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ABCB1 C3435T, G2677T/A and C1236T variants have no effect in eslicarbazepine pharmacokinetics

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ABSTRACT

Eslicarbazepine acetate is a third-generation anti-epileptic prodrug quickly and extensively transformed to eslicarbazepine after oral administration. Reduction in seizure frequency in patients managed with eslicarbazepine is only partial in the majority of patients and many of them suffer considerable ADRs that require a change of treatment. The P-glycoprotein, encoded by the *ABCB1* gene, is expressed throughout the body and can impact the pharmacokinetics of several drugs. In terms of epilepsy treatment, this transporter was linked to drug-resistant epilepsy, as it conditions drug access into the brain due to its expression at the blood-brain barrier. Therefore, we aimed to investigate the impact of three *ABCB1* common polymorphisms (i.e., C3435T, or rs1045642, G2677A or rs2032582 and C1236T or rs1128503) in the pharmacokinetics and safety of eslicarbazepine. For this purpose, 22 healthy volunteers participating in a bioequivalence clinical trial were recruited. No significant relationship was observed between sex, race and *ABCB1* polymorphism and eslicarbazepine pharmacokinetic variability. In contrast, *ABCB1* C1236T C/C diplotype was significantly related to the occurrence of ADRs: one volunteer with this genotype suffered dizziness, somnolence and hand paresthesia, while no other volunteer suffered any of these ADRs ($p < 0.045$). To the best of our knowledge, this is the first study published to date evaluating eslicarbazepine pharmacogenetics. Further studies with large sample sizes are needed to compare the results obtained here.

1. Introduction

Epilepsy is one of the most common neurological diseases, affecting more than 70 million people worldwide [1]. This disease is characterized by the predisposition to epileptic seizures. Epilepsy pathophysiology's is characterized by epileptogenesis, a process in which a group of neurons develop an abnormal excitability thus triggering spontaneous and recurrent epileptic seizures [1]. Anti-epileptic drugs aim to decrease neural excitability through blocking sodium channels or inhibiting glutamate release, one of the main neurotransmitters of the central nervous system [2]. Although these drugs help to control symptoms, none of them is able to cure the disease. Pharmacogenomics is the discipline that studies genetic biomarkers that predict drug response [3]. Pharmacogenetic testing is well implemented in epilepsy pharmacotherapy as, for instance, patients carrying the *HLA-B**15:02 allele should not receive oxcarbazepine or carbamazepine as the risk for drug-associated cutaneous adverse reactions is significantly increased [4].

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Eslicarbazepine acetate is a third-generation anti-epileptic drug. It was first approved by the European Medicine Agency [5] in 2009 and by the U.S. Food and Drug Administration as an adjuvant treatment for partial seizures [6,7]. The precise mechanism of action of eslicarbazepine remains undeciphered nowadays. However, *in vitro* studies suggest that the drug stabilizes the inactivated state of voltage-dependent sodium channels, which impedes the return to the active state and, consequently the repetitive neuronal firing is avoided [8].

After drug administration, eslicarbazepine acetate is quickly and extensively transformed to eslicarbazepine (S-licarbazepine) by first-pass hydrolytic metabolism and to other metabolites that account for < 5% of the administered dose. It shows more than 90% oral bioavailability. The maximum plasma concentration of eslicarbamazepine (C_{max}) is reached 2–3 h after oral drug administration (t_{max}). It shows low plasma protein binding (<40%) which is independent from the concentration and linear pharmacokinetics in the range of 400–1200 mg. Eslicarbazepine shows an elimination half-life ($t_{1/2}$) of approximately 20–24 h as steady state is reached 5 days after therapy start [7]. Neither eslicarbazepine acetate nor eslicarbazepine undergo significant cytochrome p450 (CYP) metabolism, however, eslicarbazepine is a weak CYP3A4 inducer and CYP2C19 inhibitor. It undergoes glucuronidation and it is mainly excreted by renal route as, of the dose recovered in urine, 61.9% corresponds to eslicarbazepine, 29.9% to eslicarbazepine glucuronide and 4.1% to oxcarbazepine glucuronide [9]. Furthermore, it is a weak *UGT1A1* inducer.

Moreover, the P-glycoprotein (P-gp) is an efflux transporter expressed in different tissues such as the blood brain barrier (BBB) cells, the luminal membrane of small intestine, the apical membrane of hepatocytes and epithelial cells of proximal renal tube [10]. It pumps xenobiotics out of the body compartment where it is expressed, modulating BBB permeation or pharmacokinetic processes of several drugs [11]. Despite eslicarbazepine drug label does not specify if it is a P-gp substrate, *in vitro* studies demonstrated that it has a high affinity for it [12]. P-gp is encoded by the *ABCB1* gene (ATP-binding cassette, subfamily B, member 1). *ABCB1* polymorphism can influence P-glycoprotein function or expression thus participating in inter-individual variability in drug absorption, BBB disposition or drug distribution [13].

The percentage of drug-resistant epilepsy patients is approximately 25–30% [14]. This variability in the response may be explained by different reasons, including genetic factors [15]. Drug disposition in the brain certainly conditions its effectiveness as this is the compartment where it exerts its mechanism of action. As mentioned, P-gp could condition this process and certain variants could be related to unresponsive patients. Moreover, the processes of drug absorption, distribution, excretion and the access to metabolizing organs could be likewise altered. Hence, the aim of this work was to evaluate the effect of the most relevant *ABCB1* variants (i.e., C3435T, or rs1045642, G2677A or rs2032582 and C1236T or rs1128503) in the pharmacokinetics and safety of eslicarbamazepine.

2. Methods

2.1. Study population

The study population comprised 24 healthy volunteers enrolled in a single-dose bioequivalence clinical trial carried out at the Clinical Trials Unit of Hospital Universitario de La Princesa (UECHUP, Madrid, Spain). The protocol complied with current Spanish legislation on clinical research in humans and was approved by the Research Ethics Committee, authorized by the Spanish Drugs Agency (AEMPS) and followed the guidelines of good clinical practice. EudraCT number was 2018-004061-14. All subjects provided their informed consent for the clinical trial, of which 22 signed the written informed consent for the pharmacogenetic study.

Inclusion criteria comprised non-smoking healthy volunteers, aged 18–55 years, body mass index (BMI) inside the 18.5–30.0 range, free from any organic or psychiatric conditions, with normal vital signs, electrocardiogram (ECG), with no clinically significant abnormalities in hematology, biochemistry, serology (Ag HBs, HC antibodies, HIV antibodies) and urine tests, with normal medical records and physical examination. No other drugs were allowed during the study. Exclusion criteria were as follows: having received prescribed pharmacological treatment, consumed controlled substances in the previous 15 days prior to the study or any kind of medication in the 48 h prior to receiving the study medication, hypersensitivity to any drug, daily consumers of alcohol, smokers, having suffered alcohol poisoning the previous week, having consumed illegal or recreational drugs recently, having donated blood in the previous month and being pregnant or breastfeeding, consumption of grapefruits and its products within a period of 48 h prior to dosing or history of difficulty in swallowing.

2.2. Study design and procedures

The clinical trial was designed as a phase I, randomized, open-label, single-dose, single-centre crossover, two-sequence, two-period study, which were separated by a 7-day washout period, with blind determination of the plasma concentrations of eslicarbazepine. The reference formulation was Zebinix ® (eslicarbazepine acetate 800 mg tablets, BIAL - Portela & C^a, SA, Portugal); the test product was another eslicarbazepine acetate 800 mg tablet formulation. In each period, either formulation was administered with 240 ml of water; in the subsequent period, volunteers received the opposite formulation. Subjects fasted from 10 h before until 5 h after drug administration. 19 blood samples for eslicarbazepine plasma determination were collected between baseline and 72 h post dose in EDTA-K2 tubes. Samples were centrifuged for 10 min at 1900g and plasma were stored at − 20ºC until their shipment to an external analytical laboratory. Drug levels were determined with a validated high-performance liquid chromatography mass spectrometry (HPLC-MS/MS) method, validated following EMA standards. The lower limit of quantification (LLOQ) was 50 ng/ml and the upper limit of quantification (ULOQ) was 20,000 ng/ml. Another EDTA-K2 tube was extracted for DNA extraction and genotyping.

2.3. Pharmacokinetic analysis

Pharmacokinetic parameters were calculated by non-compartmental methods using WinNonlin Professional, version 2.0 (Pharsight Corporation, Palo Alto, California). The maximum plasma concentration (C_{max}) and time to reach the maximum plasma concentration (t_{max}) were both obtained directly from concentration-time curves. The area under the curve (AUC) from administration (t = 0 h) to the last measured concentration (t = 72 h) (AUC_t) was calculated by linear trapezoidal integration. The remaining AUC from 72 h to infinite was obtained by dividing the last measured concentration (C_t) by the constant of elimination (k_e). k_e was the slope of the line obtained by linear regression from the points corresponding to the drug's elimination phase. The total AUC from administration to infinity (AUC_∞) was calculated as the sum of AUC_t and the residual area. Half-life ($t_{1/2}$) was calculated by dividing 0.693 by k_e. The total drug clearance adjusted for bioavailability (Cl/F) was calculated by dividing the dose by the AUC_∞ and corrected for weight (Cl/F_w). Vd adjusted for bioavailability (V_d/F) was calculated as Cl/F divided by k_e and corrected for weight (V_d/F_w).

2.4. Safety assessment

Tolerability was assessed by clinical evaluation of adverse events (AEs) and other parameters including vital sign and physical examinations. During the course of the study, volunteers were asked whether they had experienced any AEs and, additionally, those spontaneously notified by the volunteer were documented. The algorithm of Spanish pharmacovigilance system [16] was used to determine causality. According to these criteria, AEs were classified as unrelated, unlikely,

possible, probable and definite. Only those AEs that were definite, probable or possible were considered as adverse drug reactions (ADRs) and considered for statistical analysis [17]. Heart rate (HR), ECG, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were monitored before and 3 h after dosing for safety purposes.

2.5. Genotyping

DNA was extracted from 1 ml of peripheral blood samples using an automatic DNA extractor (MagNA Pure® System, Roche Applied Science, Indianapolis, Indiana) and quantified spectrophotometrically in a NanoDrop® ND-1000 Spectrophotometer (Wilmington, USA). *ABCB1* genotyping and allelic discrimination was carried out with a QuantStudio 12k Flex real-time PCR System (Thermo Fisher Scientific, Massachusetts, USA). The TaqMan assays (Applied Biosystems, California, USA) used for *ABCB1* genotyping were the following: C__7586657_20, for C3435T/rs1045642; C__7586662_10, for C1236T/rs1128503; C_11711720C_30, for G2677A/rs2032582; and C_11711720D_40 for G2677T/rs2032582. These variants were merged into an haplotype as described previously [18]. Additionally, based on prevalence and linkage disequilibrium (LD) data (available at https://ldlink.nci.nih.gov/) for Iberians, Mexicans, Puerto Ricans, Colombians and Peruvians, the following alleles were proposed: *ABCB1* *1 was considered the combination of 1236 C and 3435 C alleles; *2 the combination of 1236 T and 3435 T; *3 the combination of 1236 C and 3435 T; *4 the combination of 1236 T and 3435 C. No LD data is available for G2677T/A as this is a trialellic data. Hence, the presence of the 2677 A variant in conferred the B sub allele of each allele. Furthermore, *1 allele was assigned an activity score of 1, while *2, *3 and *4 alleles were assigned an activity score of 0.5. The sum of both allele's activity scores conferred the global activity score, which was used to infer transporter's phenotype: normal function (NF), with a global activity score of 1.5–2, and decreased function (DF), with a global activity score of 1.

2.6. Statistical analysis

Statistical analysis was performed with SPSS software (version 23). AUC and Cmax were corrected for the dose/weight (DW) ratio (AUC/DW, Cmax/DW) to correct the impact of weight on drug exposure. Pharmacokinetic parameters were logarithmically transformed for statistical analysis to normalize distributions. For the comparison of means, a *t*-test or an ANOVA test was accomplished. Chi-squared test was used to infer statistical significance in contingence tables; when more than 20% of cells had expected frequencies < 5, a Fisher exact test was used. The Hardy-Weinberg equilibrium was estimated for all analyzed variants by comparing the obtained genotype frequencies with the expected frequencies ($p^2 + 2pq + q^2 = 1$) and with a Chi-squared test. For this purpose, the De Finetti program (available at http://ihg.gsf.de/cgi-bin/hw/hwa1.p) was used. Afterwards, a multivariate analysis was performed by means of linear regression (pharmacokinetic parameters) or logistic regression (ADRs). As dependent variables, each pharmacokinetic parameter or ADR were analyzed; as independent variables, any factor with $p < 0.1$ in the univariate analysis as well as race and sex were included; for ADRs, pharmacokinetic parameters without DW correction were included. Type-1 error (α) was estimated at 0.05 and the threshold for significance at $p < 0.05$.

3. Results

A total of 22 healthy volunteers consented to participate in the pharmacogenetic study, with evenly distributed proportions of males and females and of Caucasians and Latin Americans (Table 1). Females exhibited higher age ($p = 0.027$) and lower height ($p < 0.001$) than males and a tendency towards lower weight ($p = 0.055$) (Table 1).

Mean AUC and Cmax were 287.10 ± 58.63 h* μg/ml and 13.32 ± 3.01 μg/ml, respectively; these parameters were higher in females than in males 319.91 ± 59.17 h* μg/ml and 15.41 ± 2.24 μg/ml compared to 259.76 ± 43.58 h* μg/ml and 11.57 ± 2.42 μg/ml, respectively, $p = 0.013$ and o= 0.001). Both variables were inversely and significantly correlated with weight (R2 =0.49 and 0.34, respectively; $p < 0.001$ and 0.004, respectively). After DW correction, these differences were no longer observed (Table 2). Moreover, males showed a higher Vd/Fw than females (*t*-test $p = 0.015$; multivariate analysis $p = 0.015$; unstandardized β coefficient = 0.167; R2 =0.26). No other significant relationship was observed between pharmacokinetic parameters, demographic characteristics and *ABCB1* genotypes, haplotype or phenotype (Table 2). All genetic variants were in Hardy-Weinberg equilibrium (HWE).

3.1. Safety

Both tests and reference formulations showed similar safety profile. No severe, serious or life-threatening ADRs were registered. Eslicarbazepine produced no change on HR, SBP, DBP or ECG. 7 volunteers suffered one ADR and one volunteer suffered 3. Headache was reported 6 times, while dizziness, somnolence, hand paresthesia and increased transaminases only 1 each. Dizziness, somnolence and hand paresthesia occurred exclusively in the only subject with the ABCB1 C1236T C/C genotype, while no cases of these ADRs were reported by C/T (n = 13) or T/T (n = 8) volunteers ($p = 0.045$). No other significant relationship was observed between ADR incidence and sex, race, ABCB1 genotypes, phenotype or haplotype.

4. Discussion

In certain groups of patients with epilepsy treated with eslicarbazepine in monotherapy or as an adjuvant, seizure freedom rates may be considerably low: 23.4% and ADRs occur in 11.4–28.4% of the patients [19]. Henceforth, it is crucial to search for biomarkers that could help to predict response and tolerability to eslicarbazepine treatment and adapt treatment dose to patients' genotype. To the best of our knowledge, this work is the first candidate gene pharmacogenetic study on eslicarbazepine published to date.

After an 800 mg oral dose, mean AUCinf was 287 h* μg/ml, which corresponds to 1129 μmol h/L and mean Cmax was 13.32 μg/ml, which corresponds to 52.44 μM; this is consistent with previous works, where an AUC in steady state (ss) of 1156 μmol h/L and a Cmax-ss of 87.3 μM were observed [20]. Significant differences in eslicarbazepine exposure

Table 1
Demographic characteristics of the healthy volunteers participating in this study.

	n	Age (years)	SD	Height (cm)	SD	Weight (kg)	SD	BMI (kg/m2)	SD
Sex									
Female	10	35.00*	11.22	163.20	6.29	63.49	10.86	23.89	4.10
Male	12	26.50	4.80	176.75*	6.90	72.63	10.12	23.16	1.95
Race									
Caucasian	13	28.54	8.18	172.00	7.05	66.86	11.62	22.57	3.61
Latin-American	9	33.00	10.44	168.56	12.36	70.80	10.83	24.82	1.26
Total		30.36	9.21	170.59	9.47	68.47	11.22	23.49	3.05

* $p < 0.05$ after *t*-test.

Table 2
Eslicarbazepine pharmacokinetic parameters based on demographic characteristics and *ABCB1* genotype.

Variable		n	AUC/DW (kg*h*ng/ml*mg)	SD	C_{max} /DW (kg*ng/ml*mg)	SD	t_{max} (h)	SD	$t_{1/2}$ (h)	SD	Vd/Fw (ml/kg)	SD	Cl/Fw (ml/h*kg)	SD
Sex	Female	10	24985.71	4292.34	1204.88	149.83	0.88	0.28	11.04	2.24	644.9	128.2	41.1	6.54
	Male	12	23263.48	3100.55	1039.42	196.47	1.5	0.43	12.11	1.61	754.26*,$	81.54	43.69	5.61
Race	Caucasian	13	24285.95	4057.04	1099.06	212.21	2.71	1.22	11.74	1.78	705.92	104.22	42.22	6.47
	Latin-American	9	23700.18	3324.25	1137.11	168.78	2.77	1.6	11.46	2.28	702.57	139.6	42.94	5.71
ABCB1 C3435T	C/C	4	23901.13	3106.08	1119.65	78.83	2.13	0.94	13.5	2.01	817.34	104.75	42.37	5.02
	C/T	14	24133.81	4346.6	1104.91	236.68	2.88	1.44	11.26	1.58	685.02	111.99	42.66	7.1
	T/T	4	23885.26	2073.44	1143.61	90.07	2.84	1.49	11.02	2.47	660.12	93.5	42.13	3.39
ABCB1 C1236T	C/C C/T**	8	23561.83	3421.05	1046.11	220.24	3.19	1.73	10.79	2.11	659.55	76.43	43.22	5.95
	T/T	14	24323.16	3950.35	1153.78	170.39	2.47	1.06	12.1	1.76	730.27	130.08	42.11	6.28
ABCB1 G2677TA	G/G	7	23716.44	3664.84	1068.78	227.58	2.86	1.57	10.72	2.27	650.48	77.76	43.04	6.4
	G/A	13	24039.33	3920.89	1140.6	191.06	2.83	1.32	11.91	1.38	729.63	132.13	42.55	6.19
	A/A	2	25246.28	4362.98	1106.3	60.03	1.67	0	12.93	4.02	730.78	102.56	40.41	7.09
ABCB1 haplotype	WT	3	23491.35	5806.16	969.01	342.17	2.9	2.02	10.33	2.42	637.63	67.79	44.25	10.09
	HT	8	23161.72	1684.45	1098.96	116.46	2.96	1.56	11.69	2.03	728.7	121.8	43.39	2.88
	MUT	11	24841.01	4316.58	1165.74	187.78	2.53	1.1	11.93	1.83	705.24	124.56	41.4	6.91
ABCB1 phenotype	NF	14	24323.16	3950.35	1153.78	170.39	2.47	1.06	12.1	1.76	730.27	130.08	42.11	6.28
	DF	8	23561.83	3421.05	1046.11	220.24	3.19	1.73	10.79	2.11	659.55	76.43	43.22	5.95

Abbreviations: ABCB1: ATP Binding Cassette, Family B, Member 1. AUC/DW: area under the curve corrected by dose/weight. C_{max}/DW: maximum concentration corrected by dose/weight. V_d/F_w: volume of distribution adjusted for bioavailability corrected for weight; Cl/F_w: clearance adjusted for bioavailability corrected for weight. SD: standard deviation.

* $p < 0.05$ after *t*-test;

$ $p < 0.05$ after multivariate analysis.

** Only one *ABCB1* C1236T C/C individual was observed.

were observed according to sex, however, exposure was inversely related to weight and, as expected, men's weight was higher than that of women. Congruently, after correcting for DW, no differences in these parameters according to sex were observed. However, males showed significantly higher Vd/Fw values compared to women. Unfortunately, the volume of distribution for this work was estimated by non-compartmental methods and the value of F (bioavailability) was not available. Therefore, Vd/F was corrected for weight (not for DW as dose is already used to estimate Vd/F) following the same justification as for AUC and Cmax DW corrections. Adding the limitation in the calculation of the parameter to the number of comparisons made, this association is likely to be spurious. In fact, by applying a Bonferroni correction for multiple comparisons, significance is discarded. Therefore, we can conclude that sex itself has no impact in eslicarbazepine exposure, which is consistent with previous works [21]. Likewise, race had no impact on eslicarbazepine pharmacokinetic variability, which is consistent with previous works as well [22].

Different studies underlined the importance of ABCB1 variants in drug resistant epilepsy [23–25]. In fact, a meta-analysis demonstrated that there is an association of drug resistant epilepsy and the presence of C3435T SNP (ABCB1), located on exon 26 [25]. Moreover, ABCB1 harbors a huge amount of rare and population-specific variations that may have an impact in the transporter's function [26]. We hypothesized that *ABCB1* polymorphism could influence brain permeation and, consequently, eslicarbazepine effectiveness and central nervous system (CNS) toxicity. Here, neither individual *ABCB1* SNPs nor haplotypes or phenotypes had an impact in eslicarbazepine pharmacokinetic variability. Further observational studies are warranted as, to date, no work was published with which to compare our results.

Concerning safety, the C allele at *ABCB1* C1236T (rs1128503) was related to a significantly increased risk for developing dizziness, somnolence and hand paranesthesia. Of note, all these ADRs occurred in a single individual. It is therefore difficult to assume whether this occurred by chance or not. A vast amount of observational studies analyzed the impact of this variant in a variety of substrates and clinical settings to date. Only in the Pharmacogenomics Knowledgebase (PharmGKB), 222 variant annotations are indexed for this variant (Supplementary File 1). However, no consensus was reached to date on the clinical effect of the variant in any clinical setting and for any drug. The volunteer with this genotype was not particularly overexposed to eslicarbazepine, with mean AUC and Cmax values close to the mean. Therefore, we can suggest that *ABCB1* C1236T (rs1128503) C/C diplotype may impair P-gp function at the BBB and drug disposition in the brain would be higher. Unfortunately, no works are available to corroborate or dismiss our hypothesis.

4.1. Limitations

The main limitation of our study was the small sample size. Further studies involving a higher number of subjects are required in order to provide a comparator to our results. Moreover, it would be interesting to genotype additional genes like uridine glucuronosyltransferases (including *UGT1A4, UGT1A9, UGT2B4, UGT2B7* and *UGT2B17*) as they are involved in the metabolism of eslicarbazepine [27]. Furthermore, our study was performed after a single-dose administration to healthy subjects, which does not allow assessing long-term effectiveness and safety; pharmacokinetics, pharmacodynamics, and tolerability might vary in epileptic patients receiving chronic treatment. However, our study design allows controlling other confounding factors such as smoking or concomitant treatments.

5. Conclusions

Sex, race, and *ABCB1* variants had no impact in eslicarbazepine pharmacokinetic variability. ABCB1 C1236T C/C diplotype was significantly related to the occurrence of ADRs, in particular, one volunteer with this genotype suffered dizziness, somnolence and hand paresthesia; nevertheless, this result may be a spurious finding. To the best of our knowledge, this is the first study published to date evaluating eslicarbazepine pharmacogenetics. Further studies with large sample sizes are needed to compare the results obtained here.

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CRediT authorship contribution statement

Pablo Zubiaur: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **Miriam del Peso-Casado:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Visualization, Writing – original draft. **Dolores Ochoa:** Investigation, Writing – review & editing. **Teresa Enrique-Benedito:** Investigation, Writing – review & editing. **Gina Mejía-Abril:** Investigation, Writing – review & editing. **Marcos Navares:** Investigation, Writing – review & editing. **Gonzalo Villapalos-García:** Writing – review & editing. **Manuel Román:** Investigation, Writing – review & editing. **Francisco Abad-Santos:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft. **María Carmen Ovejero-Benito:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft.

Conflict of interest statement

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. However, the work reported in this manuscript was not associated with any drug. As this work did not receive financial support from any pharmaceutical company, the authors have no conflicts to declare related to the current publication.

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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.2021.112083.

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