

NOVEL LC–MS/MS-BASED METHOD FOR THE QUANTIFICATION OF ORGANIC UV FILTERS FROM SUNSCREEN FORMULATIONS IN FISH ORGANS AND TISSUES

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Received date: Nov. 18th 2025 ; Accepted date: Jan. 22nd 2026; Published date: Sept. 30th 2026

Benzophenones are widely used as organic UV filters in sunscreens and cosmetic products. Their increasing occurrence in aquatic environments has raised concerns due to their potential endocrine-disrupting effects. Consequently, sensitive and reliable analytical methods are required for their determination at trace levels. In this study, a validated LC-MS/MS method was developed for the determination of benzophenone UV filters and their metabolites in Cyprinus carpio tissues. The method showed good linearity over the concentration range of 1-100 µg/L, with limits of quantification of 0.12–0.87 ng/g and accuracy between 97.3 and 102%. This method enables efficient trace-level monitoring of organic UV filters in fish tissues.

Keywords: method validation; LC–MS/MS; organic UV filters;

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1. Introduction

Organic UV filters are chemical agents that absorb ultraviolet (UV) A (315–400 nm) and/or ultraviolet (UV) B (280–315 nm) radiation [1]. These compounds are commonly added to sunscreens or cosmetic products [1] and protect skin from UV radiation. In addition, organic UV filters are applied as photoprotective agents in plastics, adhesives, and rubber [2]. They have been detected worldwide in several environmental compartments, including surface water [3], wastewater [3–5], seawater [6], groundwater [7], sediment [8], and biota [9]. Their toxic potential and endocrine-disrupting effects are a cause of concern. Some organic UV filters act as xenohormones, raising significant environmental impact issues [10–12].

A closer examination of specific UV filters shows their widespread use and biotransformation in living organisms. 2-Hydroxy-4-methoxybenzophenone (BP-3) is a UV filter from the benzophenone group. BP-3 is frequently used as an active ingredient in several sunscreen formulations [13-14]. Various publications have reported the degradation of BP-3 in animals and even in the human body, mediated by the cleavage of certain functional chemical groups [15-16]. Studies in rats have found important BP-3 metabolites: benzophenone-1 (BP-1), benzophenone-8 (BP-8), and 4-hydroxybenzophenone (4-OH-BP). Degradation products, generally more soluble than the parent compound, are excreted in urine. [15-16].

Recent studies have focused on the biological activity of organic UV filters and their metabolites. High estrogenic activity has been shown for octocrylene (OC), homosalate (HS), and ethylhexyl salicylate (EHS). Also, androgenic or anti-androgenic activity has been observed in in vitro experiments using human estrogen and androgen receptors [17-18]. The major concern is not the presence of these synthetic compounds in aquatic systems, but also their biologically active interactions with living organisms.

The main methods frequently used for the detection and identification of organic UV filters in biotic and abiotic samples are chromatographic methods. The need for sensitive and selective methods leads to the usual use of diode array detectors (DAD). However, the complexity of the analyzed matrices can lead to analytical interferences. In these conditions, mass spectrometric detection is more suitable and recommended, with DAD used only for clean samples with high loading of target compounds [19]. For more volatile compounds or thermostable derivatives, GC-MS/MS may be a better choice, providing efficient separation and selective detection, although derivatization is often necessary [20-21]. By contrast, LC-MS/MS is now considered the analytical reference method due to its selective detection in MRM mode and low detection limits in the ng/g range. This enables simultaneous analysis of target UV filters and their transformation products [22].

Despite growing worldwide awareness of UV filter pollution, this issue has not been extensively studied in Romania. These UV filters can easily spread throughout the environment in multiple chemical forms and are known to disrupt the endocrine system. That is why it is important to measure their levels in the environment. Therefore, this study validated an LC-MS/MS analytical method for simultaneous quantification of several commonly used UV filters in the tissues of *Cyprinus carpio* (common carp).

2. Materials and Methods

2.1 Chemicals and standards

Analytical standards included 4-hydroxybenzophenone (4-HBP), 2,4-dihydroxybenzophenone (BP-1), 2-hydroxy-4-methoxybenzophenone (BP-3),

2,2',4,4'-tetrahydroxybenzophenone (BP-2), 2,2'-dihydroxy-4-methoxybenzophenone (BP-8), 2,3,4-trihydroxybenzophenone (234-HBP), and 2-hydroxy-4-methoxy-4'-methylbenzophenone (BP-10). Benzophenone-13C (BP-13C) served as the internal standard. All standards were from Sigma-Aldrich (Germany). High-purity acetonitrile, methanol (Merck, Darmstadt, Germany), and formic acid (Sigma-Aldrich, Germany) were used for mobile-phase preparation and sample extraction.

2.2 Preparation of biological material

The biological material used in the toxicological experiments was European carp (*Cyprinus carpio*), known as common carp. The species were purchased in October 2021 from the NUCET Aquaculture Research and Development Station, in accordance with Quality Certificate No. 738/21.10.2021. Specimens used in this study showed normal morphology, with no visible lesions observed after acclimatization under laboratory conditions. Fish were subjected to controlled laboratory exposure to BP-3. During maintenance in the laboratory tanks, the fish were fed daily. Fish care and experimental procedures were carried out in accordance with the European Directive 2010/63/EU on the protection of animals used for scientific purposes. Three healthy individuals were humanely euthanized in accordance with national regulations and ethical standards. All experimental studies were approved by the Ethics Committee of the National Institute for Research and Development for Industrial Ecology – ECOIND (approval number 3557/2025).

After the fish were sacrificed, we rinsed them with ultrapure water to eliminate any surface contaminants. We dissected the fish and combined the muscle, liver, and gill tissues, which were then homogenized using a stainless-steel blender. The resulting mixture was freeze-dried at -110°C for 48 hours to ensure all moisture was removed.

Once dried, we finely ground the samples into a fine powder. This powder was stored in amber glass containers, away from light and moisture, until it was time for extraction and LC–MS/MS analysis (Fig. 1). For each analysis, we used approximately 0.5 grams of the lyophilized tissue.

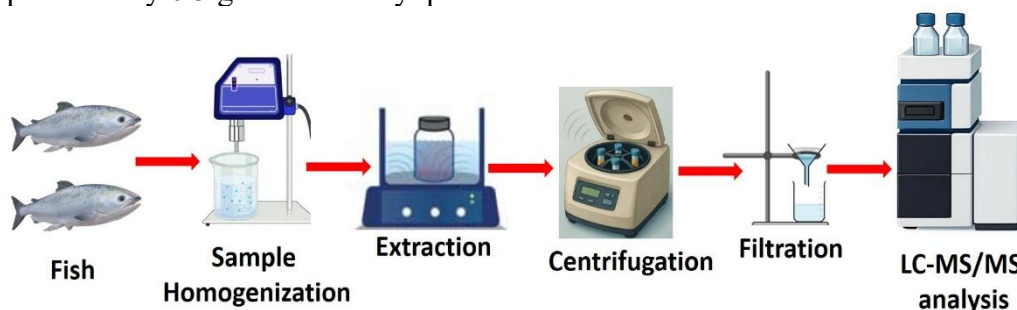


Figure 1. Fish tissue sample preparation and LC–MS/MS analysis.

Extraction of biological samples was performed using 20 mL glass vials. 0.5 g of the sample prepared according to the previous instructions was mixed with 10 mL of methanol and vortexed for 1 minute. After stirring, the mixture was placed in an ultrasonic bath for 30 minutes at 30°C. After extraction, the solid part was decanted by centrifugation at 3000 rpm for 10 minutes. The organic part was collected, and the solid part was extracted again. Finally, the extracts were mixed, passed through silica gel, and evaporated almost completely. The residue was dissolved in 1 mL of a 60/40 water-acetonitrile mixture and placed in a 2 mL vial.

2.3 LC–MS/MS Analytical Method

We conducted our analyses of BP-3 and its metabolites using an Agilent 6410B triple quadrupole LC–MS/MS system with ESI. Chromatographic separation was conducted using a Luna C18 column (150 × 2.0 mm, 3.0 µm) at 30 °C. n (150 × 2.0 mm, 3.0 µm) maintained at 30 °C. Our mobile phase was made up of 0.15% formic acid (A) in water and acetonitrile (B), with a flow rate of 0.2 mL/min, and a 1 µL sample was injected into the system by means of a gradient elution program.

For the compounds we studied, 4-HBP, BP-1, 2,3,4-HBP, and BP-2 were analyzed in negative ESI mode, while BP-3, BP-8, and BP-10 were examined in positive mode. For precise quantification and confirmation, the compound-specific Multiple Reaction Monitoring (MRM) transitions were optimized. The equipment was run with a capillary voltage of 5,000 V, a drying gas flow rate of 9 L/min at 300 °C, and a nebulizer pressure of 40 psi.

2.4 Method Validation and Quality Assurance

The validation of the analytical method performance parameters was carried out using two international reference documents, namely: ICH Q2(R2) Validation of analytical procedures - Scientific guideline [25] and ISO/IEC 17025:2017- General requirements for the competence of testing and calibration laboratories [26]. Among these parameters, the following were verified: method linearity, method detection limit (LOD), method quantification limits (LOQ), selectivity, precision (repeatability and reproducibility of the chromatographic method), recovery efficiency of the extraction method, accuracy, and matrix effects.

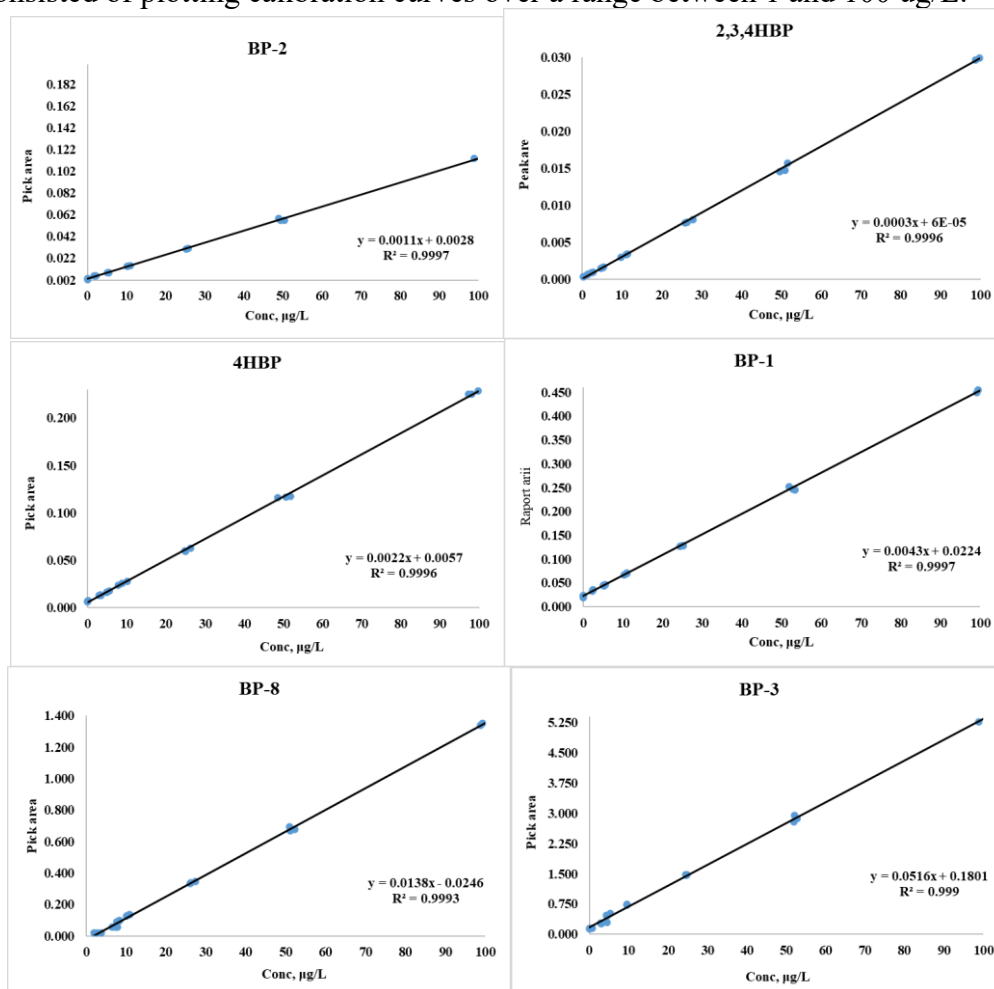
The lack of interference during the analysis of biological samples demonstrated the selectivity of the analytical method. Calibration curves were drawn on well-established concentration ranges by the pike method in the fish tissue matrix. The LOD and LOQ values were established by evaluating the signal-to-noise ratio. The other performance parameters of the chromatographic method were tested by analyzing samples spiked with a known and well-established concentration of a mixture of standard compounds. The post-extraction enrichment

method was the basis for evaluating the matrix effects to determine the potential suppression or amplification of the analytical signal. The results obtained following the verification and validation of the chromatographic method demonstrated that the developed analytical method represents a suitable method for the identification and quantification at trace levels of target compounds in fish tissue.

3. Results and Discussion

3.1 Validation and Verification of Method Performance Parameters

The verification of the first performance parameter of the analytical method consisted of plotting calibration curves over a range between 1 and 100 µg/L.



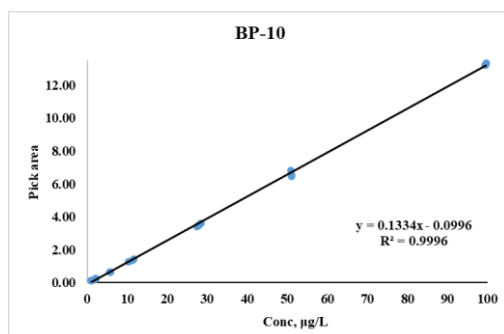


Figure 2. Calibration curves of the 7 organic UV filters.

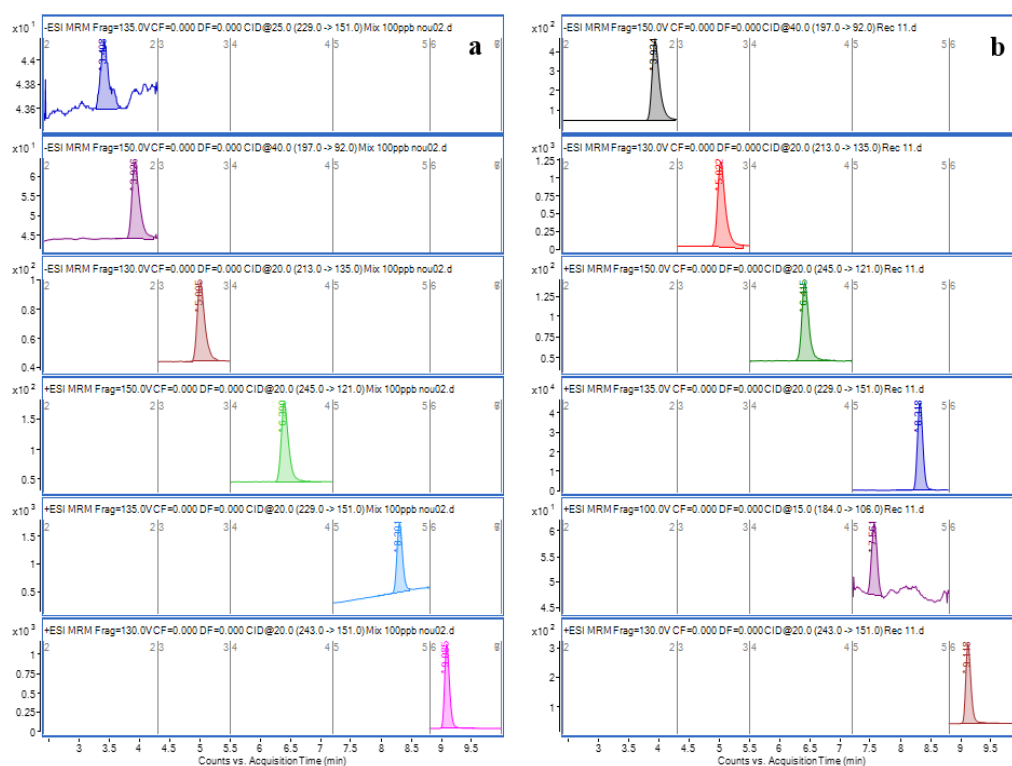


Figure 3. TIC MRM chromatograms of (a) a synthetic standard and (b) a spiked biota extract at 100 µg/L mix solution.

The precision of the LC-MS/MS method, which consists of verifying the repeatability and intermediate precision, was evaluated for two concentration levels, at 10 and 50 ng/L, respectively, according to the validation protocols existing at the international level. To test the repeatability of the analytical method, six samples prepared separately by a single analyst were injected on the same day. The results obtained, expressed as relative standard deviation (RSD, %), were between 1.52 and 2.35 % for the low concentration range, and between 1.56 and 2.04% for

the intermediate concentration range. These results support the short-term reproducibility of the method. The intermediate precision was tested by repeatedly analyzing the samples prepared separately on different days by 2 analysts, successively. The results obtained, also expressed in RSD%, were between 3.81 and 4.72% for the low concentration range and between 3.91 and 4.54% for the intermediate concentration range. In addition, the values obtained for the accuracy of the chromatographic method were between 98.3 and 103%, for both concentration ranges, the differences between the ranges being very small. The values determined for this operational parameter support the reliability of the method in the medium term (Fig. 4).

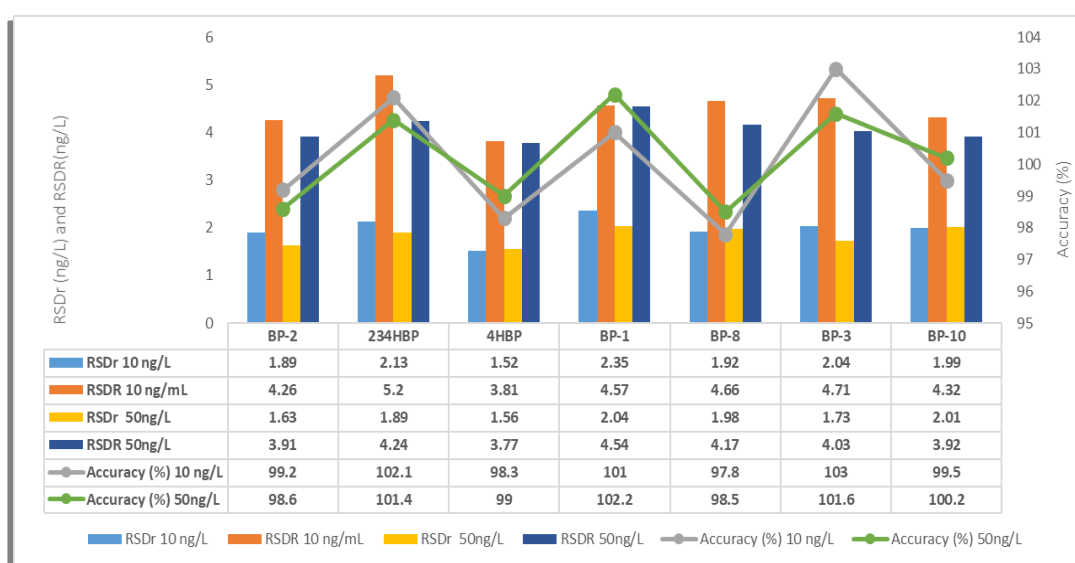


Figure 4. RSD_r, RSD_R, and Accuracy results obtained for the targeted analytes in biological tissue.

The obtained data support the fact that the new chromatographic method for the determination of target organic UV substances by LC-MS/MS can detect and quantify the target analytes in biological samples of fish tissue. The method is reproducible, generating similar results every time it is used. The values obtained for accuracy, around 100% for both concentration ranges, provide support for confidence in the results generated by the new chromatographic method. The difficulty of this method is given by the preparation of biological samples, which represent a loaded matrix due to the fats and proteins contained. However, special attention to the extraction of biological samples and the use of high-performance, high-resolution equipment can lead to the avoidance of samples generated by the complex matrix.

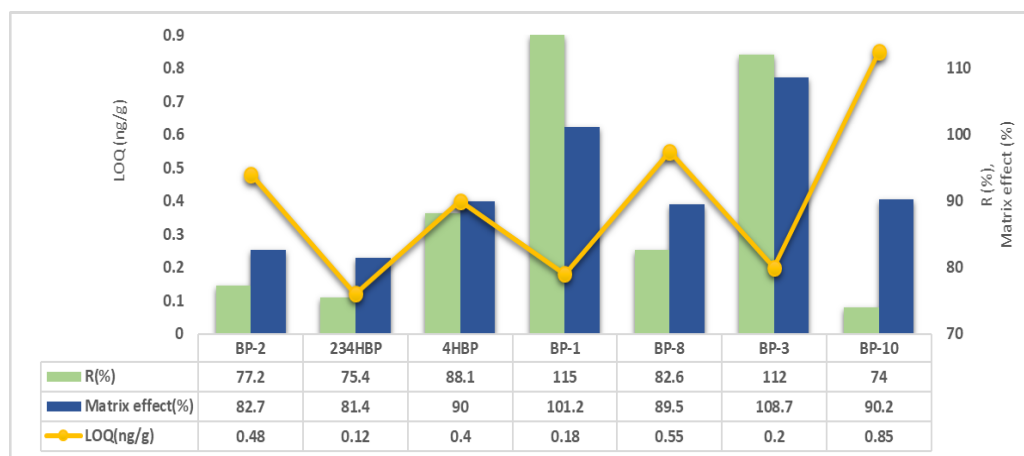


Figure 5. Correlation between Recovery, Matrix Effect, and LOQ for Benzophenone-type UV Filters in Fish tissue

The chromatographic method developed in this study generated similar results over several days of testing, demonstrating good functionality even on loaded biological matrices. These data support the fact that the new method is suitable for the precise determination of low concentration ranges of organic UV substances in aquatic organisms and can be used for ecological risk screening and assessment of the accumulation of target analytes in living beings.

The recovery yields of target analytes from fish tissue ranged from 74.0% to 115%, indicating an efficient extraction process of target chemicals from biological samples. Values above 100% obtained for BP-1 and BP-3 can be attributed to signal interference due to sample loading. In the case of values determined during the evaluation of matrix effects, they ranged from 81.4% to 108.7%, suggesting small changes in the analytical signal, but these results are within the variability ranges of a chromatographic method. The data obtained support the importance of performing calibration samples in the biological matrix to correct for differences in the samples. The limit of detection (LOD) and the limit of quantification (LOQ) were estimated using a signal-to-noise approach, the standard deviation of the response and the slope of the calibration curve. The evaluation of the quantification limits of the method was quite low, ranging between 0.12 and 0.85 ng/g, and the LOD values ranged between 0.04 and 0.30 ng/g, indicating a method with high sensitivity and suitable for the detection of traces in biological matrices (Fig. 5). The information obtained during the validation and verification process of the new chromatographic method confirms that the new method is precise and reliable for routine chromatographic analyses, allowing the determination and quantification of UV-organic substances in aquatic organisms at trace levels.

3.2 Method Applicability

The LC-MS/MS method developed in this study can be successfully applied to determine compounds used as active substances in products that protect against solar radiation, accumulated in biological samples (fish tissue). The chromatographic method is suitable for both laboratory and real-system studies, being applicable for the determination of moderate and ultra-trace concentrations, using a low amount (approximately 0.5 grams of dry tissue) and a handy extraction process. The extraction technique, chromatographic separation, and mass spectrometric detection of organic UV-filters can also be used for other types of aquatic organisms with similar tissues. Moreover, the method can be modified and upgraded at any time to include chemicals from the class of organic UV-filters, which are important for the environment. Using this methodology, target analytes can be detected and quantified in different aquatic organisms, leading to more complex studies such as evaluating differences in the accumulation of target substances between different species, the transport of these substances along the food chain, and the risk to human health.

4. Conclusions

The chromatographic method based on LC-MS/MS presented in this study offers a reliable, sensitive, and precise option for the determination of organic UV compounds of the benzophenone type in biota samples. Drawing the calibration curves directly in the biological matrix leads to the reduction of interferences due to the loaded matrix of biological samples, such as fats and proteins, allowing correct determinations over a real concentration range. The analytical method has been validated and verified according to international standards, respecting the norms of accuracy and consistency. Also, an advantage is the fact that it allows the determination of very low concentration ranges in biological tissue samples (down to 0.12 ng/g), which generates the usefulness of the method for environmental monitoring. Thus, this chromatographic method is suitable and recommended for the regular testing and identification of the presence, accumulation, and mobility of organic UV filters in aquatic organisms.

Author Contributions

Conceptualization, V.A.P., S.G., F.L.P. and C.U.; methodology, V.A.P., S.G., F.L.P. and C.U.; validation, F.L.P.; formal analysis, V.A.P., S.G., F.L.P. and C.U.; investigation, V.A.P., S.G., F.L.P. and C.U.; writing—original draft preparation, V.A.P. and F.L.P.; writing—review and editing, V.A.P., S.G., F.L.P. and C.U.; supervision, F.L.P.; funding acquisition, V.A.P., S.G. and F.L.P. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

Funding

Declared none.

Conflicts of Interest

The authors declare no conflict of interest.

Artificial Intelligence Disclosure

No artificial intelligence-based or generative tools were used in the preparation of this manuscript.

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