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# Antioxidant Status and DNA Damage in Children with Attention Deficit Hyperactivity Disorder with or without Comorbid Disruptive Behavioral Disorders

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**ABSTRACT:**

Antioxidant status and DNA damage in children with attention deficit hyperactivity disorder with or without comorbid disruptive behavioral disorders

**Objective:** The aim of this study is to investigate oxidative stress and DNA damage among children with attention deficit hyperactivity disorder (ADHD) with or without disruptive behavioral disorders (DBD).

**Methods:** A total of 49 treatment naïve children (M/F: 40/9) who were diagnosed with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria were included. The patients with ADHD were divided into two groups, those with ADHD alone (n= 25) and ADHD plus DBD (n=24). The control group consisted of 40 age- and sex-similar healthy children. The Schedule for Affective Disorders and Schizophrenia for School Aged Children- Present and Life-time version (K-SADS-PL) was applied to all children. Children's teachers completed the Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S). Serum glutathione peroxidase (GPx), coenzyme Q, 8-hydroxy-2-deoxyguanosine (8-OHdG) and superoxide dismutase (SOD) levels were measured by the ELISA method using commercial kits.

**Results:** There were no significant differences in serum GPx, SOD, CoQ and 8-OHdG levels among the pure ADHD, ADHD plus DBD and the control groups (p>0.05). No statistically significant correlations were found between the severity of ADHD symptoms and GPx, SOD, CoQ and 8-OHdG levels.

**Conclusion:** Our study suggests that oxidative stress may not play a key role in the pathogenesis of pure ADHD and ADHD plus DBD.

**Keywords:** attention deficit hyperactivity disorder, child, disruptive behavioral disorders, oxidative stress, DNA damage

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## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neuro-developmental disorder characterized by signs of attention deficit, hyperactivity and impulsivity, which accounts for 5 to 10% of school-age children[1]. Nearly 50% of the patients with ADHD present with disruptive behavioral disorders (DBD) (oppositional defiant disorder and conduct disorder)[2]. The pathogenesis of ADHD differs with the absence and presence of comorbidity[3]. Psychosocial problems, exposure to trauma, stigmatization, and poor academic success are higher in ADHD patients associated with DBD[4-6].

As there are a limited number of studies investigating the pathogenesis of ADHD, our knowledge is also limited. A strong genetic transition is known to be responsible for the disorder[7]. Some environmental risk factors have also been established[8]. Dopamine and noradrenaline

hypothesis has been suggested, and therefore some drugs increasing the exposure of these substances in the synaptic cleft were used in the treatment[9].

Oxidative stress is defined as the over production of free radicals and as a deficiency in the antioxidant defense system[10]. Brain tissue is more sensitive to oxidative stress than the other tissues due to its dense lipid content, high oxygen consumption, relatively low antioxidant level, and excessive iron content[11]. Oxidative stress is harmful to the lipid, protein, and nucleic acid components of the cell. Oxidants react with the membrane proteins, which leads to defects in enzyme and neurotransmitter transportation, resulting in a predisposition to psychiatric disorders[12]. Superoxide dismutase (SOD) and glutathione peroxidase (GPx) are the major antioxidant enzymes in the human body[13]. Coenzyme Q is a natural antioxidant[14]. 8-Hydroxy-2-deoxyguanosine (8-OHdG) is a biochemical marker of DNA damage caused by reactive oxygen species (ROS)[15]. In the studies recruited adult ADHD patients, oxidative stress was reported to be increased[16,17]. In a recent meta-analysis, although significant correlations were identified between severities of ADHD symptoms and oxidative stress; similar antioxidant levels were found in treatment-naïve ADHD patients and the control group[18]. No significant differences were found in 8-OHdG levels between the newly diagnosed ADHD patients and the control group[19].

To the best of our knowledge, oxidative stress has not been studied in ADHD children with comorbid DBD. In the present study, we aimed to examine oxidative stress and DNA damage in patients with pure ADHD, ADHD plus DBD, and in healthy individuals.

## PATIENTS AND METHODS

### Study Population

This study was performed in Dicle University, Training and Research Hospital, Department of Cild and Adolescent Psychiatry. The data were obtained between August 2013 and April 2014. The study included 49 treatment-naïve children with ADHD, of which 9 (18.4%) were girls and 40 (81.6%) were boys. The patients were recruited consecutively. The diagnosis of ADHD was based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria. The ADHD group was divided into two groups, namely pure ADHD (n=25) and ADHD plus DBD (n=24). In the pure ADHD group, 72% (n=18) of the patients had a combined type disease, and 28% (n=7) was predominantly inattentive type, whereas all patients in the ADHD plus DBD group were of the combined type. There were no cases of predominantly hyperactive-impulsive type in both groups. Individuals with an intelligence quotient below 70, epileptic episode, head trauma history with unconsciousness, encephalitis, Tourette's disorder, pervasive developmental disorder, bipolar mood disorders, psychotic disorders, history of prior or recent cortisol therapy, history of vitamin intake, morbid obesity, clinically active infection, and chronic systemic disease were excluded. Forty age- and sex-similar children living in the same region included as control group. Control subjects had no psychiatric or medical disorder. The study was reviewed and approved by the Ethics Committee of Clinical Researches, Dicle University, Faculty of Medicine. Informed consents were obtained from parents of each subject.

### Study Conduct

All subjects initially completed the sociodemographic and clinical data form. A structured psychiatric interview (K-SADS-PL) was performed. All parents and teachers completed the DSM-IV based behavior disorders screening form and rating scale for attention deficit and disruptive behavior disorders. A 2-mL venous blood sample was drawn for biochemical analysis.

### Forms and Schedules

**Sociodemographic and Clinical Data Form:** Age, sex, height, body weight and educational status of the children, education level and profession of the

parents, degree of parental consanguinity, number of siblings, psychiatric disease and criminological history in the family and relatives, drug addiction in the family, presence of intrafamily violence were recorded.

**Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (K-SADS-PL):** The original Schedule (K-SADS-PL) was developed by Kaufman et al.[20], adapted into Turkish in 2004 by Gökler et al.[21] The K-SADS-PL was administered by interviewing the parents and the children. All resources of information were assessed together. The presence of psychopathological disorders, which was frequently observed in ADHD children and adolescents were questioned.

**Turgay DSM-IV Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S):** This scale was developed using the DSM-IV criteria by Turgay, and includes a total of 41 items, of which 9 inquires attention deficiency, 6 hyperactivity, 3 impulsivity, 8 oppositional defiant disorders, and 15 conduct disorder symptoms[22]. The validity and reliability studies of this scale were performed by Ercan et al.[23].

### Biochemical Analysis

Blood samples were obtained between 10:00 and 12:00 am. The samples were collected in gel tubes and blood samples were centrifuged to separate serum from clot at 1000 g for 10 minutes after coagulation. Measurement of SOD, GPx, CoQ and 8-OHdG were done with an enzyme linked immunosorbent assay (ELISA) method (Hangzhou Eastbiopharm CO. LTD China), according to the manufacturer's instructions. Briefly, samples were added to wells, which are pre-coated with monoclonal antibody and incubated; then, antibodies labeled with biotin were added, and combined with Streptavidin-HRP to form immune complex; then incubation and washing were carried out. After that, chromogen solutions were added, and at the effect of stop solution, the color was finally become yellow. The absorbance was measured at 450 nm.

### Statistical Analysis

The chi-square test was carried out to determine the group differences in sex, parental consanguinity, psychiatric history of psychiatric disorder and criminological history in the family and relatives, drug addiction and intrafamily violence. Non-parametric continuous variables were compared by using the Kruskal Wallis, while posthoc comparisons were performed by using Bonferroni corrected Mann-Whitney U test. The Pearson's correlation analysis was used to determine the correlations between normally distributed numerical variables, whereas the Spearman's test was used to analyze non-normally distributed variables. The data were given as median (25%-75% values) values. The p-value below 0.05 was considered statistically significant.

## RESULTS

The median (25%-75% values) values for age in the pure ADHD (M/F: 18/7) group was 8 (6-10) years, in ADHD plus DBD (M/F: 23/1) group 8 (7-11.3) years, and in the control group (M/F: 32/8) was 8 (7-10) years. There were no differences in age and gender distribution between the patients and the control groups ($p>0.05$). Age, parental professions, parental relativeness, and data for intrafamily violence and drug addiction did not differ between the groups ($p>0.05$ for each). Sociodemographic characteristics of the study groups are shown in Table 1. The ratio for psychiatric disease in family and close relatives, and intrafamily violence ratio in the ADHD plus DBD group were found to be statistically significantly higher than pure ADHD and control groups ($p<0.001$, and $p=0.010$, respectively). In the pure ADHD group, the median (interquartile range) of T-DSM-IV-S scores, that filled up by the teachers, were 15 (12.5-20) for attention, 2 (1-11) for hyperactivity- impulsivity and 0 (0-3.5) for oppositional defiance; in the ADHD plus DBD group, these scores were 17.5

**Table 1: Sociodemographic data of the study groups [median (25%-75% values)]**

| | Pure ADHD (n=25) | ADHD + DBD (n=24) | Control (n=40) | p* value |
|---|---|---|---|---|
| Age (years) | 8 (6-10) | 8 (7-11.3) | 8 (7-10) | 0.70 |
| Education duration (years) | 2 (1-4) | 3 (2-5.8) | 3 (2-6) | 0.11 |
| Mother's age (years) | 31.5 (28.8-36.3) | 31.5 (28.8-35.3) | 34 (31-38.5) | 0.26 |
| Mother's education duration (years) | 5 (5-11) | 5 (0-8) | 5 (5-11) | 0.37 |
| Father's age (years) | 36 (34-44) | 37 (34-40.5) | 40 (35-47.5) | 0.38 |
| Father's education duration (years) | 9.5 (5-15) | 8 (5-15) | 8 (5-15) | 0.91 |
| BMI (kg/m$^2$) | 16.3 (14.7-16.8) | 16.5 (15.9-17.8) | 17.5(15.4-19.9) | 0.10 |

ADHD: Attention Deficit Hyperactivity Disorder, DBD: Disruptive Behavioral Disorders, BMI: Body Mass İndex, BDNF: Brain-Derived Neurotrophic Factor, *Kruskal Wallis Test.

**Table 2: Comparison of study subjects related to biochemical analyses [median (25%-75% values)]**

| | Pure ADHD (n=25) | ADHD + DBD (n=24) | Control (n=40) | p* value |
|---|---|---|---|---|
| SOD (U/L) | 33.4 (24.5-74.9) | 30.4 (23.9-75.4) | 39.9 (26.3-130.7) | 0.56 |
| GPx (U/ml) | 28.3 (17.1-35.9) | 34.9 (24.5-97.9) | 31.8 (27.9-67.3) | 0.09 |
| Coenzyme Q (ng/ml) | 11.1 (8.2-31.9) | 14.1 (9.0-32.9) | 15.9 (9.6-27.7) | 0.64 |
| 8-OHdG (ng/ml) | 5.8 (4.1-11.1) | 5.6 (4.2-16.9) | 6.9 (4.7-17.7) | 0.80 |

ADHD: Attention Deficit Hyperactivity Disorder, DBD: Disruptive Behavioral Disorders, GPx: Glutathione peroxidase, SOD: Superoxide dismutase, 8-OHdG: 8-Hydroxy-2-Deoxyguanosine, *Kruskal Wallis Test.

(14.8-23) for attention, 18 (12-22.5) for hyperactivity- impulsivity and 16 (9.5-18.3) for opposition defiance. ADHD plus DBD group had statistically significantly higher scores for hyperactivity-impulsivity and oppositional defiance compared with the pure ADHD group ($p<0.001$ and $p<0.001$, respectively). There were no significant differences in these scores between male and female subjects ($p>0.05$).

The GPx, SOD, CoQ and 8-OHdG levels did not statistically significantly differ among the ADHD+ DBD, pure ADHD and control groups ($p>0.05$ for each) (Table 2). There were no statistically significantly correlations between the severity of ADHD symptoms and serum levels of GPx, SOD, CoQ and 8-OHdG in the patients ($p>0.05$).

## DISCUSSION

The main result of our study is the lack of a significant difference in oxidative stress and DNA damage between the control group and ADHD patients with or without DBD comorbidity. To the best of our knowledge, oxidative stress variables were not studied before in patients with DBD.

It has been established that ADHD and DBD share many common genetic components[24]. However, ADHD patients with comorbid DBD were shown to have genetic differences compared to the patients with pure ADHD[3,25,26]. It has been reported that ADHD plus DBD patients have a poor prognosis when compared to pure ADHD cases, and they are exposed to more adverse critical conditions[6]. Therefore, it is hypothesized that patients with ADHD plus DBD would be exposed to higher levels of oxidative stress. Our results, however, did not support this hypothesis.

Another important finding of the present study is the lack of difference in oxidative stress variables between the patients with pure ADHD and the control group. Abnormal regulation of neurotransmitter system, particularly of dopamine, has been suggested to play a key role in the etiology of ADHD[27]. Dopamine and noradrenaline levels in the cerebrospinal fluid, as well as blood and urine, have been shown to be lower in ADHD patients, compared to the control group[28]. The cell membrane lipid component is the main structural constituent of the central nervous system and may affect the neurotransmitter functions. Lipids are more vulnerable to oxidation, and, thus, dopamine regulation may be affected[29]. Both genetic and environmental risk factors may increase oxidative

stress levels, and in many studies, increased peripheral oxidative stress levels were found in patients with ADHD[18]. Some authors suggests that excessive intracellular iron accumulation in neurons may cause oxidative stress[30,31]. However, patients with ADHD were reported to have low brain iron levels[32,33]. Additionally, brain glucose metabolism was shown to be decreased in patients with ADHD[34]. It may be reasonable to suggest that low brain iron levels and low glucose metabolism are protective against oxidative stress in patients with ADHD.

Ceylan et al. have found similar SOD levels in children with ADHD and healthy controls; in our study, there were no significant differences in SOD and GPx values between patients and control group. We were unable to find a study investigating CoQ levels in the children with ADHD in the literature. In a study, vitamin E and total antioxidant levels were reported to be lower in the children with ADHD, compared to the control group[35,36]. However, there were substantial heterogeneities in characteristics of the participants, particularly in their ages, in both studies investigating oxidative stress and antioxidants[18]. Some of previous studies have reported increased oxidative stress in children with ADHD[17,37-40], whereas others, consistent with our study results, do not agree with that result[19].

Some authors concluded that 'hypodopaminergic status' might develop as a result of oxidative stress in patients with ADHD[29]. In contrast, others have reported that oxidative stress was low due to 'hypodopaminergic status' of these patients[19].

In our study, serum 8-OHdG, which is an oxidant indicating DNA damage, was found to be not different between ADHD children and healthy controls. There is no great number of studies investigating DNA damage in children with ADHD. In a study by Oztop et al.[19], lower 8-OHdG levels were found in children with ADHD compared with healthy controls. It was also reported that DNA damage and protein oxidation increased in relation to age and the presence of neurodegenerative diseases[41,42].

On the other hand, there are some limitations of this study. Firstly, it was a cross-sectional analysis and participants were assessed only once. Secondly, only some of the oxidative stress variables were measured. All these may lead to an inadequate assessment of the condition. The biochemical parameters were analyzed in the serum samples. Bodily sources other than the brain may have effects on the measured variables. This study was not also powered with including pure DBD cases, which might have prevent establishing a definitive conclusion about the oxidative stress in patients with DBD alone.

## CONCLUSION

In conclusion, our study does not support the hypothesis that patients with ADHD would have increased oxidative stress. Our study suggests that oxidative stress may not play a key role in the pathogenesis of pure ADHD and ADHD plus DBD. Further large-scale studies are needed to establish more satisfactory conclusions in children with ADHD.

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## References:

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.
2. Wilens TE, Biederman J, Brown S, Tanguay S, Monuteaux MC, Blake C, et al. Psychiatric comorbidity and functioning in clinically referred preschool children and school-age youths with ADHD. J Am Acad Child Adolesc Psychiatry 2002;41(3):262-8. **[CrossRef]**

3. Liu L, Cheng J, Li H, Yang L, Qian Q, Wang Y. The possible involvement of genetic variants of NET1 in the etiology of attention-deficit/hyperactivity disorder comorbid with oppositional defiant disorder. J Child Psychol Psychiatry 2015;56(1):58-66. [CrossRef]

4. Andrade BF, Tannock R. Sustained impact of inattention and hyperactivity-impulsivity on peer problems: mediating Roles of prosocial skills and conduct problems in a community sample of children. Child Psychiatry Hum Dev 2014;45(3):318-28. [CrossRef]

5. Lafortune D, Meilleur D. Medically defining, screening, and treating conduct disorder: a French controversy. J Child Fam Stud 2013;23(4):728-37. [CrossRef]

6. Pardini DA, Fite PJ. Symptoms of conduct disorder, oppositional defiant disorder, attention-deficit/hyperactivity disorder, and callous-unemotional traits as unique predictors of psychosocial maladjustment in boys: advancing an evidence base for DSM-V. J Am Acad Child Adolesc Psychiatry 2010;49(11):1134-44. [CrossRef]

7. Faraone SV, Perlis RH, Doyle AE, Smoller JW, Goralnick JJ, Holmgren MA, et al. Molecular genetics of attention-deficit/hyperactivity disorder. Biol Psychiatry 2005;57(11):1313-23. [CrossRef]

8. Brassett-Harknett A, Butler N. Attention-deficit/hyperactivity disorder: an overview of the etiology and a review of the literature relating to the correlates and lifecourse outcomes for men and women. Clin Psychol Rev 2007;27(2):188-210. [CrossRef]

9. Faraone SV. Advances in the genetics and neurobiology of attention deficit hyperactivity disorder. Biol Psychiatry 2006;60(10):1025-7. [CrossRef]

10. Serafini M, Del Rio D. Understanding the association between dietary antioxidants, redox status and disease: is the Total Antioxidant Capacity the right tool? Redox Rep 2004;9(3):145-52. [CrossRef]

11. Ng F, Berk M, Dean O, Bush AI. Oxidative stress in psychiatric disorders: evidence base and therapeutic implications. Int J Neuropsychopharmacol 2008;11(6):851-76. [CrossRef]

12. Weber GF. The pathophysiology of reactive oxygen intermediates in the central nervous system. Med Hypotheses 1994;43(4):223-30. [CrossRef]

13. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39(1):44-84. [CrossRef]

14. Crane FL. Biochemical functions of coenzyme Q10. J. Am Coll Nutr 2001;20(6):591-8. [CrossRef]

15. Berk M. Neuroprogression: pathways to progressive brain changes in bipolar disorder. Int J Neuropsychopharmacol 2009;12(4):441-5. [CrossRef]

16. Selek S, Bulut M, Ocak AR, Kalenderoglu A, Savas HA. Evaluation of total oxidative status in adult attention deficit hyperactivity disorder and its diagnostic implications. J Psychiatr Res 2012;46(4):451-5. [CrossRef]

17. Selek S, Savas HA, Gergerlioglu HS, Bulut M, Yilmaz HR. Oxidative imbalance in adult attention deficit/hyperactivity disorder. Biol Psychol 2008;79(2):256-9. [CrossRef]

18. Alpak G, Selek S, Bulut M, Bulbul F, Unal A, Virit O, et al. High catalase and low thiol levels in adult-ADHD patients. Klinik Psikofarmakoloji Bulteni - Bulletin of Clinical Psychopharmacology 2014;24(2):128-34. [CrossRef]

19. Oztop D, Altun H, Baskol G, Ozsoy S. Oxidative stress in children with attention deficit hyperactivity disorder. Clin Biochem 2012;45(10-11):745-8. [CrossRef]

20. Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. J Am Acad Child Adolesc Psychiatry 1997;36(7):980-8. [CrossRef]

21. Gokler B, Unal F, Pehlivanturk B, Kultur EC, Akdemir D, Taner Y. Reliability and validity of schedule for affective disorders and schizophrenia for school age children-present and lifetime version-Turkish version (K-SADS-PL-T). Turkish Association for Child and Adolescent Psychiatry 2004;11(3):109-16. (Turkish)

22. Turgay A. Disruptive Behavior Disorders Child and Adolescent Screening and Rating Scale for Children, Adolescents, Parents, and Teachers. West Blomfield (Michigan): Integrative Therapy Institute Publication; 1994.

23. Ercan ES, Amado S, Somer O, Cikoglu S. Development of a test battery for the assessment of attention deficit hyperactivity disorder. Turkish Association for Child and Adolescent Psychiatry 2001;8(3):132-44. (Turkish)

24. Connor DF, Steeber J, McBurnett K. A review of attention-deficit/hyperactivity disorder complicated by symptoms of oppositional defiant disorder or conduct disorder. J Dev Behav Pediatr 2010;31(5):427-40. [CrossRef]

25. Malmberg K, Wargelius HL, Lichtenstein P, Oreland L, Larsson JO. ADHD and Disruptive Behavior scores - associations with MAO-A and 5-HTT genes and with platelet MAO-B activity in adolescents. BMC Psychiatry 2008;8:28. [CrossRef]

26. Salatino-Oliveira A, Genro JP, Guimaraes AP, Chazan R, Zeni C, Schmitz M, et al. Cathechol-O-methyltransferase Val (158) Met polymorphism is associated with disruptive behavior disorders among children and adolescents with ADHD. J Neural Transm (Vienna) 2012;119(6):729-33. [CrossRef]

27. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The roles of dopamine and noradrenaline in the pathophysiology and treatment of attention-deficit/hyperactivity disorder. Biol Psychiatry 2011;69(12):145-57. [CrossRef]

28. Castellanos FX, Rapoport JL. Etiology of attention deficit hyperactivity disorder. Child Adolesc Psychiatr Clin N Am 1992;1:373-84.

29. Brookes KJ, Chen W, Xu X, Taylor E, Asherson P. Association of fatty acid desaturase genes with attention-deficit/hyperactivity disorder. Biol Psychiatry 2006;60(10):1053-61. [CrossRef]

30. Galaris D, Pantopoulos K. Oxidative stress and iron homeostasis: mechanistic and health aspects. Crit Rev Clin Lab Sci 2008;45(1):1-23. [CrossRef]

31. Li J, O W, Li W, Jiang ZG, Ghanbari HA. Oxidative stress and neurodegenerative disorders. Int J Mol Sci 2013;14(12):24438-75. [CrossRef]

32. Adisetiyo V, Jensen JH, Tabesh A, Deardorff RL, Fieremans E, Di Martino A, et al. Multimodal MR imaging of brain iron in attention deficit hyperactivity disorder: a noninvasive biomarker that responds to psychostimulant treatment? Radiology 2014;272(2):524-32. [CrossRef]

33. Cortese S, Azoulay R, Castellanos FX, Chalard F, Lecendreux M, Chechin D, et al. Brain iron levels in attention-deficit/hyperactivity disorder: a pilot MRI study. World J Biol Psychiatry 2012;13(3):223-31. [CrossRef]

34. Zimmer L. Positron emission tomography neuroimaging for a better understanding of the biology of ADHD. Neuropharmacology 2009;57(7-8):601-7. [CrossRef]

35. Spahis S, Vanasse M, Bélanger SA, Ghadirian P, Grenier E, Levy E. Lipid profile, fatty acid composition and pro-and anti-oxidant status in pediatric patients with attention-deficit/hyperactivity disorder. Prostaglandins Leukot Essent Fatty Acids 2008;79(1-2):47-53. [CrossRef]

36. Dvoráková M, Sivoňová M, Trebatická J, Skodáček I, Waczuliková I, Muchová J, et al. The effect of polyphenolic extract from pine bark, Pycnogenol® on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD). Redox Rep 2006;11(4):163-72. [CrossRef]

37. Archana E, Pai P, Prabhu BK, Shenoy RP, Prabhu K, Rao A. Altered biochemical parameters in saliva of pediatric attention deficit hyperactivity disorder. Neurochem Res 2012;37(2):330-4. [CrossRef]

38. Bulut M, Selek S, Gergerlioglu HS, Savas HA, Yilmaz HR, Yuce M, et al. Malondialdehyde levels in adult attention-deficit hyperactivity disorder. J Psychiatry Neurosci 2007;32(6):435-8.

39. Ceylan MF, Sener S, Bayraktar AC, Kavutcu M. Changes in oxidative stress and cellular immunity serum markers in attention-deficit/hyperactivity disorder. Psychiatry Clin Neurosci 2012;66(3):220-6. [CrossRef]

40. Ceylan M, Sener S, Bayraktar AC, Kavutcu M. Oxidative imbalance in child and adolescent patients with attention-deficit/hyperactivity disorder. Prog Neuropsychopharmacol Biol Psychiatry 2010;34(8):1491-4. [CrossRef]

41. Gmitterová K, Heinemann U, Gawinecka J, Varges D, Ciesielczyk B, Valkovic P, et al. 8-OHdG in cerebrospinal fluid as a marker of oxidative stress in various neurodegenerative diseases. Neurodegener Dis 2009;6(5-6):263-9. [CrossRef]

42. Toda T, Nakamura M, Morisawa H, Hirota M, Nishigaki R, Yoshimi Y. Proteomic approaches to oxidative protein modifications implicated in the mechanism of aging. Geriatr Gerontol Int 2010;10(Suppl.1):S25-S31. [CrossRef]