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Effect of Diosmin on Lipopolysaccharide-induced Neuroinflammation and Cognitive Impairment in Mice

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Abstract

Context: Neuroinflammation has been linked to some neurobehavioral alterations including cognitive and memory impairment which are prominent features of many neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease.
Objective: This study explored the cognitive-enhancing properties of a flavonoid, diosmin, against lipopolysaccharide-induced cognitive impairment in mice.
Materials and Methods: Thirty-five (35) mice were divided into five groups comprising seven (7) mice each (n=7). These groups were scheduled to receive either vehicle, any of the two doses of diosmin (50 mg/kg and 100 mg/kg) or donepezil for seven (7) consecutive days. Group 1-2 received vehicle, groups 3-4 received diosmin at 50 and 100 mg/kg respectively, and group 5 was the positive control group which received 10 mg/kg donepezil. About sixty (60) minutes post-treatment, groups 2-5 were treated with lipopolysaccharide (LPS; 250 µg/kg, i.p.) daily. Afterwards, all mice were subjected to the Y-maze and the novel object recognition (NOR) tests to assess their spatial and non-spatial working memory, respectively. Subsequently, the mice were sacrificed and whole brain samples were harvested for further biochemical analysis. The data was analysed using one way analysis of variance (ANOVA) and a post hoc test. The level of significance was set at $p<0.05$.
Results: Our data shows that diosmin significantly inhibited the LPS-induced neuroinflammation by inhibiting the expression of selected proinflammatory mediators in the brain and subsequently improving memory ($p<0.05$).
Conclusion: Diosmin possesses significant anti-inflammatory and antioxidant properties that could be beneficial in management of inflammation-related cognitive disorders.

Keywords: Neuroinflammation, Neurodegeneration, Flavonoid, Diosmin, Alzheimer's disease, Memory loss

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1. Introduction

Neurodegeneration is a pathological condition affecting neurons of the brain. Although neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD),

Huntington's disease may have been associated with different pathological characteristics and pathogenic factors affecting specific neurons in the brain, they all share a common feature of chronic neuroinflammation. For instance, in the pathophysiology of AD and PD, neuroinflammation has been demonstrated to be the hallmark and main etiological factor.[1] Furthermore, Ransohoff[2] and Kheradmand et al.,[3] reported neuroinflammation as the major underlying factor of many neurodegenerative disorders such as AD, PD, multiple sclerosis. Consistently, several studies have shown active participation of cytokines such as the interleukins (ILs), tumour necrosis factors (TNFs), interferons (IFNs), and transforming growth factors (TGFs) in the pathogenesis of AD.[4]

Neuroinflammation is the cascade of events in the central nervous system (CNS) in response to certain stimuli ranging from reactive oxygen species (ROS), lipopolysaccharides (LPS), infection, formation of beta amyloid (Aβ) plaque.[5] It involves activation of immune cells in the brain especially the resident brain macrophages (also known as microglial cells). It has been implicated in pathophysiological events leading to various neurodegenerative diseases.[4] Furthermore, the therapeutic potential of neuroinflammatory signalling regulation in the management of neurodegenerative disease has however been suggested based on the evidence that individuals placed on long-term nonsteroidal anti-inflammatory drugs had as much as a 50% reduction in the risk of developing AD.[6] Thus, targeting activated immune responses and more specifically, innate immunity may give a promising approach for developing translational therapies in neurodegenerative diseases.[7]

Recently attention has shifted towards the increasing utilization of plant flavonoids with a good therapeutic benefit on brain-related diseases. Flavonoids are known to be anti-inflammatory, thus exhibiting a good therapeutic benefit against depression, AD and stroke through inhibition of neuroinflammation,[8] and polarization of microglia and astrocyte.[9] Diosmin, a naturally occurring flavonoid mainly resident in citrus fruits[10] is a potent antioxidant and anti-inflammatory compound.[11,12] It possesses numerous health benefits ranging from anticancer, antidiabetic, antibacterial, cardioprotection, hepatoprotection and neuroprotection,[11,12] making it one of the most sought-after natural compounds.[11] Convincing evidence emanating from literature, showed that diosmin significantly decreased expression of numerous proinflammatory cytokines in LPS-induced lung damage.[13] Interestingly, Sawmiller et al.,[14] demonstrated that diosmetin, a diosmin metabolite could reduce amyloid-beta (Aβ) generation, tau hyperphosphorylation and pro-inflammatory activation of microglia in the hippocampus and prefrontal cortex through inhibition of GSK-3α/β.

In addition, diosmin has been shown to slow the degenerative course of AD in an in-vitro study using hen egg white lysozyme by inhibiting protein aggregation.[15] Furthermore, studies have shown that diosmin prevented scopolamine-induced cognitive impairment in rats,[16] and inhibited LPS-induced inflammatory pain and peritonitis in a mouse model by blocking activation of NF-κB signalling.[17] These effects of diosmin thus suggest potential benefits in the management of inflammation-related cognitive disorders. The present study aimed at investigating the effect of diosmin against LPS-induced neuroinflammation and cognitive impairment in experimental animals.

LPS, an inflammation-inducing endotoxin, is a tool employed in pharmacology to investigate potential therapeutic candidates and various mechanisms involving neuroinflammation and associated alterations in the central nervous system.[18,19] In the present study, a 7-day treatment with LPS (250 μg/kg) was considered sufficient to produce symptoms such as cognitive dysfunction, memory impairment as well as the activation of specific inflammatory mediators, all indicative of AD.[20]

2. Materials and Methods

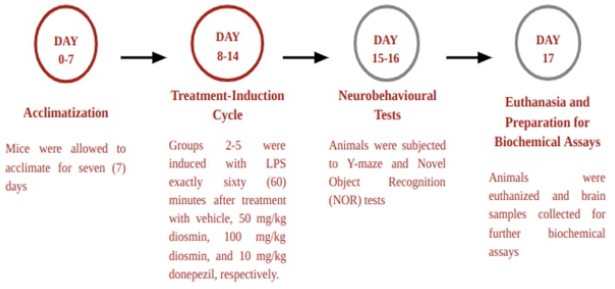
2.1 Materials

Diosmin (CAT NO.: D3525-5G), and lipopolysaccharide were obtained from Sigma-Aldrich®. Donepezil tablets were acquired from the Afe Babalola Multisystem Hospital Pharmacy, Ado-Ekiti. ELISA kits for interleukin-12 (IL-12; CAT NO.: 433607), interferon gamma (IFN-γ; CAT NO.: 430807) were obtained from BioLegend® while tumor necrosis factor-alpha (TNF-α; CAT

NO.: EM0183) was obtained from FineTest®.
Diosmin was dissolved in distilled water to a concentration of 10mg/mL stock solution. The doses (50mg/kg and 100mg/kg) were selected based on information from existing literature where oral pretreatment with both doses improved antioxidant status and delayed the development of diabetic neuropathy.[13,21]

2.2 Laboratory Animals
Thirty-five (35) Swiss mice (males, 25.0±2.0 g) were procured from Afe Babalola University Animal House, Ado-Ekiti. The animals were acclimated for one week at room temperature and allowed to have unrestricted access to standard animal chow and clean water in accordance with the National Institutes of Health (NIH) guidelines. All experimental procedures were in agreement with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines[22] and preset University rules on animal experimentation (ABUADHREC/26/03/2022/2008).

2.3 Experimental Procedure
The mice were randomly divided into five groups (n=7): groups 1 and 2 received vehicle (10 mL/kg, p.o.), groups 3 and 4 received diosmin (D) 50 mg/kg and 100 mg/kg, p.o respectively, group 5 received donepezil (DPZ)10 mg/kg, p.o. Therefore, group 1 is the control group, group 2 is the LPS-only group, group 3 is D50 group, group 4 is D100 group and group 5 is positive control/DPZ group.
Exactly, 60 min after the daily treatment with vehicle or diosmin (D), LPS (250 µg/kg, i.p.) was administered to mice in groups 2-5 only. This induction-treatment cycle (Scheme 1) was done daily throughout the duration of the study, that is seven (7) consecutive days. Afterwards, all animals were exposed to neurobehavioral tests beginning from day 8.



Scheme 1 Illustration of experimental schedule

2.4 Neurobehavioral tests
These tests were carried out to compare the pharmacodynamic manifestations of the mice from all groups. The mice were not trained beforehand, and the observers were blind to the treatments.

2.4.1 Y-Maze test
As the name implies, the apparatus is Y-shaped with the arms properly labelled. Each mouse was allowed to explore the apparatus for 5 mins while manually recording the number of arm entries as well as the alternations. The number of correct alternations (e.g. ABC, ACB, BAC, BCA, CAB, CBA) were used to calculate the percentage alternation[23] using the following formula:
Percentage alternation (%) = Number of correct spontaneous alternations x 100/Total number of arm entries — 2

2.4.2 Novel Object Recognition Test (NORT)
Each animal was placed in an open chamber with two identical objects of the same colour (labelled A and B), and the animal was allowed to explore the objects for 5 mins during the pre-test phase. After 4 hrs, the test was repeated by replacing object A with a new/different object C and the animal was allowed to explore the new setup for 5 mins. The times spent exploring both the old object (object A) and the new object (object C) were manually recorded. The discrimination ratio was calculated at the end of the test[24] using the following formula:
Novel object exploration time — Familiar object exploration time X 100 / Total exploration time

2.5 Tissue Preparation for Biochemical assays
The mice were euthanized using a high dose of an injectable anaesthetic and their whole brain samples were harvested. The brains were homogenised in 10% phosphate buffered saline (PBS, 0.1M, pH 7.4) and centrifuged at 10,000 rpm for 15 mins in a cold centrifuge (4°C). The separated supernatants were used for biochemical analysis for IL-12, TNF-α, IFN-γ using ELISA techniques as stated in the manufacturer's protocol.

2.6 Statistical Analysis

The data were analysed using one-way analysis of variance (ANOVA). The difference between the groups was analysed using Tukey's multiple comparison test. The data was presented as mean ± standard deviation (SD). The GraphPad 8 software was used for the statistical analysis, and the level of significance was set at $p<0.05$. The results were thereafter presented in graphs.

3. Results

3.1 Diosmin improves cognition in LPS-induced memory impairment

To determine the memory-enhancing effect of diosmin in mice exposed to LPS in this study, Y-maze and NOR tests were performed twenty-four hours after the last treatment. In Fig 1, one-way ANOVA showed significant difference across the groups in the Y-maze test ($F(4, 30) = 0.7490$; $p<0.0001$). A significant decrease in percentage alternation was observed with animals exposed to LPS alone compared with the control group (Fig. 1).

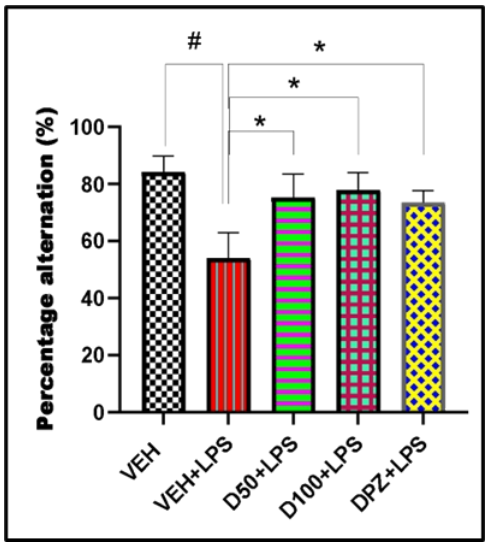


Fig. 1 Effect of diosmin on LPS-induced memory impairment in Y-Maze

Results are presented as mean±SD (n=7).
#p<0.0001 relative to normal control, *p<0.0001 relative to the LPS-only group.
VEH = Group 1; VEH+LPS = Group 2; D50+LPS = Group 3; D100+LPS = Group 4; DPZ+LPS = Group 5
VEH, vehicle; LPS, lipopolysaccharide; D50, diosmin 50 mg/kg; D100, diosmin 100 mg/kg; DPZ, donepezil.

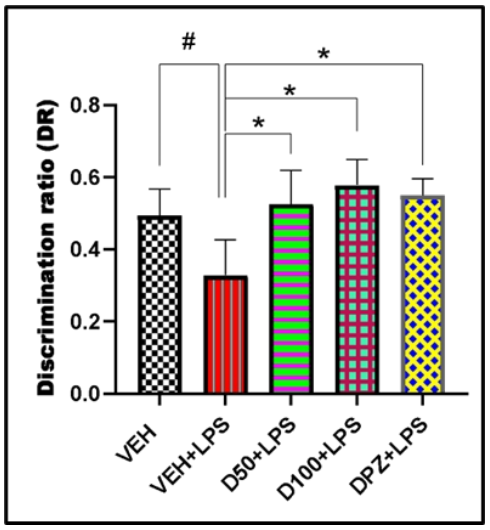


Fig. 2 Effect of diosmin on LPS-induced memory impairment in NOR test

Results are presented as mean±SD (n=7).
#p=0.0042 relative to normal control, *p<0.0006 relative to the LPS-only group.
VEH = Group 1; VEH+LPS = Group 2; D50+LPS = Group 3; D100+LPS = Group 4; DPZ+LPS = Group 5
VEH, vehicle; LPS, lipopolysaccharide; D50, diosmin 50 mg/kg; D100, diosmin 100 mg/kg; DPZ, donepezil.

Similarly, recognition memory measured by NOR test revealed that LPS caused a significant reduction in the discrimination index ($F(4, 30) = 0.6645$; $p<0.005$) when compared with the control (Fig. 2). Conversely, treatment with diosmin, like donepezil, improved cognitive performance evident by significant ($p<0.05$) increase in percentage alternation (Fig. 1) and discrimination ratio (Fig. 2) compared to the LPS-treated group.

3.2 Effect of diosmin on proinflammatory mediators

The anti-neuroinflammatory effect of diosmin was determined by analysing the brain levels of some proinflammatory mediators (TNF-α, IL-12 and IFN-γ) using ELISA technique. Mice of the LPS-only group exhibited a sustained increase in the expression of TNF-α ($F(4, 30) = 0.7386$; $p<0.0001$), IL-12 ($F(4, 30) = 0.3467$; $p<0.05$), and IFN-γ ($F(4, 30) = 0.9505$; $p<0.0001$), as shown in Figures 3-5, respectively when compared with the normal control group. However, pretreatment with doses of diosmin significantly inhibited the LPS-induced

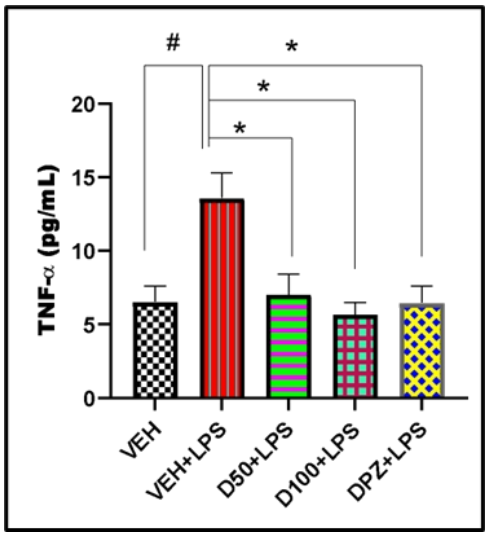


Fig. 3 Effect of diosmin on LPS-induced TNF-α expression in mice
Results are presented as mean±SD (n=7).
#p<0.0001 relative to normal control, *p<0.0001 relative to the LPS-only group.
VEH = Group 1; VEH+LPS = Group 2; D50+LPS = Group 3; D100+LPS = Group 4; DPZ+LPS = Group 5
VEH, vehicle; LPS, lipopolysaccharide; D50, diosmin 50 mg/kg; D100, diosmin 100 mg/kg; DPZ, donepezil.

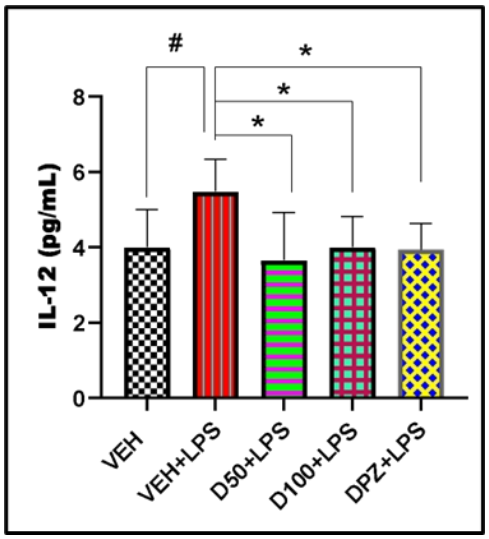


Fig. 4 Effect of diosmin on LPS-induced IL-12 expression in mice
Results are presented as mean±SD (n=7).
#p=0.0474 relative to normal control, *p<0.05 relative to the LPS-only group.
VEH = Group 1; VEH+LPS = Group 2; D50+LPS = Group 3; D100+LPS = Group 4; DPZ+LPS = Group 5
VEH, vehicle; LPS, lipopolysaccharide; D50, diosmin 50 mg/kg; D100, diosmin 100 mg/kg; DPZ, donepezil.

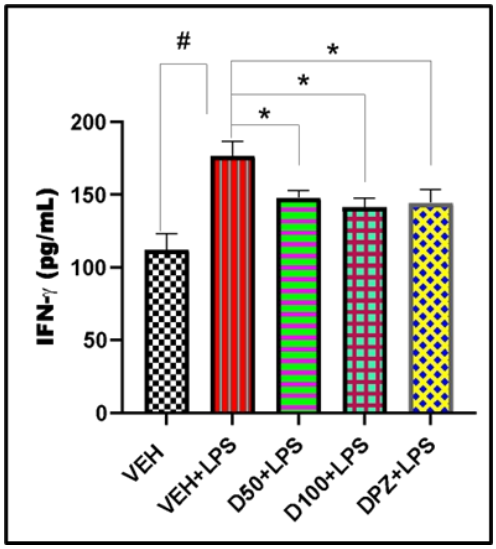


Fig. 5 Effect of diosmin on LPS-induced IFN-γ expression in mice
Results are presented as mean±SD (n=7).
#p<0.0001 relative to normal control, *p<0.0001 relative to the LPS-only group.
VEH = Group 1; VEH+LPS = Group 2; D50+LPS = Group 3; D100+LPS = Group 4; DPZ+LPS = Group 5
VEH, vehicle; LPS, lipopolysaccharide; D50, diosmin 50 mg/kg; D100, diosmin 100 mg/kg; DPZ, donepezil.

increase in TNF-α (Fig. 3), IL-12 (Fig. 4) and IFN-γ (Fig. 5) suggesting its anti-neuroinflammatory effect.

4. Discussion

Neuroinflammation is an important process in the pathogenesis of neurodegenerative diseases, involving prolonged activation microglia. Several studies have investigated the association between neuroinflammation and neurodegenerative disease[7,25] and thus giving insight into the development of promising therapeutic candidates by halting or disrupting neuroinflammation signalling during pathogenesis of

neurodegenerative disorders. The use of plant flavonoids for their anti-inflammatory properties has attracted a lot of attention. Diosmin is an example of plant flavonoid belonging to the family Rutaceae. Its anti-inflammatory effect has been demonstrated in several animal models of different diseases. This study explored the effect of diosmin against LPS-induced neuroinflammation and memory impairment in experimental animals.

The LPS model of neuroinflammation has been widely used in the study of neurodegenerative disorders given its ability to induce human-like effects.[26,27] Administration of LPS has reportedly caused significant increase in the level of cytokines, neurodegeneration and subsequent memory and cognitive impairment in various experimental models.[28,29] In consistence with previous observations, administration of LPS in this study induced marked increase in the levels of proinflammatory cytokines such as TNF-α, IL-12, and IFN-γ. This observation corroborates findings from previous studies of LPS-model of inflammation in rodents.[26,27] Peng and colleagues demonstrated disruption of the blood-brain barrier following injection of LPS which subsequently allowed entry of other proinflammatory mediators into the brain causing neuroinflammation.[30] Interestingly, the groups of animals pretreated with diosmin before exposure to LPS showed significant decrease in the level of brain cytokines compared to the group treated with LPS only, indicating its anti-inflammatory action in the brain. Diosmin as a flavonoid has been reported to possess anti-inflammatory properties.[12,31] Similarly, in scopolamine-induced cognitive impairment in rats, diosmin was demonstrated to suppress neuroinflammation.[16] Furthermore, diosmin has also been reported to block activation of NF-kB in LPS-induced inflammatory pain and peritonitis in mice.[17]

Cognitive performance of mice was assessed using Y-maze and novel object recognition tests. In this study, we observed that LPS reduced the natural ability of mice to remember the arms of the Y-maze explored and alternate accordingly, suggesting memory deficit. Similarly, cognitive deficit was observed in the group of animals treated with LPS alone as evident by significant decrease in the discrimination ratio (i.e. a below normal discrimination between familiar and novel objects in the NOR test) when compared with the normal control group. Studies have shown that exposure of rodents to LPS has led to a marked neuroinflammation and subsequent cognitive impairment and behavioural changes such as depression, anxiety and decreased appetite.[26,32] Intriguingly, we observed that the groups pretreated with diosmin before exposure to LPS significantly display improved cognitive performance compared to the group treated with LPS alone. The effect of diosmin on cognitive performance is comparable to that of donepezil which has previously been shown to also reduce LPS-induced neuroinflammation and cognitive impairment.[33]

Conclusion

This study shows that diosmin improves cognitive performance of animals and this action could be due to the inhibition of neuroinflammation. The finding also reinforces the earlier suggestion that targeting chronically activated immune responses can be a promising approach for developing translational therapies in neurodegenerative diseases. However, further investigation on the specific and underlying mechanisms of cognitive enhancing action of diosmin is required.

Declaration of interests

The authors have no relevant financial or non-financial interests to disclose.

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Authors' Contributions

AGO and AOA were responsible for the research concept and design. The methodology, investigation, data curation and analysis were done by JIP, AFR, OLO, and AOA. AGO also contributed to the analysis. OLO and AFR prepared the original draft of the manuscript, which was then edited and reviewed by AGO, AOA, AR, AIA, and BAG. Finally, all authors read and approved the final manuscript.

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