Effects of resveratrol on the acquisition and reinstatement of morphine-induced conditioned place preference in mice

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Abstract. Seeking opioids, even after a prolonged withdrawal period, is a main concern of opioid withdrawal. Resveratrol (RES) has been shown to exert inhibitory effects on glutamate release from cerebrocortical nerve terminals via *N-methyl-D-aspartate* (NMDA) antagonistic effects. In this study, the effects of RES on the acquisition and reinstatement of morphine were examined in a mouse model using the morphine-induced conditioned place preference (CPP) paradigm. In the first step, namely the acquisition phase, morphine was administered to mice for 4 consecutive days (daily 40 mg/kg, i.p. injection) and the mice were trained in a CPP chamber. In the second step, namely extinction and reinstatement, the animals underwent the same CPP training followed by extinction training on day 16 and reinstatement was investigated by CPP following the administration of a 'reminding' dose of morphine (10 mg/kg). Finally, the effects of RES (25, 50 and 75 mg/kg) on the acquisition and reinstatement induced by morphine were examined in a CPP test. Based on our data, RES (25, 50 and 75 mg/kg) reduced morphine tendency. In the second step of the experiment, after day 16 (following the 'reminder' dose of morphine at 10 mg/kg), the tendency of the animals for the white, drug-paired compartment of the CPP chamber significantly decreased following treatment with RES at 50 and 75 mg/kg (but not at 25 mg/kg). On the whole, the findings of this study demonstrate that RES decreases the acquisition and reinstatement of morphine-induced CPP in mice.

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Introduction

Morphine continues to be used a reliable painkiller for the alleviation of moderate to severe pain in acute and chronic diseases. However, tolerance and dependence limit the clinical application of morphine (1-3). Opioid dependence to occurs within a relatively short period of time following treatment initiation and is a major concern which limits opioid administration (4). Following morphine abstinence therapy, relapsing to morphine is one of the most important issues that may occur even after a long period of abstinence therapy (4,5). It is a subjective feeling that can force the objective for drug craving (1). Recently, several investigations have been conducted with an aim of finding a solution for this issue; however, these efforts have not been successful and morphine relapse is continuing (5-7). In this regard, chemicals with *N-methyl-D-aspartate* (NMDA) antagonistic effects have been examined and promising results have been achieved (8).

It has been shown that dopaminergic, GABAergic, glutamatergic, serotonergic, adrenergic and orexinergic pathways along with endogen opioid peptides are involved in the reward and reinforcement pathway (4,5,9). One of the most important systems that is involved in the addiction and relapse to drugs of abuse is the dopaminergic system, which begins from the ventral tegmental area (VTA) with projections to nucleus accumbens (NAcc).

Resveratrol (RES; trans-3,4,5-trihydroxystilbene), a natural polyphenol with the structure of phytoalexin is found in human dietary compounds and in a large numbers of plants and beverages, including peanuts, mulberries, grapes (particularly the skin of black grapes) and red wines (10-13). There is evidence to suggest that RES exerts a number of biological effects, including antioxidant, anti-inflammatory, cardiovascular protective, anti-cancer and neuroprotective and potentially analgesic effects, without any known toxic effects (14-21).

RES has been shown to exert antinociceptive effects on acute and inflammatory pain and RES pre-treatment has been shown to exert antinociceptive effects in morphine-tolerant animals (22,23). RES and long-term morphine co-administration has been shown to result in NMDAR upregulation and RES can reduce the activation of NMDA receptors; this is evidence of crosstalk between morphine tolerance and addiction (23,24).

Furthermore, RES can improve learning and memory via the microRNA-*CREB* pathway (20), prevent the increase in acetylcholinesterase (AChE) activity and decrease memory impairment (25), and improve the clearance of amyloid beta peptides (26). Moreover, it has been shown to exert cyclooxygenase and lipoxygenase inhibitory effects that justify its analgesic effects (27-29). In a study conducted by Pérez-Severiano *et al*, RES administration to the spinal cord was shown to reduce allodynia by decreasing nitric oxide synthase (NOS) activity and neuronal NOS (nNOS) expression (30). Furthermore, other studies have demonstrated that RES inhibits the expression of TNF-α, an important mediator of the induction of inflammation (26,30).

Additionally, RES exerts inhibitory effects on the release of glutamate from the cerebrocortical nerve terminals and exerts NMDA antagonistic effects in cortical neurons. In fact, drugs (e.g., haloperidol, clozapine, risperidone and SCH 23390) that antagonize NMDA receptors and exert inhibitory effects on glutamate receptors, have been shown to exert inhibitory effects on morphine tendency in animal models. The authors have previously demonstrated that *Berberis vulgaris* with NMDA antagonistic effects reduces morphine relapsing and reinstatement (31). Moreover, the prefrontal cortex and limbic area that project towards the VTA and NAcc and regulate the release of dopamine via glutamate and N-methyl-D-aspartate (NMDA) receptors, play important roles in reward processing. Memantine (an NMDA receptor antagonist), promotes the acquisition of morphine-induced CPP (5).

As RES antagonizes NMDA receptors, inhibits glutamate release in the brain and exerts anti-inflammatory, anti-neuropathic pain and neuroprotective effects, particularly in neuroglia, it was hypothesized that RES can ameliorate morphine tendency in animals using the CPP model.

Materials and methods

Animals. Fifty-six male NMRI mice (purchased from Pasteur Institute, Tehran, Iran; 23 days old weighing 25-30 g) were kept under standard conditions (at 25˚C with 12 h/12 h light/dark cycles) and had free access to food and water, *ad libitum*. All tests were performed with respect to the guidelines for the care and use of laboratory animals provided by Zabol University of Medical Sciences, Zabol, Iran. This study was approved by Ethics Committee of Zabol University of Medical Sciences, Zabol, Iran (approval no. IR.ZBMU.REC.1398.157).

Chemicals. Morphine sulfate and RES were purchased from Daropakhsh and Sigma, respectively.

Apparatus. The Plexiglas apparatus consisted of a box with three compartments (30x30x35 cm dimensions) separated by removable baffles. Two compartments were of the same size, but had different colors (black and white), floor texture (the black compartment was thicker than the white one) and odor (i.e., essence of banana in the white compartment and acetic acid in the black compartment). The third compartment, which was in gray, was in the middle of the box and was connected to the two other compartments. Following each experiment, all chambers were cleaned in order to remove any odor interventions induced by animals' feces and/or urine.

Experimental procedure. This study comprised of 6 different stages namely, pre-treatment, pre-conditioning, conditioning, post-conditioning, extinction and the reinstatement test (Table I).

Pre-conditioning phase. This part of the study comprised 3 phases. During the first 2 days, the animals were placed in the box without guillotine doors (doors were opened) and were allowed to freely move among the compartments. On day 3, the mice were placed in the box only for 20 min and were allowed to move freely in all compartments; the time each animal spent in each compartment (black, white and gray) was measured to evaluate unconditioned preference. Mice that stayed in each compartment for >600 sec were excluded from the study. During the pre-conditioning phase, there were no significant preferences of each animal for each compartment.

Conditioning phase. This phase lasted for 4 days. The animals were administered a single intra-peritoneal dose of normal saline (NS) and placed in the black chamber of CPP for 1 h. After 4 h, they received either morphine or RES, intraperitoneally. Following treatment (with morphine or RES), they were placed for 1 h inside the white CPP chamber. The animals were divided into 8 groups (n=7 per group) as follows: i) The normal saline + normal saline (SAL) group; ii) the saline + morphine 40 mg/kg group; iii) the morphine 40 mg/kg + RES 25 mg/kg group; iv) the morphine 40 mg/kg + RES 50 mg/kg group; v) the morphine 40 mg/kg + RES 75 mg/kg group; vi) the normal saline + RES 25 mg/kg group; vii) the normal saline + RES 50 mg/kg group; and viii) the normal saline + RES 75 mg/kg group. Immediately following drug administration, the animals were placed in the white compartment for 1 h.

Post-conditioning phase. The third part of this study was the post-conditioning phase. Eight days after the experiment, the mice were placed into the apparatus for 900 sec and allowed to move freely among the compartments; the time that was spent in each compartment (white, black and gray) was measured. The time that was spent in the middle chamber was equally divid¬ed between the white and black compartments. By abstracting, time spent during pre-conditioning and post-conditioning can be measured for each mouse. If the obtained result (time) is positive, it confirms that the drug can induce a preference and vice versa (8,32).

Extinction of place preference. At this stage, the animals were placed in the apparatus and allowed to move freely between the compartments for 60 min/day for 7 days in order to reverse morphine dependency. The time each mouse spent in the white compartment could not be significant between the pre-conditioning and extinction phases. The animals

Table I. Treatment schedule of the CPP experiment.

	Acquisition of place preference			Extinction phase	Reinstatement phase
Pre-treatment (2 days)	Pre-conditioning (1 day)	Conditioning (4 days)	Post-conditioning (1 day)	7 days	1 day
		Normal saline + normal saline, normal saline + morphine 40 mg/kg, morphine 40 mg/kg + Res 25, 50 and 75 mg/kg, normal saline + RES 25, 50 and 75 mg/kg			Normal saline + morphine10 mg/kg morphine 10 mg/kg + RES 25, 50 and 75 mg/kg

were then tested as described above. Following addiction, the animals were placed into the CPP apparatus (for 900 sec on day 16) for morphine reinstatement, and the time spent in the different compartments was measured (8,32). At 30 min following drug administration, morphine 10 mg/kg + normal saline (morphine group), or morphine 10 mg/kg + RES 25, 50 and 75 mg/kg were injected. The animals experienced a 15-min daily extinction session, which consisted of the placement of the animals in the apparatus (without guillotine doors separating the compartments). On the 8th day, the time spent in the white compartment for each group of animals became similar to that of pre-conditioning sessions.

Reinstatement of place preference. On day 16, from step 1, four groups namely, the morphine/saline, morphine/RES 25 mg/kg, morphine/RES 50 mg/kg and morphine/RES 75 mg/kg were used. The animals were placed into the CPP apparatus and allowed to move freely between the compartments during which time they were recorded. A reminding dose of morphine (10 mg/kg) was injected to each animal. After 30 min, RES 25, 50 and 75 mg/kg was intraperitoneally administered to each animal and the time spent in the white compartment was recorded (8,32). The time spent before and after the injection was calculated to elucidate whether the animals exhibit reinstatement or not.

Statistical analysis. To compare differences among means, one-way ANOVA with Tukey's post hoc tests were used. Results are presented as the means ± SEM. A $P<0.05$ was considered to indicate a statistically significant difference.

Results

Effects of RES on morphine acquisition of place preference test. The administration of RES (25, 50 and 75 mg/kg) alone did not cause place preference and aversion. RES at 50 and 75 mg/kg inhibited CPP (Fig. 1). In the conditioning phase, the animals were grouped as follows: SAL (received normal saline plus normal saline); morphine (received normal saline + morphine 40 mg/kg); M + RES 25 mg/kg (RES 25 mg/kg of RES plus 40 mg/kg of morphine); M + RES 50 (received RES 50 mg/kg plus morphine 40 mg/kg); M + RES 75 (received RES 75 mg/kg + morphine 40 mg/kg); RES 25 (received RES 25 mg/kg plus normal saline); RES 50 (received RES 50 mg/kg plus normal saline); and RES (received RES 75 mg/kg plus normal saline).

The extinction and pre-conditioning phases did not differ significantly after daily extinction sessions and the conditioning disappeared. The injection of the priming dose of morphine (10 mg/kg) reinstated CPP. RES at 50 and 75 mg/kg (but not 25 mg/kg) inhibited the reinstatement of place preference induced by the first dose of morphine (Fig. 2). In total, as depicted in Fig. 2, RES at all doses reduced morphine post-conditioning and at 50 and 75 mg/kg, it inhibited morphine-induced reinstatement.

Discussion

The results of this study revealed that RES decreased morphine-induced CPP, but did not cause morphine tendency

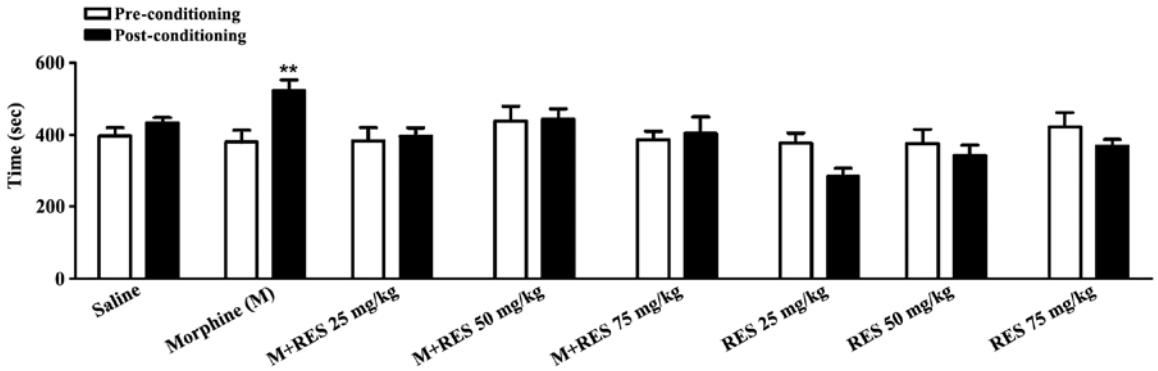

Figure 1. Effects of resveratrol (Res) on morphine-induced conditioned place preference. The time spent in the white compartment in the drug-paired compartment before conditioning (white bars) and after conditioning (black bars) is indicated. **P<0.01 represents significant differences in time spent by animals before and after conditioning.

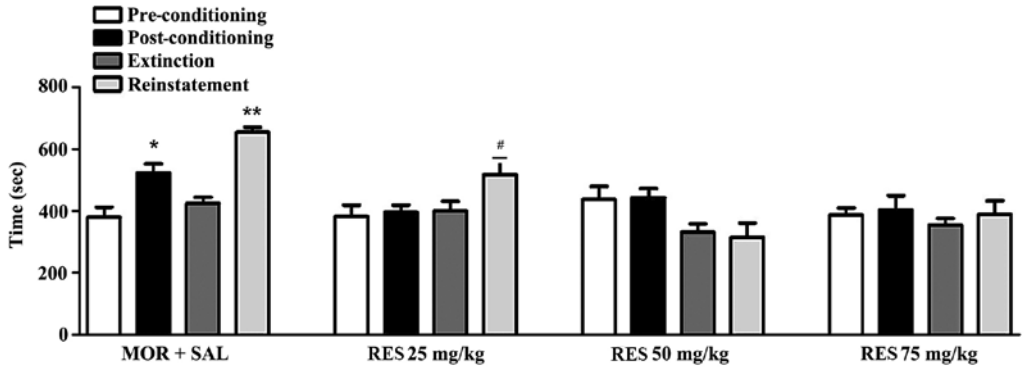

Figure 2. Effects of resveratrol (Res) on the reinstatement of morphine-induced conditioned place preferences. The four groups received morphine with either normal saline or different doses of Res. *P<0.05, significant difference between the pre-conditioning and post-conditioning phase in the MOR + SAL group; **P<0.01, significant difference at between extinction and reinstatement phase in the MOR + SAL group; and $^{\#}$P<0.05, significant difference between the extinction and reinstatement phase in the Res 25 mg/kg group. Based on this Figure, Res at all doses reduced morphine post-conditioning and at 50 and 75 mg/kg, it inhibited morphine-induced reinstatement.

or repulsion. The results of reinstatement investigation revealed that RES prevented morphine reinforcement (hedonism as well as withdrawal discomfort may lead to continued consumption) induced by the morphine (10 mg/kg) 'reminding' dose.

Similar to previous studies, repeated injections of morphine (40 mg/kg) for 4 consecutive days produced morphine dependency (27-29). At 7 days following the initiation of the experiment, the animals withdrew their morphine tendency when placed into CPP apparatus. On the 8th day of the experiment, the effects of RES on morphine tendency were examined. Following to aversion, morphine at a 10 mg/kg injection on day 16 can reinstate morphine CPP.

Opioidergic, dopaminergic and GABAergic neuronal pathways along with NAcc, VTA, the amygdala and hippocampus regulate morphine-induced CPP (30).

One of the most important systems involved in the 'rewarding' effects of morphine is the mesolimbic pathway. Moreover, NMDA antagonists can prevent morphine tendency (5,16,32). Additionally, RES exerts inhibitory effects on glutamate receptor especially NMDA receptors in cortical neurons that are involved in the rewarding system (33). This effect of RES has been shown to be mediated by the increment of glutamate release by reducing the activity of voltage-dependent Ca^{2+} channels and MAP kinase; moreover, RES inhibits glutamate release form cerebrocortical nerve terminals by reducing the activity of N- and P/Q-type Ca^{2+} channels (34). Furthermore, RES inhibits the pre-synaptic release of glutamate, although post-synaptically, it inhibits NMDA type glutamate receptor (33,34).

In acute opioid dependence, the rewarding effects along with the development and expression of behavioral and opioid neurochemical sensitization are related to glutamatergic neurotransmission, and dopamine release is under the control of glutamate and NMDA receptors (33). Opioids administration into the VTA enhances dopamine release in the NAcc (29). The data of this study are consistent with those of previous research indicating that NMDA antagonists can diminish morphine tendency, as well as tolerance and dependency (8).

Increased rates of dopamine release in the NAcc are associated with the rewarding effects of morphine addiction (31,33). The administration of MK 801, an NMDA antagonist, has been shown to boost the morphine antinociceptive effects via the suppression of calcium influx (4,7).

Similar to the results of this study, a previous study on the effect of dextromethorphan, an NMDA antagonist, on morphine demonstrated that dextromethorphan reduced morphine tolerance and dependency (29). Dextromethorphan can increase morphine antinociceptive effects and decrease tolerance and dependence towards it (29).

Excitatory neurotransmitters, including NMDA play crucial roles in hyperalgesia and morphine tolerance. It has been shown that memantine, an NMDA antagonist, decreases morphine tendency and CPP (16,33) and attenuates morphine rewarding potential, as evaluated by the method of morphine self-administration in mice (32). Other NMDA antagonists have been shown to exert inhibitory effects on morphine rewarding activity in a CPP model. Mechanistically, the activation of the morphine rewarding system requires the stimulation of NMDA receptors in the NAcc and VTA. Previously, the authors demonstrated that *Berberis vulgaris aqueous* extract reduces morphine tendency and reinstatement presumably via NMDA antagonistic effects (31).

Moreover, previous studies have shown that RES exerts antinociceptive effects on acute pain and chronic inflammation and increases the antinociceptive effects of morphine in morphine-tolerant animals (22,23). Since RES exerts antinociceptive effects, potentiates antinociceptive effects in morphine-tolerant animals and reduces morphine relapse and reinstatement, it may prove to a valuable natural product for abstinence therapy.

In conclusion, this study demonstrated that RES markedly suppressed morphine-induced CPP and improved extinction. The findings of this study demonstrate that RES can potentiate the antinociceptive effects of morphine and reduces morphine tendency and reinstatement.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article or are available from the corresponding author on reasonable request.

Authors' contributions

MH and RR were involved in the study design, and in the drafting and editing of the manuscript; SJ, SE and MAA performed the experiments; AT, DAS and CN were involved in the study design and in data interpretation. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by Ethics Committee of Zabol University of Medical Sciences, Zabol, Iran (approval no. IR.ZBMU.REC.1398.157).

Patient consent for publication

Not applicable.

Competing interests

DAS is the Managing Editor of the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

References

1. Kest B, McLemore G, Kao B and Inturrisi CE: The competitive α-amino-3-hydroxy-5-methylisoxazole-4-propionate receptor antagonist LY293558 attenuates and reverses analgesic tolerance to morphine but not to delta or kappa opioids. J Pharmacol Exp Ther 283: 1249-1255, 1997.
2. Mayer DJ, Mao J, Holt J and Price DD: Cellular mechanisms of neuropathic pain, morphine tolerance, and their interactions. Proc Natl Acad Sci USA 96: 7731-7736, 1999.
3. Tsatsakis A, Docea AO, Calina D, Tsarouhas K, Zamfira LM, Mitrut R, Sharifi-Rad J, Kovatsi L, Siokas V, Dardiotis E, *et al*: A Mechanistic and Pathophysiological Approach for Stroke Associated with Drugs of Abuse. J Clin Med 8: 1295, 2019.
4. Kratzer U and Schmidt WJ: The anti-craving drug acamprosate inhibits the conditioned place aversion induced by naloxone-precipitated morphine withdrawal in rats. Neurosci Lett 252: 53-56, 1998.
5. Theberge FR, Li X, Kambhampati S, Pickens CL, St Laurent R, Bossert JM, Baumann MH, Hutchinson MR, Rice KC, Watkins LR, *et al*: Effect of chronic delivery of the Toll-like receptor 4 antagonist (+)-naltrexone on incubation of heroin craving. Biol Psychiatry 73: 729-737, 2013.
6. Dhawan K, Kumar S and Sharma A: Reversal of Morphine Tolerance and Dependence by Passiflora incarnata - A Traditional Medicine to Combat Morphine Addiction. Pharm Biol 40: 576-580, 2002.
7. Tabatabai SM, Dashti S, Doosti F and Hosseinzadeh H: Phytotherapy of opioid dependence and withdrawal syndrome: A review. Phytother Res 28: 811-830, 2014.
8. Ribeiro Do Couto B, Aguilar MA, Manzanedo C, Rodríguez-Arias M and Miñarro J: Effects of NMDA receptor antagonists (MK-801 and memantine) on the acquisition of morphine-induced conditioned place preference in mice. Prog Neuropsychopharmacol Biol Psychiatry 28: 1035-1043, 2004.
9. Guo SJ, Cui Y, Huang ZZ, Liu H, Zhang XQ, Jiang JX and Xin WJ: Orexin A-mediated AKT signaling in the dentate gyrus contributes to the acquisition, expression and reinstatement of morphine-induced conditioned place preference. Addict Biol 21: 547-559, 2016.
10. Al-Harthi SE, Alarabi OM, Ramadan WS, Alaama MN, Al-Kreathy HM, Damanhouri ZA, Khan LM and Osman AM: Amelioration of doxorubicin induced cardiotoxicity by resveratrol. Mol Med Rep 10: 1455-1460, 2014.
11. Hamza RZ and El-Shenawy NS: Anti-inflammatory and antioxidant role of resveratrol on nicotine-induced lung changes in male rats. Toxicol Rep 4: 399-407, 2017.
12. Theodotou M, Fokianos K, Moniatis D, Kadlenic R, Chrysikou A, Aristotelous A, Mouzouridou A, Diakides J and Stavrou E: Effect of resveratrol on non-alcoholic fatty liver disease. Exp Ther Med 18: 559-565, 2019.
13. Goutzourelas N, Stagos D, Spanidis Y, Liosi M, Apostolou A, Priftis A, Haroutounian S, Spandidos DA, Tsatsakis AM and Kouretas D: Polyphenolic composition of grape stem extracts affects antioxidant activity in endothelial and muscle cells. Mol Med Rep 12: 5846-5856, 2015.
14. Hashemzaei M, Barani AK, Iranshahi M, Rezaee R, Tsarouhas K, Tsatsakis AM, Wilks MF and Tabrizian K: Effects of resveratrol on carbon monoxide-induced cardiotoxicity in rats. Environ Toxicol Pharmacol 46: 110-115, 2016.
15. Hashemzaei M, Karami SP, Delaramifar A, Sheidary A, Tabrizian K, Rezaee R, Shahsavand S, Arsene AL, Tsatsakis AM and Taghdisi SM: Anticancer effects of co-administration of daunorubicin and resveratrol in MOLT-4, U266 B1 and RAJI cell lines. Farmacia 64: 36-42, 2016.
16. Labinskyy N, Csiszar A, Veress G, Stef G, Pacher P, Oroszi G, Wu J and Ungvari Z: Vascular dysfunction in aging: Potential effects of resveratrol, an anti-inflammatory phytoestrogen. Curr Med Chem 13: 989-996, 2006.

17. Russo GL: Ins and outs of dietary phytochemicals in cancer chemoprevention. Biochem Pharmacol 74: 533-544, 2007.
18. Tabrizian K, Musavi SS, Rigi M, Hosseindadi F, Kordi S, Shamshirgaran F, Bazi A, Shahraki J, Rezaee R and Hashemzaei M: Behavioral and molecular effects of intrahippocampal infusion of auraptene, resveratrol, and curcumin on H-89-induced deficits on spatial memory acquisition and retention in Morris water maze. Hum Exp Toxicol 38: 775-784, 2019.
19. Tabrizian K, Shahraki J, Bazzi M, Rezaee R, Jahantigh H and Hashemzaei M: Neuro-Protective Effects of Resveratrol on Carbon Monoxide-Induced Toxicity in Male Rats. Phytother Res 31: 1310-1315, 2017.
20. Zhao YN, Li WF, Li F, Zhang Z, Dai YD, Xu AL, Qi C, Gao JM and Gao J: Resveratrol improves learning and memory in normally aged mice through microRNA-CREB pathway. Biochem Biophys Res Commun 435: 597-602, 2013.
21. Ghazanfarpour M, Najafi MN, Roozbeh N, Mashhadi ME, Keramat-Roudi A, Mégarbane B, Tsatsakis A, Moghaddam MMM and Rezaee R: Therapeutic approaches for neonatal abstinence syndrome: A systematic review of randomized clinical trials. Daru 27: 423-431, 2019.
22. Gentilli M, Mazoit JX, Bouaziz H, Fletcher D, Casper RF, Benhamou D and Savouret JF: Resveratrol decreases hyperalgesia induced by carrageenan in the rat hind paw. Life Sci 68: 1317-1321, 2001.
23. Tsai RY, Chou KY, Shen CH, Chien CC, Tsai WY, Huang YN, Tao PL, Lin YS and Wong CS: Resveratrol regulates N-methyl-D-aspartate receptor expression and suppresses neuroinflammation in morphine-tolerant rats. Anesth Analg 115: 944-952, 2012.
24. Shen CH, Tsai RY, Tai YH, Lin SL, Chien CC and Wong CS: Intrathecal etanercept partially restores morphine's antinociception in morphine-tolerant rats via attenuation of the glutamatergic transmission. Anesth Analg 113: 184-190, 2011.
25. Schmatz R, Mazzanti CM, Spanevello R, Stefanello N, Gutierres J, Corrêa M, da Rosa MM, Rubin MA, Chitolina Schetinger MR and Morsch VM: Resveratrol prevents memory deficits and the increase in acetylcholinesterase activity in streptozotocin-induced diabetic rats. Eur J Pharmacol 610: 42-48, 2009.
26. Marambaud P, Zhao H and Davies P: Resveratrol promotes clearance of Alzheimer's disease amyloid-β peptides. J Biol Chem 280: 37377-37382, 2005.
27. MacCarrone M, Lorenzon T, Guerrieri P and Agrò AF: Resveratrol prevents apoptosis in K562 cells by inhibiting lipoxygenase and cyclooxygenase activity. Eur J Biochem 265: 27-34, 1999.
28. Subbaramaiah K, Chung WJ, Michaluart P, Telang N, Tanabe T, Inoue H, Jang M, Pezzuto JM and Dannenberg AJ: Resveratrol inhibits cyclooxygenase-2 transcription and activity in phorbol ester-treated human mammary epithelial cells. J Biol Chem 273: 21875-21882, 1998.
29. Subbaramaiah K, Michaluart P, Chung WJ, Tanabe T, Telang N and Dannenberg AJ: Resveratrol inhibits cyclooxygenase-2 transcription in human mammary epithelial cells. Ann N Y Acad Sci 889: 214-223, 1999.
30. Pérez-Severiano F, Bermúdez-Ocaña DY, López-Sánchez P, Ríos C and Granados-Soto V: Spinal nerve ligation reduces nitric oxide synthase activity and expression: Effect of resveratrol. Pharmacol Biochem Behav 90: 742-747, 2008.
31. Imenshahidi M, Qaredashi R, Hashemzaei M and Hosseinzadeh H: Inhibitory Effect of *Berberis vulgaris Aqueous* Extract on Acquisition and Reinstatement Effects of Morphine in Conditioned Place Preferences (CPP) in Mice. Jundishapur J Nat Pharm Prod 9: e16145, 2014.
32. Qaredashi R, Hosseinzadeh H and Hashemzaei M: Inhibitory effect of *Berberis vulgaris aqueous* extract on acquisition and reinstatement effects of morphine in conditioned place preferences (CPP) in mice. Res Pharm Sci 7: S839, 2012.
33. Gao ZB, Chen XQ and Hu GY: Inhibition of excitatory synaptic transmission by trans-resveratrol in rat hippocampus. Brain Res 1111: 41-47, 2006.
34. Chang Y and Wang SJ: Inhibitory effect of glutamate release from rat cerebrocortical nerve terminals by resveratrol. Neurochem Int 54: 135-141, 2009.