BİTLİS EREN ÜNİVERSİTESİ
FEN BİLİMLERİ DERGİSİ

ISSN: 2147-3129 / e-ISSN: 2147-3188

Article Type : Research Article
Received : October 14, 2024
Revised : January 12, 2025
Accepted : January 13, 2025
DOI : 10.17798/bitlisfen.1567031

Year : 2025
Volume : 14
Issue : 1
Pages : 213-224

EFFECT OF VENLAFAXINE AND VITAMIN C ON SOME BIOCHEMICAL PARAMETERS OF SACCHAROMYCES CEREVISIAE (NRRLY-12632)

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ABSTRACT

In this study, *Saccharomyces cerevisiae* (NRLLY-12632) was grown in Yeast Extract–Peptone–Dextrose (YPD) medium containing different concentrations of venlafaxine, (RS)-1-[2-dimethylamino-1-(4-methoxyphenyl)-ethyl] cyclohexanol. To counteract the effect of venlafaxine, vitamin C were added to the growth medium of *Saccharomyces cerevisiae* (*S. cerevisiae)*. Then the antioxidant enzymes activities and stress biomarkers were investigated through the use of spectrophotometric methods and HPLC technique, respectively. Addition of venlafaxine in to growth medium of *S. cerevisiae*, significantly increased the superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GSH-Rd) and peroxidase (POD) activities ($p<0.05$). On the other hand, activities of CAT, GSH-Px, GSH-Rd and POD enzymes were decreased significantly in all vitamin C concentrations added to the growth medium containing venlafaxine ($p<0.05$). SOD activities were found to be significantly decreased at 50 and 75 ppm vitamin C concentrations ($p<0.05$). While total protein amount decreased at all venlafaxine concentrations, on the other hand amount of advanced oxidized proteins (AOP) increased significantly ($p<0.05$). Vitamin C at 25, 50 and 75 ppm concentrations with venlafaxine led to increase the total protein amount and decreased the AOP concentration ($p<0.05$). The amount of reduced glutathione (GSH) decreased in all venlafaxine concentrations while the amounts of oxidized glutathione (GSSG), malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) increased ($p<0.05$). With the addition 25, 50 and 75 ppm vitamin C to the growth medium containing venlafaxine while leading to decrease the amount of GSSG, MDA and 4-HNE, the amount of GSH increased significantly ($p<0.05$). From these findings, it can be said that the negative effect of venlafaxine on the biochemical parameters of *S. cerevisiae* is reduced by the addition of vitamin C to the medium.

Keywords: *S. cerevisiae*, Venlafaxine, Vitamin C, Antioxidant enzymes, Stress biomarkers.

1 INTRODUCTION

The term microorganism is used to describe many living things in a broad framework, including bacteria, yeast, fungi and algae. Yeasts are eukaryotic, unicellular microorganisms that reproduce by budding. Yeasts are composed of high protein, lipid, polysaccharide and nucleic acids as a cellular composition [1]. *S. cerevisiae* is commonly used in scientific studies for similarities to human genome. Yeasts are used in many industries due to their high reproduction in a short time and low cost by using cheap renewable food sources [2].

Depression is the most common complex psychiatric disorder worldwide, causing severe dysfunction in patients [3]. Depression is characterized by feelings of worthlessness, anxiety, guilt, hopelessness, suicidal ideation, loss of appetite, weight changes, constipation, agitation, and other somatic symptoms. In addition to its chronicity, depression causes significant work and social losses, resulting in negativities in current activities [4]. The most common treatment method for depression is the use of antidepressant drugs. Antidepressants are usually administered for a long time and in some cases in combination with other antidepressants [5]. It has been reported that in patients using antidepressants, normal metabolism is disrupted due to the side effects of drugs, abnormal signals reach the cell, and oxidative stress occurs as a result [6]. Antidepressants might cause oxidative stress by affecting cell metabolism, and the resulting free radicals in cell membrane, proteins, amino acids, vitamins. Determining the damage to the cells is of great importance in terms of preventing this damage [3]. Vitamin C, which is effective in the release of some hormones in the event of stress in living organism, has a strong antioxidant effect [7]. It is stated that vitamin C effectively protects DNA, proteins and lipids against oxidative damage due to its ability to actively capture reactive oxygen and nitrogen species [8].

All organisms, eukaryotic or prokaryotic, have developed complex cellular defense mechanisms to protect their cell and organ systems against the harmful effects of Reactive Oxygen Species (ROS) and other reactive species [9]. These mechanisms, which are generally referred to as antioxidant systems, contain various components of endogenous and exogenous origin, realized by enzymatic and non-enzymatic means, and have a radical scavenging effect, repair radical-induced damage and prevent mutations [10]. The most important of the enzymes that play a role in the antioxidant system are SOD, CAT, POD, GSH-Px and GSH-Rd, as well as non-enzymatic is GSH [11]. It was reported by Adwas et al. [12] that the antioxidant enzyme activity is important due to oxidative stress. In order to maintain its normal functioning, the

amount of protein must be kept at a constant level. Changes that may occur in the total amount of protein may be the harbinger of some diseases. Therefore, analysis of total protein is important. Free radicals formed as a result of different stress factors cause oxidation in proteins. Proteins damaged by oxidation are called advanced AOP. Protein oxidation can occur directly with reactive oxygen species or indirectly with secondary products of oxidative stress [13,14]. If there is no stress factor present in the cell, glutathione is in form GSH, in the event of stress glutathione is converted to GSSG by the action of the GSH-Px enzyme. Conversion of GSSG to GSH is important in terms of preventing free radical damage [15]. While GSSG is an indicator of oxidative stress, it also inhibits protein synthesis, GSH has many physiological functions like preventing the harmful effect of drugs [16]. Radicalic compounds cause lipid peroxidation of fatty acids in cell membranes. Lipid peroxides transform into compounds such as MDA and 4-HNE, which are indicative of lipid peroxidation [17]. In this work, *S. cerevisiae* was chosen for having at least 23% common genes to humans [18].

The aim of this study is to determine the effect of venlafaxine, one of the widely used antidepressants, on antioxidant enzymes and stress biomarkers in metabolism of *S. cerevisiae.* Additionally, investigating the effect of vitamin C on antioxidant enzymes and stress biomarkers that will be affected by antidepressants containing growth medium of *S. cerevisiae.*

2 MATERIAL AND METHOD

2.1 Material

S. cerevisiae (NRRLY-12632) used in this study was obtained from Fırat University, Department of Chemical Engineering, Biotechnology Laboratory. *S. cerevisiae* produced in yeast peptone dextrose (YPD) broth (10.0 g peptone, 5.0 g yeast extract, 10.0 g Dextrose per liter) was used. Solutions of 1000 ppm venlafaxine chloride and 500 ppm vitamin C were prepared freshly and used. The microorganism was produced in 250 mL flasks containing 50 mL nutrient medium. Experiments were carried out by forming the following groups for the study.

1. Control group: Microorganisms were grown by inoculating *S. cerevisiae* in the YPD medium.

2. Venlafaxine group: Microorganisms were grown by adding venlafaxine stock solution at desired concentrations (100 - 500 ppm) to the control.

3. Vitamin C group: Microorganisms were produced by adding vitamin C at the desired concentration (10-75 ppm) to the venlafaxine group.

The medium was incubated on an orbital shaker for 72 hours at 150 rpm at 30 °C. The concentration of *S. cerevisiae* was determined by measuring the absorbance at 600 nm with a spectrophotometer. After centrifugation of the medium containing the microorganism at 8000 rpm at 10 ºC for 10 minutes, the supernatant was removed, and the microorganism was washed twice with distilled water for further analysis [19].

2.2 Methods

Total protein analysis, Glutathione peroxidase, Glutathione reductase, Catalase and Peroxidase enzyme activities were performed by UV-Visible spectrophotometer according to the methods applied by İbrahim et al. [20], Superoxide dismutase activity was determined using the pyrogallol autoxidation method [21] and AOP determination was made according to the method developed by Witko-Sarsat et al. [22] by using by UV-Visible spectrophotometer. GSH, GSSG and MDA were analyzed using a Utisil-XB-C-8 column, using mobile phase as 50 mM $NaClO_4$ at pH: 4 in 0.1 % H_3PO_4 solution and 4-HNE were determinated on ODS-2 column by HPLC according to İbrahim et al. [20]. The HPLC chromatogram of GSH, GSSG and MDA is given in figure 1.

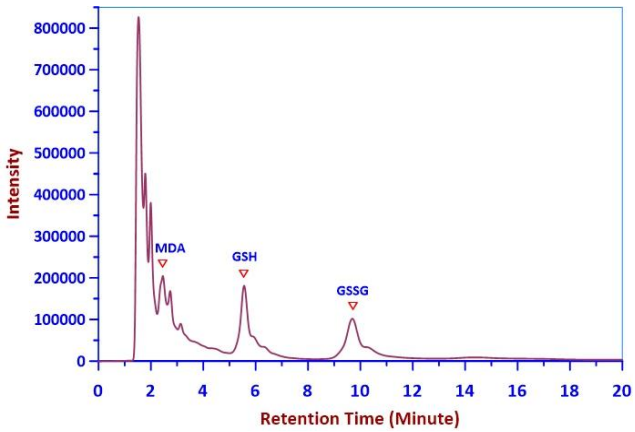

Figure 1. HPLC chromatogram of GSH, GSSG and MDA.

2.3 Statistical Analysis

All measurements were triplicated, and Mean ± Standard Deviation was determined. The results were subjected to one-way ANOVA by SPSS 26.0 for Windows. Differences between the group's means were analyzed for significance using the Tukey HSD test. The level

of statistical significance was expressed as $p<0.05$. The superscripts in the table columns are indicated as an if the effect of antidepressants compared to the control group is statistically significant ($p<0.05$), b if the effect of vitamin C in growth medium containing antidepressants is statistically significant ($p<0.05$), and c if it is not statistically significant ($p>0.05$).

3 RESULTS AND DISCUSSION

Antioxidant enzyme activities, total and oxidized protein and stress biomarkers concentrations determined in *S. cerevisiae* for different experimental groups are given in Table 1-3, respectively.

Table 1. Enzymes activities of SOD, CAT, GSH-Px, and GSH-Rd in S. cerevisiae produced in a nutrient medium.

Application	SOD (U g^{-1} dw)	CAT (U g^{-1} dw)	GSH-Px (U g^{-1} dw)	GSH-Rd (U g^{-1} dw)
Control	211.25±5.00	250.38±5.37	27.57±0.59	36.37±0.77
Ven-1	231.64±4.50 [a]	300.66±5.80 [a]	50.59±1.06 [a]	48.22±1.07 [a]
Ven-2	240.79±5.23 [a]	349.27±5.96 [a]	72.12±1.17 [a]	55.73±1.10 [a]
Ven-3	250.98±5.28 [a]	383.99±6.00 [a]	87.75±1.33 [a]	62.67±1.07 [a]
Ven-4	257.36±5.37 [a]	418.72±6.38 [a]	96.08±1.46 [a]	67.00±1.16 [a]
Ven-5	262.70±5.56 [a]	435.40±6.10 [a]	103.40±1.55 [a]	73.15±1.14 [a]
Ven-1+C10	225.48±4.93 [c]	287.64±4.70 [c]	46.86±0.88 [b]	44.10±0.93 [b]
Ven-1+C25	220.95±4.88 [c]	273.24±4.06 [b]	40.61±0.81 [b]	40.34±0.88 [b]
Ven-1+C50	216.14±4.23 [b]	255.69±3.77 [b]	35.87±0.73 [b]	36.94±0.75 [b]
Ven-1+C75	212.41±4.74 [b]	247.16±3.54 [b]	30.74±0.70 [b]	34.48±0.73 [b]
Ven-2+C10	233.58±4.97 [c]	332.15±3.49 [b]	66.95±1.07 [b]	50.56±1.02 [b]
Ven-2+C25	227.17±4.87 [c]	309.19±3.36 [b]	60.59±0.87 [b]	47.37±0.93 [b]
Ven-2+C50	222.38±4.73 [b]	289.47±2.93 [b]	54.15±0.83 [b]	43.72±0.81 [b]
Ven-2+C75	218.10±4.66 [b]	272.52±2.52 [b]	48.61±0.81 [b]	40.85±0.71 [b]
Ven-3+C10	244.84±4.81 [c]	363.44±3.64 [b]	78.71±1.29 [b]	56.41±1.04 [b]
Ven-3+C25	237.79±4.74 [c]	342.14±3.48 [b]	70.72±1.16 [b]	51.92±0.88 [b]
Ven-3+C50	233.06±4.66 [b]	313.48±3.04 [b]	61.89±1.11 [b]	47.21±0.74 [b]
Ven-3+C75	227.57±4.59 [b]	290.68±2.90 [b]	53.03±1.04 [b]	41.77±0.64 [b]
Ven-4+C10	249.89±4.85 [c]	397.99±3.42 [b]	85.33±1.28 [b]	62.47±0.96 [b]
Ven-4+C25	242.54±4.70 [c]	374.67±3.60 [b]	74.12±1.13 [b]	54.69±0.89 [b]
Ven-4+C50	236.45±4.58 [b]	345.04±3.96 [b]	65.29±1.07 [b]	49.90±0.81 [b]
Ven-4+C75	230.53±4.36 [b]	320.08±3.50 [b]	57.75±0.87 [b]	45.73±0.74 [b]
Ven-5+C10	255.25±4.11 [c]	417.16±3.76 [b]	94.90±1.42 [b]	67.25±0.99 [b]
Ven-5+C25	249.54±4.02 [c]	395.28±3.54 [b]	83.67±1.33 [b]	60.90±0.91 [b]
Ven-5+C50	242.88±4.06 [b]	373.88±3.40 [b]	73.05±1.25 [b]	56.86±0.84 [b]
Ven-5+C75	236.10±3.81 [b]	343.90±3.48 [b]	64.10±1.16 [b]	49.15±0.78 [b]

Ven-1: 100 ppm Venlafaxine, Ven-2: 200 ppm Venlafaxine, Ven-3: 300 ppm Venlafaxine, Ven-4: 400 ppm Venlafaxine, Ven-5: 500 ppm Venlafaxine, C10: 10 ppm Vitamin C, C25: 25 ppm Vitamin C, C50: 50 ppm Vitamin C, C75: 75 ppm Vitamin C.

Table 2. Peroxidase Activity, Total protein and Advanced Oxidized Protein.

Application	POD (U g^{-1} dw)	Total Prot. (mg g^{-1} dw)	AOP (µmol Cloramine T g^{-1} dw)
Control	55.63±0.97	72.76±1.46	6.75±0.12
Ven-1	80.20±1.45 [a]	65.92±0.87 [a]	8.50±0.15 [a]
Ven-2	100.55±1.80 [a]	59.38±1.06 [a]	10.10±0.19 [a]
Ven-3	110.91±1.77 [a]	54.50±1.02 [a]	11.95±0.20 [a]
Ven-4	117.54±1.82 [a]	51.14±0.96 [a]	13.10±0.21 [a]
Ven-5	124.40±1.98 [a]	48.85±0.84 [a]	14.25±0.20 [a]
Ven-1+C10	72.40±1.16 [b]	67.24±1.15 [c]	7.90±0.13 [b]
Ven-1+C25	65.51±1.13 [b]	69.30±0.82 [b]	7.41±0.11 [b]
Ven-1+C50	59.66±1.09 [b]	70.24±1.31 [b]	7.00±0.10 [b]
Ven-1+C75	56.16±1.02 [b]	72.58±1.42 [b]	6.70±0.07 [b]
Ven-2+C10	89.65±1.19 [b]	61.47±0.90 [c]	9.15±0.16 [b]
Ven-2+C25	78.21±1.10 [b]	63.78±0.96 [b]	8.53±0.15 [b]
Ven-2+C50	69.05±0.93 [b]	65.31±1.00 [b]	8.00±0.11 [b]
Ven-2+C75	60.69±0.87 [b]	67.58±1.08 [b]	7.35±0.09 [b]
Ven-3+C10	97.38±1.49 [b]	57.52±0.95 [b]	10.90±0.14 [b]
Ven-3+C25	84.59±1.17 [b]	59.78±0.98 [b]	9.76±0.12 [b]
Ven-3+C50	75.67±1.04 [b]	63.04±0.99 [b]	8.92±0.10 [b]
Ven-3+C75	67.58±0.96 [b]	65.90±1.02 [b]	8.52±0.12 [b]
Ven-4+C10	106.97±1.46 [b]	53.73±0.73 [c]	12.25±0.17 [b]
Ven-4+C25	93.47±1.45 [b]	56.87±0.88 [b]	11.54±0.15[b]
Ven-4+C50	82.85±1.04 [b]	59.15±1.02 [b]	10.95±0.13 [b]
Ven-4+C75	70.06±1.02 [b]	62.84±1.10 [b]	9.95±0.12 [b]
Ven-5+C10	109.60±1.86 [b]	51.00±0.87 [c]	13.60±0.12 [b]
Ven-5+C25	96.48±1.64 [b]	53.10±0.89 [b]	12.75±0.13 [b]
Ven-5+C50	84.80±1.62 [b]	55.90±0.93 [b]	11.50±0.15 [b]
Ven-5+C75	74.10±1.31 [b]	59.50±1.00 [b]	10.74±0.10 [b]

Ven-1: 100 ppm Venlafaxine, Ven-2: 200 ppm Venlafaxine, Ven-3: 300 ppm Venlafaxine, Ven-4: 400 ppm Venlafaxine, Ven-5: 500 ppm Venlafaxine, C10: 10 ppm Vitamin C, C25: 25 ppm Vitamin C, C50: 50 ppm Vitamin C, C75: 75 ppm Vitamin C

The effects of vitamin C on the oxidative DNA damage and mutagenesis were investigated by Nikolic et al. [23] using *S. cerevisiae* and *Escherichia coli* microorganisms, and they reported that vitamin C had a reducing effect on oxidative stress. Due to this feature of vitamin C, 10 - 75 ppm vitamin C was added to the medium containing venlafaxine.

SOD, CAT, GSH-Px, GSH-Rd and POD are very important for restoring the oxidative balance, which is disrupted as a result of metabolic events in the cell by external factors. It was determined that *S. cerevisiae*, which was stressed by adding different concentrations of venlafaxine to the medium, increased the SOD and CAT activities. Whereas vitamin C added to the medium containing venlafaxine decreased these enzyme activities depending on its concentration ($p<0.05$) (Table 1).

The SOD enzyme converts the superoxide radical anion to the less toxic hydrogen peroxide (H_2O_2) and oxygen. CAT in an important enzyme in cellular detoxification converts

H_2O_2 into water and oxygen. Another function of catalase, which is considered as a hemoprotein is present in all animal cells and aerobic microorganisms and contributes to the cell's defense system [24, 25].

In the study investigating the effect of *S. cerevisiae* against S-nitroso glutathione-induced stress, it was reported that SOD and CAT enzyme activities increased [26]. It was determined that GSH-Px and GSH-Rd activities of *S. cerevisiae* increased due to the oxidative stress caused by venlafaxine added to the medium. while vitamin C added to the medium containing venlafaxine decreased GSH-Px and GSH-Rd activities ($p<0.05$) (Table 1). According to the results of a study carried out stress caused by cadmium on *Rhizobium leguminosarum*, they reported the increased activities of GSH-Rd and GSH Px [27]. It has been reported that GSH-Rd and GSH-Px enzyme activities increased in *S. cerevisiae* cells grown in $KMnO_4$-containing medium [28].

Table 3. Concentrations of stress biomarkers in S. cerevisiae produced in a nutrient medium.

Application	GSH (µg g^{-1} dw)	GSSG (µg g^{-1} dw)	MDA (µg g^{-1} dw)	4-HNE (µg g^{-1} dw)	GSH/GSSG
Control	2950±20.30	245±2.18	8.20±0.13	4.10±0.06	12
Ven-1	2860±13.34 [a]	285±2.03 [a]	9.00±0.13 a [a]	4.60±0.05 [a]	10
Ven-2	2700±17.98 [a]	320±2.09 [a]	9.75±0.14 [a]	5.20±0.06 [a]	8.44
Ven-3	2630±18.27 [a]	360±2.20 [a]	10.30±0.14 [a]	5.90±0.08 [a]	7.31
Ven-4	2550±17.40 [a]	405±2.32 [a]	11.00±0.15 [a]	6.50±0.09 [a]	6.30
Ven-5	2480±16.70 [a]	460±2.32 [a]	11.68±0.15 [a]	7.10±0.09 [a]	5.40
Ven-1+C10	2880±18.56 [c]	273±2.03 [b]	8.75±0.12 [c]	4.52±0.06 [c]	10.55
Ven-1+C25	2907±12.76 [b]	260±1.97 [b]	8.55±0.12 [b]	4.41±0.05 [b]	11.17
Ven-1+C50	2930±17.98 [b]	253±1.86 [b]	8.40±0.11 [b]	4.36±0.05 [b]	11.58
Ven-1+C75	2955±18.27 [b]	246±1.86 [b]	8.10±0.10 [b]	4.22±0.05 [b]	12.00
Ven-2+C10	2760±16.82 [c]	305±1.91 [b]	9.45±0.12 [c]	5.12±0006 [c]	9.05
Ven-2+C25	2805±17.11 [b]	290±1.86 [b]	9.15±0.11 [b]	4.98±0.06 [b]	9.67
Ven-2+C50	2855±17.40 [b]	273±1.80 [b]	8.76±0.10 [b]	4.88±0.05 [b]	10.46
Ven-2+C75	2910±17.69 [b]	259±1.71 [b]	8.35±0.09 [b]	4.72±0.05 [b]	11.24
Ven-3+C10	2695±16.24 [b]	345±1.80 [b]	9.90±0.12[c]	5.75±0.07 [c]	7.81
Ven-3+C25	2750±15.08 [b]	330±1.74 [b]	9.50±0.12 [b]	5.62±0.06 [b]	8.33
Ven-3+C50	2810±15.20 [b]	315±1.68 [b]	9.15±0.11 [b]	5.48±0.06 [b]	8.92
Ven-3+C75	2880±15.02 [b]	292±1.51 [b]	8.70±0.10 [b]	5.34±0.06 [b]	9.86
Ven-4+C10	2605±14.50 [c]	348±2.03 [b]	10.40±0.13 [b]	6.36±0.08 [c]	7.49
Ven-4+C25	2660±14.50 [b]	331±1.97 [b]	9.95±0.12 [b]	6.15±0.06 [b]	8.04
Ven-4+C50	2705±14.21 [b]	316±1.86 [b]	9.54±0.12 [b]	5.90±0.06 [b]	8.56
Ven-4+C75	2770±14.50 [b]	298±1.74 [b]	8.90±.0.10 [b]	5.72±0.06 [b]	9.30
Ven-5+C10	2525±13.34 [c]	445±2.20 [b]	11.05±0.13 [b]	6.95±0.08 [c]	5.67
Ven-5+C25	2590±13.92 [b]	430±2.09 [b]	10.60±0.12 [b]	6.80±0.07 [b]	6.02
Ven-5+C50	2645±14.21 [b]	413±2.00 [b]	10.00±0.12 [b]	6.62±0.06 [b]	6.40
Ven-5+C75	2700±14.50 [b]	390±1.97 [b]	9.40±0.11 [b]	6.45±0.06 [b]	6.92

Ven-1: 100 ppm Venlafaxine, Ven-2: 200 ppm Venlafaxine, Ven-3: 300 ppm Venlafaxine, Ven-4: 400 ppm Venlafaxine, Ven-5: 500 ppm Venlafaxine, C10: 10 ppm Vitamin C, C25: 25 ppm Vitamin C, C50: 50 ppm Vitamin C, C75: 75 ppm Vitamin C.

Peroxidase activity is used as a stress marker by many researchers. Studies conducted on many plant species, it has been emphasized that peroxidase activity increases rapidly as a result of the plant's uptake of heavy metals [29]. In a similar way in our studies, it was observed that POD enzyme activity increased ($p<0.05$) due to oxidative stress caused by venlafaxine, while vitamin C added to the same medium caused a decrease in POD activity ($p<0.05$) (Table 2). It has been reported that there is a significant increase in POD activity of *Bacillus subtilis* and *Pseudomonas putida* bacteria under heavy metal stress [30]. It is very important to preserve the protein structure for the continuation of the functions in the cells. Proteins are highly sensitive to oxidative damage, and cellular metabolism is negatively affected when their structures are disrupted [31]. It was observed that the amount of total protein decreased and the amount of AOP increased as the increasing concentrations of venlafaxine added to the broth of *S. cerevisiae* ($p<0.05$). It was determined that vitamin C added to venlafaxine-containing media increased the total protein and decreased the amount of oxidized protein ($p<0.05$) (Table 2). It was determined that carbon tetrachloride (CCl_4) added to the nutrient medium decreased the total protein amount in *S. cerevisiae*, while clove plant extract added as an antioxidant significantly increased the total protein amount [32]. It has been reported that the amount of AOP increases at the end of the 6^{th} and 9^{th} hours in *S. cerevisiae*, which is stressed by applying a magnetic field [33].

GSH is especially important for the transport of amino acids keeping the sulfhydryl groups in proteins in a reduced state and acting as a coenzyme in some enzymatic reactions [34]. GSH and GSSG are important indicators of cellular redox status and organismal health. Therefore, reduced glutathione ratio to oxidized glutathione is also known as a stress indicator [35].

Our results showed that while amount of GSH decreased. GSSG increased due to the oxidative stress caused by the addition of venlafaxine to the medium. It was seen that the amount of GSH increased and the amount of GSSG decreased with the addition of vitamin C to media containing venlafaxine. While the ratio of GSH/GSSG, decreased depending on the concentration of venlafaxine. addition of vitamin C to medium caused to increase this ratio, due to antioxidant properties of vitamin C (Table 3). It has been reported that cadmium addition to the growth medium increases the amount of GSSG while decreasing the amount of GSH in *Citrobacter Freundii*, and this situation is reversed with the addition of vitamin C to the medium [20]. As a result of lipid peroxidation, MDA and 4-HNE, which are considered stress biomarkers, are formed [17]. It was observed that the amount of MDA and 4-HNE increased

depending on the concentration of venlafaxine added to the *S. cerevisiae* medium, on the other hand, the amount of MDA and 4-HNE decreased with the addition of vitamin C to the same medium (Table 3). It has been reported that heavy metals applied to the *S. cerevisiae* medium increase the amount of GSSG and MDA, while decreasing the GSH/GSSG ratio and the amount of GSH [36].

Vitamin C is a good singlet oxygen scavenger that neutralizes ROS, reduces oxidative stress [37]. It can be concluded that other antioxidant systems are less affected by oxidative stress due to the antioxidant effect of vitamin C.

4 CONCLUSION AND SUGGESTIONS

With the increase of venlafaxine concentration added to YPD medium, it was observed that antioxidant enzyme activities, the amounts of GSSG, AOP, MDA, 4-HNE increased, while the amount of GSH and total protein decreased.

Similarly, with the increase of vitamin C concentration in the growth medium of *S. cerevisiae*, reduced the negative effects of venlafaxine on all the measured parameters.

Conflict of Interest Statement

There is no conflict of interest between the authors.

Statement of Research and Publication Ethics

The study is complied with research and publication ethics.

Artificial Intelligence (AI) Contribution Statement

This manuscript was entirely written, edited, analyzed, and prepared without the assistance of any artificial intelligence (AI) tools. All content, including text, data analysis, and figures, was solely generated by the authors.

Contributions of the Authors

Meltem Çakmak: Resources, Methodology, Research, Formal analysis, **Dursun Özer**: Data curation, Conceptualization, Writing – original draft, Visualization, Validation, **Fikret Karataş**: Data curation, Conceptualization, Writing – original draft, Visualization, Validation, **Sinan Saydam**: Writing – review & editing, Visualization.

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