

Possible role of selective serotonin reuptake inhibitor sertraline on oxidative stress responses

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Abstract. – The naphthylamine derivative sertraline is a potent and selective inhibitor of serotonin reuptake into presynaptic terminals and the most widely used that has been shown to have both antidepressant and anti-anxiety effects. In the present study the possible role of sertraline (acute and chronically doses) was evaluated on lipid peroxidation levels and antioxidant enzyme activities in plasma and brain tissues of (10, 40, 80 mg/kg) sertraline treated Wistar albino rats (n=48). Lipid peroxidation levels (MDA) of plasma and brain tissue increased in all acute and chronic sertraline treated rats ($p < 0.05$). According to results of present study superoxide dismutase (SOD) levels of brain tissue decreased while plasma levels increased ($p < 0.05$) as compared with vehicle group. Catalase (CAT) levels of plasma and brain tissue and paraoxonase (PON) levels of plasma decreased ($p < 0.05$) as compared with vehicle group. Based on the data, it can be concluded that high dose sertraline administration enhances oxidative stress. Therefore, dose adjustment in depression patients seems significant as it may help prevention of further prognosis of the diseases.

Key Words:

Sertraline, Oxidative stress, Antioxidant, Biomarker.

Abbreviations

SOD = Superoxide dismutase; CAT = Catalase; PON = Paraoxonase; MDA = Malondialdehyde; SSRI = Selective Serotonin Re-uptake Inhibitors; ROS = Reactive oxygen species; NBT = Nitroblue tetrazolium

Introduction

The last decade has witnessed the introduction of several new antidepressant drugs for the pharmacological management of depressive disorders. In particular, selective serotonin re-uptake inhibitors (SSRI) are prescription medications used to inhibit serotonin reuptake and when used result in a potential increase in serotonin levels,

which are found lacking, and used for treatment of depression, anxiety, obsessional and impulse control disorders¹. The naphthylamine derivative sertraline, a leading antidepressant in SSRI group of medicine is the most frequently prescribed drug (Figure 1). It's well-known fact that central nervous system medication, in particular, triggers oxidative stress, causing oxidation in the lipid structure of brain tissue²⁻⁵. Sertraline was reported to have beneficial effect in transgenic animal model of Huntington's Disease. Previous reports also state that sertraline increases the neurogenesis and has antioxidant effect^{6,7}.

Reactive oxygen species (ROS) are continuously generated in physiological conditions and are effectively controlled/eliminated by intracellular and extracellular antioxidant systems^{8,9}. ROS are products of normal cellular metabolism and are well recognized for their dual role as deleterious and essential compounds, given that ROS can be harmful or beneficial^{9,10}. Beneficial effects of ROS occur at low levels and involve cell signaling and signal transduction¹¹. ROS also play an essential role in the human immune system helping killing and eliminating infectious organisms. However, elevated or chronic inflammations are major determinants of disease later in the human lifespan, ROS plays a critical role in several age-related diseases, particularly cancer, cardiac and neurodegenerative disorders^{10,12}.

There are four major sources of ROS: (1) oxidative burst (i.e., activation of immune cells by different causes); (2) oxidative process (e.g., electron transport chain, cytochrome P450 activation, and increased monoamine oxidation); (3) lipid peroxidation; and (4) oxidative stress (e.g., trauma, ischemia). There is a balance between ROS and antioxidants, such as cellular antioxidants, membrane antioxidants and extracellular antioxidants, under normal circumstances⁽¹²⁾. The term "oxidative stress" has been defined as

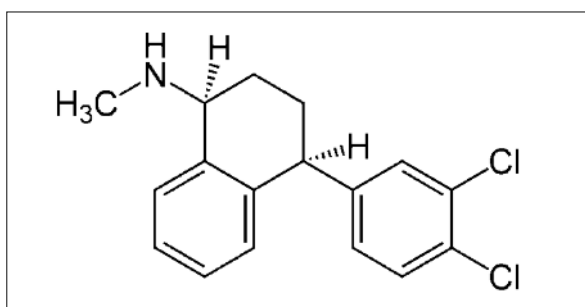


Figure 1. Chemical structure of sertraline.

an imbalance between the generation of ROS and antioxidant defenses, favouring the former¹⁰. In situations of oxidative stress, several biomolecules (e.g., lipid membrane, proteins, and DNA) can be damaged. As ROS have extremely short half-lives, their levels are difficult to measure. Therefore, most studies measure the levels of the damage induced by oxidative stress. For instance, malondialdehyde (MDA) is one of the low-molecular-weight end products formed via the decomposition of primary and secondary lipid peroxidation products¹³.

Extensive production of ROS leads to lipid peroxidation in biological membranes it causes loss of fluidity in cell membranes, decrease in membrane potential and eventual rupture leading to release of cell and organelle contents¹⁴. The brain is much more vulnerable to oxidative free radicals than other tissues since it utilizes 20% of the oxygen consumed by the body. Moreover, the brain contains great amounts of polyunsaturated fatty acids, iron and low concentration of antioxidant enzymes¹⁵⁻¹⁷. Therefore, oxidative stress in the brain tissues has been greatly increased by the antidepressants in the depression patients. Consequently, dose adjustment in antidepressant therapy might significantly reduce potential oxidative damage. The present research was designed to investigate the effect of acute, chronic and different doses therapy of SSRI sertraline on antioxidant levels and oxidative stress in rat plasma and brain tissue.

Materials and Methods

Materials

Animals

Male Wistar albino rats of 150-250 g, 5-6 weeks age, were used in this study. All animals

were obtained from Experimental Medical Research Center of Mersin University (Mersin, Turkey). Animals were acclimatized to laboratory conditions prior to experimentation. The animals were kept under standard conditions of light and dark cycle with food and water *ad libitum*. The protocol was approved by the Mersin University Animal Ethics Committee (document number is 2010/06) and carried out in accordance with the guidelines and the laws governing animal studies in Europe¹⁸.

Drugs and Treatment Schedule

Sertraline (Sigma Chemicals, St. Louis, MO, USA) was diluted with distilled water and solution was administered by oral gavage method to animal in a volume of 2 ml of groups. Each experimental group consisted of six animals. Group-1 vehicle treated group (distilled water 2 mL/day); Group-2 received low dose (10 mg/kg/day) sertraline, Group-3 received medium dose (40 mg/kg/day) sertraline; Group-4 received high dose (80 mg/kg/day) sertraline throughout 28 days (daily) of the study for chronic treatment. Group-5 vehicle treated group (distilled water 2 mL/day); Group 6 received low dose (10 mg/kg/day) sertraline; Group-7 received medium dose (40 mg/kg/day) sertraline; Group-8 received high dose (80 mg/kg/day) sertraline daily for acute treatment. In the end of the treatment periods (28th day for chronically, 24 hour for acute) all animals were sacrificed by xylazine.

Biochemical Assessment

Plasma Samples

Fasting blood samples were drawn into heparinized tubes during blood sampling for biochemical analyses. After immediate centrifugation at 1000 g for 10 min, plasma samples were stored at -20°C for further analysis.

Brain Tissue Samples

After brains of rat tissues were quickly excised, and then rinsed with ice-cold 0.175 M KCl/25 mM Tris HCl, pH 7.4, to clean the blood, weighed, finely minced in the same solution, and homogenized in a homogenizer with a Teflon pestle. Homogenates were centrifuged at 10,000 × g for 15 min and supernatants were used for lipid peroxidation and antioxidant enzymes assay.

Determination of Lipid Peroxidation

Lipid peroxidation was assayed by measuring the level of malondialdehyde (MDA) in rats. MDA

levels, as an index of lipid peroxidation, were determined by using thiobarbituric acid reaction according to the method suggested by Yagi¹⁹.

Determination of Superoxide Dismutase (SOD) Activity

SOD activity was measured through the inhibition of nitroblue tetrazolium (NBT) reduction by oxygen generation of the xanthine/xanthine oxidase system. One unit of SOD activity was defined as the amount of protein causing 50% inhibition of the NBT reduction rate²⁰.

Determination of Catalase (CAT) Activity

CAT activity was determined according to the method of Aebi²¹. The decomposition of H₂O₂ can be followed directly by the decrease in absorbance at 240 nm, resulting from enzymatic decomposition of H₂O₂. The difference in absorbance per unit time was used as a measure of CAT activity.

Determination of Paraoxonase (PON) Activity

Plasma PON activity was determined by Eckerson's modified method²². The rate of paraoxon hydrolysis was measured by monitoring the increase in absorbance at 412 nm (25°C). PON activity was expressed as U/L.

Determination of Protein Content

Tissue protein content was determined according to the method developed by Lowry et al²³ using bovine plasma albumin as standard.

Statistical Analysis

All data were statistically analyzed with a computer program SPSS version 11.5 (SPSS Inc., Chicago, IL, USA). The results were expressed as mean values \pm standard deviation. Differences in MDA levels, SOD, PON and CAT activity between the groups were analyzed and compared by One-Way ANOVA with paired samples *t* test tests for all pair mean comparison. Obtained "*p*" values of less than 0.05 were considered statistically significant.

Results

Effect of Sertraline Treatment on MDA Level

Plasma MDA levels in acute sertraline administered groups were significantly higher than

those of vehicle treated group ($p < 0.05$). Values of MDA were: 3.50 ± 0.40 nmol/mL for dose of 10 mg/kg/day, 3.67 ± 0.34 nmol/mL for dose in 40 mg/kg/day, 3.86 ± 0.35 nmol/mL for dose of 80 mg/kg/day (Figure 2a).

Brain tissue MDA level in acute and chronic sertraline administered groups were significantly higher than those of vehicle treated group ($p < 0.05$). Values of MDA levels in acute sertraline administered groups were: 0.56 ± 0.05 nmol/mg protein, 0.60 ± 0.04 nmol/mg protein and 0.69 ± 0.06 nmol/mg protein for low, medium and high doses, respectively (Figure 3a).

Effect of Sertraline Treatment on CAT Activity

Regardless of the time course of treatment, plasma CAT activities for medium and high treated doses were found to be significantly lower than those of vehicle treated group ($p < 0.05$) (Figure 2b). Values ($n=6$, mean \pm SD) of CAT activity were as following: 4.07 ± 0.32 U/L, 4.05 ± 0.30 U/L for acute medium and high doses and 3.98 ± 0.46 U/L, 3.65 ± 0.39 U/L for chronic medium and high doses. There were statistically meaningful difference between acute and chronic high dose groups ($p < 0.05$).

On the other hand, brain tissue CAT activities were significantly lower than that of controls in acute low, medium and high doses and chronic high dose sertraline administered group ($p < 0.05$) (Figure 3b). There was also statistically difference between CAT levels in acute and chronic sertraline treated (high and medium doses) rats' brain tissue. Values ($n=6$, mean \pm SD) of CAT were as following: 675.15 ± 49.88 U/mg protein, 566.26 ± 50.32 U/mg protein, 493.26 ± 33.51 U/mg protein for acute low, medium and high doses and 604.59 ± 33.82 U/mg protein chronic high dose sertraline administered respectively (Figure 3b).

Effect of Sertraline Treatment on PON Activity

Plasma PON activity of acute (low, medium and high doses) and chronic (low dose) administered groups of sertraline were significantly lower than those of vehicle treated group ($p < 0.05$) (Figure 2c). Values ($n=6$, mean \pm SD) of PON were as following: 160.56 ± 11.99 U/L, 146.55 ± 7.69 U/L, 143.48 ± 9.88 U/L for acute sertraline doses, 154.69 ± 6.87 U/L for chronic low dose administered sertraline, respectively.

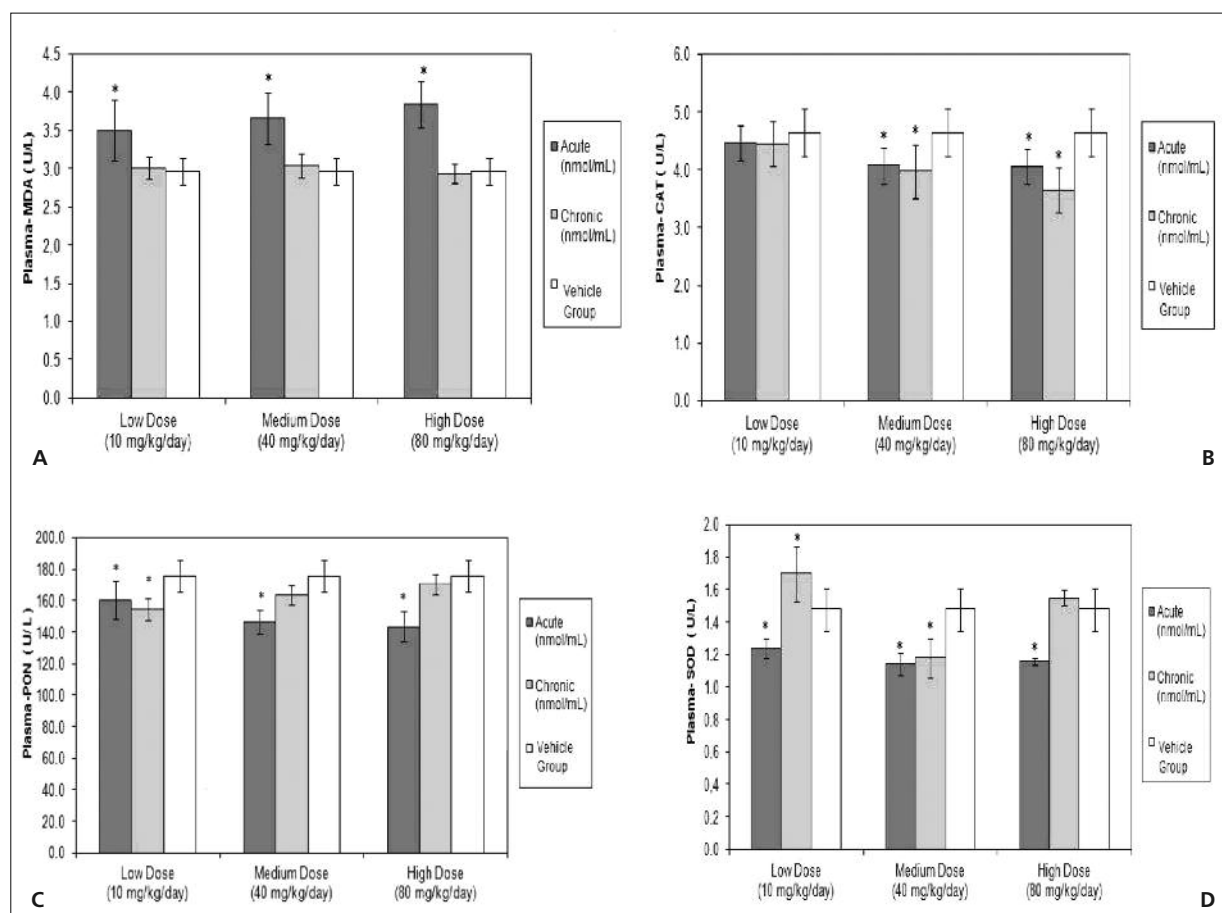


Figure 2. Plasma malondialdehyde and antioxidant enzyme levels of acute and chronic sertraline treated rats. **A**, Malondialdehyde. **B**, Catalase. **C**, Paraoxonase. **D**, Superoxide dismutase. *There is a significant difference between vehicle group and sertraline dose groups ($p < 0.05$).

Effect of Sertraline treatment on SOD Activity

Plasma SOD activities of acute doses sertraline administrated groups of rats were significantly lower than those of vehicle treated group on the other hand, chronically sertraline (low and medium doses) treated groups of rats show significantly higher plasma SOD levels than those of vehicle treated group ($p < 0.05$) (Figure 2d). Values ($n=6$, mean \pm SD) of SOD activity were found to be 1.16 ± 0.02 U/L, 1.14 ± 0.07 U/L, 1.24 ± 0.06 U/L for acute sertraline doses, 1.69 ± 0.17 U/L, 1.79 ± 0.12 U/L for chronically administered sertraline doses, of low and medium respectively.

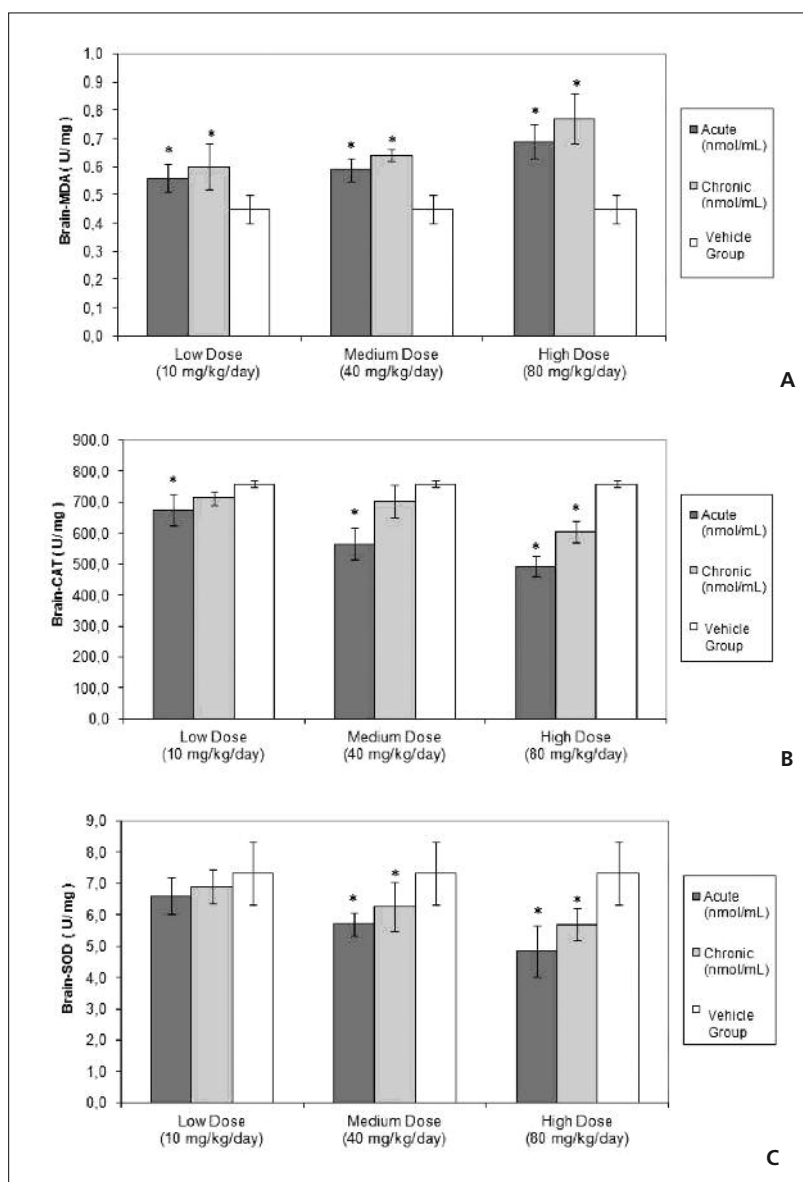
Brain tissue SOD activities were significantly lower than that of the vehicle group in both acute and chronically administered medium and high doses of sertraline ($p < 0.05$) (Figure 3c). Values ($n=6$, mean \pm SD) of SOD activity were found to

be 5.72 ± 0.37 U/mg protein, 4.86 ± 0.82 U/mg protein, 6.28 ± 0.78 U/mg protein, 5.71 ± 0.52 U/mg protein for acute medium and high doses and chronic medium and high doses sertraline administered respectively. There were statistically meaningful difference between acute and chronic high dose groups ($p < 0.05$).

Discussion

Depression is a widely seen, devastating disorder causing serious physical anomalies and psychosocial disturbances. It is characterized long term attacks, relapse and recurrence rates. Depression can occur with different symptoms at any age. Potential to overcome biological, psychological, and sociological stress sometimes becomes very low. Antidepressants are third drug among all drugs currently used in medicine. SS-

Figure 3. Brain malondialdehyde and antioxidant enzyme levels of acute and chronic sertraline treated rats. **A,** Malondialdehyde. **B,** Catalase. **C,** Superoxide dismutase. *There is a significant difference between vehicle group and sertraline dose groups ($p < 0.05$).



RI are 80% of the antidepressants. Sertraline is a leading antidepressant in SSRI group of medicine. Alterations in oxidative biology are increasingly being recognized as a critical route of damage toward the pathophysiology of depression. Enhanced oxidative stress or defective antioxidant defenses are also related to major depression²⁴⁻²⁶. In this study, the influence of the acute and chronic therapy with the different doses of sertraline on oxidative stress was investigated.

Free radicals are normal products of cellular aerobic metabolism. However, when the production of free radicals increases or defense system of the body decreases, it results in cellular dysfunction. Free radicals attack at the

polyunsaturated sites of the biological membranes, causing lipid peroxidation. The increase in levels of MDA is a marker of lipid peroxidation^{27,28}. In the present study, it was determined that plasma MDA levels were increased in acute treatment of sertraline at all (low, moderate and high) doses. In contrast, chronic sertraline administration didn't cause significant difference in MDA levels. However, increased MDA levels in brain were observed in both acute and chronic treatment groups at all doses. The highest increase was obtained by high dose sertraline therapy. This elevation in MDA might be because of the increased ROS production and lower level of antioxidant enzymes. In

contrast to our study, sertraline administration to rats at 10 or 20 mg/kg showed decrease in brain MDA levels by 40.7 and 30.0%, respectively in rat brain¹. Similar results were observed by Khanzode et al²⁹ and Bilici et al¹² in case of the 3 months antidepressant treatment³⁰.

Organisms have developed several cellular defense paths, which under normal metabolic conditions regulate the level of ROS and protect against the deleterious effects of free radicals. This defense system includes SOD, CAT, glutathione reductase and glutathione peroxidase^{31,32}.

SOD metabolizes superoxide anion, releasing hydrogen peroxide (H₂O₂)^{33,34}. SOD can act as a primary defense system and prevents further generation of free radicals. In our study, plasma SOD activities showed decrease in all dose groups of acute treatment whereas chronic administration resulted in increase. The increase in high dose was not statistically significant. Brain SOD levels were decreased in all groups, in comparison to the vehicle group. The decrease was significant in medium and high doses of acute and chronic administration. The highest decrease was observed in high dose treatment. The decreased SOD activities suggest that accumulation of superoxide anion radical might be responsible for increased lipid peroxidation following sertraline treatment.

CAT is responsible for breakdown of H₂O₂, an important ROS, produced during metabolism. CAT catalyzes the removal of H₂O₂ formed during the reaction catalyzed by SOD^{35,36}. In this study, plasma CAT activities were decreased in all groups treated with sertraline. This decrease was statistically significant in moderate and high dose groups of acute and chronic treatment. Brain CAT activities were decreased parallel to plasma CAT activities whereas this decrease was statistically significant in low, medium and high dose of acute and high dose of chronically treated groups of rats. The largest decrease was caused by high dose administration. Reduced activity of CAT could be correlated to increased generation of H₂O₂. Outcome of our research are in good agreement with that of Bilici et al¹² as they reported that 3 months of sub chronic treatment with SSRI, reduce antioxidant enzyme activities.

PON was identified as an enzyme having organophosphates as its substrates. There are three known genotypic forms of paraoxonases. They are coded for by the PON set of genes – PON1, PON2 and PON3. PON1 is synthesized in

the liver and transported along with HDL in the plasma. It functions as an antioxidant; preventing the oxidation of LDL. PON2 is a ubiquitously expressed intracellular protein that can protect cells against oxidative damage³⁷. PON3 is similar to PON1 in activity but differs from it in substrate specificity³⁸. The present study showed decreased plasma PON activity, which could be also related to a diminished antioxidative defense in all dose groups of acute and chronically treated rats. The decrease was significant at all doses of acute group whereas it was significant only in low dose group of chronically treated rats. Previous studies in literature reported that PON activity increased after 24-week antidepressant treatment whereas PON activity diminished by 6-week antidepressant treatment³⁰. In general brain has the lowest PON activity so it is not evaluated in this study. According to our literature research, there is no published study investigating the effect of sertraline on PON in rats.

Our study indicated that chronic treatment with sertraline reduced lipid peroxidation and increased SOD activity in plasma compared to acute treatment. However, lipid peroxidation increased and antioxidant enzyme activities (SOD and CAT) decreased in the brain tissues of chronically and acute sertraline treated groups of rats. Brain processes large amounts of oxygen in relatively small mass and has a high content of substrates such as polyunsaturated fatty acids available for oxidation in conjunction with low antioxidant activities, making it extremely susceptible to oxidative damage^{39,40}.

Several studies have provided evidence for the antioxidant effects of antidepressants, by demonstrating reversals of antioxidant and oxidative disturbances after antidepressant treatments, suggesting that antioxidant properties may contribute to their clinical effects^{12,24,29,41}.

Conclusions

High dose sertraline administration enhances oxidative stress. Therefore, dose adjustment in depression patients seems significant as it may help prevention of further prognosis of the diseases. Furthermore, it may be suggested that the administration of nutraceuticals with antioxidant properties may play an important role in prevention of potential oxidative damage in the depression patients under the treatment of antidepressants.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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