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Maximum tolerated dose and toxicity evaluation of orally administered docetaxel granule in mice

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ABSTRACT

Oral delivery of chemotherapy drugs is the most favorable and preferred route of drug administration. However, because of poor solubility and/or permeability, most chemotherapy drugs are given by intravenous administration. Docetaxel (DTX) is a potent chemotherapy drug that inhibits microtubular depolymerization and is widely used to treat numerous cancers. DTX is highly lipophilic and insoluble in water; thus, 50% polysorbate 80, which may cause hypersensitivity reactions and reduce drug uptake by tumor tissue, is used in the commercial DTX injection to dissolve DTX. Maximum tolerated dose (MTD) and toxicity are important to determine parameters in preclinical studies and to predict human dose in clinical trials. However, MTD and toxicity of oral DTX formulations have not been studied although various oral DTX formulations have been reported. We have previously developed oral DTX granule and demonstrated its ability to inhibit tumor growth. In this study, we aimed to systemically measure MTD and tissue distribution and evaluate the toxicity of oral DTX granule in mice. Oral DTX granule showed sex differences in toxicity and absorption. The MTD of DTX granule was determined at 50 mg/kg for female mice and 25 mg/kg for male mice. However, female mice had higher tissue absorption than male mice. At a very high dose (400 mg/kg), oral DTX granule induced kidney damage but did not influence the liver and the lungs. The study provides the fundamental data for future preclinical studies and clinical application of oral DTX formulations for cancers.

1. Introduction

Oral delivery of chemotherapy drugs is the most favorable and preferred route of drug administration. A study showed that over 90% of cancer patients preferred oral over intravenous (IV) drugs because of convenience and flexibility in timing and location of administration [1]. With the discovery of molecular-targeted agents (e.g. tyrosine kinase inhibitors) directed against specific molecular targets, oral drug usage has become the center of daily oncology practice. Indeed, almost half of the approved targeted anticancer drugs in the European Union since 2000 are exclusively available as oral formulations [2]. Chemotherapy drugs play a vital role in cancer treatments. Many studies have demonstrated that metronomic chemotherapy in which chemotherapy drugs are given frequently at low doses over a long time improved the outcomes and reduced side effects [3–6]. However, many chemotherapy drugs such as docetaxel (DTX) have been commercially formulated for IV injections because of their low solubility and/or low permeability. This revolution in cancer treatment has led to an urgent need for oral drug delivery systems.

DTX, like other taxane drugs, is a potent chemotherapy drug working as a microtubule inhibitor and is widely used to treat breast cancer, head and neck cancer, stomach cancer, prostate cancer, and non-small-cell lung cancer [7–9]. DTX is highly lipophilic (LogP 4.3) and insoluble in water (< 20 ng/mL). In addition, DTX is a substrate of efflux transporters such as P-glycoprotein and metabolism enzymes such as CYP3A4. Thus, the oral bioavailability of DTX is low and variable. DTX is given by IV infusion and commercially formulated with a 1:1 ratio of polysorbate 80/dehydrated alcohol although polysorbate 80 may cause hypersensitivity reactions and reduce drug uptake by tumor tissue. Compared to the dose at 75 mg/m^2 every 3 weeks, a weekly dose of DTX at 35 or 40 mg/m^2 showed a significantly lower rate of severe neutropenia with comparable efficacy in terms of survival [10,11]. However, DTX is still given at the dose of 75 mg/m^2 every 3 weeks in clinical practice because of the limitations of using frequent IV infusion. Various oral DTX formulations have been studied such as nanoparticles [12], microemulsions [13], solid dispersion [14], and chitosan conjugates

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Table 1
The clinical score determination.

Score	0	1	2
Body weight	No change	Loss of body weight > 10%	Loss of body weight > 20%
Body posture	Normal	Hunched	Massive hunched
Movement	Normal	Reduced or slow	Move only after stimulation
Social activity	Normal	Somehow isolated	Completely isolated

[15]. Recently, we successfully developed an oral DTX granule and demonstrated oral DTX granule given at 5 mg/kg twice per week remarkably inhibited the tumor growth in the lungs over 24 days in a mouse model of prostate cancer with lung metastasis [16].

Tumor regression is correlated to the dose used to treat the cancer in preclinical studies and the clinical setting [17,18]. To achieve systemic therapy for many cancers, treatment plans typically consist of repeated cycles of anticancer drugs at a dose as high as possible, without causing unacceptable toxicity. Maximum tolerated dose (MTD) is defined as the highest dose that is tolerated and does not produce major life-threatening toxicity for the study duration. Preclinical studies require MTD and toxicity profiles to determine dose and dose schedules for well-designed efficacy studies. Moreover, MTD and toxicity studies in preclinical studies are often used to predict those in human studies. Thus, systemic determination of MTD and evaluation of toxicity are critical for new drug formulations. However, to our knowledge, there are no reports on the MTD and toxicity of oral DTX formulations.

The objective of this study was to systemically measure MTD and tissue distribution and evaluate the toxicity of oral DTX granule in mice. Toxicity studies here included acute and short-term (one-month) toxicity studies. Acute toxicity testing was used to select doses for short-term toxicity studies for which five dose levels of the tested groups and a concurrent control group were used for both female and male mice. The MTDs with the repeated dose of oral DTX granule once per day in FVB mice were determined and measured over one month for female and male mice, respectively. In addition, dose response and tissue distribution of oral DTX granule were measured and the toxicity was evaluated based on the measurements of liver function and renal function and the histological analysis.

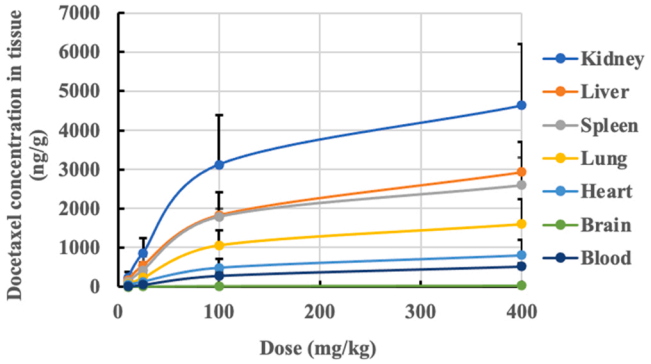


Fig. 2. The dose response curves of oral DTX granule in tissues. Male mice (n=4) were treated with oral DTX granule at 10, 25, 50, 100, 200 and 400 mg/kg. After 2 hours, tissues were collected and drug concentrations in tissues were measured by a validated LC-MS method.

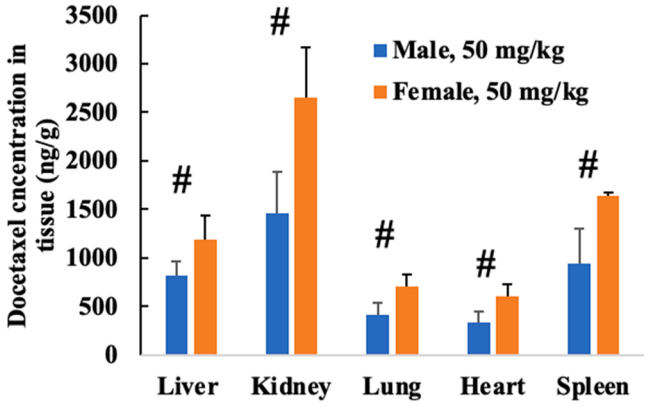


Fig. 3. The different absorption of oral DTX granule in female and male mice at 50 mg/kg (n=4). Mice were given DTX granule by oral administration. Tissue samples were collected after 2 hour of post dosing. DTX concentrations in tissue samples were measured by a validated LC-MS method and compared between female and male mice. For all tested tissues, the difference between female and male mice was significant (# $p<0.05$).

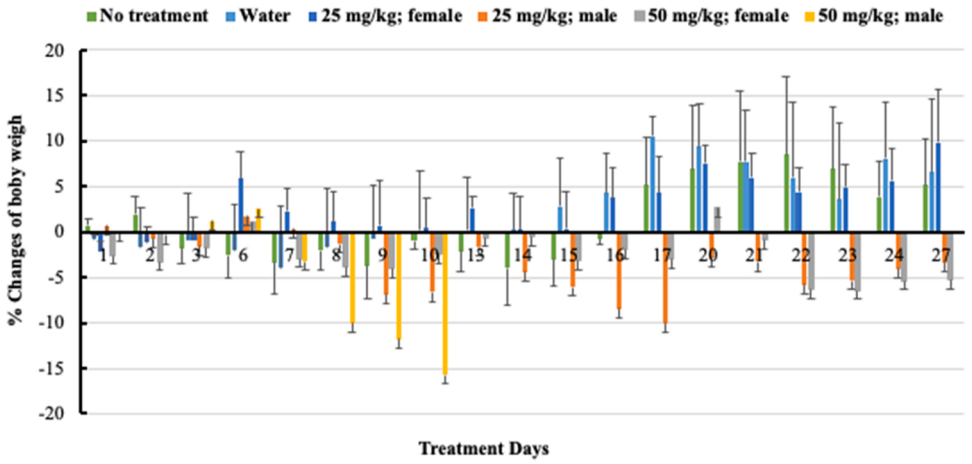
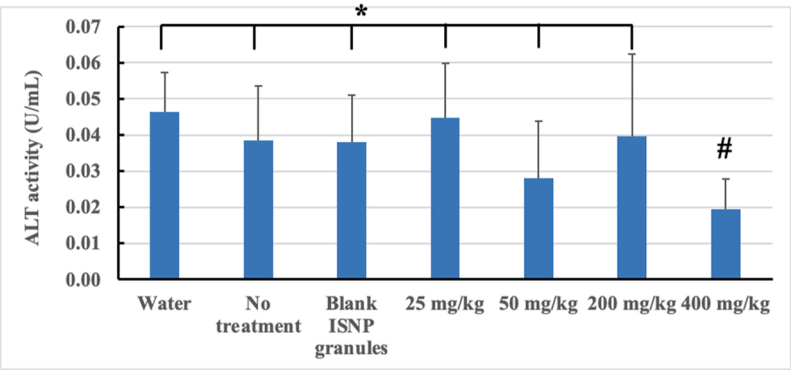
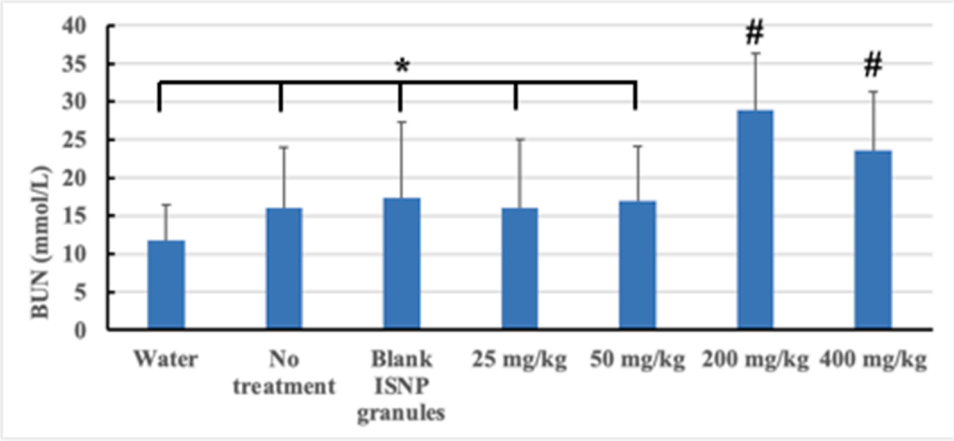


Fig. 1. The percentage change of body weight of female and male mice treated with 25 mg/kg or 50 mg/kg of DTX granule over 27 days. The body weight was compared with that on Day 0. Water and no treatment were used as controls.

A.



B.



C.

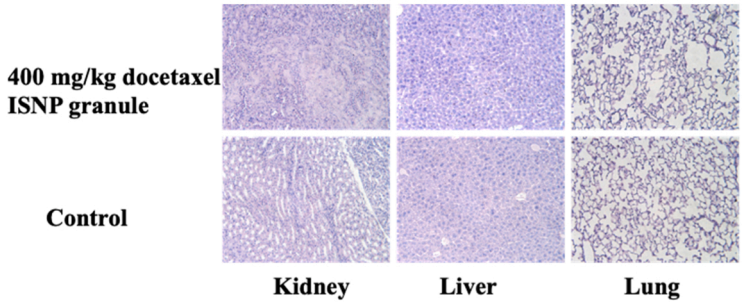


Fig. 4. The toxicity evaluation of oral DTX granule in mice. (A) the ALT activities and (B) BUN levels with the treatments of 25, 50, 200, and 400 mg/kg of DTX granule (n=4–6). (C) H&E stain for mouse kidney, liver, and lung after the treatment of 400 mg/kg of DTX granule. The mouse was sacrificed after reaching euthanasia criteria and organs were collected for H&E stain. The images of the H&E stain were taken under a microscope. Among liver, lung and kidney, kidney showed damage by the treatment of 400 mg/kg of DTX granule compared to the control. The significant difference in the measurements of the ALT activities and the BUN levels was labeled as # $p<0.05$ and * $p>0.05$.

2. Materials and method

2.1. Animals

Five-week-old FVB mice were purchased from Charles River Laboratories (Wilmington, Massachusetts). Animal experiments were conducted according to an approved protocol (IACUC-2019–0023) by the Institutional Animal Care and Use Committee at the University of North Texas Health Science Center.

2.2. Prepare blank granule and DTX granule

Blank granule and DTX granule were prepared as previously reported [16]. Briefly, for DTX granule, DTX was mixed with Miglyol 812 and TPGS at 50°C for 20 min, and then Aeroperl 300 was added, mixed and cooled to room temperature. Blank granule was prepared without DTX and used as a vehicle control.

2.3. Determine MTD of oral DTX granule

Female and male FVB mice were given the treatments by oral gavage

once per day. Mice were not restricted to food and water. IACUC protocol was approved by the UNTHSC IACUC committee. The clinical score determination is shown in Table 1. Euthanasia criteria include weight loss $\geq$ 20% or clinical score $\geq$ 2.

For the overall design, blank granule and DTX granule were firstly given to male mice (6 per group), respectively. A dose range was tested from high to low (400, 200, 100, 50 and 25 mg/kg). The dose that kept mice survival for three days was chosen for the MTD determination for multiple doses. Female and male mice were used to determine multiple dose MTD. The detailed experiments are below.

In the first cohort, a single dose in a single mouse was used to determine the dose range. Each mouse was given 400, 200, 100, 50, 25, and 10 mg/kg of DTX granule, respectively, on day one and then monitored for three days.

In the second cohort, 400 mg/kg of DTX granule or equivalent blank granule (6 male mice per group) were given daily and monitored, and the mice were sacrificed until the euthanasia criteria were reached.

In the third cohort, 200 mg/kg of DTX granule (6 male mice per group) were given daily and monitored, and the mice were sacrificed until the euthanasia criteria were reached.

In the fourth cohort, 25, 50, and 100 mg/kg of DTX granule were given to mice (one male mouse per group) daily and monitored, respectively, and the mice were sacrificed until the euthanasia criteria were reached in any one of the treatments.

In the last cohort, 25 and 50 mg/kg of DTX granule were given to mice daily, respectively, and the mice were sacrificed until the euthanasia criteria were reached in any one of the treatments. To test the difference between sexes, three female mice and three male mice were studied for each dose. Mice dosed with water and without treatment were used as control groups (3 male mice per group).

To find the MTD of blank granule, three female mice and three male mice were given a dose of blank granule equivalent to 400 mg/kg of DTX granule daily for 30 days.

2.4. Determine tissue distribution of DTX granule

Mice (male, n=4–6) were given 10, 25, 50, 100, 200 and 400 mg/kg of DTX granule. After 2 hours, mice were sacrificed. Blood and tissues including liver, lung, spleen, kidney, heart, and brain were collected. Blood was centrifuged at 400 rpm for 5 min to get plasma. Samples were stored at −80°C until analysis. The DTX concentrations in the plasma and other tissues were measured by a validated LC-MS method as previously reported[16]. The LC-MS measurement was performed using an Agilent 1260 infinity HPLC coupled with Agilent 6460 triple quadrupole mass spectrometer operated in a positive mode using multiple reaction morning (MRM). Paclitaxel was used as an internal standard. Quantification was conducted in MRM by monitoring the transition of m/z 830.3 -> 549.2 for DTX and m/z 876.3 -> 308.3 for paclitaxel. An XBridge C18 column (4.6×50mm, 3.5 μm, Waters, USA) was used to separate samples at room temperature. The mobile phase A was composed of 0.1% formic acid in water and the mobile phase B was composed of 0.1 formic acid in acetonitrile. A gradient elution was started from 50% to 20% mobile phase A within 4 min, reduced to 2% mobile phase A at 4.1 min and kept to 5 min and then increased to 50% at 5.1 min and kept until 6 min. The total run was 6 min. The injection volume as 5 μL. The flow rate was 0.5 mL/min. The retention time of DTX and paclitaxel was 3.21 min and 3.33 min, respectively.

2.5. Evaluate the toxicity of DTX granule

Blood (n=5–6) from these mice who were treated with 25, 50, 200, and 400 mg/kg of DTX granule and met euthanasia criteria was collected when the mice were sacrificed and frozen at −80°C until analysis. In addition, blood (n=5–6) in the treatment groups of water and no treatment was collected as controls. To evaluate liver function, an Alamine Transaminase (ALT) colorimetric activity assay kit (Cayman Chemical) was used. Blood urea nitrogen (BUN) was tested by using a urea colorimetric assay kit (Elabscience) to evaluate renal function. The BUN kit was modified for the measurement on 96-well plates. The DTX granule delivered most drug to the liver, lung, and kidney. Thus, liver, lung, and kidney from the treatment of 400 mg/kg DTX granule in the second cohort were collected and fixed in 10% buffered formalin and stained with hematoxylin and eosin (H&E) for microscopic examination.

2.6. Statistical analysis

The data are presented as mean ± standard deviation. A two-tailed *t-test* at 95% confidence level was used to analyze the data. The statistically significant difference was considered when $p < 0.05$.

3. Results and discussion

3.1. Maximum tolerated dose of DTX granule and sex differences in toxicity

After mice were treated with a single dose of 10, 25, 50, 100, 200, and 400 mg/kg of DTX granule in the first cohort, respectively, all mice survived over three days. Thus, we continued with the repeated doses. When mice were treated with 400 mg/kg of DTX granule daily in the second cohort, one mouse lost the body weight over 15% on day 5 and two mice lost the body weight over 15% on day 6. The same toxicity was observed for 200 mg/kg of DTX granule given daily in the third cohort. The results of 200 and 400 mg/kg indicated that these doses were too high for a daily regimen. To save animals, we started to use one mouse per dose in the fourth cohort to test daily dosing for 25, 50 and 100 mg /kg of DTX granule. The mouse given 100 mg/kg lost the body weight for 15% on the Day 4 while the mice given 25 and 50 mg/kg were normal. According to these results, the doses of 25 and 50 mg/kg of DTX granule were chosen to test in female and male mice for daily dosing, respectively.

To determine the MTD for multiple doses, female and male mice were treated with 25 mg/kg of DTX granule, 50 mg/kg of DTX granule, water, or no treatment. The mouse was individually labeled and weighed over 27 days. The percentage of average body weight loss is shown in Fig. 1. Overall, DTX granule indicated more toxicity in male mice than female mice. Two male mice at a 50 mg/kg dose lost body weight by over 15% on Day 10 and were sacrificed. All other mice were survived over 27 days. Therefore, the MTD of DTX granule for daily dose was determined at 50 mg/kg for female mice and 25 mg/kg for male mice, respectively. Even for male mice, the MTD (25 mg/kg) is much higher than the dose (5 mg/kg) we used in our previous anticancer efficacy studies in metastatic lung cancer[16]. Thus, the study here provides sufficient space to increase the dose of oral DTX granule in future efficacy studies.

Clearly, we observed the sex differences in the toxicity of oral DTX granule. It is known that chemotherapy drugs could have different responses in sex in both humans and animals[19–22]. Differences in pharmacokinetics, pharmacodynamics, and drug metabolism could generate the sex differences in toxicity of systemic treatments of chemotherapy drugs[22]. Paclitaxel has been reported to show significant sex differences in pharmacokinetics. However, the sex differences of DTX in toxicity have not been reported yet. This is the first report evidencing that DTX is one of these drugs inducing different responses in sex. The MTD of DTX granule in female mice was higher than that in male mice (50 mg/kg vs 25 mg/kg). Thus, female mice were more tolerant to oral DTX granule than male mice. If our observation in mice is correlated to clinical observation in humans, modified doses could be suggested for female and male patients. More studies on this aspect are warranted. Moreover, the National Institute of Health (NIH) emphasizes rigorous experimental design for animals. Sex difference is asked to be included in the experimental design in NIH grant applications. Our data will provide a solid foundation for other researchers to propose animal

studies for DTX.

3.2. Tissue distribution of DTX granule at different doses

To evaluate if the tested doses reached the saturation absorption, tissue distribution of DTX granule at each dose was measured and compared at 2 hours of post dosing, in which DTX granule would be fully absorbed and distributed to each organ. As shown in Fig. 2, DTX concentrations in blood and tissues increased with the dose increase of DTX granule. Moreover, the order of concentration in tissues was the same. For example, the kidney had the highest concentrations, and the liver had the second highest concentration among the tissues in the same dose. Thus, the MTD we found was reliable and did not result from the saturation of oral and tissue absorption. Comparing DTX concentrations in tissues, the heart is not a favorable tissue. Thus, the granule could be used to formulate chemotherapy drugs that induce cardiovascular toxicity. To examine the sex influence on tissue distribution, we tested the tissue distribution of DTX granule at 50 mg/kg in female and male mice, respectively. As shown in Fig. 3, female mice absorbed more DTX than male mice ($p < 0.05$). This is interesting because the MTD of DTX granule in female mice was higher than in male mice. The hepatic metabolism is different in female and male mice. DTX clearance is related to hepatic function, which leads to different pharmacokinetics, dynamics, and toxicity of DTX between Japanese and Western patients [23]. Thus, differences in hepatic metabolism could make female mice more tolerant to DTX although the absorption of DTX granules in female mice is higher than in male mice. This finding is significant and valuable for controlling side effects and reducing inter-patient variation for DTX treatment.

3.3. Toxicity evaluation of oral DTX granule

Since we observed the toxicity at 400 mg/kg of DTX granule, we measured ALT and BUN in mice treated with 25, 50, 200, and 400 mg/kg of DTX granule. As shown in Fig. 4A, only in mice who were treated with 400 mg/kg of DTX granule ALT activities significantly decreased compared to mice treated with water or no treatment ($p<0.05$). Although mice treated with 50 and 200 mg/kg met euthanasia criteria (i.e. change of body weight $>$ 15%) they did not show a significant difference in ALT activities ($p >0.05$). At 25 mg/kg, there was no significant difference compared to water and no treatment on ALT activities ($p >0.05$). For blank granule, there was no significant difference even at 400 mg/kg ($p >0.05$). ALT activity is commonly used to measure liver function. A decrease in ALT activity after treatments is considered normal, but an increase in ALT activity indicates liver damage. As shown in Fig. 4A, the ALT activity decreased for all treatments, indicating that DTX granule, even at 400 mg/kg, did not induce liver damage.

As shown in Fig. 4B, BUN levels significantly increased at 200 and 400 mg/kg ($p <0.05$), which indicated the toxicity in the kidney. Blank granule at 25 mg/kg and 50 mg/kg did not significantly change the BUN levels. If the kidneys are not to remove urea from the blood, the BUN level rises. The BUN level at 200 and 400 mg/kg of DTX granule increased (Fig. 4B). Thus, oral DTX granule induced kidney damage and alteration in renal function, which could be the reason that mice lost body weight (Fig. 1).

Liver, lung, and kidney collected from a mouse who was treated with 400 mg/kg of DTX granule were examined by H&E stain. As shown in Fig. 4C, the liver and lung did not show tissue toxicity at 400 mg/kg, but the kidney structure was damaged by the treatment, compared to the control. Thus, the aforementioned toxicity mechanism that 400 mg/kg of DTX granule induced kidney damage was confirmed by the histological analysis. Taken together, DTX granule at a very high dose (400 mg/kg) will reduce renal function and have toxicity in the kidney but will not affect liver and lung functions.

4. Conclusion

The MTD, tissue distribution, and toxicity of oral DTX granule were systemically measured and evaluated. Oral DTX granule showed sex differences in toxicity and absorption. The MTD of DTX granule was determined at 50 mg/kg for female mice and 25 mg/kg for male mice. However, female mice had higher tissue absorption than male mice. These new findings could be used to reduce inter-patient variation on efficacy and side effects associated with sex. We also observed that the oral granule delivered the lowest amount of DTX in the heart compared to the kidney, liver, lung, and spleen. Thus, the oral granule could be used for drugs that induce cardiotoxicity (e.g. doxorubicin). Overall, mice were well tolerated at the MTD doses of DTX granule over 24 days. At a very high dose (400 mg/kg), oral DTX granule induced kidney damage but did not influence the liver and lungs. The study provides the fundamental data for future preclinical studies and clinical application of oral DTX formulation for cancers.

CRediT authorship contribution statement

Jinmin Zhang: Writing – review & editing, Data curation. **Xiaowei Dong:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Xiaowei Dong reports financial support was provided by National Institute of General Medical Sciences. Xiaowei Dong reports a relationship with National Institute of General Medical Sciences that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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