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Effects of Brucea Javanica Oil Emulsion Injection Combined with Lobaplatin on Proliferation, Migration, Invasion, and Apoptosis of Hepatocellular Carcinoma Cells Via Downregulation of HIF-1α

Guangfeng Duan *

Minimally Invasive Intervention Department, Affiliated Cancer Hospital and Institute of Guangzhou Medical University, Guangzhou, Guangdong, 510000, China

*** Corresponding author Email:** dgf_0306@163.com

Abstract: Tgcjhy{j%To explore the effects of Brucea javanica oil emulsion injection combined with lobaplatin on the biological behaviors of hepatocellular carcinoma cells through downregulation of HIF-1α. **Methods:** HepG-2 cells were treated with lobaplatin combined with Brucea javanica oil emulsion injection at different concentrations. A negative control group, a positive control group, and experimental groups 1–3 were established. Cell viability was assessed by the CCK-8 assay, while cell migration and invasion abilities were evaluated by wound healing and Transwell assays, respectively. Cell apoptosis was quantified by Annexin V-FITC/PI double staining followed by flow cytometry. **Results:** Brucea javanica oil emulsion injection combined with lobaplatin inhibited the migration and invasion of hepatocellular carcinoma cells by downregulating HIF-1α ($P < 0.005$), and the inhibitory effect became stronger with increasing concentrations of Brucea javanica oil emulsion injection. Brucea javanica oil also enhanced lobaplatin-induced apoptosis in HepG-2 cells. After 24 h of drug treatment, the apoptosis rates in the negative control group (0 μg/mL Brucea javanica oil, 0 μg/mL lobaplatin), positive control group (0 μg/mL Brucea javanica oil, 5 μg/mL lobaplatin), experimental group 1 (50 μg/mL Brucea javanica oil, 5 μg/mL lobaplatin), experimental group 2 (100 μg/mL Brucea javanica oil, 5 μg/mL lobaplatin), and experimental group 3 (200 μg/mL Brucea javanica oil, 5 μg/mL lobaplatin) were 8.29 ± 0.54%, 17.84 ± 1.24%, 21.61 ± 1.49%, 31.26 ± 3.54%, and 38.05 ± 0.25%, respectively, with statistically significant differences ($P < 0.005$). **Conclusion:** Brucea javanica oil emulsion injection can enhance the inhibitory effects of lobaplatin on the proliferation, migration, and invasion of HepG-2 cells by downregulating HIF-1α, promote apoptosis, and thereby increase the sensitivity of HepG-2 cells to lobaplatin.

Keywords: Brucea Javanica Oil; Lobaplatin; Hepatocellular Carcinoma; Proliferation; Invasion; Migration; Apoptosis.

1. Introduction

Hepatocellular carcinoma (HCC), the major histological subtype of primary liver cancer, is characterized by high malignancy and strong invasiveness [1]. Due to the lack of typical symptoms in the early stage and rapid disease progression, a large proportion of patients are diagnosed at an advanced stage, leaving relatively limited therapeutic options and resulting in an overall low 5-year survival rate; among them, the median survival of patients with unresectable liver cancer is only approximately 6–20 months [2]. Surgical resection remains an effective treatment, but its indications are stringent, requiring adequate residual liver function and the absence of extrahepatic metastasis. Unfortunately, most patients with liver cancer present at an advanced stage, with a high tumor burden or decompensated liver function, leading to a low resection rate [3,4]. At present, it is widely recognized that hepatocellular carcinoma responds poorly to systemic chemotherapy and is associated with an unfavorable overall prognosis. In this context, transarterial chemoembolization (TACE), as a locoregional therapy, has been recognized as one of the important treatment options for unresectable liver cancer by selectively obstructing the tumor-feeding arteries and increasing the local concentration of chemotherapeutic drugs within the tumor [4–6]. The rational combination of chemotherapeutic agents is one of the key factors determining the efficacy of TACE and patient prognosis. Because patients with liver cancer often have impaired liver function, monotherapy not only provides limited efficacy but may also aggravate liver injury due to toxic side effects. Combination therapy, through multi-target synergistic effects, can enhance antitumor activity while reducing the toxicity of single agents. Our previous study demonstrated that a TACE regimen containing lobaplatin has definite efficacy against liver cancer, can significantly prolong survival, and shows good safety, suggesting that it may serve as a fundamental drug choice for TACE in unresectable liver cancer [7]. In recent years, accumulating evidence has indicated that traditional Chinese medicine can effectively improve survival benefits in cancer patients; however, its role is mostly limited to adjuvant treatment or purely palliative intervention in patients with advanced disease [8,9]. Brucea javanica oil emulsion injection is a natural oil emulsion preparation extracted from the dried ripe fruits of Brucea javanica [10,11]. Studies have shown that it possesses broad-spectrum antitumor activity and is currently widely used as an adjuvant antitumor drug in clinical practice. However, as an intravenous emulsion, its stability and in vivo distribution characteristics may affect its efficacy as a single agent. In addition, clinical practice has shown that it has a certain degree of vascular irritation, and its antitumor effect is relatively mild when used alone; therefore, it is often combined with other antitumor drugs or interventional approaches to enhance efficacy [12–14]. Based on our preliminary literature review, no report has yet described the

application of lobaplatin combined with Brucea javanica oil emulsion injection in the treatment of hepatocellular carcinoma. Therefore, this study aims to investigate, through in vitro experiments, the effect of Brucea javanica oil emulsion injection on the action of lobaplatin in hepatocellular carcinoma cells, and further explore the feasibility of their combined use, so as to provide experimental evidence and a theoretical basis for developing new therapeutic strategies for hepatocellular carcinoma.

2. Materials and Methods

2.1. Materials

2.1.1. Cell Line

Human hepatocellular carcinoma cell line HepG-2 was purchased from the Shanghai Institute of Life Sciences.

2.1.2. Drugs

Brucea javanica oil emulsion injection (Dalian Huali Jingang Pharmaceutical Co., Ltd., China; specification: Brucea javanica oil concentration, 3.74 mg/mL) and lobaplatin (Hainan Changan International Pharmaceutical Co., Ltd., China; 50 mg/vial) were used in this study.

2.1.3. Main Reagents and Instruments

The main reagents and instruments used in this study were as follows: high-glucose EMEM medium (Gibco, USA), fetal bovine serum (FBS, Hyclone, USA), MEM non-essential amino acid solution (Double Helix Biology, Shanghai, China), crystal violet solution (Amresco, USA), RIPA lysis buffer and pre-stained protein marker (Solarbio, Shanghai, China), penicillin-streptomycin solution and 0.25% trypsin-EDTA (Beyotime, Shanghai, China), Annexin V-FITC/PI apoptosis detection kit and CCK-8 cell proliferation and cytotoxicity assay kit (KeyGEN Biotech, Jiangsu, China). The main instruments included a flow cytometer (Essen, USA) and an inverted fluorescence microscope (Olympus, Japan).

2.2. Methods

2.2.1. Cell Culture

HepG-2 cells were cultured in high-glucose EMEM medium supplemented with 10% fetal bovine serum (FBS) in a humidified incubator at 37°C with 5% CO_2. The medium was changed regularly, and the cell status was monitored. When the confluence reached 80%–90%, cells were passaged using 0.25% trypsin-EDTA. Cells in the logarithmic growth phase with good condition were harvested for subsequent experiments.

For the CCK-8 assay, the digested cells were prepared into a single-cell suspension, counted, and seeded into 96-well plates at a density of 1×10^5 cells/mL, 100 μL per well. After 24 h of attachment, the medium was removed, and cells were treated according to the following groups: negative control group (0 μg/mL Brucea javanica oil, 0 μg/mL lobaplatin), positive control group (0 μg/mL Brucea javanica oil, 5 μg/mL lobaplatin), and experimental groups 1–3 (50, 100, and 200 μg/mL Brucea javanica oil combined with 5 μg/mL lobaplatin). Each group had five replicate wells. At 0, 24, and 48 h, 200 μL of CCK-8 working solution was added to each well, followed by incubation for 3 h. The optical density (OD) value was measured at 450 nm using a microplate reader. Cell viability (%) was calculated as follows: OD value of experimental well/OD value of control well × 100%.

2.2.2. Wound Healing Assay

Cell grouping and drug treatment were the same as described in Section 1.2.2. Cells were seeded in six-well plates at a density of 5×10^5 cells per well and incubated for 24 h. When the cell confluence reached 90%–100% under the microscope, the medium was removed, and medium containing different concentrations of Brucea javanica oil and lobaplatin was added to each group. After further incubation for 24 h, a scratch was made. The wells were washed and then replenished with FBS-free medium. Images were captured under an inverted microscope (40×) immediately before incubation (0 h) and after 48 h of incubation. The scratch width was measured to calculate the migration rate. Each experiment was independently repeated three times.

Cell migration rate (%) = (scratch width at 0 h − scratch width at 48 h) / scratch width at 0 h × 100%.

2.2.3. Transwell Assay

Cell grouping and drug treatment were the same as described above. After HepG-2 cells were treated with drugs for 24 h, they were digested and counted, and the cell concentration was adjusted to 5×10^5 cells/mL using serum-free medium. The Transwell upper chamber was precoated the day before with 50 μL Matrigel diluted at 1:8. The following day, 200 μL of cell suspension was added to the upper chamber, and 500 μL of complete medium containing serum was added to the lower chamber. After 24 h of incubation, the medium was removed, and residual fluid was gently wiped off with a cotton swab. Then, 800 μL of 4% paraformaldehyde was added for fixation for 60 min. After PBS washing, cells were stained with 0.1% crystal violet for 10 min, rinsed with running water for 0.5 h, and air-dried with cotton swabs. Invasive cells were observed and photographed under an inverted phase-contrast microscope. Each group was repeated three times.

2.2.4. Flow Cytometry

Cell grouping and drug treatment were the same as described above. HepG-2 cells were seeded in six-well plates at a density of 5×10^5 cells per well (2 mL per well) and collected after 24 h of culture. The medium was removed, and cells were washed twice with pre-cooled PBS. Then, 500 μL prewarmed trypsin without EDTA was added to each well until the cells detached completely. Digestion was terminated with complete medium, and cells were gently resuspended and transferred into centrifuge tubes. After centrifugation at 1000 r/min for 5 min, the supernatant was discarded, and the cells were resuspended in 1 mL pre-cooled PBS and counted. A suspension containing 5×10^5 cells was centrifuged again, and the supernatant was discarded. Then, 100 μL 1× binding buffer was added to resuspend the cells, which were transferred into sample tubes. Subsequently, 5 μL Annexin V-FITC and 5 μL PI were added in the dark, mixed gently, and incubated at room temperature for 15 min in the dark. Then, 400 μL binding buffer was added and mixed well. The samples were analyzed by flow cytometry within 1 h. Annexin V-FITC emits green fluorescence, and PI emits red fluorescence.

2.3. Statistical Analysis

All experiments were repeated three times. Data were analyzed using GraphPad Prism 8 software. Experimental data are expressed as mean ± standard deviation (SD). Comparisons between two groups were performed using an unpaired independent-samples t-test. For comparisons among more than two groups, one-way analysis of variance (ANOVA) was first performed, followed by Bonferroni post hoc multiple comparison tests to assess pairwise differences.

A value of *P < 0.05 was considered statistically significant.

3. Results

3.1. Cell Viability Assay

The CCK-8 assay showed that, compared with the negative control group, the cell viability of HepG-2 cells was significantly decreased in the lobaplatin group and in all Brucea javanica oil emulsion plus lobaplatin groups ($P < 0.05$). In addition, cell viability in the combination groups was significantly lower than that in the lobaplatin-alone group ($P < 0.05$). When the concentration of lobaplatin was fixed at 5 μg/mL, cell viability decreased in a concentration-dependent manner with increasing concentrations of Brucea javanica oil emulsion injection (50, 100, and 200 μg/mL) ($P < 0.05$). These findings suggest that Brucea javanica oil emulsion injection may enhance the inhibitory effect of lobaplatin on hepatocellular carcinoma cell proliferation by suppressing HIF-1α expression (Figure 1).

3.2. Comparison of Cell Migration Among Groups

The wound healing assay showed that the migration rates of HepG-2 cells in the lobaplatin group and in all Brucea javanica oil emulsion plus lobaplatin groups were significantly lower than those in the negative control group ($P < 0.05$). The migration rates in the combination groups were also significantly lower than those in the lobaplatin-alone group ($P < 0.05$). With the concentration of lobaplatin fixed, the cell migration rate decreased in a concentration-dependent manner as the concentration of Brucea javanica oil emulsion injection increased (50, 100, and 200 μg/mL) ($P < 0.05$). Meanwhile, HIF-1α protein expression in the combination groups was significantly downregulated compared with that in the lobaplatin-alone group ($P < 0.05$), suggesting that Brucea javanica oil emulsion injection combined with lobaplatin may synergistically inhibit the migration ability of hepatocellular carcinoma cells by downregulating HIF-1α expression (Figure 2, Table 1).

3.3. Comparison of Cell Invasiveness Among Groups

The Transwell assay showed that, compared with the negative control group, the number of invasive HepG-2 cells was significantly reduced in the lobaplatin group and in all Brucea javanica oil emulsion plus lobaplatin groups ($P < 0.05$). The number of invasive cells in the combination groups was also significantly lower than that in the lobaplatin-alone group ($P < 0.05$). With the concentration of lobaplatin fixed, the number of invasive cells further decreased in a concentration-dependent manner as the concentration of Brucea javanica oil emulsion injection increased (50, 100, and 200 μg/mL) ($P < 0.05$). Together with the downregulation of HIF-1α expression, these results suggest that Brucea javanica oil emulsion injection may enhance the inhibitory effect of lobaplatin on the invasiveness of hepatocellular carcinoma cells by suppressing the HIF-1α signaling pathway, and this effect appears to be concentration-dependent (Figure 3, Table 1).

3.4. Cell Apoptosis Assay

Flow cytometry analysis showed that, after 24 h of drug treatment, the apoptosis rates of HepG-2 cells in the negative control group, lobaplatin group, and experimental groups 1–3 were 8.29 ± 0.54%, 17.84 ± 1.24%, 21.61 ± 1.49%, 31.26 ± 3.54%, and 38.05 ± 0.25%, respectively. The apoptosis rates in the lobaplatin group and in the combination groups were significantly higher than those in the negative control group ($P < 0.05$). The apoptosis rate in the combination groups was also significantly higher than that in the lobaplatin-alone group ($P < 0.05$), and pairwise comparisons among groups showed statistically significant differences ($P < 0.001$). With the concentration of lobaplatin fixed, the apoptosis rate increased in a concentration-dependent manner as the concentration of Brucea javanica oil emulsion injection increased ($P < 0.001$). Together with the downregulation of HIF-1α expression, these findings suggest that Brucea javanica oil emulsion injection may synergistically enhance the pro-apoptotic effect of lobaplatin on hepatocellular carcinoma cells by inhibiting the HIF-1α signaling pathway.

4. Discussion

Transarterial chemoembolization (TACE), by combining embolization of the tumor-feeding arteries with local sustained-release chemotherapy, has become a first-line locoregional treatment option for unresectable liver cancer. The design of the chemotherapeutic regimen used in TACE directly affects therapeutic efficacy, among which platinum-based agents have always played an important role. As a third-generation platinum derivative, lobaplatin is a non-diastereomeric complex of 1,2-diaminocyclobutane-lactic acid platinum. It has excellent chemical stability and broad-spectrum antitumor activity, and has shown confirmed efficacy in the first-line treatment of malignant tumors such as non-small cell lung cancer and ovarian cancer, with increasingly widespread clinical use [15,16]. Studies have shown that lobaplatin lacks cross-resistance with cisplatin, which may be related to its unique DNA alkylation pattern—by forming specific DNA adducts, it can effectively block tumor cell proliferation. Therefore, in cisplatin-resistant tumor cells, lobaplatin can still exhibit strong cytotoxic and antitumor activity. In addition, lobaplatin shows higher in vitro sensitivity in hepatocellular carcinoma than cisplatin, and its optimized molecular structure confers stronger anticancer activity than conventional platinum agents. In terms of safety, lobaplatin has significantly lower nephrotoxicity than cisplatin and carboplatin, and does not cause obvious neurotoxicity, with good patient tolerance [17]. In addition to the above characteristics, lobaplatin also has broad-spectrum antitumor activity, good aqueous stability, and high solubility. Its gastrointestinal toxicity and myelosuppression are also lower than those of most conventional platinum drugs, making it well tolerated and highly valuable for clinical application in TACE for hepatocellular carcinoma [18]. The amino acid-derived structure of lobaplatin may also confer higher tumor cell selectivity, which is beneficial for precise targeting. However, repeated TACE treatment often leads to the development of tumor resistance, resulting in TACE resistance and becoming a major bottleneck limiting long-term efficacy [19,20]. Given the objective existence of TACE resistance, combination therapy has become an important strategy for prolonging the efficacy of TACE. Traditional Chinese medicine, as a representative intervention of Chinese medicine, has shown unique potential in cancer combination therapy due to its natural advantages of multiple components, multiple targets, low toxicity, and diverse sources, and has attracted increasing research attention [7,8]. Screening antitumor active

components from traditional Chinese medicine and clarifying the pharmacological mechanisms by which they synergistically enhance existing anticancer therapies are key links in optimizing clinical treatment strategies and improving long-term patient survival, and are therefore of considerable research value.

Brucea javanica oil emulsion injection is a self-developed antitumor phytopharmaceutical extracted from the dried ripe fruits of Brucea javanica, a traditional Chinese medicinal herb. Its main active components include oleic acid, linoleic acid, and various quassinoid compounds. It has been approved as a national Class II new drug and is widely used in clinical practice, with extensive experience accumulated particularly in the treatment of liver cancer, lung cancer, and brain metastases [21]. Studies have shown that Brucea javanica oil emulsion injection exerts antitumor effects through multiple pathways and targets in various tumors, including inhibition of cell proliferation, migration, and invasion, induction of apoptosis, blockade of tumor angiogenesis, and regulation of the immune status of the tumor microenvironment. In vitro studies have shown that it can affect tumor cell cycle distribution, arresting cells in the G0/G1 phase or S phase, thereby inhibiting DNA replication and cell division, while also modulating the secretion profile of key cytokines such as IL-6, TNF-α, IL-1β, and IL-10, thereby improving immune function. In recent years, long non-coding RNAs (lncRNAs) have been recognized as important regulatory factors in the development of hepatocellular carcinoma. Among them, highly upregulated in liver cancer (HULC), as an oncogenic lncRNA, is significantly upregulated in HCC tissues, whereas Brucea javanica oil emulsion injection can effectively reduce HULC expression, suggesting that it may suppress the malignant phenotype of HCC cells by regulating HULC [22,23]. In addition, Brucea javanica oil emulsion injection has shown unique advantages in combination therapy, as it can increase tumor cell sensitivity to chemotherapeutic and molecular targeted agents and has the potential to reverse chemoresistance, while further improving overall therapeutic effects by modulating host immune status [24]. In clinical treatment of liver cancer, some researchers have used Brucea javanica oil emulsion injection as an adjuvant drug for TACE via hepatic arterial infusion, and preliminary results have shown improved short-term efficacy without significantly increasing adverse reactions such as liver function damage, indicating good safety and promising prospects for combined application [25]. However, whether Brucea javanica oil emulsion injection can produce synergistic effects when combined with chemotherapeutic agents in liver cancer, particularly with third-generation platinum drugs such as lobaplatin, remains unsupported by systematic experimental and clinical evidence. Based on this, the present study used a hepatocellular carcinoma cell line as an in vitro model to preliminarily explore the synergistic antitumor effect of Brucea javanica oil emulsion injection combined with lobaplatin, with particular attention to its regulation of the HIF-1α signaling pathway, in order to provide experimental evidence and a theoretical basis for optimizing TACE combination regimens in hepatocellular carcinoma [26].

Based on the above background, the present study used the human hepatocellular carcinoma cell line HepG-2 to preliminarily explore the synergistic antitumor effect of Brucea javanica oil emulsion injection combined with lobaplatin. The CCK-8 assay showed that Brucea javanica oil emulsion injection could effectively enhance the inhibitory effect of lobaplatin on the proliferation of HepG-2 cells; the wound healing assay and Transwell assay confirmed that Brucea javanica oil emulsion injection could enhance the inhibitory effect of lobaplatin on the migration and invasion of HepG-2 cells; and flow cytometry revealed that Brucea javanica oil emulsion injection significantly enhanced lobaplatin-induced apoptosis in HepG-2 cells. Meanwhile, Western blot results showed that combined treatment significantly downregulated HIF-1α protein expression, suggesting that the synergistic effect may be associated with inhibition of the HIF-1α pathway. These findings are consistent with previous reports and, in an in vitro model, provide initial evidence that Brucea javanica oil emulsion injection can enhance the triple antitumor effects of lobaplatin on HCC cells, namely inhibition of proliferation, blockade of metastasis, and induction of apoptosis. This provides experimental evidence for optimizing TACE combination regimens and also offers experimental support for clinical treatment strategies and drug regimens in hepatocellular carcinoma.

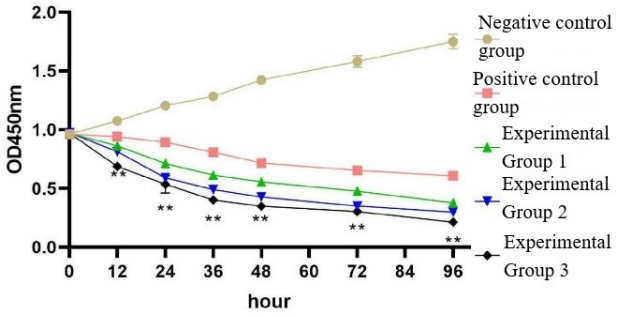


Figure 1. Growth and proliferation curves of HepG2 cells over time in different drug concentration groups.

Table 1. Cell apoptosis rate, migration rate, and number of invasive cells in each group after 24 h of drug treatment ($\bar{x} \pm s$).

Group	Cell apoptosis rate (%)	Cell migration rate (%)	Number of invasive cells (pcs)
Negative control group	8.29±0.54	49.85±0.87	106±5.86
Positive control group	17.84±1.24	41.27±1.99	61±3.61
Experimental group 1	21.61±1.49	32.07±0.78	39.67±1.20
Experimental group 2	31.26±3.54	21.87±0.51	24.67±0.33
Experimental group 3	38.05±0.25	15.51±0.69	16.33±0.88
F	44.31	284.6	129.3
P	<0.0001	<0.0001	<0.0001

Note: Pcs (pieces) is a commonly used unit for counting, indicating the number of cells in the experiment, specifically the number of invasive cells that successfully passed through the membrane structure.

Nevertheless, this study has some limitations. First, the synergistic antitumor effect of Brucea javanica oil emulsion injection on lobaplatin was only demonstrated in vitro, and only one hepatocellular carcinoma cell line was used, with only one protein being examined, making the experimental model relatively limited. In addition, the study of the underlying mechanisms was not sufficiently in depth; the specific signaling pathways and key targets involved were not further clarified in this study. Further investigation through in vivo experiments and validation in multiple cell lines is still needed.

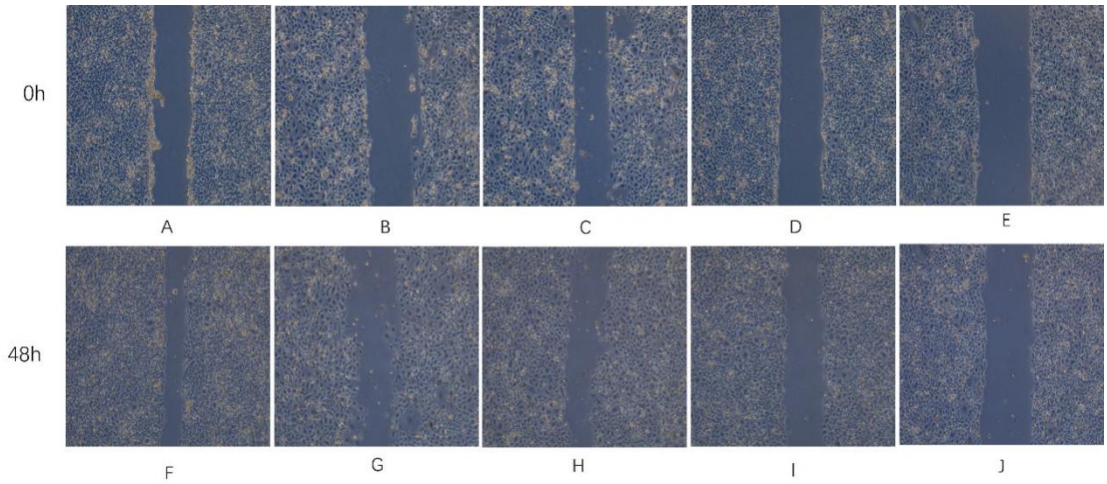


Figure 2. Wound healing assay showing the migration ability of HepG2 cells in each group at 0 h (before incubation) and 48 h (after 48 h of incubation) (40×).

Note: A: scratch width of the negative control group at 0 h; B: scratch width of the positive control group at 0 h; C: scratch width of experimental group 1 at 0 h; D: scratch width of experimental group 2 at 0 h; E: scratch width of experimental group 3 at 0 h; F: scratch width of the negative control group at 48 h; G: scratch width of the positive control group at 48 h; H: scratch width of experimental group 1 at 48 h; I: scratch width of experimental group 2 at 48 h; J: scratch width of experimental group 3 at 48 h.

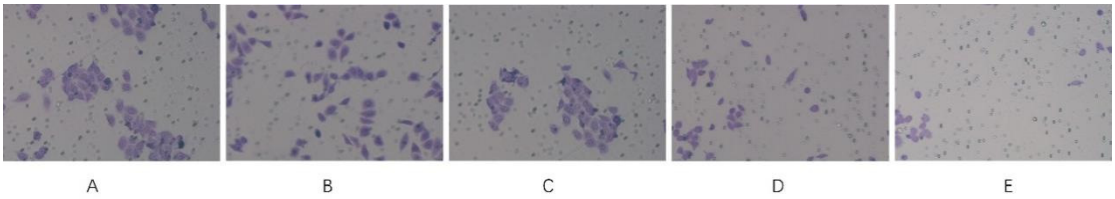


Figure 3. Transwell assay showing the invasive ability of HepG2 cells in each group (crystal violet, 100×).

Note: A: negative control group; B: lobaplatin positive control group; C: experimental group 1; D: experimental group 2; E: experimental group 3.

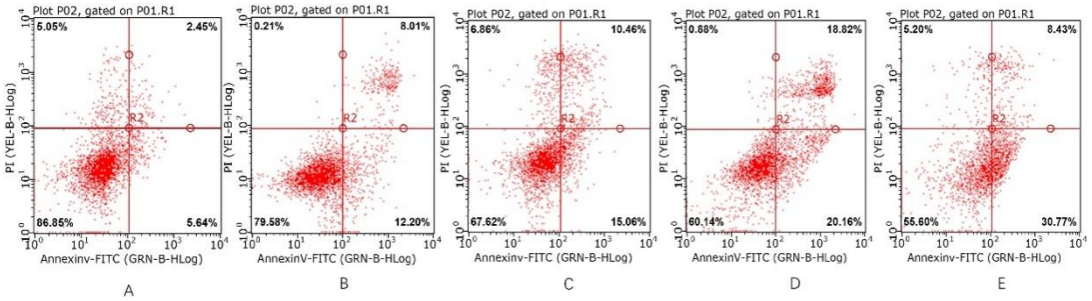


Figure 4. Flow cytometric analysis of apoptosis in HepG2 cells in each group

Note: A: negative control group; B: lobaplatin positive control group; C: experimental group 1; D: experimental group 2; E: experimental group 3.

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