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Effect of the potassium channel Kir2.1/KCNJ2 and radiation on the permeability of brain microvascular endothelial cells and its regulatory mechanism

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► ***Original article***

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ABSTRACT

Background: This study aimed to investigate the regulatory mechanisms of brain microvascular endothelial cell (BMEC) permeability, with a focus on the role of Kir2.1 (KCNJ2) potassium channels and their potential interaction with ionizing radiation (IR). ***Materials and Methods:*** BMECs were isolated from seven-day-old Sprague-Dawley rats, and cells were stimulated with lipopolysaccharide (LPS) to evaluate inflammatory responses. A 6-MV linear accelerator was used to deliver single radiation doses (0–8 Gy) to confluent BMEC monolayers to simulate clinical radiotherapy conditions. RhoA activity, p115RhoGEF expression, and tight junction (TJ) proteins (ZO-1, occludin, claudin-5) were detected by Western blotting. Transendothelial electrical resistance (TEER) was used to assess changes in barrier permeability. ***Results:*** LPS stimulation significantly increased p115RhoGEF expression at 1, 3, and 6 h compared with the control ($P<0.05$). TEER values decreased progressively after LPS exposure, indicating impaired barrier integrity ($P<0.05$). Claudin-5 levels showed no significant change, whereas ZO-1 and occludin were markedly reduced at 6 h and 12 h ($P<0.05$). Radiation exposure produced similar permeability-enhancing effects, supporting shared mechanisms of barrier disruption. ***Conclusion:*** LPS-induced inflammation increases BMEC permeability primarily through downregulation of TJ proteins. Ionizing radiation produces comparable barrier-disruptive effects, suggesting overlapping regulatory pathways. These findings support a potential role for Kir2.1 channels in modulating BMEC permeability under both inflammatory and radiation-induced stress.

INTRODUCTION

The blood-brain barrier (BBB) is composed of brain microvascular endothelial cells (BMECs), pericytes, and astrocytes [1]. Tight junctions are formed between endothelial cells, and almost only small lipophilic molecules can enter [2]. In addition to passive diffusion, the common mechanisms of material exchange between the brain and the outside world include active transport, effector transport, and carrier-mediated transcytosis (CMT) [3]. Human BMECs, the primary components of the BBB, restrict the entry of soluble substances and cells from the blood into the brain. BMECs share some of the same properties as peripheral endothelial cells, such as i) BMECs have many tight intercellular junctions, which produce high transendothelial impedance and delay paracellular flux [4, 5]; ii) BMECs lack the fenestrated structure of endothelial cells, and their pinocytosis activity is low; and iii) BMECs possess asymmetrically localized enzymes and vector-mediated transport systems, resulting in a "polarized" phenotype [6, 7]. BMECs express cell adhesion molecules on their surface to regulate leukocyte entry into the brain [8]. Due to the organ specificity of microvascular endothelial cells (MECs), endothelial cells are often derived from tissues relevant to disease research. Central nervous system diseases remain a leading cause of death globally [9, 10], and the blood-brain barrier (BBB) remains a critical barrier to drug delivery, making it a significant bottleneck in treatment development [11, 12].

Potassium channels are widely distributed on the cell membrane of vascular smooth muscle, with different subtypes expressed at varying levels. The physiological roles, structural properties, and pathological changes of these potassium channels, particularly Kir2.1, are receiving increasing attention in vascular and neurovascular research. As a major member of the Kir2 family, Kir2.1 is highly expressed in cardiovascular, skeletal muscle, and brain tissues in mammals [13]. Some studies suggest that Kir2.1 is involved in endothelial cell phenotypic changes, though the underlying mechanisms remain unclear [14]. BMECs and their tight junctions can function as a barrier under normal physiological conditions. However, when these conditions are disrupted due to ischemia or brain injury, BMEC barrier integrity is compromised, leading to increased vascular permeability, severe brain edema, and secondary brain injury [15]. Lipopolysaccharide (LPS), a potent endotoxin released into the bloodstream, plays a

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critical role in stimulating the non-specific immune response of the body [16]. Studies have shown that LPS levels are significantly elevated in central nervous system infections, and that tight junction proteins such as occludin and ZO-1 in BMECs are downregulated [17, 18]. LPS has been shown to enhance BBB permeability, potentially by disrupting tight junction proteins, a process that mirrors the permeability changes observed following ionizing radiation [19-21]. However, the precise mechanisms remain unclear. In particular, the contribution of Kir2.1 channels to BMEC permeability under combined inflammatory and radiation-induced stress has not been fully elucidated.

Therefore, this study aimed to investigate the effects of LPS and ionizing radiation on BMEC permeability and tight junction protein expression, and to explore the potential regulatory role of Kir2.1 (KCNJ2) in these processes. To our knowledge, this is the first study to link Kir2.1-mediated signaling with RhoA activation, tight junction remodeling, and blood–brain barrier dysfunction in the context of both inflammatory stimulation and radiotherapy-related radiation exposure, providing new mechanistic insight and a potential therapeutic target for protecting the BBB during brain irradiation.

MATERIALS AND METHODS

Research materials

Seven-day-old specific pathogen-free (SPF) Sprague–Dawley (SD) rats were purchased from the Animal Experimental Center of Shandong Provincial Hospital Affiliated to Shandong First Medical University. All experimental procedures were approved by the Animal Ethics Committee of Shandong First Medical University, and were performed in accordance with institutional and national guidelines for the care and use of laboratory animals.

To simulate clinical radiotherapy conditions, confluent BMEC monolayers were exposed to single doses of ionizing radiation (0, 0.5, 2, and 8 Gy) using a 6 MV linear accelerator (Clinac series, Varian Medical Systems, USA). Irradiation was delivered at a dose rate of approximately 2–4 Gy/min with a source-to-surface distance (SSD) of 100 cm and a field size of 20 × 20 cm^2. Sham-irradiated cells served as controls.

Isolation and culture of BMECs

The rats were anesthetized with 4% chloral hydrate (Sinopharm Chemical Reagent Co., China) and fixed in the supine position on a sterile bench. Hair was removed with a blade, and the skin was disinfected with 75% ethanol (Tianjin Kermel, China). The brain was removed quickly to preserve structural integrity and placed in precooled DMEM/F12 basal medium (Gibco, Thermo Fisher Scientific, USA). The meninges and external blood vessels were removed under aseptic conditions. White matter was discarded, and gray matter was retained. The tissue was rinsed several times with precooled medium at 4°C, cut into approximately 1 mm^3 pieces, and transferred into a sterile 50 mL centrifuge tube. After centrifugation (25°C, 900 rpm, 4 min), the supernatant was discarded, and 5 mL of serum-free DMEM/F12 was added.

Explants were cultured in DMEM/F12 containing 20% fetal bovine serum (FBS; Gibco, USA) and penicillin–streptomycin (Thermo Fisher Scientific, USA) at 37°C in a 5% CO_2 incubator. The medium was changed every 3 days. When cells reached 70–80% confluence, they were digested with 0.1% trypsin–EDTA (Gibco, USA) for subculture. Cells between the 2nd and 4th passages were used for all experiments.

Grouping

The 3rd - 4th generation MECs were divided into the following experimental groups. In the Control (Ctrl) group, cells were treated with 0.9% normal saline. In the Observation (Obs) group, cells were stimulated with 5 μg/mL lipopolysaccharide (LPS; Sigma-Aldrich, USA). Radiation groups were exposed to 0.5, 2, or 8 Gy of ionizing radiation alone. In the Combination group, cells received 5 μg/mL LPS followed by irradiation at the indicated doses. This design allowed assessment of Kir2.1-related responses under inflammatory stress, radiation stress, and combined conditions.

Determination of RhoA activity in cells

The pull-down method was used to detect RhoA activity, employing a commercial RhoA activation assay kit (Guangzhou Bohui Biotechnology Co., Ltd., China). After treatment, cell lysates were incubated with RhoA-binding domain beads according to the manufacturer's protocol. Expression of active GTP-bound RhoA (GTP-RhoA) and total RhoA was detected by Western blot, and RhoA activity was expressed as the ratio of GTP-RhoA to total RhoA. For irradiation experiments, RhoA activity was measured at 6 h and 24 h after exposure to ionizing radiation to capture early and intermediate signaling changes.

Cell TEER assay

Cells were seeded into Transwell culture inserts (Corning, USA) and cultured until a confluent monolayer formed. Unseeded wells containing the same culture medium were used as blank controls. Transendothelial electrical resistance (TEER) was measured using an ESR-2 resistance meter (Millipore, Japan) at room temperature. Each measurement was repeated three times, and the normalized TEER value was obtained by subtracting the blank control reading from each well reading.

For the radiation and combination groups, TEER was measured before irradiation and at 6 h, 24 h, and

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48 h post-irradiation to evaluate dynamic changes in barrier permeability.

Expression of related proteins detected by Western blot

Total protein from cells in each group was extracted using RIPA lysis buffer (Beyotime Biotechnology, China). Equal amounts of protein were separated by SDS–polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene difluoride (PVDF) membranes (Millipore, USA). Membranes were blocked with 5% skim milk in Tris-buffered saline with Tween-20 (TBST) and incubated with primary antibodies at 4°C overnight. The following primary antibodies were used: anti-RhoA (1:1000; Cell Signaling Technology, USA), anti-p115RhoGEF (1:1000; Santa Cruz Biotechnology, USA), anti-ZO-1 (1:1000; Invitrogen, USA), anti-occludin (1:1000; Abcam, UK), anti-claudin -5 (1:1000; Abcam, UK), and anti–phospho-myosin light chain (p-MLC, 1:1000; Cell Signaling Technology, USA). After washing, membranes were incubated with HRP-conjugated goat anti-rabbit or goat anti-mouse IgG secondary antibodies (1:10,000; ZSGB-BIO, China) for 1 h at room temperature. Protein bands were visualized using an enhanced chemiluminescence (ECL) kit (Thermo Fisher Scientific, USA) and quantified using ImageJ software (National Institutes of Health, USA).

Method of statistics

Statistical analyses were performed using SPSS software, version 22.0 (IBM Corp., Armonk, NY, USA). Measurement data were expressed as mean ± standard deviation (SD). The t test or χ^2 test was used to compare differences between groups, as appropriate. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Morphology of BMECs

During primary culture, BMECs adhered to the culture surface within approximately 24 hours and initially displayed a spindle-shaped or elongated morphology. After routine medium replacement, cell proliferation became more pronounced, and cells exhibited uniform spindle or polygonal shapes. Confluence of 70%–80% was typically achieved within 5–7 days, allowing for passage.

Expression of p115RhoGEF protein

Western blot analysis showed low basal expression of p115RhoGEF in the Ctrl group, while LPS stimulation significantly increased p115RhoGEF levels at 1, 3, and 6 h, followed by a gradual decline toward baseline at 12 h ($P < 0.05$). These findings indicate a time-dependent activation of the RhoA regulatory pathway under inflammatory stimulation (figure 1).

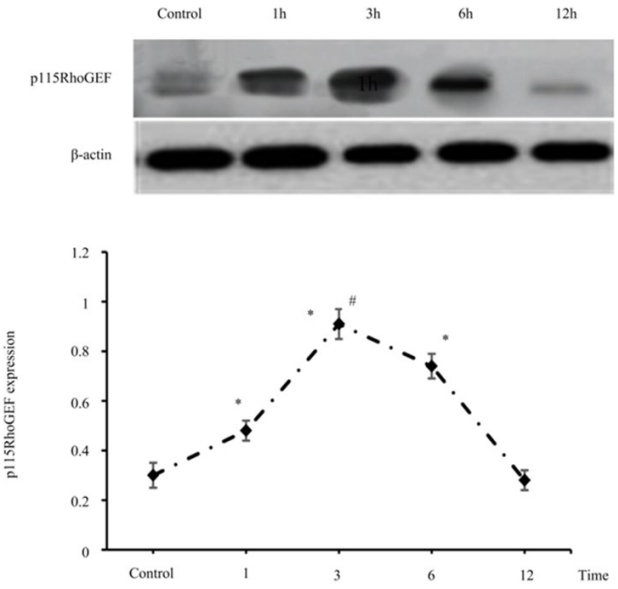

Figure 1. Expression of p115RhoGEF in BMECs after LPS treatment. Western blot analysis shows time-dependent upregulation of p115RhoGEF at 1, 3, and 6 h, with levels returning toward baseline at 12 h. *P < 0.05 vs. Ctrl; #P < 0.05 vs. earlier time points in the Obs group.

RhoA activity in BMECs

GTP-RhoA levels were low in Ctrl cells but markedly increased in the Obs group after 5 and 15 minutes of LPS exposure, confirming rapid activation of RhoA signaling in response to endotoxin stimulation (figure 2).

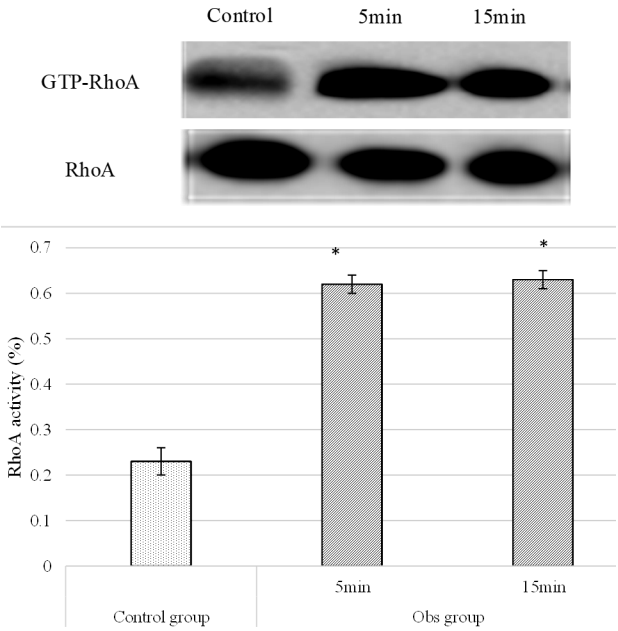

Figure 2. RhoA activity in BMECs. GTP-RhoA levels were elevated at 5 and 15 min following LPS stimulation, indicating rapid activation of RhoA signaling.

TEER measurements

Baseline TEER values were similar between groups ($P > 0.05$). After LPS stimulation, TEER values decreased progressively at 3, 6, and 12 h, indicating

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time-dependent impairment of barrier integrity ($P < 0.05$). In contrast, TEER values in the Ctrl group remained stable throughout the same time intervals. For radiation-exposed groups, TEER values measured before irradiation and at 6 h, 24 h, and 48 h post-irradiation also demonstrated a dose-dependent decline, confirming that ionizing radiation impaired endothelial barrier function similarly to LPS (figure 3).

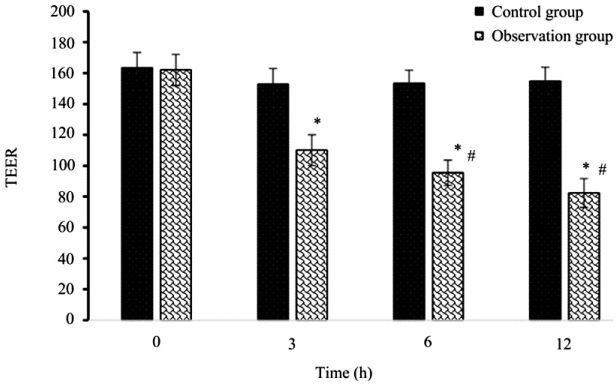

Figure 3. Transendothelial electrical resistance (TEER) in BMECs. LPS treatment significantly reduced TEER at 3, 6, and 12 h, indicating impaired barrier function.

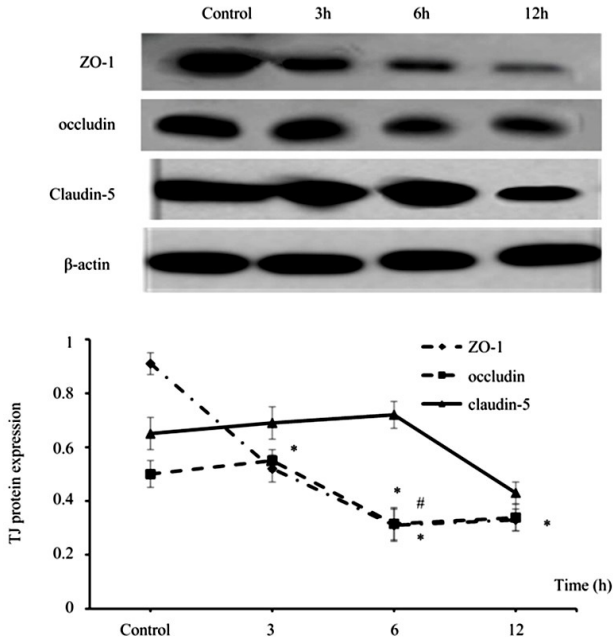

Figure 4. Expression of tight junction proteins ZO-1, occludin, and claudin-5. LPS induced significant reductions in ZO-1 and occludin at 6 and 12 h; claudin-5 expression remained unchanged.

Tight junction protein expression

Western blot analysis of tight junction proteins ZO-1, occludin, and claudin-5 revealed that LPS stimulation significantly reduced ZO-1 and occludin expression at 6 h and 12 h compared with the Ctrl group ($P < 0.05$). Claudin-5 levels did not differ significantly between groups at any time point ($P > 0.05$). These findings indicate that LPS selectively disrupts components of the tight junction complex that are critical for maintaining BMEC barrier integrity. Radiation-exposed groups showed similar reductions in ZO-1 and occludin expression in a dose-dependent manner, further supporting radiation-induced disruption of tight junction integrity (figure 4).

DISCUSSION

The blood–brain barrier (BBB), formed primarily by brain microvascular endothelial cells (BMECs), plays a crucial role in regulating the movement of substances between the blood and the brain. The integrity of the BBB is essential for maintaining brain homeostasis, and its dysfunction is associated with various neurological conditions, including neuroinflammation, ischemia, and neurodegenerative diseases. In this study, we investigated the impact of lipopolysaccharide (LPS) treatment on BMEC permeability and the role of Kir2.1 (KCNJ2) channels in regulating endothelial function under both inflammatory and radiation-induced stress. The results suggest that LPS treatment significantly impairs tight junction integrity and disrupts endothelial barrier function, leading to increased permeability in BMEC monolayers.

Our findings are consistent with previous studies indicating that LPS-induced inflammation contributes to BBB disruption through the regulation of tight junction proteins such as ZO-1, occludin, and claudin-5 [17, 18]. These proteins form a critical component of the endothelial cell junctions, and their downregulation is a hallmark of BBB breakdown. In this study, we observed significant reductions in the levels of ZO-1 and occludin following LPS treatment, similar to what has been reported in other inflammatory models of BBB dysfunction [16]. Moreover, the observation that ionizing radiation (IR) produced comparable changes in tight junction protein expression and TEER further supports the concept that different stressors may converge on common signaling pathways to compromise BBB integrity. The combination of LPS treatment with IR led to a more pronounced decrease in barrier function than either stimulus alone, further supporting the idea that radiation can enhance inflammation-induced barrier disruption.

Radiation and inflammatory stress: a synergistic effect on the BBB

Our data demonstrate that IR induces dose-dependent decreases in TEER and further diminishes the expression of tight junction proteins, similar to the effects seen with LPS treatment. This supports the growing body of literature showing that radiation-induced BBB dysfunction can significantly contribute to neurological damage, including edema, inflammation, and impaired drug delivery [22]. We observed that higher doses of radiation (8 Gy) led to the most severe reduction in TEER, which aligns with

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findings from other studies demonstrating that radiation doses above 2 Gy cause significant structural and functional changes in endothelial cell barriers [23]. In the context of radiotherapy for brain tumors, the combination of radiation and inflammatory processes such as those triggered by infection or injury may amplify damage to the BBB. These findings have important implications for radiation therapy, where the treatment of brain tumors can inadvertently compromise the BBB, complicating drug delivery and exacerbating the risk of neurotoxicity [24]. In clinical practice, whole-brain radiotherapy and local boost treatments are widely used in patients with brain metastases [26], and our findings suggest that, beyond tumor control, strategies to preserve BBB integrity during these treatments may be important [25] Our results therefore highlight the need to consider both radiation dose and the inflammatory status of the microenvironment when designing radiotherapy protocols.

Kir2.1 as a potential regulator of BBB integrity Kir2.1 channels have been implicated in regulating endothelial cell function by modulating membrane potential, calcium influx, and RhoA/ROCK signaling pathways, which are crucial for maintaining tight junction integrity. Our study suggests that Kir2.1 may play a significant role in regulating the permeability of BMECs under both inflammatory and radiation-induced stress. This is supported by the finding that RhoA activity, a key regulator of cytoskeletal dynamics and tight junction remodeling, was elevated after both LPS treatment and radiation exposure, indicating activation of a common downstream signaling cascade [26].

Interestingly, the combination of LPS treatment and radiation resulted in a significantly higher RhoA activity than either stimulus alone, suggesting that Kir2.1 may act as a modulator of RhoA/ROCK signaling. This aligns with previous studies suggesting that potassium channels, including Kir2.1, influence endothelial barrier function through the regulation of intracellular calcium levels and the activation of RhoA/ROCK pathways [27]. These findings imply that Kir2.1 may offer a novel target for protecting the BBB from radiation-induced damage and improving drug delivery in radiotherapy settings. Taken together, our data support a model in which Kir2.1-dependent modulation of RhoA/ROCK signaling contributes to tight junction disruption and increased BMEC permeability during both inflammatory and radiation stress.

The findings of this study underscore the importance of understanding the molecular mechanisms underlying BBB dysfunction in the context of radiotherapy and neuroinflammation. Therapeutic strategies aimed at stabilizing the BBB, such as modulating Kir2.1 activity or targeting the RhoA/ROCK pathway, could offer promising avenues for improving treatment outcomes in patients undergoing brain irradiation [12]. Additionally, combination therapies that address both the inflammatory and radiation-induced effects on the BBB may be essential for mitigating the side effects of radiotherapy, such as edema and neurocognitive decline. Future studies should focus on exploring the protective effects of Kir2.1 agonists or RhoA inhibitors in preclinical models of radiation-induced BBB disruption, as well as evaluating the impact of these interventions on drug delivery across the BBB [28].

This study has several limitations that should be considered when interpreting the results. First, all experiments were performed *in vitro* using rat BMECs, which may not fully recapitulate the complexity of the *in-vivo* neurovascular unit, including interactions with astrocytes, pericytes, and immune cells. Second, although we observed associations between Kir2.1 activity, RhoA signaling, and tight junction protein expression, direct genetic or pharmacological manipulation of Kir2.1 was not performed, and thus causality remains to be conclusively demonstrated. Third, only a limited range of radiation doses and time points was examined; more detailed dose–response and time-course studies are needed to better define the dynamics of BBB disruption after irradiation. Finally, we did not assess functional neurological outcomes or *in-vivo* BBB permeability, which will be important to address in future animal studies to translate these findings into clinically relevant strategies.

CONCLUSION

This study demonstrates that lipopolysaccharide (LPS) and ionizing radiation both disrupt tight junction integrity and increase the permeability of brain microvascular endothelial cells (BMECs), with combined exposure producing greater barrier impairment. The findings indicate that Kir2.1 (KCNJ2) channels may contribute to these permeability changes through modulation of RhoA/ROCK signaling. Kir2.1 therefore represents a potential therapeutic target for protecting the blood–brain barrier during radiotherapy. Further studies using direct modulation of Kir2.1 and *in-vivo* validation are needed to clarify its mechanistic role and therapeutic potential.

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***Conflict of Interest*:** The authors declare that they

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have no conflict of interest related to this work.

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***Ethical Consideration*:** All animal experimental procedures were conducted in accordance with the guidelines for the care and use of laboratory animals and were approved by the Animal Ethics Committee of Affiliated Hospital of Jianghan University. All efforts were made to minimize the number of animals used and their suffering.

***Authors' Contribution*:** L.D., contributed to the conception and design of the study, performed the experiments, and collected the data. D.W., supervised the project, contributed to data interpretation, and critically revised the manuscript. Both authors participated in drafting and revising the manuscript, approved the final version, and agree to be accountable for all aspects of the work.

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