Original Article

Induction of ferroptosis in oxaliplatin-resistant colorectal cancer cells by extract from *Actinidia chinensis* Planch radix

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Background: Colorectal cancer (CRC) is the third most common cancer worldwide, and there is growing number of reports on the emergence of chemoresistance among patients with CRC. Oxaliplatin, a common chemotherapeutic agent used to treat CRC, has been linked to the emergence of drug-resistant tumor cells. While traditional Chinese medicines have gained attention for their multi-target anticancer properties, *Actinidia chinensis* Planch radix, despite its documented anti-inflammatory and hepatoprotective effects, remains unexplored in the context of oxaliplatin resistance modulation. This study aims to investigate whether *Actinidia chinensis* Planch radix extract can reverse oxaliplatin resistance in CRC cells and determine its mechanistic relationship with ferroptosis—an iron-dependent form of regulated cell death implicated in chemoresistance.

Methods: Oxaliplatin-resistant HT29 CRC cells were generated by increasing the concentration of oxaliplatin in the culture media. Cell viability was measured via MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium-bromide) assay, while proliferation was assessed via wound healing assays. Gene expression was determined with quantitative polymerase chain reaction and Western blotting. Extract from *A. chinensis* Planch radix was achieved by hydrophilic extraction.

Results: Treatment with *A. chinensis* Planch radix extract significantly inhibited the overgrowth of oxaliplatin-resistant HT29 cells, suggesting a potential reversal of chemoresistance. The extract induced ferroptosis, a type of programmed cell death dependent on iron and characterized by lipid peroxidation in oxaliplatin-resistant HT29 cells. The extract modified the expression of several key genes and proteins associated with chemoresistance and cell survival, including ubiquitin-specific-processing protease 7 (*USP7*), wild-type tumor suppressor protein 53 (*p53*), and transferrin receptor 1 (*TFRC1*). Changes were observed at both the messenger RNA and protein levels, indicating a direct regulatory effect.

Conclusions: *A. chinensis* Planch radix extract effectively reverses oxaliplatin resistance in CRC cells by inducing ferroptosis and modulating the expression of crucial genes including as *USP7*, wild-type *p53*, and *TFRC1*. These findings suggest that this traditional Chinese medicine could be a promising therapeutic agent to overcome chemoresistance in CRC.

Keywords: Colorectal cancer (CRC); *Actinidia chinensis* Planch radix; ubiquitin-specific-processing protease 7 (*USP7*); protein 53 (*p53*); transferrin receptor 1 (*TFRC1*)

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide. Although progress has been made in the screening and treatment of patients with CRC, the prevalence and mortality associated with this disease are increasing worldwide and affecting patients in both developing and industrialized countries. Moreover, CRC is the second most common cause of cancer-related death (1), and recent research has reported a rise in the incidence of early-onset CRC (2). Therefore, the development of additional therapeutic options for CRC is imperative.

Chemotherapy remains a mainstream treatment for advanced CRC, and cytotoxic agents with or without anti-epidermal growth factor receptor (*EGFR*) treatment remain the first-line chemotherapy for advanced CRC (3,4). Among the cytotoxic agents, oxaliplatin is one of the most critical to therapy, as indicated in clinical trials (5,6). However, resistance to oxaliplatin in patients with CRC can arise due to the selection against oxaliplatin-sensitive cancer cells (7,8). When chemoresistance occurs, patients experience a poorer outcome and have fewer therapeutic alternatives, and thus it is crucial that the means to restoring the responsiveness to oxaliplatin is clarified.

Traditional Chinese medicine has been historically used for the treatment of chronic disorders including cancer. *Actinidia chinensis* Planch radix is plentiful in the southern part of China, and its root can be used for medical purposes. According to traditional Chinese medicine book "*The Yellow Emperor's Inner Canon*", *A. chinensis* Planch radix exerts therapeutic effects in those with cancer, fever, toxicity, etc. (9), and *A. chinensis* Planch radix has been used in cancer treatment in modern laboratory settings (10,11). However, whether *A. chinensis* Planch radix can reverse resistance to oxaliplatin in CRC remains unclear.

Ferroptosis is a recently discovered iron-mediated cell death process and is characterized by the accumulation of intracellular reactive oxygen species (ROS) (12). Downregulation of glutathione peroxide (*GPX*), especially *GPX4*, is a characteristic marker of ferroptosis (13), and a decrease in the expression of transferrin receptor 1 (*TFRC1*) induces ferroptosis (14). It has been reported that ferroptosis might have a role in the anticancer effect in oxaliplatin-resistant CRC (15). Ubiquitin-specific protease (*USP7*), a member of the deubiquitinase protein family (DUB), has been extensively studied. It is highly expressed in multiple cancers, is regarded as a biomarker for poor outcomes in patients with cancer (16,17), and more importantly, is involved in chemoresistance (16,17). It has also been reported that the presence of the wild-type protein 53 (*p53*) protein is correlated with responsiveness to oxaliplatin in CRC cells (18,19). However, whether *A. chinensis* Planch radix induces ferroptosis in oxaliplatin-resistant CRC remains unclear.

In this study, we tested our hypothesis that extract from *A. chinensis* Planch radix can induce ferroptosis in oxaliplatin-resistant CRC cells by increasing the expression of *p53* and decreasing that of *USP7* and *TFRC1*. The findings of this study provide insights into the potential clinical applications of traditional Chinese medicine in incurable oxaliplatin-resistant CRC.

Highlight box

Key findings

- Extract from *Actinidia chinensis* Planch radix significantly inhibited the proliferation of oxaliplatin-resistant colorectal cancer (CRC) cells, suggesting its potential to reverse drug resistance. The extract triggered ferroptosis, a type of iron-dependent cell death, characterized by lipid peroxidation, in the resistant CRC cells, indicating a novel mechanism for overcoming chemoresistance. These findings indicate that *A. chinensis* Planch radix extract could serve as a potential therapeutic strategy for overcoming oxaliplatin resistance in CRC through ferroptosis induction and gene modulation.

What is known and what is new?

- Oxaliplatin, a standard chemotherapeutic drug for CRC, often leads to the emergence of drug-resistant cancer cells, reducing treatment efficacy. Ferroptosis, a form of programmed cell death dependent on iron and characterized by lipid peroxidation, has been identified as a potential mechanism for killing cancer cells, but its role in overcoming chemoresistance is still under investigation.
- This study is the first to demonstrate that *A. chinensis* Planch radix can target oxaliplatin-resistant CRC cells, highlighting its potential use as an adjuvant therapy in patients with treatment-resistant CRC.

What is the implication, and what should change now?

- Our results may provide a new approach for the future treatment of CRC and inform the development of novel drugs and therapeutic technologies. Further clinical trials are warranted to further validate these findings.

Methods

Preparation of A. chinensis Planch radix root extracts

To prepare the *A. chinensis* Planch radix root extracts, roots (donated by Zhengjiang Traditional Chinese Medical

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University) were washed, chopped, and placed in double-distilled water. The mixture was heated to 100 ℃ for 1 h under reflux condensation to prevent solvent loss, followed by filtration through a 0.22 μm cellulose membrane (MilliporeSigma, Burlington, MA, USA). The aqueous extract was freeze-dried using a Labconco FreeZone 2.5 L lyophilizer (−50 ℃, 48 h), yielding a dry powder. The final concentration of extract was 500 μg/mL.

Cell culture

HT29, a human colorectal adenocarcinoma cell line, was purchased from the American Type Culture Collection (Manassas, VA, USA). Cells were cultured in McCoy's 5A medium supplemented with 10% of fetal bovine serum (FBS) (Gibco, Thermo Fisher Scientific, Waltham, MA, USA). Cells were cultured at 37 ℃ and 5% CO_2 in a cell culture incubator. To generate an oxaliplatin-resistant daughter cell line, parental CRC cells were chronically exposed to stepwise increasing concentrations of oxaliplatin (Sigma-Aldrich, St. Louis, MO, USA) dissolved in serum-free Dulbecco's modified Eagle's medium (DMEM) containing 0.1% dimethyl sulfoxide (DMSO) as vehicle. Starting from the baseline half maximal inhibitory concentration (IC50) concentration (0.1 μM) determined by preliminary Cell Counting Kit-8 (CCK-8) assay, the exposure gradient was progressively escalated over 8 weeks (0.1→0.5→1.0→5.0→10 μM) with medium replacement every 3 days. Prior to each concentration increment, cells underwent serum starvation for 24 h in 1% FBS medium to synchronize cell cycle progression. Drug resistance was confirmed through three consecutive passages showing >5-fold increase in IC50 (0.52±0.07 μM in parental *vs.* 2.89±0.12 μM in resistant cells, P<0.001) and maintained in 1.0 μM oxaliplatin during routine culture (20).

MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium-bromide) assay

Cell proliferation was measured by MTT assays. Different types of cells seeded in 96-well plates and treated with various conditions were used for the MTT assays. At designated time points, cell culture medium was removed, and 100 μL of diluted MTT (Sigma-Aldrich) solution was added to each well. The plates were then placed in the incubator at 37 ℃ and 5% CO_2 for another 2 h. At the end of the culture, DMSO was added to the system to dissolve the crystals. The absorbance at 540 nm was obtained from a plate reader.

Wound healing assay

Cells were seeded into six-well plates and cultured to complete confluence. Cells were then serum starved in serum-free medium. Artificial wounds were induced using as sterile 200-μL pipette tip. Cells were then washed using serum-free culture medium. Images were obtained at 0 and 36 h using an inverted microscope (Olympus, Tokyo, Japan). Migration ability was calculated according to changes in the size of the wound.

Quantitative polymerase chain reaction

Total RNA was isolated using a commercial RNA extraction kit (RNeasy Kit, Qiagen, Hilden, Germany). Complementary DNA was generated with PrimeScrip RT Reagent Kit (Takara Bio, Kusatsu, Japan) according to the manufacturer's guidelines. The expression of genes of interest was examined via quantitative real-time polymerase chain reaction with Power SYBR Green PCR master mix (Applied Biosystems, Thermo Fisher Scientific). All primers were purchased from OriGene (Rockville, MD, USA).

Western blotting

Total protein was obtained using cell lysis buffer (KeyGene, Wageningen, The Netherlands), and the concentration of protein was measured using the Lowry method. Proteins were loaded and separated in 8% sodium dodecyl-sulfate polyacrylamide gel for electrophoresis. They were then transferred to polyvinylidene fluoride (PVDF) membranes (MilliporeSigma, Burlington, MA, USA). Membranes were blocked using 5% bovine serum albumin for 1 h before primary antibodies (Abcam, Cambridge, UK) were applied overnight at 4 ℃. After thorough washing, horseradish peroxidase-conjugated secondary antibodies (Abcam) were incubated to the membranes for 1 h at room temperature. Bands were visualized using an enhanced chemiluminescence reagent (MilliporeSigma).

Statistical analysis

Data are presented as the mean ± standard deviation (SD). Differences between more than two groups were compared using Student's *t*-test (two-tailed, unpaired) to compare differences between two experimental groups. All statistical analyses were conducted using GraphPad Prism version 8.0 (GraphPad Software, La Jolla, CA, USA) for Windows.

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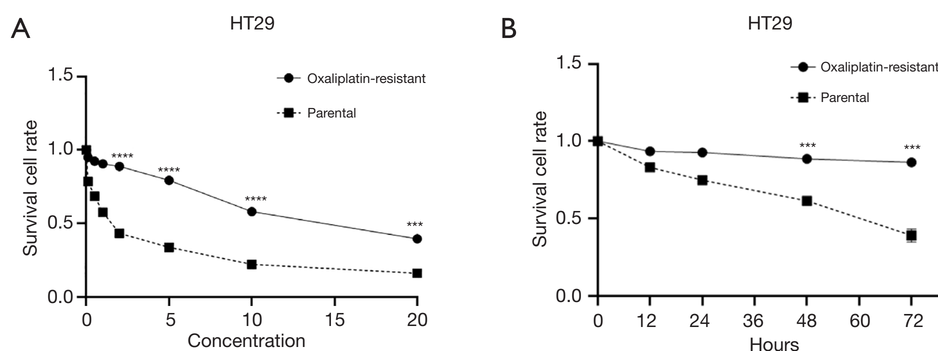

Figure 1 Generation of oxaliplatin-resistant HT29 cells. (A) The concentration-effect curve indicated that the IC50 values of oxaliplatin for oxaliplatin-resistant HT29 were significantly higher than HT29 parental cells. (B) Oxaliplatin-resistant HT29 cell lines showed elevated cell viability compared to the HT29 parental cells at different time. ***, P<0.001 by the Student *t*-test at the same time point; ****, P<0.0001 by the Student *t*-test at the same time point. IC50, half maximal inhibitory concentration.

A P value of less than 0.05 was considered to indicate statistical significance.

Results

Generation of oxaliplatin-resistant CRC cells

In order to test the effects of *A. chinensis* Planch radix extract on oxaliplatin-resistant CRC cell lines, we sought to first generate such cell lines. As described above, we used an escalated gradient of oxaliplatin in the cell culture media to generate chemotherapy-resistant cell lines. A gradient between 3 and 20 µM was chosen. As shown in *Figure 1*, oxaliplatin-resistant HT29 cells were generated, which showed an increased ability to survive in various concentrations of oxaliplatin (*Figure 1A*) and at different time points (*Figure 1B*). These cells were examined in the subsequent experiments.

Extract from A. chinensis Planch radix inhibited the proliferation of oxaliplatin-resistant CRC cells

Next, we sought to determine if extract from *A. chinensis* Planch radix could suppress increased levels of proliferation in oxaliplatin-resistant CRC. When cultured in oxaliplatin-free culture media, oxaliplatin-resistant cells showed a fast rate of growth at 48 h after seeding (*Figure 2A*). As shown in *Figure 2A*, with the presence of oxaliplatin in the cell culture medium (10 µM), oxaliplatin-resistant HT29 cells showed enhanced survival over time; application of extract from *A. chinensis* Planch radix (treatment), however, decreased the rates of survival in oxaliplatin-resistant CRC cells (green line in *Figure 2*). It is worth noting that treatment did not decrease the survival rate of oxaliplatin-sensitive parent cells. We also conducted wound healing assays using oxaliplatin-resistant cells and their parental controls. As demonstrated in *Figure 2B*, oxaliplatin-resistant HT29 cells showed an increased ability to heal the artificial wounding in culture with the presence of oxaliplatin, but application of extract from *A. chinensis* Planch radix reduced the speed of healing to the levels of parental cells. These data indicate that extract from *A. chinensis* Planch radix is effective in reversing drug resistance in oxaliplatin-resistant HT29 cells.

Extract from A. chinensis Planch radix induced ferroptosis in oxaliplatin-resistant CRC cells

We next aimed to clarify the mechanisms related to the reversal of responsiveness in oxaliplatin-resistant HT29 cells mediated by extract from *A. chinensis* Planch radix. It has been reported that extract from *A. chinensis* Planch induces ferroptosis in gastric cancer cells by decreasing the expression of *GPX4* (21). We sought to determine whether a similar mechanism would apply in the context of oxaliplatin resistance in CRC cells. We added extract from *A. chinensis* Planch radix in the cell culture media with the presence of oxaliplatin. As shown in *Figure 3A,3B*, the expression of transferrin—a ferroptosis marker—was significantly elevated in oxaliplatin-resistant HT29 cells treated with the extract. Conversely, GPX4 expression was reduced in resistant cells supplemented with the extract (*Figure 3A,3C*). Notably, the 'Parent + treatment'

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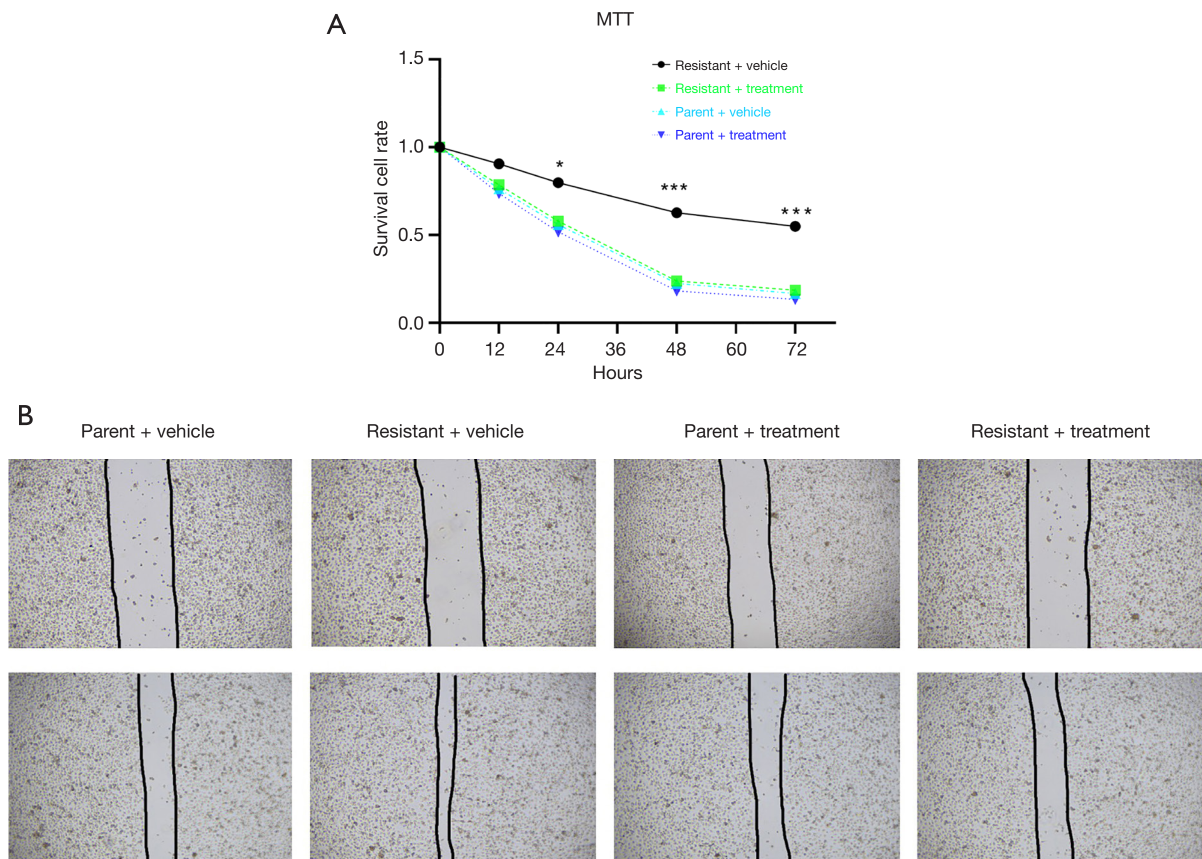

Figure 2 Oxaliplatin-resistant HT29 cells harbored a higher ability for proliferation. (A) MTT assay. The graph shows the survival cell rate over time (0 to 72 h) for different treatment groups using the MTT assay. The legend includes four groups: resistant + vehicle (black circles), resistant + treatment (green squares), parent + vehicle (blue triangles), parent + treatment (purple diamonds). Statistical significance is denoted by asterisks: *, P<0.05 and ***, P<0.001 by one-way ANOVA at the same time point. (B) Wound healing assay. A representative images of cell migration results, scale bar =5 µm. There are four columns corresponding to the four treatment groups: parent + vehicle, resistant + vehicle, parent + treatment, resistant + treatment. The MTT assay shows that resistant cells maintain higher survival rates over time, especially when treated with vehicle compared to treatment. The wound healing assay illustrates that resistant cells (both with vehicle and treatment) exhibit faster and more extensive migration compared to parental cells, indicating enhanced migratory capacity. ANOVA, analysis of variance; MTT, 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide.

group exhibited lower transferrin levels compared to the 'Parent + vehicle' group (*Figure 3B*), suggesting that the extract may exert distinct regulatory effects on ferroptosis markers in parental versus resistant cells. While GPX4 levels remained unchanged in parental cells, the observed reduction in transferrin implies that the treatment could modulate iron metabolism or ferroptosis sensitivity in a cell type-specific manner. This differential response may reflect inherent variations in redox homeostasis or iron-handling pathways between parental and resistant cells, potentially linked to oxaliplatin resistance mechanisms. Further investigation into the interplay between transferrin regulation, GPX4-independent ferroptosis pathways, and drug-resistant phenotypes is warranted to elucidate these findings.

Gene expression profiles altered by extract from A. chinensis Planch radix

We then attempted to characterize the changes in gene expression associated with the addition of extract from *A. chinensis* Planch radix in the context of oxaliplatin. It has been reported that *USP7* (16,17), wild-type *p53* (18,19), and *TFRC1* (22) are associated with chemoresistance. We

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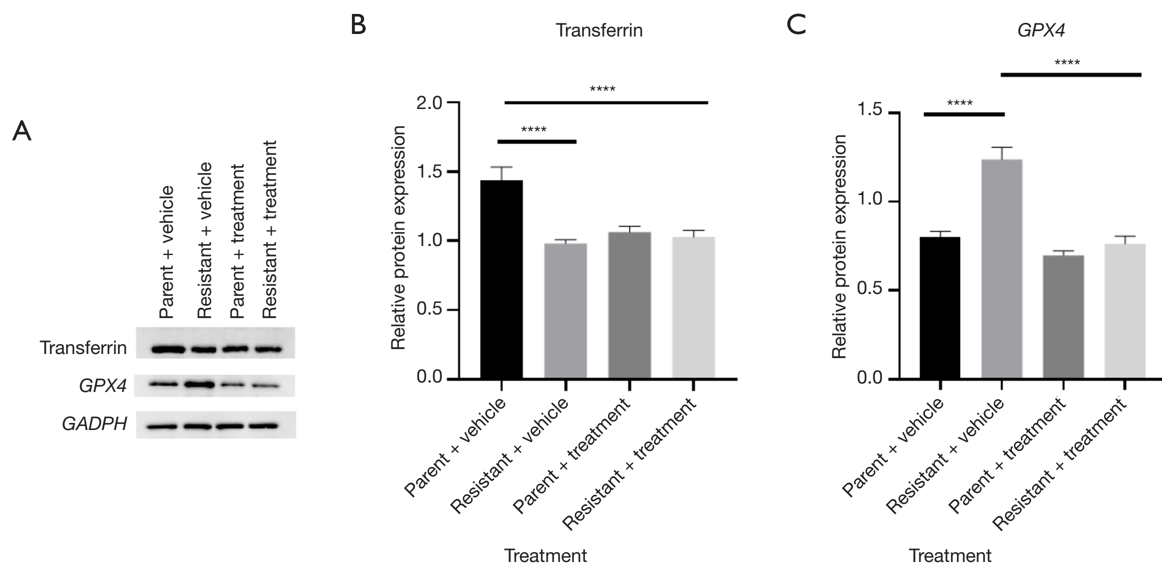

Figure 3 Extract from *Actinidia chinensis* Planch radix induces ferroptosis. (A) Expression of *GPX4* measured by Western blotting. (B) Expression of transferrin. (C) Expression of GPX4. ****, P<0.001 by one-way ANOVA. ANOVA, analysis of variance; *GADPH*, glyceraldehyde-3-phosphate dehydrogenase; *GPX*, glutathione peroxide.

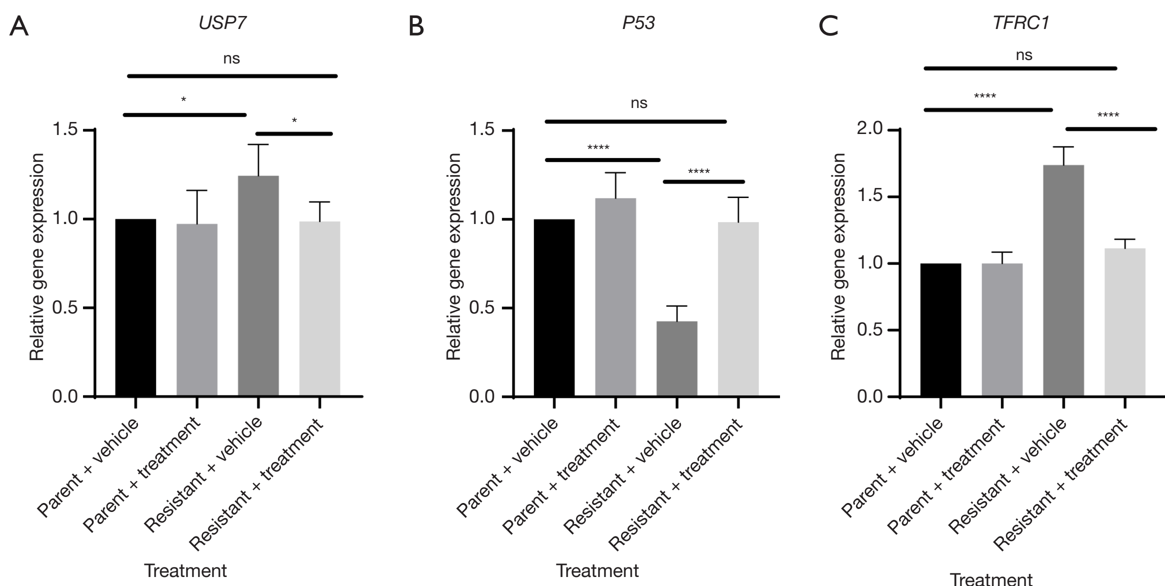

Figure 4 Expression of *USP7*, *P53*, and *TFRC1* at the mRNA level. (A) Expression of *USP7*. (B) Expression of *P53*. (C) Expression of *TFRC1*. ns, no significance; *, P<0.05 by one-way ANOVA; ****, P<0.001 by one-way ANOVA. ANOVA, analysis of variance; mRNA, messenger RNA; *P53*, protein 53; *TFRC1*, transferrin receptor 1; *USP7*, ubiquitin-specific-processing protease 7.

subsequently examined the expression of these genes at the messenger RNA (mRNA) level. As shown in *Figure 4*, USP7 and *TFRC1* were significantly upregulated in oxaliplatin-resistant HT29 cells, but application of extract remarkably reversed this increase, returning it to the baseline level. Moreover, the expression of wild-type *p53* was reduced in oxaliplatin-resistant HT29 cells, and administration of extract increased its expression to reach that of parent cells.

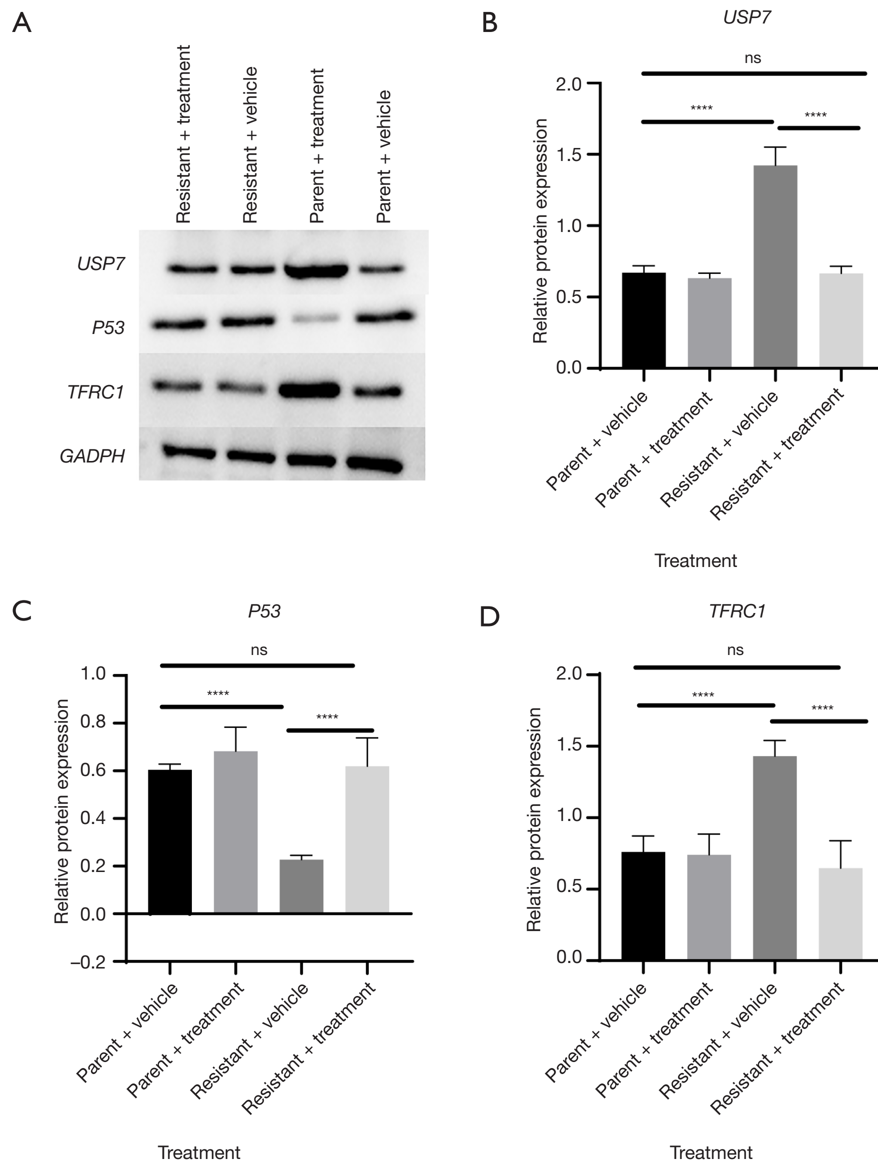

Figure 5 Expression of *USP7*, *P53*, and *TFRC1* at the protein level. (A) Western blotting. (B) Expression of *USP7*. (C) Expression of *P53*. (D) Expression of *TFRC1*. ns, no significance; ****, P<0.001 by one-way ANOVA. ANOVA, analysis of variance; *GADPH*, glyceraldehyde-3-phosphate dehydrogenase; *P53*, protein 53; *TFRC1*, transferrin receptor 1; *USP7*, ubiquitin-specific-processing protease 7.

Protein levels of gene expression

We additionally examined the protein levels of gene expression mediated by extract from *A. chinensis* Planch radix. As shown in *Figure 5*, at the protein level, extract from *A. chinensis* Planch radix increased expression of *USP7* and *TFRC1* in oxaliplatin-resistant HT29 cells and decreased that of wild-type *p53*. These data, along with those provided in *Figure 4*, indicate that extract from *A. chinensis* Planch radix mediates the change in key elements associated with chemoresistance.

Discussion

In this study, we found that extract from *A. chinensis* Planch radix reversed chemoresistance in oxaliplatin-resistant CRC cells. This reversal was achieved via the induction of ferroptosis and the alteration of chemoresistance-related genes.

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CRC, which accounts for approximately 10% of all cancer cases worldwide, is common in both genders. Although the primary treatment option for CRC is surgery, chemotherapy or radiotherapy can be used for adjuvant therapy. However, due to heterogeneity of tumors and repeated application of chemotherapy reagents, the prevalence of chemoresistant CRC has been increasing. Given that oxaliplatin-based regimens are involved in first-line chemotherapy, it is important to clarify the mechanism by which chemoresistance arises in order to develop novel treatments for patients.

In our study, we first established an oxaliplatin-resistant cell line. As shown in *Figure 1*, oxaliplatin-resistant HT29 cells. Upon being exposed to elevated concentrations of oxaliplatin in the culture medium, the selected cells exhibited resistance to oxaliplatin in cell culture.

Unsurprisingly, these oxaliplatin-resistant cells were proliferative and had an increased ability to migrate during wound healing assays. In the oxaliplatin-resistant CRC cells were generated, key genes related to chemoresistance, including *USP7*, *TFRC1*, and wild-type *p53*, showed different expression profiles compared to parental cells at both the mRNA and protein levels, indicating these oxaliplatin-resistant CRC cells harbor different transcription regulations. More importantly, when extract from *A. chinensis* Planch radix was applied to oxaliplatin-resistant CRC cells in our experimental system, the changes in expression of these abovementioned gene changes were reversed (*Figures 4,5*). Moreover, extract from *A. chinensis* Planch radix induced ferroptosis in oxaliplatin-resistant CRC cells, proposing a mechanism to suppress the proliferation of oxaliplatin-resistant CRC cells.

Extract from *A. chinensis* Planch radix has been shown to be effective in killing cancer cells, including hepatocellular carcinoma (9,23), gastric cancer (24), lung cancer (10,25), and others. In this study, we also found that extract from *A. chinensis* Planch radix reverses oxaliplatin resistance in CRC cells, suggesting this plant might have broader applications in cancers. *A. chinensis* Planch is an angiosperm grown in southern China, and its root extract has considerable medical value; however, given the complexity of the chemical composition of this extract, it is extremely difficult to identify the specific molecular components responsible for its anticancer properties. Triterpenes, flavonoids, phenolics, polysaccharides, and steroids have been speculated to be responsible for these anticancer effects (10). In our study, we were unable to isolate those chemical compounds with anticancer features, and thus additional studies involving chemical isolation and purification are needed.

A few other limitations to this study should also be acknowledged. Firstly, how extract from *A. chinensis* Planch radix induces ferroptosis remains unclear. It is possible that the application of extract from *A. chinensis* Planch radix renders cancer cells more sensitive to iron, but more studies are needed to confirm this. Secondly, it remains unclear whether the administration of *A. chinensis* Planch radix extract can suppress cancer in animal models. Therefore, it is imperative to conduct preclinical experiments to elucidate its potential anticancer properties.

Conclusions

Application of extract from *A. chinensis* Planch radix induces ferroptosis in oxaliplatin-resistant CRC cells by altering gene expression profiles. Once the specific anticancer reagents are identified, it may be possible to apply treatments based on *A. chinensis* Planch radix in cancer therapy.

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None.

Footnote

Data Sharing Statement: Available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2567/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-2024-2567/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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