# ETOXEC

Environmental Toxicology and Ecology

© Environmental Toxicology and Ecology
2022, Vol. 2 (1)
e-ISSN: 2757-9719

Research Article

# Effect of Amitriptyline on Serum Biochemistry of Gilthead Sea Bream (*Sparus aurata*)

Osman Nezih KENANOĞLU[1], Nihan AKINCI KENANOĞLU[2*], Sevdan YILMAZ[3], Soner BİLEN[1]

**Article Info**

*Corresponding author*:

**Institution:**[2] *Çanakkale Onsekiz Mart University, Faculty of Arts and Sciences, Department of Biology, Çanakkale, Turkey*

**e-mail:** nihanakinci2@gmail.com

**ORCID:** 0000-0002-3917-6412

[1] *Kastamonu University, Faculty of Aquaculture and Fisheries*
[3]*Çanakkale Onsekiz Mart University, Marine Science and Technology Faculty*

**Article history**

*Received*: 30.03.2022

*Accepted:* 13.04.2022

*Available online*: 29.04.2022

**Keywords:**

Antidepressant, Biochemical activity, Aquatic environment

**Anahtar Kelimeler:**

Antidepresan, Biyokimyasal aktivite, Akuatik çevre

***How to Cite:*** *O.N. Kenanoğlu, N Akıncı Kenanoğlu, S. Yılmaz, S. Bilen, "* Effect of Amitriptyline on Serum Biochemistry of Gilthead Sea Bream (*Sparus aurata*)*", Environmental Toxicology and Ecology, c. 2, sayı. 1, ss. 66-75, Nis. 2022.*

## ABSTRACT

Amitriptyline is a tricyclic antidepressant that is frequently used in the treatment of many neuropathic and inflammatory diseases as well as depression. As a result of contamination to the aquatic environment, the effects of amitriptyline antidepressant, which has long lasting properties, on the serum biochemistry of gilthead sea bream fish was investigated in this study. For this purpose, gilthead sea bream were exposed to amitriptyline concentrations of 0.2 µg/L, 10 µg/L, 100 µg/L and 1000 µg/L for 14 days. Glucose, albumin, globulin, total protein, triglyceride, cholesterol, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and lactate dehydrogenase biochemical parameters were determined from the blood serum samples of the fish taken on the 7$^{th}$ and 14$^{th}$ days of the study. Significant changes occurred on the 14$^{th}$ day in the values of triglyceride, cholesterol, aspartate aminotransferase, alkaline phosphatase and lactate dehydrogenase, which did not show a significant difference on the 7$^{th}$ day. These results reveal that different amitriptyline concentrations cause negative changes in the fish biochemistry.

## Amitriptilinin Çipura (*Sparus aurata*) Serum Biyokimyası Üzerindeki Etkisi

## ÖZET

Amitriptilin, depresyonun yanında, birçok nöropatik ve inflamatuar hastalığın tedavisinde sıklıkla kullanılan trisiklik antidepresandır. Bu çalışmada, sucul ortama karışması sonucunda uzun süre kalıcılık gösterme özelliğine sahip olan amitriptilin antidepresanının çipura (*Sparus aurata*) balıklarının serum biyokimyasına olan etkisi araştırılmıştır. Bu amaçla çipura balıkları 14 gün boyunca 0,2 µg/L, 10 µg/L, 100 µg/L ve 1000 µg/L'lik amitriptilin konsantrasyonlarına maruz bırakılmıştır. Çalışmanın 7. ve 14. gününde alınan balıkların kan serum örneklerinden glukoz, albumin, globulin, total protein, trigliserid, kolesterol, aspartat aminotransferaz, alanin aminotransferaz, alkalen fosfataz ve laktat dehidrogenaz biyokimyasal parametreleri belirlenmiştir. 7. günde anlamlı bir farklılık göstermeyen tüm serum biyokimya parametrelerinden, trigliserid, kolesterol, aspartat aminotransferaz, alkalen fosfataz ve laktat dehidrogenaz değerlerinde 14. günde anlamlı değişimler meydana gelmiştir. Bu sonuçlar farklı amitriptilin konsantrasyonlarının balık biyokimyasında olumsuz yönde değişimlere neden olduğunu ortaya koymaktadır.

© Environmental Toxicology and Ecology
2022, Vol. 2 (1)
e-ISSN: 2757-9719

Research Article

## 1. INTRODUCTION

Amitriptyline is a tricyclic antidepressant that has been widely used in the world for many years due to its high efficacy and low cost [1-3]. Acting as a serotonin and noradrenaline reuptake inhibitor, amitriptyline is widely prescribed to treat depression, severe neuropathic and inflammatory diseases in both humans and animals [2-5]. It is known that amitriptyline ranked 56$^{th}$ (5.91 tonnes) among the 100 most consumed pharmaceutical compounds by mass in the UK in 2000 [6].

Studies of amitriptyline on aquatic organisms are very scarce [2]. However, it has been reported that amitriptyline is present in low detectable concentrations in aquatic environment [2,4]. Amitriptyline can be detected up to 72 ng/L in surface waters and up to 223 ng/L in wastewater treatment plant wastes [7-10]. Amitriptyline at concentrations as low as 10 ng/L can impair the immune system of aquatic organisms and affect their reproduction, growth and development [2,10-12]. Along with these findings, it is stated that amitriptyline has the potential to bioaccumulate and is observed up to 1.8 ng/g in aquatic organisms [9-10,13-14]. It has been reported that amitriptyline is one of the five substances that may cause problems on aquatic organisms in the future, based on accumulation and biodegradation in sewage treatment plants [6]. In addition, the classification of chronic aquatic toxicity of amitriptyline hydrochloride is indicated as very toxic effect, long-term persistence in the aquatic environment [15].

It has been reported that gilthead sea bream exposed to amitriptyline at doses of 0.2 µg/L and 10 µg/L for 7 days had residues in the brain and gill tissues, and 33 amitriptyline metabolites were encountered in gall, liver and plasma [10]. In another study, it was determined that sea bream exposed to 0.2 µg/L amitriptyline for 7 days had changes in the brain and liver metabolome [14].

In a study on investigating the effect of amitriptyline at 1, 10, 100 ng/L, 1, 10, 100 µg/L and 1 mg/L concentrations on zebrafish (*Danio rerio*) embryos, it was determined that both incubation time and body length in embryos were significantly reduced due to increasing concentrations of amitriptyline [2]. They also found that amitriptyline caused changes in physiological and biochemical parameters in zebrafish embryos [2]. In the mentioned study, it was stated that the negative effects of amitriptyline on fish embryos could be measured at concentrations as low as ng/L levels [2].

When the results of these studies are evaluated together, amitriptyline, which is used extensively in veterinary and medicine, can cause various problems on aquatic organisms with the increasing residue problem as a result of contamination to wastewater, however, it is seen that the studies in this field are quite limited. The aim of this study is to determine the biochemical effects of 0.2 µg/L, 10 µg/L, 100 µg/L and 1000 µg/L concentrations of amitriptyline antidepressant, which is reported to have long-term persistence in sea water and in the aquatic environment, on gilthead sea bream fish.



## 2. MATERIAL and METHODS

The fish, obtained from Çanakkale İda Gıda Tarımsal Üretim İç ve Dış Pazarlama A.Ş., were brought to Çanakkale Onsekiz Mart University Faculty of Marine Sciences and Technology Live Source Laboratory, where the study was carried out, for acclimatisation. At the end of the 2-week acclimatisation period, 150 *Sparus aurata* with an average weight of 20 ± 5 g (average mean ± S.D.) were used for the study. After an adaptation period, the fish were transferred into 15 tanks (180 L) as 10 for each group in triplicate. The natural sea water used for the experiment was transferred to the aquariums after the necessary filtration processes. The temperature, salinity and pH of the sea water was determined as 22±0.5°C, ‰26 and 8.04, respectively. Photoperiod was set to 14 hr:10 hr (light:dark). Required ethics committee approval was approved by Çanakkale Onsekiz Mart University Animal Experiments Local Ethics Committee with the decision numbered 2021/08-07.

### 2.1. Chemical Used in the Study and Its Application

Amitriptyline antidepressant was used in this study. For this purpose, a commercial preparation containing 28.30 mg of amitriptyline hydrochloride equivalent to 25.0 mg of amitriptyline was obtained. Dose range was determined and implemented in experimental aquariums as 0 µg/L(control), 0.2 µg/L, 10 µg/L, 100 µg/L and 1000 µg/L concentrations based on previous studies [2,10]. Water inlet and outlet were stopped in the aquariums for 14 days during the experiment.

On the $7^{th}$ and $14^{th}$ blood sampling days, fish were anesthetized with 20 mg/mL clove oil, which is a natural product and widely used [16]. Then, in order not to mix the blood with the mucous membrane, after thoroughly cleaning the posterior part of the anal fin with alcohol, approximately 500 µL of blood was collected by entering the caudal vein with an insulin injector without harming the fish. Blood samples were placed in serum tubes and centrifuged at 5000 g for 10 minutes. Obtained serum samples were stored at -80 °C until the time of biochemical analysis.

### 2.2. Biochemical Analysis

Biochemical analyzes of blood serum were performed spectrophotometrically using a commercial kit (Bioanalytic) used in fish experiments [17]. Glucose (GLU), albumin (ALB), globulin (GLO), total protein (TP), triglyceride (TG), cholesterol (CHO), Aspartate transaminase (AST), alanine aminotransaminase (ALT), alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) biochemical parameters were determined.

### 2.3. Statistical Analysis

SPSS v.17 package program (SPSS Inc., Chicago, IL, USA) was used to statistical analyze of all data obtained from this study. Tukey test was performed at 95% confidence level to determine the differences between the groups.

© Environmental Toxicology and Ecology
2022, Vol. 2 (1)
e-ISSN: 2757-9719

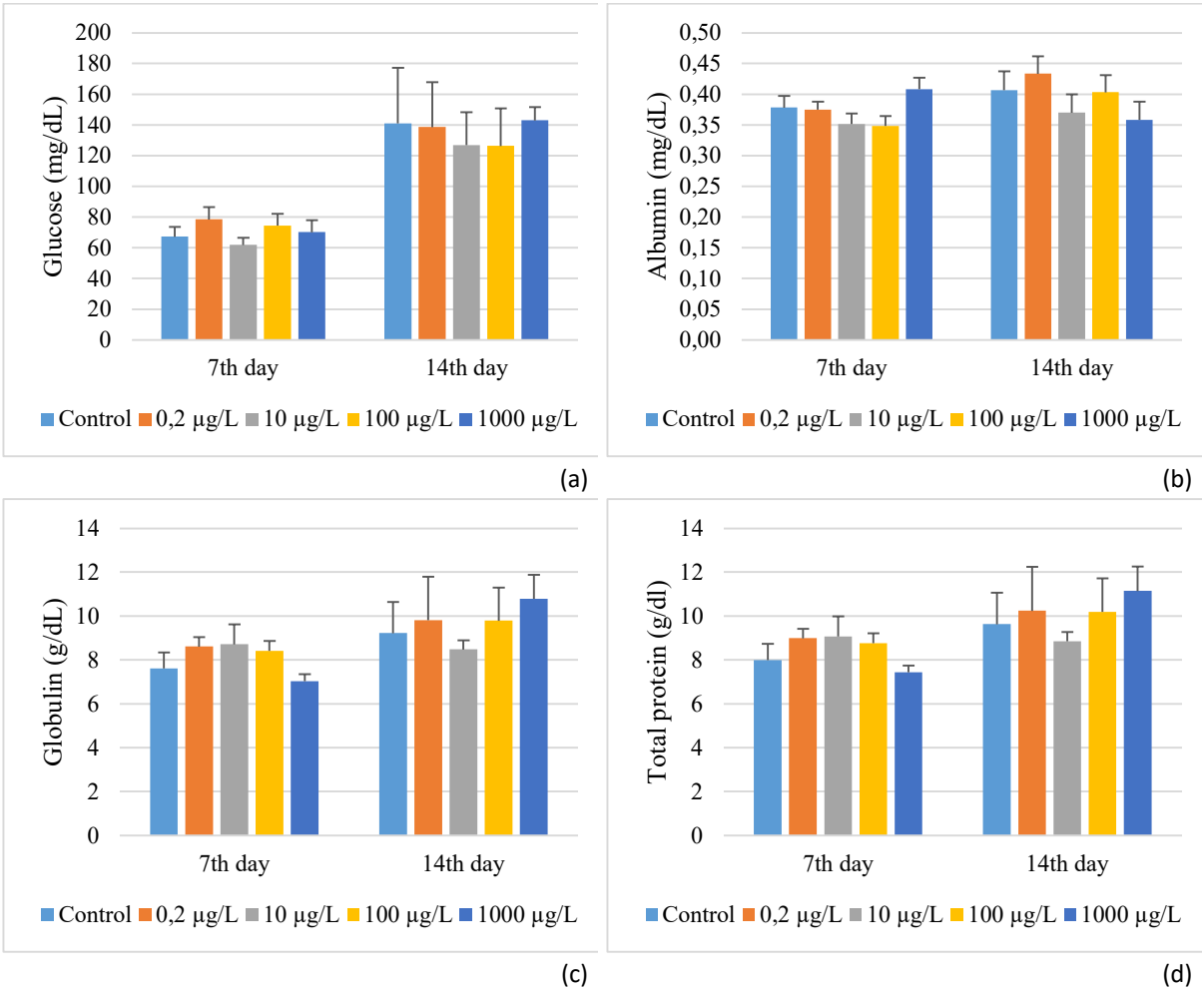
Research Article

## 3. RESULTS and DISCUSSION

It is known that blood parameters of fish are affected by various factors as health status, season, age, water quality variables, sex, genetic characteristics, nutrition, transportation, other environmental factors, sampling and laboratory analysis methods [18-20]. While amitriptyline can be found at low concentrations in aquatic environments, it has been reported in various studies that it causes damage to aquatic organisms even at these concentrations [2,7-12]. The aim of this study is to reveal the changes in the biochemical parameters of gilthead sea bream, caused by amitriptyline antidepressant.

At the end of the study, the changes in biochemical parameters of GLU, ALB, GLO, TP, TG, CHO, AST, ALT, ALP and LDH from biochemical analyzes are given in Figure 1, respectively.

In this study, it was determined that GLU levels did not differ significantly on the 7$^{th}$ and 14$^{th}$ days compared to the control (P>0.05) (Fig. 1a). The amount of GLU in the blood is the most important parameter that determines the stress status of fish [21-22]. It is known that increased GLU affects stress hormones, such as adrenaline, in muscle and liver [22-23]. It has been reported that persistent hyperglycemia often causes slow growth in fish [22,24].



© Environmental Toxicology and Ecology
2022, Vol. 2 (1)
e-ISSN: 2757-9719

Research Article

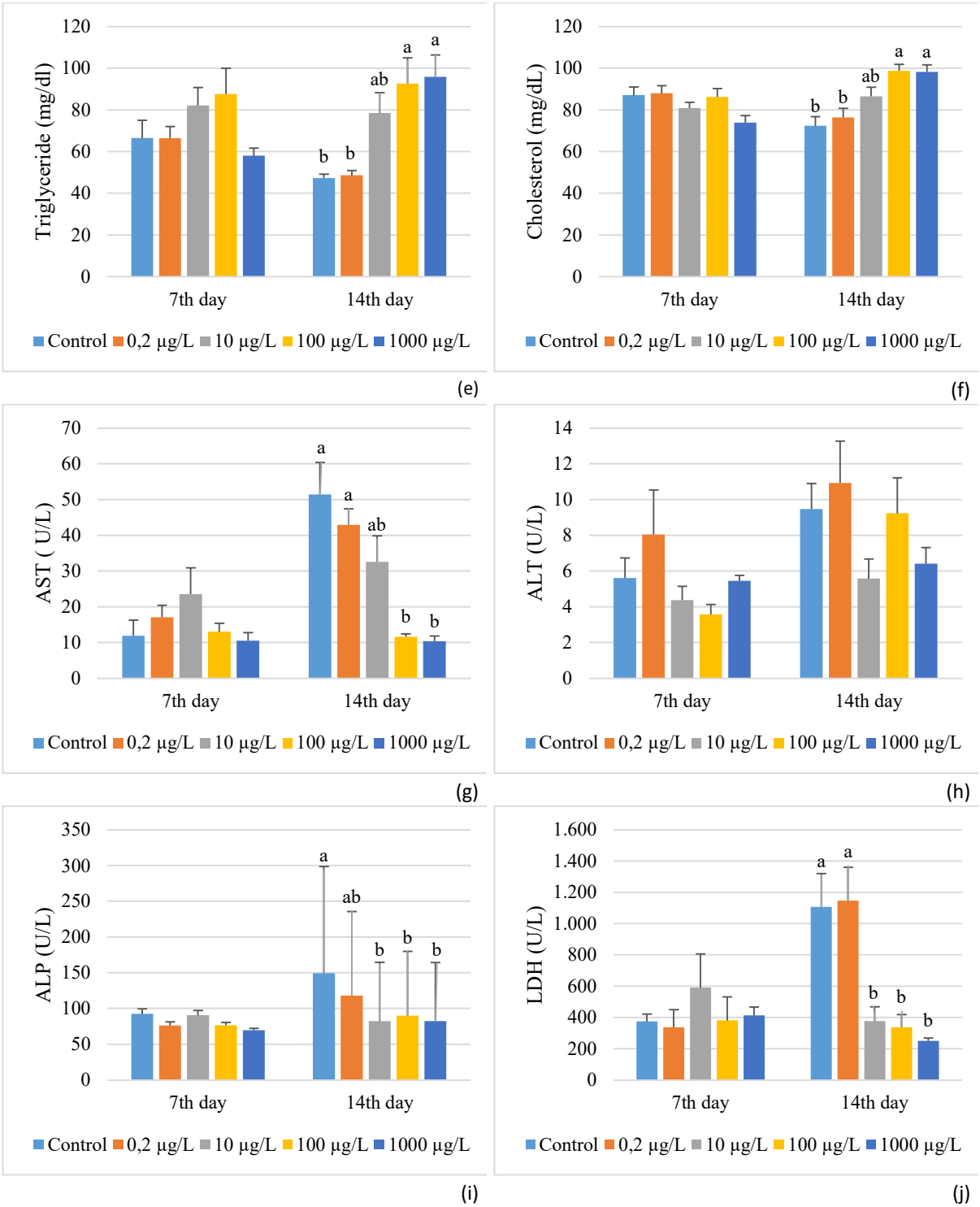



**Figure 1.** The serum parameters of gilthead sea bream exposed to amitriptyline on days 7th and 14th, a) GLU, b) ALB, c) GLO, d) TP, e) TG, f) CHO, g) AST, h) ALT, i) ALP and j) LDH (P<0,05)

According to our findings, there was no significant change in the GLO levels of gilthead sea bream exposed to amitriptyline compared to the control (Fig. 1c) (P>0.05). GLO, a protein that is insoluble in water but soluble in dilute salt water, is a simple protein that precipitates in a medium semi-saturated with ammonium sulfate or saturated with sodium and magnesium



sulfate [28]. In some immune system diseases, an increase in the amount of GLO occurs [28-29].

In the present study, no significant change was found between the groups in TP values on the 7th and 14th days (P>0.05) (Fig. 1d). TP in the blood is considered as an element of the non-specific immune system and provides information about the state of the immune system [22,27,30]. Serum protein is suppressed as a result of various stress sources and prolonged fasting conditions [21-22,26]. Therefore, the increase in TP will enable the fish to be more resistant to stress conditions.

Considering the TG values on day 14th of our study, it was determined that the doses of 100 µg/L and 1000 µg/L showed a significant increase compared to the control group (P<0.05) (Fig. 1e). With its high caloric value and low water content, TGs (triglycerides) are fatty acid esters of glycerol, where energy is actively stored in the fat storage [28,31]. There is a positive correlation between plasma TGs and CHO concentrations, which vary with age, gender, and diet [28,32]. TG values decrease in long-term fasting conditions [28,29].

In this study, there was no change in CHO values on the 7th day. A difference was detected in the 100 µg/L and 1000 µg/L dose groups compared to control and 0.2 µg/L doses on the 14th day and this difference was in the form of an increase (P<0.05) (Fig. 1f). CHO, a component of plasma membranes in all eukaryotic organisms, is essential for cell survival and growth in higher organisms. However, the buildup of CHO ester plaques can cause atherosclerosis, so excess CHO can be lethal. CHO is also a precursor to steroid hormones such as testosterone, progesterone, estradiol, and cortisol [33-34]. In a study on human CHO and fatty acid biosynthesis of antidepressant drugs, it was determined that antipsychotic drugs activate sterol regulatory element binding protein (SREBP) transcription factors in human and rat glial cells, resulting in upregulation of many downstream genes involved in CHO and fatty acid biosynthesis [35].

ALT, AST, ALP and LDH enzymes found in blood serum have been accepted as stress indicators and are widely used in the diagnosis of fish diseases and in the detection of tissue damage caused by environmental pollution [36]. As a result of this study, no change was observed in the AST, ALT, ALP and LDH values between all groups on the 7th day, while a decrease was observed in the AST, ALP and LDH values on the 14th day of the 100 µg/L and 1000 µg/L dose groups compared to the control group (P<0.05) (Fig. 1g, Fig. 1h, Fig. 1i, Fig.1j). These results showed that sea bream exposed to high concentrations of amitriptyline for 14 days became stressed. In a study of hematological and biochemical changes induced by the antidepressant amitriptyline in male rats, it has been reported that significant increases in ALP, AST, lipid profiles (CHO, TGs, LDL and HDL) in amitriptyline-treated rats compared to the control group [37].

Unlike our results (P>0.05), which found that amitriptyline caused significant changes in AST, ALP, LDH and cholesterol values in gilthead sea bream, in a study on examining the changes in biochemical parameters of trout (*Oncorhynchus mykiss*) as a result of contamination of sertraline antidepressant with water from food sources, no significant difference was found between the control and experimental groups for these parameters [38]. Similar to our results,



it was also stated that there was no dose-related change in GLU, ALB and TP values, the difference between the control and experimental groups was insignificant [38]. In a study on investigating the effect of amitriptyline on the liver of male rats, it was determined that high dose of amitriptyline increased affect the liver activity by increasing all liver enzymes due to the cytotoxic effects of amitriptyline [37,39].

## 1. CONCLUSIONS and FUTURE OUTLOOK

As a result, according to the findings obtained in this study, it was determined that there were significant changes in some serum biochemical parameters of fish exposed to amitriptyline antidepressant for 14 days. We think that there is a need to investigate the physiological, hematological and genotoxic effects of amitriptyline in fish in future studies.

***Acknowledgments***

Authors are grateful to İDA GIDA TARIMSAL ÜRETİM İÇ VE DIŞ PAZARLAMA A.Ş., Bülent SAVAŞ, İsmail AVCILAR and Irmak YAYIN for procure fish.

***Funding***

The author (s) has no received any financial support for the research, authorship or publication of this study.

***The Declaration of Conflict of Interest/Common Interest***

No conflict of interest or common interest has been declared by the authors.

***The Declaration of Ethics Committee Approval***

This study was conducted with the approval of the Animal Experiments Local Ethics Committee of Çanakkale Onsekiz Mart University, with the decision number 2021/08-07 dated 24/09/2021.

***The Declaration of Research and Publication Ethics***

The authors of the paper declare that they comply with the scientific, ethical and quotation rules of ETOXEC in all processes of the paper and that they do not make any falsification on the data collected. In addition, they declare that Environmental Toxicology and Ecology and its editorial board have no responsibility for any ethical violations that may be encountered, and that this study has not been evaluated in any academic publication environment other than Environmental Toxicology and Ecology.

## REFERENCES

[1] C. Barbui, M. Hotopf, "Amitriptyline v. the rest: still the leading antidepressant after 40 years of randomised controlled trials" Br J Psychiatry, vol. 178, pp. 129-144, Feb 2001, doi: 10.1192/bjp.178.2.129. PMID: 11157426.

[2] M. Yang, W. Qiu, J. Chen, J. Zhan, C. Pan, X. Lei, M. Wu, "Growth inhibition and coordinated physiological regulation of zebrafish (*Danio rerio*) embryos upon sublethal exposure to antidepressant amitriptyline". Aquat Toxicol., vol. 151, pp 68-76, Jun 2014

[3] K.A. Demin, T.O Kolesnikova., S.L. Khatsko, D.A. Meshalkina, E.V. Efimova, Y.Y. Morzherin, A.V. Kalueff, "Acute effects of amitriptyline on adult zebrafish: Potential relevance to antidepressant drug screening and modeling human toxidromes" Neurotoxicol Teratol., vol. 62, pp. 27-33, Jul 2017, doi: 10.1016/j.ntt.2017.04.002. Epub 2017 Apr 22. PMID: 28438663.

[4] V. Calisto, V.I. Esteves, "Psychiatric pharmaceuticals in the environment". Chemosphere, vol: 77 (10), pp. 1257–1274, 2009.

[5] M.R. Bautista-Ferrufino, M.D. Cordero, J.A. Sánchez-Alcázar, M. Illanes, A. Fernández-Rodríguez, P. Navas, M. de Miguel, "Amitriptyline induces coenzyme Qdeficiency and oxidative damage in mouse lung and liver" Toxicol. Lett., vol. 204 (1), pp. 32–37, 2011.

[6] I. M. Sebastine, R. J. Wakeman. "Consumption and environmental hazards of pharmaceutical substances in the UK." Process Safety and Environmental Protection vol. 81.4, pp. 229-235, 2003.

[7] A. Lajeunesse, C. Gagnon, S. Sauvé, "Determination of Basic Antidepressants and Their N-Desmethyl Metabolites in Raw Sewage and Wastewater Using Solid-Phase Extraction and Liquid Chromatography−Tandem Mass Spectrometry". Anal. Chem., vol. 80 (14), pp. 5325–5333, 2008, doı: 10.1021/ac800162q

[8] D. R. Baker, B. Kasprzyk-Hordern, "Multi-residue analysis of drugs of abuse in wastewater and surface water by solid-phase extraction and liquid chromatography– positive electrospray ionisation tandem mass spectrometry". J. Chromatogr., vol. 1218 (12), pp. 1620–1631, 2011, doı: 10.1016/j.chroma.2011.01.060

[9] H. Ziarrusta, L. Mijangos, A. Prieto, N. Etxebarria, O. Zuloaga, M. Olivares, "Determination of tricyclic antidepressants in biota tissue and environmental waters by liquid chromatography-tandem mass spectrometry". Anal. Bioanal. Chem., vol., 408 (4), pp. 1205–1216, 2016. doı: 10.1007/s00216-015-9224-y.

[10] H. Ziarrusta, L. Mijangos, U. Izagirre, M.M. Plassmann, J.P. Benskin, E. Anakabe, M. Olivares, O. Zuloaga, "Bioconcentration and biotransformation of amitriptyline in gilthead bream". Environmental science & technology, vol. 51(4), pp. 2464-2471, 2017.

[11] P. P. Fong, A. T. Ford, "The biological effects of antidepressants on the molluscs and crustaceans: A review". Aquat. Toxicol., vol. 151, pp. 4−13, 2014.

[12] L. Minguez, E. Farcy, C. Ballandonne, A. Lepailleur, A. Serpentini, J-M. Lebel, R. Bureau, M-P. Halm-Lemeille, "Acute toxicity of 8 antidepressants: What are their modes of action?" Chemosphere, vol. 108, pp. 314−319, 2014.



[13] S.L. Klosterhaus, R. Grace, M.C. Hamilton, and D. Yee, "Method validation and reconnaissance of pharmaceuticals, personal care products, and alkylphenols in surface waters, sediments, and mussels in an urban estuary" Environment international, vol. 54, pp.92-99, 2013.

[14] H. Ziarrusta, A. Ribbenstedt, L. Mijangos, S. Picart-Armada, A. Perera-Lluna, A. Prieto, U. Izagirre, JP Benskin, M. Olivares, O. Zuloaga, N. Etxebarria, "Amitriptyline at an Environmentally Relevant Concentration Alters the Profile of Metabolites Beyond Monoamines in Gilthead Bream". Environ Toxicol Chem., vol. 38(5): pp. 965-977, May 2019. doi: 10.1002/etc.4381. Epub 2019 Apr 2. PMID: 30702171.

[15] https://assets.lgcstandards.com/sys-master%2Fpdfs%2Fh17%2Fhb6%2F10373775786014%2FSDS_BP+016_ST-WB-MSDS-3547340-1-1-1.PDF (Erişim Tarihi: 01.03.2022)

[16] M. Iversen, B. Finstad, R. S. McKinley, R.A. Eliassen, "The efficacy of metomidate, clove oil, Aqui-S™ and Benzoak® as anaesthetics in Atlantic salmon (*Salmo salar* L.) smolts, and their potential stress-reducing capacity". Aquaculture, vol. 221: pp. 549-566, 2003.

[17] S. Yılmaz, S. Ergün, "Effects of garlic and ginger oils on hematological and biochemical variables of sea bass *Dicentrarchus labrax"*. Journal of Aquatic Animal Health, vol. 24: pp. 219-224, 2012.

[18] C.E. Bond,. "Circulation, respiration, and the gas bladder". In C. E. Bond (ed.) Biology of Fishes. W. B Saunders Company Press, London, UK, 1979, pp. 347-374.

[19] G. Rey Vázquez, G.A. Guerrero, "Characterization of blood cells and hematological parameters in *Cichlasoma dimerus* (Teleostei, Perciformes)". Tissue and Cell, vol. 39, pp. 151-160, 2007.

[20] M. Kanyılmaz, N. Tekellioğlu, "Effects of dietary zeolite levels on some blood parameters of gilthead seabream (*Sparus aurata*) juveniles". Journal of Aquaculture Engineering and Fisheries Research, vol. 2(3), pp. 119-127, 2016.

[21] D.G. McDonald, C.L. Milligan, "Chemical Properties of the Blood". Academic Press, Inc., California. pp. 56-113, 1992.

[22] O. Demir, "Tilapia Oreochromis mossambicus (Peters, 1852) Balıklarının Yemlerinde Balık Yağı Yerine Yerfıstığı Yağı Kullanılmasının Büyüme Performansı, Yem Değerlendirme, Vücut Kompozisyonu Ve Serum Biyokimyasına Etkisi", Muğla Sıtkı Koçman Üniversitesi Fen Bilimleri Enstitüsü Su Ürünleri Mühendisliği Anabilim Dalı, 2019, Muğla.

[23] J.D. Morgan, G.K. Iwama, " Measurements of Stressed States in the Field". Cambridge University Press, Cambridge. pp. 247-270, 1997.

[24] T.W. Moon, "Glucose Intolerance in Teleost Fish: Fact or Fiction?". Comp Biochem Phys B, vol. 129: pp. 243-249, 2001

[25] G.G. Gunter, L. L Sulya, B. E. Box, "Some Evolutionary Patterns in Fishes' Blood". Biological Bulletin. pp. 121. 1961, 10.2307/1539434.

[26] G.H. Satchell, "Physiology and Form of Fish Circulation" Cambridge University Press, Cambridge. 1991, pp. 235.



[27] G.F.Wiegertjes, R.J.M. Stet, H.K. Parmentier, W.B. Van Muiswinkel, "Immunogenetics of disease resistance in Changes in biochemical, histological and specific immune parameters 151 fish; a comparable approach". Dev. Comp. Immunol. 20, pp. 365–381, 1996.

[28] E. Ş. Çelik, S. Bilgin, "Bazı balık türleri için kan protein ve lipidlerinin standardizasyonu". Erciyes Üniversitesi Fen Bilimleri Enstitüsü Fen Bilimleri Dergisi, vol. *23*(1), pp. 215-229, 2007.

[29] S. Mayer, "A review of the scientific justifications for Maintaining cetaceans in captivity, (edit. By Frances Clarke), A report for the whale and dolphin conservation society (WDCS)", 35 p., 1998

[30] B. Magnadottir, "Innate Immunity of Fish (overview)". Fish Shellfish Immun, vol. 20(2): pp. 137–151, 2006.

[31] M.F. Laker, "Klinik Biyokimya" (Ulukaya, E., Tokullugil A., Gür, E., Dirican, M., Tuncel, P., Ulukaya, E., vd. çev.), s. 343, Uludağ Üniv. Tıp Fak. Biyokimya ABD., Nobel Tıp Kitapevleri Ltd.Şti., İstanbul, 1996.

[32] H. Karagül, A. Altıntaş, U.R. Fidancı, T. Sel, "Klinik Biyokimya", s. 430, Cilt 1, Medisan Yayın Evi, Yayın No: 45, Ankara, 2000.

[33] L. Stryer, "Biochernistry", Freeman and Company, San Francisco, pp 470-476. 1975.

[34] M. Atamanalp, M. Yilmaz, H.İ. Haliloğlu, "Comparing Serum Cholesterol Types and Levels of Three Trout Species (*Salvelinus alpinus, Salmo trutta fario and Oncorhynchus mykiss*)", Journal of Applied Animal Research, vol. 23:2, pp. 223-226, 2003. doi: 10.1080/09712119.2003.9706425

[35] M. B. Raeder, J. Fernø, M.Glambek, C.Stansberg, & V. M. Steen, "Antidepressant drugs activate SREBP and up-regulate cholesterol and fatty acid biosynthesis in human glial cells." Neuroscience letters, 395(3), 185-190, 2006.

[36] Ö. Fırat, H.Y. Cogun, T.A. Yüzereroğlu, G. Gök, Ö. Fırat, F. Kargin, Y. Kötemen, "A comparative study on the effects of a pesticide (cypermethrin) and two metals (copper, lead) to serum biochemistry of Nile tilapia, *Oreochromis niloticus*". Fish Physiology and Biochemistry, vol. *37*(3), pp. 657-666, 2011

[37] A. El Atrash, E. Tousson, A. Gad, & S.Allam, "Hematological and biochemical changes caused by antidepressants amitriptyline induced cardiac toxicity in male rats". Asian Journal of Cardiology Research, 23, 1-6, 2019.

[38] J. Vaclavik, P. Sehonova, N. Hodkovicova, L. Vecerkova, J. Blahova, A. Frangi, P. Marsalek, J. Mares, F. Tichy, Z. Svobodova, C. Faggio, "The effect of foodborne sertraline on rainbow trout (*Oncorhynchus mykiss*)". Science of the Total Environment, vol. 708, 135082, 2020

[39] M. Afify, M.D.E. Abd Elmaksoud, T. Mosa, M. Elshaer, N. Kotb, "Differential effects of amitriptyline treatment on testicular and liver functions". New York Science Journal,3(3): pp. 10-182010