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# Status of antioxidant defense and lipid peroxidation in schizophrenics with positive, negative and cognitive symptoms

Paul Sunday Ogunro [a,c,*], Benjamin Adekunle Eegunranti [b], Adeniran Samuel Atiba [a], Elizabeth Olufunke Oke [a], Joel Olufunminiyi Akande [a]

[a] Department of Chemical Pathology, College of Health Sciences, Ladoke Akintola University of Technology, Osogbo 3456, Nigeria
[b] Department of Psychiatry, College of Health Sciences, Ladoke Akintola University of Technology, Osogbo 3456, Nigeria
[c] Malaria Research and Clinical Laboratory, College of Health Science, Ladoke Akintola University of Technology, Osogbo 5623, Nigeria

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ABSTRACT

*Introduction:* The etiology of schizophrenic is still remains elusive. In the last few decades, dopamine hyperactivity hypothesis predominates in the research field. Impaired antioxidant defenses are suggested to participate in the pathophysiology of schizophrenia. The aim of this study is to elucidate whether oxidative stress may have a pathophysiological role in schizophrenia and in clinical course.
*Methods:* A total of 48 schizophrenic patients of age group 18–55 years (30M: 18F) were recruited. The patients were divided into three groups: 18 subjects with positive symptoms, 14 with negative symptoms and 16 with cognitive symptoms. The control groups consist of 48 healthy individuals that were recruited from general population with similar socio-economic status. Total antioxidant ststus (TAS), erythrocyte malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione (GSH) and glucose-6-phosphate dehydrogenase (G6PD) were measured using standard methods.
*Results:* Erythrocyte MDA concentration was significantly increased in schizophrenic subjects with positive, negative and cognitive symptoms. Contrarily, the erythrocyte antioxidant enzymes GSH-Px and CAT were significantly reduced among schizophrenic subjects. Erythrocyte GSH and plasma TAS concentrations were also significantly reduced in schizophrenic subjects. Likewise, secondary antioxidant enzymes activity G6PD was significantly reduced ($p < 0.01$) among schizophrenic subjects.
*Conclusion:* Our finding reveals that maintenance of redox balances within cells is a primary component of homeostasis underlying neuronal survival. Studies are pointing to oxidative stress as a part of the pathology in schizophrenia. Therefore, identifying viable therapeutic strategies to tackle oxidative stress and the resulting physiological disturbances will provide an exciting opportunity for the treatment and ultimately prevention of schizophrenia.


## 1. Introduction

Reactive oxygen species (ROS), collectively described as oxygen free radicals (OFR) as well as reactive nitrogen species (RNS), are products of normal cellular metabolism.[1] ROS and RNS are well recognized for playing a dual role as both deleterious and beneficial species, since they can be either harmful or beneficial to living systems.[1] Beneficial effects of ROS occur at low/moderate concentrations and involve physiological roles in cellular responses to noxia, as in defense against infectious agents and in the function of a number of cellular signaling systems.[2] One further beneficial example of ROS at low/moderate concentrations is the induction of a mitogenic response. The harmful effect of free radicals causing potential biological damage is termed oxidative stress and nitrosative stress.[2] This occurs in biological systems when there is an overproduction of ROS/RNS on one side and a deficiency of enzymatic and non-enzymatic antioxidants on the other. In other words, oxidative stress results from the metabolic reactions that use oxygen and represents a disturbance in the equilibrium status of pro-oxidant/antioxidant reactions in living organisms.[2] The activities of free radicals in many age-related diseases have long been of interest, and there is substantial evidence linking cancer, diabetes mellitus, atherosclerosis, neurodegenerative diseases (Alzheimer's

* Corresponding author. Department of Chemical Pathology, College of Health Sciences, Ladoke Akintola University of Technology, Osogbo, Nigeria. Tel.: +234 (0) 8033061119 (mobile).
*E-mail address:* ogunrops@yahoo.com (P.S. Ogunro).

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and Parkinson's disease), rheumatoid arthritis, ischemic/reperfusion injury, obstructive sleep apnea, cardiovascular disease, hypertension and aging to free radical-induced alterations.[3,4] The brain makes up about 2% of body mass but consumes 20% of metabolic oxygen. The vast majority of energy is used by the neurons.[5] Due to the lack of glutathione-producing capacity by neurons, the brain has a limited capacity to detoxify ROS. Therefore, neurons are the first cells to be affected by the increase in ROS and shortage of antioxidants and as a result, are most susceptible to oxidative stress.

The concept of oxidative stress is intimately linked with the notion that, in many psychiatric disorders, there is an abnormality in mitochondrial energy generation.[6] For example, molecular and genetic studies indicate that disturbances in redox reactions are part of the pathophysiology of schizophrenia, including evidence of changes in elements of the genetic transcript, protein and metabolite levels that are involved in mitochondrial function, energy metabolism and oxidative stress responses.[7] Recent studies have implicated these mechanisms in the control of brain pathology, raising the possibility that altered regulation of fundamental mechanisms of oxidative stress may contribute to the pathogenesis of schizophrenia and related disorders.[8,9]

Schizophrenia, the most common of the major mental disorders, is also one whose clinical symptomatology, etiology, prognosis and successful treatment are fraught with confusion. It is a devastating mental disorder, expressed in the form of abnormal mental functions and disturbed behavior. It has a life-time prevalence of approximately 1% of the world's population.[10] Cardinal symptoms of schizophrenia include positive symptom, negative symptoms, cognitive dysfunction, and deterioration in social and occupational functioning.[11]

Recently, reduced levels of the antioxidant enzymes, SOD, CAT and GSH-Px are reported in patients with schizophrenia compared with controls,[12,13] although there are both negative studies and studies that have only partially replicated the positive findings.[14,15] An inverse relationship between blood GSH-Px and structural measures of brain atrophy has been documented, suggesting a link between oxidative dysregulation and progressive structural changes.[16] Studies also shows that antioxidant systems, including the antioxidant proteins albumin, bilirubin, uric acid, and the plasma total antioxidant status are lower in schizophrenia than controls[17,18] and also in first episode patients schizophrenic on neuroleptic.[19] The definite etiology of schizophrenia is still a mirage and the chemical nature of schizophrenic brain is still not completely understood. The brain and nervous system are particularly prone to lipid peroxidation since the membrane lipids are very rich in polyunsaturated fatty acid chains, and areas of human brain are very rich in iron, which plays an essential role in generating free radical species. However, the status of antioxidants and the extent of lipid peroxidation in erythrocytes have not been fully investigated so far in schizophrenia patients with different symptoms. Therefore, the aim of this study is to examine the erythrocyte antioxidant status and lipid peroxidation in the schizophrenics and correlate with positive, negative and cognitive symptoms.

## 2. Materials and methods

A total of 48 schizophrenic patients of age group 18–55 years of both sexes were selected from the psychiatric department of Ladoke Akintola University of Technology teaching hospital Osogbo, Osun state, Nigeria. The patients were divided into three groups: 18 subjects with positive symptoms, 14 with negative symptoms and 16 with cognitive symptoms. Any patient with combination of the above symptoms was not included in this study, but in future study base on the outcome of the present study. All the selected subjects met the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 2000) for schizophrenia.[20] Those excluded from the study are all subjects on any antioxidant supplements such as vitamin C, vitamin E, β-carotene, any natural herbs or other similar substances within one month prior to the day blood was collected. Patients with a history of drug abuse or dependence, serious medical conditions, severe head injury or seizure disorders were also excluded from the study.

Informed and written consent was obtained from all subjects/subject's guardian prior to examination. The control groups consist of 48 healthy individuals that were recruited from general population with similar socio-economic status, control with familial history of mental illness was also eliminated from participating in the study. Fasting blood samples was obtained by venepuncture from patients and controls into heparinised bottle which was centrifuged at 2000 *g* for 15 min, plasma was carefully removed and the erythrocyte pellet was washed three times with equal volumes of saline and centrifuged at 2000 *g* for 15 min. The washed red blood cells were then haemolyzed in distilled water (1:4, v/v) and by freezing and thawing. The haemolysate was centrifuged and the supernatant and plasma was then stored at −20 °C until they were analyzed.

Since neuronal oxidative injury processes and underlying dynamic molecular regulatory mechanisms are reflected in peripheral blood cells, we could use red blood cells, platelets, lymphocytes and cultured skin fibroblasts as "window" to the CNS.

Erythrocyte MDA levels was determined using the method of Draper and Hadley[21] based on the reaction of MDA with thiobarbituric acid (TBA) at 95 °C. In the TBA test reaction, MDA and TBA react to form a pink pigment with an absorption maximum at 532 nm. The reaction was performed at pH 2–3 at 95 °C for 15 min. The sample was mixed with 2.5 volumes of 10% (w/v) trichloroacetic acid to precipitate the protein. The precipitate was pelleted by centrifugation and an aliquot of supernatant was reacted with 0.67% TBA in a boiling water-bath for 15 min. After cooling, the absorbance was read at 532 nm. Arbitrary values obtained were compared with a series of standard solutions (1,1,3,3 tetramethoxypropane). Measurement of TAS in the plasma was performed using a commercial kit from Randox Laboratories (Randox Laboratories Ltd, Diamond Road, Crumlin, Co. Antrim, Ireland).[22] The assay was calibrated using 6-hydroxy-2, 5, 8- tetra-methylchroman-2-carboxylic acid (trolox). The results were expressed as mmol/L of trolox equivalent. Measurement of erythrocyte GSH-Px (EC# 1.11.1.9) activity was performed using a commercial kit RANSEL from Randox Laboratories (Randox Laboratories Ltd, Diamond Road, Crumlin, Co. Antrim, Ireland). GSH-Px catalyzes the oxidation of GSH to glutathione disulphide (GSSG) by cumene hydroperoxide, in the presence of glutathione reductase and NADPH, GSSG is immediately converted to GSH with a concomitant oxidation of NADPH to $NADP^+$ according to the method of Paglia and Valentine.[23] The concentration of GSH-Px activity is assessed from the decrease in absorption at 340 nm and at 37 °C using Humalyzer 2000 analyzer. A standard curve was prepared by using the standard provided in the kit, and the value for each sample was read from this curve. SOD (EC. 1.15.1.1) activity was estimated by employing xanthine/xanthine oxidase assay commercial kit RANSOD from Randox Laboratories (Randox Laboratories, Crumlin, Antrim, UK).[24] The results of SOD activity were normalized to the hemoglobin content in the erythrocyte lysate and expressed as U/g Hb. The CAT (EC 1.11.1.6) peroxidative activity was measured by the reaction of formaldehyde produced from methanol with purpald to produce a chromophore according to the method of Johansson and Hakan Borg.[25] Quantitation was carried out by measuring the absorbance at 540 nm and comparing the results with those obtained with formaldehyde calibrators. GSH

concentration in erythrocytes was determined in the presence of low-molecular-mass free thiol groups, mercuric salt and sulfanilamide, in a highly acidic medium, biazonian salt was produced. The salt so obtained was conjugated with amine salt, producing a colored complex, the absorbance of which was measured at 535 nm and calculations were made according to the model curve for GSH and expressed in μmoles GSH/g Hb.[26] G6PD activities will be assayed according to the procedure described by Beutler.[27]

### 2.1. Statistical analysis

All values were expressed as the mean ± standard deviation. Data was analyzed using one-way ANOVA followed by the post-hoc Duncan multiple range test for analysis of biochemical data using SPSS version 11 (SPSS Inc Chicago, Ilinois). Method of correlation analysis (PEARSON) was also used to determine the degree of association between variable of interest. Values were considered statistically significant at $p < 0.05$.

## 3. Results

The anthropometric measurements and physical clinical parameters of the subjects and the controls were depicted in Table 1. All the studied subjects and the controls were non-obese and normotensive.

Erythrocyte MDA concentration of 4.51 ± 0.72 nmol/g Hb for positive symptom was significantly increased ($p < 0.01$); 4.07 ± 0.46 nmol/g Hb for negative symptom and 3.99 ± 0.18 nmol/g Hb for cognitive symptom were significantly increased ($p < 0.05$) when they were compared to 2.71 ± 0.41 nmol/g Hb for the controls. The mean plasma TAS concentration of 1.25 ± 0.15 mmol/L for positive symptom, 1.30 ± 0.08 mmol/L for negative symptom and 1.25 ± 0.15 mmol/L for cognitive symptom were significantly decreased ($p < 0.05$) compared to 1.98 ± 0.18 mmol/L for the controls. Likewise, erythrocyte antioxidant GSH-Px activity of 20.09 ± 2.29 U/g Hb for positive symptom and 19.85 ± 2.17 U/g Hb for negative symptom were significantly decreased ($p < 0.01$); 22.46 ± 3.80 U/g Hb for cognitive symptom was significantly decreased ($p < 0.05$) when compared to 38.07 ± 4.25 U/g Hb for the controls. However, erythrocyte activity of SOD for schizophrenic subjects did not show any significant when compared to the control. Erythrocyte GSH concentration of 4.01 ± 0.4 μmol/g Hb for positive symptom and 4.25 ± 0.6 μmol/g Hb for cognitive symptom were significantly decreased ($p < 0.05$); 3.52 ± 0.3 μmol/g Hb for negative symptom and was significantly decreased ($p < 0.01$) when both were compared to 6.05 ± 0.9 μmol/g Hb for the controls. Similarly, erythrocyte CAT activity of 1271.09 ± 45.8 U/g Hb for positive symptom, 1197.23 ± 63.7 U/g Hb for negative symptom and 1201.49 ± 44.9 U/g Hb for cognitive symptom were significantly reduced ($p < 0.05$) compared to 1426.72 ± 80.9 U/g Hb for the controls. Likewise, erythrocyte G6PD activity of 9.02 ± 1.17 U/g Hb for positive symptom, 8.79 ± 1.09 U/g Hb for negative symptom and 8.19 ± 1.12 U/g Hb for cognitive symptom were significantly reduced ($p < 0.01$) compared to 18.98 ± 2.05 U/g Hb for the controls [Table 2].

Table 3 shows the correlation coefficient analysis between the levels of antioxidant level and the marker of oxidative stress of schizophrenic subjects. Marker of oxidative stress (MDA) recorded inverse correlation with other antioxidants in the three major symptoms of schizophrenic mental disorder.

## 4. Discussion

Most measurements of oxidative stress in patients with schizophrenia have been made on peripheral tissues. There is a lack of information on oxidative processes in cerebrospinal fluid and brain. RBCs have often been used for evaluation of oxidative stress in patients with schizophrenia. Some illness-related abnormalities in RBCs may reflect equivalent abnormalities in the neurons, which are hard to examine *in vivo*.[14,28] Because of its accessibility, the RBC membrane is commonly used as a "window" into the CNS. In the present study the erythrocyte MDA, a marker of oxidative stress was significantly increased in schizophrenic subjects with the three major symptoms, this finding was in agreement with the recent studies[29,30] in which they reported elevated levels of MDA in plasma, erythrocytes, leucocytes and platelets of patients with schizophrenia. It is believed that a high level of MDA is a sign of peroxidative injury to membrane phospholipids. Neuronal functioning is affected by this injury either by changes in membrane fluidity or by alterations in membrane receptors,[31] which can cause neurotransmitter uptake, release impairment and even cell death.[32] It was further demonstrated that the extent of lipid peroxidation is positively correlated with the severity of symptoms in never-medicated patients and inversely with the levels of membrane-essential polyunsaturated fatty acids.[9]

Human body has a complex defense system of antioxidant enzymes, including SOD, GSH-Px, and CAT. These enzymes block the initiation of ROS/RNS chain reactions.[33] The non-enzymatic antioxidant components are compounds such as GSH, vitamin E, vitamin C and β-carotene, which react with ROS/RNS and thereby prevent the propagation of chain reactions.[34] The presence of SOD in various compartments of our body enables it to dismutate superoxide radicals immediately they are produce and protects the cells from oxidative damage. SOD activities observed in this study among the schizophrenic patients with positive, negative, and cognitive symptoms show no significant difference from the controls although SOD activity was marginal reduced; contrary to the studies conducted by researchers[12,13,15,30] in which they reported decreased SOD activity and other studies[35–37] reported increased SOD activity among schizophrenic patients compared to the control

**Table 1**
Anthropometric and clinical parameters (mean ± SD) of the controls and subjects with their presentation.

| | Controls ($n = 48$) | Schizophrenic subjects ($n = 48$) 2.975625 | | | | | |
|---|---|---|---|---|---|---|---|
| | | Positive symptom ($n = 18$) | $p_1$ Value | Negative symptom ($n = 14$) | $p_2$ Value | Cognitive symptom ($n = 16$) | $p_3$ Value |
| Age (years) | 31.7 ± 7.5 | 32.5 ± 9.2 | ns | 30.4 ± 8.8 | ns | 33.7 ± 7.16 | ns |
| Height (cm) | 173.1 ± 1.4 | 171.8 ± 1.9 | ns | 168.9 ± 1.6 | ns | 172.5 ± 1.9 | ns |
| Weight (kg) | 72.0 ± 2.7 | 69.9 ± 1.2 | ns | 69.3 ± 0.9 | ns | 71.1 ± 1.1 | ns |
| BMI (Kg/m2) | 24.0 ± 0.3 | 23.7 ± 0.5 | ns | 24.3 ± 0.1 | ns | 23.9 ± 0.7 | ns |
| Systolic BP (mmHg) | 119.9 ± 2.1 | 120.8 ± 3.8 | ns | 117.2 ± 2.7 | ns | 122.2 ± 3.1 | ns |
| Diastolic BP (mmHg) | 77.8 ± 1.7 | 80.3 ± 2.1 | ns | 81.7 ± 1.9 | ns | 79.5 ± 2.4 | ns |

$p_1$ Value = when schizophrenics with positive symptom was compared with controls; $p_2$ value = when schizophrenics with negative symptom was compared with controls; $p_3$ value = when schizophrenics with cognitive symptom was compared with controls; ns = not significant, $p > 0.05$.

**Table 2**
$p$ Value (mean ± SD) of the measured parameters for subjects were compared to controls.

| | Controls ($n = 48$) | Schizophrenic subjects ($n = 48$) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Positive symptom ($n = 18$) | $p_1$ Value | Negative symptom ($n = 14$) | $p_2$ Value | Cognitive symptom ($n = 16$) | $p_3$ Value |
| Plasma-MDA (nmol/ml) | 2.71 ± 0.41 | 4.51 ± 0.72 | 0.0060** | 4.07 ± 0.46 | 0.0243* | 3.99 ± 0.18 | 0.0405* |
| Plasma TAS (mmol/L) | 1.98 ± 0.18 | 1.25 ± 0.15 | 0.0304* | 1.30 ± 0.08 | 0.0411* | 1.21 ± 0.09 | 0.0405* |
| Eryth-GSH-Px (U/g Hb) | 38.07 ± 4.25 | 20.09 ± 2.29 | 0.0097** | 19.85 ± 2.17 | 0.0083** | 22.46 ± 3.80 | 0.0205* |
| Eryth-SOD (U/g Hb) | 913.04 ± 79.41 | 899.83 ± 69.07 | 0.0590 | 878.97 ± 47.53 | 0.0671 | 891.07 ± 58.14 | 0.0603 |
| Eryth GSH (μmol/g Hb) | 6.05 ± 0.9 | 4.01 ± 0.4 | 0.0412* | 3.52 ± 0.3 | 0.0090** | 4.25 ± 0.6 | 0.0442* |
| Eryth-CAT (U/g Hb) | 1426.72 ± 80.9 | 271.09 ± 45.8 | 0.0407* | 197.23 ± 63.7 | 0.0151* | 1201.49 ± 44.9 | 0.0374* |
| Eryth-G6PD (U/g Hb) | 18.98 ± 2.05 | 9.02 ± 1.17 | 0.0053** | 8.19 ± 1.12 | 0.0039** | 8.79 ± 1.09 | 0.0047** |

Eryth: Erythrocyte. $p_1$ value = when schizophrenics with positive symptom was compared with controls; $p_2$ value = when schizophrenics with negative symptom was compared with controls; $p_3$ value = when schizophrenics with cognitive symptom was compared with controls; Significant level at the ($p < 0.01$) ** and ($p < 0.05$ *).

subject; there were a lot contradictions in the activity of SOD in schizophrenic patients.

GSH-Px neutralizes hydrogen peroxide by taking hydrogen from two GSH molecules resulting in two $H_2O$ and one GSSG. The enzyme GSH-Px then regenerates GSH from GSSG with NADPH as a source of hydrogen. In the present study erythrocyte GSH concentration and the activity of GSH-Px were significantly reduced in shizophrenic subjects with the three major symptoms, this was in agreement with recent studies[12,13,15,30] in which they reported decreased activity of GSH-Px in schizophrenic patients; likewise, other researchers[35,38,39] reported reduction in concentration GSH in their studies. CAT activity is one of the most important mechanisms by which RBC dispose of $H_2O_2$ produce by dismutation reaction of $O_2$ in a cell. We recorded a significant reduction in the activity of CAT in the present study among the schizophrenic subjects compared to the healthy controls; this was in conformity with other studies[12,13,15,30] which reported reduction in the activity of CAT among schizophrenic disorder, but Rukmini et al[40] reported otherwise in their study.

The secondary antioxidant enzyme (G6PD) activity, in the body system in the present study decreased significantly and G6PD activity was found to be lowest in subjects with negative symptoms. The role of G6PD deficiency in psychiatric disorders has not been fully established. The first study dates back to 1962, when Dern et al[41] reported that there was a decrease in the activity of G6PD among subjects who suffered from acute psychosis. Interestingly, the activity of the hexose monophosphate shunt, whose first step is catalyzed by G6PD, can be stimulated in the brain by monoamine transmitters, perhaps in relation with the detoxication of monoamine-oxidase-dependent metabolites.[42]

Our results are consistent with recent study which stated that G6PD deficiency is the most peculiar pattern of acute psychiatrimanic episodes, mostly characterized by loosening of association, agitation, catatonic symptoms, and/or transient confusion, concurrent hyperbilirubinemia, positive psychiatric family history, and partial response to long term lithium treatment.[43]

**Table 3**
Correlation coefficient analysis between marker of oxidative stress (MDA) and and antioxidant level.

| | MDA | | | | | |
|---|---|---|---|---|---|---|
| | Positive symptom | | Negative symptom | | Cognitive symptom | |
| | "$r$"-Value | $p$ Value | "$r$"-Value | $p$ Value | "$r$"-Value | $p$ Value |
| TAS | -0.3419 | 0.0281 | −0.3053 | 0.0423 | −0.3107 | 0.0411 |
| GSH-Px | −0.4618 | 0.0046 | −0.4390 | 0.0058 | −0.3772 | 0.0214 |
| SOD | −0.2183 | 0.1097 | −0.2339 | 0.0998 | −0.2285 | 0.1003 |
| GSH | −0.3091 | 0.0415 | −0.4297 | 0.0063 | −0.3348 | 0.0315 |
| CAT | −0.3568 | 0.0240 | −0.3914 | 0.0129 | −0.3865 | 0.0191 |
| G6PD | −0.4599 | 0.0048 | −0.4690 | 0.0035 | −0.4729 | 0.0014 |

Plasma TAS includes the antioxidant effects of all the antioxidants in the plasma including albumin, haptoglobin, uric acid, and vitamin E, together with other undetected substances. The total antioxidant plasma capacity is not a simple sum of the various antioxidant substances, but includes a dynamic equilibrium that is influenced by the interactions between different serum antioxidant constituents. The present study demonstrated a significant reduction in plasma TAS of patients with schizophrenia compared to healthy controls, this finding was in agreement with similar study conducted by Ustundag et al.[44] The brain is preferentially susceptible to oxidative damage since it is under very high oxygen tension and highly enriched in reactive oxygen species (free radicals), susceptible proteins, lipids and poor DNA repair.[45]

## 5. Conclusion

In the present study, we analyzed the various disturbances of the antioxidant systems in schizophrenics with various symptoms; it was obvious that there was increased oxidative stress and decreased antioxidants among schizophrenic subjects. The maintenance of redox balance within cells is a primary component of homeostasis underlying neuronal survival. It may not be too surprising therefore that any process that leads to a disruption of the redox balance can drastically interfere with a range of other biochemical processes and result in neuronal deficits and dysfunction. Our findings support the hypothesis of a state dependent process of oxidative stress in schizophrenia, which might be related to the known neurodegenerative process. Our data support the notion that interventions at the level of oxidative stress may be of potential value in the management of schizophrenic disorder.

## Conflicts of interest

All authors have none to declare.

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