

Antidepressant-like effect of resveratrol in a subchronic model of depression

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Background and aim

Depression is one of the most serious and common mental diseases with major negative social consequences. Transresveratrol (trans-3,5,4'-trihydroxystilbene) is a polyphenolic compound with a broad spectrum of pharmacological activities. It has been detected in some fruits and herbs, including the Asian plant *Polygonum cuspidatum*. The aim of this study was to assess the antidepressant-like effect of transresveratrol in a reserpine subchronic model of depression.

Materials and methods

Depression-like behaviours were induced in rats by reserpine injection (0.25 mg/kg, subcutaneously) every 48 h, for 20 days. Transresveratrol (60 and 120 mg/kg) and fluoxetine (10 mg/kg) were administered orally daily during the 20 days of the study. Behavioural tests, namely, open-field test and forced swimming test, as well as brain neurotransmitters levels and antioxidant contents and liver functions, were assessed.

Results

Data revealed that transresveratrol improved the rats' behaviour in both the open-field test and forced swimming test, and also elevated the brain's neurotransmitter content, normalized the liver enzymes level, and improved the antioxidant status of both the brain and liver, compared with those of fluoxetine.

Conclusion

The present study provided a clear evidence for the antidepressant-like of transresveratrol in the experimental model of depression. Further investigations are required to investigate the mechanism of action of transresveratrol as well as its applicability to be used as an antidepressant.

Keywords:

behaviour, depression, neurotransmitters, *Polygonum cuspidatum*, transresveratrol

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Introduction

Depression is a prevalent psychiatric disease affecting the quality of life of many people. On the basis of the latest available data from the WHO, depression is expected to become the second leading cause of disease-related disability by the year 2020 [1]. It is one of the top 10 causes of morbidity and mortality worldwide, and despite the exponential increase in the number of antidepressants over the years, the prevalence of the disorder remains the same, which could be because of the unclear pathophysiology. Multiple pathogenic factors are involved in depression; although there are several molecular targets available for the development of new antidepressant drugs, most of the current treatments for depression directly or indirectly affect the monoaminergic system [2,3]. Many synthetic antidepressant drugs show low response rates and even produce adverse side effects such as cardiotoxicity, hypertensive crisis, sexual dysfunction and sleep disorders in depressed patients. Moreover, 15% of the depressed patients are resistant to all known therapies [4]. Therefore, it is desirable to

seek antidepressants in natural products; such materials are expected to show fewer side effects [5,6].

Transresveratrol (trans-3,5,4'-trihydroxystilbene) is a natural polyphenolic compound belonging to the family of phytoalexins, which are low molecular weight secondary metabolites produced by plants for defense against stresses such as wounding, pathogen attack and UV irradiation. It was first isolated from the roots of white hellebore (*Veratrum grandiflorum* O. Loes) in 1940 and later, in 1963, from the roots of *Polygonum cuspidatum*, a plant used in traditional Chinese and Japanese medicine. It is also found in grapes, red wine, a variety of berries and peanuts, and is regarded as the main factor in the French paradox, which is the observation that French people suffer a relatively low incidence of coronary heart disease, despite having a diet rich in saturated fats. Therefore, it has received considerable attention owing to its beneficial effects on human health, such as protective effects against inflammation, hepatic injuries, carcinogenesis, oxidation, aging, diabetes and neurodegenerative diseases [7–11].

Fluoxetine is an antidepressant drug of the selective serotonin reuptake inhibitor class, which is commonly prescribed to treat depression [12]. However, it has recently been postulated to induce liver damage and mediates free radical reactions owing to its fluorine content [13].

The present study was conducted to assess the antidepressant and hepatoprotective effects of transresveratrol in comparison with fluoxetine in an experimental subchronic reserpine model of depression.

Materials and methods

Animals used were adult male Wistar rats, weighing 130–150 g each, purchased from the Animal House at the National Research Centre, Giza, Egypt. All animals received human care in compliance with the guidelines of the animal care and use committee of the NRC. Upon arrival, the animals were kept in a quiet place, housed eight per cage, and acclimatized to a colony room with controlled ambient temperature ($22 \pm 1^\circ\text{C}$), humidity ($50 \pm 10\%$) and a 12 h natural light/dark cycle. They were fed a standard diet, water was provided *ad libitum*, and they were acclimated for 7 days before entry into the subsequent study. They were allowed free access to water and food throughout the period of investigation. The experiments were conducted on 16 rats per treatment group according to a randomized schedule. In behavioural tests, animals in every group were intermixed during the observation and the observers were unaware of the treatment conditions. All experiments were conducted according to the National Regulations on Animal Welfare and National Research Centre-Medical Research Ethics Committee for the use of Human or Animal Subjects.

Drugs used were fluoxetine hydrochloride (Prozac 20 mg dispersible tablets; Lilly, Alcobendas, Spain). The tablets were freshly suspended in distilled water before oral administration and transresveratrol that was provided as a generous gift from Jing Tea LLC (Sidney, Australia); it was provided as Harmoni-T micronized transresveratrol capsules for ingestion. The powder in the capsules was freshly dissolved in distilled water just before oral administration. Reserpine was a generous gift from Novartis Co. (Cairo, Egypt): it was provided as pure powder for injection and it was freshly dissolved in a dimethyl sulfoxide (DMSO)/saline mixture (0.1 : 10 ml) before subcutaneous injection.

Rats were divided into five different groups (16 rats each) and were treated as follows: group 1, normal control (DMSO/saline group); group 2, depressed group (reserpine group); group 3, received fluoxetine

(10 mg/kg orally) [14]; and groups 4 and 5 received transresveratrol (60 and 120 mg/kg orally, respectively).

Groups 2, 3, 4 and 5 received reserpine (0.25 mg/kg subcutaneously) every 48 h, for 20 days to induce depression-like symptoms [15]. Group 1 received DMSO/saline every 48 h, for 20 days. Group 1 was kept in separate cages and had free access to food and water till the end of the experiment. Group 2 received only the reserpine with no treatments. All other groups received the corresponding drugs daily starting from day 1 to day 20. On day 21, eight rats were chosen from each group randomly to perform the behavioural tests, namely, open-field test (OFT) and forced swimming test (FST). After 24 h, eight rats from each group were chosen randomly and killed by decapitation. Their brain and liver tissues were isolated, and the tissues were washed with cold sterile physiological saline, blotted between two damp filter papers and stored at -80°C until use for biochemical analyses. Lipid peroxide levels [measured as malondialdehyde (MDA) and reduced glutathione (GSH)] were taken as in-vivo reliable indices for the contribution of free radical generation in oxidative stress. Blood samples were collected from the other eight rats in each group using the retro-orbital venous plexus and were used in measuring aspartate aminotransferase (AST) and alanine aminotransferase (ALT).

Behavioural tests included the OFT and the FST. The OFT was carried out in a square wooden arena ($80 \times 80 \times 40$ cm high) with red walls and white smooth polished floor divided by black lines into 16 equal squares. The test was conducted under white light in a quiet room. Each rat was placed at the same corner square and observed during 5 min. The floor and walls were cleaned after testing each rat. The following parameters were recorded during the 5 min observation period: latency: time taken by each animal till it starts moving in the arena; ambulation frequency: number of squares crossed by the animal; rearing frequency: number of times the animal stood stretched on its hind limbs with or without forelimb support; and grooming frequency: the number of face scratching and washing with the hind limbs and licking of the forelimbs [16–19].

The FST was conducted according to the method described by Porsolt *et al.* [20]. Each rat was placed for 5 min in a cylindrical water tank (70 cm high, 40 cm diameter), where the water level was about 40 cm and water temperature was maintained at $23\text{--}25^\circ\text{C}$. The total duration of immobility of each animal was recorded. The tank was emptied and washed with fresh water flush between each rat to remove any traces of urine or faeces.

Biochemical analyses included the determination of brain monoamine levels and the determination of brain and liver MDA and GSH levels. Each brain tissue was weighed individually and divided into two longitudinal halves, of which one half was homogenized in 75% aqueous high-performance liquid chromatography grade methanol (10% w/v). The homogenate was spun at 4000 rpm for 10 min and the supernatant was isolated. Brain monoamines were detected by high-performance liquid chromatography according to a method described by Pagel *et al.* [21]. The other half was homogenized in ice-cold saline (20% w/v); each liver tissue was also isolated and homogenized in ice-cold saline (20% w/v). The brain and liver homogenates were divided into two portions for the determination of MDA and GSH levels. The level of MDA was determined according to the method of Ruiz-Larea *et al.* [22]. The level of GSH was determined according to the method of Ellman [23] modified by Bulaj *et al.* [24].

Serum activities of AST and ALT were estimated according to Reitman and Frankel [25].

Statistical analyses was carried out by nonparametric K-independent samples Kruskal–Wallis *H*-test, followed by two independent samples Mann–Whitney *U*-test in case of ambulation, rearing and grooming frequencies in the OFT, and one-way analysis of variance followed by the least significant difference post-hoc multiple comparisons test to calculate significance in the neurotransmitters levels. For all the other parameters, statistical analyses were carried out using one-way analysis of variance, followed by Tukey's HSD post-hoc multiple comparisons test. Data were

expressed as mean $\pm$ SEM. Significances were expressed at a *P* value less than 0.05.

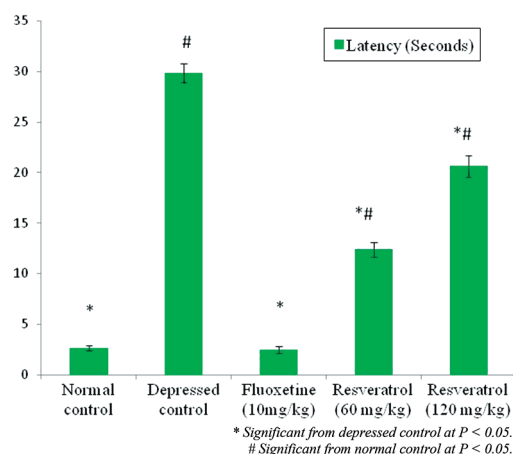
Results

The results of the OFT are represented in Figures 1 and 2. Depression-like behaviour induced by reserpine could be clearly demonstrated by the significant decrease in the activity of all rats compared with vehicle control values. Transresveratrol (60 and 120 mg/kg, orally) increased the rats' activity significantly compared with the depressed control. Fluoxetine (10 mg/kg, orally) treatment retrieved the normal levels of the open-field parameters.

Figure 3 showed the effects of transresveratrol (60 and 120 mg/kg, orally) and fluoxetine (10 mg/kg, orally) on the duration of immobility in the FST. Post-hoc analysis revealed that transresveratrol, at a dose of 60 mg/kg, and the classic antidepressant fluoxetine (10 mg/kg, orally), normalized the immobility time. On the contrary, although transresveratrol (120 mg/kg, orally) showed a significant reduction in the immobility duration compared with the depressed control, it is worth mentioning that it recorded higher immobility duration than the lower dose of transresveratrol.

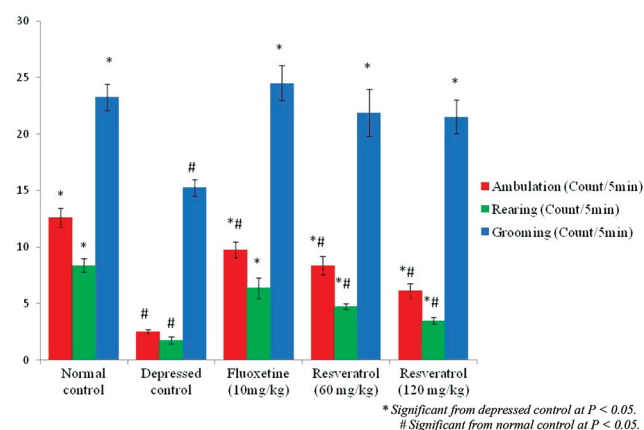
The levels of monoamines detected are summarized in Figure 4. Statistics revealed that serotonin, norepinephrine and dopamine levels were decreased significantly compared with the normal levels after reserpine injection. Oral administration of fluoxetine (10 mg/kg) and the two-dose levels of transresveratrol restored the normal values of the three neurotransmitters.

Figure 1



Effect of transresveratrol on the latency time in the OFT in depressed rats using the subchronic reserpine injection model of depression. *Significant from depressed control at $P < 0.05$. #Significant from normal control at $P < 0.05$. OFT, open-field test.

Figure 2



Effect of transresveratrol on the ambulation, rearing and grooming frequencies in the OFT in depressed rats using the subchronic reserpine injection model of depression. *Significant from depressed control at $P < 0.05$. #Significant from normal control at $P < 0.05$. OFT, open-field test.

Table 1 shows that chronic administration of reserpine significantly decreased liver GSH content and increased liver MDA level as compared with the normal control group. Treatment of animals with transresveratrol at two-dose levels normalized the liver GSH and MDA levels. Fluoxetine normalized MDA level and significantly increased GSH level compared with the depressed control. Moreover, the obtained data showed that there was no significant difference in the brain contents of GSH and MDA between the normal and the depressed control groups.

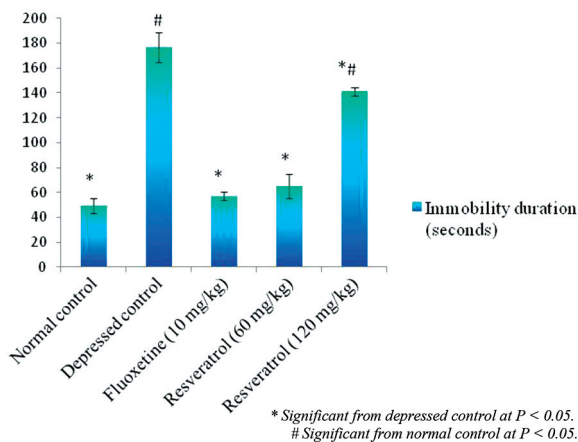
Table 2 shows that chronic administration of reserpine significantly increased serum levels of ALT and AST as compared with the normal control group. Treatment of animals with fluoxetine and resveratrol at two-dose levels significantly decreased liver enzyme levels as compared with depressed control values. The hepatotoxicity indices (ALT and AST) reached 81.8 and 85.1% for fluoxetine (10 mg/kg), 74.1 and 85.8% for resveratrol (60 mg/kg body weight), and 70.3 and 84.2% for resveratrol (120 mg/kg body weight), respectively, as compared with the depressed

control group. It is noteworthy that the higher dose of resveratrol (120 mg/kg body weight) showed better protection against increased serum level of ALT than fluoxetine.

Discussion

This study was planned to investigate the antidepressant and hepatoprotective effects of transresveratrol against fluoxetine in a subchronic reserpine model of depression. Reserpine, a well-known antihypertensive drug, is also famous for inducing depression in patients being treated for hypertension, as well as in normal subjects, owing to its capability to pass the blood–brain barrier and depleting the peripheral monoamine stores, which account for much of the beneficial antihypertensive effect used over the years. However, depletion of central stores of neurotransmitter amines is responsible for the antipsychotic effects and consequently its adverse side effects such as depression [15]. Reserpine model is based on the ability of antidepressants to reverse the behavioural and biochemical depressive-like syndrome induced by reserpine in rodents [26–29]. In the present investigation, reserpine resulted in significant

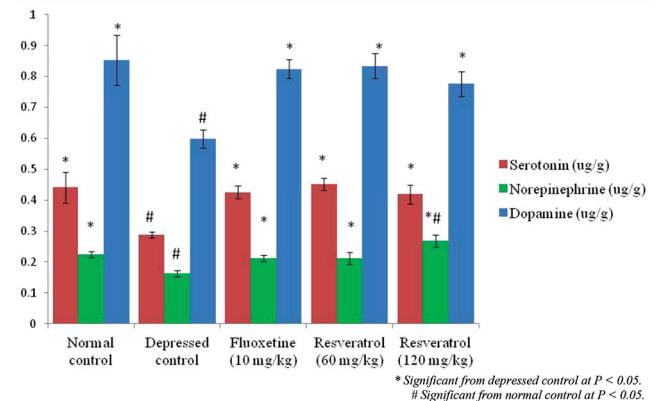
Figure 3



* Significant from depressed control at $P < 0.05$.
Significant from normal control at $P < 0.05$.

Effect of transresveratrol on the immobility duration in the forced swimming test in depressed rats using the subchronic reserpine injection model of depression. *Significant from depressed control at $P < 0.05$. #Significant from normal control at $P < 0.05$.

Figure 4



* Significant from depressed control at $P < 0.05$.
Significant from normal control at $P < 0.05$.

Effect of transresveratrol on the neurotransmitters levels in depressed rats using the subchronic reserpine injection model of depression. *Significant from depressed control at $P < 0.05$. #Significant from normal control at $P < 0.05$.

Table 1 Effect of transresveratrol on the brain and liver antioxidant parameter levels in depressed rats using the subchronic reserpine injection model of depression

Groups	Liver		Brain	
	GSH ($\mu\text{mol/g tissue}$)	MDA (nmol/g tissue)	GSH ($\mu\text{mol/g tissue}$)	MDA (nmol/g tissue)
Normal control	$15.57 \pm 0.39^*$	$11.25 \pm 1.45^*$	1.28 ± 0.09	44.42 ± 0.66
Depressed control	$8.51 \pm 0.71^{\#}$	$45.82 \pm 9.12^{\#}$	1.17 ± 0.05	50.96 ± 1.28
Fluoxetine (10 mg/kg)	$12.7 \pm 0.57^{*\#}$	$11.63 \pm 1.33^*$	1.42 ± 0.07	43.08 ± 2.94
Transresveratrol (60 mg/kg)	$14.16 \pm 0.82^*$	$14.18 \pm 1.78^*$	1.33 ± 0.06	$38.23 \pm 3.34^*$
Transresveratrol (120 mg/kg)	$16.25 \pm 0.63^*$	$14.02 \pm 2.28^*$	1.42 ± 0.07	$38.13 \pm 4.41^*$

GSH, glutathione; MDA, malondialdehyde; *Significant from depressed control at $P < 0.05$; #Significant from normal control at $P < 0.05$.

Table 2 Effect of transresveratrol on the serum ALT and AST levels in depressed rats using the subchronic reserpine injection model of depression

Groups	ALT (U/l)	AST (U/l)
Normal control	29.52 ± 1.09*	94.28 ± 2.32*
Depressed control	51.29 ± 1.21 [#]	126.68 ± 1.42 [#]
Fluoxetine (10 mg/kg)	41.95 ± 0.75**	107.80 ± 1.57**
Resveratrol (60 mg/kg)	38.00 ± 0.76**	108.79 ± 1.64**
Resveratrol (120 mg/kg)	36.10 ± 1.41**	106.66 ± 5.98*

ALT, alanine aminotransferase; AST, aspartate aminotransferase;

*Significant from depressed control at $P < 0.05$; [#]Significant from normal control at $P < 0.05$.

hypolocomotor activity in the OFT and also a pronounced increase in the immobility duration in the FST as compared with vehicle control. This result is consistent with Qingjun *et al.* [30] who reported that reserpine increased floating time in the Porsolt swim test in a dose-dependent and time-dependent manner in rats. Moreover, reserpine was found to induce a syndrome of locomotor hypomotility in the OFT and an increase in the immobility period in the tail suspension test [31–33]. Furthermore, biochemical analysis revealed that chronic reserpine treatment significantly decreased the three neurotransmitters under investigation compared with normal control but had no effect on brain MDA or GSH levels. On the contrary, it induced lipid peroxidation and decreased GSH level in the liver.

Previous investigations revealed that different dose levels of transresveratrol, ranging from 10 to 100 mg/kg, showed antioxidant capability as well as neuroprotective and hepatoprotective effects [11,34–38]. Transresveratrol treatment also reduced immobility time in the FST. However, results obtained from open field are controversial depending on the dose, route and duration of administration, wherein some cases of transresveratrol enhanced locomotor activity in the OFT and in other cases it had no effect on the locomotor activity [39–42]. The present study demonstrated that transresveratrol (60 and 120 mg/kg orally) reversed reserpine-induced depression-like behavioural symptoms in the OFT and FST in a manner comparable to that of fluoxetine; however, it is worth mentioning that the lower dose showed better response. In addition, transresveratrol (60 and 120 mg/kg) reversed the reserpine-induced reduction in the brain's neurotransmitter content. Former studies reported that the effect of transresveratrol on depressive-like behaviours may be partly because of the potentiated activation of monoaminergic system in the brain. Neurochemical assays showed transresveratrol (80 mg/kg) and produced a marked increase of 5-HT levels in the brain's frontal cortex, hippocampus and hypothalamus. Norepinephrine and dopamine levels were also increased in both the frontal

cortex and striatum. Furthermore, chronic treatment with transresveratrol was found to inhibit monoamine oxidase-A (MAO)-A activity, particularly in the frontal cortex and hippocampus, whereas MAO-B activity was not affected. These findings indicate that the antidepressant-like effect of transresveratrol involves the regulation of the central serotonin and norepinephrine levels and the related MAO-A activities [43,44].

Fluoxetine has recently been postulated to induce liver damage and mediates free radical reactions owing to its fluorine content [13,45]. However, Zafir and Banu [46] reported that fluoxetine ameliorated stress-induced oxidative damage. In the present study, fluoxetine ingestion for 20 days normalized liver MDA level and resulted in a significant decrease in serum ALT and AST levels, and significant increase in the GSH level compared with the depressed group. On the contrary, transresveratrol at both dose levels normalized the serum and brain's MDA and GSH levels, as well as ALT and AST contents. It is worth mentioning that the higher dose of transresveratrol showed better hepatoprotective effect than fluoxetine.

Conclusion

The present study revealed that subchronic ingestion of transresveratrol (60 and 120 mg/kg body weight) for 20 days prevented the depression-like symptoms induced by reserpine. Both the dose levels also showed a hepatoprotective effect. The obtained results were comparable to those of fluoxetine. Further studies are required to investigate the possible mechanism of action as well as safety of using transresveratrol as antidepressant and the exact dose to be used.

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Conflicts of interest

None declared.

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