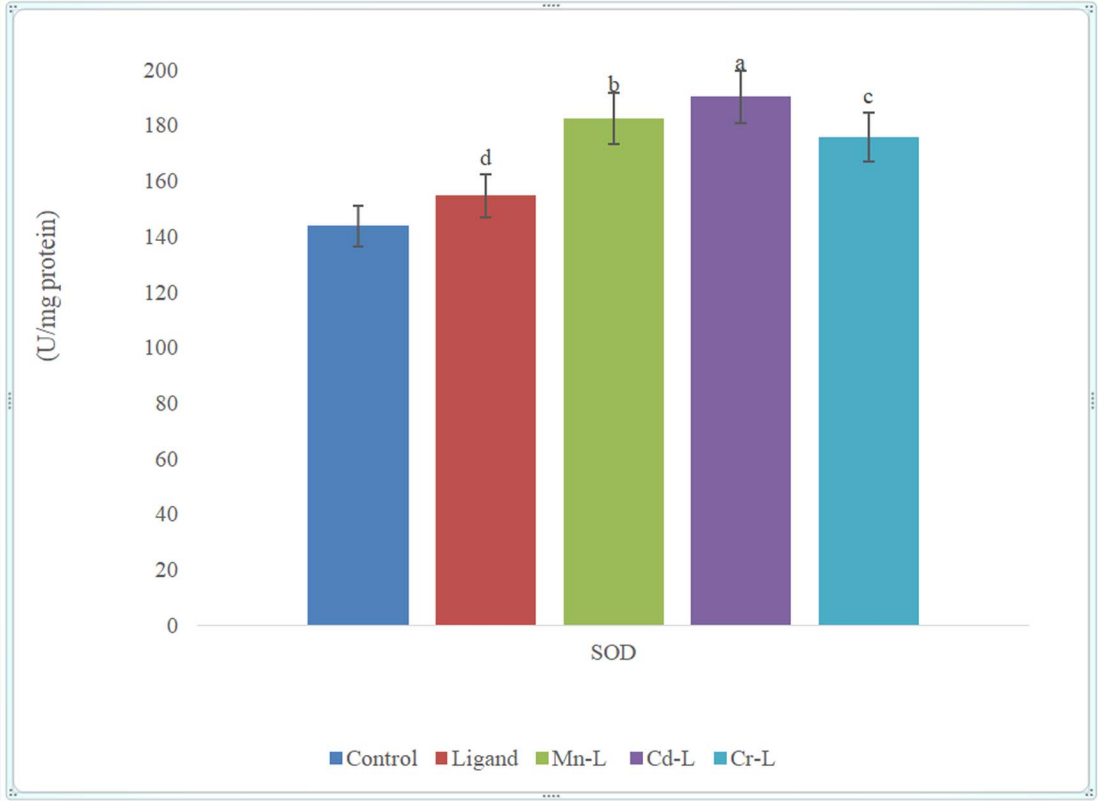
E-ISSN: 2149-7222 (Online)

Journal Cellular Neuroscience and Oxidative Stress

http://dergipark.gov.tr/jcnos

Former name; Cell Membranes and Free Radical Research



OPEN ACCESS and NO PUBLICATION FEE

Editor in Chief
Prof.Dr. Mustafa NAZIROĞLU

Volume 11, Number 1, 2019

Journal of Cellular Neuroscience and Oxidative Stress

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BSN Health Analyses, Innovation, Consultancy, Organization, Industry and Trade Limited Company

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Formerly known as:

Cell Membranes and Free Radical Research (2008 - 2014)

Volume 11, Number 1, 2019

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Volume 11, Number 1, 2019
E-ISSN Number: 2149-7222 (Online)
Indexing: Google Scholar, Index Copernicus, Chemical Abstracts, Scopus (Elsevier),
EBSCOhost Research Database, Citation Index Database,

AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A- Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D- Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

READERSHIP

Biophysics	Biochemistry
Biology	Biomedical Engineering
Pharmacology	PhysiologyGenetics
Cardiology	Neurology
Oncology	Psychiatry
Neuroscience	Neuropharmacology

Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

RESEARCH ARTICLE

J Cell Neurosci Oxid Stress 2019;11(1): 797-804.

Relationship between some element levels and oxidative stress parameters in rats liver treated with hydroxyurea derivative compounds

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Received 18 January 2019; ***Accepted*** 15 May 2019

Abstract

In this study, effects of hydroxyurea derivatives 1, 3, 4 - thiadiazole and schiff base compounds on some element levels and antioxidant enzyme activities in rat liver and on antioxidant enzyme levels that are parameters of oxidative stress were investigated. For this purpose, iron (Fe), zinc (Zn) and copper (Cu) concentrations were analyzed by using atomic absorption spectroscopy superoxide dismutase (SOD) and catalase (CAT) activities were measured by using a UV spectrophotometer. Fe, Zn and Cu concentrations in the liver of rats treated with these compounds were compared with levels of SOD and CAT statistically. As a result, the increase in the antioxidant activities of SOD and CAT metalloenzymes together with decrease in levels of Cu, Zn and Fe elements observed may suggest that the elements be bound to these enzymes.

Keywords: Some element, oxidative stress, rat, liver, hydroxyurea

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List of Abbreviations;

CAT, catalase; **Cu,** copper; **DMSO,** dimethylsulphoxide; **Fe,** iron; **G-Px**, glutathione peroxidase; **H_2O_2,** hydrogen peroxide; **O_2,** molecular oxygen; **O_2-,** superoxide; **KCl,** potassium chloride; **MUFA,** monounsaturated fatty acids; **SOD,** superoxide dismutase; **Zn,** zinc

Introduction

Thiadiazole derivatives are used as therapeutic in many diseases due to their antifungal (Kikelj and Urleb 2002), antiviral (Kritsanida et al. 1993), antibacterial (Amorim et al. 1992), anticonvulsant (De Lima et al. 1994), antimicrobial and anti-inflammatory (Kadi et al. 2007), properties. Thiadiazole derivatives are also said to show antithyroid activity (Jackson et al. 2007). It was determined that some thiadiazole derivatives (2, 2-bis-1,3,4-thiadiazole) showed antitumor and immunosuppressive activities against leukemia types such as L1210 leukemia 6C3HED/OG lymphosarcomata, C1498 myeloid leukemia, Ehrlich carcinoma, sarcoma 180, B16 melanoma and X5563 myeloma in BALB/3T3 rats applied in vivo (Matsumoto et al. 1974, Stewart et al. 1986). In particular, N-substitute 2-amino-1,3,4-thiadiazole derivatives were examined in terms of showing antiproliferative activity (Borras et al. 1996). It was observed in in vivo studies that thiadiazole ligands inhibited carbonic anhydrase enzyme (CA, EC 4.2.1.1) (Devasagayam et al. 1983). It is also indicated that it exhibits antioxidative activity by inhibiting lipid peroxidation (Yoshikawa et al. 2000) and protein oxidation (Oner et al. 2005). It is indicated that schiff bases and metal complexes have antitumor (Yang et al. 2000), antiviral (Das et al. 1999), antimicrobial (Fioravanti et al. 1996), antineoplastic properties (Sur et al. 1990). In addition, it was reported that, when high dose of schiff base derivative Cd (II) metal complex containing thiosemicarbazone derivative was injected to rats, Cd (II) metal complex created oxidative stress and on the other hand, damage occurred in testicular tissue (Karatepe and Karatas 2006). In another study, it was reported that schiff base derivative did not affect antioxidant parameters of synthesized ligand, and Cu (II) complex and Cd (II) complex behaved like antioxidants. It was also reported that Zn (II) complex did not create any oxidative stress, but acted like an antioxidant, and did not result in any damages in liver, kidney and adrenal tissues (Varvaresou et al. 2000).

In this study, the objective was to determine effects of hydroxyurea derivative 1, 3, 4- thiadiazole and schiff base compounds, known to have many biologic activities, on activities of antioxidant enzymes in rat liver tissues including superoxide dismutase (SOD), catalase (CAT) and element concentrations (Fe, Zn and Cu).

Materials and Methods

Experimental protocol

In the research, a total of 84 adult Wistar male rats that were 12-14-week-old with average weight of 250 g and grown in Experimental Research Center, Faculty of Medicine, Fırat University (FÜTDAM) were used as animal material. Rats were kept in room temperature under light for 12 hours and under dark for 12 hours. Rats were given feed and water as much as requested. The experimental protocol was approved (protocol number: 2008/255 and date of approve: 04.07.2008) by the Ethical Committee of Animal Experiments, Fırat University. The study was conducted in accordance with ethical rules. Since thiadiazole complexes dissolve in dimethylsulphoxide (DMSO), it was diluted with maize oil in a way to keep the amount of DMSO under 10% (Cesur et al. 2002). Animal were divided into 1 control and 4 practice groups containing 7 animals in each group for hydroxyurea derivative 1,3,4-thiadiazole compounds, and they were divided into 1 control and 6 practice groups for hydroxyurea derivative schiff base compounds. Control group was injected with DMSO only diluted with maize oil. Ligand and other metal complex groups were injected subcutaneously with 0,5 ml DMSO in a way to achieve 25 mg/kg every three days for a period of 15 days.

Chemical compounds

Structure of hydroxyurea derivative 1, 3, 4 - thiadiazole (Figure 1) and schiff base (Figure 2) compounds that are used in applications and characterized by pre-synthesizing are presented below (Çetin et al. 2006, Turan and Sekerci 2009, Adıguzel et al. 2011, Esener et al. 2011).

Analysis of antioxidant enzymes and lipid peroxidation

Preparation of tissue homogenization

Tissue samples were weighed, potassium chloride (KCl) of 3 times the weight per gram was added on the tissue inside the glass tube. After homogenizing the tissues with homogenizer, it was centrifuged for 60 minutes by 4000 cycles per minute. In the study, the clear supernatant portion of the homogenized tissue

above was taken, its protein values were measured, and the results were given per protein.

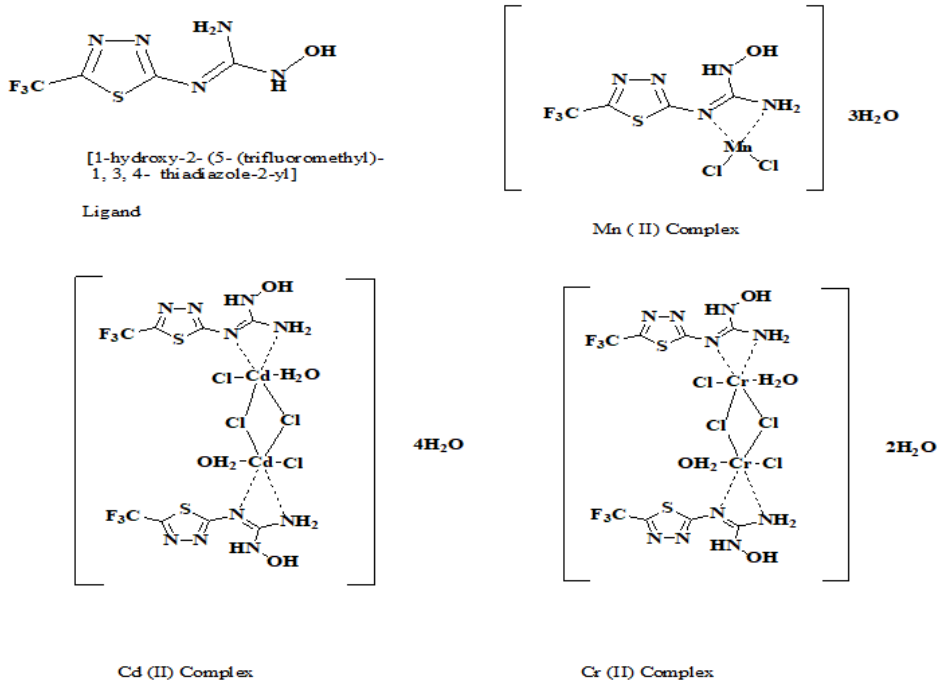

Figure 1. Chemical structure of hydroxurea derivative 1,3,4-thiadiazole and its complexes

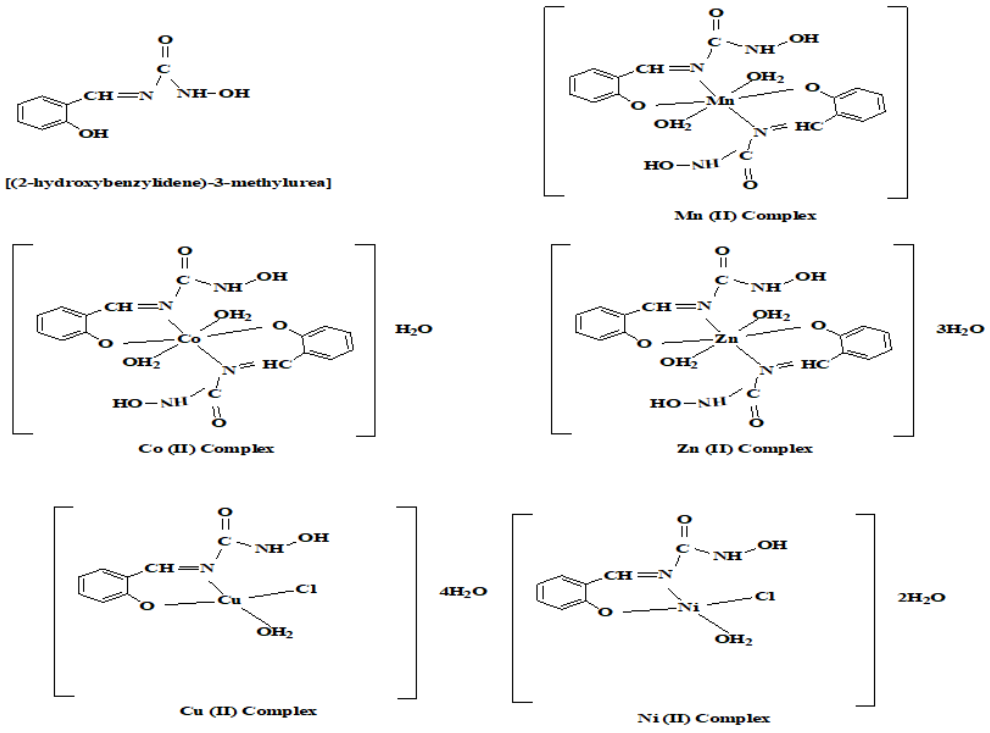

Figure 2. Chemical structure of hydroxyurea derivative schiff base and its complexes

Superoxide dismutase (SOD) assay

The method was adopted for the determination of SOD, which operates by detecting O_2-• by oxidation of hydroxylamine HCl to 2 nitrites. The measurement of the colored product resulted at 560 nm calorimetrically. 100 µl of 5% liver homogenate in 0.2 M sucrose was included in 1 mL of sodium carbonate, 0.4 mL of nitro blue tetrazolium (NBT) and 0.2 ml of EDTA and zero-minute reading was determined at 560 nm. 0.4 ml of hydroxylamine (1 mM) was included in the reaction mixture, following the incubation for 5 min at 25°C, the colored product acquired was measured to be at 560 nm by using Schimadzu UV 1201 version spectrophotometer colorimetrically. SOD activity was determined in units/mg protein as the quantity of protein in 1000 µl of 5% liver homogenate that prevented the reduction of 24 mM NBT by 50%. SOD was measured using the SOD assay kit provided by Randox company (Ransod SD125, Elazig, Turkey). (Muradian et al. 2002).

Catalase (CAT) assay

The method was adopted in order to determine the decomposition of hydrogen peroxide by tissue catalase. 100 µL of 5% liver homogenate in 0.15 M KCl was included in 1.9 mL of phosphate buffer (0.25 M, pH 7) and the absorbance level was measured to be 240 nm. 1 mL of hydrogen peroxide solution (0.34 mL of 30% H_2O_2 in 100 mL distilled water) was included in the 2:2 reaction mixture and the absorbance level was determined after 1 min at 240 nm by using Schimadzu UV 1201 version spectrophotometer during shattering of H_2O_2 into H_2O and O_2 with catalase enzyme. The activity of catalase was indicated as U/mg of protein. 1 international unit of CAT equals to the amount that catalyzes 1 mM of H_2O_2 per minute at 37°C (Sinha 1972).

Analysis of trace elements

On 0.1 grams weighed tissue samples, 1.5 ml of mixed nitric acid was placed, then it remained in the incubator at 100 °C around 2 hours until half of the total volume was left. 1.5 ml of concentrated perchloric acid was added to the tubes, which were expected to be removed from the incubator and cooled at room temperature. After the samples were left again in the incubator for approximately 2 hours until half of the total volume was left, the total volume of the sample in the cooled tubes was filled with distilled water up to a specific ml. After mixing process, the levels of iron, zinc and copper in these tissues (ATI-UNICAM 929 Model) were measured by an atomic absorption spectrophotometer device (Brown and Taylor 1985, Aydemir et al. 2006, Ölçücü and Çağlar 1993)

Statistical analysis

Experimental data was analyzed using SPSS 15.0 statistical package program, and the results were presented as mean value ± standard deviation. The degree of significance among differences among group averages were revealed with analysis of variance (ANOVA) and Duncan multiple comparison test. $P<0.05$ values for statistical results found were considered significant.

Results

There was no statistically significant change in all application groups according to the control in the Fe, Zn and Cu element levels of rats treated with some compounds of hydroxyurea derivative 1, 3, 4-thiadiazole and schiff ($p > 0.05$) (Table 1 and 2). There was not a statistically significant decreased or increased values in the levels of Fe, Zn and Cu between the control and the other application groups. A statistically significant change was not detected in all application groups according to the CAT activity values in rat livers treated with hydroxyurea derivative 1,3,4-thiadiazole compounds ($p>0.05$). On the other hand, a statistically significant increase was found in SOD activity values, ($p<0.05$) (Figure 3). In the CAT activity values in rat livers treated with some hydroxyurea derivative schiff based compounds, there was no statistically significant change in the application groups compared to the control group ($p>0.05$). In contrast, a statistically significant increase was found in the SOD activity ($p<0.05$) (Figure 4).

Parameters (n =7)	Groups					P
	Control	Ligand	Mn-L	Cd-L	Cr-L	
SOD (U/mg protein)	143.82±1.15	154.71±3.68^{d}	182.65±1.02^{b}	190.34±1.14^{a}	175.79±2.24^{c}	(P<0.05)
CAT (U/mg protein)	69.46±0.85	73.37±0.98	70.34±0.57	71.72±0.50	73.74±0.87	(P>0.05)
Fe (µg/g)	12.50±0.25	66.32±4.26	24.79±1.94	5.80±0.56	2.66±0.44	(P>0.05)
Cu (µg/g)	15.33±0.45	10.35±0.42	3.01±0.16	4.14±0.09	4.51±0.18	(P>0.05)
Zn (µg/g)	6.55±0.25	29.07±0.49	2.31±0.06	2.49±0.09	3.28±0.01	(P>0.05)

Table 1. Superoxide dismutase (SOD), catalase (CAT) activities, iron (Fe), copper (Cu) and zinc (Zn) concentrations in liver of rats with treated hydroxyurea derivative 1, 3, 4 - thiadiazole compounds. (Mean ± SD). Each mean represents analyses of five independent samples (a, b, c, d) Variation in the following letters between samples indicates significant of difference by Duncan's test at 5% level (p<0.05). P: Statistical values. L:Ligand

Parameters (n =7)	Groups							P
	Control	Ligand	$Mn(L)_2$	$Cu(L)_2$	$Ni(L)_2$	$Co(L)_2$	$Zn(L)_2$	
SOD (U/mg protein)	50.89±1.70	56.76±0.61^{f}	74.13±0.64^{b}	84.23±0.65^{a}	62.39±0.67^{d}	59.27±1.19^{e}	67.62±0.46^{c}	(P<0.05)
CAT (U/mg protein)	39.77±0.26	35.20±0.37	23.87±0.22	26.20±0.42	32.97±0.20	37.01±0.43	29.08±0.45	(P>0.05)
Fe (µg/g)	50.75±1.57	57.56±1.54	35.54±1.47	20.47±1.58	8.57±1.41	42.58±1.46	37.43±1.70	(P>0.05)
Cu (µg/g)	10.48±1.56	4.58±1.98	3.23±1.74	4.00±1.41	4.61±1.18	5.10±2.25	11.21±2.62	(P>0.05)
Zn (µg/g)	12.42±1.63	7.35±1.52	1.48±0.97	1.45±0.51	7.57±1.40	2.40±1.26	5.36±1.69	(P>0.05)

Table 2. Superoxide dismutase (SOD), catalase (CAT) activities, iron (Fe), copper (Cu) and zinc (Zn) concentrations in liver of rats with treated hydroxyurea derivative schiff base compounds. (Mean ± SD). Each mean represents analyses of five independent samples (a, b, c, d, e and f) Variation in the following letters between samples indicates significant of difference by Duncan's test at 5% level (p<0.05). P: Statistical values. L:Ligand

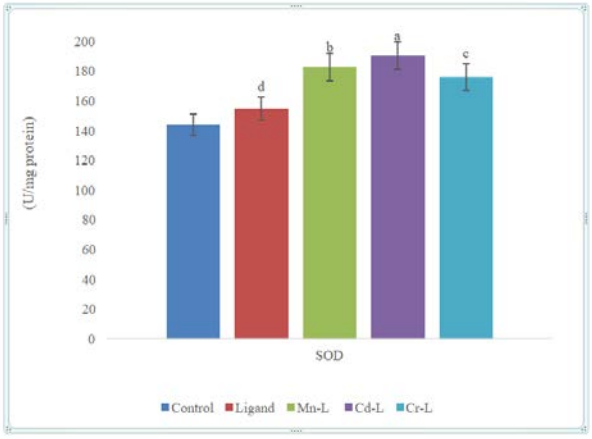

Figure 3. Superoxide dismutase **(**SOD) and catalase (CAT) activities in liver of rats with treated hydroxyurea derivative 1, 3, 4 - thiadiazole compounds (mean ± SD and n=7). Each mean represents analyses of five independent samples (a, b, c, d) Variation in the following letters between samples indicates significant of difference by Duncan's test at 5% level ($p<0.05$). P: Statistical values. L:Ligand.

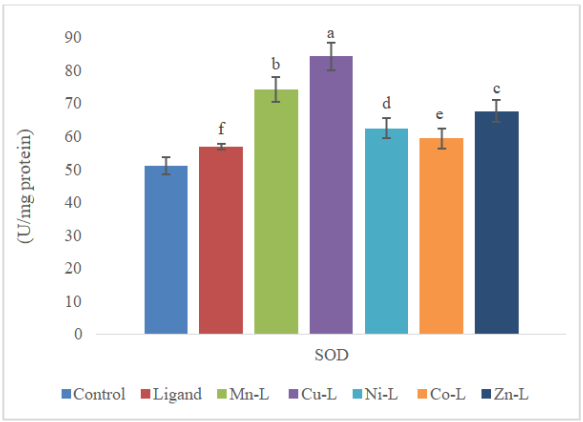

Figure 4. Superoxide dismutase **(**SOD) and catalase (CAT) activities in liver of rats with treated hydroxyurea derivative schiff base compounds. (mean ± SD and n=7). Each mean represents analyses of five independent samples (a, b, c, d, e and f) Variation in the following letters between samples indicates significant of difference by Duncan's test at 5% level ($p<0.05$). P: Statistical values. L:Ligand

Discussion

Hydrogen peroxide forming with the reaction in which SOD catalyzes superoxide radical (O_2.-) to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2) is eliminated from the medium with CAT or glutathione peroxidase (G-Px) enzymatic antioxidants (Young and Woodside 2001). Hydrogen peroxide in non-radicalic characteristic results in formation of hydroxyl radical (OH) which is the most reactive among free radicals with Fenton reaction under catalyst of Fe and Cu metal ions (Cheung et al. 2001, Larson 1988). Hydrogen peroxide is expelled from medium by degrading to water with G-Px and fragmenting into water and oxygen with CAT enzyme (Sen and Chakraborty 2011, Reiter et al. 1995).

While Cu and Zn regarded as important trace elements are required for activity of SOD enzyme, Fe element has also effects on antioxidant system by joining the structure of CAT enzyme (Steinkühler et al. 1991). Besides, Fe and Cu redox active materials initiate radicalic reactions by locking on DNA and RNA; thus, these reactions result in damaging nucleic acids. There are study results available reporting that Fe and Cu redox active transition metals increase oxidative damage or result in antioxidant defense in their absence (Nasr et al. 2002, Chan et al. 1999, Ashour et al. 1999).

In a study brought about by Parlak et al. (2018) investigated effects of hydroxyurea derivative 1,3,4 - thiadiazoles on fatty acids and lipophilic vitamins in rats liver. In this study, it was indicated that, while amounts of oleic acid (18: 1, n-9) and monounsaturated fatty acids (MUFA) increased significantly in Mn complex group compared to the control group, arachidonic acid amount (20: 4, n-6) in ligand group increased significantly, in addition, α-tocopherol amounts and K_2 and D_3 vitamins increased significantly in all groups compared to the control group, increases of α-tocopherol amounts in both Mn and Cr complex groups were found closer to each other compared to the control group, and retinol amount in Mn complex group was lower compared to other groups. In a similar study brought about by Turkoglu et al. (2014) investigated effects of hydroxyurea derivative schiff base compounds on fatty acids and lipophilic vitamins in rat liver and it was indicated that, when compared with the control group, while amounts of monounsaturated fatty acids (MUFA) decreased significantly in Mn, Ni and Zn complex groups, amount of linoleic acid (18:3) and eicosatrienoic acid (20:3) increased significantly, besides, amounts of K_2 and D_2 vitamins increased significantly in Mn and Ni groups compared to the control group, and increase in α-tocopherol amounts in both Ni and Co complex groups were found closer to each other compared to control group. In another study in which antioxidant and antitumor effects of these complex compounds were examined, it was reported that, while there was too much decrease in antioxidant vitamin A and E levels in rat serums in the group

applied with Cd complex compared to other groups, again this complex exhibited the highest antitumor activity against MCF-7 breast cancer cells (Karagozoglu et al. 2015).

In studies conducted with both hydroxyurea derivative 1,3,4-thiadiazole and schiff base compounds, the fact that SOD enzyme activity is high in practice groups and free radical production of liver tissue increases may be an indicator of lipid peroxidation. It can be said that CAT enzyme offers protective effect depending upon increase in level, however, increase in SOD enzyme activity is an indicator of high amount of superoxide radical in the medium (Karagozoglu et al. 2013, Parlak et al. 2017).

The increase in SOD and CAT activities suggests that superoxide radicals in environment are transformed into hydrogen peroxides, and hydrogen peroxides are transformed into water molecules. There may be many reasons for the increase of hydroxyl radical; hydrogen peroxide, which accumulate in the environment, are reduced by transition metals such as Fe and Cu, or react with superoxides to form hydroxyl radicals. As a result, the increase in the antioxidant activities of SOD and CAT metalloenzymes together with decrease in levels of Cu, Zn and Fe elements observed may suggest that the elements be bound to these enzymes. In this regard, more extensive research is needed to determine the exact role of antioxidant enzymes and the elements in the formation of oxidative damage.

Finding and financial disclosure: There is no financial support and disclosure for the current study.

Conflict of interest statement: The author declares that he has no conflict of interest in the current study.

ORCHID

Yusuf Karagözoğlu

References

Adiguzel R, Esener H, Ergin Z, Aktan E, Turan N, Sekerci M. 2011. Synthesis and Characterization of Novel Ni(II), Cu(II) and Cd(II) Complexes of 4-(2-clorphenylazo)-1hpyrazole-3,5-diamine. Asian J Chem. 23:1846-1850.

Amorim E, LC, Brandao SSF, Cavalcanti COM. 1992. Synthesis and structure of substituted bromo and nitrobenzyl benzylidene imidazolidinediones and thiazolidinediones Ann Pharm Fr. 50 (2): 103-111.

Ashour MN, Salem SI, El-Gadban HM, Elwan NM, Basu TK. 1999. Antioxidant status in children with protein-energy malnutrition (PEM) living in Cairo, Egypt. Eur J Clin Nutr. 53:669-673.

Aydemir B, Kızıler AR, Onaran I, Alici B, Ozkara H, Akyolcu MC. 2006. Impact of Cu and Fe concentrations on oxidative damage in male infertility. Biol Trace Elem Res. 112:193-204.

Borras J, Cristea T, Gheorghe A, Scozzafava A, Supuran CT, Tudor V. 1996. Complexes With Biologically Active Ligands. Part 6 Ni(II) Coordination Compounds of Hydrazine and Heterocyclic Sulfonamides as Inhibitors of the Zinc Enzyme Carbonic Anhydrase. Metal Based Drugs. 3:143-148.

Brown A and Taylor A. 1985. Applications of aslotted quartz tube and flame atomic absorption spectrophatometry to the analysis of biological samples. Analyst. 110: 579-582.

Cesur N, Birteksöz S, Ötük G. 2002. Synthesis and Biological Evaluation of some new thiosemicarbazide, 4-thiazolidinone, 1,3,4-oxadiazole and l,2,4-triazole-3-thione derivatives bearing imidazo[l,2-a]pyridine moiety. Acta PharmTurcica. 44: 23-41.

Cheung CCC, Zheng GJ, Li AMY, Richardson BJ, Lam PKS. 2001. Relationship Between Tissue Concentrations of Polycylic Aromatic Hydrocarbons and Antioxidative Responses of Marine Mussels, Perna viridis. Aquat Toxicol. 52(3-4): 189-203.

Chan AC, Chow CK, Chiu D. 1999. Interaction of antioxidants and their implication in genetic anemia. Proc Soc Exp Biol Med. 222:274-282.

Çetin A, Cansız A, Koparır M, Kazaz C. 2006. The Synthesis And Spectral Investigations Of New Derivatives Of 1,3,4-Oxadiazole, 1,3,4-Thiadiazole, And 1,2,4-Triazole. Organic Chem: An Indian Journal. 2(5-6): 140-149.

Das A, Trousdale MD, Ren S, Lien EJ. 1999. Inhibition of Herbes Simplex Virus type 1 and Adeno Virus Type 5 by Heterocyclic SchifF base of Aminohydorxy Guanidine Tosylate. Antiviral Research. 44: 201-208.

De Lima, JG, Perrissin M, Chantegrel J, Luu-Duc C, Rousseau A, Narcisse G. 1994. Synthesis and pharmacological evaluation of some 3-phenacyl-5-benzylidene- thiazolidine- 2,4-diones. Arzneim Forch Drug Res. 44 (22): 831-834.

Devasagayam TPA, Pushpendran CK, Eapen J. 1983. Differences in lipid peroxidation of rat liver rough and smooth microsomes. Biochim Biophys Acta. 750: 91-97.

Diurno MV, Mazzoni O, Piscopo E. 1993. On antimicrobial activity of 3- phenylspiro [3H-indole - 3, 2 – thiazolidine] - 2, 4 (1H) – diones. Farmaco. 48 (3): 435-441.

Esener H, Adiguzel R, Ergin Z, Aktan E, Turan N, Sekerci M. 2011. Synthesis and Characterization of Novel Mn(II), Co(III), Ni(II) and Cd(II) Complexes from 4-(2-nitrophenylazo)-1H-pryazole-3,5- diamine. Advanced Sci Let. 4:3669-3675.

Fioravanti R, Biava M, Donnarumma S, Porretta GC, Simonetti N, Villa A, Porta-Puglia A, Deiddo D, Maullo C, Pompei R. 1996. Synthsesis and microbiological Evaluations of (N- Heteroaryl) Arylmethamines and their their Schif Base. IL Farmoco. 51(10): 643-652.

Jackson T, Woo LW, Trusselle MN, Chander SK, Purohit A, Reed MJ, Potter BV. 2007. Dual aromatase-sulfatase inhibitors based on the anastrozole template: synthesis, in vitro SAR, molecular

modelling and in vivo activity. Org Biomol Chem. 5(18): 2940- 2952.

Kadi AA, El-Brollosy NR, Al-Deeb OA, Habib EE, Ibrahim TM, El-Emam AA. 2007. Synthesis, antimicrobial, and anti-inflammatory activities of novel 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles. European Journal of Medicinal Chemistry. 42 (2): 235-242.

Kritsanida M, Mouroutsou A, Marakos P, Papakonstantinou-Garoufalias S, Pannecouque C, Witvrouw M, De Clercq E. 2002. Antiviral Synthesis and antiviral activity evaluation of some new 6-substituted 3-(1-adamantyl) - 1, 2, 4 – triazolo [3,4-b] [1, 3, 4] thiadiazoles. Il Farmaco. 57 (3): 253-257.

Karagozoglu Y, Turkoglu S, Parlak AE, Alayunt NÖ. 2013. The Effects of Hydroxyurea Derivative 1, 3, 4- Thiadiazoles on Serum Biochemical Parameters and Antioxidant Status in Liver of Rats. Digest Journal of Nanomaterials and Biostructures. 8(1): 247 - 253.

Karagozoglu Y, Alayunt NO, Karatepe M. 2015. Effects of the hydroxyurea derivative 1, 3, 4- thiadiazoles on antioxidant vitamins, MDA in serums of rats and cell viability of MCF-7 breast cancer cells J Cell Neurosci Oxid Stress. 7(2): 439-445.

Karatepe M, Karatas F. 2006. Antioxidant, pro-oxidant effect of the thiosemicarbazone derivative schiff base (4-(1–phenylmethylcyclobutane–3–yl)–2-(2hydroxybenzylidenehy-drazino) thiazole) and and its metal complexes on rats. Cell Biochem and Function. 24 (6): 547-554.

Larson RA. 1988. The antioxidants of higher plants. Phytochemistry. 27(4): 969-978.

Matsumoto T, Ootsu K, and Okada Y. 1974. Effects of 2,2-(Methylenediimino)bis-l,3,4-thiadiazole (NSC-143019) on Tumor Growth and Immune Responses in Mice. Cancer Chemotherapy Rept. 58: 331-334.

Muradian KK, Utko NA, Fraifeld V, Mozzhukhine TG, Pishel IN. 2002. Superoxide dismutase, catalase and glutathione peroxidase activities in the liver of young and old mice: linear regression and correlation. Arch Gerontology Geriatrics. 35: 205-214.

Nasr MR, Ali S, Shaker M, Elgabry E. 2002. Antioxidant micronutrients in children with thalassaemia in Egypt. East Mediterr Health J. 8:490-495.

Oner H, Karatepe M, Karatas F, Yilmaz I, Cukurovali A. 2005. Effects on the Rat Testes of Thiosemicarbazone Derivative Schiff Base (4-(1-Phenyl- Methylcyclobutane-3-yl)-2-(2-Ydroxybenzylidenehydrazino)Thiazole) and its Cadmium (II) Complex. Cell Biochem Func. 23(6):427-433.

Ölçücü A, Çağlar P. 1993. The Zinc Levels in Human Hair and Blood Serum of Infants and Their Relationship to Various Diseases in the Upper Euprates Basin. J. Trace Elem Exp Med. 6(4): 141-145.

Parlak AE, Karagozoglu Y, Alayunt NO, Turkoglu S, Yildirim I, Karatepe M, Koparir M. 2017. Biochemical evaluation of hydroxyurea derivative schiff bases in liver of rats. Cell Mol Biol. 63(10)11:.5-10.

Parlak AE, Karagozoglu Y, Alayunt NO, Turkoglu S, Yildirim I, Karatepe M, Koparir M. 2018. The determination of the effect of some 1, 3, 4 - thiadiazole derivatives on biochemical content (Fatty Acids, Sterols, Lypophilic Vitamins) in rat liver. Cell Mol Biol. 64(3)3: 35-39.

Reiter RJ, Melchiorri D, Sewerynek E, Poeggeler B, Barlow-Walden L, Chuang J, Ortiz GG, Acuna-Castroviejo D. 1995. A review of the evidence supporting melatonin‘s role as an antioxidant. J Pineal Res. 18(1): 1-11.

Sen S, Chakraborty R. 2011. The Role of Antioxidants in Human Health. American Chemical Society, Oxidative Stress: Diagnostics, Prevention and Therapy. (1): 1-37.

Sinha AK. 1972. Colorimetry assay of catalase. Anal.Biochem. 47: 380.

Stewart JA, Ackerly CC, Myers CC, Newman RA, Krakoff IH. 1986. Clinical and clinical pharmacologic studies of 2-amino-1,3,4-thiadiazole. J Cancer Chemother Pharmacol. 16: 287-291.

Steinkühler C, Pedersen JZ, Weser U, Rotilio G. 1991. Oxidative stress induced by a di-Schiff base copper complex is both mediated and modulated by glutathione. Biochem Pharmacol. 42:1821-1827.

Sur B, Chatterjee SP, Sur P, Maity T, Roychoudhury S. 1990. Studies on the Antiplasticty of Schiff bases Containing 5- Nitrofuran and pyrimidine. Oncology. 47: 433-438.

Turan N, Sekerci M. 2009. Synthesis and Characterization of Co (II), Ni (II), Cd (II) and Cu (II) Complexes of Bis-Schiff Bases obtained from 1,8-Diaminonaphthalene. J Chem Soc Pakistan. 31:564-568.

Turkoglu S, Karagozoglu Y, Parlak AE, Alayunt NO, Yildirim I. 2014. The Effects of Hydroxyurea Derivative Schiff Bases on Fatty Acids and Lypophilic Vitamins in Liver of Rats. Digest J Nanomaterials Biostructures. 9(1):159-165.

Varvaresou A, Tsantili-Kakoulidou A, Siatra-Papastaikoudi T, Tiligada E. 2000. Synthesis and biological evaluation of indole containing derivatives of thiosemicarbazide and their cyclic 1,2,4-triazole and 1,3,4-thiadiazole analogs. Arzneimittelforschung. 50:48-54.

Yang ZY, Yang RD, Li, FS, Yu KB. 2000. Crystal Structure and antitumour Activity of some Rare Earth Metal Complexes with Schiff base. Polyhedron. 19: 2599-2604.

Young IS, Woodside JV. 2001. Antioxidants in Health and Disease. J Clin Pathol. 54(3): 176-186.

Yoshikawa T, Toyokuni S, Yamamoto Y, Naito Y. 2000. Free radicals in Chemistry, Biology and Medicine. OICA International,London pp 580.