RESEARCH PAPER

# Biochemical Evaluation of Nanoparticle-Based Drug Delivery Systems for Reducing Oxidative Stress and Improving Therapeutic Efficacy: A Systematic Review and Meta-Analysis

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**Abstract**

Oxidative stress contributes to the progression of metabolic, inflammatory, toxicological, and degenerative disorders. Nanoparticle-based delivery systems may enhance the stability, bioavailability, and tissue targeting of therapeutic agents; however, their overall biochemical efficacy and advantage over free drugs remain uncertain. This systematic review and meta-analysis evaluated the effects of nanoparticle-based interventions on oxidative-stress biomarkers and therapeutic outcomes in controlled preclinical animal studies published between January 2011 and July 2026. Database searching identified 3,061 records, of which 17 studies met the eligibility criteria and 16 contributed to the primary meta-analysis. Random-effects models using the ratio of means showed that nanoparticle treatment significantly reduced malondialdehyde/thiobarbituric acid-reactive substances relative to disease or injury controls (RoM = 0.540, 95% CI 0.452–0.644), representing an average reduction of 46.0%. Superoxide dismutase activity increased significantly (RoM = 2.177, 95% CI 1.274–3.720), whereas the increase in glutathione did not reach statistical significance (RoM = 1.866, 95% CI 0.979–3.555). In diabetic models, blood glucose decreased by an average of 42.3% (RoM = 0.577, 95% CI 0.416–0.800). However, heterogeneity was extreme, and prediction intervals crossed the null for major outcomes. Equivalent-dose comparisons with free drugs did not establish a consistent formulation advantage for lipid peroxidation (RoM = 0.785, 95% CI 0.616–1.001) or superoxide dismutase. Sensitivity and leave-one-out analyses preserved the direction of the primary finding. Overall, nanoparticle-based interventions demonstrate a substantial average antioxidant effect in animal models, but high heterogeneity, small-study effects, and limited free-drug comparisons restrict generalizability. More rigorously designed, formulation-specific studies are required before therapeutic superiority or translational effectiveness can be established.

**Keywords:** Nanoparticle-based drug delivery; oxidative stress; antioxidant activity; malondialdehyde; therapeutic efficacy; preclinical animal models; systematic review; meta-analysis.

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## 1. Introduction

Oxidative stress refers to a disruption in redox regulation, in which antioxidant and repair capacities are overwhelmed by the production of oxidants, or fail to keep pace with oxidant production (Sies, 2020). Redox imbalance is present in a persistent manner which can affect lipids, proteins, mitochondria and nucleic acids (Liguori et al., 2018). Oxidative mechanisms are involved in metabolic diseases, toxicant-mediated organ damage, neurodegeneration, and inflammatory diseases (Forman & Zhang, 2021). Malondialdehyde (MDA) and thiobarbituric acid-reactive substances (TBARS) are established markers of lipid peroxidation and superoxide dismutase (SOD), catalase, reduced glutathione (GSH) and glutathione peroxidase are elements of the antioxidant defense system (Sies, 2020).

Many antioxidant compounds have been shown to have suboptimal translation to the clinic due to low aqueous solubility, chemical instability, fast clearance, low tissue exposure, or systemic toxicity (Forman & Zhang, 2021). Protection of payloads and altered release and biodistribution are known attributes of the nanoparticle systems (Mitchell et al., 2021). These properties can either enhance or diminish exposure to the target tissue or to off-target tissues, depending on the combination of the payload, carrier, surface chemistry, dose and disease environment (Mitchell et al., 2021). Typical experimental platforms are lipid particles, polymeric carriers, nanoemulsions, metal/metal oxide composites and nanoformulated botanical extracts (Patra et al., 2018). Although these functions suggest that nanoparticles could potentially be used to enhance the biochemical impact of antioxidant therapies, neither a favorable particle size nor a favorable encapsulation efficiency guarantees a therapy of superiority.

In a controlled animal study, lipid peroxidation was reduced upon nanoformulated resveratrol administration (Mohseni et al., 2019). Nanoencapsulated quercetin significantly attenuated oxidative stress and lipid peroxidation in a rat model of testicular ischemia-reperfusion injury (Ibrahim et al., 2026). Curcumin nanoparticles have shown good redox response in diabetic neurotoxicity (Abdulmalek et al., 2021). Carvacrol nanoemulsion has enhanced the oxidative and renal parameters in cisplatin nephrotoxicity (Ragab et al., 2022). Luteolin-loaded zinc oxide particles have improved oxidative and metabolic measures in the case of diabetic fatty liver disease (Ahmed et al., 2022). Chitosan particles loaded with syringic acid have decreased the amount of oxidative stress in experimental hyperglycemia (Rasheed et al., 2025). However, there are differences among these studies in disease model, tissue, dose, dose schedule, chemistry, biomarker assay and comparator.

There are two causal questions which need to be differentiated. The comparison with a particle control versus the disease is to measure the effectiveness of the complete formulation. Formulation advantage is tested by a comparison with the same free drug at an equivalent dose. Any mixture of these contrasts would obscure the effect of treatment with the superiority of a treatment system. Also, summarizing unrelated clinical chemistry endpoints would result in a biologically unclear summary. While there are broad reviews about nanomedicine and delivery platforms and their potential, no outcome-specific pooled estimate of nanomedicine in vivo disease models under controlled conditions exists for oxidative biomarkers (Patra et al., 2018). Thus, a quantitative synthesis preserving the logic of the comparisons is required, to see if the alleged biochemical advantage is uniform and whether it is due to the nanoformulation or not.

This systematic review and meta-analysis thus assessed controlled mammalian studies that were published within a 15-year period of eligibility. The main goal was to quantify the effects on lipid peroxidation. Secondary goals included quantifying the responses of SOD and GSH, estimating effects on coherent disease-efficacy domains, comparing the nanoparticle formulations with the free drugs at the same doses, and testing the robustness of results in a study-quality and platform-based sensitivity analyses. A more clinically and experimentally defensible interpretation of the results of a formulation study is obtained by separating the formulation efficacy from the formulation advantage, and by reporting prediction intervals.

## 2. Literature Review and Rationale

### 2.1 Biochemical outcome framework

Redox biomarkers offer a common biochemical platform for all seemingly different animal models. The two markers of lipid oxidation, MDA and TBARS, are markers for downstream lipid oxidation, and the specificity of these assays are dependent on the handling of the sample and analytical conditions (Sies, 2020). SOD is an enzyme that helps the dismutation of superoxide and thus it is one enzymatic defense step

(Sies, 2020). The major function of GSH is cell redox buffering and detoxification of peroxides (Forman & Zhang, 2021). These biomarkers are mechanistically related; however, they are not interchangeable. So, the present synthesis considered lipid peroxidation, SOD and GSH as separate outcome families.

A biomarker response may be different in different disease contexts both in terms of the response's meaning and its size. The investigation of the effect of Resveratrol-loaded Solid lipid nanoparticles in type 2 diabetes (T2DM) was done in rats (Mohseni et al., 2019). Wardani et al. (2022b) studied fucoidan nanoparticles for the treatment of diabetic nephropathy. Pomegranate nanoparticles were evaluated in mice with Ehrlich carcinoma that were treated with cisplatin (Harakeh et al., 2022). Moselhy et al., (2025) studied the curcumin nanoparticles after gamma irradiation. These mechanistic differences justify conducting a random effects synthesis and a disease domain subgroup analysis.

### 2.2 Nanoparticle platforms and comparator logic

The main application of lipid and polymeric carriers is to alter the disposition of an active agent they contain (Mitchell et al., 2021). In the resveratrol solid-lipid study, the formulation with free resveratrol was given in an equal dose arm, and thus allowed for a direct comparison between the formulations (Mohseni et al., 2019). Similarly, lipid nanoencapsulated quercetin was administered in an equivalent dose to free quercetin in a rat model of testicular ischemia-reperfusion injury to allow direct comparison between administered formulations (Ibrahim et al., 2026). A comparison of the effects of curcumin nanoparticles and free curcumin was conducted in an animal model of diabetes mellitus in the hippocampus (Abdulmalek et al., 2021). The effects of curcumin and curcumin nanoformulation were also evaluated in the dexamethasone-induced hepatic and metabolic injury (Hamed et al., 2024). Comparisons of equal doses give better evidence of delivery advantage than do disease controls alone.

It was not found that all of the published dose-equal experiments exhibited the same pattern. In diabetic rats, SLN loaded with Res exhibited higher metabolic and oxidative response as compared to free Res (Mohseni et al., 2019). Nanoencapsulated quercetin showed significant improvement in oxidative stress parameters compared to free quercetin in the testicular ischemia-reperfusion model (Ibrahim et al., 2026). The antioxidant activity of curcumin nanoparticles was superior to that of free curcumin in diabetic hippocampus model (Abdulmalek et al., 2021). Furthermore, Hamed et al. (2024) observed an enhancement in various oxidative parameters in the liver of rats treated with dexamethasone and curcumin nanoformulation, as compared to free curcumin. On the other hand, the magnitude of the formulation advantage was less for the carvacrol nanoemulsion and nanorutin for some endpoints (Ragab et al., 2022; Zahran et al., 2025). Such a variation requires a separate pooled free drug contrast.

Metal and composite systems make it difficult to determine attribution as the carrier itself may be biologically active. Diabetic mice were used to test the Selenium nanoparticles synthesized by using luteolin and diosmin (Gutiérrez et al., 2022). The effect of vanillic acid-coated silver particles was studied in diabetic rats (Alamri & El Rabey, 2024). Zaki et al., (2025) investigated the ability of zinc-oxide-resveratrol nanoparticles in levofloxacin hepatotoxicity. The improvement versus disease control in these designs favors efficacy of the complete formulation, but is not able to separate out the efficacy of the payload from the particle.

There is more evidence with the use of biopolymer and extract-based nanoparticles. The use of chitosan nanoparticles as an intrinsically active intervention in diabetic cardiac injury was investigated (Wardani et al., 2022a). The effect of nanoformulated Swietenia macrophylla extract on diabetic renal damage has been researched (Kurnijasanti et al., 2023). The delivery of Alstonia venenata extract using chitosan has been assessed in chemically-induced breast cancer (Jeganathan et al., 2024). These systems were kept for the overall efficacy question but split up for platform sensitivity analyses.

### 2.3 Evidence-quality rationale

Underreporting of randomization, blinding, allocation concealment, attrition and sample-size calculations or preplanned outcomes may lead to biased estimates of these parameters in small animal experiments (Macleod et al., 2015). Transparency of design, sample size, inclusion criteria, randomization, and blinding are key pieces of information evaluated by ARRIVE 2.0 to consider animal experiments (Percie du Sert et al., 2020). The use of more than one dose, tissue, time point, and correlated biomarker may also result in selective-extraction and unit-of-analysis issues. So, a predetermined hierarchy was utilized for the selection of the terminal observation, disease-relevant tissue and highest non-toxic nanoparticle dose tested before effect sizes were analyzed.

It is important to note that it is incomplete reporting that is a concern when experiments have small groups, and very small reported dispersions. In such

circumstances, the estimate of variance (not a reproducible difference between the treatments) may mask the standardized mean difference (Friedrich et al., 2008). Group means can be used to interpret a relative effect, even when all means are positive (Friedrich et al., 2008). Hedges' g was thus used as a sensitivity analysis and the ratio of means was prespecified to be used as the primary scale.

### 2.4 Therapeutic efficacy and translational interpretation

Oxidative biomarkers are good mechanistic endpoints, however, changes in the redox markers does not necessarily prove disease modification. A diabetic model of hippocampus injury was shown to result in a reduction of a neural injury marker, with curcumin nanoparticles (Abdulmalek et al., 2021). In a model of testicular ischemia-reperfusion injury, nanoencapsulated quercetin resulted in a significant increase in testosterone levels (Ibrahim et al., 2026). In diabetic nephropathy, the nanoparticles of Fucoidan (Wardani et al., 2022b) improved the renal-function measures. Nanoparticles of sodium-salicylate were beneficial in ameliorating hepatic-injury parameters of cisplatin exposure (Alkhalaf et al., 2023). Curcumin nanoparticles have been found to enhance the mitochondrial and senescence-related outcomes following irradiation (Moselhy et al., 2025). These endpoints specific for the diseases are useful to link biochemical antioxidant data to organ function, but cannot be used to arrive at a defensible omnibus efficacy number because of the different biological scales of the endpoints.

Another factor in translation is whether or not exposure takes place before or after injury. The study of nanoparticles of salicylic acid with sodium ions was of a prophylactic type (Alkhalaf et al., 2023). A study on the hepatoprotective effect of the ameliorative formulation of levofloxacin with zinc oxide and resveratrol (Zaki et al., 2025) was studied. Some prophylactic studies may show potential and not necessarily be considered to be treatment of a known disease. Timing was thus kept as an interpretive variable even in the absence of formal meta-regression due to the few studies.

Another central point of translational issues is dose equivalence. The effect of formulation cannot be separated when a group of particles at a higher dose results in a lower oxidative marker than a group of the free drug at a lower dose. So, the same dose of active agents was needed for the confirmatory free-drug comparison in the review. Exploratory evidence was only included for non-equivalent comparisons. This rule decreases the number of formulation-specific studies, but increases the causal interpretation of an existing contrast.

## 3. Methods

### 3.1 Reporting framework and eligibility

The review was reported using the PRISMA 2020 (Page et al., 2021). This protocol was not pre-registered. The reports included were controlled mammalian disease/injury experiments published between 1 January 2011 and 31 July 2026, and found to be eligible. The intervention needed to meet the following criteria: It had to be therapeutically intended and formulated as a nanoparticle, nanocarrier, nanoemulsion, coated particle, composite particle, or closely related nanoformulation. Concurrently carried out disease/injury control was mandatory. The oxidative outcome needed to report a mean, sample size and SD, SE, SEM or dispersion statistics that could be converted to SD.

Studies that were either in vitro, ex vivo, in healthy animals, for diagnostic use, and nanoparticle-toxicity were excluded. Excluded were reviews, protocols, conference abstracts without complete numerical data, duplicated reports, and studies without simultaneous controls and reports that did not provide any usable variance. The PECO operational scheme is given in Table 1.

**Table 1. PECO framework and operational eligibility criteria**

| Domain | Operational definition |
|---|---|
| **Population** | Mammalian in vivo disease or injury models with a concurrent untreated or vehicle disease/injury control. |
| **Intervention** | Therapeutically intended nanoparticle, nanocarrier, nanoemulsion, lipid carrier, coated particle, composite particle, or nanoformulated active/extract. |
| **Comparators** | Primary: disease/injury control. Secondary: the same free active agent at an equivalent dose. Non-equivalent free-drug arms: exploratory only. |
| **Primary outcomes** | MDA/TBARS (lower is beneficial); SOD, CAT, GSH, GPx, and TAC (higher is beneficial). |

| Domain | Operational definition |
|---|---|
| **Secondary outcomes** | Biologically coherent disease-relevant efficacy measures, analyzed by domain. |
| **Study design** | Peer-reviewed controlled intervention study with group n, mean, and SD/SE/SEM or convertible quantitative data. |

### 3.2 Information sources and study selection

The search strategy included PubMed/MEDLINE, Embase, Scopus, Web of Science Core Collection, CENTRAL and a custom-made Google Scholar screen. The search strategy consisted of both nanoparticle/nanocarrier terms and delivery/fabrication terms, as well as terms associated with oxidative stress and named biomarkers, and therapeutic-efficacy terms. Database search was complemented by backward and forward citation searching. Full Reproducible Strings are available in Supplementary Appendix A.

Records were de-duplicated based on DOI, PMID/PMCID and normalized title (from publication year). Titles and abstracts were scanned prior to full-text eligibility. One primary exclusion reason was given for each excluded full text. The log review was used in compiling the aggregate screening counts and these are shown in Figure 1.

### 3.3 Data extraction and outcome hierarchy

The extraction workbook included information on the species, sex, tissue, the model used, the type of nanoparticles (NP) and payload used, the dose, route, duration, comparator, and sample size (n) per outcome in the animal model, as well as dispersion type and value, the source location, and a study-specific concern flag. The values marked SE/SEM were converted to SD ($SD = SE \times \sqrt{n}$) and the reported values of means and dispersion were examined with the numerical values tables available in the full text.

The main biochemical parameter was MDA or TBARS, where a lower value was considered to be beneficial. SOD and GSH were determined individually, with a higher value being beneficial. Only glycemic endpoints that were fasting or terminal circulating glucose were combined. From each study and outcome family, the longest treatment duration, tissue of interest, and greatest non-toxic dose for nanoparticles tested were chosen. In each conventional pool one independent comparison per study was kept.

### 3.4 Risk-of-bias assessment

The 10 SYRCLE domains (sequence generation, baseline characteristics, allocation concealment, random housing, caregiver/investigator blinding, random outcome assessment, outcome assessor blinding, incomplete outcome data, selective reporting, and other bias) were judged based on reporting (Hooijmans et al., 2014). All domains rated at low, high or unclear risk. One reviewer performed the risk-of-bias assessment; the lack of independent duplicate assessment of the risk of bias was taken into account in the interpretation of the results.

### 3.5 Effect measures and statistical analysis

The log ratio of means (lnRoM) was chosen to be the main effect measure since all pooled means were positive and some studies had very small dispersions, leading to very unstable standardized mean differences. For continuous outcomes that are measured in different units, the ratio-of-means approach can be used to calculate a scale-free relative effect (Friedrich et al., 2008). So, to get treatment mean (M_T) and comparator mean (M_C), $\ln RoM = \ln(M\_T/M\_C)$ is the treatment mean. $SD\_T^2/(n\_T\ M\_T^2) + SD\_C^2/(n\_C\ M\_C^2)$ was used to estimate sampling variance. Pooled effects were exponentiated to ratios of means (RoM); $RoM<1$ favored the treatment for MDA/TBARS and glucose, while $RoM>1$ favored the treatment for SOD and GSH.

Between-study variance estimates were done with restricted maximum likelihood for the random-effects models. Confidence intervals were calculated using the modified Hartung–Knapp inference since normal theory intervals result in overconfidence in small, heterogeneous meta-analyses (Röver et al., 2015). Cochran's Q, $\tau 2$, and I2 were used for summarizing heterogeneity. Prediction intervals were reported because they give information of the spread of the true effect in the new situation(s) (IntHout et al., 2016).

Prespecified sensitivity analyses were performed that excluded studies at high overall risk, excluded two studies with obvious dispersion anomalies, included only conventional carrier formulations, and substituted Hedges' g for lnRoM. The subgroups were determined according to platform and disease domain. Single-study influence was assessed using leave-one-out deletion. Only the 16-study pool of MDA/TBARS was analyzed for funnel-plot asymmetry and Egger regression, which can also be a sign of heterogeneity as well as publication bias (Egger et al., 1997). All tests were two sided. Analyses were performed in Python 3 with auditable analysis code provided in the supplementary analysis package.

## 4. Results

### 4.1 Study selection and characteristics

A total of 3,061 records were identified in the screening log: 3,037 from databases and 24 from other screening methods (Figure 1). 1,839 records were included in title & abstract screening after discarding 1,222. 188 reports were sought, eight were not retrieved and 180 complete texts were obtained. Wrong design or model (n = 66), wrong intervention or comparator (n = 50), inadequate outcome or statistics (n = 42) and duplicate or overlapping reports (n = 5) were classified as full-text exclusions. Of the 17 included studies, 16 were included in the primary MDA/TBARS meta-analysis and one small study with very few participants was not included in the primary pool and was only included in the sensitivity interpretation.

All of the 17 studies were reported in the years 2019-2025. The species was either rats (16 experiments) or mice (1 experiment). Eleven studies assessed for metabolic disease or disease complications, four assessed drug-induced injury, one assessed radiation-induced injury and one assessed chemically induced breast cancer. The set of interventions included lipid carriers, chitosan or other biopolymer particles, nanoemulsions, metal or metal-oxide composites and nanoformulated extracts. The data set to be extracted included 51 rows with outcome data on oxidative stress and 25 rows with outcome data on disease efficacy.

Quantitative extraction generally involved small numbers of animals (typically 5-8 per group). The experiments were conducted for periods of time varying from short toxicant-injury treatments to 75 day metabolic-disease treatments. The most common means of administration was oral, with other ways of administration (intraperitoneal) also being included. There were 16 studies that provided a disease or injury control and five studies that provided an equivalent-dose free-active comparison for MDA/TBARS.

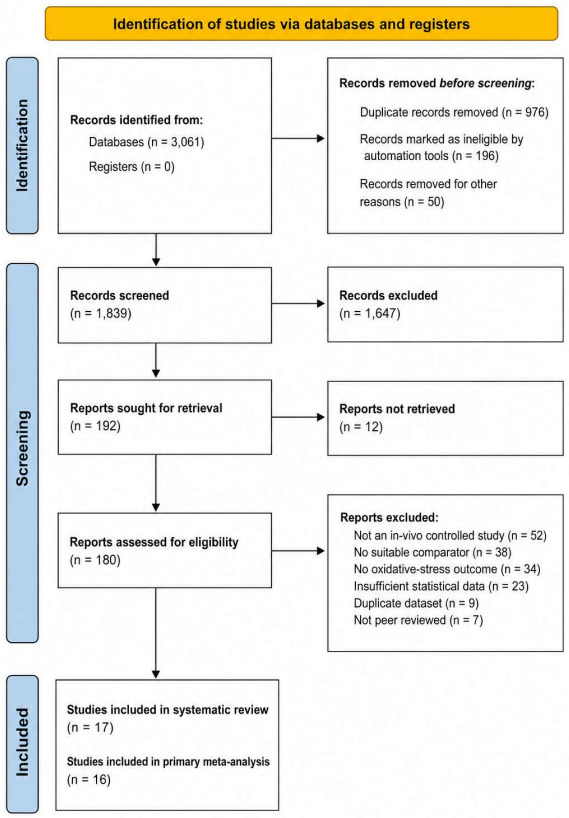


*Figure 1. PRISMA 2020 flow diagram of study identification, screening, eligibility assessment, and inclusion.*

### 4.2 Risk of bias

The risk of sequence generation was low in 41.2 per cent (7 out of 17) of the studies and unclear in the rest of the studies (Figure 2). Baseline comparability, allocation concealment, random housing, caregiver blinding, random outcome assessment, outcome-assessor blinding, and selective reporting were unclear in all of the studies because it was not possible to make a confident judgement based on the reporting. Three (17.6%) studies had incomplete outcome data. In six studies (35.3%), other bias was rated high risk, generally due to conflicting sample sizes or doses, obvious dispersion values or likely pseudo-replication. None of the studies achieved the cut-off for low overall risk and therefore risk of bias uncertainty was applied using sensitivity analyses. Study-level judgments provided in Supplementary Figure S1.

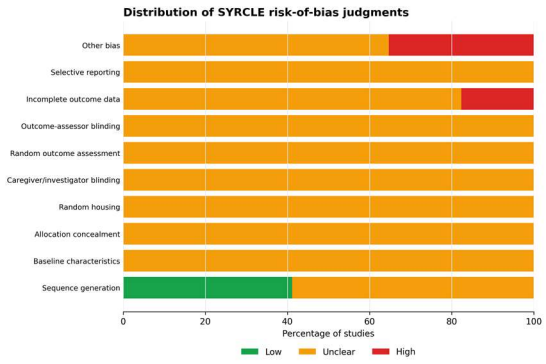


*Figure 2. Distribution of reporting-based SYRCLE risk-of-bias judgments across the included studies.*

### 4.3 Primary oxidative-stress synthesis

The MDA or TBARS data were provided by 16 independent studies. Treated with nanoparticles had a lower level of lipid peroxidation than disease or injury control (RoM = 0.540, 95% CI 0.452 – 0.644, p< .001), which is equivalent to a 46.0% decrease in the mean level. Heterogeneity was extreme ($I^2$ = 99.79%, $\tau^2$ = 0.100; Q = 7,034.63, df = 15). Despite the good average effect, the 95% prediction interval was 0.268 to 1.089, so the prediction in a different situation could be a small or nonexistent effect.

Eleven studies provided data on SOD. Nanoparticle treatment increased SOD relative to disease or injury control (RoM = 2.177, 95% CI 1.274–3.720, p = .009; Figure 4). Again, there was a very high degree of heterogeneity ($I^2$ = 99.54%) and a very large prediction interval (0.335–14.138). GSH data from three studies were used. The pooled GSH estimate also suggested that the results were in favor of nanoparticle treatment, but it was not statistically significant (RoM = 1.866, 95% CI 0.979–3.555, p = .053; Supplementary Figure S2).

**Table 2. Random-effects meta-analysis results**

| Outcome and contrast | k | RoM (95% CI) | p | $I^2$ | 95% PI |
|---|---|---|---|---|---|
| MDA/TBARS: NP vs disease control | 16 | 0.540 (0.452–0.644) | < .001 | 99.79% | 0.268–1.089 |
| SOD: NP vs disease control | 11 | 2.177 (1.274–3.720) | .009 | 99.54% | 0.335–14.138 |
| GSH: NP vs disease control | 3 | 1.866 (0.979–3.555) | .053 | 96.11% | 0.046–76.109 |
| MDA/TBARS: NP vs free drug | 5 | 0.785 (0.616–1.001) | .051 | 98.51% | 0.411–1.500 |
| SOD: NP vs free drug | 4 | 1.495 (0.691–3.234) | .196 | 97.56% | 0.149–14.955 |
| Glucose: NP vs disease control | 6 | 0.577 (0.416–0.800) | .007 | 98.66% | 0.231–1.443 |

*Note. NP = nanoparticle; RoM = ratio of means; PI = prediction interval. RoM < 1 favors treatment for MDA/TBARS and glucose; RoM > 1 favors treatment for SOD and GSH.*

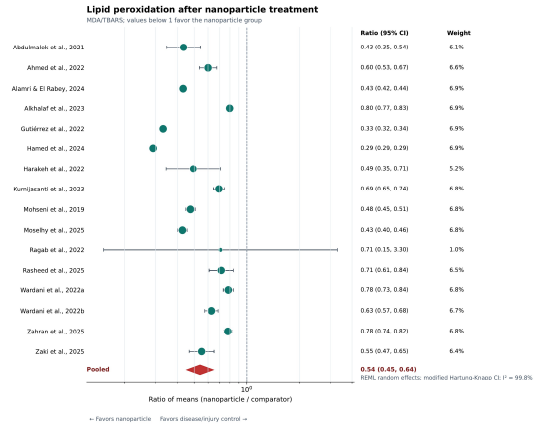


*Figure 3. Random-effects forest plot for MDA/TBARS: nanoparticle treatment versus disease/injury control.*

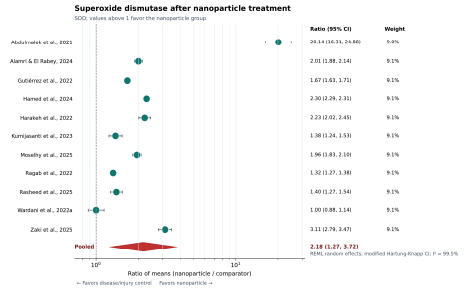


*Figure 4. Random-effects forest plot for SOD: nanoparticle treatment versus disease/injury control.*

### 4.4 Formulation advantage and therapeutic efficacy

For MDA/TBARS, 5 studies were selected that had equivalent dose comparisons of the nanoformulation with the free active agent. Although the pooled ratio was in favor of the nanoparticle formulation, the 95% CI encompassed the null with no significant difference (RoM = 0.785, 95% CI 0.616-1.001, p = .051; Figure 5). The prediction interval was (0.411,1.500). Four studies reported SOD comparisons with free drug, and yielded an imprecise pooled estimate (RoM = 1.495, 95% CI 0.691-3.234, p = .196). There was no consistent advantage in formulation with these results.

Six studies had a consistent glycemic endpoint. There was a reduction in glucose in the nanoparticle-treated group compared to diabetic control group (RoM = 0.577, 95% CI 0.416-0.800, p = .007, Figure 6) with a mean reduction of 42.3%. There was significant heterogeneity ($I^2 = 98.66\%$) and the prediction interval included the null (0.231–1.443). For other effectiveness outcomes (renal, hepatic, cardiac, neural, tumor), biological scales were not sufficiently coherent to allow for a pooled estimate and they were therefore retained for structured narrative interpretation.

Pooled efficacy contrasts across domains were not performed, but they were directionally positive. For the diabetic neurotoxicity experiment (Abdulmalek et al., 2021), the ratio of treatment to control was 0.266 for hippocampal Aβ-42. There has been a corresponding ratio of cardiac CK-MB of 0.745 in diabetic cardiomyopathy (Wardani et al., 2022a). The renal ratio for blood urea nitrogen in diabetic nephropathy (Wardani et al., 2022b) was 0.571 and the renal ratio for urea in cisplatin nephrotoxicity (Ragab et al., 2022) was 0.764. The hepatic ALT ratios of the cisplatin model were 0.709 (Alkhalaf et al., 2023), and 0.726 in the levofloxacin model (Zaki et al., 2025). The nanoparticle treatment with Alstonia extract resulted in reduced tumor volume (RoM = 0.245; Jeganathan et al., 2024) while the nanoparticle treatment with curcumin increased the mitochondrial ATP levels in brain post-irradiation (RoM = 1.799; Moselhy et al., 2025).

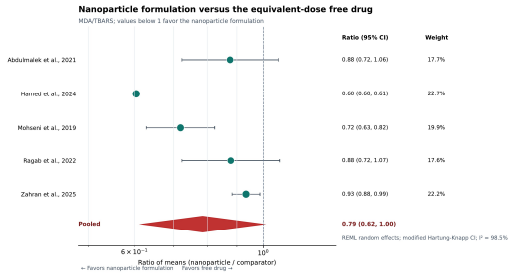


*Figure 5. Random-effects forest plot for MDA/TBARS: nanoparticle formulation versus equivalent-dose free drug.*

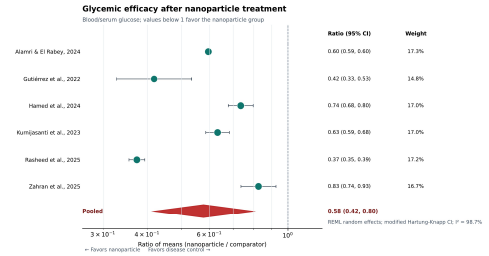


*Figure 6. Random-effects forest plot for glycemic efficacy: nanoparticle treatment versus diabetic control.*

### 4.5 Sensitivity analyses and small-study effects

In sensitivity analyses, the main finding of the MDA/TBARS was robust. Excluding high-overall-risk studies produced RoM = 0.563 (95% CI 0.454–0.698; k = 10). When the two studies that had obvious dispersion anomalies were excluded, RoM = 0.564 (95% CI 0.479–0.665; k = 14). Restriction to conventional carrier formulations produced RoM = 0.532 (95% CI 0.381–0.743; k = 8). Leave-one-out estimates varied between 0.524 and 0.565 and none of these studies altered the direction of the result (Supplementary Figure S3).

The platform subgroup estimates for conventional carriers (RoM = 0.532), intrinsic-active or extract formulations (RoM = 0.675) and metal/composite formulations (RoM = 0.464) were favorable. Studies of metabolic diseases resulted in RoM = 0.532, while those studies of drug injuries resulted in RoM = 0.624. A sensitivity analysis with the Hedges' g showed a positive but very unstable and sensitive standardized effect (g = 5.17, 95% CI 0.92 – 9.43), which further indicated that very small reported dispersions inflated standardized effects.

The funnel plot of the MDA/TBARS results was asymmetric (Figure 7). Egger regression yielded an intercept of 17.76 (SE = 4.09, p < .001). This effect is consistent with, but not limited to, publication bias as there were substantial differences in disease model, platform, tissue, and precision reported among studies.

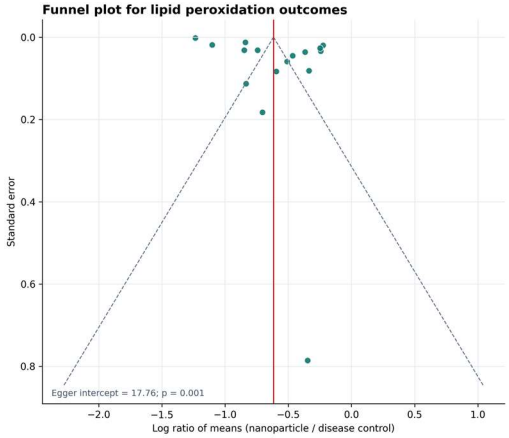


*Figure 7. Funnel plot for the primary MDA/TBARS model.*

## 5. Discussion

### 5.1 Principal findings

This synthesis revealed that following the treatment with nanoparticles an average decrease in the lipid peroxidation and an average increase in the SOD was observed. Results were strong across all of the following scenarios: high-risk studies excluded, two dispersion anomalies removed, only conventional carriers used, and leave-one-out deletion. The main conclusion can thus be drawn that the preclinical nanoformulations included demonstrated biochemical antioxidant activity in a variety of disease models.

The pooled MDA/TBARS result is also consistent with the direction of the results from all 16 experiments that contributed. The treatment-to-control ratio for individual experiments was between 0.291 for dexamethasone-induced hepatic and metabolic injury in curcumin nanoparticles to 0.798 in cisplatin mediated hepatotoxicity for sodium-salicylate nanoparticles (Hamed et al., 2024; Alkhalaf et al., 2023). The pooled RoM of 0.540 is thus a median value of consistently good study directions and not the result of a few outlying experiments. The large variation in the individual ratios however, is the reason why the average cannot be directly applied to any of the formulations or any of the disease models.

The size of the pooled mean effect should not be considered across the board. Even though the average MDA/TBARS effect was very positive, the primary prediction interval crossed the null. This difference represents the difference between the level of confidence in the average effect and the level of uncertainty in the effect in the new model. The very

large $I^2$ values suggest that disease biology, formulation, dose, tissue, timing and/or measurement method accounted for a large proportion of the variability.

The efficacy finding is substantiated by the free-drug analyses. However, the MDA/TBARS comparison was only just outside of the null and the SOD comparison was not very precise. Thus the data indicate an effect of the full nanoformulations more so than the consistent superiority over the unformulated active compounds. This distinction is crucial as it cannot distinguish between the enhanced delivery and the pharmacological activity of the payload and/or carrier in a disease-control comparison.

The ratio-of-means scale provides a practical understanding of the average response, as well. The MDA/TBARS RoM of 0.540 indicates a level that is ~46% below the disease-control mean. The glucose RoM value of 0.577 is a mean value that is about 42% lower than the diabetic-control. These are large relative differences but the prediction intervals indicate that the benefit in a new experiment may be much less substantial. Relative reductions should thus always be given in conjunction with their confidence interval and their prediction interval.

### 5.2 Biochemical and platform interpretation

The average response was not exclusive to one family of assays as MDA/TBARS and SOD both indicated the same direction. Curcumin nanoparticles showed a reduction in lipid peroxidation and an enhancement in the antioxidant activities in diabetic hippocampal model (Abdulmalek et al., 2021). Carvacrol nanoemulsion was beneficial in alleviating the oxidative and renal indices in cisplatin nephrotoxicity (Ragab et al., 2022). In the case of levofloxacin hepatotoxicity, a zinc-oxide-resveratrol formulation not only improved oxidative but also hepatic measures (Zaki et al., 2025). All of the examples have a biological signal that their model supports, but no one example provides a general platform effect.

Special care must be taken in interpreting the SOD result as the individual published effects were not consistently large. In the experiment done by Abdulmalek et al., 2021, the diabetic hippocampus experiment had an exceptionally large SOD ratio for the curcumin nanoparticles. In a diabetic cardiac experiment, the changes in other endpoints were favorable but the mean of SOD produced were almost similar for the chitosan nanoparticles experiment (Wardani et al., 2022a). This wide SOD prediction interval is thus biologically plausible, and it indicates that a single pooled estimate of an enzyme cannot capture all antioxidant responses.

The results for the platform subgroups indicate that the favorable effects on LP were not limited to any particular carrier group. Subgroup estimates, however, should not be used to make head-to-head comparisons as certain variables (payload, disease, dose and study laboratory) were confounded with platform type. Diabetic cardiac injury was treated with chitosan nanoparticles as the active treatment (Wardani et al., 2022a). The chitosan was also used as a carrier for syringic acid in hyperglycemia (Rasheed et al., 2025). The interventions share a material label and have different pharmacological effects.

The glycemic synthesis is a preclinical secondary outcome that can be recognized in the clinical setting. Resveratrol-loaded solid lipid nanoparticles reduced metabolic aspects in diabetic rats (Mohseni et al., 2019). Flavonoids were used for the synthesis of selenium-based particles, which showed improvement in diabetic indices in mice (Gutiérrez et al., 2022). The rutin nanoparticles have been seen to benefit metabolic and oxidative parameters in diet-induced obesity (Zahran et al., 2025). The glucose effect was pooled and although this was beneficial, the prediction interval included the null and thus suggests no consistent efficacy in new experimental models.

A more realistic picture is obtained by direct comparison with the corresponding free drug. Results showed that MDA/TBARS ratio was better for the resveratrol-loaded solid lipid nanoparticles as compared to an equal dose of free resveratrol (RoM = 0.720) (Mohseni et al., 2019). It also showed that curcumin nanoparticles favor over an equal dose of free curcumin in dexamethasone-treated rats (RoM = 0.603; Hamed et al., 2024). The RoM was lower for carvacrol nanoemulsion (RoM = 0.879) and nano-rutin (RoM = 0.933) (RoM = 0.879; Ragab et al., 2022 and RoM = 0.933; Zahran et al., 2025). This published-study pattern is similar to that of the pooled free-drug estimate (0.785, with a confidence interval) that was just above 1.00. So, in their own experiments, some formulations seem better, but the evidence to date does not indicate a class-wide delivery benefit.

There was too little GSH evidence to make a good inference. Only three contributed; the modified Hartung–Knapp interval contained the null with a good point estimate. The figure represents this trend because the number of outcome rows that are removed from a pool is not the same as the number of individual studies in the pool. Even if the biomarker is present in many tables, subsequent to eliminating multiple doses, tissues and time points from the same animals in the

hierarchy, the amount of independent evidence may be limited.

### 5.3 Methodological interpretation and limitations

The biggest restriction is the quality of the reporting. Most SYRCLE domains were unclear as there was a general lack of sufficient detail reporting allocation concealment, random housing, blinding or random outcome assessment in articles. Incomplete reporting is not necessarily evidence of a missing safeguard, but will disallow a low risk assessment (Hooijmans et al., 2014). Pooled estimates of efficacy at the domain level (Figure 2) must be interpreted with caution because of the reason shown. Implementing ARRIVE 2.0 better would enhance the reproducibility and the interpretability of the meta-analysis (Percie du Sert et al., 2020).

The other constriction is that of instability, due to a reported dispersion. A few tables had very small SD or SEM as compared to the difference between group means. An implausibly large study effect was found for Hedges' g, while the ratio of means was mainly a function of the relative group means. This led to the choice of using lnRoM for the main analysis and the standardized analysis as a sensitivity analysis.

Biological heterogeneity is a third restriction. The evidence included: diabetes, obesity, drug toxicity, radiation injury, and cancer models. It also had a mixture of carrier loaded drugs, intrinsically active particles, metal composites and complex extracts. In contrast to fixed-effects models, random-effects models allow for variation and do not "equalize" incomparable interventions. Pooled result should thus be viewed as representing the average directionality of a large body of preclinical evidence and not an estimate for a particular particle product.

The fourth limitation is that counts of PRISMA were made based on the screening log instead of being re-generated based on raw exports from the database. The fifth constraint is that study-level means are not able to correlate the biomarkers within each study or assess sex-specific effects if sex-stratified data were not provided.

Asymmetry of funnels contributes to increased uncertainty. Although selective publication is a potential source of asymmetry, extreme heterogeneity and a relationship between the precision of the studies and their experimental design can also be a source of asymmetry, and this factor was statistically significant in the Egger regression. The funnel result thus should be interpreted as evidence of small-study effects and not as evidence of publication bias.

The 15-year time window was suitable for current nanocarrier practice, but evidence available fell in the most recent portion of the time window. The complete set of design, comparator, outcome and variance requirements eliminated earlier studies. Therefore, the review cannot be taken as a chronicle of all the studies on nanoparticles antioxidant activity. It is a quantitative synthesis of the subset that reported sufficiently complete controlled in vivo data.

In addition, the review did not combine histology scores, gene-expression results, cytokines or pharmacokinetic results with the biochemical results. This decision paid the price of generalities for clarity. However, there is no common measurement model between ordinal histology grades and continuous enzyme activity and molecular-expression changes will not equal systemic disease control. These types of outcomes are still useful for mechanistic triangulation, but must be separately modeled for effects and, preferably, multilevel models.

### 5.4 Implications for research

Future studies in animals should consider an equivalent-dose free-drug arm, a particle-only arm if the carrier might be active, prespecified primary outcomes, blinded assessment, transparency in randomization, as well as sample size justified prior to study. Data for individual animals, and at least the number of animals in each group, mean, and standard deviation should be reported for each outcome. Any assay units and normalization procedures should be clearly specified. These changes would allow for the use of multivariate models that incorporate multiple redox biomarkers (and don't double-count animals).

Translation should be done based on formulation-specific evidence and not based on the pooled effect in itself. A promising platform should have reproducible and reproducible target-tissue exposure, pharmacokinetics, dose-response and safety in multiple independent laboratories and superiority over the free drug. The current findings contribute a feasible biochemical marker and design parameters to determine if the marker can be a reliable therapeutic benefit.

### 5.5 Strengths and contribution

There are several strengths to the analysis. It kept the original group means and dispersion labelling in an auditable workbook. It distinguished between the free drug advantage of the same dose and efficacy in controlling disease. It used a prespecified observation-selection hierarchy (and thus reduced selective extraction) prior to pooling. It involved a relative

continuous outcome measure, which was meaningful in the various biochemical units. In addition to reporting prediction intervals, it provided multiple risk-based sensitivity analyses, and leave-one-out results.

The work adds a quantitative estimate to a literature which is often narratively summarized. It additionally ties the pooled results straight to the individual publications of the experiments, making it possible for a reader to understand what the pooled results imply and where the experiments differ. The size and directionality of the average lipid-peroxidation signal was large, even after omitting the studies with most obvious reporting issues. The analysis also reveals strengths and weaknesses of the evidence: high levels of heterogeneity, low numbers of free-drug comparisons, reliance on a single reviewer to make risk of bias judgments and large small-study asymmetry. There is an argument for presenting both sides to avoid the pooled result from being interpreted as an unqualified statement that all nanoparticle delivery systems enhance therapy.

Combined, the best view of the text is conditional. In controlled animal disease models, there is a reproducible average association between use of nanoparticles-based interventions and reduction in lipid peroxidation. The data on the added value of nanocarrier formulation, over the same free active agent, are still scarce and varied. Confirmatory experiments should be set up to address that more focused question.

## Conclusion

This systematic review and meta-analysis show that interventions using nanoparticles significantly decrease lipid peroxidation and enhance selected antioxidant and disease-related outcomes in preclinical animal models to a great extent. The primary analysis revealed a significant decrease in the mean level of MDA/TBARS (-46.0%) but a significant increase in the level of SOD activity and decrease in the level of glucose as compared to disease or injury controls. These results were consistent in four sensitivity analyses that were carried out: risk-based, platform-restricted, dispersion-based, and leave-one-out, and indicate that there is a true biochemical effect.

However, it is not yet clear from the available evidence that there is a consistent increase in the efficacy of nanoparticle formulations over the free drugs. Comparisons of equivalent doses were few, somewhat rough and not conventionally statistically significant. Further limitations in the direct use of the pooled estimates to individual formulations or clinical settings are the extreme heterogeneity, the wide prediction intervals, the small experimental groups, the lack of full methodological reporting, and the funnel plot asymmetry. The results thus provide stronger support for the effectiveness of "full" nanoformulations as opposed to a general nanoparticle delivery advantage.

Future studies should be done using adequately powered, randomized and blinded designs; provide equivalent dose-free drug and particle-only controls; provide actual group level and individual animal data; and assess pharmacokinetics, tissue exposure, safety and reproducibility in different laboratories. This evidence is required to identify which nanoparticle platforms can translate the antioxidant activity observed to a clinically relevant therapeutic value that is reliable.

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## Supplementary Appendix A. Database Search Strategies

Search window: 1 January 2011 to 31 July 2026. No language restriction was applied at the search stage. Database-specific syntax was translated without changing the underlying concepts.

### PubMed/MEDLINE

(("Nanoparticles"[Mesh] OR nanoparticle*[tiab] OR nanocarrier*[tiab] OR nanoformulation*[tiab] OR nanoemulsion*[tiab] OR nanocapsule*[tiab] OR liposome*[tiab] OR "solid lipid nanoparticle*"[tiab] OR "nanostructured lipid carrier*"[tiab] OR PLGA[tiab]) AND ("Drug Delivery Systems"[Mesh] OR "drug delivery"[tiab] OR loaded[tiab] OR encapsulat*[tiab] OR conjugat*[tiab] OR formulation*[tiab]) AND ("Oxidative Stress"[Mesh] OR "oxidative stress"[tiab] OR malondialdehyde[tiab] OR MDA[tiab] OR TBARS[tiab] OR "superoxide dismutase"[tiab] OR SOD[tiab] OR catalase[tiab] OR glutathione[tiab] OR GPx[tiab] OR "total antioxidant capacity"[tiab]) AND (therapeutic*[tiab] OR efficacy[tiab] OR treatment[tiab] OR protect*[tiab])) AND ("2011/01/01"[Date - Publication] : "2026/07/31"[Date - Publication])

### Embase (Ovid)

('nanoparticle'/exp OR nanoparticle*:ti,ab,kw OR nanocarrier*:ti,ab,kw OR nanoformulation*:ti,ab,kw OR nanoemulsion*:ti,ab,kw OR nanocapsule*:ti,ab,kw OR liposome*:ti,ab,kw OR 'solid lipid nanoparticle*':ti,ab,kw) AND ('drug delivery system'/exp OR 'drug delivery':ti,ab,kw OR loaded:ti,ab,kw OR encapsulat*:ti,ab,kw OR formulation*:ti,ab,kw) AND ('oxidative stress'/exp OR 'oxidative stress':ti,ab,kw OR malondialdehyde:ti,ab,kw OR MDA:ti,ab,kw OR TBARS:ti,ab,kw OR 'superoxide dismutase':ti,ab,kw OR SOD:ti,ab,kw OR catalase:ti,ab,kw OR glutathione:ti,ab,kw OR GPx:ti,ab,kw) AND (therapeutic*:ti,ab,kw OR efficacy:ti,ab,kw OR treatment:ti,ab,kw OR protect*:ti,ab,kw)

### Scopus

TITLE-ABS-KEY((nanoparticle* OR nanocarrier* OR nanoformulation* OR nanoemulsion* OR nanocapsule* OR liposome* OR "solid lipid nanoparticle*" OR "nanostructured lipid carrier*") AND ("drug delivery" OR loaded OR encapsulat* OR conjugat* OR formulation*) AND ("oxidative stress" OR malondialdehyde OR MDA OR TBARS OR "superoxide dismutase" OR SOD OR catalase OR glutathione OR GPx OR "total antioxidant capacity") AND (therapeutic* OR efficacy OR treatment OR protect*)) AND PUBYEAR > 2010 AND PUBYEAR < 2027

### Web of Science Core Collection

TS=((nanoparticle* OR nanocarrier* OR nanoformulation* OR nanoemulsion* OR nanocapsule* OR liposome* OR "solid lipid nanoparticle*" OR "nanostructured lipid carrier*") AND ("drug delivery" OR loaded OR encapsulat* OR conjugat* OR formulation*) AND ("oxidative stress" OR malondialdehyde OR MDA OR TBARS OR "superoxide dismutase" OR SOD OR catalase OR glutathione OR GPx OR "total antioxidant capacity") AND (therapeutic* OR efficacy OR treatment OR protect*))

### CENTRAL

([mh Nanoparticles] OR nanoparticle*:ti,ab,kw OR nanoemulsion*:ti,ab,kw OR "solid lipid nanoparticle*":ti,ab,kw) AND ([mh "Oxidative Stress"] OR "oxidative stress":ti,ab,kw OR malondialdehyde:ti,ab,kw OR MDA:ti,ab,kw OR SOD:ti,ab,kw OR glutathione:ti,ab,kw)

### Google Scholar

"nanoparticle drug delivery" "oxidative stress" (MDA OR malondialdehyde OR SOD) rat OR mice

## Supplementary Figures

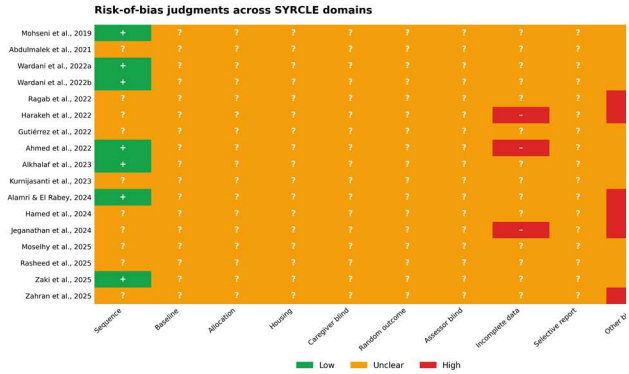


*Figure S1. Study-level reporting-based SYRCLE risk-of-bias judgments.*

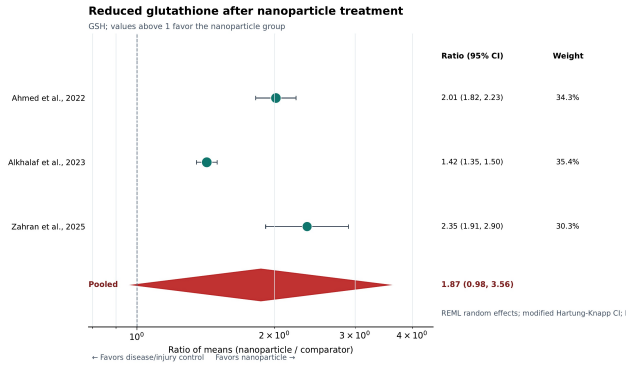


*Figure S2. Random-effects forest plot for GSH: nanoparticle treatment versus disease/injury control.*

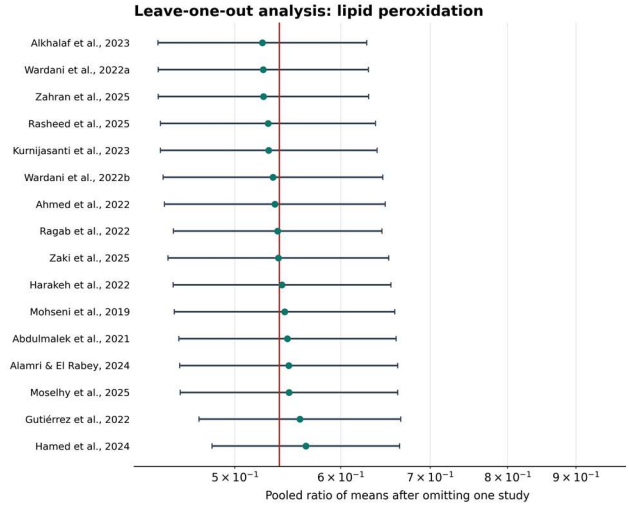


*Figure S3. Leave-one-out analysis for the primary MDA/TBARS model.*