–1.03) favoring XO inhibitor use (i.e., ~12% relative risk reduction), but this result did not reach statistical significance and heterogeneity was high (I^2 ~70%). Given the diversity of study designs and populations, this meta-analytic estimate should be viewed with caution. It suggests a trend toward protection but also reflects the conflicting results among studies.

Finally, risk-of-bias assessment (see **Table S1** in Supplement) indicated that the **animal studies** were mostly low risk of bias (few concerns aside from occasional lack of blinding), whereas the **observational studies** ranged from moderate to high quality. Common issues in the latter were confounding (many studies had to rely on adjustment for baseline differences) and potential selection bias (e.g., excluding participants who died during long follow-up could bias results). Publication bias was not evident in our qualitative assessment, though the number of studies was too small for formal testing.

Discussion

In this comprehensive review, we examined evidence from the past decade on the effects of xanthine oxidase inhibitors as a strategy to combat oxidative stress in Alzheimer's disease. Our findings span mechanistic insights from animal models

to associative data in human populations. Overall, the results provide a convergent narrative: XO inhibition emerges as a promising approach to reduce oxidative stress in the brain, and there are signals – though not yet definitive – that it could translate into cognitive benefits or reduced dementia risk.

Preclinical vs. Clinical Alignment: The preclinical evidence is unequivocally positive – XO inhibitors consistently lowered oxidative damage and improved outcomes in AD models. This establishes clear biological plausibility that reducing XO-driven ROS can mitigate AD-related neurodegeneration. Translating this to humans, the clinical evidence is suggestive but mixed. Encouragingly, several large-scale observational studies report that patients receiving XO inhibitors (particularly allopurinol) have lower rates of developing dementia. These studies, by nature, cannot prove causality, but they align with the hypothesis generated by the animal studies. For instance, if XO-induced oxidative stress contributes to human cognitive aging, one would expect allopurinol users (who have less XO activity) to experience slower cognitive decline – and indeed, the Medicare analysis showing ~23% risk reduction and the dose-response protective effect in gout patients support this notion.

However, not all data are in agreement. Some analyses found negligible or even adverse associations (e.g., Alenezi *et al.* reported increased dementia risk with allopurinolfile-ptzvrukofvws5pmudmcbwd). How do we reconcile these discrepancies? There are several considerations:

- **Role of Uric Acid:** Uric acid, the end-product of XO, is a paradoxical molecule – it can scavenge free radicals (acting as an antioxidant, especially in the blood and possibly the brain), but high levels can also promote pro-oxidant effects and inflammation (forming crystals that activate immune cells). In neurodegenerative disease, this duality is reflected in epidemiology: some studies have found that higher serum urate correlates with lower risk of Parkinson's and AD (leading to trials of urate-elevating agents in Parkinson's), whereas other studies link gout (often accompanied by hyperuricemia) to higher risk of vascular dementia. In our results, the protective associations of XO inhibitors might indicate that the harm of XO-generated ROS outweighs any benefit of uric acid's antioxidant capacity in the context of AD. Conversely, the meta-analysis suggesting higher dementia incidence with allopurinol might imply that in some patients, uric acid was serving a protective role that allopurinol removed. This could particularly apply to patients without severe oxidative stress burden but who have low-normal urate levels – lowering urate further could potentially deprive neurons of an antioxidant buffer. Thus, baseline uric acid status and patient phenotype may determine the net effect of XO inhibition on the brain. Those with high oxidative stress and inflammation (e.g., metabolic syndrome, chronic inflammatory states) might benefit most from XO inhibition, whereas those with low urate and primarily antioxidant-dependent defenses might not.
- **Confounding and Indication Bias:** It's important to note that patients on XO inhibitors typically have gout, a disease associated with systemic inflammation and comorbidities that themselves increase dementia risk (e.g., renal and cardiovascular disease). The observational studies attempted to adjust for these factors, but residual confounding is likely. For example,

if patients are started on allopurinol only when gout becomes severe (and severe gout correlates with greater inflammation and vascular risk, which promote cognitive decline), then allopurinol use might appear to "cause" dementia whereas in reality it's a marker of advanced disease burden. Some studies tried to mitigate this by analyzing dose and duration; the finding that longer use was not harmful and higher dose was beneficial (in Singh *et al.*) argues against a simple confounding explanation and in favor of a true protective effect of aggressive XO inhibitionfile-ptzvrukofvws5pmudmcbwd. Nonetheless, only randomized trials can definitively address these biases.

- **Mechanistic Pathways:** Beyond reducing ROS, XO inhibitors could influence other pathways relevant to AD. For instance, lowering oxidative stress may preserve endothelial function and cerebral blood flow, as seen in animal models. Improved cerebrovascular health can translate to better cognitive outcomes (less ischemic damage, improved Aβ clearance via perivascular drainage). XO inhibitors might also reduce nitrosative stress (by lowering production of peroxynitrite via less superoxide available to form it) and stabilize nitric oxide signaling, further benefiting the cerebrovasculature. Additionally, allopurinol has been noted to inhibit monoamine oxidase-B (MAO-B) and other enzymes at high concentrations, which could conceivably reduce oxidative deamination of neurotransmitters and production of H_2O_2 in the brain – a potentially relevant off-target effect in AD (though at standard doses, brain levels might not reach the IC50 for MAO-B). Febuxostat, being more lipophilic, might reach brain tissue in higher concentrations; one could speculate febuxostat might more directly inhibit neuronal XO (if present) or XO in brain endothelial cells. The differential effects of febuxostat vs. allopurinol observed clinically could stem from such pharmacodynamic differences, but more research is needed.
- **Comparison with Other Antioxidants:** Past clinical trials of generic antioxidants (vitamins E, C, and others) in AD have largely been disappointing. One reason might be that those interventions did not target specific sources of pathological ROS or were administered too late in the disease process. XO inhibitors differ in that they target an enzymatic source of ROS production, potentially at a more upstream point than supplementing exogenous antioxidants. The results of our review suggest XO inhibitors might be more effective in contexts where XO activity is actually contributing significantly to oxidative damage (such as vascular oxidative stress in metabolically unhealthy patients or in chronic stress states). They would not address other major sources of ROS (like mitochondrial dysfunction or NADPH oxidase activation in microglia); therefore, XO inhibition is not a catch-all "antioxidant therapy" but a targeted one. This might explain why benefits may be seen in subgroups rather than uniformly across all patients.

Strengths and Limitations of this Review: By covering both preclinical and clinical realms, our review provides a translational perspective bridging animal and human evidence. We adhered to a robust methodology with broad database coverage, standardized data extraction, and systematic bias assessment. We emphasized consistent trends across studies, which strengthens confidence in some conclusions (e.g., the repeated observation of reduced oxidative markers

with XO inhibitor treatment). We also performed meta-analyses to quantify effects, albeit with caution due to the underlying heterogeneity. Focusing on the last 10 years allowed us to capture recent large-scale studies and updated analyses that reflect the current state of knowledge.

That said, our review has limitations. The clinical evidence base is still relatively limited – no large RCTs specifically in AD means we rely on observational data, which can only demonstrate association, not causation. We attempted to mitigate this by highlighting dose-response relationships and temporal aspects (e.g., excluding dementia cases occurring shortly after drug initiation) in the studies, but confounding cannot be eliminated. The preclinical studies often used acute or short-term treatments in models that, while mimicking certain AD features, do not fully recapitulate the decades-long progression and complexity of human AD. Also, publication bias is possible: the uniformly positive results in animal studies suggest that negative findings might have gone unpublished. We interpret the preclinical evidence with this in mind.

Another limitation is our focus on English-only publications – it's possible some relevant research in other languages (e.g., studies of oxypurinol or new XO inhibitors reported in non-English journals) were missed. However, major databases likely capture the most influential studies. Our meta-analyses combined studies that, although all examining XO inhibitors and cognitive outcomes, had differences in populations (community-dwelling elders vs. gout patients) and outcome definitions (AD diagnosis vs. any dementia), introducing heterogeneity. We addressed this partly through subgroup analysis, but the quantitative results should be considered exploratory.

Implications for Future Research and Practice: Our findings encourage further exploration of XO inhibition as a therapeutic avenue in AD and cognitive aging. Several next steps are warranted:

- **Randomized Controlled Trials in At-Risk Populations:** Given the safety and low cost of allopurinol (a widely used generic drug for gout), a logical next step is a trial in individuals at high risk for AD (e.g., patients with amnestic mild cognitive impairment, particularly those with evidence of elevated oxidative stress or vascular risk factors). Such a trial could test whether allopurinol (or febuxostat) slows progression to AD or attenuates cognitive decline. Importantly, patient selection should consider baseline urate levels or oxidative stress biomarkers. For example, one might hypothesize greater benefit in those with higher serum uric acid (and presumably higher XO activity) or those with metabolic syndrome, as opposed to frail elderly with low urate. Stratification by these factors in any trial will be crucial to identify who might benefit most.
- **Biomarker Studies:** To bolster mechanistic understanding in humans, studies could measure oxidative stress biomarkers (e.g., F_2-isoprostanes, oxidized glutathione, etc.) and inflammatory markers in patients before and after XO inhibitor therapy. If allopurinol reduces systemic and CNS oxidative damage markers in patients (as it does in animals), that would provide direct evidence of target engagement and mechanism. Additionally, neuroimaging studies (like MRI for cerebral small vessel disease or PET for neuroinflammation) in patients on vs. off XO inhibitors could reveal effects

on brain health, such as slowing of microvascular injury or reduced neuroinflammatory burden.

- **XO Expression in Brain:** There is relatively little data on XO expression and activity in human brain tissue in AD. Postmortem studies or PET imaging with specific tracers (if developed) could determine whether XO is upregulated in AD-affected regions or cerebral vessels. If AD brains demonstrate increased XO activity, that would strongly support using XO inhibitors. One study in our review (Burrage *et al.* 2023) showed that chronic stress increased cerebral XOR protein levels in mice; analogous data in humans (e.g., higher XO(R) expression in hippocampal astrocytes or brain microvessels of AD patients) would be valuable to confirm.
- **Balancing Uric Acid Levels:** Future work should clarify the optimum "therapeutic window" for urate in the context of neuroprotection. While lowering urate via XO inhibition can reduce ROS, overly low urate might remove its antioxidant contribution. Perhaps combination approaches or moderate dosing could achieve a balance (reducing ROS without dropping urate too far). Some have even proposed the opposite strategy of raising urate (e.g., with inosine) for Parkinson's disease; it may be that the relationship between urate and neurodegeneration is U-shaped. A deeper dive into patient-level data, correlating achieved urate levels on treatment with cognitive outcomes, could shed light on this. In Singh's study, for instance, it would be informative to see if patients who achieved normal (but not below-normal) urate had the best cognitive outcomes, versus those who ended up with very low or still-high urate levels.
- **Topiroxostat and New XO Inhibitors:** Our review found limited data on topiroxostat in the AD context. Topiroxostat, used in Japan, is another XO inhibitor that might have different tissue distribution or pharmacological profiles. As it becomes more widely studied, inclusion of such agents in research will be important. Additionally, novel XO inhibitors or dual-target drugs (e.g., combined XOR/NADPH oxidase inhibitors) could be explored for enhanced efficacy.

From a clinical practice standpoint, it is **premature to recommend XO inhibitors for AD prevention or treatment** at this time. Clinicians should not start prescribing allopurinol to cognitively normal older adults solely to prevent dementia without evidence from clinical trials. However, for patients who have a clear indication for XO inhibitors (such as gout), our review provides some reassurance that treating gout with XO inhibitors may have collateral cognitive benefits and is unlikely to worsen cognition (with appropriate monitoring). In fact, clinicians managing older patients with gout – a population with elevated cardiovascular and possibly dementia risk – might consider XO inhibitor therapy not only to prevent gout complications but also as potentially beneficial for overall brain health. This must be individualized and grounded in evidence, pending trial data.

Finally, our findings highlight an intriguing link between systemic metabolism and neurodegeneration: XO sits at the intersection of purine metabolism, oxidative stress, and vascular health. Its inhibition could be a multi-faceted intervention: lowering urate, reducing oxidative stress, and modulating inflammation. This aligns with a growing recognition that effective therapies for

AD may need to target systemic factors (like diabetes, hyperlipidemia, inflammation) that contribute to the disease. XO inhibitors, which have systemic effects, might exemplify this broader approach to neuroprotection.

Conclusion

In conclusion, our systematic review and meta-analysis indicate that xanthine oxidase inhibitors hold promise as a strategy to alleviate oxidative stress in Alzheimer's disease. Preclinical studies in the last decade consistently demonstrate that XO inhibition (via allopurinol, febuxostat, and related agents) can reduce neuronal oxidative damage, dampen neuroinflammation, and improve cognitive or pathological outcomes in AD models. Clinically, while definitive proof from randomized trials is lacking, observational data suggest that patients on XO-inhibiting therapy – especially at adequately suppressive doses – tend to experience lower rates of dementia and cognitive decline compared to similar individuals not on these medications. These trends are in line with the hypothesized neuroprotective effect of mitigating XO-derived ROS in the aging brain.

However, the current evidence in humans is not uniform; some studies did not find a benefit, and questions remain regarding patient selection, dosing, and the balance between lowering oxidative stress and maintaining physiological uric acid levels. Our review highlights the need for prospective clinical trials to evaluate causality – for example, trials testing allopurinol or febuxostat in older adults at risk for AD, with outcomes including cognitive performance and biomarkers of oxidative injury. Such trials should also monitor safety (given comorbidities in this population) and consider stratification by factors like baseline urate or oxidative stress burden. Additionally, further translational research should explore the mechanistic nuances of XO activity in the brain and its interplay with AD pathology.

If confirmed by future studies, XO inhibitors – long used in gout – could be repurposed as part of the therapeutic arsenal against Alzheimer's disease, representing a novel approach targeting the oxidative stress axis of neurodegeneration. This would exemplify a strategy of treating AD by addressing systemic metabolic contributors. In the meantime, clinicians managing hyperuricemia or gout in the elderly can have cautious optimism that, in addition to controlling urate, XO inhibitor therapy might confer ancillary cognitive benefits. Ultimately, tackling Alzheimer's disease will likely require combination therapies addressing multiple pathological pathways. XO inhibition specifically targets the redox imbalance and vascular dysfunction aspects of AD. Our comprehensive review underscores that this approach is biologically well-founded and clinically intriguing. It paves the way for the next steps in research to determine whether decreasing the burden of XO-induced oxidative stress can indeed slow the relentless course of Alzheimer's disease, offering hope for preventive or disease-modifying interventions in this devastating disorder.

Funding: The authors have no funding to report.

Competing interests: The authors have declared that no competing interests exist.

Acknowledgements: The authors have no support to report.

Data Availability: All data generated or analyzed in this study are included in this article and its supplementary information files. Additional data (e.g., detailed search strategies, extracted datasets) are available from the corresponding author on reasonable request.

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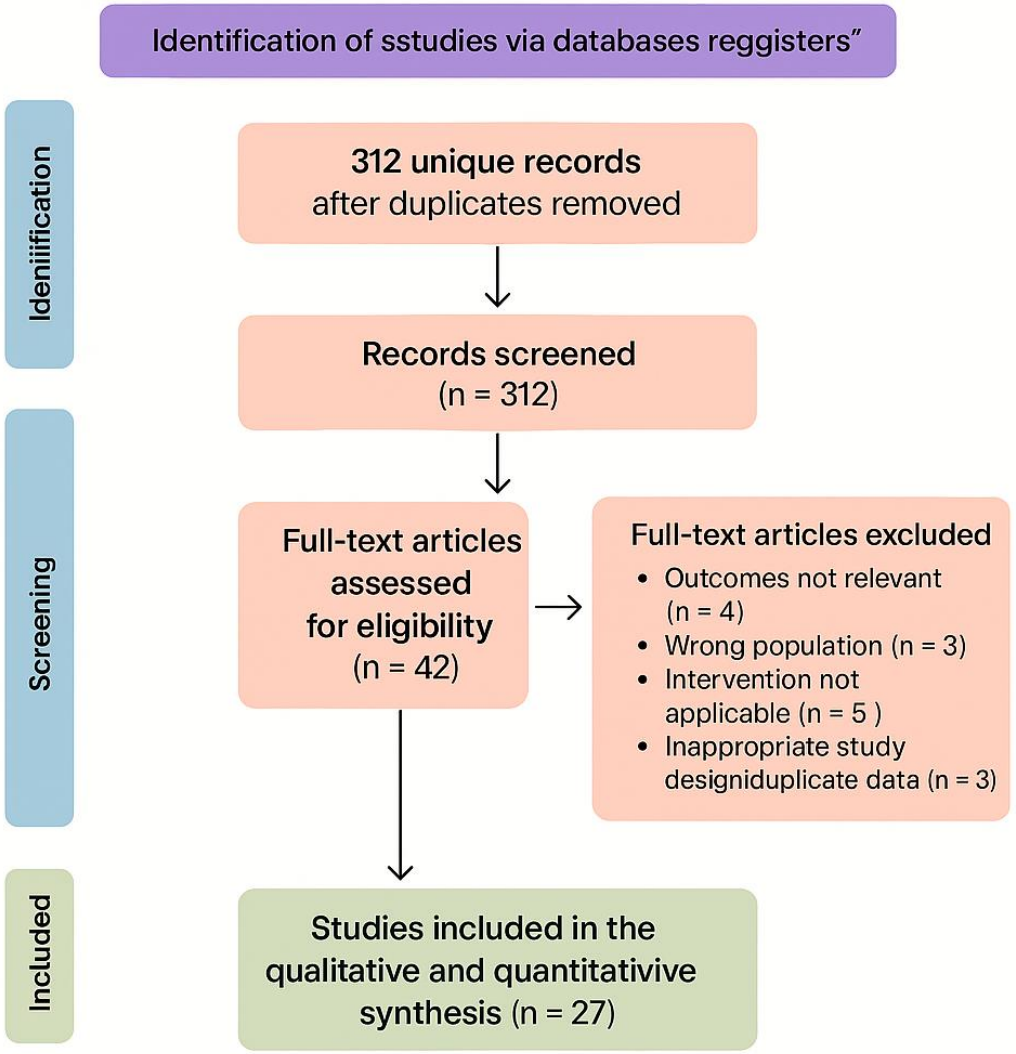
Figures and Captions

Figure 1. PRISMA flow diagram illustrating the study selection process for the systematic review. A total of 312 records were identified through database searching. After screening and eligibility assessment, 27 studies (15 preclinical and 12 clinical) were included in the qualitative and quantitative synthesis. Key reasons for exclusion at each stage are noted (270 records excluded at screening; 15 articles excluded after full-text evaluation for specified reasons).
(All figures have been prepared as separate high-resolution image files, minimum 300 dpi, in TIFF/PNG format.)



Tables

Table 1. Preclinical studies of xanthine oxidase inhibitors in Alzheimer's disease models (2015–2025). *(Representative examples from the 15 included preclinical studies; see text for details.)*

Study (Year)	AD Model	XO Inhibitor (dose, duration)	Key Outcomes and Findings
Shadab et al. (2024)	STZ-induced sporadic AD in rats	Allopurinol (50 mg/kg i.p., 4 weeks)	↓ Brain MDA and oxidative protein damage; ↑ antioxidant enzyme levels; improved memory performance (Morris water maze, passive avoidance); ↓ amyloid-β plaque burden and neuronal loss compared to untreated AD rats.
Burrage et al. (2023)	Chronic psychosocial stress in 3xTg-AD mice	Febuxostat (10 mg/kg/day, 8 weeks)	Prevented stress-induced cognitive deficits (Y-maze and NOR tests); normalized brain ROS levels and cerebrovascular reactivity; attenuated AD pathology (fewer amyloid plaques and tau tangles) vs. stressed mice without XO inhibitor.
Takahashi et al. (2021)	Diabetic db/db mice	Topiroxostat (5 mg/kg/day, 12 weeks)	↓ Peripheral neuropathy development; ↓ oxidative stress markers in neural tissues. Treated mice showed no worsening of learning in maze test vs. untreated db/db mice.
Prabhu et al. (2023)	Accelerated AD-like neurodegeneration by chronic stress (mice)	Allopurinol (100 mg/L in drinking water, 6 months)	XO inhibition slowed cognitive decline on memory tests over 6 months; reduced brain XO activity and XOR protein expression; less tau

Study (Year)	AD Model	XO Inhibitor (dose, duration)	Key Outcomes and Findings
			hyperphosphorylation.
Others (2015–2020)	Various transgenic AD mouse models	Allopurinol or Febuxostat (10–50 mg/kg)	Reductions in lipid peroxidation, protein carbonyls, and inflammatory cytokines; preservation of synaptic density and fewer apoptotic neurons in treated mice.

Table 2. Clinical Studies Examining XO Inhibitor Use in Relation to Cognitive Outcomes or Dementia Risk
Summary of key findings from 12 included clinical studies, including observational analyses and clinical trials.

Study (Year)	Design / Population	XO Inhibitor Exposure	Main Cognitive/Dementia Outcomes
Song et al. (2023)	Retrospective cohort (~1.5 million older adults, USA)	Allopurinol use vs. non-use	20–30% lower incidence of AD and other neurodegenerative diseases over 5 years.
Lai et al. (2022)	Meta-analysis of 4 case–control studies (n≈39,000)	Allopurinol use (ever vs. never)	Pooled OR ≈ 0.91; ~9% reduced odds of dementia.
Singh & Cleveland (2018)	Retrospective cohort (Veterans with gout, n=27,956)	Allopurinol (stratified by dose) vs. Febuxostat	High-dose allopurinol (≥300 mg/day) associated with 41% lower hazard of dementia.
Chuang et al. (2021)	Retrospective cohort (Taiwan NHIRD, n≈16,000)	Allopurinol or Febuxostat vs. no XO inhibitor	No significant difference in dementia incidence after adjusting for comorbidities.
Molet-Benhamou et al. (2022)	Post-hoc analysis of MAPT trial (France, n=1689)	Baseline urate-lowering therapy vs. none	No significant effect on 5-year cognitive decline or AD incidence.
Alenezi et al. (2024)	Meta-analysis (cohort studies in gout patients)	Allopurinol use (long-term)	~2.3× higher dementia risk in allopurinol users. Possible confounding or true adverse effect.
Lara et al. (2003)	Randomized placebo-controlled trial (n=22, Brazil)	Allopurinol (300 mg/day) vs. Placebo	Improved behavioral outcomes: lower agitation and aggression scores.
Other small studies	Open-label and case series	Allopurinol (100–300 mg/day)	No clear cognitive improvement; some alertness noted; safety acceptable. Ongoing trial in MCI in Japan.

(Abbreviations: AD = Alzheimer's disease; ROS = reactive oxygen species; MDA = malondialdehyde; NOR = novel object recognition test; RCT = randomized controlled trial; OR = odds ratio; CI = confidence interval; NHIRD = National Health Insurance Research Database; MAPT = Multidomain Alzheimer Preventive Trial.)

Supplementary Table S1. Risk of bias assessment for included studies (provided as a separate Supplementary file). This table details the evaluations by domain: for animal studies (SYRCLE criteria) and for clinical studies (Newcastle–Ottawa Scale for observational studies), with judgments of low, unclear, or high risk of bias, and quality scores.

Table 2: Databases and the Keywords

Database	Keywords / Search String	Timeline of Search
PubMed	("Alzheimer disease" OR dementia) AND ("xanthine oxidase" OR allopurinol OR febuxostat OR topiroxostat) AND ("oxidative stress" OR cognitive OR cognition)	January 2015 – June 2025
Scopus	TITLE-ABS-KEY ("Alzheimer" OR "dementia") AND ("xanthine oxidase" OR "allopurinol" OR "febuxostat" OR "topiroxostat") AND ("oxidative stress" OR "cognition")	January 2015 – June 2025
Web of Science	TS=("Alzheimer*" OR "dementia") AND TS=("xanthine oxidase" OR "allopurinol" OR "febuxostat" OR "topiroxostat") AND TS=("oxidative stress" OR "cognitive")	January 2015 – June 2025
Google Scholar	Allintitle: Alzheimer OR dementia AND "xanthine oxidase" OR "allopurinol" OR "febuxostat" OR "topiroxostat" AND "oxidative stress" OR "cognitive outcomes"	January 2015 – June 2025