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Antidepressant-like activity of red wine phenolic extracts in repeated corticosterone-induced depression mice via BDNF/TrkB/CREB signaling pathway

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Abstract. The aim of this study was to investigate the antidepressant-like effect of red wine phenolic extracts in mouse model exposed to exogenous corticosterone. The results showed that 3-week corticosterone injections caused depression-like behavior in mice, as indicated by the significant decrease in sucrose consumption and increase immobility time in the forced swim test. Red wine phenolic extracts treatment significantly reduced serum corticosterone levels. Moreover, it was found that red wine phenolic extract increased the brain-derived neurotrophic factor protein (BNDF) and Tropomyosin-related kinase B (TrkB) phosphorylation and cAMP-responsive element binding protein (CREB) phosphorylation levels in the hippocampus and prefrontal cortex. However, K252a, an inhibitor of TrkB, completely abolished those antidepressant-like effects. These results suggested that the red wine phenolic extracts produce an antidepressant-like effect in corticosterone-treated mice, at least in part, which is possibly mediated by modulating hypothalamic-pituitary-adrenal (HPA) axis, BDNF, TrkB and CREB phosphorylation levels in the brain region of mice.

1. Introduction

Major depression disorder (MDD) is one of the most common debilitating mood disorders worldwide and becoming the second leading disease contributing to the years lived with disability by 2013 (Cai, Huang, & Hao, 2015). The prominent and persistent low mood, mental retardation, cognitive impairment, volitional decline and somatic symptoms companied the patients lifelong and impaired their social functions. The lifetime and 12-month prevalence estimates for MDD were 5.8% and 2.2% in an Asian multi-racial population, respectively (Chong, Vaingankar, Abdin, & Subramaniam, 2012). And on the other aspect, diabetes, cardiometabolic disease, obesity and other comorbidity associated with MDD (Deschenes, Burns, & Schmitz, 2015; Gelaye et al., 2015), emerges as a serious health concern.

Despite its higher prevalence, the mechanisms associated with the pathogenesis of MDD have yet to be completely understood and current treatments remain ineffective in a large subset of patients (Menard, Hodes, & Russo, 2015). A growing literature has shown that the HPA axis plays a major role in the regulation of a variety of physiological disorders, such as depression (Kuepper, 2015; Wieczorek, Fish, O'Leary-Moore, Parnell, & Sulik, 2015). In this classic neuroendocrine circuit, limbic and hypothalamic brain structures coordinate emotional, cognitive, neuroendocrine and autonomic inputs, which together determine the magnitude and specificity of an individual's behavioral, neural and hormonal responses to stress. This response is mediated by glucocorticoid hormones (corticosterone in rodents and cortisol in humans) (Lucassen et al., 2014). Increased level of corticosterone has mostly been ascribed to impaired feedback regulation of the HPA axis, possibly caused by altered function of the glucocorticoid receptor and induced depressive disorder (Lee, Sur, Shim, Lee, & Hahm, 2015).

Moreover, BDNF and its receptor, TrkB downstream signaling are integral to a range of neural functions, including synaptic plasticity and exhibits activity-dependent regulation of expression. The neurotrophic model of depression hypothesizes that the level of BDNF is decreased during depression, which has been certified by the concentration of BDNF detected in the serum and hippocampus of postmortem in several publications (Buttenschon et al., 2015; Reinhart et al., 2015). Additionally, CREB signaling also can increase the transcription of BDNF in the soma or transportation

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to dendrites (Duman & Voleti, 2012), contributes to the actions of antidepressant treatments.

A depression animal model by repeated corticosterone treatment has been performed widely in mice, which resulted in depressive-like behavior marked by significant changes in behavioral traits, neurochemistry and brain (Ali et al., 2015). Corticosterone-induced depression model has advantages over the stress models (such as restraint stress exposure) that it avoid the possibility of potential habituation effects and variation in HPA axis response to stress stimuli (Gupta, Radhakrishnan, & Kurhe, 2015). Previous reports have shown that exogenous corticosterone administration develops depression-like behavior in mice during forced swim test, sucrose consumption test and tail suspension test (Fenton et al., 2015; Zhang, Zhao, & Wang, 2015). Therefore, these findings suggest that a chronic corticosterone treatment appears to model depression-like state in mice is suitable for evaluating the efficacy of potential antidepressant candidates and to explore the mechanism of action of antidepressants.

Recent studies have shown that plant polyphenols possess a number of beneficial properties, such as reducing the risks of cancer and heart diseases (Aravindan, Ramraj, Somasundaram, Herman, & Aravindan, 2015; Ko et al., 2015), green tea and grape powder have shown effects on alleviating cognitive impairments and leading to a lower prevalence of depressive symptoms (Mulero et al., 2015; Patki, Ali, Pokkunuri, Asghar, & Salim, 2015; Solanki, Alkadhi, Atrooz, Patki, & Salim, 2015). It has been recognized that red wines are one of the richest sources in polyphenols and thus possess beneficial effects on human health when drunk in moderation (Edmands et al., 2015; Urquiaga et al., 2015). However, it is unknown whether red wine has a potential effect on alleviating depressive disorder, and the impact of polyphenols content of antidepressant-like effect. Therefore, the objective of this study was to verify the antidepressant-like effects of red wine phenolic extracts in a mouse model of depression induced by repeated injections of corticosterone. Further investigate the direct link between BDNF signaling and the antidepressant-like effect of red wine phenolic extracts.

2. Methods and materials

2.1. Red wine phenolic extracts

The two tested red wine phenolic extracts, one from red wine at 2 days of maceration (TPx-MT2) and another from red wine at 7 days of maceration (TPx-MT7), were obtained as described in our previous work (Sun et al., 2011). Both red wine phenolic extracts present high purity in polyphenols (>91%; w/w) but TPx-MT2 (14.00%; w/w) contains more anthocyanins than TPx-MT7 (8.43%; w/w) while TPx-MT7 (4.61%; w/w) contains more proanthocyanidins than TPx-MT2 (6.17%; w/w) (Sun et al., 2011).

2.2. Animals

Adult male Kunming mice (weighing 20 ± 2g) were purchased from the Experimental Animal Center of Shenyang Pharmaceutical University (Shenyang, China). All of them were maintained under standard laboratory conditions of constant temperature ($23 \pm 1\,^{\circ}$C), relative humidity ($50 \pm 10\%$) and a 12h light/dark cycle (light from 7:00 a.m. to 7:00 p.m.) with food and water available *ad libitum* and were allowed to habituate to the novel environment for 1 week prior to use in experiments. The experiment was carried out in compliance with the National Institutes of Health and institutional guidelines for the humane care of animals and was approved by the Animal Care Committee of Shenyang Pharmaceutical University. Every effort was made to minimize the number of animals used and any pain and discomfort experienced by the subjects.

2.3. Drug administration and experimental groups

The mice were randomly assigned 12 groups (n=8/group): control group, vehicle group, corticosterone groups: corticosterone only, TPx-MT2 (10 mg/kg), TPx-MT2 (10mg/kg) + K252a, TPx-MT2 (20 mg/kg), fluoxetine (10 mg/kg), TPx-MT2 (20 mg/kg) + K252a, TPx-MT7 (10 mg/kg), TPx-MT7 (10 mg/kg) + K252a, TPx-MT7 (20 mg/kg), TPx-MT7 (20 mg/kg) + K252a. Corticosterone (TCI, Japan) was dissolved in saline containing 0.1% dimethyl sulfoxide (DMSO) and 0.1% Tween-80. Corticosterone was injected subcutaneously once a day, between 09:00 and 11:30 a.m. (Sousa et al., 2015), at 40 mg/kg in a volume of 1 ml/kg as this dose reliably increases depression-like behavior in mice without altering the nonspecific motor activity (Fenton et al., 2015). Control mice received the same volume of saline. Mice in the vehicle group received only vehicle without corticosterone for the same period. TPx-MT2 and TPx-MT7, Castelao and Tinta Miuda red wine extract (INIA Dois Portos, Instituto Nacional de Recursos Biológicos, Portugal) and fluoxetine (Melone, China) was suspended in saline and administered by gavage 30 min prior to the corticosterone injection. K252a (Santa Cruz, USA), an inhibitor of BDNF receptor TrkB, was dissolved in 0.1% DMSO in saline and injected i.p. in a volume of 10 ml/kg before 30min of gavage administration (Luo et al., 2015). The dose of TPx-MT was chosen based on the results of preliminary experiment. The repeated drug treatment was performed once daily and continuously for 21 days. The behavioral tests were carried out 24 h after the last injection. One animal from each group was tested in sequence.

2.4. Sucrose preference test

Sucrose preference test was carried out 24h after the last injection as described previously (Chiba et al., 2012). Briefly, prior to testing, mice were trained to adapt to the sucrose solution (1%, w/v): two bottles of sucrose solution were placed in each cage for 24 h, and then one bottle of sucrose solution was replaced with water for 24 h. After adaptation, mice were deprived of water and food for 24 h. Sucrose preference test was conducted with mice housed in individual cage and free access to the two bottles, one containing 100 ml of sucrose solution (1% w/v) and the other 100 ml of water. After 1 h, the volumes of the consumed sucrose solution and water were recorded and the sucrose preference was calculated as the sucrose preference(%) = sucrose consumption/(sucrose consumption + water consumption) × 100%.

2.5. Forced swim test

FST was carried out on mice, according to the method of Kruk-Slomka et al. (Kruk-Slomka, Michalak, & Biala, 2015). Briefly, individual mouse was subjected to swimming stress session for 15 min (pre-test), in a vertical glass cylinder (25 cm high, 14 cm in diameter) containing 10 cm of water, maintained at 25 ± 2°. After 24 h, FST was carried out and the total duration of immobility (seconds) was recorded during the last 4 min of a single 6 min test session. A mouse was judged to be immobile when it ceased struggling and remained floating motionless in the water, making only small movements necessary to keep its head above water. The water in the container was changed after each trial.

2.6. Serum corticosterone measurement

After the behavioral test, mice were euthanized by decapitation and blood was collected (Yu, Zhang, Li, He, & Tai, 2015). Serum corticosterone level was measured using a commercially customized ELISA kit (Liyu Bioengineering Ltd., Shanghai, China) according to the manufacturer's protocol. Briefly, 50 μl of sample and standard solutions were added to the already precoated antibody plate provided with the kit and incubated for 30 min at 37°. The reaction was terminated and followed by washing, 50 μl of the TMB color reagent was added and incubated for 20 min without shaking. The reaction was stopped by adding 50 μl of stop solution and absorbance was read at 450 nm using a microplate reader (Varioskan flash, Thermoscientific, USA).

2.7. Tissue collection and biochemical analysis

24 hours after the completion of the behavioral test, the mice were sacrificed by decapitation. Whole brains were rapidly removed from the mice and chilled in an ice-cold saline solution. Brain regions of the hippocampus and prefrontal cortex were dissected on a cold plate and immediately frozen in liquid nitrogen. The tissue samples were stored at −80 °C until assay.

The level of BDNF, pCREB, CREB, pTrkB and TrkB were measured using commercially available enzyme-linked immunosorbent assay ELISA kits (Liyu Bioengineering Ltd., Shanghai, China) according to the manufacturer's instructions. Absorbance was measured at 450 nm using a microplate reader (Varioskan flash, Thermoscientific, USA).

2.8. Statistical analysis

All data were analyzed using one-way analysis of variance (ANOVA) with repeated measures, followed by Tukey HSD post-hoc test when significant main effects were indicated. All analyses were two-tailed and *p $<$ 0.05 was considered significant a priori.

3. Results

3.1. Sucrose consumption

As shown in Fig. 1, a 3-week corticosterone exposure significantly reduced the percentage of sucrose consumption in the stressed mice in comparison with the control animals [F (11, 84) = 2.981, p $<$ 0.01]. However, post-hoc analysis revealed that long-term treatment of corticosterone mice with TPx-MT7 (10, 20 mg/kg) and fluoxetine (10 mg/kg) increased sucrose preference, as compared to corticosterone-exposed mice (respectively, F (11, 84) = 2.981, p$<$ 0.05; p $<$ 0.01; p $<$ 0.01). But with TPx-MT2 treatment, there are no similar results obtained. Chronic treatment with TPx-MT2 or TPx-MT7 showed no effects on sucrose preference of K252a-injected animals.

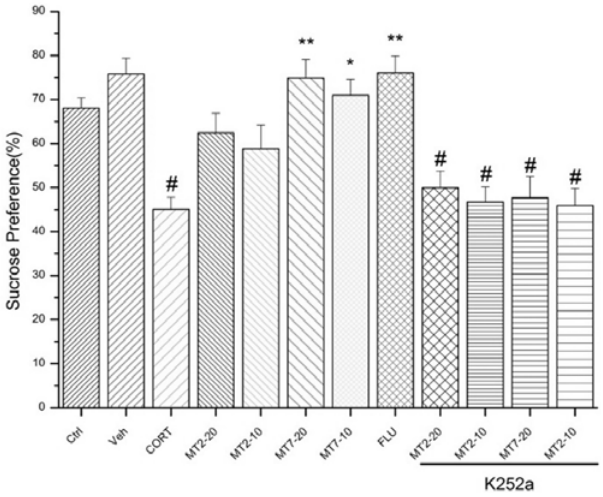

Figure 1. Effect of TPx-MT2 and TPx-MT7 on sucrose consumption. All the values are given as mean±SEM(n=8), $*P < 0.05$ and $*P < 0.01$ vs. CORT control; $^{\#}P < 0.05$ vs. control.

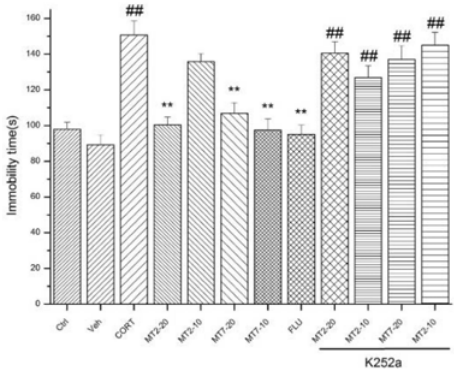

Figure 2. Effect of TPx-MT2 and TPx-MT7 on the immobility time in forced swimming test. All the values are given as mean±SEM(n=8), $**P < 0.01$ vs. CORT control, $^{\#\#}P < 0.01$ vs. control.

3.2. Immobility time in the FST

The effects of treatment with TPx-MT2 and TPx-MT7 on the immobility time were presented in Fig. 2. Fluoxetine (10 mg/kg), TPx-MT2 (20 mg/kg) and TPx-MT7 (10, 20 mg/kg) treatment significantly increased the immobility time of stressed animals compare to the corticosterone – treated only group [F (11, 84) = 20.077, p $<$ 0.01]. On the contrary, the immobility time between K252a-treated groups and corticosterone -treated group is no considerable difference, also including TPx-MT2 (10 mg/kg) group.

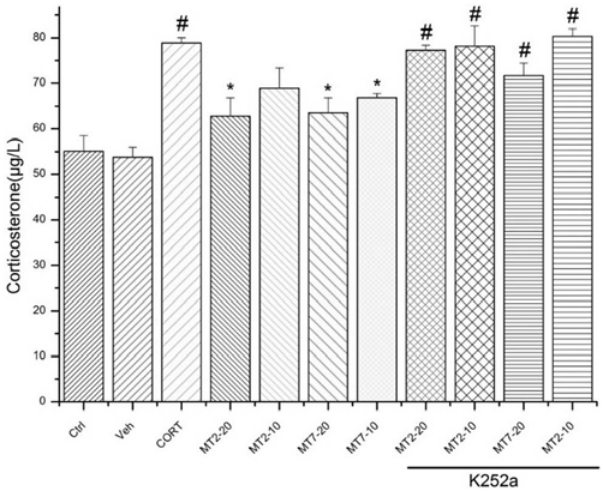

Figure 3. Effect of TPx-MT2 and TPx-MT7 on serum corticosterone concentration. All the values are given as mean±SEM(n=8), $^{*}P < 0.05$ vs. CORT control; $^{\#}P < 0.05$ vs. control.

3.3. Serum corticosterone levels

As shown in Fig. 3, there was a significant effect of corticosterone exposure on serum corticosterone concentrations [F (10.77) = 10.092, p < 0.05]. The corticosterone-induced increases in serum corticosterone levels were significantly reduced in mice treated with TPx-MT2 (20 mg/kg) [F (10.77) = 10.092, p < 0.05] and TPx-MT7 (10, 20 mg/kg) [F (10.77) = 10.092, p < 0.05]. However, these reductions were robust by K252a injection. Chronic treatment with TPx-MT2 (10 mg/kg) showed no effect on the serum corticosterone level of corticosterone-treated animals.

3.4. BDNF levels

As shown in Fig. 4, exposure to corticosterone significantly decreased both hippocampal [F (10.77) = 9.531, p < 0.01] (Fig. 4A) and prefrontal cortex BDNF levels [F (10.77) = 9.416, p < 0.05] (Fig. 4B) as compared to the control animals. Treatment with a daily dose of TPx-MT2 (20 mg/kg) and TPx-MT7 (20 mg/kg) significantly attenuated the decrease in BDNF protein level [F (10.77) = 9.531, p < 0.05 and p <0.05, respectively] in the hippocampus as compared to the only corticosterone-treated mice. And this attenuated effect in the hippocampus was blocked by K252a. But the BDNF levels in prefrontal cortex of both TPx-MT2 and TPx-MT7 treatment groups have no alterations compare to the corticosterone-treated group.

3.5. Phosphorylation TrkB / TrkB

As shown in Fig. 5, the ratio of pTrkB/TrkB in the hippocampus [F (10.77) = 4.199, p < 0.05] (Fig. 5A) and prefrontal cortex [F (10.77) = 4.012, p < 0.05] (Fig. 5B) of the corticosterone-treated mice were significantly decreased as compared to the control mice. Chronic administration of TPx-MT2 (20 mg/kg) (p < 0.05) and TPx-MT7 (20 mg/kg) (p < 0.01) increased the ratio of pTrkB/TrkB in the hippocampus. TrkB expressions in the K252a-injected mice were similar to that in corticosterone-treated mice. However the ratio of pTrkB/TrkB in the

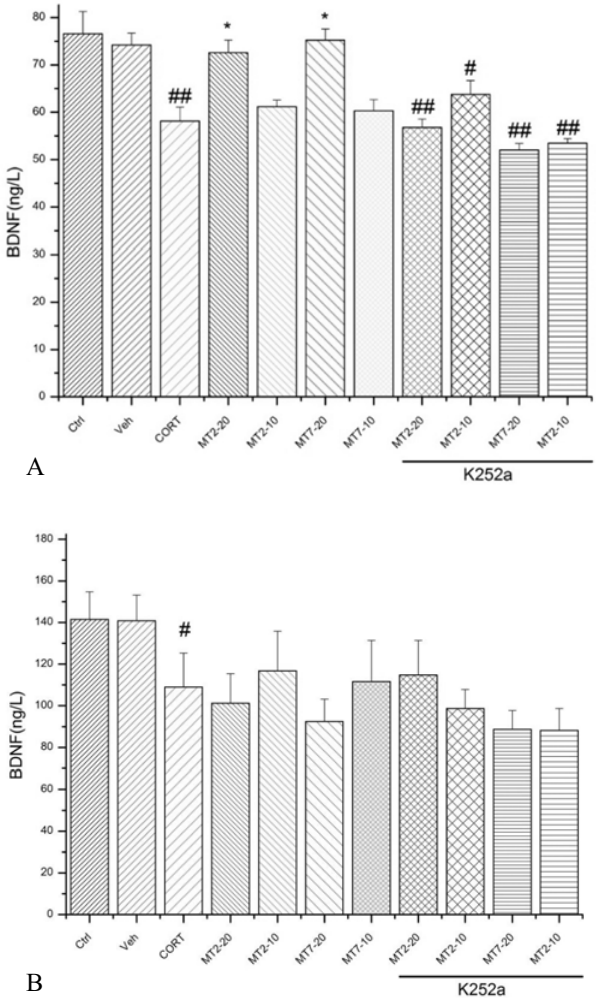

Figure 4. Effect of TPx-MT2 and TPx-MT7 on BDNF level of hippocampus (A) and prefrontal cortex (B). All the values are given as mean±SEM(n=8), $^{*}P < 0.05$ vs. CORT control; $^{\#}P$ <0.05 vs. control; $^{\#\#}P < 0.01$ vs. control.

prefrontal cortex among all other groups was similar to the control group, despite TPx-MT2 or TPx-MT7 administrated or K252a treated.

3.6. Phosphorylation CREB / CREB

As shown in Fig. 6A, the ratio of pCREB/CREB in the hippocampus [F (10.77) = 5.472, p < 0.01] of corticosterone-treated mice was significantly decreased as compared to the control group. TPx-MT2 or TPx-MT7 up-regulated the ratio of pCREB/CREB, and K252a has not abolished it. Similar results were obtained in the prefrontal cortex, all treated groups were no difference compared to the control group.

4. Discussion

The sucrose preference test is an indicator of anhedonia-like behavioral change. Anhedonia, a core symptom of major depression among humans, is modeled by inducing a decrease in responsiveness to rewards, as reflected by the reduced consumption of and/or preference for sweetened solutions (Q. Q. Mao, Huang, Zhong, Xian, & Ip, 2014). In the present study, our data are in line with classical antidepressant fluoxetine showing

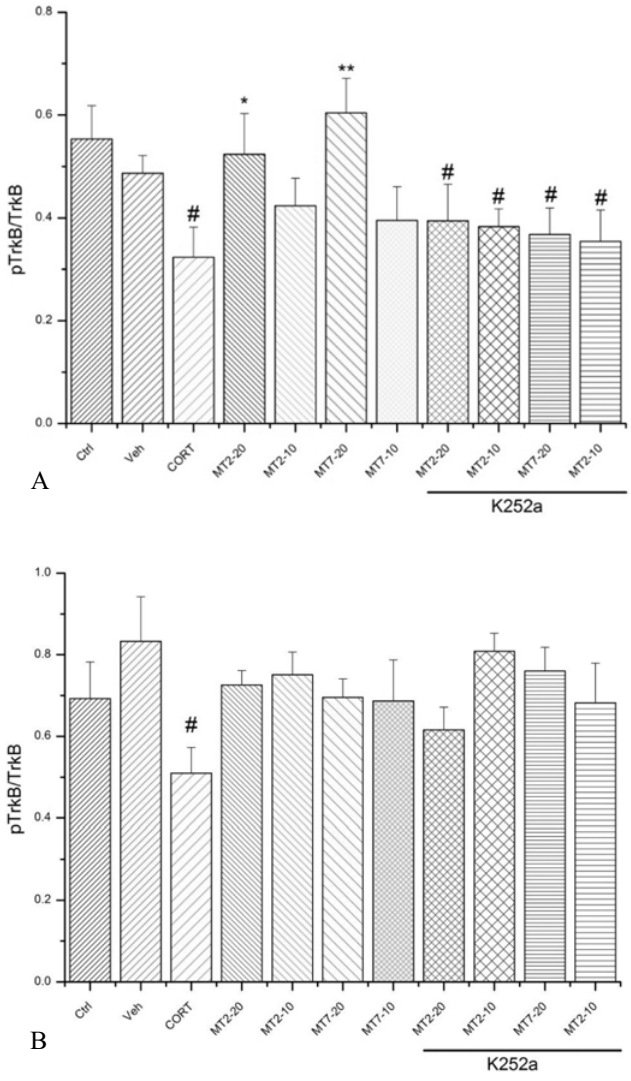

Figure 5. Effect of TPx-MT2 and TPx-MT7 on the ratio of pTrkB/TrkB of hippocampus (A) and prefrontal cortex (B). All the values are given as mean ± SEM(n = 8), $^{*}P < 0.05$, $^{**}P < 0.01$ vs. CORT control; $^{\#}P < 0.05$ vs. control.

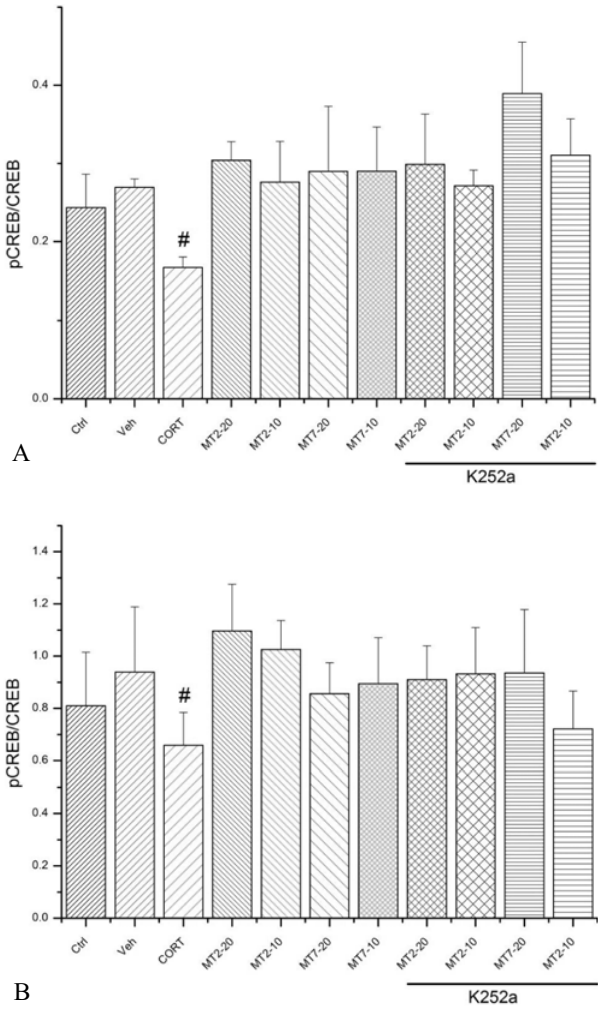

Figure 6. Effect of TPx-MT2 and TPx-MT7 on the ratio of pCREB/CREB of hippocampus (A) and prefrontal cortex (B). All the values are given as mean±SEM (n=8).

that a significant decrease in the percentage of sucrose consumption of mice (Wu et al., 2013). Red wine extract significantly reversed this behavioral change which suggested the antidepressant-like effect.

Further, the mice under 21-day corticosterone treatment exhibited significant behavioral despair, as shown by the significantly increased immobility time in the FST. FST is a behavioral despair test useful for probing the pathological mechanism of depression and for the evaluation of antidepressant drugs (Álvarez-Suárez, Banqueri, Vilella, Méndez, & Arias, 2015). This neurobehavioral alteration was also ameliorated by red wine extract, thereby underlining the effectiveness of red wine as an antidepressant candidate.

Nearly all psychiatric disorders present with circadian disruption, such as abnormalities in the timing of the sleep-wake cycle, core body temperature rhythms, and melatonin and cortisol secretion (Jones & Benca, 2015). Chronic CORT administration induces high emotionality, associated with a decrease in neurogenesis and altered pain sensitivity. And a flattened circadian rhythm and decreased activity in the home-cage observed in this model, especially during the dark phase (Le Dantec et al., 2014). Circadian rhythm is modulated by corticosteroids secretion, which is regulated by the hypothalamus-pituitary-adrenal gland axis (Llansola et al., 2013). It was observed in our study that repeated corticosterone treatment caused an elevation of serum corticosterone levels in mice, which was consistent with the previous studies (Sousa et al., 2015). This means that exogenous corticosterone results in an absolute increase in circulating serum corticosterone levels, an indicator of stress and depression in mice. Thus, the present study revealed that the behavioral consequences of repeated corticosterone administration were accompanied by dysregulation of the HPA axis.

The role of BDNF in the pathogenesis of depression and in the mechanism of action of antidepressants has been well appreciated. In humans, brain BDNF levels have been found to be reduced in postmortem samples from depressed patients, and antidepressant therapies restored brain BDNF level to the normal range (Matrisciano et al., 2009). As well as clinical studies, it has also been shown that BDNF expression was decreased in the

hippocampus and prefrontal cortex of depressive animals, which could be reversed by long term antidepressant treatment (Mendez-David et al., 2015; Sahin et al., 2015). Therefore, when we examined the effects of red wine extract on the corticosterone-mediated decrease in BDNF protein levels, the results of long-term red wine extract treatment reversing the reduction suggested that the behavioral improvement in the model may be concurrent with increased BDNF levels.

Growing evidence suggests that BDNF-TrkB signaling serves an important role in the regulation of many of the behavioral and molecular mechanism of antidepressant. BDNF mitigates depressive symptoms mainly by binding to TrkB, leading to the autophosphorylation of TrkB, and the activation of downstream signaling molecules (X. Y. Mao et al., 2015). To further confirm that the effect of red wine extract was implemented by BDNF signaling, we investigated the contribution of BDNF-TrkB signaling to antidepressant-like effect by using a TrkB receptor antagonist K252a. Previous studies found that blockade of BDNF-TrkB signaling by K252a abolished the effects of antidepressants in depression-like models (Jiang et al., 2012). Consistent with previous findings, in the present study, we found that K252a prevents the behavioral effects of red wine extract on sucrose preference and immobility time in FST. Moreover, the antagonist also inhibited the decrease of serum corticosterone level and the increase of hippocampal and prefrontal cortex BDNF levels and the pTrkB/TrkB ratio. Considering that there is clear evidence that BDNF signaling through TrkB is involved in the action mechanisms of antidepressants, as mentioned above, our current point is that the BDNF signaling pathway is necessary for the antidepressant-like effect of red wine extracts.

CREB is up-regulated by chronic antidepressant treatment, and increasing CREB levels in rodent model results in antidepressant-like behaviors. Furthermore, postmortem studies indicate that CREB levels are increased in subjects taking antidepressants at the time of death ((Réus et al., 2015). In agreement with that, in our present study the red wine extract significantly increased the ratio of pCREB/CREB in the hippocampus and prefrontal cortex. And no reverse effects of K252a observed. Thus, it is possible that red wine extract-induced antidepressant-like effect is likely through modulation of CREB signaling pathway also.

Based on the different preparation procedure, both red wine phenolic extracts present high purity in polyphenols (>91%; w/w), TPx-MT2 contains more anthocyanins than TPx-MT7 while TPx-MT7 contains more proanthocyanidins than TPx-MT2 (Sun et al., 2011). Compare the red wine extract treatment groups, we found that BDNF level and pTrkB/TrkB ratio in hippocampus of TPx-MT7 is higher than TPx-MT2, especially in TPx-MT7 (20 mg/kg) group. All these results together, we can draw the conclusion that proanthocyanidins is exerting greater antidepressant-like effect than anthocyanins, which consistent with the data of antioxidant activities *in vitro* (Sun et al., 2009). However, we also found that the ratio of pCREB/CREB among TPx-MT2 and TPx-MT7 treatment groups both in the hippocampus and prefrontal cortex is similar, this may be caused by the dose or other involved mechanisms and should be investigated in our further studies.

5. Conclusions

In summary, although both red wine phenolic extracts showed their potent reversing the anhedonia effects in the depressed mouse model, TPx-MT7 containing more proanthocyanidins appeared more effective on the antidepressant-like activity than TPx-MT2 containing anthocyanins, indicating that proanthocyanidins would have greater antidepressant-like effect than the anthocyanins. The antidepressant-like effects may be speculated to be mediated by its modulator action on the HPA axis function and its ability to prevent the alterations of BDNF, pTrkB/TrkB and pCREB/CREB levels in the hippocampus and prefrontal cortex of depressed mice. These findings more generally support the role of red wine in preventative therapy for depression

6. Conflict of interest statement

The authors have no conflict of interest to declare.

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