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Research Article

Epigallocatechin Gallate Sensitizes Breast Cancer Cells to Cisplatin Through the Induction of Ferroptosis

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Abstract

Background and Objective: This study aimed to investigate the mechanisms through which epigallocatechin gallate (EGCG), a green tea polyphenol, enhances the antitumor activity of cisplatin (diamminedichloroplatinum, DDP) in breast cancer cells *in vitro*. **Methods**: Cytotoxicity assays and Western blotting were used to evaluate the effects of EGCG on DDP-mediated anticancer activity. Ferroptosis was assessed in MDA-MB-231 cells treated with DDP in the presence or absence of ferroptosis inhibitors using lipid peroxidation assays and Western blotting. **Results**: EGCG significantly sensitized MDA-MB-231 cells to cisplatin-induced cytotoxicity. Moreover, EGCG augmented cisplatin-induced increases in reactive oxygen species and lipid peroxides, elevated malondialdehyde content, and reduced glutathione levels. Western blot analysis revealed that EGCG promoted cisplatin-mediated upregulation of 4-HNE and downregulation of the anti-ferroptotic proteins SLC7A11 and GPX4. The ferroptosis inhibitor deferoxamine reversed EGCG/DDP-induced ferroptosis. **Conclusions**: EGCG enhances the efficacy of DDP by downregulating SLC7A11 and inducing ferroptosis at the cellular level. To our knowledge, this is the first study to clarify the synergistic mechanism between EGCG and DDP; thus, this work presents new pharmacological targets for the antitumor application of EGCG.

Keywords: breast cancer; ferroptosis; cisplatin; epigallocatechin gallate

1. Introduction

Breast cancer continues to be one of the most prevalent malignancies among women and a major cause of cancer-related deaths globally, with incidence rates showing a persistent upward trend year by year [1,2]. In China, both the occurrence and mortality associated with breast cancer are rising, and the average age at diagnosis is roughly ten years younger than that observed in Western populations [3,4]. According to NCCN guidelines, endocrine therapy is the standard treatment for ER-positive breast cancer, and anti-human epidermal growth factor receptor 2 (HER2) targeted therapy is routinely used for HER2-positive cases. However, effective targeted therapeutic options remain unavailable for triple-negative breast cancer (TNBC), which consequently correlates with elevated recurrence rates and a poorer prognosis [3,4]. Drug resistance represents a major obstacle in breast cancer treatment, underscoring the urgent need to identify novel therapeutic strategies and resistance mechanisms [5].

Chemotherapy remains a cornerstone in the management of advanced breast cancer. Platinum-based agents, as common chemotherapeutic drugs, require standardized clinical application. A clear understanding of their treatment protocols, efficacy, and adverse effects can help optimize clinical practice and promote rational use [6]. Platinum drugs are cell cycle non-specific agents that form covalent cross-links with DNA, creating platinum-DNA adducts that inhibit DNA replication and suppress tumor proliferation. These drugs exhibit potent antitumor activity across various cancers. In HER2-positive breast cancer, platinum-based regimens combined with targeted therapy are prioritized as neoadjuvant options. For HER2-negative breast cancer, particularly TNBC, chemotherapy remains the mainstay of treatment, with anthracycline- and taxane-based regimens being conventional neoadjuvant approaches. The incorporation of platinum drugs into these regimens or the use of platinum-alone chemotherapy has gained increasing clinical acceptance.

Cisplatin, a platinum-based chemotherapeutic, remains a standard treatment for breast cancer and is often used in combination with other agents [7]. However, patients with advanced disease or poor general condition may struggle to tolerate the side effects of combination therapy. Resistance to diamminedichloroplatinum (DDP) frequently arises through enhanced apoptotic resistance and reprogramming of redox homeostasis, which significantly limit its efficacy. Thus, agents capable of triggering non-apoptotic cell death or disrupting redox balance may help overcome cisplatin resistance.

Ferroptosis is an emerging form of regulated cell death (RCD) characterized by the iron-dependent accumulation of lethal lipid peroxides [8–12]. Numerous conventional

cancer therapies—such as chemotherapy, radiotherapy, immunotherapy, and targeted treatments—have been shown to exert their antitumor effects, in part, through the induction of ferroptosis [9,13–16]. Targeting ferroptosis thus represents a promising strategy, especially for cancers resistant to standard therapies, including breast cancer [10,11,17]. A deeper understanding of the molecular regulation of ferroptosis in breast cancer may lead to more effective treatment approaches.

Epigallocatechin gallate (EGCG), the major polyphenolic catechin in green tea, has demonstrated multiple anticancer properties [18]. Studies showed that EGCG blocks cell cycle progression, modulates proliferative and differentiation pathways, induces apoptosis, inhibits metastatic processes, and suppresses angiogenesis by downregulating VEGF. *In vivo*, oral EGCG administration reduces tumor growth in xenograft and allograft models, exhibiting antimetastatic and anti-angiogenic effects [19].

Given that DDP can induce ferroptosis in various cancers, this study aims to investigate whether EGCG enhances the sensitivity of breast cancer cells to DDP by promoting ferroptosis and to elucidate the underlying mechanisms. Our findings reveal a novel role for EGCG in triggering ferroptosis and enhancing the antitumor activity of DDP in breast cancer cells.

2. Materials and Methods

2.1 Materials

The human breast cancer cell line MDA-MB-231 was acquired from the China Center for Type Culture Collection (CCTCC). The cell line was validated by STR profiling and tested negative for mycoplasma. Complete Protease Inhibitor was obtained from Roche Diagnostics GmbH (Penzberg, Germany). Hoechst 33258 (C1018, Beyotime, Beijing, China) and the ECL detection kit (Wanleibio, Shenyang, China, Cat.WLA006) were obtained from Beyotime. Modified Dulbecco's Eagle's medium was purchased from Gibco Invitrogen Corporation. All other chemicals were of commercially available high-grade purity.

2.2 Cell Culture and Treatment

MDA-MB-231 cells were cultured in high-glucose DMEM containing 10% fetal bovine serum (Gibco, Thermo Fisher Scientific, NY, USA), along with 1% penicillin and 1% streptomycin (KeyGEN, Jiangsu, China). The cells were maintained at 37 °C in a humidified incubator with 5% CO_2.

2.3 Determination of Cell Viability

Cytotoxicity was evaluated using the CCK-8 assay (Wanleibio, Shenyang, China, Cat. WLA074). Cells were plated in 96-well plates at a density of 1.5×10^4 cells per well and left to attach overnight. Following this, the cells were exposed for 24 hours to EGCG (100 µM), DDP (20 µM), or a combination of both. In the rescue experiments, cells received combined treatment with EGCG and DDP along with the ferroptosis inhibitor deferoxamine (DFO, 100 µM) for 24 hours. Subsequently, 10 µL of CCK-8 solution was introduced to each well, and the plates were incubated for 2 hours at 37 °C. Absorbance was then recorded to determine cell viability.

2.4 Clonogenic Assay

For the clonogenic assay, MDA-MB-231 cells (1×10^3 cells/well) were seeded in 12-well plates and incubated for 24 hours. The medium was then replaced with fresh complete culture medium containing EGCG (100 µM), DDP (20 µM), or a combination of both, in the presence or absence of 100 µM DFO, and the cells were cultured for an additional 3 days. After incubation, the colonies were washed with PBS, fixed with 4% paraformaldehyde, and stained with 0.1% crystal violet for 30 minutes.

2.5 Edu Incorporation Assay

The cell proliferation capacity of MDA-MB-231 cells treated with EGCG alone, DDP alone, or their combination in the presence or absence of 100 µM DFO was assessed using the 5-ethynyl-2′-deoxyuridine (EdU) incorporation assay, performed in accordance with the manufacturer's instructions. Immunofluorescence images were subsequently visualized and captured using a fluorescence microscope.

2.6 Intracellular Reactive Oxygen Species (ROS) Generation Detection

Total intracellular ROS levels were measured using an H_2DCFDA-based intracellular ROS fluorescence assay kit (Wanleibio, Shenyang, China, Cat. WLA131) according to the manufacturer's instructions. H_2DCFDA is a cell-permeable probe that is deacetylated by intracellular esterases and oxidized by a broad range of ROS, primarily hydrogen peroxide, to yield the fluorescent product DCF. Fluorescence intensity was quantified to reflect overall ROS levels.

2.7 GSH and MDA Analysis

Logarithmically growing MDA-MB-231 cells were seeded into 6-well plates at a density of 3×10^5 cells/mL (5 mL per well). The cells were then treated for 24 h with 100 µM EGCG, 20 µM DDP, or their combination, in the presence or absence of 100 µM DFO. After washing with PBS, the cells were harvested, sonicated, and centrifuged to collect the supernatants. The levels of MDA (WLA048, Wanleibio, China) and GSH (WLA105, Wanleibio, China) were measured, respectively, according to the manufacturers' instructions.

2.8 Detection of Cellular Lipid Peroxidation Levels by Flow Cytometry

Collect cells from each group after treatment, centrifuge at 150 g for 5 minutes, carefully aspirate the super-

natant, wash the cells once with PBS, and centrifuge at 150 g for 5 minutes to collect cells from each group. Add C11 BODIPY 581/591 (MX5211, MkBio, Shanghai, China) at a concentration of 5 µM, mix well, and incubate in a 37 °C incubator for 30 minutes. Wash the cells three times with PBS, resuspend the cells in 500 µL of PBS, and perform flow cytometry analysis (NovoCyte, Agilen, San Diego, CA, USA).

2.9 Western Blot Analysis

Total protein was extracted from treated cells using RIPA lysis buffer (Solarbio Life Sciences, Beijing, China), and the protein concentration was measured with a BCA assay kit (Beyotime, China). Equal amounts of protein (20 µg per lane) were separated by SDS-PAGE on 10% or 15% gels and then electrotransferred onto PVDF membranes. After blocking, the membranes were incubated overnight at 4 °C with primary antibodies recognizing 4-HNEmodified proteins (Novus Biologicals, CO, USA; 1:1000), GPX4 (Wanleibio; 1:500), and SLC7A11 (Abclonal, Woburn, MA, USA; 1:2000). Subsequently, the membranes were incubated with HRP conjugated secondary antibodies (Proteintech, Rosemont, IL, USA; 1:5000). Immunodetection was performed using an enhanced chemiluminescence (ECL) kit (Wanleibio), and images were acquired with a Chemi-Doc MP Imaging System (BioRad). βActin (Wanleibio; 1:1000) was used as the loading control.

2.10 Statistical Analysis

All data are presented as mean $\pm$ S.E.M. Statistical analyses were performed using one-way ANOVA or Student's *t*-test with GraphPad Prism 6.0 (GraphPad Software, Inc., San Diego, CA, USA). Differences were considered statistically significant at $p < 0.05$.

3. Results

3.1 EGCG Significantly Enhances the Inhibitory Effect of DDP on MDA-MB-231 Cells

We evaluated the effects of EGCG and DDP, both alone and in combination, on human MDA-MB-231 cells. Cytotoxicity was assessed via CCK-8 assay, which revealed that EGCG and DDP each inhibited MDA-MB-231 cell growth. Moreover, EGCG increased the sensitivity of these cells to cisplatin-induced cytotoxicity (Fig. 1A). A colony formation assay was used to examine long-term cell survival following treatment. After 3 days of combination treatment, both the number and size of colonies were significantly reduced compared with single-agent treatments (Fig. 1B). Furthermore, EdU incorporation assays indicated that either agent alone reduced EdUlabeled nuclei, while the combination treatment caused a more pronounced decrease in EdUpositive cells, confirming effective suppression of cell proliferation (Fig. 1C). To explore the mechanism underlying this synergy, we performed Annexin V FITC/PI double staining and Calcein AM/PI live/dead staining. The results demonstrated that the combination of EGCG and DDP synergistically increased cell death (Fig. 1D) and decreased viable cells (Fig. 1E). In summary, EGCG significantly sensitized MDA-MB-231 cells to cisplatin, thereby enhancing its cytotoxic effects.

3.2 EGCG Enhances the Anti-cancer Effect of DDP by Inducing Ferroptosis

In MDA-MB-231 cells, EGCG enhanced cisplatin-induced elevation of ROS (measured by H_2DCFDA fluorescence, Fig. 2A) and lipid peroxides levels (Fig. 2B), increased malondialdehyde MDA content (Fig. 2C), and decreased GSH/GSSG (Fig. 2D). Western blot analysis further revealed that EGCG promoted the upregulation of 4-HNE (Fig. 2E) and downregulated the anti-ferroptosis proteins SLC7A11 and GPX4 (Fig. 2F). Together, these results indicate that EGCG potentiates the cytotoxic effect of cisplatin by inducing ferroptosis.

3.3 Ferroptosis Inhibitor Attenuates the Anti-cancer Effects Of EGCG and Cisplatin

To further validate that EGCG promotes cytotoxicity in MDA-MB-231 cells by inducing ferroptosis, the ferroptosis inhibitor deferoxamine (DFO) was applied to cells treated with EGCG and DDP. DFO was found to reverse EGCG/DDP-induced ferroptosis, which was supported by the following observations: rescued cell viability (Fig. 3A), enhanced colony formation ability (Fig. 3B), increased percentage of EdU-positive cells (Fig. 3C), as well as reduced levels of ROS (Fig. 3D), lipid peroxides (Fig. 3E), and MDA content (Fig. 3F). Western blot analysis further demonstrated that DFO suppressed the accumulation of 4-HNE (Fig. 3G) and restored the expression of the anti-ferroptosis proteins SLC7A11 and GPX4 (Fig. 3H). Collectively, these results confirm that EGCG enhances the cytotoxic effect of cisplatin by activating the ferroptosis pathway.

4. Discussion

Chemotherapy resistance, both intrinsic and acquired, often arises during treatment and leads to poor prognosis in breast cancer patients. Ferroptosis, a recently characterized form of RCD, is distinct from other forms of cell death in its morphological, biochemical, and genetic features, representing a unique cell death pathway [11]. Growing evidence indicates that pharmacological induction of ferroptosis offers a promising strategy to eradicate cancer cells, including those resistant to conventional chemotherapy [11]. In this study, we demonstrate for the first time that EGCG enhances the antitumor effect of cisplatin by triggering ferroptosis in breast cancer cells. Mechanistically, EGCG treatment downregulates SLC7A11 and GPX4, key regulators of glutathione metabolism. These findings provide new insights into targeting ferroptosis via EGCG for breast cancer treatment and highlight a potential therapeutic strategy to overcome chemoresistance.

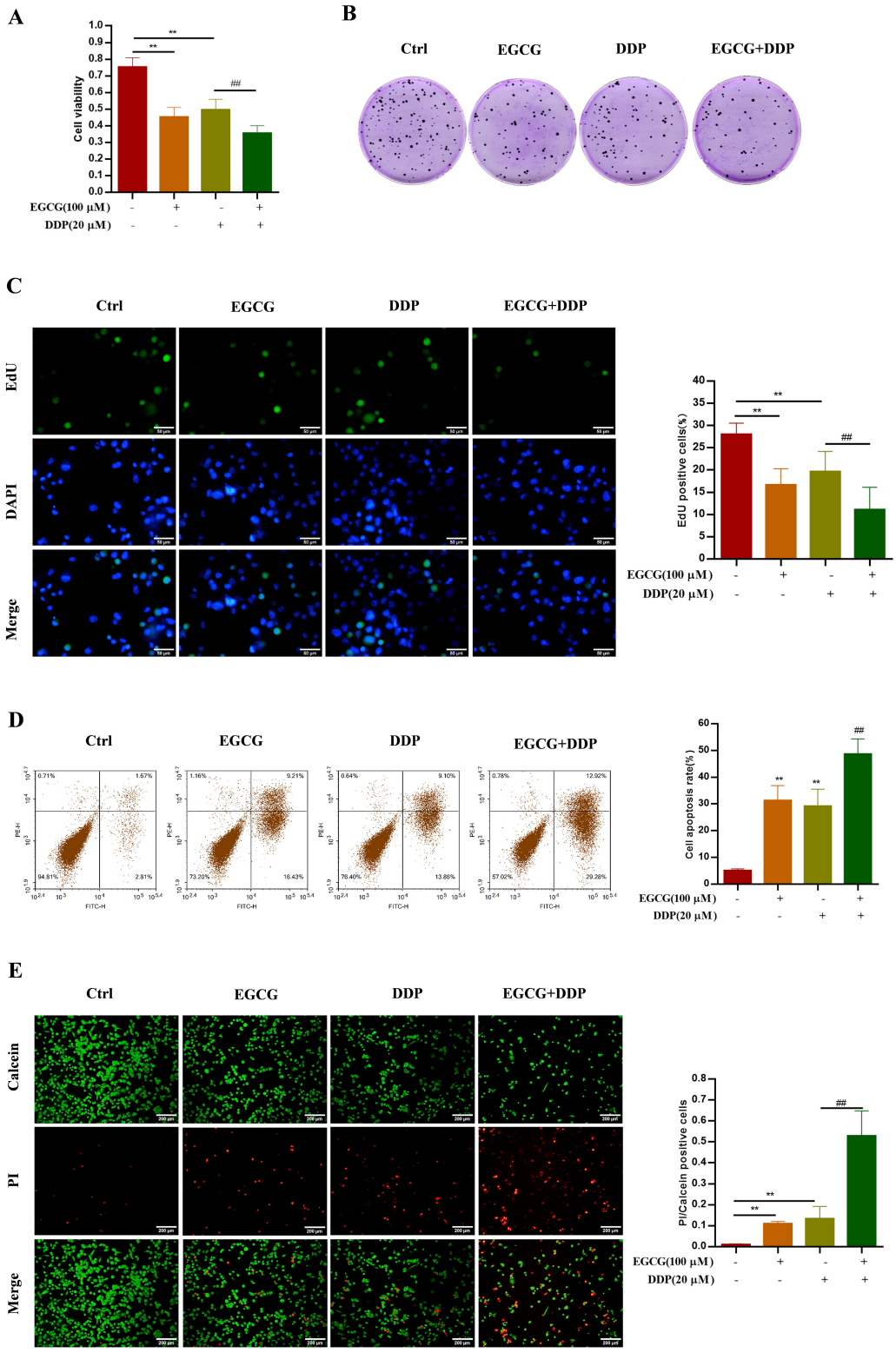

Fig. 1. EGCG synergistically enhances the inhibitory effects of cisplatin (DDP) on MDA-MB-231 human breast cancer cells. Cells were treated with EGCG (100 μM), DDP (20 μM), or their combination for 24 h. (A) Cell viability was assessed using the CCK-8 assay. (B) Colony formation assay: representative images and quantitative data from three independent experiments are presented as mean ± SEM. (C) Proliferation was evaluated using the EdU incorporation assay. Scale bar: 50 μm. (D) Apoptosis was detected by Annexin V-FITC/PI double staining. (E) Live/dead cell staining was performed with Calcein-AM (live cells, green) and PI (dead cells, red). Scale bar: 200 μm. $^{\#\#}p < 0.01$; $^{**}p < 0.01$. EGCG, epigallocatechin gallate; DDP, diamminedichloroplatinum; PI, Propidium Iodide.

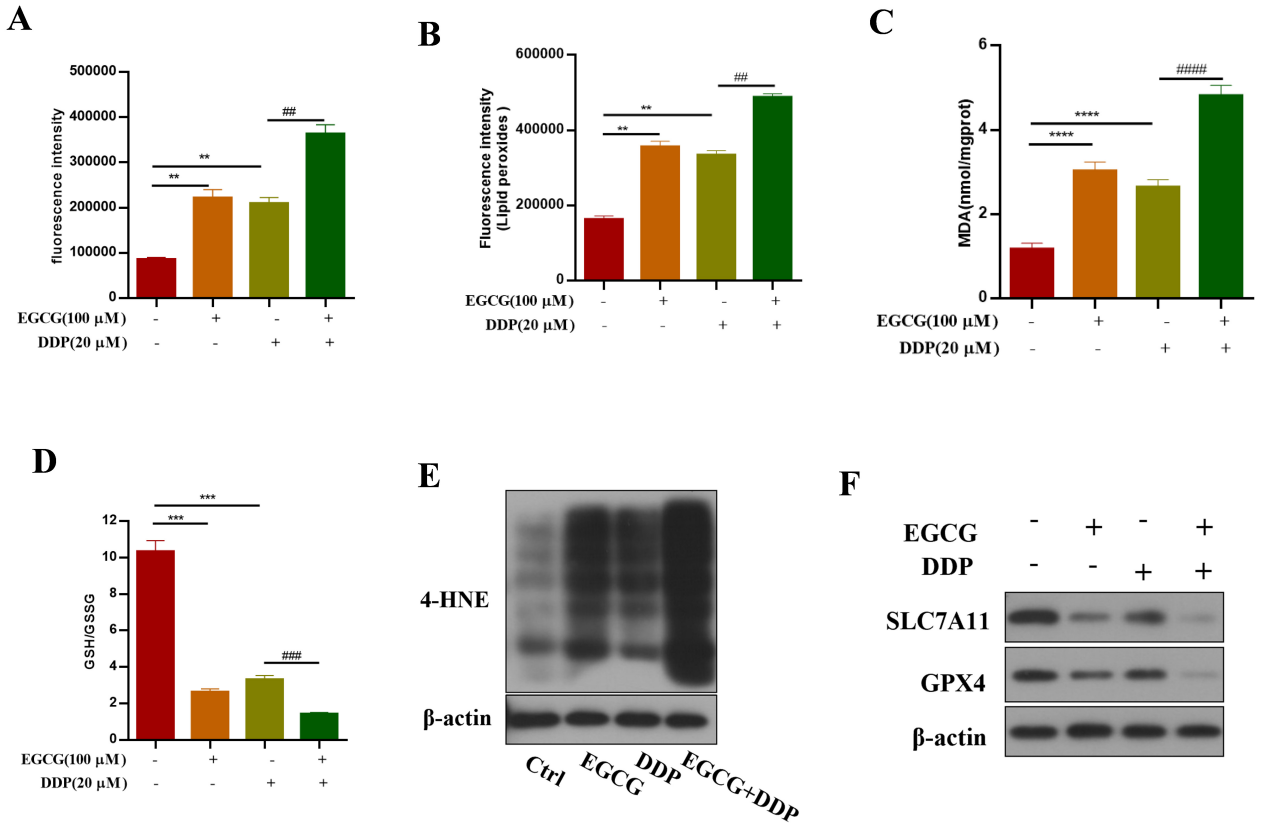

Fig. 2. EGCG enhances the anti-cancer effect of DDP by inducing ferroptosis in MDA-MB-231 cells. Cells were treated with EGCG (100 μM), DDP (20 μM), or their combination for 24 h. (A) Intracellular ROS was measured by flow cytometry using the H_2DCFDA probe, with fluorescence intensity quantified accordingly. (B–D) Levels of lipid peroxides, MDA, and GSH/GSSG were detected using specific assay kits, with statistical results shown. (E,F) Western blot analysis of 4-HNE-modified proteins, SLC7A11, and GPX4 expression in MDA-MB-231 cells. $^{\#\#}p < 0.01$; $^{**}p < 0.01$; $^{\#\#\#}p < 0.005$; $^{***}p < 0.005$; $^{****}p < 0.001$; $^{\#\#\#\#}p < 0.001$.

Platinum-based chemotherapy remains a cornerstone of systemic therapy for advanced breast cancer, especially in triple-negative subtypes, and is frequently recommended in first-line regimens [7]. However, resistance to platinum drugs greatly limits clinical efficacy and poses a major therapeutic challenge [20]. Combining platinum-based chemotherapy with EGCG has emerged as a promising approach to improve outcomes. There is an urgent need to identify novel mechanisms that address unmet clinical needs in breast cancer management. Recent advances suggest that ferroptosis induction can bypass drug resistance and promote tumor cell death [11]. Compounds with ferroptosis-inducing activity may enhance the efficacy of conventional therapies by activating this iron-dependent cell death pathway [11]. Here, we further investigated whether EGCG increases cisplatin sensitivity in breast cancer cells through ferroptosis induction, providing a mechanistic basis for future therapeutic development.

The GPX4-dependent pathway, particularly the GPX4-GSH axis, plays a critical role in regulating ferroptosis [9,21]. The SLC7A11-GSH-GPX4 system constitutes a major cellular defense against ferroptosis, with its inhibition—alongside the accumulation of free iron—serving as key signals for ferroptosis induction [22]. Our results revealed that EGCG reduces protein levels of SLC7A11 and GPX4 and synergizes with cisplatin to further downregulate these proteins. This suggests that EGCG induces ferroptosis by inactivating the SLC7A11-GPX4 axis, thereby sensitizing breast cancer cells to cisplatin.

5. Limitations

While this study provides the first evidence that EGCG enhances cisplatin sensitivity by inducing ferroptosis in breast cancer cells, several limitations must be acknowledged. First, all experiments were conducted exclusively in the MDA-MB-231 triple-negative breast cancer cell line. Although this model is highly relevant for studying aggressive breast cancer subtypes, the absence of additional breast cancer cell lines—including hormone receptor-positive and HER2-positive models—limits the generalizability of our findings. It remains unclear whether the observed synergistic effect of EGCG and cisplatin is

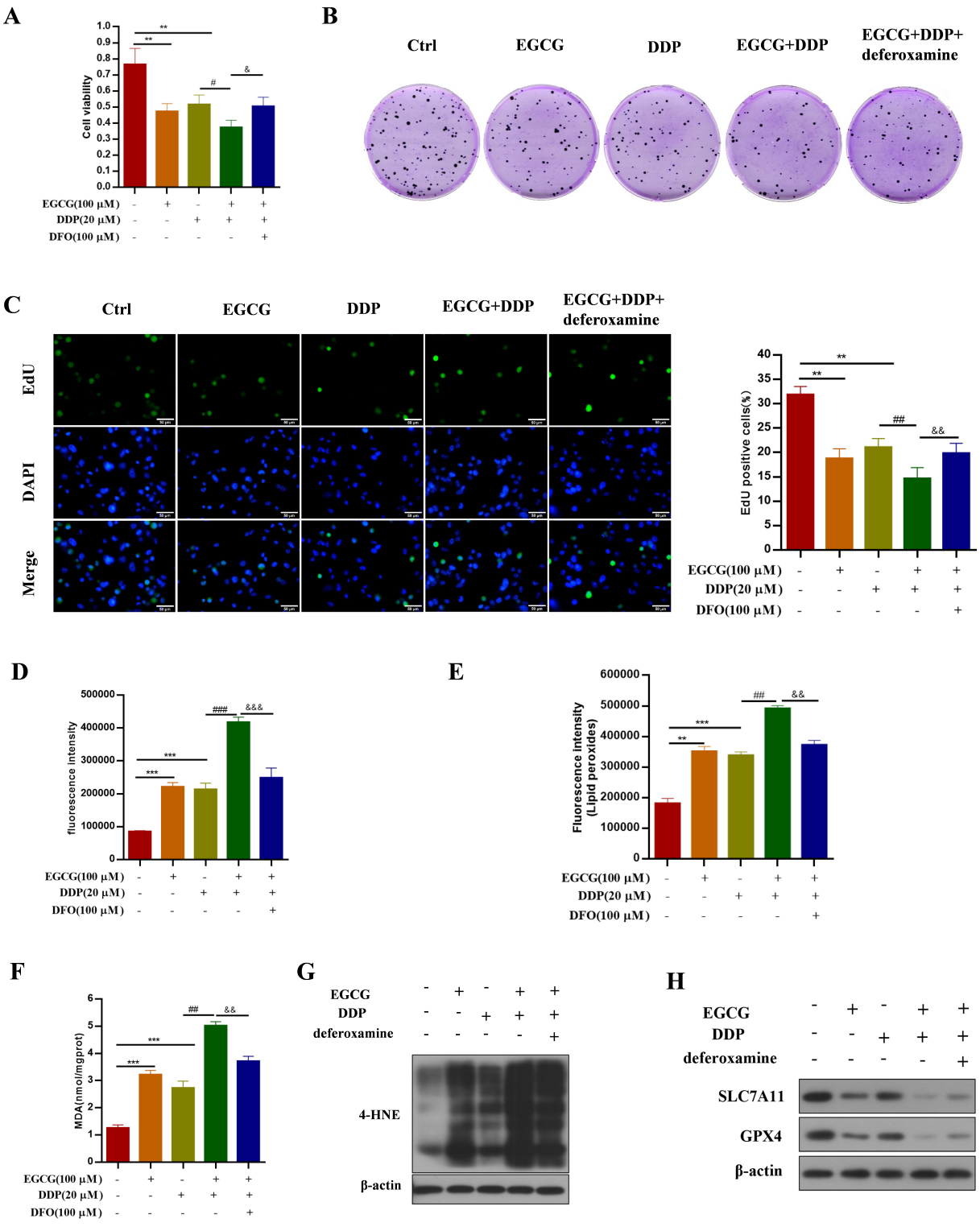

Fig. 3. Ferroptosis inhibitor attenuates the anticancer effects of EGCG and cisplatin. MDAMB231 cells were pretreated with ferroptosis inhibitors for 2 h, followed by exposure to EGCG (100 μM), DDP (20 μM), or their combination for 24 h. (A) Cell viability was measured by CCK8 assay. (B) Colony formation ability was assessed. (C) Cell proliferation was evaluated using the EdU incorporation assay. Scale bar: 50 μm. (D–F) Levels of ROS (detected by H_2DCFDA probe), lipid peroxides, and MDA were detected with corresponding assay kits and statistically analyzed. (G,H) Western blot was performed to detect 4-HNE-modified proteins and SLC7A11/GPX4 expression in MDAMB231 cells. $^{\#}p < 0.05$; $^{\#\#}p < 0.01$; $^{\#\#\#}p < 0.005$; $^{**}p < 0.01$; $^{***}p < 0.005$; $^{\&}p < 0.05$; $^{\&\&}p < 0.01$; $^{\&\&\&}p < 0.005$.

consistent across the heterogeneous spectrum of breast cancer molecular subtypes. Second, this investigation was restricted to *in vitro* experiments. While our data clearly demonstrate the induction of ferroptosis at the cellular level, we did not validate these mechanisms in an *in vivo* model, such as a xenograft mouse model. Consequently, we cannot confirm whether the EGCG/cisplatin combination effectively suppresses tumor growth or induces ferroptosis in a living system, nor can we assess potential pharmacokinetic interactions or off-target toxicities that might arise *in vivo*. Third, the concentrations of EGCG (100 μM) and cisplatin (20 μM) used in this study, while effective *in vitro*, may not be directly translatable to clinically achievable concentrations in humans. The bioavailability of EGCG is known to be limited, and achieving such concentrations in tumor tissue could be challenging. Further studies using clinically relevant dosing regimens are necessary to determine the therapeutic potential of this combination. Finally, although we identified the downregulation of SLC7A11 and GPX4 as a key mechanism, our study did not employ genetic approaches—such as siRNA-mediated knockdown or overexpression of these genes—to definitively establish their causal role in EGCG/DDP-induced ferroptosis. Future work should include such loss- and gain-of-function experiments to confirm the necessity and sufficiency of the SLC7A11-GPX4 axis in this synergistic interaction. Addressing these limitations in future research will be essential to fully evaluate the therapeutic promise of combining EGCG with cisplatin for breast cancer treatment.

6. Conclusion

In summary, this study uncovers a novel mechanism by which EGCG kills breast cancer cells *in vitro*: it induces ferroptosis through inactivation of SLC7A11/GPX4, thereby enhancing cisplatin-mediated antitumor activity in breast cancer cells.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

YG and YW designed and conceived the review. YW wrote the manuscript. YG and YW generated the figures. Both authors contributed to the review and/or editing of the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest.

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