Letters & Reviews in Neurological Sciences

Gold in Different Forms for the Treatment of Amyotrophic Lateral Sclerosis / Motor Neuron Disease: A Narrative Review of Nanocrystalline, Molecular and Ayurvedic (Swarna Bhasma) Gold

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ABSTRACT

Background: Amyotrophic lateral sclerosis (ALS), termed motor neuron disease (MND) in many countries, is a fatal neurodegenerative disorder with very few disease-modifying treatments. Impaired neuronal bioenergetics, oxidative stress and protein misfolding recur in ALS biology, and gold in several chemical forms has been proposed to act on these processes.

Aim: To review critically the experimental and clinical evidence for gold in nanocrystalline, functionalised-nanoparticle, molecular gold (I) and traditional (Ayurvedic/Siddha) forms in ALS/MND.

Methods: Narrative review of peer-reviewed articles, trial reports and company disclosures located up to September 2026; bibliographic details of the key sources were checked against the original records.

Findings: The best-characterised agent is CNM-Au8, an oral suspension of ~13 nm clean-surfaced gold nanocrystals that catalyses the oxidation of NADH to NAD^+. In the phase 2 RESCUE-ALS trial (n = 45) and the phase 2/3 HEALEY ALS Platform Trial (n = 161) the primary endpoints were not met. Open-label analyses against external controls suggest a survival signal and lower neurofilament light chain, but these are hypothesis-generating. In non-ALS cohorts CNM-Au8 raised the brain NAD^+/NADH ratio by 10.4%. Preclinical studies support gold-nanoparticle conjugates in SOD1 G93A mice and auranofin effects on thioredoxin reductase/Nrf2 signalling and TDP-43 self-interaction in cell models. Swarna bhasma contains nanoscale gold with antioxidant activity in animals, but no ALS-specific studies were identified and heavy-metal content is a concern.

Conclusions: Gold-based approaches are mechanistically attractive but clinically unproven. Confirmatory randomised trials, dose-finding, standardised characterisation and neuron-specific testing of traditional preparations are the priorities.

Key words: Amyotrophic lateral sclerosis; motor neuron disease; gold nanoparticles; CNM-Au8; auranofin; Swarna bhasma; NAD^+; neuroprotection.

1. Introduction

ALS is a progressive disease in which upper and lower motor neurons degenerate, producing weakness, paralysis and, in most patients, death from respiratory failure [1]. Riluzole, the first licensed drug, prolongs survival only modestly [2]. Edaravone, a free-radical scavenger, slowed functional decline in a carefully selected group of patients [3], and the antisense oligonucleotide tofersen is directed at the rare SOD1-mutant form [4]. For the great majority of patients the therapeutic gap remains large.

Several convergent mechanisms are implicated in motor neuron loss. Mitochondrial dysfunction, including altered bioenergetics, calcium buffering and organelle dynamics, has been described extensively in patients and models [5]. Oxidation of cysteine residues in TDP-43, the major component of cytoplasmic inclusions, promotes disulphide cross-linking and loss of solubility [6,7]. These features make redox-active and metabolism-modulating agents plausible therapeutic candidates.

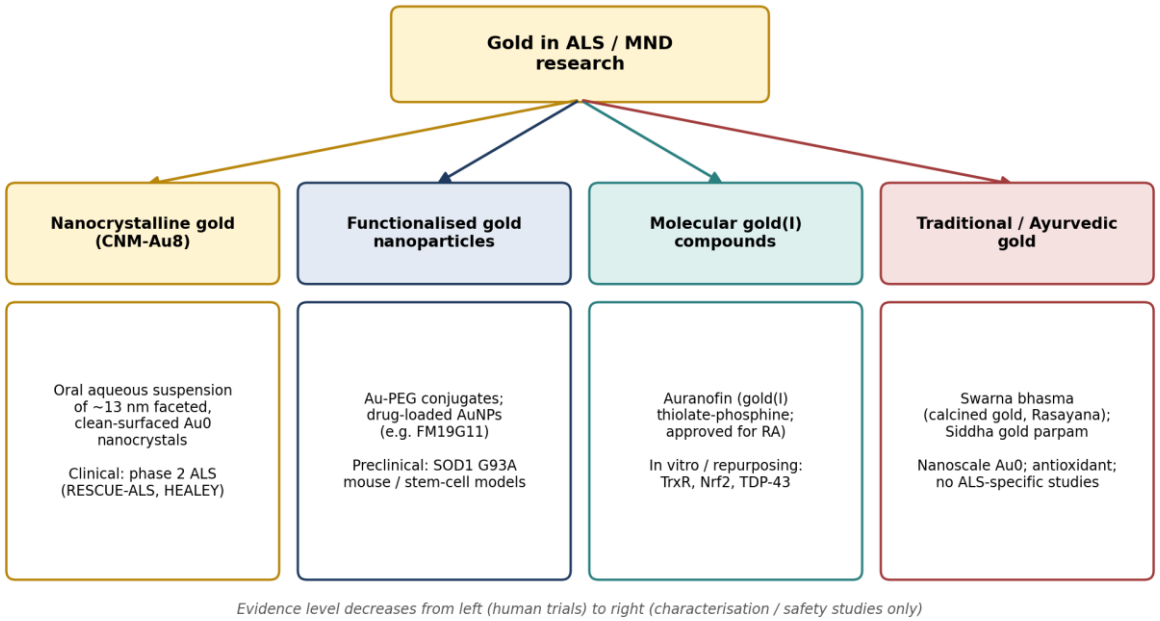
Gold has a long history in medicine. Auranofin, an oral gold(I) compound, is approved for rheumatoid arthritis and has since been investigated for other indications, including neurodegenerative disorders [8]. More recently, engineered gold nanocrystals have entered clinical trials in ALS, while traditional

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gold preparations (bhasma) remain in widespread use in Ayurveda. This review brings these strands together, separating what is established in patients from what is mechanistic or preclinical, and highlights the evidence gaps for each form of gold.

2. Forms of gold relevant to ALS/MND

Four groups of gold agents have been studied or proposed for ALS/MND (Scheme 1, Table 1): catalytically active nanocrystalline gold; functionalised gold nanoparticles used as therapeutics or carriers; molecular gold (I) compounds; and traditional calcined gold preparations. They differ in oxidation state, size, route of delivery and, above all, in the quality of evidence.



Scheme 1. *Classification of the gold-based agents studied or proposed for ALS/MND, with the current level of evidence for each group.*

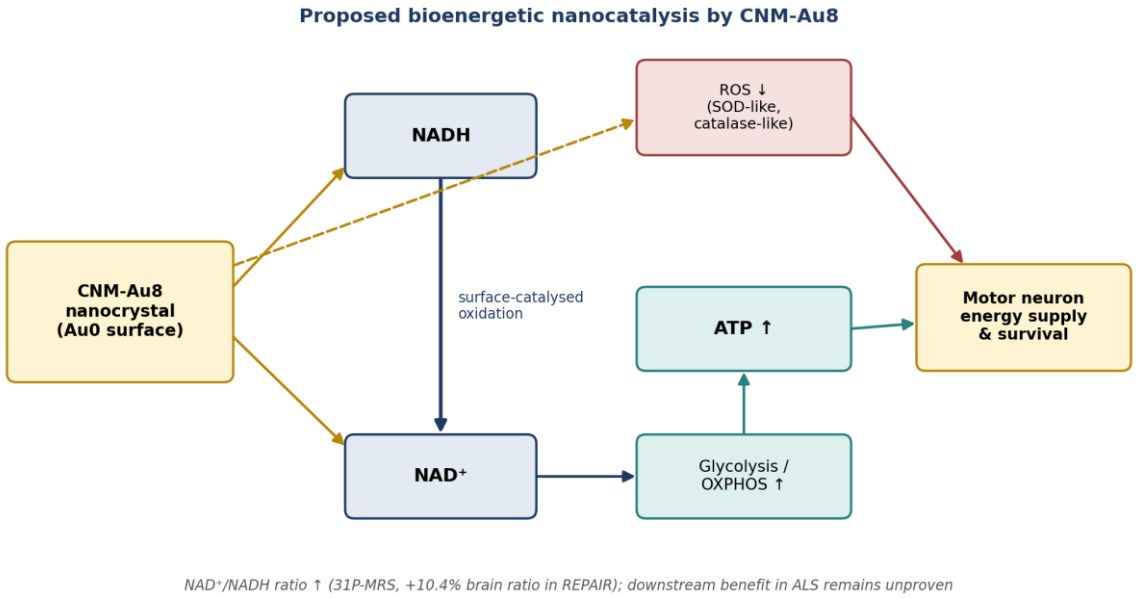
Table 1. Forms of gold considered for ALS/MND.

Form	Example	Size / chemistry	Proposed action	Evidence in ALS/MND
Nanocrystalline gold	CNM-Au8 (oral suspension)	~13 nm faceted, clean-surfaced Au^0 nanocrystals [9]	Catalyses NADH → NAD^+; raises ATP; SOD-/catalase-like activity [10,11]	Two phase 2 trials; phase 3 planned [10,12,13]
Functionalised gold nanoparticles	Au-PEG; FM19G11-loaded AuNPs	PEG-coated or drug-loaded Au^0 particles	Correction of SOD1-linked transport defects (in silico/in vivo); stem-cell modulation [14,15]	Preclinical only
Molecular gold (I)	Auranofin	Gold(I) thiolate-phosphine complex	TrxR inhibition, Nrf2 activation, lower TDP-43 self-interaction [16–18]	In vitro / non-ALS animal data; no ALS trial identified
Traditional gold	Swarna bhasma (Ayurveda); gold parpam (Siddha)	Calcined gold; 5–35 nm crystallites, larger aggregates [19–21]	Antioxidant enzyme induction in animals [22]	Characterisation and safety studies; no ALS-specific data identified

3. Nanocrystalline gold: CNM-Au8

3.1 Physicochemical basis and proposed mechanism

CNM-Au8 is an aqueous suspension of faceted gold nanocrystals whose surfaces are free of the chemical modifications that accompany other production methods [13]. The nanocrystals are about 13 nm in diameter [9]. Their surfaces are reported to catalyse the conversion of NADH to NAD^+, increasing cellular ATP production [10,23], and to reduce oxidative stress through superoxide dismutase-like and catalase-like activity [11] (Scheme 2). The rationale is that bioenergetic failure has been proposed as a driver of ALS [10], and that restoring NAD^+/NADH balance in energy-hungry motor neurons might slow degeneration [23].



Scheme 2. *Proposed bioenergetic mechanism of CNM-Au8: surface-catalysed oxidation of NADH to NAD^+, increased ATP availability and reduced reactive oxygen species (ROS)* [10,11].

3.2 Preclinical evidence

In rodent and human-cell models of ALS, CNM-Au8 improved motor neuron survival after glutamate excitotoxicity or amyloid-β oligomer exposure, reduced cytoplasmic TDP-43 aggregates, protected SOD1 G93A rat motor neurons in a cAMP-dependent manner, prevented death of C9ORF72 iPSC-derived neurons under trophic-factor withdrawal, and improved survival and neurite outgrowth of iPSC motor neurons co-cultured with toxic SOD1 A4V astrocytes [9] (Table 2). These findings come from a conference presentation, and the RESCUE-ALS protocol cited the astrocyte co-culture data as a manuscript in preparation [23]; the full peer-reviewed dataset should therefore be sought before these results are treated as established.

Table 2. Principal preclinical findings for gold agents in ALS-relevant and related models.

Model	Agent	Main finding	Reference
Rat primary spinal motor neurons	CNM-Au8	Improved survival after glutamate or Aβ1-42 injury; preserved neurites; fewer cytoplasmic TDP-43 aggregates	[9]
SOD1 G93A rat motor neurons	CNM-Au8	Protection from excitotoxicity (cAMP-dependent); less SOD1 accumulation (cAMP-independent)	[9]
C9ORF72 iPSC-derived neurons; iPSC motor neurons with SOD1 A4V astrocytes	CNM-Au8	Prevented stress-induced death; dose-dependent gain in survival and neurite outgrowth	[9]
SOD1 G93A mice	Au-PEG	Differences in symptom onset and progression on rotarod and walking tests; docking suggested improved kinesin–tubulin binding in the presence of A4V SOD1	[14]

Model	Agent	Main finding	Reference
G93A-SOD1 ependymal stem progenitor cells	FM19G11-loaded AuNPs	Increased SOX2, OCT4, AKT1 and AKT3; altered miR-19a/PTEN expression	[15]
N2a cells (TDP-43 NanoBiT assay)	Auranofin	Dose-dependent fall in TDP-43 self-interaction; shift to PBS-soluble pool; lower reduced glutathione	[17]
Mouse relapsing–remitting EAE (non-ALS)	Auranofin	TrxR inhibition with Nrf2 up-regulation in the CNS	[18]
Rats (blood–brain barrier)	Gold nanoparticles	Spontaneous BBB penetration; biological half-life 12.9 ± 4.9 h	[24]
Animal models (acute and chronic dosing)	Swarna bhasma	Higher SOD and catalase activity; no toxicity on liver/kidney markers or histology	[22]

3.3 Brain target engagement

The REPAIR studies used 7-tesla ^{31}P magnetic resonance spectroscopy in 11 participants with relapsing multiple sclerosis and 13 with Parkinson's disease. After 12 or more weeks of daily CNM-Au8 the brain NAD^+/NADH ratio rose by 10.4% ($p = 0.037$, paired t-test); the individual cohorts were not significant ($p = 0.11$ and 0.14), and the ratio returned to baseline six weeks after withdrawal in the MS cohort [11]. A later company release of an expanded analysis (n = 39) reported an 8.65% rise [25] (Figure 1A). These data are open-label, non-ALS and small, but they are the main human evidence that the proposed mechanism is engaged in the brain.

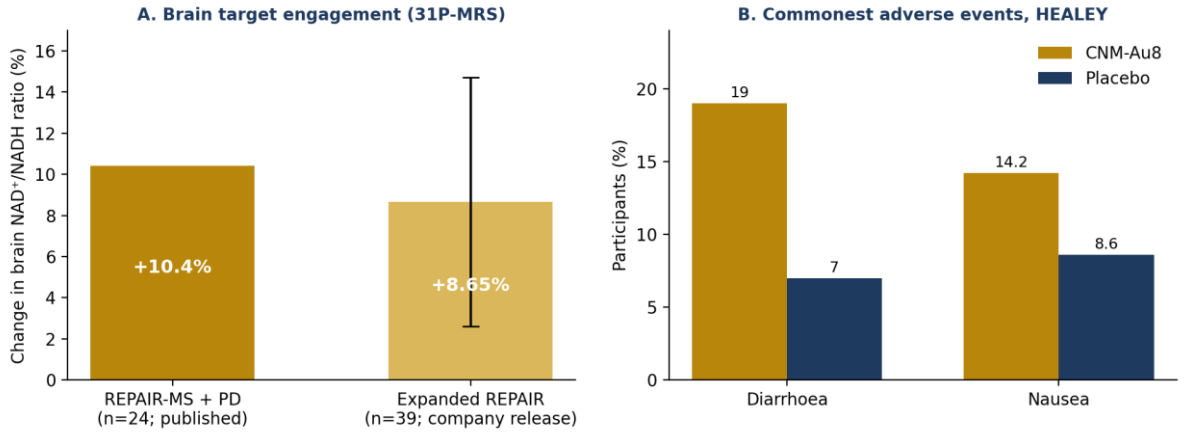


Figure 1. (*A) Change in brain NAD^+/NADH ratio with CNM-Au8 in the REPAIR studies; error bar shows the 95% confidence interval reported for the expanded analysis* [11,25]. *(B) Commonest adverse events in the HEALEY CNM-Au8 regimen* [10].

3.4 RESCUE-ALS (phase 2)

RESCUE-ALS randomised 45 adults with early symptomatic ALS 1:1 to CNM-Au8 30 mg daily or placebo for 36 weeks, on a background of riluzole, at two clinics in Sydney; the primary outcome was change in the motor unit number index (MUNIX), an electrophysiological measure of lower motor neuron loss [12,23]. The primary and secondary outcomes were not significant. Exploratory analyses of disease-progression events, and an open-label extension in which 36 participants continued, suggested slower progression in those initially assigned to CNM-Au8; the drug was well tolerated [12] (Table 3, Figure 2).

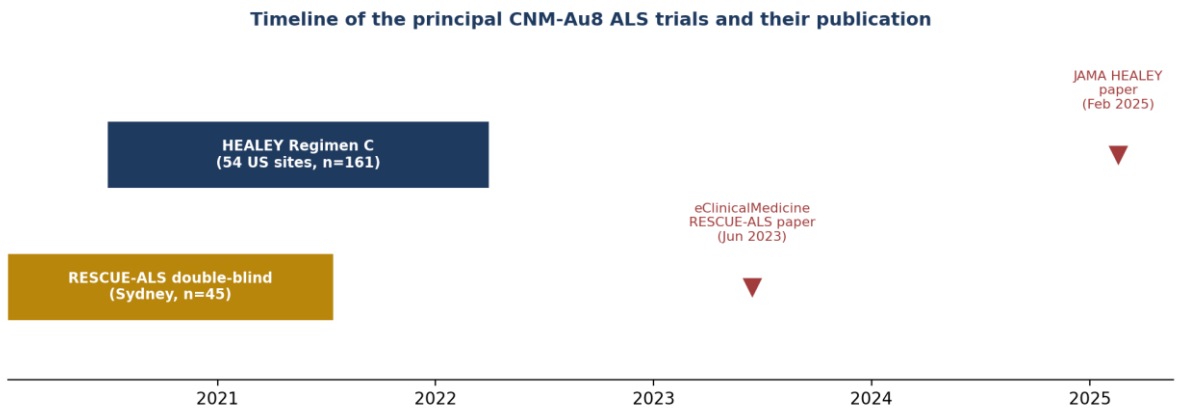


Figure 2. *Timeline of the double-blind periods of RESCUE-ALS (16 January 2020 to 13 July 2021) and HEALEY Regimen C (July 2020 to March 2022) and of their principal publications* [10,12].

3.5 HEALEY ALS Platform Trial (phase 2/3)

In the HEALEY ALS Platform Trial, 161 participants were randomised 3:3:2 to CNM-Au8 60 mg (n = 61), 30 mg (n = 59) or placebo (n = 41) daily for 24 weeks, with 123 concurrently randomised placebo participants from other regimens contributing to the analyses [10]. The primary endpoint, a Bayesian measure combining function and survival, showed no benefit (disease rate ratio 0.97; 95% credible interval 0.783–1.175), and the three secondary endpoints likewise showed neither benefit nor harm [10] (Figure 3). The pooled CNM-Au8 group had more participants with clinically definite ALS and fewer in King's stage 1 than the shared placebo group, a baseline imbalance towards more advanced disease [10]. A topline analysis adjusted for baseline risk reported a lower risk of death, or death or permanent assisted ventilation, at 30 mg but not at 60 mg [26]. Diarrhoea and nausea were more frequent with CNM-Au8 (Figure 1B) [10].

3.6 Long-term analyses and regulatory status

Open-label extension analyses compared 30 mg CNM-Au8 recipients with matched controls from the PRO-ACT database. Reported hazard ratios for death were 0.431 (95% CI 0.276–0.672) over up to 3.5 years in HEALEY participants [27] and 0.406 (95% CI 0.220–0.749) in a pooled HEALEY and RESCUE-ALS analysis [28]; plasma neurofilament light chain also fell [27]. These analyses are non-randomised, open-label, and company-reported, so selection and ascertainment bias cannot be excluded, and they should be read as hypothesis-generating (Figure 3). According to the company's September 2026 prospectus, an application for accelerated approval supported by neurofilament light and clinical data was planned for early in the fourth quarter of 2026, with a confirmatory phase 3 trial (RESTORE-ALS) planned for the second quarter of 2027 [13]; the earlier planned filing date has moved, and current status should be verified before submission of this manuscript.

Table 3. Clinical studies of CNM-Au8 relevant to ALS.

Study	Design and population	Intervention	Main results	Safety / comment
REPAIR-MS / REPAIR-PD (non-ALS)	Phase 2 open-label; 7T ^{31}P-MRS; 11 relapsing MS + 13 PD	30 mg daily, ≥12 weeks	Brain NAD^+/NADH +10.4% (p = 0.037); cohorts alone p = 0.11 and 0.14 [11]	Target engagement; not an efficacy trial
RESCUE-ALS	Phase 2, randomised, double-blind; n = 45 early symptomatic ALS; 36 weeks + OLE	30 mg daily vs placebo, with riluzole	Primary (MUNIX) and secondary outcomes not significant; exploratory signals for slower progression [12]	Well tolerated; adverse events balanced between arms
HEALEY Regimen C	Phase 2/3 platform; 54 US sites; n = 161 (mean age 58.4 y; 37.9% female)	60 mg (n = 61), 30 mg (n = 59), placebo (n = 41) for 24 weeks	DRR 0.97 (0.783–1.175); secondary endpoints no benefit [10]	Diarrhoea 19% vs 7%; nausea 14.2% vs 8.6%
HEALEY OLE and pooled analyses	Open-label; external PRO-ACT matched controls	30 mg daily	Death HR 0.431 (0.276–0.672) to 3.5 y; pooled HR 0.406 (0.220–0.749) [27,28]	Company-reported; hypothesis-generating

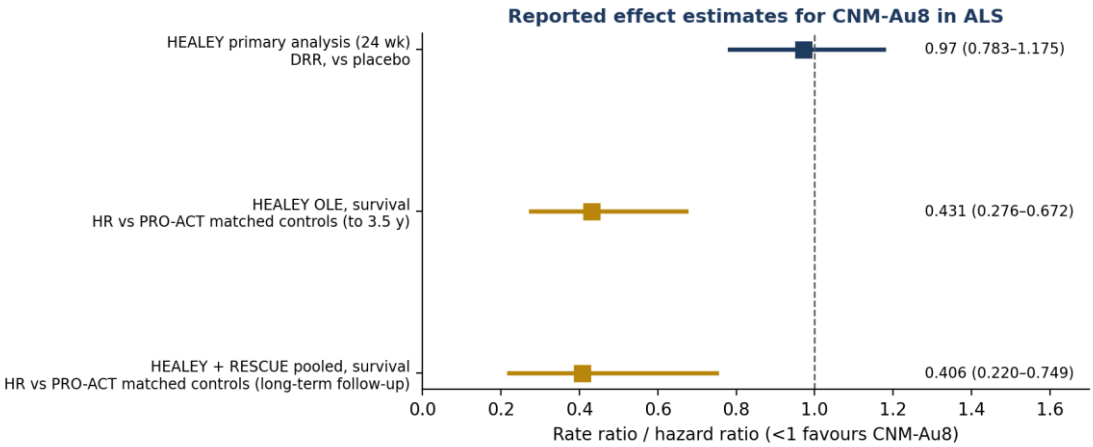


Figure 3. *Reported effect estimates for CNM-Au8 in ALS. The blinded randomised comparison (blue; 95% credible interval) is null, whereas open-label analyses against external controls (gold; 95% CI) favour treatment but are susceptible to bias* [10,27,28].

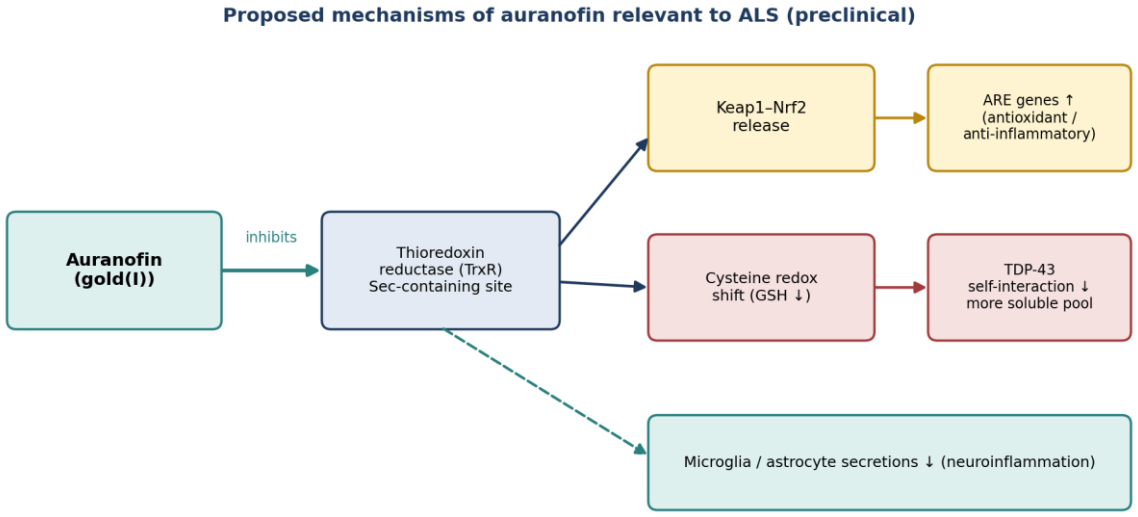
4. Functionalised gold nanoparticles

Gold nanoparticles can cross the blood–brain barrier. After intraperitoneal injection in rats, gold reached brain regions, penetration was reduced by about half by ion-channel blockers, and the biological half-life was about 13 hours, although much of the gold detected sat in blood vessels until perfusion was performed [24]. This property underlies the use of gold particles as carriers and as therapeutics in their own right.

A PEGylated gold nanoconjugate (Au-PEG) was tested in SOD1 G93A mice after earlier in vitro work reported that a gold ‘nano-chaperone’ restored motor processivity that mutant SOD1 had impaired; treated animals differed from controls in the onset and progression of behavioural deficits, and docking suggested that gold improved kinesin–tubulin binding in the presence of A4V SOD1 [14]. The supplementary data indicate small groups (6 control and 9 treated mice) [14], and the docking results are computational. FM19G11-loaded gold nanoparticles increased pluripotency and proliferation markers in ependymal stem progenitor cells from G93A-SOD1 mice [15], illustrating a regenerative rather than purely protective strategy. Neither approach has reached clinical testing in ALS.

5. Molecular gold (I): Auranofin

Auranofin’s principal mechanism is inhibition of redox enzymes that regulate intracellular reactive oxygen species [8]. Its main target is thioredoxin reductase (TrxR), which it inhibits through the selenocysteine-containing active site [16]. In a screen of pharmacologically active compounds, auranofin gave the strongest dose-dependent reduction of TDP-43 self-interaction without overt toxicity, moved TDP-43 from insoluble to PBS-soluble fractions in N2a cells and lowered reduced glutathione, consistent with oxidative modification of TDP-43 cysteines [17]. Inhibition of TrxR also releases Nrf2 signalling; auranofin raised Nrf2 activity in the CNS of mice with relapsing–remitting EAE [18], and astrocytic Nrf2 over-expression protected motor neurons and extended survival in ALS mouse models through increased glutathione secretion [29]. Auranofin has additionally been reported to inhibit cytotoxic secretions from human astrocytes and to be directly neuroprotective [30] (Scheme 3).



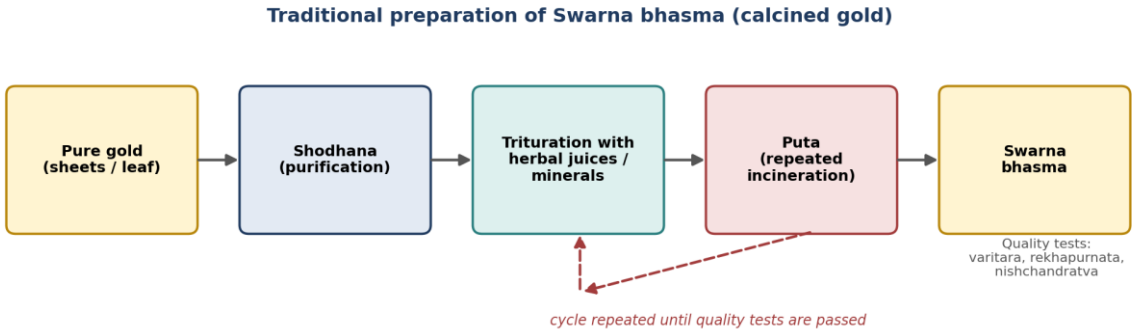
Scheme 3. Proposed mechanisms of auranofin relevant to ALS, derived from cell and non-ALS animal studies [16–18,30].

A translational gap exists. The TDP-43 effects were measured at micromolar concentrations (1.6–62.5 µM), whereas oral dosing in rodents has been reported to give CNS concentrations above only about 0.1 µM [17,30]. Because TrxR is ubiquitous, systemic redox disturbance is also a concern, and the toxicity profile established in rheumatoid arthritis would need to be re-evaluated in ALS [8]. No ALS clinical trial of auranofin was identified in the sources reviewed.

6. Ayurvedic and other traditional gold preparations

6.1 Swarna bhasma: Preparation and composition

Swarna bhasma (calcined gold) is a classical Ayurvedic Rasayana, described in the Rasashastra literature as a rejuvenating and longevity-promoting drug [19]. About twenty-five preparation methods are documented, using substances such as mercury, sulphur, lead and plant materials with repeated calcination [19]. In the Putapaka process, purified gold is ground with herbal extracts and incinerated at about 1000 °C in repeated cycles, reducing particle size by successive comminution [21] (Scheme 4). Siddha medicine uses analogous incinerated metal preparations [21]. Classical indications cited for Swarna bhasma include loss of memory, nervous disorders, rheumatoid arthritis and early ageing [22].



Scheme 4. *Outline of the traditional preparation of Swarna bhasma, from purification (Shodhana) through trituration with herbal juices or minerals and repeated incineration (Puta)* [19,21].

6.2 Physicochemical characterisation and safety studies

Modern analysis shows that Swarna bhasma is largely metallic gold at the nanoscale, but the product is not uniform (Table 4, Figure 4). X-ray diffraction and electron microscopy of an industrial sample showed highly crystalline spherical gold particles of 5–20 nm and about 95% gold by gravimetry, whereas other studies report gold contents from about 20% to about 90% depending on the method [19]. Two batches examined for blood compatibility had crystallite sizes of 28–35 nm, were non-cytotoxic, caused negligible complement or platelet activation, and opened tight junctions in a Caco-2 model [20]. Incinerated gold particles entered human cells through vesicles without noticeably altering cell activity, although they formed aggregates larger than 2 µm, unlike dispersed citrate-capped nanoparticles [21].

Table 4. Characterisation, toxicity and biological findings for Swarna bhasma.

Study	Material	Findings
Patil-Bhole et al. [19]	Industrial Swarna bhasma	XRD: principally pure nanoscale gold; FE-TEM: spherical particles 5–20 nm; gravimetric gold ~95%; traditional bhasma tests applied; gold content in earlier studies ~20%, ~52% and ~90%
Paul and Sharma [20]	Two batches	Crystallite size 28–35 nm; non-cytotoxic; no blood-cell aggregation or protein adsorption; negligible complement/platelet activation; tight-junction opening in Caco-2 cells
Beaudet et al. [21]	Incinerated gold particles vs citrate-capped AuNPs	Cell entry by vesicles in HeLa and HFF-1 cells; no noticeable effect on cell activity; particles aggregate (>2 µm)
Mitra et al. [22]	Swarna bhasma prepared with realgar, lead oxide, gold and Calotropis latex	Gold plus trace elements (Fe, Al, Cu, Zn, Co, Mg, Ca, As, Pb); no acute mortality in mice; no chronic toxicity by SGPT, SGOT, creatinine, urea or histology; higher SOD and catalase activity

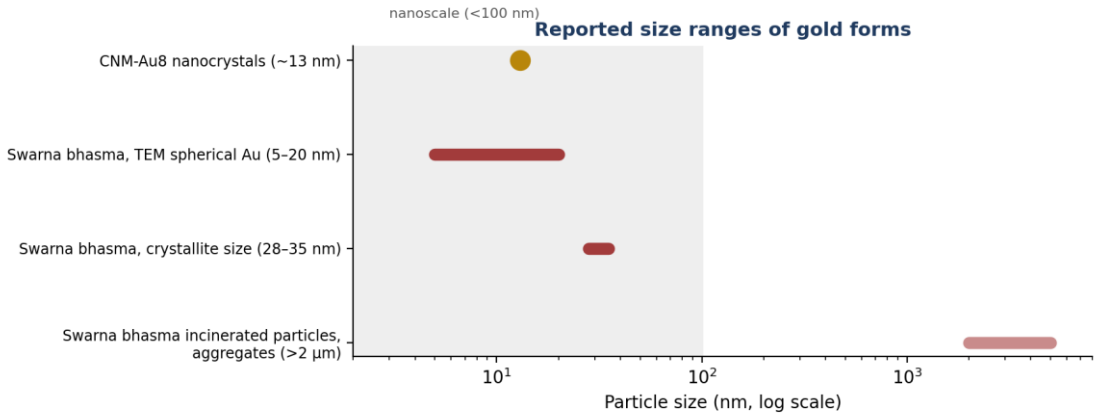


Figure 4. *Reported particle-size ranges of CNM-Au8 and of Swarna bhasma by different methods* [9,19–21]. *For aggregates the figure gives only the reported lower bound (>2 µm); the upper end of the bar is illustrative.*

6.3 Relevance to ALS/MND

No ALS-specific or motor-neuron-specific study of Swarna bhasma or other traditional gold preparations was identified in the literature reviewed. The existing biological data are indirect: higher SOD and catalase activity in animals [22], absence of cytotoxicity in cell lines and blood [20,21], and the traditional use of gold in nervine and rejuvenative regimens [19,22]. Ayurvedic practitioners often interpret progressive neuromuscular wasting within the framework of vata disorders, but this is an interpretive correlation rather than a validated equivalence with ALS. Two safety issues are central. First, mercury-based processing is documented [19], and at least one classical formulation contained arsenic- and lead-based ingredients, with arsenic and lead detected in the product [22]. Second, composition varies widely between preparations [19], so results from one batch cannot be extrapolated to another. Unregulated colloidal gold supplements lack controlled data and should not be conflated with either CNM-Au8 or well-characterised bhasma.

7. Integrated view of mechanisms

The four gold groups act on partly overlapping nodes of ALS pathobiology (Figure 5). CNM-Au8 is directed at bioenergetic failure and oxidative stress [10,11]; auranofin at redox signalling, TDP-43 solubility and glial inflammation [17,30]; gold-nanoparticle conjugates at SOD1-related transport defects [14]; and Swarna bhasma, on current evidence, at antioxidant defences [22]. Only the NAD^+/NADH change with CNM-Au8 has been demonstrated in the human brain [11], and no study has shown that engaging any of these nodes slows ALS.

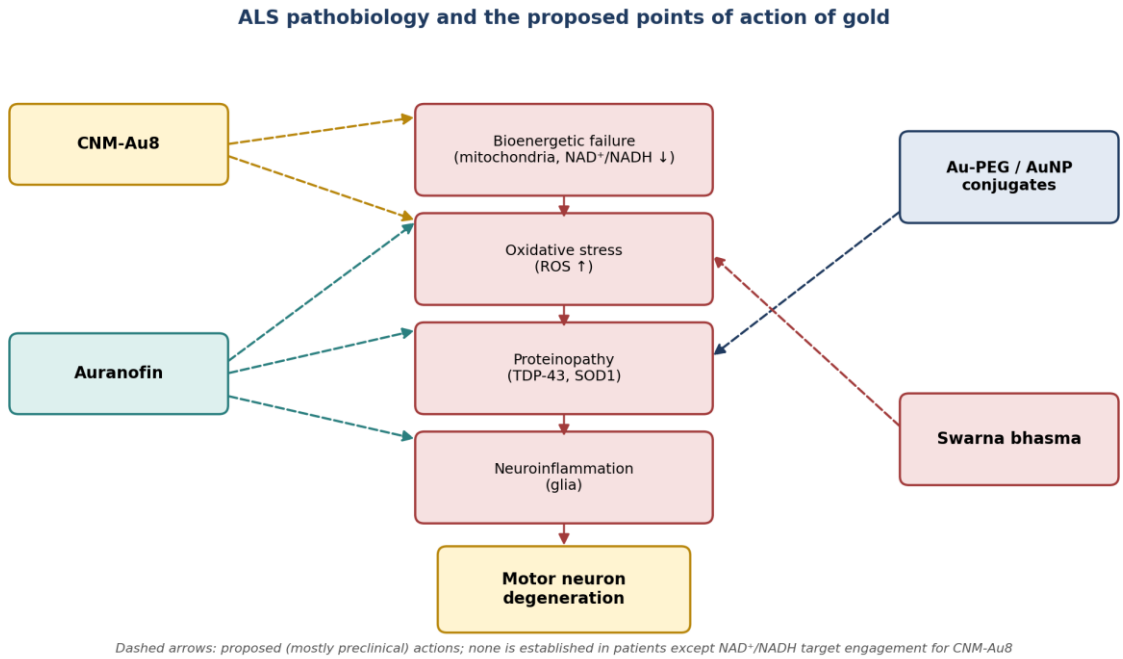


Figure 5. *Integrated scheme of ALS pathobiology and the proposed points of action of each gold agent. Dashed arrows indicate proposed, largely preclinical actions* [10,11,14,17,22].

8. Critical appraisal, limitations and future directions

The clinical story of CNM-Au8 illustrates the difficulty of interpreting early-phase ALS data. The pre-specified primary endpoints of both randomised trials were not met [10,12], while survival and biomarker signals emerged in secondary, exploratory or open-label analyses with baseline imbalance and external controls [10,27,28]. The absence of a survival benefit at 60 mg, the higher of two doses [26], also needs explanation through pharmacokinetic and pharmacodynamic work. Table 5 summarises the main limitations and the evidence needed to resolve each.

Table 5. Key limitations and suggested next steps.

Issue	Evidence	Suggested next step
Efficacy signal *vs* failed primary endpoint	Null blinded primary results; survival signal only in secondary/open-label analyses [10,27]	Adequately powered confirmatory phase 3 (RESTORE-ALS is planned) [13]
Biomarker as surrogate	Neurofilament light reductions reported by the sponsor [13,27]	Independent validation against clinical outcomes
Dose–response	No survival benefit at 60 mg [26]	Dose-ranging pharmacokinetic/pharmacodynamic studies
Auranofin exposure gap	Effective in vitro at µM levels; CNS ~0.1 µM in rodents [17,30]	Exposure-guided dosing and safety studies in ALS models
Nanoparticle biodistribution	BBB penetration with substantial gold in blood and organs [24]	Long-term biodistribution and clearance studies
Standardisation of bhasma	Gold content ~20–95%; arsenic, lead, mercury concerns [19,22]	Batch standardisation, elemental analysis, neuron-specific preclinical testing
No ALS data for traditional gold	None identified	Controlled SOD1 G93A studies before any clinical use

Priorities for future work are: (i). completion of confirmatory randomised trials for CNM-Au8 with survival-based and functional endpoints; (ii). peer-reviewed publication of the preclinical ALS dataset for CNM-Au8; (iii). exposure-matched testing of auranofin in ALS models; (iv). head-to-head characterisation of gold nanoparticle forms for brain delivery and clearance; and (v). neuron-specific and safety testing of standardised Ayurvedic gold preparations before any clinical evaluation.

9. Conclusions

Gold in its different forms engages biologically plausible targets in ALS, including NAD^+/NADH metabolism, redox balance, TDP-43 solubility and glial inflammation. For nanocrystalline CNM-Au8, brain target engagement has been shown, but the two randomised trials did not meet their primary endpoints, and survival signals await confirmation. Functionalised gold nanoparticles and auranofin remain preclinical for ALS, and Swarna bhasma lacks ALS-specific evidence and standardisation. Patients should not take unregulated gold preparations in the expectation of benefit; further controlled research is required.

Declaration, Conflict of interest and funding

The content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological sciences.

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Conflict of interest: The author declares no conflict of interest.
Ethics approval: Not applicable; this article is a literature-based narrative review and contains no new human or animal data.
Data availability: No new datasets were generated or analyzed.

Author Note

This manuscript is a literature review and is not a treatment recommendation for an individual patient. Mineral supplementation or chelation should be undertaken only for a clinically justified indication and with appropriate medical monitoring.

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