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Laboratory Investigation

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Investigating the Impact of Turmeric on Neuroinflammation and Degenerative Changes in Repetitive Traumatic Brain Injuries: Insights from Murine Model

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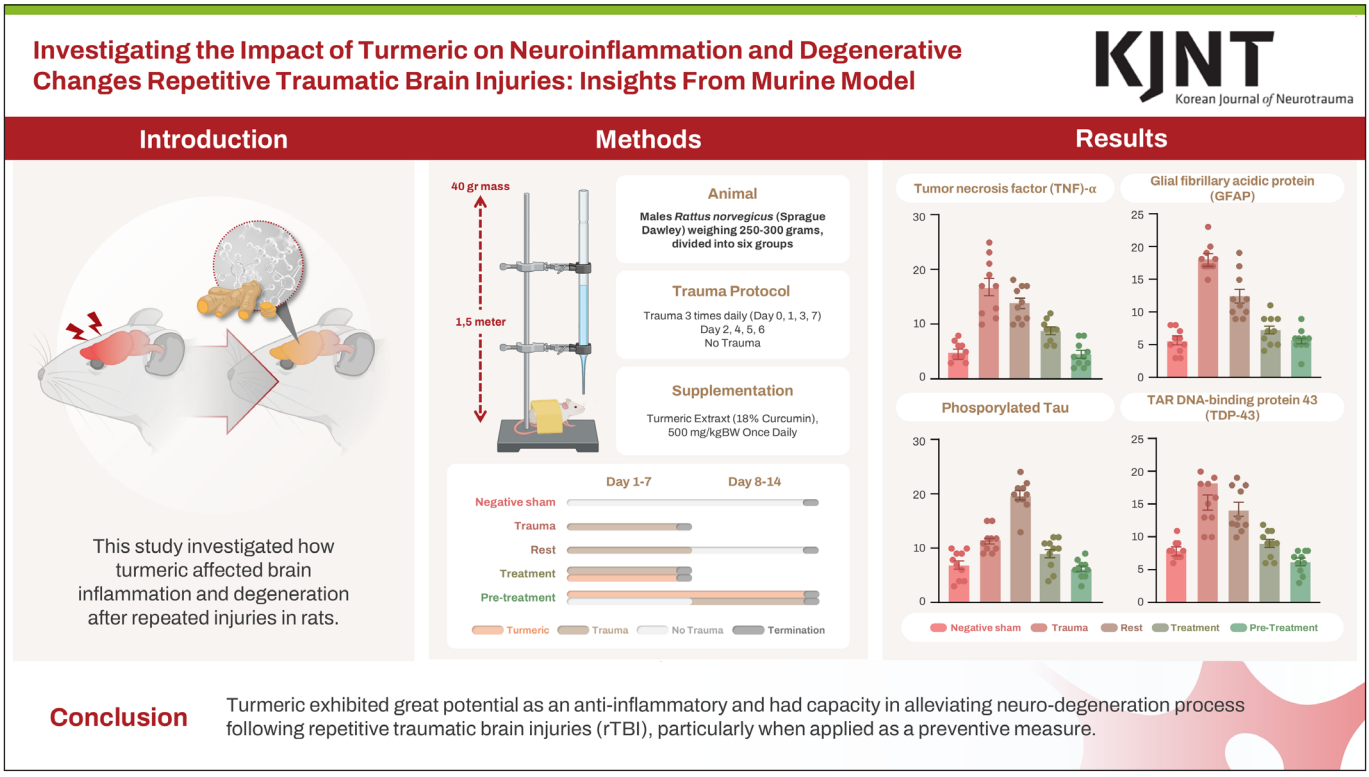
ABSTRACT

Objective: Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Preclinical and clinical studies investigating the effects of curcumin on TBI indicate that curcumin can modulate essential signaling pathways and molecules that mediate neuroinflammation in TBI. This study aimed to explore the effects of turmeric on neuroinflammation and neurodegenerative disorder following repetitive traumatic brain injuries (rTBIs) in a rat model.
Methods: Sixty male *Rattus norvegicus* were housed in a controlled environment. A modified Marmarou weight drop model was used. Turmeric extract was administered once daily in the morning. The avidin-biotin-peroxidase complex technique was used to evaluate the expression of all markers. Following incubation with normal rabbit serum, the slides were subsequently incubated with monoclonal antibodies targeting tau protein (AT-8), TAR DNA-binding protein 43 (TDP-43), glial fibrillary acidic protein (GFAP), and tumor necrosis factor (TNF)-α.
Results: rTBI significantly increased the levels of inflammatory markers, such as TNF-α and GFAP. A substantial decrease of TNF-α expression was observed in the treatment group. A distinct trend was observed for GFAP expression, which was markedly decreased after the rest period compared to that in the trauma group. Phosphorylated tau expression decreased in both the treatment and pretreatment groups relative to that in the trauma and rest groups. TDP-43 expression was also significantly decreased in the treatment and pretreatment groups.
Conclusion: In conclusion, Turmeric demonstrates significant potential as a neuroprotective and anti-inflammatory agent in rTBI, especially when used as a preventive measure. Our findings challenge the significance of rest in concussion management.

Keywords: Turmeric; Traumatic brain injury; Neuroinflammation; Neuroprotective agent; Neurodegenerative disorder

GRAPHICAL ABSTRACT



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Funding
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Conflict of Interest
The authors have no financial conflicts of interest.

Informed Consent
No humans were involved in this study, and our study was a primarily performed using a murine model. Informed consent was not provided or required for this study.

Ethics Approval
This study followed ethical animal experimentation guidelines, and the Institutional Animal Ethics Committee of Universitas Sumatera Utara approved the protocol.

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide. Annually, 50–60 million individuals sustain TBIs, resulting in an economic burden of approximately US$400 billion worldwide. Among prevalent neurological illnesses, TBI has the highest frequency and represents a significant public health challenge.[35] Mild traumatic brain injury (mTBI), defined as a Glasgow Coma Score of 14–15, is the most prevalent form of TBI in clinical settings, with an estimated annual incidence of up to 600 per 100,000 individuals.[21] mTBI typically result in temporary and nonspecific signs and symptoms, including headache, dizziness, fatigue, nausea, and attentional impairment.[57] Rest and symptomatic therapies remain the primary modalities for managing this condition.[50] In most cases, symptoms may subside within 2 weeks[48]; however, approximately 16% of patients with mTBI encounter persistent problems.[33]

Despite being considered “mild,” mTBI involves a complex sequence of pathological processes. Mechanical forces applied to the brain cause a breakdown of cellular homeostasis, excitotoxicity, depletion of intracellular glucose reserves, excessive lactate accumulation, mitochondrial dysfunction, and neuroinflammation.[22] In the acute phase, the initial impact releases damage-associated molecular patterns that induce an intricate immune response after a single mTBI. The complex inflammatory response involves the activation of microglia and astrocytes and the release of a variety of inflammatory mediators, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α. Neural disruption following a single mTBI event can last weeks after the initial impact. Furthermore, the inflammatory process can persist for a few months after the initial impact.

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Interest in repetitive traumatic brain injury (rTBI) has grown in recent decades, especially in high-risk populations. Professional contact sports athletes and military personnel are susceptible to mTBI,[15,33] and rTBIs are prevalent in these individuals.[1,45] A single TBI increases vulnerability to subsequent TBI, and the occurrence of a second mTBI before the complete resolution of pathological changes from the initial injury may result in accumulating damage to the brain and prolonged recovery.[7] rTBIs are associated with persistent, chronic neurodegenerative changes. Although the mechanisms underlying chronic changes after rTBIs are poorly understood, animal studies have shown the effects of inflammation on brain vulnerability after a single impact,[25] which leads to white matter degeneration, significant neuronal loss, and alterations in glial cell populations.[8,40] These degenerative changes are associated with cognitive difficulties, depressive emotional and behavioral impairments, and increased suicidality.[23,29] While degenerative changes are primarily associated with older age,[13,39] a recent study showed that this condition may also manifest in individuals under the age of 30.[37]

Degenerative changes have been associated with hyperphosphorylated tau protein and the accumulation of abnormally aggregated proteins, such as TAR DNA-binding protein 43 (TDP-43).[38] Tau is a microtubule-associated protein primarily expressed in neurons, with limited expression in glial cells. The accumulation of hyperphosphorylated tau in the form of tangles is a well-established hallmark of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases,[62] as well as conditions resulting from TBI.[2] TDP-43 is an interesting novel biomarker that was explored in our study. TDP-43 is an RNA-binding protein involved in various critical cellular processes, including RNA biogenesis and processing and the regulation of mRNA alternative splicing.[20] TDP-43 is activated by IL-1 and TNF-α, which in turn activates c-Jun N-terminal kinases and increases TDP-43 levels. This suggests that TDP-43 is involved in the final cascade of inflammation. Studies have found a correlation between TDP-43 mislocalization or excessive production and synaptic, cognitive, and neurological deficits following TBI.[6,20] These findings highlight the role of TDP-43 in neuroinflammation and neurodegeneration.

Curcuma longa, commonly known as turmeric, is one of the most studied medicinal plants that is recognized for its potential anticancer, anti-inflammatory, and neuroprotective properties. Curcumin, an essential active compound in *C. longa*, is a low-molecular-weight polyphenol that plays a central role in its antioxidant and anti-inflammatory effects.[41] Turmeric is well known in the medicinal world, and a review has pinpointed its broad range of clinical properties, owing to its considerable antioxidative and anti-inflammatory actions. Preclinical and clinical studies investigating the effects of curcumin on TBI indicate that curcumin can modulate essential signaling pathways and molecules that mediate the neuroinflammation in TBI.[30] Turmeric is readily available as a food additive and condiment and is therefore not a problematic plant source for the general population.[54] In addition, turmeric can penetrate the blood-brain barrier.[55]

However, the role of turmeric in TBI in relation to neurodegeneration has not been elucidated. Although curcumin, the main active compound of turmeric, has been shown to have beneficial properties *in vitro*, *in vivo*, and in clinical studies of TBI, its neuroprotective effect on rTBI or chronic TBI has not been sufficiently elucidated.[30] Curcumin is a well-known substance that has the potential to protect against and prevent neurodegenerative changes associated with abnormal neuronal proteinopathies such as Alzheimer's disease.[11] Moreover, turmeric has a good safety profile in humans, even after long-term use. This study

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aimed to explore the effects of turmeric on neuroinflammation and degenerative changes following rTBI in a rat model.

MATERIALS AND METHODS

Animals

Sixty male *Rattus norvegicus* (Sprague-Dawley strain), aged 1.5–2 months and weighing 250–300 g, were housed in polypropylene cages measuring 30×40×15 cm^3, with 2–3 individuals per cage. Body weights of the animals were evenly distributed to ensure compatibility. We calculated the sample size based on an *a priori* analysis using G*power,[18] considering an α of 0.05, 1-β of 0.80, and an effect size of 0.5. Each group was housed in separate cages to avoid cross-group contamination. The cages were lined with rice husk bedding, which was replaced every three days. An ambient temperature of 22°C–24°C and a 12-hour light/dark cycle were maintained to ensure a consistent environment for all animals. The diet consisted of antibiotic-free commercial wet chicken feed, and each cage received 100–150 g of food daily. Water was provided ad libitum throughout the study, to ensure adequate hydration.

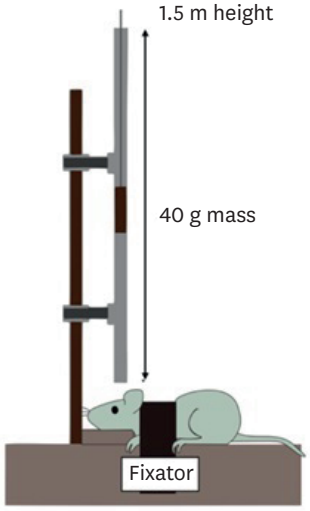
rTBI experimental model

The rTBI protocol used in this study was based on a previous model of neuroinflammation and neurodegeneration.[60] A modified Marmarou weight drop model was used to induce rTBI. A 40 g weight was dropped from a height of one meter directly onto the vertex of the skull, producing a blunt-force impact. This procedure was performed three times daily on days 0, 1, 3, and 7, resulting in 12 trauma episodes. A metal plate was attached to the vertex before the trauma procedure to prevent skull fracture (**FIGURE 1A & B**). The animal was comfortably restrained using a restraint bag tied for immobilization. No anesthesia was used in this study. This study followed ethical animal experimentation guidelines, and the Institutional Animal Ethics Committee approved the protocol.

A

Day	Trauma	Turmeric extract
0	3 times	500 mg/kg per oral once daily
1	3 times	
2	-	
3	3 times	
4	-	
5	-	
6	-	
7	3 times	

B



C

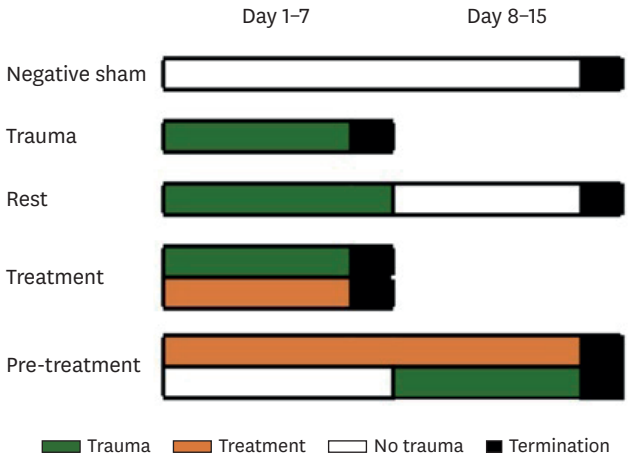


FIGURE 1. Model of mild repetitive traumatic brain injury adopted in the study.

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Turmeric extract treatment protocol

Turmeric extract (18% curcumin) was administered orally once daily in the morning, at a dose of 500 mg/kg body weight. This dosing was consistent with the turmeric administration performed without the need for a bioavailability enhancer (e.g., piperine) in a previous study.[17] A previous study demonstrated that a 500 mg/kg body weight dose improved neutrophil infiltration and reduced levels of apoptosis-related proteins in a murine weight drop model of TBI.[30] Based on the conversion of animal doses to human equivalent doses using the body surface area (BSA), a dose of 500 mg/kg body weight in animals is equivalent to 4.8 g/kg body weight in humans with a body weight of 60 kg (BSA of 1.6).[47] Notably, 4.8 g/kg is also the median lethal dose value for curcumin in humans.[27]

Grouping

The animals were divided into 5 groups, each consisting of 10 rats, as follows: 1) Negative sham: No trauma and no turmeric administration on days 0–15; 2) Trauma: Trauma was induced from day 0 to day 7, followed by sacrifice on the last day; 3) Rest: Trauma was induced from day 0 to day 7, followed by no intervention from day 8 to day 15; 4) Treatment: Trauma was induced and turmeric was administered from day 0 to day 7; and 5) Pretreatment: Turmeric administration was initiated 7 days before the trauma and continued throughout the trauma (**FIGURE 1C**).

Immunohistochemical staining

The avidin-biotin-peroxidase complex technique was used to evaluate the expression of all markers. Paraffin blocks were sectioned into 5 μm thick slices and rehydrated. The endogenous peroxidase activity of the sections was inhibited with hydrogen peroxide for 10 minutes, followed by washing with phosphate-buffered saline (PBS) for 25 minutes. Following incubation with normal rabbit serum, the slides were subsequently incubated with monoclonal antibodies targeting tau protein (AT-8; Thermo Fisher Scientific, Waltham, MA, USA), TDP-43 (Santa Cruz Biotechnology, Dallas, TX, USA), glial fibrillary acidic protein (GFAP; Santa Cruz Biotechnology), and TNF-α (Abcam, Cambridge, UK). After additional washes with PBS, the slices were incubated with a secondary antibody for 30 minutes, developed with 3,3'-diaminobenzidine tetrahydrochloride, and counterstained.

All proteins were quantitatively assessed based on positively stained cells in the cortical area. Cells exhibiting positive staining were counted under a light binocular microscope at 1,000× magnification in 20 high-power fields.

Statistical analysis

The total numbers of stained cells for all markers are reported as means and standard deviations. The Shapiro-Wilk test was used to determine whether the data were normally distributed. The significance of the variability between groups was evaluated using one-way analysis of variance, followed by Tukey's *post hoc* analysis. If the data were abnormally distributed, the significance of the variability was evaluated using the Kruskal-Wallis test, followed by the Mann-Whitney *post hoc* analysis. Differences were considered statistically significant at $p<0.05$.

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RESULTS

Fifty rats were categorized into the negative sham, trauma, rest, treatment, or pretreatment groups. None of the rats died during the follow-up. We evaluated the expression of two markers associated with brain inflammation (TNF-α and GFAP) and 2 proteins associated with neurodegenerative processes (phosphorylated tau [pTau] and TDP-43). Detailed results are presented in **TABLE 1** and **FIGURE 2**.

TABLE 1. Results and standard deviation of GFAP, TDP-43, pTau, and TNF-α levels in trauma, rest, treatment and pre-treatment models

Models	TNF-α	GFAP	pTau	TDP-43
Negative sham	3.60±1.78	5.50±1.84	7.00±2.62	8.00±1.41
Trauma	16.80±5.22	18.10±2.18	11.50±2.17	15.20±3.61
Rest	13.70±3.13	12.40±3.47	19.70±2.91	14.20±3.39
Treatment	8.80±1.99	7.20±2.25	9.10±2.85	9.00±2.11
Pre-treatment	4.50±2.22	5.70±1.77	6.20±1.69	6.20±1.75

GFAP: glial fibrillary acidic protein, TDP-43: TAR DNA-binding protein 43, pTau: phosphorylated tau, TNF: tumor necrosis factor.

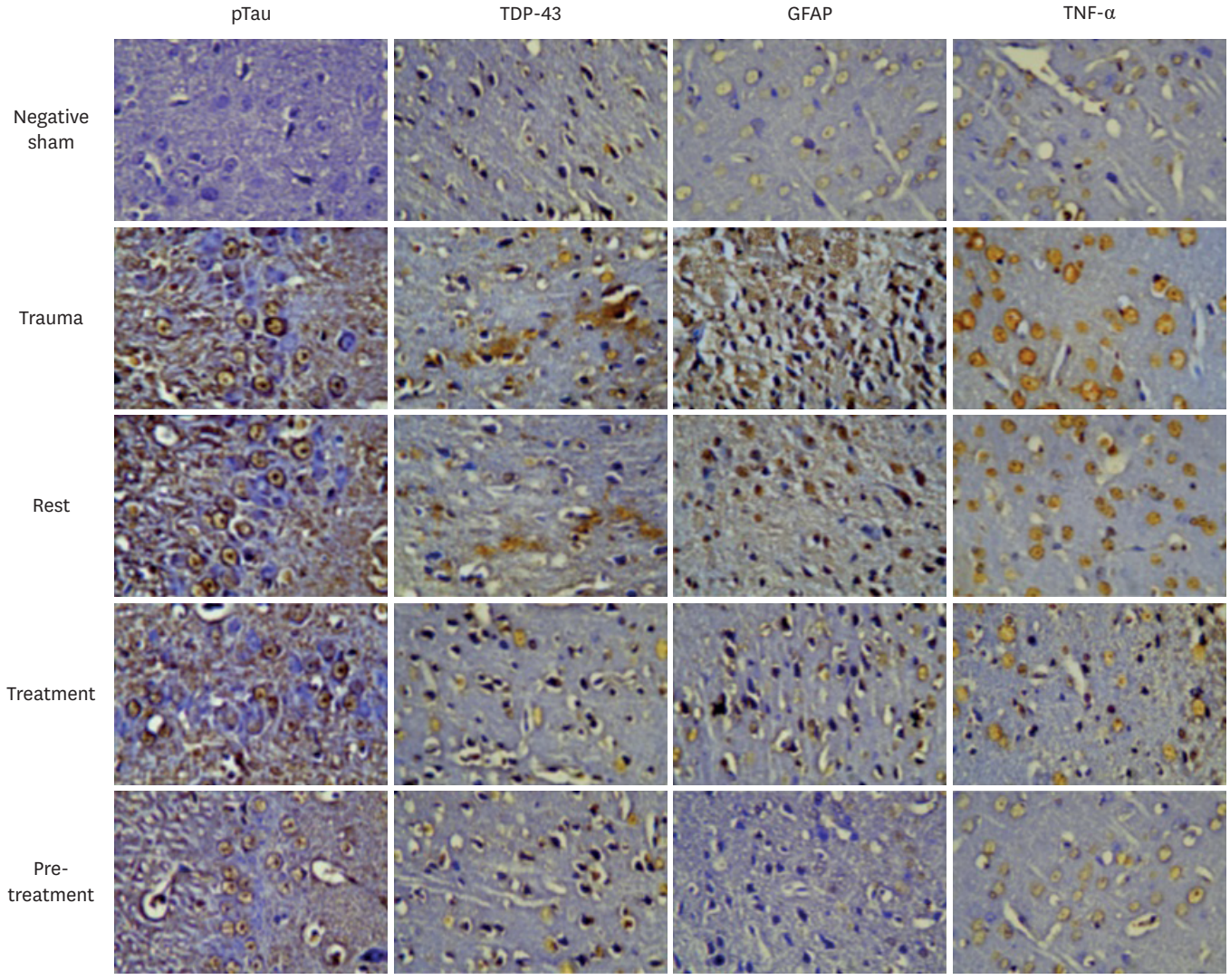

FIGURE 2. Immunohistochemical study in control and experimental groups revealing pTau, TDP-43, GFAP, and TNF-α expression.
pTau: phosphorylated tau, TDP-43: TAR DNA-binding protein 43, GFAP: glial fibrillary acidic protein, TNF: tumor necrosis factor.

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rTBI increased the expression of inflammatory markers

rTBI significantly increased the levels of inflammatory markers, such as TNF-α and GFAP. After 7 days of repeated trauma, TNF-α levels were significantly higher than those of the negative sham group. On the rest group, the TNF-α levels were reduced; however, it was not significant compared to the trauma group (**FIGURE 3A**).

Similarly, GFAP expression was significantly increased in the trauma group. After 7 days of rest, the GFAP expression was significantly lower (**FIGURE 3B**).

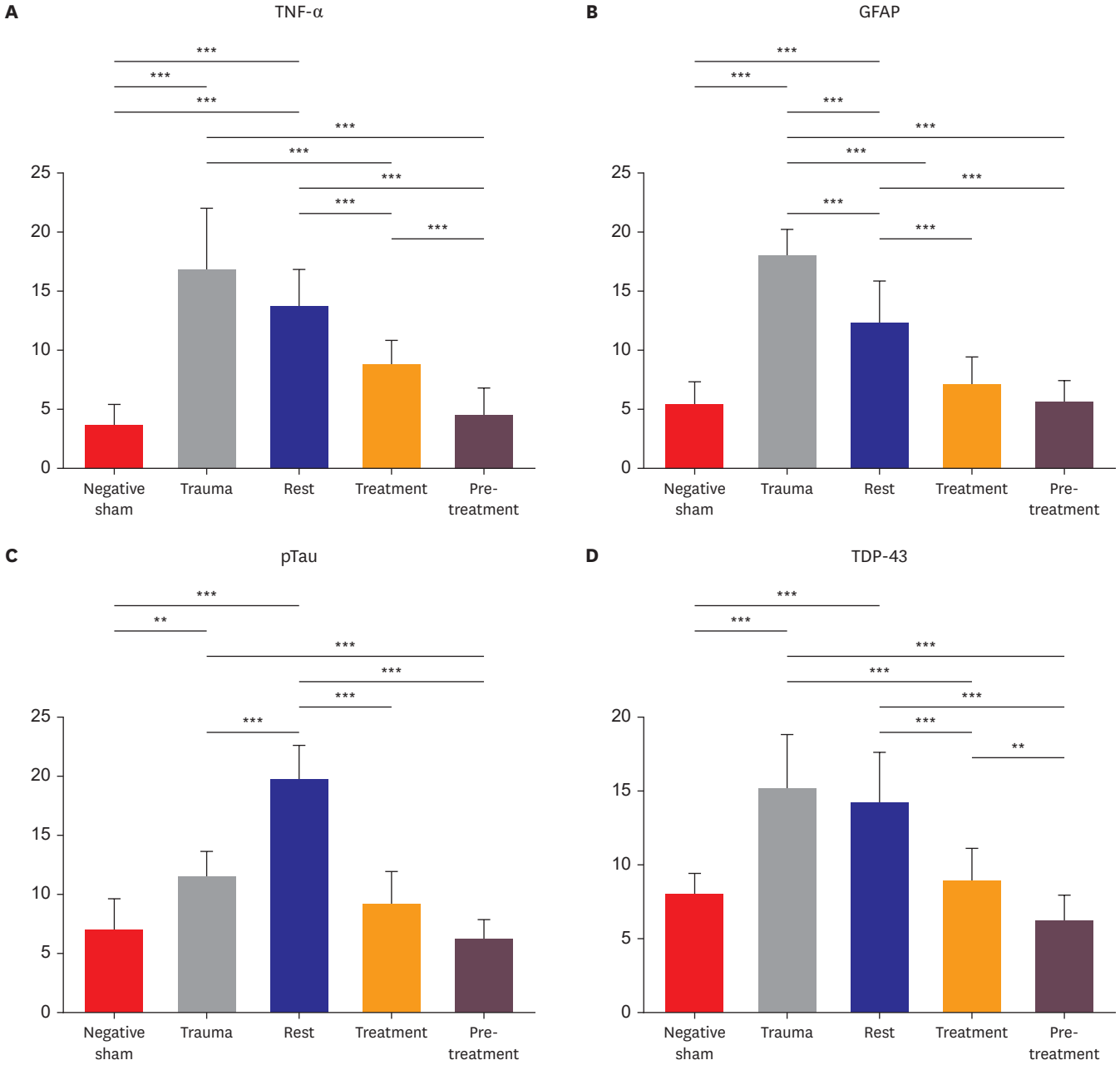

FIGURE 3. *Post-hoc* test visualization. Comparing TNF-α (A), GFAP (B), pTau (C), and TDP-43 (D) in all groups.
TNF: tumor necrosis factor, GFAP: glial fibrillary acidic protein, pTau: phosphorylated tau, TDP-43: TAR DNA-binding protein 43.
$^{**}p<0.01$, $^{***}p<0.001$.

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rTBI elevated the levels of pTau protein and TDP-43

rTBI significantly increased the levels of pTau and TDP-43, two essential proteins associated with neurodegenerative disorders. pTau expression was significantly higher in the trauma group than in the negative sham control group. Interestingly, the pTau expression was elevated in the rest group (**FIGURE 3C**).

An increasing trend was also observed for TDP-43 levels. Repetitive trauma resulted in increased TDP-43 expression on day seven. However, unlike with pTau, a trend of decreased TDP-43 expression was observed in the rest group, although this decrease was not substantially different from that observed in the trauma group (**FIGURE 3D**).

Turmeric treatment reduced inflammatory markers following rTBI

As mentioned previously, the rest group showed a nonsignificant decrease in TNF-α expression. In contrast, a significant decrease in TNF-α expression was observed in the treatment group. Furthermore, the reduction in TNF-α expression was significantly lower in the pretreatment group than in the treatment group (**FIGURE 3A**).

A distinct trend was observed for the GFAP expression. The GFAP expression was markedly decreased after the rest period compared to that in the trauma group. Compared with the control group, both the treatment and pretreatment groups had markedly reduced GFAP expression. The pretreatment group showed a nonsignificant trend of decreased GFAP expression compared with that of the treatment group (**FIGURE 3B**).

Turmeric treatment affected the expression of tau protein and TDP-43

As previously stated, pTau expression was elevated in the rest group compared with that in the trauma group. In contrast, pTau expression was decreased in both the treatment and pretreatment groups compared with that in the trauma or rest groups. The expression of pTau in the pretreatment group was lower than that in the treatment group, although the difference was not statistically significant (**FIGURE 3C**).

The TDP-43 expression was significantly decreased in the treatment and pretreatment groups compared with that in the trauma and rest groups. Moreover, the TDP-43 expression was notably decreased in the pretreatment group compared with that in the treatment group (**FIGURE 3D**).

DISCUSSION

Impact of rTBIs on neuroinflammation and neurodegeneration

Activation of the innate immune system is a crucial factor in TBI that is associated with subsequent morbidity.[51] Microglial activation has been observed for up to 17 years after moderate and severe head injuries.[46] Moreover, there is increasing evidence of persistent neuroinflammation following a single mTBI. Glial activation has been observed for up to 18 days after the initial insult in an animal model of blast TBI.[44] Clinical research faces challenges when investigating cerebral neuroinflammation following mTBI. However, systemic inflammation may persist for up to 1 year following damage, even after a single mTBI.[10] The complexity of this issue increases in rTBI; following a single mTBI, a temporal window of brain vulnerability emerges, during which a subsequent impact is highly correlated with more severe outcomes, prolonged recovery, and potentially extended

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inflammation.[24,56] Janković and Pilipović[26] demonstrated that microglial activation occurs following the initial brain trauma, initiating a cascade of inflammatory responses, including the release of cytokines, chemokines, and other proinflammatory mediators that contribute to neurodegeneration. Repeated brain trauma prevents the transition of microglia from a proinflammatory state (M1) to a neuroprotective state (M2). This finding explains why mild repetitive brain trauma, even when subsequent injuries occur several months apart, is associated with a higher incidence of prolonged neurological consequences than a single brain trauma.[26]

We found increased TNF-α expression after rTBI that persisted after a 7-day recovery interval. This is not an unexpected finding, as solid evidence supports the critical role that TNF-α plays in mTBI progression[43] and its potential as a therapeutic target.[3,63] We also noted a sustained increase in GFAP, a marker of astrogliosis, following rTBI, which was significantly reduced after recovery. In response to head trauma, astrocytes become reactive, creating a glial scar that functions as a physical barrier between injured and healthy tissues.[9] This process, astrogliosis, may be associated with TNF-α through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway.[34] However, reactive astrogliosis can also be detrimental. In clinical studies involving subjects exposed to repetitive head impacts, persistent elevation of plasma GFAP levels correlates with progressive atrophy of the thalamus and corpus callosum and cognitive decline.[5]

This study demonstrated a considerable increase in tau protein and TDP-43 levels following rTBI. Interestingly, the tau protein expression was significantly increased in the rest group, raising doubts regarding the efficacy of rest in managing rTBI. Adopting rest in concussion care appears reasonable, as it reduces the energy demand[4]; nevertheless, strict rest is no longer advised.[31] Increasing evidence supports the role of neuroinflammation in degenerative diseases. The inadequate healing of damaged tissues may result in chronic low-grade irritation that triggers chronic inflammation and aberrant proteinopathy.[61] TBI itself is a recognized risk factor for several neurodegenerative diseases associated with proteinopathies, including Alzheimer's and Parkinson's diseases, and chronic inflammation is considered a potential connection.[14,28] Another study found that the abnormal accumulation of tau protein occurs due to intra-axonal microtubule destruction, which leads to axonal apoptosis.[32] Amyloid-β plaques have also been identified in approximately one-third of individuals with fatal TBI, a finding supported in TBI survivors who have undergone decompressive craniectomy.[14,36]

Potential role of turmeric in rTBI

Curcumin, an active compound in turmeric, has shown substantial promise in mitigating the inflammatory effects associated with TBI. The beneficial effect of curcumin has been observed in several animal models of single TBI, mainly through immunomodulatory properties, including NF-κB and nuclear factor erythroid 2 related factor 2 (**FIGURE 4**).[12,53] Reductions in several neuroinflammation-associated markers (e.g., IL-1β, IL-6, IL-18, and TNF-α) and reactive astrogliosis (GFAP) after curcumin administration have also been reported in several animal models of single TBI.[56] In this study, we observed the same effect when turmeric was administered in an rTBI model.

As previously stated, given that neuroinflammation is closely associated with the development of aberrant proteinopathies, the observed decreases in tau protein and TDP-43 following turmeric administration in this study are reasonable. Hyperphosphorylated

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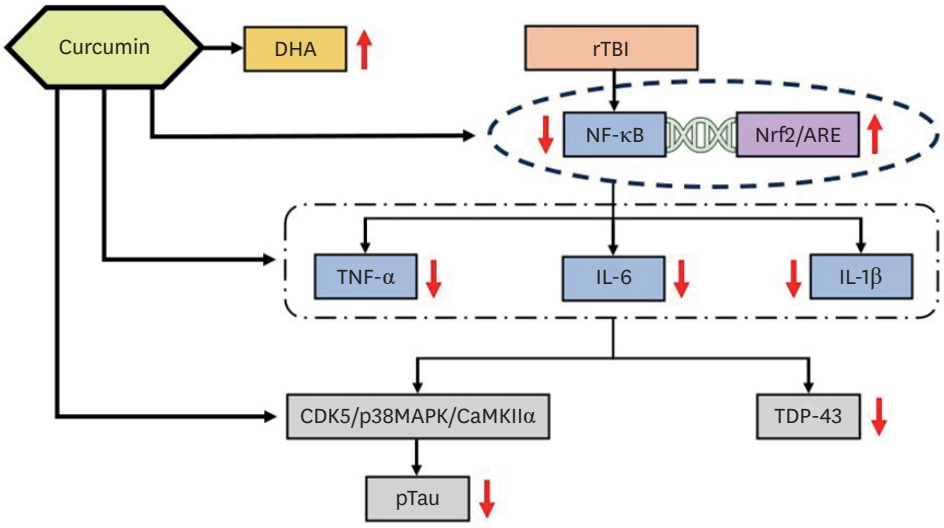

FIGURE 4. Flow diagram describing curcumin pharmacodynamics in reducing neuroinflammation and enhancing neuroprotective effects.
DHA: docosahexaenoic acid, rTBI: repetitive traumatic brain injury, NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells, Nrf2: nuclear factor erythroid 2 related factor 2, ARE: antioxidant responsive element, TNF: tumor necrosis factor, IL: interleukin, CDK5: cyclin-dependent kinase 5, p38MAPK: p38 mitogen-activated protein kinase, CaMKIIα: calcium/calmodulin-dependent protein kinase type IIα, TDP-43: TAR DNA-binding protein 43, pTau: phosphorylated tau.

tau proteins can misfold and form neurofibrillary tangles, which are a characteristic feature of various neurodegenerative diseases that is known as tauopathy. Although the precise mechanism of tau aggregation remains unclear, increasing evidence indicates that neuroinflammation is involved. TNF-α and IL-1β can activate several protein kinases associated with tau protein, including p38 mitogen-activated protein kinase, cyclin-dependent kinase 5, and calcium/calmodulin-dependent protein kinase type II α. This is a tightly regulated mechanism, and any disruption in its stability, such as chronic neuroinflammation in rTBI, may lead to abnormal proteinopathy.[16] Numerous studies indicate the beneficial effects of the TNF-α inhibitors on proteinopathy, including Alzheimer's disease.[42,49] Further research is required to elucidate the role of immunomodulatory agents in rTBI.

In this study, we observed that the pretreatment group had the most significant reduction in inflammation and degeneration, indicating the potency of turmeric in increasing neuroplasticity and responding to trauma. This effect may be mediated through docosahexaenoic acid (DHA). DHA is the predominant omega-3 fatty acid in brain tissues and the most-studied supplement for treating concussions. Supplementation with omega-3 fatty acids, as a preventative measure in young athletes, has been linked to decreased levels of neurofilament light chain, an indicator of brain injury.[19] Curcumin has been shown to augment hepatic and cerebral DHA levels in multiple animal experiments.[58,59] Turmeric has a good safety profile, and its possible use as a preventative measure in rTBI should be investigated.[52]

Study strengths

Our study was the first to assess TDP-43 in TBI interventional studies, even though TDP-43 has been established as a neurodegenerative biomarker. The role of TDP-43 in rTBI remains unknown, and interventions to inhibit TDP-43 are scarce in neuroscience. Another strength

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of our study is the follow-up period and grouping. Owing to our grouping and experimental model, we found that rest alone was not sufficient to alleviate the destructive effects of rTBI at the biomolecular level, which in turn may have a long-term effect on humans.

Limitations and future directions

Although these findings highlight the potential of curcumin for preventing and mitigating the effects of rTBI, several limitations should be considered. First, the study was conducted using animal models, and although the results are promising, they can only be directly translated to human applications through further clinical trials. Additionally, this study focused on short-term inflammatory responses, and the long-term effects of curcumin treatment require further research. Second, our study did not analyze the neurological function of the sample through cognitive or behavioral assessments. The results of a neurological function examination could be correlated with biomarker and immunohistochemistry changes, to support further biomolecular research on TBI. Third, while rest was analyzed in our study on rTBI, several neuroinflammatory and neurodegenerative effects may persist for some time; thus, a more extended follow-up period with multiple examinations to confirm the results may be necessary. Fourth, we did not analyze the curcumin concentration in the brain. Although curcumin can cross the blood-brain barrier, its bioavailability in the brain is low. Hence, the optimal dose required to treat rTBI remains unclear.

Future research should investigate the prolonged use of curcumin in populations at a high risk of rTBI, such as athletes and military personnel, and its effects on cognitive and behavioral outcomes over extended periods, particularly as a preventive measure. Optimizing dosing regimens and exploring alternative curcumin formulations to improve bioavailability may also enhance their efficacy in clinical settings.

CONCLUSION

In conclusion, curcumin demonstrates significant potential as a neuroprotective and anti-inflammatory agent in rTBI, especially when used as a preventive measure. Our findings challenge the significance of rest in concussion management. However, more extensive studies, particularly in humans, are required to understand its therapeutic potential and optimize its clinical use.

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