RESEARCH PAPER

Effects of Nigella Sativa Extract on Brain-Derived Neurotrophic Factor Levels and Histopathological Necrosis in a Wistar Rat Model of Traumatic Brain Injury

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ABSTRACT

Background: Traumatic brain injury (TBI) triggers secondary injury mechanisms including oxidative stress, neuroinflammation, and neuronal necrosis, which contribute to poor neurological outcomes. Brain-derived neurotrophic factor (BDNF) plays an essential role in neuronal survival and neuroregeneration. Nigella sativa possesses antioxidant and anti-inflammatory properties that may provide neuroprotective effects following TBI. This study evaluated the effects of Nigella sativa extract on serum BDNF levels and histopathological necrosis in a Wistar rat model of TBI.

Methods: A true experimental randomized pretest–posttest control group study was conducted using 16 male Wistar rats with induced TBI via the Marmarou weight-drop model. Rats were randomly assigned into two groups: TBI treated with Nigella sativa extract (200 mg/kg/day orally for 7 days) and placebo-treated TBI rats. Serum BDNF levels were measured at baseline, day 1, day 3, and day 7 using ELISA. Histopathological examination and necrotic cell quantification were performed on day 7.

Results: Significant differences in serum BDNF levels were observed between the Nigella sativa and placebo groups on day 3 ($p=0.018$) and day 7 ($p<0.001$). Rats receiving Nigella sativa demonstrated progressive increases in BDNF levels, whereas placebo-treated rats showed continuous declines. Necrotic cell counts were significantly lower in the Nigella sativa group compared with placebo (3164.13 ± 771.38 vs 4028.38 ± 204.58; $p=0.008$). Serum BDNF levels were negatively correlated with necrotic cell counts ($r=-0.659$; $p=0.006$).

Conclusion: Administration of Nigella sativa extract increased serum BDNF levels and reduced histopathological necrosis in Wistar rats with TBI, suggesting potential neuroprotective and neurotrophic effects.

Keywords: *Traumatic Brain Injury; Brain-Derived Neurotrophic Factor; Nigella sativa; neuroprotection; histopathological necrosis*

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1. INTRODUCTION

Traumatic brain injury (TBI) is a major cause of mortality and long-term disability worldwide, particularly among individuals younger than 35 years old [1,2]. The World Health Organization estimates that approximately 150–300 per 100,000 people experience TBI annually (Chen et al., 2022) [3]. Beyond acute neurological impairment, TBI is associated with chronic neurodegeneration, cognitive decline, and poor functional outcomes [4].

The pathophysiology of TBI consists of primary and secondary injury mechanisms. Primary injury results from direct mechanical trauma, whereas secondary injury involves excitotoxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, apoptosis, and neuronal necrosis [5]. Excessive glutamate release and intracellular calcium influx activate apoptotic signaling pathways and promote neuronal cell death [6]. Activated microglia further exacerbate brain injury through the release of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α [5].

Brain-derived neurotrophic factor (BDNF) is an essential neurotrophin involved in neuronal survival, synaptic plasticity, and neuroregeneration [7]. Activation of the BDNF/TrkB signaling pathway promotes neuronal

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survival through PI3K/Akt and CREB-mediated pathways, whereas reduced BDNF expression has been associated with apoptosis and impaired neurological recovery after TBI [8]. Clinical studies have shown significantly lower serum BDNF levels in TBI patients compared with healthy individuals [9]. Therefore, therapies targeting BDNF modulation may provide neuroprotective benefits in TBI management.

Nigella sativa (Habbatussauda) is a medicinal plant known for its antioxidant, anti-inflammatory, and neuroprotective properties [10]. Its major bioactive compound, thymoquinone, has been reported to suppress oxidative stress, inhibit NF-κB-mediated neuroinflammation, and activate prosurvival pathways including Nrf2/ARE and PI3K/Akt signaling [11]. Experimental studies demonstrated that *Nigella sativa* administration increased BDNF levels and reduced neuronal apoptosis in animal models of traumatic brain injury [12,13].

However, evidence regarding the combined effects of *Nigella sativa* extract on BDNF levels and histopathological necrosis in traumatic brain injury remains limited. Therefore, this study aimed to evaluate the effects of *Nigella sativa* extract on brain-derived neurotrophic factor (BDNF) levels and histopathological necrosis in a Wistar rat model of traumatic brain injury.

2. MATERIALS AND METHODS

Study Design and Setting

This study employed a true experimental laboratory design using a randomized pretest–posttest control group approach. The study was conducted from January to February 2026 at the Laboratory of the Faculty of Veterinary Medicine, Hasanuddin University, Makassar, Indonesia. Biomolecular examinations were performed at the Microbiology Laboratory, Faculty of Medicine, Hasanuddin University, while histopathological analysis was conducted at the Laboratory of the Faculty of Veterinary Medicine, Hasanuddin University.

Experimental Animals

The study utilized male Wistar rats (*Rattus norvegicus*) aged 3–4 months with body weights ranging from 200–250 g. All animals were healthy and active prior to the experiment. The rats were acclimatized for two weeks under controlled laboratory conditions with a temperature of 28 ± 2°C, 12-hour light/dark cycle, and ad libitum access to food and water.

Sample Size Determination

Sample size calculation was performed according to the formula proposed by Pakgohar and Mehrannia. The minimum number of animals required per group was seven rats, while the maximum was eleven rats. To anticipate potential dropouts, an additional 10% was added, resulting in a total sample size of 16–24 rats divided equally into two groups.

Group Allocation

The animals were randomly assigned into two experimental groups. Group A consisted of TBI rats treated with *Nigella sativa* extract, whereas Group B consisted of TBI rats receiving placebo treatment with distilled water.

Induction of Traumatic Brain Injury

Traumatic brain injury was induced using the Marmarou weight-drop model. Following intraperitoneal anesthesia using ketamine cocktail (0.2 mL/50 g body weight), the scalp was shaved and disinfected with povidone-iodine. A midline scalp incision was made to expose the skull, and a metal disc was attached between the bregma and lambda. A 30 g metal weight was then dropped from a height of 80 cm onto the metal disc to induce diffuse brain injury. Body temperature was maintained at 37°C throughout the procedure.

Administration of Nigella sativa Extract

One hour after TBI induction, rats in Group A received *Nigella sativa* extract orally at a dose of 200 mg/kg body weight/day for seven consecutive days. The extract was diluted in 1 mL of distilled water before administration using an oral gavage needle. Rats in Group B received 1 mL distilled water as placebo for the same duration.

Blood Sampling and BDNF Measurement

Venous blood samples were collected from the orbital venous plexus before TBI induction (baseline), 24 hours after injury, and on days 3 and 7 after treatment. Serum BDNF levels were measured quantitatively using a Rat BDNF ELISA kit according to the manufacturer's instructions. The results were expressed in ng/mL.

Histopathological Examination

On day 7, all animals were euthanized ethically, and brain tissues were collected for histopathological evaluation. Tissue samples were stained using hematoxylin–eosin staining and examined microscopically. Necrotic cells were quantified using digital pathology analysis with ImageJ software and subsequently verified by a blinded veterinary pathologist.

Statistical Analysis

All data were tabulated and analyzed using SPSS version 27 for Windows. Normality testing was performed using the Shapiro–Wilk test. Independent sample *t*-test or Mann–Whitney U test was used to compare differences between groups, depending on data distribution. Within-group comparisons were analyzed using paired *t*-test or Wilcoxon signed-rank test. A *p*-value <0.05 was considered statistically significant.

3. RESULTS

Characteristics of Experimental Animals

This study was conducted on 16 male Wistar rats (*Rattus norvegicus*) with TBI, consisting of 8 rats treated with *Nigella sativa* extract at a dose of 200 mg/kg body weight/day orally for 7 consecutive days and 8 rats receiving placebo treatment. Serum BDNF levels were

measured before treatment (H0), 24 hours after treatment (H1), day 3 after treatment (H3), and day 7 after treatment (H7). Histopathological examination of brain tissue and necrotic cell assessment were also performed on day 7 after treatment.

All experimental animals were healthy and active male Wistar rats aged 3–4 months with body weights ranging from 200–250 g. Comparison of baseline body weight between the *Nigella sativa* and placebo groups is presented in Table 1. The analysis showed no statistically significant difference in body weight between the two groups ($p > 0.05$), indicating that both groups had homogeneous baseline characteristics prior to intervention.

Comparison of BDNF Levels Before and After Treatment with Nigella sativa Extract and Placebo

The comparison of serum BDNF levels before and after treatment in the *Nigella sativa* and placebo groups is presented in Table 2. Statistical analysis demonstrated significant changes in BDNF levels over time in both groups ($p < 0.05$). In the *Nigella sativa* group, no significant difference in serum BDNF levels was observed between baseline and day 1 after treatment ($p > 0.05$), as well as between baseline and day 3 after treatment ($p > 0.05$). However, serum BDNF levels on day 7 were significantly different compared with baseline ($p < 0.05$). In contrast, the placebo group demonstrated significant differences in serum BDNF levels between baseline and day 1, day 3, and day 7 after treatment (all $p < 0.05$).

As illustrated in Figure 8, BDNF levels in the *Nigella sativa* group initially decreased on day 1, followed by progressive increases on days 3 and 7 compared with baseline values. Conversely, the placebo group showed a continuous decline in BDNF levels over time. These findings indicate that administration of *Nigella sativa* for 7 days increased serum BDNF levels in Wistar rats with traumatic brain injury. The effect appeared to emerge from day 3 of treatment, although the increase was not statistically significant at that time point, while a significant increase was observed on day 7.

Comparison of Changes in BDNF Levels Between the Nigella sativa and Placebo Groups

The comparison of serum BDNF levels between the *Nigella sativa* and placebo groups is presented in Table 3. The analysis showed no significant difference in BDNF levels between the two groups at baseline and on day 1 after treatment ($p > 0.05$). However, significant differences in BDNF levels were observed between the groups on day 3 and day 7 after treatment ($p < 0.05$).

Evaluation of BDNF level changes demonstrated that the decrease in BDNF levels on day 1 did not differ significantly between the *Nigella sativa* and placebo groups, as both groups experienced reductions in serum BDNF levels. In contrast, significant differences in BDNF changes were identified on days 3 and 7 after treatment ($p < 0.05$). Rats treated with *Nigella sativa* extract showed progressive increases in BDNF levels, whereas rats receiving placebo exhibited continuous declines in BDNF levels over time. These findings indicate that administration of *Nigella sativa* extract exerted a positive effect on serum BDNF levels in Wistar rats with traumatic brain injury, with observable effects beginning on day 3 and becoming more pronounced after 7 days of treatment.

Comparison of Histopathological Necrosis Between the Nigella sativa and Placebo Groups

The comparison of histopathological findings, represented by the number of necrotic cells between the *Nigella sativa* and placebo groups after 7 days of treatment, is presented in Table 4. The results demonstrated a significant difference in the number of necrotic cells between rats treated with *Nigella sativa* extract and those receiving placebo ($p < 0.05$). The *Nigella sativa* group exhibited a lower number of necrotic cells compared with the placebo group, as illustrated in Figure 9. Furthermore, Table 5 shows a significant correlation between serum BDNF levels and the number of necrotic cells in Wistar rats with traumatic brain injury after 7 days of intervention ($p < 0.05$). The correlation coefficient was −0.659, indicating a moderate negative correlation between BDNF levels and necrotic cell count. These findings suggest that higher BDNF levels were associated with lower numbers of necrotic cells. The scatter plot illustrating the relationship between BDNF levels and necrotic cell count is presented in Figure 11.

4. DISCUSSION

The study showed a significant rise in serum BDNF levels after 7 days of *Nigella sativa* extract in Wistar rats with TBI, aligning with prior research on its neuroprotective effects. Nazwar (2023) found that doses of 200, 300, and 400 mg/kg significantly boosted BDNF in head-injured rats, with 400 mg/kg being most effective [14]. Kulsum et al. (2024) noted 500 mg/kg of *Nigella sativa* had better neuroplastic and neuroprotective effects than propofol in a TBI model [13]. Increased BDNF levels and neuronal repair suggest *Nigella sativa's* neuroprotective potential. Thymoquinone, *Nigella sativa's* main component, is crucial for BDNF modulation. Mamun et al. (2022) showed 25 mg/kg/day of thymoquinone for 12 weeks raised hippocampal BDNF via CREB phosphorylation [15]. Kozak et al. (2022) reported intraperitoneal thymoquinone increased serum BDNF in a methanol intoxication model, reducing inflammation and lipid peroxidation, enhancing neuroprotection [16].

Evidence from other conditions supports *Nigella sativa's* role in regulating BDNF expression. In an LPS-induced neuroinflammation model, *Nigella sativa* oil increased BDNF, with thymoquinone as the active compound [17]. In rats with metabolic syndrome, *Nigella sativa* oil for four weeks maintained BDNF regulation and reduced oxidative stress from fructose [18]. Ustunova et al. (2020) reported restored cerebral BDNF after pentylenetetrazol induction with *Nigella sativa* [19]. Clinically, *Nigella sativa's* benefits on BDNF are demonstrated. Zadeh et al. (2022) found 1000 mg/day of *Nigella sativa* oil for 10 weeks increased serum BDNF and improved depressive symptoms compared to placebo [20].

Previous findings support this study, indicating *Nigella sativa* and thymoquinone can enhance BDNF expression in neurological injury. This study showed a lower dose of *Nigella sativa* extract (200 mg/kg) for a short duration increased BDNF levels in TBI rats. Although the day 3 increase was not statistically significant, an upward trend was evident, with significant elevation on day 7. These findings suggest short-term, low-dose *Nigella sativa* can exert neurotrophic effects in traumatic brain injury. BDNF, a major neurotrophin produced by glial cells, is essential for neuronal survival, synaptic plasticity, and neurotransmitter regulation. Reduced BDNF levels are linked to neurodegenerative processes and increased neuronal vulnerability. In TBI, inflammation and oxidative stress decrease BDNF expression, worsening neuronal damage [17]. Anti-inflammatory agents like *Nigella sativa* may enhance BDNF under pathological conditions.

Nigella sativa's neuroprotective effects involve multiple pathways, with thymoquinone as the dominant component among over 35 bioactive compounds. These compounds affect inflammation, oxidative stress, and neurotrophic signaling, including BDNF regulation. Thymoquinone stimulates BDNF mRNA and protein in the hippocampus [17]. In chronic mild stress models, *Nigella sativa* reversed decreased hippocampal BDNF levels [21]. Quercetin may also enhance BDNF signaling via the TrkB receptor, stimulating ERK1/2, PI3K/Akt/mTOR, and PLCγ/IP3 pathways, promoting neuronal survival, synaptic plasticity, and apoptosis inhibition [22]. This study showed fewer necrotic cells in *Nigella sativa*-treated rats than in placebo-treated ones, indicating its neuroprotective effect against neuronal damage in TBI, especially necrotic cell death.

This result aligns with Kulsum et al. (2024), who found 500 mg/kg *Nigella sativa* extract for 7 days reduced neuronal necrosis in TBI rats more effectively than propofol or combined propofol–*Nigella sativa* therapy [13]. Though limited, evidence suggests *Nigella sativa's* dose-dependent BDNF increase reduces neuronal apoptosis, enhancing survival through BDNF regulation and reducing structural damage and necrosis [14]. This supports the present study showing higher BDNF levels correlate with fewer necrotic cells. Necrosis, an irreversible cell death, involves organelle swelling, cellular enlargement, membrane rupture, and release of components into tissues. In TBI, it occurs acutely due to impaired blood and oxygen supply with neuronal damage [23]. Histopathological studies show higher degeneration, necrosis, apoptosis, congestion, inflammatory infiltration, and hemorrhage in TBI animals than non-TBI controls [24].

At the molecular level, TBI involves multiple regulated cell death pathways: necroptosis, pyroptosis, ferroptosis, parthanatos, and cyclophilin D-mediated necrosis, which interact to worsen brain injury. Necroptosis via RIP1/RIP3 signaling may increase inflammation, release DAMPs, and inhibit autophagy through NF-κB [25]. Ferroptosis and pyroptosis worsen neuronal injury by generating ROS, lipid peroxidation, and activating the NLRP3 inflammasome. High ROS levels damage proteins, DNA, and cell membranes, accelerating necrosis. Blood–brain barrier disruption allows Ca2+ and Na+ ions in, causing mitochondrial dysfunction, ATP depletion, and neuronal death [26]. *Nigella sativa* may offer neuroprotection through antioxidant, anti-inflammatory, immunomodulatory, and neurotrophic effects. Thymoquinone reduces ROS and prevents lipid peroxidation, suppressing membrane damage and necrosis. *Nigella sativa* also inhibits nitric oxide by reducing iNOS expression and suppressing 5-lipoxygenase, lowering inflammatory leukotrienes that harm tissue [14]. Overall, this study suggests *Nigella sativa* has strong neuroprotective potential by enhancing BDNF expression and reducing neuronal necrosis in TBI.

5. LIMITATIONS

This study did not evaluate different doses of *Nigella sativa* extract administration. Another limitation of this study was that only BDNF levels were assessed without evaluating other biomarkers related to TBI. In addition, the study measured serum BDNF levels only and did not assess BDNF expression in brain tissue.

6. CONCLUSIONS

Based on the findings of the present study, it can be concluded that administration of *Nigella sativa* extract significantly increased serum BDNF levels after 7 days in Wistar rats with TBI. In contrast, placebo-treated rats demonstrated significant reductions in BDNF levels on days 1, 3, and 7 after treatment. Significant differences in BDNF changes were observed between the *Nigella sativa* and placebo groups on days 3 and 7, indicating a neurotrophic effect of *Nigella sativa* administration. Histopathological examination further revealed lower necrotic cell counts in rats treated with *Nigella sativa* compared with placebo-treated rats, suggesting a potential neuroprotective effect against neuronal damage in traumatic brain injury.

DECLARATIONS

Ethics Approval and Consent to Participate

All experimental procedures involving animals were conducted in accordance with institutional guidelines for the care and use of laboratory animals and were approved by the Ethics Committee of the Faculty of Medicine, Hasanuddin University, Makassar, Indonesia (Approval No. 42/UN4.6.4.5.31/PP36/2026).

Consent for Publication

Not applicable.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Authors' Contributions
AZM Conceptualization, methodology, investigation, data curation, formal analysis, writing—original draft preparation.

WD: Supervision, methodology, writing—review and editing.

NS: Histopathological analysis, validation, writing—review and editing.

JH: Supervision, project administration, writing—review and editing.

All authors have read and approved the final manuscript.

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7. REFERENCES

1. Sempere L, Rodríguez-Rodríguez A, Boyero L, Egea-Guerrero JJ. Experimental models in traumatic brain injury: from animal models to in vitro assays. Med Intensiva. 2019;43(6):362-372. doi:10.1016/j.medin.2018.04.012
2. Gustafsson D, Klang A, Thams S, Rostami E. The Role of BDNF in Experimental and Clinical Traumatic Brain Injury. Int J Mol Sci. 2021;22(7). doi:10.3390/IJMS22073582
3. Chen C, Hou J, Lu J, et al. A novel simple traumatic brain injury mouse model. Chinese Neurosurgical Journal 2022 8:1. 2022;8(1):8-. doi:10.1186/S41016-022-00273-5
4. Khan RU, Jawad SM, Kiyani MM, Shah SA, Bashir S, Khan H. Nigella sativa extract abrogates traumatic brain injury-induced memory impairment in adult mice. Heliyon. 2024;10(18). doi:10.1016/j.heliyon.2024.e38106
5. Kumar M, Chaudhary J, Jain A. The Intricacy of Subsequent Pathway Resulting from Traumatic Brain Injury: Pathophysiology and Possible Interventions. Curr Behav Neurosci Rep. 2025;12(1). doi:10.1007/S40473-025-00300-6
6. Ng SY, Lee AYW. Traumatic Brain Injuries: Pathophysiology and Potential Therapeutic Targets. Front Cell Neurosci. 2019;13. doi:10.3389/FNCEL.2019.00528
7. Mihaylova A, Doncheva N, Vlasheva M, et al. Investigation of the Immunomodulatory and Neuroprotective Properties of Nigella sativa Oil in Experimental Systemic and Neuroinflammation. Int J Mol Sci. 2025;26(5). doi:10.3390/IJMS26052235
8. Giesler LP, Mychasiuk R, Shultz SR, McDonald SJ. BDNF: New Views of an Old Player in Traumatic Brain Injury. Neuroscientist. 2024;30(5):560-573. doi:10.1177/10738584231164918;PAGE:STRING:ARTICLE/CHAPTER
9. Korley FK, Diaz-Arrastia R, Wu AHB, et al. Circulating Brain-Derived Neurotrophic Factor Has Diagnostic and Prognostic Value in Traumatic Brain Injury. J Neurotrauma. 2016;33(2):215-225. doi:10.1089/NEU.2015.3949
10. Ramadan MFawzy. Black cumin (Nigella sativa) seeds : chemistry, technology, functionality, and applications. Published online 2021.
11. Gawas CG, Mathur S, Wani M, Tabassum H. Nigella sativa and its nano-mediated approach toward management of neurodegenerative disorders: A review. Ibrain. 2023;9(1):111-123. doi:10.1002/IBRA.12091
12. KAMASAK K, BASARSLAN K, DAGLI AT, et al. Effects of Nimodipine and Nigella sativa on Oxidative Stress and Apoptosis in Serum and Brain Tissue of Rats with Experimental Head Trauma. Turk Neurosurg. 2021;31(1):8-17. doi:10.5137/1019-5149.JTN.25523-19.3
13. Kulsum K, Syahrul S, Hasbalah K, Balqis U. Effect of ethanol extract of nigella sativa L seeds and propofol on BDNF protein level as neuroplasticity and neuroprotection of traumatic brain injury in rats. F1000Res. 2024;13. doi:10.12688/F1000RESEARCH.142054.2/DOI
14. Alfandy Nazwar T, Balafif F, Wisnu Wardhana D, et al. Potential of Nigella Sativa on Anti or Pro-apoptotic Pathway After Brain Injury Via Brain-derived Neurotrophic factor on Rattus Norvegicus Wistar. Teikyo Medical Journal. 2023;46(1):7683-7696.
15. Al Mamun A, Matsuzaki K, Islam R, et al. Chronic Administration of Thymoquinone Enhances Adult Hippocampal Neurogenesis and Improves Memory in Rats Via Regulating the BDNF Signaling Pathway. Neurochem Res. 2022;47(4):933-951. doi:10.1007/S11064-021-03495-8
16. Kozak HH, Kilinc I, Ozkurkculer A. Acute and subacute effects of thymoquinone on acute methanol intoxication: An assessment based on serum TBARS and BDNF levels in rat model. Marmara Medical Journal. 2022;35(2):127-131. doi:10.5472/MARUMJ.1089689

17. Mihaylova A, Doncheva N, Vlasheva M, et al. Investigation of the Immunomodulatory and Neuroprotective Properties of Nigella sativa Oil in Experimental Systemic and Neuroinflammation. International Journal of Molecular Sciences 2025, Vol 26, Page 2235. 2025;26(5):2235. doi:10.3390/IJMS26052235

18. Alayunt NO, Kayaoglu Y, Yilmaz M, Ustundag B. Nigella Sativa Oil Improves Oxidative Stress, Inflammation and Changes in Neurotransmitter Structures in Fructose-Induced Metabolic Syndrome. Euroasia Journal of Mathematics, Engineering, Natural & Medical Sciences International Indexed and Refereed. 2023;10(29):128-138. doi:10.5281/zenodo.8416168

19. Ustunova S, Meral İ, Koçyiğit A, et al. Effects of Nigella sativa on Plasma Oxidative Stress, and Some Apoptotic Protein Markers in Cerebrum and Hippocampus in Pentylenetetrazol Induced-Kindling Rats. European Journal of Biology. 2020;79(2):124-131. doi:10.26650/EurJBiol.2020.0088

20. Zadeh AR, Eghbal AF, Mirghazanfari SM, Ghasemzadeh MR, Nassireslami E, Donyavi V. Nigella sativa extract in the treatment of depression and serum Brain-Derived Neurotrophic Factor (BDNF) levels. J Res Med Sci. 2022;27(1):28. doi:10.4103/JRMS.JRMS_823_21

21. Nazir S, Farooq RK, Nasir S, Hanif R, Javed A. Therapeutic effect of Thymoquinone on behavioural response to UCMS and neuroinflammation in hippocampus and amygdala in BALB/c mice model. Psychopharmacology (Berl). 2022;239(1):47-58. doi:10.1007/S00213-021-06038-9

22. Andriana K, Nurdiana, Barlianto W, Wiyasa IWA, Rahayu M. Effect of Nigella sativa L. extract on improving memory function through reducing GSK3β activation and Aβ42/40 ratio. J Pharm Pharmacogn Res. 2022;10(2):328-337. doi:10.56499/JPPRES21.1211_10.2.328

23. Osier ND, Carlson SW, DeSana A, Dixon CE. Chronic Histopathological and Behavioral Outcomes of Experimental Traumatic Brain Injury in Adult Male Animals. J Neurotrauma. 2015;32(23):1861-1882. doi:10.1089/NEU.2014.3680

24. Suryadi T, Kulsum K. Comparison between premortem histopathology findings in rats with and without traumatic brain injury: prospective application in forensic medicine. F1000Research 2024 12:1311. 2024;12:1311. doi:10.12688/f1000research.140718.2

25. Nie Z, Tan L, Niu J, Wang B. The role of regulatory necrosis in traumatic brain injury. Front Mol Neurosci. 2022;15:1005422. doi:10.3389/FNMOL.2022.1005422/FULL

26. Kursancew ACS, Faller CJ, Bortoluzzi DP, et al. Neuroinflammatory Response in the Traumatic Brain Injury: An Update. Neurochem Res. 2025;50(1). doi:10.1007/S11064-024-04316-4

Tables and Figures

Table 1: Comparison of Body Weight Between the Two Groups

Group	Body Weight (Mean ± SD)	Shapiro–Wilk Normality Test (*p*-value)	Independent Sample *t*-test (*p*-value)
Nigella sativa	237.00 ± 14.97	0.909	0.320
Placebo	228.75 ± 16.97	0.690	

Table 2. Comparison of BDNF Levels Before and After Treatment in the Nigella sativa and Placebo Groups

BDNF Levels (ng/mL)	*Nigella sativa*		Placebo	
	Mean ± SD	*p*-value	Mean ± SD	*p*-value
All time points[a]				
H0, H1, H3, H7	–	0.009	–	< 0.001
Between time points[b]				
H0 and H1	−0.001 ± 0.008	0.720	−0.005 ± 0.004	0.005
H0 and H3	0.002 ± 0.007	0.526	−0.008 ± 0.006	0.007
H0 and H7	0.007 ± 0.008	0.031	−0.012 ± 0.007	0.001

Notes: [a]Repeated Measures ANOVA; [b]Paired *t*-test; H0 = before treatment (day 0), H1 = day 1 after treatment, H3 = day 3 after treatment, H7 = day 7 after treatment.

Table 3. Comparison of BDNF Levels Between the Nigella sativa and Placebo Groups

Time Point	*Nigella sativa* Extract (n = 8) Mean ± SD	Placebo (n = 8) Mean ± SD	*p*-value
H0	0.133 ± 0.007	0.135 ± 0.007	0.637

H1	0.132 ± 0.005	0.129 ± 0.009	0.495
H3	0.135 ± 0.005	0.127 ± 0.006	0.018
H7	0.140 ± 0.006	0.122 ± 0.007	< 0.001
Delta H0–H1	−0.001 ± 0.008	−0.005 ± 0.004	0.182
Delta H0–H3	0.002 ± 0.007	−0.008 ± 0.006	0.013
Delta H0–H7	0.007 ± 0.008	−0.012 ± 0.007	< 0.001

Independent sample t-test.

Table 4. Comparison of Necrotic Cell Counts Between the Nigella sativa and Placebo Groups

Parameter	*Nigella sativa* Extract (n = 8) Mean ± SD	Placebo (n = 8) Mean ± SD	*p*-value
Necrotic cell count	3164.13 ± 771.38	4028.38 ± 204.58	0.008

Independent sample t-test.

Table 5. Correlation Between BDNF Levels and Necrotic Cell Counts

Variable	N	Mean	r	*p*-value
BDNF	8	0.131	−0.659	0.006
Necrotic cell count	8	3596.25		

Pearson correlation test.

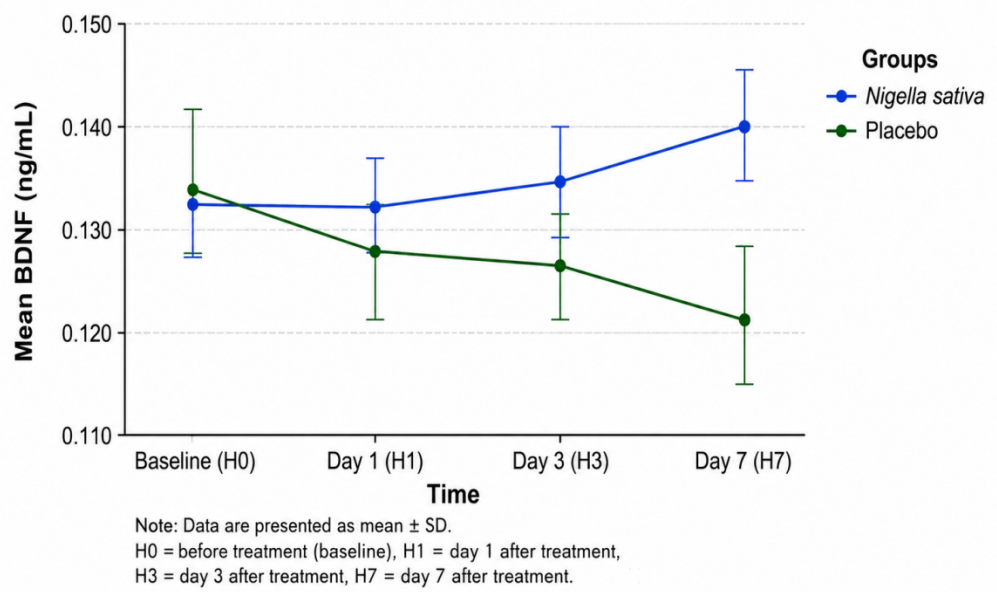

Figure 1. Changes in Mean Serum BDNF Levels Between the Nigella sativa and Placebo Groups

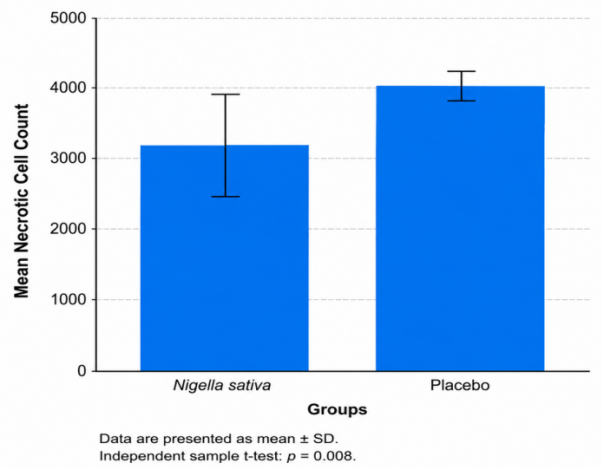

Figure 2. Comparison of Necrotic Cell Counts After 7 Days of Treatment Between the Nigella sativa and Placebo Groups

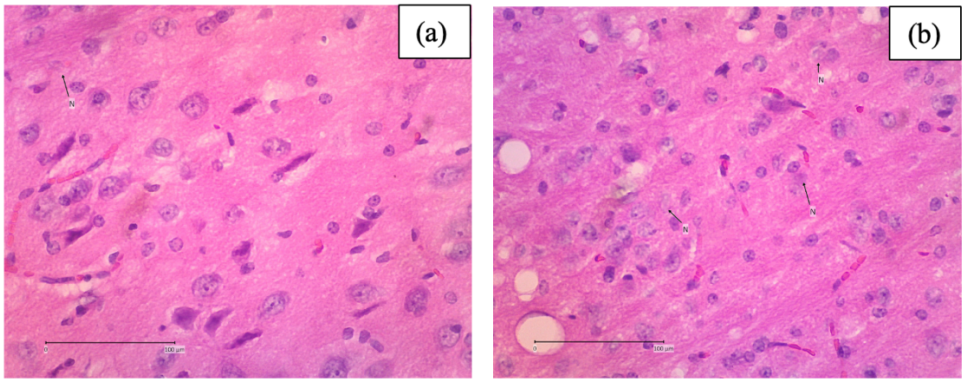

Figure 3. Histopathological Findings of Brain Tissue in TBI Rats After Treatment: (a) Nigella sativa Group and (b) Placebo Group, with Necrotic Cells Indicated by Arrows (40× Magnification)

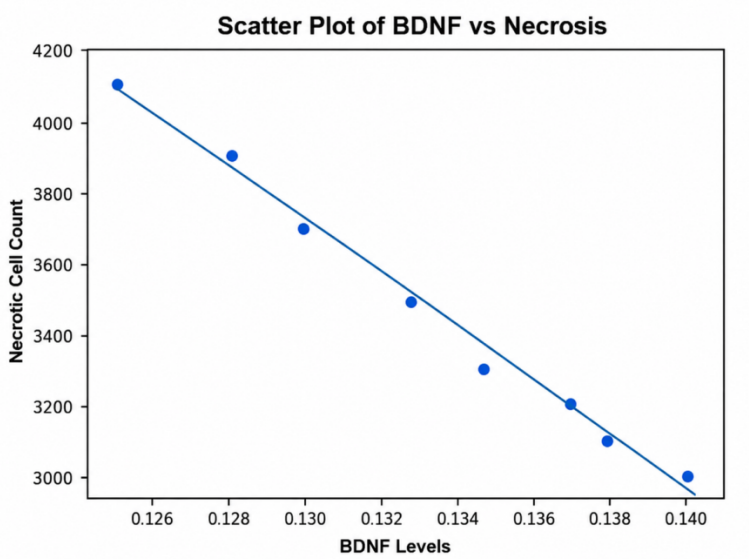

Figure 4. Interpolation Line Scatter Plot Showing the Relationship Between BDNF Levels and Necrotic Cell Counts