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Potential Therapeutic Agent in Psychiatric and Neurological Diseases: Alpha Lipoic Acid

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Abstract

Alpha lipoic acid (ALA) which is known by its antioxidant properties can lead to positive reflections through various mechanisms of action in nervous system diseases. ALA can create privileges in the treatment of neurological and psychiatric diseases through the vital features such as prevention of formation of reactive oxygen species (ROS), having a mission as a cofactor in various enzyme complexes, promotion the level of antioxidants and neurotransmitters in brain. It has also been shown to be responsible for regulation the nerve growth factor, prevention of neuronal damage and neuronal loss, and vitalization of damaged tissues. Hence, the implementation of ALA as a therapeutic substance in the therapy of neurological and psychiatric diseases is promising in the treatment of diseases. Finally, ALA can prevent diseases related with nervous system.

Keywords: Alpha lipoic acid; Neurorestoration; Neuroprotection; Alzhemier's disease; Depression; Parkinson's disease; Schizophrenia; Multiple sclerosis

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Introduction

Alpha lipoic acid (ALA) which is characterized by its therapeutic effects, is described as a potent antioxidant derived from octanoic acid [1]. ALA which has 8 carbons containing 2 sulfur atoms in the dithiol ring structure is an essential substrate for energy metabolism of carbohydrates, proteins and fats [2]. It can naturally be synthesized by a number of enzymatic reactions from octanoic acid and cysteine in the liver and supplied a limited amount by *de novo* catabolism for the human body [2]. Except for the synthesis of a limited amount in the body, it is present in some nutritional sources, such as red meat, liver, heart, kidney, spinach, tomato, broccoli, brussel sprouts and rice bran in small quantities [3,4]. The ratio of ALA naturally synthesized by human tissues is low level in the total body pool [4]. Thus, ALA is regarded as an essential nutrient [2]. For this reason, the possible health effects of ALA are seen only after dietary reinforcement at 600-1800 mg/day [4]. Besides, It has been reported that doses of 600-2400 mg per day are safe [5]. While absorption mechanism is not clearly known, it may be absorbed by multiple carriers such as monocarboxylic and sodium-dependent multivitamin carrier. Because of the confusing routes in absorption, it is considered that the absorption of ALA may be negatively affected by means of substrate competition. Moreover, it may be subject to transcriptional regulation of specific carrier proteins [4].

When the potential health effects of ALA are evaluated; its antioxidant properties have been revealed to have positive effects on many diseases such as inflammatory diseases, neurological and psychiatric diseases, obesity, diabetes and cardiovascular diseases. ALA which is accepted as a scavenger free radicals and modulating various signal transduction pathways, provides to the improvement oxidative stress parameters and reduction of inflammation in inflammatory disorders. In presence of sepsis, ALA reduces both inflammation and oxidative stress in some organs such as liver and kidney through reducing myeloperoxidase activity and lipid peroxidation, increasing superoxide dismutase activity and catalase activity [6].

While ALA is traditionally known by its antioxidant features, it has recently been suggested that ALA has therapeutic potential implications for the treatment of dyslipidemia. ALA modulates cholesterol homeostasis in many ways, including reduction of cholesterol synthesis, attenuation of bile acid synthesis, and enhancement of cholesterol clearance [7]. In addition, the supplementation with ALA can cause to significant weight loss and importantly can decrease body mass index [8]. Weight loss caused by ALA may restore the level of thyroid hormone levels in plasma and diminish oxidative stress and thus it is suggested that ALA may act as a therapeutic potential agent in heart diseases [9].

Potential Therapeutic Effects of Alpha Lipoic Acid in Psychiatric and Neurological Diseases

ALA can act as a vital role for the treatment of various nervous system diseases by fighting against free radicals, acting as a cofactor in many enzyme complexes, supporting the reduction of lipid peroxidation, and regenerating damaged tissues. Because of its potent antioxidant effect, ALA can inhibit neuron damage caused by ROS manufactured throughout neurodegenerative diseases. ALA is associated with neurodegenerative diseases because of anti-inflammatory activity and behaves like a metal chelator that diminishes oxidative processes [10]. Except some features like reducing lipid peroxidation and enhancing antioxidants and neurotransmitters in brain, it also supports regulation of nerve growth factor. In addition, it provides the expression of superoxide dismutase gene [11] and helps to maintain blood glucose balance as affecting the signal pathways of insulin [5]. The reduction of oxidative stress and sustaining blood glucose balance by ALA can prevent neurodegenerative diseases [5].

ALA is regarded as biological thiol antioxidants which are located at the center of antioxidant defenses mechanism in nervous system tissues. Because of neuroprotective effects, it is thought to be a therapeutic agent in a lot of neurotraumatic models [12]. ALA exerts a definite protective effect on the tissues and thus may resist neurotoxicity. It also have anti-apoptotic influences on hippocampal neurons. Especially, it provides to the inhibition neuronal apoptosis by means of Caspase 3 pathway and NF KappaB dependent pathway [13]. ALA decelerates the brain atrophy rate, reduces demyelination and axonal loss in spinal cords, stabilizes blood-brain barrier, and improves the progression of multiple sclerosis. Therefore, ALA has been recomended for clinical benefit in multiple sclerosis [14-16].

Chronic administration of ALA supplementation supports cognitive function and memory. It has been proven that the supplemention of ALA improves cognitive function by increasing total antioxidant capacity, decreasing peripheral oxidative damage, and reducing neurodegeneration in the hippocampal region [5]. Besides, ALA has a potential role in cognitive and behavioural functions via the enhancement of the cholinergic process. Thus, it is an desirable curative agent for the cure of neurvous system disorders [17]. ALA has been demonstrated to have a mechanism of action interfered with pathogenic results of Alzhemier's disease which is also characterized by both a cholinergic deficit, and senile plaques (accumulation of betaamyloid). ALA can be a therapeutic candidate for the treatment of Alzhemier's disease through protecting neurons from betaamyloid neurotoxicity and inhibiting the formation of betaamyloid fibrils [18]. It greatly improves cerebral damage, preserves the cortical neurons, and inhibits inflammatory responses and oxidative stress [19]. In addition, ALA improves the clinical alterations of Parkinson's disease which is associated with dopaminergic mechanism. It protects dopaminergic neurons against neurotoxicity, upregulates DNA repair protein, and reduces mitochondrial transmembrane permeability which held responsible for pathogenesis of Parkinson's disease [20,21].

When the relationship between ALA and psychiatric disorders is examined; it is suggested that ALA have important effects on psychiatric disorders. Especially, the possible effects of ALA are evident in schizophrenia. The existance of an oxidative instability has been increasingly highlighted in pathophysiological process of schizophrenia. Thus, the use of antioxidant substances may have a powerful effect for schizophrenia treatment [22]. It has been announced that ALA inhibits the inflammatory and oxidative damage induced by myeloperoxidase which is found in high concentrations in the serum of schizophrenia patients. Besides, except of inhibiting myeloperoxidase, it can promotes the regulation in gene expression and transcription of pro-inflammatory factors [22]. ALA can also reduce oxidative stress which has been responsible for the pathogenesis of main psychiatric disorders, such as schizophrenia, bipolar disorder and major depression. Especially, major depression disorder is related to free radicals and oxidative imbalance [23] and ALA is a promising substance for the therapy of depression through enhancement of glutathione levels in the prefrontal cortex and striatum. Moreover, it reverses the decline in neurotrophic factor in the hippocampus and striatum, and reduces whole brain total nucleoside triphosphate levels [23-25].

Results

In this review study, thirty-four research articles related to ALA and the nervous system were examined **(Table 1)**. Research results show that; ALA has visible and assertive effects on neurological diseases including multiple sclerosis, Alzhemier's disease, Parkinson's disease, as well as psychiatric disorders such as depression, schizophrenia, and anxiety. In addition, ALA helps to repair or prevent damage related to nervous system such as traumatic brain injury, neuronal apoptosis, neurotoxicity, spinal cord injury and neuropathy. It acts as an reputable role in the management of the nervous system diseases by its properties such as neuronal damage inhibitor, neurorestorative and nervous system supporter.

Conclusion

Although antioxidants such as ALA are known to be beneficial for our health, it is unclear how useful and effective it is in the nervous system. In particular, it is thought that it can play a role in prevention of neurological and psychiatric diseases and in reducing the reflection of diseases. In the course of the management of nervous system diseases, the necessary medical treatment together with ALA administration may alleviate the clinical reflection of neurologic and psychiatric diseases. Therefore, ALA can be shown as an effective therapeutic agent for the therapy of nervous system diseases.

Table 1 The studies examining the therapeutic effects of alpha lipoic acid in nervous system diseases.

Disorders	Subjects	Results	References
Schizophrenia	Schizophrenia model in male Wistar rats (n=130)	ALA (100mg/kg/day) inhibited behavioral impairments accompanied by hippocampal oxidative alterations, possibly related to NMDA receptors hypofunction, demonstrating a beneficial effect as antipsychotic agent.	[22]
Traumatic brain injury	Traumatic brain injury weight-drop model in male rats	ALA (20 or 100 mg/kg) enhanced neuronal survival by the downregulation of caspase-3 expression. In addition, it diminished malondialdehyde level, Bcl-2-associated X protein, and glutathione peroxidase activity. Thus, ALA heals neurological results and inhibits apoptosis by a action related to mitochondria.	[1]
Schizophrenia	Adult male Swiss mice induced by ketamine.	ALA (100 mg/kg) assumed a antipsychotic role via reversing behavioral alterations by the mechanism of neurotrophic and nitrergic pathways. Besides, the administration of clozapine together with ALA improves most of the parameters without causing motor impairment.	[26]
Stroke	Adult male Sprague-Dawley (n=201) induced by clinical stroke	ALA implementation was responsible for decreased mortality, reduced infarction, reduced neurological deficit score. Besides, it caused the rise in count of cells in the borderline (more double-labeled cells) and infarct nucleus regions. Moreover, it was demonstrated that the brain metabolism in ALA group markedly improved. The implementation of ALA for ischemic injury treatment has important restorative effects on neurons due to insulin receptor activation.	[27]
Memory	Aluminium induced neurotoxicity in BALB/c mice (n=24)	ALA (25 mg/kg/day) caused a significantly rise in the expression of muscarinic receptor genes and choline acetyltransferase comparative to the control group. ALA improved fear memory and social novelty preference comparative. ALA remarkably repaired to the fear extinction memory.	[17]
Depression	Depression model in male Swiss mice (n= 295)	The administration of mirtazapine combined with ALA reversed behavioral and oxidative alterations such as anxiety and depression via their central antioxidant effects.	[28]
Memory	Albino Charles-Foster rats	The antioxidant supplement which contains ALA prevented age-dependent alterations in synaptosomal parameters. The age-dependent deficit of learning and memory functions was remarkably prevented through antioxidant supplement which contains ALA.	[29]
Alzheimer's disease	11 month old SAMP8 mice	ALA (100 mg/kg/day) ameliorated memory in the test of object-place recognition paradigm, and also improved learning in the Barnes maze test. It resulted significantly rise in glutathione levels, and decline glutathione peroxidase and malondialdehyde. ALA reversed oxidative stress in the brain tissue.	[30]
Dementia	Dementia model in adult male Wistar rats	ALA (50 mg/kg/day) has potential therapeutic effects on dementia via behavioral alterations, protection of oxidative stress, and restoration of cholinergic pathway. ALA elevated acetylcholine and choline acetyltransferase level, and also reduced the action of acetycholinesterase.	[31]
Schizophrenia	Schizophrenia model in male Wistar rats	The administration of ALA potentiated the inhibitory effects of chlorpromazine on gamma low-band oscillations. The alterations on EEG induced by ketamine were prevented by ALA.	[32]
Depression	Depression model in Swiss mice	ALA reversed the decline of the hippocampal glutathione and also it improved glutathione levels in the prefrontal cortex and striatum. ALA can take place as a promising substance for the therapy of depression.	[23]
Spinal cord injury	Spinal cord injury model in male Wistar albino rats	ALA (50 mg/kg/day) conversely altered histological and impairment of functions such as contraction and relaxation caused by spinal cord injury via its antioxidant and anti-inflammatory actions, however, It did not improve neurological functions.	[12]
Alzheimer's disease	Male Wistar rats	ALA is an impressive candidate for the enhancement of cognitive functions and healing neurochemical defects in Alzhemier's disease via improving neuronal insulin resistance and neuronal insulin signalling. In addition, ALA assists cognitive function.	[3]
Neuronal apoptosis and neurotoxicity	Neonatal mice	ALA demonstrated an significant anti-apoptotic effect on hippocampal neurons. Thus, it may be an ambitious candidate for intervention against neuronal damage.	[13]
Multiple sclerosis	Multiple sclerosis patients aged 40–70 years	ALA which known as a slowing the brain atrophy rate proved a 68% reduction in annualized percent change brain volume. Furthermore, using of ALA for over 2 years has been recomended for clinical benefit in secondary progressive multiple sclerosis.	[14]
Multiple sclerosis	Multiple sclerosis model in SJL mice	ALA significantly prevented clinical alterations based multiple sclerosis via reducing demyelination, axonal loss in spinal cords, CD3+ T cells, and inflammation.	[16]
Multiple sclerosis	Lewis rats	Because of influencing the migration capacity of monocytes and balance of the blood-brain barrier, ALA should be considered as an strong therapeutic substance for the management of multiple sclerosis.	[33]
Multiple sclerosis	52 multiple sclerosis patients	While the implementation of ALA (1200 mg) resulted in an enhancement of total antioxidant capacity, whereas it did not positively affect oxidative stress parameters.	[34]

Multiple sclerosis	52 multiple sclerosis patients	While the levels of INF-γ, TGF-β, IL-4 and ICAM-1 were significantly decreased by ALA (1200 mg) whereas the levels of EDSS, TNF-α, IL-6, and MMP-9 did not significantly alter in the patients of multiple sclerosis.	[35]
Multiple sclerosis	39 multiple sclerosis patients	ALA demonstrated an improvement the progression of multiple sclerosis by significantly reduction EDSS in the patients which EDSS is more than zero.	[15]
Parkinson's disease	Early Parkinson's disease model in rat	ALA (100mg/kg) significantly alleviated alterations related with neurodegeneration by preventing loss of neurons, and decreasing MDA and nitrite. Thus, ALA can afford neuroprotection against neurotoxicity via attenuation of oxidative stress.	[36]
Parkinson's disease	Male C57BL6J and Swiss albino mice	ALA terminates the cascade which mitochondrial permeability transition pore triggers death the signal pathway by activation apoptosis signal regulating kinase such as ASK1 and translocating Daxx. Thus, ALA can afford neuroprotection in dopaminergic neurons.	[37]
Parkinson's disease	PC12 cell cultures	ALA protects dopaminergic neurons from oxidative damage via inhibiting development of ROS levels and reducing mitochondrial transmembrane permeability which held responsible for pathogenesis of Parkinson's disease.	[21]
Spinal cord injury	Spinal cord injury model in rats	ALA therapy reversed all of histopathologic alterations and biochemical parameters in spinal cord injury. It reduced oxidative stress and also provided neuroprotection by limiting lipid peroxidation and DNA fragmentation.	[38]
Spinal cord injury	48 Wistar albino rats	Histopathological examination results showed that ALA did not prevent necrosis and destruction of neural tissue.	[39]
Cerebral ischemia	Cerebral ischemia/ reperfusion model in male rats	ALA attenuated oxidative stress and apoptosis. Hence, it protected cerebral damage. Moreover it has demonstrated neuroprotective action via activation of the BDNF-PI3K/ Akt-ERK1/2 pathway.	[40]
Parkinson's disease	PC12 cell culture	ALA protected dopaminergic neurons against neurotoxicity through up-regulation of DNA repair protein.	[20]
Alzheimer's disease	Wistar rats	The implementation of an antioxidant suplement that contains ALA substantially inhibited to deterioration of spatial learning and memory in elderly rats. In addition, ALA alleviated the age-related clinical alterations in amyloid beta metabolism.	[41]
Parkinson's disease	Human neuroblastoma cell line SH-SY5Y	While R form of ALA upregulates mitochondrial regulatory protein PGC-1α, whereas it downregulates the autophagy-related proteins except LC3 expression. Hence, ALA has neuroprotective mechanism with prevention autophagy and the amelioration of mitochondrial function.	[42]
Alzheimer's disease	ApoE-4 transgenic mice	The R form of ALA and acetyl-L-Carnitine healed cognitive function in spatial memory and temporal memory tests.	[43]
Bipolar depression	40 patients with bipolar depression	The phosphocreatine levels in the parieto-occipital cortex was reduced by ALA suplementation (600–1800 mg/day). The Montgomery-Asberg Depression Rating Scale scores of patients which treated with ALA reduced and these alterations was associated with decline in whole brain total nucleoside triphosphate levels from baseline.	[25]
Depression	Depression model in female Swiss mice	ALA (200 mg/kg) showed an antidepressant-like effect by decreasing the preference of sucrose and reversing immobility time in the forced swimming test. It also reversed corticosterone-induced decrease in neurotrophic factor in the striatum and hippocampus.	[24]
Traumatic brain injury	42 Wistar albino rat pups	ALA therapy significanttly decreased neuronal loss in the hippocampus, parietal cortex and prefrontal cortex.	[44]
Neuropathy	Neuropathy model in 40 male rats	ALA therapy improved brain enzymatic biomarkers and also attenuated lipid peroxidation in neuropathic rats. Besides it increased antioxidant activities in neuropathic rats.	[45]

Abbreviations: ALA: Alpha-lipoic acid, ASK1: Apoptosis signal-regulating kinase 1, EDSS: Expanded disability status scale, EEG: Electroencephalographic, ICAM-1 : İntercellular adhesion molecule-1, IL-4: **/nterleukin 4,** IL-6: **Interleukin 6,** INF-γ: Interferon-gamma, **MMP-9:** Matrix metallopeptidase 9, NMDA: N-methyl-D-aspartate, ROS: Reactive oxygen species, TGF-β: **Transforming growth factor** beta, TNF-α: **Tumor necrosis factor-alpha**

References

1 Wei W, Wang H, Wu Y, Ding K, Li T, et al. (2015) Alpha lipoic acid inhibits neural apoptosis via a mitochondrial pathway in rats following traumatic brain injury. Neurochem Int 87: 85-91.

2 Seifar F, Khalili M, Khaledyan H, Moghadam SA, Izadi A, et al. (2017) α-Lipoic acid, functional fatty acid, as a novel therapeutic alternative for central nervous system diseases: a review. Nutr Neurosci 29: 1-11.

3 Rodriguez-Perdigon M, Solas M, Moreno-Aliaga MJ, Ramirez MJ (2016) Lipoic acid improves neuronal insulin signalling and rescues cognitive function regulating VGlut1 expression in high-fat-fed rats: implications for Alzheimer's disease. Biochimica Biophysica Acta 1862: 511-517.

4 Carrier B, Rideout TC (2013) Anti-obesity and lipid-lowering properties of alpha-lipoic acid. J Hum Nutr Food Sci 1: 1002.

5 Yürük AA, Ayaz A (2014) The health effects of alpha lipoic acid. Hacettepe Üniversitesi Sağlık Bilimleri Fakültesi Dergisi 1: 11-23.

6 Petronilho F, Florentino D, Danielski LG, Vieira LC, Martins MM, et al. (2016) Alpha-lipoic acid attenuates oxidative damage in organs after sepsis. Inflammation 39: 357-365.

7 Rideout TC, Carrier B, Wen S, Raslawsky A, Browne RW, et al. (2016) Complementary cholesterol-lowering response of a phytosterol/α-lipoic acid combination in obese zucker rats. J Diet Suppl 13: 283-299.

8 Namazi N, Larijani B, Azadbakht L (2017) Alpha-lipoic acid supplement in obesity treatment: A systematic review and meta-analysis of clinical trials. Clin Nutr 37: 419-428.

9 Cheserek MJ, Wu G, Li L, Li L, Karangwa E, et al. (2016) Cardioprotective effects of lipoic acid, quercetin and resveratrol on oxidative stress related to thyroid hormone alterations in long-term obesity. J Nutr Biochem 33: 36-44.

10 de Araújo DP, Camboim TGM, Silva APM, Silva CDF, de Sousa RC, et al. (2017) Behavioral and neurochemical effects of alpha lipoic acid associtated ted with omega-3 in tardive dyskinesia ınduced by chronical haloperidol in rats. Can J Physiol Pharmacol 95: 837-843.

11 Dixit S, Dhar P, Mehra RD (2011) Protective role of exogenous α-lipoic acid (ALA) on hippocampal antioxidant status and memory function in rat pups exposed to sodium arsenite during the early post-natal period. Toxicol Mech Methods 21: 216-224.

12 Ekiz A, Özdemir-Kumral ZN, Erşahin M, Tuğtepe H, Velioğlu Öğünç A, et al. (2017) Functional and structural changes of the urinary bladder following spinal cord injury; treatment with alpha lipoic acid. Neurourol Urodyn 36: 1061-1068.

13 Zhao H, Bu M, Li B, Zhang Y (2018) Lipoic acid inhibited desflurane-induced hippocampal neuronal apoptosis through Caspase3 and NF-KappaB dependent pathway. Tissue Cell 50: 37-42.

14 Spain R, Powers K, Murchison C, Heriza E, Winges K, et al. (2017) Lipoic acid in secondary progressive MS: a randomized controlled pilot trial. Neurol Neuroimmunol Neuroinflamm 4: e374.

15 Khalili M, Eskandari G, Ghajarzadeh M, Azimi A, Eghtesadi S, et al. (2012) Lipoic acid and multiple sclerosis: a randomized controlled clinical trial. Curr Top Nutraceutical Res 10: 95-100.

16 Marracci GH, Jones RE, McKeon GP, Bourdette DN (2002) Alpha lipoic acid inhibits T cell migration into the spinal cord and suppresses and treats experimental autoimmune encephalomyelitis. J Neuroimmunol 131: 104-114.

17 Mahboob A, Farhat SM, Iqbal G, Babar MM, Zaidi NSS, et al. (2016) Alpha-lipoic acid-mediated activation of muscarinic receptors improves hippocampus- and amygdala-dependent memory. Brain Res Bull 122: 19-28.

18 Venigalla M, Sonego S, Gyengesi E, Sharman MJ, Münch G (2016) Novel promising therapeutics against chronic neuroinflammation and neurodegeneration in Alzheimer's disease. Neurochem Int 95: 63-74.

19 Liu Y, ZhangQ, Wang L, Wang H, Sun T, et al. (2017) The α-lipoic acid improves high-fat diet-induced cerebral damage through inhibition of oxidative stress and inflammatory reaction. Environ Toxicol Pharmacol 56: 219-224.

20 Li DW, Wang YD, Zhou SY, Sun WP (2016) α-lipoic acid exerts neuroprotective effects on neuronal cells by upregulating the expression of PCNA via the P53 pathway in neurodegenerative conditions. Mol Med Rep 14: 4360-4266.

21 Li DW, Li G-R, Lu Y, Liu Z-Q, Chang M, et al. (2013) α-lipoic acid protects dopaminergic neurons against MPP+- induced apoptosis by attenuating reactive oxygen species formation. Int J Mol Med 32: 108-114.

22 Sampaio LRL, Cysne Filho FMS, de Almeida JC, Diniz DDS, Patrocínio CFV, et al. (2018) Advantages of the alpha-lipoic acid association with chlorpromazine in a model of schizophrenia ınduced by ketamine in rats: behavioral and oxidative stress evidences. Neuroscience 373: 72-81.

23 Silva MCC, de Sousa CNS, Gomes PXL, de Oliveira GV, Araújo FYR, et al. (2016) Evidence for protective effect of lipoic acid and desvenlafaxine on oxidative stress in a model depression in mice. Prog Neuropsychopharmacol Biol Psychiatry 64: 142-148.

24 de Sousa CN, Meneses LN, Vasconcelos GS, Silva MC, da Silva JC, et al. (2015) Reversal of corticosterone-induced BDNF alterations by the natural antioxidant alpha-lipoic acid alone and combined with desvenlafaxine: emphasis on the neurotrophic hypothesis of depression. Psychiatry Res 230: 211-219.

25 Brennan BP, Jensen JE, Hudson JI, Coit CE, Beaulieu A, et al. (2013) A placebo-controlled trial of acetyl-l-carnitine and α-lipoic acid in the treatment of bipolar depression. J Clin Psychopharmacol 33: 627-635.

26 Vasconcelos GS, Ximenes NC, de Sousa CNS, de Queiroz Oliveira T, Lima LLL, et al. (2015) Alpha-lipoic acid alone and combined with clozapine reverses schizophrenia-like symptoms induced by ketamine in mice: participation of antioxidant, nitrergic and neurotrophic mechanisms. Schizophr Res 165: 163-170.

27 Choi KH, Park MS, Kim HS, Kim KT, Kim HS, et al. (2015) Alpha-lipoic acid treatment is neurorestorative and promotes functional recovery after stroke in rats. Mol Brain 8: 9.

28 Oliveira TQ, Sousa CNS, Vasconcelos GS, de Sousa LC, de Oliveira AA, et al. (2017) Brain antioxidant effect of mirtazapine and reversal of sedation by its combination with alpha-lipoic acid in a model of depression induced by corticosterone. J Affect Disord 219: 49-57.

29 Thakurta IG, Banerjee P, Bagh MB, Ghosh A, Sahoo A, et al. (2014) Combination of N-acetylcysteine, α-lipoic acid and α-tocopherol substantially prevents the brain synaptosomal alterations and memory and learning deficits of aged rats. Exp Gerontol 50: 19-25.

30 Farr SA, Price TO, Banks WA, Ercal N, Morley JE (2012) Effect of alpha-lipoic acid on memory, oxidation, and lifespan in SAMP8 mice. J Alzheimers Dis 32: 447-455.

31 Zhao RR, Xu F, Xu XC, Tan GJ, Liu LM, et al. (2015) Effects of alpha-lipoic acid on spatial learning and memory, oxidative stress, and central cholinergic system in a rat model of vascular dementia. Neurosci Lett 587: 113-119.

32 Sampaio LR, Borges L, Barbosa TM, Matos NCB, Lima RF, et al. (2017) Electroencephalographic study of chlorpromazine alone or combined with alpha-lipoic acid in a model of schizophrenia induced by ketamine in rats. J Psychiatr Res 86: 73-82.

33 Schreibelt G, Musters RJ, Reijerkerk A, de Groot LR, van der Pol SM, et al. (2006) Lipoic acid affects cellular migration into the central nervous system and stabilizes blood-brain barrier integrity. J Immunol 177: 2630-2637.

34 Khalili M, Eghtesadi S, Mirshafiey A, Eskandari G, Sanoobar M, et al. (2014) Effect of lipoic acid consumption on oxidative stress among multiple sclerosis patients: a randomized controlled clinical trial. Nutr Neurosci 17: 16-20.

35 Khalili M, Azimi A, Izadi V, Eghtesadi S, Mirshafiey A, et al. (2014) Does lipoic acid consumption affect the cytokine profile in multiple sclerosis patients: a double-blind, placebo-controlled, randomized clinical trial. Neuroimmunomodulation 21: 291-296.

36 Jalali-Nadoushan M, Roghani M (2013) Alpha-lipoic acid protects against 6-hydroxydopamine-induced neurotoxicity in a rat model of hemi parkinsonism. Brain Res 1505: 68-74.

37 Karunakaran S, Diwakar L, Saeed U, Agarwal V, Ramakrishnan S, et al. (2007) Activation of apoptosis signal regulating kinase 1 (ASK1) and translocation of deathassociated protein, Daxx, in substantia nigra pars compacta in a mouse model of Parkinson's disease: protection by α- lipoic acid. FASEB J 21: 2226-2236.

38 Toklu HZ, Hakan T, Celik H, Biber N, Erzik C, et al. (2010) Neuroprotective effects of alpha-lipoic acid in experimental spinal cord injury in rats. J Spinal Cord Med 33: 401-409.

39 Tas N, Bakar B, Kasimcan MO, Gazyagci S, Ayva SK, et al. (2010) Evaluation of protective effects of the alpha lipoic acid after spinal cord injury: an animal study. Injury 41: 1068-1074.

40 Deng H, Zuo X, Zhang J, Liu X, Liu L, et al. (2015) α-lipoic acid protects against cerebral ischemia/reperfusion-induced injury in rats. Mol Med Rep 11: 3659-3665.

41 Sinha M, Bir A, Banerjee A, Bhowmick P (2016) Multiple mechanisms of age-dependent accumulation of amyloid beta protein in rat brain: prevention by dietary supplementation with N-acetylcysteine, a-lipoic acid and a-tocopherol. Neurochem Int 95: 92-99.

42 Zhao H, Zhao X, Liu L, Zhang H, Xuan M, et al. (2017) Neurochemical effects of the R form of α-lipoic acid and its neuroprotective mechanism in cellular models of Parkinson's disease. International J Biochem Cell Biol 87: 86-94.

43 Shenk JC, Liu J, Fischbach K, Xu K, Puchowicz M, et al. (2009) The effect of acetyl-L-carnitine and lipoic acid treatment in ApoE4 mouse as a model of human alzheimer's disease. J Neurol Sci 283: 199-206.

44 Ozbal S, Cankurt U, Tugyan K, Pekcetin C, Sisman AR, et al. (2015) The effects of α-lipoic acid on immature rats with traumatic brain injury. Biotech Histochem 90: 206-215.

45 Lebda MA, Gad SB, Rashed RR (2015) The effect of lipoic acid on acrylamide-induced neuropathy in rats with reference to biochemical, hematological, and behavioral alterations. Pharm Biol 53: 1207-1213.