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Original Article

Neuroprotective nanotherapy of *Paraboea leuserensis* in traumatic brain injury: Modulation of oxidative stress, inflammation, and apoptosis

[Nanoterapia neuroprotectora de *Paraboea leuserensis* en lesión cerebral traumática: modulación del estrés oxidativo, inflamación y apoptosis]

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Abstract

Context: Traumatic brain injury (TBI) is a major cause of disability and mortality worldwide. In addition to the primary insult, secondary mechanisms such as oxidative stress, neuroinflammation, and neuronal apoptosis worsen neurological outcomes. Existing treatments like corticosteroids offer limited protection, underscoring the need for novel therapies.

Aims: To investigate the neuroprotective potential of nanoformulated *Paraboea leuserensis* B.L.Burtt, an Indonesian medicinal plant with antioxidant and anti-inflammatory properties, in a rat TBI model.

Methods: Thirty male Wistar rats were randomly assigned into six groups: control, untreated TBI, TBI + methylprednisolone (10 mg/kg), and TBI + *P. leuserensis* nanoparticles (150, 250, or 350 mg/kg). Biomarkers of oxidative stress (GSH), inflammation (IL-6, IL-1β, HIF-1α), neurotrophic factor (BDNF), and apoptosis (TUNEL assay) were measured using ELISA and immunohistochemistry. Regression analysis was applied to evaluate correlations between apoptosis and biomarker changes.

Results: TBI increased IL-6, IL-1β, HIF-1α, and apoptosis, while decreasing GSH and BDNF. Treatment with nanoformulated *P. leuserensis* reduced oxidative stress, inflammation, and apoptosis in a dose-dependent manner, with optimal effects at 250 mg/kg. Regression showed apoptosis positively correlated with IL-1β and HIF-1α, and negatively with BDNF.

Conclusions: Nanoformulated *P. leuserensis* demonstrated significant neuroprotection, supporting its potential as an adjunct therapy for TBI.

Keywords: apoptosis; neuroprotection; nanoparticles; oxidative stress; *Paraboea leuserensis*; traumatic brain injury.

Resumen

Contexto: La lesión cerebral traumática (TBI) es una causa importante de discapacidad y mortalidad en todo el mundo. Además del daño primario, los mecanismos secundarios, como el estrés oxidativo, la neuroinflamación y la apoptosis neuronal, empeoran los resultados neurológicos. Los tratamientos existentes, como los corticosteroides, ofrecen una protección limitada, lo que subraya la necesidad de nuevas terapias.

Objetivos: Investigar el potencial neuroprotector de *Paraboea leuserensis* B.L.Burtt nanoformulada, una planta medicinal indonesiana con propiedades antioxidantes y antiinflamatorias, en un modelo de TBI en ratas.

Métodos: Treinta ratas Wistar machos fueron asignados aleatoriamente a seis grupos: control, TBI sin tratamiento, TBI + metilprednisolona (10 mg/kg) y TBI + nanopartículas de *P. leuserensis* (150, 250 o 350 mg/kg). Se midieron biomarcadores de estrés oxidativo (GSH), de inflamación (IL-6, IL-1β, HIF-1α), de factor neurotrófico (BDNF) y de apoptosis (ensayo TUNEL) mediante ELISA e inmunohistoquímica. Se aplicó un análisis de regresión para evaluar las correlaciones entre la apoptosis y los cambios en los biomarcadores.

Resultados: TBI aumentó IL-6, IL-1β, HIF-1α y apoptosis, mientras que disminuyó GSH y BDNF. El tratamiento con *P. leuserensis* nanoformulada redujo el estrés oxidativo, la inflamación y la apoptosis de forma dosis-dependiente, con efectos óptimos a 250 mg/kg. La regresión mostró que la apoptosis se correlacionaba positivamente con IL-1β y HIF-1α, y negativamente con BDNF.

Conclusiones: La nanoformulación de *P. leuserensis* demostró una neuroprotección significativa, lo que respalda su potencial como terapia complementaria para la lesión cerebral traumática.

Palabras Clave: apoptosis; estrés oxidativo; lesión cerebral traumática; nanopartículas; neuroprotección; *Paraboea leuserensis*.

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INTRODUCTION

Traumatic brain injury (TBI) represents a growing global health concern, with incidence increasingly driven by road traffic accidents, sports injuries, violence, and falls. Beyond the primary insult, secondary mechanisms—including oxidative stress, neuroinflammation, and apoptosis—intensify neuronal damage and contribute to long-term neurological impairment (Howlett et al., 2022; Mohammed et al., 2023). Despite advances in clinical management, existing treatments remain largely supportive and fail to halt progressive deterioration. This therapeutic gap highlights the need for innovative strategies, including the exploration of nanoformulated medicinal plants such as *Paraboea leuserensis*, which possesses recognized antioxidant and anti-inflammatory potential.

Paraboea leuserensis B.L.Burtt (*Gesneriaceae*) is an endemic species of the Leuser ecosystem in North Sumatra, Indonesia, where it has long been applied in ethnomedicine to treat inflammatory and degenerative conditions. Phytochemical studies reveal that it is rich in antioxidants and bioactive metabolites with anti-inflammatory and anti-apoptotic potential (Abd El Salam et al., 2023; Situmorang & Ilyas, 2018; Xiaobo et al., 2023). Despite this pharmacological promise, its neuroprotective effects in traumatic brain injury have not been examined. Addressing this gap not only provides a novel therapeutic candidate but also establishes a scientific basis for validating traditional medicinal knowledge within the framework of modern neurotherapeutics.

Over the last decade, nanotechnology-based drug delivery has emerged as a promising strategy to overcome major barriers in neurotherapeutics. Nanoparticle systems improve the bioavailability, stability, and controlled release of bioactive compounds while facilitating their passage across the blood–brain barrier (Alqahtani et al., 2024; Aqel et al., 2024; Fathy et al., 2023; Mohammed et al., 2023; Sheweita et al., 2023). These advantages are particularly relevant for plant-derived extracts, which often suffer from poor solubility and limited absorption. In this context, nanoformulation offers a critical opportunity to enhance the therapeutic efficacy of *P. leuserensis* and enable its application as a targeted intervention for secondary injury after TBI (Howlett et al., 2022; Thoma et al., 2022).

Previous studies on plant extract-based therapies for TBI have primarily investigated well-characterized compounds such as curcumin and resveratrol. However, to date, no study has evaluated the neuroprotective potential of *P. leuserensis*, particularly in a nanoformulated form. This research, therefore, addresses a clear gap by combining an endemic Indonesian medicinal plant with nanotechnology while simultaneously assessing oxidative stress, inflammation, and apoptotic pathways (Heryani et al., 2024). We hypothesize that nanoformulated *P. leuserensis* significantly attenuates secondary brain injury in TBI by modulating these interconnected mechanisms, thereby advancing natural compound-based therapeutic strategies (Abd El Salam et al., 2023; Shati et al., 2024).

Despite significant advancements in nanotechnology-based therapies for various neurological conditions, research on the effectiveness of nanoparticles derived from natural compounds for TBI remains limited (Jarrahi et al., 2020). Existing studies have predominantly focused on single bioactive compounds, such as polyphenols or flavonoids, and have often assessed only one or two isolated mechanisms. In contrast, the potential of *P. leuserensis*, which contains potent antioxidant and anti-inflammatory secondary metabolites (Marbun et al., 2024; Rahmawaty et al., 2015), has not yet been examined in the context of TBI. Importantly, TBI-induced damage is multifactorial, involving oxidative stress, inflammation, and apoptosis simultaneously. Therefore, a more comprehensive study is required to determine how *P. leuserensis* extract nanoparticles could provide neuroprotection through these interconnected mechanisms. Investigating this plant in TBI not only advances pharmacological research but also strengthens the scientific validation of Indonesian ethnomedicinal knowledge.

This study aims to investigate the effects of *P. leuserensis* extract nanoparticles in a rat model of TBI, focusing on three key mechanisms contributing to secondary injury. Biomarkers were selected based on their established role in TBI pathology: oxidative stress will be assessed through malondialdehyde (MDA) as a marker of lipid peroxidation, and superoxide dismutase (SOD) and glutathione peroxidase (GPx) as indicators of endogenous antioxidant defense (Jena et al., 2023; Liu et al., 2024; Sheweita et al., 2023). Inflammation was evaluated by measuring pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, which are consistently elevated in post-TBI neuroinflammation (Adeyi et al., 2023; Dutta & Bishayi, 2023; Johra et al., 2023; Koshak et al., 2023; Shen et al., 2023). Apoptotic pathways were explored by quantifying the expression of pro-apoptotic proteins Bax and caspase-3 (Ilyas et al., 2013), alongside the anti-apoptotic protein Bcl-2 (Borkar et al., 2022), as these are critical regulators of neuronal survival. Through this multidimensional analysis of oxidative stress, inflammation, and apoptosis, the study seeks to provide deeper insights into the neuroprotective mechanisms of *P. leuserensis* nanoparticles. Ultimately, this research highlights a natural compound-based therapeutic approach with promising potential to be developed into a safe neuroprotective

drug candidate for TBI patients (Akamatsu & Hanafy, 2020; Aqel et al., 2024; Bramlett & Dietrich, 2015).

Beyond its pharmacological significance, the study contributes to advancing novel therapies, leveraging local natural resources, and integrating nanotechnology into neuroprotection. The findings are expected to provide a foundation for further investigations into nanoparticle-based natural compound therapies for the treatment of traumatic brain injury.

MATERIAL AND METHODS

Reagents

The reagents used in this study included: Glutathione (GSH) ELISA kit (Cat# EKU04473), Mouse IL-6 ELISA kit (Cat# KE10007), BDNF Polyclonal Antibody for IHC (Cat# 28205-1-AP), IHC Easy HIF1AN Ready-To-Use IHC kit (Cat# KHC1968), and APO-BRDU-IHC (TUNEL) kit (Cat# NBP2-31164). All kits and reagents were used according to the manufacturer's protocols.

Plant material

Samples of *Paraboea leuserensis* B.L.Burtt were collected from the rainforest of Gunung Leuser, Bahorok District, Langkat Regency, North Sumatra Province, Indonesia. Fresh leaves were washing and air-drying, drained, and weighed. The leaves were dried in a drying cabinet at ±40°C, ground into powder, and stored in airtight containers at room temperature until use. The plant was taxonomically identified and authenticated by the Management of Scientific Collections, National Research and Innovation Agency, Jakarta (voucher number B-1216/II.6.2/IR.01.02/ 6/2023).

P. leuserensis nanoformulation

Nanoformulation of *P. leuserensis* was prepared using high-energy milling (HEM; Emax [4292201006-AL2-106857201], Germany). A ball-to-powder mass ratio of 1:20 was applied, with milling durations of 3, 6, or 9 h, as previously described (Irianti et al., 2020; Seo et al., 2023). During milling, cycles consisted of 10 minutes of operation followed by a 1 h rest period to prevent overheating. The powder was processed to obtain a nano-sized herbal extract with enhanced bioavailability and stability, following standardized procedures to ensure a concentrated and bioactive form suitable for experimental use.

Experimental animals

Thirty male Wistar rats (200–250 g, 10–15 weeks old) were obtained from the Biology Laboratory of Universitas Sumatera Utara (USU). The rats were acclimated for 2 weeks in the Animal Physiology Laboratory of the Biology Department at USU. Housing conditions were maintained at a 12 h light/dark cycle, 35–60% humidity, and standard temperature. Animals were provided with *ad libitum* access to water, corn, and pellet feed. Rats were housed in sterilized plastic cages (40 × 30 × 15 cm^3). All procedures were conducted under the approval of the Health Research Ethics Committee, Faculty of Mathematics and Natural Sciences, USU (Approval No. 0422/KEPH-FMIPA/2024).

Group allocation and treatment protocol

The rats were randomly assigned to five experimental groups (n = 5/group) following Federer's formula for experimental design: C0 (negative control); C+ (TBI, traumatic brain injury); M.pred. (TBI + methylprednisolone 10 mg/kg body weight); P.leu150 (TBI + *P. leuserensis* 150 mg/kg BW); P.leu250 (TBI + *P. leuserensis* 250 mg/kg BW); and P.leu350 (TBI + *P. leuserensis* 350 mg/kg BW).

Blood sample collection

At the end of the experimental period, rats were euthanized with a lethal intramuscular injection of anesthetic overdose (applied to the thigh muscle), a method considered ethically acceptable though slower than intravenous administration. Blood was collected by cardiac puncture, allowed to clot, and centrifuged to obtain serum for biochemical analyses (Borkar et al., 2022; Sheweita et al., 2023).

Quantification of brain cell biomarkers as indicators of damage

Serum levels of oxidative stress and inflammatory biomarkers, including glutathione (GSH) and interleukin-6 (IL-6), were quantified using commercially available ELISA kits, following the manufacturer's instructions (Adeyi et al., 2023; Dutta & Bishayi, 2023). These biomarkers were selected as sensitive indicators of neuronal injury and systemic inflammatory responses.

IHC analyses

Brain tissues were harvested and fixed in 10% neutral-buffered formalin, dehydrated, and embedded in paraffin blocks. Sections (4 µm thick) were prepared and subjected to immunohistochemical staining to evaluate the expression of the following markers: HIF-1α and IL-1β: markers of hypoxic and inflammatory responses, BDNF: neurotrophic factor associated with neuronal survival, and TUNEL assay: detection of DNA fragmentation as an indicator of apoptosis. All staining procedures followed the protocols provided in the reagent kits (Abd El Salam et al., 2023; Jena et al., 2023; Xiaobo et al., 2023). Positive signals were quantified in ImageJ (NIH, USA) to determine the

percentage of positive cells per field across standardized brain regions.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Prior to statistical testing, data distribution was assessed for normality (Shapiro–Wilk test) and homogeneity of variances (Levene's test). Comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test for multiple comparisons. Correlation analyses between apoptosis (TUNEL assay) and biomarker levels (IL-1β, HIF-1α, BDNF) were performed using linear regression analysis. All statistical analyses were conducted with SPSS software (IBM SPSS Statistics, Version 25.0), and significance was set at $p<0.05$ (Ilyas et al., 2025).

RESULTS

Particle size analysis of nanoherbal

The particle size distribution of the nanoherbal formulation was assessed using laser diffraction. The distribution curve is shown on Fig. 1. The results demonstrate that the preparation had a median particle size of 64.79 µm, a mean size of 117.10 µm, and a mode of 82.68 µm. The geometric mean diameter was 46.90 µm, with a geometric standard deviation of 4.78 µm, suggesting a broad distribution. In addition, the overall standard deviation of 138.26 µm indicates variability among particle sizes. According to the cumulative undersize data, 10% of particles measured less than 5.16 µm, whereas 90% measured less than 344.61 µm.

Evaluation of the neuroprotective potential of *P. leuserensis*

The neuroprotective potential of *P. leuserensis* against TBI-induced neurotoxicity was evaluated across six experimental groups: C0, C+, M.pred, P.leu150, P.leu250, and P.leu350.

Glutathione (GSH) and IL-6

TBI significantly reduced serum GSH levels compared with C0 ($p<0.05$), confirming the presence of oxidative stress. Treatment with methylprednisolone partially restored GSH levels but did not reach baseline values. Administration of *P. leuserensis* nanoparticles significantly increased GSH in a dose-dependent manner, with P.leu250 and P.leu350 showing the greatest improvements ($p<0.05$ vs. C+). The increase in GSH levels in these groups was comparable to that of the M.pred group (Fig. 2A).

IL-6 concentrations were significantly elevated in the C+ group compared to C0 ($p<0.05$), indicating an enhanced inflammatory response. Methylprednisolone significantly reduced IL-6 expression ($p<0.05$ vs. C+). Treatment with *P. leuserensis* also lowered IL-6 levels, although the reductions were less pronounced than with M.pred. Among the nanoparticle-treated groups, P.leu250 and P.leu350 achieved significant decreases compared to C+ ($p<0.05$), while P.leu150 did not differ significantly from C+ (Fig. 2B).

Brain-derived neurotrophic factor (BDNF) expression

TBI (C+) resulted in a significant reduction of BDNF-positive cells compared with C0 ($p<0.05$), indicating impaired neurotrophic support following injury (Fig. 3A). Treatment with methylprednisolone significantly restored BDNF expression compared to C+ ($p<0.05$).

Administration of *P. leuserensis* nanoparticles at 150, 250, and 350 mg/kg BW also increased BDNF expression relative to C+. Among these, P.leu250 produced the most consistent and significant improvement ($p<0.01$ vs. C+), whereas P.leu150 and P.leu350 showed moderate increases that were not always statistically significant (ns) (Fig. 3B).

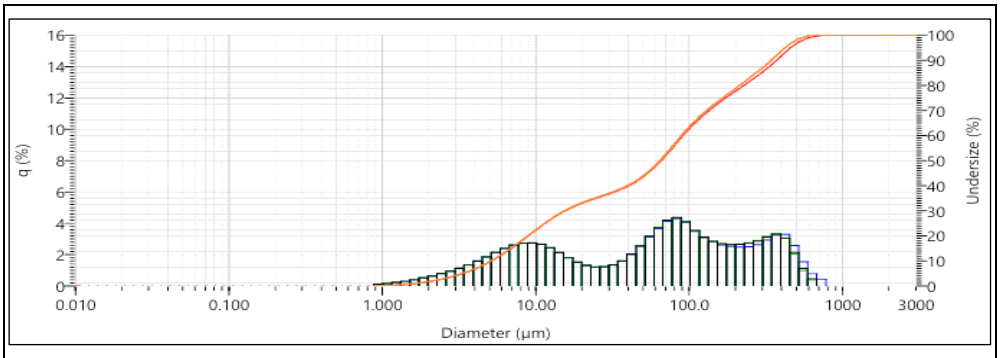

Figure 1. Particle size distribution curve of the nanoherbal formulation.

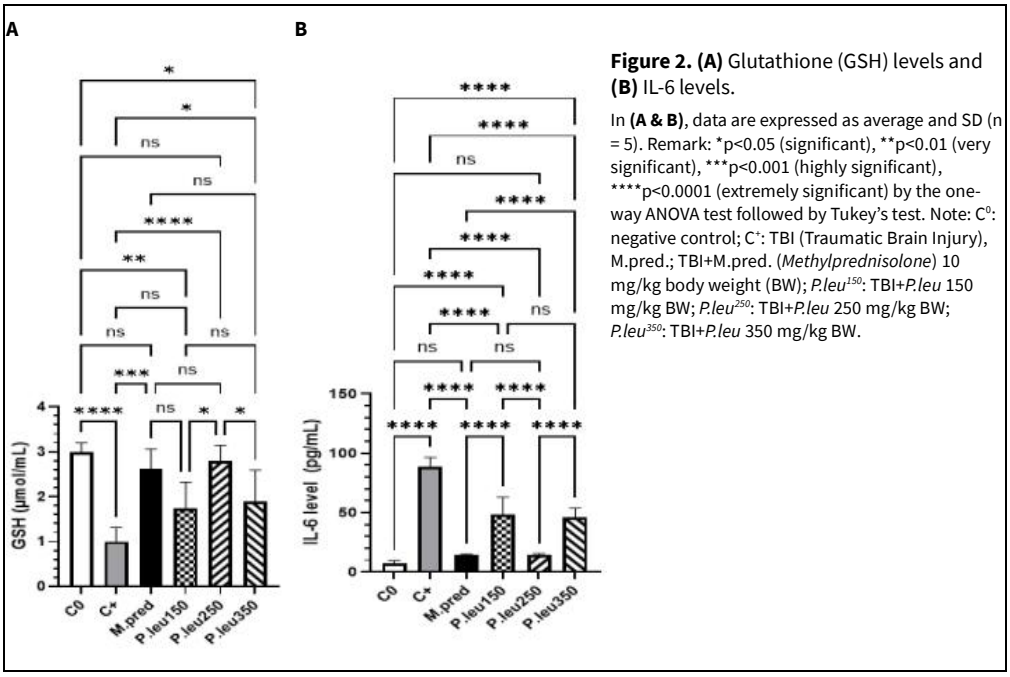

Figure 2. (A) Glutathione (GSH) levels and **(B)** IL-6 levels.

In **(A & B)**, data are expressed as average and SD (n = 5). Remark: *p<0.05 (significant), **p<0.01 (very significant), ***p<0.001 (highly significant), ****p<0.0001 (extremely significant) by the one-way ANOVA test followed by Tukey's test. Note: C^0: negative control; C^+: TBI (Traumatic Brain Injury), M.pred.; TBI+M.pred. (*Methylprednisolone*) 10 mg/kg body weight (BW); *P.leu*^{150}: TBI+*P.leu* 150 mg/kg BW; *P.leu*^{250}: TBI+*P.leu* 250 mg/kg BW; *P.leu*^{350}: TBI+*P.leu* 350 mg/kg BW.

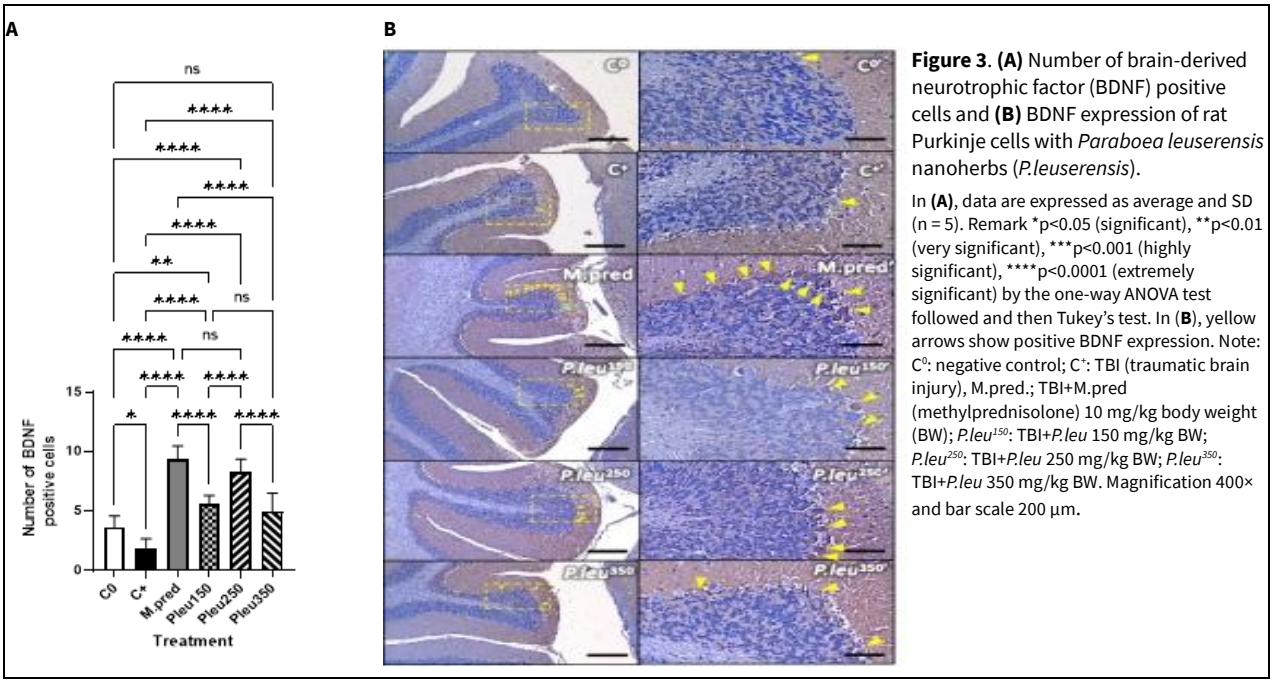

Figure 3. **(A)** Number of brain-derived neurotrophic factor (BDNF) positive cells and **(B)** BDNF expression of rat Purkinje cells with *Paraboea leuserensis* nanoherbs (*P.leuserensis*).

In **(A)**, data are expressed as average and SD (n = 5). Remark *p<0.05 (significant), **p<0.01 (very significant), ***p<0.001 (highly significant), ****p<0.0001 (extremely significant) by the one-way ANOVA test followed and then Tukey's test. In (**B**), yellow arrows show positive BDNF expression. Note: C^0: negative control; C^+: TBI (traumatic brain injury), M.pred.; TBI+M.pred (methylprednisolone) 10 mg/kg body weight (BW); *P.leu*^{150}: TBI+*P.leu* 150 mg/kg BW; *P.leu*^{250}: TBI+*P.leu* 250 mg/kg BW; *P.leu*^{350}: TBI+*P.leu* 350 mg/kg BW. Magnification 400× and bar scale 200 µm.

Inflammatory marker IL-1β expression

Fig. 4A-B shows that TBI (C+) significantly increased the number of IL-1β-positive cells compared with C0 (****p<0.0001). Treatment with methylprednisolone (M.pred) significantly reduced IL-1β expression compared with C+ (p<0.01).

The *P. leuserensis*-treated groups (150, 250, 350 mg/kg BW) also reduced IL-1β expression compared with C+, although the reductions were less pronounced than with methylprednisolone. Statistical analysis indicated that these reductions were not consistently significant (ns), and no significant differences were observed among the three doses.

Hypoxia-inducible factor-1 Alpha (HIF-1α) expression

As shown in Fig. 5A, the untreated TBI group (C+) displayed a significant increase in HIF-1α expression compared to the negative control (C0) (****p<0.0001), confirming the induction of hypoxia following brain injury. Treatment with methylprednisolone (M.pred) significantly reduced HIF-1α levels compared to C+ (**p<0.01), demonstrating its protective effect.

Similarly, *P. leuserensis* at 150, 250, and 350 mg/kg BW reduced HIF-1α expression relative to C+, although the differences between doses were not significant (ns). P.leu250 and P.leu350 showed lower expression than C+ but remained higher than M.pred. Overall, these findings indicate that *P. leuserensis* confers partial protection against hypoxia, though less effectively than methylprednisolone.

Apoptosis marker (TUNEL-positive cells) expression

As shown in Fig. 6A-B, the untreated TBI group (C+) displayed the highest number of TUNEL-positive cells compared to the negative control (C0) (****p<0.0001), confirming a marked increase in apoptosis following brain injury. Methylprednisolone (M.pred) significantly reduced the number of apoptotic cells compared to C+ (**p<0.01), demonstrating its protective effect. Similarly, treatment with *P. leuserensis* at 150, 250, and 350 mg/kg BW decreased apoptosis relative to C+, with P.leu250 and P.leu350 showing greater reductions than P.leu150. However, differences between the *P. leuserensis* doses were not statistically significant (ns).

Statistical analysis revealed highly significant differences (****p<0.0001, ***p<0.001) between several groups, whereas some comparisons were not statistically significant (ns). These findings confirm that TBI markedly increases apoptosis, that methyl-prednisolone effectively reduces it, and that *P. leuserensis* provides protective effects against apoptosis, particularly at higher doses (250 and 350 mg/kg BW).

Based on multiple linear regression analysis, the equation for predicting apoptosis based on IL-1β, BDNF, and HIF-1α was:

Apoptosis = 1.7204 + (0.4911 × IL-1β) − (0.2951 × BDNF) + (1.0253 × HIF-1α)

The coefficient interpretation indicates that IL-1β (0.4911) and HIF-1α (1.0253) contribute positively to apoptosis, with HIF-1α being the strongest predictor. Conversely, BDNF (−0.2951) exerts a protective effect by reducing apoptosis.

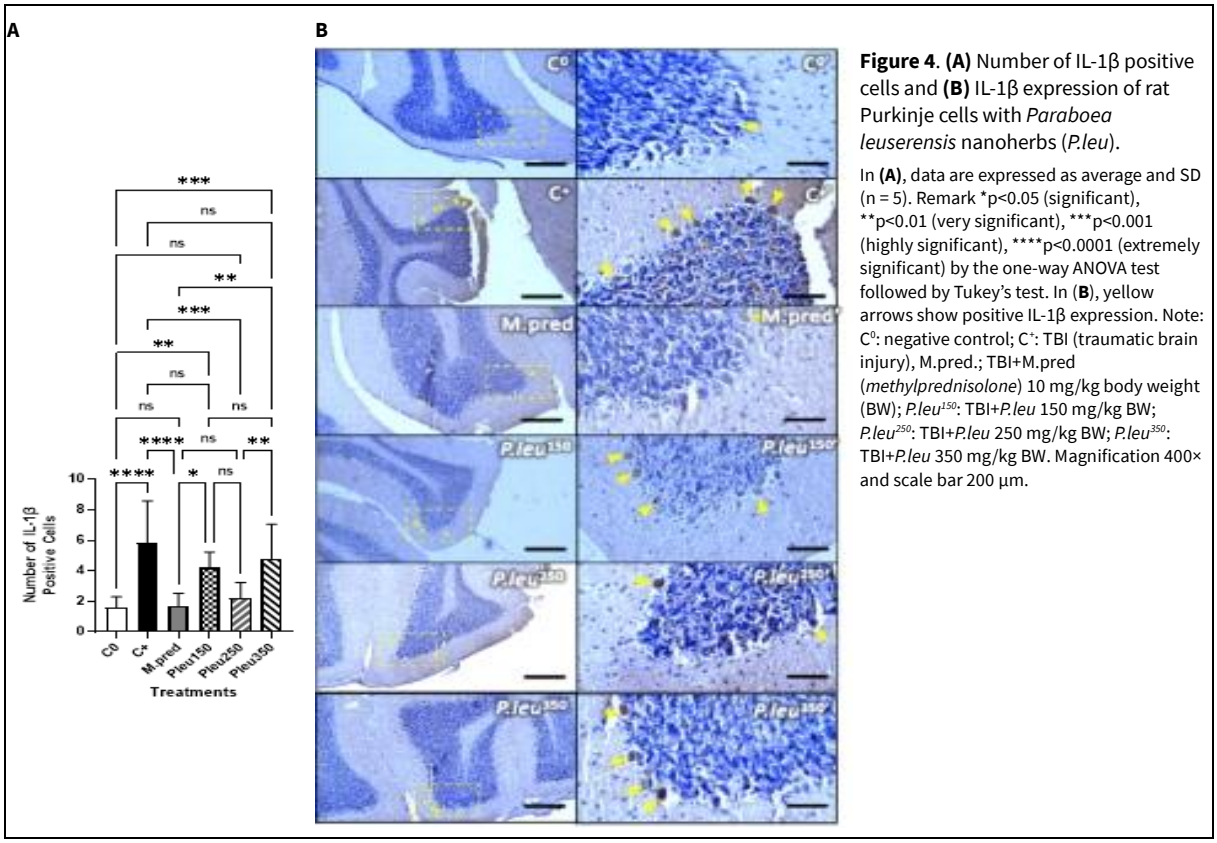

Figure 4. **(A)** Number of IL-1β positive cells and **(B)** IL-1β expression of rat Purkinje cells with *Paraboea leuserensis* nanoherbs (*P.leu*).

In **(A)**, data are expressed as average and SD (n = 5). Remark *p<0.05 (significant), **p<0.01 (very significant), ***p<0.001 (highly significant), ****p<0.0001 (extremely significant) by the one-way ANOVA test followed by Tukey's test. In (**B**), yellow arrows show positive IL-1β expression. Note: C^0: negative control; C^+: TBI (traumatic brain injury), M.pred.; TBI+M.pred (*methylprednisolone*) 10 mg/kg body weight (BW); $P.leu^{150}$: TBI+*P.leu* 150 mg/kg BW; $P.leu^{250}$: TBI+*P.leu* 250 mg/kg BW; $P.leu^{350}$: TBI+*P.leu* 350 mg/kg BW. Magnification 400× and scale bar 200 µm.

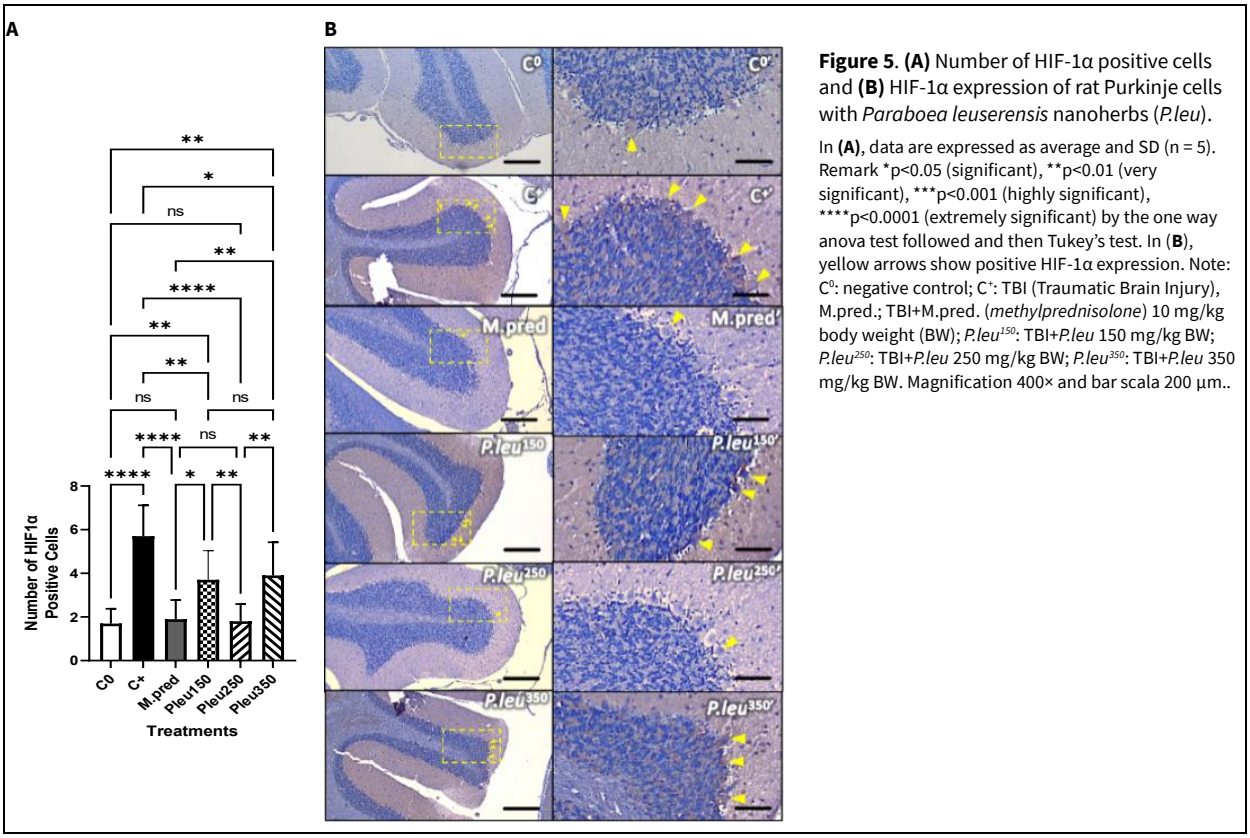

Figure 5. **(A)** Number of HIF-1α positive cells and **(B)** HIF-1α expression of rat Purkinje cells with *Paraboea leuserensis* nanoherbs (*P.leu*).

In **(A)**, data are expressed as average and SD (n = 5). Remark *p<0.05 (significant), **p<0.01 (very significant), ***p<0.001 (highly significant), ****p<0.0001 (extremely significant) by the one way anova test followed and then Tukey's test. In (**B**), yellow arrows show positive HIF-1α expression. Note: C^0: negative control; C^+: TBI (Traumatic Brain Injury), M.pred.; TBI+M.pred. (*methylprednisolone*) 10 mg/kg body weight (BW); $P.leu^{150}$: TBI+*P.leu* 150 mg/kg BW; $P.leu^{250}$: TBI+*P.leu* 250 mg/kg BW; $P.leu^{350}$: TBI+*P.leu* 350 mg/kg BW. Magnification 400× and bar scala 200 µm..

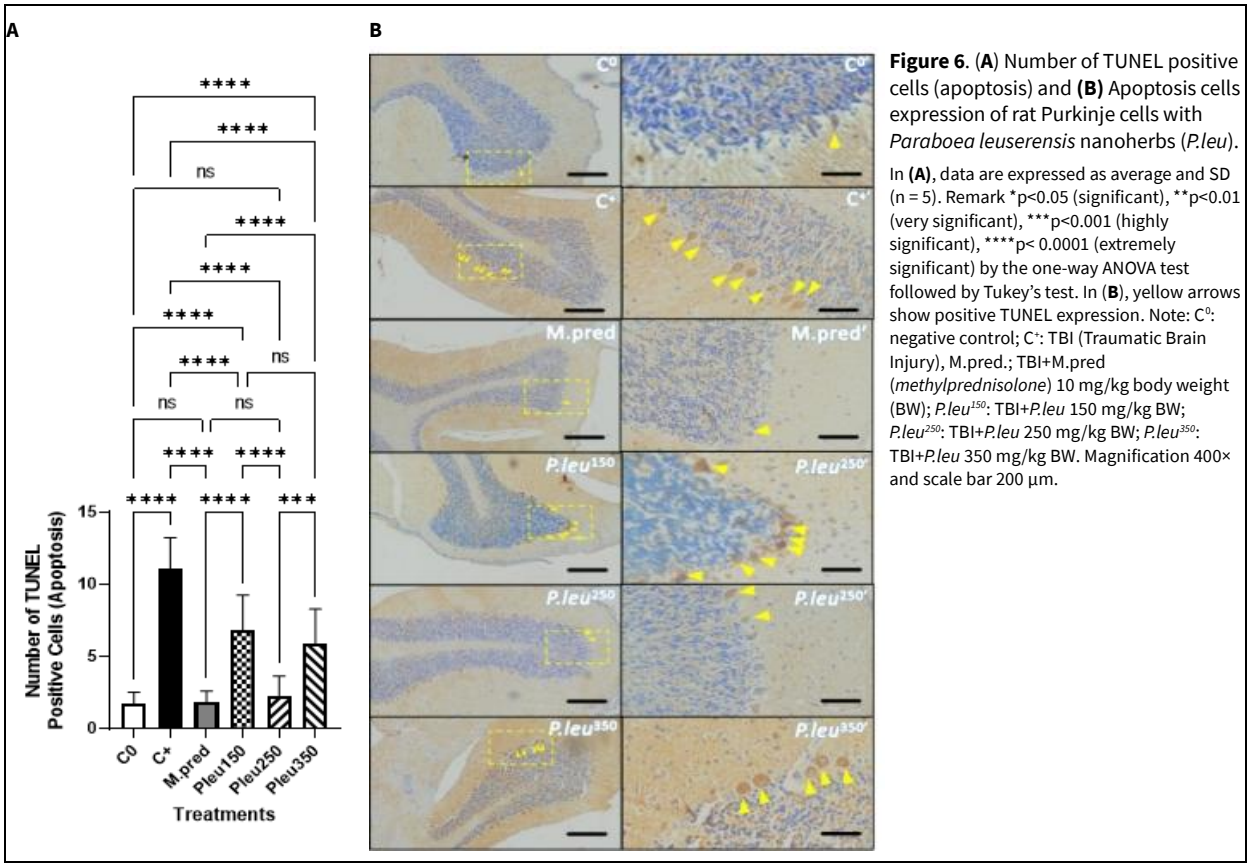

Figure 6. (**A**) Number of TUNEL positive cells (apoptosis) and **(B)** Apoptosis cells expression of rat Purkinje cells with *Paraboea leuserensis* nanoherbs (*P.leu*).

In **(A)**, data are expressed as average and SD (n = 5). Remark *p<0.05 (significant), **p<0.01 (very significant), ***p<0.001 (highly significant), ****p< 0.0001 (extremely significant) by the one-way ANOVA test followed by Tukey's test. In (**B**), yellow arrows show positive TUNEL expression. Note: C^0: negative control; C^+: TBI (Traumatic Brain Injury), M.pred.; TBI+M.pred (*methylprednisolone*) 10 mg/kg body weight (BW); $P.leu^{150}$: TBI+*P.leu* 150 mg/kg BW; $P.leu^{250}$: TBI+*P.leu* 250 mg/kg BW; $P.leu^{350}$: TBI+*P.leu* 350 mg/kg BW. Magnification 400× and scale bar 200 µm.

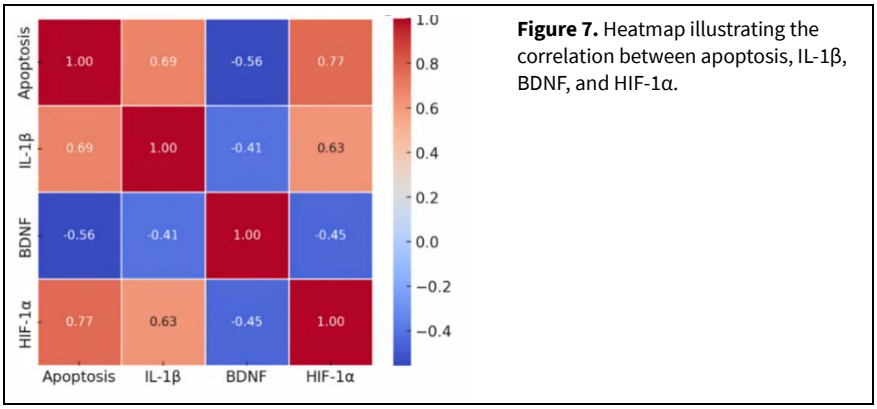

Figure 7. Heatmap illustrating the correlation between apoptosis, IL-1β, BDNF, and HIF-1α.

Table 1. Effect of *P. leuserensis* nanoherbal on biochemical and cellular parameters in TBI rat model.

Biomarker	C0 (Negative control)	C+ (TBI)	M.pred (10 mg/kg)	P.leu150	P.leu250	P.leu350
GSH	Normal	Low	Higher	Low–Normal	Normal	High
IL-6	Normal (Low)	High	Lower	High–Normal	Normal	Low
IL-1β	Normal (Low)	High	Lower	High–Normal	Normal	Low
HIF-1α	Normal	High	Lower	High–Normal	Normal	Low
BDNF	Normal	Low	Higher	Low–Normal	Normal	High
Apoptosis (TUNEL)	Normal	High	Lower	High–Normal	Normal	Low

Normal: baseline level (healthy control, C0).

Low / High: significantly different from the negative control (C0).

Higher / Lower: indicates an increase or decrease compared to the positive TBI control(C+), usually trending toward normalization.

The heatmap in Fig. 7 shows the correlation among apoptosis, IL-1β, BDNF, and HIF-1α. The color scale represents correlation values, with red indicating a strong positive correlation and blue representing a negative correlation. Apoptosis shows strong positive correlations with HIF-1α (0.77) and IL-1β (0.69), suggesting that increased hypoxia and inflammation contribute to cell death. BDNF exhibits negative correlations with apoptosis (−0.56), IL-1β (−0.41), and HIF-1α (−0.45), indicating its protective role against neuroinflammation and hypoxia-induced damage. IL-1β and HIF-1α are positively correlated (r = 0.63), supporting the link between inflammation and hypoxia in TBI pathology. Overall, the data suggest that inflammation and hypoxia drive apoptosis, while BDNF plays a protective role in reducing neuronal damage.

Table 1 summarizes the effects of *P. leuserensis* nanoherbal treatment at different doses on key biomarkers related to oxidative stress, inflammation, and neuronal survival in a traumatic brain injury (TBI) model. The untreated TBI group (C+) showed elevated pro-inflammatory markers (IL-6, IL-1β, HIF-1α) and apoptosis, along with reduced GSH and BDNF levels. Methylprednisolone (M.pred) and *P. leuserensis* treatment partially restored these alterations, with the highest dose (350 mg/kg BW) demonstrating the most consistent normalization across all parameters.

DISCUSSION

Particle size distribution is an essential parameter that determines dissolution, bioavailability, and therapeutic performance of nanoherbal formulations. The PSA results revealed a broad distribution with a mean size of 117.10 µm and a median of 64.79 µm, indicating a polydisperse system. A fraction of fine particles (<10 µm) may improve surface area and dissolution, while the presence of larger particles (>300 µm) suggests aggregation or incomplete reduction.

Optimization techniques such as homogenization or ultrasonication could help achieve a narrower distribution and improve consistency. Having established the physical characteristics of the nanoherbal preparation, the subsequent analysis focused on its biological effects in a traumatic brain injury (TBI) model.

This study investigated multiple biochemical and cellular parameters in a traumatic brain injury (TBI) model, including glutathione (GSH), interleukin-6 (IL-6), interleukin-1β (IL-1β), hypoxia-inducible factor-1α (HIF-1α), brain-derived neurotrophic factor (BDNF), and apoptosis (TUNEL-positive cells). The experimental groups comprised a negative control (C0), untreated TBI (C+), TBI treated with methylprednisolone

(M.pred), and TBI treated with *P. leuserensis* at three different doses (150, 250, and 350 mg/kg BW).

GSH, a central intracellular antioxidant, plays a critical role in neutralizing reactive oxygen species and maintaining cellular redox balance (Zhu et al., 2024). Consistent with this role, the C0 group displayed the highest GSH levels, while the untreated TBI group (C+) showed a marked reduction, reflecting elevated oxidative stress. Both methylprednisolone and *P. leuserensis* increased GSH levels, with the strongest effects observed at 250 and 350 mg/kg BW. These findings align with the phytochemical profile of *P. leuserensis*, which contains alkaloids, flavonoids, glycosides, saponins, tannins, and steroids/triterpenoids. In particular, flavonoids are known to enhance endogenous antioxidant defenses and inhibit oxidative stress, supporting the protective effect observed in this study. Prior phytochemical investigations have demonstrated the strong antioxidant activity of *P. leuserensis* ethanol extract (IC_{50}: 45.95 µg/mL) (Marbun et al., 2024).

Conversely, IL-6 levels were markedly elevated in the untreated TBI group compared to C0, indicating a strong inflammatory response. Treatment with methylprednisolone significantly suppressed IL-6, while *P. leuserensis* also reduced IL-6 levels, albeit less effectively. This pattern supports the proposed link between oxidative stress and inflammation in TBI pathology, where GSH depletion contributes to pro-inflammatory cytokine activation.

IL-1β is a key pro-inflammatory cytokine that plays a central role in neuroinflammation following TBI (Borkar et al., 2022; Situmorang & Ilyas, 2018). In this study, the untreated TBI group (C+) exhibited the highest IL-1β expression, confirming the strong inflammatory response induced by injury. Both methylprednisolone and *P. leuserensis* reduced IL-1β levels, although the effect of *P. leuserensis* was less pronounced than that of methylprednisolone. These findings indicate that *P. leuserensis* exerts anti-inflammatory activity, possibly through mechanisms distinct from glucocorticoid pathways. Prior phytochemical reports support this, showing that *P. leuserensis* leaves contain flavonoids such as myricetin, myricitrin, quercetin, kaempferol, and ellagic acid, which are known to modulate inflammation, oxidative stress, and immune responses (Heryani et al., 2024; Marbun et al., 2024).

HIF-1α, a transcription factor and marker of cellular hypoxia (Hou et al., 2023; Jena et al., 2023; Wróbel-Nowicka et al., 2024), was markedly increased in the untreated TBI group, consistent with the hypoxic environment caused by brain injury. Both methylprednisolone and *P. leuserensis* reduced HIF-1α expression, with more potent effects observed at 250 and 350 mg/kg BW. The observed correlation between IL-1β and HIF-1α further supports the notion that neuroinflammation and hypoxia act synergistically to exacerbate neuronal injury, and that *P. leuserensis* provides partial protection against this process.

BDNF is a neurotrophic factor essential for neuronal survival, plasticity, and regeneration (Alqahtani et al., 2024; Aqel et al., 2024; Ding et al., 2017; Silvestro & Mazzon, 2023). In line with previous studies, BDNF expression was markedly suppressed in the untreated TBI group, indicating impaired neuroregeneration. Both methylprednisolone and *P. leuserensis* restored BDNF levels, with the most pronounced effect observed at 250 mg/kg BW. This suggests that *P. leuserensis* supports neuronal recovery not only through antioxidant and anti-inflammatory mechanisms but also by promoting neurotrophic signaling.

Apoptosis is a programmed cell death pathway that is markedly enhanced following TBI due to oxidative stress, inflammation, and hypoxia (Akamatsu & Hanafy, 2020; Aqel et al., 2024; Mohammed et al., 2023; Silvestro & Mazzon, 2023). In this study, the untreated TBI group (C+) exhibited the highest proportion of apoptotic (TUNEL-positive) cells, reflecting substantial neuronal loss. Treatment with methylprednisolone markedly reduced apoptosis, consistent with its well-established neuroprotective effects. *P. leuserensis* also decreased apoptosis in a dose-dependent manner, with the most pronounced reduction observed at 250 and 350 mg/kg BW, indicating its potential in mitigating neuronal cell death. These findings align with the concept that secondary injury, driven by delayed neurochemical and molecular processes after the initial trauma, is a major contributor to poor TBI outcomes (Alqahtani et al., 2024; Aqel et al., 2024; Kurniawan et al., 2022). Unlike primary damage, which is irreversible, secondary brain injury may be alleviated through antioxidant, anti-inflammatory, and neurotrophic interventions.

The correlation analysis further supports this mechanism: depletion of GSH (oxidative stress), elevated IL-6 and IL-1β (inflammation), and increased HIF-1α (hypoxia) were closely associated with neuronal apoptosis. Conversely, higher BDNF levels were linked to reduced apoptosis, underscoring the role of neurotrophic support in neuronal survival. Both methylprednisolone and *P. leuserensis* attenuated apoptosis by modulating these interconnected pathways, though methylprednisolone remained more potent. The neuroprotective potential of *P. leuserensis* can be attributed to its flavonoid content, particularly quercetin, which has been reported to counteract oxidative stress and inhibit apoptotic signaling (Fathy et al., 2023; Prakash, 2017; Situmorang & Ilyas, 2018). These phytoconstituents provide a mechanistic basis for the observed effects and highlight *P. leuserensis* as a

promising candidate for complementary therapy in TBI management.

The correlation analysis indicates that GSH plays a central role in regulating oxidative stress, which, in turn, modulates inflammation and apoptosis in TBI. In this study, *P. leuserensis* demonstrated neuroprotective effects by enhancing BDNF levels and reducing apoptosis, suggesting its therapeutic potential. Importantly, the flavonoid content, particularly quercetin, is likely a key contributor to these effects. Quercetin has been reported to enhance BDNF expression in neuronal cells, thereby promoting neuronal survival and reducing apoptosis (Alqahtani et al., 2024; Majeed et al., 2023; Mohammed et al., 2023; Xiaobo et al., 2023).

As shown in Fig. 7, apoptosis showed strong positive correlations with IL-1β (0.69) and HIF-1α (0.77), suggesting that neuroinflammation and hypoxia are major contributors to neuronal death following TBI. Conversely, BDNF showed negative correlations with apoptosis (−0.56), IL-1β (−0.41), and HIF-1α (−0.45), underscoring its protective role in limiting neuronal damage. The positive correlation between IL-1β and HIF-1α (r = 0.63) indicates a close relationship between inflammation and hypoxia in the pathophysiology of TBI (Silvestro & Mazzon, 2023; Wu et al., 2022).

Treatment with *P. leuserensis* significantly reduced IL-1β and HIF-1α levels while increasing BDNF expression, thereby reducing neuronal apoptosis. These findings suggest that *P. leuserensis* mitigates secondary brain injury in TBI by modulating oxidative stress, inflammation, hypoxia, and apoptosis. The presence of quercetin, a major flavonoid, may play a key role in these mechanisms, given its previously demonstrated antioxidant, anti-inflammatory, and neuroprotective activities. Supporting this, several studies have shown that quercetin facilitates neuronal repair and recovery after TBI-induced injury (Fathy et al., 2023). However, additional studies, including clinical validation and mechanistic investigations, are required to confirm these findings.

CONCLUSION

Traumatic brain injury was shown to induce oxidative stress, inflammation, and hypoxia, leading to neuronal apoptosis and impaired recovery. Methylprednisolone demonstrated significant neuroprotective effects by reducing these pathological processes. Importantly, administration of *P. leuserensis* extract, particularly at doses of 250 and 350 mg/kg BW, attenuated inflammation, enhanced antioxidant activity, and reduced neuronal apoptosis. The flavonoid content, especially quercetin, was suggested to contribute to these effects by enhancing BDNF expression, thereby supporting neuronal survival and regeneration. Collectively, these findings indicate that *P. leuserensis* possesses neuroprotective potential and may serve as a complementary therapeutic candidate in the management of TBI. Further studies are warranted to clarify the molecular mechanisms and to validate these effects in clinical settings.

CONFLICT OF INTEREST

The research was conducted entirely free from any involvement in commercial, financial, or personal matters that might be perceived as a possible conflict of interest or that could have influenced the outcomes or interpretation of the study.

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GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

The authors used ChatGPT (Open AI) to improve the language and readability of the manuscript. The authors reviewed and edited the content and take full responsibility for its accuracy. No images were generated or manipulated using AI tools.

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AUTHOR CONTRIBUTION:

Contribution	Midoen YH	Ilyas S	Safni S
Concepts or ideas	x	x	
Design	x	x	
Definition of intellectual content		x	x
Literature search			x
Experimental studies			x
Data acquisition	x	x	
Data analysis	x	x	
Statistical analysis	x		
Manuscript preparation	x		x
Manuscript editing	x		
Manuscript review	x	x	x

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