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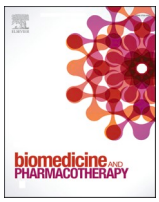

Intraperitoneal pharmacokinetics of systemic oxaliplatin, 5-fluorouracil and bevacizumab in patients with colorectal peritoneal metastases

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ABSTRACT

Background: Peritoneal metastases (PM) commonly occur in colorectal cancer patients. Systemic chemotherapy yields poor outcomes for these patients. It is hypothesised that traditional systemic chemotherapy is not very effective for this patient population. This study investigates to what extent systemic anti-cancer therapy crosses the peritoneal barrier.

Methods: In a Phase I study, eighteen patients received systemic oxaliplatin, 5-FU, and bevacizumab. Plasma and peritoneal fluid samples were collected to measure drug concentrations. A non-compartmental analysis determined the Area Under the Curve (AUC) for oxaliplatin and 5-FU in both matrices. Intraperitoneal (IP) and intravenous (IV) exposure ratios were calculated, along with the bevacizumab concentration IP/IV ratio. The relationship between tumour load and IP/IV ratios and the correlation between the IP/IV ratios of different treatments were assessed statistically.

Results: A total of 438 5-FU samples and 578 oxaliplatin samples were analysed in plasma and peritoneal fluid. Bevacizumab was quantified with 17 measurements in plasma and 15 measurements IP. Median IP/IV ratios were 0.143, 0.352 and 0.085 for 5-FU, oxaliplatin and bevacizumab, respectively. Oxaliplatin exhibited a longer IP half-life than 5-FU. A correlation was found between oxaliplatin and bevacizumab IP/IV ratios ($R=0.69$, $p=0.01$). No statistical correlations were found between the other investigated drugs.

Conclusions: Our findings indicate that only a small percentage of systemically administered anti-cancer treatment reaches the IP cavity, questioning their efficacy against PM. This strengthens the hypothesis for repeated intraperitoneal chemotherapy to reach adequate anti-cancer drug levels.

1. Introduction

Peritoneal metastases (PM) are relatively common in patients with colorectal cancer (CRC), with 5 % of the patients having PM at diagnosis and another 4–19 % developing PM during follow-up [1–3]. The only potentially curative treatment for patients with PM of CRC consists of treatment with cytoreductive surgery in combination with hyperthermic intraperitoneal (IP) chemotherapy (CRS-HIPEC), but this approach is only beneficial for patients with limited peritoneal disease (Peritoneal Cancer Index (PCI)$\leq$ 20) [4,5]. For patients with more extensive peritoneal disease, only systemic chemotherapy, often containing (a combination of) a fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab remains as a palliative treatment [6]. However, when treated with systemic chemotherapy outcomes were shown to be worse in patients with PM compared to patients with other distant metastases, such as lung or liver metastases [3,7,8]. Therefore, it is hypothesised that traditional systemic therapy is not very effective for this patient population, which calls for exploring alternative solutions such as

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repeated IP chemotherapy [9].

The peritoneum is a complex diffusion barrier which is a three-dimensional organ that forms a layer over the abdominal wall and the abdominal-pelvic organs [10]. This physiological barrier regulates the movement of medications from the bloodstream into the peritoneal cavity. Owing to the relatively small molecular weight of both commonly used chemotherapeutics (oxaliplatin: 397 g/mol; 5-fluorouracil: 130 g/mol), movement over the peritoneal plasma barrier is anticipated. Furthermore, the hydrophilic characteristics of both medications suggest favourability towards watery environments, such as the IP cavity [11,12]. Bevacizumab, on the other hand, is a large monoclonal immunoglobulin (IgG) targeting vascular endothelial growth factor A (VEGF-A) and does not readily cross cell membranes [13].

The first INTERACT trial for colorectal cancer patients was a phase I study of IP irinotecan administered through a peritoneal catheter in addition to standard systemic oxaliplatin, 5-fluorouracil (5-FU) and bevacizumab [14]. This study provided the opportunity to explore the IP pharmacokinetics of systemic anticancer treatment [15]. The aim of the current analysis is to explore to what extent the systemic chemotherapy crosses the peritoneal barrier.

2. Methods

2.1. Patients & treatment

Patients who participated in the INTERACT phase I trial were eligible for this secondary analysis. The trial adhered to Good Clinical Practice guidelines and the Declaration of Helsinki, with all patients providing written informed consent before study-related procedures (ICTRP Search Portal; NTR7177) [14]. This trial aimed to determine the safety and maximum tolerated dose of IP administered irinotecan besides systemic FOLFOX-bevacizumab. Patients with CRC with peritoneal metastases and a PCI above 20, a life expectancy of at least 3 months, normal organ function, and adequate bone marrow reserve were eligible for this study [14]. In total, 18 patients were included. Each systemic chemotherapy cycle consisted of oxaliplatin 85 mg/m^2, a bolus 5-FU (400 mg/m^2), leucovorin 200 mg/m^2, and bevacizumab (5 mg/kg) followed by either a 22-h infusion of 5-FU (600 mg/m^2) on day 1 plus a bolus 5-FU (400 mg/m^2) and a 22-h infusion of 5-FU (600 mg/m^2) on day 2 or a 44-h 5-FU infusion (1200 mg/m^2) (Fig. 1). A dose of 50, 75 or 100 mg irinotecan was administered intraperitoneally on day 1 in 1.5 h.

Peritoneal fluid samples were collected through a peritoneal access port that was connected to a catheter with a multi-fenestrated tip positioned within the pouch of Douglas. This port served a dual purpose as both the entry point for administering the treatment and for PK sample collection. Samples were taken pre-dose, 30 min, 1, 1.5, 2, 3, 4, 6, 22.5, and 46.5 h after IP irinotecan infusion. Samples were drawn in a lithium-heparin tube and stored at T≤-70 °C until analysis. Oxaliplatin and 5-FU were measured at all available time points in plasma and peritoneal fluid. Bevacizumab concentrations were measured in plasma and in peritoneal fluid at 24 h after the first dose.

2.2. Analysis

Plasma samples were centrifuged (10 min at 2500*g, 4°C) following analysis of both plasma and peritoneal fluid samples. 5-FU was measured using a validated liquid chromatography-mass spectrometry (LC-MS/MS) method with a Lower Limit of Quantitation of 1.00 ng/mL. The platinum concentration of plasma and peritoneal fluid was determined by validated atomic absorption spectrometric analyses (AAS) with a LOQ of 50.0 ng/mL. The monoclonal antibody bevacizumab was quantified using the mABXmise monoclonal antibodies quantification kit multiplex (Promise Proteomics, France) which is based on the stable isotope dilution coupled to mass spectrometry analysis [16]. The internal standard is a Stable-Isotopically-Labelled mAb (SIL-mAb), with a sequence highly similar to the one of targeted mAb and coated at the same amount in each well of the 96 well-plate. Calibration ranged from 2.00 μg/mL to 100 μg/mL. Quantification was performed by using a UPLC-MS/MS system, purchased from Waters Chromatography B.V (Etten-Leur, The Netherlands).

2.3. Pharmacokinetic analysis

Analysis of PK data was performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria) and, PKNCA version 0.10.1. The Area Under the Curve (AUC) values for oxaliplatin and 5-FU in both plasma and peritoneal fluid were determined through Non-Compartmental Analysis. Subsequently, the ratio between IP exposure (AUC_{IP}) and intravenous exposure (AUC_{IV}) was calculated. For bevacizumab, the concentration at 24 h IP/IV ratio was calculated.

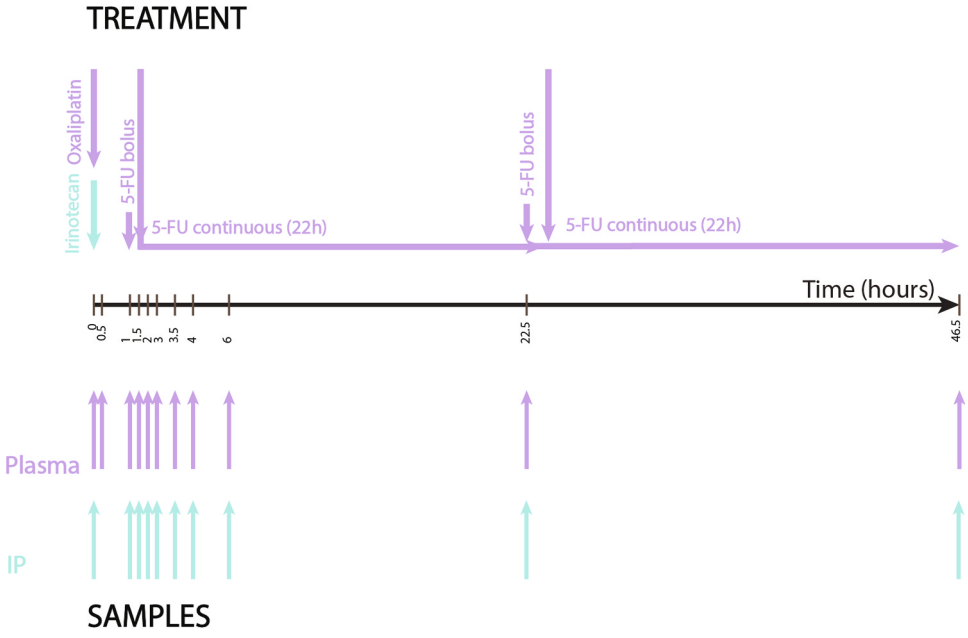

Fig. 1. Graphical representation of administered chemotherapeutics and collected plasma (purple) and peritoneal fluid (green) samples.

2.4. Tumour load

Given the non-normal distribution of the data, a Spearman's rank correlation test was performed. The PCI score and plasma albumin were statistically tested to examine the correlation with IP/IV exposure ratio. The statistical analysis was carried out using R packages stats (version 4.2.1) and nnet (version 7.3–19). Initial tests involved assessing the normality of parameters through a Shapiro-Wilk test and visual inspection.

2.5. Ratio correlation

In order to determine if an elevated IP exposure was primarily attributed to the patient's peritoneal plasma barrier characteristics, rather than a specific response to the administered intravenous chemotherapy, a Spearman's rank correlation test was conducted. This test aimed to assess the correlation between the $AUC_{IP/IV}$ ratio of 5-FU with the $AUC_{IP/IV}$ ratio of oxaliplatin and the $C_{t=24}$ IP/IV ratio of bevacizumab with the exposure ratios of 5-FU and oxaliplatin from the first treatment cycle.

3. Results

3.1. Patients and samples

Table 1 presents the baseline patient characteristics. Drug concentrations of 5-FU and oxaliplatin were measured at 11 time points in plasma (236 5-FU samples, 328 oxaliplatin samples) and peritoneal fluid (203 5-FU samples, 250 oxaliplatin samples) as depicted in Figure A.1. Bevacizumab was quantified with 17 measurements in plasma and 15 measurements IP at a time point 24 h after dose.

3.2. Pharmacokinetic analysis

The pharmacokinetic parameters for 5-FU, oxaliplatin and bevacizumab are presented in Table 2. The median $AUC_{IP/IV}$ ratio of 5-FU was 0.14 (range: 0.0005–1.1), with a median IP half-life of 6.3 h. For oxaliplatin, the median $AUC_{IP/IV}$ ratio was 0.35 (range: 0.06–0.9). Elimination from the peritoneal cavity occurred at a median elimination half-life of approximately 137 h. Bevacizumab IP exposure at 24 h after infusion was low compared to plasma exposure. The median Ratio IP/IV was 0.085 and interpatient variability was relatively low (Table 2), as indicated by the narrow density plot in Fig. 2.

Table 1
Baseline patient characteristics of study population.

	Overall (n = 18)
Sex	
Female	6
Male	12
Age (years), median (i.q.r.)	64 (57–68)
PCI score, median (i.q.r.)	29 (24–33)
Peritoneal metastases timing	
Synchronous	12
Metachronous	6
Primary tumour resected	
Yes	8
No	10
Weight (kg), median (i.q.r.)	79.7 (70–98)
Smoking status	
Smoker	4
Ex-smoker	6
Non-smoker	6
Unknown	2
ECOG performance score	
0	12
1	6
5-Fluorouracil regimen	
Day 1: 5-FU bolus + continuous infusion (22 h). Day 2: 5-FU bolus + continuous infusion (22 h)	10
Day 1: 5-FU bolus + continuous infusion (44 h)	8
Plasma albumin levels baseline (g/L), median (i.q.r.)	41 (37–42)

Abbreviations: PCI, Peritoneal Cancer Index; BMI, Body Mass Index; BSA, Body Surface Area; ECOG, Eastern Cooperative Oncology Group performance status; i.q.r, Interquartile range

3.3. Tumour load

For all anti-cancer therapies, no significant correlation was found between IP/IV ratios and PCI score or albumin levels.

3.4. Ratio correlation

The Spearman-Rank analysis revealed no significant correlation between the $AUC_{IP/IV}$ ratio of oxaliplatin and the $AUC_{IP/IV}$ ratio of 5-FU. Accordingly, patients with elevated IP exposure to 5-FU did not necessarily exhibit a corresponding increase in IP exposure to oxaliplatin. However, a significant correlation ($R=0.69$, $p=0.01$) was observed for the bevacizumab concentration ratio with the oxaliplatin IP/IV exposure ratio (Figure A.2).

4. Discussion

This study focused on the pharmacokinetics involved in the diffusion through the peritoneal plasma barrier of systemically administered chemotherapeutics. Oxaliplatin exhibited best reach into the IP compartment evidenced by a median IP/IV ratio of 0.35 compared to 0.14 for 5-FU and 0.085 for bevacizumab. Additionally, oxaliplatin showed a long residence time in the IP compartment with a median half-life of 136 h. In contrast, 5-FU, characterised by rapid IP distribution, faces fast clearance, resulting in a median IP half-life of 6.3 h, even during continuous infusion. Although both 5-FU and oxaliplatin exhibited inter-individual variability in exposure ratio and half-life, 5-FU showed the greatest variability, as evidenced by a notably flatter density curve.

A potential explanation for the brief cumulative IP exposure of 5-FU is the extremely short half-life of approximately 12 min, due to fast metabolisation into active metabolites and degradation products [17]. Additionally, due to its small molecular size, when 5-FU enters the peritoneal cavity, it may be rapidly reabsorbed into the bloodstream and transported to the liver. Oxaliplatin also distributes to the peritoneal cavity after IV administration. As a result of its high reactivity, oxaliplatin forms reactive platinum complexes, that contribute to prolonged retention within the peritoneal space [18]. Due to its large antibody structure, bevacizumab is not anticipated to effectively traverse the peritoneal plasma barrier, aligning with our findings. Furthermore, as a concentration gradient influences the distribution of molecules, it is important to consider the treatment schedule in addition to the specific drug properties. Here we have three different medicines, each with a unique method of administration, requiring careful comparison of IV/IP ratios.

Moreover, our results show that the peritoneal barrier potentially prevents penetration of both oxaliplatin and bevacizumab to some degree. This assumption is based on the found correlation between the IP/IV ratio of bevacizumab and the IP/IV ratio of oxaliplatin. Nevertheless, It is important to keep in mind, that the ratios of the three distinct drugs cannot be directly compared because the ratio that is found depends on the administration and sampling procedures.

The peritoneal barrier's impact on PK is most effectively expressed by comparing the IP AUC of a drug to its IV AUC. A high IP AUC indicates high local drug exposure and potential effectiveness against peritoneal metastases [19]. For platinum-based antineoplastic drugs, relatively low AUC ratios after IP administration are reported compared to other

Table 2
Intraperitoneal exposure and AUC ratios for 5-FU and oxaliplatin. Bevacizumab IP concentrations, IV concentrations and ratio at 24 h after infusion.

	Parameter	*Min*	*Q1*	*Median*	*Q3*	*Max*
5-FU						
	*AUC IP (ng*h/mL)*	302	$1.02*10^3$	$2.76*10^3$	$4.46*10^3$	$8.66*10^3$
	*AUC IV (ng*h/mL)*	$3.59*10^3$	$7.41*10^3$	$11.6 *10^3$	$16.2*10^3$	$6.54*10^6$
	Ratio IP/IV	0.000488	0.0528	0.143	0.378	1.11
	Tmax IP	0.45	1.1	1.38	1.84	5.62
	Half-life IP (hours)	0.58	3.56	6.32	12.5	34.9
Oxaliplatin						
	*AUC IP (μg*h/mL)*	6.84	18.3	23.5	40.3	60.8
	*AUC IV (μg*h/mL)*	49.1	56.7	80.7	98.4	149
	Ratio IP/IV	0.0644	0.249	0.352	0.461	0.907
	Tmax IP (hours)	2.07	2.93	3.67	4.53	49
	Half-life IP (hours)	8.04	92.9	137	251	$1.39*10^3$
Bevacizumab						
	$C_{t=24}$ IP (μg/mL)	2.1	3.92	7.92	15.1	25.6
	$C_{t=24}$ IV (μg/mL)	61.5	84.1	90.9	95.8	106
	Ratio IP/IV	0.02	0.04	0.085	0.17	0.27

Abbreviations: AUC, Area Under the Concentration-Time Curve; IP, Intraperitoneal; IV, Intravenous; Tmax, Time to peak drug concentration; $C_{t=24}$, concentration at time 24 h after dose.

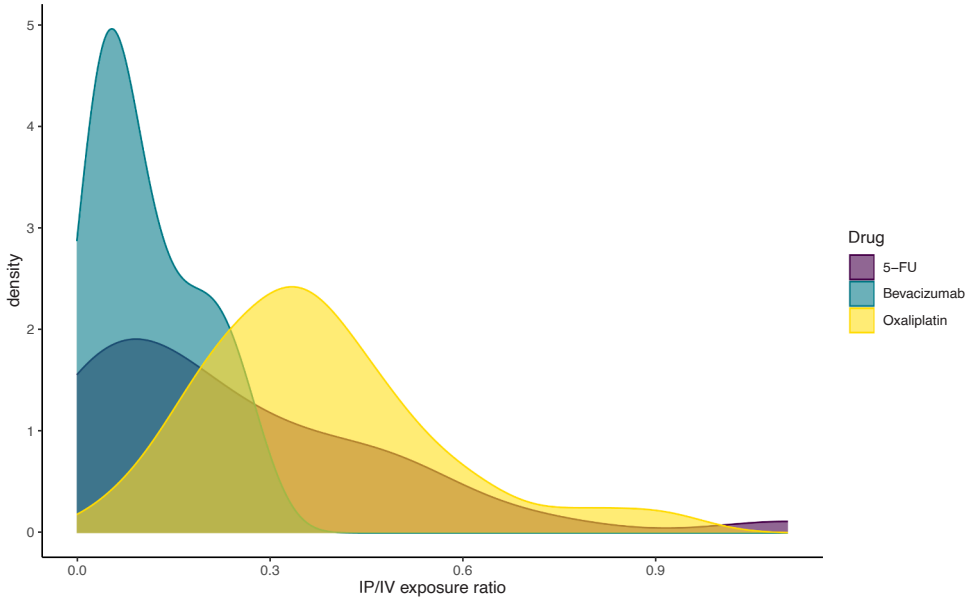

Fig. 2. Kernel density estimation plot of systemic anti-cancer therapy exposure ratios. The plot visualises the estimated probability density functions for exposure ratios of oxaliplatin ($AUC_{IP/IV}$) in yellow, 5-FU ($AUC_{IP/IV}$) in purple and bevacizumab ($C_{IP/IV}$) in green.

chemotherapeutics [20]. Furthermore, in a clinical setting, it was observed that approximately half of the administered oxaliplatin was absorbed from the IP compartment into the central compartment [20,21]. Paradoxically, the capacity to cross the peritoneal-plasma barrier with ease is advantageous for targeting peritoneal metastases when administered IV. In a study from 2011, oxaliplatin was administered IV at 85 mg/m^2 over a 2-h infusion, resulting in an $AUC_{IP/IV}$ (0–26 h) ratio of 0.26 [22]. Our estimated oxaliplatin IP/IV ratio of 0.35 slightly favours exposure in peritoneal fluid, possibly influenced by the extended sample times up to 48 h. Typically, for small molecules, diffusion is the predominant mechanism to penetrate tissue [18]. Therefore, higher drug concentrations in the peritoneal fluid results in higher drug concentrations in tumour tissue. De Jong *et al.* reported high IP exposures in 0.5 h of sampling after an oxaliplatin-based HIPEC (460 mg/m^2), with $AUC_{0–0.5\ h}$ for total platinum in peritoneal fluid at 75.9 μg*h/mL [23]. Additionally, increasing oxaliplatin IP doses led to elevated intratumoural concentrations, indicating a dose-exposure effect [21,24]. However, it is important to note that despite relatively high oxaliplatin concentrations, the effect of this drug on peritoneal metastases is least likely. A mutation analysis showed that CRC-derived PM are predominant of the Consensus Molecular Subtype 4 (CMS4) combined with increased KRAS pathway activation [25]. Moreover, in CRC-PM derived organoids, it was demonstrated that a clinically relevant oxaliplatin HIPEC dose had a minor effect on the viability of different organoid lines [26]. This is probably due to the relative resistance of CMS4 tumours to oxaliplatin [27,28].

A clinical trial investigating 5-FU pharmacology revealed rapid transfer of 5-FU from plasma to peritoneal fluid in the 1.5 h of sampling, resulting in an $AUC_{IP/IV}$ ratio of 2.3 [29]. During this early phase, relatively high concentrations of 5-FU in the peritoneal cavity were observed in our study as well. Prolonged exposure to the drug increases the likelihood of effectively inhibiting DNA synthesis in cancer cells during their growth phase (S-phase) [17]. Yet, only approximately 14 % of IV 5-FU reached the peritoneal metastases, and its levels decreased rapidly thereafter. Administering 5-FU directly into the abdomen achieves higher local drug concentrations at these cancer sites. However, similar considerations as to systemic 5-FU apply to IP 5-FU; while initial high IP/IV ratios suggest favourable pharmacologic properties, a short

retention time is a drawback [20,29].

The effectiveness of bevacizumab relies on prolonged exposure to consistently inhibit VEGF. Poor prognosis in various tumours has been linked to low trough serum concentrations [30]. In our study, we found that the IP concentration of bevacizumab at 24 h after dose is approximately 8.5 % of the IV concentration. However, since bevacizumab primarily operates in the plasma, its effectiveness against peritoneal metastases may not necessarily correlate with high concentrations in the abdominal cavity.

The original purpose of the INTERACT I study was to evaluate the safety and PK of IP administered chemotherapy. This design introduces certain limitations to the present study. Given the very short half-life of 5-FU, there is a potential for missing a portion of its PK profile when sampling times are not specifically tailored to this drug. Additionally, the simultaneous administration of IP irinotecan may impact the pharmacokinetics of IV-administered drugs, likely due to dilution from the extra volume. Nonetheless, irinotecan is not expected to interact with the IV administered treatments [31,32].

Our study shows that only a minor fraction of systemically administered anti-cancer treatment reaches the IP space. This raises questions regarding local efficacy against peritoneal metastases. As the ideal tissue concentration for anti-cancer effects on peritoneal metastases is unknown, the need for maximising local concentration while minimising systemic exposure is emphasised. This strengthens the hypothesis for repeated intraperitoneal chemotherapy to reach adequate anti-cancer drug levels.

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CRediT authorship contribution statement

Cornelis Verhoef: Writing – review & editing, Investigation. **Birgit C.P. Koch:** Writing – review & editing, Supervision. **Eva V. E. Madsen:** Writing – review & editing, Investigation. **Sebastiaan D. T. Sassen:** Writing – review & editing, Supervision. **Niels A.D. Guchelaar:** Writing – review & editing, Investigation. **Stijn L.W. Koolen:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Pascale C.S. Rietveld:** Writing – review & editing, Writing – original draft, Validation, Project administration, Investigation, Formal analysis, Conceptualization. **Ron H.J. Mathijssen:** Writing – review & editing, Supervision, Investigation. **Jacobus W.A. Burger:** Writing – review & editing, Investigation. **Ruben A. G. van Eerden:** Writing – review & editing, Investigation. **Peter de Bruijn:** Writing – review & editing, Validation, Resources. **Nadine L. de Boer:** Writing – review & editing, Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2024.116820.

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