RESEARCH PAPER

Neuroprotective Effects of Pinoresinol Diglucoside in Lipopolysaccharide-Induced Cognitive Impairment: Behavioral, Biochemical and Molecular Evidences

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ABSTRACT
Cognitive impairment progressively manifests in neurodegenerative diseases such as aging, moderate cognitive impairment, Alzheimer's disease, perioperative neurocognitive disorders, and stroke, imposing a substantial socioeconomic burden. This model demonstrates that cholinergic agonist, antioxidant, and anti-neuroinflammatory therapies yield beneficial outcomes. Pinoresinol diglucoside (PDG) exhibits numerous pharmacological actions. Nonetheless, there is a lack of evidence on the efficacy of PDG in ameliorating cognitive impairment induced by lipopolysaccharide (LPS). Consequently, we assessed its efficacy in mitigating cognitive impairment induced by LPS at a dosage of 1 mg/kg administered intraperitoneally in Wistar rats. To evaluate learning and memory performance, the Y-maze paradigm was employed. Oxidative stress was assessed by measuring the activities of superoxide dismutase (SOD) and catalase (CAT), along with the level of malondialdehyde (MDA), to determine their role in ameliorating cognitive decline. In addition, cholinergic function was examined through choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) levels, while neuroinflammatory status was determined by estimating interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) concentrations. PDG administration considerably improved behavioral performance in the Y-maze test. In addition, PDG modulated oxidative stress markers, as evidenced by changes in SOD, CAT, and MDA levels, and improved cholinergic function through regulation of AChE and ChAT activity. Furthermore, the levels of pro-inflammatory cytokines, including IL-6, TNF-α, and IL-1β, were significantly altered following treatment. Overall, these findings suggest that PDG exerts a protective effect against LPS-induced cognitive dysfunction.

Keywords: *Lipopolysaccharide; Cognitive impairment; Pinoresinol Diglucoside; Oxidative stress; Pro-inflammatory cytokines.*
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INTRODUCTION

Cognitive impairment progressively manifests in neurodegenerative diseases such as aging, moderate cognitive impairment, Alzheimer's disease, perioperative neurocognitive disorders, and stroke, imposing a substantial socioeconomic burden [1, 2]. Options for treatment in these circumstances are constrained due to the incomplete understanding of the underlying mechanisms. Neuroinflammation has been identified as a prevalent and significant mediator in various disorders associated with cognitive loss [3]. Research demonstrates that the prevalence of cognitive impairment following surgery varies between 13% and 50%, and it roughly doubles the one-year death rate within three months post-operation [4, 5]. The restricted treatment alternatives are partially attributable to the ambiguous neuronal etiology underlying cognitive impairment.

Lipopolysaccharide (LPS) is an endotoxin derived from Gram-negative bacteria that stimulates the synthesis of pro-inflammatory cytokines [6]. Numerous investigations have indicated that systemic LPS injection replicates specific clinical, immunological, and histological characteristics of these illnesses, primarily through the

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activation of glial cells and the subsequent immune response in the central nervous system [7, 8]. Moreover, systemic administration of LPS correlates with neuroinflammation in brain regions essential for memory functions, such as the hippocampus [9], results in cognitive impairment [10]. Increased oxidative stress [11], diminished antioxidant system [12] and elevated activity of the acetylcholinesterase (AChE) enzyme [13]. LPS induces cognitive deterioration in rats and has predominantly been utilized in paradigms for Alzheimer's disease. Systemic LPS induces the production of many inflammation-promoting mediators and cytokines, including tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), and the nuclear factor-kappa B (NF-κB) system, which are associated with microglial activation [14].

Pinoresinol diglucoside (PDG), a lignan from Eucommia ulmoides, shows promise in supporting cognitive functions through anti-inflammatory, antioxidant, and anti-apoptotic effects in preclinical models [15, 16]. In MCAO mice, intravenous pinoresinol diglucoside improved neurological outcomes, reduced infarction and neuronal injury, attenuated oxidative-inflammatory responses, and activated Nrf2/HO-1 while inhibiting NF-κB signaling, mitigating post-ischemic cognitive deficits [17]. Oral pinoresinol diglucoside ameliorated Aβ1–42-induced cognitive impairment by reducing neuroinflammation, oxidative stress, and apoptosis through TLR4/NF-κB inhibition and Nrf2/HO-1 activation, supporting therapeutic potential in Alzheimer’s disease [18]. Pinoresinol enhances hippocampal long-term potentiation, inhibits acetylcholinesterase, and promotes calcium influx, suggesting PDG’s therapeutic potential against ischemic and neurodegeneration-associated cognitive impairment [19].

These data proposed that PDG may exert beneficial effects against LPS-induced cognitive impairment. However, to date, no published studies have specifically addressed this aspect. Therefore, the present study was designed to evaluate the protective effects of PDG against LPS-induced cognitive deficits in rodents through behavioral, biochemical, and molecular assessments. Collectively, the current evidence indicates that PDG is a promising experimental neuroprotective agent with the potential to mitigate neuroinflammation-associated cognitive impairment induced by LPS through multiple underlying protective mechanisms.

EXPERIMENTS

Subjects

We employed male Wistar rats with a weight range of 200±20 g. The animals were maintained in a standard laboratory environment with pellet food and unrestricted access to water, adhering to natural light and dark cycles. In accordance with the "CCSEA Guidelines for Laboratory Animal Facilities," the requisite approvals were secured (IAEC/DRGCOP/2024/03).

Drugs

LPS (Escherichia coli) was procured from Merck India, while pinoresinol diglucoside (PDG) was purchased from Sigma-Aldrich, USA. Commercial assay kits for the estimation of neuroinflammatory cytokines IL-6, IL-1β, and TNF-α were obtained from MyBioSource. All remaining chemicals employed in the study were of analytical grade.

Experimental protocol

Following a 7-day dilution in saline (pH 7.4), LPS was injected intraperitoneally at a dosage of 1 mg/kg to induced cognitive impairments in the experimental subjects [20]. A total of 24 animals were randomly allocated into five experimental groups (n = 6 per group). Group-I served as the normal control and given normal saline. Group-II served as the LPS control and given LPS. Group-III served as LPS + PDG 5 and given LPS along with PDG at the dose of 5 mg/kg p.o., Group-IV served as LPS + PDG 10 and given LPS along with higher dose of PDG 10 mg/kg p.o., PDG was administered orally once daily for 7 consecutive days at doses of 5 and 10 mg/kg, 1 hour prior to LPS administration. Behavioral assessments were performed on the 7th day following completion of treatment, after which the animals were sacrificed for biochemical analysis [20].

Behavioral Parameters

Y-maze test

Y-maze assessment was employed to analyze behavioral traits. The Y-maze consists of three black acrylic arms (A, B, and C) of a timber structure, each capable of rotating across a 120° angle. The rats were permitted to traverse freely at the conclusion of the maze. In the 5-minute interval, we recorded the number of visits per arm. Upon concluding the training session, the animals were administered the intervention medicine, followed by a repetition of the testing procedure. Subsequent to each activity, the instrument was sanitized with 10% ethanol to eradicate odors. The total number of entries in the arms was recorded while all paws were positioned on the ground. Rats were enumerated for successive admissions into each group upon their entry into that group in an alternating sequence. To assess the learning capacity of disease-controlled (e.g., ABC, CAB, or BCA) and treated animals, the spontaneous alternation percentage was computed, and total entrances were documented [21, 22].

Biochemical estimation

Forming brain tissue homogenate

Subsequent to the behavioral test, the entire brains of the euthanized animals were excised and preserved at a temperature below -50 °C. Physiological saline was employed to meticulously cleanse the brains of the animals. The brain tissues were consolidated utilizing a neutral pH phosphate buffer. The samples were subjected to centrifugation, and biochemical analysis was performed on the supernatant [23].

Estimation of AChE and choline-acetyltransferase (ChAT)

An approach related to that described by Ellman (1961) was used to measure AChE level expressed as μmol/min/mg of protein [24, 25]. Commercial kits and hydroxylamine procedures were used to measure the amounts of brain ChAT activity.

Estimation of level of malondialdehyde (MDA)
The supernatant was treated with trichloroacetic acid and TBARS, boiled for 90 minutes, cooled, centrifuged, and measured at 532 nm to quantify MDA in μmol per gram of brain tissue [26].

Estimation of level of superoxide dismutase (SOD)
Xanthine oxidase and xanthine were added to the supernatant and incubated for 30 minutes in potassium phosphate buffer. Nitro blue tetrazolium was then added, and absorbance at 550 nm was measured to calculate SOD activity based on NBT reduction inhibition [27].

Estimation of level of catalase (CAT)
Phosphate buffer and brain homogenate supernatant (50 nM each) were mixed with H_2O_2, and absorbance at 240 nm was measured every 15 seconds to quantify enzyme activity in μmoles per minute per gram of brain tissue [28].

Pro-inflammatory Cytokines
The pro-inflammatory markers IL-1β, TNF-α, and IL-6 were assessed with an immunoassay kit. Indicator concentrations were calculated using calibration curves and expressed as pg/ml protein.

Statistical analysis
The values of results were analysis using GraphPad Prism-9 (GraphPad Software Inc., USA), and represented as mean ± SEM. The data were examined for MWM test by two-way ANOVA followed by Bonferroni *post hoc* test and one-way ANOVA followed by Tukey's *post hoc* test.

RESULTS

Effect of PDG on Y-maze test
In Y-Maze test, LPS control rats considerably decline SAP% as compared to the normal control rats (P<0.001). PDG-treatment (5 and 10 mg/kg) elevated SAP%, as compared to LPS control rats [F (3, 20) = 10.44, (P=0.0002)] (Figure 1).

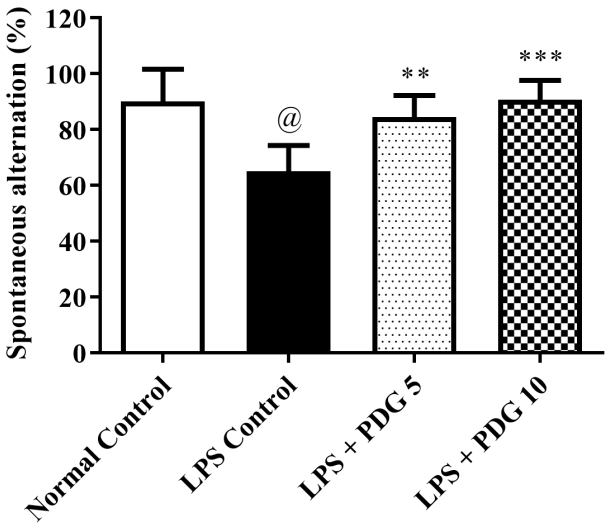

Figure 1: Displays the effect of PDG on Y-maze tests. Mean ± S.E.M. (n = 6). @P < 0.001 vs. normal control, **P<0.01 and ***P<0.001 vs LPS control. One-way ANOVA was followed by Tukey's test.

Effect of PDG on concentration of AChE and ChAT
The level of AChE was significantly elevated in the brain region of LPS control rats compared to normal control rats (P<0.0001). PDG therapy (5 and 10 mg/kg) significantly reduced AChE activity compared to LPS control rats [F (3, 20) = 15.39, (P<0.0001)] (Figure 2A). Activity of ChAT significantly decreased in the brain region of LPS control rats compared to normal control rats (P<0.0001). PDG administration (5 and 10 mg/kg) markedly increased ChAT activity relative to LPS control rats [F (3, 20) = 17.79, (P<0.0001)] (Figure 2B).

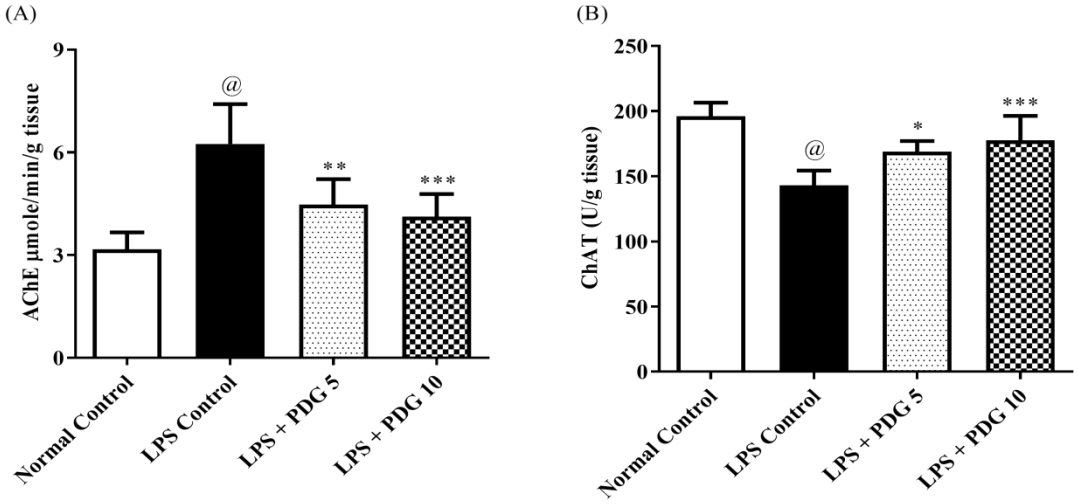

Figure 2 (A-B): Displays the effect of PDG on levels of A) AChE and B) ChAT. Mean ± S.E.M. (n = 6). @P < 0.001 vs. normal control, *P< 0.05, **P<0.01 and ***P<0.001 vs LPS control. One-way ANOVA was followed by Tukey's test.

Effect of PDG on MDA, SOD, CAT

Figure 3A showed that the LPS control rats exhibited significantly elevated MDA levels in the brain area compared to normal control rats (P < 0.001). However, PDG (5 and 10 mg/kg) therapy markedly diminished MDA levels in the brain area of LPS control rats [F (3, 20) = 13.99, (P < 0.0001)]. The disparity observed that the levels of SOD and CAT were substantially lower in the brain region of LPS control rats compared to normal control rats. PDG therapy markedly restored the levels of SOD [F (3, 20) = 14.13, P < 0.0001] and CAT [F (3, 20) = 12.16, P < 0.0001] in the brain areas of LPS control rats (Figure 3 B, C).

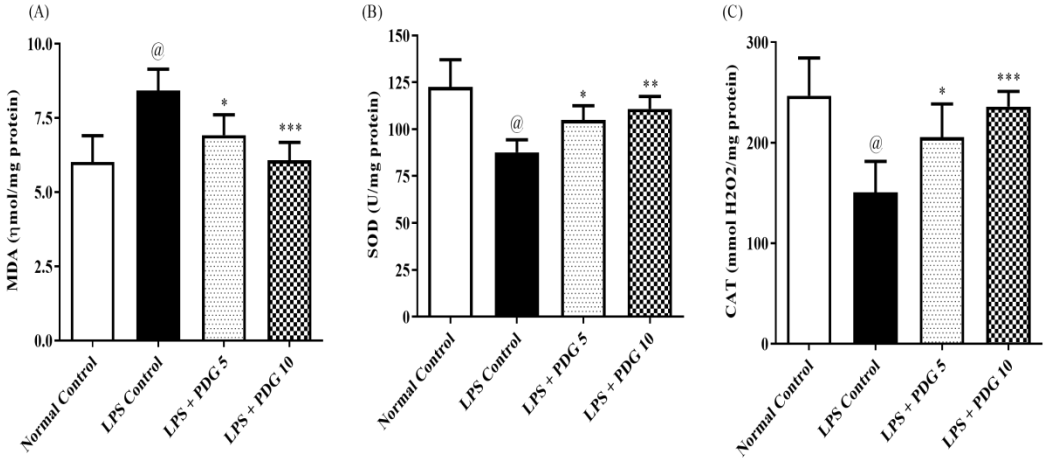

Figure 3 (A-C): Displays the effect of PDG on levels of A) MDA, B) SOD and C) CAT. Mean ± S.E.M. (n = 6). @P < 0.001 vs. normal control, *P< 0.05, **P<0.01 and ***P<0.001 vs LPS control. One-way ANOVA was followed by Tukey's test.

Effect of PDG on IL-1β, TNF-α and IL-6

The influence of PDG on the inflammation caused by LPS was also observed in our current investigation. The levels of IL-1β, TNF-α and IL-6 were significantly enhanced in the brain region of LPS control rats in comparison to normal control rats (P<0.001). PDG (5 and 10 mg/kg) treatment significantly decreased the levels of IL-1β, TNF-α and IL-6 in brain region of LPS control rat IL-1β [F (3, 20) = 14.20, P<0.0001)], TNF-α [F (3, 20) = 29.77, P<0.0001)] and IL-6 [F (3, 20) = 26.22, P < 0.0001)] (Figure 4 A-C).

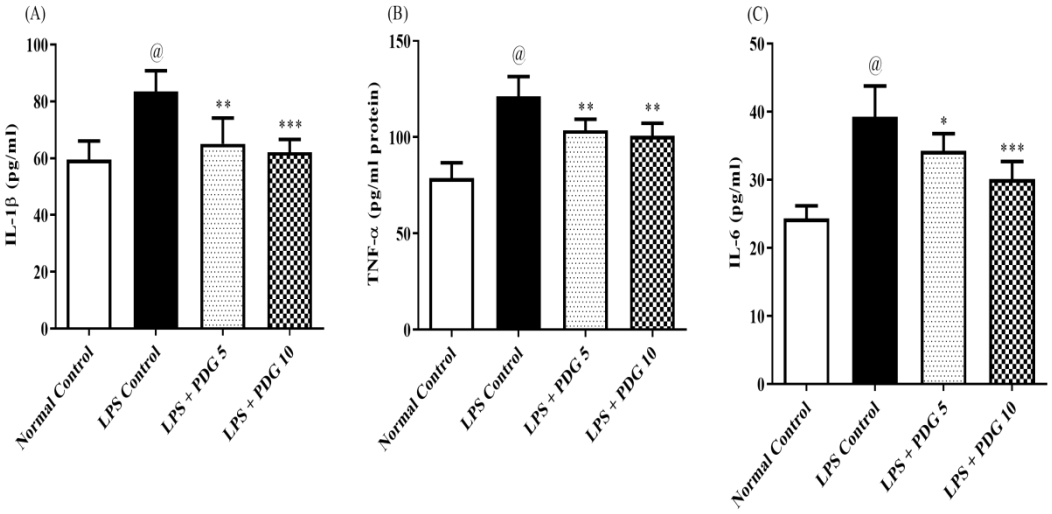

Figure 4 (A-C): Displays the effect of PDG on levels of A) IL-1β, B) TNF-α and C) IL-6. Mean ± S.E.M. (n = 6). @P < 0.001 vs. normal control, *P< 0.05, **P<0.01 and ***P<0.001 vs LPS control. One-way ANOVA was followed by Tukey's test.

DISCUSSION

This study demonstrated that PDG exerts protective effects against LPS-induced cognitive impairment by modulating both physiological and behavioral alterations. LPS administration significantly impaired cholinergic neurotransmission and enhanced oxidative stress and neuroinflammatory cytokine production in the brain, leading to marked deterioration in cognitive performance. PDG treatment significantly reversed these pathological changes, as evidenced by improvement in cognitive function, attenuation of cholinergic dysfunction, reduction of oxidative stress, and suppression of neuroinflammatory cytokines in LPS-induced cognitively impaired rats.

The Y-maze test is widely employed to assess spontaneous alternation behavior and short-term spatial working memory in rodents. In LPS-induced neuroinflammatory models, reduced spontaneous alternation percentage reflects hippocampal dysfunction and impaired working memory resulting from elevated oxidative stress and pro-inflammatory cytokine production [29, 30]. LPS-treated rats had a notable decrease in spontaneous alternation % and total arm entries in the Y-maze, signifying compromised working memory and diminished exploratory behavior. PDG therapy markedly reinstated both indices, indicating enhanced cognitive function in LPS-induced cognitively impaired rats.

The cholinergic system is implicated in the cognitive functions of memory and attention [31]. PDG therapy diminished the primary enzyme responsible for catalyzing the degradation of acetylcholine (ACh) induced by LPS. Cognitive deficits were induced by reduced levels of ACh in the central nervous system [32]. In this study, LPS administration significantly increased AChE activity and decreased ChAT levels in rats. PDG treatment at both doses (5 and 10 mg/kg) significantly attenuated AChE activity while enhancing ChAT expression in the brain. These results are in agreement with previously reported studies [16].

Chronic inflammation and oxidative stress are mutually reinforcing processes wherein persistent inflammation stimulates the production of reactive oxygen species (ROS) and the release of pro-inflammatory cytokines, establishing a self-perpetuating cycle. This oxidative imbalance has a role in the etiology of neurodegenerative illnesses, and brain oxidative damage is closely linked to LPS-induced deficits in learning and memory [33]. The hippocampus is crucial for learning and memory but is vulnerable to oxidative stress. Previous studies indicated that LPS-induced memory impairment correlated with elevated nitric oxide (NO) and MDA metabolites, alongside diminished SOD, CAT, and thiol levels in the hippocampus [34]. Our investigation demonstrated a considerable increase in brain MDA levels, whereas the activities of antioxidant enzymes (CAT and SOD) markedly decreased in the LPS-treated rats. This can be elucidated by the observation that, in LPS-induced cognitive impairments, heightened inflammation and oxidative stress markers may result from the dysfunction of anti-inflammatory and antioxidant processes. PDG treatment markedly decreased MDA levels while augmenting the activities of CAT and SOD.

The treatment of LPS markedly increases the concentrations of pro-inflammatory cytokines and mediators, such as TNF-α, TLR4, NF-κB, [12], and IL-6 [35]. Consistently, Jiang et al. reported that LPS exposure markedly upregulated TNF-α, IL-1β, and IL-6 expression [36]. The present study demonstrated that PDG treatment markedly attenuated neuroinflammation by significantly reducing IL-1β, IL-6, and TNF-α level in brain tissue, indicating its anti-inflammatory potential in an LPS-induced model of cognitive impairment.

In conclusion, the present findings suggest that the antioxidant, AChE-inhibitory, and anti-neuroinflammatory properties of PDG may underlie its protective effects against LPS-induced cognitive decline, supporting its potential therapeutic value in neurological and cognitive impairments associated with AD.

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Conceptualization, Data curation, Methodology, Investigation and Writing-original draft: Shaktipal Patil; Methodology, Writing-review and editing: Ujashkumar Shah, Hirenkumar Chaudhary and Snigdha Das Mandal.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY
Data will be provided upon request.

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