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A new tumor-treating device OM-100 with low-frequency magnetic fields inhibits proliferation and metastasis in liver cancer

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Abstract

Background This study aims to investigate a novel instrument OM-100 with low-frequency magnetic fields (LFMFs) for its potential applicability in the treatment of liver cancer.

Methods Liver cancer cell lines (HepG2 and Huh7) and normal liver cell line THLE-2 were exposed to OM-100 at LFMFs of 0, 10, 25, 50, and 100 kHz for 2 h in the morning, noon, and evening, respectively. The effects of LFMF on cell viability, apoptosis, migration, and invasion capabilities were examined. Additionally, impacts of LFMF on ROS production was assessed. In vivo studies were conducted to examine the safety profile of OM-100 and its effects on tumor growth.

Results In vitro, OM-100 reduced the viability of liver cancer cells, increased cell apoptosis, and inhibited cell migration and invasion abilities in a frequency-dependent manner ($P < 0.05$). In vivo, OM-100 significantly slowed down tumor growth and promoted apoptosis in liver tumors ($P < 0.05$). Moreover, OM-100 rarely affected the viability of normal liver cells, as well as the health of normal mice. Finally, we further found that OM-100 significantly increased the production of ROS in liver cancer cells ($P < 0.05$), a key factor in inducing autophagy, which is very important for the progression of liver cancer.

Conclusion Our findings reveal the safety of OM-100 and its frequency at 100 kHz significantly inhibits liver cancer progression.

Keywords Tumor treating instrument, Low-frequency magnetic fields, Liver cancer, Proliferation, Migration, Invasion, Xenograft tumor model

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Background

Liver cancer, a prevalent health dilemma worldwide, is a significant global health issue [1]. Occupying the third position in terms of fatal outcomes, it is responsible for approximately 8.3% of all worldwide cancer deaths and emerges as the principal cause of cancer-related mortality among men globally [2]. Even with advancements in diagnosis and various treatment modalities—ranging from surgical intervention and liver transplants to chemotherapeutic and targeted approaches—the five-year survival statistics remain notably poor [3]. Only 5-15% of patients are eligible for surgical options, but which are generally limited to early-stage patients, and the utility of liver transplantation is further restricted by a shortage of donor organs [4]. Additionally, chemotherapy often leads to severe side effects and eventual drug resistance [5]. Although targeted therapies have ushered in a new era for liver cancer treatment, drug resistance, and tumor heterogeneity often limit their long-term efficacy [6]. Given these challenges, it is a pressing need to explore innovative and effective strategies for liver cancer treatment.

Low-frequency magnetic fields (LFMFs) have emerged as a potential treatment method for liver cancer, primarily due to their non-invasive and localized application [7]. These magnetic fields (MFs) are believed to exert their anti-cancer effects by interfering with ion channels and cellular membranes, consequently disrupting key signaling pathways that control cell proliferation and survival [8]. MF disruption promotes apoptosis, offering a level of selective cytotoxicity that traditional treatments often fail to achieve [9, 10]. Preliminary studies have confirmed the targeted action of LFMFs, providing promising preclinical evidence of LFMFs retarding tumor growth and enhancing the effects of existing chemotherapies [8, 11]. LFMF is reported to inhibit proliferation of breast cancer cells [12] and improve general symptom of advanced gastric cancer [13]. A previous study demonstrates the enhance effect of LFMFs on antitumor immune response in hepatocellular cancer [14]. Although still underexplored, LFMF presents an attractive avenue for the treatment of liver cancer that warrants comprehensive future research.

This article aims to discuss the development and therapeutic potential of a novel tumor treatment device, OM-100, that utilizes LFMF (1.066–16.983 mT, 20–200 kHz) for the treatment of liver cancer. OM-100 device is illustrated in Fig. 1 and the magnetic field in device is evenly distributed (Fig. S1). The features of OM-100 include non-contact operation, no heat generation, and precise, small-area targeting of lesions. OM-100 utilizes the LFMF generated by the rotation of high-field magnets to exert an inhibitory effect on tumor cell growth. In our study, we explored effects of OM-100 on cell apoptosis, migration, invasion, and reactive oxygen species (ROS) production in vitro and further extended our investigations to in vivo studies, examining the safety and efficacy of OM-100 in both healthy mice and a liver cancer xenograft model. Our findings intend to clarify the efficacy of OM-100 in preclinical, and its potential as an adjunct or alternative to conventional liver cancer treatment strategies.

Materials and methods

Cell lines and culture conditions

Human liver cancer cell lines (HepG2 and Huh7) and normal human liver cell line (THLE-2) were purchased from Meisen Cell (Zhejiang, China). All cells were cultured in Dulbecco's modified eagle medium (DMEM). The cell cultures were maintained at 37 °C in a humidified incubator with 5% CO_2.

Cell treatment

LFMFs were generated using OM-100. THLE-2 cells were treated with 1.066 mT LFMF at 0 kHz, 10 kHz, 25 kHz, 50 kHz, 100 kHz, and 150 kHz for 0, 24, 48, and 72 h; HepG2 and Huh7 cells were treated with 1.066 mT LFMF at 0 kHz, 10 kHz, 25 kHz, 50 kHz, and 100 kHz for varying durations (0, 24, 48, and 72 h).

Cell viability assay

To evaluate cell viability, we employed the CCK-8 assay. Totally 100 μL cells (2×10^3 cell/well) were seeded in 96-well plates and exposed to LFMF for different frequency and different duration as mentioned before. Subsequently, 10 μL of CCK-8 solution was introduced to each well, and the cells were incubated for another 2 h at 37 °C. The optical density was then ascertained at a wavelength of 450 nm utilizing a microplate reader.

Apoptotic activity assay

Apoptotic cells were identified using an Annexin V-FITC/PI apoptosis detection kit. Post exposure to OM-100 for 72 h, cells were collected, washed with cold PBS, and then labeled with 5 μL Annexin V-FITC and 10 μL PI as per the kit guidelines.

Cell proliferation assay

Colony formation was employed for cell proliferation assay. Cells were dispersed in 6-well plates. Following a 14-day incubation, the colonies were set with methanol for 15 min and tinted with crystal violet for additional 20 min. The colony count was done using microscopic analysis.

Cell migration and invasion assay

The Transwell apparatus was utilized to evaluate both cellular migration and invasion. For the migration assay,

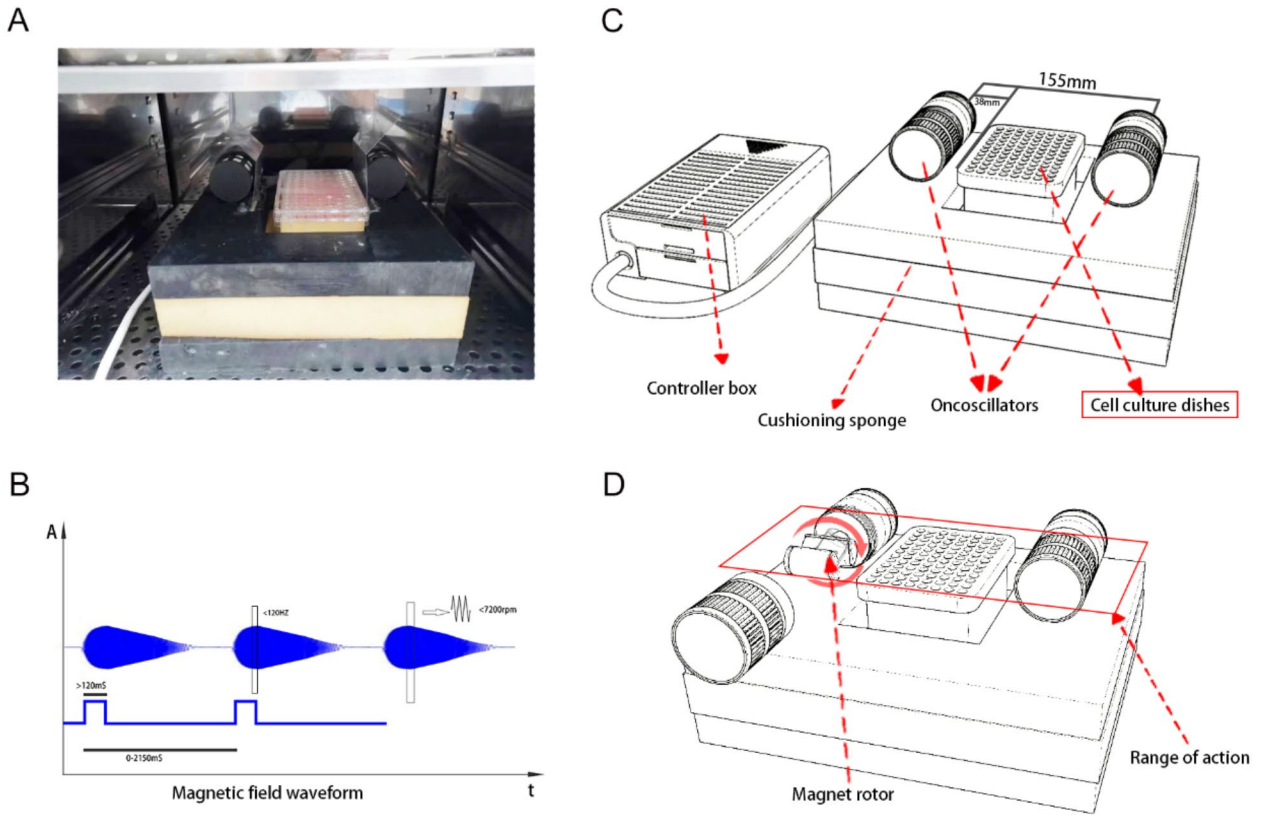

Fig. 1 Exposure system and low-frequency magnetic fields (LFMFs) of OM-100. **A** Photo of the exposure system. **B** Magnetic field waveform. X-axis represents the time unit; y-axis represents gain mV. **C**, **D** Scheme of the exposure system. According to the experiment results, the effects of continuous wave and pulse wave are basically same. To save energy, pluse wave was used in this device

the cells were treated with OM-100 for 72 h, and then 200 µL cells (1×10^5 cell/mL) were plated in non-coated upper chamber. For invasiveness, chambers were pre-treated with Matrigel. After incubation for 24 h, cells adhering to the upper membrane surface were eradicated, while the cells that had migrated or invaded through to the lower membrane surface were dyed with crystal violet for a span of 20 min. Three fields of view per group were randomly selected to observe the cells and take photos. The cell number was calculated using Image J software.

ROS quantification

For the detection of intracellular ROS, a DCFH-DA probe was employed. After treatment with OM-100, cells were exposed to 10 µM DCFH-DA for a half-hour at 37 °C. The resultant fluorescence intensity was then quantified via flow cytometry.

In vivo tumor xenograft model

All experimental setup were shown in Fig. 2A. BALB/c nude mice (6-week-old, male, $n=12$) were purchased from Yangzhou University Laboratory Animal Center. Mice were subcutaneously injected with 100 µL 5×10^5 HepG2 cells to establish a liver cancer xenograft model. Once tumor volume reached approximately 100 mm^3, the mice were randomly divided into the model group (LC: liver cancer) and the OM-100-treated group (LC+24 d). Tumor growth was monitored every three days, and the tumor volume was calculated using the formula $V=0.5\times L\times W^2$, where L is the length and W is the width of the tumor. OM-100-treated mice received a treatment of 1.066 mT magnetic fields at 100 kHz for 24 days with 2 h at morning (7:00 to 9:00), noon (12:00 to 14:00), and evening (17:00 to 19:00). Mice without any treatment were used as controls.

Upon completion of the treatment, 800 µL of blood was collected from the orbital sinus of a mouse. EDTA-K2 anticoagulant was added to 150 µL of this whole blood, and then the levels of blood routine indicators, including granulocytes (Gran), hematocrit (HCT), hemoglobin (HGB), lymphocytes (Lymph), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), platelets (PLT), red blood cells (RBC), platelet distribution width (PDW), mean platelet volume (MPV), and white blood cells (WBC), were analyzed using an automatic hematology analyzer. The remaining 650 µL of blood was

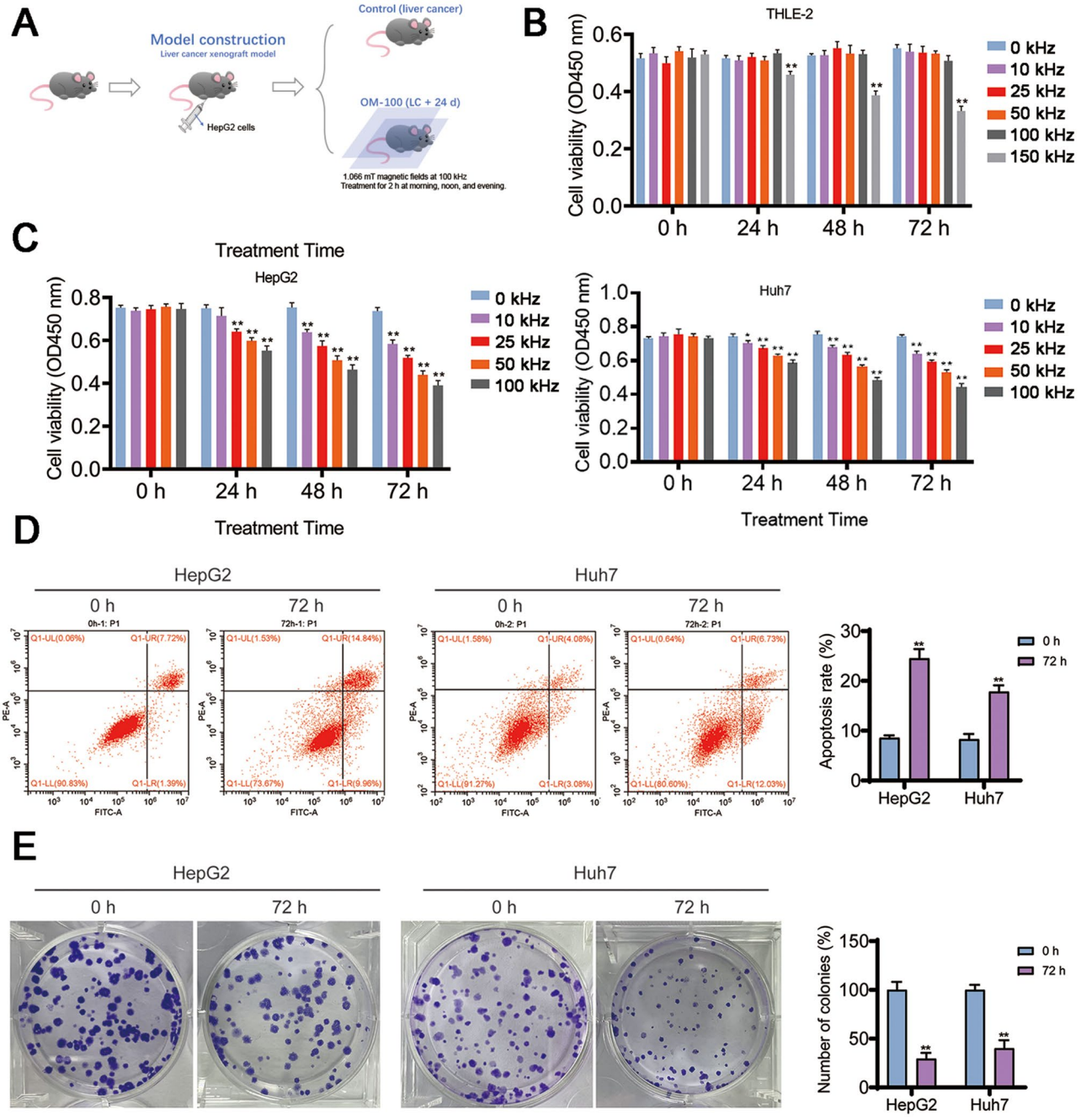

Fig. 2 OM-100 inhibits cell proliferation and promotes apoptosis in liver cancer cell lines. **A** The animal experiment. **B** Cell viability of normal human liver cells (THLE-2) under varying LFMF frequencies (0, 10, 25, 50, 100, and 150 kHz) at 0, 24, 48, and 72 h. **C** Cell viability of liver cancer cell lines (HepG2, Huh7) under varying LFMF frequencies (0, 10, 25, 50, and 100 kHz) at 0, 24, 48, and 72 h. . **D** Apoptosis rates in HepG2 and Huh7 cells following OM-100 treatment at a 100 kHz frequency for 72 h. **E** Colony formation capability of HepG2 and Huh7 cells after OM-100 treatment at a 100 kHz frequency for 72 h. *$P < 0.05$, **$P < 0.01$. HepG2 and Huh7 cells were treated with 100 kHz and 1.066 mT of OM-100 for 72 h

allowed to stand for 30 min, followed by centrifugation at 10,000 r/min for 2 min. The serum was then taken and tested for biochemical indicators, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T-BIL), creatinine (CREA), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c), using an automatic biochemistry analyzer.

At last, mice were anesthetized using 10% sodium pentobarbital solution, and euthanized by cervical dislocation. The tumors were excised, photographed, and weighed. The animal experiments were approved by

Yangzhou University Laboratory Animal Center (No. 202311014).

Histopathological analysis

Heart, liver, spleen, lung, and kidney were harvested and fixed in 10% formalin. These tissues were then embedded in paraffin, sectioned, and stained with hematoxylin and eosin for histological examination as previous described [15].

Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assessment

TUNEL assay was conducted to detect cell apoptosis in tumor tissues of the xenograft model. After deparaffinization and rehydration, tumor sections were treated with proteinase K for 30 min. Then, slides were incubated with the TUNEL reaction mixture for 60 min. The nuclei were counterstained with DAPI for 10 min. Apoptotic cells were visualized and quantified under a fluorescence microscope. Percentage of TUNEL-positive cells was calculated to assess the extent of apoptosis.

Statistical analysis

All data are presented as the mean ± standard deviation. Differences between two groups were analyzed using Student's t-test, those among multiple groups were evaluated through a one-way analysis of variance followed by Tukey's test. $P<0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad 8.0.

Results

OM-100 inhibited cell proliferation of the liver cancer cells

To explore the effects of OM-100 on cell proliferation, in vitro experiments were conducted using normal human liver cells (THLE-2) and liver cancer cell lines (HepG2, Huh7). The results revealed that cell viability of THLE-2 cells (normal human liver cell) remained virtually unchanged at frequencies form 0–100 kHz across all time points (Fig. 2B, $P>0.05$). However, when at 150 kHz OM-100 treatment, cell viability significantly reduced (Fig. 2B, $P<0.05$), suggesting that 150 kHz OM-100 may cause damage to normal liver cells. Therefore, treatment with OM-100 at 150 kHz was then excluded in further analysis. After treatment with OM-100, HepG2 and Huh7 cells (human liver cancer cells) exhibited a frequency-dependent reduction in cell viability (Fig. 2C, $P<0.05$). Specifically, at the 100 kHz frequency, the most substantial decrease in cell viability was observed (Fig. 2C, $P<0.05$). These indicate that higher frequencies and prolonged exposure to OM-100 has the most profound anti-proliferative effects. Therefore, cells treated with OM-100 at 100 kHz frequency were selected for further exploration.

To investigate the mode of cell death, we performed apoptosis assays following OM-100 treatment (100 kHz, 72 h). Compared to cells receiving no treatment (0 h), both HepG2 and Huh7 cells showed significantly increased apoptosis rates post-OM-100 treatment (Fig. 2D, $P<0.01$). Moreover, colony-forming ability, a marker of proliferative capacity, was assessed. HepG2 and Huh7 cells displayed a significant decrease in colony formation after OM-100 treatment compared to the cells that received no treatment (Fig. 2E, $P<0.01$). The results revealed that OM-100 effectively inhibited liver cell proliferation, with this inhibitory effect being most pronounced at 100 kHz.

OM-100 inhibited migration and invasion of the liver cancer cells

We further evaluated the role of OM-100 on metastatic potential of liver cancer cells. In migration assay, there was a significant reduction in the number of migrating cells in both HepG2 and Huh7 cells after OM-100 treatment (Fig. 3A, $P<0.01$). The invasion assays showed a similar pattern, with a significant decrease in the number of invasive cells after OM-100 treatment (Fig. 3B, $P<0.01$). These results showed that OM-100 treatment effectively inhibits the migratory and invasive potential of liver cancer cells.

OM-100 promoted ROS in liver cancer cells

ROS plays a significant role in progression of liver cancer by inducing oxidative stress that can lead to genomic instability and promote carcinogenesis. ROS production was significantly increased both in the HepG2 and Huh7 cells following OM-100 treatment in this study (Fig. 4, $P<0.01$). This implies that OM-100 might exert its anticancer effects by inducing oxidative damage within liver cancer cells, inhibiting their proliferation and metastatic potential.

OM-100 had no effects on normal mice

Cell experiments revealed the safety of OM-100 in normal liver cells. An in vivo examination was performed to further validate the safety of OM-100 in normal mice. Normal nude mice were exposed to 1.066 mT 100 kHz OM-100. The results showed no significant differences in body weight and behavioral state between the OM-100-treated mice and the untreated controls over the course of the 24-day period (Fig. 5A). HE staining on organ tissues from the heart, liver, spleen, lung, and kidney revealed that no discernible pathological alterations were observed as a result of OM-100 treatment compared to untreated mice (Fig. 5B). Additionally, there were no obvious difference in the levels of blood routine indicators (Gran, HCT, HGB, Lymph, MCH, MCV, PLT, RBC, PDW, MPV, and WBC) and biochemical indicators

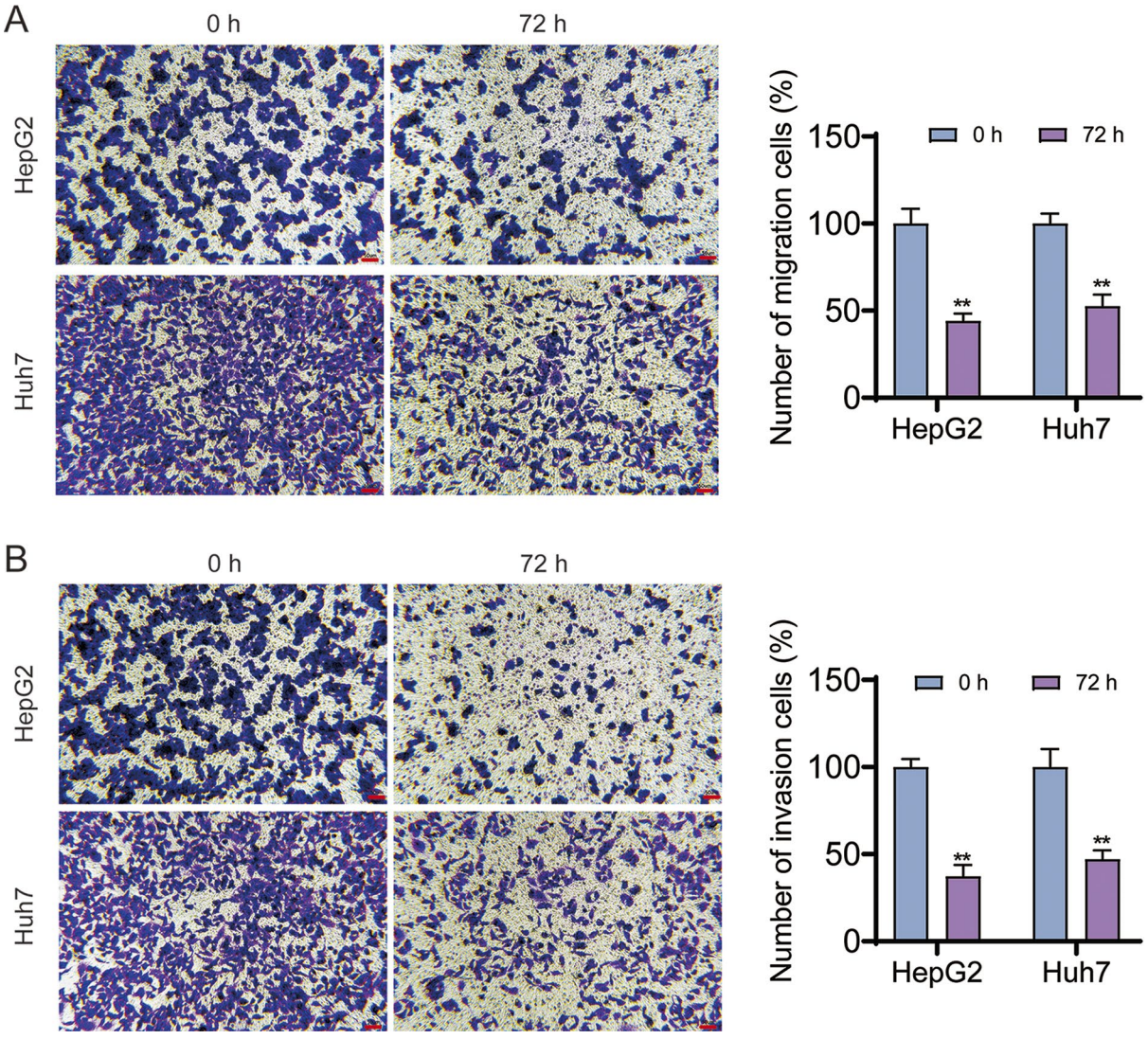

Fig. 3 OM-100 inhibits migration and invasion in the liver cancer cell lines. **A** Transwell migration assay results for HepG2 and Huh7 cells. **B** Transwell invasion assay results for HepG2 and Huh7 cells. Scale bar = 50 μm; $^{**}P < 0.01$. HepG2 and Huh7 cells were treated with 100 kHz and 1.066 mT of OM-100 for 72 h

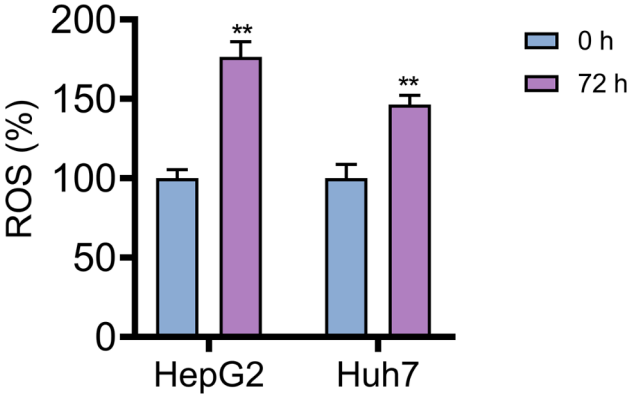

Fig. 4 OM-100 induces ROS production in liver cancer cell lines. Comparative ROS levels in HepG2 and Huh7 cells. $^{**}P < 0.01$. HepG2 and Huh7 cells were treated with 100 kHz and 1.066 mT of OM-100 for 72 h

between control mice and OM-100 treated mice (Fig. 6A and B). These results substantiate safety of OM-100, reinforcing that they do not cause detrimental organ damage, even with prolonged exposure.

OM-100 suppressed tumor growth and promoted apoptosis in liver xenograft tumor model mice

Following the establishment of a liver cancer xenograft model in mice, model mice were treated with OM-100 at a frequency of 100 kHz. The tumor growth curves depicted a clear divergence, with the OM-100-treated mice showing a slower tumor progression rate than untreated model mice (Fig. 7A, B and $P < 0.01$). Moreover, the tumors in OM-100-treated mice weighed significantly less than those in the untreated group at the end of the 24-day period (Fig. 7C, $P < 0.01$). Additionally,

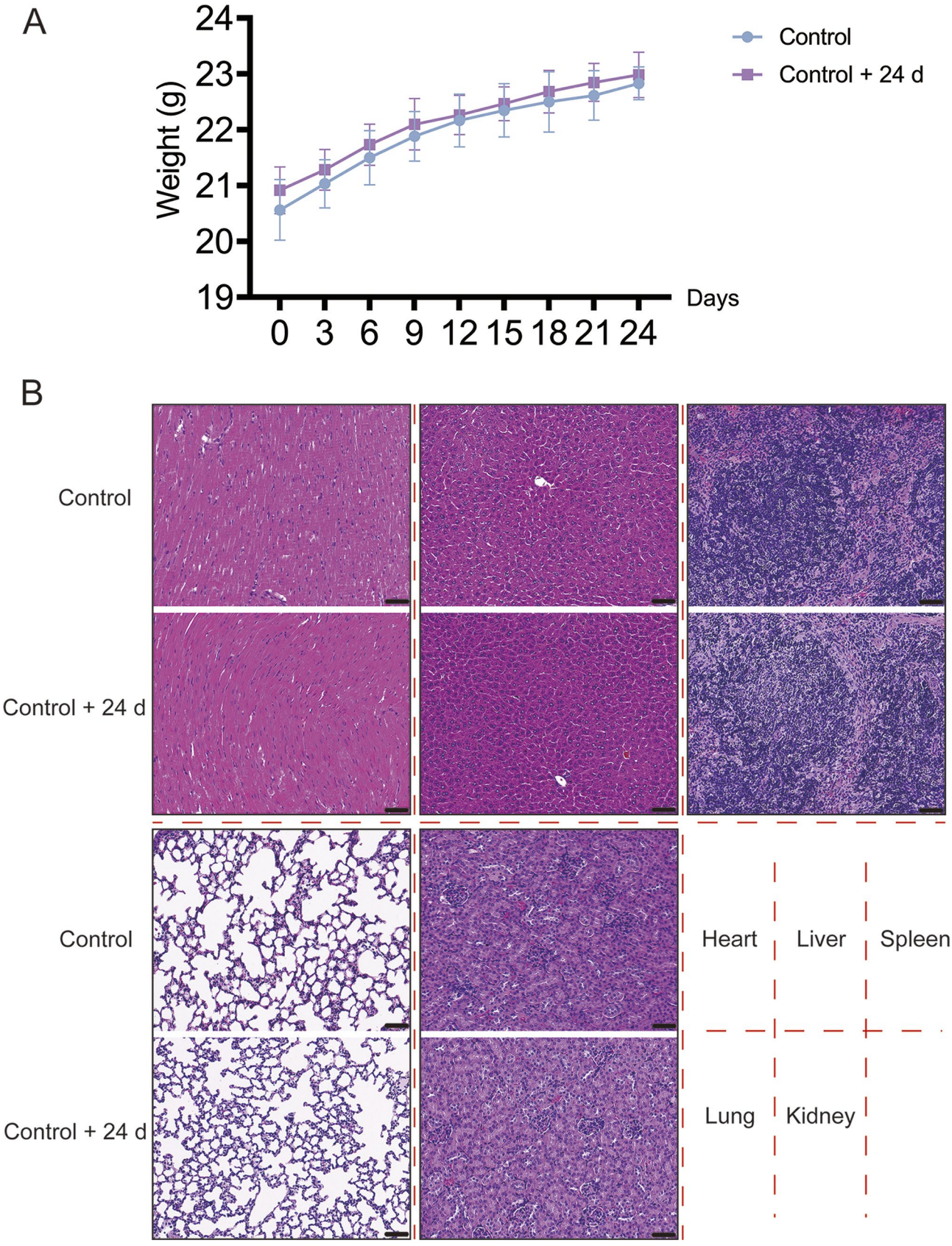

Fig. 5 Impacts of OM-100 on normal mice. **A** Body weight of normal nude mice. **B** Histopathological examination of organ tissues. Scale bar = 50 μm; Mice were treated with 1.066 mT of OM-100 at 100 kHz for 24 days

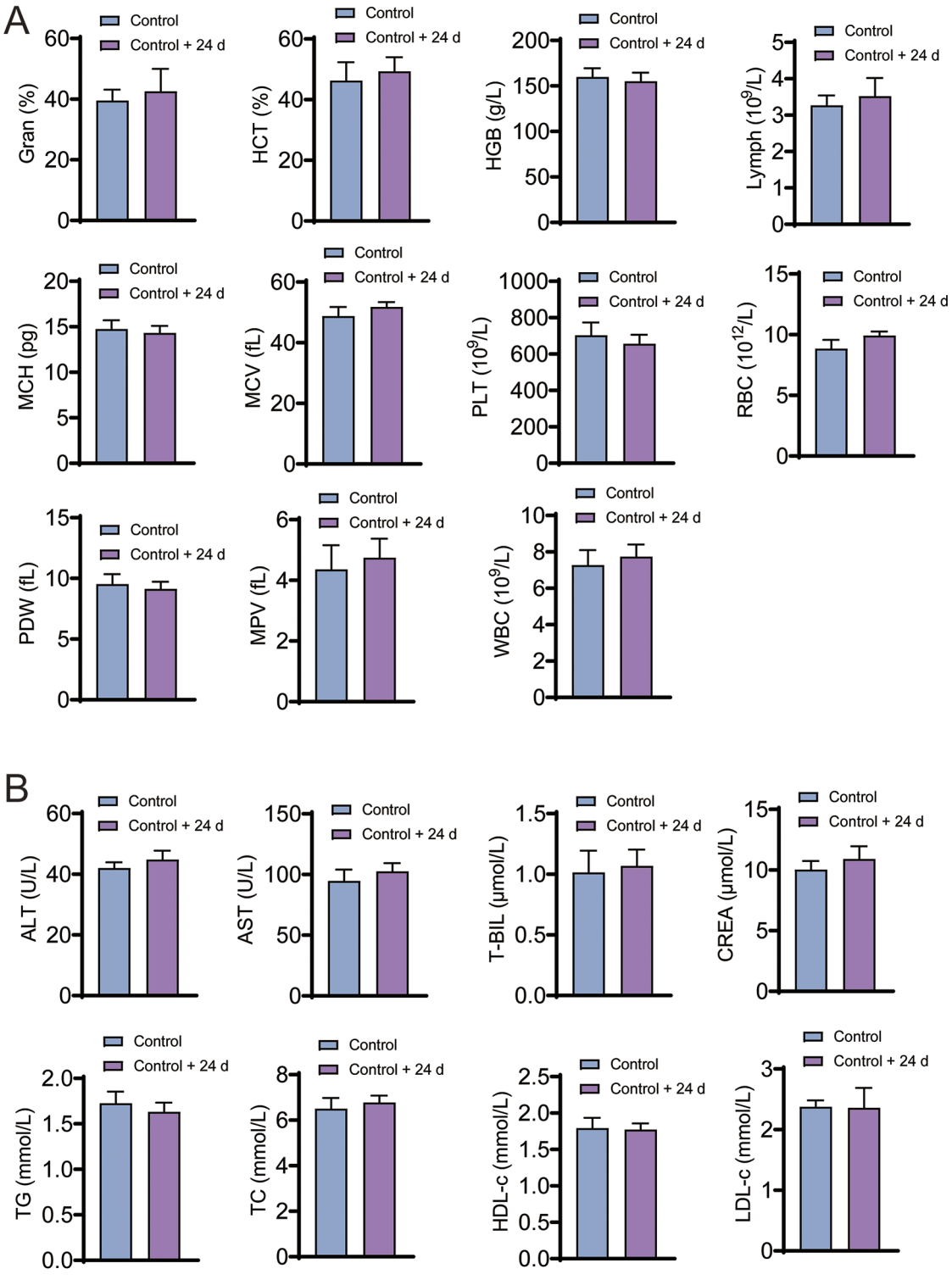

Fig. 6 Effects of OM-100 on blood routine indicators and biochemical indicators in normal mice. **A** Levels of blood routine indicators in mice. **B** Levels of biochemical indicators in mice. Mice were treated with 1.066 mT of OM-100 at 100 kHz for 24 days

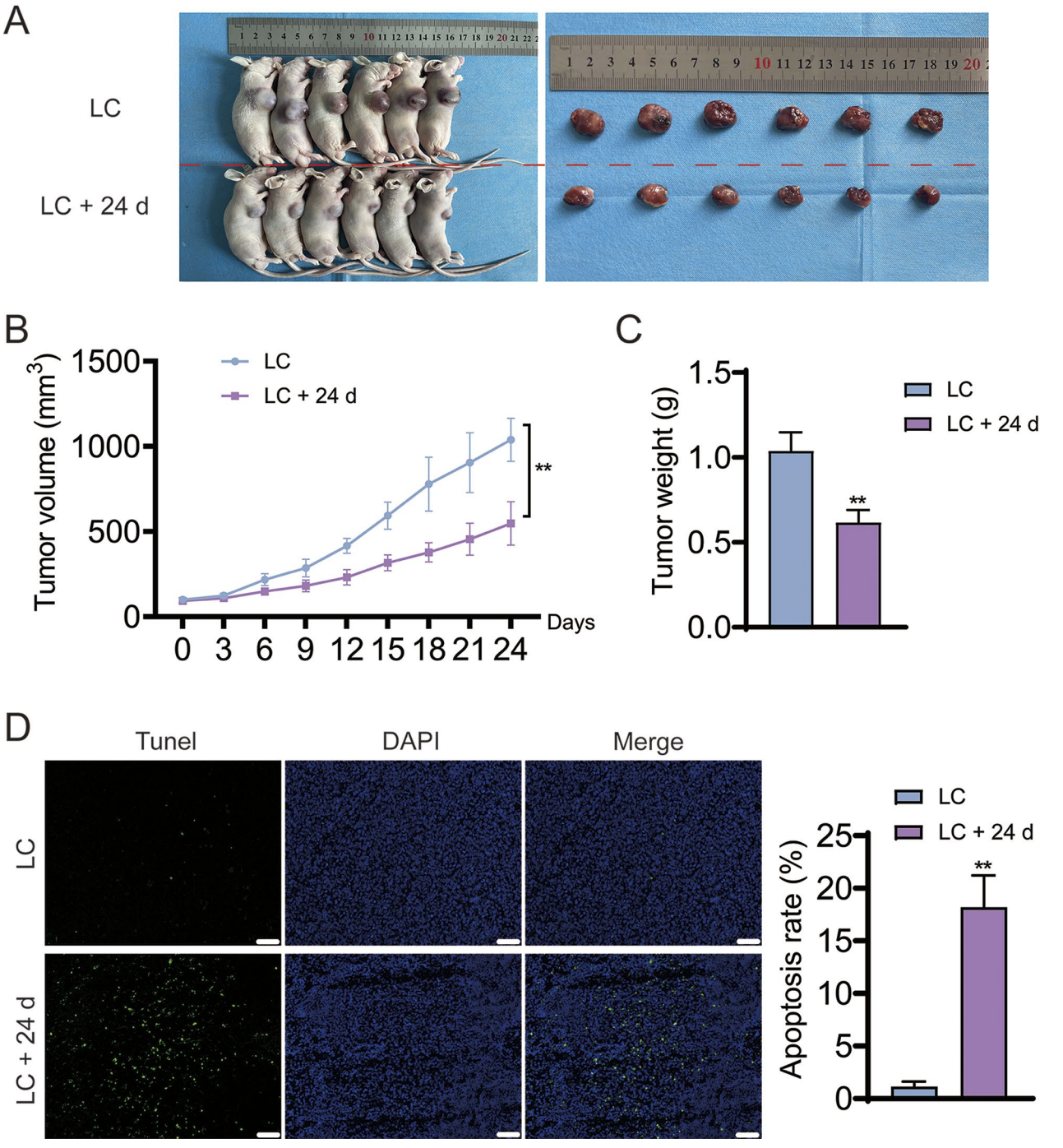

Fig. 7 OM-100 suppresses tumor growth and promotes apoptosis in liver xenograft tumor model mice. **A** Model mice and tumors. **B** Tumor volume in liver cancer xenograft mice. **C** Tumor weights of OM-100-treated and untreated liver cancer xenograft mice after 24 days. **D** Apoptosis levels in tumor tissues of OM-100-treated and untreated liver cancer xenograft mice; Scale bar = 50 μm. $^{**}P < 0.01$. Liver tumor xenograft model mice were treated with 1.066 mT of OM-100 at 100 kHz for 24 days

we performed TUNEL staining on the tumor tissues to assess the extent of apoptosis. Our findings revealed an increased rate of apoptosis in the tumors of OM-100-treated mice compared to untreated mice (Fig. 7D).

Discussion

Liver cancer is a key global health problem due to its increasing incidence, high mortality rate, and limited effective therapeutic options [16]. The inefficacy of conventional treatments underscores the need for innovative approaches that can offer therapeutic benefits with

minimized side effects [17]. In this context, our study explored the potential of OM-100, a device utilizing LFMF, as a promising avenue for liver cancer treatment. Our study successfully demonstrated the inhibitory effects of OM-100 on liver cancer cells and in a xenograft mouse model, providing substantial evidence for the potential of OM-100 application as a therapeutic approach for liver cancer. Preferential inhibition of liver cancer cell malignance by OM-100, along with the enhanced apoptosis and ROS production, highlights the specific anti-cancer effects of this treatment.

MF is viewed as a novel, patient-compatible approach for enhancing the efficacy of traditional cancer treatments while overcoming their limitations [18]. Studies have demonstrated the antitumor effects of LFMF in multiple cancers, including lung cancer [11], gastric cancer [13], neuroblastoma [19], and breast cancer [20]. LFMF effectively inhibited lung cancer cell proliferation and suppressed tumor growth [11]. Our findings demonstrated that OM-100 also effectively inhibited liver cell proliferation. Mechanically, LFMF exerts its effects on cells undergoing division, impairs mitotic spindle formation, as well as impairs organelles and biomolecules by impairing chromosome separation and cell division through mesoelectrophoretic effects during telophase/cytoplasmic division [21, 22]. Furthermore, the underlying mechanisms of LFMF is also involved in cellular processes interferences such as ion channels and signaling pathways, thereby apoptosis occurred [12, 23]. Beyond inhibiting cell proliferation, our study showed that OM-100 could effectively curtail the metastatic potential of liver cancer cells. Both migration and invasion assays confirmed the suppressive effect of OM-100 on the metastatic traits of the cancer cell lines. This dual action against proliferation and metastasis presents OM-100 as a comprehensive tool in combating liver cancer. Importantly, our study also provided evidence supporting the safety of OM-100. Both in vitro and in vivo tests revealed rarely adverse effects on normal liver cells or in vital organs, strengthening the case for its clinical applicability. The safety and nontoxicity of LFMF have been proposed in vitro and in vivo studies [24]. The safety of LFMF has also been emphasized in an earlier pilot study from advanced cancer, which shows no obvious toxicity and adverse side effects [25]. Some studies considered that tumor cells are attacked mainly results from that tumor-specific LFMF frequencies [26]. Under the tumor-specific frequencies, LFMF, shows to be nonthermal, and selectively affects dividing cells (uncontrolled growth cancer cells) while quiescent cells are left intact [24].

Moreover, the anti-proliferative effects of OM-100 is frequency-dependent, which exhibited as higher frequencies treatment with OM-100 has more profound anti-proliferative effects when the frequency. This is coincidence with a previous study conducted in lung cancer [27], which also demonstrates the frequency-dependent inhibitory effects of LFMF under 150 kHz. Different suitable frequences might divers from different cancer cell type. Kirson et al. propose that intermediate frequency (100–300 kHz) electric fields exhibit profoundly inhibitory effect on the growth rate of various tumors [24], further providing clarification for the better inhibitory role of OM-100 at 100 kHz in this study.

ROS production in tumor microenvironment plays a central role in the regulation and induction of apoptosis [28]. Interestingly, we noted a significant increase in ROS production following OM-100 treatment. ROS mediates many biological responses, such as cell proliferation, apoptosis, and gene expression [29]. High levels of ROS can induce oxidative stress, which in turn cause substantial harm to cellular components and initiate apoptosis [30, 31]. Modulating the intricate equilibrium of ROS generation and clearance in cancer cells is emerging as a viable therapeutic strategy, influencing a range of cellular mechanisms including apoptosis and cell dissemination [32, 33]. ROS is a key factor in inducing autophagy and cell apoptosis through mitochondrial connections in liver cancer cells [34]. At the molecular level, MF suppresses tumors by interfering with ROS levels [7]. Lazzarini et al. find that MF induced increase of ROS levels in the mitochondria of breast cancer cells [35]. Additionally, long-term exposure to MF in adherent cells effectively inhibits proliferation levels by arresting the cell population at the G2/M phase and increasing intracellular ROS, leading to morphological changes and cell death [36]. Hence, the elevated ROS production observed in this study might contribute to the anti-cancer effects of OM-100 by inducing oxidative damage within the liver cancer cells. Of course, there are many factors that cause cancer cell apoptosis by LFMF, and ROS may be only one of them. Reportedly, LFMF may inhibit cancer progression through regulating ferroptosis, angiogenesis, and immune response, as well as physiology and electrochemistry [37–39]. For example, Ren et al. demonstrated that LFMF suppresses lung cancer by inhibiting cellular iron metabolism, stabilizing P53 protein and activating p53-related pathway [37]. Nie et al. demonstrated that LFMF inhibits melanoma through regulating production of immune cells (like Treg and dendritic cells) and cytokines [38]. A recently study has also implied that LFMF can enhance the antitumor effect of anti-PD-1 immunotherapy on the growth of glioblastoma [40]. Although the anti-tumor mechanism of LFMF is complex, its anti-tumor effect is beyond doubt.

In our study, OM-100, a novel tumor treatment device, represents a promising new modality for the treatment of liver cancer without toxicity for non-cancerous cells. Nevertheless, there are some limitations. First, although

we emphasized the ROS action in the LFMF treatment on the liver cancer, other potential mechanism like immune, ferroptosis, and angiogenesis also should be conducted in future. Second, the clinical application of MF therapy in oncology is still limited, and only several studies mentioned [26, 41]. Hence, how to introduce MF therapy into clinical application is a major difficulty and emphasis in future research.

Conclusion

In summary, our study has shown that OM-100 represents a promising new modality for the treatment of liver cancer. This device effectively targets multiple hallmarks of cancer, including cell proliferation and metastatic potential, while maintaining a strong safety profile. These findings suggest that OM-100 and its application of LFMF could serve as a valuable adjunct to current liver cancer treatment options. Given these encouraging results, further investigations and larger clinical trials are warranted to establish OM-100 as a therapeutic strategy for liver cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12885-024-13121-9.

Supplementary Fig. S1 The distribution of the magnetic field in OM-100 device.

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Author contributions
Xin Zhang: Conceptualization, Data curation, Investigation, Writing-original draft, Validation. Lifa Huang: Conceptualization, Data curation, Software, Validation. Zhaoxian Yan: Data curation, Investigation, Investigation, Validation. Xinyan Yu: Data curation, Formal analysis, Methodology, Visualization, Validation. Rui Huang: Conceptualization, Methodology, Writing-review & editing. All authors have read and approved the final manuscript.

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Data availability
The data used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All experiments were approved by the Institutional Animal Care and Use Committee of Yangzhou University (202311014).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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