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p53 promote oxidative stress, neuroinflammation and behavioral disorders via DDIT4-NF-κB signaling pathway

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ABSTRACT

Depression is a mood disorder characterized by persistent emotional and behavioral dysregulation. Oxidative stress-induced neuronal damage is increasingly recognized as a critical risk factor contributing to the pathogenesis of depression. However, the potential molecular mechanisms and therapeutic targets underlying brain homeostasis disruption induced by neuroinflammatory responses remain unclear. The polyphenolic compound curcumin has been shown to exert neuroprotective effects and partially alleviate depression-related behavioral symptoms through its anti-oxidative properties. However, the molecular mechanisms and therapeutic targets underlying curcumin's ability to ameliorate oxidative stress-induced behavioral abnormalities in specific brain regions remain insufficiently defined. In this study, we demonstrate that chronic administration of corticosterone (CORT) induces pronounced depression- and anxiety-like behaviors in mice, accompanied by marked oxidative stress, neuroinflammation, and disrupted synaptic plasticity within the medial prefrontal cortex (mPFC). Curcumin treatment significantly ameliorated these behavioral and neuropathological abnormalities by enhancing antioxidant capacity, suppressing inflammatory cytokine production and restoring dendritic architecture. Transcriptomic profiling and network pharmacology identified the p53-DDIT4-NF-κB signaling as a key signaling hub underlying these effects. Pharmacological inhibition of p53 with pifithrin-α (PFT-α) mimicked the antidepressant-like effects of curcumin, whereas activation with NSC697923 abolished them. These findings support curcumin may serve as a promising strategy for anti-oxidative stress and *anti*-neuroinflammation in depression via targeting p53-DDIT4-NF-κB signaling.

1. Introduction

Depression is one of the most prevalent psychiatric disorders [1]. The neuropathological mechanism of depression remains unclear, seriously hindering the development of targeted therapy and becoming an urgent problem to be solved in the field of neuropsychiatry [2,3]. Recent evidence indicates that depression is associated with alterations in brain function, neuronal plasticity, and reduced volume of the prefrontal cortex and hippocampus, with oxidative stress (OS) emerging as a primary contributor to these structural and functional disruptions in major depressive disorder (MDD) [4,5]. Preclinical and clinical studies have revealed that the increased generation of reactive oxygen species (ROS) and the depletion of antioxidative defenses are key factors underlying the structural alterations observed in the brain [6,7]. Increased OS

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activates proinflammatory signaling pathways, which elevate cytokine levels, impair neurogenesis, and drive neuroprogression, thereby exacerbating the pathophysiology of MDD [8,9].

DNA Damage-Inducible Transcript 4 (DDIT4) is a highly expressed response gene under various cellular stress conditions, and it is widely involved in metabolic regulation, stress responses, and the pathological processes of neurological and psychiatric disorders [10,11]. In mouse models of depression, stress-induced upregulation of DDIT4 suppresses mechanistic target of rapamycin complex 1 (mTORC1) mediated protein synthesis, which leads to synaptic loss and the manifestation of depressive-like behaviors [12]. Furthermore, the expression of DDIT4 is regulated by p53. The p53 directly activates the transcription of DDIT4 and participates in cell repair and stress responses [11]. The synergistic effect between DDIT4 and p53 plays a crucial regulatory role in processes such as DNA damage, oxidative stress, and inflammatory responses [13]. It also affects the occurrence and progression of tumors and neurological diseases [14,15].

Curcumin is a natural polyphenol active component extracted from the rhizome of Curcuma longa, a plant of the Zingiberaceae [16]. It has been proven to have antioxidant, anti-inflammatory, anti-tumor, immunomodulatory and neuroprotective effects [17–19]. Curcumin has shown potential in the treatment of cancer, metabolic diseases, neurodegenerative diseases and depression through multiple target mechanisms such as inflammatory pathways and oxidative stress [20,21]. Although several clinical trials on the potential effectiveness of Curcumin in depression have produced conflicting results [22,23]. However, it is worth noting that recent clinical and animal research results have all emphasized the effective role of curcumin in anti-depression [24–26]. Curcumin significantly improved depressive-like behaviors in animal models of rats and mice by regulating the monoamine system, reducing inflammatory signals, lowering corticosterone (CORT) levels, enhancing synaptic plasticity and antioxidant effects [27–31]. Some clinical evidence also shows that curcumin, as an adjunctive treatment, has a significant role in improving the core symptoms of depression [32].

In this study, we observed that curcumin pretreatment significantly alleviated CORT- or lipopolysaccharide (LPS) -induced depressive-like behaviors, while reducing oxidative stress, inflammation and neuronal morphological damage in the mPFC. Further mechanistic investigations revealed that the alleviation of depressive-like behaviors in the inflammation-related subtype was mediated through the regulation of the p53-DDIT4-NF-κB axis. Upon activation of p53 activity, oxidative stress and neuroinflammatory responses were exacerbated, morphological plasticity was impaired, and depressive-like behaviors were aggravated. In summary, this study provides novel insights into the neuroimmune mechanisms underlying curcumin's antidepressant effects and supports its potential therapeutic value in depression through its antioxidant stress-removing action.

2. Methods

2.1. Animals

Male C57/BL 6J mice (weighing 25–30 g, 6–8 weeks old) were purchased from Jinan Peng-yue Experimental Animal Breeding Co., Ltd. The animals were housed in a facility designed to simulate a natural light-dzark cycle (lights on at 8:00 a.m. and off at 8:00 p.m.) and were maintained under standard laboratory conditions at 22 °C and a humidity of 35–40 %. Ad libitum access to food and water was provided at all time. Mice were randomly assigned to different experiments groups. Before behavioral test, mice were acclimatized under laboratory environment for one week. All experimental procedures were approved by the Ethics Committee of Shandong University (ECSBMSSDU-2022-2-65), and were conducted according to the International Guiding Principles for Animal Research provided by the International Organizations of the Medical Sciences Council.

2.2. Regents and antibodies

Corticosterone (CORT) was purchased from MedChemExpress (USA). Lipopolysaccharide (LPS) were purchased from Sigma-Aldrich (St. Lous, USA). Curcumin and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (St. Lous, USA). Pifithrin-α (PFT-α) was purchased from Sellcek (USA). NSC697923 was purchased from MedChemExpress (USA). The polyclonal rabbit anti-ionized calcium binding adaptor molecule-1 (Iba-1) (019–19741) was purchased from Wako (Japan) and the DAPI was purchased from Beyotime Biotechnology (Shanghai, China). Alexa Fluor 568 Donkey anti-Rabbit IgG secondary antibody was purchased from Thermo Fisher Scientific (Waltham, USA).

2.3. LPS-induced depression model

The LPS-induced mouse model of depression was established following previously described methods with minor modifications. In this protocol, mice underwent daily intraperitoneal (i.p.) injections of freshly prepared LPS (1 mg/kg) administered consecutively for 14 days. Control group animals received equivalent volumes of normal saline following identical injection schedules. All solutions were prepared immediately prior to daily administration to ensure stability. The experiment was maintained consistency in dosage frequency and preparation timing between the LPS-treated and saline-treated groups.

2.4. CORT-induced depression model

A CORT-induced mouse model of depression was established in male C57BL/6J mice through oral administration. Freshly prepared CORT solution (dissolved in 0.1 % DMSO-saline) was provided as the exclusive drinking source with progressive dose reduction: 12 mg/480 mL during first week, decreased to 6 mg/480 mL in second week, and further reduced to 3 mg/480 mL (6.25 mg/kg/day) in third week. The control group freely drank the vehicle solution.

2.5. Drug treatments

From the second week of oral administration of CORT in mice, Curcumin (50 mg/kg) was intraperitoneally injected every day for 2 weeks until the end of CORT-induced modeling. For the two groups of p53 inhibitors (PFT-α) and agonists (NSC697923), both were intraperitoneally injected with PFT-α (5 mg/kg) or NSC697923 (2 mg/kg) respectively 30 min after Curcumin treatment for 2 weeks.

2.6. Behavioral tests

To verify the effect of curcumin treatment on depressive symptoms induced by oral CORT. All behavioral evaluations are conducted in dedicated testing facilities to eliminate external interference. Behavioral assessment was conducted by independent investigators under blinding conditions.

2.7. Open field test

OFT is used to assess the motor ability and anxiety levels of mice. Mice were gently placed in the center of a square box (50 × 50 × 50, L × W × H in cm). Spontaneous locomotor activity was automatically recorded for 10 min with a video camera positioned above the box and analyzed with the tracking software (SMART 2.5, Panlab). The locomotor activity was evaluated by using the total traveled distance.

2.8. Sucrose preference test

The sucrose preference test was conducted following a previously described protocol with certain modifications. For the first 24 h, the animals were acclimated in two bottles of 2 % sucrose solution. Next 24

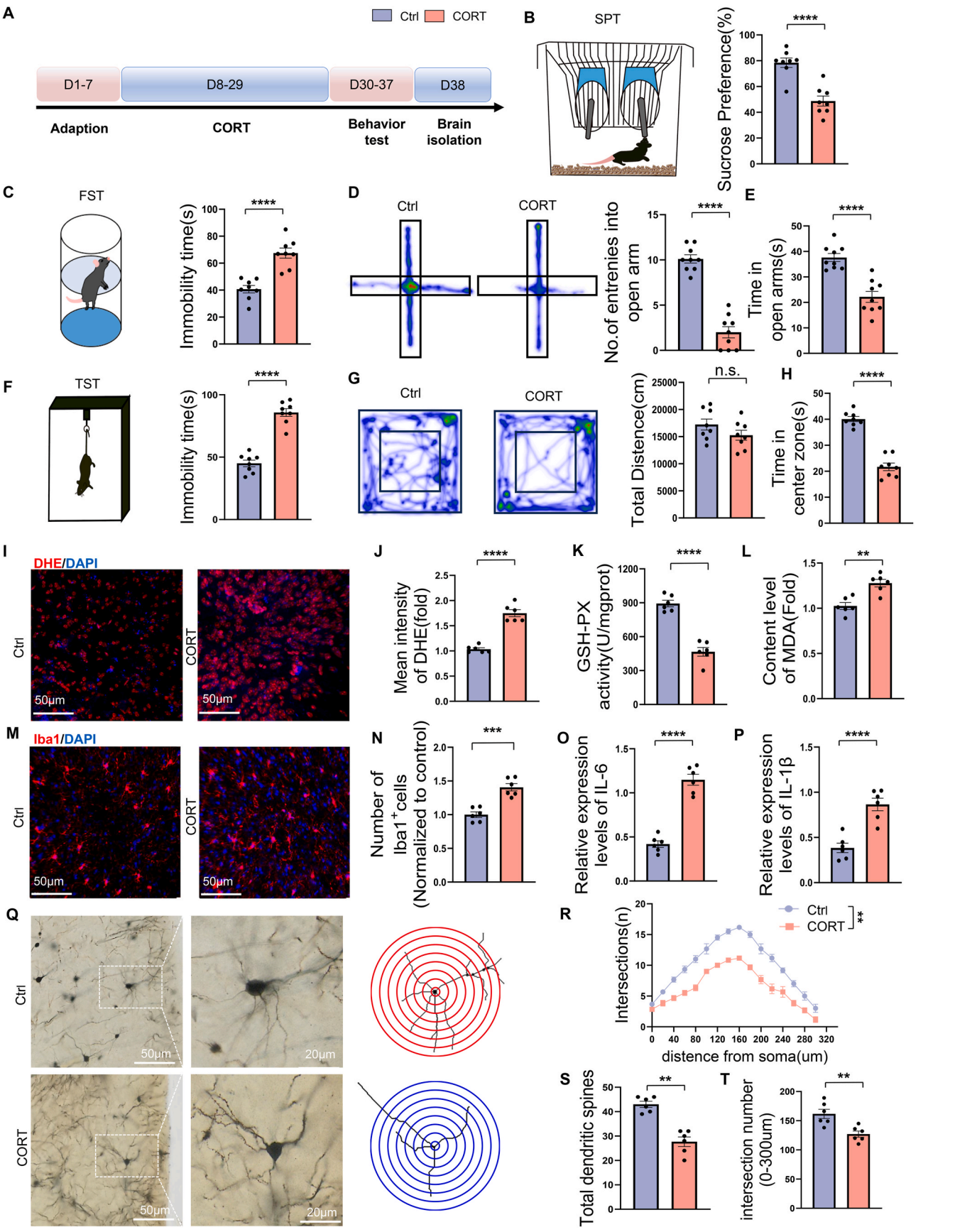

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Fig. 1. Chronic CORT administration induces depression- and anxiety-like behaviors, neuroinflammation, oxidative stress, and impaired neuronal morphological plasticity in **the mPFC.** (**A**) Schematic diagram of the experimental design for the mouse depression model induced by corticosterone (CORT). (**B**) Sucrose preference test (SPT) showed a significant reduction in sucrose preference in the CORT group. (**C**) Forced swim test (FST) showed significantly increased immobility time in CORT mice. (**D, E**) Elevated plus maze (EPM) test showed that both the time spent and the number of entries into open arms were significantly reduced in CORT mice. (**F**) Tail suspension test (TST) showed significantly increased immobility time in CORT mice. (**G, H**) Open field test (OFT) results showed that the total distance traveled by the CORT mice remained unchanged, but the time spent in the central area was significantly reduced. (**I, J**) DHE fluorescence intensity was higher in the CORT + Cur + NSC group, indicating increased ROS accumulation. (**K, L**) Biochemical analysis showed reduced GSH-PX activity and elevated MDA levels. (**M, N**) Immunofluorescence staining demonstrated an increased number of Iba1-positive microglia in the mPFC of CORT mice. (**O, P**) qPCR analysis of mPFC tissue showed significant upregulation of pro-inflammatory cytokines interleukin-6 and interleukin-1β in the CORT group. (**Q, R**) Sholl analysis showed a significant reduction in dendritic intersections as a function of radial distance from the soma in CORT mice. (**S, T**) Quantification showed significantly reduced total dendritic spines and intersections within 300 μm in the mPFC neurons of CORT mice. Data are presented as mean ± SEM. N = 8 per group. NS, not significant ($P > 0.05$); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

h, replace one of the bottles of sucrose solution with water. Following a 12 h period of fluid deprivation, the intake of sucrose was measured during a 6 h test. Sucrose preference was calculated as a percentage by (100 × volume of sucrose consumed/total volume consumed).

2.9. Forced swimming test

The forced swimming test assesses depression-like behaviors by the measuring the immobility time and is used to characterize desperate behaviors. Individual mice were placed in a cylinder measuring 25 cm in height and 20 cm in diameter, filled with water to a depth of 10 cm at a temperature of 23–25 °C to prevent the animal from touching the bottom with its hind limbs. All animals underwent a 6 min swimming test, with their immobility time recorded during the final 5 min.

2.10. Tail suspension test

The experiment was used to assess desperate behaviors in order to measure the degree of depression in animal models. Fix the place 1 cm away from the tip of the mouse tail to the hook inside the tail suspension device with tape, and it should be at least 20 cm above the ground. The absence of any body activity in mice and their passive suspension state are defined as immobility. Test the immobility time of each mouse within 5 min to evaluate helpless and desperate behaviors.

2.11. The elevated plus maze test

The elevated plus maze (EPM) is used to assess the anxiety levels of animals. The device consists of three parts: two open arms (35 × 6 cm), two closed arms (35 × 6 × 20 cm) and a central area (6 × 6 cm). At the beginning of the test, each mouse was placed in the central area of the maze, with its head facing the open arms, and freely explored the maze for 5 min. Time spent in the open arms and the number of entries into open arms in 5 min were recorded by tracking software (SMART 2.5, Panlab).

2.12. Immunofluorescence staining

Mice were anesthetized with isoflurane and subsequently sacrificed. They were perfused with 0.9 % saline, followed by 4 % paraformaldehyde (PFA) in phosphate-buffered saline (PBS). The brains were postfixed in 1 × PFA solution at 4 °C overnight, then cryoprotected by immersed in 30 % sucrose until they sank. Coronal brain sections (30 μm thick) encompassing mPFC were obtained using a cryostat (CM1950, Leica, Germany). Sections were permeabilized with PBST (0.1 m PBS with 0.3 % Triton X-100) for 30 min and blocked with PBST containing 5 % normal goat serum for 1 h at room temperature to block nonspecific staining. On the second day, slices were incubated with matched secondary antibody (1:1000, Invitrogen) in the blocking solution at 4 °C for 1 h and 5 min in DAPI (Beyotime Biotechnology C1002). Images were obtained from highspeed confocal platform (Dragonfly 200).

2.13. Western blotting

Mice were anesthetized with sodium pentobarbital (50 mg/kg, i.p.), and the mPFC regions were carefully dissected for Western blot analysis at 24 h after behavioral tests. The brain tissues were sonicated in RIPA lysis buffer containing protease and phosphatase inhibitors. Following sonication, the samples were centrifuged at 12,000g for 20 min at 4 °C, and the supernatant was collected and quantified using the BCA assay (Beyotime). The protein sample (30 μg) was separated by SDS-PAGE, followed by transferring onto PVDF membranes. Target protein detection was performed using HRP-conjugated polyclonal goat anti-rabbit secondary antibodies and polyclonal goat anti-mouse secondary antibody. The enhanced chemiluminescence kit (Vazyme, catalog no. E412-01) was utilized for blot detection. Protein band intensities were analyzed with Image-J software, and experiments involving samples from each mouse were independently repeated a minimum of three times.

2.14. Real-time quantitative PCR

Brain tissue RNA was isolated via the TRIzol method (ACCURATE BIOLOGY, catalog no. AG21102). RNA concentration was measured using a NanoDrop ND-1000 spectrophotometer (Thermo Fisher Scientific, Wilmington, DE), and 500 ng of total RNA was reverse-transcribed into cDNA. Target gene expression was analyzed by quantitative real-time PCR (qPCR) with the $2-\Delta\Delta Ct$ method. For mRNA quantification, qPCR reactions (20 μL total volume) comprised 10 μL SYBR Green Master Mix (Nobelab Biotech, catalog no. R605, China) and were run for 40 cycles (95 °C for 15 s, 60 °C for 1 min), with GAPDH mRNA serving as the endogenous control. miRNA expression was assessed using the All-in-One™ miRNA RT-PCR Kit (GeneCopoeia, catalog no. QP010, USA) on a Bio-Rad CFX96 system (Hercules, CA), normalized to Rno-U6.

2.15. Golgi staining

Golgi staining was conducted following established protocols. Fresh rat brain tissues were processed using the FD Rapid Golgi Stain™ kit (FD Neuro Technologies, catalog no. PK401) in accordance with the manufacturer's guidelines. Tissue samples were sectioned coronally into 150-μm slices with a vibratome (Leica VT1200S,Germany), mounted on gelatin-coated slides, dehydrated through a gradient alcohol series, cleared in xylene, and ultimately cover slipped. Prepared slides were stored at room temperature in light-protected conditions. mPFC neurons were imaged using an digital slide scanner (Olympus VS120, Japan), and dendritic spine densities were determined by counting spines per 10 μm dendritic segment. All images underwent processing with Fiji software (ImageJ, NIH), incorporating Sholl analysis for morphological quantification.

2.16. Oxidative stress experiment

The extent of DNA oxidative damage in the mPFC tissue was assessed by measuring the content of its specific biomarker, 8-

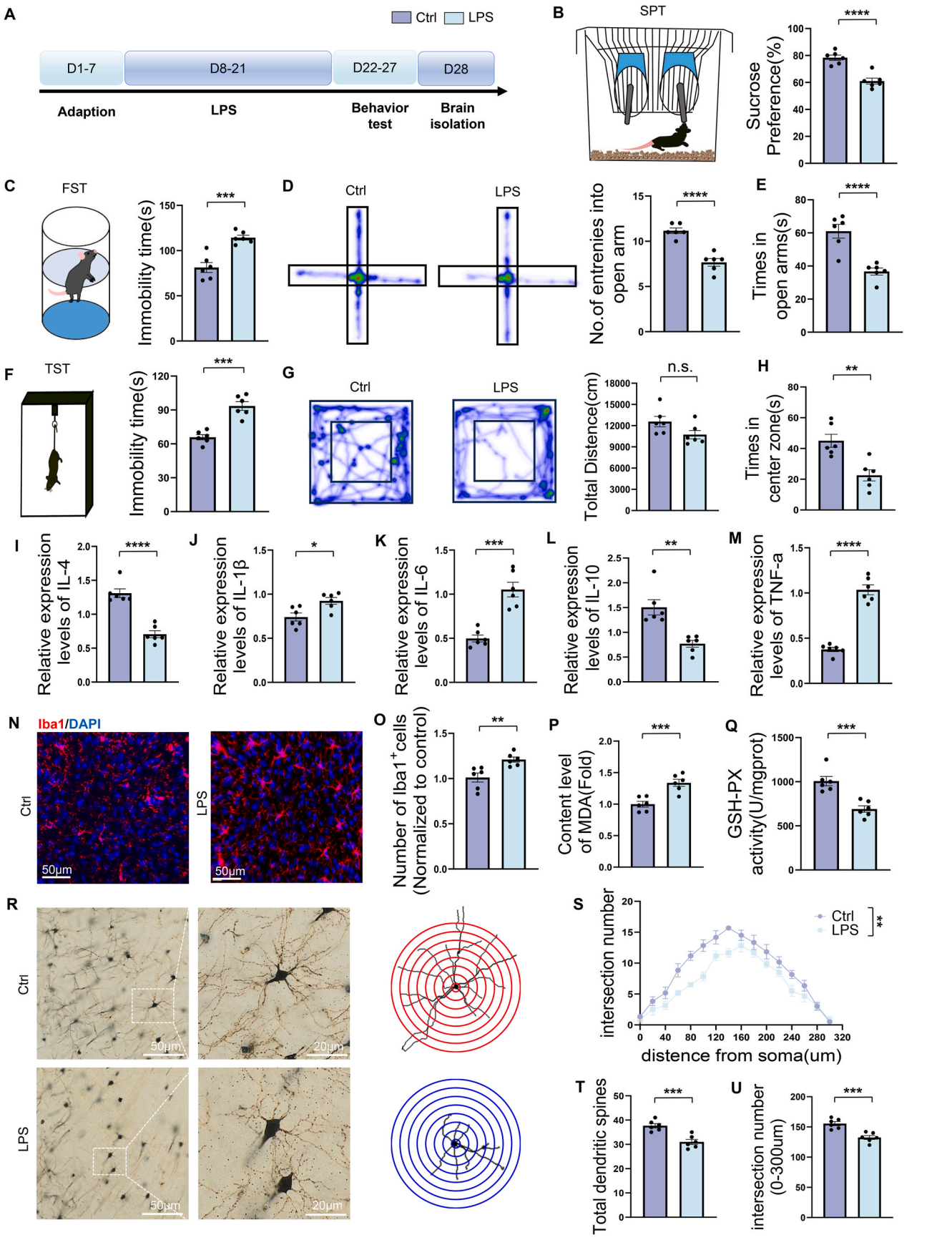

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Fig. 2. Chronic LPS exposure induces depression- and anxiety-like behaviors, neuroinflammation, and altered morphological p**lasticity.** (**A**) Schematic diagram of the experimental design for the mouse depression model induced by chronic Lipopolysaccharide (LPS). (**B**) Mice exposed to LPS showed significantly reduced sucrose preference. (**C**) Immobility time in the forced swim test was significantly increased in LPS mice. (**D, E**) Elevated plus maze test showed that both the time spent and the number of entries into open arms were significantly reduced in LPS mice. (**F**) Immobility time in the tail suspension test was significantly increased in the LPS mice. (**G, H**) Open field test results showed that the total distance traveled by the LPS mice remained unchanged, but the time spent in the central area was significantly reduced. (**I, M**) qPCR analysis of mPFC showed significant increase of pro-inflammatory cytokines interleukin-1β, interleukin-6, and tumor necrosis factor-α, decrease the anti-inflammatory cytokines interleukin-4 and interleukin-10 in LPS mice. (**N**) Representative immunofluorescence images of $Iba1^+$ microglia in the PFC of LPS mice. Scale bar = 50 μm. (**O**) Quantification of the number of $Iba1^+$ cells showed a significant increase in the LPS group. (**P, Q**) Biochemical analysis revealed a significant decrease in glutathione peroxidase (GSH-PX) activity and an increase in malondialdehyde (MDA) levels. (**R**) Representative images of Golgi-stained neurons in the PFC and Sholl analysis. Scale bar = 50 μm (left), 20 μm (right). (**S**) Sholl aignificnalysis showed a sant reduction in dendritic intersections in the LPS group, with fewer intersections observed at increasing distances from the soma. (**T, U**) The total number of dendritic spines and the number of dendritic intersections within a 300 μm radius from the soma were significantly reduced in LPS mice. Data are presented as mean ± SEM. n = 6 per group. NS, not significant ($P > 0.05$); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

hydroxydeoxyguanosine (8-OHDG), using an 8-hydroxydeoxyguanosine Assay Kit (No. H165-1-1). All assay kits were obtained from Jiancheng Bioengineering Institute (Nanjing, China), and all experimental procedures were strictly performed in accordance with the manufacturer's guidelines.

2.17. Molecular docking

We used the UniProt database (https://www.uniprot.org/) to obtain the structures of Curcumin and p53 to further investigate the possible interaction between the two proteins. This database integrates literature-derived protein sequences and associated functional information. Next, we through the GRAMM-X web server (http://vakser.bioinformatics.ku.edu/resources/gramm/grammx) for protein molecular docking between. Curcumin was defined as a receptor while p53 as a ligand. The initial output model was selected as the final structure and visualized using PyMOL and LigPlot+.

2.18. Statistical analysis

All data were present as the means ± SEMs, and statistical analyses were performed using GraphPad Prism software version 8.0.1. Comparisons between two independent groups were analyzed using two-tailed independent Student's t-tests. For analyses involving three or more groups, one-way or two-way ANOVA was employed, with Tukey's honestly significant difference (HSD) post hoc test applied for multiple comparisons.

3. Result

Chronic CORT Induces Depression- and Anxiety-like Behaviors Accompanied by Oxidative Stress, Neuroinflammation and Impairs Structural Plasticity within the mPFC Region.

Mouse models of depression induced by chronic corticosterone administration were assessed using five distinct behavioral tests to evaluate depression-like and anxiety-like behaviors (Fig. 1A). In the sucrose preference test, CORT mouse displayed a significant reduction in sucrose preference compared to the control group (Fig. 1B). In the forced swim test, CORT mouse exhibited increased immobility times and decreased swimming times compared to controls (Fig. 1C). The results of these two behavioral tests indicate that CORT mouse displayed anhedonia and behavioral despair, which are typical depression-like behaviors. The results of the elevated plus maze test showed that the duration of open arm in CORT mice was significantly reduced (Fig. 1D and E). In the tail suspended test, compared with the control group, the immobility time of CORT mice was significantly prolonged (Fig. 1F). The results of the open field test showed that the total distance traveled by the CORT mice remained unchanged, but the exploration time in the central area of the open field significantly decreased (Fig. 1G and H). These results indicate that the anxiety levels associated with depression in CORT mice were also significantly increased.

Due to the neuroinflammatory responses often associated with specific brain regions in depression, we next examined the mRNA expression of key proinflammatory cytokines in the medial prefrontal cortex (mPFC). DHE fluorescence staining revealed a significantly stronger DHE signal in the CORT group, indicating higher ROS accumulation in the mPFC than in curcumin-treated mice (Fig. 1I and J). Correspondingly, we observed significantly decreased glutathione peroxidase (GSH-PX) activity and elevated malondialdehyde (MDA) levels in CORT mice, demonstrating impaired antioxidant capacity and exacerbated oxidative damage in this depressive model (Fig. 1K and L). Immunofluorescence staining showed that the number of $Iba1^+$ microglia in the mPFC region of CORT mice increased significantly, indicating that microglia were activated (Fig. 1M and N). Our qPCR results showed that the levels of several key pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and interleukin-6 (IL-6) in the mPFC region were significantly elevated in the CORT mice (Fig. 1O and P). Subsequently, we examined whether chronic CORT-induced stress would produce abnormal synaptic morphological plasticity in neurons of the mPFC. Golgi staining results revealed that, compared to the control group, mPFC neurons in CORT mouse exhibited the dendritic intersections against the radial distance from the soma of mPFC neurons (Fig. 1Q and R) and the intersection number within 300 μm (Fig. 1S and T) were significantly decreased. These results indicate that oxidative stress, inflammatory responses, impaired structural plasticity of neurons, and accompanied by depressive and anxiety-like behaviors occur in the mPFC region of mice induced by chronic CORT.

Chronic LPS Induces Depression- and Anxiety-like Behaviors Accompanied by Oxidative Stress Neuroinflammation and Altered Structural Plasticity within the mPFC Region.

We evaluated the impact of chronic lipopolysaccharide (LPS) exposure on depression-like and anxiety-like behaviors using a battery of behavioral tests (Fig. 2A). In the sucrose preference test, mice exposed to LPS showed a significant decrease in sucrose preference compared to controls (Fig. 2B). The forced swim test revealed that LPS mice had increased immobility time, indicative of behavioral despair (Fig. 2C). The results from the elevated plus maze test showed that LPS mice spent significantly less time in the open arms, suggesting increased anxiety (Fig. 2D and E). Similarly, in the tail suspended test, LPS mice exhibited a significantly higher immobility time compared to the control group, further confirming the presence of depressive-like behaviors (Fig. 2F). Furthermore, the open field test showed that the total distance of movement in LPS mice remained unchanged, while the exploration time in the central area of the open field decreased, further supporting the presence of heightened anxiety (Fig. 2G and H). The levels of IL-1β, TNF-α and IL-6 in the mPFC region were significantly increased, while IL-4 and IL-10 were significantly decreased in LPS mice (Fig. 2I–M). Immunofluorescence staining showed a marked increase in $Iba1^+$ microglia in the PFC of LPS mice, indicating microglial activation (Fig. 2N and O). Next, we also observed a significant decrease in GSH-PX activity and an increase in MDA level in LPS mice, indicating impaired antioxidant capacity and aggravated oxidative damage (Fig. 2P and Q). To further investigate the effects on neuronal structure, we assessed dendritic spine morphology using Golgi staining. The results showed a significant

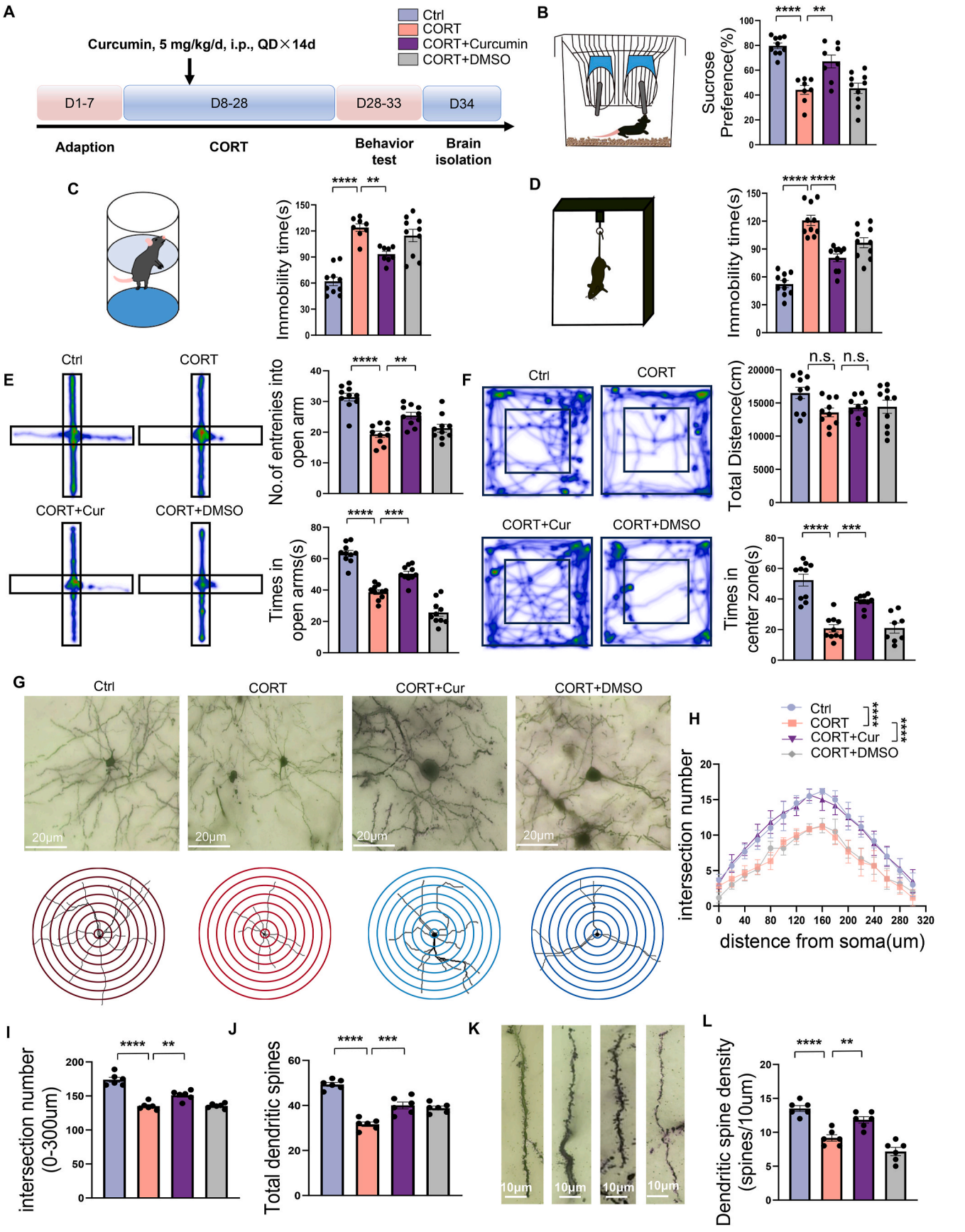

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Fig. 3. Curcumin alleviates depression- and anxiety-like behaviors and restores morphological plasticity in the mPFC of **CORT mice.** (**A**) Schematic diagram of the experimental timeline. (**B**) In the SPT, curcumin treatment significantly increased sucrose preference in CORT mice. (**C-D**) In the FST and TST, curcumin treatment significantly reduced immobility time. (**E**) Representative movement tracks and statistical results in the elevated plus maze (EPM) showed that curcumin significantly increased both the time spent and the number of entries into the open arms in CORT mice. (**F**) In the open field test (OFT), the total distance of movement in the curcumin treatment group remained unchanged, but it significantly increased the time spent in the central area and the distance moved. (**G**) Representative images of Golgi-stained pyramidal neurons in the mPFC and corresponding Sholl analysis diagrams. Scale bar = 20 μm. (**H**) Sholl analysis showed a sant reduction in dendritic intersections in the LPS group, with fewer intersections observed at increasing distances from the soma. (**I**) Quantification of dendritic intersections within 300 μm from the soma showed significant improvement following curcumin treatment. (**J**) Total dendritic spine number was significantly increased in the Cur group compared to the CORT group. (**K**) Representative images of dendritic spines in each group. Scale bar = 10 μm. (**L**) Dendritic spine density was significantly restored in curcumin-treated mice compared to the CORT group. Data are presented as mean ± SEM. N = 8–10 per group. NS, not significant ($P > 0.05$); $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

decrease in the total number of dendritic spines and a reduction in the number of dendritic intersections within a 300 μm radius from the soma in LPS mice, suggesting impaired synaptic plasticity in the mPFC (Fig. 2R–U). Collectively, these findings indicate that chronic LPS exposure induces both behavioral and neurobiological changes that are characteristic of depression and anxiety, accompanied by significant neuroinflammation and oxidative stress.

3.1. Curcumin alleviates depression- and anxiety-like behaviors and remodel mPFC structural plasticity in CORT-treated mice

The natural compound curcumin has shown potential as an adjunctive treatment for depression in both animal models and clinical trials [23,25]. To further investigate the therapeutic effect of curcumin in the oxidative stress-induced depression model, we evaluated the therapeutic effects of curcumin on CORT mice using five different behavioral paradigms and neuronal morphological analysis (Fig. 3A). In the sucrose preference test, curcumin treatment significantly increased the percentage of sucrose intake in CORT mice, indicating an improvement in anhedonia (Fig. 3B). Results from the forced swim test and tail suspended test demonstrated that curcumin markedly reduced immobility time (Fig. 3C and D). In both the elevated plus maze and open field test, CORT mice exhibited significantly decreased time spent in the open arms and the center area, respectively, whereas curcumin administration significantly increased these parameters, indicating its anxiolytic properties (Fig. 3E and F).

Morphologically, the Golgi staining results showed that compared with CORT mice, after curcumin intervention, mPFC pyramidal neurons exhibited the dendritic intersections against the radial distance from the soma of mPFC neurons (Fig. 3G and H) and the intersection number within 300 μm (Fig. 3I) were significantly increased, And the density of dendritic spines was restored (Fig. 3J–L). These findings suggest that curcumin may promote synaptic remodeling and enhance functional connections between neurons, thereby improving behavioral symptoms.

3.2. Curcumin mitigates mPFC oxidative stress and neuroinflammation in CORT-induced depressive mice

Depression is commonly characterized by oxidative stress and neuroinflammation in distinct brain regions and the excessive activation of microglia [33,34]. We assessed the mRNA expression levels of inflammation-associated cytokines and the morphological alterations of microglia. The qPCR analysis revealed that, compared to CORT mice, curcumin intervention significantly decreased the relative expression levels of the pro-inflammatory cytokines IL-1β, TNFα, and IL-6 in the mPFC, while it significantly increased the expression levels of the anti-inflammatory cytokines IL-4 and IL-10. In contrast, DMSO treatment had no observable effect, highlighting the specificity of curcumin's anti-inflammatory action. (Fig. 4A–E). Immunofluorescence staining results revealed a significantly higher number of $IBA1^{+}$ microglia (Fig. 4F and G), along with a decrease in intersections, shorter processes, and reduced endpoints (Fig. 4H–K), in the mPFC region of the curcumin-treated group compared to the control group. Oxidative stress (OS) drives brain structural and functional impairments by activating pro-inflammatory cascades that contribute to depression pathogenesis [35,36]. Through the oxidative stress experiment, compared with the control group, we also observed an increase in MDA level (Fig. 4L), a decrease in GSH-PX activity (Fig. 4M), and an increase in the average fluorescence intensity of 8-OHDG in the mPFC region of CORT mice (Fig. 4N and O). However, after curcumin intervention, all the above results were significantly reversed. These results highlight the neuroprotective antioxidant potential of curcumin in counteracting oxidative stress-induced damage in the mPFC.

3.3. DDIT4 and p53 identified as potential targets of curcumin in depression via RNA-seq and network pharmacology

To further clarify the molecular mechanisms underlying curcumin's antidepressant effects, we integrated transcriptomic analysis, network pharmacology, and data from publicly available databases. Based on RNA-seq data, we identified 1317 upregulated and 1309 downregulated genes in the depression model, indicating widespread transcriptomic alterations following chronic CORT exposure (Fig. 5A). To predict curcumin-related therapeutic targets, we conducted a systematic data mining and target screening using the ChEMBL, GeneCard, and PubMed databases. Through Venn diagram analysis, we identified 45 overlapping targets associated with curcumin, depression, and differentially expressed genes in the dataset (Fig. 5B and C). Among these, p53 emerged as a key intersection node, suggesting it may serve as a critical regulatory hub mediating the antidepressant effects of curcumin.

Protein-protein interaction (PPI) network analysis showed TP53, DDIT4, and MTOR as core hubs closely linked to neuroinflammatory and stress response pathways. Molecular docking further confirmed that curcumin could directly bind to p53, interacting with critical residues such as Gln 2.9 and Thr 2.92 (Fig. 5D). Molecular dynamics simulations demonstrated that the curcumin-p53 complex was stable over time, with consistent hydrogen bonding, solvent accessibility, and low RMSD fluctuations (Fig. 5E–G). Additionally, the free energy surface of the curcumin-p53 complex shows lower free energy regions at different binding states, indicating a strong binding affinity and good binding stability between curcumin and p53 (Fig. 5H). Western blot analysis validated that p53 and DDIT4 protein levels were significantly upregulated in the CORT group compared to controls (Fig. 5I–K), supporting the bioinformatics predictions. Collectively, these findings suggest that curcumin may alleviate depression-like behaviors by modulating p53-DDIT4 signaling, restoring neuronal function, and reducing neuroinflammation and oxidative stress. In addition, GO enrichment analysis revealed that these differentially expressed genes (DEGs) were significantly associated with inflammatory response, cellular stress, apoptotic processes, and synaptic function (Supplementary Fig. 1A–D).

3.4. Pharmacological inhibition of p53 alleviates CORT-induced oxidative stress and neuroinflammation within mPFC and behavioral deficits in mice

Based on RNAseq and network pharmacological analysis, we conducted pharmacological experiments using the p53 inhibitor PFT-α (5 mg/kg/d, i.p) to evaluate the functional role of p53 in the pathogenesis

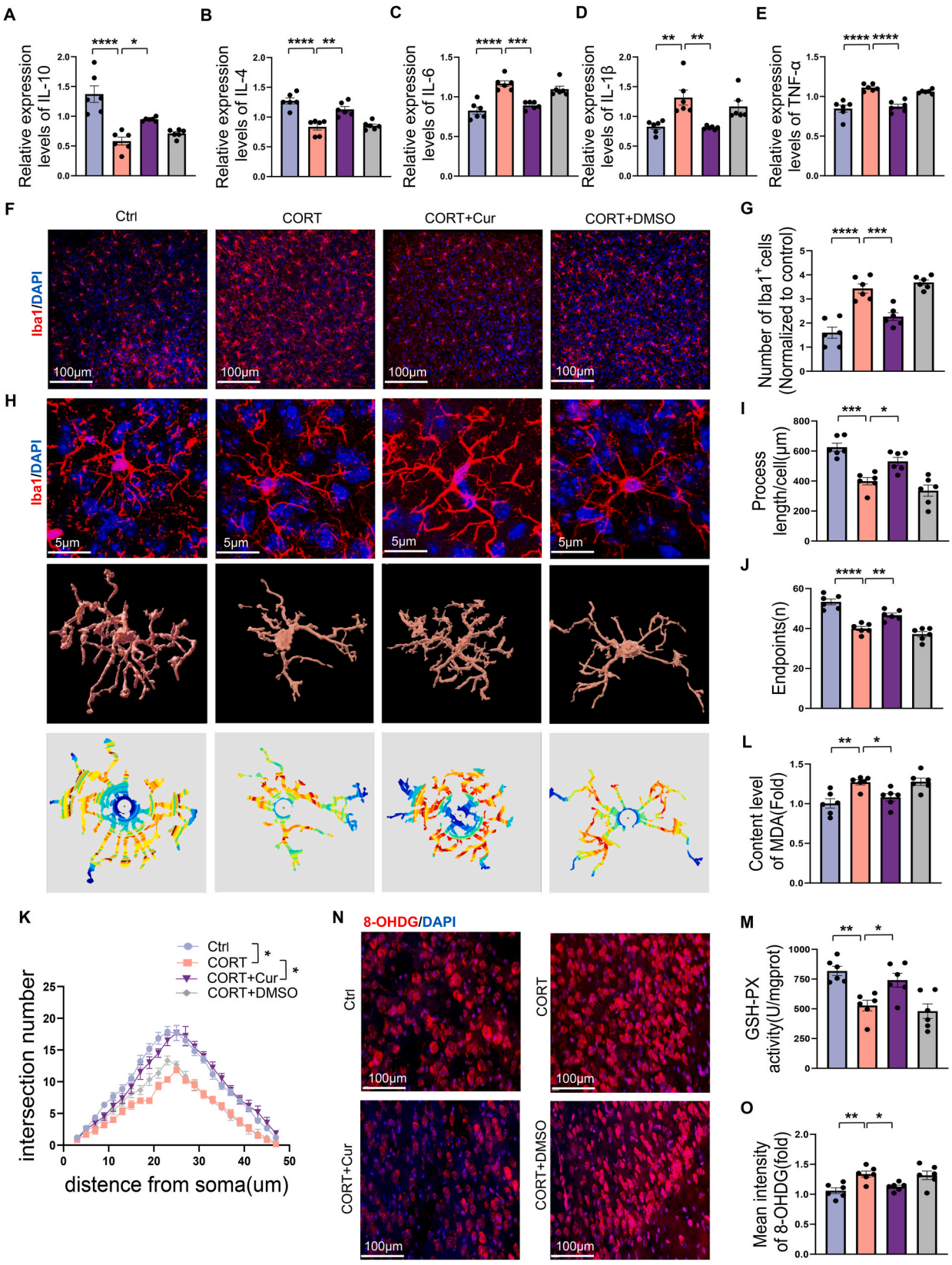

Fig. 4. Curcumin reduces mPFC neuroinflammation and oxidative stress in CORT mice. (**A-E**) qPCR analysis showed that curcumin decreased interleukin-1β, tumor necrosis factor-α, interleukin-6 and increased anti-inflammatory cytokines interleukin-4, interleukin-10 compared to CORT mice. DMSO treatment had no effect. (**F**) Immunofluorescence staining revealed increased Iba1^{+} microglia in curcumin-treated mice. Scale bar = 100 μm. (**G**) Quantification of Iba1^{+} cells showed a significant increase in the curcumin group. (**H, J**) Curcumin increased microglial process length and endpoint number. (**K**) Sholl analysis showed reduced dendritic intersections in microglia after curcumin treatment. Scale bar = 5 μm. (**L**) MDA levels were reduced following curcumin treatment. (**M**) GSH-PX activity was significantly restored by curcumin. (**N, O**) 8-OHDG staining intensity was lower in curcumin-treated mice. Scale bar = 100 μm. Data are presented as mean ± SEM. n = 6 per group. NS, not significant ($P > 0.05$); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

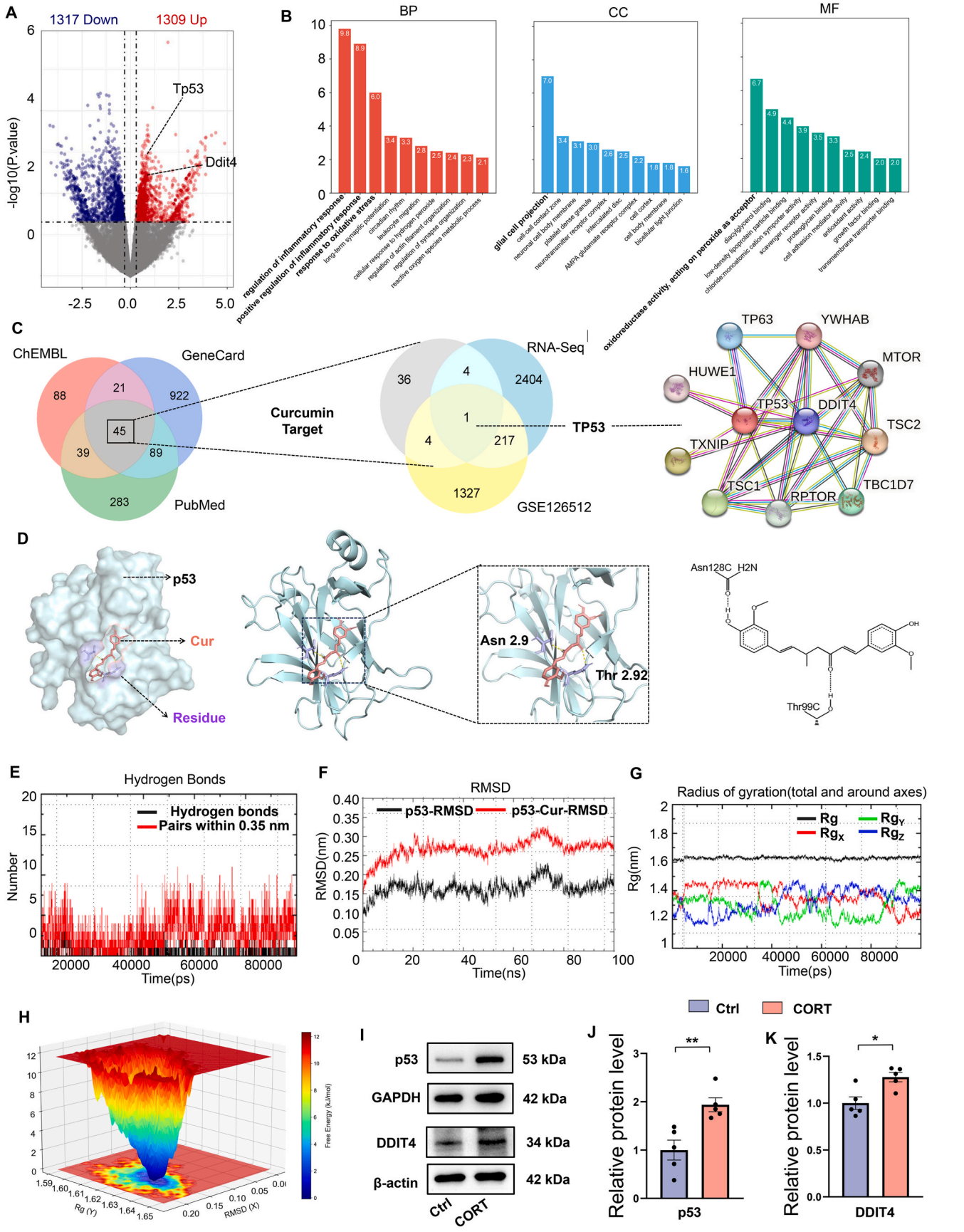

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Fig. 5. Identification of p53 and DDIT4 as potential curcumin targets via RNA-seq and network pharmacology. (**A**) Volcano plot showing 1317 upregulated and 1309 downregulated genes in CORT mice. (**B**) GO enrichment analysis of differentially expressed genes (DEGs) in biological processes (BP), cellular components (CC), and molecular functions (MF). (**C**) Venn diagram showing 45 overlapping genes from ChEMBL, GeneCard, PubMed, and RNA-seq datasets; p53 identified at the intersection. (**D**) Molecular docking showing curcumin binding to p53, with key interaction residues Gln 2.9 and Thr 2.92. (**E**) Hydrogen bond number between curcumin and p53 during molecular dynamics simulation. (**F**) RMSD of p53 and the curcumin-p53 complex during simulation. (**G**) Radius of gyration (Rg) of the curcumin-p53 complex across simulation time. (**H**) Free energy surface (FES) of the curcumin-p53 complex. (**I–K**) Western blot analysis of DDIT4 and p53 protein expression. Both DDIT4 and p53 protein levels were significantly increased in the CORT group compared to the control group. Data are presented as mean ± SEM. n = 5 per group. NS, not significant ($P > 0.05$); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

of depression and neuroinflammation (Fig. 6A). The mechanism of action of the p53 inhibitor PFT-α is shown in the figure (Fig. 6B). Behaviorally, compared with the CORT group, administration of PFT-α significantly restored the sucrose preference of CORT mice in sucrose preference test and significantly reduced the immobility times in forced swim test and tail suspended test (Fig. 6C–E). In both the EPM and OFT, compared with the CORT group, the PFT-α group mice exhibited significantly increased time spent in the open arms and the center area respectively, indicating that inhibiting p53 activity improved anxiety-like behaviors (Supplementary Fig. 2A–D).

The qPCR analysis showed that compared with the CORT group, the PFT-α group significantly downregulated the expression of IL-1β and TNF-α in mPFC, indicating effective inhibition of neuroinflammatory responses (Fig. 6F and G). PFT-α can also reduce the level of MDA and restore the activity of GSH-PX, reflecting the improvement of oxidative stress (Fig. 6H and I). Immunofluorescence staining showed that compared with the CORT group, after PFT-α treatment, a decrease in the fluorescence intensity of 8-OHDG was observed, indicating a reduction in DNA oxidative damage (Fig. 6J and K). Meanwhile, the number and activation of $IBA1^+$ microglia in mPFC were significantly reduced (Fig. 6L and M). Furthermore, the results of the Western blot experiment showed that compared with the CORT group, the DDIT4 protein level in the PFT-α group was significantly downregulated (Fig. 6N and O). These results indicated that inhibiting the p53 activity in the mPFC region of CORT mice would reduce the expression of DDIT4, alleviate the inflammatory response and oxidative stress, and improve depressive-like behaviors.

3.5. Activation of p53 reverses the antidepressant and neuroprotective effects of curcumin in CORT-treated mice

As previously stated, p53 serves as a critical target of curcumin, and PFT-α mitigates oxidative stress and neuroinflammation-associated depression-like behaviors by suppressing DDIT4 expression. To further explore this, we conducted pharmacological experiments utilizing the p53 activator NSC697923 (NSC) (2 mg/kg/d, i.p) to assess whether activation of p53 would counteract the beneficial effects of curcumin in CORT mice (Fig. 7A and B). The behavioral experiment results showed that, compared with the CORT + Cur group, NSC co-treatment significantly reduced sucrose preference in the sucrose preference test and increased immobility time in both the forced swim test and tail suspended test (Fig. 7C–E). These changes indicate that p53 activation effectively reversed the antidepressant-like behavioral improvements conferred by curcumin. In both the EPM and OFT, compared with the CORT + Cur group, the NSC co-treatment exhibited significantly decreased time spent in the open arms and the center area respectively, indicating that activating p53 activity induced anxiety-like behaviors (Supplementary Fig. 3A–D).

The results of qPCR showed that the relative mRNA expression levels of proinflammatory cytokines TNF-α and IL-1β were significantly elevated in the mPFC of the NSC group compared to the CORT + Cur group (Fig. 7F and G), indicating a resurgence of neuroinflammatory responses. Consistently, NSC treatment led to a marked increase in MDA levels and a decrease in GSH-PX activity relative to curcumin alone (Fig. 7H and I), reflecting aggravated oxidative stress and impaired antioxidant defenses. Correspondingly, DHE fluorescence staining revealed a significantly stronger DHE signal in the CORT + Cur + NSC group, indicating higher ROS accumulation in the mPFC than in curcumin-treated mice (Fig. 7J and K). In parallel, immunofluorescence analysis showed that NSC reversed curcumin's suppressive effect on microglial activation. The number of $Iba1^+$ microglia in the mPFC was significantly increased in the NSC group compared with the CORT+Cur group (Fig. 7L and M), approaching the heightened microglial activation observed in the CORT group.

NF-κB is a heterodimeric transcription factor formed by subunits such as p65/RelA paired with p50 or c-Rel [37]. The p65 subunit provides the principal transactivation function. Its activity is governed by post-translational modifications; phosphorylation at Ser536, in particular, drives p65 nuclear translocation and transcriptional activation [38]. Therefore, total p65 abundance does not indicate NF-κB activation. Activation requires liberation from IκB and acquisition of activating modifications, notably Ser536 phosphorylation, which together enable nuclear accumulation and gene regulation [39].

Furthermore, Western blot results demonstrated that p53 protein levels were significantly upregulated by NSC697923, confirming effective p53 activation, and the expression of the DDIT4, p65 and p-p65 was also increased in the CORT + Cur + NSC group (Fig. 7N–Q). These findings suggest that pharmacological activation of p53 reverses the antidepressant and neuroprotective effects of curcumin by upregulating the expression of DDIT4, p65 and p-p65, indicates that the activation of the p53-DDIT4 axis and its downstream NF-κB signaling pathway may represent a potential target for the action of curcumin.

4. Discussion

Depression remains the leading cause of disability worldwide, contributing to an overwhelming public health burden [40]. While effective treatments have been available for decades, remission rates remain low, relapse rates are high, and the prevalence of the disorder remains notably stagnant, with only 12.7 % of patients receiving minimally adequate treatment [41]. The overactive of oxidative stress and neuroinflammation, characterized as an aberrant response in the brain, has been demonstrated to contribute to the pathogenesis of major depressive disorder through diverse neurobiological mechanisms [42]. Curcumin exerts antidepressant effects by modulating inflammatory responses, oxidative stress, and neurotrophic signaling pathways, functioning as a multi-target therapeutic agent in depression [43,44]. The present study explored the neuroimmune mechanisms underlying the antidepressant effects of curcumin, focusing on the p53–DDIT4–NF-κB signaling axis in the medial prefrontal cortex. Our data show that curcumin can reverse the depressive-like behaviors caused by cortisol, restore synaptic structure, and reduce the activation of microglia and oxidative stress. Mechanistically, curcumin suppressed p53-dependent DDIT4 expression and inhibited NF-κB activation, both of which were elevated under chronic stress. These findings suggest that curcumin alleviates behavioral deficits by targeting convergent oxidative stress and inflammatory pathways, highlighting the p53–DDIT4–NF-κB axis as a promising therapeutic target for mood disorders.

Dysfunction of the mPFC impairs emotional regulation, decision-making, and stress responses, contributing significantly to the pathophysiology of depression [45]. Recent evidence suggests that neuroinflammatory responses and microglial activation in the mPFC region contribute to the induction of depressive-like behaviors in animal

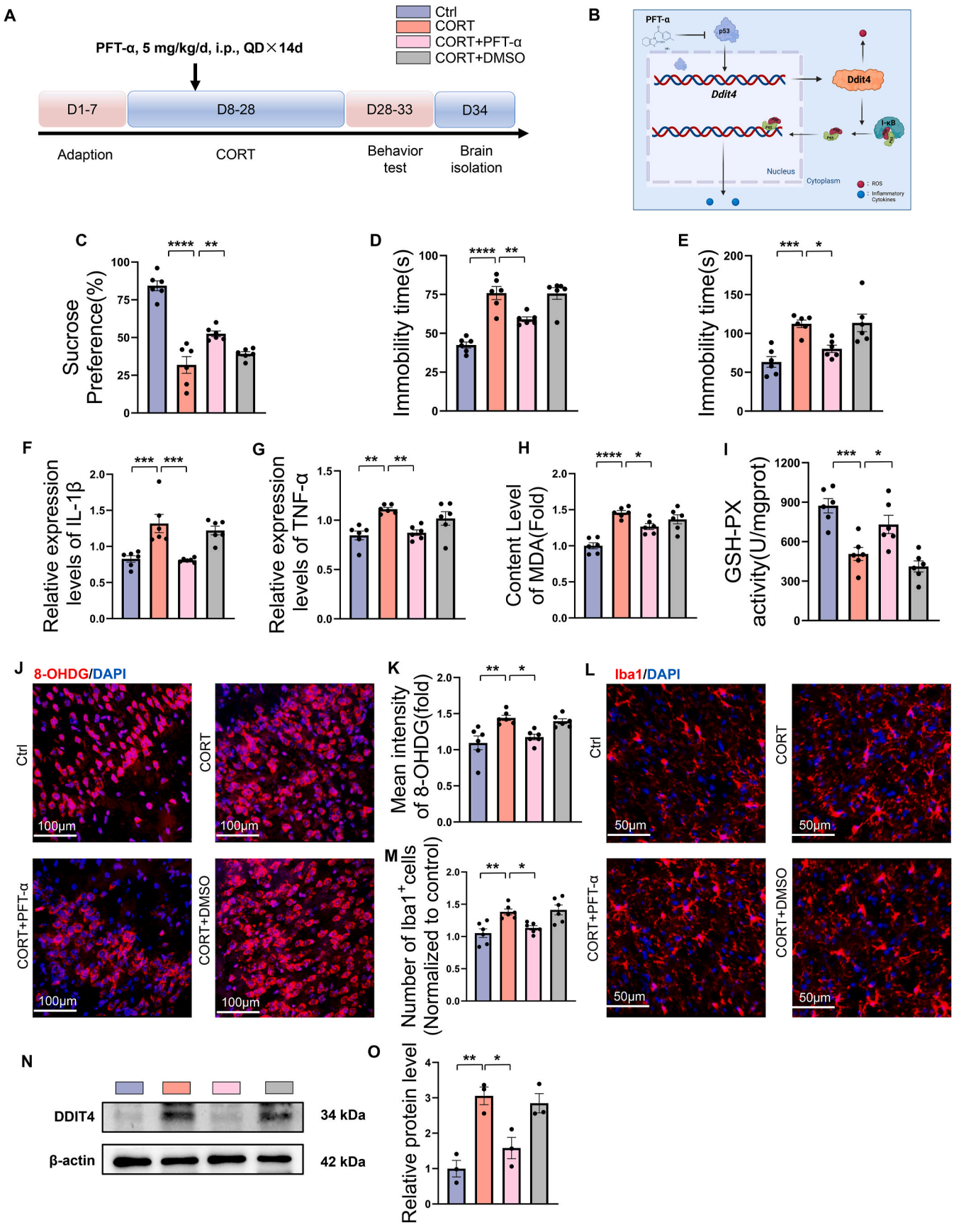

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Fig. 6. PFT-α treatment modulates depression-like behaviors, neuroinflammation, and oxidative stress in **CORT mice.** (**A**) Experimental timeline of PFT-α treatment (5 mg/kg/day, i.p.) in CORT mice. (**B**) The mechanism diagram of the p53 agonist PFT-α. (**C**) SPT showed increased sucrose preference in the PFT-α treatment group compared to CORT mice. (**D**) Immobility time in the FST was reduced in the PFT-α group compared to the CORT group. (**E**) Immobility time in the TST was significantly reduced in the PFT-α treatment group. (**F, G**) qPCR analysis indicated that PFT-α treatment significantly decreased the mRNA levels of pro-inflammatory cytokines IL-1β and TNF-α in the mPFC region compared to CORT mice. (**H**) MDA levels were significantly decreased in the PFT-α group compared to the CORT group. (**I**) GSH-PX activity was higher in the PFT-α treated group compared to CORT mice. (**J**) Immunofluorescence staining of 8-OHDG showed lower oxidative damage in the PFT-α group. Scale bar = 100 μm. (**K**) Quantification of 8-OHDG intensity revealed a reduction in oxidative stress in the PFT-α group. (**L**) Representative images of $Iba1^+$ microglia in the mPFC showed reduced microglial activation in the PFT-α treated group. Scale bar = 50 μm. (**M**) Quantification of $Iba1^+$ cells showed a reduction in the number of activated microglia in the PFT-α group compared to the CORT group. (**N**) Western blot analysis showed that compared with the CORT group, the DDIT4 relative protein level in the PFT-α group was significantly decreased. Data are presented as mean ± SEM. n = 4–6 per group. NS, not significant ($P > 0.05$); *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

models to varying extents [46,47]. Although significant progress has been made in preclinical studies on the antidepressant effects of curcumin [28,48], the mechanisms and signaling pathways through which it exerts neuroprotective effects remain unclear. Our previous studies have shown that curcumin alleviates chronic stress-induced depression-like behaviors by inhibiting IL-1β-mediated neuroinflammation and modulating the NF-κB/SSH1/cofilin pathway in the mPFC [49]. This preliminary finding suggests that curcumin's modulation of neuroinflammation in the mPFC may be key to alleviating depressive-like behaviors, providing a research direction for the treatment of depression. The CORT administration is a useful experimental system for preclinical studies of stress-induced mood disorders, with mice treated with corticosterone demonstrating good face and construct validity as an animal model for studying depression [50,51]. Previous studies have shown that chronic corticosterone administration induces anxiety- and depression-like behaviors alongside neuroinflammatory responses in mice, evidenced by increased forced swim test immobility, reduced sucrose preference, prolonged novelty-suppressed feeding latency, and elevated pro-inflammatory cytokine levels [52,53]. It is well known that lipopolysaccharide (LPS) can affect the central immunity by inducing pro-inflammatory factors and activating inflammasomes, thereby causing depressive-like behaviors in mice [54,55]. Our findings demonstrate that both chronic CORT exposure and repeated LPS administration robustly induced depression- and anxiety-like phenotypes in mice, as reflected by reduced sucrose preference, increased immobility in the forced swim and tail suspension tests, and diminished exploratory behavior in the open field and elevated plus maze. These abnormal behaviors are accompanied by an increase in the expression levels of pro-inflammatory cytokines (IL-1β, TNF-α and IL-6) in the mPFC region, as well as an increase in the number of $Iba1^+$ microglial cells. The results of further Sholl analysis demonstrated that, compared to the control group, CORT administration led to a significant reduction in the number of intersections, a shortening of microglial processes, and a decrease in the number of endpoints in $IBA1^+$ microglia within the mPFC. However, curcumin treatment markedly reversed these alterations, restoring microglial morphology to a less activated state. These results validate the utility of both CORT and LPS paradigms as reliable inflammation-related models of depression. Importantly, curcumin administration significantly ameliorated CORT-induced behavioral deficits, including anhedonia, behavioral despair, and anxiety-like symptoms. This behavioral rescue was associated with a down-regulation of pro-inflammatory cytokine expression and suppression of microglial activation in the mPFC. Together, these data suggest that curcumin exerts antidepressant and neuroprotective effects by targeting neuroimmune dysregulation within the mPFC, supporting its potential therapeutic value in inflammation-driven subtypes of depression.

Excessive oxidation or impaired antioxidative defense leads to the accumulation of free radicals, thereby disrupting cellular homeostasis, a condition known as oxidative stress (OS) [56,57]. Animal studies have further elucidated stress-induced abnormalities in specific brain subregions, including decreased GSH and SOD activity, as well as elevated levels of ROS, MDA, and carbonyl, in the prefrontal cortex (PFC) and hippocampus of depressed rats subjected to chronic unpredictable mild stress (CUMS), chronic restraint stress (CRS) [58–60]. Our study demonstrates that chronic CORT and LPS exposure induce oxidative stress in the mPFC, as shown by increased MDA levels and decreased GSH-PX activity. Of note, curcumin treatment reversed these oxidative alterations in CORT-induced mice, reducing MDA levels, restoring GSH-PX activity, and decreasing oxidative DNA damage (8-OHdG). These results indicate that chronic exposure to CORT not only triggers neuroinflammation but also exacerbates oxidative stress. Curcumin exerts its antidepressant effect at least in part by reducing oxidative damage and enhancing the antioxidant defense capacity.

Human and mouse studies indicate that p53 exerts a context-dependent dual effect on oxidative stress. Under mild stress, p53 transcriptionally upregulates antioxidant defense genes – for example, Sestrin1/2, glutathione peroxidase (GPX1), aldehyde dehydrogenase 4 (ALDH4A1) and TIGAR– which together scavenge reactive oxygen species and promote cell survival [61–63]. In contrast, under severe oxidative stress p53 shifts to a pro-oxidant/apoptotic program. It induces targets such as PIG3 (TP53I3), proline oxidase (POX/PRODH), PUMA and BAX, amplifying ROS levels and triggering mitochondrial apoptosis [64]. This functional switch is biologically significant: it allows damaged cells to be eliminated while permitting mild stress to be countered, integrating redox control with cell-fate decisions. Indeed, murine studies suggest that a proper balance of p53's antioxidant and pro-oxidant activities can influence aging and longevity [64]. Importantly, natural compounds can modulate this p53/ROS axis. For example, the dietary polyphenol curcumin has been reported to elevate ROS, promote mitochondrial translocation of p53, and enhance apoptosis in tumor cells [65]. Taken together, p53 acts as a redox rheostat: depending on stress intensity and post-translational modifications, it directs transcription toward either antioxidant, pro-survival repair or pro-oxidant, apoptosis-driven elimination, thereby maintaining tissue homeostasis and limiting irreversible damage.

At the cellular level, depression is marked by neuronal atrophy and synaptic dysfunction, particularly in the mPFC and hippocampus [66]. Moreover, chronic stress leads to activation of microglia, the brain's resident immune cells, which engulf synapses on nearby pyramidal neurons and thereby contribute to neuronal atrophy [67]. Our study demonstrates that chronic CORT and LPS administration significantly impair morphological plasticity of mPFC neurons, curcumin intervention not only reversed CORT-induced dendritic complexity deficits but also restored spine density. This indicates that curcumin may reverse neuronal atrophy and restore synaptic and structural plasticity by inhibiting the activation of microglia cells induced by chronic stress.

Cells and organisms are continuously exposed to environmental and physiological stressors, including OS, hypoxia, osmotic imbalances, and nutrient fluctuations [68,69]. In response, adaptive pathways are activated, primarily through the induction of stress-responsive proteins, such as DDIT4 (DNA Damage-Inducible Transcript 4) [14]. Previous studies have shown that DDIT4 is upregulated in response to LPS and CORT, thereby enhancing the oxidative and inflammatory response [70,71]. The pioneering research by Ota, K. T. et al. demonstrated that in mice exposed to CUS, the mRNA and protein levels of DDIT4 in the PFC significantly increased, the activity of mTORC1 decreased, and the synaptogenesis dependent on protein synthesis was reduced. Moreover, the high expression of DDIT4 was positively correlated with the

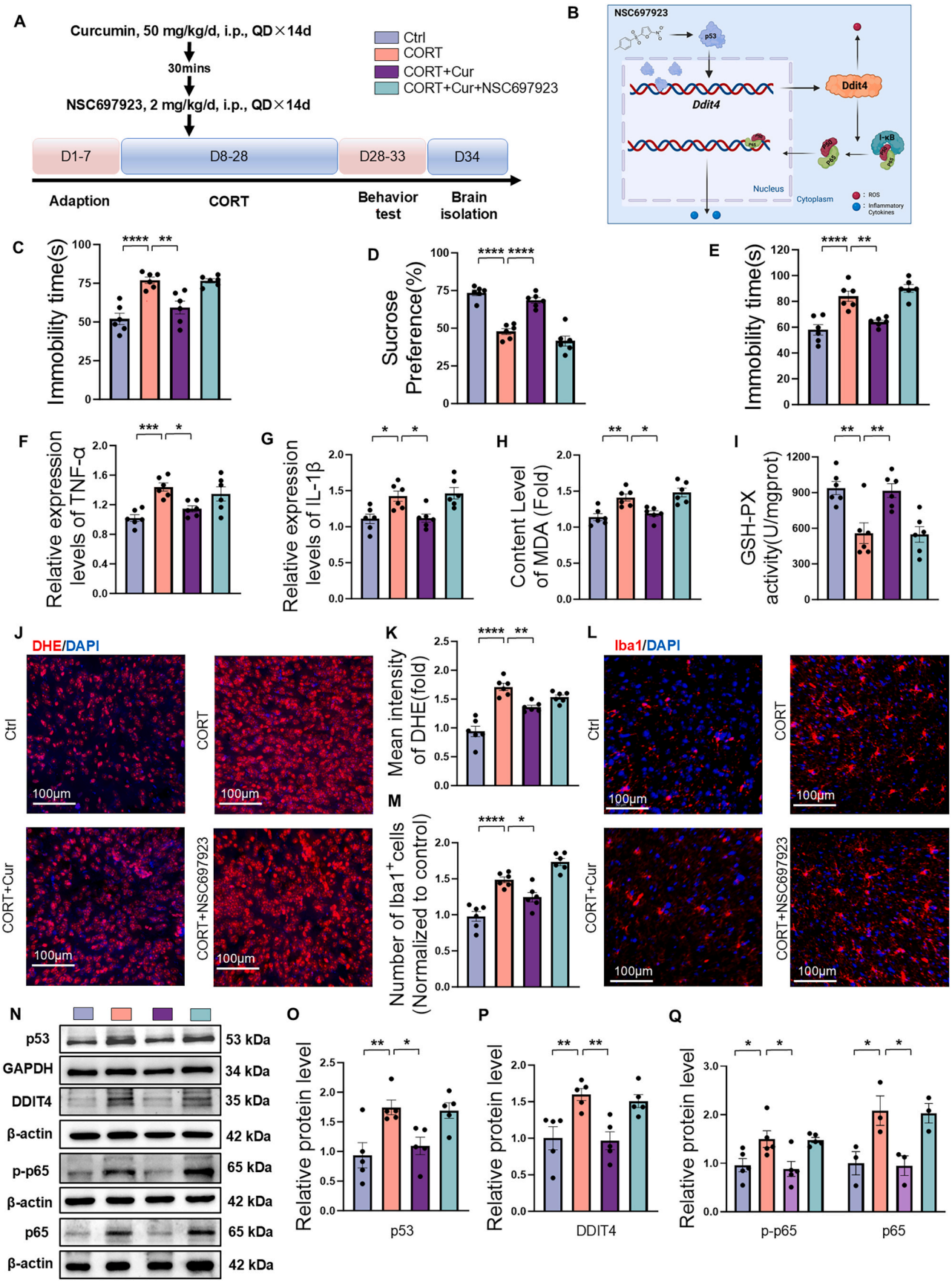

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Fig. 7. Activation of p53 reverses the antidepressant and neuroprotective effects of curcumin in CORT mice. (**A**) Experimental timeline showing curcumin (Cur) and p53 activator NSC697923 (NSC) treatment in corticosterone (CORT) mice. (**B**) The mechanism diagram of the p53 antagonist NSC. (**C**) Immobility time in the forced swim test was significantly higher in the CORT + Cur + NSC group compared to the CORT + Cur group. (**D**) The sucrose preference test showed that, compared with the CORT + Cur group, the sucrose consumption in the CORT + Cur + NSC group was significantly lower. (**E**) Immobility time in the tail suspended test was significantly higher in the CORT + Cur + NSC group compared to the CORT + Cur group. (**F, G**) qPCR analysis indicated higher mRNA levels of TNF-α and IL-1β in the CORT + Cur + NSC group compared to the CORT + Cur group. (**H, I**) MDA levels were significantly higher, and GSH-PX activity was lower in the CORT + Cur + NSC group compared to the CORT + Cur group. (**J, K**) DHE fluorescence intensity was higher in the CORT + Cur + NSC group, indicating increased ROS accumulation. (**L, M**) Immunofluorescence staining of $Iba1^+$ microglia showed significantly more activated microglia in the CORT+Cur + NSC group compared to the CORT + Cur group. n = 6 per group (**N-Q**) Western blot analysis showed increased p53, DDIT4, p-p65 and p65 protein levels in the CORT + Cur + NSC group compared to the CORT + Cur group. For Western blotting, n = 3–5 per group. Data are presented as mean ± SEM. NS, not significant ($P > 0.05$); $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

depressive-like behavior of the mice [13]. However, there are also studies suggesting that DDIT4 may regulate depression-related behaviors through the Akt/FoxO3a signaling pathway rather than the mTORC1 signaling pathway [72]. When exposed to various stressors, multiple transcription factors including p53 and their related upstream signals may affect the expression of DDIT4 [10]. However, it remains unclear whether the upregulation of DDIT4 expression by p53 through direct transcriptional activation is directly involved in the occurrence of neuroinflammatory responses and depressive-like behaviors. Additionally, whether curcumin, through the p53-DDIT4 axis, can alleviate the inflammatory responses and behavioral disorders in CORT mice also requires further investigation. Our bioinformatics results indicate that the p53-DDIT4 axis may be the core hub mediating the antidepressant effect of curcumin. RNA sequencing revealed that the transcriptome of the mPFC was disrupted after exposure to corticosterone, and network pharmacology prioritized p53 from 45 overlapping targets. Protein-protein interaction (PPI) analysis further demonstrated that the p53/DDIT4 axis is a key neuroinflammatory and stress-related module. Molecular docking confirmed the high affinity binding of curcumin to p53, with a stable and dynamic binding, and functional enrichment analysis linked the identified targets to inflammation and synaptic pathways. Western blotting verified the upregulation of p53 and DDIT4 induced by corticosterone. The above results indicate that the p53-DDIT4 axis, this molecular pathway, may be the key target for the therapeutic effect of curcumin in inflammation-related depression. The p53 inhibitor PFT-α can reverse the behavioral defects and neuroinflammation induced by corticosterone. Administration of PFT-α significantly restored the sucrose preference in CORT mice and reduced the immobility time in the FST and TST, indicating that both euphoric disorder and behavioral despair have improved. Moreover, PFT-α treatment reduced the expression of pro-inflammatory cytokines and decreased the number of activated microglia in the mPFC, further demonstrating that p53 is a key regulatory factor for stress-induced neuroinflammation and behavioral changes. In contrast, the p53 activator NSC697923 reversed the therapeutic effect of curcumin. After NSC treatment, mice exhibited more severe depressive-like and anxiety-like behaviors, as well as stronger oxidative and neuroinflammatory responses. In summary, these results emphasize that curcumin, by inhibiting the p53-DDIT4 axis, can effectively alleviate oxidative stress and neuroinflammation, restore synaptic plasticity, and improve depressive-like behaviors. This indicates that curcumin has potential in treating emotional disorders caused by oxidative stress and inflammation, and inhibiting or regulating the p53-DDIT4 axis provides a promising strategy for intervention in such diseases.

Therefore, the inhibitory effect of curcumin on the p53-DDIT4 axis is mediated through which downstream signaling pathways to exert its anti-oxidative, anti-inflammatory and antidepressant effects? Previous studies have shown that activated microglia in the hippocampus enhance cognitive deficits and inflammation in depressive-like mice via NF-κB signaling [73]. In CRS mice, activation of the mTOR/NF-κB/IL-1β pathway in the dentate gyrus promotes neurogenesis, suppresses neuroinflammation, and improves depressive-like behaviors [74]. Our Western blot results show that, compared to the CORT + CUR group, the expression of p65 was significantly reduced in the NSC697923 treatment group. These results suggest that curcumin regulates NF-κB signaling via the p53-DDIT4 axis, alleviating corticosterone-induced neuroinflammation and improving depressive-like behaviors. Targeting the p53-DDIT4 axis may offer a promising therapeutic strategy for inflammation-related mood disorders.

Despite the valuable insights provided by this study into the anti-oxidative and *anti*-neuroinflammation mechanisms underlying curcumin's antidepressant effects, several limitations must be acknowledged. First, while we employed CORT and LPS-induced mouse models to simulate inflammation-driven depression, these models may not fully replicate the complexity of human depression, particularly with respect to the heterogeneous nature of the disease, which involves genetic, environmental, and social factors. In addition,the exact role of p53-DDIT4-NF-κB signaling remains to be fully understood, as this mechanism may be influenced by other co-factors or pathways not yet explored in this study. Future studies should expand the molecular framework by incorporating multi-omics approaches to gain a more comprehensive understanding of curcumin's mechanism of action. In particularly, single-cell RNA sequencing could offer deeper insights into the cellular diversity and specific cell-type interactions within the mPFC and other brain regions involved in depression, thereby revealing the fine-grained molecular changes induced by curcumin treatment. The mechanistic basis underlying why curcumin binding to p53 leads to a reduction in its expression remains insufficiently defined. This phenomenon may be attributable to the pleiotropic nature of curcumin, which, as a multi-target compound, can indirectly suppress the expression and activity of p53 through diverse signaling pathways [75–79]. Lastly, although curcumin shows promise in preclinical models, clinical trials are necessary to assess its safety, efficacy, and potential synergistic effects when combined with other therapeutic agents. Taken together, the findings in the present study support curcumin may serve as a promising strategy for anti-oxidative stress and anti-neuroinflammation in depression via targeting p53-DDIT4-NF-κB signaling.

CRediT authorship contribution statement

Kaiqi Zhang: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation. **Yongsi Zhao:** Writing – original draft, Software, Methodology, Investigation, Formal analysis. **Xiao Chen:** Methodology, Investigation, Formal analysis. **Ye Li:** Methodology, Investigation. **Tian Lan:** Methodology, Investigation. **Mengni Chang:** Methodology, Investigation. **Wenjing Wang:** Methodology, Investigation. **Changmin Wang:** Methodology, Investigation. **Xianghua Zhuang:** Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Bin Zhang:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Conceptualization. **Shuyan Yu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Study approval

The Ethics Committee at Shandong University Animal Care and Use Committee (Jinan, China) approved the protocols of this study

(Approval No.: ECSBMSSDU-2022-2-65). All experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (National Research Council, 1996).

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.redox.2025.103836.

Data availability

Data will be made available on request.

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