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Article

Evaluation of the Influence of some Antioxidant Agents in Patients with Schizophrenia: A Case–Control Study

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ABSTRACT

Schizophrenia is a psychical disorder with abnormality in social behavior and failure to understand what is real. Despite considerable efforts that have been made from a lot of researchers, there are still delays in the diagnosis and treatment of schizophrenia. Therefore, this study has been focused to investigate the expected association between the levels of antioxidant agents (Vitamin E, Vitamin A, glutathione [GSH], and uric acid) and the risk of schizophrenia. Levels of these variables were determined in sera of 60 patients with schizophrenia, and then, the variations in their levels were analyzed in comparison with 60 healthy volunteers to try to predict of occurrence and progression of disease. The results obtained showed a significant decrease in the levels of Vitamin E, GSH, uric acid, and urea, in contrast to non-significant change in the levels of Vitamin A in schizophrenic patients compared to the healthy group. Data analysis also revealed the presence of a valuable correlation between most of variables in schizophrenic patients. Accordingly, it can be suggested that these variables may have a vital role and prognostic value against schizophrenia. Furthermore, it can be suggested that vitamin supplementation, in particular Vitamin E, may play a crucial role in the treatment of schizophrenia or reduce the risk of schizophrenia. The real mechanism responsible for the variations in the levels of these parameters in patients with schizophrenia is unclear and requires additional evaluation by further comprehensive studies.

Key words: Schizophrenia, Antioxidants, Vitamin E, Vitamin A, Glutathione, Uric acid.

1. INTRODUCTION

Antioxidants are substances that have the ability to protect cells from damage caused by unstable free radicals, by interacting with or neutralizing these radicals [1]. Antioxidant defense system includes a diversity of components that function interactively and synergistically to neutralize free radicals, for example, (a) nutrient-derived antioxidants such as Vitamin C, Vitamin E, and glutathione (GSH) and (b) antioxidant enzymes such as superoxide dismutase, GSH peroxidase, and GSH reductase [2].

Vitamins are one of the most fundamental nutrients found in foods, which are required in sufficient amounts to maintain the body health. They play fateful functions in a diversity of body systems, for example, Vitamins E and C that function as antioxidant agents. According to their solubility characteristics, vitamins are classified into two groups: Group 1 – fat-soluble vitamins which include A, D, E, and K and Group 2 – water-soluble vitamins which include B-complex vitamins and Vitamin C [3].

Vitamin E is a fat-soluble vitamin, also called tocopherol; molecular formula is $C_{19}H_{50}O_2$ with molar mass of 430.717 g/mol. Vitamin E has four isomeric forms: α, ß, γ, and δ – tocopherol [4]. Vitamin E seems to be the most important micronutrient involved in the protection of low-density lipoprotein from oxidation [5]. Simply, α-tocopherol is capable readily of trapping peroxyl radical, which is produced by peroxidation of membrane [6]. It is notable that α-tocopherol protects the polyunsaturated fatty acid from peroxidation even at a concentration as low as 0.005 mol/l [7]. Vitamin E is synthesized only by plants and, therefore, is found primarily in plant products such as nuts and leafy vegetables. Significant amounts of this vitamin are also available in some foods, for example, eggs, milk, corn, seaweed, meat, and brown rice [8]. Although Vitamin E deficiency is rare in humans, the deficiency can surly result from insufficient Vitamin dietary intake. The deficiency of Vitamin E is mainly occured as a result of genetic abnormalities in α-tocopherol transfer protein [9].

Vitamin A is a fat-soluble vitamin, also called retinol (the active form of Vitamin A), and the molecular formula is $C_{20}H_{30}O$ with molar mass of 286.45 g/mol. The main sources of Vitamin A are foods of animal origin such as fish, liver, chicken, and dairy products. Furthermore, some plant-based foods such as fruits and vegetables contain beta-carotene as an antioxidant which mainly converts in the body into Vitamin A [10]. Vitamin A has many functions in the human body. It is essential for vision, where it promotes good vision, especially in the dark. Furthermore, it plays an important function in tooth development, bone growth, reproduction, cell division, and regulation of immune system [11,12]. Vitamin A deficiency usually results from inadequate vitamin intakes from animal products, fruit, and vegetables. Vitamin A deficiency contributes mainly to blindness. In addition,

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Vitamin A deficiency can cause erratic tooth development and slower bone growth [13].

GSH is a tripeptide that named L-γ-glutamyl-L-cysteinylglycine, and the molecular formula is $C_{10}H_{17}N_3O_6S$ with molar mass of 307.32 g/mol [14]. GSH has an active thiol group of the cysteine residue in its structure, and therefore, it acts as antioxidant agent by interacting directly with reactive oxygen species (ROS) and reactive nitrogen species or indirectly as a cofactor with various enzymes [15].

Schizophrenia is a psychical disorder with an abnormality in social behavior and failure to understand what is real. It has been reported that approximately 1% of the population worldwide is affected with schizophrenia; for example, more than 2 million cases of disease were recorded in the United States alone [16]. Furthermore, it has been found that the incidence of schizophrenia in male is more likely to develop than female [17]. In fact, schizophrenia may be result of both genetics and environmental factors, and these causal factors may act either together or in sequence to initiate or promote the development of disease [18].

Although several studies have been conducted to assess and try to early detection of persons under the risk of developing schizophrenia, most of these studies are still incomplete [19,20]. In fact, despite considerable efforts that have been made from a lot of researchers, there are still delays in the diagnosis and treatment of schizophrenia. Therefore, this study has been focused to investigate the expected association between the levels of antioxidant agents (Vitamin E, Vitamin A, GSH, and uric acid) and the risk of schizophrenia. And the benefit of monitoring these parameters to predict the disease.

2. EXPERIMENTAL

This research was carried out in 2017, in Nutrition Research Institute and Chemistry Department, College of Science, Mustansiriyah University, Baghdad, Iraq. Sixty patients, 20 females and 40 males, with schizophrenia (age ranging from 42 to 60 years and 49.6 years) and sixty volunteers, 20 females and 40 males, of healthy group (age ranging from 44 to 61 years and the mean age 50.9 years) were included in this study. Patient samples were collected from Al-Rashad Psychiatric Hospital, Ministry of Health, Baghdad, Iraq. 5 ml of blood were collected from each individual. Sera were separated after allowed the blood to clot for 15–20 min at room temperature and then centrifuged for 10 min at 3000 g. The sera were stored at −20°C in refrigerator for subsequent analysis.

High-performance liquid chromatography (HPLC) technique was carried out, in the present study, to measure Vitamin (A and E) levels in the sera of patient subjects diagnosed with schizophrenia and then compare with the vitamin levels measured in sera of volunteers' subjects. All serum pre-treatment samples were subjected to reverse-phase HPLC analysis using a Knauer HPLC System (Berlin, Germany) with an analytical C18, 5 µm (250 mm×4.6 mm) reverse phase KNAUER column, under PC control. Methanol was used as mobile phase with 1.2 ml/min flow rate and ultraviolet–visible detection at wavelength 286 nm.

The serum GSH concentration was measured using a slightly modified form of the method previously described [21] as follows: 20 µl of serum was added to 1000 µl of distilled water in a test tube. Then, 1000 µl of phosphate buffer, 0.2 M at pH= 8, was added and mixed well. 1500 µl were drawn from this mixture and 200 µl of DTNB reagent were added. The solution was mixed well and incubated at 37°C for 60 min. Blank was prepared as the same procedure with the exception that the same volume of distilled water was added instead of serum. The absorbance was read at wavelength 420 nm and the GSH concentration was calculated according to the following equation:

$$\text{GSH con. in serum } \mu\text{mol/L} = (\text{T - B}) \times \frac{\text{d.f}}{\varepsilon} \times 10^6$$

Where T: Test absorbance, B: Blank absorbance, e: Extinction coefficient = 13600 $M^{-1}.cm^{-1}$, and d.f: Dilution factor =102.

Colorimetric method (BIOLABO SAS-URIC ACID Uricase method) for quantitative determination of uric acid concentrations in human serum was carried out following the protocol of the commercially available BIOLABO kit supplied by BIOLABO SAS, Les Hautes Rivers, Maizy, France, while serum urea concentration was measured by spectrophotometry according to the colorimetric method protocol (UREA/BUN-Color UREASA/SALICYLATE) of the commercial BioSystems kit supplied by Biosystems SA, Barcelona, Spain.

Statistical analysis was performed by descriptive statistics, independent samples Student's *t*-test, and Pearson's correlation analysis using SPSS program version 22.0. The results were expressed as mean ± standard deviation (SD), and $p<0.05$ with 95% confidence interval was considered as statistically significant.

3. RESULTS AND DISCUSSION

3.1. Results

The concentrations of Vitamins (A and E) for patients and healthy groups were calculated from HPLC through the standard calibration curve, and the collective data are presented in Table 1.

The mean ± SD values of Vitamin A for schizophrenic patients and healthy were found to be 47.40±17.45 µg/dl and 50.41±20.55 µg/dl, respectively (Table 1). The results revealed no significant differences in Vitamin A concentration between patients and healthy ($p=0.392$). Furthermore, the calculated results of Vitamin A for patients and healthy (male and female) were found (52.02±16.68 µg/dl and 38.40±15.60 µg/dl and 56.16±21.19 µg/dl and 38.90±11.41 µg/dl), respectively (Table 2 and Figure 1). The results revealed the presence of a significant decrease in the concentration of Vitamin A of female in patients and healthy compared with the concentration of those of male ($p<0.05$).

The calculated values of Vitamin E for patients and healthy were 268±74 µg/dl and 1049±371 µg/dl, respectively (Table 1), and these values revealed the presence of a highly significant decrease in Vitamin E concentration of schizophrenic patients in comparison with healthy group ($p<0.001$). The data analysis according to gender (male and female) for patients and healthy was found (286±141 µg/dl and 197±64 µg/dl and 1182±389 µg/dl and 785±379 µg/dl), respectively (Table 2 and Figure 1). Statistically, the results showed significant differences in Vitamin E values between male and female ($p<0.05$).

The calculated mean ± SD values of GSH for patients and healthy were found (625±113 µmole/L and 1303±311 µmole/L), respectively (Table 3). The data revealed the presence of a highly significant decrease in GSH concentration of schizophrenic patients in comparison with healthy group ($p<0.001$). The results recorded for schizophrenic patients and healthy according to gender (male and female) were 619±178 µmole/L and 636±155 µmole/L and 1292±381 µmole/L and 1317±303 µmole/L, respectively (Table 4 and Figure 2). Statistically, no significant differences were found between GSH values in male and female.

The mean ± SD values calculated for uric acid of healthy and schizophrenic patients were 5.23±1.92 µg/dl and 2.26±1.15 µg/dl, respectively, as shown in Table 3. These results indicated that the difference between healthy and patient groups is highly significant ($p<0.001$). Furthermore, the data showed that there is no effect to the gender on the values of uric acid, where almost the same declined were

Table 1: Levels of Vitamins (A and E) in sera of schizophrenic patients and healthy control.

Vitamin	Healthy group n=60			Patient group n=60			p value
	Mean±SD	Upper limit	Lower limit	Mean±SD	Upper limit	Lower limit	
Vitamin A (µg/dl)	50.41±20.55	77.9	33.97	47.4±18.45	73.79	35.55	0.392
Vitamin E (µg/dl)	1049±371	1425	720	268±74	358	196	<0.001

SD: Standard deviation

Table 2: Levels of Vitamins (A and E) in sera of schizophrenic patients and healthy control (male and female).

Vitamin	Gender	Healthy group n=60			Patient group n=60			p value
		Mean±SD	Upper limit	Lower limit	Mean±SD	Upper limit	Lower limit	
Vitamin A (µg/dl)	Male	56.16±21.19	78.78	41.42	52.02±16.68	73.91	36.59	0.338
	Female	38.9±11.41	48.39	30.83	38.4±15.6	66.24	28.63	0.914
Vitamin E (µg/dl)	Male	1182±389	1497	807	286±141	417	159	<0.001
	Female	785±379	1018	504	197±64	264	143	<0.001

SD: Standard deviation

Table 3: Serum levels of GSH, uric acid, and urea in patients of schizophrenia and healthy group.

Parameter	Healthy group n=60			Patient group n=60			p value
	Mean±SD	Upper limit	Lower limit	Mean±SD	Upper limit	Lower limit	
GSH (µmole/L)	1303±311	1529	1089	625±113	727	563	<0.001
Uric acid (µg/dl)	5.23±1.92	5.72	4.73	2.26±1.15	2.56	1.96	<0.001
Urea (µg/dl)	29.12±3.77	30.09	28.14	19.99±5.25	21.35	18.64	<0.001

SD: Standard deviation, GSH: Glutathione

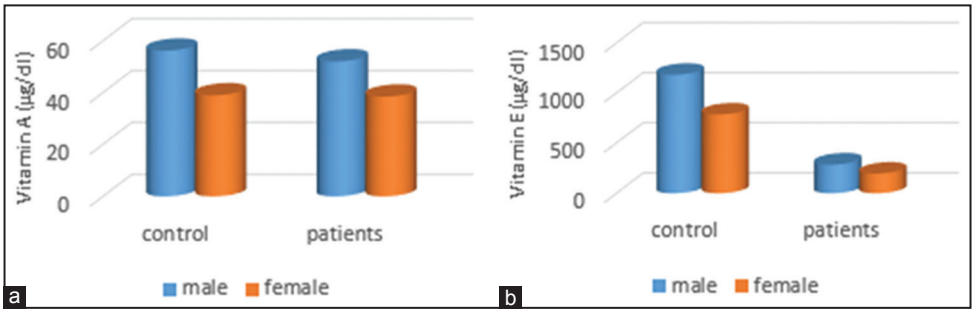

Figure 1: The differences in mean values of serum (a) Vitamin A (µg/dl) and (b) Vitamin B (µg/dl) between schizophrenic patients and healthy groups *t*-test.

recorded for uric acid level in patients (male and female) compared to healthy subjects (Table 4 and Figure 2).

The urea values of healthy and patients were 29.12±3.77 µg/dl and 19.99±5.25 µg/dl, respectively [Table 3]. From these results, it appears clearly the highly significant difference in urea levels between healthy and schizophrenic patients. According to the gender factor (male and female), the final results of the healthy and schizophrenic patients were 29.95 ± 3.87 µg/dl and 27.45 ± 2.99 µg/dl and 22.23 ± 2.76 µg/dl and 15.54 ± 2.39 µg/dl, respectively (Table 4 and Figure 2). It was found that the urea level measured in male patients was lower than the male healthy and this was statistically significant ($p<0.05$). Almost, the same declined was recorded in female gender.

The relationship between all parameters included in the present work was studied using Pearson's correlation analysis. The collective results are presented in Table 5. A negative correlation has shown between GSH level and the levels of Vitamin E, uric acid as well as urea. The results also revealed the presence of a positive correlation for Vitamin A concentration with Vitamin E, Vitamin E with uric acid, and Vitamin E with urea. Furthermore, the results revealed the presence of a positive correlation between urea and uric acid.

3.2. DISCUSSION

Several studies have indicated that oxidative damage, result of decline in antioxidant defense system, is present in patients with schizophrenia [22-24]. It is found, in the current study, that the levels of

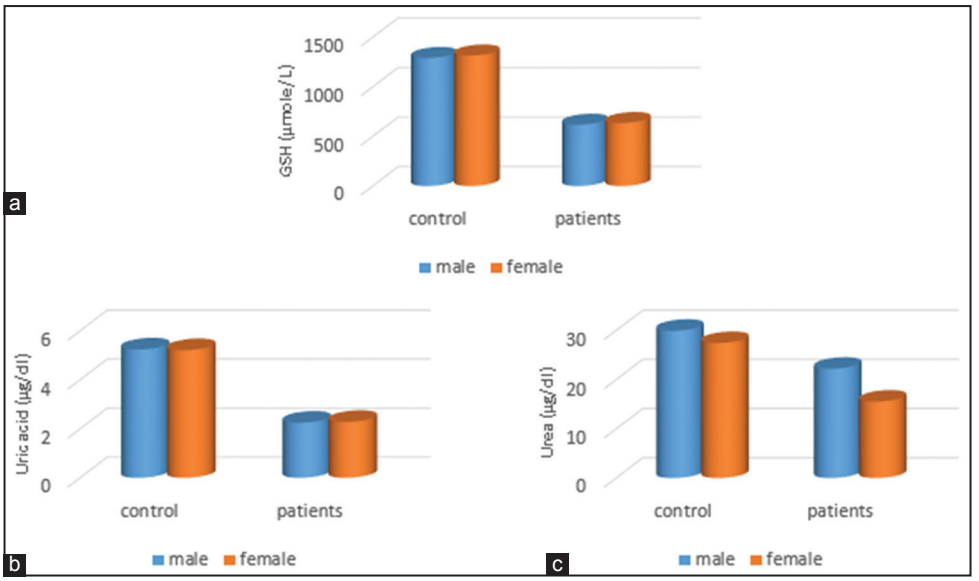

Figure 2: The differences in mean values of serum (a) glutathione (µmole/L), (b) uric acid (µg/dl), and (c) urea (µg/dl) between schizophrenic patients and healthy groups *t*-test.

Table 4: Serum levels of GSH, uric acid, and urea in patients with schizophrenia and healthy group (male and female).

Parameter	Gender	Healthy group			Patient group			p value
		n=60			n=60			
		Mean±SD	Upper limit	Lower limit	Mean±SD	Upper limit	Lower limit	
GSH (µmole/L)	Male	1292±381	1518	1063	619±178	749	537	<0.001
	Female	1317±303	1547	1094	636±155	723	558	<0.001
Uric acid (µg/dl)	Male	5.24±1.81	5.82	4.66	2.25±1.28	2.66	1.84	<0.001
	Female	5.21±2.16	6.22	4.19	2.28±0.87	2.69	1.87	<0.001
Urea	Male	29.95±3.87	31.19	28.71	22.23±2.76	23.75	20.71	<0.05
(µg/dl)	Female	27.45±2.99	28.85	26.04	15.54±2.39	16.85	14.23	<0.001

SD: Standard deviation, GSH: Glutathione

Table 5: Correlations between all study parameters in schizophrenic patients' group (r value).

Parameter	GSH	Vitamin A	Vitamin E	Uric acid	Urea
GSH	1	−0.157	−0.344**	−0.329**	−0.236**
Vitamin A	−0.157	1	0.203*	0.069	0.129
Vitamin E	−0.344**	0.203*	1	0.595**	0.580**
Uric acid	−0.329**	0.069	0.595**	1	0.467**
Urea	−0.236**	0.129	0.580**	0.467**	1

*Correlation is significant at the 0.05 level. **Correlation is significant at the 0.01 level. GSH: Glutathione

these some antioxidant parameters, for example, Vitamin E, GSH, and uric acid in schizophrenic patients differ significantly in comparison with those in controls. Therefore, follow-up of these variables could be a significant factor in the early diagnosis, progression, and treatment of schizophrenia.

The present findings indicated that there is no clear effect of Vitamin A in the etiology of schizophrenia, where it was found that the level of Vitamin A of healthy people is not affected compared to patients with schizophrenia. However, at the same time, these results indicate the presence of clear differences in Vitamin A levels between male and female, which may be the result of physiological differences between them. Although Vitamin A supplementation has been proposed as therapeutic agents for psychiatric pathologies including schizophrenia and Alzheimer's disease [25], the data available to describe the association of Vitamin A with schizophrenia are limited and unclear. Therefore, according to available information, this may be the first attempt to study the relationship between Vitamin A and schizophrenia.

The data obtained of the present work are in agreement with the data recorded of the previous study, and lower levels of Vitamin E were found in schizophrenia patients than in controls [20]. Therefore, the reduced levels of Vitamin E recorded in the present study may be due to the significant contribution of Vitamin E in the antioxidant defense system

against oxidative stress. Recently, a significant relationship between the disturbances of Vitamin D levels with major depressive disorder (MDD) has been reported, where it was found that the reduction in the antioxidant Vitamin E leads to increased risk of MDD [26].

Vitamin E is an antioxidant agent which protects against cellular damage that occurs by molecules containing highly reactive oxygen. The most important benefit of Vitamin E is to diminish the toxic effects of reactive species, especially to prevent the oxidation of polyunsaturated fatty acids [27]. In fact, the brain has a high proportion of readily oxidizable membrane polyunsaturated fatty acids, which make it more susceptible to oxidative stress [22]. It has been found that the human body needs large quantities of Vitamin E whenever the intake of unsaturated fatty acids [7]. Moreover, any deficit of Vitamin E can reduce the defense ability against oxidative stress [23]. In fact, Vitamin E can interact with peroxyl radicals generated from membrane polyunsaturated fatty acids to give more stable α-tocopheroxyl radicals, thereby protecting tissues from lipid free radical attack [7].

GSH is considered the most important endogenous scavenger for free radical in the human body. In the case of low GSH levels, there is an increased risk of cellular oxidative stress which is characterized by an increase and accumulation of ROS. The lack of GSH levels leads to limited free radical detoxification capacity that may lead to several psychiatric disorders including schizophrenia [28,29]. In this study, the results give further evidence that low levels of GSH were associated with an increased risk of schizophrenia, which are consistent with the results reported by previous studies [30,31].

Uric acid is a heterocyclic compound that is created as a final product of the breakdown of purine nucleotides. It is one of the most important antioxidants in plasma that protects cells from oxidative stress [32]. A previous study has reported significantly lower levels of plasma uric acid than in schizophrenic patients normal control subjects [33]. The same results were recorded in the present study, thus providing additional support that oxidative stress induced in schizophrenia may be caused by a defect in an antioxidant defense system.

A previous study showed no significant difference in urea levels between schizophrenic patients and healthy control [34]. In the present study, decreased levels of urea were found in patients with schizophrenia compared to healthy controls. This finding seems to be resulting from dysregulation in urea or might be attributed due to disease itself or lifestyle changes.

4. CONCLUSION

Antioxidants have an important influence and play a major role in a variety of processes necessary for life. The findings of the current work indicated that the levels of Vitamin E, GSH, uric acid, and urea were significantly lower in serum samples of schizophrenic patients in comparison with healthy controls. They also indicated a non-significant difference in Vitamin A levels among patients and controls. These results reflect the protective role that these variables may play in the resistance of schizophrenia. In fact, the reduced levels of Vitamin E and GSH recorded in the present study may be due to the significant contribution of them in the antioxidant defense system against oxidative stress induced in schizophrenia. More studies to estimate the status of trace elements and find the correlation with the antioxidants agents in schizophrenic patients are highly recommended [35-37].

The most important conclusion of the current work is giving new information for understanding the relationship between Vitamin E, GSH, and uric acid and their role in schizophrenia. It can be suggested that these variables may have a vital role as a prognostic biomarkers against schizophrenia. The real mechanism responsible for the alterations in the levels of these parameters in patients with schizophrenia is unclear and requires additional evaluation by further comprehensive studies. Finally, it can be suggested that vitamin supplementation, in particular Vitamin E, may play a substantial role in the treatment of schizophrenia or reduce the risk of schizophrenia. More studies are needed to prove that.

5. ACKNOWLEDGMENTS

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6. REFERENCES

1. H. Sies, (1997) Oxidative stress: Oxidants and antioxidants, ***Experimental Physiology,* 82(2)**: 291-295.
2. S. J. Flora, (2009) Structural, chemical and biological aspects of antioxidants for strategies against metal and metalloid exposure, ***Oxidative Medicine and Cellular Longevity,* 2(4)**: 191-206.
3. A. B. David, (2003) ***Nutritional Biochemistry of the Vitamins***, 2nd ed. U.K: Cambridge University Press.
4. C. K. Sen, S. Khanna, S. Roy, (2006) Tocotrienols: Vitamin E Beyond Tocopherols, ***Life Sciences*, 78(18)**: 2088-2098.
5. S. P. Fortmann, B. U. Burda, C. A. Senger, J. S. Lin, E. P. Whitlock, (2013) Vitamin and mineral supplements in the primary prevention of cardiovascular disease and cancer: An updated systematic evidence review for the U.S. preventive services task force, ***Annals of Internal Medicine*, 159(12)**: 824-834.
6. J. G. Bieri, R. K. Poukka, (1970) *In vitro* hemolysis as related to rat erythrocyte content of alpha-tocopherol and polyunsaturated fatty acids, ***The Journal of Nutrition*, 100(5)**: 557-564.
7. D. Raederstorff, A. Wyss, P. C. Calder, P. Weber, M. Eggersdorfer, (2015) Vitamin E function and requirements in relation to PUFA, ***The British Journal of Nutrition*, 114(8)**: 1113-1122.
8. Sight and Life. (2016) ***Vitamins and Minerals: A Brief Guide***. Basel, Switzerland: Sight and Life/DSM Nutritional Products Ltd.
9. Institute of Medicine (USA). (2000) ***Panel on Dietary Antioxidants and Related Compounds. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids. 6, Vitamin E***. Washington (DC): National Academies Press (USA).
10. S. S. Gropper, J. L. Smith, J. L. Groff, (2009) ***Advanced Nutrition and Human Metabolism.*** 5th ed. Belmont, CA: Wadsworth Cengage Learning, p373-1182.
11. L. Bellows, R. Moore, (2013) ***Fat-Soluble Vitamins: A, D, E, and K.*** Colorado State University. Fact Sheet.
12. S. W. Alexander, (1995) Specific nutrients in the immune response, ***Journal of Human Nutrition*, 11:** 229-230.
13. H. Glerup, K. Mikkelsen, L. Poulsen, E. Hass, S. Overbeck, J. Thomsen, P. Charles, E.F. Eriksen, (2000) Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited, ***Journal of Internal Medicine,* 247(2):** 260-268.
14. P. D. Vivancos, T. Wolff, J. Markovic, F. V. Pallardo, C. H. Foyer, (2010) A nuclear glutathione cycle within the cell cycle, ***Biochemical Journal*, 431(2)**: 169-178.
15. P. Maher, (2005) The effects of stress and aging on glutathione metabolism, ***Ageing Research Reviews,* 4(2):** 288-314.
16. U. S. Department of Health and Human Services, National

Institutes of Health, National Institute of Mental Health (2016) ***Schizophrenia***, USA: National Institutes of Health, National Institute of Mental Health.
17. World Health Organization (2015) ***Schizophrenia Fact sheet: WHO's Mental Health Action Plan 2013-2020***, Geneva: World Health Organization.
18. M. M. Picchioni, R. M. Murray (2007) Schizophrenia. ***British Medical Journal***, **335(7610):** 91-95.
19. F. S. Al-Fartusie, S. N. Mohssan, A. R. Farhan, (2017) Estimation of total thyroxine, prolactin and testosterone hormones in sera of Iraqi schizophrenic patients, ***Journal of. Basic and Applied Chemistry,*** **7(2):** 1-7.
20. B. D'Souza, V. D'Souza, (2003) Oxidative injury and antioxidant Vitamins E and C in Schizophrenia, ***Indian Journal of Clinical Biochemistry,*** **18(1):** 87-90.
21. M. L. HU, (1994) Measurement of protein thiol groups and glutathione in plasma, ***Methods Enzymol***, **233:** 380-385.
22. S. P. Mahadik, S. Mukherjee, (1996) Free radical pathology and antioxidant defense in schizophrenia: A review. ***Schizophrenia Research,*** **19(1):** 1-17.
23. Y. Gilgun-Sherki, E. Melamed, D. Offen, (2001) Oxidative stress induced neurodegenerative diseases: The need for antioxidants that penetrate the blood brain barrier. ***Neuropharmacology***, **40(8):** 959-975.
24. I. Perez-Neri, J. Ramirez-Bermudez, S. Montes, C. Rios, (2006) Possible mechanisms of neurodegeneration in schizophrenia, ***Neurochemical Research***, **31(10):** 1279-1294.
25. A. Malaspina, A. T. Michael-Titus, (2008) Is the modulation of retinoid and retinoid-associated signaling a future therapeutic strategy in neurological trauma and neurodegeneration? ***Journal of Neurochemistry***, **104:** 584-595.
26. F. S. Al-Fartusie, H. K. Al-Bairmani, Z. S. Al-Garawi, A. H. Yousif, (2018) Evaluation of some trace elements and vitamins in major depressive disorder patients: A case-control study, ***Biological Trace Element Research,*** **189(2):** 412-419.
27. M. Bošković, T. Vovk, B. K. Plesničar, I. Grabnar, (2011) Oxidative stress in Schizophrenia, ***Current Neuropharmacology,*** **9(2):** 301-312.
28. O. M. Dean, M. van den Buuse, A. I. Bush, D. L. Copolov, F. Ng, S. Dodd, M. Berk, (2009) A role for glutathione in the pathophysiology of bipolar disorder and schizophrenia? Animal models and relevance to clinical practice, ***Current Medicinal Chemistry***, **16(23):** 2965-2976.
29. K. Q. Do, A. H. Trabesinger, M. Kirsten-Krüger, C. J. Lauer, U. Dydak, D. Hell, F. Holsboer, P. Boesiger, M. Cuénod, (2000) Schizophrenia: Glutathione deficit in cerebrospinal fluid and prefrontal cortex *in vivo*, ***European Journal of Neuroscience,*** **12(10):** 3721-3728.
30. Z. Nahar, M. S. Sarwar, M. S. Islam, A. Rahman, S. N. Islam, M. S. Islam, A. Hasnat, (2013) Determination of serum antioxidant vitamins, glutathione and MDA levels in panic disorder patients, ***Drug Research (Stuttg)***, **63(8):** 424-428.
31. J. K. Yao, S. Leonard, R. Reddy, (2006) Altered glutathione redox state in schizophrenia, ***Disease Markers***, **22(1-2):** 83-93.
32. B. N. Ames, R. Cathcart, E. Schwiers, P. Hochstein, (2006) Uric acid provides an antioxidant defense in humans against oxidant- and radical-caused aging and cancer: A hypothesis, ***Proceedings of the National Academy of Sciences of the United States of America***, **78:** 6858-6862.
33. J. K. Yao, R. Reddy, D. P. Van Kammen, (1998) Reduced level of plasma antioxidant uric acid in schizophrenia, ***Psychiatry Research,*** **80(1):** 29-39.
34. V. Devaramane, B. Vanishree, Y. Nagalakshmi, A. Natarajan, S. Vivek, C. Abhishek, K. Jeevan, V. Panambur, P. Mungli, V. Nayak, (2013) Oxidative stress in Schizophrenia patients with and without diabetes mellitus, ***Asian Journal of Biomedical and Pharmaceutical Sciences,*** **3(18):** 29-32.
35. F. S. Al-Fartusie, S. N. Mohssan, (2017) Essential trace elements and their vital roles in human body, ***Indian Journal of Advances in Chemical Science,*** **5(3):** 127-136.
36. F. S. Al-Fartusie, A. T. Marzook, T. S. Morad, (2012) Study of some trace elements and antioxidant vitamins in sera of Iraqi women with toxoplasmosis, ***Al-Mustansiriyah Journal of Science,*** **23(3):** 199-206.
37. F. S. Al-Fartusie, A. Hafudh, N. Mustafa, H. K. Al-Bairmani, A. Y. Mustafa, (2017) Levels of some trace elements in sera of patients with lung cancer and in smokers, ***Indian Journal of Advances in Chemical Science,*** **5(4)**: 344-352.

****Bibliographical Sketch***

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