Homoeopathic Medicines in Experimental Models of Alzheimer's Disease and Dementia: A Narrative Mini-Review with Evidence from Alumina Preclinical Studies

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ABSTRACT

Background: Alzheimer's disease remains without a disease-modifying treatment despite decades of intensive drug development effort. A small number of research groups have begun testing homoeopathic preparations in controlled animal models, generating a limited but internally consistent body of evidence. We reviewed this literature and incorporated two original preclinical Alumina studies from our own group to assess whether potentised preparations produce biologically detectable responses under defined experimental conditions.

Methods: We searched PubMed, Scopus, Google Scholar, and homoeopathy-specific databases through February 2026, using Boolean terms across homoeopathy, ultra-dilution, Alzheimer's disease, dementia, scopolamine, and streptozotocin. Seven controlled animal studies with quantitative outcomes met all inclusion criteria. Design heterogeneity precluded meta-analysis; Cohen's d was calculated for select oxidative stress comparisons from the Alumina dataset, and retrospective power analysis was performed for the n = 6/group design.

Results: Potency-related biological gradients were recorded independently for Lycopodium clavatum, Mercurius solubilis, Gelsemium sempervirens, and Alumina Metallicum across cholinergic and oxidative endpoints. Scopolamine produced a large MDA elevation (Cohen's d = 5.3 vs. normal controls). Alumina 10M partially reversed this, approaching donepezil values (d = 0.4, $p > 0.05$), though these figures come from six animals per group at a single institution and must be read accordingly.

Conclusions: The available evidence is hypothesis-generating only preliminary cholinergic model data, not proof of disease modification. The Nrf2/HO-1 pathway hypothesis that emerges from the oxidative results warrants direct testing via Western blot and Nrf2 reporter assays in pre-registered, independent studies with adequate power and both sexes. No clinical translation is justified on present evidence.

Keywords: Alzheimer's disease; potentised preparations; scopolamine model; Alumina; oxidative stress; Nrf2/HO-1 pathway; potency-dependent response; homoeopathy

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INTRODUCTION

Alzheimer's disease is the leading cause of dementia globally affecting an estimated 57 million people in 2019, with projections exceeding 152 million by 2050.[1] Despite sustained research investment, no pharmacological agent has been shown to modify disease progression; acetylcholinesterase inhibitors and memantine offer modest symptomatic benefit at best.[2,3] This gap has kept interest alive in alternative pharmacological strategies, including preparations used in complementary medicine systems.

Within homoeopathic pharmacology, a small number of groups have published controlled animal studies examining cognitive and neuroprotective endpoints.[4,7,9] Two gaps in this body of work stood out when we began this project. First, no single study had assessed a potency-dependent biological gradient across both behavioural and biochemical outcomes in one experimental cohort. Second, no proposed mechanism had been subjected to direct testing. This review takes stock of existing evidence, reports original data from two Alumina studies conducted by members of our group, and frames a testable Nrf2/HO-1 mechanistic hypothesis for future investigation.

Scope: All evidence reviewed here derives from a cholinergic blockade model. Scopolamine does not reproduce amyloid or tau pathology, and these findings cannot be taken as evidence of disease-modifying activity. What they may provide is a foundation for more rigorous work.

Methods

Search strategy

We searched PubMed, Scopus, Google Scholar, the Liga Medicorum Homoeopathica Internationalis database, and the Indian Journal of Research in Homoeopathy archive with no date restriction through February 2026. The primary search combined: (homeopathy OR high dilution OR ultra-dilution OR potentised) AND (Alzheimer's disease OR dementia OR cognitive impairment OR scopolamine OR streptozotocin). Separate targeted searches covered Lycopodium clavatum, Mercurius solubilis, Gelsemium sempervirens, and Alumina Metallicum individually. Reference lists of retrieved articles were screened by hand.

Eligibility criteria

We included studies using a controlled animal design with at least one treated and one disease group, a homoeopathic or ultra-high-dilution preparation, pharmacological or surgical induction of a dementia relevant condition and quantitative behavioural or biochemical data available as full English text. We excluded cell-line and in silico work, studies without a concurrent disease control, conference abstracts without peer-reviewed full text, and combination preparations precluding attribution to a single substance. Seven studies met all criteria. A PRISMA flow diagram is provided as Supplementary Figure S1.

Quantitative synthesis

Design variation across studies precluded pooled analysis. Where the Alumina primary papers reported means and standard deviations with sufficient precision, we calculated Cohen's d post hoc for two comparisons of interest: scopolamine disease control vs. normal control, and Alumina 10M vs. the donepezil reference. These figures supplement the primary study statistics; no new inferential conclusions are drawn from them.

We also ran a retrospective power analysis for the $n = 6$/group design used in the Alumina studies (two-tailed $\alpha = 0.05$, $d = 1.0$). The result approximately 42% power means a real large effect would have been missed more than half the time. We include this calculation because it directly shapes how the non-significant donepezil comparisons should be interpreted.

Results

Summary of included studies

Table 1 lists the five experimental entries drawn from seven eligible publications. All were conducted in CPCSEA-accredited facilities under IAEC-approved protocols. The two Alumina investigations additionally followed ARRIVE 2.0 reporting standards. In those studies, 36 adult male Wistar rats were randomised to six groups of six; biochemical analysts were blinded to group identity. Blinding the drug administrator was not feasible given preparation-specific dosing volumes, and this residual performance bias cannot be ruled out.

No included study performed an a priori power calculation. Our retrospective estimates suggest roughly 42% power at $n = 6$ for large between-group differences which means non-significant results against donepezil are inconclusive, not negative. None of the studies have been replicated by an independent laboratory, and that remains the single most important gap in this field.

Table 1: Preclinical Investigations of Homoeopathic Medicines in Dementia Models

Remedy	Potency	Model	Parameters	Key Findings	n/group	Reference	p vs. Donepezil
Lycopodium clavatum	30C, 200C	Scopolamine (rat)	Memory, AChE, CBF	200C outperformed 30C on memory, AChE activity, and CBF vs. disease control	6	Hanif et al. 2015 [8]	NR

Mercurius solubilis	6C–1M	ICV-STZ (rat)	Memory, CBF, antioxidants, AChE	Improved memory and perfusion; antioxidant enzyme levels and AChE activity restored toward normal	6	Hanif et al. 2016, 2017 [9]	NR
Gelsemium sempervirens	Mother tincture	Scopolamine (mouse)	Memory, AChE, BACE1, GSH	~60% in vivo neuroprotection; AChE IC_{50} 9.25 µg/ml; BACE1 IC_{50} 16.25 µg/ml; GSH elevated	Not reported	Palit et al. 2015 [10]	NR
Alumina	200C, 1M, 10M	Scopolamine (rat)	OFT, NOR, BCT, Y-Maze	Ascending 200C→1M→10M gradient on OFT, NOR, BCT; 10M approached donepezil; Y-Maze reversed (200C > 1M > 10M)	6	Zagday et al. 2026 [11]	$p > 0.05$ (OFT, NOR, BCT)
Alumina	200C, 1M, 10M	Scopolamine (rat)	MDA, Catalase, GSH	Monotonic 200C→1M→10M reversal of oxidative injury; 10M approached donepezil on all three markers (d = 0.4 for MDA)	6	Bidiwale et al. 2026 [12]	$p > 0.05$ (MDA, catalase, GSH)

AChE: acetylcholinesterase; BCT: bar catalepsy test; CBF: cerebral blood flow; GSH: reduced glutathione; ICV-STZ: intracerebroventricular streptozotocin; MDA: malondialdehyde; NOR: novel object recognition; NR: not reported; OFT: open field test. $p > 0.05$ by post-hoc Tukey test vs. donepezil standard. Refs 11 and 12 include authors from the present review team; see Declarations.

Lycopodium clavatum and Mercurius solubilis

The first controlled homoeopathic dementia study we found was published by Hanif et al. in 2015.[7] In scopolamine-treated rats, Lycopodium clavatum 200C produced better outcomes than 30C on memory, AChE activity, and cerebral blood flow the first published example of a potency-dependent gradient in this model. The same group extended the work to Mercurius solubilis in the ICV-STZ rat model across two further papers[8,9] reporting improvements in working memory, antioxidant enzyme activity, AChE output, and regional brain perfusion. That a potency-graded effect appeared in two pharmacologically distinct models from one laboratory reduces though does not eliminate the likelihood of coincidence. External replication has not yet appeared.

Gelsemium sempervirens

Palit et al. tested a reconstituted Gelsemium sempervirens mother tincture in scopolamine-treated mice and reported approximately 60% in vivo neuroprotection.[10] The enzyme inhibition assays were the most noteworthy finding: an AChE IC_{50} of 9.25 µg/ml and BACE1 IC_{50} of 16.25 µg/ml, with concurrent GSH elevation, suggest activity at both a cholinergic and an amyloidogenic target within one preparation. Whether potentised forms replicate this dual-target activity in transgenic models is an open question worth pursuing.

Alumina preclinical studies

The behavioural study[11] (IAEC protocol No. Biotox/IAEC/06/2025/RP-35; ARRIVE 2.0 compliant) randomised 36 adult male Wistar rats to six groups of six: normal control, scopolamine disease control, donepezil positive control, and Alumina at 200C, 1M, and 10M. Oral Alumina was given for 14 days, with scopolamine (1 mg/kg i.p.) on Day 15. OFT, NOR, and BCT all produced the ascending 200C < 1M < 10M pattern; Alumina 10M was statistically indistinguishable from donepezil on all three tests ($p > 0.05$, post-hoc Tukey). Y-Maze diverged: 200C gave the highest spontaneous alternation score (67.17 ± 2.40%), with 10M lower. We address this in the Discussion.

Brain tissue from the same animals was assayed for oxidative markers by Bidiwale et al.[12] Scopolamine nearly tripled MDA relative to normal controls (1.25

to 4.12 ng/ml; Cohen's d = 5.3), approximately halved catalase (59.17 to 28.83 ng/ml; d = 59.5), and more than halved GSH (6.92 to 3.18 ng/ml; d = 52.9) all significant at $p < 0.001$. Alumina reversed all three markers monotonically across potencies, with 10M reaching non-significant distance from donepezil on MDA (d = 0.4, $p > 0.05$). Three independent analytes, all moving in the same direction at every potency tested: that consistency is what motivates the mechanistic hypothesis that follows. We are equally clear that this is n = 6 from one laboratory, with authors overlapping the present review preliminary data, and nothing more.

We selected Alumina on the basis of its symptom correspondence in the classical homoeopathic Materia Medica,[13–15] where progressive motor slowing, incoordination, and cognitive dulling are prominent features closely matching the scopolamine phenotype in rodents. This is essentially reverse pharmacology: matching a symptom library to a target phenotype rather than engineering a ligand against a receptor.

Figure 1

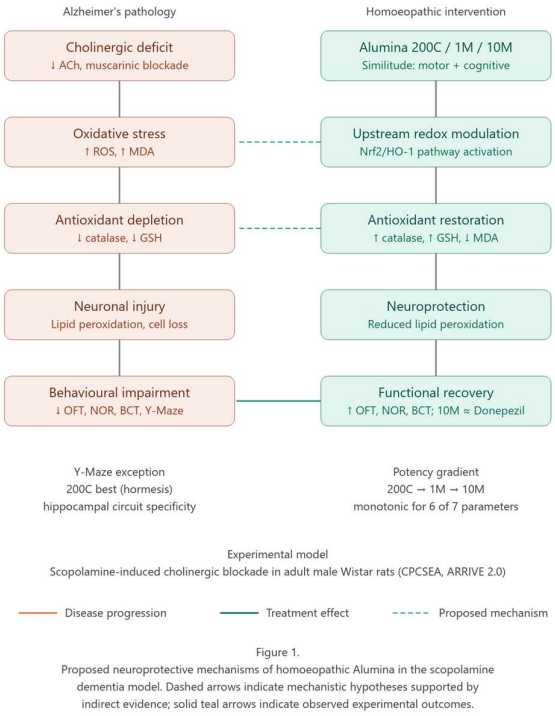

Figure 1.
Proposed neuroprotective mechanisms of homoeopathic Alumina in the scopolamine dementia model. Dashed arrows indicate mechanistic hypotheses supported by indirect evidence; solid teal arrows indicate observed experimental outcomes.

Discussion

Three patterns emerge across the seven studies. Potency-dependent biological responses were recorded independently for Lycopodium clavatum, Mercurius solubilis, and Alumina, in different laboratories and with different animal models. The oxidative markers MDA, catalase, GSH shifted in the same protective direction at every Alumina potency, without exception. Behaviour and biochemistry aligned: higher potencies generally performed better, with 10M approaching donepezil on most endpoints. This consistency is what makes the dataset worth taking seriously. It is also what limits it a small cluster of studies largely corroborating each other, without any independent external validation.

What the scopolamine model can and cannot tell us

Scopolamine produces its cognitive effects by blocking muscarinic acetylcholine receptors, impairing memory acquisition, consolidation, and retrieval. It is a well-validated proxy for the cholinergic dimension of AD pharmacology, widely used in screening.[5,6] What it does not produce is amyloid-β plaque deposition, tau hyperphosphorylation, or progressive neurodegeneration the defining features of clinical Alzheimer's disease. The appropriate characterisation of everything reviewed here is: preliminary cholinergic model evidence, not disease-modifying evidence. Moving beyond that framing requires validation in transgenic amyloid models (e.g., 5×FAD, APP/PS1) and tauopathy paradigms.

A working hypothesis: Nrf2/HO-1 pathway

Three oxidative analytes reversed simultaneously across three potency levels. Direct radical scavenging is an unlikely explanation for that degree of coordination. A more tractable account involves the Nrf2/antioxidant response element (ARE) pathway. Al-Omairi et al. produced essentially the same reversal pattern—same model, same three markers using a plant extract reported to act via Nrf2/HO-1 pathways,[16]while Nrf2 insufficiency and altered redox

markers are documented in AD brain.[17]

The experimental path is well-defined: (i) Western blot or ELISA for nuclear Nrf2 translocation in hippocampal lysates; (ii) immunoblot for downstream targets HO-1, NQO1, and γ-GCS; (iii) Nrf2 luciferase reporter assays in primary neuronal cultures; and (iv) co-treatment with the Nrf2 inhibitor ML385 to confirm pathway specificity. All four should be built into the next round of studies from the outset.

The Y-Maze result and potency specificity

The Y-Maze result cut against the pattern: 200C gave the best spontaneous alternation score, not 10M. Hippocampal networks driving spatial working memory are anatomically and pharmacologically distinct from the cortical and subcortical circuits engaged by OFT, NOR, and BCT. It is plausible that hippocampal cholinergic or redox systems have a different potency-sensitivity threshold (circuit-specific potency response). We advance this only as a testable hypothesis, not as a finding.

Limitations

Authorship overlap: Refs 11 and 12 were co-authored by A. Zagday, T. Bidiwale, V. Vaishampayan, V. Upadhyay, and others from the present review team. This constitutes a direct conflict of interest, declared explicitly here. The Alumina data have not been reproduced by any independent group. Every numerical claim we derive from those two references should be read with that in mind. Independent replication is not a formality it is the only thing that will determine whether these results generalise. We specifically recommend the first replication be led by a team with no author overlap with ours.

Statistical power: No included study used an a priori power calculation. Retrospective power at $n = 6$ for $d = 1.0$ is approximately 42%, meaning over half of real effects of that magnitude would have been missed. The $p > 0.05$ Alumina 10M vs. donepezil result is therefore indeterminate, not evidence of equivalence. Adequately powered studies require $n \geq 15$/group for $d = 0.8$ at 80% power (G*Power 3.1), with pre-specified sample sizes and a registered protocol.

Other constraints: All animals were male. Sex differences in cholinergic sensitivity and antioxidant defence are documented and female cohorts must be included from the design stage in future work. Single-blind methodology leaves room for performance bias. Observer variability in behavioural scoring persists even under blinding. The scopolamine model limitation applies throughout.

The priority list for future work is clear: pre-registered studies with both sexes, $n \geq 10$/group, a priori power calculations, full mechanistic panels (AChE, Nrf2/HO-1, neuroinflammatory markers), and a shift toward transgenic amyloid or tau models.

Conclusion

Across seven controlled animal studies, potentised preparations of Lycopodium clavatum, Mercurius solubilis, Gelsemium sempervirens, and Alumina have each produced biologically detectable, preparation-specific responses in standardised dementia models, with potency-related gradients appearing independently across cholinergic and oxidative endpoints.[7–12]

The Alumina preclinical data add a potency-graded profile spanning both behaviour and oxidative stress in one cohort. Alumina 10M approached donepezil reference values on most endpoints ($p > 0.05$; $d = 0.4$ for MDA), but the data come from six animals per group at one institution with author overlap with this review.[11,12] These are preliminary observations, held as such.

The Nrf2/HO-1 hypothesis is biologically plausible and directly testable with defined methods. Establishing it requires pre-registered, independently run, adequately powered studies with both sexes, the molecular panel described above, and eventual evaluation in transgenic disease models. Until that evidence exists, no clinical inference is warranted from the current literature.

Declarations

Conflict of Interest: Refs 11 and 12 are co-authored by A. Zagday, T. Bidiwale, V. Vaishampayan, V. Upadhyay, and other members of the present author group. This overlap constitutes a potential conflict of interest and is explicitly declared. The Alumina dataset has not been independently validated. All other authors declare no conflicts.

Independent Validation Statement: The Alumina data in Refs 11 and 12 have not been reproduced by any unaffiliated laboratory. The authors consider this the primary limitation of the current evidence base and recommend that the first replication study be led by a group with no author overlap with our team, under a pre-registered protocol.

Funding: No external funding was received.

ARRIVE 2.0 Compliance: The animal studies in Refs 11 and 12 were designed and reported according to ARRIVE 2.0 guidelines.

Protocol Registration: Refs 11 and 12 were not prospectively registered. We recommend all future studies be registered on OSF, PROSPERO, or AsPredicted prior to data collection.

Ethical Approval: Approved by the Institutional Animal Ethics Committee, Biotox Laboratories, Nashik (No. Biotox/IAEC/06/2025/RP-35); all procedures under CPCSEA guidelines.

Author Contributions (CRediT): Avishkar Zagday: conceptualisation, literature review, writing – original draft. Tazeen Bidiwale: writing – review and editing, validation. Vaishali Vaishampayan, Samidha Mumbaikar, Manisha Soni, Samreen Kavare, Pulin KS, Dipak Patel, Tushar Patil: writing – review and editing. Vinay Upadhyay: supervision, writing – review and editing. All authors approved the final version.

AI Assistance: Language editing tools were used for copyediting and structural revision. All scientific content, data, and interpretations are the authors' own.

AI use is limited to editing and does not constitute authorship.

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