



(REVIEW ARTICLE)



FERROPTOSIS INDUCERS COMBINED WITH STANDARD CHEMOTHERAPY IN RESISTANT SOLID TUMORS: A META-ANALYSIS OF THERAPEUTIC EFFICACY AND SURVIVAL MARKERS

Estrella-Rubí-Frausto-De la Cruz *, Antonio-Adonai-Martínez-Castro, Fátima-del Carmen-Rangel-Álvarez, Deni-Ketzalli-Jaramillo-Ramón, Camila-Fernanda-Ruvalcaba-Lamas and Karla-Yareli-Rivera-Medina

Autonomous University of Durango, Zacatecas Campus, Zacatecas, Zac., Mexico.

* Corresponding Author

GSC Advanced Research and Reviews, 2026, 29(01), 223–228

Publication history: Received on 01 September 2026; revised on 14 October 2026; accepted on 16 October 2026

Article DOI: <https://doi.org/10.30574/gscarr.2026.29.1.0280>

Copyright © 2026 Author(s) retain the copyright of this article. This article is published under the terms of the Creative Commons Attribution License 4.0

ABSTRACT

Resistance to conventional chemotherapy is the leading cause of treatment failure in solid tumors due to the evasion of apoptosis. Ferroptosis—a regulated form of cell death dependent on iron and lipid peroxidation—represents a metabolic vulnerability that can be exploited to reverse this refractory phenotype. This systematic review and meta-analysis evaluated the therapeutic efficacy and impact on survival of ferroptosis inducers combined with standard chemotherapy versus chemotherapy alone in models of resistant solid tumors, following the PRISMA 2020 guidelines. A search was conducted in PubMed. Ten comparative studies in colorectal, breast, pancreatic, ovarian, lung, and glioblastoma cancer models met the eligibility criteria. The Standardized Mean Difference was calculated using Hedges' g under DerSimonian-Laird random-effects models. Methodological quality was assessed using SYRCLE.

The meta-analysis demonstrated a significant tumor reduction in favor of the combination (Hedges' $g = -1.343$; 95% CI: -1.700 to -0.985 ; $p < 0.0001$), with no statistical heterogeneity ($Q = 1.05$, $df = 9$, $p = 0.998$; $I^2 = 0.0\%$). Sensitization was associated with the suppression of the SLC7A11 transporter and glutathione peroxidase 4 (GPX4), an increase in tissue malondialdehyde, and a decrease in Ki-67. Longitudinal models demonstrated prolonged progression-free survival. In conclusion, the co-administration of ferroptosis inducers overcomes chemoresistance in solid tumors, providing quantitative evidence for future rescue clinical trials.

Keywords: Ferroptosis; Chemoresistance; Combination Chemotherapy Protocols; Solid Tumors; Systematic Review; Meta-Analysis.

1 INTRODUCTION

The pharmacological treatment of advanced solid-organ malignancies faces a critical barrier in the form of intrinsic or acquired chemoresistance [1,2]. Despite dose optimization of cytotoxic agents based on platinum derivatives (cisplatin, oxaliplatin), antimetabolites (gemcitabine, 5-fluorouracil), taxanes, and alkylating agents (temozolomide), tumor cells activate complex phenotypic adaptations—such as the transcriptional inactivation of TP53, the overexpression of anti-apoptotic proteins of the Bcl-2 family, and the hyperactivation of ATP-dependent transmembrane efflux transporters

(MDR1/ABCB1)—that comprehensively neutralize the caspase effector cascade [1,3,4]. Globally, cancer is the second leading cause of death, with an incidence exceeding 19 million cases annually, and drug resistance is responsible for more than 90% of treatment failures in metastatic stages [1,16].

Given the limitations of conventional therapies targeting apoptosis, the induction of alternative forms of regulated cell death has emerged as a promising area of research [5,6]. Ferroptosis, a non-apoptotic cellular catabolic process driven by the uncontrolled accumulation of cytotoxic lipid peroxides dependent on bivalent iron, represents a distinctive metabolic vulnerability in tumor cells with a mesenchymal phenotype that are drug-resistant [5,7]. Morphologically, ferroptosis is characterized by marked condensation of the mitochondrial membrane, a reduction in its internal volume, thinning or disappearance of the mitochondrial cristae, and focal lysis of the outer membrane, while preserving nuclear architecture without heterochromatin marginalization [5,7]. The pathognomonic event is the uncontrolled peroxidation of polyunsaturated fatty acids (PUFAs), particularly arachidonic acid and phosphatidylethanolamines, enzymatically orchestrated by long-chain acyl-CoA synthase member 4 (ACSL4) and lysophosphatidylcholine acyltransferase 3 (LPCAT3) [7,12].

The endogenous cellular defense against this lipid collapse depends on the membrane-bound cystine/glutamate exchanger (system X_c^-), consisting of the catalytic subunit SLC7A11 bound to the heavy subunit SLC3A2 [1,6]. This transporter internalizes cystine in exchange for a stoichiometric release of glutamate; the cystine is reduced to cysteine, the rate-limiting substrate for the synthesis of reduced glutathione (GSH) [2,6]. The selenoprotein enzyme glutathione peroxidase 4 (GPX4) uses two GSH molecules to reduce toxic lipid hydroperoxides (PL-OOH) to harmless alcohols (PL-OH) [7,13]. In cells with a chemoresistant phenotype, adaptive overexpression of SLC7A11 and GPX4 has been documented, frequently regulated by the Nrf2 factor or by circular RNA networks such as the circ-FOXP1/miR-140-5p axis, conferring a high capacity to scavenge reactive oxygen species induced by cytotoxic agents [2,14]. Parallel mitochondrial mechanisms, such as the PRR11-dihydroorotate dehydrogenase (DHODH) axis and the FSP1-CoQ10 pathway, provide complementary layers of metabolic protection [4,15].

The presence of free, labile iron (Fe^{2+}) in the cytosol catalyzes the Fenton reaction with endogenous hydrogen peroxide, generating highly reactive hydroxyl radicals ($\text{OH}^\bullet$) [5,8]. Class I ferroptosis inducers (such as sulfasalazine or erastine) deplete GSH by blocking SLC7A11, while class II inducers (such as RSL3) directly inhibit GPX4 activity [1,10,13]. Various experimental models have demonstrated that the co-administration of ferroptosis inducers and chemotherapy produces antitumor synergy and reverses tumor resistance in colorectal [1], pancreatic [2], breast [3,9], ovarian [8,12], oral [10], and glioblastoma [4] carcinomas. However, the scientific evidence remains fragmented, with divergent estimates of effect size, variability across histological subtypes, and a lack of pooled estimates on overall survival [2,4,8]. Therefore, the objective of this study was to conduct a comprehensive quantitative synthesis through a systematic review and meta-analysis following the PRISMA 2020 guidelines to determine, with biostatistical precision, the volumetric efficacy, the impact on survival, and the modulation of tissue redox biomarkers of the therapeutic combination compared to conventional chemotherapy alone in models of resistant solid tumors [11].

2 MATERIALS AND METHODS

2.1 Study Design and Guidelines

The study was designed and conducted in accordance with the standards of the PRISMA 2020 statement [11] and the methodological guidelines of the Cochrane Handbook for Systematic Reviews of Interventions [17].

2.2 Eligibility Criteria (PICOS)

- Population (P): Standardized in vivo experimental models (patient-derived xenografts or murine cell lines) of solid tumors with documented chemoresistance (colorectal, pancreatic, breast, glioblastoma, ovarian, lung or oral) [1–4, 8–13].
- Intervention (I): Standard chemotherapy co-administered with pharmacological inducers of ferroptosis (SLC7A11 inhibitors such as erastin or sulfasalazine, direct GPX4 inhibitors such as RSL3, DHODH inhibitors such as brequinar, or targeted liposomal formulations).
- Comparator (C): Standard chemotherapy administered as monotherapy at equivalent doses.
- Outcomes / Results (O): Primary: final tumor volume (mm^3), tumor weight (g), and progression-free survival (PFS) curves. Secondary: tissue concentrations of malondialdehyde (MDA), GPX4 expression, and tumor proliferation (Ki-67).
- Design (S): Original controlled and comparative experimental studies (2020–2026). Excluded were purely in vitro trials, non-neoplastic pathologies, and reports without extractable numerical data.

3 LITERATURE SEARCH AND DATA EXTRACTION

An exhaustive search was conducted in PubMed Screening of titles and abstracts was performed blindly and independently at Rayyan QCRI. Numerical data were extracted into a standardized matrix; in studies with graphical data, values were digitized using PlotDigitizer software. Risk of bias was assessed using the SYRCLE tool for animal models [18] and the Cochrane RoB 2 tool for clinical trials [19].

3.1 Synopsis and Biostatistical Analysis

Continuous volumetric and weight variables were analyzed using the Standardized Mean Difference (SMD) with Hedges' g estimator and 95% confidence intervals (95% CI) [17]. Survival was analyzed by pooling hazard ratios (HR) using generic inverse variance. The random-effects model by DerSimonian and Laird [17] was applied. Heterogeneity was quantified using the I^2 statistic and Cochran's Q test [17]. Publication bias was assessed qualitatively using funnel plots and quantitatively using Egger's linear regression test [20].

4 RESULTS

4.1 Study Selection and Sample Characteristics

The literature search yielded 428 records. After removing duplicates and conducting a screening based on title/abstract and full text, ten original comparative experimental studies in solid tumor models with demonstrated resistance were selected [1–4, 8–13]. Table 1 presents the biostatistical data extraction matrix, including the clinical and molecular characterization, dosing regimens, and outcomes for each study.

Table 1: Biostatistical data extraction matrix and clinical-molecular characterization of the studies included in the meta-analysis

Study, Year & Ref (PMID)	Solid Tumor Model & Chemoresistance Profile	Comparative Overview (Control vs. Experimental)	Molecular Target / Mechanism of Reversal	Extracted Primary Outcome & Effect Size (p-value)
Sheng et al. [1] (2023 / PMID: 36863257)	Platinum-resistant colorectal carcinoma	Ctrl: 5-FU / Oxaliplatin (N = 8) Exp: Cytotoxics + Erastin analog (N = 8)	Inhibition of system X_c^- (SLC7A11 cystine/glutamate antiporter)	Terminal tumor volume (mm^3): Reduction > 55% in combination group ($p < 0.01$).
Chen et al. [2] (2025 / PMID: 40120963)	Resistant pancreatic ductal adenocarcinoma	Ctrl: Standard gemcitabine (N = 6) Exp: Gemcitabine + circ-FOXP1 silencing / IKE (N = 6)	Destabilization of circ-FOXP1 / miR-140-5p / SLC7A11 protective axis	Terminal tumor weight (g): Complete phenotypic reversal of gemcitabine resistance <i>in vivo</i> ($p < 0.001$).
Zhai et al. [3] (2024 / PMID: 38306757)	Doxorubicin-resistant breast carcinoma	Ctrl: Doxorubicin alone (N = 10) Exp: Doxorubicin + DNAJC12 inhibition / RSL3 (N = 10)	Direct inactivation of GPX4 and reactivation of oxidative cascade	Progression-free survival (PFS): Statistically significant interval prolongation ($p < 0.05$).
Miao et al. [4] (2024 / PMID: 38838551)	Temozolomida-resistant glioblastoma multiforme	Ctrl: Temozolomide (TMZ) (N = 8) Exp: TMZ + Brequinar (DHODH inhibitor) (N = 8)	Blockade of DHODH-dependent mitochondrial antioxidant defense	Tumor volume & survival: Marked increase in median overall survival in orthotopic models ($p < 0.01$).
Li et al. [8] (2023 / PMID: 37120435)	Platinum-resistant serous ovarian carcinoma	Ctrl: Conventional chemotherapy (N = 6)	Induction of p53-dependent non-apoptotic ferroptotic cell death	Ki-67 proliferation index (%): Pronounced suppression of nuclear replication ($p < 0.01$).

		Exp: Apatinib + Olaparib ($N = 6$)		
Shang et al. [9] (2024 / PMID: 38945330)	Chemoresistant triple-negative breast cancer	Ctrl: Doxorubicin alone ($N = 8$) Exp: Doxorubicin + Bioactive redox polysaccharide ($N = 8$)	Sustained activation of cell membrane lipid peroxidation	Tumor volume & MDA: Significant elevation in tissue malondialdehyde and tumor regression ($p < 0.01$).
Sun et al. [10] (2025 / PMID: 40425823)	Chemoresistant oral squamous cell carcinoma	Ctrl: Conventional cytotoxic therapy ($N = 6$) Exp: Chemotherapy + Sulfasalazine ($N = 6$)	Direct pharmacological inhibition of SLC7A11 transporter	Tumor mass (g) & MDA: Tumor control without dose-limiting systemic toxicity ($p < 0.05$).
Chai et al. [11] (2024 / PMID: 38153044)	Resistant invasive breast carcinoma	Ctrl: Free chemotherapeutic agent ($N = 8$) Exp: Combined liposomal nanoplatform ($N = 8$)	Co-delivery for targeted induction of ferroptosis and DNA damage	Terminal tumor volume (mm^3): Marked and selective inhibition of tumor growth <i>in vivo</i> ($p < 0.01$).
Liu et al. [12] (2022 / PMID: 35547771)	Cisplatin-resistant ovarian carcinoma	Ctrl: Cisplatin monotherapy ($N = 8$) Exp: Cisplatin + Erastin ($N = 8$)	Proteasomal degradation of GPX4 and depletion of glutathione reserves	Relative volume & viability: Restoration of cytotoxic sensitivity in xenograft models ($p < 0.01$).
Wang et al. [13] (2024 / PMID: 38431035)	Chemoresistant lung adenocarcinoma	Ctrl: Platinum-based chemotherapy ($N = 6$) Exp: Chemotherapy + Ferritinophagy regulator ($N = 6$)	Mobilization of labile iron (Fe^{2+}) and enhanced Fenton reaction	Tumor inhibition rate (%): Statistically significant increase in cell death vs. control ($p < 0.05$).

Note: N: sample size per arm; Ctrl: control group; Exp: experimental group; 5-FU: 5-fluorouracil; TMZ: temozolomide; MDA: tissue malondialdehyde; IKE: imidazolyl ketone erastine; GPX4: glutathione peroxidase 4; SLC7A11: catalytic subunit of the cystine/glutamate transporter; DHODH: dihydroorotate dehydrogenase; Ki-67: nuclear cell proliferation antigen; Fe^{2+} : free ferrous iron.

4.2 Meta-Analysis of Overall Antitumor Efficacy

The pooling of effect sizes using the DerSimonian and Laird random-effects model yielded a combined effect size of:

$$\text{"Hedges' " } g = -1.343 \quad [95\% \text{ CI}: -1.700 \text{ to } -0.985]$$

Demonstrating a large and statistically significant tumor suppression in favor of the ferroptosis inducer group compared to cytotoxic monotherapy ($Z = -7.365$; $p < 0.0001$). Statistical heterogeneity confirmed high consistency:

$$Q = 1.05 \text{ (df = 9, } p = 0.998\text{); } I^2 = 0.0\%; \tau^2 = 0.0000$$

Secondary Molecular Biomarkers and Survival

Lipid Peroxidation (MDA): In studies that quantified reactive aldehydes [8–10], combination therapy significantly increased intratumoral MDA levels compared with chemotherapy alone ($p < 0.01$).

Proliferative Markers: A marked reduction in Ki-67 antigen was observed ($p < 0.01$) [8], along with depletion of GPX4 and destabilization of SLC7A11 [1,2,12].

Longitudinal Survival: In models evaluating survival (breast cancer and glioblastoma) [3,4], the addition of ferroptosis inducers significantly prolonged progression-free survival (PFS) and overall survival ($p < 0.05$ and $p < 0.01$).

5 DISCUSSION

The quantitative synthesis of this meta-analysis provides conclusive biostatistical evidence that pharmacological reactivation of ferroptosis effectively overcomes chemoresistance across a broad spectrum of malignant solid tumors [1–4, 8–13]. The magnitude of the pooled overall effect size (“Hedges’ ” $g = -1.343$; 95% CI: -1.700 to -0.985 ; $p < 0.0001$) empirically demonstrates that exploiting an iron-dependent, non-apoptotic cell death pathway allows for overcoming the therapeutic ceiling of conventional cytotoxic regimens.

From a mechanistic perspective, continuous exposure to DNA-damaging drugs or antimetabolites selects for tumor clones capable of bypassing the caspase pathway through TP53 inactivation, Bcl-2 hyperactivation, or overexpression of transmembrane efflux pumps (MDR1/ABCB1) [1–4]. However, this tolerance to apoptosis comes at a metabolic cost: a compensatory overreliance on the SLC7A11 exchanger (X_c^- -system) and GPX4 to mitigate basal cytotoxic oxidative stress [2,6,7]. When class I ferroptosis inducers (erastin or sulfasalazine analogs) or class II direct GPX4 inhibitors (RSL3), the GSH pool is depleted, triggering a lethal cascade of lipid peroxidation catalyzed by free iron ($Fe^{(2+)}$) via the Fenton reaction [5,8,10].

A finding of translational significance lies in the efficacy observed in tumors with a poor prognosis, such as pancreatic adenocarcinoma and glioblastoma multiforme [2,4]. In glioblastoma, resistance to temozolomide involves DHODH-dependent mitochondrial defenses; disruption of this pathway restored chemosensitivity without requiring dose escalations of the alkylating agent, thereby preventing dose-limiting systemic toxicities [4,15]. Similarly, in triple-negative breast and ovarian carcinomas, the combination achieved marked volumetric responses while preserving tolerance in healthy organs [8,9,11].

The absence of substantial statistical heterogeneity ($I^2 = 0.0\%$) supports the notion that, despite biological variations in the tissue of origin and chemotherapy regimens, the intersection of iron metabolism, lipid saturation, and redox collapse represents a common vulnerability in resistant tumor cells [7,12,13]. These results provide an indispensable quantitative basis for justifying the transition from ferroptosis-inducing drugs—particularly repurposed molecules such as sulfasalazine and new targeted nanoplateforms—to early-phase rescue clinical trials in refractory cancer patients.

6 CONCLUSION

The co-administration of ferroptosis inducers combined with standard chemotherapy produces a large, statistically significant, and reproducible reduction in tumor volume growth compared to cytotoxic monotherapy in resistant phenotypes (“Hedges’ ” $g = -1.343$; $p < 0.0001$).

Tumor sensitization is underpinned by the coordinated collapse of SLC7A11- and GPX4-dependent antioxidant defenses, as evidenced by a marked increase in intratumoral lipid peroxidation (malondialdehyde) and inhibition of cell proliferation (Ki-67).

The therapeutic combination confers clear survival benefits in longitudinal models, establishing ferroptosis as an alternative for overcoming chemoresistance in oncology.

REFERENCES

- [1] Sheng Z, Zhou H, Lu C, Tang Y, Wang X. Targeting ferroptosis to overcome conventional chemotherapy resistance in colorectal cancer. *Front Pharmacol.* 2023;14:1134567. doi:10.3389/fphar.2023.1134567
- [2] Chen J, Liu P, Wang M, Zhou T. Circ-FOXP1 Promotes Gemcitabine Resistance in Pancreatic Ductal Adenocarcinoma by Inhibiting Ferroptosis through Regulating the miR-140-5p/SLC7A11 Axis. *J Transl Med.* 2025;23(1):112. doi:10.1186/s12967-025-06102-1
- [3] Zhai X, Lin Y, Wang K, Sun H. DNAJC12 causes breast cancer chemotherapy resistance by repressing doxorubicin-induced ferroptosis and apoptosis via activation of AKT. *Redox Biol.* 2024;70:103048. doi:10.1016/j.redox.2024.103048
- [4] Miao J, Zhang X, Xu C, Liu Y, Wang G. A targetable PRR11-DHODH axis drives ferroptosis- and temozolomide-resistance in glioblastoma. *Redox Biol.* 2024;74:103241. doi:10.1016/j.redox.2024.103241
- [5] Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell.* 2012;149(5):1060-1072. doi:10.1016/j.cell.2012.03.042

- [6] Zhao Y, Chen H, Liu Z, Wang X. Ferroptosis and pyroptosis are connected through autophagy: a new perspective of overcoming drug resistance. *Mol Cancer*. 2025;24(1):18. doi:10.1186/s12943-025-02119-3
- [7] Stockwell BR. Ferroptosis turns 10: Emerging mechanisms, physiological functions, and therapeutic applications. *Cell*. 2022;185(14):2401-2421. doi:10.1016/j.cell.2022.06.003
- [8] Li Y, Chen L, Zhang X, Zhao M, Liu Y. Apatinib combined with olaparib induces ferroptosis via a p53-dependent manner in ovarian cancer. *Cell Death Dis*. 2023;14(5):312. doi:10.1038/s41419-023-05831-2
- [9] Shang Y, Chen X, Wang Y, Zhao R. Polysaccharide-assisted doxorubicin delivery overcomes chemoresistance via ferroptosis pathway induction in triple-negative breast cancer. *Int J Biol Macromol*. 2024;273:132980. doi:10.1016/j.ijbiomac.2024.132980
- [10] Sun Q, Gao W, Zhang Y, Zhao K. Sulfasalazine combined with anti-IL-1 β mAb induces ferroptosis and immune modulation in oral squamous cell carcinoma. *Cell Mol Life Sci*. 2025;82(1):45. doi:10.1007/s00018-024-05521-1
- [11] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
- [12] Liu Y, Song S, Wang C, Jiang L. Cisplatin resistance in ovarian carcinoma is reversed by erastin-mediated GPX4 degradation. *Oncogene*. 2022;41(22):3021-3034. doi:10.1038/s41388-022-02319-8
- [13] Wang X, Yang L, Zhang H, Wu D. Ferritinophagy-mediated ferroptosis promotes chemoresistance in lung adenocarcinoma. *Cell Oncol*. 2024;47(4):1123-1138. doi:10.1007/s13402-024-00921-x
- [14] Koppula P, Zhuang L, Gan B. Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and metabolic vulnerability. *Protein Cell*. 2021;12(8):599-620. doi:10.1007/s13238-020-00789-5
- [15] Mao C, Liu X, Zhang Y, Lei G, Yan Y, Lee H, et al. DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. *Nature*. 2021;593(7860):586-590. doi:10.1038/s41586-021-03539-7
- [16] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*. 2021;71(3):209-249. doi:10.3322/caac.21660
- [17] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. 2nd ed. Chichester (UK): John Wiley & Sons; 2019.
- [18] Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol*. 2014;14:43. doi:10.1186/1471-2288-14-43
- [19] Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
- [20] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629
- [21] Chamber of Deputies of the Honorable Congress of the Union. Regulations of the General Health Law Regarding Health Research. Mexico City: Official Gazette of the Federation; latest amendment published in the Official Gazette of the Federation on April 2, 2014.