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ORIGINAL ARTICLE

# Rhynchophylline Attenuates Tourette Syndrome via BDNF/NF-κB Pathway In Vivo and In Vitro

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## Abstract

Tourette syndrome (TS) is characterized by one of the chronic neuropsychiatric disorders in multiple children, and the pathogenesis of Tourette syndrome (TS) has not been previously elucidated.

The aim of this study was designed to investigate the effects of rhynchophylline (RH) on Tourette syndrome (TS) in rats.

TS model was established in rats and BV2 cells by the selective 5-HT2A/2C agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI). Behavior evaluations including stereotypy recording and autonomic activity test were performed. Inflammatory cytokine levels such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) in serum, striatum, and cell supernatant were detected. The expression levels of BDNF/NF-κB pathway in striatum and BV2 cells were measured by Western blot. Dopamine (DA) and dopamine receptor D 2 (D2) in striatum were also measured.

Data indicated that RH significantly decreased IL-6, IL-1β, and TNF-α in serum, striatum, and cell supernatant of TS model, with altered expression of P-NF-κBp65, P-IκBα, and BDNF in TS rats, and DOI-induced BV2 cells, as evidenced by Western blot analysis and immunohistochemistry analysis. RH also significantly reduced the levels of DA and D2 in striatum.

Our results shown that the regulation of BDNF/NF-κB pathway might be involved in the effects of RH on TS model.

**Keywords** Rhynchophylline · Tourette syndrome · BDNF/NF-κB

## Introduction

Tourette syndrome (TS) is characterized by one of the chronic neuropsychiatric disorders in multiple children (Zinna and Kyriakopoulos 2016). In most cases, TS firstly shows symptoms of a blink of eye with facial tic. However, as the condition progresses, TS presents with the multiple motor tics plus one or more vocal (phonic) tics, which characteristically wax and wane spontaneously (Hawksley et al. 2015). The underlying mechanism of TS remains largely unknown. Previous studies have demonstrated that the pathogenesis of TS mainly involves neurobiochemical factors, environment factors, and hereditary factors (Ben-Shlomo et al. 2016). Besides, numerous studies have revealed that TS is associated with malfunctions in the cortico-basal ganglia pathway (Worbe et al. 2015), especially reducing inhibition within the striatum, the primary input nucleus of the basal ganglia (BG). Two sorts of ways can be applied to fiddle with the output of BG by striatum. The striatum can directly output the nucleus of BG, the plobus pallidus internus (GPi). Additionally, it can control the output of BG by indirect pathway to the GPi via the globus pallidus externus (GPe) (Chang et al. 2002).

Gambirplant (Gouteng), one of the traditional Chinese medicines belonging to the plants of Rubinaceae genus, exerts multiple pharmacological properties. So far, it has been mainly applied to treat ailments in the cardiovascular (Zhang and Sun 2010) and central nervous systems, such as lightheadedness, convulsions, numbness, and hypertension (Zhou and Zhou 2012). Rhynchophylline (RH) is considered as the most active pharmacological component in Gouteng. In consideration of the activities of Gouteng, we hypothesized that RH was also conductive to the treatment of TS.

Inflammation is involved in the pathophysiological process of Tourette's disease. In addition, recent clinical studies have

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indicated that patients with inflammation may tend to present several neurological disorders with the spillover of the inflammatory cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) (Ma et al. 2017). NF-κB is a classic pro-inflammatory transcription factor which contains p50/p65 and IκBα. Meanwhile, multiple studies have demonstrated that NF-κB could trigger and regulate the transcription as well as the expressions of downstream pro-inflammatory cytokines (Lu et al. 2017). Brain-derived neurotrophic factor (BDNF) plays a protective role on nervous system through various mechanisms, which can be combined with Trk receptor to exert the biological effects (Sleiman et al. 2016). The Trk receptor tyrosine kinase family is consisted of TrkA and TrkC, receptors for NGF, and neurotrophic factor 3 (NT3) respectively (Guo et al. 2018), as well as TrkB which mediates the effect of BDNF and also neurotrophic factor 4/5 (NT 4/5). BDNF-TrkB pathway can reduce inflammation (Xu et al. 2017). And inflammation plays an important role in TS (Long et al. 2017b); also BDNF-TrkB pathway was involved in TS. Based on the above, we assumed that BDNF-TrkB signaling pathway plays a role in TS through inflammation.

However, the pathogenesis of Tourette syndrome (TS) has not been previously elucidated. Therefore, the present work was aimed to further illustrate the mechanisms of rhynchophylline (RH) on Tourette syndrome (TS) and its anti-inflammatory activity through BDNF/NF-κB signaling pathway.

## Material and Methods

### Chemicals and Reagents

RH was purchased from Tianjin Chase Sun Pharmaceutical. Co., Ltd. (Tianjin, China). The selective 5-HT2A/2C agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI) was purchased from Sigma–Aldrich (Shanghai, China). Enzyme-linked immunosorbent assay (ELISA) kits for the detection of IL-6, IL-1β, and TNF-α were obtained from Nanjing KeyGEN Biotech. CO., LTD. (Nanjing, China).

### Animals

A total of 50 male Wistar rats (8 weeks, 180–200 g) were purchased from Beijing Vital River Co., LTD (License number: SCXK (Jing) 2012-0001) and maintained under specific pathogen-free conditions in GLP laboratory in accordance with institutional guidelines. The animals were kept in a conventional animal facility with a 12 h light/12 h dark cycle circumstance at a constant temperature of 22–24 °C. The rats had free access to standard water and food pellets ad libitum. All of the experiments were performed in full compliance with the guidelines of the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals approved by the National Institutes of Health (NIH Publication No. 85-23, revised 1996). Animal care and experimental protocols were approved by the Nanjing University of Chinese Medicine Committee.

### Experimental Protocols

Rats were randomly separated into five groups (10 rats in each group): control group, DOI-treated group, DOI+ tiapride (25 mg/kg) group, DOI + RH (20, 40 mg/kg) group. DOI was intraperitoneally injected with 1 mg/kg once a day for 21 days to induce Tourette syndrome in rats. The control group and DOI group were intraperitoneal injected with normal saline or DOI. RH group were treated with RH orally, and RH was given 2 h before DOI was administrated. While tiapride group were treated with drugs orally as the positive and also was given 2 h before DOI administration. These protocols were according to our previous reports (Long et al. 2017a, b).

### Behavioral Experiment

#### Stereotypy Recording

Stereotypy recording was conducted according to previous report (Zhang et al. 2016). Briefly, in order to evaluate stereotypes, each animal was observed for 2 min after DOI injection and drug administrations. The average score was calculated for each rat.

#### Autonomic Activity Test

We connected the animal behavior analysis system with the spontaneous activity video analysis system (Zhang et al. 2016). Each group is a random sequence. One rat was placed in each active compartment. Rats were conditioned for 5 min before recording. The activity of each rat was then recorded for 5 min. We chose the total distance as an objective index to judge the autonomous activity of rats. The box was kept in a cool place and the environment was quiet.

### Cell Culture

BV2 cells were cultured in a moist incubator composed of 95% air and 5% CO2 at 37 °C in an improved eagle culture medium (DMEM) in Dulbecco with 10% fetal bovine serum and 1% antibiotic (penicillin/streptomycin).

## Cell Viability Assay

Cell viability was determined by MTT assay. BV2 cells were placed in RH (1, 2, 4, 8, 16, 32, 64 μM) at different concentrations for 2 h and then incubated with 1 μM DOI for 4 h. The cells were incubated with 20 μL MTT (5 mg/mL) solution for 4 h and 150 μL dimethyl sulfoxide (DMSO) was added after co-incubation. The absorbance value was measured with a microplate spectrophotometer at a test wavelength of 570 nm. The data is expressed as a percentage of the average absorbance of the control. Cell survival rate (%) = (*A* treatment / *A* control) × 100%.

## Inflammatory Cytokines in Serum, Striatum, and Cell Supernatant

The level of IL-1β, IL-6, TNF-α in serum, striatum, and cell supernatant was detected by enzyme-linked immunosorbent assay (ELISA) kits, according to the manufacturer's instructions (Nanjing KeyGEN Biotech. CO., LTD., Nanjing, China). The results of the concentrations of inflammatory cytokines were expressed as pictograms per milligram protein.

## Western Blot

Striatum tissue and BV2 cells were homogenized in ice-cold RIPA buffer containing 0.1% phenylmethylsulfonyl fluoride. The total protein content was quantified by Bicinchoninic acid (BCA) protein assay kits (Beyotime, Nanjing, China) Equal amounts of protein were loaded on 8% to 12% SDS-polyacrylamide gel electrophoresis. The transferred PVDF membranes from SDS-polyacrylamide gel electrophoresis were blocked in skim milk at room temperature over 2 h. Then, the PVDF membranes were incubated with the appropriate concentration of specific antibodies overnight at 4 °C. On the second day, PVDF membranes were incubated with second antibody at room temperature for 1 h after washing three times by TBST. The immunoreactive bands were interacted with an enhanced chemiluminescence (ECL) kit and visualized on a gel imaging system (Tanon Science & Technology Co., Ltd., China).

## Immunohistochemistry

The expressions of BDNF and P-P65 in the striatum were evaluated by immunohistochemistry staining. In brief, the striatum tissues were embedded in paraffin and sectioned. Then, the paraffin sections were deparaffinized in xylene, rehydrated by ethanol, and incubated with 3% hydrogen peroxide. Striatum samples were blocked with 3% BSA and incubated with respective primary antibody at 4 °C overnight. After incubated with secondary and three antibodies, samples were stained with DAB and observed under a microscope.

## Determination of DA in the Striatum

Striatum tissue samples were homogenized with 1:3 (g:mL) normal saline. After centrifugation at 12000 rpm for 20 min, supernatant was collected, then 100-μL sample was mixed with 10 μL of internal standard solution (2 g/mL, paracetamol). The mixture was deproteinized with 300 μL of acetonitrile, vortexed for 5 min, and then centrifuged at 15000 rpm for 10 min. One hundred fifty microliters of water was added to dilute 150 μL of supernatant. After vortex mixing for 5 s, the mixture was transferred to an autosampler vial and 10 μL was injected into the LC-MS/MS system for analysis.

## Statistical Analyses

Results were presented as mean ± S.D. Multiple comparisons were performed by analysis of variance (ANOVA) with Newman–Keuls post hoc test by SPSS 17.0 (SPSS Inc., USA). A $p$ value less than 0.05 was considered statistically significant.

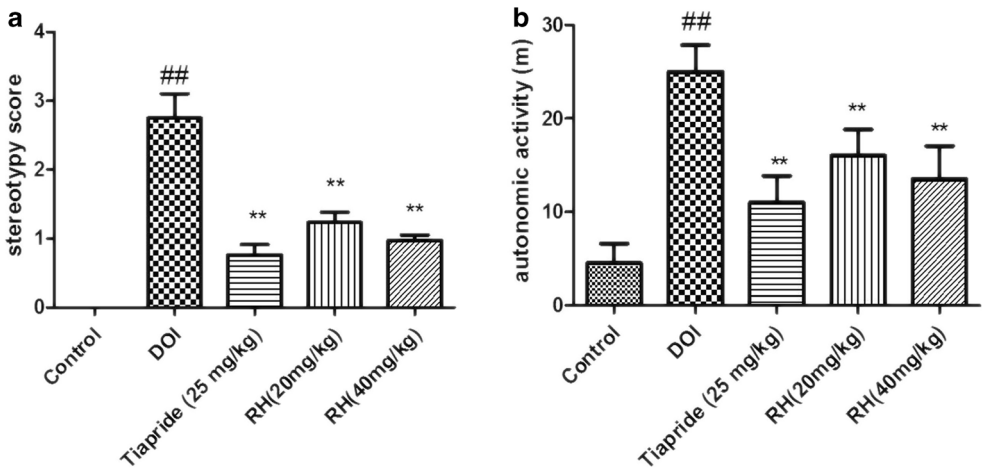


**Fig. 1** The effects of RH on stereotypy score (**a**) and autonomic activity (**b**) ($n = 10$). The data are expressed as mean values ± SDs. $^{\#\#}p < 0.01$ compared with control group; $^{\#}p < 0.05$ compared with control group; $^{**}p < 0.01$ compared with model group; $^{*}p < 0.05$ compared with model group

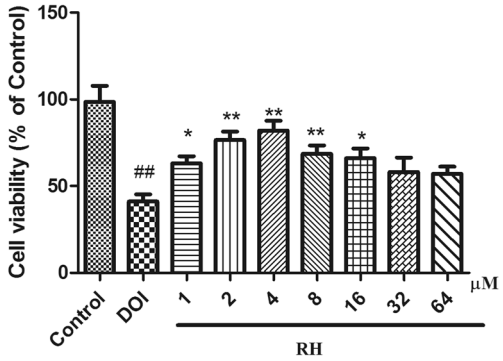


**Fig. 2** Effects of RH on cell viability. The data are expressed as mean values ± SDs. $^{\#\#}p < 0.01$ compared with control group; $^{\#}p < 0.05$ compared with control group; $^{**}p < 0.01$ compared with model group; $^{*}p < 0.05$ compared with model group

## Results

### The Effects of RH on Stereotypy Score

As shown in Fig.1a, the TS rat induced by DOI showed abnormal stereotypy score compared with the control group, and RH significantly decreased stereotypy score compared with the TS group.

### The Effects of RH on Autonomic Activity

As shown in Fig.1b, the total distance of TS rats showed a significant increase compared with the control group, and RH significantly decreased the total distance compared with the TS group.

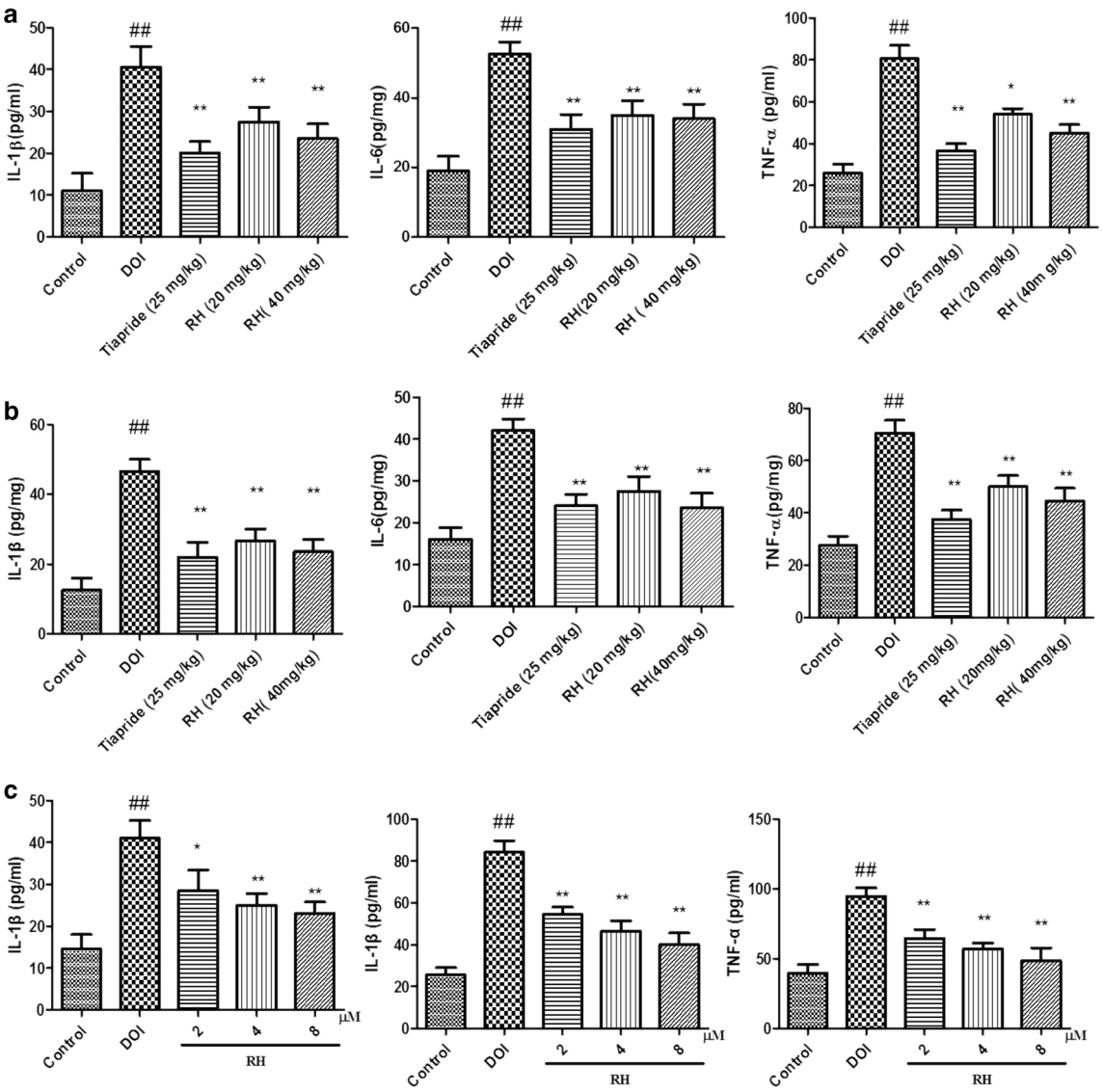


**Fig. 3** Effects of RH on the contents of TNF-α, IL-1β, and IL-6 in serum (**a**), striatum (**b**), and cell supernatant (**c**) ($n = 10$). The data are expressed as mean values ± SDs. $^{\#\#}p < 0.01$ compared with control group; $^{\#}p < 0.05$ compared with control group; $^{**}p < 0.01$ compared with model group; $^{*}p < 0.05$ compared with model group

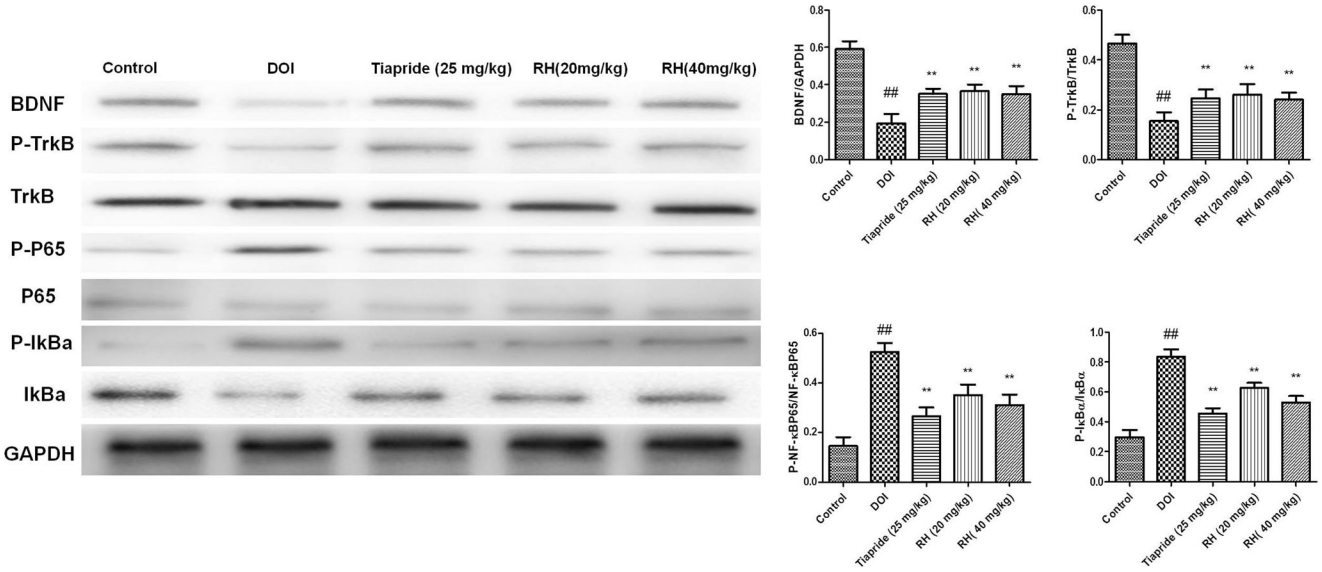


**Fig. 4** Effects of RH on BDNF-mediated NF-κB pathway in striatum ($n = 6$). The data are expressed as mean values ± SDs. $^{\#\#}p < 0.01$ compared with control group; $^{\#}p < 0.05$ compared with control group; $^{**}p < 0.01$ compared with model group; $^{*}p < 0.05$ compared with model group

## Effects of RH on Cell Viability

MTT results showed that DOI significantly reduced the cell viability of BV2 cells and increased the cell viability to varying degrees. Our data show that DOI leads to a loss of cell viability of BV2 cells and can be effectively restored by RH (2, 4, 8 uM) (Fig. 2).

## Effects of RH on Inflammatory Cytokines in Serum, Striatum, and Cell Supernatant

The levels of IL-1β, IL-6, TNF-α in serum, striatum, and cell supernatant were detected. As expected, the levels of IL-1β, IL-6, and TNF-α were significantly increased in serum, striatum, and cell supernatant in TS rats compared with the control group. RH or tiapride significantly decreased the levels of IL-1β, IL-6, and TNF-α in serum, striatum, and cell supernatant induced by DOI exposure (Fig. 3).

## Effects of RH on BNDF/NF-κB Pathway in Striatum

As shown in Fig. 4, increased levels of p-NF-κBp65 and p-IκBα, and decreased levels of BNDF, P-TrkB, and TrkB were observed in DOI rats compared with those in the control group. In contrast, RH (20, 40 mg/kg) and tiapride (25 mg/kg) were able to reverse the changes.

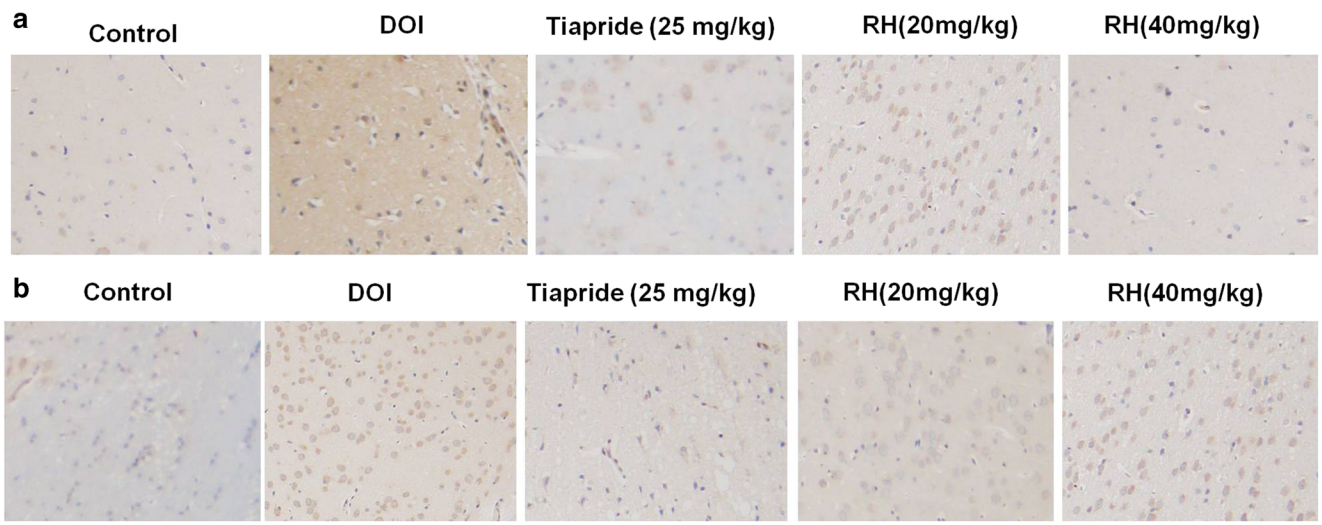


**Fig. 5** Effects of RH on BDNF (**a**) and p-NF-κB (**b**) pathway in striatum (× 200) ($n = 6$)

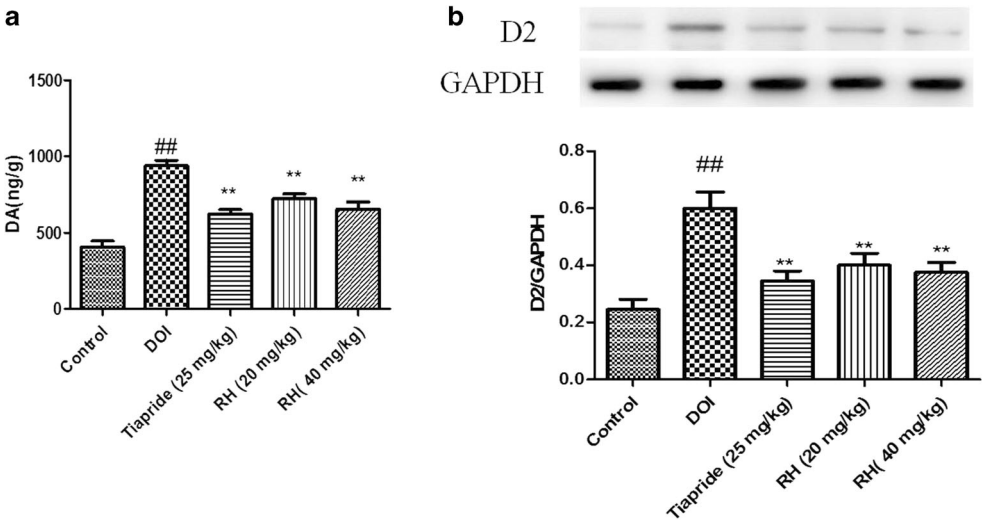


**Fig. 6** Effects of RH on DA (**a**) and D2 (**b**) in striatum ($n = 10$). The data are expressed as mean values ± SDs. $^{\#\#}p < 0.01$ compared with control group; $^{\#}p < 0.05$ compared with control group; $^{**}p < 0.01$ compared with model group; $^{*}p < 0.05$ compared with model group

### Effects of RH on BDNF and p-NF-κBp65 Pathway in Striatum

The increased level of p-NF-κBp65 and the decreased level of BDNF in DOI-stimulated rats from immunohistochemistry are shown in Fig. 5. RH reduced the levels of p-NF-κBp65 and increased levels of BNDF.

### Effects of RH on DA and D2 in Striatum

As shown in Fig. 6, the level of DA and the expression of D2 in striatum were increased in DOI-induced TS rats, while RH (20, 40 mg/kg) and tiapride (25 mg/kg) were able to reduce the level of DA and the expression of D2 in striatum.

### Effects of RH on BNDF/NF-κB Pathway in BV2 Cells

As shown in Fig. 7, increased levels of p-NF-κBp65 and p-IκBα, and decreased levels of BNDF, P-TrkB, and TrkB were observed in DOI-induced BV2 cells compared with those in the control group. In contrast, RH (2, 4, 8 uM) was able to reverse the changes.

## Discussions

As a Chinese traditional medicine, Rubiaceae is capable of clearing-heat and planning-liver, dispelling wind, and relieving convulsion with wide application to treat hypertension, cerebral neurologic diseases, and cerebrovascular

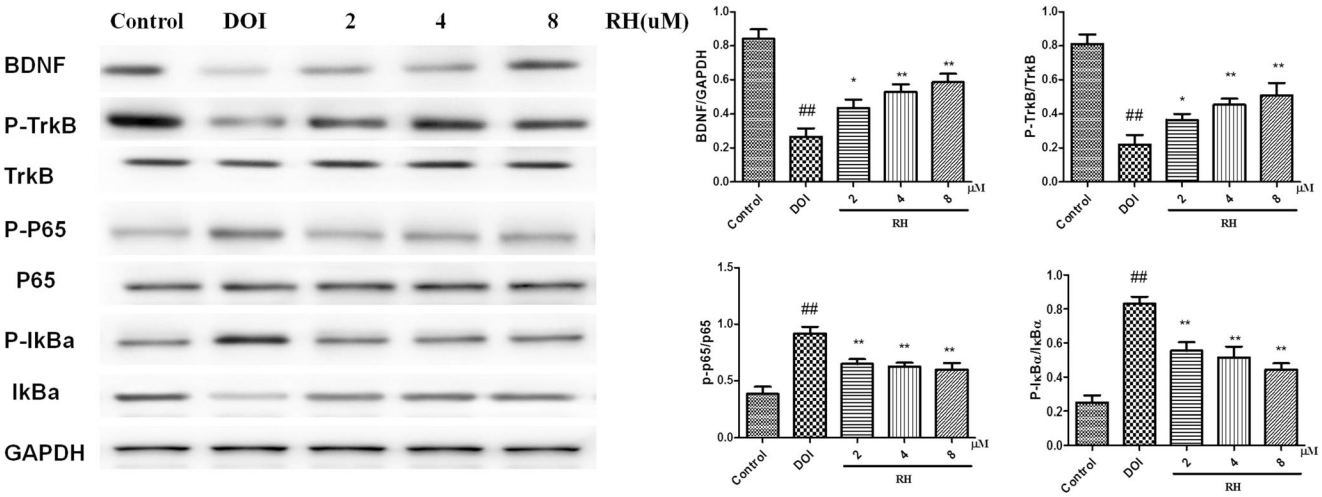


**Fig. 7** Effects of RH on BNDF/NF-κB pathway in BV2 cells. The data are expressed as mean values ± SDs. $^{\#\#}p < 0.01$ compared with control group; $^{\#}p < 0.05$ compared with control group; $^{**}p < 0.01$ compared with model group; $^{*}p < 0.05$ compared with model group

diseases (Sakakibara 1994). Rhynchophylline (RH) is the major ingredient in Rubiaceae. Until now, numerous studies have proved that RH exerts effects on cardiovascular and central nervous systems including anti-epileptic (Zhou and Zhou 2010). However, the function of RH on TS has not been well characterized. Herein, our research attempted to investigate the protective effect of RH on DOI-induced TS in rats.

Tourette syndrome (TS) is a common disease, which is mainly manifested by involuntary motor and phonic tics as the main symptom. Tics are involuntary, repetitive muscle contractions that produce stereotyped movements (motor tics) or sounds (vocal tics) (Fründt et al. 2017). According to clinical studies, patients undergoing TS may exhibit attention deficit hyperactivity disorder (ADHD), obsessive compulsive disorder (OCD), and even self-injurious behaviors which cause serious injury to patients [20]. In addition, TS is associated with dysfunctional signaling by the neuromodulator dopamine. However, despite extensive studies concerning the relevant pathogenesis has been reported to date, there has no effective treatment for TS. At present, the establishment of model of TS is mainly achieved via injection of the selective 5-HT2A/2C agonist 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane (DOI), which is obvious and stable compared with other models (Tizabi et al. 2001).

In most recent studies, the pathological process of TS is accompanied with inflammation. Meantime, recent clinical studies have also shown that when suffering from the inflammation, circulating pro-inflammatory cytokines can trigger extensive changes in serum and striatum, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). TNF-α is produced by monocytes, with immunomodulatory and inflammatory regulatory effects. IL-1β is a pro-inflammatory cytokine involved in tissue destruction or edema. IL-6 exhibits a variety of immune regulatory functions, which enhance the immune function of the body (Bellinghausen et al. 2005). The result indicated that the inflammatory cytokines IL-1β, IL-6, and TNF-α were significantly increased in serum, striatum, and cell supernatant. However, the levels of inflammatory cytokines were significantly decreased by RH or tiapride.

Many studies show that dysfunction of dopaminergic system plays an important role in the pathophysiology of TS. As a result, people have carried out a lot of clinical and animal experimental studies on the DA production, release, transport, transporters and their genes, the relationship between DA receptor and receptor genes, and TS, but the research results are not consistent. Most scholars believe that hyperactivity of the dopamine system is the cause of Tourette syndrome. In this study, the levels of DA and the expression of D2 were increased after DOI stimulated. However, the levels of DA and the expression of D2 were significantly decreased by RH (20, 40 mg/kg) or tiapride (25 mg/kg). The above shown that rhynchophylline could improve Tourette syndrome by regulating dopaminergic nervous system.

Finally, Western blot was used to explore the mechanism of RH on DOI-induced TS. NF-κB is a classic pro-inflammatory transcription factor activated by IκBα (Fan et al. 2017). Nuclear factor (NF)-κB, a pro-inflammatory transcription factor, is one of the most important factors participating in regulating the generation of pro-inflammatory mediators generation (Ho et al. 2017). Besides, brain-derived neurotrophic factor (BDNF) is one of the most important members of the neurotrophin family. The neurotrophic and neuroprotective effects of BNDF are mediated by combining with the high affinity receptor TrkB. The current study indicated that increased levels of p-NF-κBp65 and p-IκBα, and decreased levels of BNDF, P-TrkB, and TrkB were observed in DOI-induced rats and BV2 cells. In contrast, administration of RH or tiapride treatment was capable of reversing the effects of DOI injection on inflammation-related proteins. And Western blot analysis showed that the mechanism of TS may be related to BDNF/NF-κB pathway. In conclusion, RH has positive effects on DOI-induced TS, where the regulation of BDNF/NF-κB pathway may be involved in the pathological progression.

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**Authors' Contributions** Long Hongyan and Ruan Jie designed the experiments and wrote articles, Zhang Mengjiao and Wang Chunyan performed the experiments, and Huang Yaruo analyzed and processed data.

## Compliance with Ethical Guidelines

All of the experiments were performed in full compliance with the guidelines of the Principles of Laboratory Animal Care and the Guide for the Care and Use of Laboratory Animals approved by the National Institutes of Health (NIH Publication No. 85-23, revised 1996). Animal care and experimental protocols were approved by the Nanjing University of Chinese Medicine Committee.

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