Research article

Antidepressant effect of teriflunomide via oligodendrocyte protection in a mouse model

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A B S T R A C T

Addressing the treatment of depression is crucial; nevertheless, the etiology and pathogenesis remain unelucidated. Therefore, this study investigated the effects of teriflunomide (TF) on corticosterone (CORT)-induced depression-like behaviors in mice. Notably, TF administration resulted in a substantial amelioration of anxiety and depression-like behaviors observed in CORT-treated mice. This was evidenced by behavioral assessments conducted via the sucrose preference test (SPT), open-field test (OFT), novelty-suppressed feeding test (NSFT), forced swimming test (FST), and tail suspension test (TST). The administration of CORT inflicts damage upon oligo-dendrocytes and neurons within the hippocampus. Our findings indicate that TF offers significant protective effects on oligodendrocytes, mitigating apoptosis both *in vivo* and *in vitro*. Additionally, TF was found to counteract the CORT-induced neuronal loss and synaptic damage, as demon-strated by an increase in Nissl-positive cells across hippocampal regions CA1, CA3, and the dentate gyrus (DG) alongside elevated levels of synapse-related proteins including PSD-95 and synaptophysin. Additionally, TF treatment facilitated a reduction in the levels of apoptosis-related proteins while simultaneously augmenting the levels of Bcl2. Our findings indicate that TF administration effectively mitigates CORT-induced depression-like behaviors and reverses dam-age to oligodendrocytes and neurons in the hippocampus, suggesting TF as a promising candidate for depression.

1. Introduction

Major depressive disorder (MDD) presents substantial challenges to the physical and mental health of patients and is thus cate-gorized as a serious emotional and mental ailment. Individuals diagnosed with MDD are frequently confronted with an elevated risk of suicide, underscoring the gravity of this condition [1,2]. The advent of the COVID-19 pandemic has only served to intensify adverse social determinants, taking a significant toll on the mental well-being of populations worldwide [3,4]. Given these circumstances, it is imperative to prioritize the prevention, identification, and effective treatment of depression [5].

The hippocampus stands as a crucial neural structure that is intricately connected to both cognitive and emotional processes. This structure plays a pivotal role in modulating stress responses and memory functions, rendering it susceptible to a spectrum of internal

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Abbreviations

CORT	corticosterone
CUS	chronic unpredictable stress
CNS	central nervous system
FST	forced swimming test
LPS	lipopolysaccharide
MBP	Myelin basic protein
MDD	Major depressive disorder
MS	multiple sclerosis
NAc	nucleus accumbens
NSFT	novelty-suppressed feeding test
OFT	open-field test
OPCs	oligodendrocyte precursor cells
PFC	prefrontal cortex
PVDF	polyvinylidene difluoride
SPT	sucrose preference test
TF	teriflunomide
TST	tail suspension test

and external stressors [6–8]. Autopsy and neuroimaging studies have consistently demonstrated a reduction in hippocampal volume in patients with MDD, further solidifying the link between hippocampal atrophy and this psychiatric disorder [9–11]. While hippocampal atrophy in animal models of depression is prevalent, suggesting a strong correlation with the pathological trajectory of depression, initial attributions of this atrophy to extensive neuronal death have been revised [12–14]. Subsequent research endeavors have unearthed the pivotal role of glial cells in this context, particularly highlighting their contribution to hippocampal atrophy [15]. It has become increasingly evident that disruptions in the homeostasis of cellular composition within the hippocampus may render individuals more vulnerable to psychiatric conditions [16].

Recent scientific explorations have shifted toward understanding the pathogenesis and potential preventative measures for depression through the lens of interactions between glial cells and neurons. As a specific type of glial cell, oligodendrocytes function in tandem with neurons, playing a vital role in sustaining normal brain functionality and behavior [17,18]. The primary function of oligodendrocytes is to support and protect neurons by creating myelin sheaths, which help to accelerate nerve impulse transmission and maintain the overall function and balance of the nervous system [19]. A notable reduction in oligodendrocyte number has been observed in the amygdalae of patients diagnosed with MDD, accompanied by a significant downregulation of genes and proteins associated with oligodendrocytes in the ventral prefrontal white matter [20]. Such diminished oligodendrocyte functionality is not confined to human subjects; rodent models of stress-induced depression-like phenotypes have also exhibited this trait [21]. Furthermore, preclinical studies have demonstrated that exposure to chronic unpredictable stress (CUS) precipitates a decrease in both the number and proliferation of glial cells within the prefrontal cortex (PFC) [22]. Various established models of depression, ranging from CUS to lipopolysaccharide (LPS) exposure, feature demyelination and synaptic deficits as direct consequences of oligodendrocyte damage [23,24]. This has led to the proposition that safeguarding oligodendrocytes may unlock new avenues for the development of innovative antidepressant therapies [25].

Recognized as an oral immunomodulatory agent, teriflunomide (TF) has been approved for treating multiple sclerosis (MS). Upon reaching serum concentrations between 1 % and 2 %, TF is capable of traversing the blood-brain barrier and directly impacting the central nervous system (CNS) [26,27]. Empirical evidence from *Xenopus laevis* and mouse studies showed TF to protect oligodendrocytes while mitigating demyelination at nanomolar concentrations [28,29]. In rodent models specific to MS, TF has demonstrated efficacy in preserving myelin and oligodendrocytes, largely by curtailing the influx of immune cells into the CNS [30]. Moreover, TF actively promotes oligodendrocyte formation through the modulation of critical transcription factors, including the p73 signaling pathway [28]. Despite these promising findings, a knowledge gap exists regarding TF's potential to alleviate depression via oligodendrocyte protection.

Clinical studies have shown that serum cortisol levels are elevated in patients with depression, and long-term administration of glucocorticoids such as CORT can induce depressive-like behaviors in experimental animals [31]. In the present study, a mouse model of depression was established by chronic administration of corticosterone (CORT), and changes in the hippocampal oligodendrocytes of depressed mice were observed. In addition, the study investigated whether TF can prevent depression-like behaviors and pathological changes in depressed mice. Our results indicated that TF administration ameliorated CORT-induced depression-like behaviors, and reversed oligodendrocyte damage and synaptic abnormalities in the hippocampus. These results indicated that TF may be an effective therapeutic agent for depression. Our study provides evidence for the novel clinical value of TF in treating depression.
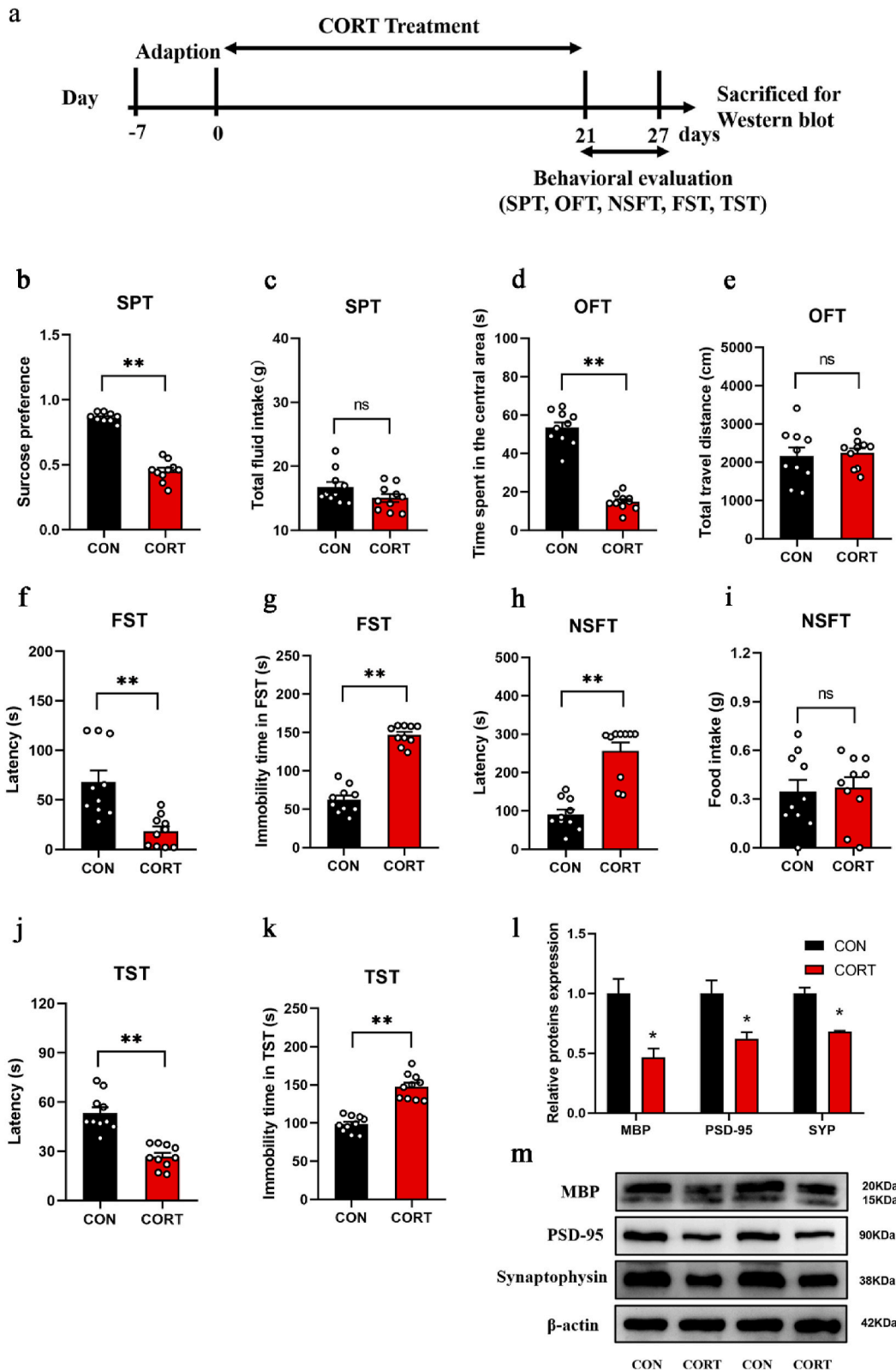
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Fig. 1. Chronic and continuous CORT treatment induced depression-like behaviors and hippocampal oligodendrocyte damage in mice. (a) Experiment procedure. Sucrose preference (b) and total fluid consumption (c) in SPT. Time spent in the central area (d) and total travel distance (e) in OFT. The latency to immobility (f) and immobility time (g) in FST. The latency to feed (h) and home cage consumption (i) in NSFT. The latency to immobility (j) and immobility time (k) in TST (n = 10). Levels of MBP, PSD-95, and Synaptophysin were measured by Western blotting (m) and quantified (l) (n = 3). Data were expressed as mean ± SEM. *$p < 0.05$, **$p < 0.01$ vs. CON group; ns means *$p > 0.05$*, no statistical difference.

2. Materials and methods

2.1. Animals

C57BL/6J male mice (8 weeks old) were procured from Hunan Slake Jingda Laboratory Animal Co. LTD and acclimatized for 1 week under controlled conditions (12 h light/dark cycle starting at 21:00, 60 % humidity, and 24 ± 1 °C temperature), with free access to food and water. All experimental procedures adhered to the Hunan Province's Guide for the Care and Use of Laboratory Animals, and the Local Committee on Animal Care, Use, and Protection at Hunan Normal University granted approval.

2.2. Reagents

CORT (T0948L, TargetMol, USA) and TF (T7534, TargetMol, USA) were administered following the protocols of previous studies in dosage [32,33]. Subcutaneous administrations of CORT (20 mg/kg, 1 ml/kg, dissolved in 5 % DMSO and 95 % corn oil) and intragastric administrations of (10 mg/kg, 1 ml/kg, dissolved in saline with 0.6 % sodium carboxymethyl cellulose and 5 % DMSO) TF were performed daily. The corresponding solvent in the control group was consistent with that in the administration group.

2.3. Experimental design

Experiment 1 involved two groups: CON (n = 10) and CORT (n = 10), with the latter receiving subcutaneous CORT injections for 21 days and the former receiving vehicle. Behavioral tests occurred on day 22 and lasted for 6 days. The animals were sacrificed 24 h after the last behavioral test (Fig. 1a).

In Experiment 2, animals were categorized into four groups: CON (n = 9), CON + TF (n = 9), CORT (n = 9), and CORT + TF (n = 9). For 21 days, the CON and CON + TF groups received subcutaneous vehicle injections, with CON + TF also receiving intragastric TF for the last 10 days. The CORT and CORT + TF groups received subcutaneous CORT injections for 21 days, with CORT + TF also receiving intragastric TF for the preceding 10 days. Behavioral tests for depression-like behaviors were conducted sequentially starting from the 33rd day and lasted for 6 days. The animals were sacrificed 24 h after the last behavioral test (Fig. 3a).

2.4. Behavioral evaluation

All behavioral tests occurred during the dark phase (9:00 a.m.–9:00 p.m.), following this order: sucrose preference test (SPT), open field test (OFT), novelty-suppressed feeding test (NSFT), forced swimming test (FST), and tail suspension test (TST). To avoid interference between tests as much as possible, a 24-h interval was maintained between different tests.

2.4.1. Sucrose preference test

The Sucrose Preference Test followed an established and optimized protocol [34] in which mice adapted to 1 % sucrose water for 48 h followed by a 24-h deprivation. Testing involved single housing and provision of two bottles, one with 1 % sucrose and the other with tap water, for 12 h. Bottle positions were swapped after 6 h to prevent side preference. Consumption of sugar water and pure water was calculated based on post-experiment bottle weights.

2.4.2. Open field test

To assess general locomotion and anxiety-like behavior, an Open Field Test (OFT) was conducted in accordance with a modified version of a previously established procedure [35]. The apparatus comprised a square arena (50 × 50 × 40 cm) with an open top. Mice were then individually placed at the center in a dark environment, and their movements were tracked for 5 min using a camera system. The apparatus was thoroughly cleaned with 75 % ethanol between tests to eliminate olfactory cues. Parameters such as time spent in the central area and total distance traveled were quantified using the SuperMaze video analysis software (Shanghai XinRuan Information Technology Co., Ltd).

2.4.3. Novelty-suppressed feeding test

The NSFT was conducted to evaluate the animals' anxiety-like behavior under novel conditions, following protocols established in previous studies [36]. Mice underwent a 24-h period of food deprivation prior to the test. During the 5-min test session, mice were then placed in one corner of an open-field arena (50 × 50 × 40 cm) which contained small food pellets placed at the center on a white paper sheet (10 × 10 cm). Latency to feed, defined as the time taken by the mice to initiate feeding, was recorded. To control for potential effects of food deprivation, total food consumption was measured for 5 min after returning the animals to their home cages.

2.4.4. Forced swimming test

The FST was utilized to assess depressive-like behavior, and the procedure was conducted as per previously established guidelines [37]. Mice were individually placed in a transparent cylindrical container filled with water (temperature: 23 ± 2 °C) maintained at a depth of 15–18 cm. The test duration was 6 min, during which the time is taken by the mice to exhibit immobility in the initial 2 min, as well as the total duration of immobility in the final 4 min, were meticulously recorded. Immobility was defined as minimal movement, sufficient only to keep the mice afloat, with occasional gentle movements to prevent submersion.

2.4.5. Tail suspension test

Depressive-like behavior was further evaluated using the TST, performed in accordance with established protocols [38]. Each mouse was suspended by its tail in a specialized enclosure ($60 \times 60 \times 40$ cm), ensuring that its head was elevated above the enclosure's floor. The test lasted for 6 min, during which both the latency to immobility within the initial 2 min and the total immobility time in the last 4 min were recorded.

2.5. Nissl staining

Following behavioral assessments, mice were euthanized and perfused with 4 % paraformaldehyde, and their brains were subsequently harvested. Brain tissue underwent a series of gradient dehydration steps using 10 % and 30 % sucrose solutions, followed by freezing and sectioning into 25-μm slices. The hippocampal regions of these sections were then stained using a Nissl Staining Kit (G1430, Solarbio, China) as per the manufacturer's protocol. The stained sections were then imaged, and subsequent analyses were conducted using ImageJ software.

2.6. Cell culture and treatments

The OLN-93 cell line, a permanent oligodendroglial cell line derived from neonatal rat brains, serves as a valid model for studying oligodendrocyte proliferation and differentiation [39–41]. These oligodendrocyte cells were cultured in Dulbecco's Modified Eagle's Medium (DMEM; Gibco) supplemented with 10 % fetal bovine serum (FBS; Biological Industries) and maintained at 37 °C in a humidified incubator with 5 % CO2. The medium was refreshed every 2 days, and the cells were subcultured at a 1:4 ratio bi-daily. For experimental treatments, cells were pre-exposed to TF at concentrations of 12.5 μM and 50 μM for 1 h, followed by a 24-h incubation with CORT at a concentration of 250 μM. A CCK-8 assay was subsequently employed to assess the impacts of these specific concentrations of CORT and TF on cell viability.

2.7. Cell counting kit-8 assay

The CCK-8 assay was conducted using a CCK-8 kit (C0005; TargetMol, USA) and commenced with seeding 100 μL of the cell suspension in each well of a 96-well plate, followed by a 24-h incubation at 37 °C in a 5 % CO2 incubator. Subsequently, 10 μL of CCK-8 solution was added directly to each well, with thorough mixing ensured. The plate was incubated for an additional 3 h, shaken for approximately 1 min, and the absorbance at 450 nm was measured using a microplate reader. This process facilitated the calculation of cell activity.

2.8. Western blot analysis

Proteins were extracted from both whole hippocampal tissues of mice and the treated cell samples. The protein concentrations in the supernatants were determined using a BCA protein assay kit (Solarbio, PC0020, Beijing, China), with the manufacturer's instructions followed. The proteins were then separated via 10 % SDS-PAGE (Seven, SW143-02, Beijing, China) and transferred onto polyvinylidene difluoride membranes. The membranes were subsequently cut based on molecular weight in accordance with the protein marker and blocked with 5 % BSA in TBST (TBS containing 0.1 % Tween-20). Overnight incubation at 4 °C was carried out using a variety of primary antibodies: anti-MBP (1:800, 10458-1-AP, Proteintech, USA), anti-Bcl2 (1:800, A20736, ABclonal, China), anti-Bax (1:1000, AF1270, Beyotime, China), anti-Caspase-3 (1:1000, AF0081, Beyotime, China), anti-cleaved Caspase-3 (1:1000, 9664, Cell Signaling Technology, USA), anti-β-actin (1:40000, AC026, ABclonal, China), anti-PSD-95 (1:1000, AF1096, Beyotime, China), Anti-Iba1 (1:4000, ET1705-78, HUABIO, China) and anti-Synaptophysin (1:1000, AF8091, Beyotime, China). This was followed by a 90-min incubation with anti-rabbit or anti-mouse secondary antibodies, and the membranes were subsequently scanned using the Tanon-5200 imaging system (Shanghai, China). After synaptophysin imaging, the membrane underwent immersion in an antibody eluent, facilitating antibody elution. Additionally, 1-h incubation with anti-β-actin was carried out at room temperature followed by a 90-min incubation with rabbit II antibody (1:1000, A0208, Beyotime) and subsequent imaging. ImageJ software was utilized for the quantification of all images.

2.9. Statistical analysis

The data are presented as mean $\pm$ SEM and were analyzed using GraphPad Prism 5.01 and Microsoft Office 2016 software. Statistical evaluations were conducted employing either one-way or two-way ANOVA, followed by Tukey's post-hoc test. A p-value less than 0.05 was considered to denote statistical significance.

3. Results

3.1. Chronic and continuous CORT treatment induced depression-like behaviors and nerve cells hippocampal oligodendrocyte damage in mice

When used for an extended period, glucocorticoids such as CORT have been associated with the induction of depression-like behaviors in animal models [31]. Preliminary experiments showed that TF had no statistical difference on the microglia marker (Iba1) (Fig. 5j–k). Previous research has shown that there are no effects of TF on astrocytes in culture or *in vivo* models [42]. To validate our animal model and investigate the impact on oligodendrocytes associated with depression, we conducted a series of behavioral tests 21 days post-CORT administration (Fig. 1a). The results revealed a significant decrease in sucrose preference values in the CORT group compared with those in the CON group (Fig. 1b, **$p < 0.01$), while the total fluid intake of the CON group and the CORT group remained unchanged (Fig. 1c, $p > 0.05$), indicative of anhedonia, a core symptom of depression. Additionally, the CORT group displayed increased immobility time and reduced latency to immobility in both the FST and TST, further confirming the presence of depression-like behaviors (Fig. 1f, g, j, k, **$p < 0.01$).

Analysis of anxiety-like behaviors showed that the CORT group spent less time in the central area of the OFT (Fig. 1d, **$p < 0.01$), despite no changes in overall locomotion (Fig. 1e, $p > 0.05$). In the NSFT, the CORT group exhibited increased latency to feed (Fig. 1h, **$p < 0.01$), while total food intake remained constant (Fig. 1i, $p > 0.05$), suggesting an increase in anxiety-like behaviors. Collectively, these behavioral tests demonstrated the successful induction of anxiety- and depression-like behaviors in the mice following chronic CORT treatment.

On examining the hippocampus for changes in oligodendrocyte integrity, we observed a reduction in Myelin Basic Protein (MBP)
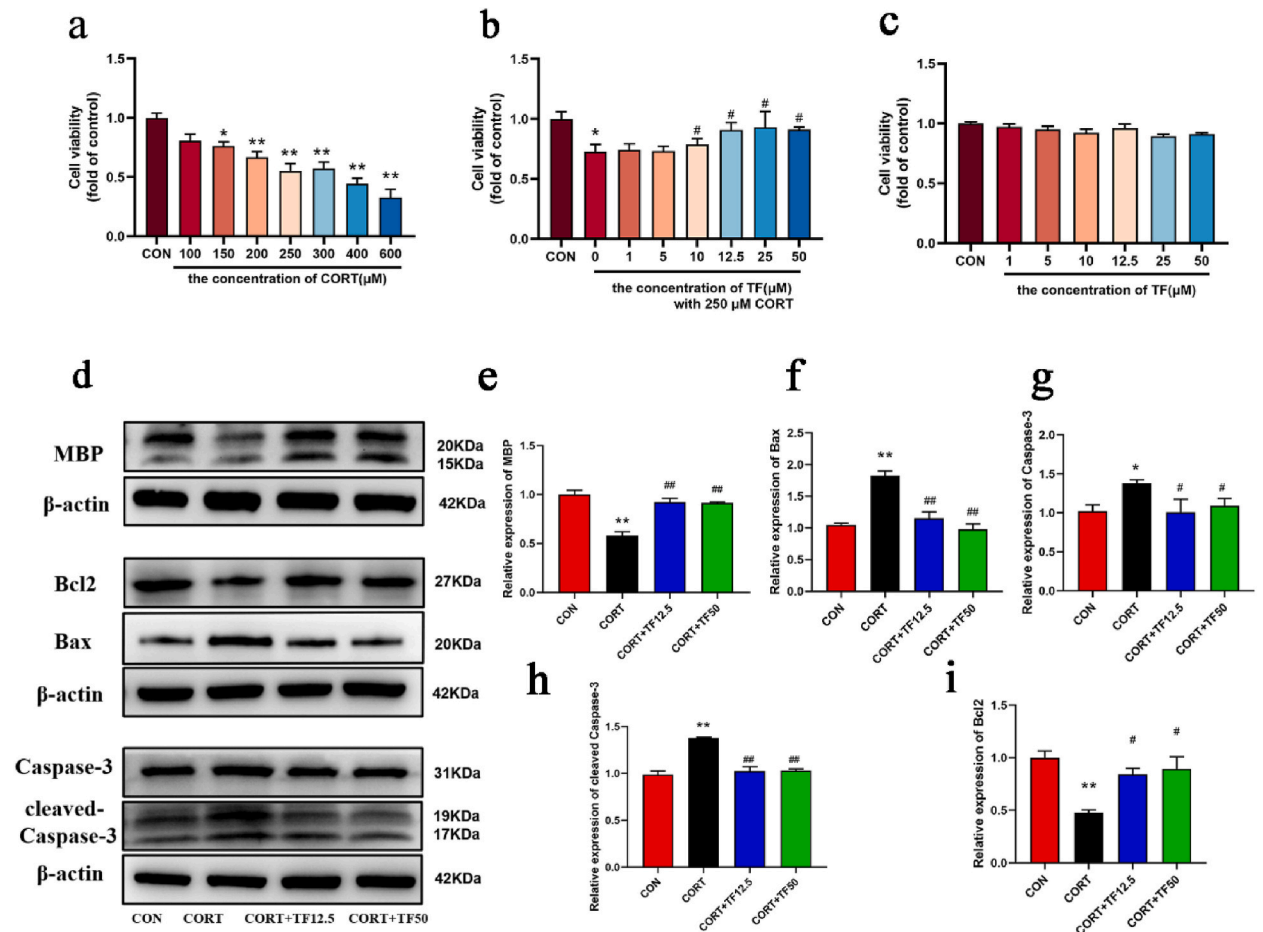

Fig. 2. TF ameliorated CORT-induced cytotoxicity in OLN-93 cells. (a) OLN-93 cells were treated with different concentrations (0, 100, 150, 200, 250, 300, 400, or 600 μM) of CORT for 24 h, and the cell viability was measured by CCK-8. (b) OLN-93 cells were treated with 250 μM CORT and TF at different concentrations (0, 1, 5, 10,12.5, 25, or 50 μM) for 24 h, and the cell viability was assessed by CCK-8. (c) OLN-93 cells were treated with different concentrations (0, 1.5, 10,12.5, 25, or 50 μM) of TF for 24 h, and cell viability was assessed by CCK-8. Measurements of CCK-8 assays were presented as mean ± SEM (n = 6). (d–i) Levels of apoptosis-related proteins and MBP were measured by Western blotting and quantified. Results were expressed as mean ± SEM (n = 4). *$p < 0.05$, **$p < 0.01$ vs. CON group; # $p < 0.01$ vs. CORT group.
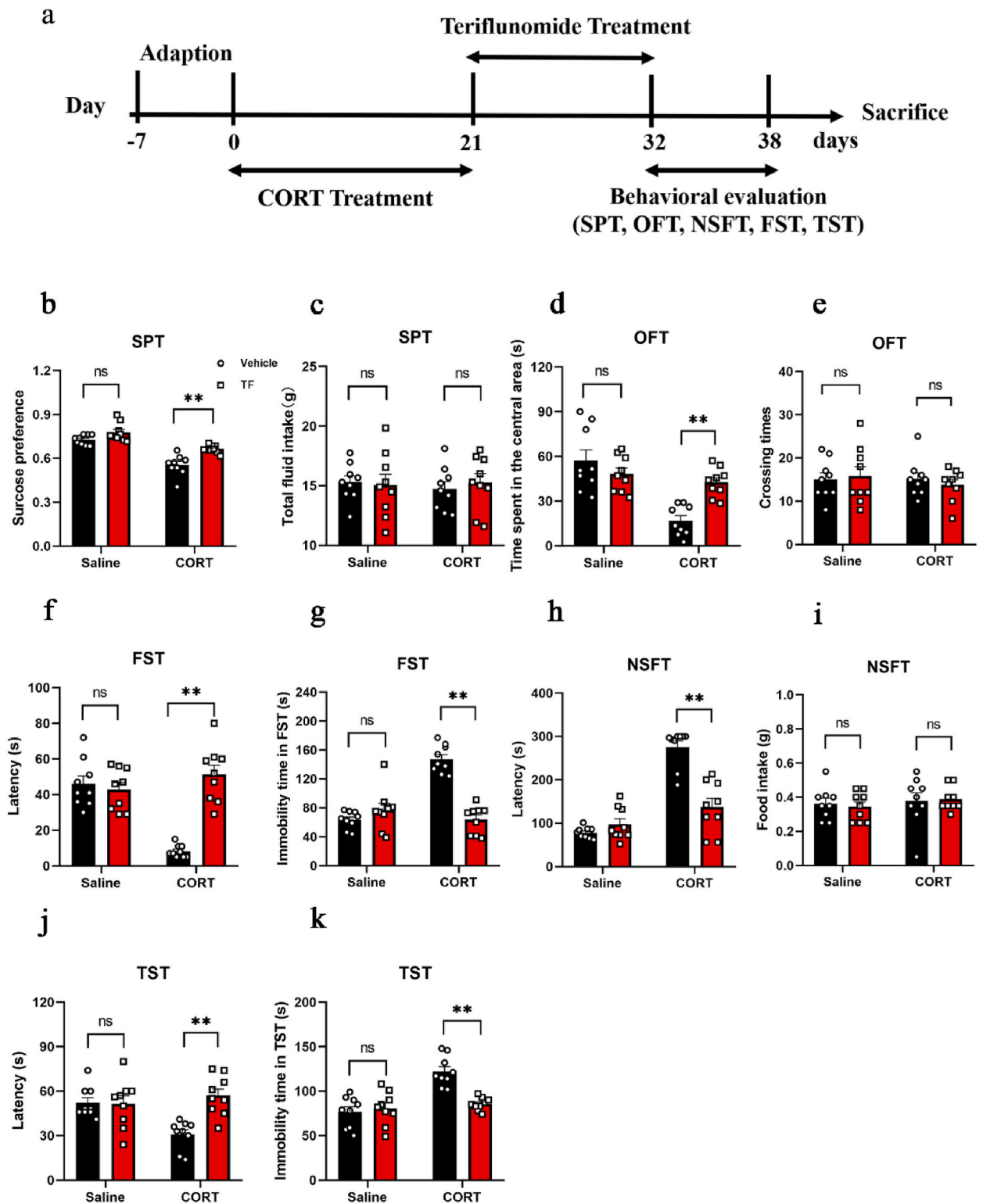
Fig. 3. TF mitigated CORT-induced depression-like behaviors in mice. (a) Experiment procedure. Sucrose preference (b) and total fluid consumption (c) in SPT. Time spent in the central area (d) and crossing times (e) in OFT. The latency to immobility (f) and immobility time (g) in FST. The latency to feed (h) and home cage consumption (i) in NSFT. The latency to immobility (j) and immobility time (k) in TST. Data were expressed as mean ± SEM (n = 9). *$p < 0.05$, **$p < 0.01$ vs. CON group; #$p < 0.05$, ##$p < 0.01$ vs. CORT group; ns means $p < 0.05$ no statistical difference; the CON group: saline + vehicle; the TF group: saline + TF; the CORTgroup: CORT + Vehicle; the CORT + TF group: CORT + TF.
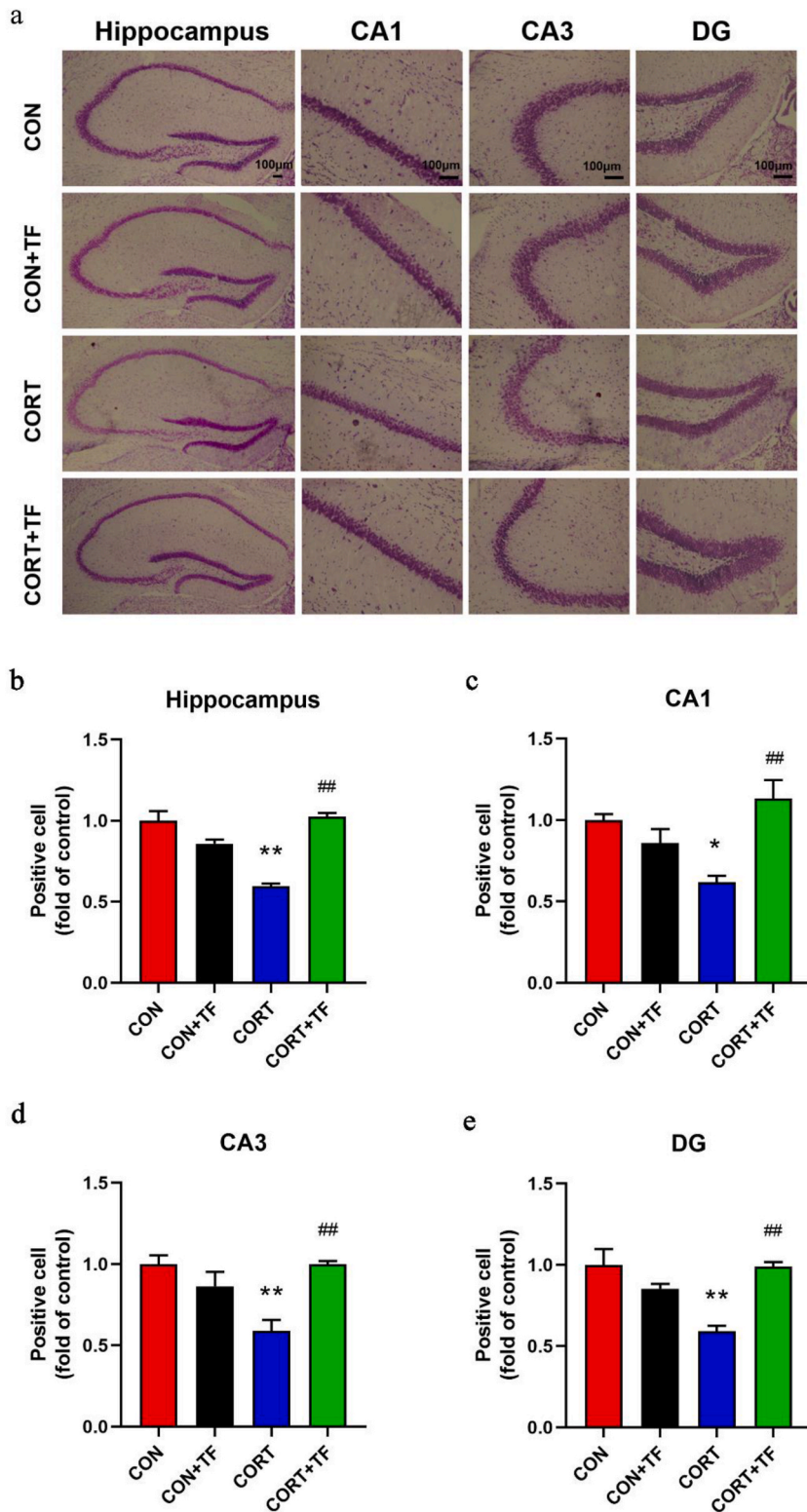
Fig. 4. TF attenuated CORT-induced hippocampal neuronal damage. (a) Neurons in the hippocampus, CA1, CA3, and DG regions were detected by Nissl staining. (b–e) The Nissl-positive cells in the hippocampus were quantified by ImageJ. Scale bar = 100 μm. Data were expressed as mean ± SEM (n = 3). *$p < 0.05$, **$p < 0.01$ vs. CON group; ##$p < 0.01$ vs. CORT group.

levels, a typical marker of oligodendrocytes [39], in the CORT group compared with that in the control, suggesting oligodendrocyte damage in this depression model ($p < 0.05$; Fig. 1l and m). In addition, levels of PSD-95 and Synaptophysin (SYP), markers of synaptic integrity, were reduced in the CORT group, indicating impaired synaptic plasticity ($p < 0.05$; Fig. 1l and m). Given the role of oligodendrocytes in maintaining neural homeostasis and supporting synaptic communication [19,43], our data suggest that protecting oligodendrocytes may also confer protection to hippocampal neurons from stress-induced injury.

3.2. TF ameliorated CORT-induced cytotoxicity in OLN-93 cells

To assess the protective effects of TF against CORT-induced cellular damage, we utilized the OLN-93 oligodendrocyte cell line. Fig. 2a demonstrates the dose-dependent cytotoxic effects of CORT, with concentrations ranging from 100 to 600 µM. Based on these results, we selected 250 µM CORT for subsequent experiments, as it induced a roughly 45 % reduction in cell viability. Co-treatment with TF (10–50 µM) in the presence of CORT resulted in a dose-dependent increase in cell survival, indicating the protective effects of TF (Fig. 2b). Notably, TF treatment alone did not affect cell viability (Fig. 2c).

Further exploration of TF's protective mechanisms using concentrations of 12.5 µM and 50 µM revealed its impact on apoptosis-related proteins in OLN-93 cells (Fig. 2d). Quantitative analysis demonstrated that CORT treatment upregulated pro-apoptotic markers including Bax (F [3,8] = 26.17, $p < 0.01$), Caspase-3(F [3,8] = 8.388, $p < 0.01$), and cleaved Caspase-3(F [3,8] = 32.32, $p < 0.01$), and downregulated the anti-apoptotic marker Bcl2(F [3,8] = 9.77, $p < 0.01$) (Fig. 2f–i). TF treatment significantly mitigated these changes, reducing apoptosis marker expression to near control levels (Fig. 2d–h). Additionally, the reduction in MBP levels (F [3,8] = 26.18, $p < 0.01$) caused by CORT was effectively reversed by TF treatment (Fig. 2d and e). These results collectively indicate that while CORT treatment promotes apoptosis and oligodendrocyte damage, TF functions to counteract these effects, enhancing oligodendrocyte survival and function *in vitro*.
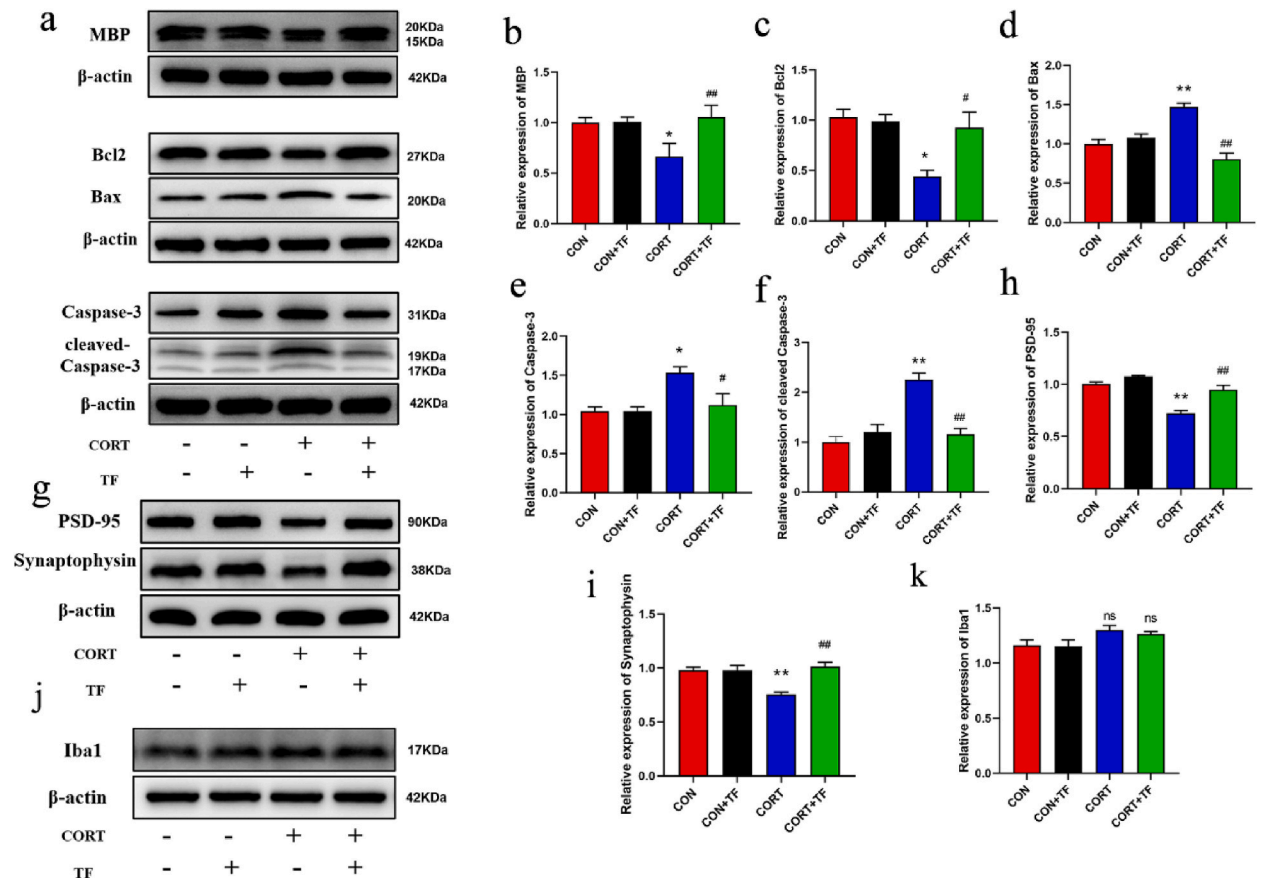
Fig. 5. TF attenuated hippocampal cell apoptosis and enhanced synaptic protein expression in depressed mice. (a–f) Levels of MBP and apoptosis-related protein were measured by Western blotting and quantified. (g–i) Levels of PSD-95 and Synaptophysin were measured by Western blotting and quantified. (j–k) Levels of Iba1 were measured by Western blotting and quantified. Results were expressed as mean ± SEM (n = 4). *$p < 0.05$, **$p < 0.01$ vs. CON group. #$p < 0.05$, ##$p < 0.01$ vs. CORT group.

3.3. TF mitigated CORT-induced depression-like behaviors in mice

Following chronic CORT administration, mice exhibited discernible anxiety and depression-like behaviors as illustrated in the behavioral tests (Fig. 1). To assess the antidepressant properties of TF, we administered TF treatment 21 days post-CORT administration and conducted behavioral tests on day 32 to evaluate its impact on CORT-induced depressive behaviors in mice. The experimental timeline is depicted in Fig. 3a. No significant differences were noted between the TF and CON groups across all behavioral outcomes (Fig. 3b–k). In the SPT, the CORT + TF group demonstrated a substantial increase in sucrose preference compared to the CORT group, indicating an improvement in anhedonia (F $[1,32] = 21.86$, $p < 0.01$, Fig. 3b). Assessment of despair-like behavior through immobility duration in both the FST and TST revealed a significant increase in latency. The CORT + TF group observably increased the latency in FST (F $[1,32] = 24.83$, $p < 0.01$, Fig. 3f) and TST (F $[1,32] = 8.988$, $p < 0.01$, Fig. 3j) compared to the CORT group. The CORT + TF group observably decreased the duration of immobility in FST (F $[1,32] = 25.99$, $p < 0.01$, Fig. 3g) and TST (F $[1,32] = 9.618$, $p < 0.01$, Fig. 3k) compared to the CORT group. Moreover, the CORT + TF group spent more time in the central area of the OFT, without changes in overall locomotion, indicating a reduction in anxiety-like behavior (F $[1,32] = 23.59$, $p < 0.01$, Fig. 3d). Latency to feed in the NSFT was considerably reduced in the CORT + TF group (F $[1,32] = 18.63$, $p < 0.01$, Fig. 3h), while total food intake remained constant (Fig. 3i). These behavioral assessments collectively highlight the efficacy of TF treatment in reversing the anxiety- and depression-like behaviors instigated by CORT in mice.

3.4. TF attenuated hippocampal cell apoptosis and enhanced synaptic protein expression in depressed mice

Given TF's protective role in oligodendrocytes *in vitro*, we examined MBP levels in the hippocampi of depressed mice (Fig. 5a). The CORT + TF group displayed elevated MBP levels compared to the CORT group, suggesting that TF safeguarded oligodendrocytes against CORT-induced damage (F $[3,8] = 9.019$, $p < 0.01$, Fig. 5b). Nissl staining was employed to observe changes in hippocampal neuronal cells, revealing a notable reduction in Nissl-positive cells in the CORT group compared to the control (F $[3,13] = 31,66$, $p < 0.01$, Fig. 4a and b). This reduction was apparent in the CA1 (F $[3,13] = 8.249$, $p < 0.01$, Fig. 4a–c), CA3(F $[3,13] = 9.582$, $p < 0.01$, Fig. 4a–d), and DG regions (F $[3,13] = 11.86$, $p < 0.01$, Fig. 4a–e). Conversely, TF treatment significantly mitigated the loss of Nissl-positive cells induced by chronic CORT, with TF treatment alone having no impact on the number of hippocampal neurons (Fig. 4a–e). These findings underscore TF's capacity to preserve oligodendrocyte and neuronal integrity in the face of CORT-induced damage.

Apoptosis in glial cells and neurons plays a crucial role in depression pathology [44–46], with apoptosis and necroptosis of oligodendrocytes in the hippocampus contributing to demyelination and synaptic dysfunction [15,47,48]. We examined apoptosis-related proteins in the hippocampus using western blotting (Fig. 5a). Quantitative analysis revealed an upregulation of Bax (F $[3,8] = 22.48$, $p < 0.01$), Caspase-3 (F $[3,8] = 6.745$, $p < 0.05$), and cleaved Caspase-3 levels (F $[3,8] = 19.42$, $p < 0.01$), and downregulation of Bcl2 (F $[3,8] = 7.678$, $p < 0.01$) in the CORT group compared with controls (Fig. 5c–f). TF treatment significantly reversed these alterations, highlighting its role in mitigating CORT-induced apoptosis in the hippocampi of mice with depression.

Owing to the regulatory role of oligodendrocytes in synaptic plasticity, we evaluated hippocampal synapse-related protein expression. In mice with CORT-induced depression, there was a notable decrease in both PSD-95 (F $[3,8] = 34.30$, $p < 0.01$, Fig. 5h) and SYP levels (F $[3,8] = 11.10$, $p < 0.01$, Fig. 5i) in the hippocampus. Following 10 days of TF treatment, levels of both PSD-95 and SYP saw a significant upswing (Fig. 5g–i), suggesting a synaptic protective effect of TF in mice suffering from CORT-induced depression.

4. Discussion

Our preliminary findings suggest that intragastric administration of TF exhibits an antidepressant effect in a mouse model of CORT-induced depression. Concurrently, this effect is associated with a reduction in hippocampal oligodendrocyte damage and apoptosis, alongside an increase in the levels of PSD-95 and SYP in the hippocampi of the depressed mice. Previous research has established that chronic stress-induced depression can harm oligodendrocytes. Our study is unique in demonstrating that TF can ameliorate these effects in a CORT-induced depression model, protecting oligodendrocytes and reducing hippocampal apoptosis.

Oligodendrocytes are the primary myelin-forming cells of the CNS, and play a crucial role in the regulation of myelin development and maturation; damage to these cells is a hallmark of several psychiatric disorders. Research has linked abnormalities in myelin and oligodendrocytes in white matter to the pathology of Alzheimer's disease [49,50]. In a mouse model of multiple sclerosis (MS), a 12-week exposure to the oligodendrocyte toxin cuprizone resulted in over 90 % demyelination of the hippocampus, leading to impairments in memory and learning [15]. The importance of oligodendrocytes in depression has been recognized in previous studies [51]. The pathogenesis of depression is believed to be influenced by the loss of myelin and dysfunction of oligodendrocytes. This is further supported by the co-morbidity of demyelinating diseases and depression in both humans and rodents [52]. For instance, a study found a significant reduction in oligodendrocyte density in the prefrontal cortex (PFC) of individuals with depression, alongside ultrastructural signs of apoptosis and necrosis in these cells [53]. Autopsy reports have also revealed notable morphological changes in the brains of patients with depression, including a reduced number of glial cells in the PFC [21]. Preclinical studies support these findings, illustrating the crucial role of oligodendrocytes in depression's development. For example, 15 days of chronic unpredictable stress (CUS) led to a significant decrease in oligodendrocyte numbers, a change that was reversible with a three-week fluoxetine treatment [54].

The hippocampus, highly sensitive to stress and particularly prone to stress-induced damage, has been extensively studied in

depression research [55]. In our study, we observed reduced levels of MBP, PSD-95, and SYP in the hippocampus of depressed mice, indicating damage to both oligodendrocytes and synapses. Evidence suggests that protecting hippocampal oligodendrocytes from damage can reverse depression-like behavior. For instance, Yuan et al. demonstrated that fluoxetine treatment in diabetic mice prevented MBP loss, mitigated oligodendrocyte damage, and concurrently alleviated anxiety and cognitive dysfunction [56]. Another study found that 3 weeks of fluoxetine treatment protected oligodendrocytes in the CA1 and CA3 regions of the hippocampus in CUS-exposed rats, reversing depression-like behavior [57]. Furthermore, exercise has been shown to promote oligodendrocyte differentiation and myelination in the hippocampi of depressed male mice [58], with 4 weeks of running significantly reducing depression-like behaviors and increasing the total number of oligodendrocytes in the CA3 and dentate gyrus (DG) regions of the hippocampus in CUS rats [59].

Collectively, the dysfunction of oligodendrocytes is intricately linked to the pathogenesis of depression, highlighting the potential of strategies aimed at preventing oligodendrocyte damage as alternative treatments for depression.

TF is a clinically approved drug for treating MS that has demonstrated a robust clinical profile having earned approval for pediatric MS treatment in Europe in 2021 [60]. In our study, TF displayed no detrimental effects, either *in vitro or in vivo*. Specifically, *in vivo* investigations revealed that TF ameliorates depression-like behavior by safeguarding hippocampal oligodendrocytes. The CORT group exhibited a notable reduction in MBP content within the hippocampus, compared with the CON group, highlighting oligodendrocyte damage. In contrast, TF administration normalized MBP levels suggesting its protective role in oligodendrocytes, which corresponded with a reversal in depression-like behaviors in mice. Additionally, we observed that CORT diminished oligodendrocyte activity *in vitro* while TF administration enhanced cell viability. Chronic psychosocial stress is known to trigger prolonged loss and transient proliferation of oligodendrocyte precursor cells (OPCs) [57], leading to morphological OPC damage, excessive oxidative stress, and oligodendroglial apoptosis [61]. Consistent with these findings, our results indicate that TF protects against OLN-93 apoptosis under CORT influence marked by an increased Bcl2/Bax ratio and decreased levels of Caspase-3 and cleaved Caspase-3. TF treatment at concentrations of 12.5 μM or 50 μM reversed these damages and increased MBP level.

As highly susceptible cells within the CNS, oligodendrocytes exhibit heightened sensitivity to excitotoxic damage, oxidative stress, and cytokines [62]. TF's protective effects on oligodendrocytes may be attributed to its anti-neuroinflammatory properties, as it has been reported to mitigate neuroinflammation in various brain disorders including ischemic stroke and traumatic brain injury [30,33, 63,64]. Consequently, future investigations will focus on elucidating the anti-inflammatory roles of TF in depression. Oligodendrocytes play a key role in creating and maintaining myelin sheaths in the central nervous system, supporting and safeguarding neurons from harm and external stimuli. These myelin sheaths not only offer protection but also aid in speeding up nerve signal conduction, which is essential for effective communication and information transmission between nerve cells [65]. As such, we propose that teriflunomide's protective impact on mouse oligodendrocytes establishes optimal conditions for the proper functioning and safeguarding of nerve cells, ultimately ensuring the smooth operation of the nervous system.

Previous research has established the impairment of synaptic plasticity in depression [66,67]. Our current study corroborates these findings, showing synaptic toxicity in CORT-treated mice, evident from the significant reduction in PSD-95 and SYP levels. Oligodendrocytes are crucial for preserving the integrity and survival of axons [68], modulating axonal outgrowth in the CNS and preventing extensive axonal degeneration through demyelination [69–71]. Post-TF treatment, we observed a significant enhancement in the levels of PSD-95 and SYP in the hippocampus, suggesting that oligodendrocyte protection aids in the recovery from synaptic damage. Neurons, characterized by high energy demands and limited energy storage capabilities [72,73], rely on oligodendrocytes to fulfill their metabolic requirements through myelin-axon-connected structures [71]. Metabolites such as lactic acid are transported to neurons from oligodendrocytes, supporting neuronal metabolic needs [62,74]. The maintenance of brain function necessitates bidirectional communication between oligodendrocytes and neurons, with disruptions in this communication commonly observed in neurological disorders [75,76]. Oligodendrocyte injury leads to the disintegration of oligodendrocyte-neuron units, contributing to CNS degeneration [77]. Previous reports have documented hippocampal neuron loss in both depression patients and animal models [78,79], but have also highlighted the reversal of neuronal loss and improvement in depressive symptoms through oligodendrocyte protection [80].

Our findings from the mouse model in this study indicate that CORT-induced depression results in neuronal damage and increased apoptosis in the hippocampus, which may be mitigated by TF treatment. This treatment not only protects oligodendrocytes but also reduces hippocampal cell apoptosis and reverses neuronal loss, demonstrating the potential of TF in improving depression-like behavior induced by CORT in mice. Moreover, our data indicate that TF treatment diminishes oligodendrocyte damage in the hippocampus of depressed mice. Nissl staining results further confirm the neuroprotective effects of TF, showing an increase in hippocampal CA1, CA3, and DG neurons alongside a marked increase in the Bcl2/Bax ratio and a decrease in Caspase-3 and cleaved Caspase-3 levels. This suggests that TF treatment helps to restore the homeostatic balance between oligodendrocytes and neurons in the brain. We propose that the elevation in synapse-related protein levels could be attributed to the protective effects of TF on oligodendrocytes, although further research is required to elucidate the specific molecular mechanisms underpinning the interaction between TF's protective role in oligodendrocytes and neurons. In previous studies, oligodendrocytes were also damaged in the CUS depression model [81], and exercise could improve the depressive-like behavior of rats by protecting hippocampal oligodendrocytes in this model [59]. However, whether teriflunomide improves CUS- and LPS-induced depression symptoms by protecting oligodendrocytes in different depression models requires further experimental verification.

Distributed across various brain regions, oligodendrocytes exhibit responsiveness to stress, demonstrating unique gene expression patterns that are specific to each region [82]. Transcriptional analyses of the PFC and nucleus accumbens (NAc) have unveiled a downregulation in transcripts pertinent to myelin and oligodendrocytes. In contrast, the corpus callosum witnessed an upregulation of myelin-associated transcripts, although these changes were not statistically significant. Notably, no evident alterations were detected

in the amygdala. A critical observation was the reduction in oligodendrocyte- and myelin-specific gene transcripts in both the PFC and NAc that occurred as early as one week following exposure to stress [82]. This highlights the intricate and nuanced role of oligodendrocytes in depression, suggesting a complex relationship that necessitates consideration of the specific brain regions involved. Given the prominent role of the hippocampus in MDD, our study focused on this particular region. Nonetheless, it is paramount to acknowledge that oligodendrocytes' responses to depression may vary across different brain regions, underscoring the need for further research to comprehensively understand these region-specific changes and their implications for depressive disorders.

5. Conclusions

The findings of this study demonstrate that administration of TF mitigates CORT-induced depressive-like behaviors while also rectifying damage to oligodendrocytes and synaptic irregularities in the hippocampus. These outcomes suggest that TF holds potential as an efficacious therapeutic agent in combating depression, and provide evidence in support of the clinical utility of TF in the management of depressive disorders.

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Institutional review board statement

The animal study protocol was approved by the Medical Research Ethics Committee of Hunan Normal University (protocol code 2020 No. 397, approval of date September 1, 2020).

Informed consent statement

Not applicable.

Data availability statement

The dataset supporting the findings of this study is available from the corresponding author upon reasonable and justified request.

CRediT authorship contribution statement

Shuting Luo: Writing – original draft, Visualization, Supervision, Software, Methodology, Conceptualization. **Feilong Wu:** Writing – original draft, Software, Methodology, Formal analysis, Conceptualization. **Qian Fang:** Writing – original draft, Validation, Methodology, Formal analysis. **Yue Hu:** Software, Methodology, Investigation. **Huihui Zhang:** Validation, Supervision, Investigation. **Shishan Yuan:** Visualization, Resources, Project administration. **Chang Yang:** Supervision, Software, Resources. **Yan Shi:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition. **Yixiao Luo:** Writing – review & editing, Visualization, Supervision, Project administration, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e29481.

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