VERIZONA PUBLISHER
Publishing Your Ideas

www.verizonaonlinepublishing.com
Vol: 1, Issue: 1

Chemistry of Compounds Journal

Evidence for the Use of Rosmarinic Acid as a Neuroprotective Agent: A Review

Marcos Roberto de Oliveira

Department of Chemistry/ICET, Postgraduate Program in Chemistry (PPGQ), Federal University of Mato Grosso (UFMT)

***Corresponding author:** Marcos Roberto de Oliveira, Department of Chemistry/ICET, Postgraduate Program in Chemistry (PPGQ), Federal University of Mato Grosso (UFMT), Av. Fernando Corrêa da Costa, 2367, CEP 78060-900, Cuiaba, MT, Brazil; Tel: +55-65-36158765; E mail: mrobioq@gmail.com;mrobioq@yahoo.com.br

Article Type: Review, **Submission Date**: 05 May 2016, **Accepted Date:** 07 June 2016, **Published Date:** 25 October 2016.

Citation: Marcos Roberto de Oliveira (2016) Evidence for the Use of Rosmarinic Acid as a Neuroprotective Agent: A Review. Chemi. Compol. J 1(1): 1-5.

Copyright: © 2016 Marcos Roberto de Oliveira. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

Rosmarinic acid (RA; $C_{18}H_{16}O_8$), a phenolic ester derived from caffeic acid, is found in several vegetal species, including *Rosmarinus officinalis* L., *Perilla frutescens* Britton, *Mentha* spp., and *Melissa officinalis* L. RA exerts antioxidant, anti-inflammatory, and antimutagenic activities, to cite a few. Moreover, RA has been viewed as a neuroprotective agent in both *in vitro* and *in vivo* experimental models. In spite of the efforts made to understand how RA protects brain cells against certain insults, the full mechanism by which RA rescued these cells was not elucidated yet. In the present review, the effects of RA upon brain cells are described and discussed, summarizing the findings obtained by several research groups.

Keywords: Rosmarinic acid, Brain, Neuroprotection.

Introduction

Rosmarinic acid (RA; $C_{18}H_{16}O_8$; Figure 1), which is an ester derived from caffeic acid, is present in several plant species, such as *Rosmarinus officinalis* L, *Perilla frutescens* Britton, *Mentha* spp, and *Melissa officinalis* L. [1]. RA exhibits antioxidant, anti-inflammatory, antimicrobial, and antimutagenic activities, among others [1]. Moreover, RA has been viewed as a neuroprotective agent in both *in vitro* and *in vivo* experimental models. In this review, it is discussed the mechanisms by which RA elicits neuroprotection in several studies.

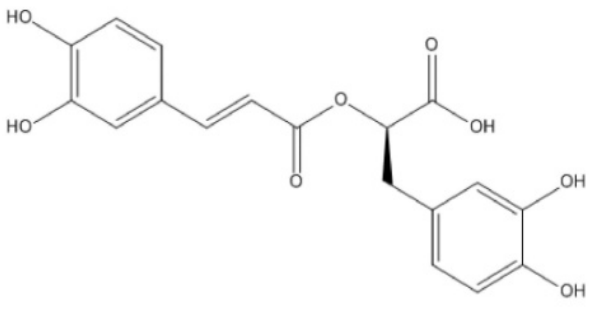

Figure 1: The chemical structure of rosmarinic acid

Data regarding RA bioavailability are limited; however, some research groups demonstrated that RA is metabolized in mammals, including humans. Al Sereiti et al. demonstrated that RA is absorbed from both gastrointestinal tract and skin [2]. Ritschel et al. found that the absolute bioavailability of RA after topical administration in rat skin was 60% and, importantly, RA was found in brain, lung, heart, liver, spleen, and bone tissue of rats after a 0.5-h intravenous administration [3]. In humans, RA and its metabolites are excreted in the urine (6.3 ± 2.2% of the total dose) within 6 h after RA administration (RA at 200 mg through oral route) [4]. Therefore, RA reaches mammalian brain cells and elicits several effects through a panoply of mechanisms as will be briefly analyzed here.

Rosmarinic Acid Effects in *In vitro* Experimental Models

RA at 5 μM for 24 h did increase neither antioxidant response element (ARE) binding activity nor reduced glutathione (GSH) synthesis in HT22 cells. Additionally, RA (0.1 – 10 μM) failed to prevent glutamate-induced toxicity in HT22 neuronal cells, as assessed through MTT assay [5]. In the same work, the authors demonstrated that other polyphenol components of rosemary, including genkwanin, verbenone, and caffeic acid did not activate ARE and did not cause any effect in GSH synthesis. Moreover, these polyphenols (0.1 – 10 μM) were not effective in preventing toxicity elicited by glutamate in HT22 cells. In spite of this, Lee et al. described that RA (14 – 56 μM 30 min before the induction of pro-oxidant challenge) exhibited cytoprotective effects in SH-SY5Y neuroblastoma cells exposed to hydrogen peroxide (H_2O_2). RA (56 μM) blocked caspase-3 activation and apoptosis in H_2O_2-treated SH-SY5Y cells [6]. RA (28 and 56 μM, but not 14 μM) prevented the increase in ROS production induced by H_2O_2. At least in part, the antioxidant effect of RA was promoted by induction of HO-1 expression, since zinc protoporphyrin (ZnPP; a HO-1 inhibitor) abolished the protective effects elicited by RA upon SH-SY5Y cells. RA induced HO-1 expression through a mechanism associated with protein kinase A (PKA) and phosphoinositide-3-kinase (PI3K) activation, because a co-treatment with PKI (PKA inhibitor) or LY294002 (an inhibitor of the phosphoinositide-3-kinase, PI3K) partially suppressed the

effects of RA on HO-1. Indeed, the authors observed increased apoptotic cell death in the RA and H_2O_2-treated cells that were treated with protein kinases inhibitors.

In this regard, Fallarini et al. demonstrated that a RA (10 – 100 μM) co-treatment protected neuronal cells (differentiated SH-SY5Y and SK-N-BE (2) neuroblastoma cell lines) from different pro-oxidant insults (*tert*-butylhydroperoxide–*t*-BOOH, L-glutamate, and oxygen-glucose deprivation, OGD for 5h/re-oxygenation for 20h) with low EC_{50} values (0.9 – 3.7 μM) [7]. RA induced cytoprotective effects by preventing LDH release in *t*-BOOH-treated SH-SY5Y cells. A similar preventive effect was seen in SK-N-BE(2) cells exposed to L-glutamate. Antioxidant effects were elicited by RA in SH-SY5Y cells: RA caused a dose-dependent increase in GSH levels and a decrease in the levels of markers of lipid peroxidation. RA (10 μM) prevented the increase in intracellular Ca^{2+} ions levels induced by L-glutamate in SK-N-BE(2) neuronal cells. RA (0.1 – 100 μM) was also effective in preventing the increase in c-fos expression elicited by L-glutamate in SK-N-BE(2) cells. However, c-jun expression levels were not affected in that experimental model. On the other hand, RA (10 μM) inhibited nuclear factor-κB (NF-κB) activation by decreasing the amounts of both p50 and p65 in the nucleus of SH-SY5Y cells. Additionally, RA (10 μM) up-regulated peroxisome proliferator-activated receptor γ (PPARγ) expression in SH-SY5Y cells. The stimulation of PPARγ leads to neuroprotection *in vitro* and *in vivo* by increasing the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (CAT), among other effects [8-10]. Furthermore, PPARγ activation causes down-regulation in the translocation of NF-κB to cell nucleus [11,12]. Therefore, RA caused protective effects to neuronal cells, at least in part, by the activation of PPARγ and inhibition of NF-κB and c-fos, which play a role in oxidative stress and neuroinflammation [13].

Du et al. demonstrated that RA (10^{-9} mol/L for 30 min) pretreatment was able to protect MES23.5 dopaminergic cells against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced toxicity [14]. RA prevented loss of cell viability and lactate dehydrogenase (LDH) release, as well as blocked the decreased in dopamine content in MES23.5 exposed to MPTP. RA elicited an antioxidant effect by decreasing ROS production induced by MPTP. RA attenuated MPTP-triggered loss of mitochondrial membrane potential (MMP) and Bcl-2-associated X protein (Bax) expression and increased B-cell lymphoma 2 (Bcl-2) mRNA levels, leading to decreased caspase-3 activity in MES23.5 cells. Accordingly, Dashti et al. found that RA protected primary culture of mice cerebellar granule cells against potassium dichromate ($K_2Cr_2O_7$)-related toxicity [15]. RA (30 and 100 μM for 24h) co-treatment counteracted loss of cell viability induced by $K_2Cr_2O_7$ in mature cerebellar granule cells, but failed to protect immature neurons. RA at lower doses (3 and 10 μM) did not exert any beneficial effect on cerebellar cells in that experimental model. Nonetheless, RA (30 and 100 μM for 24h) suppressed the increase in reactive oxygen species (ROS) production in the $K_2Cr_2O_7$-treated mature cells. Loss of MMP was blocked by RA (30 and 100 μM) in the cells that were exposed to $K_2Cr_2O_7$. The authors did not measure the effects of RA on immature cerebellar cells regarding ROS production and MMP in this model of $K_2Cr_2O_7$-induced neurotoxicity.

Utilizing N2A mouse neuroblastoma cell line, Ghaffari et al. described that RA counteracted the pro-oxidant and cytotoxic effects triggered by H_2O_2 [16]. RA co-treatment (24 h) inhibited the decrease in cell viability induced by H_2O_2 in a concentration-dependent manner (1 – 50 μM). Moreover, RA was effective in suppressing LDH release in cells exposed to H_2O_2. RA (1 – 25 μM for 24 h) prevented both H_2O_2-dependent increase in ROS production and loss of MMP in N2A cells. RA also inhibited genotoxicity induced by H_2O_2 in that experimental model. Interestingly, RA (25 μM for 24 h) caused an increase in the expression of tyrosine hydroxylase (TH) and brain-derived neurotrophic factor (BDNF) in N2A cells. Therefore, RA was effective in protecting N2A neuroblastoma cells against a pro-oxidant agent and also modulated affected parameters associated with neurotransmission and neurotrophic signaling. Even though the exact mechanism by which RA exerted such effects was not elucidated in that work, data obtained by the authors may be useful in the interpretation of results obtained from *in vivo* experimental models in which RA elicited anti-depressive effects, for example.

RA also exerted neuroprotection in an experimental model utilizing primary human neurons obtained from human foetal brains. Authors found that RA (0.01 – 0.1 mg/mL) pre-treatment (for 1 h) protected primary neurons against ciguatoxin (CTX, a toxic molecule obtained from the dinoflagellate microalgae *Gambier discuss* pp. and causes neurological disturbances in humans) [17]. RA decreased LDH release from primary neurons and protected neuronal cells against the CTX-induced nicotinamide adenine dinucleotide (NAD^+) depletion. Moreover, RA was effective in preventing DNA damage elicited by CTX in that experimental model. NAD^+ levels are associated with DNA repair by NAD^+-dependent poly (ADP-ribose) polymerase (PARP) enzyme [18-21]. Additionally, NAD^+ is associated with the function of sirtuins and of the tumour suppressor protein, p53 [22,23].

Rosmarinic Acid Effects in *In vivo* Experimental Models

RA effects were seen also in *in vivo* experimental models regarding its ability in rescuing brain cells from chemical insults, among other conditions. For example, RA exerted anti-depressive effects *in vivo*, as will be discussed here. Takeda et al. reported that mice that received RA (2 mg/kg i.p. administrated 30 min before the start of the behavioral analyses) presented decreased immobility in the forced swimming test [24]. In the same study, authors observed that caffeic acid (4 mg/kg i.p. 30 min before the start of behavioral tasks), the major metabolite of RA, exerted a similar effect in mice. Interestingly, RA and caffeic acid did not affect synaptosomal uptake of the monoamines norepinephrine, dopamine, and 5-hydroxytryptamine (5-HT). Additionally, neither RA nor caffeic acid changed monoamine oxidase B (MAO-B) enzyme activity in that experimental model. However, RA (40.4%) and caffeic acid (35.5%) inhibited MAO-A enzyme activity. Data obtained by the authors demonstrated that RA and its metabolite caffeic acid would exert anti-depressive effects by distinct mechanisms when compared to inhibitors of monoamine transporter or MAO enzyme.

Ito et al. showed that RA (1 – 4 mg/kg.bw^{-1}i.p. for 7 or 14 days) induced anti-depressive effects by accelerating the proliferation of newborn cells in the dentate gyrus of mice hippocampus [25].

Accordingly, Nie et al. reported RA (10 mg/kg i.p. for 14 days) elicited anti-depressant effects by an extracellular signal-regulated kinase (ERK1/2)-dependent mechanism in the rat model of post-traumatic stress disorder (PTSD) [26]. RA (5 and 10 μg/mL for 5 days) promoted cell proliferation in hippocampal neural stem cells by a mechanism dependent on ERK1/2 signaling pathway. Jin et al. described that RA (10 mg/kg i.p. once a day for 14 days) exerted anti-depressive effects in an experimental model of chronic unpredictable stress utilizing rats [27]. A lower RA dose (5 mg/kg) did not elicit anti-depressive effects in that experimental model. RA elicited the anti-depressive effects, at least in part, by activation of ERK1/2 phosphorylation and up-regulation of BDNF expression in rat hippocampus. U0126 (an inhibitor of ERK1/2 phosphorylation) blocked the protective effects of RA on rat behavior and BDNF expression. RA also activated ERK1/2 phosphorylation (20 and 40 μg/mL) and increased BDNF levels (20 μg/mL) in cultured astrocytes. Therefore, RA did act as an anti-depressive agent through ERK signaling pathway activation leading to augmented BDNF levels in the rat hippocampus.

Wang et al. published that RA (20 mg/kg once a day by intragastric administration for 21 days) protected rat striatum against 6-hydroxydopamine (6-OHDA)-induced lesion [28]. RA prevented the decrease in dopamine contents and in TH levels elicited by 6-OHDA. Consequently, RA prevented loss in TH positive neurons in striatum of 6-OHDA treated rats. RA protected striatal cells from 6-OHDA-induced cell death by increasing Bcl-2 and decreasing Bax proteins levels. RA was also effective in decreasing the number of iron-positive cells in the striatum exposed to 6-OHDA. In this context, RA was able to protect striatal cells against iron overload caused by 6-OHDA, probably decreasing the rate of reaction of iron with H_2O_2 by Fenton reaction [13]. However, additional data regarding redox environment related parameters, as for instance oxidative damage to lipids, proteins, or DNA were not investigated in that work. In another study, Mushtaq et al. reported an antioxidant effect of RA in the brain of rats exposed to streptozotocin (STZ). RA (10 mg/kg by intragastric administration for 21 days) suppressed lipid peroxidation induced by STZ in rat hippocampus, striatum, and cerebral cortex [29]. RA also prevented the increase in acetylcholinesterase activity elicited by STZ in the same rat brain areas.

Shimojo et al. found that RA was effective in protecting mice in an experimental model of familial amyotrophic lateral sclerosis (FALS) utilizing human SOD1 G93A transgenic mice [30]. Humans with FALS presented impaired SOD1 function (the cytosolic isoform of SOD). Moreover, microglial activity is increased in FALS patients, indicating a role for neuroinflammation in the pathology [31-33]. Thus, a compound that exerts antioxidant and anti-inflammatory effects would be an interesting strategy in the treatment of FALS. The authors observed that FALS mice that received RA (0.13 mg/kg i.p. twice a week for 14 days) presented a significant increase in survival, as well as exhibited ameliorations regarding behavior in several tasks. CA at the same dose did not alter survival rate in this experimental model. Additionally, neurons from the anterior horn of the lumbar spinal cord presented augmented size when compared to the FALS control (that did not receive RA). Therefore, RA treatment attenuated motor neurons degeneration leading to an improvement in behavior in an experimental model of FALS.

Luan et al. reported that RA exhibited anti-inflammatory effects *in vitro* (in SH-SY5Y neuroblastoma cells) and *in vivo* (in a rat experimental model of diabetes) [34]. RA (3 – 81 μM for 12 h after a 3-h period under OGD; RA at 1 μM did not protect SH-SY5Y from OGD) was effective in decreasing the loss of cell viability caused by OGD in SH-SY5Y cells, as well as induced cytoprotective effects by partially inhibiting LDH leakage in that experimental model. RA inhibited cell apoptosis and the tumor necrosis factor-α (TNF-α)-induced activation of NF-κB, as well as partially abrogated NF-κB binding activity. RA (25 – 200 mg/kg by intravenous route 30 min after induction of cerebral ischemia/reperfusion, I/R) decreased infarct volume and brain water content in experimental animals. Moreover, RA (50 mg/kg by intravenous route at 1 h, 3 h, 5 h, and 7 h after I/R induction) elicited very similar effects in that experimental model. Authors also described that RA (50 mg/kg by intravenous route 30 min after reperfusion) decreased Evans blue extravasation (an index to assess BBB integrity) and myeloperoxidase (MPO) activity (an index of inflammation) *in vivo*. RA also suppressed NF-κB activation under the same conditions. Thus, RA exhibited anti-inflammatory effects *in vivo* by modulation of a signaling pathway associated with neuroinflammation. In agreement with those data, Swarup et al. previously observed that RA (25 mg/kg i.p. twice a day after virus inoculation during the period in which no deaths were registrated – after the first death in the infected group that did not receive RA, the animals were killed and the samples were collected) exerted anti-inflammatory effects on mice infected with Japanese encephalitis virus by decreasing the number of activated microglia and downregulating the expression of pro-inflammatory cytokines [35]. Moreover, RA inhibited NF-κB activation in that experimental model. RA was effective in reducing brain viral replication and the consequent inflammation resulting from virus inoculation.

Conclusion and Future Needs

RA presents antioxidant and anti-inflammatory actions in brain cells, but the mechanisms involved in these effects are not completely understood yet. Therefore, further research needs to be performed in the "mechanistic field" in order to clarify several questions related to the use of RA as a neuroprotective agent. It is important to mention that the RA concentrations utilized in *in vitro* experimental models are not commonly observed *in vivo*, *i.e.* these concentrations are sometimes very high when compared to the concentrations reached *in vivo*, as demonstrated in the bioavailability studies. In this context, the protective effects seen in *in vitro* studies may not be observed in humans utilizing purified RA in the form of supplements, for example. Really, toxicological analyses need to be performed due to the risk in RA inducing intoxication, as is common to other natural compounds. Furthermore, studies involving strategies to increase RA bioavailability would be very useful, as well as research developed to create ways to target RA to specific cells and tissues.

References

1. Amoah SK, Sandjo LP, Kratz JM, Biavatti MW. Rosmarinic Acid - Pharmaceutical and Clinical Aspects. Planta Med. 2016; 82(5):388-406. doi: 10.1055/s-0035-1568274.
2. al-Sereiti MR, Abu-Amer KM, Sen P. Pharmacology of rosemary (Rosmarinus officinalis Linn.) and its therapeutic potentials. Indian J Exp Biol. 1999; 37(2):124-130.
3. Ritschel WA, Starzacher A, Sabouni A, Hussain AS, Koch HP. Percutaneous absorption of rosmarinic acid in the rat. Methods Find. Exp. Methods Find Exp Clin Pharmacol. 1989; 11(5):345-52.
4. Baba S, Osakabe N, Natsume M, Yasuda A, Muto Y, Hiyoshi K, etal. Absorption, metabolism, degradation and urinary excretion of rosmarinic acid after intake of Perilla frutescens extract in humans. Eur J Nutr. 2005; 44:1-9.
5. Tamaki Y, Tabuchi T, Takahashi T, Kosaka K, Satoh T. Activated glutathione metabolism participates in protective effects of carnosic acid against oxidative stress in neuronal HT22 cells. Planta Med. 2010; 76(7):683-688.
6. Lee HJ, Cho HS, Park E, Kim S, Lee SY, Kim CS, et al. Rosmarinic acid protects human dopaminergic neuronal cells against hydrogen peroxide-induced apoptosis. Toxicology. 2008; 250(2-3):109-115. doi: 10.1016/j.tox.2008.06.010.
7. Fallarini S, Miglio G, Paoletti T, Minassi A, Amoruso A, Bardelli C, et al. Clovamide and rosmarinic acid induce neuroprotective effects in in vitro models of neuronal death. Br J Pharmacol. 2009; 157(6):1072-1084. doi: 10.1111/j.1476-5381.2009.00213.x.
8. Jung TW, Lee JY, Shim WS, Kang ES, Kim SK, Ahn CW, et al. Rosiglitazone protects human neuroblastoma SH-SY5Y cells against MPP^+ induced cytotoxicity via inhibition of mitochondrial dysfunction and ROS production. J Neurol Sci. 2007; 253(1-2):53-60.
9. Dehmer T, Heneka MT, Sastre M, Dichgans J, Schulz JB. Protection by pioglitazone in the MPTP model of Parkinson's disease correlates with I kappa B alpha induction and block of NF kappa B and iNOS activation. J Neurochem. 2004; 88(2):494-501.
10. Schütz B, Reimann J, Dumitrescu-Ozimek L, Kappes-Horn K, Landreth GE, Schürmann B, et al. The oral antidiabetic pioglitazone protects from neurodegeneration and amyotrophic lateral sclerosis-like symptoms in superoxide dismutase-G93A transgenic mice. J Neurosci. 2005; 25(34):7805-7812.
11. Culman J, Zhao Y, Gohlke P, Herdegen T. PPAR-gamma: therapeutic target for ischemic stroke. Trends Pharmacol Sci. 2007; 28(5):244-249.
12. Kim EJ, Park KS, Chung SY, Sheen YY, Moon DC, Song YS, et al. Peroxisome proliferator-activated receptor-gamma activator 15-deoxy-Delta12,14-prostaglandin J2 inhibits neuroblastoma cell growth through induction of apoptosis: association with extracellular signal-regulated kinase signal pathway. J Pharmacol Exp Ther. 2003; 307(2):505-517.
13. Halliwell B. Oxidative stress and neurodegeneration: where are we now? J Neurochem. 2006; 97(6):1634-1658.
14. Du T, Li L, Song N, Xie J, Jiang H. Rosmarinic acid antagonized 1-methyl-4-phenylpyridinium (MPP+)-induced neurotoxicity in MES23.5 dopaminergic cells. Int J Toxicol. 2010; 29(6):625-633. doi: 10.1177/1091581810383705.
15. Dashti A, Soodi M, Amani N. Cr (VI) induced oxidative stress and toxicity in cultured cerebellar granule neurons at different stages of development and protective effect of Rosmarinic acid. Environ Toxicol. 2016; 31(3):269-277. doi: 10.1002/tox.22041.
16. Ghaffari H, Venkataramana M, Jalali Ghassam B, Chandra Nayaka S, Nataraju A, Geetha NP, et al. Rosmarinic acid mediated neuroprotective effects against H2O2-induced neuronal cell damage in N2A cells. Life Sci. 2014; 113(1-2):7-13. doi: 10.1016/j.lfs.2014.07.010.
17. Braidy N, Matin A, Rossi F, Chinain M, Laurent D, Guillemin GJ. Neuroprotective effects of rosmarinic acid on ciguatoxin in primary human neurons. Neurotox Res. 2014; 25(2):226-234. doi: 10.1007/s12640-013-9429-9.
18. Braidy N, Gai WP, Xu YH, Sachdev P, Guillemin GJ, Jiang XM, et al Alpha-synuclein transmission and mitochondrial toxicity in primary human foetal enteric neurons in vitro. Neurotox Res. 2014; 25(2):170-182. doi: 10.1007/s12640-013-9420-5.
19. Boesten DM, von Ungern-Sternberg SN, den Hartog GJ1, Bast A. Protective Pleiotropic Effect of Flavonoids on NAD (+) Levels in Endothelial Cells Exposed to High Glucose. Oxid Med Cell Longev. 2015; 2015:894597. doi: 10.1155/2015/894597.
20. Gerö D, Szabo C. Salvage of nicotinamide adenine dinucleotide plays a critical role in the bioenergetic recovery of post-hypoxic cardiomyocytes. Br J Pharmacol. 2015; 172(20):4817-32. doi: 10.1111/bph.13252.
21. Martire S, Mosca L, d'Erme M. PARP-1 involvement in neurodegeneration: A focus on Alzheimer's and Parkinson's diseases. Mech Ageing Dev. 2015; 146-148:53-64. doi: 10.1016/j.mad.2015.04.001.
22. Braidy N, Guillemin GJ, Mansour H, Chan-Ling T, Poljak A, Grant R. Age related changes in NAD+ metabolism oxidative stress and Sirt1 activity in Wistar rats. PLoS One. 2011; 6(4):e19194. doi: 10.1371/journal.pone.0019194.
23. Braidy N, Jayasena T, Poljak A, Sachdev PS. Sirtuins in cognitive ageing and Alzheimer's disease. Curr Opin Psychiatry. 2012; 25(3):226-230. doi: 10.1097/YCO.0b013e32835112c1.
24. Takeda H, Tsuji M, Inazu M, Egashira T, Matsumiya T. Rosmarinic acid and caffeic acid produce antidepressive-like effect in the forced swimming test in mice. Eur J Pharmacol. 2002; 449(3):261-267.
25. Ito N, Yabe T, Gamo Y, Nagai T, Oikawa T, Yamada H, et al. Rosmarinic acid from Perillae Herba produces an antidepressant-like effect in mice through cell proliferation in the hippocampus. Biol Pharm Bull. 2008; 31(7):1376-1380.
26. Nie H, Peng Z, Lao N, Wang H, Chen Y, Fang Z, et al. Rosmarinic acid ameliorates PTSD-like symptoms in a rat model and promotes cell proliferation in the hippocampus. Prog Neuropsychopharmacol Biol Psychiatry. 2014; 51:16-22. doi: 10.1016/j.pnpbp.2014.01.002.
27. Jin X, Liu P, Yang F, Zhang YH, Miao D. Rosmarinic acid ameliorates depressive-like behaviors in a rat model of CUS and Up-regulates BDNF levels in the hippocampus and hippocampal-derived astrocytes. Neurochem Res. 2013; 38(9):1828-1837. doi: 10.1007/s11064-013-1088-y.
28. Wang J, Xu H, Jiang H, Du X, Sun P, Xie J. Neurorescue effect of rosmarinic acid on 6-hydroxydopamine-lesioned nigral dopamine neurons in rat model of Parkinson's disease. J Mol Neurosci. 2012; 47(1):113-119. doi: 10.1007/s12031-011-9693-1.
29. Mushtaq N, Schmatz R, Pereira LB, Ahmad M, Stefanello N, Vieira JM, et al Rosmarinic acid prevents lipid peroxidation and increase in acetylcholinesterase activity in brain of streptozotocin-induced diabetic rats. Cell Biochem Funct. 2014; 32(3):287-293.
30. Shimojo Y, Kosaka K, Noda Y, Shimizu T, Shirasawa T. Effect of rosmarinic acid in motor dysfunction and life span in a mouse model of familial amyotrophic lateral sclerosis. J Neurosci Res. 2010; 88(4):896-904. doi: 10.1002/jnr.22242.

31. Engelhardt JI, Appel SH. IgG reactivity in the spinal cord and motor cortex in amyotrophic lateral sclerosis. Arch Neurol. 1990; 47(11):1210-1216.

32. McGeer PL, McGeer EG. Inflammatory processes in amyotrophic lateral sclerosis. Muscle Nerve. 2002; 26(4):459-470.

33. Henkel JS, Engelhardt JI, Siklós L, Simpson EP, Kim SH, Pan T, et al. Presence of dendritic cells, MCP-1, and activated microglia/ macrophages in amyotrophic lateral sclerosis spinal cord tissue. Ann Neurol. 2004; 55(2):221-235.

34. Luan H, Kan Z, Xu Y, Lv C, Jiang W. Rosmarinic acid protects against experimental diabetes with cerebral ischemia: relation to inflammation response. J Neuroinflammation. 2013; 10:28. doi: 10.1186/1742-2094-10-28.

35. Swarup V, Ghosh J, Ghosh S, Saxena A, Basu A. Antiviral and anti-inflammatory effects of rosmarinic acid in an experimental murine model of Japanese encephalitis. Antimicrob Agents Chemother. 2007; 51(9):3367-3370.