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Resveratrol upregulates brain-derived neurotrophic factor (BDNF) levels in reserpine-induced mice: A mechanistic extension study

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Multiple research reports have shown that resveratrol exerts antidepressant-like effects through upregulation of brain-derived neurotrophic factor (BDNF) in various depression models. However, the operation of this mechanism in the classic reserpine-induced model, which depletes monoamines via inhibition of the vesicular monoamine transporter, remains poorly understood. Twenty-five mice served as subjects: The control group (group I, n=5) was treated orally with mormal saline (0.9% W/V). The remaining 20 mice were injected intraperitoneally with reserpine (0.2 mg/kg/day) for 16 days to induce depressive-like symptoms. Afterward, they were randomly divided into 4 groups (groups II-V, n=5). They were treated every other day with intraperitoneal injections of 0.2 mg/kg reserpine and once daily with 20 mg/kg fluoxetine, along with graded doses of resveratrol (30 mg/kg, 60 mg/kg). The treatment regimen lasted 15 days. Reserpine significantly ($p < 0.05$) reduced whole-brain BDNF levels and this reduction was significantly attenuated by resveratrol 60 mg/kg ($p < 0.05$) compared with the reserpine group alone. This study provides evidence that resveratrol at a higher dose upregulates BDNF in the reserpine model, thereby extending the neurotrophic mechanism to this classic monoamine-depletion paradigm.

Key words: Resveratrol, reserpine, brain-derived neurotrophic factor (BDNF), hippocampus, neurotrophic hypothesis, depression.

INTRODUCTION

Depression is a leading cause of disability worldwide, and the neurotrophic hypothesis proposes that reduced brain-derived neurotrophic factor (BDNF) contributes to hippocampal atrophy and depressive symptoms. The restoration of BDNF is considered a key mechanism of antidepressant efficacy (Arosio et al., 2021; Crawford et al., 2023; Varghese et al., 2025). Resveratrol, a natural polyphenol, has been extensively documented to exert antidepressant-like effects through upregulation of BDNF in various preclinical models, including lipopolysaccharide-induced (Liu et al., 2016), chronic unpredictable mild stress (Yang et al., 2017), chronic restraint stress (Zhang

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et al., 2017), and ovariectomy-combined stress models (Hiu et al., 2025). Despite this extensive evidence across multiple models, including inflammation-induced lipopolysaccharide (LPS), stress-induced (Chronic Unpredictable Mild Stress (CUMS), chronic restraint stress (CRS)), and surgical ovariectomy (OVX) models (Liu et al., 2016; Yang et al., 2017; Zhang et al., 2017; Hiu et al., 2025), the literature shows that no study has examined whether resveratrol modulates BDNF in the reserpine model, a classic pharmacological model of monoamine depletion (Moore et al., 2018). Reserpine induces depression through a distinct mechanism: irreversible inhibition of the vesicular monoamine transporter (VMAT), leading to monoamine depletion and secondary oxidative stress (Zhao et al., 2019; Alwindi and Bizanti, 2023). This model remains relevant for understanding depression pathophysiology and testing potential therapeutics (Strawbridge et al., 2023). While extensive behavioral evidence has established resveratrol's antidepressant-like effects across multiple rodent models (Zhang et al., 2012; Moore et al., 2018; Wu et al., 2025; Kharazmi et al., 2026), the present study focuses specifically on the neurotrophic mechanism in the reserpine model; a context where BDNF modulation by resveratrol remains unexplored (Wu et al., 2025; Kharazmi et al., 2026). The study aims to investigate whether resveratrol upregulates BDNF expression in reserpine-treated mice, thereby extending the neurotrophic mechanism in this classic pharmacological model.

MATERIALS AND METHODS

Animal cages and feeders, syringes and cannula, cotton wool, towel, weighing balance, Stopwatch, 70% alcohol, and brain-derived neurotrophic factor ELISA assay kit.

Chemical and drug preparation

Reserpine (Sigma-Aldrich, USA), Tween 80, Resveratrol, Fluoxetine and all other chemicals were of analytical grade. Reserpine was dissolved in 0.1 mg/mL of distilled water + 1% Tween 80 (0.1 mg/mL). Resveratrol was reconstituted in distilled water (15 mg/ml) and 0.1 mL of Tween 80, to enhance resveratrol's solubility for oral administration. While, fluoxetine was dissolved in distilled water (4 mg/ml). The use of Tween 80 is a standard and accepted practice for administering lipophilic compounds orally (Fine-Shamir and Dahan, 2024). The drug doses used were carefully selected following a preliminary study (Khadrawy et al., 2018).

Experimental animals

Twenty-five male Swiss mice were obtained from the animal house of the Department of Human Physiology, Ahmadu Bello University, Zaria. The animals were housed and maintained under experimental conditions at room temperature (25 to 26°C), relative humidity, and light. The animals were allowed to acclimatize for one week before the experiment began and were fed food and water *ad libitum*. Ethical approval for the experimental protocol was sought and obtained from the Ahmadu Bello University Animal Ethical Committee, with approval number ABUCAUC/2024/019.

Experimental design and grouping

At the beginning of the experiment, five mice were randomly selected to serve as the control group. They were fed pelletized feed and provided with tap water during the induction phase, and were administered normal saline orally during the treatment phase. Depressive-like symptoms were induced in the remaining twenty mice by daily injections of reserpine (0.2 mg/kg/day) for sixteen days. Thereafter, the twenty reserpine-induced mice were randomly divided into four groups of five mice each (n = 5) and treated for fifteen days according to the following regimen (Antkiewicz-Michaluk et al., 2014; Khadrawy et al., 2018; Fahmy et al., 2022). The technician administering the injections and oral treatments was not blinded to group allocation due to logistical constraints. However, the researcher who conducted the biochemical assays was blinded, as all samples were coded until the completion of the experiment. The overall groupings were as follows:

i) Group 1: normal control treated with 0.9 % saline
ii) Group 2: negative control, treated every two successive days with i.p injection of reserpine (0.2 mg/kg).
iii) Group 3: positive control, treated every two successive days with an i.p. injection of reserpine (0.2 mg/kg) and daily oral administration of fluoxetine 20 mg/kg.
iv) Group 4: Treated every two successive days with an i.p. injection of reserpine (0.2 mg/kg) and daily oral administration of resveratrol 30 mg/kg reconstituted with 0.1 ml Tween 80.
v) Group 5: Treated every two successive days with an i.p. injection of reserpine (0.2 mg/kg) and daily oral administration of resveratrol 60 mg/kg reconstituted with 0.1 ml Tween 80 (Antkiewicz-Michaluk et al., 2014; Khadrawy et al., 2018; Fahmy et al., 2022).

Preparation of brain homogenates

All mice were fasted overnight and subsequently anaesthetized with a combination of ketamine (25 mg/kg) and diazepam (3 mg/kg), administered intraperitoneally, after which they were sacrificed by cervical dislocation. Each mouse was then decapitated, and the whole brain was removed and homogenized in ice-cold phosphate buffer (pH 7.4). The homogenate was centrifuged to obtain a clear supernatant, which was used to estimate brain-derived neurotrophic factor (BDNF) levels using an enzyme-linked immunosorbent assay (Kuzay et al., 2022).

Estimation of brain-derived neurotrophic factor content

The BDNF content in the brain homogenates was estimated using a mouse BDNF ELISA Kit (Wuhan Fine Biotech Co., Ltd., Wuhan, China), based on the manufacturer's instructions. Whole-brain tissue samples were homogenized in ice-cold RIPA buffer containing protease inhibitor cocktail (1:100) and phosphatase inhibitors (1:100). The homogenization volume was fixed at 200 µL per 10 mg of tissue wet weight. Homogenates were centrifuged at 12,000 × g and 4°C for 5 min, and the supernatant was collected. The same volume of supernatant (50 µL) was used for BDNF ELISA in all

Table 1. Effect of resveratrol on brain-derived neurotrophic factor in reserpine-induced depression-like phenotype in mice.

Groups	BDNF (ng/ml)
NS	71.24±2.94[a]
RESP	65.91±1.26[a]
FLUX20	81.93±0.67[b]
RESV30	66.59±1.63[a]
RESV60	86.11±3.68[b]

a-b = Means with different superscript letters are significantly ($p < 0.05$) different. BDNF = Brain-derived neurotrophic factor; NS = normal saline, RESP = reserpine 0.2mg/kg, FLUX20 = fluoxetine 20 mg/kg, RESV30 = resveratrol 30 mg/kg, RESV60 = resveratrol 60 mg/kg, n = 5.

samples. All steps were performed on ice to prevent protein degradation. Briefly, antibody was pre-coated unto a 48-well plate and the biotin conjugated antibody was used as detection antibiodies. The standards, test samples and biotin conjugated detection antibody were added to the wells subsequently, and washed with wash buffer. Tetramethylbenzidine (TMB) substrates were used to visualize Horseradish Peroxidase (HRP) enzymatic reaction. TMB was catalyzed by HRP to produce a blue colour product that changed into yellow after adding acidic stop solution. The density of yellow was proportional to the target amount of sample captured in the plate. The absorbance was read off at a wavelength of 450 nm in a microplate reader and the concentration of the target was then calculated.

Data analyses

Data obtained from each group were expressed as mean ± SEM. The data were analyzed using one-way ANOVA with Tukey's post-hoc test to determine the levels of significance between the control and experimental groups. All analyses were performed using IBM SPSS Statistics for Windows, version 22. 0 (NY, USA: IBM Corp, 2013). Values of $p < 0.05$ were considered significant.

RESULTS

Table 1 and Figure 1 show the effect of resveratrol on BDNF levels in mice with reserpine-induced depressive-like phenotypes. The BDNF concentration significantly ($p < 0.05$) decreased in mice treated with 0.2 mg/kg reserpine alone (65.91 ± 1.26 ng/mL) compared to mice that received 0.2 mg/kg reserpine + 20 mg/kg fluoxetine (81.93 ± 0.67 ng/mL) and 0.2 mg/kg reserpine + 60 mg/kg resveratrol (86.11 ± 3.68 ng/mL). The significant difference between 0.2 mg/kg reserpine + 60 mg/kg resveratrol (86.11 ± 3.68 ng/mL) and 0.2 mg/kg reserpine + 60 mg/kg resveratrol (66.59 ± 1.63 ng/mL) shows a dose-dependent effect of resveratrol administration.

DISCUSSION

The present study demonstrates that resveratrol, at a higher concentration, upregulates whole-brain BDNF levels in reserpine-induced mice. This finding extends the well-established neurotrophic mechanism of resveratrol (Moor et al., 2018; Colucci-D'Amato et al., 2020; Kharazmi et al., 2026). Reserpine treatment produced a numerical reduction in BDNF levels compared to normal saline; however, this difference was not statistically significant. Fluoxetine (20 mg/kg) and resveratrol at 60 mg/kg (but not 30 mg/kg) significantly increased BDNF levels compared to the reserpine-treated group ($p < 0.05$). The observed upregulation of BDNF in response to a high dose of resveratrol in a reserpine-induced depression model is consistent with multiple studies demonstrating similar effects in other models (Basta et al., 2023; Lazarova et al., 2024; Fiore et al., 2025; Jie et al., 2025). Xu et al. (2025) reported BDNF upregulation in ovariectomized mice; Ge et al. (2015) showed comparable effects in a lipopolysaccharide model; and Yan et al. (2017) demonstrated BDNF upregulation in a chronic unpredictable mild stress model. Resveratrol has also been shown to induce BDNF/p-cofilin1 upregulation in chronic restraint stress (Chen et al., 2021). These findings extend to the reserpine model, confirming that the BDNF-related mechanism is robust across diverse depression paradigms (Numakawa et al., 2025; Toader et al., 2025). Resveratrol at a higher dose restored BDNF levels in this model, suggesting that the neurotrophic mechanism operates independently of the primary insult, whether inflammatory (LPS) (Lis et al., 2025), stress-induced (CUMS/CRS) (Moore et al., 2018; Chen et al., 2021), hormonal (OVX) (Xu et al., 2025), or pharmacological (reserpine) (Govindarajulu et al., 2021).

Several limitations should be acknowledged. Behavioral endpoints (e.g., forced swim test, sucrose preference test, tail suspension test) were not assessed to directly correlate BDNF changes with antidepressant-like effects (Wang et al., 2013; Kristiyani et al., 2024). Additionally, a power analysis was not performed. The sample size (n = 5 per group) was selected based on widely accepted standards in rodent biochemical studies (Kramer and Front, 2017). The non-significant difference between reserpine and normal saline groups may therefore reflect insufficient statistical power to detect a modest reduction in BDNF, rather than a true absence of effect.

Furthermore, total protein normalization was not conducted. However, all samples were processed under identical conditions (same tissue weight per volume of homogenization buffer and same aliquot volume for ELISA), and no significant differences in tissue weight or homogenate protein yield were observed between groups. Although this does not replace formal normalization, it reduces the likelihood of systematic bias. Extensive literature linking BDNF to antidepressant efficacy (Chen et al., 2021; Lis et al., 2025; Xu et al., 2025) provides strong correlational and indirect support for the translational relevance of these findings. Future studies using the

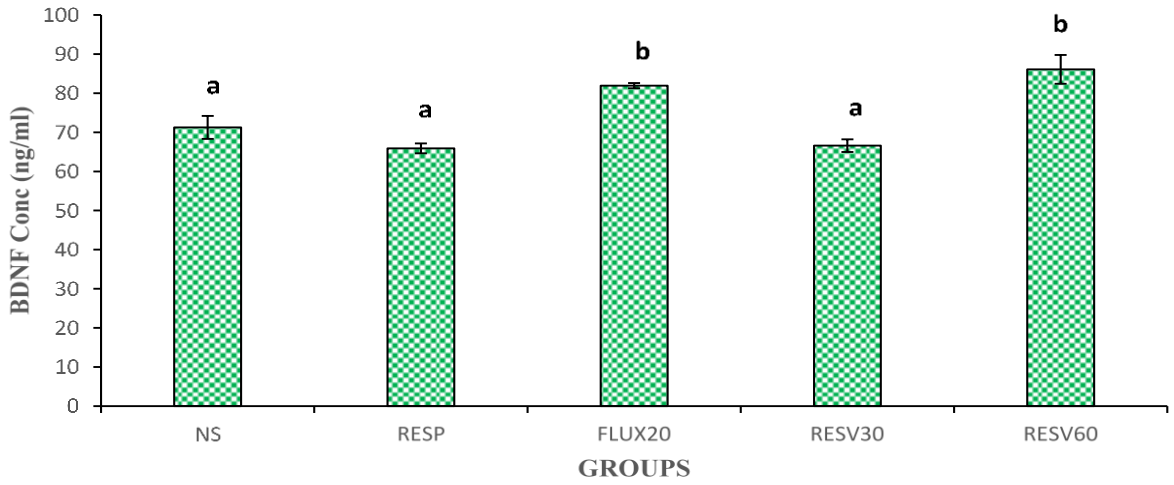

Figure 1. Effect of resveratrol on brain-derived neurotrophic factor in the brain of reserpine-induced depression-like mice.
[a-b] = Means with different superscript letters are significantly ($p < 0.05$) different. BDNF= Brain-derived neurotrophic factor; NS= normal saline, RESP= reserpine 0.2mg/kg, FLUX20=fluoxetine 20mg/kg, RESV30= resveratrol 30mg/kg, RESV60=resveratrol 60mg/kg, n = 5.

reserpine model should combine BDNF measurement with behavioral assessments (forced swim, sucrose preference, tail suspension tests) to establish a direct correlation (Ge et al., 2015; Yang et al., 2017). In addition, investigation of upstream signaling pathways such as cAMP response element-binding protein, extracellular signal-regulated kinase, and protein kinase B (Wan et al., 2016; Shen et al., 2019; Cubillos et al., 2022), as well as downstream structural changes, including dendritic spine remodeling and neurogenesis, would provide deeper mechanistic insight (Hiu et al., 2025).

Conclusion

This study demonstrates that resveratrol, at a higher dose, upregulates BDNF in a reserpine-induced depression model. These findings extend the neurotrophic mechanism to this classic monoamine depletion paradigm and support the broader relevance of BDNF as a therapeutic target for depression, providing mechanistic evidence for the potential antidepressant effects of resveratrol in this model.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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