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Mefloquine enhances radiosensitivity of glioma cells through ROS-dependent apoptosis

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► ***Original article***

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ABSTRACT

Background: Radiosensitizers enhance the effectiveness of radiation therapy by reducing the radio-resistance of cancer cells. A key advantage of traditional drug repositioning over the development of new drugs is the rapid repurposing of existing medications for new therapeutic applications. Mefloquine, a classical antimalaria drug, has also demonstrated anti-tumor activity through various mechanisms. The goal of this study is to investigate the potential of mefloquine as a radiosensitizer on gliomas. ***Materials and Methods:*** Gliomas were pre-treated with mefloquine prior to X-ray irradiation. The radiosensitization of mefloquine on these cells was first estimated using a clonogenic formation assay. To determine the mode of cell death, apoptosis and autophagy were measured in U251 gliomas at different intervals after mefloquine-mediated radiosensitization. Additionally, intracellular levels of reactive oxygen species and calcium ions were measured to explore the molecular mechanism during mefloquine-mediated radiosensitization. ***Results:*** Mefloquine was demonstrated to present a notable radiosensitizing effect on gliomas. However, the enhancement of protective autophagy diminished the radiosensitizing effect on the first day following combined treatment with mefloquine and X-rays. From the third day onward, the radiosensitization became more pronounced, attributed to a reduction in protective autophagy and an increase in apoptosis. Further study revealed that the increased apoptosis during mefloquine-mediated radiosensitization was dependent on intracellular reactive oxygen species levels, as the apoptotic response was inhibited by glutathione. ***Conclusion:*** Our findings demonstrate that mefloquine can elevate the radiosensitivity of gliomas through reactive oxygen species-dependent apoptosis.

INTRODUCTION

Malignant gliomas represent about 29% of all brain tumors [1]. Despite advancements in treatment strategies (surgical resection, chemotherapy, and radiotherapy) [2], patients with gliomas face a poor prognosis, with a median survival of only around fifteen months [3, 4] and a five-year survival of less than 19% [5]. Radiotherapy remains a cornerstone in the treatment of malignant glioma, utilizing ionizing radiation to kill tumor cells and reduce tumor masses. However, the inherent radio-resistance of gliomas significantly limits the effectiveness of this approach [6]. A radiosensitizer is a pharmacological or chemical agent that can greatly enhance the radiosensitivity of tumor cells when used alongside ionizing radiation. Thus, identifying effective radiosensitizers for gliomas continues to be a major challenge in improving the outcomes of radiotherapy.

Cell death induced by ionizing radiation can be classified into various types based on morphological features, including apoptosis, autophagy, senescence, mitosis catastrophe, ferroptosis, and necrosis [7-13]. Among these, apoptosis is a primary mechanism through which cells undergo self-destruction if their deoxyribonucleic acid damage remains unrepaired [14]. Apoptosis is sometimes considered a form of reproductive cell death, often linked to mitotic catastrophe and senescence [15]. Studies have also demonstrated a potential interplay between apoptosis and autophagy [16]. Consequently, apoptosis is recognized as the most prominent form of radiation -induced cell death. Several factors influence this process, with reactive oxygen species (ROS) [17, 18] and calcium ions [19, 20] playing critical roles in regulating radiation-induced apoptosis.

Mefloquine has been used to treat malaria since 1984 [21] and has also been reported to exhibit notable anti-cancer properties [22]. Its anti-neoplastic mechanisms include the induction of apoptosis [23], inhibition of angiogenesis [24], suppression of protective autophagy [25, 26], and interference with

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protein synthesis [27]. In addition, as one of the components of mefloquine, the fluorine atom has a high electronegativity and a small atomic radius [28], which enhances the permeability and lipid solubility of the compound, facilitating efficient cellular uptake. Despite these promising attributes, few studies have investigated mefloquine's potential as a radiosensitizer in combination with radiotherapy. In this work, we explored the radiosensitizing effects of mefloquine on gliomas and the underlying mechanisms. We found that pre-treatment with mefloquine significantly increased the sensitivity of gliomas to X-rays, an effect associated with a marked increase in apoptosis driven by elevated intracellular ROS levels. These findings indicate that mefloquine could serve as a promising radiosensitizer for glioma treatment. Notably, this research represents the first time mefloquine, an anti-malaria medication, has been used as a radiosensitizer in glioma cells due to its capacity to induce apoptosis.

MATERIALS AND METHODS

Glioma cells and reagents

Two glioma cell lines, U251 and C6, were kindly provided by the School of Biological Science and Medical Engineering at Southeast University (Nanjing, Jiangsu, China). Dulbecco's Modified Eagle's Medium (DMEM; 11965118) was sourced from Thermo Fisher Scientific (Austin, TX, USA). Mefloquine (PC404546) was purchased from J&K Scientific (Shanghai, China). The Annexin V-FITC Apoptosis Detection Kit (C1062L), Cell Counting Kit-8 (CCK-8; C0038), and Fluo-4 AM (S1060) were obtained from Beyotime Biotechnology (Shanghai, China). The 2',7'-dichlorodihydrofluorescein diacetate (DCF-DA; ALX-610-022) and Cyto-ID Autophagy Detection Kit (ENZ-51031) were procured from Enzo Life Sciences (Farmingdale, NY, USA). 3-methyladenine (3-MA; 189490) was obtained from Sigma Aldrich (St. Louis, MO, USA). Propidium iodide (PI; P266304) and Glutathione (GSH; G105427) were acquired from Shanghai Aladdin Bio-Chem Technology Co., Ltd. (Shanghai, China).

Cell culture and irradiation procedure

U251 and C6 cells were cultured in DMEM supplemented with 10% fetal bovine serum, 100 U/mL penicillin, and 100 U/mL streptomycin. The cells were maintained in an incubator at 37°C with 5% CO_2 and 95% air.

X-ray irradiation (6 MV) was performed using a linear accelerator (Varian, Palo Alto, CA, USA). A radiation dose of 6 Gy [29] was applied in most experiments, while the clonogenic formation assay included doses of 0, 2, 4, 6, and 8 Gy. The dose rate was set at 200 cGy/min.

U251 cells were exposed to X-ray irradiation after being treated with mefloquine for 1 hour. After a 24-hour incubation period, the mefloquine-containing medium was removed. The cells were then visualized and photographed using an inverted microscope (IX71, Olympus Optical Co., Tokyo, Japan).

Evaluation of cell viability

The cytotoxic effects of mefloquine on glioma cells were assessed using a cell viability assay. U251 cells were treated with mefloquine at 0, 20, 40, 60, 80, and 100 μM, while C6 cells were treated with 0, 30, 60, 90, 120, and 150 μM. After 24 hours of incubation, cell viability was measured using the CCK-8 kit according to the producer's protocols.

To evaluate the impact of mefloquine-mediated radiosensitization over time, U251 cells were treated with mefloquine (20 or 40 μM) in combination with X-rays, and cell viability was assessed on days 1, 3, and 6 post-treatments.

Additionally, to investigate the role of autophagy, U251 cells were sequentially treated with 3-MA (1 mM), mefloquine (20 or 40 μM), and X-rays, and cell viability was measured 24 hours later.

Clonogenic formation assay

The clonogenic formation assay was performed as previously described [30]. Glioma cells were pre-treated with mefloquine at two concentrations (20 or 40 μM for U251 cells and 60 or 90 μM for C6 cells) for one hour, followed by exposure to different doses of X-ray irradiation. After an additional eight days of incubation, cell colonies were stained and counted to assess the colony-forming ability of U251 and C6 cells.

Evaluation of apoptosis rate

Apoptosis rates were assessed at various time points after mefloquine-mediated radiosensitization using an apoptosis detection kit, following the producer's protocols. U251 cells were sequentially treated with mefloquine (20 or 40 μM) followed by X-ray irradiation. At days 1, 3, and 6 post-treatments, the cells were stained with Annexin V/ PI, and apoptosis levels were analyzed using a flow cytometer (BD Biosciences, Franklin Lakes, NJ, USA).

Additionally, to evaluate the role of intracellular ROS in apoptosis induction, the apoptosis rate was measured on the third day after U251 cells were treated sequentially with GSH, (1 mM), mefloquine (20 or 40 μM), and X-ray irradiation.

Measurement of autophagy

After the induction of radiosensitization by mefloquine, U251 cells were cultured for either one or three days. After the incubation period, cells were stained with Cyto-ID dye and autophagy levels were evaluated according to the manufacturer's instructions.

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Determination of ROS

After undergoing mefloquine-mediated radiosensitization, U251 cells were cultured for three days. The intracellular ROS levels were then evaluated using the DCF-DA method [31].

Measurement of intracellular calcium ions

U251 cells were incubated with Fluo-4 AM (5 μM) on the third day after they were co-treated with mefloquine (20/40 μM) and X-ray irradiation, and the level of intracellular calcium ions was measured using the flow cytometer according to the manufacturer's instructions.

Statistical analysis

All experiments were performed in triplicate. Data are expressed as mean ± standard deviation and were analyzed using OriginPro 8.0 software (OriginLab Corporation, Northampton, MA, USA). Statistical comparisons were conducted using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Radiosensitizing effect of mefloquine on gliomas

The cytotoxic effect of mefloquine on gliomas after their 24-hour incubation was estimated using the CCK-8 counting assay before investigating its radiosensitizing effect. Mefloquine caused a concentration-dependent reduction in cell viability in both U251 and C6 cell lines (figure 1A, 1B). The effective concentration for 20% of maximal cytotoxicity (EC20), defined as the concentration at which 20% of cells remain viable, was determined to be 43 μM for U251 cells and 95 μM for C6 cells. Since effective radiosensitizers should exhibit minimal cytotoxicity on their own, concentrations below the EC20 threshold, specifically 20 and 40 μM for U251 cells and 60 and 90 μM for C6 cells were selected for subsequent radiosensitization experiments.

The clonogenic formation assay was conducted to evaluate the radiosensitizing effect of mefloquine on glioma cells. Figure 1C and 1D present the survival fractions of U251 and C6 cells. The survival fractions were significantly lower in the mefloquine-treated, irradiated groups compared to those exposed to X-rays alone, with the reductions being both dose- and concentration-dependent. These results collectively indicate that mefloquine enhances the radiosensitivity of gliomas.

Increase of protective autophagy on day one following mefloquine's radiosensitization

U251 cells were used as a model to explore the mechanism underlying the radiosensitization of mefloquine. The reduction in survival fraction observed after mefloquine treatment combined with irradiation reflected the viability of U251 cells on day 8 (figure 1C). To gain a deeper understanding of the radiosensitizing activity of mefloquine, it was important to assess cell viability at different time points and explore the associated mechanisms. Hence, using the CCK-8 assay, we evaluated the viability of U251 cells on day 1 following co-treatment with mefloquine and 6 Gy X-ray irradiation. The viability of U251 cells did not decrease on day 1(figures 2A). The result indicates no radiosensitization occurs on U251 cells on the first day after combined treatment with mefloquine and X-rays.

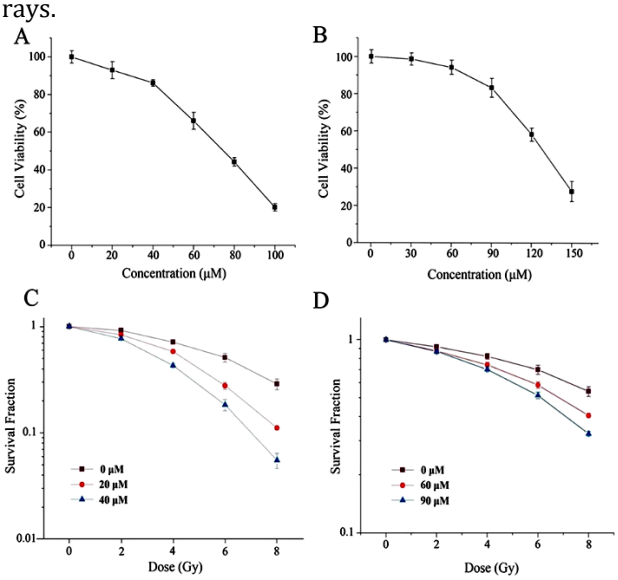

Figure 1. Radiosensitization effect of mefloquine on glioma cells. **A:** Viability of U251 cells decreased with increasing mefloquine concentrations. The viability of U251 cells was assessed 24 h following the treatment of mefloquine at 0, 20, 40, 60, 80, and 100 μM. **B:** Viability of C6 cells decreased with increasing mefloquine concentrations. The viability of C6 cells was assessed 24 h following the treatment of mefloquine at 0, 30, 60, 90, 120, and 150 μM. **C:** Survival fraction of U251 cells decreased in concentration- and dose- dependent manners. **D:** Survival fraction of C6 cells decreased in concentration- and dose-dependent manners. Three replicates were included in each group. Error bars mean standard errors of the mean.

To investigate the mechanisms behind the viability of U251 cells on day one following mefloquine-mediated radiosensitization, apoptosis and autophagy were examined. As shown in figures 2B and 2C, mefloquine increased apoptosis in irradiated U251 cells, however, this increase was not significant. In contrast, autophagy levels were significantly elevated in the mefloquine plus X-ray group compared to the X-ray-only group (figures 2D and 2E). Autophagy plays a complex role in cancer, potentially supporting either tumor cell survival or suppression. Therefore, the significance of the increase in autophagy during mefloquine-mediated radiosensitization warranted further investigation. To assess the role of this autophagy, 3-MA, an autophagy inhibitor, was employed. As shown in figure 2F, the U251 cell viability markedly declined

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following treatment with 3-MA in combination with mefloquine and X-rays. This finding indicates that the increased autophagy induced by mefloquine and radiation is protective. Collectively, the results suggest that apoptosis and autophagy are activated in U251 cells on day 1 post-treatment. However, the elevated protective autophagy counteracts the apoptosis, resulting in no significant radiosensitization on U251 cells.

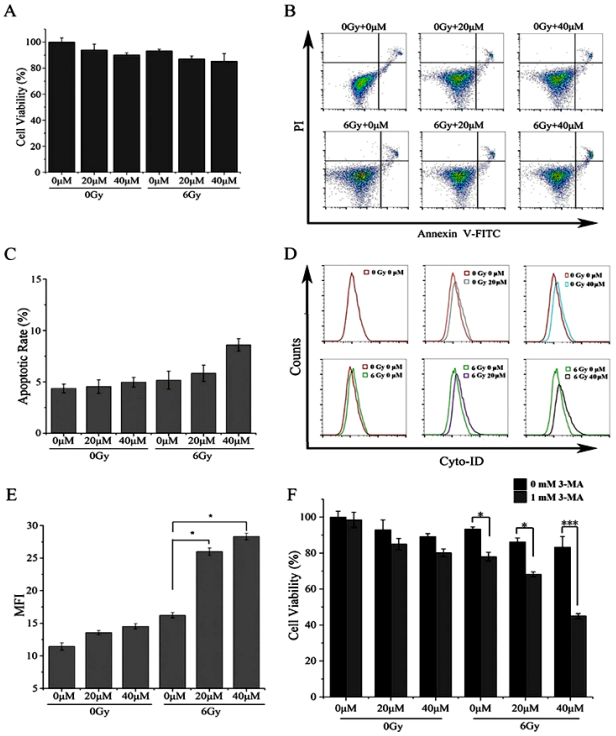

Figure 2. No significant change in the viability of U251 cells on the first day due to the increase in protective autophagy. **A:** Viability of U251 cells did not decrease after mefloquine-mediated radiosensitization. U251 cells' viability was measured on the first day following the treatment of mefloquine (20 and 40 μM) and 6 Gy of X-rays. **B:** Apoptosis in U251 cells did not significantly increase after mefloquine-mediated radiosensitization. **C:** U251 cells' apoptosis rate did not significantly increase after mefloquine-mediated radiosensitization. The apoptosis was evaluated on the first day after U251 cells were subjected to mefloquine (20 and 40 μM) and X-rays (6 Gy). **D:** Autophagic U251 cells increased after mefloquine-mediated radiosensitization. **E:** Mean fluorescent intensity (MFI) of autophagy in U251 cells increased after mefloquine-mediated radiosensitization. MFI of autophagy was measured on the first day after U251 cells were subjected to mefloquine (20 and 40 μM) and X-rays (6 Gy). **F:** 3-MA decreased U251 cells' viability during mefloquine -mediated radiosensitization. U251 cells' viability was measured on the first day following the treatment with 3-MA (1 mM), mefloquine (20 and 40 μM), and X-rays (6 Gy). Three replicates were included in each group. Statistics performed by a one-way analysis of variance and a Tukey test, *p<0.05 and ***p<0.001.

Elevated apoptosis rate from the third Day after mefloquine-mediated radiosensitization

We next examined the viability of U251 cells on the third day following mefloquine-mediated radiosensitization. A significant reduction in cell viability was observed in the group treated with mefloquine and 6 Gy X-ray irradiation (figures 3A), suggesting that the radiosensitizing effect of mefloquine becomes prominent around day three post-treatment. To further explore this effect, apoptosis and autophagy levels were assessed. Apoptosis increased notably, reaching 25.68% following treatment with 40 μM mefloquine and 6 Gy X-rays (figures 3B and 3C). In contrast, autophagy levels returned to those observed in cells subjected to X-rays alone (figures 3D and 3E). These findings indicate that the reduced viability of U251 cells on day three is primarily driven by enhanced apoptosis and a decline in protective autophagy.

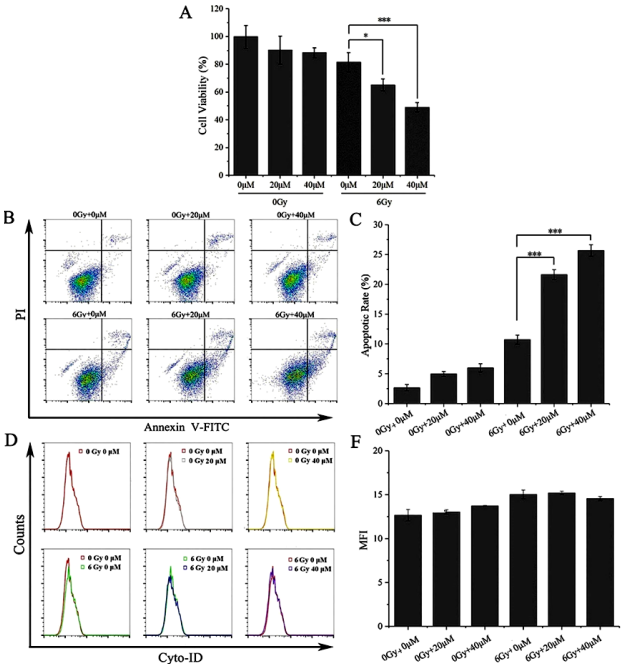

Figure 3. U251 cells' viability of decreased on the third day due to the increase in the apoptosis rate. **A:** Viability of U251 cells decreased after mefloquine-mediated radiosensitization. U251 cells' viability was measured on the third day following the treatment of mefloquine (20 and 40 μM) and X-rays (6 Gy). **B:** Apoptosis in U251 cells increased after mefloquine-mediated radiosensitization. **C:** Apoptosis rate increased after mefloquine-mediated radiosensitization. Apoptosis was evaluated on the third day after U251 cells were subjected to mefloquine (20 and 40 μM) and X-rays (6 Gy). **D:** Autophagic U251 cells did not significantly increase after mefloquine-mediated radiosensitization. **E:** Mean fluorescent intensity (MFI) of autophagy in U251 cells did not significantly increase after mefloquine-mediated radiosensitization. Autophagy was measured on the third day after U251 cells were subjected to mefloquine (20 and 40 μM) and X-rays (6 Gy). Three replicates were included in each group. Statistics performed by a one-way analysis of variance and a Tukey test, *p<0.05 and ***p<0.001.

Finally, we assessed the radiosensitizing effect of mefloquine on day six. As shown in figure 4A and 4B, the apoptosis rate increased significantly, reaching 55.53% in the group treated with 40 μM mefloquine

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combined with X-rays. This result suggests the radiosensitizing effect of mefloquine was primarily due to increased apoptosis.

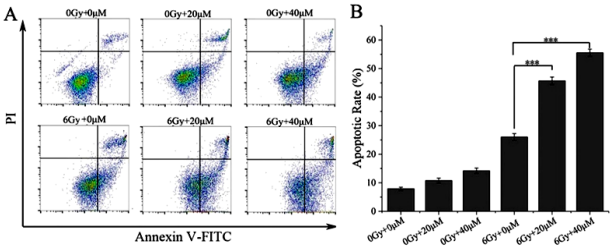

Figure 4. Continual increase in the apoptotic U251 cells on the sixth day after mefloquine-mediated radiosensitization. **A:** Increased apoptotic U251 cells. **B:** Increased apoptosis rate. Apoptosis was evaluated on the sixth day after U251 cells were subjected to mefloquine (20 and 40 μM) and X-rays (6 Gy). Three replicates were included in each group. Statistics performed by a one-way analysis of variance and a Tukey test, ***p<0.001.

Elevated intracellular ROS levels trigger apoptosis

To explore the mechanism behind the increased apoptosis rate, we examined key apoptosis-related factors, specifically intracellular ROS and calcium ions. As shown in Figures 5A and 5B, intracellular ROS levels in U251 cells were significantly elevated on the third day following mefloquine-mediated radiosensitization. To estimate the role of ROS, U251 cells were pre-treated with GSH and mefloquine one hour prior to exposure X-rays. Figures 5C and 5D show that GSH treatment markedly reduced the apoptosis rate induced by the combined treatment, indicating that elevated intracellular ROS is responsible for the increased apoptosis observed in radiosensitized U251 cells. Figures 5E and 5F display intracellular calcium levels on the third day after co-treatment. Compared to the X-ray-only group, no significant difference in calcium ion concentration was found in the mefloquine plus X-ray groups. This suggests that calcium ions do not contribute to the enhanced apoptosis rate under these conditions. Collectively, these findings demonstrate that the increased apoptosis in U251 cells following mefloquine-mediated radiosensitization is primarily driven by elevated intracellular ROS levels, rather than changes in calcium ion concentration.

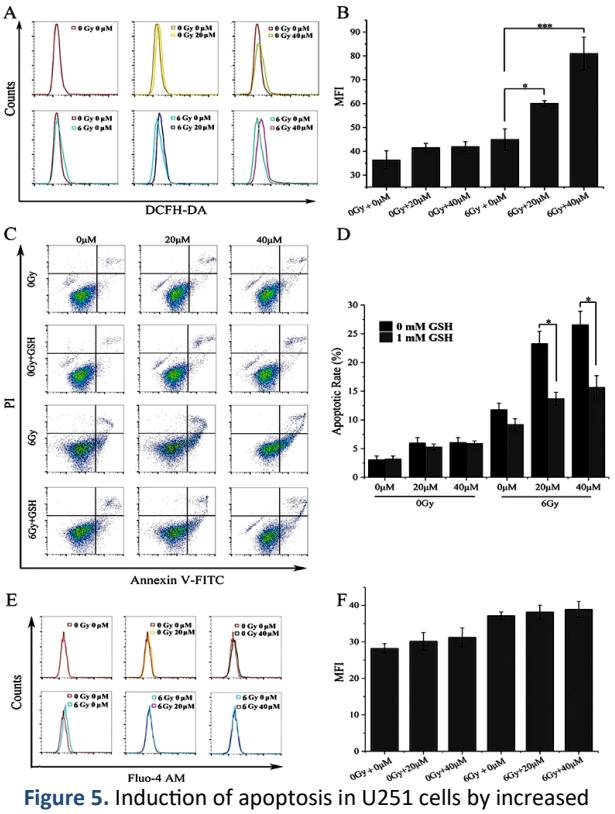

Figure 5. Induction of apoptosis in U251 cells by increased levels of intracellular ROS. **A:** Intracellular ROS-containing U251 cells increased after mefloquine-mediated radiosensitization. **B:** Mean fluorescent intensity (MFI) for intracellular ROS in U251 cells increased after mefloquine-mediated radiosensitization. Intracellular ROS was evaluated on the third day after U251 cells were subjected to mefloquine (20 and 40 μM) and X-rays (6Gy). **C:** GSH decreased the apoptotic U251 cells during mefloquine-mediated radiosensitization. **D:** GSH decreased the apoptosis rate of U251 cells during mefloquine-mediated radiosensitization. Apoptosis was measured on the third day after U251 cells were subjected to GSH (1 mM), mefloquine (20 and 40 μM), and X-rays (6 Gy). **E:** Calcium ion-containing U251 cells did not change after mefloquine-mediated radiosensitization. **F:** MFI for calcium ion in U251 cells did not change after mefloquine-mediated radiosensitization. Levels of calcium ion were determined on the third day after U251 cells were subjected to mefloquine (20 and 40 μM) and X-rays (6 Gy). Three replicates were included in each group. Statistics performed by a one-way analysis of variance and a Tukey test, *p<0.05 and ***p<0.001.

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DISCUSSION

A key advantage of traditional drug repurposing is rapidly applying established medications to new therapeutic indications. Mefloquine, a well-known antimalarial agent, was investigated in this study for its potential as a radiosensitizer in glioma treatment. Our findings demonstrate that mefloquine enhances the radiosensitivity of gliomas by triggering apoptosis through a mechanism dependent on ROS.

The reduction in the survival fraction of U251 cells in the groups treated with mefloquine and X-rays (figures 1C and 1D) indicates that mefloquine possesses a radiosensitizing effect on glioma cells. Over time, the number of apoptotic cells increased progressively (figures 3C and 4B), establishing apoptosis as the primary mode of cell death during mefloquine-mediated radiosensitization. This is consistent with previous reports showing that either X-ray irradiation [8] or mefloquine [32] can independently induce apoptosis. Hence, the predominance of apoptosis in this context is a logical outcome. On the first day post-treatment, autophagy levels increased but returned to baseline by the third day (figures 2E and 3E). When cells were treated with 3-MA, the survival rate of U251 cells significantly declined (figure 2F), indicating that the early autophagy observed was protective. Protective autophagy has also been observed during the radiosensitization of U251 cells by deferoxamine [29] and Ag nanoparticles [31]. Numerous works have demonstrated that autophagy can promote cancer cell survival following radiotherapy, thereby contributing to radioresistance [33,34]. The simultaneous presence of apoptosis and protective autophagy highlights the complexity of the radiosensitizing mechanism of mefloquine in U251 cells. A similar coexistence of apoptosis and protective autophagy has been reported in glioma cells treated with deferoxamine [29]. The damage mechanism caused by deferoxamine is distinct from mefloquine, which chelates ferric ions from proteins in tumor cells. These observations suggest that the concurrent induction of apoptosis and protective autophagy may represent a general phenomenon in the radiosensitization of U251 cells. We intend to conduct experiments to validate this hypothesis in future studies. Thus, given our finding that protective autophagy is activated during the early phase of mefloquine-induced radiosensitization, combining mefloquine with an autophagy inhibitor may serve as a promising strategy to further enhance its radiosensitizing effect on U251 cells.

The loss of proliferative ability is a key indicator of tumor cell death. Hence, to assess the radiosensitization of mefloquine on gliomas, we conducted a colony formation assay, quantifying the number of U251 cell colonies on day 8 following mefloquine-mediated radiosensitization.

Additionally, we monitored radiation-induced cell death mechanisms, specifically apoptosis and autophagy at days 1, 3, and 6, respectively, in U251 cells. This time-course analysis offers a comprehensive overview of the cell death pathways activated during mefloquine-mediated radiosensitization. Our findings indicate that apoptosis is the predominant mode of cell death in this context. However, the apoptosis rate observed on day 6 was approximately 55.53 ± 1.26% (figure 4B), suggesting that other radiation-induced death mechanisms, such as mitotic catastrophe [11] and ferroptosis [12], might also be occurring. Consequently, a noted limitation of this study is that it did not encompass the full spectrum of radiation-associated cell death pathways.

Intracellular levels of ROS and calcium ions are closely associated with radiation-induced apoptosis. Although mefloquine has been shown to elevate both ROS and calcium ion levels [35], our findings indicate that only ROS contributed to the apoptosis induced by the combined treatment of mefloquine and X-rays (figures 5B and 5D). Calcium ions did not appear to play a role in this process. Future investigations will focus on elucidating the underlying mechanism by which calcium ions are not involved in apoptosis triggered by the co-treatment.

In conclusion, our study demonstrated that mefloquine exerts a significant radiosensitizing effect on glioma cells. This enhanced radiosensitivity was primarily associated with increased apoptosis, which was driven by elevated levels of intracellular ROS. These results provide novel insights into the potential therapeutic application of mefloquine beyond its established use as an antimalarial drug. However, to fully validate the clinical potential of mefloquine as a radiosensitizer, further in vivo studies using animal models are essential. Such studies will be critical for evaluating the therapeutic efficacy of mefloquine in a more physiologically relevant context.

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Conflicts of interests: The authors declare no conflicts of interest.

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Ethical considerations: The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Bengbu Medical University.

Author contributions: Conceptualization, A.W. and X.Z.; methodology, A.W. and Y.M.; original draft preparation, A.W., A.G., and Z.D.; supervision, X.H. and X.Z.

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