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Original article

The Noradrenergic System is Partly Involved in Resveratrol Antidepressant and Anti-Obsessive Like Effects in Mice Model

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Abstract

Background and objectives: Resveratrol is a natural phenol in food particularly the skin of fruits like red grapes. It has shown biological, and antidepressant effects. The objective of the present study was to evaluate the role of adrenergic system on antidepressant and anti-obsessive effect of resveratrol. **Methods:** Male mice (weighing 27±2 g) were used. A tyrosine hydroxylase inhibitor, α-methyl-p-tyrosine (AMPT 100 mg/kg), α1 adrenergic receptors (AR) antagonist (prazosin, 1 mg/kg), α2-AR antagonist (yohimbine, 1 mg/kg), β-AR antagonist (propranolol, 2 mg/kg) and a tricyclic antidepressant (imipramine, 5 mg/kg), were injected before resveratrol (60 mg/kg). Locomotor activity, burring behavior during marble burring test, and immobility time during forced swimming test (FST) were evaluated. **Results:** No significant difference was observed in the locomotor activity between groups. The immobility time increased following pretreatment with AMPT (147.3±6.35s vs resveratrol alone 85.67±4.51s, $p<0.001$); marble burring behavior increased significantly, indicating the possible role of norepinephrine in resveratrol antidepressant and anti-obsessive-like effects. Propranolol (163.8±8.25 s, $p<0.001$) and yohimbine (151.0±6.47s, $p=0.0030$) pretreatment increased immobility in the FST compared to resveratrol. Pretreatment with prazosin did not cause important change in FST. Pretreatment with propranolol slightly increased marble burring behavior while no changes were observed following yohimbine or prazosin administration. Imipramine pretreatment did not have additive antidepressant effect with resveratrol and increased immobility time (136.1±16.88 s, $p=0.014$ vs resveratrol). **Conclusion:** Resveratrol antidepressant-like effect is partly mediated by the noradrenergic system, and interaction with β-AR and α2-AR. Additionally, resveratrol anti-obsessive-like property involves noradrenergic system but not the β or α-AR.

Keywords: adrenergic antagonists; alpha-methyltyrosine; depression; norepinephrine; resveratrol

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Introduction

Depression is a common mood affective illness that is often chronic and since it may lead into suicide, it can be life-threatening. Although new antidepressant drugs have been approved in the last decades, the prevalence of depressive disorder has increased recently due to the outbreak of Covid-19. The pandemic has put a burden on societies, and because of the illness, social, and financial problems, anxiety, and depression have become prominent [1]. One form of anxiety disorder is characterized by obsession or compulsive behavior. Patients suffering from obsessive- compulsive disorder (OCD) often show counting, frequent hand washing, and checking [2]. Synthetic antidepressant drugs that are usually prescribed for depression and OCD may not be

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suitable to suggest for preventing depression during hard times. They not only can expose individuals to unneeded chemicals, but also, they can cause undesirable side effects. It has been shown that phytomedicines influence the central nervous system and exert antidepressant effects in different ways [3,4]. Safe and available organic compounds could treat depression even at lower concentrations compared to clinical doses of standard antidepressant drugs [5]. Therefore, supplements and medicinal plants are preferred namely for prevention of psychological illness and depression.

An ample number of natural derivatives have been studied and introduced as neuroprotective or antidepressant agents. Among them, polyphenols have been particularly popular, for instance, curcumin [6] and resveratrol [7,8]. Resveratrol is ubiquitous in plants, especially red grapes, peanut products, and other fruit skins. In recent studies, it has been shown to have numerous biological properties such as anti-oxidant, anti-inflammatory [9], cardioprotective [10], anticancer [11], and anti-aging [12] activities.

Since the 1950s, norepinephrine (NE), a catecholamine neurotransmitter, has been supposed to have a major role in depressive disorders. The first enzyme in the NE synthesis pathway is tyrosine hydroxylase that converts amino acid tyrosine to DOPA. NE exerts its effects by binding to G-protein coupled α- and β-adrenergic receptors (ARs) [13]. NE signaling is auto-regulated by presynaptic α2- ARs and β2-ARs [14]. The noradrenergic system is also regulated by other neurotransmitters, such as the excitatory glutamate and the inhibitory gamma-aminobutyric acid system [13]. In this study, to complete previous studies regarding the antidepressant effect of resveratrol, we focused on the possible involvement of noradrenergic system on its antidepressant potential in mice. The changes in resveratrol induced behavioral effects were observed following pretreatment with α-methyl-p-tyrosine (AMPT), a selective inhibitor of tyrosine hydroxylase, prazosin (α1-AR antagonist), yohimbine (α2-AR antagonist), propranolol (β-AR antagonist), and finally imipramine (a tricyclic antidepressant). Besides, resveratrol effect on mice obsessive-compulsive behavior, and the role of noradrenergic system role was evaluated.

Material and Methods

Ethical consideration

All animal experiments were performed according to the guidelines for the Care and Use of Laboratory Animals issued by The National Ethical Committee of Iran (Date: 2020-07-22); Ethical code approval number: IR.MUI.REC.1399.187). Co2 chamber was used for euthanasia. Determination was made as to minimize animal suffering and to reduce the number of animals used in the experiments.

Chemicals

The following drugs were used: AMPT, yohimbine, and imipramine (Sigma, Germany), prazosin (gift from Amin industry, Iran), propranolol (1 mg/mL ampule POLFA, Poland).

Plant material

Resveratrol powder was provided as a gift from Shari Company, Iran.

Experimental design

Animals

Male NMRI mice (weighing 27±2 g, 6-8 weeks old) were used for the experiments. Six mice were kept together in each cage at room temperature 21± 2 ºC on a 12 h light and 12 h dark cycle (lights on at 06:00) and free access to standard mice chow and tap-water. Cages were placed in the behavioral laboratory 24 h prior to the experiments to acclimate. The behavioral experiments were performed during the morning until 14:00.

Treatment design

According to previous studies, yohimbine and prazosin 1 mg/kg; imipramine 5 mg/kg; and propranolol 2 mg/kg, were injected 30 min before resveratrol [15,16]. AMPT 100 mg/kg was freshly prepared in dimethyl sulfoxide solution (DMSO, 0.1%) and was injected 3 h before resveratrol. Control animals received the relevant vehicle (normal saline or DMSO 0.1% solution). Since the results for the control DMSO solution were not different from the normal saline group; they were not reported separately. Resveratrol 60 mg/kg was prepared in ethanol (10% v/v), the dose was selected according to previous studies [17,18]; control animals received the vehicle. The volume for all injections was 10 mL/kg and, they were all injected intraperitoneally (IP).

In the experimental groups, after measuring animals' locomotor activity to evaluate obsessive-compulsive and depressive behavior, the marble burring test (MBT) and forced swimming test (FST) were conducted, respectively in the same day. According to previous studies, the tests were started 30 min after injecting imipramine, prazosin, yohimbine, or propranolol alone and 3 h after injecting AMPT alone [15,16]. In groups that were treated with resveratrol, the tests started 3 h after resveratrol injection.

Totally, 14 groups of animals consisting six mice in each group were studied, including six separate groups of animals that were treated with imipramine, prazosin, yohimbine, propranolol or AMPT alone and the control (normal saline) group; the resveratrol alone group and the vehicle group (ethanol 10% v/v solution); other five groups were pretreated separately with imipramine, prazosin, yohimbine, propranolol or AMPT before resveratrol; and finally a group that was co-injected with prazosin and yohimbine before resveratrol.

Locomotor test

The locomotor activity was measured in an open field (Borj Sanat, Iran) with dark walls and a white floor that was divided into 15 zones by the red beams crossing the floor. Each mouse was placed at the corner of the apparatus to explore the area for 3 min. The device automatically counted the number of zone entries when the mouse passed through red beams while rears on hind legs were recorded manually. Finally, total activity was measured by summing the zone entries (horizontal movements) and the rears (vertical movements) [3].

Marble burying test

During MBT, the number of marbles buried by mice for 30 min was counted each 10 min. This test was conducted in an open, transparent plastic box (29 cm×34 cm, depth 18 cm) covered with 5 cm deep sawdust. Twelve blue marbles (15 mm diameter) were evenly placed on sawdust, and each animal was placed in the arena for 30 min [19].

Forced swimming test

FST was performed after MBT (16-19). The mice were forced to swim for 6 min in a 2-liter Pyrex beaker (diameter 12.5 cm, depth 12 cm) filled with water (25 ºC). The first 2 min was considered for the habituation period and immobility time was measured during the last 4 min. The immobility time that shows animal despair behavior was considered when the mouse had no extra activity than that essential to keep the animals' head above the water. To avoid hypothermia after the test, the animals were dried carefully and returned to their cage. The entire experiment was recorded by a camera and evaluated later.

Data processing and statistical analysis

Data processing and statistical analysis were carried out by using Excel 2010 and the GraphPad Prism 8 software (La Jolla, USA). All results are expressed as group mean ± SEM. The results of each of the drugs including imipramine, prazosin, yohimbine, propranolol and AMPT were compared with the control group and the results of pretreatment with each of the drugs before resveratrol, with resveratrol alone and vehicle groups were compared by one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. Values of $p<0.05$ were defined as statistically significant.

Results and Discussion

The locomotor activity needs to be verified before behavioral tests in rodents since deviations in locomotor activity might nonspecifically affect the results in many behavioral analyses. Animals', locomotor activity count is shown in Table 1; the locomotor activity of resveratrol treated group had insignificant difference from the vehicle group. Ethanol was chosen for resveratrol as the solvent (1 mL/kg), the locomotor activity in vehicle-treated animal did not differ from the control group [19]. Also, the total activity count following treatments with imipramine, prazosin, yohimbine, propranolol, or AMPT alone was not significantly different compared with the control group. This was in line with previous studies that used the similar drugs in order to understand the possible mechanism involved in the anti-immobility effect of minocycline during FST [20]. The locomotor activity in animal groups that received imipramine, prazosin, yohimbine, propranolol, or AMPT before resveratrol was not significantly different from the vehicle group. There was only significantly lower locomotor activity when prazosin and yohimbine were co-injected before resveratrol ($p=0.0055$). Meanwhile, by comparing this group locomotor activity with zero locomotor activity by using the one-sample t-test, it was

significantly higher than zero (t=5.717, df=5, p=0.0023) which showed that the animals were not sedated, and it would not interact with FST results. Therefore, variations in the immobility time observed during FST could be referred as animals' despair behavior.

The results depicted in Figure 1(a-d) show that resveratrol significantly reduced the immobility time during FST (85.67±4.51 s, compared to vehicle 187.5±6.56 s, p<0.001); therefore, it has an antidepressant-like effect. Previously, the antidepressant effect of resveratrol was proven, it was shown to be related partly to the increase in the serotonin neurotransmitter and increased expression of neuropeptide Y in the brain [21]. It was shown earlier that trans- resveratrol inhibited the immobility time of mice during FST, and tail suspension tests; trans- resveratrol results were comparable to that observed for the classical antidepressant drugs such as fluoxetine [17]. This effect was prevented by pre-treatment with p-chlorophenyl-alanine, an inhibitor of serotonin synthesis [17].

Figure 1a shows that AMPT alone does not change immobility time during FST, which was similar to previous research results [15,16,20]. While pretreatment with AMPT significantly increased the immobility time (147.3±6.35 s, compared to resveratrol 85.67±4.51s, p<0.001) in the FST, although the anti-immobility effect of resveratrol persisted since immobility time remained lower than vehicle (vehicle 187.5±6.56 s, p<0.001). Pretreatment with AMPT clearly showed that NE is at least partly involved in the antidepressant like effects of resveratrol since by tyrosine hydroxylase inhibition, resveratrol antidepressant effect reduced. Our study proved that the NE neurotransmitter system is essential for resveratrol antidepressant effect. This is supported by earlier findings that following high dose of trans-resveratrol (80 mg/kg) administration, NE level increased in the frontal cortex [7]. The tyrosine hydroxylase enzyme is also essential in dopamine synthesis; therefore, it may be concluded that dopamine may have a role in the antidepressant-like effects of resveratrol [13]. According to previous results, unlike the serotonin system, the dopaminergic system is not involved in trans-resveratrol antidepressant-like effect [18]. To further investigate the adrenergic role in the antidepressant effect of resveratrol the AR-specific antagonists were studied.

The results depicted in Figure 1b shows that pretreatment with propranolol, a nonselective β-AR antagonist, significantly increased the immobility time during the FST (163.8±8.25 s, p<0.001 compared with resveratrol); thus, propranolol reversed the antidepressant-like effect of resveratrol. Like previous results, propranolol on its own did not change the immobility time compared with the control group (192.2±8.94 s vs 184.7±7.88 s) [16,20]. All the ARs that mediate physiological responses to NE belong to the G-protein coupled receptors family. The β1-AR is the most plentiful β-AR subtype in mammalian brain, which is potently involved in regulating synaptic plasticity [22]. There are numerous studies about the modifications of β-ARs sensitivity, density, and signal transduction pathways in emotional illnesses [23]. Therefore, part of resveratrol the antidepressant-like effects is mediated through β-AR. The role of α-AR on resveratrol anti-depressive effect during FST is presented in Figure 1c, by pretreatment with prazosin (α1-AR antagonist) and yohimbine (α2-AR antagonist).

Table 1. Effect of different treatments on the locomotor activity

Groups (n=6)	No. Total activity	Groups (n=6)	No. Total activity
Control	172.70±16.81	Imipramine+RSV	141.7±25.22
Imipramine	163.5±21.82	Yohimbine+RSV	100.7±12.99
Yohimbine	187.7±16.91	Propranolol+RSV	131.7±22.90
Propranolol	203.0±22.13	Prazosin+RSV	102.5±9.97
Prazosin	118.7±23.42	AMPT+RSV	129.5±21.25
AMPT	126.2±12.0	Yohimbine+ Prazosin +RSV	66.33±11.60**, #
Vehicle	158.3±20.38	RSV	148.5±18.47

Total activity= horizontal exploration + vertical exploration. Yohimbine and prazosin 1 mg/kg; imipramine 5 mg/kg, propranolol 2 mg/kg, AMPT: α-methyl-p-tyrosine 100 mg/kg; and the control group received normal saline. RSV: resveratrol; vehicle group ethanol 10% v/v. Results are expressed as group mean ± SEM tested by ANOVA followed by Tukey's comparison tests. # p<0.05 compared to RSV; **p<0.01 compared to vehicle group

Yohimbine alone significantly reduced the immobility time (148.0±6.66 s vs control group 185.0±7.88 s, p=0.0079); prazosin alone did not cause a noticeable change in immobility time. While prazosin pretreatment did not change the resveratrol anti-immobility effect, yohimbine pretreatment significantly increased the immobility time (151.0±6.47 s, p=0.0030 compared with resveratrol). The result was similar when prazosin and yohimbine were administered together prior to resveratrol. Contrary to α2-AR, α1-AR does not underlie anti-immobility effect of resveratrol. Clonidine is an α2-AR agonist, also decreases the immobility time in the mice FST, and this effect was reversed by yohimbine [24]. Yohimbine also reversed the antidepressant-like effect of lamotrigine in the mice FST [17]. A literature review has revealed that α2-AR desensitization triggers the enhancing effect of NE reuptake inhibitors after chronic consumption and may also be related to the delayed onset of the antidepressant effect [25]. As proved previously, in addition to the presynaptic α2-AR that facilitates NE release, the postsynaptic α2-AR also has an essential role in desipramine antidepressant effect [26].

The results depicted in Figure 1d shows that the co-administration of imipramine also had anti-immobility effect (136.1±16.88 s, p=0.0078 vs vehicle), but the immobility time was significantly higher than resveratrol alone (85.67±4.51 s, p=0.014). This showed that imipramine and resveratrol do not have additive effects, perhaps somehow, they share similar mechanisms that may compete when they are co-administered. In this work, only a single dose of imipramine and resveratrol were co-administered, further studies about the chronic administration of resveratrol and common antidepressant drugs are suggested.

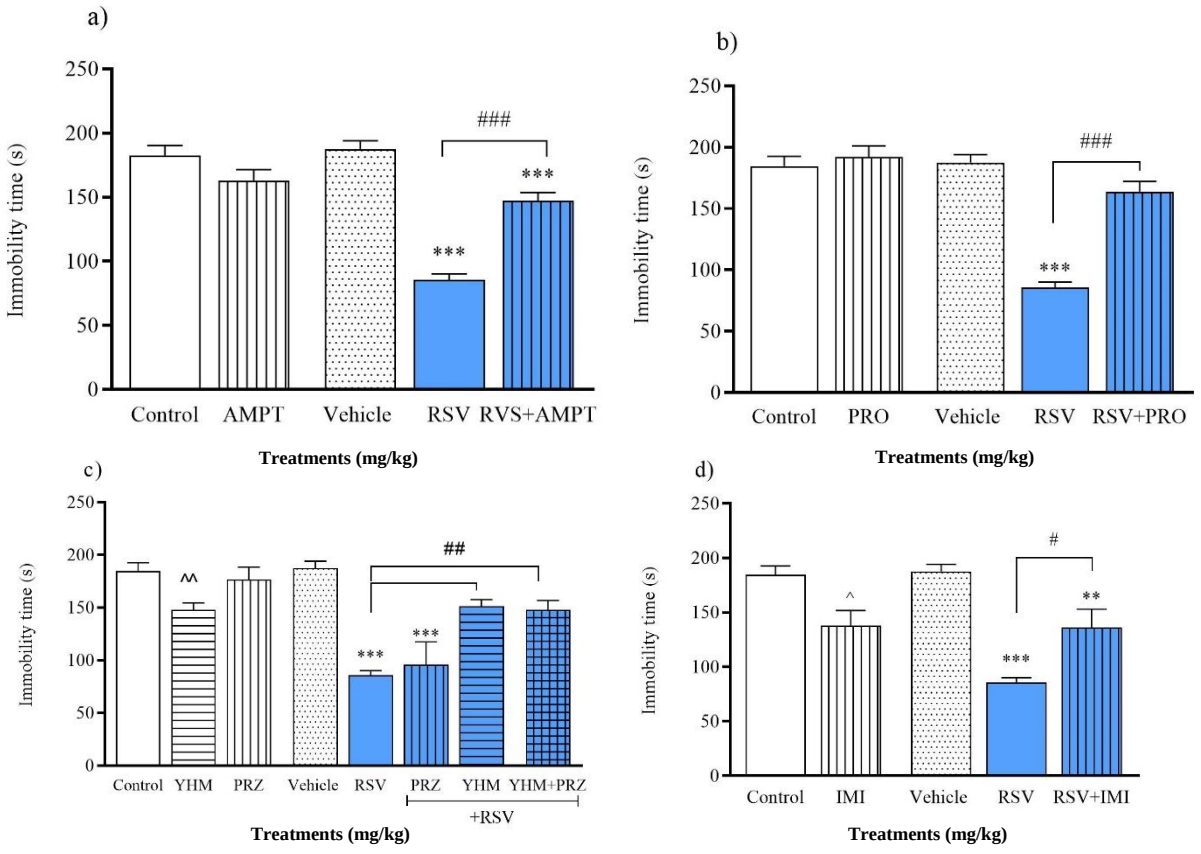

Figure 1. The effect of adrenergic receptor inhibitors and AMPT on immobility time during the FST; (a): AMPT: α-methyl-p-tyrosine, 100mg/kg (b): PRO: propranolol, 2 mg/kg; (c): YHM: yohimbine and PRZ: prazosin, 1 mg/kg; (d): IMI: imipramine, 5 mg/kg; control group: normal saline, RSV: resveratrol, 60 mg/kg; vehicle group: ethanol 10% v/v. Results are expressed as group mean ± SEM (n=6) and tested by ANOVA followed by Tukey's comparison tests. ^ P<0.05, ^^ p<0.01 compared to control group; # p<0.05, # # p<0.01, ### p<0.001 compared to RSV; **p<0.01, *** p<0.001 compared to vehicle group

The burying of harmless objects like marbles by mice was measured as an animal model for OCD [27,28]. This behavior is attenuated by treatment with selective serotonin reuptake inhibitors and anxiolytics drugs [29]. As shown in Figure 2(a-d), resveratrol significantly reduced the number of marbles buried after 30 min (0.50±0.34 vs vehicle 3.7±1; p=0.0148). Pretreatment with AMPT significantly increased the marbles burying behavior by resveratrol after 20 min (3.0±1.5, p= 0.0234 compared with resveratrol) (Figure 1a). This finding shows that resveratrol anxiolytic effects is at least partly related to the catecholamine neurotransmitter system.

The results in Figure 2b shows that propranolol on its own significantly reduced the number of marbles buried after 20 min (1.80±1.1 vs control 5.30±1.80, p=0.0268), this could be related to propranolol anxiolytic effects [30]. By pretreatment with propranolol, the number of marbles buried increased insignificantly compared with resveratrol alone. As shown in Figure 2c, pretreatment with the α-AR drugs did not reverse resveratrol anti-marbles burying behavior. While prazosin on its own significantly reduced the number of marbles buried after 30 min (3.0±1.4 vs control 6.70±2.20, p=0.0168).

This finding agreed with previous results suggesting that the prazosin anxiolytic effect may be helpful in reducing responses to stress related to alcohol use and during repetitive alcohol withdrawals that lead to increased anxiety [31,32]. Although the catecholamine neurotransmitter system was vital in anti-marbles burying behavior, this effect was not reversed by the α or β-AR antagonists which suggests that the serotonergic system is also crucial in resveratrol anxiolytic effects.

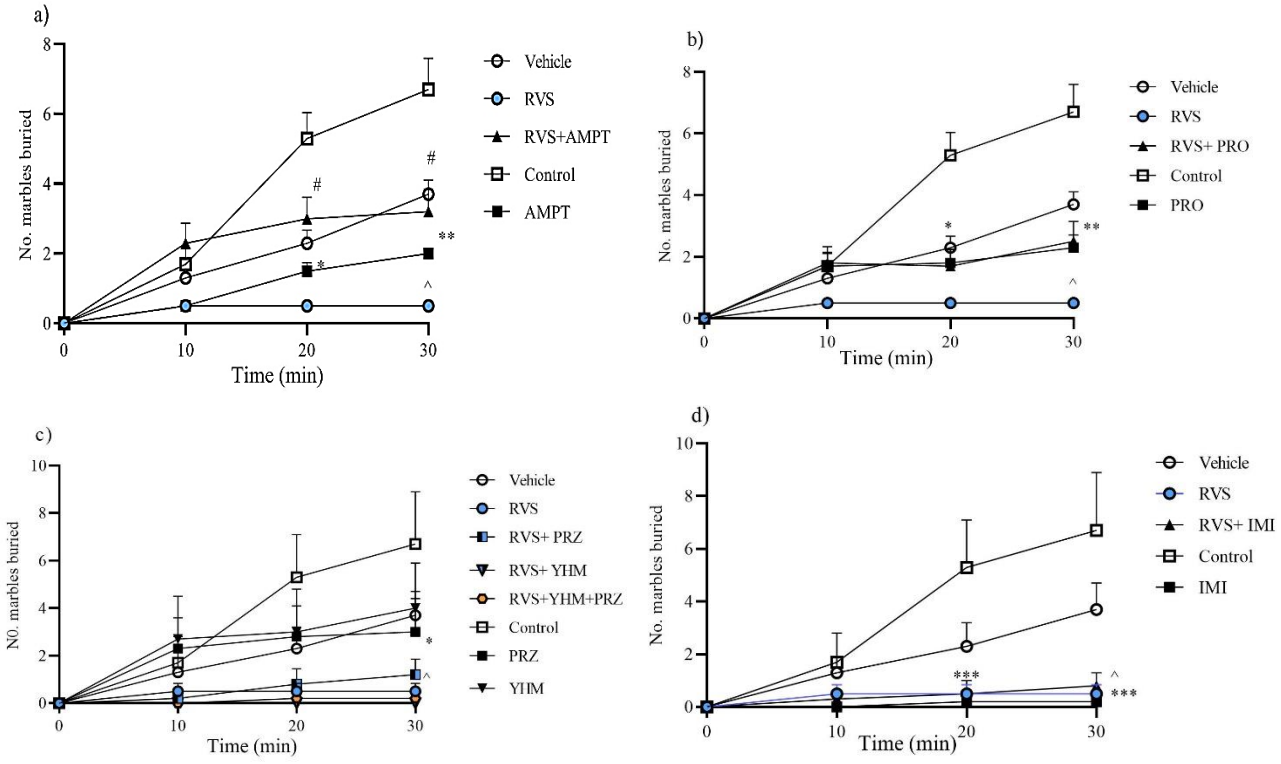

Figure 2. The effect of adrenergic receptor inhibitors and AMPT on MBT; (a): AMPT: α-methyl-p-tyrosine, 100mg/kg; (b): PRO: propranolol, 2 mg/kg; (c): YHM: yohimbine and PRZ: prazosin, 1mg/kg; (d): IMI: imipramine, 5 mg/kg; control group: normal saline; RSV: resveratrol, 60 mg/kg; vehicle group: ethanol 10% v/v. Results are expressed as group mean ± SEM (n=6) and tested by ANOVA followed by Tukey's comparison tests. ^ P<0.05, compared to vehicle group; # p<0.05, compared to RSV; *p<0.05, **p<0.01, *** p<0.001 compared to control group

Previous results have also shown that trans-resveratrol dose-dependently increased the serotonin levels in cortex, hippocampus, and hypothalamus brain regions [17]. On the other hand, the dopaminergic system may be involved in resveratrol reducing marble burring effect since this effect was only reversed by AMPT. Although serotonin regulatory neurotransmitter is the most crucial part of the pathophysiology of OCD, the dopaminergic system is also involved in OCD pathophysiology [33].

Figure 1d also supports antianxiety effect of resveratrol that is similar to imipramine alone. Twenty min after imipramine injection marbles burring behavior significantly reduced compared to control (0.20±0.17 vs 5.30±1.80, $p<0.001$), by co-administrating imipramine with resveratrol marble burring behavior remained unchanged compared to resveratrol alone.

Conclusion

Our results showed that resveratrol reduced immobility time during FST, and in agreement with previous studies indicated its antidepressant-like efficacy. Furthermore, this study extended previous findings giving convincing evidence that resveratrol effect in the FST is partly mediated by the noradrenergic system and by interaction with the postsynaptic and presynaptic β-AR and α2-AR. On the other hand, these results confirmed that resveratrol has an anxiolytic property by reducing obsessive-like behavior during MBT. The results obtained in this test also highlighted the role of the noradrenergic system, but not the β or α-AR involvement. Therefore, it could underline the possible role of the dopaminergic system in resveratrol anti-obsessive effect during MBT.

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Author contributions

Azadeh Mesripour was involved in supervision, conception, design, execution, and interpretation of the study and writing and editing of the manuscript; Fatemeh Payandekhah contributed to the experiments and writing of the manuscript.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the accuracy and integrity of the paper content.

References

[1] Shigemura J, Ursano RJ, Morganstein JC, Kurosawa M, Benedek DM. Public responses to the novel 2019 coronavirus (2019-nCoV) in Japan: mental health consequences and target populations. *Psychiatry Clin Neurosci*. 2020; 74(4): 281–282.

[2] Radua J, Van den Heuvel OA, Surguladze S, Mataix-Cols D. Meta-analytical comparison of voxel-based morphometry studies in obsessive-compulsive disorder vs other anxiety disorders. *Arch Gen Psychiatry*. 2010; 67(7): 701–711.

[3] Mesripour A, Almasi M. Flaxseed prevents interferon-alpha induced depressive behavior in mice: the α-linolenic acid is essential. *Res J Pharmacogn*. 2021; 8(1): 63–71.

[4] Rafieian-Kopaei M. Medicinal plants and the human needs. *J Herbmed Pharmacol*. 2012; 1(1): 1–2.

[5] Ogle WO, Speisman RB, Ormerod BK. Potential of treating age related depression and cognitive decline with nutraceutical approaches: a mini-review. *Gerontology*. 2013; 59(1): 23–31.

[6] Hurley LL, Akinfiresoye L, Nwulia E, Kamiya A, Kulkarni AA, Tizabi Y. Antidepressant-like effects of curcumin in WKY rat model of depression is associated with an increase in hippocampal BDNF. *Behav Brain Res*. 2013; 239: 27–30.

[7] Finnell JE, Lombard CM, Melson MN, Singh NP, Nagarkatti M, Nagarkatti P, Fadel JR, Wood CS, Wood SK. The protective effects of resveratrol on social stress-induced cytokine release and depressive-like behavior. *Brain Behav Immun*. 2017; 59: 147–157.

[8] Rania FA, Rehab Fawzy A, Omar AHA F, Salma AE, Alyaa FH. Combined hepatoprotective and antidepressant effects of resveratrol in an acute model of depression. *Bull Fac Pharm Cairo Univ*. 2014; 52(2): 191–197.

[9] Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov*. 2006; 5(6): 493–506.

[10] Bradamante S, Barenghi L, Piccinini F, Bertelli AA, De Jonge R, Beemster P, De Jong DW. Resveratrol provides late-phase

cardioprotection by means of a nitric oxide- and adenosine-mediated mechanism. *Eur J Pharmacol*. 2003; 465(1-2): 115–123.

[11] Wu X, Xu Y, Zhu B, Liu Q, Yao Q, Zhao G. Resveratrol induces apoptosis in SGC-7901 gastric cancer cells. *Oncol Lett*. 2018; 16(3): 2949–2956.

[12] Tresguerres IF, Tamimi F, Eimar H, Barralet J, Torres J, Blanco L, Tresguerres JAF. Resveratrol as anti-aging therapy for age-related bone loss. *Rejuvenation Res*. 2014; 17(5): 439–445.

[13] Maletic V, Eramo A, Gwin K, Offord SJ, Duffy RA. The role of norepinephrine and its α-adrenergic receptors in the pathophysiology and treatment of major depressive disorder and schizophrenia: a systematic review. *Front Psychiatry*. 2017; 8: 1–12.

[14] Hein L. Adrenoceptors and signal transduction in neurons. *Cell Tissue Res*. 2006; 326(2): 541–551.

[15] Brocardo PS, Budni J, Kaster MP, Santos ARS, Rodrigues ALS. Folic acid administration produces an antidepressant-like effect in mice: evidence for the involvement of the serotonergic and noradrenergic systems. *Neuropharmacology*. 2008; 54(2): 464–473.

[16] Mesripour A, Sajadiyan S, Hajhashemi V. Antidepressant-like effect of vitamin B6 in mice forced swimming test and the possible involvement of the noradrenergic system. *J Rep Pharm Sci*. 2019; 8(2): 133–138.

[17] Xu Y, Wang Z, You W, Zhang X, Li S, Barish PA, Vernon MM, Du X, Li G, Pan J, Ogle WO. Antidepressant-like effect of trans-resveratrol: Involvement of serotonin and noradrenaline system. *Eur Neuropsychopharmacol*. 2010; 20(6): 405–413.

[18] Gad SC, Cassidy CD, Aubert N, Spainhour B, Robbe H. Nonclinical vehicle use in studies by multiple routes in multiple species. *Int J Toxicol*. 2006; 25(6): 499–521.

[19] Mesripour A, Hajhashemi V, Kuchak A. Effect of concomitant administration of three different antidepressants with vitamin B6 on depression and obsessive compulsive disorder in mice models. *Res Pharm Sci*. 2017; 12(1): 46–52.

[20] Mesripour A, Kaviyanpour M, Hajhashemi V. Antidepressant-like effect of minocycline in mice forced swimming test: minor involvement of the noradrenergic system. *Thai J Pharm Sci*. 2019; 43(3): 125–130.

[21] Gu Z, Chu L, Han Y. Therapeutic effect of resveratrol on mice with depression. *Exp Ther Med*. 2019; 17(4): 3061–3064.

[22] Zill P, Baghai TC, Engel R, Zwanzger P, Schüle C, Minov C, Behrens S, Bottlender R, Jäger M, Rupprecht R, Möller HJ, Ackenheil M, Bondy B. Beta-1-adrenergic receptor gene in major depression: influence on antidepressant treatment response. *Am J Med Genet B Neuropsychiatr Genet*. 2003; 120B(1): 85–89.

[23] Manji HK, Lenox RH. Signaling: cellular insights into the pathophysiology of bipolar disorder. *Biol Psychiatry*. 2000; 48(6): 518–530.

[24] O'Neill MF, Osborne DJ, Woodhouse SM, Conway MW. Selective imidazoline I2 ligands do not show antidepressant-like activity in the forced swim test in mice. *J Psychopharmacol*. 2001; 15(1): 18–22.

[25] Invernizzi RW, Garattini S. Role of presynaptic alpha2-adrenoceptors in antidepressant action: recent findings from microdialysis studies. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004; 28(5): 819–827.

[26] Zhang HT, Whisler LR, Huang Y, Xiang Y, O'Donnell JM. Postsynaptic alpha-2 adrenergic receptors are critical for the antidepressant-like effects of desipramine on behavior. *Neuropsychopharmacology*. 2009; 34(4): 1067–1077.

[27] Deacon RMJ. Digging and marble burying in mice: simple methods for in vivo identification of biological impacts. *Nat Protoc*. 2006; 1(1): 122–124.

[28] Gawali NB, Chowdhury AA, Kothavade PS, Bulani VD, Nagmoti DM, Juvekar AR. Involvement of nitric oxide in anti compulsive‐like effect of agmatine on marble‐burying behaviour in mice. *Eur J Pharmacol*. 2016; 770: 165–171.

[29] Sugimoto Y, Tagawa N, Kobayashi Y, Hotta Y, Yamada J. Effects of the serotonin and noradrenaline reuptake inhibitor (SNRI) milnacipran on marble burying behavior in mice. *Biol Pharm Bull*. 2007; 30(12): 2399–2401.

[30] Merali Z, Levac C, Anisman H. Validation of a simple, ethologically relevant paradigm for assessing anxiety in mice. *Biol Psychiatry*. 2003; 54(5): 552–565.
[31] Skelly MJ, Weiner JL. Chronic treatment with prazosin or duloxetine lessens concurrent anxiety-like behavior and alcohol intake: evidence of disrupted noradrenergic signaling in anxiety-related alcohol use. *Brain Behav*. 2014; 4(4): 468–483.
[32] Rasmussen DD, Kincaid CL, Froehlich JC. Prazosin prevents increased anxiety behavior that occurs in response to stress during alcohol deprivations. *Alcohol Alcohol*. 2017; 52(1): 5–11.
[33] Koo MS, Kim EJ, Roh D, Kim CH. Role of dopamine in the pathophysiology and treatment of obsessive-compulsive disorder. *Expert Rev Neurother*. 2010; 10(2): 275–290.

Abbreviations

AMPT: α-methyl-p-tyrosine; RSV: resveratrol; AR: adrenergic receptor; CNS: central nervous system; FST: forced swimming test; IDO: indoleamine 2, 3-dioxygenase; MBT: marble burring test, NE: norepinephrine; TH: tyrosine hydroxylase