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Berberine Effect on GPX4 Axis in Pancreatic Ductal Adenocarcinoma Cancer

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Abstract. Pancreatic Ductal Adenocarcinoma Cancer (PDAC) treatment has always been a major milestone in clinical trials due to its high resistance to multiple forms of conventional treatment. Recent studies have identified ferroptosis as an alternative cell death mechanism. Unlike apoptosis, this iron-dependent process induces cell death through lipid peroxidation. Its independence of caspase activation allows it to bypass pancreatic cancer cells that are resistant to conventional apoptosis medication, offering a potential solution for treatment-resistant cases. Likewise, Berberine, a traditional Chinese medicine, has exhibited a positive impact in preventing cancer metastasis and inducing cell death in both in vitro and vivo studies while sparing healthy body cells. It has been found that Berberine can modulate oxidation-reduction homeostasis and lipid metabolism, which is a key component of the ferroptosis pathway. Thus, this study aims to highlight the therapeutic potential of using a combination of glutathione peroxidase 4 (GPX4) axis and Berberine as a novel treatment for PDAC by focusing on lipid peroxidation in ferroptosis.

Keywords: Pancreatic cancer, Berberine, Ferroptosis, GPX4

1. Introduction

Pancreatic cancer, known as the “king of cancers,” is one of the most lethal and aggressive types of cancer that affects the secretion of digestive juice and blood sugar levels [1]. It is notoriously famous for being resistant to many current cancer treatments due to its resistance to traditional apoptosis-inducing therapies. Thus, the combined five-year survival rate for pancreatic cancer is only 12 percent since more patients are diagnosed during later stages when it has already metastasized. During stage IV (the last stage), the five-year survival rate is down to only 1 percent, and the average diagnosed patient will live for about one year due to a metastasized tumor. The absence of noticeable symptoms accounts for the status quo of pancreatic cancer diagnosis. Mutations are reported at Kirsten rat sarcoma (KRAS), Tumor Protein 53 (TP53), cyclin-dependent kinase inhibitor 2A (CDKNA2A), transforming growth factor (TGF), signaling molecule SMAD, and cell migration-inducing hyaluronan-binding protein (CEMIP) [2]. Patients of pancreatic cancer suffer from jaundice, stomach and back pain, weight loss, gastrointestinal problems, fatigue, and potentially diabetes [3].

Specifically, pancreatic ductal adenocarcinoma cancer (PDAC) is the most common type of cancer that accounts for more than 90 percent of pancreatic cancer diagnoses [4]. The molecular and

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cellular features of PDAC are aggressive and have several levels of therapeutic resistance, such as stromal proliferation, reduced vascular density, and immune suppression. Several conventional treatment methods include surgery, chemotherapy, and radiation, yet they have minimal contribution to the recovery of pancreatic cancer patients. As mentioned above, most pancreatic cancer patients are diagnosed in old age, when the tumor is malignant and has metastasized to critical vessels and neighboring organs. Not to mention the difficulty of gaining access to sufficient medical treatment and skilled surgeons, only a small portion of patients have tumors that are amenable to surgery (able to conduct surgery) [5]. However, even in the most experienced centers, long-term survival after surgery is poor due to the high recurrence rate [6-7].

Chemotherapy and radiation function to target fast-growing cells in your body, but also kill healthy cells that divide quickly, such as hair cells, intestinal cells, and mouth cells. This causes side effects such as exhaustion, hair loss, and nausea [8]. Moreover, clinical studies of patients with chemotherapy reflect disappointing results. Very few patients treated have an effective decrease in tumor size. Thus, it is concluded that pancreatic cancer has an initial resistance to chemotherapy rather than acquired resistance, which is observed in most cancers [9].

Hence, it is important to consider other cellular therapies for pancreatic cancer: ferroptosis. Ferroptosis is a non-apoptotic cell death in cancer cells with RAS mutations that involves the production of iron-dependent reactive oxygen species (ROS) [10-11]. As a classical GPX4 inhibitor, RSL3 inhibits the antioxidant system as it increases intracellular iron accumulation [10]. RSL3 targets an enzyme with a nucleophilic active site, such as serine, threonine, cysteine, or selenocysteine, and covalently binds to one or more proteins to induce the inactivation of peroxidase activity of GPX4 [12]. This generates excessive ROS through the Fenton reaction that increases oxidative damage and increases the activity of lipoxygenase (ALOX) or EGLN prolyl hydroxylase (PHD), which are enzymes involved in lipid peroxidation and oxygen homeostasis [13]. This causes oxidative damage to cells, ultimately resulting in cell death.

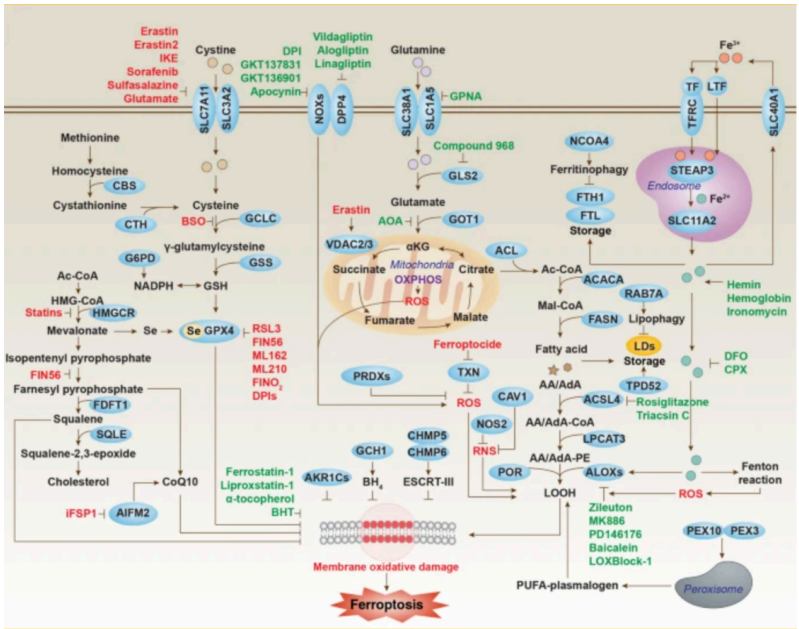

Figure 1: Signaling regulation of ferroptosis pathway [14] A summary of both the extrinsic and intrinsic pathways of ferroptosis

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The level of ferroptosis in PDAC cells can be regulated in multiple ways, such as autophagic degradation, transcription factors, and metabolic pathways. In this study, we focused on the glutathione metabolism pathway involving the inactivation of glutathione peroxidase 4 (GPX4) and its inhibitor RSL3. This crucial antioxidant enzyme maintains redox balance by reducing lipid hydroperoxides through the protection of neurons [14]. This treatment mechanism enables the specificity of cancer treatment and minimizes side effects compared with conventional treatment methods.

Berberine (BBR), a naturally occurring plant-derived polyphenol that is being used in Traditional Chinese Medicine (TCM) [15], has been found to exhibit antibacterial, antidiabetic, anti-inflammatory, and fungicidal properties [16]. The anticancer properties are mediated through the regulation of different molecular pathways that induce cell death [17]. In Nasopharyngeal carcinoma (NPC), for example, BBR has experimentally been shown to suppress cell proliferation, with ferroptosis being the predominant cell death program [18]. Specifically in the System Xc^-/GSH axis, NPC cells have exhibited a decreased level of GPX4, SLC7A11, and SLC3A2 after treatment with various concentrations of BBR. BBR has promoted autophagy to activate ROS-mediated ferroptosis, thus inducing lipid peroxidation that promotes cell proliferation and prevents further metastasis [18-19]. Thus, by incorporating this mechanism into PDAC cells, BBR may similarly act on GPX4 and induce lipid peroxidation through ferroptosis when combined with RSL3 treatment.

2. Hypothesis

Using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3, it can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone.

2.1. Materials and methods

We first measure the viability of BBR treatment on PC3 cell lines by MTT assay. Then lipid oxidation is measured by BODIPY, and ROS is measured through the DCFDA assay. The positive control is ML 162, a GPX4 inhibitor; the negative control is phosphate-buffered saline (PBS); the control group is the general concentration of RSL3. Before the experiment, all PC3 cell lines will be cultured at 37°C in a humidified 5% CO_2 incubator for 24 hours. For the control groups, RSL3 will be added after 24 hours and continued to culture for 24 hours. For the experimental groups, BBR and RSL3 will be added and continued to culture.

2.2. Concentration

A specific concentration of Berberine between 1μM to 100μM will be chosen to conduct the experiment, which will be later referred to as the general concentration. For simplification purposes, the concentration of all other chemicals is used in their general concentration: 1x PBS, 20μM of BBR, and 2μM of RSL3.

2.3. Method 1

MTT assay will be used to measure the viability of BBR treatment on PC3 cell lines. This is a colorimetric assay that is commonly used to assess cell viability, proliferation, and cytotoxicity

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based on the reduction of MTT compound by mitochondrial enzymes in living cells. Negative control will be PBS, while positive control is ML 162.

For the control group, only RSL 3 added in PC3 cell lines with PBS is present. The MTT reagent will be added to the cell culture medium to reach a final concentration of 0.5mg/mL, and then incubated for 4 hours. After incubation, DMSO will be added to dissolve formazan crystals, which creates a colored solution used to measure absorbance at 570 nm in the spectrophotometer to measure the number of viable cells in the sample. Higher absorbance indicates more viable cells.

For the experimental group, BBR will be added together with ML 162 in the PC3 cell lines with PBS. The MTT reagent will be added to the cell culture medium to reach a final concentration of 0.5mg/mL, and then incubated for 4 hours. After incubation, DMSO will be added to dissolve formazan crystals, which creates a colored solution used to measure absorbance at 570nm in the spectrophotometer to measure the number of viable cells in the sample. Higher absorbance indicates more viable cells.

2.4. Method 2

BODIPY will be used to measure the lipid peroxidation of the test groups. BODIPY is a class of fluorescent dyes that act as a ratio metric probe to detect lipid peroxidation through changing color when detecting oxidation.

For the control group with only RSL3 added in PC3 cell lines with PBS present, it will be incubated with 2mM BODIPY 581/591 C11 reagent for 30 minutes at 37°C. The lipid peroxides generated during oxidative damage to lipids will react with the BODIPY reagent since peroxide groups can form adducts with the reagent. It will then undergo a chemical transformation that results in a fluorescent signal, which will be measured with a fluorescence spectrophotometer with green fluorescence at 510 nm and red fluorescence at 590 nm. Then, measure the green-red fluorescence ratio using fluorescence microscopy. A higher ratio indicates an increased lipid peroxidation.

For the experimental group, it is the culture of PC3 cell lines treated with both RLS3 and BBR with PBS present. It will also be incubated with 2mM BODIPY 581/591 C11 reagent for 30 minutes at 37°C. The lipid peroxides generated during oxidative damage to lipids will react with the BODIPY reagent since peroxide groups can form adducts with the reagent. It will then undergo a chemical transformation that results in a fluorescent signal, which will be measured with a fluorescence spectrophotometer with green fluorescence at 510 nm and red fluorescence at 590 nm. Then, measure the green-red fluorescence ratio using fluorescence microscopy. A higher ratio indicates an increased lipid peroxidation.

2.5. Method 3

The DCFDA assay will be used to measure ROS concentration in the experiment. DCFDA is a non-fluorescent molecule that penetrates cell membranes and gets hydrolyzed to DCFH. ROS is a highly reactive molecule that can cause cellular death. ROS oxidizes DCFH to produce a highly fluorescent compound. This will be measured using a fluorescence plate reader or a flow cytometer, where the intensity will be directly proportional to the amount of ROS in the cells in the given PC3 cell line.

For the control group, PC3 cells are cultured with RSL3 and PBS only. 10mM DCFDA reagent will be added to the cultured cells and incubated for 30-45 minutes at 37°C. The DCFDA solution will then be removed, and a fluorescence plate reader or flow cytometer will be used to measure

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DCF fluorescence intensity with excitation wavelength at 485 nm and emission wavelength at 530 nm.

For the experimental groups, BBR will be added together with RSL3 and PBS to culture the PC3 cell line. 10mM DCFDA reagent will be added to the cultured cells and incubated for 30-45 minutes at 37°C. The DCFDA solution will then be removed, and a fluorescence plate reader or flow cytometer will be used to measure DCF fluorescence intensity with excitation wavelength at 485 nm and emission wavelength at 530 nm.

2.6. Statistical analysis

For all experimental groups, data will be analyzed to compare BBR treatment with RSL3 and with RSL3 alone on cell viability, lipid peroxidation, and ROS levels in PC3 cell lines. Each experiment will be replicated three times to obtain accurate results for each condition. The data will be analyzed using one-way ANOVA, followed by Tukey's post-hoc test for multiple comparisons between the experimental and control groups. Each of the experiment methods will be conducted three times to ensure the validity of the results. Statistical significance will be controlled by the experimenter to have a p-value under 0.05 to reflect significant results.

2.7. Possible results

Figure 2: Possible Results Table for the Three Methods

Combination of possible results (CR)	berberine+RSL3 kills PC3 by MTT more than RSL3 alone	berberine+RSL3 increases lipid peroxidation by BODIPY more than RSL3 alone	berberine+RSL3 increases ROS by DCFDA assay more than RSL3 alone	Support hypothesis
CR1	+	+	+	Fully yes
CR2	+	+	-	Partial
CR3	+	-	+	Partial
CR4	-	+	+	Partial
CR5	-	-	+	Partial
CR6	+	-	-	Partial
CR7	-	+	-	Partial
CR8	-	-	-	Fully no

+ indicates the measurement changes in the direction indicated in the column header, similar to the positive control (ML162) and the opposite of the negative control in PBS.

- indicates the measurement changes in the opposite direction of the direction indicated in the column header, similar to the negative control (PBS) and the opposite of the positive control (ML162).

3. Results

3.1. Concentration

As we increase the concentration of BBR, it is possible to observe both a general increase and decrease in cell death measured by MTT, both an increase and decrease in lipid peroxidation measured by BODIPY assay, and both an increase and decrease in ROS levels measured by DCFDA assay.

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3.2. Duration time

As we increase the treatment duration time of BBR to the cells, we should observe an increase in cell death measured by MTT, an increase in lipid peroxidation measured by the BODIPY assay, and an increase in ROS levels measured by the DCFDA assay.

It is also possible to observe a decrease in cell death measured by MTT, a decrease in lipid peroxidation measured by BODIPY assay, and a decrease in ROS levels measured by DCFDA assay.

3.3. Combination of possible results (CR)

CR1

The addition of BBR has proven to kill PC3 cells more than RSL3 alone, increase lipid peroxidation more than RSL3 alone, and increase ROS more than RSL3 alone.

CR2

The addition of BBR has been proven to kill PC3 cells more than RSL3 alone and increase ROS more than RSL3 alone, yet it fails to demonstrate an increase in lipid peroxidation more than RSL3 alone.

CR3

The addition of BBR has been proven to kill PC3 cells more than RSL3 alone and increase lipid peroxidation more than RSL3 alone, yet it fails to demonstrate an increase in ROS more than RSL3 alone.

CR4

The addition of BBR has proven to increase lipid peroxidation more than RSL3 alone and increases ROS more than RSL3 alone, yet fails to demonstrate more PC3 cell deaths than RSL3 alone.

CR5

The addition of BBR has only proven to increase ROS more than RSL3 alone, but fails to demonstrate more PC3 cell deaths than RSL3 alone, and an increase in lipid peroxidation more than RSL3 alone.

CR6

The addition of BBR has only proven to kill more PC3 cells than RSL alone, but fails to prove a greater increase in lipid peroxidation and increase in ROS than RSL3 alone.

CR7

The addition of BBR has only been proven to increase lipid peroxidation more than RSL3 alone, yet it fails to show more PC3 cell deaths than RSL3 alone, and an increase in ROS more than RSL3 alone.

CR8

The addition of BBR has shown no increase in lipid peroxidation compared to RSL3 alone, no increase in ROS compared to RSL3 alone, and no greater PC3 cell deaths compared to RSL3 alone.

4. Discussion

4.1. Concentration

An increase in the concentration of Berberine serves to eliminate the false negative that not enough BBR was added to observe the desired result.

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If an increased cell death compared with only RSL3 had been observed, it is because more BBR is available in the cell lines to induce greater levels of lipid peroxidation. However, it is also possible that the cells might have undergone significant cytotoxicity. Instead of lipid peroxidation, cell death might be due to apoptosis. This disrupts the accuracy of our study of the relationship between BBR and cell death exclusively, which makes it equally important to observe the degree of lipid peroxidation and ROS level to make experimental conclusions valid. Similarly, if an increase in lipid peroxidation and ROS level was observed, it signifies the exclusivity of BBR on the ferroptosis pathway, which is likely due to greater interactions between BBR and PC3 cell lines.

If a decreased effect in lipid peroxidation and ROS level was observed, it also indicates that the cells did not have an increase in ferroptosis-induced cell death. Moreover, if a decreased cell death is also observed, then it is likely that the addition of BBR had activated a protective mechanism in PC3 cells. Instead of inducing cell death, an increase in the concentration of BBR promoted protection for PC3 cells via reducing ferroptosis sensitivity, clearing oxidative damages, or mediating defensive mechanisms.

4.2. Duration time

With the experimental groups, the cell lines will be treated for up to 24 hours with BBR.

As we increase the treatment time, an increase in cell death, lipid peroxidation, and ROS levels might be observed. There is more time for the PC3 cell lines to contact BBR, which leads to an increase in the accumulation of ROS, thus increasing lipid peroxidation and cell death. Similarly, more exposure to BBR can also promote the incorporation of PUFA into membranes by altering lipid metabolism. This increases lipid peroxidation, and once it reaches a threshold, cells will undergo ferroptosis.

If there is an observed decrease in cell death, lipid peroxidation, and ROS level, BBR likely triggered antioxidant responses that shifted lipid metabolism away from ferroptosis susceptibility. Similarly, the addition of BBR had likely activated a protective mechanism in PC3 cells. Instead of inducing cell death, an increase in the concentration of BBR promoted protection for PC3 cells via reducing ferroptosis sensitivity, clearing oxidative damages, or mediating defensive mechanisms.

4.3. Combination of possible results (CR)

CR1

This result fully supports the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. This is likely due to Berberine's positive effect on the GPX4 pathway, which decreases GPX4 activity. This increases intracellular iron levels, which triggers oxidative damage and increases the activities of ALOX and PHD. Together with an increase in ROS level, lipid peroxidation is induced, thus killing more PC3 cells. This result fully supports the hypothesis that a combination of berberine and GPX4 inhibitor RSL3 kills PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone.

CR2

This result only partially supports the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. Berberine does increase lipid peroxidation and lead to more cell death, but a lack of increased ROS level may be BBR's role in

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modulating antioxidant defenses. BBR might have activated the NRF2 pathway that uses the excess ROS produced, so the overall ROS levels did not rise significantly.

CR3

This result only partially supports the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. Berberine may have an impact on increasing ROS levels that increase oxidative damage, but ferroptosis may not be the major cell death pathway. The PC3 cell lines might undergo mitochondrial dysfunction as an increase in ROS level is also observed in this pathway, which triggers cell death.

CR4

This result only partially supports the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. PC3 cells might have a higher threshold for ferroptosis induction, so lipid peroxidation induced by BBR is insufficient for ferroptosis. PC3 cells' antioxidant defenses might also be reasons that mediated the increase in ROS, which avoids ferroptosis despite lipid peroxidation. Thus, this result only partially supports the hypothesis.

CR5

This result only partially supports the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. Aside from lipid peroxidation, BBR also triggers fatty acid metabolism, which reduces the abundance of polyunsaturated fatty acids (PUFAs). Even with a high ROS level, there will be less lipid available for lipid peroxidation. Another reason could be that an increase in ROS levels also poses a risk to further tumor development as it may damage DNA and lead to metastasis.

CR6

This result only partially supports the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. BBR might induce cell death via apoptosis and autophagy, which leads to mitochondria-mediated apoptosis that is independent of ROS levels and lipid peroxidation. Ferroptosis is not the major cell death pathway because BBR does not inhibit GPX4 activity as well as RSL3.

CR7

This result only partially supports the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. This suggests that lipid peroxidation may not have a strong correlation with ROS levels and cell death. BBR might be signaling for autophagic cell death, which shows a similar increase in lipid peroxidation but different ROS levels from ferroptosis. Moreover, BBR may increase the incorporation of PUFAs into membrane phospholipids, which enhances lipid peroxidation susceptibility and leads to increased oxidized lipids even if the total ROS level does not increase.

CR8

This result fully negates the hypothesis that using a combination of berberine and the glutathione peroxidase 4 (GPX4) inhibitor RSL3 can kill PC3 cells through ferroptosis, elevated lipid peroxidation, and elevated ROS better than RSL3 alone. This experimental result shows that the addition of Berberine does not affect pancreatic cancer treatment as it fails to increase ferroptosis

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and lead to cell death. The excessive ROS level might be neutralized and consumed in the NRF2 pathway, which leads to no overall increase in ROS level observed. At the same time, decreased ROS levels also reduced lipid peroxidation, which decreased observed PC3 cell deaths. Moreover, instead of assisting PC3 cell death, BBR may also promote PC3 growth as it can activate AMPK signaling that clears damaged organelles, fails to induce cell death, and aids the development of pancreatic cells.

5. Conclusions

In this study, we aimed to investigate the effect of Berberine, a traditional Chinese medicine, on the treatment of pancreatic cancer. We qualified the effect of Berberine by designing an experimental group with Berberine added with RSL3 and used MTT assay to assess cell viability, BIPOD assay to measure lipid peroxidation, and DCFDA assay to quantify ROS levels. These experimental results can then be used to assess the degree of ferroptosis in these PC3 cell lines compared with the control group, at only a concentration of RSL3. If the experimental results matched with possible result 1 (CR1), then it fully supports the hypothesis that Berberine and RSL3 are an effective combination in killing PC3 cells through ferroptosis. Furthermore, it indicates that Berberine itself also has a significant positive impact on inducing ferroptosis in pancreatic cancer cells. This research further confirmed the viability of using ferroptosis as an alternative treatment for pancreatic cancer, which introduced traditional Chinese medicine, an often neglected and mysterious approach, as a therapeutic strategy for cancer treatment. Further research can focus on the possible side effects that Berberine has on the human body to test the safety of applying Berberine to pancreatic cancer treatment.

Future studies should first experiment using different concentrations of BBR, varying from 1μM to 100μM, and vary the treatment concentration of PC3 cell lines with BBR for up to 24 hours. We could obtain more precise results regarding the effect of an increase in concentration and treatment duration, which can indicate the optimal condition of BBR and its effect in inducing pancreatic cell death via the ferroptosis pathway. Secondly, future studies can also apply the BBR induction mechanisms to other types of diseases with similar mechanisms: oxidative stress regulation, ferroptosis susceptibility, and metabolic dysfunction. Other types of cancer, such as prostate cancer, breast cancer, and colorectal cancer, can also be regulated via the GPX4 pathway and lipid peroxidation.

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