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ORIGINAL ARTICLE

Binding interactions with sevelamer and polystyrene sulfonate *in vitro*

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Abstract

This study explored the binding of 28 drugs, which were selected based on frequency of concomitant use and chemical properties, to sevelamer and polystyrene sulfonate *in vitro*. The relative binding was determined by dissolving the investigated drugs alone (=control), together with 800 mg of sevelamer and 15 g of polystyrene sulfonate at different pH levels (1.5, 5.5, and 7.4), respectively. After incubation at 37°C and shaking for 60 min, the solutions were diluted and centrifuged, and the drug concentrations were quantified with validated analytical assays. The binding assays were performed in threefold. The mean relative binding (MRB) at each pH level was calculated, with a MRB >20% for at least one pH level to be considered as relevant binding. Fourteen and 23 potentially new binding interactions were identified with sevelamer and polystyrene sulfonate, respectively. These potentially new binding interactions have to be studied *in vivo* to assess their clinical relevance.

KEYWORDS
absorption, chronic kidney disease, clinical pharmacy, drug interactions

1 | INTRODUCTION

Resins, such as sevelamer and polystyrene sulfonate, are used to treat hyperphosphatemia and hyperkaliaemia in patients with chronic kidney disease (CKD).[1,2] Sevelamer and polystyrene sulfonate bind phosphate and potassium in the gastrointestinal tract, respectively, preventing their absorption and thereby reducing elevated phosphate and potassium levels, which may cause serious complications in CKD patients.[3–5] In addition to its phosphate binding properties, sevelamer acts as a bile acid sequestrant and significantly reduces low-density lipoprotein cholesterol levels.[3] Because of their binding properties, resins are known to bind other drugs in the gastrointestinal tract, decreasing their bioavailability and clinical effectiveness.

Clinical studies and case reports have shown that sevelamer binds to levothyroxine, ciprofloxacin, mycophenolic acid, tacrolimus, cyclosporine, vitamin D analogues, lipid soluble vitamins like vitamins A, E, and K, folic acid, quetiapine, furosemide, and levetiracetam.[6-21] For polystyrene sulfonate, binding interactions have been described with lithium, quetiapine, and levothyroxine.[21-23] CKD patients often use many different drugs (average of eight drugs a day), and the prevalence of potential drug–drug

Abbreviations: MRB, mean relative binding; CKD, chronic kidney disease; RB, relative binding.

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interactions in CKD patients is high (75%–91%).[24-30] Therefore, probably more drug binding interactions with sevelamer and/or polystyrene sulfonate than already described in literature may be of clinical relevance.

Previously, we performed an in silico study, analyzing drug utilization data and chemical properties of these co-dispensed drugs, and identified various drugs that potentially may bind to sevelamer or polystyrene sulfonate.[31] A next step to study binding interactions is performing *in vitro* experiments in which gastrointestinal conditions are simulated in the laboratory and binding of different drugs is tested by determining drug concentrations with and without the presence of sevelamer or polystyrene sulfonate. *In vitro* testing provides a valuable tool whereby numerous drugs can be tested relatively quickly to limit the number of candidates taken forward into clinical drug interaction studies.[32]

The aim of this study was to identify potential new binding interactions with sevelamer and with polystyrene sulfonate by assessing the relative *in vitro* binding of different drugs to these resins.

What is already known about this subject?

- Sevelamer and polystyrene sulfonate are used in chronic kidney disease patients for binding phosphate and potassium.
- These drugs are known for binding interactions, decreasing the bioavailability and clinical effectiveness of concomitantly administered drugs.
- *In vitro* testing is a valuable tool to identify potentially new binding interactions.

What does this study add?

- Fourteen potentially new binding interactions were identified with sevelamer by performing *in vitro* experiments.
- For polystyrene sulfonate, 23 potentially new binding interactions were identified.
- pKa values may be used to predict binding to these resins *in vitro*.

2 | MATERIALS AND METHODS

2.1 | Selection of the investigated drugs

We used the list of drugs co-dispensed in patients using sevelamer/polystyrene sulfonate from our previous study.[31] Assessment of the chemical properties, pKa-, and log P-values of these drugs, in combination with the available validated analytical methods to quantify these drugs in the laboratory of the Deventer Teaching Hospital, led to the selection of 28 drugs for the current study, depicted in Table 1.[33] Salicylic acid was used to represent acetylic salicylic acid because *in vivo* exposure to acetylic salicylic acid is measured by measuring salicylic acid, and therefore the available analytical method was for quantifying salicylic acid and not acetylic salicylic acid. This was justified because the potential binding is based on the carboxylic acid group and not the acetylic group.

2.2 | Prediction of binding

Drugs negatively charged at gastrointestinal pH levels based on the pKa value potentially bind to sevelamer. In addition, drugs with log P-value ≥2.0 potentially bind to sevelamer.[3,32,33] For polystyrene sulfonate, drugs potentially bind when positively charged at gastrointestinal pH levels based on pKa value.[4,5,33] In Table 1, the predicted binding of the investigated drugs to sevelamer/polystyrene sulfonate is presented.

2.3 | Experimental procedure

The relative binding (RB) of 28 drugs (Table 1) to sevelamer and polystyrene sulfonate was determined by performing *in vitro* binding experiments at simulated gastrointestinal environment conditions. The intraluminal pH of the gastrointestinal tract varies from pH < 3 in the stomach to 7.4 in the terminal ileum. To simulate the different pH environments of the gastrointestinal tract, which may affect binding, the assays were executed at pH 1.5, 5.5, and 7.4. The pH-adjusted aqueous solutions were prepared by adjusting the pH of Milli-Q®-water with sodium hydroxide 2 M and hydrochloric acid 2 M. The investigated drugs (Table 1) were disintegrated/dissolved in 50.0 ml pH-adjusted aqueous solution alone (control), in 50.0 ml pH-adjusted aqueous solution together with 800 mg of sevelamer (Renvela® sachet 2.4 g), and in 100.0 ml pH-adjusted aqueous solution together with 15 g of polystyrene sulfonate sodium (Resonium A®). These solutions were incubated at 37°C and shaken for 60 min. The solutions of the investigated drugs were further diluted in 10.0 ml of the corresponding pH-adjusted aqueous solution. Each diluted solution was centrifuged at 4000 rpm for 5 min. Finally, the concentrations of the investigated drugs were measured with validated analytical assays that are routinely used in the laboratory of the Deventer Teaching Hospital for therapeutic drug monitoring and clinical toxicology. The used analytical techniques were liquid chromatography tandem mass-spectrometry and liquid chromatography with diode array detection. For each drug, the binding assays were performed in threefold at each pH level. The experimental procedure is graphically depicted in Figure 1.

2.4 | Data analysis

The RB is calculated as follows:

$$RB = 100\% \times (U - T)/U,$$

where U is the mean measured concentration of the investigated drug in the control solution and T is the measured concentration of the

investigated drug combined with sevelamer/polystyrene sulfonate. The mean relative binding (MRB) and the standard deviations were calculated for each drug–resin combination, for each pH value. A MRB > 20% for at least one pH level was considered as relevant binding. This cut-off was chosen by analogy with requirements in bioequivalence studies in which an exposure of less than 80% or more than 125% is considered not bio-equivalent. An exposure of <80% may result in clinically relevant less effectiveness, and an exposure of >125% may result in clinically relevant more adverse effects. Because binding to resins in the gastrointestinal tract will result in less exposure, the lower cut-off level of 20% was used.

3 | RESULTS

The results of the drugs with relevant binding (MRB > 20% for at least one pH level) are presented in Table 2. The drugs in this table are ordered from the highest MRB to the lowest MRB.

3.1 | Sevelamer

Salicylic acid, flucloxacillin, and sulfamethoxazole showed relevant binding to sevelamer as predicted based on pKa value at pH levels 5.5 and 7.4. In contrast, valproic acid showed no relevant binding. Amitriptyline and haloperidol had a MRB of about 40% and 22% at all pH levels, respectively. Binding of these drugs to sevelamer was predicted based on log P-value. This also counts for amiodarone, sertraline, imipramine, mirtazapine, clomipramine, duloxetine, fluvoxamine, and phenytoin. These drugs showed a MRB > 20% at one pH level but not at the other two pH levels. In some of these drugs, the standard deviation of the MRB was high (Table 2). The MRB of trimethoprim of 53% at pH level 1.5 was not predicted. For the investigated drugs (Table 1) not mentioned in Table 2, the MRB to sevelamer was ≤20% at all three pH levels. Carbamazepine, citalopram, clonazepam, clozapine, fluoxetine, nortriptyline, paroxetine, risperidone, valproic acid, and venlafaxine, predicted to bind based on log P-value, showed no relevant binding. For amiodarone,

TABLE 1 Investigated drugs and predicted binding to sevelamer and polystyrene sulfonate

Drug	Product	pKa beneath Binding prediction sevelamer	Log P beneath Binding prediction sevelamer	pKa beneath Binding prediction polystyrene sulfonate
Amiodaron	Amiodarone HCl TEVA 200 mg	No	Yes	Yes
Amitriptyline	Amitriptyline HCl CF 50 mg	No	Yes	Yes
Aripiprazole	Aripiprazole DMB 2.5 mg	No	Yes	Yes
Carbamazepine	Carbamazepine CF 200 mg	No	Yes	No
Citalopram	Citalopram CF 10 mg	No	Yes	Yes
Clomipramine	Clomipramine Sandoz 25 mg	No	Yes	Yes
Clonazepam	Rivotril® 0.5 mg	No	Yes	No
Clozapine	Clozapine Sandoz 25 mg	No	Yes	Yes
Duloxetine	Duloxetine CF 30 mg MSR	No	Yes	Yes
Flucloxacillin	Flucloxacillin Mylan 500 mg	Yes	Yes	No
Fluoxetine	Fluoxetine CF 20 mg	No	Yes	Yes
Fluvoxamine	Fluvoxamine maleate CF 50 mg	No	Yes	Yes
Haloperidol	Haloperidol PCH 1 mg	No	Yes	Yes
Imipramine	Imipramine CF 25 mg	No	Yes	Yes
Lamotrigine	Lamictal® dispers 50 mg	No	No	Yes
Metformin	Metformin TEVA 500 mg	No	No	Yes
Mirtazapine	Mirtazapine Mylan 15 mg	No	Yes	Yes
Nortriptyline	Nortrilen® 25 mg	No	Yes	Yes
Paroxetine	Paroxetine PCH 10 mg	No	Yes	Yes
Phenytoin	Diphantoine-Z–75®	No	Yes	No
Pipamperone	Dipiperon® 40 mg	No	No	Yes
Risperidone	Risperidone PCH 0.5 mg	No	Yes	Yes
Salicylic acid	Acidum salicylicum (90) Fagron BV	Yes	No	No
Sertraline	Sertraline PCH 50 mg	No	Yes	Yes
Sulfamethoxazole	Cotrimoxazol 480 mg	Yes	No	Yes
Trimethoprim	Cotrimoxazol 480 mg	No	No	Yes
Valproic acid	Depakine Enteric® 150 mg	Yes	Yes	No
Venlafaxine	Venlafaxine PCH 37.5 mg retard	No	Yes	Yes

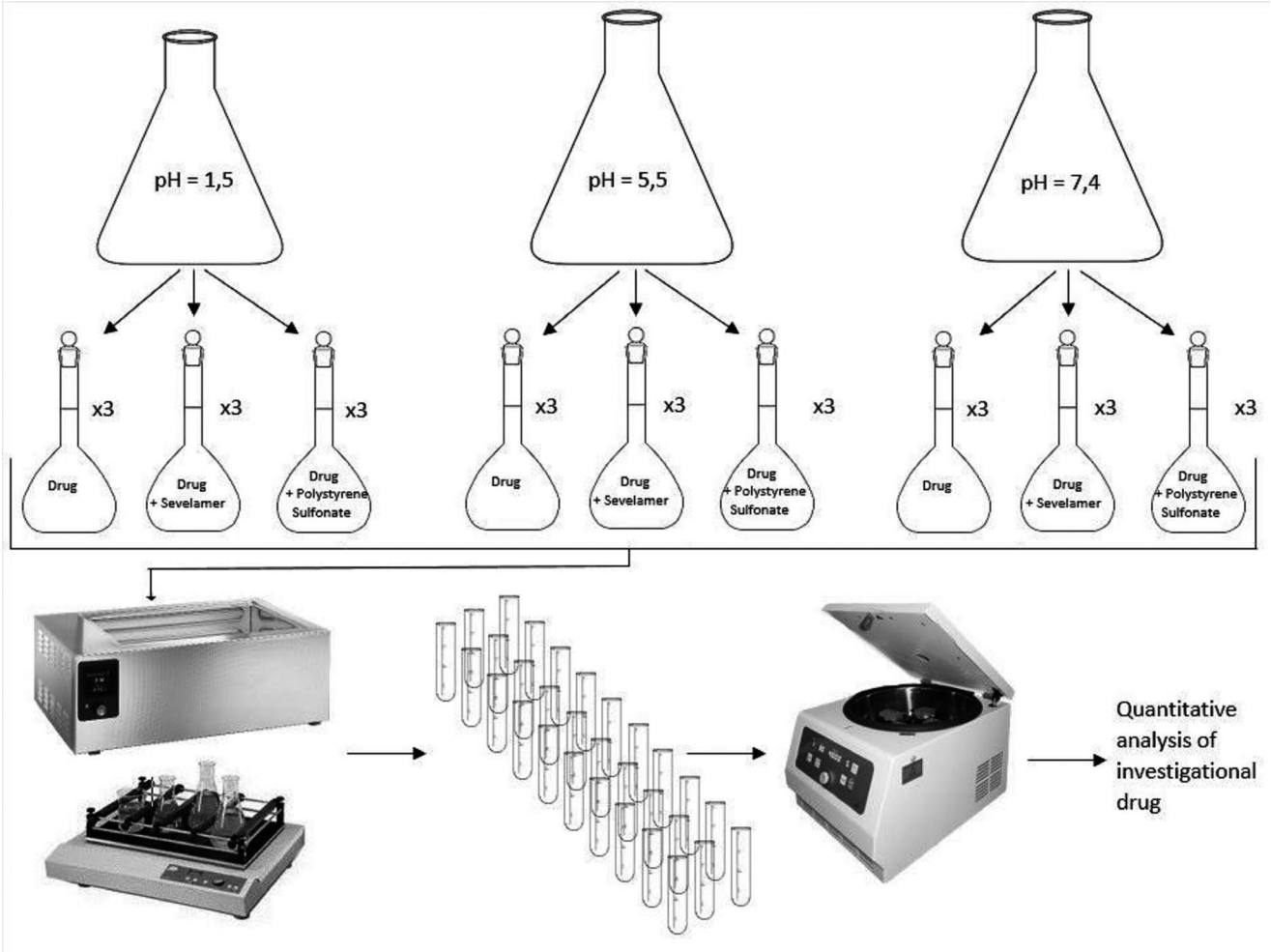

FIGURE 1 Experimental procedure.

aripiprazole, and flucloxacillin, not all results were available because of solubility or stability issues.

3.2 | Polystyrene sulfonate

All investigated drugs predicted to bind to polystyrene sulfonate based on pKa value showed relevant bindings of 48%–100% at all three pH levels. The drugs not predicted to bind to polystyrene sulfonate (Table 1) showed MRBs ≤ 20% at all three pH levels with the exception of clonazepam, which showed a MRB > 70% independent of pH level. For carbamazepine, there were no results due to solubility issues.

4 | DISCUSSION

In this study, 14 and 23 relevant candidates were identified for binding interactions with sevelamer and polystyrene sulfonate, respectively, based on *in vitro* binding.

In vitro experiments, to assess binding to resins, have been described in literature before.[21,23,32,34-43] The sensitivity of *in vitro* studies for identifying compounds binding to resins is high, but the specificity may be low.[32] Studies confirming that *in vitro* binding is also clinically relevant *in vivo* have been described for different drug–resin combinations.[21,22,32,39,40,42,43] However, there are also several studies in which *in vitro* binding could not be confirmed *in vivo* to the same extent.[32,34,36,41,44-46] This can be explained by the fact that drug absorption from the gastrointestinal tract is affected by many different factors such as absorptive surface area, pH, food effects, co-medication, intestinal transit time, passive intestinal permeability, intestinal transporters, and enzymes that are not accounted for *in vitro*.[47]

To select candidates for confirmatory *in vivo* studies, drugs with the highest *in vitro* binding should be given priority. For polystyrene sulfonate, all candidates showed high MRBs of 48%–100% at all three pH levels, while for sevelamer, flucloxacillin, acetylic salicylic acid, amiodarone, and sulfamethoxazole showed the highest binding. However, also the therapeutic window of the drug and the absence of a clinical effect parameter determine the clinical relevance of a binding interaction.

For polystyrene sulfonate, binding results with investigated drugs were in accordance with predictions based on pKa values, with the exception of clonazepam, that unexpectedly showed binding to polystyrene sulfonate. Polystyrene sulfonate lowers the

TABLE 2 Mean relative binding to sevelamer/polystyrene sulfonate

	RB to sevelamer (mean (%) ± SD)				RB to polystyrene sulfonate (mean (%) ± SD)		
Drug/pH	**1.5**	**5.5**	**7.4**	**Drug/pH**	**1.5**	**5.5**	**7.4**
Salicylic acid	NB[a]	85 ± 2	73 ± 2	Duloxetine	100 ± 0	100 ± 0	100 ± 0
Flucloxacillin	NA[b]	65 ± 3	74 ± 6	Sertraline	99 ± 0	99 ± 1	100 ± 0
Amiodarone	NB	NA	58 ± 20	Amitriptyline	96 ± 1	99 ± 0	98 ± 1
Sulfamethoxazole	NB[a]	54 ± 3	48 ± 4	Aripiprazole	99 ± 0	69 ± 7	76 ± 9
Trimethoprim	53 ± 4	NB	NB	Citalopram	99 ± 0	99 ± 0	99 ± 0
Sertraline	45 ± 22	14 ± 3	NB	Clomipramine	99 ± 0	99 ± 0	99 ± 0
Amitriptyline	43 ± 24	37 ± 5	44 ± 14	Clozapine	99 ± 0	80 ± 0	72 ± 0
Imipramine	38 ± 7	12 ± 10	NB	Imipramine	99 ± 0	99 ± 0	99 ± 0
Mirtazapine	11 ± 40	38 ± 1	NB	Nortriptyline	99 ± 0	99 ± 0	99 ± 0
Clomipramine	9 ± 11	31 ± 13	6 ± 12	Risperidone	99 ± 0	99 ± 0	99 ± 0
Duloxetine	7 ± 8	29 ± 12	21 ± 3	Venlafaxine	96 ± 1	99 ± 0	99 ± 0
Haloperidol	20 ± 7	24 ± 6	24 ± 40	Fluoxetine	98 ± 0	98 ± 0	98 ± 0
Fluvoxamine	NB	22 ± 6	8 ± 7	Fluvoxamine	97 ± 0	98 ± 0	98 ± 0
Phenytoin	21 ± 10	NB	NB	Haloperidol	98 ± 0	97 ± 0	98 ± 0
				Mirtazapine	98 ± 0	98 ± 0	96 ± 1
				Pipamperone	98 ± 0	98 ± 0	98 ± 0
				Lamotrigine	97 ± 0	52 ± 4	48 ± 5
				Clonazepam	96 ± 0	74 ± 2	72 ± 3
				Metformin	96 ± 0	96 ± 0	86±17
				Paroxetine	93 ± 2	94 ± 2	95 ± 2
				Trimethoprim	89 ± 0	94 ± 0	94 ± 0
				Amiodarone	57 ± 0	71 ± 3	87 ± 4
				Sulfamethoxazole	86 ± 4	NB[c]	NB[c]

Abbreviations: NA, not available; NB, no binding; RB, relative binding; SD, standard deviation.

[a]Salicylic acid and sulfamethoxazole are negatively charged at pH 5.5 and 7.4 but not at pH 1.5.

[b]Flucloxacillin was not stable at pH 1.5.

[c]Sulfamethoxazole is positively charged at pH 1.5 but not at pH 5.5 and 7.4.

plasma potassium concentration through exchange of potassium and sodium/calcium ions in the gastrointestinal tract, which explains the binding with positively charged drugs at gastrointestinal pH levels.[4,5] Sevelamer is a polymer containing several amines that become partially protonated in the gastrointestinal tract and interact with phosphate molecules through ionic and hydrogen binding.[3] Compounds negatively charged in the gastrointestinal tract may bind to sevelamer, indicating that pKa values may be predictive for binding capacity. In this study, this was confirmed in three out of four of the investigated drugs. Flucloxacillin, salicylic acid, and sulfamethozazole showed a MRB of 80%, 70%, and 50%, respectively, where as the MRB of valproic acid was ≤20% at all pH levels. In addition, sevelamer acts as a bile sequestrant and may also bind lipophilic compounds.[3] Prediction of binding based on log P-value was less accurate, that is, only 50% of the investigated drugs predicted to bind to sevelamer showed a MRB of >20% for at least one pH level. These findings were not consistent at all pH levels, and variation in MRB was high. Furthermore, the high trimethoprim MRB of 53% to sevelamer at pH level 1.5 cannot be explained by pKa or log P-value. Possibly, there is an interaction based on hydrogen binding.

A strength of this study is the selection of the investigated drugs from a large database study of co-dispensed drugs in patients using sevelamer/polystyrene sulfonate. We selected drugs regularly used in patients with CKD, taking into account their chemical properties (pKa and log P), as potential binding candidates for performing these *in vitro* experiments. We have shown that *in vitro* experiments represent a relatively quick and simple tool to identify many potential novel drug binding interactions. This study has resulted in 37 potentially new binding interactions and also provides information on drugs not binding to these resins. The latter is also clinically relevant information when establishing dosing regimens for patients. The well-described design of the study, mimicking gastrointestinal environment, is easy to reproduce in clinical pharmacy laboratories performing routine therapeutic drug monitoring. However, this design does not reflect all physiological factors influencing absorbance of drugs, which is a limitation of this study. More sophisticated *in vitro* and computational designs have been described to study drug binding and drug absorbance, which are worthwhile to investigate, because they may reduce the necessity of confirmatory *in vivo* studies.[47,48] However, the facilities needed for these designs are mostly not available in routine

daily practice of clinical pharmacists. Another limitation of our study was low recovery found for some of the investigated drugs, for example amiodarone. This may be due to low water solubility of some of the lipophilic investigated drugs because we measured lower concentrations in the aqueous solutions than theoretically calculated. Additionally, instability may be a cause for the low recovery found as we observed for flucloxacilline in solution pH 1.5. We believe that these results are still valid because we measured relevant decreased concentrations incubated together with the resins compared with control. However, the results that show high variation in binding within the triplicate should be interpreted more cautiously.

CKD patients, the main users of sevelamer and polystyrene sulfonate, use many different drugs for comorbidities such as cardiovascular disease, diabetes mellitus, metabolic disorders, gout, and anaemia.[24,25] Binding interactions with sevelamer or polystyrene sulfonate may lead to ineffective treatment of these comorbidities. In the Netherlands, electronic medication surveillance systems containing information about known drug interactions are used by physicians and pharmacists during prescribing and dispensing. In general, for binding interactions, the advice is to stagger dosing between the drugs.[24,25] More knowledge of new binding interactions with sevelamer and polystyrene sulfonate will improve treatment of CKD patients significantly. Therefore, the potentially new binding interactions that were identified in the current study should be further studied *in vivo* to assess the clinical relevance. We suggest to perform prospective cross-over studies in healthy volunteers in which participants ingest the investigated drug alone on one day and simultaneously with sevelamer of polystyrene sulfonate on another day, after which bloodsamples are taken on different time points during both days. The effect of combined intake on exposure of the investigated drug can be measured by comparing the maximum concentration and the area under the curve for the investigated drug taken together with the resin and the investigated drug taken alone. The advantage of healthy volunteers is that variation in binding can be minimized by exclusion of co-medication and standardization of food intake. A disadvantage is that the effect of CKD itself or other comorbidities on exposure of the investigated drug is not accounted for.

5 | CONCLUSION

This study identified 14 and 23 potentially new binding interactions with sevelamer and polystyrene sulfonate, respectively, in *in vitro* experiments. Further research *in vivo* is necessary to assess the clinical relevance of these results.

ETHICS STATEMENT

No ethics committee approval is needed for performing *in vitro* research.

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DISCLOSURE

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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