Curcumin Attenuates Lipopolysaccharide-Induced Neuroinflammation and Memory Deficiency by Inhibiting Microglia Activation in Mice Hippocampus

Kingsley Iteire1, Raphael Uwejigho1*, Glory Okonofua1

Abstract

Background. Curcumin has a variety of properties, including antioxidant and anti-inflammatory ones, and has demonstrated some protective prospects on neurological conditions.

Aim: This study explored the neuroprotective ability of curcumin in lipopolysaccharide-induced neuroinflammation in an animal model.

Methods. A total of thirty-two adult male mice were randomly assigned to four groups (A, B, C, and D, n=8): Group A (Control) received distilled water; Group B was administered lipopolysaccharide (LPS) only to induce neuroinflammation for seven days; Group C was treated with both LPS and curcumin simultaneously for fourteen days; Group D received only curcumin for fourteen days. After appropriate exposure to the mice, their cognitive abilities were assessed using the Y-maze and novel object recognition tests. At the termination of the administration period, the mice were sacrificed, and the hippocampi were dissected for histology and immunostaining using GFAP and Iba1. Statistical analysis for the data generated was done with GraphPad prism. Tests of significance were with one-way ANOVA and Tukey tests for post-hoc.

Results. Curcumin significantly (p < 0.05) increased object recognition, mean alternation, and markedly restored neuronal distortion caused by LPS toxicity in the CA3 region and the dentate gyrus of the hippocampus of Group C animals as compared to Group B. In addition, curcumin significantly down-regulated Iba1 expression and GFAP cell activities of both the CA3 region and the dentate gyrus.

Conclusions. Curcumin showed a promising role in attenuating LPS-induced neuroinflammation in the brain by inhibiting microglial activation and improving memory of neurotoxic mice.

Keywords
Curcumin; Lipopolysaccharide; Neuroinflammation; Hippocampus; Immunohistochemistry

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Introduction

Curcumin, a diferuloylmethane, is a substantive active component of turmeric (Curcuma longa) with anti-inflammatory properties [1]. It has been reported to decrease microglial activation following lipopolysaccharide (LPS) -induced neurotoxicity in rodent neuronal culture [2]. Although curcumin possesses anti-inflammatory and neuroprotective hallmarks, there is diminutive evidence of its exact mechanism of action, notably in the ambient hippocampal microglia and astrocyte expression levels. Neuroinflammation plays a crucial role in the neuropathogenesis of neurodegenerative diseases. In the central nervous system (CNS), a large portion of neuroinflammatory reactions is mediated by microglia and astrocytes [3, 4]. A few corroborations support the overexpression of microglia and astrocytes because of certain natural poisons, like LPS. These cells, astrocytes, and microglia are exhibited by the immunoeexpression of glial fibrillary acidic protein (GFAP) and ionized calcium-binding adaptor molecule (Iba1) separately [5–7]. Studies have shown that LPS initiates neuroinflammation in the hippocampus [8, 9]. Inflammation of the CNS plays an imperative role in the development of chronic neurodegeneration. In most chronic neurodegenerative diseases, the inflammatory response is subjigated by microglia and astrocytes [3, 4]. Mounting evidence suggests overexpression of microglia and astrocytes due to certain natural toxins and endogenous proteins [6, 7]. These proteins re-
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Neurodegeneration is an attribute of diverse age-related ravaging diseases. The most common chronic neurodegenerative disease (AD) accounts for 60-70% of dementia cases [10, 11]. AD symptoms are distinguished by fluctuating cognitive abilities and hindering social and behavioral activities. The major histopathological features of AD are amyloid-β (Aβ) plaques, occasioned by altered proteolysis of amyloid precursor protein (APP) and neurofibrillary tangles (NFTs) due to excessively phosphorylated tau protein [12]. The World Health Organization (WHO) chronicled that 35.6 million people worldwide are plagued with AD. As the lifespan of the elderly population appreciates, its frequency is estimated to double by 2030 and triple by 2050 [10]. Currently, no pharmacological treatments are aimed at preventing or curing cognitive decline. Although cognitive enhancers (donepezil and galantamine) being currently in use for AD may delay cognitive deterioration, several patients still do not respond to them. The beneficial effects are characterized by temporal relief and several adverse effects [13]. The deficiency of effectual pharmacotherapy has necessitated the search for alternative approaches to alleviate the effects of AD.

In the present study, GFAP and Iba1 sensitivity in the mouse hippocampus was determined and measured to appraise the attenuating influence of curcumin on LPS-induced neuroinflammation in mice.

Materials and Methods

Care and Management of Experimental Animals
Thirty-two mice (20-32 g), including 20 males and 12 females, were enrolled in this study. The animals were obtained from the animal house at the University of Medical Sciences (Ondo State, Nigeria). The experimental animals used in this research were cared for and maintained in the animal facility following regulations, guidelines, and policies governing the use of animals in research as described in the Public Health Service Policy on Human Care and Use of Laboratory Animals, as approved by the Institute of Laboratory Animal Resource, National Research Council [14]. They were acclimatized for two weeks preceding the inception of the experiment and reserved under standard laboratory conditions at 25.5-27.0 degrees Celsius, 12-hour light: 12-hour darkness cycle.

Drug Preparation
LPS and curcumin were purchased from Boster Biological Technology Co., LTD. The stock of LPS was opened and reconstituted in water to the concentration of 5 mg/mL. The LPS stock was then diluted with sterile phosphate-buffered saline (PBS) to the working concentration of 0.2 μg/μl and administered at a dose of 10 μl/g [15]. All solutions were prepared fresh on the day of treatment and administered by cannula in a final volume of 0.1–0.15 ml.

The volume given to the animals was determined by the formula stated below:

\[
\text{Volume of curcumin (ml)} = \frac{\text{weight of animal (kg)} \times \text{dosage of curcumin (mg/kg)}}{\text{Concentration of curcumin (mg/ml)}}
\]

The weight of the animals was determined shortly before treatment.

Experimental Procedures
The experimental animals were acclimatized to handling once daily for about a week, during which the intake of food and weight were documented daily. They were arbitrarily divided into four experimental groups (A-D, n=8):

- **Group A (Control)** received distilled water;
- **Group B (LPS group)** was intraperitoneally injected with only LPS for seven days;
- **Group C (LPS and curcumin group)** was treated with both LPS and curcumin simultaneously for fourteen days;
- **Group D (curcumin group)** received only curcumin for fourteen days.

All solutions were prepared fresh on the day of treatment and administered by cannula in a final volume of 0.1–0.15 ml. A suspension of curcumin in 1% methylcellulose was administered at 50 mg/kg body weight by cannula to Group D after periodic daily fasting for fourteen days sequentially. Group A was treated with 50 mg/kg of water for fourteen days. Group B was given a single intraperitoneal injection of 5 mg/kg of LPS once daily for seven days. In Group C, a single intraperitoneal injection (5 mg/kg of LPS) was given after administering curcumin and water one hour later for fourteen consecutive days. The dose of LPS used has been chronicled to cause brain inflammatory response, as well as modifications in behavior and perpetual neurodegeneration in rodents [16–19]. Animals with severe deteriorating health conditions and moribundity that required euthanasia were less than 10% after LPS injection. The weight of the animals, cage activity, and overall appearance at 2, 8, and 24 h were evaluated daily for one week after LPS therapy. Biochemical and molecular examinations and behavioral tests were carried out at stipulated time points after LPS intervention. A summary is given in Table 1.

Behavioral Testing

Y-Maze Test
Behavioral tasks in preclinical studies are assessed using the Y-maze, specifically for studying spatial learning and memory. The test is done in a Y-shaped maze having three identical arms at an angle of 120° from each other. Initially, the animals are introduced to the maze centre and then they are given free access to all three arms. If the animal decides to go through a different arm than it came, it is termed an alteration and considered the right response. Still, returning through the same arm it arrived, it is a deliberate error. The percentage of alternation is then calculated by noting and recording the total number of arm entries and the sequence of entries [20].

Novel Object Recognition Test
The novel object recognition (NOR) test is divided into three different sessions, each section with a duration of
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Table 1. Groups of animals: summary.

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Substance Administered</th>
<th>Mode of Administration</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Control</td>
<td>Water</td>
<td>Orogastric cannula</td>
<td>-</td>
<td>14 days</td>
</tr>
<tr>
<td>B</td>
<td>LPS only</td>
<td>LPS</td>
<td>Intraperitoneal injection</td>
<td>5 mg/kg</td>
<td>7 days*</td>
</tr>
<tr>
<td>C</td>
<td>LPS + curcumin</td>
<td>LPS</td>
<td>Intraperitoneal injection</td>
<td>5 mg/kg</td>
<td>14 days**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Curcumin</td>
<td>Orogastric cannula</td>
<td>A suspension of curcumin in 1% methylcellulose administered at 50 mg/kg body weight</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Curcumin only</td>
<td>Curcumin</td>
<td>Orogastric cannula</td>
<td>A suspension of curcumin in 1% methylcellulose administered at 50 mg/kg body weight</td>
<td>14 days</td>
</tr>
</tbody>
</table>

Notes: * – timeframe is adequate for neuroinflammation development according to Miryam et al. [33]
** – LPS administration was performed one hour after curcumin administration.

10 minutes for two sequential days. First, the animals were allowed to explore the exposed field arena without objects freely and then placed back in their cages. This step is called the habitation session. After twenty-four hours, the second session commences with mice individually placed in the arena and exposing them to two identical items (in this case, two rectangular boxes being 3 cm long, 3 cm broad, and 6 cm high). The two items are deposed at two corners of the open field apparatus at a distance of 8 cm from the sidewalls. The duration of exploration was canned with the aid of a video camera placed aloft in the chamber, the moment the animals come in contact with the item (with its nose) at a spacing of less than 1 cm, this session is known as the training session. The animal is taken back to its home cage after this session.

The third session commences two hours later; mice are taken back into the arena but with two different items: the first item is exactly alike the familiar ones but not formally used to preclude olfactory cues, while the second is a new item of the same size but distinct in color and shape, (laboratory flask of 4 cm in length, 3 cm in breadth, and 6 cm in height). The two items are deposed at a coverslip. Antibody (G 0650) or Negative Control were then applied development. When the slides were sufficiently stained, they were then counterstained with Mayer’s hematoxylin. Glycerol gelatin or other aqueous mounting medium was applied and covered with a coverslip.


def T_{novel}/(T_{novel} + T_{familiar})

Tissue Collection
At the end of the experimental procedure, the mice were euthanized by cervical dislocation to mitigate stress, suffering, and discomfort. After the animals were sacrificed, blood samples were collected by cardiac puncture for plasma separation and stored at -80°C to measure curcumin concentration. Animals were then decapitated, whole brains removed, and fixed in 10% neutral buffered formalin for later histological (H&E) and immunohistochemical tissue processing.

Glial Fibrillary Acidic Protein (GFAP) Stain for Astroglia Activity Staining Procedure
This immunohistochemical technique was done to precisely identify tissue components and to check if cells contain GFAP [21]. The sections were deparaffinized and hydrated. Two drops of 3% hydrogen peroxide were added for 5 minutes, and the slides were washed and wiped. They were then incubated with blocking reagent for 10 minutes and excess reagent was wiped off. Two drops of Primary Antibody (G 0650) or Negative Control were then applied and incubated for 60 minutes, and the slides were washed and wiped.

Further, two drops of Biotinylated Secondary Antibody (B 1425) and Peroxidase Reagent (E 1267) were added and incubated for 20 minutes, and the slides were washed and wiped. Two drops of substrate reagent were added and incubated for up to 10 minutes. The slide was then checked microscopically for adequate chromogen development. When the slides were sufficiently stained, they were rinsed in deionized water for 5 minutes to wipe off excess stains. They were then counterstained with Mayer’s hematoxylin for 2 minutes and rinsed in gently running tap water to “blue” hematoxylin. Glycerol gelatin or other aqueous mounting medium was applied and covered with a coverslip.

Iba1 (Ionizing Calcium-Binding Adaptor Molecule 1) Staining Procedure
Iba1 in microglial and macrophage-specific calcium-binding protein involves membrane ruffling and phagocytosis in activated microglia. In this research, Iba1 was used to show the expression of microglia in neuroinflammation [22]. The sections were deparaffinized in xylene and taken to water with descending grades of alcohol, and then antigen retrieval was executed. The slides were rinsed in PBS for 2 minutes, after which endogenous peroxidase blocking was applied using 0.3% hydrogen peroxide in PBS for 10 minutes. The sections were incubated in primary antibody (anti-Iba1) at 1:1250 for 2 hours at room temperature and
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washed in PBS for 5 minutes. After that, sections were incubated in ImmPRESS (Peroxidase) Polymer Anti-Mouse IgG Reagent, made in a horse for 30 minutes, and washed twice, 5 minutes at a time. The color was developed with DAB Peroxidase (HRP) Substrate Kit (Vector®) and properly washed in tap water for excessive staining. The slides were counter-stained in hematoxylin, dehydrated using graded alcohols, cleared with xylene, mounted, and coverslipped with Distyrene Plasticizer Xylene (DPX). Before photomicrography, the quality of the slides was assessed and they were stored at room temperature.

Photomicrograph of Histological and Histochemical Stain
The Leica DM750 digital microscope was used to visualize the sections. A light microscope with a digital camera (MV500 Cameroscope, 5.1MP) connected to the PC was used to capture and store the digital images. The images were captured with X40 and X100 objective lenses and X10 of a phototube of the MV 500 digital inspection camera. The images were saved in JPEG format for analysis.

Statistical Analysis
Results generated from the cognitive studies were presented as Mean ± Standard Error of Means (SEM). All statistical analysis was done with GraphPad Prism (version 10) software manufactured by GraphPad Software Inc. 7825 Fay Avenue, Suite 230 La Jolla, CA 92037, USA. The obtained datasets were normally distributed (confirmed by the Kolmogorov-Smirnov test). The significance of the differences in the means of all parameters was determined using a one-way analysis of variance (ANOVA; 95% confidence interval) for more than two sets of data comparison and a t-test for two data sets. A Post hoc test was carried out using the Tukey’s test for all groups and compared with the Control. Statistical significance was considered with a p-value < 0.05.

Results

Behavioral Test
Novel Object Recognition Test
After appropriate exposure to the mice and the assessment of their cognitive activities by the NOR test, there was a significant decrease in recognition (p < 0.05) in Group B as compared to the other groups. In addition, it was observed that curcumin improved the object recognition test in Group C as compared to Group B (Fig. 1, chart 1).

Y-Maze Test
Animals in Group A had a mean alternation of 53.00 ± 3.27, this significantly reduced to 17.30 ± 3.78 (p=0.0092) in Group B. In Group C, the mean alternation increased to 51.65 ± 9.44 (p=0.0114) as compared to Group B (Fig. 1, chart 2).

Histology of the Hippocampus CA3 Region
The hippocampal histology of the CA3 region is shown in Fig 2. There are three distinct layers of the hippocampal

Figure 1. Discrimination ratio of novel object recognition test and Y-maze test. Bars are Mean ± SEM. ** – a significant decrease (p < 0.05) as compared to Group A (Control). * – a significant increase (p < 0.05) as compared to Group B. One-way ANOVA preceded by the Tukey test.

CA3: the pyramidal layer containing large pyramidal neurons; stratum oriens with sparse cells; stratum radiatum containing hippocampal neural projections (Group A, Fig. 2A). Group B shows obvious disorganization of the pyramidal neurons in the pyramidal layer (Fig. 2B). Treatment with curcumin restored the CA3 histology in Group C (Fig. 2C).
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Dentate Gyrus

There are three distinct layers: the granule layer containing small, tightly packed rounded granular neurons with deeply stained acidophilic nuclei; the polymorphic layer lying between the CA3 and the granular layer; the molecular layer with sparse cells. All groups presented intact histology of the dentate gyrus (Fig. 3).

Immunohistological Staining and Quantification of Immune-Expressed Iba1 Cells in the CA3 Region of the Hippocampus

There was evidence of increased Iba1 expression in Group B (Fig. 4B) as compared to the Control Group and other treatment groups. The chart shows increased Iba1 immunoreactivity in Group B (9.39 ± 0.57) as compared to the Control Group (5.44 ± 0.63), Group C (3.29 ± 0.36) and Group D (3.30 ± 0.42).
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**Figure 4.** Groups A-D: photomicrographs of the hippocampal CA3 region (x400). Brown arrows represent Iba1 expressing microglia cells, blue arrows denote other hippocampal cells. The bar chart depicts the number of Iba1 immunoreactive cells in the CA3 of the experimental groups; bars are Mean ± SEM. ** – a significant increase (p < 0.05) as compared to Group A (Control). * – a significant decrease (p < 0.05) as compared to Group B. One-way ANOVA preceded by the Tukey test.

**Figure 5.** Groups A-D: photomicrographs of the dentate gyrus (x400). Brown arrows represent Iba1 expressing microglia cells, blue arrows denote other hippocampal cells. The bar graph depicts the number of Iba1 immunoreactive cells in the dentate gyrus of the experimental groups; bars are Mean ± SEM. * – a significant increase (p < 0.05) as compared to Group A (Control). ** – a significant decrease (p < 0.05) in comparison with Group B. One-way ANOVA preceded by the Tukey test.

**Immunohistological Staining and Quantification of Iba1 Immune-Expressed Cells in the Dentate Gyrus of the Hippocampus**

There was evidence of increased Iba1 expression in Group B as compared to the Control Group and other treatment groups (Fig. 5B). The bar chart shows increased Iba1 immunoreactivity in Group B (7.40 ± 0.73) as compared to Group A (5.00 ± 1.14), Group C (3.44 ± 0.75), and Group D (4.46 ± 0.40).

**Immunohistological Staining and Quantification of Immune-Expressed Cells in the CA3 Region of the Hippocampus**

There was evidence of increased GFAP expression in Group B as compared to the Control Group and other treatment groups (Fig. 6B). The present study shows no significant increase in GFAP immunoreactivity in Group B (16.00 ± 1.81) as compared to the Control Group (14.14 ± 1.41). However, a significant decrease in GFAP
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Figure 6. Groups A-D: photomicrographs of the hippocampal CA3 region (x400). Brown arrows represent GFAP expressing astrocytes, blue arrows denote other hippocampal cells. The bar graph depicts the number of GFAP immunoreactive cells in the CA3 of the experimental groups; bars are Mean ± SEM. * – a significant decrease (p < 0.05) in comparison with Group B. One-way ANOVA preceded by the Tukey test.

Figure 7. Groups A-D: photomicrographs of the dentate gyrus (x400). Brown arrows represent GFAP expressing astrocytes, blue arrows denote other hippocampal cells. The bar chart depicts the number of GFAP immunoreactive cells in the dentate gyrus of the experimental groups; bars are Mean ± SEM. ** – a significant increase (p < 0.05) as compared to Group A (Control). * – a significant decrease (p < 0.05) as compared to Group B. One-way ANOVA preceded by the Tukey test.

Immunohistological Staining and Quantification of Immune-Expressed GFAP in the Dentate Gyrus Region of the Hippocampus

There was evidence of increased GFAP expression in Group B as compared to the Control Group and other treatment groups (Fig. 7B). The bar chart shows increased GFAP immunoreactivity in Group B (16.42 ± 1.15) as compared to the Control Group (10.67 ± 0.33), Group D (11.60 ± 1.30), and Group C (12.30 ± 1.09). Group D (11.60 ± 1.30) and Group C (12.30 ± 1.09) showed a significant decrease in immunoreactivity as compared to Group B (16.42 ± 1.15) and no significant difference as compared to Group A (10.67 ± 0.33).
Discussion

In the current study, the cognitive activities of the mice were assessed using the NOR test, a significant decrease in object recognition was observed in groups treated with LPS, but this deteriorative effect was ameliorated with the introduction of curcumin. Curcumin has been documented to have a beneficial effect on cognitive deficits [23]; it can reduce neuronal apoptosis by increasing the levels of Bcl2 protein and down-regulating caspase-3 mRNA and, eventually, stimulating neurogenesis. Moreover, it is known to meliorate cerebral blood flow after ischemia by forbidding neutrophil adhesion in the cerebral circulation, ensuring better microcirculation in the brain [23]. The learning and memory functions of the animals were ascertained using the Y-maze test as well [24, 25]. Curcumin was observed to attenuate learning and memory shortfalls induced by LPS in mice; this gives new information on the ameliorative effect of curcumin on learning and memory impairment. In addition, LPS treatment was observed to prompt a diminished unconstrained rotation in the Y-maze [26]. Research has shown that fiery cytokines can result in emotional and cognitive disturbances in rodents and people. LPS can influence memory and intellectual capacities in various social ideal models in rodents and mice [27]. In the Y-maze task, mice tend to explore the maze by efficiently visiting each arm. The ability to substitute necessitates that the mice realize which arms they have already entered. Thus, alternation behavior is regarded as an action involving spatial working memory [24, 28]. The domination of the inflammatory response by the microglia and astrocytes is indicative that CNS inflammation is involved in the advancement of chronic neurodegenerative disease [3, 4].

Mounting evidence shows that microglia and astrocytes are overexpressed when responding to certain environmental toxins and endogenous proteins [6, 7]. These proteins discharge inflammatory mediators and receptive oxygen/nitrogen species, bringing about neurodegeneration seen in AD, PD, MS, and amyotrophic lateral sclerosis [5]. Investigations have shown that LPS initiates neuroinflammation in the hippocampus [8, 9]. Accordingly, blocking the activation of microglia and astrocytes and the resulting discharge of inflammatory mediators could be a promising therapeutic approach against an assortment of neurodegenerative diseases [29].

Curcumin is a significant dynamic component of the food flavor turmeric (Curcuma longa) that has been proven to have anti-inflammatory effects [1, 30]. Curcumin is known to decrease microglia initiation following LPS-induced neuroinflammation in rodents’ neuronal culture [2]. Even though it is realized that curcumin possesses anti-inflammatory and neuroprotective properties, there is fiddling evidence with regards to its definite basic mechanism of action, especially concerning hippocampal microglia and astrocyte articulation levels [31]. This study explored the impacts of curcumin on LPS-induced hippocampal microglial and astrocyte actuation, neuroinflammation, neurodegeneration, and memory impairment. As a result of the attenuating potentials of curcumin on neuroinflammation, as observed in this study, natural compounds (such as curcumin) can be utilized as options in contrast to artificial and semisynthetic medications for the treatment of neuroinflammatory disorders.

In the present work, examining H&E stained hippocampal CA3 sections showed dysmorphology in the pyramidal layer, which was subsequently restored when curcumin was administered. However, there was no significant alteration in dentate gyrus histomorphology. These data suggest that curcumin possesses a protective influence on the hippocampal cytotoxic architecture against LPS-induced neurotoxicity. In the CNS, most neuroinflammatory reactions are mediated by microglia and astrocytes [3, 4]. Studies have confirmed the overexpression of microglia and astrocytes in the light of specific natural toxins, like LPS [6, 7, 32]. These cells, astrocytes, and microglia are shown by the immunoexpression of GFAP and Iba1 proteins, respectively [5]. Moreover, LPS is known to incite neuroinflammation in the hippocampus [8, 9].

Iba1 is expressed in all microglia and is a major contributor to the regulation of activated microglia activity [33]. From this study, a significant increase in Iba1 expression was observed in the dentate gyrus and CA3 of LPS-induced mice. This suggests an overexpression or overactivation of astrocytes in these regions. This result conforms with a study where neurotoxicity was induced with methamphetamine in Wistar rats. It was observed that curcumin significantly reduced Iba1, GFAP, and caspase-3 positive cells in the hippocampus [33].

The mice brain tissues also exhibited an increased number and reactivity of microglia. Microglia are the resident immune cells of the brain. They are demonstrated by the immune-expression of Iba1. When activated, they trigger the innate immune response by sensing exogenous neurotoxic substances, such as LPS. Activated microglia lead to neuroinflammatory responses, neuronal damage, and cognitive dysfunction [34, 35]. M1/pro-inflammatory and M2/anti-inflammatory phenotypes are characteristics of activated microglia; M1 is activated in the progression of neurodegenerative disease and responsible for the discharge of pro-inflammatory cytokines with the elevated manifestation of an accumulation of differentiation markers, such as CD16 [32].

In this study, there was an increase in GFAP (a marker of astrocytes) expression in the dentate gyrus region of the hippocampus following LPS-induced neuroinflammation, though no significant increase in GFAP immunoreactivity was observed; curcumin was found to significant decrease GFAP immunoreexpression. Chronic curcumin exposure has been documented to increase synaptophysin and actin expression and reduce GFAP expression in the hippocampus [36, 37], while simultaneously reducing the reactive oxygen species (ROS) -related molecule, metallothionein 3 expression in the prefrontal cortex (PFC) and hippocampus [36]. This curcumin administration has been proposed to be a promising agent to attenuate memory deterioration in mice by inhibiting the HMGB1-RAGE/TLR4-NF-κB inflammatory signaling pathway [37]. A study of the exposure to pyrethroids in the development of Alzheimer’s type neurodegeneration by analyzing β-amyloid, tau, and...
Curcumin has been documented to react with and influence the mechanism of diverse target molecules associated with both acute and neuroinflammation [41] and, also regulate the inflammatory response in the CNS since it can traverse the blood-brain barrier. In addition, the neuroprotective impact of short-term treatment using curcumin has been elucidated with the aid of various experimental simulations of neurodegeneration and neuroinflammation in research [23, 42–44]. Conversely, the neuro-ameliorative role in short-term treatment has not been broadly examined. In the current study, we theorize that a short-term administration of curcumin to adult mice after inflammatory induction will ameliorate neuroinflammation and microglia enactment. When the mice were physically evaluated, mice treated with LPS were found to express an intense sickness response such as body weight loss, anorexia, decreased motor activity [45–47], and anxiety-like behavior. Mice are naturally constrained on encroachment to exposed spaces, and the decreased time spent in the focal space of the test field is deciphered as uneasiness-like conduct; notwithstanding, further examination using other tests of anxiety-like behavior (such as the elevated plus maze) is expected to more readily appraise the outcome of curcumin on LPS-induced anxiety.

**Conclusions**

This study showed that curcumin has attenuating potentials on LPS-induced neuroinflammation and neurodegeneration in the dentate gyrus and the CA3 district of the hippocampus of exploratory mice, as evidenced by the decreased expression of astrocyte and microglia. Nonetheless, curcumin was not observed to completely reestablish impaired cognitive functions induced by LPS. This could result from insufficient recuperation time for mice following treatment with curcumin. This research presents novel information that upholds the possible potential and the mitigating action of curcumin in the neuroprotection of the hippocampus.

**Ethical Statement**

The experiment was performed according to regulations, guidelines, and policies governing the use of animals in research as described in the Public Health Service Policy on Human Care and Use of Laboratory Animals, approved by the Institute of Laboratory Animal Resource, National Research Council.
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