

Quercetin inhibits breast cancer progression by inducing ferroptosis *via* the NEDD4L–SLC7A11 axis

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Abstract. Breast cancer remains one of the most serious malignancies threatening women's health. Quercetin, a major active component found in various Chinese herbal medicines, has shown anti-tumor potential; however, its specific role and underlying mechanisms in breast cancer require systematic investigation. This study demonstrated through MTT, colony formation, wound healing, and Transwell assays that quercetin significantly inhibits the viability, proliferation, and migration capabilities of breast cancer cells. Transcriptome sequencing combined with biochemical assays, qPCR, and Western blot further indicated that quercetin can induce ferroptosis, which is likely the key mechanism underlying its suppression of malignant progression in breast cancer cells. Mechanistically, by promoting the binding between the E3 ubiquitin ligase NEDD4L and SLC7A11, quercetin induces the ubiquitin-proteasome degradation of SLC7A11, ultimately leading to ferroptosis. Notably, quercetin maintained a significant inhibitory effect even during the malignant transformation of breast cancer cells induced by heavy metal lead (Pb) exposure. Collectively, these findings suggest a potential mechanism by which quercetin may inhibit breast cancer progression through ferroptosis activation *via* the NEDD4L/SLC7A11 axis, offering preliminary evidence that could support its possible therapeutic application in breast cancer.

Key words: Breast cancer — Quercetin — Ferroptosis — SLC7A11

Highlights

- Quercetin promotes the ubiquitination and degradation of SLC7A11 by enhancing its interaction with NEDD4L.
- NEDD4L-mediated SLC7A11 degradation triggers ferroptosis in breast cancer cells.
- Quercetin suppresses malignant progression of breast cancer *via* the NEDD4L/SLC7A11-ferroptosis axis.

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Introduction

Breast cancer remains one of the most prevalent malignant tumors among women worldwide, posing a serious threat to women's health globally. According to the latest statistics from the International Agency for Research on Cancer (IARC), breast cancer ranks first in global incidence and among the top in mortality rates among female malignancies (Cañeque et al. 2025), primarily due to its high metastatic potential (Nguyen et al. 2022; Boire et al. 2024). It is projected that both the incidence and mortality rates of breast cancer will continue to rise in the future (Xu et al. 2023). Data from 2024 indicate a sustained increase in the incidence of female breast cancer over the past decade, making it the most common malignant tumor among Chinese women (Han et al. 2024). The mechanisms underlying the development and progression of breast cancer are highly complex, with increasing attention being paid to the impact of environmental pollutants, particularly lead, on the malignant course of the disease. Studies have shown that heavy metal lead can upregulate the expression of ER α , thereby activating the PI3K/Akt/mTOR signaling pathway and accelerating breast cancer progression. In addition, lead exposure may indirectly contribute to the onset and progression of breast cancer by affecting lipid profiles and other small molecule metabolites. Against this backdrop, how to develop effective treatments for such environmentally associated breast cancers has become an important subject worthy of in-depth exploration. Current treatment strategies for breast cancer predominantly rely on chemotherapy, which is often associated with significant toxicity and the development of drug resistance. Consequently, exploring natural compounds with improved efficacy and reduced side effects is of great importance for breast cancer therapy.

Quercetin is a naturally occurring flavonoid compound widely found in fruits and vegetables. It exhibits significant anti-inflammatory, antioxidant, and antiviral activities and is considered a promising natural drug candidate (Li et al. 2023; Carrillo-Martinez et al. 2024). In recent years, quercetin has gained considerable attention in the field of oncology due to its ability to exert anti-tumor effects by interfering with various biological processes, including cell proliferation, apoptosis, and angiogenesis (Asgharian et al. 2022; Lotfi et al. 2023; Kumar and Sharma 2024). It has demonstrated anti-tumor efficacy in various cancer models, such as lung, liver, colon, and bladder cancers. The underlying mechanisms involve the modulation of multiple signaling pathways, including Wnt/ β -catenin, PI3K/AKT, JAK/STAT, MAPK, p53, and NF- κ B, thereby influencing the malignant progression of tumor cells (Asgharian et al. 2022; Tan et al. 2025). In breast cancer research, existing findings have primarily focused on the inhibitory effects of quercetin on cell proliferation and its role in inducing apoptosis. Kundur

et al. reported that quercetin suppresses breast cancer cell proliferation by enhancing histone H3 acetylation at the BRCA1 promoter, leading to the upregulation of BRCA1 expression (Kundur et al. 2019). Another study indicated that quercetin activates the GRB2/ERK/MAPK signaling pathway to promote apoptosis (Hosseini et al. 2023). Furthermore, the combination of quercetin with lonidamine was shown to downregulate MMP-2/9 protein level, inhibiting proliferation and inducing apoptosis (Ozkan and Bakar-Ates 2020). A similar synergistic effect was observed when quercetin was combined with naringenin (Umar et al. 2022). Although existing studies have demonstrated that quercetin influences breast cancer cell functions such as proliferation and apoptosis through multiple pathways, the identification of its specific molecular targets and the precise mechanisms of action remain critical questions to be addressed in current research.

Ferroptosis is an iron-dependent form of regulated cell death, distinct from apoptosis, pyroptosis, and autophagy. Its hallmark feature is the occurrence of iron-dependent lipid peroxidation, a process accompanied by the accumulation of reactive oxygen species (ROS) and depletion of glutathione (GSH) (Lei et al. 2022; Stockwell 2022; Dixon and Pratt 2023). Ferroptosis is significantly implicated in the progression of various diseases, including cancer, cardiovascular, and neurological disorders. Compared to normal cells, cancer cells, which exhibit more active metabolism and consequently higher basal levels of ROS, are generally more susceptible to ferroptosis (Xiang et al. 2024). The cystine/glutamate antiporter (system Xc⁻), composed of SLC7A11 and SLC3A2, regulates the process of ferroptosis through multiple mechanisms (S. Li et al. 2024; Zheng and Conrad 2025). SLC7A11 serves as the catalytic subunit of this transporter system and plays a central role in maintaining GSH synthesis and intracellular redox homeostasis. It is frequently overexpressed in various cancer cells (Koppula et al. 2021; Dixon and Olzmann 2024). Studies have shown that inhibiting SLC7A11 expression reduces cystine uptake, increases susceptibility to ferroptosis, and consequently suppresses tumor development (Yan et al. 2023). Conversely, high expression of SLC7A11 can inhibit ferroptosis and promote tumor progression. For instance, in liver and gastric cancers, its elevated expression leads to increased GSH, decreased ROS, and suppression of ferroptosis (Ding et al. 2024). In breast cancer, SLC7A11 is regulated at multiple levels. Transcriptionally, it is controlled by factors such as P53, BAP1, and SP1 (Xia et al. 2024). Post-translationally, the deubiquitinase OTUD5 can enhance the resistance of triple-negative breast cancer cells to ferroptosis by inhibiting the ubiquitination-mediated degradation of SLC7A11 protein (Liu et al. 2024). Compared to traditional tumor treatment methods, targeting the key regulatory protein SLC7A11 in the ferroptosis pathway to induce tumor cell

death can serve as a highly promising novel therapeutic strategy. However, the upstream regulatory network of SLC7A11 has not been fully elucidated, which hinders the development of drugs targeting this pathway.

In this work, human breast cancer cell lines were treated with the natural compound quercetin, and subsequent changes in cellular functions were evaluated. Based on these findings, transcriptome sequencing was performed to identify differentially expressed genes and enriched signaling pathways. To further elucidate the underlying mechanisms, sequencing data were integrated with measurements of key intracellular biochemical markers and molecular biology analyses to validate the effects of quercetin. Our results demonstrate that quercetin effectively inhibits the proliferation and migration of breast cancer cells and retains its suppressive activity on malignant progression even under lead-induced stress. Mechanistically, quercetin targets the NEDD4L–SLC7A11 axis, promotes ubiquitin–proteasome-mediated degradation of SLC7A11, triggers ferroptosis, and ultimately suppresses breast cancer malignancy.

Materials and Methods

Materials and reagents

The primary reagents used included: RPMI-1640 medium (PM150113, Pricella), DMEM medium (PM150217, Pricella), fetal bovine serum (FSP500, ExCell Bio), penicillin-streptomycin solution (P1400, Solarbio), quercetin (C14950778, Macklin), lead acetate (316512, Sigma-Aldrich), MTT (ST1537, Beyotime), DMSO (CD4731, Coolaber), crystal violet (ST1537, Beyotime), Reactive Oxygen Species Assay Kit (S0033S, Beyotime Biotechnology), Total Glutathione Assay Kit (S0052, Beyotime Biotechnology), Lipid Peroxidation Assay Kit (S0043S, Beyotime Biotechnology), Cell Ferrous Colorimetric Assay Kit (E-BC-K881-M, Elabscience), RNAiso Plus (9108, Takara), Reverse Transcription Kit (AU341, TransGenBiotech), Real-Time PCR Kit (RR420A, Takara), RIPA Lysis Buffer (C190419, YangGuangBio), IP Lysis Buffer (G2038, Servicebio), PMSF Inhibitor (C210111, YangGuangBio), SLC7A11 antibody (26864-1-AP, Proteintech), GPX4 antibody (Huabio, ET1706-45), ACSL4 antibody (Huabio, ET7111-43), TFRC antibody (Huabio, ET1702-06), NEDD4L antibody (13690-1-AP, Proteintech), HRD1 antibody (13473-1-AP, Proteintech), GAPDH antibody (GB15002, Servicebio), HRP-conjugated goat anti-mouse antibody (GB23301, Servicebio), β -Tubulin antibody (GB152667, Servicebio), rabbit IgG control antibody (GB111738, Servicebio), Protein A/G Magnetic Beads (HY-K0202, MCE), and Lipo6000 Transfection Reagent (C0526-1.5mL, Beyotime Biotechnology).

Cell culture

The human breast cancer cell line MCF-7 and the human embryonic kidney cell line 293T were purchased from the American Type Culture Collection (ATCC). The BT-549 cell line was a generous gift from the Cancer Metastasis and Metabolism research group at the Southern University of Science and Technology (Shenzhen, China). 293T cells were cultured in DMEM medium, while MCF-7 and BT-549 cells were maintained in RPMI-1640 medium. All cell lines were incubated at 37°C in a humidified atmosphere containing 5% CO₂.

MTT assay

Cells in the logarithmic growth phase were seeded into 96-well plates. After complete adherence, the cells were treated with the respective compounds for 48 hours. Subsequently, 5 mg/ml MTT solution was added to each well, and the plates were incubated at 37°C for 4 hours. Then, 100 μ l of dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazan crystals. The absorbance of each well was measured at a wavelength of 570 nm using a microplate reader. For evaluating the half-maximal inhibitory concentration (IC₅₀) of quercetin, experimental groups included a control group and groups treated with various concentrations of quercetin. To assess the combined effects of lead (Pb) and quercetin, the experimental setup included a control group, a lead-treated group, a quercetin-treated group, and a combination treatment group (lead plus quercetin). Each group contained six replicate wells. Cell viability was calculated using the following formula: Cell Viability = [(As – Ab)/(Ac – Ab)] $\times$ 100%. (Where As represents the absorbance of the experimental group, Ab represents the absorbance of the blank group, and Ac represents the absorbance of the control group.)

Colony formation assay

Cells in the logarithmic growth phase were seeded into 6-well plates. After the cells had completely adhered, they were treated with the respective compounds for 48 hours. The medium was then replaced with fresh medium containing 10% fetal bovine serum, and the cells were cultured continuously for two weeks. Once macroscopic colonies had formed, the cells were fixed with ice-cold methanol for 15 minutes and then stained with a 0.1% crystal violet solution for 15 minutes. The colony formation in each group was subsequently quantified.

Wound healing assay

Cells in the logarithmic growth phase were seeded into 6-well plates. After the cells reached full confluence, they were treated with the respective compounds. A straight wound was created in the cell monolayer using a sterile

pipette tip, and the detached cells were gently washed away with phosphate-buffered saline (PBS). The cells were then photographed under an inverted fluorescence microscope immediately (0 hours) after creating the wound. Subsequent images were captured at 24 and 48 hours post-wounding. The cell migration rate was calculated using the following formula: Migration rate (%) = (Wound area at 0 h – Wound area at 24 h)/Wound area at 0 h × 100%. Quantifications were performed based on three independent experiments and used for statistical analysis.

Transwell assay

Cells in the logarithmic growth phase were treated with the respective compounds for 48 hours before being seeded into the upper chamber of a Transwell insert. The lower chamber was filled with 500 µl of medium containing 10% fetal bovine serum. After 24 hours of incubation, the upper chamber was removed. The cells on the upper surface of the membrane were carefully wiped away with a cotton swab. The cells that had migrated to the lower surface were fixed with 4% paraformaldehyde for 15 minutes and then stained with a 0.1% crystal violet solution for 15 minutes. After washing with PBS, the membranes were photographed under a microscope. The migratory ability was assessed by counting the average number of stained cells in five randomly selected fields. For statistical analysis, data from three independent biological replicate experiments were used.

Transcriptome sequencing analysis

MCF-7 cells in the logarithmic growth phase were treated for 48 hours. Total RNA was then isolated using RNAiso Plus reagent. For each condition, RNA samples from three biological replicates were aliquoted, snap-frozen on dry ice, and shipped to Personalbio (Shanghai, China) for RNA sequencing. Sequencing was carried out on the Illumina NovaSeq X Plus platform, and differential gene expression analysis was performed using DESeq2 with a threshold of $|\log_2\text{FoldChange}| > 2$ and a p -value < 0.05 .

Detection of intracellular ROS

Cells in the logarithmic growth phase were seeded into 96-well plates. After complete adherence, the cells were treated with the respective compounds for 48 hours. Subsequently, an appropriate concentration of a fluorescent probe was added to each well, and the plates were incubated at 37°C for 30 minutes. The cells were then washed with serum-free medium. Finally, the fluorescence intensity of each group was measured using a fluorescence microplate reader. Each group contained three replicate wells, and data from three independent biological replicate experiments were used for statistical analysis.

Detection of intracellular malondialdehyde (MDA)

Cells in the logarithmic growth phase were seeded into 100 mm cell culture dishes. After the cells had completely adhered, they were treated with the respective compounds for 48 hours. The cells were collected into centrifuge tubes and lysed by adding an appropriate amount of the provided reagent. The supernatant was then collected, mixed with the assay working solution, and heated in a 100°C water bath for 40 minutes. Finally, the absorbance of each group was measured at 532 nm, and the MDA concentration was calculated based on a standard curve. Data from three independent biological replicate experiments were used for statistical analysis.

Detection of intracellular ferrous ion (Fe²⁺)

Cells in the logarithmic growth phase were seeded into 60 mm cell culture dishes. After the cells had completely adhered, they were treated with the respective compounds for 48 hours. The cells were collected into centrifuge tubes and lysed by adding an appropriate amount of Reagent 1 (E-BC-K881-M, Elabscience). The supernatant was then collected, mixed with Reagent 3, and incubated at 37°C for 10 minutes. Finally, the absorbance of each group was measured at 593 nm, and the Fe²⁺ concentration was calculated based on a standard curve. Data from three independent biological replicate experiments were used for statistical analysis.

Detection of intracellular total GSH content

Cells in the logarithmic growth phase were seeded into 60 mm cell culture dishes. After the cells had completely adhered, they were treated with the respective compounds for 48 hours. The cells were collected into centrifuge tubes and lysed by adding an appropriate amount of protein removal reagent, followed by three rapid freeze-thaw cycles. After centrifugation, the total glutathione assay solution and 0.5 mg/ml NADPH were added to the supernatant, and the mixture was incubated at 25°C for 5 minutes. Finally, the absorbance of each group was measured at 412 nm, and the GSH concentration was calculated based on a standard curve. Data from three independent biological replicate experiments were used for statistical analysis.

Quantitative real-time PCR (qRT-PCR)

Cells in the logarithmic growth phase were seeded into 6-well plates. After complete adherence, the cells were treated with the respective compounds for 48 hours. Total RNA was then extracted from the cells using RNAiso Plus reagent and reverse-transcribed into cDNA. Quantitative

PCR was performed using a commercial kit, with GAPDH serving as the endogenous control for normalization. The relative expression levels of the target genes were calculated using the $2^{-\Delta\Delta C_t}$ method. The primer sequences used are listed in Table 1.

Western blot analysis

Cells in the logarithmic growth phase were seeded into 60 mm culture dishes. After complete adherence, the cells were treated with the respective compounds for 48 hours. Total protein was extracted using RIPA lysis buffer containing PMSF inhibitor. The protein samples were separated by SDS-PAGE and subsequently transferred onto PVDF membranes. The membranes were then blocked with 5% non-fat milk. After washing with TBST, the membranes were incubated with appropriately diluted primary antibodies at 4°C overnight. Following another wash step, the membranes were incubated with diluted HRP-conjugated goat anti-mouse secondary antibody at 37°C for 30 minutes. After a final wash, the protein bands were visualized using an enhanced chemiluminescence (ECL) substrate, and the expression levels of the target proteins were analyzed.

Cell transfection

Cells were seeded into 6-well plates and cultured until they reached approximately 70% confluence prior to transfection. The transfection reagent Lipo6000 was mixed with DNA or small interfering RNAs (siRNAs) at concentrations specified by the manufacturer's instructions. The mixture was then co-incubated with the cells. After 6 hours, the medium was replaced with complete medium.

Co-immunoprecipitation (Co-IP) assay

Cells were lysed using IP lysis buffer. The supernatant was incubated with SLC7A11 antibody or rabbit IgG antibody at 4°C overnight. The mixture was then incubated with Protein A/G magnetic beads at 4°C for 4 hours. After magnetic separation, the beads were washed with PBST buffer and then boiled in loading buffer for 10 minutes. Finally, the samples were prepared for subsequent Western blot analysis.

Molecular docking

Using the PubChem database (<https://pubchem.ncbi.nlm.nih.gov/>) to obtain the molecular structure of quercetin, after optimization with Chem3D, it is converted into a .pdbqt format file using AutoDockTools. Using the RCSB PDB database (<https://www.rcsb.org/>) to download the molecular structure of the key regulatory factor, PyMOL 2.5.7 is used to remove water molecules and small molecule impurities

Table 1. Primer sequences for qRT-PCR

Gene	Primer sequence
GPX4	F: 5'-GAGGCAAGACCGAAGTAAACTAC-3'
	R: 5'-CCGAACTGGTTACACGGGAA-3'
SLC7A11	F: 5'-TCTCCAAAGGAGGTTACCTGC-3'
	R: 5'-AGACTCCCCTCAGTAAAGTGAC-3'
ACSL4	F: 5'-CATCCCTGGAGCAGATACTCT-3'
	R: 5'-TCACTTAGGATTTCCTGGTCC-3'
TFRC	F: 5'-ACCATTGTCATATACCCGGTTCA-3'
	R: 5'-CAATAGCCCCAAGTAGCCAATCAT-3'
AGR3	F: 5'-ATCACCTGATGGGCAATATGTG-3'
	R: 5'-GAGTATCTTCCAGCTATGTCAGC-3'
CYP1A1	F: 5'-ACATGCTGACCCTGGGAAAG-3'
	R: 5'-GGTGTGGAGCCAATTCGGAT-3'
GDF15	F: 5'-GACCCTCAGAGTTGCACTCC-3'
	R: 5'-GCCTGGTTAGCAGGTCCTC-3'
AKR1C1	F: 5'-GGCTTTGTTAGGCAACTGTGT-3'
	R: 5'-AAGGCAGCGAAGGATTCAGA-3'
ATF3	F: 5'-GTGCCGAAACAAGAAGAAGG-3'
	R: 5'-TCTGAGCCTTCAGTTCAGCA-3'
GAPDH	F: 5'-GGAGCGAGATCCCTCCAAAAT-3'
	R: 5'-GGCTGTTGTCATACTTCTCATGG-3'

F, forward; R, reverse.

from the protein structure, which is then imported into AutoDockTools and converted into a .pdbqt format file. Finally, molecular docking is performed, and visualization is carried out using PyMOL 2.5.7.

Bioinformatics analysis of core genes

The UALCAN database (<https://ualcan.path.uab.edu/>), which focuses on cancer gene expression data, is an online platform for TCGA gene expression analysis. In this study, the UALCAN database was used to analyze the differential expression of the screened core genes between tumor tissues and normal tissues, and to construct survival curves for these core genes. The TIMER database (<https://timer.cistrome.org/>) is an online platform dedicated to the analysis of cancer gene expression and the tumor immune microenvironment. It integrates cancer gene expression data and immune cell infiltration data, providing research analysis on various cancer types and the immune microenvironment. This study utilized the TIMER database to conduct a pan-cancer analysis of the core genes, examining their expression across multiple types of tumor tissues and normal tissues.

Statistical analysis

Experimental data are presented as the mean $\pm$ standard deviation (SD). Multi-group comparisons are performed

using analysis of variance (ANOVA). A probability (p) value of less than 0.05 was considered statistically significant and is denoted by *; $p < 0.01$ is denoted by **, and $p < 0.001$ is denoted by ***. Statistical analyses were performed using GraphPad Prism software (version 9.5).

Results

Quercetin inhibits the proliferation and migration of breast cancer cells

To investigate the effects of quercetin on breast cancer cell functions, we selected two human breast cancer cell lines, MCF-7 and BT-549, and treated them with varying concentrations of quercetin for 48 hours. The results indicated that quercetin significantly induced cell death at concentrations above 160 μM in a dose-dependent manner (Fig. 1A). MTT assay results showed that the IC_{50} values of quercetin for MCF-7 and BT-549 cells were 125.6 μM and 192.8 μM , respectively (Fig. 1B). Based on these findings, subsequent experiments utilized quercetin concentrations of 80 μM for MCF-7 and 120 μM for BT-549 cells for further investigation. Colony formation assays further demonstrated that quercetin significantly inhibited the proliferative capacity of the cells (Fig. 1C). Alterations in the motility of breast cancer cells represent another critical factor influencing their malignant progression. To evaluate the impact of quercetin on this process, we assessed the migratory ability of MCF-7 and BT-549 cells using wound healing and Transwell assays. The Transwell assay showed that the migratory capacity of both cell types was significantly inhibited after 48 hours of quercetin treatment (Fig. 1D). To further validate these findings, the wound healing assay similarly demonstrated that quercetin markedly reduced the migration rate of both cell types (Fig. 1E), further confirming the inhibitory effect of quercetin on the migration of breast cancer cells.

Transcriptomic alterations induced by quercetin in breast cancer cells

To elucidate the molecular mechanism of quercetin's action on breast cancer cells, we treated MCF-7 cells with 80 μM quercetin and performed transcriptome sequencing analysis. The results indicated that the quercetin-treated group exhibited significant changes at the transcriptional level compared to the control group. Volcano plot analysis revealed a large number of differentially expressed genes (DEGs) between the two groups (Fig. 2A). Cluster heatmap analysis further demonstrated a clear separation in the expression patterns of these DEGs between the treated and control groups (Fig. 2B). Principal component analysis confirmed distinct clustering of the samples from the two groups, supporting the reliability

of the transcriptome data (Fig. 2C). To validate the accuracy of the sequencing results, we randomly selected four DEGs and detected their mRNA expression levels in quercetin-treated cells by qRT-PCR. The results were consistent with the sequencing data (Fig. 2D), further confirming the credibility of the dataset.

GO functional enrichment analysis showed that the DEGs were primarily involved in biological processes such as cell migration, transcription factor binding, and plasma membrane composition (Fig. 2E). KEGG pathway analysis suggested that the DEGs were significantly enriched in ferroptosis, PI3K-Akt signaling, p53 signaling, and multiple cancer-related pathways (Fig. 2F). Among these, the ferroptosis pathway was notably prominent. Considering the reported important role of ferroptosis in suppressing tumor progression, together with our observation that quercetin induces cell death, we hypothesize that quercetin may inhibit the malignant progression of breast cancer cells by regulating the ferroptosis pathway.

Quercetin induces ferroptosis in breast cancer cells

To validate whether quercetin suppresses the malignant progression of breast cancer cells through the ferroptosis pathway, we measured key biochemical indicators of ferroptosis, including ferrous ion (Fe^{2+}), MDA, GSH, and ROS levels. The results showed that in MCF-7 cells, treatment with 80 μM quercetin significantly increased the contents of Fe^{2+} , MDA, and ROS, while markedly reducing GSH levels (Fig. 3A). Similarly, in BT-549 cells, treatment with 120 μM quercetin also led to a significant rise in Fe^{2+} , MDA, and ROS levels, accompanied by a decrease in GSH (Fig. 3B). Furthermore, we examined the expression of ferroptosis-related regulatory genes TFRC, ACSL4, and SLC7A11. In MCF-7 cells, quercetin up-regulated the expression of these genes (Fig. 3C), which aligns with features of ferroptosis. However, the upregulation of SLC7A11 is inconsistent with the typical ferroptosis response. In BT-549 cells, up-regulation of TFRC and SLC7A11 was observed, while ACSL4 showed no significant change (Fig. 3D).

In summary, these findings indicate that quercetin induces iron accumulation, enhanced lipid peroxidation, and reduced antioxidant capacity in breast cancer cells, exhibiting typical features of ferroptosis. Combined with the earlier transcriptome sequencing and qPCR results, it is suggested that quercetin may inhibit the malignant progression of breast cancer cells by triggering ferroptosis.

Quercetin promotes ferroptosis by enhancing NEDD4L–SLC7A11 interaction and protein degradation

Previous studies have indicated that downregulation of SLC7A11 can induce ferroptosis in cells. In this study, we

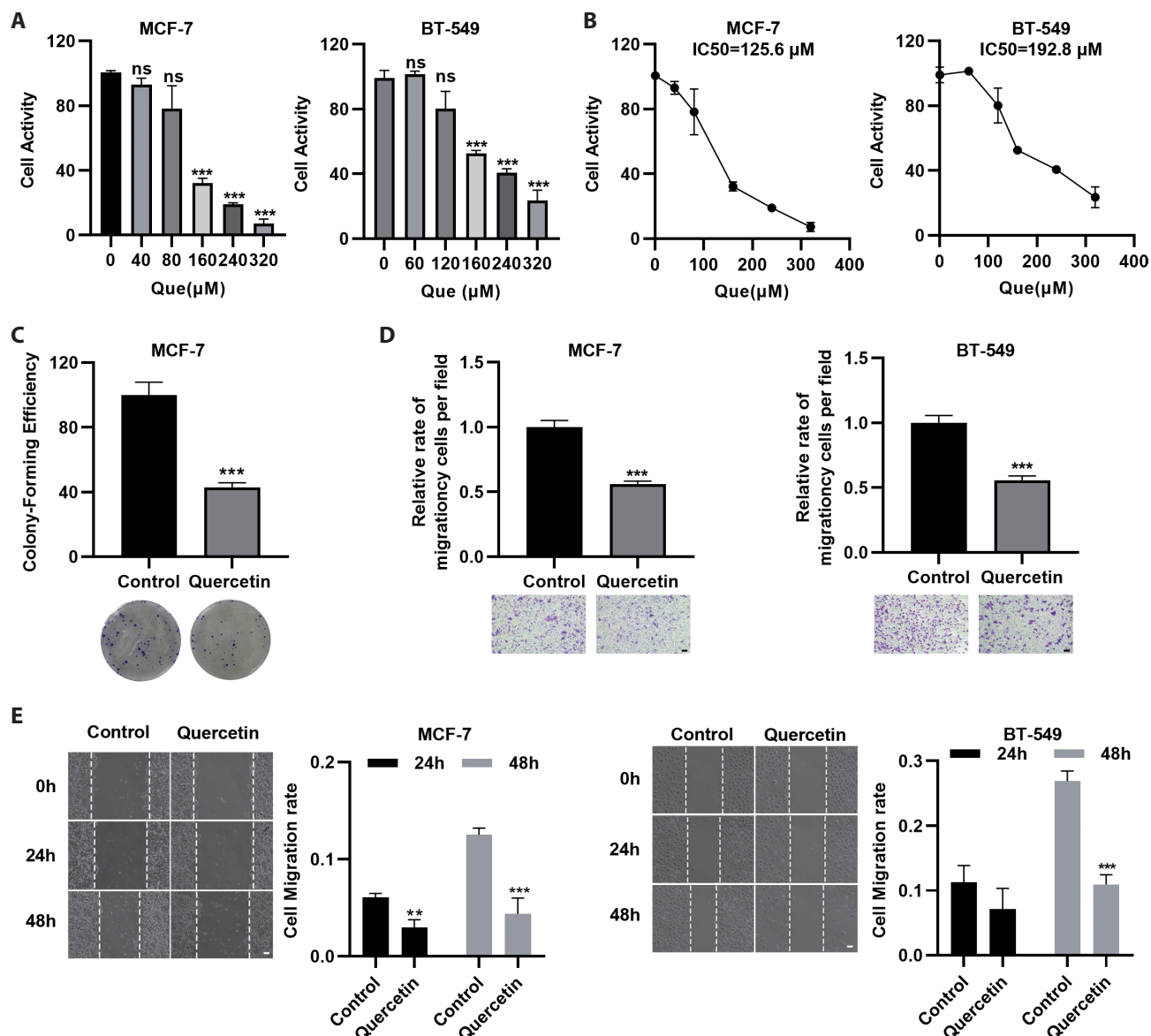


Figure 1. Effect of quercetin on the proliferation and migration of breast cancer cells. **A.** Viability of MCF-7 and BT-549 cells after treatment with indicated concentrations of quercetin for 48 h, as measured by MTT assay. **B.** Dose-response curves and corresponding half-maximal inhibitory concentration (IC₅₀) values of quercetin in MCF-7 and BT-549 cells, calculated from the data in (A). **C.** Colony formation assay of MCF-7 cells treated with 80 μM quercetin for two weeks. **D.** Migration ability of MCF-7 and BT-549 cells treated with 80 μM and 120 μM quercetin, respectively, for 48 h, evaluated by Transwell assay. **E.** Migration ability of MCF-7 and BT-549 cells treated with 80 μM and 120 μM quercetin, respectively, for 48 h, assessed by wound healing assay. Data are presented as mean ± SD; *n* = 3 experimental replicates; scale bars = 100 μm; ** *p* < 0.01, *** *p* < 0.001, ns, not significant.

found that although quercetin can trigger ferroptosis, it concurrently led to an increase in SLC7A11 expression at the transcriptional level. To further investigate this paradoxical phenomenon, we examined the protein expression levels of TFRC, ACSL4, and SLC7A11. Notably, quercetin treatment resulted in a significant decrease in SLC7A11 protein levels (Fig. 4A), which was inconsistent with the transcriptome

sequencing and qRT-PCR results. We speculated that this likely results from post-translational regulation and proteasome-dependent degradation of SLC7A11. To explore the mechanism underlying this protein downregulation, we treated the cells with the proteasome inhibitor MG-132 in combination with quercetin. The results showed a marked recovery of SLC7A11 protein levels (Fig. 4B), suggesting

that quercetin promotes the degradation of SLC7A11 *via* the ubiquitin-proteasome pathway. Subsequently, potential E3 ubiquitin ligases interacting with SLC7A11 were predicted using the Ubibrowser database, and the screening results indicated that NEDD4L is the most likely candidate for such interaction (Fig. 4C). Molecular docking results

further revealed that NEDD4L can form a stable complex with quercetin through residues Ile-487, Arg-486, and Glu-932, with a binding energy of -7.2 kcal/mol (Fig. 4D). Co-immunoprecipitation (Co-IP) experiments demonstrated that quercetin enhances the interaction between NEDD4L and SLC7A11 (Fig. 4E). To validate the functional necessity

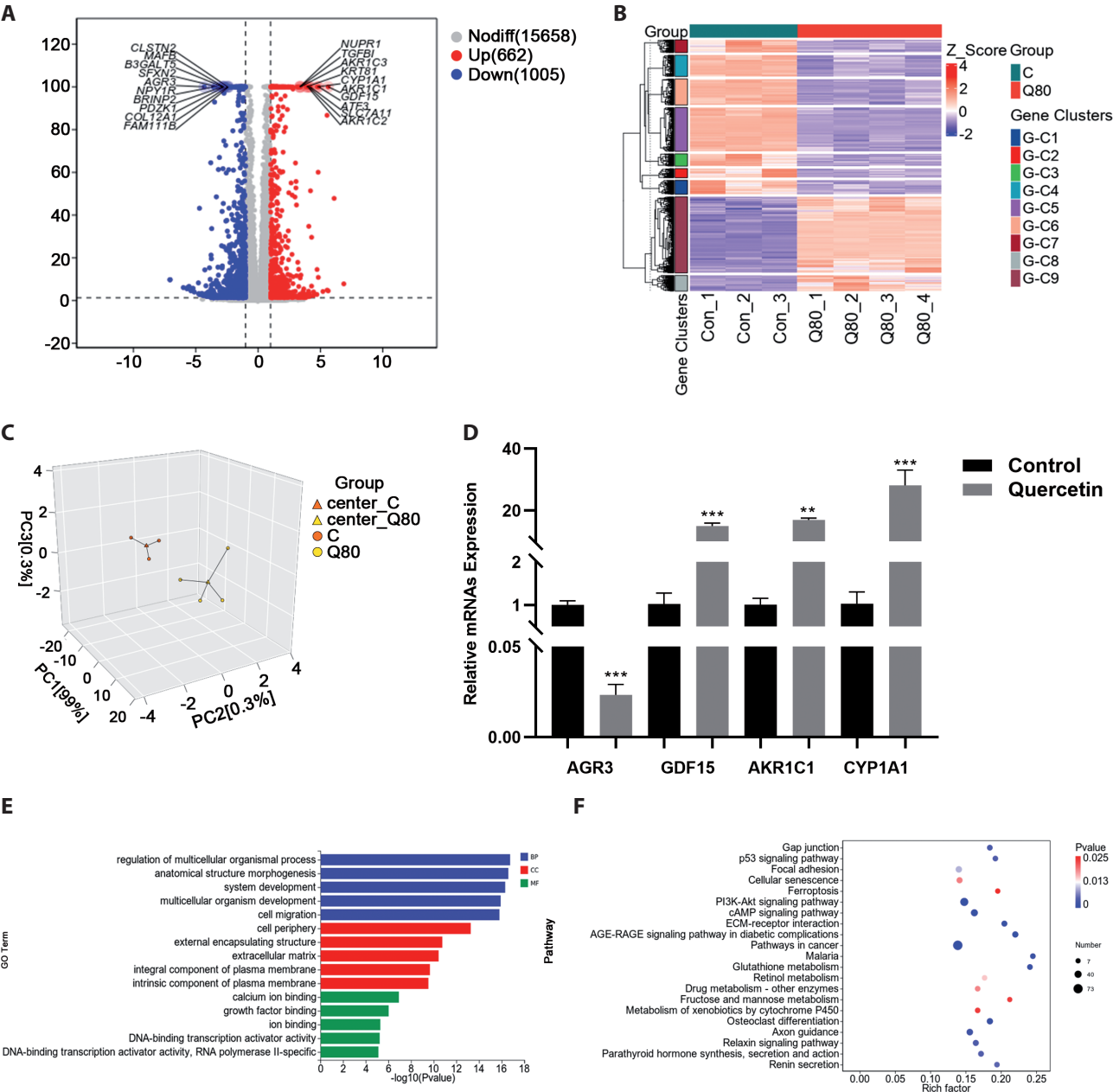


Figure 2. Transcriptome analysis of quercetin-treated MCF-7 cells. Transcriptomic sequencing analysis of MCF-7 cells treated with 80 μM quercetin. **A.** Volcano plot of differentially expressed genes ($|\text{Log}_2\text{FC}| > 2$ set as the threshold). **B.** Cluster heatmap of differentially expressed genes. **C.** Principal component analysis (PCA). **D.** qRT-PCR validation of mRNA expression levels of AGR3, GDF15, AKR1C1, and CYP1A1 in MCF-7 cells treated with quercetin (80 μM , 48 h). Functional enrichment analysis of differentially expressed genes after treatment with 80 μM quercetin. **E.** GO enrichment analysis. **F.** KEGG pathway enrichment analysis. Data are presented as mean $\pm$ SD; $n = 3$ experimental replicates; ** $p < 0.01$, *** $p < 0.001$.

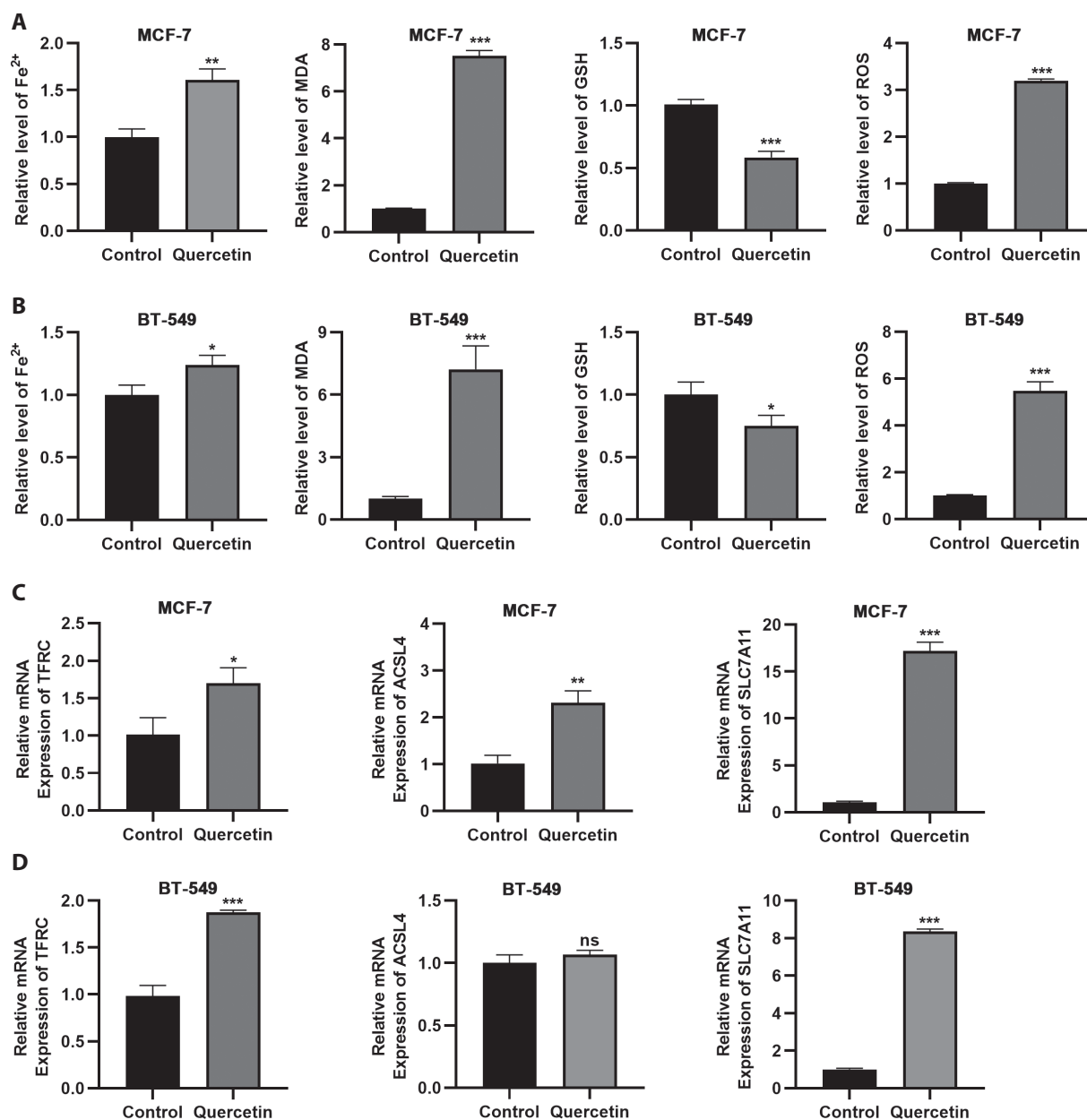
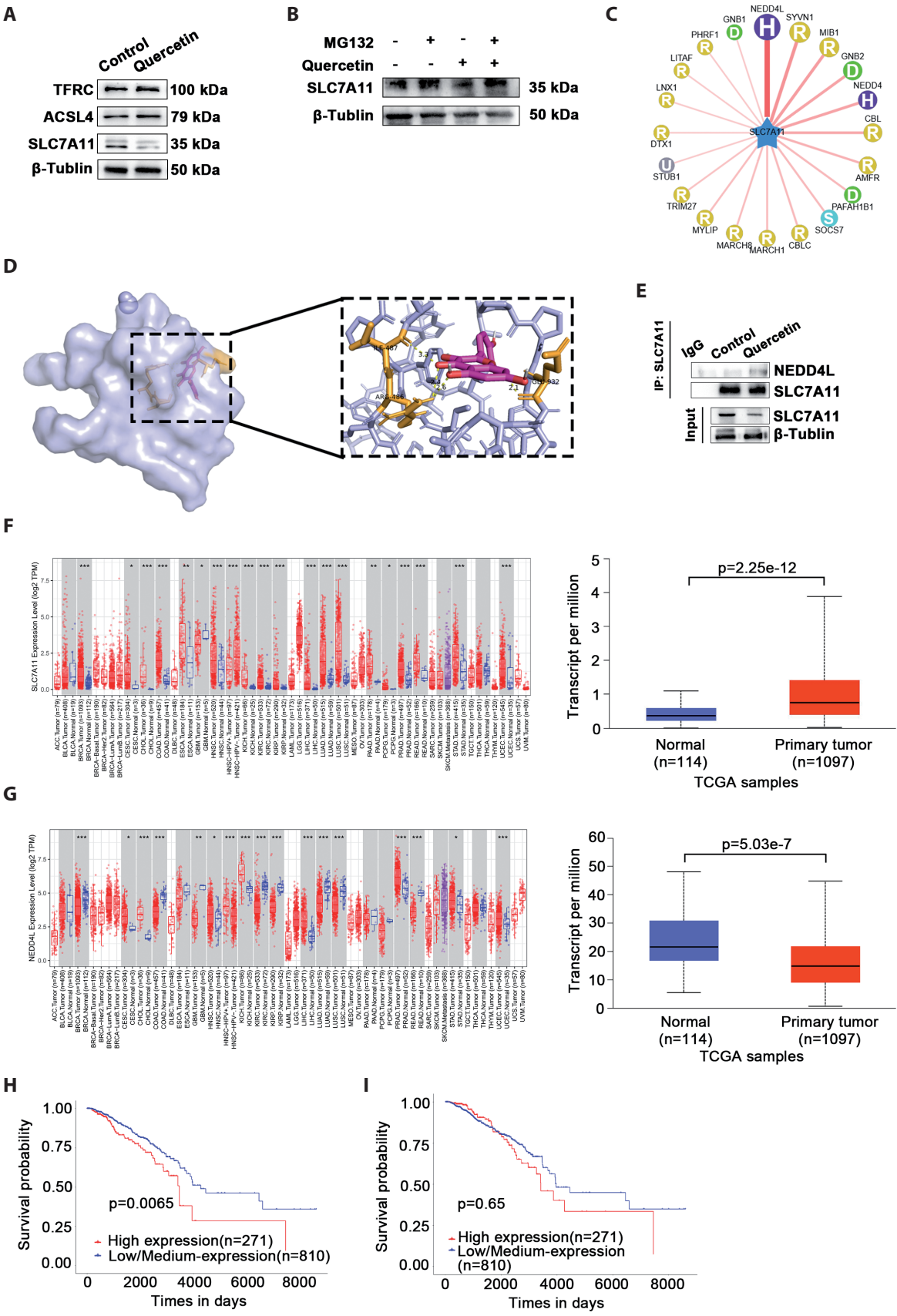


Figure 3. Effects of quercetin on ferroptosis-related markers and genes in breast cancer cells. Effects of quercetin treatment (48 h) on ferroptosis-related markers: Fe²⁺ content, MDA content, GSH level and ROS level in MCF-7 (A) and BT-549 (B) cells. The mRNA expression levels of ferroptosis-related genes (TFRC, ACSL4 and SLC7A11) after 48 h quercetin treatment in MCF-7 (C) and BT-549 (D) cells. Data are presented as mean $\pm$ SD; $n = 3$ experimental replicates; * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; ns, not significant.

of NEDD4L in quercetin-induced ferroptosis, we knocked down NEDD4L expression using siRNAg. Western blot results showed that NEDD4L knockdown reversed the down-regulation of SLC7A11 protein levels induced by quercetin (Fig. 4E). Moreover, after NEDD4L knockdown, quercetin treatment no longer triggered intracellular Fe²⁺ accumulation or elevated ROS levels, indicating that quercetin induces ferroptosis in an NEDD4L-dependent manner. Analysis

based on the TCGA database indicated that SLC7A11 is generally highly expressed in various tumor tissues, whereas NEDD4L expression is significantly lower compared to normal tissues (Fig. 4F,G). This trend was also observed in breast cancer samples: SLC7A11 showed high expression, while NEDD4L expression was low. Survival analysis revealed that high expression of SLC7A11 is significantly associated with poorer overall survival in patients (Fig. 4H), whereas the



expression level of NEDD4L, while showing a certain trend, did not reach statistical significance (Fig. 4I). In summary, our findings suggest that quercetin promotes the binding of NEDD4L, a key E3 ubiquitin ligase regulating SLC7A11, to SLC7A11, thereby mediating the degradation of SLC7A11 *via* the ubiquitin-proteasome pathway and ultimately inducing ferroptosis.

Quercetin counteracts lead-induced malignant phenotypes and enhances ferroptosis in breast cancer cells

Our previous research demonstrated that exposure to the heavy metal lead promotes malignant transformation of breast cancer cells. Building on this finding, the present study further examined the effects of quercetin on breast cancer cell function under lead exposure conditions. The results showed that quercetin effectively inhibited cell proliferation even in the presence of lead (Fig. 5A). Transwell assays revealed that quercetin markedly suppressed the migratory capacity of both MCF-7 and BT-549 cells under lead exposure (Fig. 5B). Consistent with this, wound-healing assays confirmed that quercetin significantly reduced the migration of both cell lines (Fig. 5C). To further clarify the underlying mechanism, we assessed ferroptosis-related biochemical indicators in MCF-7 and BT-549 cells treated with quercetin during lead exposure. In MCF-7 cells, quercetin treatment resulted in increased levels of Fe^{2+} , MDA, and ROS, accompanied by reduced GSH levels, indicating that quercetin can effectively trigger ferroptosis even under lead-induced stress (Fig. 5D). Similar changes were observed in BT-549 cells, where Fe^{2+} , MDA, and ROS levels were elevated and GSH levels were decreased following quercetin treatment (Fig. 5E). Collectively, these findings demonstrate that quercetin suppresses the proliferation and migration of breast cancer cells and efficiently induces ferroptosis, even in a heavy-metal lead exposure environment.

Quercetin promotes NEDD4L-mediated ubiquitination and degradation of SLC7A11 to induce ferroptosis

Quercetin treatment markedly enhanced the interaction between NEDD4L and SLC7A11, resulting in increased

ubiquitination and subsequent degradation of SLC7A11 (Fig. 6). Consistent with the loss of SLC7A11, quercetin-treated breast cancer cells exhibited elevated intracellular levels of Fe^{2+} , MDA, and ROS, along with a significant reduction in GSH, indicating the induction of ferroptosis. These results establish the quercetinNEDD4L–SLC7A11 axis as a key regulatory pathway governing ferroptotic cell death in breast cancer cells. Additionally, the degradation of SLC7A11 by quercetin was maintained under conditions of environmental stress, suggesting that this regulatory mechanism remains functional in co-exposure contexts. Together, these findings reveal a previously unrecognized mechanism through which quercetin drives ferroptosis *via* NEDD4L-dependent proteasomal degradation of SLC7A11.

Discussion

Breast cancer incidence and mortality continue to rise globally, underscoring the urgent need for more effective therapeutic strategies (Trapani et al. 2022). Metastatic dissemination and the development of drug resistance remain major contributors to treatment failure. Quercetin, a major bioactive compound in *Astragalus membranaceus*, has demonstrated broad pharmacological activities, with potent anti-tumor effects reported across multiple cancer types (Zhang et al. 2022). In this study, we systematically characterized the anti-cancer effects of quercetin on breast cancer cells and elucidated its underlying mechanisms. Quercetin markedly reduced cell viability and significantly inhibited malignant proliferation, as evidenced by colony formation, wound healing, and Transwell assays. Transcriptome sequencing provided deeper mechanistic insights, revealing that ferroptosis-related pathways were significantly enriched following quercetin treatment. Consistent with these transcriptomic findings, biochemical measurements confirmed hallmark features of ferroptosis, including increased Fe^{2+} accumulation, enhanced lipid peroxidation, and GSH depletion. These results validate ferroptosis as a central mode of quercetin-induced cell death in breast cancer. Notably, our study also found that even in the context of enhanced migration and invasion of breast cancer cells induced by lead

◀ **Figure 4.** NEDD4L-mediated ubiquitin–proteasome degradation of SLC7A11 induced by quercetin. **A.** MCF-7 cells were treated with 80 μM quercetin, and the expression levels of ferroptosis-related proteins were detected by Western blot. **B.** MCF-7 cells were treated with 80 μM quercetin in the presence of the proteasome inhibitor MG-132, and SLC7A11 protein levels were assessed. **C.** Potential E3 ubiquitin ligases interacting with SLC7A11 were predicted using the Ubibrowser database. **D.** The molecular structures of quercetin and NEDD4L were obtained from the PubChem and RCSB PDB databases, respectively. Molecular docking was performed and visualized using PyMOL 2.5.7. **E.** MCF-7 cells were treated with 80 μM quercetin for 48 h, and co-immunoprecipitation (Co-IP) was performed using an SLC7A11 antibody to examine the interaction between SLC7A11 and NEDD4L. Pan-cancer analysis of SLC7A11 (**F**) and NEDD4L (**G**) expression levels was conducted using the TIMER database. Expression levels of SLC7A11 and NEDD4L in breast cancer tissues were analyzed. The correlation between SLC7A11 (**H**) and NEDD4L (**I**) expression levels and overall survival in breast cancer patients was analyzed using the UALCAN database. (Data are presented as mean $\pm$ SD; $n = 3$ experimental replicates.

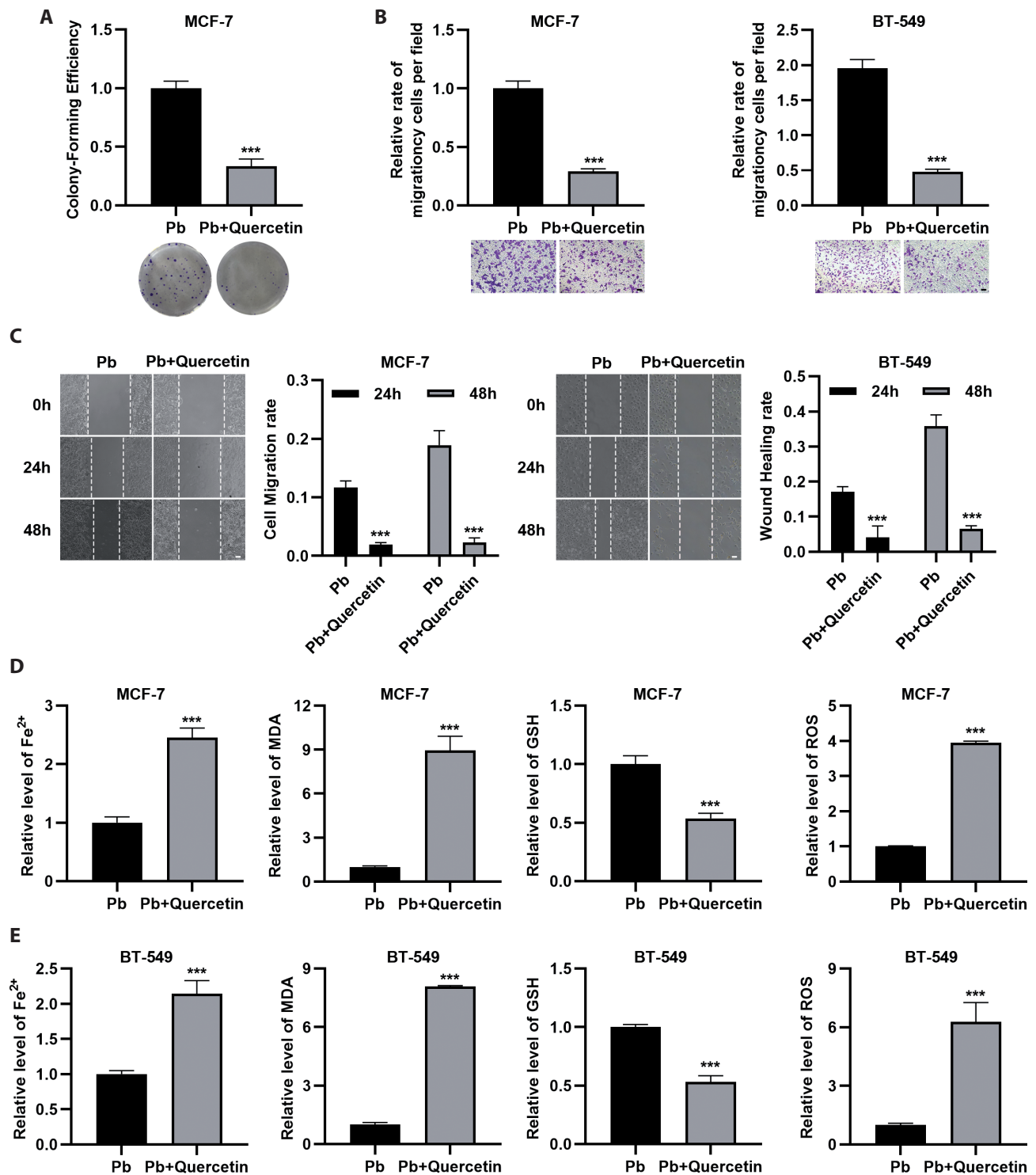


Figure 5. Quercetin inhibits proliferation and migration and induces ferroptosis in breast cancer cells under lead exposure. **A.** Colony formation ability of MCF-7 cells treated with 80 μ M quercetin under 20 μ M lead acetate exposure (plate cloning formation assay, cultured for two weeks). **B.** Effects of quercetin on the migration ability of MCF-7 (80 μ M) and BT-549 (120 μ M) cells under 20 μ M lead acetate exposure (Transwell assay, 48 h treatment). **C.** Effects of quercetin on the migration ability of MCF-7 (80 μ M) and BT-549 (120 μ M) cells under 20 μ M lead acetate exposure (wound healing assay, 48 h treatment). Effects of 48 h quercetin treatment on ferroptosis-related markers (Fe^{2+} content, MDA content, GSH level and ROS level) under 20 μ M lead acetate exposure in MCF-7 (**D**) and BT-549 (**E**) cells. Data are presented as mean $\pm$ SD; $n = 3$ experimental replicates; Scale bars = 100 μ m; *** $p < 0.001$.

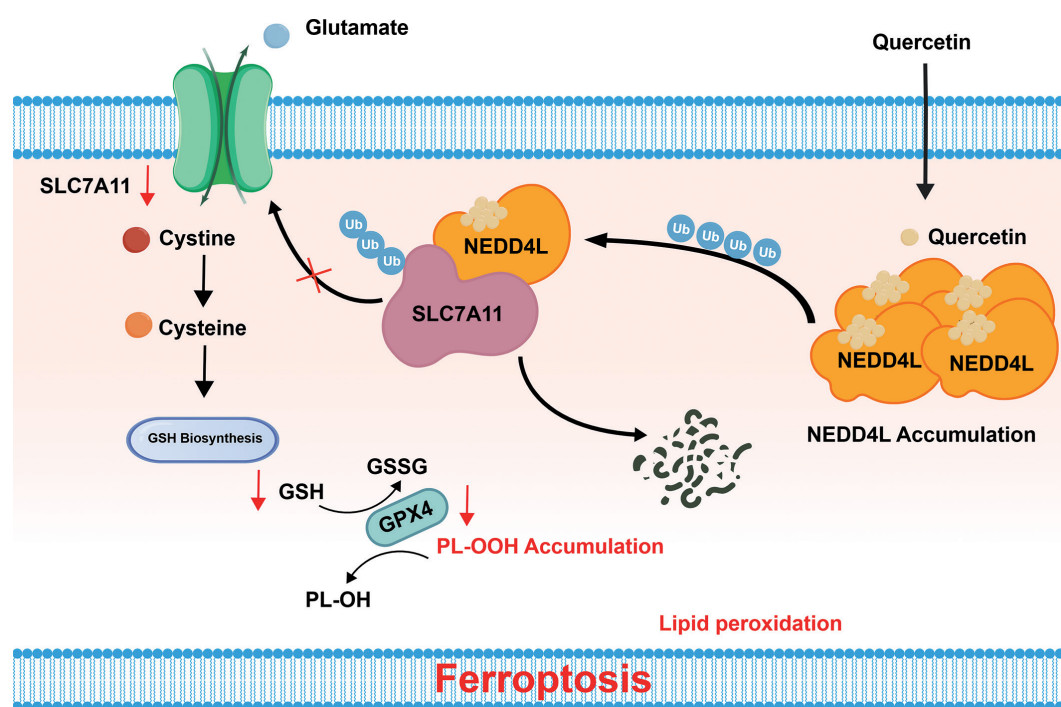


Figure 6. Schematic model illustrating how quercetin inhibits the malignant progression of breast cancer cells by inducing ferroptosis through the NEDD4L/SLC7A11 axis.

exposure, quercetin remains effective in reversing this malignant phenotype and activating the ferroptosis process. This finding further highlights the broader therapeutic potential of quercetin in the prevention and treatment of breast cancer.

Ferroptosis has emerged as a critical form of regulated cell death with substantial therapeutic implications. Several ferroptosis inducers have already demonstrated promising anti-tumor efficacy and entered clinical evaluation (Yin et al. 2022; Zhou et al. 2024). SLC7A11, a key component of system Xc⁻, plays a pivotal role in resisting ferroptosis by maintaining intracellular redox homeostasis; its high expression is closely associated with ferroptosis resistance in tumor cells (Koppula et al. 2021; Zhou et al. 2024). Our findings reveal that quercetin induces ferroptosis by promoting ubiquitination-mediated degradation of SLC7A11. It is worth noting that we observed that quercetin treatment led to an increase in the mRNA level of SLC7A11 while decreasing its protein level. The underlying mechanism may be that under ferroptosis stress, cells initiate compensatory transcriptional upregulation in an attempt to enhance SLC7A11 synthesis; meanwhile, quercetin more strongly activates the ubiquitin-proteasome pathway, mediating accelerated degradation of SLC7A11 protein. Ultimately, the degradation effect predominates, resulting in a net decrease in protein levels. Interestingly, previous studies have reported the dual regulatory role of quercetin in ferroptosis depending on the disease context. While quercetin promotes

ferroptosis in liver cancer, cholangiocarcinoma, and gastric cancer cells (Huang et al. 2024; Song et al. 2023; Xu et al. 2025), on the other hand, it exerts anti-ferroptotic effects in non-malignant pathological models. For instance, studies have shown that quercetin can inhibit ferroptosis both *in vivo* and *in vitro* via the Sirt1/Nrf2/Gpx4 pathway, thereby ameliorating the progression of acute lung injury (Deng et al. 2023). Additionally, quercetin suppresses ferroptosis by activating the Nrf2/HO-1 signaling pathway, improving diabetic kidney injury (Feng et al. 2023) and mitigating cerebral ischemic injury (Peng et al. 2024). This context-specific behavior suggests that the ferroptosis-modulating effects of quercetin are highly dependent on cellular state and microenvironmental cues, warranting further investigation.

Despite elucidating a previously unrecognized NEDD4L–SLC7A11 regulatory axis underlying quercetin-induced ferroptosis, several limitations remain. Firstly, environmental pollutants – including cadmium and lead – have been shown to promote breast cancer progression and interfere with therapeutic response (Lequy et al. 2023; Li J et al. 2024). Our preliminary experiments confirmed that lead exposure enhances breast cancer cell migration; however, quercetin retained potent inhibitory effects on both proliferation and migration, and robustly induced ferroptosis even under lead exposure conditions, as evidenced by elevated Fe²⁺, MDA, and ROS levels along with further GSH depletion (Lin et al. 2020; Liu et al. 2020). These results suggest that querce-

tin may remain effective in environmentally co-induced carcinogenic settings, though the detailed mechanisms require additional study. Secondly, the present findings are primarily based on *in vitro* assays. The therapeutic efficacy, metabolism, and biodistribution of quercetin within the tumor microenvironment remain to be evaluated *in vivo*. Thirdly, although quercetin was shown to enhance the interaction between NEDD4L, a key E3 ligase involved in regulating SLC7A11, and SLC7A11, leading to SLC7A11 degradation, the structural determinants underlying this enhanced protein–protein interaction remain unclear. Further studies involving *in vivo* validation, structural biology, and investigations across diverse breast cancer subtypes will be essential for advancing quercetin toward clinical application as a ferroptosis-modulating therapeutic. Finally, in this study, we have established a multi-layered chain of evidence supporting the core conclusion that quercetin induces ferroptosis in breast cancer cells, through the detection of key biochemical indicators such as lipid peroxidation, ROS, and Fe²⁺, combined with transcriptomic analysis. Notably, future rescue experiments employing ferroptosis-specific inhibitors could provide more causal validation for this mechanism.

In summary, this study identifies a previously unrecognized ferroptosis-regulatory mechanism through which quercetin exerts its anti-tumor effects in breast cancer. We demonstrate that quercetin facilitates the interaction between the E3 ubiquitin ligase NEDD4L and SLC7A11, thereby promoting SLC7A11 ubiquitination and degradation, disrupting redox homeostasis, and ultimately triggering ferroptotic cell death. Importantly, quercetin retains its inhibitory efficacy even under heavy-metal lead exposure, suggesting potential therapeutic value in environmentally co-induced carcinogenesis. These findings not only highlight the “quercetin–NEDD4L–SLC7A11” axis as a critical regulatory pathway in ferroptosis, but also provide a theoretical foundation for developing ferroptosis-targeted strategies in breast cancer. Future *in vivo* studies and structural investigations will be essential for advancing quercetin toward clinical translation.

Author contributions. Conceptualization: JL; Methodology: ZL and YD; Formal analysis: YZ and SS; Data curation: RM and YL; Writing – original draft: JL and ZL; Writing – review & editing: SX and GL; Supervision: SL and YL; Project administration: XH and LM; Funding acquisition: JL, SL, XH, LM, and GL. All authors have read and approved the final version of the manuscript.

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