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Original Research Article

Effectiveness of nab-paclitaxel versus traditional paclitaxels in the treatment of ovarian cancer

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Abstract

Purpose: *To evaluate the effect of four taxane drugs, namely, paclitaxel, docetaxel, paclitaxel liposomes (Lipusu), and nab-paclitaxel (Keaili) on ovarian cancer cells both in vivo and in vitro.*
Methods: *BALB/c-nu/nu female mice were used to develop mouse xenograft models. The mice were randomized to 5 groups (4 in each group), namely, control (PBS) group, paclitaxel group, docetaxel group, liposomal paclitaxel group and nab-paclitaxel group. The effect of four taxane drugs were determined via cell proliferation and toxicity tests. Mouse xenograft models were employed to assess the efficacy of four taxane drugs in inhibiting tumor growth.*
Results: *Nab-paclitaxel has a significant ovarian growth-reducing effect in vitro. In vivo, no significant differences were observed in tumor volume among the four groups ($p < 0.05$). Nab-paclitaxel produced the lowest animal toxicity when compared with other three drugs as the mice in nab-paclitaxel treatment group showed no significant alterations in body weight ($p < 0.05$). Hematoxylin and eosin (H & E) staining revealed the lowest degree of liver tissue damage in mice treated with nab-paclitaxel compared to mice administered the other three paclitaxels.*
Conclusion: *Nab-paclitaxel is more effective in mice with ovarian cancer than traditional paclitaxels. Thus, it promises to offer a viable alternative as first-line chemotherapy for epithelial ovarian cancer in humans, as it has low systemic toxicity and fewer hypersensitivity reactions. However, further investigations, including clinical trials in humans, are required.*

Keywords: *Paclitaxel, Docetaxel, Paclitaxel liposome, Nab-paclitaxel, Epithelial ovarian cancer*

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INTRODUCTION

Epithelial ovarian cancer (EOC) is the eighth leading cause of cancer-related death among women [1], and advanced ECO is associated with poor 5-year survival [2]. It is clinically managed by cytoreduction and subsequent adjuvant chemotherapy. Paclitaxel or docetaxel (in combination with cisplatin) has been

investigated as a potential first-line therapy for ovarian cancer [3].

Paclitaxel is commonly utilized in the clinical management of solid tumors [4]. Nonetheless, the solvent used, viz: polyoxyethylated castor oil (Kolliphor® EL, BASF SE, Ludwigshafen, Germany), has been linked to severe hypersensitivity reactions [5-7]. To minimize the risk of such reactions with solvent-based paclitaxel, patients are typically given corticosteroids and antihistamines as a pre-treatment measure [4]. Research indicates that Kolliphor EL traps paclitaxel in solvent micelles, thereby limiting its therapeutical potential [7-9].

Docetaxel is a semi-synthetic paclitaxel. Despite their common use in cancer treatment, there are distinct pharmacological and mechanistic differences between docetaxel and paclitaxel. Research indicates that docetaxel exhibits a higher affinity for β-tubulin than paclitaxel. Furthermore, docetaxel is more effective than paclitaxel in inducing bcl-2 phosphorylation [10]. Similar to paclitaxel, docetaxel promotes microtubule assembly and stabilizes polymers to protect against depolymerization, thereby inducing cell cycle arrest and cell death. However, docetaxel is known for its poor solubility and can cause a range of adverse effects [11]. To solve these problems, several alternative formulations, including liposomes, microspheres, nanoparticles, and polymeric micelles, have been investigated for the solubilization of paclitaxel. For example, China has developed its own paclitaxel formulation, Lipusu®. This formulation involves solubilizing paclitaxel in liposomes with a diameter of 400 nm, which are created using a combination of lecithin and cholesterol in 87/13 weight (%) ratio [12]. Liposomal paclitaxel, which has been approved in China as an EOC first-line chemotherapy option, retains the growth-inhibitory activity of free drugs while having reduced toxicity.

In 2005, the introduction of nab-paclitaxel (Abraxane) reduced Taxol's paclitaxel monopoly. Paclitaxel molecules in Abraxane non-covalently bind to albumin molecules [13], creating a primary paclitaxel-albumin aggregate measuring 4 – 14 nm [14,15]. Abraxane (nab-paclitaxel) is a member of the nano-chemotherapeutic drug family. In 2018, China developed its own version of Abraxane named Keaili.

There have been some undocumented observational advantages of nab-paclitaxel in clinical practice, but it is not first-line chemotherapy. This study was designed to evaluate the effectiveness of four taxane drugs, namely, paclitaxel, docetaxel, paclitaxel liposomes (Lipusu®), and nab-paclitaxel (Keaili®), on ovarian cancer cells both *in vivo* and *in vitro*.

EXPERIMENTAL

Reagents

Paclitaxel was obtained from Haicou Medicine Co. Ltd (Haikou, China). The source of docetaxel used in this study was Hengrui Medicine Co. Ltd (Jiangsu, China). Paclitaxel liposomes (Lipusu®) were obtained from Ivye Medicine Co Ltd (Nanjing, China). Nab-paclitaxel (Keaili®) was from Shijiazhuang Medicine Co. Ltd (Shijiazhuang, China). To conduct the *in vitro* experiments, the four drugs were dissolved in dimethyl sulfoxide (DMSO) at a concentration of 1 mM and were diluted with Dulbecco's modified Eagle's medium (DMEM) to achieve the desired concentration. The study was executed in compliance with ARRIVE 2.0 guidelines [16].

Cell culture

The SKOV3 human ovarian cancer cell line and the LO2 human normal liver cell line were procured from the American Type Culture Collection and cultured in DMEM obtained from Gibco, USA. The medium was added with 10 % FBS from Gibco, USA, 100 U/mL penicillin, and 100 µg/mL streptomycin (penicillin-streptomycin-glutamine, Gibco, USA). The cells were maintained at a temperature of 37 °C and in a humidified environment with 5 % CO_2 using a Forma Steri-Cycle CO_2 incubator (Thermo Fisher Scientific, Massachusetts, USA).

Cell proliferation and toxicity test

The cell counting kit-8 (CCK-8) assay was conducted to determine the proliferation of SKOV3 ovarian cancer cells and LO2 normal liver cells treated with four taxane drugs: paclitaxel, docetaxel, liposomal paclitaxel, and nab-paclitaxel. SKOV3 and LO2 cells were treated with different concentrations of paclitaxel for varying durations, and cell viability was measured. Specifically, cells were seeded in a 96-well plate at a density of 3×10^3 cells per well and allowed to attach for 24 h. Afterward, cells were subject to 200 µL of culture medium containing paclitaxel at concentrations ranging from 0.1 to 100 nmol/L for 24, 48, 72, and 96 h. Following each incubation period, the old culture medium was aspirated, and 100 µL of fresh medium containing 10 µL of CCK-8 reagent was introduced into each well. The cells were then

incubated for an additional 2 h. Absorbance was determined at 450 nm using a microplate reader (Varioskan Flash, Thermo, USA).

Mouse xenograft model

All experiments involving animals were conducted following the "Guidelines and suggestions for the care and use of laboratory animals" [17,18]. Ethical approval for animal studies was obtained from the Ministry of Science and Technology of the People's Republic of China, in 2006 (approval no. 2018-033). To create SKOV3 xenograft models, female BALB/c-nu/nu mice, aged between 4 to 6 weeks and weighing 16 to 20 g, were procured from Beijing Vital River Laboratory Animal Technology Co. Ltd (Beijing, China).

The mice were kept in a germ-free environment and given standard rodent chow and sterile water *ad libitum*. The tumor cells were suspended in 200 µL of phosphate-buffered saline (PBS) and subcutaneously injected into the right flanks of the nude mice at a dose of 5×10^6 cells. Once the tumors reached a mean diameter of 6 mm, the mice were randomized to 5 groups (4 in each group), namely, control (PBS) group, paclitaxel group (5 mg/kg), docetaxel group (5 mg/kg), liposomal paclitaxel group (5 mg/kg) and nab-paclitaxel group (5 mg/kg) [17]. The treatments were administered by intraperitoneal injection on alternating days. During the course of the experiment, the mice were regularly weighed, and their tumors were measured using a caliper every 3 days. tumor volume (V) was calculated as shown in Eq 1.

$V = D(d^2)/2\ mm^3$ …… (1)

where D is larger diameter and d is smaller diameter

At the end of 40-day treatment period, the mice were humanely euthanized by cervical dislocation while under anesthesia (intraperitoneal injection of 3 mg/100 g chloral hydrate (Lierkang, China). The tumors that were transferred were removed, weighed, and stored either at -80 °C or in 4 % paraformaldehyde.

TUNEL staining

An *in situ* cell death detection kit (Fluorescein; Roche, Nutley, NJ, USA) was utilized to perform the TUNEL assay based on Roche's method. Cell slides were prepared by deparaffinization and rehydration, followed by incubation with 20 µg/mL proteinase K for 15 min. Following PBS rinsing, the cells were subjected to an incubation step with a TUNEL reaction mixture containing TdT and fluorescein-dUTP. Subsequently, cells were washed, and fluorescence microscopy was used to visualize the label that was incorporated at the DNA damage sites.

Immunohistochemical staining

Paraffin-embedded tumors were cut into longitudinal sections (5 µm) and placed in an oven at 60 °C for 24 h. Deparaffinization was carried out with xylene, followed by hydration with a gradient of ethanol (100 - 70 %). Heat-induced antigen retrieval was performed in citrate buffer in an MLS-3750 autoclave (Sanyo, Japan) for 2 min. The slides were first incubated with 3 % H_2O_2 for 10 min, followed by rinsing with water.

They were then incubated overnight at 4 °C with a primary antibody (Ki-67 (1:100)). Thereafter, the slides were washed and incubated with secondary antibodies (Beijing Zhongshan Golden Bridge Biotechnology Co., Ltd., Beijing, China) for 30 min and then stained with 3,3'-diaminobenzidine (DAB) and hematoxylin. The Axion Observer A1 microscope (Zeiss, Germany) was used to examine and photograph the slides.

Hematoxylin and eosin (H&E) staining

The liver samples were subjected to H&E staining according to standard protocols. The process involved deparaffinizing and rehydrating longitudinal sections that were 5-µm thick. The sections were then stained with hematoxylin solution for 5 min. Following the previous step, the tissue sections were washed with 1 % acid ethanol (1 % HCl in 70 % ethanol) and distilled water and were subsequently stained with eosin solution for 8 min. Following dehydration using graded alcohol and clearance in xylene, the slides were mounted and observed under a fluorescence microscope (Zeiss, Germany).

Statistics analysis

Statistical Package for the Social Sciences (SPSS) 26.0 was used for statistical analysis. Differences between groups were compared using multivariate repeated measures ANOVA. Normal distribution of the grouped data was confirmed and covariance matrix full football shape test was employed to test for the intra-subject effect. If the test value did not meet this requirement, a multivariable test was used instead. Intra-group comparison was performed using the LSD method, and differences with $p < 0.05$ were considered statistically significant.

RESULTS

All four taxane drugs inhibit proliferation of SKOV3

Findings indicated that all four drugs significantly reduced the growth of SKOV3 cells in a concentration-dependent manner (Figure 1 A). When the concentration was less than 10 nM, nab-paclitaxel was less lethal to tumor cells than other three taxane drugs. At concentrations 10 and 20 nM, the differences between nab-paclitaxel and paclitaxel as well as docetaxel were not significant ($p > 0.05$, Figure 1 B). At 1 and 5 nM, the cell-lethality value of nab-paclitaxel group was smaller than that of the other three groups ($p < 0.05$). As the concentration increased to 10 and 20 nM, the lethality of nab-paclitaxel group was not significantly lower than that of paclitaxel and docetaxel groups ($p > 0.05$).

Nonlinear regression analysis was used to calculate the half-maximal inhibitory concentration (IC_{50}) (Table 1). The IC_{50} results showed that nab-paclitaxel had a slightly higher IC_{50} than the other three drugs, while such disparity progressively disappeared over time. At 96 h, no significant difference was observed between the IC_{50} of nab-paclitaxel and those of paclitaxel and docetaxel. These results show that nab-paclitaxel also has a significant ovarian cancer-inhibiting effect *in vitro*.

Table 1: The IC_{50} of four taxane drugs in ovarian cancer cell line (SKOV3)

IC_{50} (nM)	24 h	48 h	72 h	96 h
Paclitaxel	1482	17.84	3.681	3.264
Docetaxel	1011	22.44	3.769	3.063
Nab-paclitaxel	543.7	20.15	5.326	3.908
Liposomal paclitaxel	1205	5.521	1.8	0.266

All four taxane drugs inhibited the proliferation of LO2

The results showed that all four drugs appreciably suppressed the proliferation of LO2 cells in a dose-dependent manner (Figure 2 A), but nab-paclitaxel showed the weakest inhibitory effect. The inhibitory effect of nab-paclitaxel was observed to decrease significantly at a concentration of 1 nM, whereas the other three drugs still exhibited strong inhibitory effects on the proliferation of LO2 cells.

Cytotoxicity results showed that nab-paclitaxel group had the lowest cytotoxicity at all four-time points in LO2 cells (Figure 2 B). Then, to compare the effects of four drugs on LO2 cell proliferation, IC_{50} was calculated using nonlinear regression analysis (Table 2). The IC_{50} results showed that compared with the other three taxane drugs, nab-paclitaxel had a higher IC_{50} at all time points, further indicating that nab-paclitaxel may have lower cytotoxicity in normal cells.

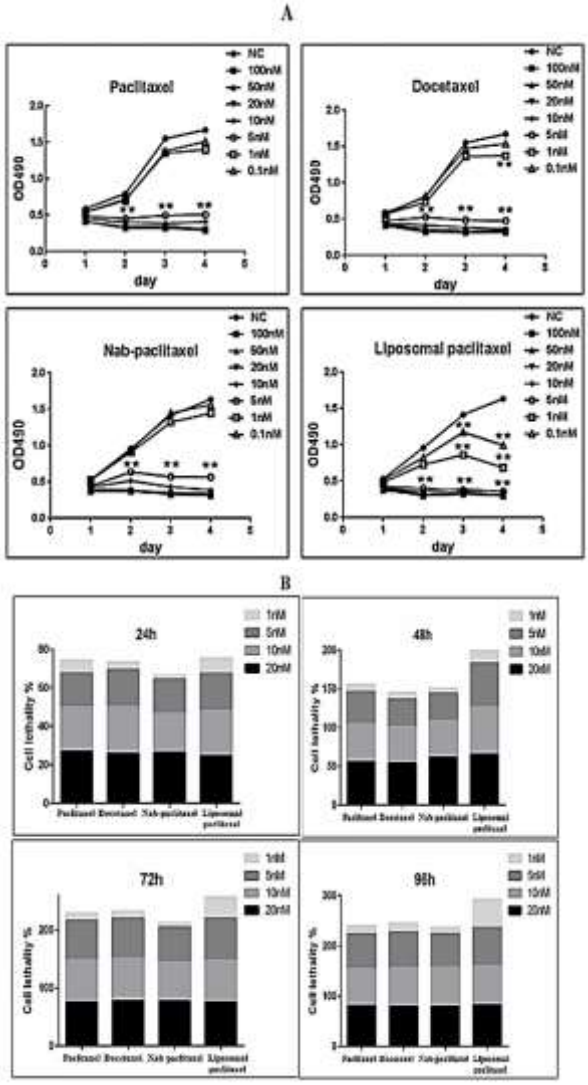

Figure 1: Effect of taxane drugs on the proliferation of human ovarian cancer cells *in vitro*. (**A)** The cell proliferation curves of SKOV3 cells after treatment with four taxane drugs in different concentrations for four days. $^{**}P < 0.05$ versus control. (**B)** The cell lethality of SKOV3 cells after treatment with four taxane drugs

All four taxane drugs inhibit tumor growth *in vivo*

As displayed in Figure 3A, intraperitoneal injection of the four taxane drugs significantly suppressed SKOV3 tumor growth when compared to that in control mice. No significant difference was detected in tumor volume among the four groups (Figure 3A). Except for control group, there was no significant difference in

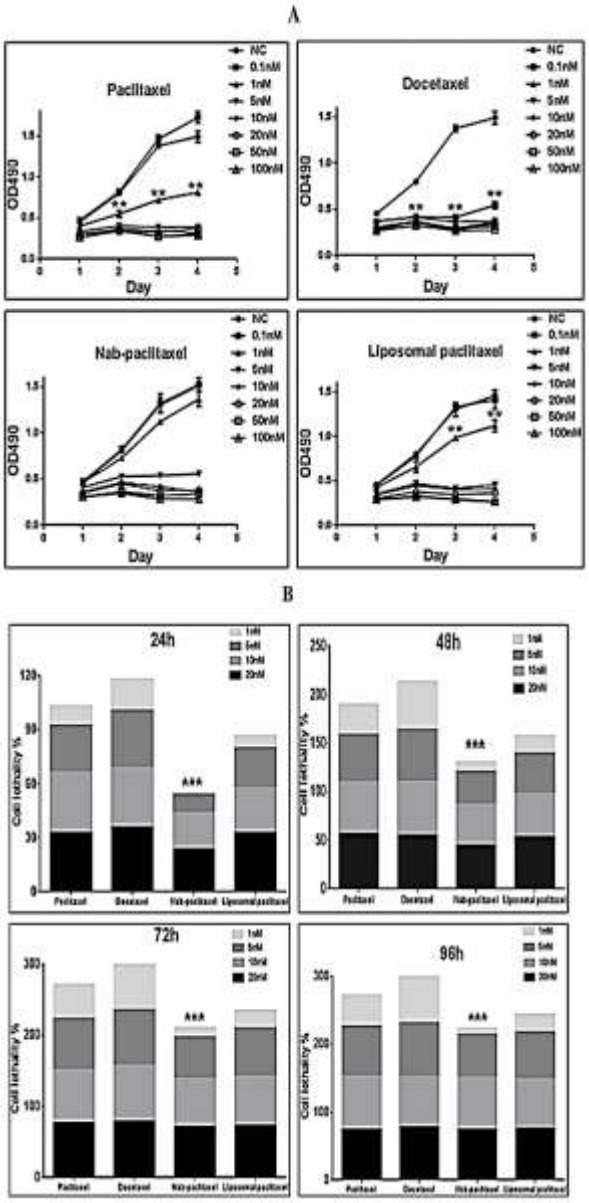

Figure 2: Effect of taxane drugs on the proliferation of normal human liver cells *in vitro*. (**A)** The cell proliferation curves of LO2 cells after treatment with four taxane drugs in different concentrations. ***P* < 0.05 versus control. **B**. The cell lethality of LO2 cells after treatment with four taxane drugs. ****P* < 0.05 versus control. In concentrations of 1, 5, 10, and 20 nM groups, nab-paclitaxel was greater than the other three groups in inhibiting the proliferation of normal human liver cells *in vitro*, and the difference was statistically significant ($p < 0.05$). Compared with the other three groups, nab-paclitaxel had the lowest toxicity to LO2 ($p < 0.05$; Table 2).

tumor volume among the other four groups after treatment ($p > 0.05$). To further confirm the anticancer effects of the four taxane drugs, TUNEL staining of tumor tissue (Figure 3 B) and immunohistochemical staining of Ki-67 (Figure 3 C) results showed that nab-paclitaxel induced more tumor cell apoptosis *in situ*. The four taxane drugs significantly lowered the expression level of Ki-67 in tumor tissues, and no significant difference was found in the inhibitory effects of the four taxane drugs.

Table 2: The IC_{50} of four taxane drugs in human liver normal cell line LO2

IC_{50} (nM)	24 h	48 h	72 h	96 h
Paclitaxel	136.7	14.05	2.082	2.224
Docetaxel	229.9	0.7052	<0.1	<0.1
Nab-paclitaxel	277.4	33.64	5.421	6.267
Liposomal paclitaxel	238	20.41	3.77	4.93

Docetaxel-treated animals had the most significant weight loss. Body weights of animals in paclitaxel and liposomal paclitaxel treatment groups were also lower than that of control mice. Nab-paclitaxel treatment group did not show a downward trend in body weight, indicating that nab-paclitaxel has the lowest animal toxicity (Figure 4 A). Hematixolin and Eosin results showed that nab-paclitaxel-treated mice exhibited the mildest degree of liver tissue damage among the four paclitaxel-treated groups (Figure 4 B).

DISCUSSION

The most significant problem with paclitaxel is its hydrophobicity and poor solubility. Therefore, Cremophor EL was added as a solvent. Paclitaxel or docetaxel may cause allergic reactions, which require anti-allergic pre-treatment 30 min before their medication. The development of nab-paclitaxel was aimed at mitigating the adverse effects that are commonly associated with solvent-based paclitaxel due to Cremophor EL, which is a toxic substance [19]. Albumin is a natural transporter in the human body and is responsible for transporting nutrients to organs. Albumin carries hydrophobic substances through blood vessels and reaches tissues. Utilizing albumin as a delivery vehicle for paclitaxel offers several advantages when compared to solvent-based paclitaxel. It is highly convenient for both patients and medical staff.

The findings from this study indicate that all four taxane drugs effectively inhibited the growth of SKOV3 cells in a dose-dependent manner. Interestingly, no significant difference in tumor volume was observed among the four treatment groups, suggesting that all four drugs may have similar antitumor efficacy *in vivo*. Clinical data leading to the approval of nab-paclitaxel demonstrated that it is superior to solvent-based paclitaxel in terms of reducing toxicity, resulting in a higher maximum tolerated dose for nab-paclitaxel. Therefore, in clinical application, the

killing effect of nab-paclitaxel is better than that of paclitaxel, docetaxel, and liposomal paclitaxel.

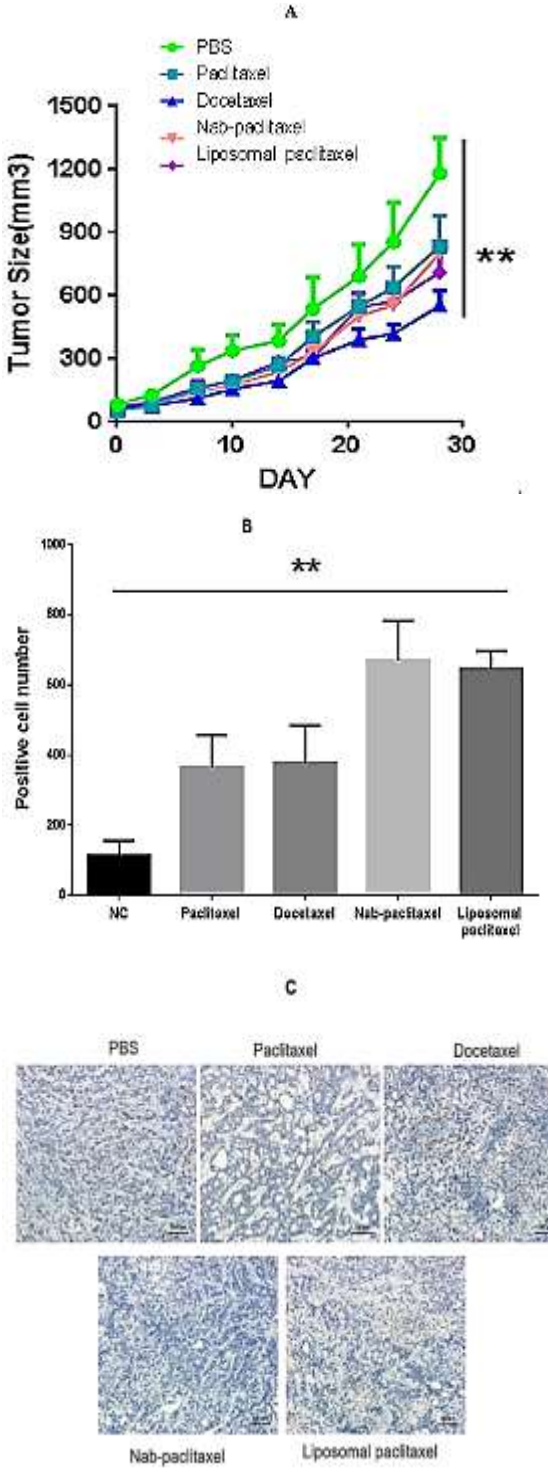

Figure 3: Effect of four taxane drugs on tumor growth *in vivo*. (A) Graph of tumor sizes in SKOV3 ovarian cancer xenograft model mice treated with PBS and 50 mg/kg paclitaxel. (B) TUNEL staining of ovarian tumor tissue from each group. Nab-paclitaxel induced more tumor cell apoptosis *in situ*. **$P < 0.05$ versus control. (C) Ki-67 immunohistochemical staining of ovarian tumor tissue from each group

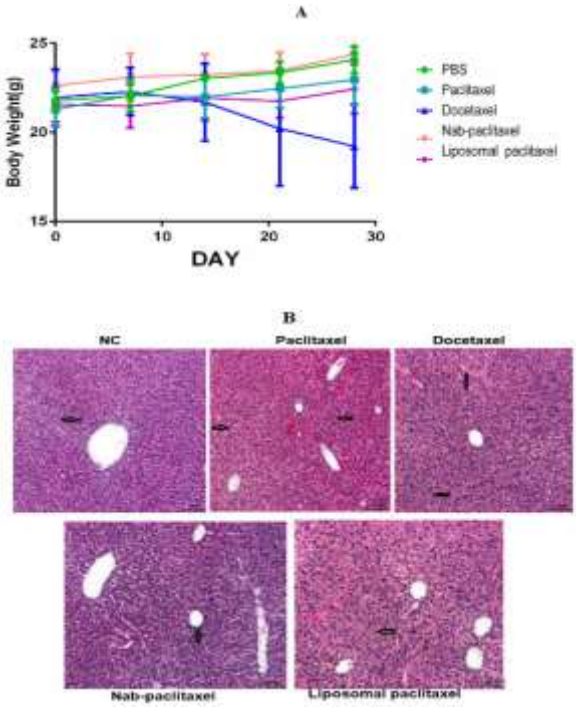

Figure 4: (A) Analysis of mouse body weight for each group. Nab-paclitaxel treatment group was the only group that did not show a downward trend in body weight ($p < 0.05$ versus control). (**B)** H&E staining of the liver from each group

Moreover, the four taxane drugs appreciably suppressed the proliferation of LO2 cells in a dose-dependent manner, but nab-paclitaxel showed the weakest inhibitory effect. When the concentration was 1 nM, nab-paclitaxel had no effect, but the other three drugs completely inhibited the proliferation of LO2 cells. The cytotoxicity results also showed that nab-paclitaxel had the lowest cytotoxicity in LO2 cells at all four-time points. Compared with the other 3 taxane drugs, nab-paclitaxel had a higher IC_{50} at all time points. *In vivo*, the body weight of animals in the nab-paclitaxel treatment group did not show a downward trend, indicating that nab-paclitaxel has the lowest toxicity in animals. Haematoxylin and Eosin staining showed that nab-paclitaxel treated group had the lowest degree of liver tissue damage among the four paclitaxel treated groups. Tumors need more nutrients than normal tissues, resulting in a higher volume of uptake of albumin than normal tissue. Thus, nab-paclitaxel accumulates in tumor tissue at a higher concentration [20,21]. The formulation of nab-paclitaxel offers several advantages over solvent-based paclitaxel, primarily due to higher fraction of unbound paclitaxel that it delivers (6.3 % vs. 2.4 %). This study revealed that nab-paclitaxel exhibited a maximal concentration of unbound paclitaxel that was about 10 times higher than other taxane drugs tested. Furthermore, the systemic

exposure, as measured by AUCinf, of unbound paclitaxel was approximately 3 times higher for nab-paclitaxel than for other drugs [22]. Micellar entrapment in Cremophor EL-based micelles has been reported to affect the pharmacokinetic (PK) linearity of solvent-based paclitaxel, which may explain the observed differences between nab-paclitaxel and solvent-based paclitaxel [23-25]. The PK linearity of solvent-based paclitaxel may be affected by micellar entrapment, whereas nab-paclitaxel's advantageous pharmacokinetic profile and more efficient use of albumin-based transport may contribute to its 33 % higher tumor uptake compared to solvent-based paclitaxel in preclinical studies. Because of the characteristics of targeting tumors, nab-paclitaxel can be enriched in tumor tissues, but its concentration in normal tissues is relatively low. Therefore, the curative effect is good, and the incidence of side effects, the most common of which was bone marrow suppression, is relatively low. Nab-paclitaxel has obvious advantages over traditional drugs.

An optimal paclitaxel formulation would exhibit a high ratio of drug to material, causing minimal to no systemic toxicity, and lead to targeted and concentrated drug accumulation in primary solid tumors and/or metastatic lesions. The addition of nano-albumin alters the tissue distribution, *in vivo* metabolism, efficacy, and side effects of paclitaxel. In essence, nab-paclitaxel is a completely different drug.

Limitations

The sample size of experimental animals is small. It will be better to have scale bars for tumor size.

CONCLUSION

Nab-paclitaxel is more effective in treating ovarian cancer in mice than traditional paclitaxels. In China, it is a first-line chemotherapy for epithelial ovarian cancer, as it has low systemic toxicity and induces limited hypersensitivity reactions. However, further investigations, including clinical trials in humans, are required.

DECLARATIONS

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Funding

None provided.

Ethical approval

None provided.

Availability of data and materials

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

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. J Ding: Protocol development, data collection, data analysis, and manuscript writing, W Xu: Data collection, X-y Cheng: Data collection, data analysis, and manuscript writing, X-h Chen: Data collection, data analysis, W-j Zhou: Data collection, data analysis, R Ma: Protocol development, F-l Meng: Protocol development. Jing Ding and Wei Xu contributed equally to this work.

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