Anticonvulsant Effect of Hydroalcoholic Extract of *Heracleum Persicum* Seed on Pentylenetetrazol-Induced Seizures across the Estrous Cycle in Female Rats

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Abstract

Catamenial epilepsy, a subtype of seizure disorder influenced by hormonal fluctuations during the menstrual cycle, remains a therapeutic challenge, particularly in women with fluctuating seizure thresholds. *Heracleum persicum* (Persian Hogweed), a traditional medicinal plant, has demonstrated anticonvulsant properties, but its efficacy under varying hormonal states has not been systematically evaluated. This study assessed the anticonvulsant effects of hydroalcoholic extract of *H. persicum* seeds on pentylenetetrazol (PTZ)-induced seizures in adult female rats across distinct stages of the estrous cycle. Ninety-six rats were synchronized to the estrous cycle and grouped by phase: proestrus, estrus, metestrus, and diestrus. Each group included one control (saline) and three treatment subgroups receiving *H. persicum* extract intraperitoneally (IP) at doses of 150, 300, or 600 mg/kg. Fifteen minutes post-treatment,

seizures were induced by PTZ injection (80 mg/kg, IP), and initiation time of myoclonic seizures (ITMS), initiation time of tonic–clonic seizures (ITTS), seizures duration and mortality rate were recorded over a 30-minute observation window. Findings showed that extract significantly delayed ITMS and ITTS in a dose-dependent manner ($P<0.05$), with effects observed consistently across all estrous phases. Notably, the treatment abolished estrous-phase-dependent variability in seizure thresholds observed in control animals. Seizure durations and mortality rates were also significantly reduced at all doses ($P<0.05$). These findings strongly suggest that *H. persicum* extract exhibits short-term, hormone-independent anticonvulsant activity, highlighting its potential as an adjunct therapy for catamenial epilepsy. Further investigation into its active constituents and long-term safety profile is warranted to better understand its clinical applicability and mechanisms in hormone-influenced seizure disorders.

Keywords: Catamenial Epilepsy, Pentylenetetrazol, Estrous Cycle, Seizure, Anticonvulsant

1. Introduction

Epilepsy is a widespread neurological disorder affecting approximately 60 million people worldwide and is considered the second most common chronic neurological condition after stroke, according to global epidemiological data (1). In women, seizure frequency often fluctuates with hormonal changes during the menstrual cycle, a phenomenon known as catamenial epilepsy, which affects up to 70% of women diagnosed with epilepsy (2). This condition is primarily mediated by variations in steroid hormones, particularly estrogen and progesterone, which exert opposing effects on neuronal excitability. Estrogen enhances excitatory neurotransmission by modulating N-methyl-D-aspartate (NMDA) receptor activity, lowering seizure thresholds, whereas progesterone and its neuroactive metabolite allopregnanolone potentiate gamma-aminobutyric acid (GABA)-ergic inhibition, exerting anticonvulsant effects (3). Consequently, hormonal fluctuations create windows of increased seizure susceptibility, particularly during estrogen-dominant phases such as proestrus and estrus.

Despite advances in antiepileptic drug (AED) therapy, only about 40% of patients achieve complete seizure control, and many experience significant side effects—highlighting the need for safer, more effective treatments, particularly for catamenial epilepsy (4). Given the limitations of conventional AEDs in addressing hormonal influences, there is growing interest in adjunct therapies derived from medicinal plants with neuroactive properties.

Heracleum persicum (Persian Hogweed), a plant native to Iran, has been traditionally utilized for the treatment of epilepsy and various other neurological conditions (5). Its seeds and roots contain bioactive

compounds such as furanocoumarins (e.g., bergapten, isopimpinellin), terpenoids, and flavonoids, which contribute to its anticonvulsant, antioxidant, and anti-inflammatory effects (6). Essential oils from the plant are rich in hexyl butyrate and octyl acetate, and the hydroalcoholic extract exhibits strong antioxidant, analgesic, and anti-inflammatory activities (7). The plant also shows notable antimicrobial and antifungal properties (8). Immunomodulatory activity has been observed, possibly linked to its flavonoid and coumarin content, which enhance both cellular and humoral immune responses (9). Animal studies have demonstrated that *H. persicum* extracts reduce seizure susceptibility, likely due to their modulation of neurotransmitter systems (10). However, no study has systematically evaluated its efficacy across the hormonally dynamic stages of the female reproductive cycle, a critical gap given the role of hormonal fluctuations in catamenial epilepsy.

To address this, the present study investigates the anticonvulsant effects of *H. persicum* seed extract on pentylenetetrazol (PTZ)-induced seizures in adult female rats during distinct estrous cycle phases. By examining how the extract interacts with endogenous hormonal variations, this research aims to uncover novel, hormone-sensitive therapeutic strategies. The findings could pave the way for more effective, tailored treatments for women with catamenial epilepsy, ultimately improving seizure control and quality of life.

2. Materials and Methods

2.1. Animals

Ninety-six adult female Wistar rats weighing between 200-250 grams were sourced from the Laboratory Animal Breeding Unit at the Faculty of Veterinary Medicine, University of Tehran. Given the study's focus on catamenial epilepsy and hormonal influences on seizure susceptibility, only female rats were included to evaluate estrous cycle-dependent effects. The animals were housed in groups of four per cage under standard laboratory conditions: 12-hour light/dark cycle, ambient temperature of 22 ± 3 °C, and unrestricted access to food and water. All experimental protocols were approved by the Institutional Animal Care and Use Committee of the University of Tehran (approval code: IR.UT.REC.1399.180) and were conducted in accordance with the guidelines outlined by the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Estrous Cycle Synchronization

To synchronize the estrous cycle, male rat pheromones were introduced using the Whitten effect. Specifically, 200 g of bedding from uncleaned male rat cages (retained for 7 days) was placed in each

female rat cage for three consecutive days (11). This method has been shown to reliably induce estrous cycling without pharmacological interference.

2.3. Determination of Estrous Cycle Stage

Vaginal smears were collected daily between 09:00 and 10:00 AM using a modified Pasteur pipette with a smoothed tip. The pipette was rinsed with alcohol, distilled water, and normal saline before each sampling. Approximately 100 μL of sterile saline was gently injected into the vagina, and the fluid was then aspirated. Smears were prepared on glass slides, allowed to dry naturally, treated with methanol for fixation, and then stained with Giemsa dye (1:10 dilution) for 10 minutes. Slides were rinsed with distilled water and examined under a light microscope at 100x and 250x magnification. The stage of the estrous cycle was determined based on the predominant cell types, as described previously (12). A trained observer, blinded to the treatment groups, performed all cytological analyses.

2.4. Preparation of *H. persicum* Extract

Seeds of *H. persicum* were obtained from an accredited local herbal market and verified by a botanist. A voucher specimen was deposited in the herbarium of the Faculty of Pharmacy, University of Tehran. The hydroalcoholic extract was prepared by macerating ground seeds in 70% ethanol for 72 hours at ambient temperature. Following filtration, ethanol was evaporated under reduced pressure using a rotary evaporator. The remaining extract was freeze-dried and stored at −20 °C. Immediately before administration, the extract was reconstituted in sterile normal saline (10). Preliminary phytochemical screening of *H. persicum* seed extract identified furanocoumarins (UV fluorescence), flavonoids (NaOH test), monoterpenes (thin-layer chromatography (TLC)), terpenoids (Salkowski test), and alkaloids (Mayer's reagent), consistent with prior reports (6, 10).

2.5. Experimental Design

This study consisted of four estrous phase-specific experiments (proestrus, estrus, metestrus, diestrus). In the first experiment (proestrus phase), rats were randomly divided into four groups, each consisting of six animals (n=6 per group): saline control, or treatment with *H. persicum* extract at 150, 300, or 600 mg/kg administered intraperitoneally (IP). Fifteen minutes post-treatment, seizures were induced with an 80 mg/kg IP injection of PTZ (Sigma-Aldrich, USA), a convulsant dose selected based on prior literature (13) (Table 1).

Table 1. Infusion protocol in the initial experiment (proestrus phase)*

Groups	First infusion	Second infusion
Control	CS**	Pentylenetetrazol (80 mg/kg)
Treatment 1	*H. persicum* extract (150 mg/kg)	Pentylenetetrazol (80 mg/kg)
Treatment 2	*H. persicum* extract (300 mg/kg)	Pentylenetetrazol (80 mg/kg)
Treatment 3	*H. persicum* extract (600 mg/kg)	Pentylenetetrazol (80 mg/kg)

*Identical protocols were followed for subsequent experiments in estrus, metestrus, and diestrus phases.
**: control solution (normal saline 0.9%)

Rats were monitored for 30 minutes post-PTZ for the following endpoints:

- Initiation time of myoclonic seizures (ITMS)
- Initiation time of tonic–clonic seizures (ITTS)
- Seizure duration (SD)
- Mortality rate (MR)

Seizure severity was classified using the Racine scale (14). All observers were blinded to group assignment. The subsequent experiments followed the same protocol as the first, but were conducted during the estrus, metestrus, and diestrus phases, respectively. Before administration, all compounds were solubilized in sterile normal saline solution to ensure proper preparation for use (12). Experimental sessions were conducted between 09:00 and 12:00 to minimize circadian variability in seizure susceptibility.

2.6. Statistical Analysis

All statistical analyses were performed using GraphPad Prism 9.0 (GraphPad Software, San Diego, CA, USA). Data were expressed as mean ± standard error of the mean (SEM). One-way ANOVA was used to compare groups within each estrous phase, followed by Tukey's post hoc test. Statistical significance was defined as $P<0.05$.

3. Results

3.1. Latency to Myoclonic and Tonic–Clonic Seizures

Administration of hydroalcoholic *H. persicum* seed extract significantly delayed the ITMS and ITTS in PTZ-challenged rats across all estrous cycle stages ($P<0.05$; Figure 1 and Figure 2). The findings demonstrate that infusion of a hydroalcoholic extract of *H. persicum* seeds at three distinct dosages significantly prolonged the latency to both myoclonic and tonic–clonic seizure onset across all phases of the estrous cycle in treatment groups compared to cycle-matched control treatments ($P<0.05$; Figure 1 and Figure 2). Notably, while control animals displayed inherent phase-specific variability in seizure thresholds, with significantly prolonged latencies during metestrus and diestrus relative to proestrus and estrus ($P<0.05$), no statistically significant interphase differences were observed in the magnitude of seizure threshold elevation induced by *H. persicum* extract administration at equivalent doses ($P\geq0.05$). Furthermore, the extract eliminated the physiological disparity in seizure susceptibility between estrous phases.

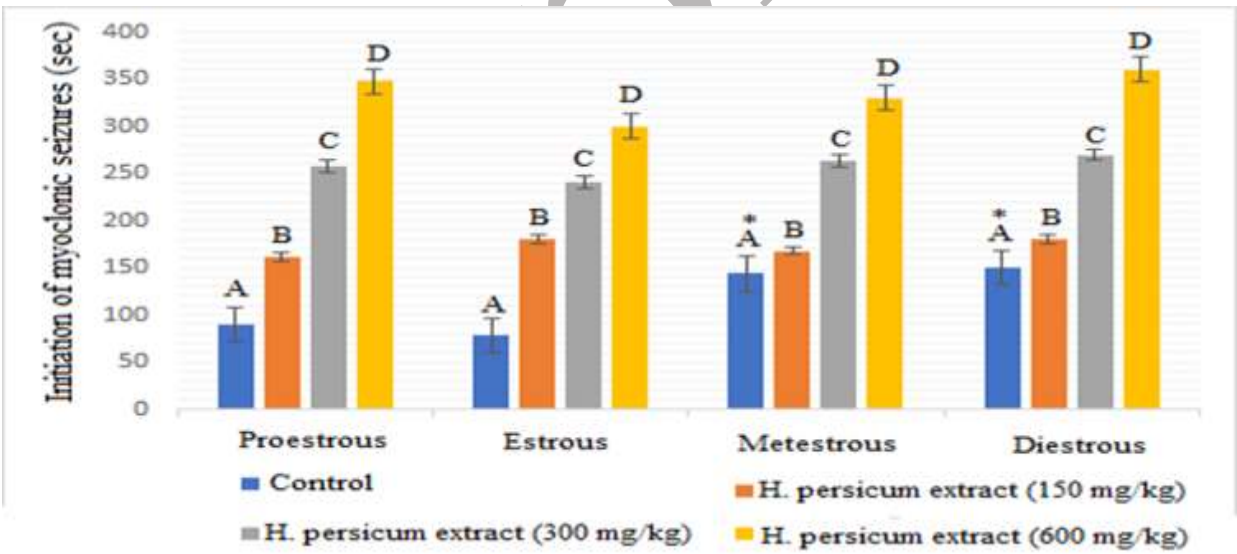

Figure 1 Antiepileptic effects of *H. persicum* extract (at doses of 150, 300, and 600 mg/kg) on the ITMS throughout estrous cycle in rats. Distinct letter labels (A–D) denote statistically significant variations in each estrous phase relative to the control treatment ($P<0.05$). Asterisks highlight significant differences between identical treatment regimens administered during distinct estrous phases ($P<0.05$). Data are reported as mean ± SEM.

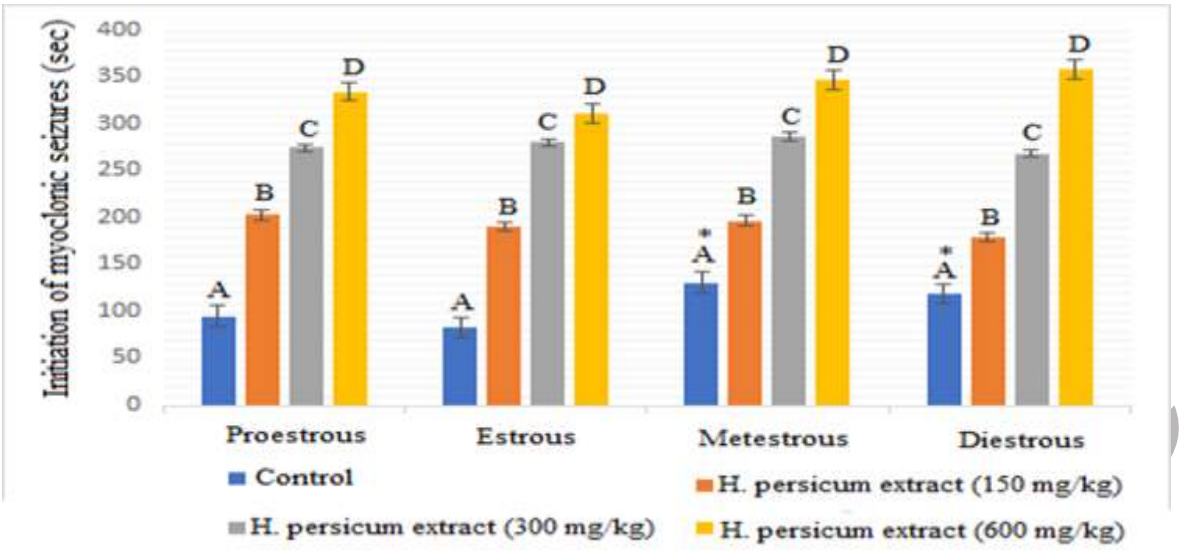

Figure 2 Antiepileptic effects of *H. persicum* extract (at doses of 150, 300, and 600 mg/kg) on the ITTS throughout estrous cycle in rats. Distinct letter labels (A–D) denote statistically significant variations in each estrous phase relative to the control treatment ($P<0.05$). Asterisks highlight significant differences between identical treatment regimens administered during distinct estrous phases ($P<0.05$). Data are reported as mean ± SEM.

3.2. Seizure Duration

Table 2 shows the effects of *H. persicum* extract on seizure duration during different estrous phases. In the control group, seizure durations were significantly longer in proestrus and estrus phases compared to metestrus and diestrus phases ($P<0.05$), indicating phase-dependent variability.

Treatment with *H. persicum* at all doses (150, 300, and 600 mg/kg) significantly reduced seizure duration compared to control in each phase ($P<0.05$). Importantly, seizure durations did not differ significantly among estrous phases within each treatment group ($P\geq0.05$), indicating the extract abolished phase-dependent variability.

Table 2. Effects of *H. persicum* extract (at doses of 150, 300, and 600 mg/kg) on seizure duration (Sec) throughout the estrous cycle in rats

Estrous phase	Control	*H. persicum* extract (150 mg/kg)	*H. persicum* extract (300 mg/kg)	*H. persicum* extract (600 mg/kg)
Proestrus	710 ± 48^{A}	$410 \pm 62^{A*}$	$320 \pm 75^{A*}$	$210 \pm 12^{A*}$
Estrous	730 ± 40^{A}	$419 \pm 98^{A*}$	$332 \pm 23^{A*}$	$219 \pm 34^{A*}$
Metestrus	460 ± 29^{B}	$371 \pm 42^{A*}$	$298 \pm 80^{A*}$	$204 \pm 18^{A*}$
Diestrus	451 ± 40^{B}	$359 \pm 60^{A*}$	$279 \pm 09^{A*}$	$195 \pm 32^{A*}$

Asterisks denote statistically significant variations within each estrous phase relative to the control treatment ($P<0.05$). Distinct letter labels (A & B) highlight significant differences between identical treatment regimens administered during distinct estrous phases ($P<0.05$). Results are reported as mean ± SEM.

3.3. Mortality Rate

Mortality rates mirrored the effects on seizure severity. In proestrus controls, 33.3% mortality was observed, which was completely abolished at all extract doses (0% mortality; $P<0.05$). Estrus controls exhibited the highest mortality (50%), significantly reduced to 16.7% at 150 and 300 mg/kg, and eliminated entirely at 600 mg/kg ($P< 0.05$; Table 3). In metestrus and diestrus, control mortality rates (16.7%) were also reduced to 0% at all doses ($P<0.05$). These findings indicate that *H. persicum* extract not only mitigates seizure severity but also prevents lethal outcomes, particularly in hormonally vulnerable phases like estrus.

Table 3. Effects of *H. persicum* extract (at doses of 150, 300, and 600 mg/kg) on mortality rate (%) throughout the estrous cycle in rats

Estrous phase	Control	*H. persicum* extract (150 mg/kg)	*H. persicum* extract (300 mg/kg)	*H. persicum* extract (600 mg/kg)
Proestrus	33.3^{A}	0^{A*}	0^{A*}	0^{A*}
Estrous	50^{A}	16.7^{B*}	16.7^{B*}	0^{A*}
Metestrus	16.7^{B}	0^{A*}	0^{A*}	0^{A*}
Diestrus	16.7^{B}	0^{A*}	0^{A*}	0^{A*}

Asterisks denote statistically significant variations within each estrous phase relative to the control treatment ($P<0.05$). Distinct letter labels (A & B) highlight significant differences between identical treatment regimens administered during distinct estrous phases ($p < 0.05$). Results are reported as mean ± SEM.

4. Discussion

The present study demonstrates that hydroalcoholic extract of *H. persicum* seeds exerts robust, dose-dependent anticonvulsant effects across all phases of the estrous cycle in seizures induced by PTZ. Notably, the extract not only delayed seizure onset (ITMS, ITTS) and reduced seizure duration and mortality rate but also abolished hormonal phase-dependent differences in seizure susceptibility. These findings suggest that *H. persicum* acutely modulates seizure thresholds through mechanisms that override

or compensate for fluctuations in neuroactive steroid levels, offering potential therapeutic utility for catamenial epilepsy.

In untreated controls, seizure susceptibility followed expected hormonal patterns: shorter ITMS and ITTS latency during estrogen-dominant phases (proestrus, estrus) compared to progesterone-dominant phases (metestrus, diestrus) (10). This aligns with the established role of estrogen in enhancing NMDA-mediated excitability and progesterone-derived neurosteroids like allopregnanolone in potentiating GABAergic inhibition (15). Remarkably, *H. persicum* treatment eliminates seizure susceptibility differences across estrous phases during the acute treatment window assessed in current study. This phase-independent efficacy suggests a multimodal mechanism targeting both excitatory and inhibitory pathways. For instance, monoterpenes such as linalool and cineol, identified in *H. persicum* essential oils, mirror the GABAergic activity of Lavandula and Melissa species, where linalool enhances chloride influx at GABAA receptors (16). Similarly, furanocoumarins like bergapten, reported in *H. persicum* roots and fruits, attenuate neuroinflammatory pathways by suppressing IL-1β-induced cyclooxygenase-2 (17). These mechanisms may synergize with the extract's antioxidant properties, attributed to its high phenolic content, which mitigate oxidative stress, a known driver of seizure propagation (18).

The extract's ability to counteract estrogen-driven hyperexcitability while amplifying inhibitory neurotransmission distinguishes it from botanicals with narrower mechanistic profiles. For example, *Valeriana officinalis* shows preferential efficacy in limbic seizure models (19), whereas *H. persicum*'s broad-spectrum action parallels *Nigella Sativa*, which suppresses hippocampal hyperexcitability via nitric oxide (NO) modulation (20). Indeed, *H. persicum*'s effects may involve NO signaling, as inhibition of NO synthase attenuates anticonvulsant activity. This broad-spectrum activity with dual modulation of GABAergic system combined with NO pathway engagement, positions *H. persicum* closer to *Ginkgo biloba*, surpassing botanicals like *Valeriana officinalis*, which targets limbic seizures selectively (19).

Methodological nuances further contextualize these findings. While *Artemisia dracunculus* exerts PTZ protection without motor impairment (21), *H. persicum*'s triterpene-rich profile may confer additional neuroprotective benefits, albeit with potential sedation risks akin to *Piper methysticum* (22). Hydroalcoholic extraction, as used here, likely optimizes bioavailability of polar antioxidants and non-polar monoterpenes compared to essential oil preparations, a critical factor also observed in Curcuma longa, where ethanolic extracts enhance curcuminoid potency (23). Such solvent-dependent bioactivity underscores the need for standardized extraction protocols to ensure reproducible therapeutic effects.

Clinically, the normalization of seizure thresholds across hormonal phases addresses a key limitation of current catamenial epilepsy therapies, such as progesterone supplementation, which exhibits variable efficacy due to fluctuating hormone levels (24). *H. persicum*'s phase-independent action could provide a more stable alternative, particularly given its immunomodulatory flavonoids and coumarins (6), which may synergize with antiepileptic drugs. However, safety concerns persist: furanocoumarins like bergapten are phototoxic and hepatotoxic at high doses (17, 25), necessitating rigorous toxicological profiling to balance efficacy and risk.

Limitations include the absence of direct hormonal assays or neurochemical analyses to elucidate precise mechanisms. To advance translational potential, subsequent studies should isolate active compounds (e.g., bergapten, linalool) to delineate their individual contributions, assess chronic toxicity, and evaluate interactions with standard antiepileptics like valproate. Direct measurement of estrogen/progesterone levels in treated animals could clarify whether *H. persicum* modulates hormone synthesis or receptor activity, while chronic epilepsy models would reveal its neuroprotective potential.

In conclusion, this study demonstrates that hydroalcoholic extract of *H. persicum* seeds exerts potent, hormone-independent anticonvulsant effects across all estrous cycle phases. The extract's ability to acutely stabilize seizure thresholds across hormonal states, coupled with its multimodal neuroprotective potential (including GABAergic modulation and anti-inflammatory activity), suggests it could address a critical gap in catamenial epilepsy management. These findings establish *H. persicum* as a compelling candidate for further development as an adjunct therapy for hormone-sensitive seizure disorders.

Declaration

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Ethics statement

All procedures adhered to the animal care regulations established in Iran and the guidelines provided by the National Institutes of Health (USA) for the care and use of laboratory animals. The Animal Ethics Committee of the Tehran University, Tehran, Iran (IR.UT.REC.1399.180) granted approval for all experimental procedures.

Authors' Contribution

Study concept and design: M. Z, M. KH.

Analysis and interpretation of data: M. Z, M. KH.

Drafting of the manuscript: E.KH, M. Z, M. KH, Z. SH, K. M.

Acquisition of Data: M. Z.

Critical revision of the manuscript for important intellectual content: K.M.

Study Supervision: M. KH.

Ethics

All procedures adhered to the animal care regulations established in Iran and the guidelines provided by the National Institutes of Health (USA) for the care and use of laboratory animals. The Animal Ethics Committee of the Tehran University, Tehran, Iran (IR.UT.REC.1399.180) granted approval for all experimental procedures.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Data availability

NO data was used for the research described in the article.

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

During the preparation of this manuscript, the author(s) used Perplexity AI, based on large language models as of July 2025 (version details not publicly disclosed), to assist in identifying and correcting potential grammatical errors and to improve the overall flow and readability of the text. The AI tool did not generate original content nor influence the scientific interpretation of the study. Following the use of this AI tool, the author(s) thoroughly reviewed and edited the manuscript as necessary and take full responsibility for the accuracy and integrity of the final published article.

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