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Ion release from bioactive dental liner materials by ion chromatography

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ABSTRACT

Objective: Bioactive liner materials are used to promote dentine bridge formation, reduce early pulp inflammation, and support remineralization. Ion release is a key factor in understanding their role in biomineralization processes. This study is the first to employ a single method to quantitatively and qualitatively analyze the simultaneous release of multiple ions from various liner materials.

Methods: Ion chromatography was used to measure the release of 16 anions and cations into water, along with pH changes, on days 1, 4, 7, 14, and 30. The tested liner materials included an experimental liner/base from Solventum (EXP), TheraCal LC (TC), Dycal (DY), Lime-Lite Enhanced (LL), Fuji Lining LC Paste Pak (FL), and Medcem MTA (MC). Statistical analysis included the Shapiro-Wilk, Kruskal-Wallis, and Friedman-tests ($\alpha = 0.05$).

Results: DY exhibited the highest pH (~12) after 30 days, followed by MC (~10), both significantly higher than FL. Of 16 tested ions, 9 were cumulatively released in quantifiable amounts. FL showed the highest F^- (279 µg/mL) and Sr^{2+} (128 µg/mL) release. LL released the most Cl^- (101 µg/mL) and PO_4^{3-} (31 µg/mL), while SO_4^{2-} peaked in TC (111 µg/mL). DY released the most Ca^{2+} (950 µg/mL). EXP showed the highest NH_4^+ levels, MC the highest K^+, and LL the highest Na^+.

Significance: The differences in ion release and pH values represent a mosaic stone in understanding the biomineralization effects of liner materials, particularly when considered alongside monomer release data in future studies addressing biological and clinical contexts.

1. Introduction

Liners are commonly used in restorative dentistry and dental traumatology to cover exposed pulp tissue or dentin near the pulp. Indications include the removal of carious tissue in deep cavities, accidental pulp exposure, or trauma-related fractures, with the goal of preserving vital pulp tissue and avoiding root canal treatment [1]. Liners, also called base or pulp-capping materials, protect the pulp from restoration chemicals, promote hard tissue formation, may reduce incipient inflammation adjacent to the dentine, and may offer antimicrobial effects [2–6]. Challenges such as material properties and handling influence success rates, along with pulp status and microbial seal integrity provided by final restorations [7]. Effective liners must adhere tightly to dentin, be mechanically stable, easy to apply, and set within a reasonable time [1,8]. Bioactivity in both liners and contemporary restorative materials stems from complex interactions between cells, matrices, and released ions, as reviewed earlier [9]. This research has especially gained importance in the context of modern concepts of carious tissue removal [10]. Various bioactive, ion-releasing materials have been studied, including glass-ionomer cements (GICs), zinc polycarboxylate cements (ZPCs), glass carbomers, bioactive glasses, giomers, composites, adhesives, calcium silicate-based cements, and silver diamine fluoride [9,11]. Key ions involved in dentine biomineralization include calcium, phosphorus, zinc, silicon, fluoride, magnesium, and sodium, along with their salts. For liners, the pulpal interface is critical. Key material classes include calcium hydroxide ($Ca(OH)_2$), calcium silicate-based cements, dentine adhesives, and resin composites [8].

$Ca(OH)_2$ remains the most common material for pulp capping, promoting reactionary or reparative dentinogenesis [12]. While its effect is closely linked to the pulp's natural healing capacity, even without medication, as demonstrated in well-known studies on germ-free animals [13,14], it involves biochemical processes like cell recruitment,

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adhesion, and differentiation into odontoblast-like cells under the superficial layer of necrosis, leading to dentin-like tissue formation within 8–30 days [7]. Its effectiveness is partly due to high concentrations of calcium and hydroxyl ions and alkaline conditions, which stimulate markers such as alkaline phosphatase activity (ALP) and mRNA expression of BMP-2 and fibronectin, along with calcified nodule formation [4,15–19]. Calcium silicate-based cements are considered to be well-suited for pulp capping due to their antimicrobial properties, biocompatibility, bioactivity, mechanical strength, and lower solubility compared to $Ca(OH)_2$ [12]. Liners containing resin monomers been questioned due to limited bioactivity and risks associated with incomplete polymerization [9].

Previous studies investigating ion release from dental materials have employed various analysis techniques (e.g. ICP/MS, colorimetric assay [20,21]) for each species and thus usually only one released ion species was determined per specimen. Another limitation of ICP/MS, for instance, is that it detects elemental atoms and not the specific ionic species and charge states. Likewise, colorimetric assays may be less reliable, as they do not consistently account for potential interfering ions. The ion chromatography (IC) method used in this study represents a significant advancement, as it allows for the simultaneous detection of all ions released from different liner material species in water. IC, an analytical technique, facilitates the simultaneous chromatographic separation of anions and cations in aqueous samples. Therefore, the actual ion species without interfering ions is detected. It operates based on the interaction of ions with an ion-exchange resin inside a chromatographic column, followed by detection, usually through conductivity. IC offers sensitive, multi-ion analysis in a single run without extensive sample preparation, making it particularly suitable for evaluating the intricate ion release profiles of dental materials [22].

This in vitro study aims to address the current lack of comprehensive multi-ion profiling across different classes of liner materials by applying a robust and interference-free analytical method to analyze ion release over a period of up to 30 days. The released ions are of particular interest, as they may contribute to bioactivity and support dentin remineralization processes. At the same time, additional factors - such as the release of resin monomers, which were not assessed here - may also modulate biological effects. Taken together, these parameters may form the basis for future correlations between chemical release profiles and biological responses, ultimately supporting evidence-based criteria for material selection in deep carious lesions and regenerative strategies.

2. Material and methods

The in vitro release of the cations ammonium (NH_4^+), barium (Ba^{2+}), calcium (Ca^{2+}), lithium (Li^+), magnesium (Mg^{2+}), manganese (Mn^{2+}), potassium (K^+), sodium (Na^+), and strontium (Sr^{2+}), as well as the anions bromide (Br^-), chloride (Cl^-), fluoride (F^-), nitrate (NO_3^-), nitrite (NO_2^-), phosphate (PO_4^{3-}), and sulfate (SO_4^{2-}), along with pH values, was measured over a period of 1–30 days for the following bioactive dental liner materials (Table 1, [19,23,24]): experimental liner/base (EXP) (Solventum, St. Paul, MN, USA), TheraCal LC® (Bisco Inc., Schaumburg, IL, USA) (TC), Dycal® (Dentsply- Caulk, Milford, DE, USA) (DY), Lime-Lite Enhanced™ (Pulpdent Corporation, Watertown, MA, USA) (LL), and Fuji Lining LC Paste Pak (GC Corporation, Tokyo, Japan) (FL), and Medcem MTA (Medcem GmbH, Weinfelden, Switzerland) (MC).

2.1. Sample preparation

Zirconia molds (6 mm diameter, 1 mm thickness, surface area 75.4 mm^2, 0.75 cm^2/mL) were used to prepare samples. Each mold was placed on a plastic matrix strip (Frasaco, Tettnang, Germany) and filled with uncured material. After covering with another plastic strip, samples were polymerized for 20 s using a high-intensity LED lamp (Elipar STM10, 1200 mW/cm^2, 3 M ESPE, Seefeld, Germany) in accordance with manufacturer's instructions. Light intensity was verified with a Demetron radiometer (Kerr, Brea, CA, USA).

Four samples were prepared for each material (n = 4). To ensure that equal amounts of material were used, the dry weight was measured immediately after curing. For material MC, specimens were additionally stored at 37 °C,100 % humidity for 4 h prior to incubation to allow for complete setting according to manufacturer's instruction. Samples were then immediately transferred to plastic vials (screw-neck vial, N 9, PP; Macherey-Nagel, Düren, Germany), incubated in 1 mL of deionized water (<18 MΩ·cm; Barnstead Micropure Water Purification System, Thermo Fisher Scientific, Waltham, MA, USA) and stored in the dark at 37°C. At intervals of 1, 4, 7, 14, and 30 days, eluates were removed from vails, and specimen were incubated with 1 mL of fresh deionized water at 37 °C in the dark. Eluates were analyzed for cation and anion concentrations using ion chromatography.

In addition, a procedural blank (negative control) was included to monitor any potential contamination or background ion contributions from the preparation process or storage conditions. As negative control Cenit L (Dreve, Germany; LOT 304080 ×0) a light-cured PMMA resin

Table 1
Bioactive liner materials used in this study and their chemical composition.

Liner material	Type	Composition	References	Manufacturer	Lot number
EXP Liner/Base (EXP)	hybrid resin modified Glass ionomer cement (RMGIC)	experimental		Solventum, St. Paul, MN, USA	NF48558
TheraCal LC® (TC)	Resin-modified Calcium Silicate- based cement	CaO, Sr glass, fumed silica, barium sulfate, barium zirconate, Portland cement type III and resin containing Bis-GMA, PEGDMA	[23,24]	Bisco Inc, Schaumburg, IL, USA	220007329
Dycal® (DY)	Calcium hydroxide	Base paste: 1,3-butylene glycol disalicylate, zinc oxide, calcium phosphate, calcium tungstate, and iron oxide pigments Catalyst paste: calcium hydroxide,N-ethyl-o/p-toluene sulphonamide, zinc oxide, titanium oxide, zinc stearate, and iron oxide pigments	[24]	Dentsply- Caulk, Milford, DE, USA	00114933
Lime-Lite Enhanced™ (LL)	Resin-modified Calcium hydroxide	Hydroxyapatite in a urethane dimethacrylate resin (Blend of diurethane and other methacrylate resins), amorphous Silica	[19]	Pulpdent Corporation, Watertown, MA, USA	220824
Fuji Lining LC Paste Pak (FL)	Resin-modifiedGlass ionomer cement	Paste A: Fluoro-Alumino-silicate glass, HEMA, Dimethacrylic acid ester, initiator, pigment, Paste B: Polyacrylic acid, destilled water, methacrylic acid ester, initiator	Safety Data Sheet 2021	GC Corporation, Tokyo, Japan	2109171
Medcem MTA® (MC)	Hydraulic silicate cement	Portland cement: tricalcium aluminate and silicate, dicalcium silicate, tetracalcium aluminoferrite, calcium oxide + zirconium oxide	Manufacturer Data Sheet 2022	Medcem GmbH, Weinfelden, Switzerland	RX210503

was used. Sample preparation and elution were carried out accordingly.

2.2. Ion chromatography analysis

All equipment parts were purchased from Thermo Fisher Scientific, except mentioned otherwise. Eluate analysis was conducted using an Ion Chromatography (IC) system comprising a Dionex Integrion IC connected to a Dionex AS-AP Autosampler and a Masterflex Ismatec Pump (VWR International GmbH, Darmstadt, Germany). The column flow rate was set to 0.25 mL/min, and eluents were generated from deionized water (<18 MΩ·cm; Barnstead Micropure Water Purification System). The compartment temperature was maintained at 20°C, the cell heater at 35°C, and the column operated at 30°C. Samples (10 µL) were injected in push partial mode for analysis.

Cations were separated using a Dionex IonPac GC12A Guard Column (2 × 50 mm) and a Dionex IonPac CS12A Capillary Column (2 × 250 mm). The eluent, methane sulfonic acid (MSA), was supplied by a Dionex EGC 500 MSA Cartridge and a Dionex CR-CTC 600 Trap Column. The chromatography was performed isocratically with a 20 mM MSA eluent over 25 min. A suppressor (Dionex CSRS 300, 2 mm) was set to 15 mA. Conductivity was recorded continuously for 25 min.

Anions were separated using a Dionex IonPac AG27 Guard Column (2 × 50 mm), a Dionex IonPac AS27 Capillary Column (2 × 250 mm), and a Dionex IonPac CR-ATC 600 Trap Column. The eluent, potassium hydroxide (KOH), was generated with a Dionex EGC 500 KOH Cartridge. The chromatography followed a multi-step gradient protocol with dynamic eluent concentrations and suppressor currents (Dionex ASRS 300, 2 mm). It began at 10 mM KOH with a 13 mA suppressor current, held for 4 min. The eluent concentration increased to 20 mM over 7 min and was maintained for 9 min. It was then raised to 60 mM over 20 min, with the suppressor current set to 35 mA after 1.5 min. After holding at 60 mM for 4 min, the suppressor current was reduced to 13 mA, and the concentration lowered to 10 mM in 1 min. The system was reconditioned at 10 mM for 10 min. Conductivity was recorded for 55 min.

Aliquots of 10 µL were analyzed using the Ion Chromatography (IC) system, with data recorded in Chromeleon 7.2 ES. Cat-/anion identification was based on retention times compared to multi-element reference standards. Calibration was done by correlating peak areas of ten different multi-element reference standard concentrations (0.1 – 10 µg/mL, n = 4).

To validate the method, spiked samples were used to confirm accuracy for ion identification. All elution samples were prepared independently, and observed variability was low across the replicates. Considering the method's robustness and the exploratory nature of the study, four independent experiments were conducted (n = 4) per time point and material. The sample size of n = 4 and surface area-to-volume ratio was adopted in accordance with our previous peer-reviewed studies using GC-MS, and HPLC, where it proved sufficient for evaluating the release of dental composite components such as methacrylates [25–27].

The Limit Of Detection (LOD) was calculated according to the IUPAC definition [28], using the standard deviation of the residuals of the calibration curve (SDr) and the slope of calibration curve (slope): LOD= 3·(SDr)/(slope). This approach reflects the minimum concentration that can be reliably distinguished from background noise, though not necessarily quantified with acceptable accuracy. The Limit Of Quantification (LOQ) was determined using the statistical method of Hubaux and Vos [29], which considers the intersection of the upper confidence interval of the blank response with the lower 99.5 % confidence interval of the calibration curve. This method provides a statistically robust estimate of the point at which quantification becomes reliable within a defined probability range. Since the measurements were performed in a matrix-free system (deionized water), spike/recovery testing was not required. Quantification accuracy was ensured through precise calibration with certified standards and excellent linearity (Table 2).

2.3. pH analysis

The pH of each eluate was measured using a pH 320 Meter (Xylem Analytics, Weilheim, Germany) with an InLab Ultra-Micro-ISM Electrode (Mettler Toledo, Columbus, OH, USA). Eluates were equilibrated to room temperature prior to measurement.

2.4. Statistical evaluation

Data were analyzed using Excel (Microsoft Corporation, Redmond, WA, USA) and SPSS 27.0 (IBM Corporation, Redwood, USA).

The intra-assay variability for ion release measurements was assessed using intraclass correlation coefficients (ICC) with 95 % confidence intervals (CI) [30]. In addition, the median of absolute differences between duplicate measurements was calculated exemplarily for Na^+, F^-, Ca^{2+}, and SO_4^{2-} on day 7.

Given the low intra-assay variability and the high analytical

Table 2
Analytical Performance Parameter for the quantification of anions and cations by ion chromatography (IC), including coefficient of determination (R^2), residual standard deviation of calibration curve (SDr), limit of detection (LOD), and limit of quantification (LOQ). LOD was calculated according to the IUPAC definition using the standard deviation of the residuals of the calibration curve (SDr) and the slope of the calibration curve (slope): LOD = 3 × (SDr) / slope. LOQ was determined using the Hubaux and Vos method at a 99.5 % confidence level. These parameters define the reliability and sensitivity of the quantification method across all measured ions.

	Calibration curve x = µg/mL; Y = µS*min	Coefficient of Determination	SDr [µg/mL]	LOD [µg/mL]	LOQ [µg/mL]
Anions					
Cl^-	$y = 0.000001*x^2 + 0.00366*x + 0.0063$	0,99995	0,0012	0,0984	0,19779
F^-	$y = 0.00666*x + 0.0144$	0,99993	0,0022	0,0991	0,19688
$(NO_2)^-$	$y = 0.00276*x + 0.0039$	0,9999	0,0013	0,1413	0,30928
Br^-	$y = 0.00154*x + 0.0034$	0,99995	0,0006	0,1169	0,23495
NO_3^-	$y = 0.000001*x^2 + 0.00189*x + 0.0048$	0,99996	0,0007	0,1111	0,37107
$(PO_4)^{3-}$	$y = 0.0011*x + 0.0039$	0,99993	0,0005	0,1364	0,27776
$(SO_4)^{2-}$	$y = 0.000001*x^2 + 0.00258*x + 0.0146$	0,99992	0,0012	0,1395	0,31591
Cations					
Li^+	y = 0,01181x−0,0312	0,99999	0,0061	0,1550	0,29142
NH_4^+	y = 0,00208x+ 0,0672	0,9826	0,0096	1,3846	2,64667
Ca^{2+}	y = 0,00452x−0023	0,99997	0,0018	0,1195	0,22269
K^+	y = 0,00248x−0,0204	0,99993	0,0030	0,3629	0,66781
Mg^{2+}	y = 0,00703x−0,0226	0,99999	0,0033	0,1408	0,2641
Na^+	y = 0,00394x−0,0132	0,99997	0,0032	0,2437	0,4647
Mn^{2+}	y = 0,00274x−0,0021	0,99916	0,0029	0,3175	0,59031
Sr^{2+}	y = 0,00214x−0031	0,99989	0,0033	0,4626	0,86117
Ba^{2+}	y = 0,00131x−0,0346	0,99972	0,0034	0,7786	1,44297

precision of the ion chromatography system, data are presented as mean ± standard deviation (SD) to illustrate central tendency and dispersion. This applies equally to pH measurements. However, due to the sample size (n = 4) and limited power to assess normality (Shapiro-Wilk test: 80.3 % of data are statistically consistent with a normal distribution), group comparisons were performed using non-parametric statistical methods. Values determined by IC lower than limit of quantification (LOQ) were excluded from statistical analysis. Cumulative ion releases over 30 days were calculated as the mean of summed releases from each independent experiment. For independent samples, the non-parametric Kruskal-Wallis test was applied, while dependent samples were analyzed using the Friedman test. Post hoc pairwise comparisons were adjusted with Dunn-Bonferroni correction for multiple testing. The significance level was set at $\alpha = 0.05$.

3. Results

3.1. pH values

The pH values measured over time showed that the eluates of all materials, except LL and FL, had lower pH on day 1 compared to the corresponding later measurement intervals (Fig. 1; Friedman test, $p < 0.05$). Significant differences in pH values were observed between materials on day 1 and day 30 (Kruskal-Wallis test). On day 1, DY exhibited a significantly higher pH than all other materials. By day 30, EXP, TC, and LL showed similar pH values around 8, while DY maintained significantly higher values (~12) compared to all other materials. MC also exhibited a significantly higher pH (~10) than EXP, TC, LL, and FL. Notably, FL remained the only material with a clearly acidic pH slightly below 6.

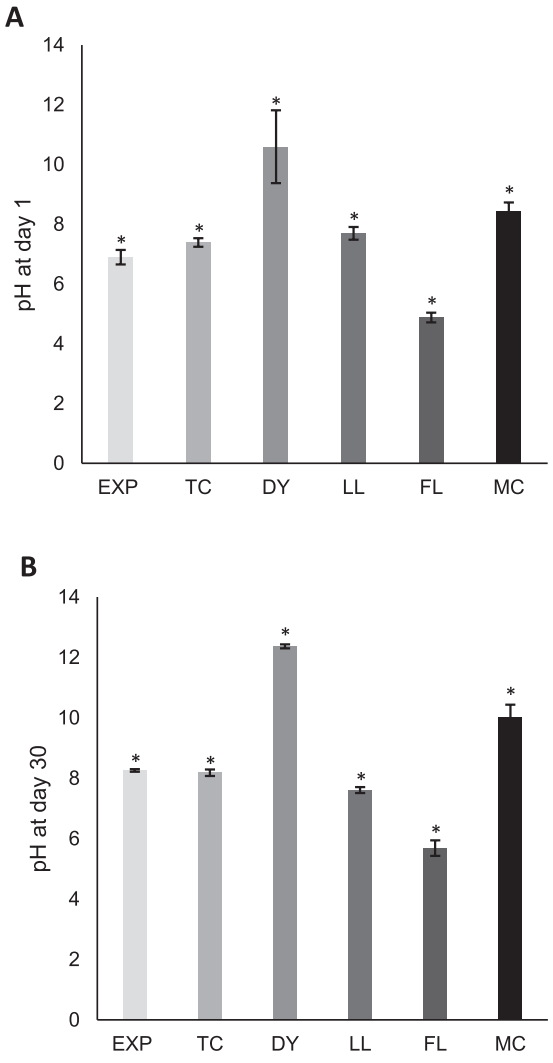

Fig. 1. pH levels of liner eluates at days 1 (A) and 30 (B) (mean ± SD; n = 5). (*) denotes significant differences ($p < 0.05$).

3.2. Ion release

The intra-assay variability was found to be excellent, with an ICC of 0.995 (95 % CI: 0.992–0.997; $p < 0.001$). The corresponding median of absolute differences across the tested ions (Na^+, F^-, Ca^{2+}, and SO_4^{2-}) was 0.11 µg/mL, indicating high analytical precision.

The anions Br^-, NO_3^-, and NO_2^-, as well as the cations Ba^{2+}, Li^+, Mg^{2+}, and Mn^{2+}, were not detected in any material (<LOD across all experiments and time intervals). Detected ions are listed in Table 3 for days 1, 4, 7, 14, and 30, including cumulative values over 30 days. The cumulative release of anions and cations over time is shown in Fig. 2 A-D (anions) and E-I (cations), while Fig. 3 provides an overview. Significant differences in anion and cation release among the tested materials were observed exemplarily on day 1 and for cumulative values after 30 days, as determined by the Kruskal–Wallis test. Corresponding pairwise differences ($p < 0.05$) are detailed in Table 3.

The negative control showed no detectable signal above the determined LODs and LOQs, confirming that no background noise contributed and that the measurements exclusively reflect the release from the tested materials.

3.3. Anions

On day 1, LL exhibited the highest initial **Cl^-** release (24.90 µg/mL), which was significantly higher than the release from EXP (2.75 µg/mL), TC (0.94 µg/mL), FL (3.77 µg/mL), and MC (0.56 µg/mL) ($p < 0.05$). This trend persisted over 30 days, with LL showing a significantly higher cumulative **Cl^-** release (100.84 µg/mL) than all other materials ($p < 0.05$), which exhibited only minimal release.

On day 1, FL released the highest amount of **F^-** (76.48 µg/mL), followed by EXP (10.64 µg/mL), LL (2.33 µg/mL), and MC (0.25 µg/mL). **F^-** concentrations in DY and TC were below LOQ. Subsequent daily **F^-** releases (days 4, 7, 14, and 30) remained mostly consistent across materials. Over 30 days, the cumulative **F^-** release was again highest from FL (278.85 µg/mL), significantly exceeding all other materials ($p < 0.05$), including EXP (66.26 µg/mL), LL (14.15 µg/mL), and MC (0.25 µg/mL), while TC and DY remained below the LOQ throughout the observation period.

LL released the highest amounts of **PO_4^{3-}** (4.86 µg/mL on day 1; 31.38 µg/mL cumulatively over 30 days). EXP released **PO_4^{3-}** only on day 1 (2.71 µg/mL). FL released minimal amounts (0.40 µg/mL), and **PO_4^{3-}** concentrations in TC, DY, and MC remained below the LOD throughout.

SO_4^{2-} release differed significantly between materials on day 1 and cumulatively after 30 days. TC showed the highest cumulative **SO_4^{2-}** release (111.17 µg/mL), followed by EXP (48.14 µg/mL) and FL (15.92 µg/mL). In contrast, DY released only 0.38 µg/mL by day 30, while LL and MC showed no detectable **SO_4^{2-}** release (below the LOD).

3.4. Cations

NH_4^+ was released in decreasing amounts by EXP (9.12 µg/mL), FL (7.08 µg/mL), and LL (5.16 µg/mL) on day 1. Cumulatively, EXP released the highest amount (31.60 µg/mL), followed by LL (22.42 µg/mL) and FL (9.18 µg/mL). No **NH_4^+** release was detected from TC, DY, or MC.

Ca^{2+} release was highest from DY, both initially (66.26 µg/mL) and cumulatively over 30 days (949.91 µg/mL). TC ranked second

Table 3
Quantity of released anions and cations (μg/mL) in eluates of six liner materials (EXP, TC, DY, LL, FL, MC) (n = 4 independent experiments, mean ± SD, and lower/upper limit of 95 % confidence intervals (95 % CI)) after 1, 4, 7, 14, and 30 days. Cumulative release (cum.) after 30 days is shown. Anions: Cl^-, F^-, PO_4^{3-}, SO_4^{2-}; cations: NH_4^+, Ca^{2+}, K^+, Na^+, and Sr^{2+}. <LOD = below limit of detection; LOD < x < LOQ;.

Material		1 d	4 d	7 d	14 d	30 d	cum.
	Anions:						
	Cl^- [μg/mL]						
EXP	mean	$2.75^{b,d,e,f}$	0.43	x	x	x	$3.50^{b,c,d,e,f}$
	SD	0.03	0.17	-	-	-	0.21
	95 % CI	2.70/2.80	−0.25/0.79	-	-	-	2.97/3.93
TC	mean	$0.94^{a,d,e,f}$	x	x	x	x	$0.94^{a,c,d,e,f}$
	SD	0.03	-	-	-	-	0.03
	95 % CI	0.89/0.98	-	-	-	-	0.89/0.98
DY	mean	x	x	x	0.22	0.55	$0.74^{a,b,d,e,f}$
	SD	-	-	-	0.02	0.08	0.10
	95 % CI	-	-	-	0.18/0.26	0.37/0.74	0.41/0.97
LL	mean	$24.90^{a,b,e,f}$	18.02	13.26	20.46	24.21	$100.84^{a,b,c,e,f}$
	SD	1.09	0.27	0.35	0.71	2.19	4.06
	95 % CI	23.16/26.63	17.59/18.45	12.70/13.82	19.32/21.59	20.72/27.69	94.37/107.30
FL	mean	$3.77^{a,b,d,f}$	0.30	x	x	0.53	$4.72^{a,b,d,e,f}$
	SD	0.41	0.01	-	-	0.02	0.28
	95 % CI	3.11/4.42	0.29/0.32	-	-	0.50/0.56	4.27/5.16
MC	mean	$0.56^{a,b,d,e}$	x	x	x	x	$0.56^{a,b,c,d,f}$
	SD	0.19	-	-	-	-	0.19
	95 % CI	0.09/1.02	-	-	-	-	0.09/1.02
	F^- [μg/mL]						
EXP	mean	$10.64^{d,e,f}$	21.43	12.13	10.78	11.28	$66.26^{d,e,f}$
	SD	1.41	3.01	0.62	0.45	0.18	4.20
	95 % CI	8.40/12.88	16.64/26.23	11.14/13.11	10.07/11.50	10.99/11.57	59.58/72.93
TC	mean	x	x	x	x	x	x
	SD	-	-	-	-	-	-
	95 % CI	-	-	-	-	-	-
DY	mean	x	x	x	x	x	x
	SD	-	-	-	-	-	-
	95 % CI	-	-	-	-	-	-
LL	mean	$2.33^{a,e,f}$	2.40	2.02	3.12	4.27	$14.15^{a,e,f}$
	SD	0.34	0.13	0.08	0.25	0.40	0.86
	95 % CI	1.80/2.86	2.20/25.99	1.90/2.14	2.72/3.52	3.64/4.90	12.78/15.51
FL	mean	$76.48^{a,d,f}$	56.99	38.26	47.57	59.55	$278.85^{a,d,f}$
	SD	11.79	12.81	8.59	10.19	11.56	53.93
	95 % CI	57.73/95.24	36.62/77.37	24.59/51.92	31.36/63.78	41.15/77.94	193.03/364.66
MC	mean	$0.25^{a,d,e}$	x	x	x	x	$0.25^{a,d,e}$
	SD	0.03	-	-	-	-	0.03
	95 % CI	0.20/0.31	-	-	-	-	0.20/0.31
	PO_4^{3-} [μg/mL]						
EXP	mean	$2.71^{c,d,e}$	<LOD				$2.71^{c,d,e}$
	SD	0.33					0.33
	min/max	2.18/3.23					2.18/3.23
TC	mean	<LOD					
	SD						
	95 % CI						
DY	mean	<LOD					
	SD						
	95 % CI						
LL	mean	$4.86^{a,d,e}$	4.74	4.30	7.09	8.97	$31.38^{a,b,e}$
	SD	0.76	0.18	0.21	0.57	1.40	2.50
	95 % CI	3.64/6.08	4.456/5.02	3.97/4.63	6.18/8.00	6.75/11.20	27.40/35.35
FL	mean	$0.40^{a,c,d}$	x	x	x	x	$0.40^{a,c,d}$
	SD	0.10	-	-	-	-	0.10
	95 % CI	0.23/0.56	-	-	-	-	0.14/0.80
MC	mean	<LOD					
	SD						
	95 % CI						

Statistical analysis was performed separately for the columns "day 1" and "cum." Letters a-f represent materials appearing in order in the column, indicating difference to the regarding material. E.g. value of material (a) is significantly different to value of material (c), the first value is depicted with the letter of the latter material (c).

(41.56 μg/mL; 171.86 μg/mL), followed by EXP (2.03 μg/mL; 135.73 μg/mL). MC showed moderate cumulative **Ca^{2+}** release (20.98 μg/mL), while LL released only minimal amounts (0.39 μg/mL), and FL remained below the LOD.

MC showed the highest overall **K^+** release (32.26 μg/mL on day 1; 52.72 μg/mL cumulatively). **K^+** was initially detected only in EXP (0.96 μg/mL), increasing to 2.23 μg/mL cumulatively. DY released only 0.71 μg/mL by day 30. No **K^+** release was detected from TC, LL, or FL.

Na^+ release on day 1 was highest in MC (32.68 μg/mL), followed by FL (27.18 μg/mL), EXP (24.92 μg/mL), LL (18.17 μg/mL), and DY (2.68 μg/mL). Over 30 days, LL showed the highest cumulative **Na^+** release (86.72 μg/mL), followed by EXP (62.39 μg/mL), MC (60.88 μg/mL), and FL (57.32 μg/mL). DY released significantly less (36.82 μg/mL), while TC remained below the LOQ.

Sr^{2+} was most pronounced in FL eluates (41.32 μg/mL on day 1; 127.72 μg/mL cumulatively), significantly higher than values observed in EXP (57.06 μg/mL), TC (86.71 μg/mL), and DY (8.60 μg/mL). **Sr^{2+}** release from MC and LL remained below the detection limits.

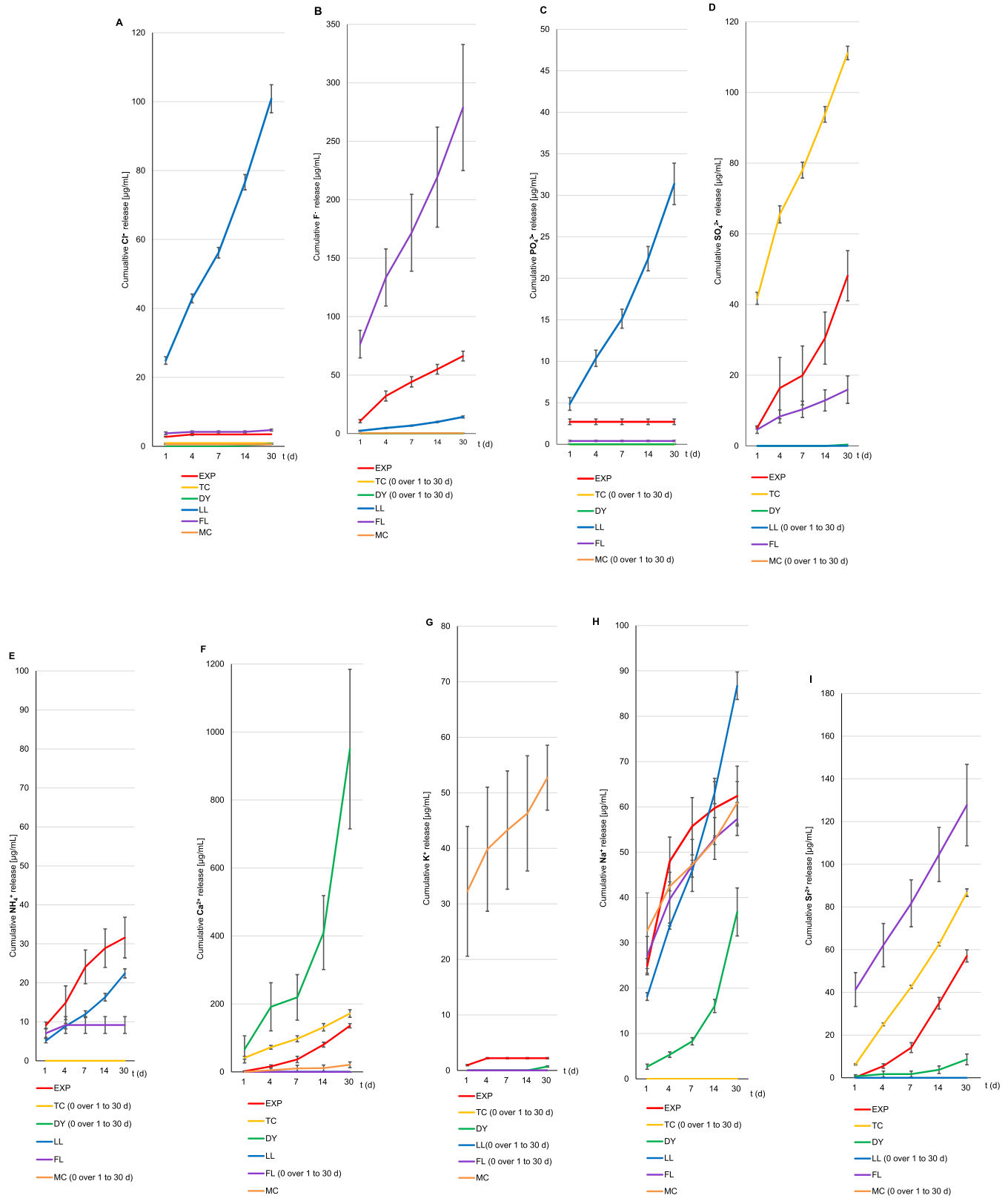

Fig. 2. Cumulative release of anions and cations from different liner materials over time (µg/mL): A) Cl^-, B) F^-, C) PO_4^{3-}, D) SO_4^{2-}, E) NH_4^+, F) Ca^{2+}, G) K^+, H) Na^+, and I) Sr^{2+}. Depicted are cumulative concentrations in the liner eluates from day 1 to day 30 (mean ± SD; n = 4).

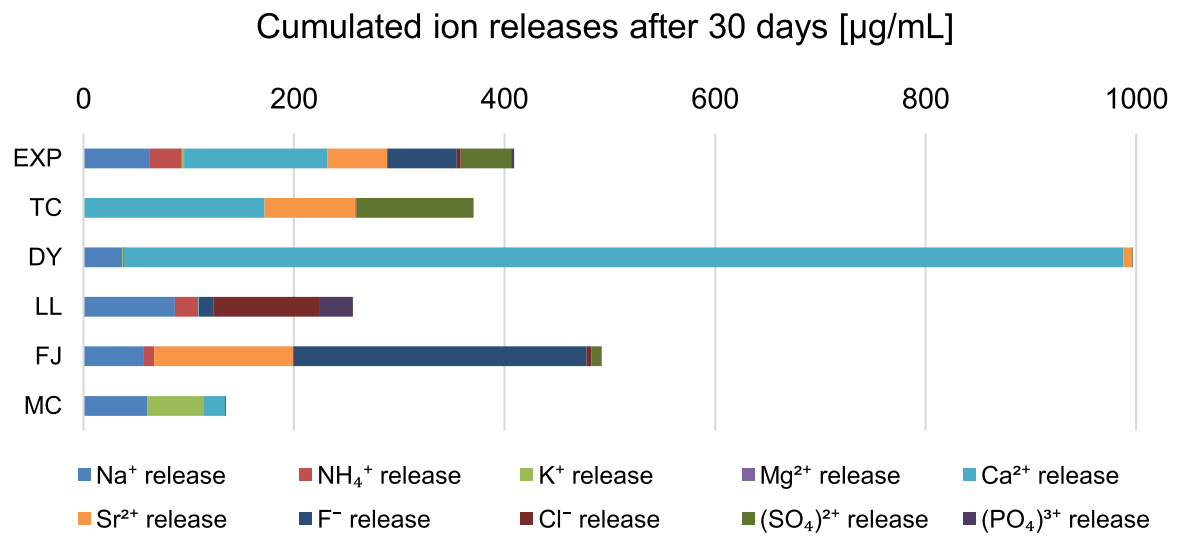

Fig. 3. Overview of the cumulative release of anions and cations (Cl^-, F^-, PO_4^{3-}, SO_4^{2-}, NH_4^+, Ca^{2+}, K^+, Na^+, Sr^{2+}) from different liner materials (µg/mL) after 30 days (mean ± SD; n = 4).

4. Discussion

This study investigated the in vitro ion release from dental liner materials using IC. While liners are not directly exposed to the oral environment and saliva, their released components may still affect pulp vitality and regeneration by diffusing through dentinal tubules or through direct contact with vital pulp tissue [19]. To reflect this physiological interface, deionized water was chosen as the extraction medium. As shown by Pashley et al. [31], dentinal fluid - an ultrafiltrate of plasma - is primarily composed of water and electrolytes, with minimal protein content and low buffering capacity. This composition closely resembles deionized water and thus allows for a relevant physiological comparison to pulp chamber conditions. The choice of elution time intervals (1, 4, 7, 14, and 30 days) was based on the study by Ruengrungsom et al. [20], reflecting a key physiological characteristic of the dentin-pulp complex: an interstitial environment with continuous fluid exchange driven by dentinal fluid dynamics and pulp perfusion [32]. At the dentine interface, released ions may promote remineralization and help prevent caries progression, potentially delaying the need for re-restoration [9,33,34]. Six liner materials were selected for this study: a resin-modified calcium silicate cement (TC), resin-modified $Ca(OH)_2$ (LL), resin-modified GIC (FL), modified $Ca(OH)_2$ (DY), an experimental hybrid resin modified glass ionomer cement (RMGIC) (EXP), and a calcium silicate-based material without resin components (MC). These materials were chosen due to their widespread clinical use and differing chemical compositions, which are expected to influence ion release behavior. To ensure valid inter-material comparisons, all materials were applied in standardized quantities that reflect typical clinical handling and were tested under identical experimental conditions. For IC calibration, 16 ions were selected based on two criteria: firstly, the compositions reported by manufacturers of the tested liner materials, and secondly, the inclusion of ions that could theoretically originate from trace impurities introduced during manufacturing or present in the raw materials (educts), as even high-purity reagents may contain low-level contaminants. Given the high sensitivity of our method, it was essential to include such ions to rule out unexpected impurities and to ensure a comprehensive chemical safety assessment.

The liners showed significant pH differences over 30 days, with DY maintaining a highly alkaline pH (11–12) and FL being the only acidic material (pH < 6). This is relevant for liner effects like dentin bridge formation. The critical pH for dentin demineralization ranges from 6.2 to 6.7 (enamel: 5.2–5.7). Higher (alkaline) pH levels have been reported to enhance the mineralization potential of human dental pulp cells (hDPCs), with optimal effects observed after 15 days [17,35]. Okabe et al. demonstrated increased ALP activity, BMP-2 mRNA expression, and calcified nodule formation at pH 7.8 compared to 7.2, noting that hDPCs survive within a pH range of 6.6–7.8 [17]. The high pH observed for Dycal is consistent with its composition, which is mainly based on calcium hydroxide. While pure $Ca(OH)_2$ suspensions reach pH values of ≥ 12.5 [36], Dycal typically shows slightly lower values (pH 11–12) due to its composition. Nonetheless, the alkaline environment it creates is sufficient to induce superficial cell necrosis, followed by dentinal repair beneath the necrotic zone - an effect that has been demonstrated in early studies and interpreted as part of a regenerative response [37]. From a clinical perspective, Dycal has been criticized due to its disintegration over time, limited sealing ability, and modest mechanical properties [38].

The following ions – Br^-, NO_3^-, NO_2^-, Ba^{2+}, Li^+, Mg^{2+}, and Mn^{2+} - were not detected in any sample eluate. However, significant differences were observed in the release of Ca^{2+}, PO_4^{3-}, and F^-.

Ca^{2+} release ranged from undetectable levels in the GIC FL to 949.91 µg/mL in DY (mainly based on $Ca(OH)_2$). While the DY samples were manufactured to be as dimensionally stable as possible in this study to avoid fragments, the high release of Ca^{2+} could be explained by DY's characteristic poor dimensional stability and mechanical integrity [38]. Concentrations of Ca^{2+} above 650 µg/mL (16.2 mM) have been linked to increased osteopontin/osteocalcin mRNA expression, indicating osteogenic differentiation, and enhanced mineralized matrix formation, which contributes to dentin bridge formation [39]. Ca^{2+} has also been reported to inhibit dentine collagenolytic enzymes, which are responsible for collagen degradation at restoration interfaces [40]. A previous study reported Ca^{2+} releases from Fuji II LC [20]. This contrasts with the findings of the present study, which showed that Ca^{2+} releases for FL were below LOQ. These materials are both resin-modified GICs from manufacturer GC but optimized for different applications (restorative vs liner material). However, direct comparison with our study is challenging, as different detection methods, sample sizes and storage media (e.g. lactic acid) were used. Of interest as well seems that the Ca^{2+} gradient at the application site itself may stimulate migration of stem cells, osteoblasts, and fibroblasts from deeper pulp tissue [7]. The highest gradient in Ca^{2+} release in our study was observed for EXP and DY, while TC exhibited a more consistent release over time. MC, a resin-free calcium silicate cement, was included as a representative of modern hydraulic cements. It released a cumulative amount of 20.98 µg/mL Ca^{2+} over 30 days, which was lower than values observed for DY, TC, and EXP. This is in line with previous reports on MTA

materials showing moderate but sustained Ca^{2+} release, which may still suffice to support mineralization-related cell responses [41,42]. While the potential effects of different Ca^{2+} release profiles on cellular response require further investigation, a systematic review found calcium silicate cements to be more effective than pure $Ca(OH)_2$ for dentin bridge formation, with bonding agents performing less favorably [43].

Another noteworthy cation is Sr^{2+}, which was primarily detected in FL eluates (41.32 µg/mL after 1 day; 127.72 µg/mL over 30 days cumulatively), followed by TC, EXP, and DY, while none was found in LL and MC. Interestingly, we observed an increasing release profile across the five time intervals. Sr^{2+} is commonly used in dentifrices for hypersensitivity and erosion, alongside compounds like arginine, potassium nitrate, or tin monofluorophosphate [44]. Sr^{2+} can replace Ca^{2+} to form strontium-apatite and promote the precipitation of organic components into the dentin matrix, activating odontoblasts [45,46]. It also supports dental pulp stem cells in differentiating into mineralizing cell types, as indicated by odontogenic markers such as dentin matrix protein and dentin sialophosphoprotein [47–49]. These properties suggest Sr^{2+} could be useful in liners for pulp capping.

The anion PO_4^{3-} plays a key role in apatite formation by binding Ca^{2+} on one hand and OH^- or F^- on the other, thereby contributing to tooth and bone mineralization [50,51]. So-called biomimetic materials, incorporating PO_4^{3-}, Ca^{2+}, and silica, have been found to promote mineral deposition in exposed collagen and inhibit collagen-degrading enzymes [52]. Among the investigated liner materials of the present study, LL released the most PO_4^{3-} (31.38 µg/mL over 30 days). In a previous study, the concentration of PO_4^{3-} from the resin-modified GIC Fuji II LC (0.83 ± 0.01 µg/cm^2) was investigated [20]. Compared to the resin-modified GIC FL (0.62 ± 0.28 µg/cm^2) of the present study, the values do not indicate any significant difference. However, as discussed earlier, because of differences in methods of both studies and optimization of both GICs for different applications, comparison is challenging.

The beneficial role of F^- in remineralization and its anticariogenic potential have been demonstrated in several studies [50,53]. Among the tested materials, the GIC-based liner FL exhibited the highest F^- release, both after 1 day (76.48 µg/mL) and cumulatively over 30 days (278.85 µg/mL). Its consistent release across all five investigated time intervals suggests sustained availability, which is considered beneficial for the adjacent tissues [50]. In terms of F^- release, FL was followed by the experimental liner EXP (66.26 µg/mL over 30 days), then LL and MC, while no release was detected from TC or DY. These findings align with a previous study showing higher F^- release from GICs (e.g., Ketac Cem EasyMix: 6.0 µg/cm^2 in water, 19.3 µg/cm^2 in acid) than from self-adhesive resin cements (0.1–1.5 µg/cm^2 in water, 2.1–10.7 µg/cm^2 in acid) (SeT PP, SDI; RelyX Unicem2, 3 M Espe, and others) [54]. Another study [20] reported cumulative F^- release from the resin-modified GIC Fuji II LC of 39.6 µg/cm^2 after 7 days and 59.0 µg/cm^2 after 14 days. Notably, F^- release is enhanced in acidic conditions, suggesting that F^- release in the present study may have been higher under acidic eluates [20,54].

The in vitro design limits the study's clinical relevance. The static setup does not mimic the dynamic oral environment with changing pH and temperature, and the 30-day observation period is rather short to assess long-term ion release. Standardized curing may overlook clinical variations, and ion chromatography's sensitivity limits detection. Additionally, pH measurements do not reflect real-time changes influenced by temperature or bacterial activity.

Furthermore, our investigation focused exclusively on ionic species and did not include the release of resin monomers. Since the latter may have a significant biological impact, future studies should aim to complement our findings by including these components.

5. Conclusion

The observed differences in ion release and pH values represent an important aspect of the broader understanding of biomineralization and should be interpreted in conjunction with data on resin monomer release in the biological environment. These findings may serve as a foundation for future studies aimed at optimizing material formulations to enhance their therapeutic potential.

CRediT authorship contribution statement

Florian Konstantin Stangl: Investigation, Methodology, Formal analysis, Visualization. Karin Christine Huth: Formal analysis, Visualization, Writing – original draft, Writing – review & editing. Christof Högg: Funding acquisition, Resources, Conceptualization, Supervision, Methodology, Project administration, Validation.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used DeepL in order to improve English. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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Disclosure statement

The authors do not have any financial interest in the companies whose products are included in this article.

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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