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Short Communication

Preliminary Evaluation of Cytotoxic and Metabolic Modulatory Activities of *Mentha cordifolia* Opiz Leaf Crude Extract on Human Peripheral Blood Mononuclear Cells

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Abstract

Mentha cordifolia Opiz (yerba buena) is traditionally used for its antimicrobial and therapeutic properties. The cytotoxic and metabolic modulatory effects of the buffered leaf crude extract of *M. cordifolia* Opiz on human peripheral blood mononuclear cells (PBMCs) were evaluated using a Water-Soluble Tetrazolium (WST-8)–based colorimetric assay. Phytochemical characterization revealed a total phenolic content of 0.1304 mg GAE/g extract. Among the tested concentrations (25–200 µg/mL), the extract exhibited minimal-to-mild cytotoxic effects, with no evident dose-dependent toxicity. Because the same donors were evaluated across all treatment conditions, repeated-measures one-way analysis of variance (ANOVA) was performed using donor identity as the repeated factor. The Shapiro–Wilk test did not indicate a significant deviation from normality ($W = 0.9855$, $p = .9891$), which supported the use of a parametric analysis. Repeated-measures one-way ANOVA revealed a statistically significant overall effect of treatment on the PBMC metabolic activity ($F(5,10) = 6.441$, $p = .0063$). Post hoc paired comparisons using Bonferroni correction demonstrated that the positive control (PC) exhibited significantly increased metabolic activity relative to the negative control (adjusted $p = .025$), whereas no other pairwise comparisons reached statistical significance after multiple-comparison correction. Under phytohemagglutinin-stimulated conditions, the 50 and 100 µg/mL concentrations showed comparatively moderate metabolic activity, whereas the 200 µg/mL concentration demonstrated reduced metabolic activity relative to that of the PC. The PC demonstrated increased metabolic activity, confirming the assay's responsiveness. Inter-individual variability in metabolic responses was observed among the donors, particularly at higher extract concentrations. The modest metabolic modulatory activity observed may be related to the phytochemical composition of the buffered extract. Overall, this preliminary in vitro study extends our previous findings and highlights the low cytotoxicity and modest donor-dependent metabolic modulatory effects of *M. cordifolia* Opiz, warranting further mechanistic and phytochemical investigations to confirm these findings.

Keywords

Mentha cordifolia Opiz, peripheral blood mononuclear cells, cytotoxicity, metabolic modulatory effects

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Introduction

Natural products have long been recognized as important sources of bioactive compounds with therapeutic potential.[1,2] Medicinal plants represent a rich reservoir of phytochemicals, such as flavonoids, alkaloids, phenolic acids, and terpenoids, many of which exhibit antioxidant, anti-inflammatory, and cytotoxic properties.[3] The growing interest in plant-derived compounds is driven by their structural diversity,

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cytotoxic and metabolic modulatory activity, and relatively favorable safety profiles compared with those of synthetic agents.

Mentha cordifolia Opiz (commonly known as yerba buena) is a widely used medicinal plant in Southeast Asia, particularly in the Philippines, where it has been traditionally employed for its analgesic, anti-inflammatory, and antimicrobial properties.[4] Phytochemical studies have shown that *Mentha* species are rich in bioactive compounds, including phenolic acids, flavonoids, and essential oils, which contribute to their antioxidant and therapeutic effects.[5] Previous studies have reported that *M. cordifolia* exhibits antimicrobial activity against a range of pathogenic microorganisms and may modulate biological systems.[4,6] Despite its widespread traditional use and emerging pharmacological evidence, limited information is available on its direct effects on human immune cells.

In recent years, there has been increasing attention directed toward identifying plant extracts capable of modulating cellular viability and growth.[3,7,8] In vitro cell-based assays provide a reliable and reproducible platform for evaluating the cytotoxic and metabolic modulatory activity of natural products and screening potential therapeutic candidates.[9] Assessing changes in cell viability following treatment with plant extracts is a critical first step in determining their cytotoxic or cytoprotective potential and guiding further mechanistic investigations.[10,11]

Our previous study demonstrated the antibiotic resistance modulatory activity of the buffered leaf crude extract of *M. cordifolia* Opiz against methicillin-resistant *Staphylococcus aureus* (MRSA) phenotypes, highlighting its antimicrobial potential.[12] However, the cellular effects of this extract on human immune cells remain largely unknown. While other *Mentha* species have been extensively investigated for their immunomodulatory effects on peripheral blood mononuclear cells (PBMCs) and related models, direct studies on *M. cordifolia* Opiz using PBMCs are limited. Building on our prior findings, the present study shifted from a pathogen-centered approach to a host cell model, enabling the evaluation of cytotoxicity and metabolic modulation in human PBMCs. This approach provides complementary insights into the cellular compatibility and dose-dependent immunometabolic effects of the extract within a physiologically relevant system, thereby bridging antimicrobial activity with host cell response and contributing to a more integrated assessment of its therapeutic potential.

Materials and Methods

Plant Materials

Fresh *M. cordifolia* Opiz leaves were purchased from a local plant vendor along Boulevard–Artiaga Street, Davao City, Philippines. The plant materials consisted of fresh, mature, and visibly healthy leaves that were free from mechanical damage, pest infestation, or signs of disease. Leaves were collected during the day under ambient environmental conditions and transported to the laboratory in clean, ventilated containers to prevent moisture accumulation and degradation. Upon arrival, the leaves were processed immediately to preserve phytochemical integrity. Botanical authentication was performed by a botanist, and a certificate of authentication was issued to confirm species identity. The leaves were then rinsed thoroughly with distilled water, air-dried at room temperature (RT) for 4 days, pulverized using a pestle and mortar, sieved to obtain a fine powder, and stored in clean containers before extraction.

Buffered Extraction of M. cordifolia Opiz

Buffered extraction was performed with minor modifications to our previously described method.[12] Briefly, 25 g of pulverized leaf material was blended with 100 mL of 0.1 M phosphate buffer (pH 7.0). A higher plant-to-solvent ratio was used to obtain a more concentrated crude extract for downstream in vitro assays. The phosphate buffer system was selected to maintain a stable, near-neutral pH, which helps preserve the integrity and solubility of bioactive compounds during extraction. The homogenized mixture was first filtered using a sterile muslin cloth to remove coarse plant debris, followed by vacuum filtration through Whatman No. 1 filter paper using a Büchner funnel. The filtrate was then air-dried under sterile conditions at RT. Subsequently, the dried extract was lyophilized using a freeze dryer (ScanVac CoolSafe; Labogene, Denmark) to obtain a powdered crude extract. The lyophilized material was stored at 4 °C until use. Two-fold serial dilutions were prepared to obtain final working concentrations of 25, 50, 100, and 200 µg/mL for in vitro assays.

Total Phenolic Content

The total phenolic content (TPC) of *M. cordifolia* Opiz leaf crude extract was determined using the Folin–Ciocalteu colorimetric method, with gallic acid as the reference standard. Briefly, 100 mg of crude extract was dissolved in 10 mL of 99% methanol and subsequently diluted 1:10 with distilled water. An aliquot (100 µL) of the diluted extract was mixed with 500 µL of Folin–Ciocalteu reagent and 500 µL of a 7% sodium carbonate solution. After incubation for color development, the absorbance was measured at 760 nm using a Shimadzu UV-1900i UV–Vis spectrophotometer. Gallic acid standard solutions (0.05–0.50 mg/L) were used to generate a calibration curve ($y = 2.2676x - 0.0531$, $R^2 = 0.9869$), where y represents the corrected absorbance, and x represents the gallic acid concentration. The phenolic content of the extract was calculated from the regression equation of the standard curve and expressed as milligrams of gallic acid equivalents per gram of crude extract (mg GAE/g extract).

Blood Collection and Isolation of PBMCs

Peripheral blood (12 mL per donor) was collected from three healthy volunteers after obtaining written informed consent. Blood samples were collected in lithium heparin anticoagulant tubes and maintained at RT before processing. All samples were processed immediately after collection to preserve the viability of the cells. PBMCs were isolated using density gradient centrifugation with Histopaque-1077 (density: 1.077 g/mL; Sigma-Aldrich). Briefly, whole blood was carefully layered over Histopaque-1077 and centrifuged at 400 × g for 30 min at RT. The mononuclear cell layer at the plasma–Histopaque interface was carefully aspirated, washed twice with isotonic phosphate-buffered saline at 300 × g for 10 min, and resuspended in Dulbecco's Modified Eagle Medium (DMEM-High; Sigma-Aldrich) supplemented with 10% heat-inactivated fetal bovine serum and 1% penicillin–streptomycin.

Baseline cell viability was determined using the Trypan Blue exclusion assay before cell plating. All experiments were performed using PBMCs from three independent donors (biological replicates). For each donor and treatment condition, measurements were obtained in technical duplicate.

WST-8-based Cellular Metabolic Activity Assay

Cellular metabolic activity was assessed using a WST-8 colorimetric assay (Cell Counting Kit-8; Dojindo Laboratories, Kumamoto, Japan) under both unstimulated and mitogen-stimulated conditions. PBMCs were seeded into 48-well plates at a density of 1×10^5 cells per well in complete DMEM and incubated for 24 h at 37 °C in a humidified atmosphere with 5% CO_2 to allow cell stabilization. The buffered *M. cordifolia* Opiz extract was reconstituted in distilled water and added to culture wells to achieve final concentrations of 25, 50, 100, and 200 µg/mL.

For cytotoxicity assessment, cells were treated with the extract without mitogenic stimulation. For mitogen-induced metabolic activity, cells were stimulated with 10 µg/mL phytohemagglutinin (PHA) and concurrently treated with the extract at the indicated concentrations. After 4 h of treatment, 10 µL of WST-8 reagent was added to each well and incubated for 1 h at 37 °C. Absorbance was measured at 450 nm using a microplate reader (Bio-Rad iMark). The buffered Mentha cordifolia Opiz extract was visually colorless following reconstitution and contained a relatively low total phenolic content (0.1304 mg GAE/g extract); therefore, substantial optical interference at 450 nm was considered unlikely. Media-only background wells were included to correct for baseline absorbance from the culture medium. However, cell-free extract-specific wells containing the extract and WST-8 were not included; therefore, direct optical interference or chemical reduction of WST-8 by extract constituents cannot be completely excluded, and the observed absorbance changes should be interpreted cautiously. The measured absorbance reflects mitochondrial metabolic activity associated with cellular activation rather than the direct quantification of cell proliferation. For each donor and treatment condition, assays were performed in technical duplicate.

Data Analysis

Statistical analysis was performed using repeated-measures one-way analysis of variance (ANOVA), with donor identity as the repeated factor. The experimental design consisted of three biological replicates (independent donors), with two technical replicates per donor and treatment condition. Technical duplicate measurements were averaged to generate a single donor-level value for each treatment condition before statistical analysis. All statistical analyses were performed using donor-level data ($n = 3$ donors). Residual normality was assessed using the Shapiro–Wilk test. When a significant overall treatment effect was detected, post hoc pairwise comparisons were performed using paired t tests with Bonferroni corrections. Data are presented as mean ± standard deviation or standard error of the mean as appropriate. Statistical significance was set at $p < .05$. Statistical analyses were performed using Stata version 14 (StataCorp LP, College Station, TX, USA), and graphical visualizations were generated using *R* version 4.5.1 (*R* Foundation for Statistical Computing, Vienna, Austria).

Results

Phytochemical Characterization

The TPC of the buffered crude extract, determined using the Folin–Ciocalteu method, was 0.1304 mg GAE/g extract.

Cytotoxic Activity of M. cordifolia *Opiz Leaf Crude Extract on Human PBMCs*

As shown in Figure 1A, the crude extract exhibited minimal cytotoxicity against human PBMCs. At 25 µg/mL, a mild cytotoxic effect (~20%–25%) was observed. At 50–200 µg/mL, the mean cytotoxicity values remained low and showed variability among donors, including slightly negative values at 100 µg/mL. Overall, no substantial reduction in cell viability or dose-dependent cytotoxicity was observed across the tested concentrations. The absence of pronounced cytotoxic effects at increasing concentrations suggests that the extract does not exert dose-dependent toxicity on PBMCs under the experimental conditions tested. The dashed horizontal line at 100% represents the theoretical maximum cytotoxic threshold, and the raw cytotoxicity data corresponding to these observations are provided in Supplementary Table S1.

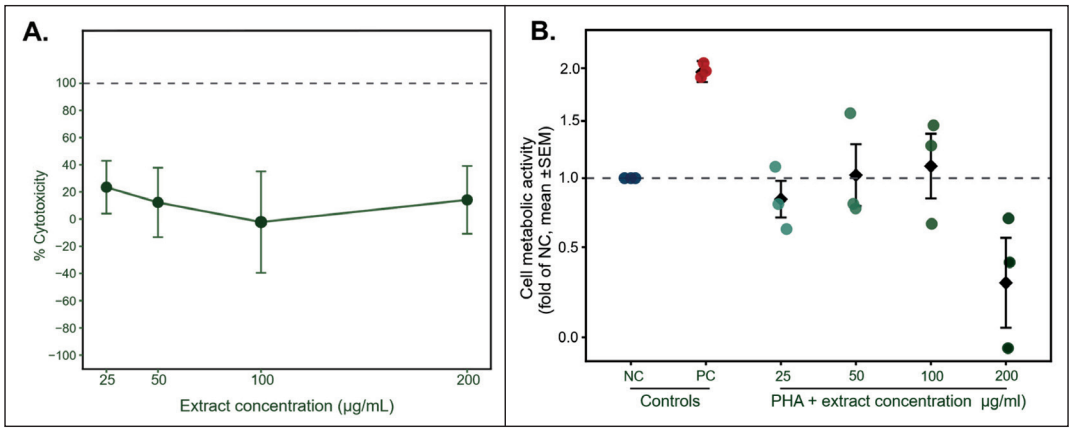

Figure 1. Cytotoxic and Metabolic Modulatory Effects of *Mentha cordifolia* Opiz Leaf Crude Extract on Human Peripheral Blood Mononuclear Cells (PBMCs): (A) Concentration-dependent Cytotoxic Activity Assessed Using the WST-8 Assay; and (B) Metabolic Activity of PBMCs Following Treatment, Expressed as a Fold Change from the Negative Control (NC). Overall Group Differences were Evaluated Using a Repeated-measures one-way ANOVA. Individual Dots Represent Independent Donors (n = 3). Technical Duplicate Measurements were Averaged Before Plotting, and Error Bars Indicate the Standard Error of the Mean.

Note: NC: Negative control, PC: Positive control.

Table 1. Post Hoc Pairwise Comparisons of PBMC Metabolic Activity Following Treatment with *Mentha cordifolia* Opiz Leaf Crude Extract.

Comparison	Mean Difference†	95% CI	Bonferroni-adjusted p Value
Negative control vs. positive control	−0.969	−1.140 to −0.798	.025
Negative control vs. 25 µg/mL	−0.050	−0.983 to 0.883	1.000
Negative control vs. 50 µg/mL	−0.168	−0.839 to 0.503	1.000
Negative control vs. 100 µg/mL	−0.207	−0.706 to 0.291	1.000
Negative control vs. 200 µg/mL	0.473	−0.954 to 1.900	1.000
Positive control vs. 25 µg/mL	0.919	0.038 to 1.800	.693
Positive control vs. 50 µg/mL	0.801	−0.016 to 1.620	.779
Positive control vs. 100 µg/mL	0.761	0.118 to 1.400	.547
Positive control vs. 200 µg/mL	1.440	0.174 to 2.710	.590
25 µg/mL vs. 50 µg/mL	−0.118	−1.150 to 0.916	1.000
25 µg/mL vs. 100 µg/mL	−0.157	−1.550 to 1.230	1.000
25 µg/mL vs. 200 µg/mL	0.523	−0.510 to 1.560	1.000
50 µg/mL vs. 100 µg/mL	−0.040	−0.740 to 0.661	1.000
50 µg/mL vs. 200 µg/mL	0.640	−1.250 to 2.530	1.000
100 µg/mL vs. 200 µg/mL	0.680	−1.230 to 2.590	1.000

Notes: Values are expressed as fold changes relative to the negative control. Post hoc comparisons were performed using paired t tests with Bonferroni correction following repeated-measures one-way ANOVA. Technical duplicates were averaged before analysis, and donor-level values (n = 3 donors) were used.

†Mean difference was calculated as the first treatment group minus the second treatment group. Confidence intervals represent 95% confidence intervals for the paired mean difference.

Metabolic Modulatory Activity of M. cordifolia *Opiz Leaf Crude Extract on Human PBMCs*

Figure 1B shows the effects of *M. cordifolia* Opiz leaf crude extract on PBMC metabolic activity, as assessed by the WST-8 assay (complete data are provided in Supplementary Table S2). Because the same donors were evaluated across all treatment conditions, a repeated-measures one-way ANOVA was performed using donor identity as the repeated factor. Before inferential analysis, residual normality was assessed using the Shapiro–Wilk test, which did not indicate a significant deviation from normality (W = 0.9855, p = .9891). Therefore, a parametric repeated-measures analysis was considered appropriate.

Repeated-measures one-way ANOVA revealed a statistically significant overall effect of treatment on PBMC metabolic activity ($F(5,10)$ = 6.441, p = .0063), indicating that at least one treatment group differed significantly from the others. Post hoc paired comparisons were performed using paired t tests with Bonferroni correction (Table 1).

The positive control (PC) exhibited higher metabolic activity than the negative control, and this difference remained statistically significant after correction for multiple comparisons (adjusted $p = .025$). No other pairwise comparisons reached statistical significance after Bonferroni correction.

Consistent with these findings, the PC (10 µg/mL PHA) demonstrated increased metabolic activity, confirming assay responsiveness. The 25 µg/mL concentration reduced metabolic activity relative to the PC, whereas the 50 and 100 µg/mL concentrations showed comparatively moderate metabolic responses. The 200 µg/mL concentration showed the greatest reduction in metabolic activity compared to the PC. Notably, inter-individual variability in metabolic responses was observed among donors, particularly at 50–200 µg/mL concentrations, as reflected by the dispersion of the individual data points. As the WST-8 assay primarily reflects mitochondrial metabolic activity rather than cell proliferation, the observed changes were interpreted as modulation of cellular metabolism rather than proliferative responses. Overall, the extract demonstrated modest, non-significant modulatory effects on PBMC metabolic activity after correction for multiple comparisons.

Discussion

This study aimed to provide a preliminary in vitro evaluation of the biological effects of *M. cordifolia* Opiz leaf crude extract on primary human immune cells. While our previous work demonstrated the antibiotic resistance modulatory activities of *M. cordifolia* Opiz buffered leaf crude extract against MRSA phenotypes,[12] the current investigation extends these findings to a host cell context. Although PBMCs provide a biologically relevant model, the findings should be interpreted within the limitations of in vitro systems.

The cytotoxicity results demonstrated that the crude extract exerted minimal-to-mild cytotoxic effects on PBMCs across the tested concentration range. Notably, no pronounced dose-dependent toxicity was observed, particularly at higher concentrations, suggesting that the extract did not compromise the viability of primary immune cells under the experimental conditions employed. These findings indicate that the extract is relatively well tolerated under the conditions tested; however, direct extrapolation to in vivo safety requires further validation. From a translational perspective, these observations provide preliminary support for further investigation of plant-derived compounds as potential adjunctive agents.[13] The relatively low cytotoxic profile observed in this study complements our earlier findings on antimicrobial resistance modulation, collectively suggesting that *M. cordifolia* Opiz may exert biological effects without substantially deleterious effects on human immune cells.

In terms of metabolic activity, the extract demonstrated modest modulatory effects on PBMCs, as measured using the WST-8 assay. Although increases in metabolic activity at certain concentrations were not consistently statistically significant compared with the untreated controls, the relative fold changes were appreciable and, in some instances, showed a trend toward increased metabolic activity, although the difference was not statistically significant. These findings suggest that the extract may influence cellular metabolic activity rather than directly inducing cell proliferation. Given that WST-8 reflects mitochondrial dehydrogenase activity, the observed increases should be interpreted as alterations in the cellular metabolic status rather than as definitive evidence of proliferative responses.[14] Such metabolic modulation may reflect subtle cellular changes; however, further mechanistic studies are required to confirm this interpretation. A relatively short treatment duration (4 h) was selected to capture early cellular metabolic responses rather than long-term outcomes, such as proliferation or sustained activation. While this design is suitable for the preliminary screening of acute cellular effects, it does not reflect longer-term immunological responses, which should be addressed in future studies using extended incubation periods.

To date, direct studies on *M. cordifolia* Opiz using PBMC have been limited. However, related *Mentha* species have demonstrated immunomodulatory activity in PBMC models. For example, *Mentha piperita* essential oil has been shown to influence cytokine responses, particularly IL-6, IL-10, and IL-8, in sheep PBMCs.[15] On the other hand, *Mentha pulegium* L. extract has been reported to modulate inflammatory responses in human PBMCs by suppressing pro-inflammatory mediators, including TNF-α, IL-1β, and IL-6.[16]

The relatively modest magnitude of metabolic modulation may be partly related to the phenolic content of the buffered crude extract. Phenolic compounds are widely recognized for their antioxidant and bioactive properties, including their ability to regulate redox-sensitive signaling pathways and mitochondrial function.[17–19] Therefore, the phenolic composition of the extract may have contributed to the observed cellular response. This observation highlights the critical role of extraction methodology in shaping the phytochemical composition and downstream biological responses. Given that a buffered extraction approach was intentionally employed to preserve physiological compatibility and translational relevance, this approach may be suitable for controlled in vitro applications; however, further optimization is required before broader application of this approach. Strategies such as adjusting buffer composition and pH, modifying extraction time and solid-to-solvent ratios, or incorporating gentle assisted techniques under buffered conditions may improve phenolic yield while maintaining biocompatibility.[20] Such refinements could enhance phenolic recovery and potentially strengthen the cellular modulatory effects observed in this study.

A limitation of this study is the lack of a direct assessment of endotoxin contamination in the plant extract, which may influence PBMC activation. Although precautions were taken during sample preparation, their contribution cannot be

fully excluded. In addition, the use of PBMCs from a limited number of donors may not fully capture the inter-individual variability. Future studies should include larger donor cohorts and complementary immunological assays, such as cytokine profiling and flow cytometry, to provide a more comprehensive evaluation of the immunomodulatory effects of the extract.

Conclusion

The buffered crude extract of *M. cordifolia* Opiz exhibited low cytotoxicity and modest effects on PBMC metabolic activity under in vitro conditions. Repeated-measures ANOVA revealed a significant overall treatment effect, although most pairwise comparisons involving the extract were not statistically significant after Bonferroni correction. These findings suggest that the extract is biologically compatible with human PBMCs and exerts limited modulatory effects on cellular metabolic activity under the tested conditions. Further studies are warranted to clarify the underlying mechanisms and potential immunological relevance of these effects on the host.

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Authors' Contribution

Alfredo A. Hinay Jr. and Camela Mae A. Northrup conceived and designed the study. Camela Mae A. Northrup, Ralph Allen G. Villa, Raijen Kaye A. Ampoloquio, Lou Jane G. Cajandig, Nikki Jean M. Gerona, Trixie Mie A. Lumanao, and Pressamae C. Pedrera performed the experiments and collected the data. Alfredo A. Hinay Jr. and Camela Mae A. Northrup analyzed and interpreted the data. Alfredo A. Hinay Jr., Camela Mae A. Northrup, and Ralph Allen G. Villa drafted the manuscript. All the authors have reviewed, revised, and approved the final version of the manuscript.

Consent to Participate

All participants provided informed consent before they participated in the study.

Consent for Publication

Not applicable.

Data Availability Statement

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of the Immaculate Conception Research Ethics Committee (Protocol Code: UG-0088-04-24).

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Informed Consent

Written informed consent was obtained from all participants before their enrollment in the study.

Use of Artificial Intelligence-assisted Tools

Artificial intelligence-based language assistance tools were used solely for improving the clarity of language, grammar, and overall readability of the manuscript. All such suggestions were carefully reviewed, critically evaluated, and edited by the authors to ensure accuracy, scientific integrity, and consistency with the original work. The authors take full responsibility for the content of the manuscript, and all revisions reflect the authors' scientific judgment and expertise.

Supplemental Material

Supplemental material for this article is available online.

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