Physiology and Pharmacology 27 (2023) 296-306
Original Article

Neuroprotective effects of *Tacca chantrieri* Andre against lipopolysaccharide-induced cognitive impairment and neuroinflammation

Utcharaporn Kamsrijai*, Benjamard Thaweethee-Sukjai, Narudol Teerapattarakan, Keerati Wanchai, Poonyawee Jirarattanawan

School of Medicine, Mae Fah Luang University, Muang, Chiang Rai 57100, Thailand

ABSTRACT

Introduction: *Tacca chantrieri* Andre is frequently used by traditional healers to alleviate pain and fever, primirily by reducing inflammation. Its rhizome extract possesses remarkable peripheral anti-inflammatory and antioxidant bioactivities. However, there is limited information available regarding its potential anti-neuroinflammation effects. This study aimes to assess the neuroprotective effects of *T. chantrieri* rhizome ethanol extract (TCE) against lipopolysaccharides (LPS)-induced neuroinflammation.

Methods: Rats were orally administered with TCE at doses of 50, 100, and 200 mg/kg continually for 9 days. On the 7th day of treatment, each rat received a single intraperitoneal injection of LPS (0.83 mg/kg). Cognitive performance was assessed using the Y-maze test and novel object recognition (NOR) test. Thereafter, the proinflammatory cytokine level in the hippocampus was measured by ELISA.

Results: Systemic LPS administration induced sickness behavior, cognitive impairment, and neuroinflammation. TCE at doses of 100 and 200 mg/kg reversed the LPS-induced behavioral deficits, showing improvements in spontaneous alternation in the Y-maze test and discrimination index in the NOR test. Additionally, pretreatment with TCE at doses of 100 and 200 mg/kg significantly attenuated the LPS-induced increase in protein expression of TNF-α.

Conclusion: TCE exhibited neuroprotective effects against LPS-induced cognitive deficits and suppressed the production of pro-inflammatory mediators in a dose-dependent manner. These findings indicate that TCE may hold therapeutic potential in preventing neuroinflammation-associated cognitive impairment. However, further studies are necessary to validate the possible mechanisms of its neuroprotective effects.

Keywords:
Tacca chantrieri Andre
Neuroinflammation
Lipopolysaccharides
Cognitive deficits

Introduction

Neuroinflammation constitutes a common hallmark of pathologic changes linked to the onset of various neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD) (Chen et al, 2016). Robust evidence from epidemiological studies has shown that inflammatory co-morbidities are significant risk factors for dementia (Reitz et al, 2011; Calsolaro and Edison,

* Corresponding author: Utcharaporn Kamsrijai, utcharaporn.kam@mfu.ac.th
Received 1 June 2022; Revised from 23 November 2022; Accepted 31 december 2022

Citation: Kamsrijai U, Thaweethee-Sukjai B, Teerapattarakan N, Wanchai K, Jirarattanawan P Neuroprotective effects of *Tacca chantrieri* Andre against lipopolysaccharide-induced cognitive impairment and neuroinflammation. Physiology and Pharmacology 2023; 27: 296-306. http://dx.doi.org/10.61186/phypha.27.3.296

2016). Furthermore, the treatment with non-steroidal anti-inflammatory drugs has been shown to reduce the risk of AD development (Benito-León et al, 2019). Lipopolysaccharide (LPS), an endotoxin derived from the outer membrane of Gram-negative bacteria, is a widely used experimental model of neuroinflammation (Zakaria et al, 2017; Zhao et al, 2019). Peripheral administration of LPS effectively triggers brain glial activity (Huang et al, 2020), resulting in the production of proinflammatory cytokines in the brain, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) (Marefati et al, 2020). Excessive induction of these cytokines following systemic LPS challenge is associated with hippocampal atrophy (Zakaria et al, 2017) and an accelerated progression of cognitive deficits (Sparkman et al, 2005; Czerniawski et al, 2015; Yin et al, 2019; Zhao et al, 2019; Lopez-Rodriguez et al, 2021).

Tacca chantrieri Andre is an herbaceous perennial plant native to Asia and the Pacific islands. Its rhizomes are used for the treatment of various diseases, such as colds, burns, gastric ulcers, hepatitis, and high blood pressure (Yokosuka et al, 2002a; Tiamjan et al, 2007). Saponins and glycosides are the of T. chantrieri (TCE) (Yokosuka et al, 2002a; Rujjanawate and Chairat, 2018), that show a variety of bioactivities including anti-inflammatory and antioxidant properties (Yokosuka et al, 2002a; Yokosuka et al, 2002b). Notably, the neuroprotective effects of saponin from ginseng roots have been extensively explored, demonstrating their capability to suppress the secretion of inflammatory cytokines such as IL-1β and TNF-α, and inhibit inflammation-promoting pathways like the nuclear factor kappa B (NF-κB) pathway in astrocyte and microglia cells (Wu et al, 2007; Miao et al, 2017; Liu et al, 2020; Madhi et al, 2021). There is a growing interest in the neuroprotective potential of herbal medicinal plants, however, only one study has hinted at TCE's ability to protect neuronal cells and inhibit of microglial activation following LPS exposure (Yang et al, 2020). Therefore, the present study aimes to investigate whether pretreatment with TCE can effectively confer neuroprotection against LPS-induced neuroinflammation.

Material and methods

Preparation of Herbal Extract

The fresh rhizomes of T. chantrieri were collected from Chiang Rai province. After collection, the rhizomes were dried and then ground into a coarse powder. Ethanol was added to the coarse powder, and the mixture was filtered to obtain the T. chantrieri ethanol extract (TCE). Thereafter, the filtrate was heated in a rotary evaporator at 55°C and lyophilized to obtain a dried form. The TCE was subsequently reconstituted in normal saline to achieve the required concentrations for the experiments.

Animals

Male Sprague Dawley rats (6-week-old) were purchased from Nomura Siam International Co., Ltd. (Thailand). All experimental procedures were carried out in accordance with the National Institutes of Health guidelines for the Care and Use of Laboratory Animals and approved by "details omitted for double-blind reviewing". All animals were housed in a controlled environment at a temperature of 25±2°C under a 12 h:12 h light:dark cycle. They were fed standard laboratory chow and had unlimited access to food and water.

Experimental Design

After the habituation period, the rats were randomly assigned to five groups (n=6). The control group (CON) received oral administration of normal saline (0.5 mL per rat) for 9 consecutive days, along with a single intraperitoneal (i.p.) injection of saline (0.5 mL per rat) on day 7. The lipopolysaccharide-treated group (LPS) received oral normal saline for 9 consecutive days followed by a single i.p. injection of LPS (0.83 mg/kg) on day 7. The other three treatment groups (TCE50+LPS; TCE100+LPS; TCE200+LPS) were orally administered TCE at doses of 50, 100, or 200 mg/kg, respectively, for 9 consecutive days with LPS-induced neurotoxicity (0.83 mg/kg, i.p.) on day 7. LPS (Sigma-Aldrich, St.Louis, MO, USA) was dissolved in 0.9% normal saline solution at a concentration of 1 mg/ml before injection. The neurotoxic dose of LPS was chosen based on a previous report (Yin et al, 2019). TCE was dissolved in 0.9% normal saline and administered once daily by oral gavage. Behavioral assessments were conducted on day 8 and 9. After completion of the behavioral tests, the rats were sacrificed. Brain tissues were immediately removed, and the hippocampus was collected and subjected to ELISA testing. The experimental design schedule is shown in Figure 1.

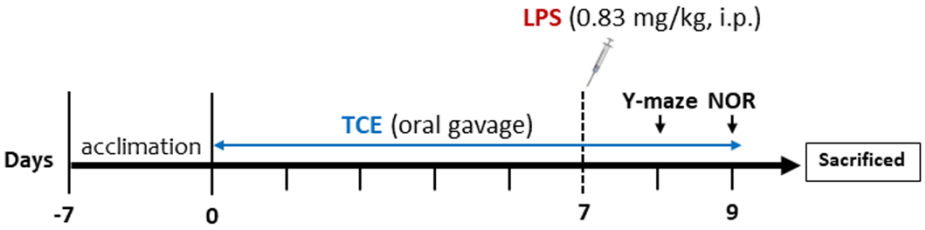

FIGURE 1. Schematic timeline illustrating drug administration and behavioral assessments.

Y-Maze Test

The Y-maze test was employed to assess Working memory and exploratory activity. The Y-maze apparatus consisted of three symmetrical arms at a 120° angle from each other. Each arm measured 30 cm in height, 50 cm in length, and 11 cm in width, with a central equilateral triangular area. The Y-maze procedure was performed according to the previously described method (Jin et al, 2017), with some modifications. Briefly, rats were positioned in the central area and allowed to explore the apparatus freely for 5 min. The maze was cleaned with 70% ethanol between tests. Entries into the arm and alternations were recorded via an overhead camera. An alteration was counted when the rat entered the three different arms in overlapping triplet sets during a triad. The spontaneous alternation behavior was defined as consecutive entries into each of the three arms without repetition. The percentage of spontaneous alternation behavior was calculated by the following formula: alternation (%) = 100 x [(number of alternations)/(total arm entries - 2)].

Novel Object Recognition Test

The novel object recognition (NOR) test was used to evaluate learning and memory ability, as described previously (Yin et al, 2019). NOR trials were conducted in square boxes of 40 cm in length, 40 cm in width, and 35 cm in height. A centrally positioned camera recorded the trials. Objects were meticulously cleaned with 70% ethanol between trials to remove olfactory cues. On day 8, rats were allowed to explore the 2 familiar objects in the box for 7 min to familiarize themselves. On day 9, the novel object trial involved replacing one familiar object with a novel object. Rats were reintroduced into the box to explore the objects for 5 min. Exploration of the novel object was defined as the rat touching the object with the nose or pointing the head within 2 cm of the object. Sitting or leaning against the object was not counted as exploration time. Discrimination index (%) was calculated using the formula: Discrimination index (%) = TN * 100/(TN + TF) (TN = time spent on the novel object; TF = time spent on the familiar object).

Enzyme-Linked Immunosorbent Assay (ELISA)

Frozen hippocampus tissue was homogenized in phosphate-buffered saline (PBS) containing a 1x protease inhibitor cocktail, resulting in a 10% tissue homogenate. The homogenate was then centrifuged at 5000 rpm for 5 min at 4 °C, and the supernatant was retained. Protein concentration was determined by the BCA method. ELISA was then conducted to quantitatively detect TNF-α proteins using a rat TNF-α ELISA kit (Elabscience Biotechnology Co. Ltd., Wuhan, China).

Statistical Analysis

All data are presented as mean ± S.E.M. All statistical analyses were performed using GraphPad software (GraphPad Prism 6.0, San Diego, CA, USA). Data were analyzed with one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. Paired t-tests was used to analyze NOR data comparing the time spent sniffing each object during NOR phases. A P-value less than 0.05 was considered statistically significant.

Results

The effect of TCE pretreatment on LPS-induced body weight loss of rats

Following LPS injection, all rats showed sickness behaviors, including decreased locomotion, a hunched posture, and weight loss. The body weight of the rats was recorded at 0 (before LPS injection), 24 h (day1), and 48 h (day 2) following the injection. LPS injection resulted in a significant weight loss 9.01% over 24 h and 8.87% over 48 h compared to the saline-treated con-

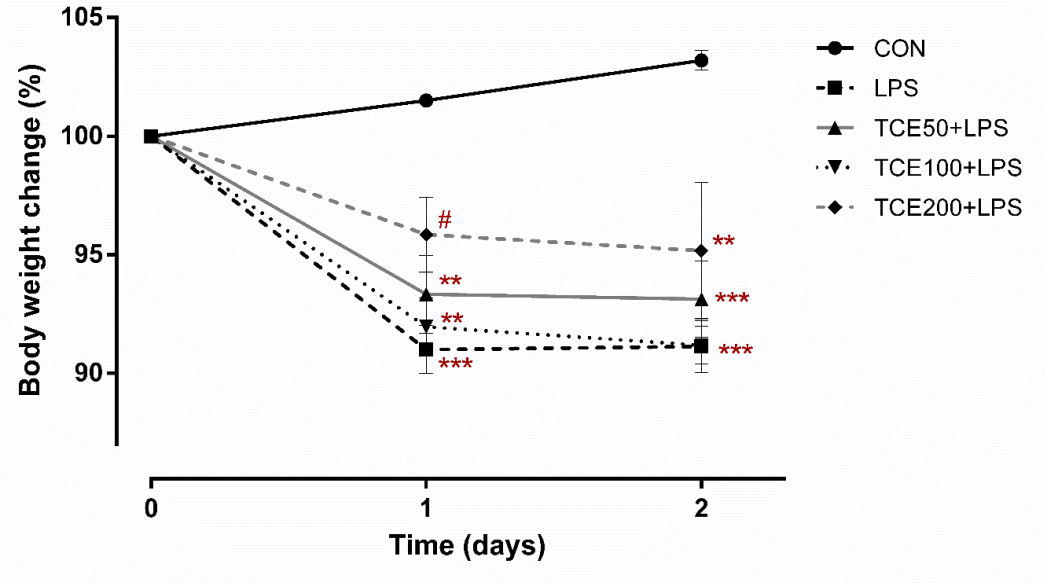

FIGURE 2. Percentage of body weight changes following LPS injection. The initial body weight on the day of LPS injection (day 0) was considered 100%. Relative body weight was calculated as a percentage of this measurement after 24 h (day 1) and 48 h (day 2) post LPS injection. Data are presented as means ± SEM (n=6). Data were analyzed by one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. $^{**}P< 0.01$ and $^{***}P< 0.001$ compared to the control group; $^{\#}P < 0.05$ compared to the LPS group.

trol group, which experienced weight gains of 1.50% over 24 h and 3.19% over 48 h ($F_{4,25}$ = 11.44, P<0.001; $F_{4,25}$ = 9.293, P<0.001, respectively)(Figure 2). Interestingly, pretreatment with TCE at a dose of 200 mg/kg halted the body weight drop, resulting in a significant difference in the percentage weight change between the TCE200+LPS group and the LPS group (P<0.05).

The effect of TCE pretreatment on LPS-induced memory impairment in the Y-maze test

The Y-maze test was performed to observe the spatial working memory of rats. The number of total entries into the arms and the percentage of triads of arm entries, in which the rats sequentially visited each possible arm without repetition, were recorded (Figure 3A). Systemic LPS administration had an influence on the total number of arm entries in the Y-maze test ($F_{4,25}$ = 7.704, P<0.001) (Figure 3B), suggesting an effect on motor activities. in terms of spontaneous alternation, the LPS-injected group exhibited a significant decrease in the percentage of spontaneous alternations when compared with the control group ($F_{4,25}$ = 5.908, P<0.01). However, TCE pretreatment at doses of 100 mg/kg (P<0.5) and 200 mg/kg (P<0.5) prior to LPS injection hindered the cognitive dysfunction induced by LPS administration (Figure 3C).

The effect of TCE pretreatment on LPS-induced memory impairment in the NOR test

Recognition memory was assessed using the NOR test. The rats were tested in an open field arena containing two identical (familiarization phase) or different (test phase) objects (Figure 4A). Analysis of the total time spent exploring the objects in the open arena during the familiarization training phase revealed no significant difference in the total time exploring the old object and novel object between animal groups (data not shown). Afterward, during the test phase, the rats in the control and TCE pretreatment groups significantly discriminated between the familiar and novel objects ($t_{1,11}$ = 4.949, P<0.01 to P<0.001)(Figure 4B), while the LPS-injected group did not. Indeed, the injection of LPS significantly impaired the discrimination index when compared with that of rats in the control group ($F_{4,25}$ = 6.220, P<0.01) (Figure 4C). TCE pretreatment at doses of 100 and 200 mg/kg significantly prevented the LPS-induced reduction in the discrimination index during the long-term memory (P<0.05 to P<0.01, respectively).

The effect of TCE pretreatment on expression levels of TNF-α in the rat hippocampus

To investigate the systemic effects of LPS exposure on the brain, the expression levels of TNF-α were determined using ELISA. Protein levels of TNF-α were significantly increased in the hippocampus of LPS-treat-

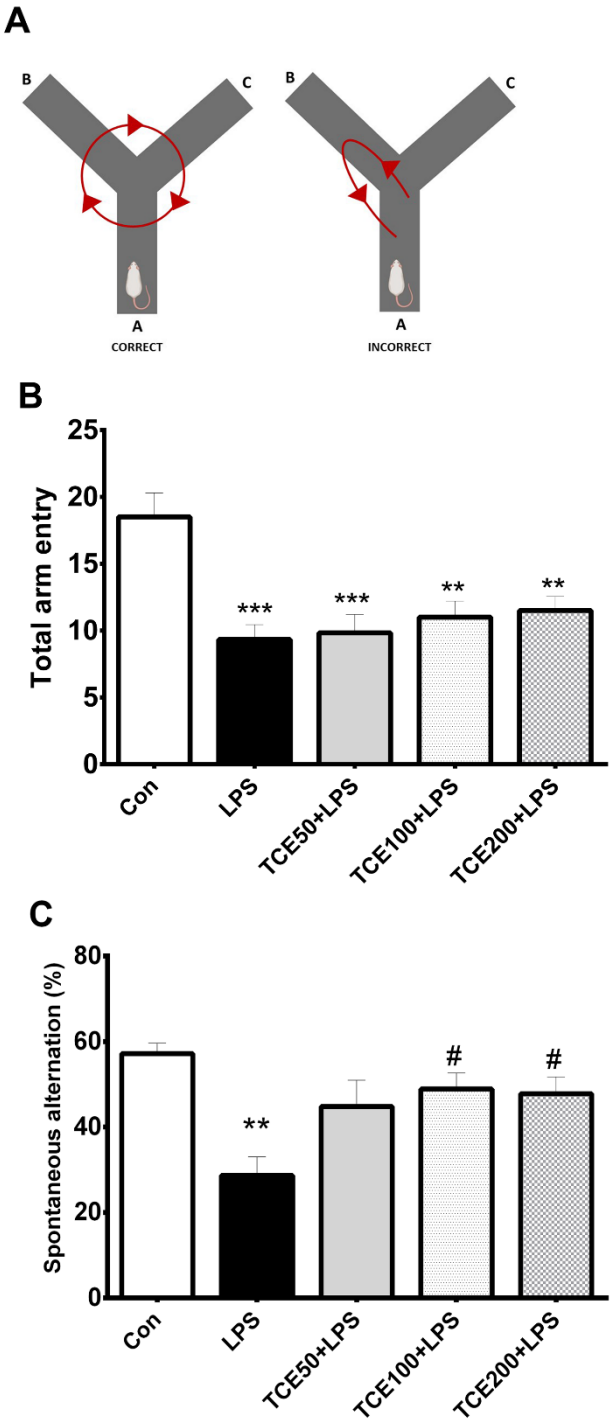

FIGURE 3. Effects of TCE on Y-maze test in LPS-injected rats. Rat received intraperitoneal LPS injection (0.83 mg/kg). TCE was orally administered at the doses of 50, 100, or 200 mg/kg seven days prior to LPS injection. The Y-maze test assessed working memory activity. (A) Diagram depicting correct and incorrect alternations in the Y-maze test. (B) Number of arm entries and (C) spontaneous alternation behavior in the Y-maze test. Data are presented as mean ± SEM (n=6). Data were analyzed by one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. $^{**}P< 0.01$ and $^{***}P< 0.001$ compared to the control group; $^{\#}P< 0.05$ compared to the LPS group. Figure 3A was created with BioRender.com.

ed rats after LPS injection ($F_{4,25} = 7.406$, $P<0.05$) compared to the control group (Figure 5). TCE pretreatment at doses of 100 and 200 mg/kg significantly attenuated LPS-induced increases in the levels of TNF-α in the hippocampus compared to the the LPS-injected group ($P<0.01$).

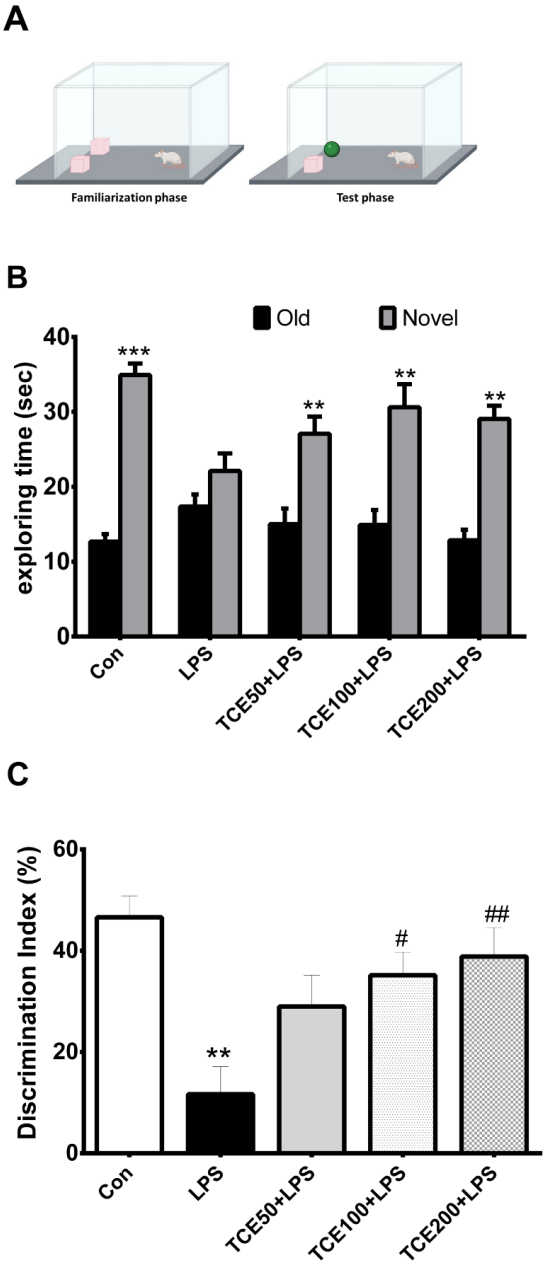

FIGURE 4. Effects of TCE on novel object recognition (NOR) in LPS-injected rats. Rats received intraperitoneal LPS injection (0.83 mg/kg). TCE was orally administered at doses of 50, 100, or 200 mg/kg seven days prior to LPS injection. (A) Schematic illustration of the NOR test evaluating recognition memory in rats. The test comprised two phases: familiarization and test. During familiarization, rats were placed in a box with two identical objects for 5 min. On the test phase, the rat looked over the box in the attendance of one novel object and a known object for 5 min. (B) Exploration time indicating time spent investigation the old and novel objects during the test phase. Data are presented as mean ± SEM (n=6). Data were analyzed by paired t-test. $^{**}P < 0.01$ and $^{***}P < 0.001$ for the comparison between the old and novel objects. (C) The discrimination index indicating the exploration time difference, calculated as (novel object exploration time)/(familiar object + novel object exploration time) across four groups during the test phase. Data are presented as mean ± SEM (n=6). Data were analyzed by one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared to the the control group; $^{\#\#}P < 0.05$ and $^{\#\#}P < 0.01$ compared to the LPS group. Figure 4A was created with BioRender.com.

Discussion

Previous studies have indicated that TCE possesses effective neuroprotective and anti-inflammatory properties against LPS-induced inflammation in SH-SY5Y neuronal cells and BV-2 microglial cells (Yen et al, 2016; Yang et al, 2020). However, it is currently unknown whether TCE treatment can improve cognitive impairment induced by LPS injection in rats. The purpose of this study was to investigate the anti-inflammatory effects of TCE in the rat brain. The results demonstrated that LPS-induced cognitive impairment was associated with deficits in learning and memory function, including

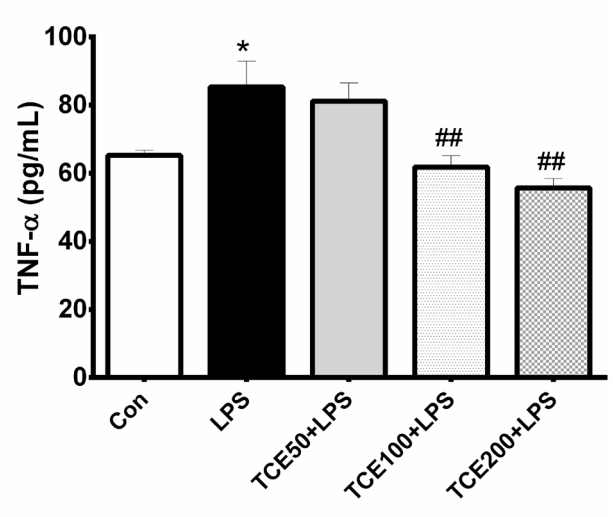

FIGURE 5. Effects of TCE on the TNF-α expression level in LPS-injected rats. At the end of the behavioral test, all rats were sacrificed. Hippocampus was homogenized and the expression levels of TNF-α were examined using ELISA kit. Data are presented as mean ± SEM (n=6). Data were analyzed by one-way analysis of variance (ANOVA) followed by post hoc Tukey's test. $^{*}P<0.05$ compared to the control group; $^{\#\#}P< 0.01$ compared to the LPS group.

both spatial working memory and recognition memory, as well as increased levels of proinflammatory cytokines in the rat hippocampus. However, pretreatment with TCE dose-dependently mitigated LPS-induced cognitive dysfunction. Additionally, TCE treatment inhibited the increase of TNF-α levels in the hippocampus of rats exposed to LPS-induced neuroinflammation.

Systemic inflammation induced by peripheral injection of LPS has been widely used as an experimental model to induce acute and subacute neuroinflammation (Zakaria et al, 2017). The results of current study demonstrated that LPS-treated rats exhibited pronounced sickness-like behavior, including decreased body weight, food consumption, and exploratory behavior following LPS injection. Sustained inflammation induced by LPS led to fat loss, likely due to reduced food intake, altered lipid anabolism, and increased lipid catabolism (Yang, Zhong et al. 2022). However, treatment with a high dose (200 mg/kg) of TCE effectively reversed the LPS-induced body weight loss. Notably, the results of the recognition test were even more pronounced at this higher dose, indicating better improvement following administration. Therefore, it is plausible that the potential effect of TCE at this high dose (200 mg/kg BW) was sufficient to ameliorate both LPS-induced sickness-like behavior and cognition deficits, potentially through modulation of proinflammatory cytokines like TNF-α.

As previously reported, peripheral immune challenges with LPS disrupt blood-brain barrier integrity (Banks et al, 2015). Moreover, LPS triggers excessive activation of microglia, shifting them from a 'resting' to an 'activated' phenotype through the Toll-like receptor 4 (TLR4)-mediated pathway (Vargas-Caraveo et al; 2020, Li et al, 2021). Activated TLR4 signaling affects NF-κB and mitogen-activated protein kinase (MAPK) pathways, including P38, AKT, ERK, and JNK (Li et al, 2021), accompanied by the release of diverse neurotoxic factors such as TNF-α, IL-1β, reactive oxygen species (ROS), and reactive nitrogen species (RNS). Accumulation of these neurotoxic factors causes long-term damage to hippocampal neurons and affects complex CNS functions like depression, sleep, and cognition (Zakaria et al, 2017; Liu et al, 2018). Interestingly, clinical studies have reported elevated LPS levels in brain samples from late-onset AD patients (increased 3-10 times) (Zhan et al, 2016; Emery et al, 2017), suggesting a potential link between LPS and cognitive impairment in AD. The modulation of LPS-releasing gram-negative bacteria has emerged as a novel therapeutic strategy for AD (Kim et al, 2021). Therefore, this study treated rats with various doses of TCE before subjecting them to LPS to stimulate neuroinflammation associated with cognitive decline.

The Y-maze test and NOR test were employed to assess spatial working memory and recognition memory, respectively. These tests are well documented and reliable behavioral paradigms to assess learning and memory (Wahl et al, 2017). The Y-maze test evaluates spa-

tial working memory associated with the hippocampus (Kraeuter et al, 2019). In this study, systemic LPS administration led to spatial working memory impairment, consistent with previous findings (Jin et al, 2017; Yin et al, 2019). Spatial learning deficit was significantly more pronounced after exposure to LPS, as indicated by a significant reduction in the percentage of spontaneous alternations. The study revealed profound hippocampal deterioration after LPS injection, resulting in diminished spatial memory. However, pretreatment with TCE at doses of 100 and 200 mg/kg significantly improved spontaneous alternation compared to rats injected with LPS alone. These results support the notion that medium and high doses of TCE could prevent spatial learning and memory impairment. Additionally, the NOR test examined TCE effects on episodic memory and recognition capacity. This test relies on synaptic connections between hippocampal neurons in CA3−CA1 (Wahl et al, 2017; Clarke et al, 2010). LPS injection significantly reduced exploration of the novel object and the discrimination index. In contrast, TCE-treated rats interacted more with the novel object, leading to an increased the discrimination index. Thus, TCE pretreatment protected against learning and memory impairments, supporting the hypothesis that TCE rescued a deficit in cognitive functions induced by LPS.

In addition, a single systemic LPS injection induced a dramatic increase in hippocampal TNF-α levels in rats, potentially deriving persistent neuroinflammation. Previous reports have demonstrated that chronic TNF-α production contributes to the onset and progression of neuroinflammatory and neurodegenerative diseases (Belarbi et al, 2012; Baj and Seth, 2018). Smaller hippocampal volume and elevated systemic TNF-α levels are associated with an increased risk of conversion from mild cognitive impairment to AD (Sudheimer et al, 2014). Notably, TNF-blocking agents are being investigated as potential therapeutic interventions for neurodegenerative diseases (Frankola et al, 2011, Belarbi et al, 2012; Zhou et al, 2020). Thus, inflammatory reactions have been associated neurodegeneration and behavioral dysfunction (Passamonti et al, 2019; Zhao et al, 2019). In this study, LPS induced cognitive impairment and elevated proinflammatory cytokine TNF-α expression. However, TCE pretreatment significantly attenuated LPS-induced neuroinflammatory changes, suggesting an anti-inflammatory potential of TCE. As previously reported, TCE protects neuronal cells from Aβ and inhibits of microglial activation following LPS exposure (Yang et al, 2020). In AD, Aβ accumulation further activates microglia to release pro-inflammatory cytokines, initiating a cascade that contributes to neuronal damage (Wang et al,2015). Additionally, soluble factors released by microglia and Aβ oligomers can induce loss of neuronal synapses (Rajendran et al, 2018), leading to synaptic dysfunction and hippocampal neuronal damage, ultimately impairing cognitive function (Passamonti et al,2019). Thus, TCE may inhibit inflammatory response, protecting hippocampal neuronal cells and promoting learning and memory improvement.

A potential limitationof this study is the lack of the identification of bioactive compounds and relevant molecular mechanisms underlying the observed effects. However, given the demonstrated neuroprotective activity of TCE against neuroinflammation, further investigations are warranted to elucidate the main bioactive compounds and mechanisms through which TCE modulates microglial activation. Future studies should focus the possible role of TCE in inhibiting the NF-κB pathway, which is a viable target for reducing the expression of proinflammatory mediators.

Conclusion

The present study demonstrated that pretreatment with TCE effectively ameliorated cognitive impairments induced by LPS injection in rats. Moreover, TCE inhibited the increase of proinflammatory cytokine TNF-α expression level, a robust deriver of neuroinflammation within the rat hippocampus. These results imply that TCE holds promising therapeutic potentials in the prevention of LPS-induced neuroinflammation-linked memory impairments.

Conflict of interest

The authors declare that there is no conflict of interest.

Acknowledgement

This work was supported by a research grant from Mae Fah Luang University, Chiang Rai, Thailand (Grant number 641A07012). The authors gratefully acknowledge Dr.Roger Timothy Callaghan for proofreading the article.

Ethics approval

All the experimental procedures were carried out in accordance with the National Institutes of Health guidelines for the Care and Use of Laboratory Animals and approved by the Animal Ethics Committee of Mae Fah Luang University (AR03-63).

References

Baj T, Seth R. Role of Curcumin in Regulation of TNF-α Mediated Brain Inflammatory Responses. Recent Pat Inflamm Allergy Drug Discov. 2018; 12(1):69-77. https://doi.org/10.2174/1872213X12666180703163824

Banks WA, Gray AM, Erickson MA, Salameh TS, Damodarasamy M, Sheibani N, Meabon JS, Wing EE, Morofuji Y, Cook DG, Reed MJ. Lipopolysaccharide-induced blood-brain barrier disruption: roles of cyclooxygenase, oxidative stress, neuroinflammation, and elements of the neurovascular unit. J Neuroinflam. 2015; 25: 12: 223. https://doi.org/10.1186/s12974-015-0434-1

Belarbi K, Jopson T, Tweedie D, Arellano C, Luo W, Greig NH, Rosi S. TNF-α protein synthesis inhibitor restores neuronal function and reverses cognitive deficits induced by chronic neuroinflammation. J Neuroinflam 2012; 25: 9-23. https://doi.org/10.1186/1742-2094-9-23

Benito-León J, Contador I, Vega S, Villarejo-Galende A, Bermejo-Pareja F. Non-steroidal anti-inflammatory drugs use in older adults decreases risk of Alzheimer's disease mortality. PLoS One 2019; 17: 14(9): e0222505. https://doi.org/10.1371/journal.pone.0222505

Calsolaro V, Edison P. Neuroinflammation in Alzheimer's disease: Current evidence and future directions. Alzheimers Dement 2016; 12(6): 719-32. https://doi.org/10.1016/j.jalz.2016.02.010

Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep 2016; 13(4):3391-6. https://doi.org/10.3892/mmr.2016.4948

Clarke JR, Cammarota M, Gruart A, Izquierdo I, Delgado-García JM. Plastic modifications induced by object recognition memory processing. Proc Natl Acad Sci USA. 2010 Feb 9; 107(6):2652-7. https://doi.org/10.1073/pnas.0915059107

Czerniawski J, Miyashita T, Lewandowski G, Guzowski JF. Systemic lipopolysaccharide administration impairs retrieval of context-object discrimination, but not spatial, memory: Evidence for selective disruption of specific hippocampus-dependent memory functions during acute neuroinflammation. Brain Behav Immun 2015; 44: 159-66. https://doi.org/10.1016/j.bbi.2014.09.014

Emery DC, Shoemark DK, Batstone TE, Waterfall CM, Coghill JA, Cerajewska TL, Davies M, West NX, Allen SJ. 16S rRNA Next Generation Sequencing Analysis Shows Bacteria in Alzheimer's Post-Mortem Brain. Front Aging Neurosci 2017; 20; 9: 195. https://doi.org/10.3389/fnagi.2017.00195

Frankola KA, Greig NH, Luo W, Tweedie D. Targeting TNF-α to elucidate and ameliorate neuroinflammation in neurodegenerative diseases. CNS Neurol Disord Drug Targets 2011; 10(3): 391-403. https://doi.org/10.2174/187152711794653751

Huang HT, Kuo YM, Tzeng SF. Intermittent peripheral exposure to lipopolysaccharide induces exploratory behavior in mice and regulates brain glial activity in obese mice. J Neuroinflam 2020; 17(1): 163. https://doi.org/10.1186/s12974-020-01837-x

Jin Y, Peng J, Wang X, Zhang D, Wang T. Ameliorative Effect of Ginsenoside Rg1 on Lipopolysaccharide-Induced Cognitive Impairment: Role of Cholinergic System. Neurochem Res 2017; 42(5): 1299-1307. https://doi.org/10.1007/s11064-016-2171-y

Kim HS, Kim S, Shin SJ, Park YH, Nam Y, Kim CW, Lee KW, Kim SM, Jung ID, Yang HD, Park YM, Moon M. Gram-negative bacteria and their lipopolysaccharides in Alzheimer's disease: pathologic roles and therapeutic implications. Transl Neurodegener 2021; 10(1): 49. https://doi.org/10.1186/s40035-021-00273-y

Kraeuter AK, Guest PC, Sarnyai Z. The Y-Maze for Assessment of Spatial Working and Reference Memory in Mice. Methods Mol Biol 2019; 1916: 105-111. https://doi.org/10.1007/978-1-4939-8994-2_10

Lee JW, Nam H, Kim LE, Jeon Y, Min H, Ha S, Lee Y, Kim SY, Lee SJ, Kim EK, Yu SW. TLR4 (toll-like receptor 4) activation suppresses autophagy through inhibition of FOXO3 and impairs phagocytic capacity of microglia. Autophagy 2019; 15(5): 753-770. https://doi.org/10.1080/15548627.2018.1556946

Li W, Ali T, He K, Liu Z, Shah FA, Ren Q, Liu Y, Jiang A, Li S. Ibrutinib alleviates LPS-induced neuroinflammation and synaptic defects in a mouse model of depression. Brain Behav Immun 2021; 92: 10-24. https://doi.org/10.1016/j.bbi.2020.11.008

Liu JQ, Zhao M, Zhang Z, Cui LY, Zhou X, Zhang W, Chu SF, Zhang DY, Chen NH. Rg1 improves LPS-induced Parkinsonian symptoms in mice via inhibition of NF-κB signaling and modulation of M1/M2 polarization. Acta Pharmacol

Sin 2020; 41(4): 523-534. https://doi.org/10.1038/s41401-020-0358-x

Liu Y, Zhang Y, Zheng X, Fang T, Yang X, Luo X, Guo A, Newell KA, Huang XF, Yu Y. Galantamine improves cognition, hippocampal inflammation, and synaptic plasticity impairments induced by lipopolysaccharide in mice. J Neuroinflam 2018; 18; 15(1): 112. https://doi.org/10.1186/s12974-018-1141-5

Lopez-Rodriguez AB, Hennessy E, Murray CL, Nazmi A, Delaney HJ, Healy D, Fagan SG, Rooney M, Stewart E, Lewis A, de Barra N, Scarry P, Riggs-Miller L, Boche D, Cunningham MO, Cunningham C. Acute systemic inflammation exacerbates neuroinflammation in Alzheimer's disease: IL-1β drives amplified responses in primed astrocytes and neuronal network dysfunction. Alzheimers Dement 2021; 17(10): 1735-1755. https://doi.org/10.1002/alz.12341

Madhi I, Kim JH, Shin JE, Kim Y. Ginsenoside Re exhibits neuroprotective effects by inhibiting neuroinflammation via CAMK/MAPK/NF-κB signaling in microglia. Mol Med Rep 2021; 24(4): 698. https://doi.org/10.3892/mmr.2021.12337

Miao HH, Zhang Y, Ding GN, Hong FX, Dong P, Tian M. Ginsenoside Rb1 attenuates isoflurane/surgery-induced cognitive dysfunction via inhibiting neuroinflammation and oxidative stress. Biomed Environ Sci 2017, 30(5): 363-372. https://doi.org/10.3967/bes2017.047

Marefati N, Beheshti F, Memarpour S, Bayat R, Naser Shafei M, Sadeghnia HR, Ghazavi H, Hosseini M. The effects of acetyl-11-keto-β-boswellic acid on brain cytokines and memory impairment induced by lipopolysaccharide in rats. Cytokine 2020; 131: 155107. https://doi.org/10.1016/j.cyto.2020.155107

Passamonti L, Tsvetanov KA, Jones PS, Bevan-Jones WR, Arnold R, Borchert RJ, Mak E, Su L, O'Brien JT, Rowe JB. Neuroinflammation and Functional Connectivity in Alzheimer's Disease: Interactive Influences on Cognitive Performance. J Neurosci 2019; 4; 39(36):7218-7226. https://doi.org/10.1523/JNEUROSCI.2574-18.2019

Rajendran L, Paolicelli RC. Microglia-Mediated Synapse Loss in Alzheimer's Disease. J Neurosci. 2018;38(12):2911-2919. https://doi.org/10.1523/JNEUROSCI.1136-17.2017

Reitz C, Brayne C, Mayeux R. Epidemiology of Alzheimer disease. Nat Rev Neurol 2011; 7(3):137-52. https://doi.org/10.1038/nrneurol.2011.2

Rujjanawate C, Chairat N. Use of bat flower's rhizome powder to relieve muscle inflammation." J Community Develop Life Qual 2018; 1(1): 91-96.

Sparkman NL, Martin LA, Calvert WS, Boehm GW. Effects of intraperitoneal lipopolysaccharide on morris maze performance in year-old and 2-month-old female C57BL/6J mice. Behav Brain Res 2005; 159(1): 145-51. https://doi.org/10.1016/j.bbr.2004.10.011

Sudheimer KD, O'Hara R, Spiegel D, Powers B, Kraemer HC, Neri E, Weiner M, Hardan A, Hallmayer J, Dhabhar FS. Cortisol, cytokines, and hippocampal volume interactions in the elderly. Front Aging Neurosci 2014; 3; 6:153. https://doi.org/10.3389/fnagi.2014.00153

Tiamjan R, Panthong A, Taesotikul T, Rujjanawate C, Taylor WC, Kanjanapothi D. Hypotensive activity of Tacca chantrieri. and its hypotensive principles. Pharma Biol 2007; 45(6): 481-485. https://doi.org/10.1080/13880200701389375

Vargas-Caraveo A, Sayd A, Robledo-Montaña J, Caso JR, Madrigal JLM, García-Bueno B, Leza JC. Toll-like receptor 4 agonist and antagonist lipopolysaccharides modify innate immune response in rat brain circumventricular organs. J Neuroinflam 2020; 17(1): 6.

Wahl D, Coogan SC, Solon-Biet SM, de Cabo R, Haran JB, Raubenheimer D, Cogger VC, Mattson MP, Simpson SJ, Le Couteur DG. Cognitive and behavioral evaluation of nutritional interventions in rodent models of brain aging and dementia. Clin Interv Aging 2017; 8; 12: 1419-1428. https://doi.org/10.2147/CIA.S145247

Wang WY, Tan MS, Yu JT, Tan L. Role of pro-inflammatory cytokines released from microglia in Alzheimer's disease. Ann Transl Med. 2015; 3(10): 136. https://doi.org/10.3978/j.issn.2305-5839.2015.03.49

Wu CF, Bi XL, Yang JY, Zhan JY, Dong YX, Wang JH, Wang JM, Zhang R, Li X. Differential effects of ginsenosides on NO and TNF-alpha production by LPS-activated N9 microglia. Int Immunopharmacol. 2007; 7(3): 313-320. https://doi.org/ 10.1016/j.intimp.2006.04.021

Yang Y, Gong Q, Wang W, Mao YL, Wang XR, Yao S, Zhang HY, Tang C, Ye Y. Neuroprotective and anti-inflammatory ditetrahydrofuran-containing diarylheptanoids from Tacca chantrieri. J Nat Prod. 2020; 83(12): 3681-3688. https://doi.org/10.1021/acs.jnatprod.0c00901

Yang Y, Zhong W, Zhang Y, Cheng Y, Lai H, Yu H, Feng N, Han Y, Huang R, Zhai Q. Sustained Inflammation Induced by LPS Leads to Tolerable Anorexia and Fat Loss via Tlr4 in Mice." J Inflamm Res. 2022; 15: 5635-5648.

Yen PH, Chi VT, Kiem PV, Tai BH, Quang TH, Nhiem NX, Anh Hle T, Ban NK, Thanh BV, Minh CV, Park S, Kim SH. Spirostanol saponins from Tacca vietnamensis and their an-

ti-inflammatory activity. Bioorg Med Chem Lett 2016; 1; 26(15): 3780-4. https://doi.org/10.1016/j.bmcl.2016.05.048

Yin S, Shao J, Wang X, Yin X, Li W, Gao Y, Velez de-la-Paz OI, Shi H, Li S. Methylene blue exerts rapid neuroprotective effects on lipopolysaccharide-induced behavioral deficits in mice. Behav Brain Res 2019; 1; 356: 288-294. https://doi.org/10.1016/j.bbr.2018.08.037

Yokosuka A, Mimaki Y, Sashida Y. Spirostanol saponins from the rhizomes of Tacca chantrieri and their cytotoxic activity. Phytochemistry 2002a; 61(1): 73-8. https://doi.org/10.1016/s0031-9422(02)00168-1

Yokosuka A, Mimaki Y, Sashida Y. Steroidal and pregnane glycosides from the rhizomes of Tacca chantrieri. J Nat Prod 2002b; 65(9):1293-8. https://doi.org/10.1021/np020094l

Zakaria R, Wan Yaacob WM, Othman Z, Long I, Ahmad AH, Al-Rahbi B. Lipopolysaccharide-induced memory impairment in rats: a model of Alzheimer's disease. Physiol Res 2017; 22; 66(4):553-565. https://doi.org/10.33549/physiolres.933480

Zhan X, Stamova B, Jin LW, DeCarli C, Phinney B, Sharp FR. Gram-negative bacterial molecules associate with Alzheimer disease pathology. Neurology 2016; 29: 87(22): 2324-2332. https://doi.org/10.1212/WNL.0000000000003391

Zhao J, Bi W, Xiao S, Lan X, Cheng X, Zhang J, Lu D, Wei W, Wang Y, Li H, Fu Y, Zhu L. Neuroinflammation induced by lipopolysaccharide causes cognitive impairment in mice. Sci Rep 2019; 9:5790. doi: https://doi.org/10.1038/s41598-019-42286-8

Zhou M, Xu R, Kaelber DC, Gurney ME. Tumor Necrosis Factor (TNF) blocking agents are associated with lower risk for Alzheimer's disease in patients with rheumatoid arthritis and psoriasis. PLoS One 2020; 23:15(3): e0229819. https://doi.org/10.1371/journal.pone.0229819