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Molecular Mechanism of the Protective Effect of Tianeptine Against Ketamine-Induced Cardiac Injury in Rats

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***SUMMARY*. Ketamine is a short-acting anesthetic drug that is derived from phencyclidine. Ketamine is used to treat depression and chronic pain disorders, as well as for anesthesia, analgesia, and sedation. Ketamine's sympathomimetic characteristic causes cardiotoxicity. The pathophysiology of ketamine's harmful impact has been linked to reactive oxygen species (ROS) and proinflammatory cytokines such as interleukin 1 beta (IL-1), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α). Tianeptine is an antidepressant that works similarly to tricyclic antidepressants. According to studies, tianeptine reduces the production of proinflammatory cytokines such as ROS, IL-1, IL-6, and TNF-α. Tianeptine has a sympatholytic action as well. All of this evidence suggests that tianeptine might help to reduce ketamine cardiotoxicity. The goal of our research is to use biochemical and histological techniques to see how tianeptine affects ketamine-induced cardiotoxicity in rats.**

RESUMEN. La ketamina es un fármaco anestésico de acción corta que se deriva de la fenciclidina. La ketamina se usa para tratar la depresión y los trastornos de dolor crónico, así como para la anestesia, analgesia y sedación. La característica simpaticomimética de la ketamina causa cardiotoxicidad. La fisiopatología del impacto dañino de la ketamina se ha relacionado con especies reactivas de oxígeno (ROS) y citocinas proinflamatorias como la interleucina 1 beta (IL-1), la interleucina 6 (IL-6) y el factor de necrosis tumoral alfa (TNF-α). La tianeptina es un antidepresivo que funciona de manera similar a los antidepresivos tricíclicos. Según estudios, la tianeptina reduce la producción de citocinas proinflamatorias como ROS, IL-1, IL-6 y TNF-α. La tianeptina también tiene una acción simpaticolítica. Toda esta evidencia sugiere que la tianeptina podría ayudar a reducir la cardiotoxicidad de la ketamina. El objetivo de nuestra investigación es utilizar técnicas bioquímicas e histológicas para ver cómo la tianeptina afecta la cardiotoxicidad inducida por ketamina en ratas.

INTRODUCTION

Ketamine is a phencyclidine derivative that was created as a short-acting alternative anesthetic in the 1960s [1]. The fact that ketamine produces dissociative anesthesia is an essential characteristic [2]. Ketamine is frequently referred to be a "one-of-a-kind drug" because of its hypnotic, analgesic, and amnesic characteristics [3]. Ketamine has been utilized to treat chronic pain syndromes, anesthesia, analgesia, and sedation until recently. Its unique pharmacodynamic characteristics, on the other hand, have increased its usage [4].

KEY WORDS: cardiotoxicity, ketamine, tianeptine.

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In treatment-resistant individuals, clinical trials have demonstrated that a subanesthetic dosage of ketamine produces fast and persistent antidepressant benefits [5]. Furthermore, because of its pleasant impact, its misuse is steadily rising [6]. The main mechanism of ketamine's pharmacological action is the blocking of N-methyl-D-aspartate (NMDA); other mechanisms include opioid receptor blockage, gamma aminobutyric acid suppression, and changes in central nervous system (CNS) and peripheral autonomic neurotransmitter levels [7]. Because it decreases catecholamine reuptake, ketamine has sympathomimetic effects [8]. This characteristic of ketamine has been identified as one of the reasons of cardiotoxicity [9]. According to studies, ketamine induces oxidative cardiac injury in rats by increasing catecholamine levels such as adrenaline (ADR), noradrenaline (NDR), and dopamine (DOP) [10-12]. In addition, ketamine-related oxidative stress was observed to raise blood creatine kinase-MB (CK-MB) and cardiac troponin-I (TP I) levels [13]. Proinflammatory cytokines such as reactive oxygen species (ROS), interleukin 1 (IL-1) and interleukin 6 (IL-6) as well as tumor necrosis factor alpha (TNF-α) have also been implicated in the pathophysiology of ketamine-related cell damage [14].

Tianeptine is an unusual antidepressant that resembles tricyclic antidepressants in structure [15]. At the same time, tianeptine is an agonist for the mu-opioid receptor [16]. It enhances the absorption of serotonin 5-hydroxytryptamine; 5-HT in the brain and decreases stress-induced dendritic atrophy [17]. In comparison to selective serotonin reuptake inhibitors and tricyclic antidepressants, it has anxiolytic benefits and has less adverse effects [18]. Tianeptine has also been proven to be beneficial in treating depression that is resistant to therapy [19]. Previous research has found that tianeptine has antioxidant action and protects stomach tissue from oxidative damage [20]. It's also been discovered that tianeptine has anti-inflammatory effects [21]. It has been observed that tianeptine has an anti-inflammatory impact by lowering the production of proinflammatory cytokines such as reactive oxygen species (ROS), interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF-α) [22]. One of tianeptine's most notable side effects is that it lowers high plasma NDR levels and suppresses neural sympathetic hyperactivity [23]. It's even been proven that tianeptine lowers ADR and NDR levels, which rise with stress [24]. All of these evidence from the literature suggests that tianeptine may be useful in decreasing ketamine cardiotoxicity. As a result, the goal of our research is to use biochemical and histological approaches to examine the effect of tianeptine on ketamine-induced cardiotoxicity in rats.

MATERIALS AND METHODS

Animals

In the experiment, 18 albino male Wistar rats weighing between 280 and 289 g were used. All of the animals were received from the Medical Experimental Application and Research Center of Atatürk University. Before the trial, the animals were kept and fed in groups at room temperature (22 °C).

Chemicals

The ketamine utilized in the experiment came from Pfizer Limited Company in Turkey, while the tianeptin came from Servier Istanbul (Turkey).

Animal Groups

Animals were divided into three groups as ketamine alone (KG), Ketamine+Tianeptine administered (KTG) and healthy group (HG).

Experiment procedure

The CTG (n-6) group was given tianeptine at a dosage of 5 mg/kg orally by gavage into the stomach in this research. The same procedure was used to apply an equal volume of distilled water as a solvent in the KG and HG groups. 30 mg/kg ketamine was administered intraperitoneally (ip) into the KG and KTG group rats one hour after they were given tianeptine and distilled water. For 30 days, this process was done once a day. On day 31, blood samples were collected from the animals' tail veins, and their hearts were extracted shortly after they were murdered by decapitation. Blood samples were examined for CK-MB and TP-I levels. Malondialdehyde (MDA), total glutathione (tGSH), TNF-α, IL-1, and IL-6 parameters were all measured in cardiac tissues. Histopathological examinations of heart tissues were also performed. All of the HG and KTG groups' experimental findings were compared to those of the KG group.

Biochemical analysis

Tissue MDA and tGSH determination

The spectrophotometric measurement of the absorbance of the pink colored complex produced by thiobarbituric acid (TBA) and MDA utilized by Ohkawa *et al.* as the basis for MDA tests [25]. The tGSH was measured using the method described by Sedlak & Lindsay [26].

TNF-α, IL-1β, and IL-6 analysis

After weighing the samples and cutting all of the tissues, we quickly frozen them with liquid nitrogen and homogenized them with a pestle and mortar; after melting, we kept the samples at 2-8 ºC. We added 1/10 (w/v) PBS (pH 7.4), vortex for 10 s, centrifuged for 20 min at 10000 × *g*, and carefully collected the supernatants. The levels of Tumor Necrosis Factor (TNF-; ng/L), Interleukin 1 beta (IL-1beta; pg/L), and Interleukin 6 (IL-6; ng/L) were determined using an ELISA kit provided by Eastbiopharm Co Ltd, China.

CK-MB determination

The Roche/Hitachi cobas c 701 system was used to test creatine kinase MB in plasma collected from animals. All phases of the immunologic UV test were completed in accordance with the method using ready-made test reagents. The CK-MB isoenzyme is made up of two subunits: CK-M and CK-B, each with an active site. With the use of CK-M specific antibodies, the catalytic performance of the CK-M subunits in the sample is decreased to 99.6%, without affecting the CK-B subunits. The residual CK-B activity, which is half of the CK-MB activity, is determined using the total CK technique.

TP-I determination

Troponin I levels in animal plasma were evaluated using the ELFA (Enzyme-Linked Fluorescent Assay) technique with the VIDAS Troponin I Ultra kit. Using the test reagents included in the kit, all phases of the test were completed automatically in the VIDAS device. The material was transferred to a well containing alkaline phosphatase-labeled anti-cardiac troponin I antibodies (conjugate). To allow the antigen to bind to troponin I and conjugate connected to the inner wall of the solid phase binder, the sample conjugate mixture was removed and released into the solid phase donor. Washing was used to eliminate any unbound material. The conjugate enzyme catalyzes the hydrolysis of the substrate, 4-methyl umbelliferyl phosphate, to produce 4-methyl umbeliferone, a product with a 450 nm fluorescence. Fluorescence intensity is proportional to the amount of antigen present in the sample.

Histopathological method

The heart tissues of the rats were necropsied and preserved in a 10% neutral formalin solution. Following normal alcohol-xylol follow-up procedures, tissues were placed in paraffin blocks. In terms of hemorrhage, degeneration, and mononuclear cell infiltrations, 5 sections on slides were stained with hematoxylin-eosin and rated as absent (-), mild (+), moderate (++), and severe (+++).

Statistical analysis

The Statistical Package for Social Sciences for Windows version 22.0 was used to conduct statistical analyses (IBM Corp. Released 2013 IBM SPSS Statistics for Windows, Version 22.0. IBM Corp. Armonk, NY, USA). For continuous variables, the mean and standard deviation (SD) were recorded. The one-way analysis of variance (ANOVA) test was used to evaluate the significance of differences between groups, followed by Tukey's analysis. A p value of less than 0.05 was deemed significant.

Histopathological statistical analysis

The data was analyzed using the SPSS 20.0 software. The Kruskal Wallis test, a nonparametric test, was used to assess the difference between the groups, as was the Mann Whitney U test for the group that caused the difference ($p < 0.05$).

RESULTS

Biochemical results

As shown in Fig. 1, ketamine significantly increased the amount of MDA in the heart tissue of rats compared to the HG ($p < 0.001$). Tianeptine significantly inhibited the increase of MDA by ketamine in the heart tissue ($p < 0.001$). There was no significant difference in the MDA levels between the KTG and HG ($p > 0.05$). The levels of tGSH significantly decreased in the ketamine group compared to HG ($p < 0.001$). Tianeptine

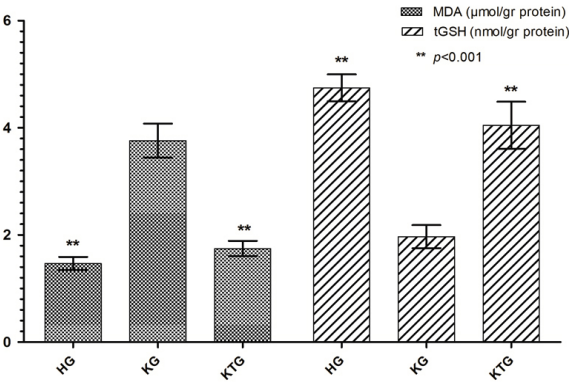

Figure 1. The effects of tianeptine on MDA and tGSH levels in the heart tissues of rats given ketamine. Bars are mean ± SD. The ketamine group (KG) is compared with the HG and KTG groups. MDA: malondialdehyde; tGSH: total glutathione; HG: healthy group; KG: ketamine group; KTG: ketamine + tianeptine group.

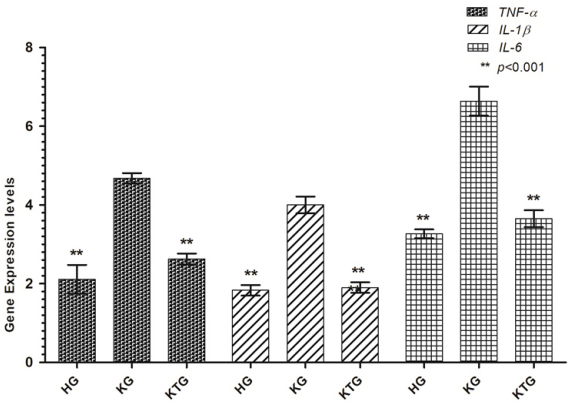

Figure 2. The effects of tianeptine on TNF-α, IL-1β and IL-6 levels in heart tissues of rats given ketamine. Bars are mean±SD. The ketamine group (KG) is compared with the HG and KTG groups. TNF-α: Tumor necrosis factor-alpha; IL-1β: interleukin-1beta; IL-6: interlekin-6; HG: healthy group; KG: ketamine group; KTG: ketamine+tianeptine group.

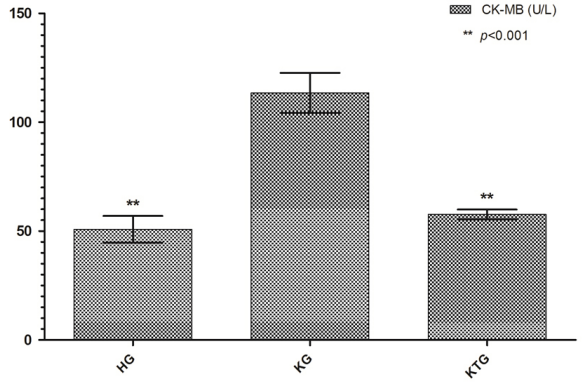

Figure 3. The effects of tianeptine on CK-MB serum levels of rats given ketamine. Bars are mean ± SD. The ketamine group (KG) is compared with the HG and KTG groups. CK-MB: creatine kinase-MB; HG: healthy group; KG: ketamine group; KTG: ketamine + tianeptine group.

significantly inhibited the decrease of tGSH levels by ketamine ($p < 0.001$; Fig. 1).

TNF-α, IL-1β, and IL-6 gene expression levels were found to be higher in the heart tissue of the rats that received ketamine, compared to the KTG and HG ($p < 0.001$; Fig. 2). The differences between the KTG and HG in terms of IL-1β were not

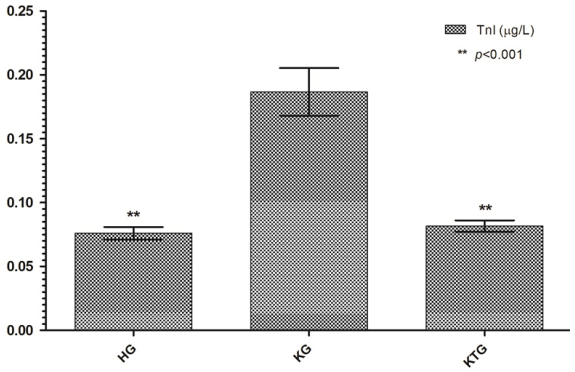

Figure 4. The effects of tianeptine on TnI serum levels of rats given ketamine. Bars are mean ± SD. The ketamine group (KG) is compared with the HG and KTG groups. TnI: Troponin I; HG: healthy group; KG: ketamine group; KTG: ketamine + tianeptine group.

statistically significant ($p > 0.05$) Ketamine caused a significant increase in the levels of TNF-α, IL-1β and IL-6. Tianeptine significantly inhibited the increase of TNF-α, IL-1β, and IL-6 levels in the heart tissues of rats ($p < 0.001$; Fig. 2).

CK-MB levels were found to be higher in the ketamine group, compared to other groups ($p < 0.001$; Fig. 3). We did not find statistically significant difference between the HG and KTG groups in terms of CK-MB ($p > 0.05$). Tianeptine prevented the increase of serum CK-MB levels of rats.

As shown in Fig. 4, ketamine significantly increased the levels of TnI of rats compared to the HG ($p < 0.001$). Tianeptine significantly inhibited the increase of TnI by ketamine. ($p < 0.001$). There was no valuable difference in the TP-I levels between the KTG and HG ($p > 0.05$).

Histopathological results

Statistically significant differences were found between the groups in histopathological examinations (Table 1, $p < 0.05$).

The histological appearance of the control group was normal. While hemorrhage and mononuclear cell infiltrations were seen in the ketamine group, it was observed that in the ketamine + tianeptine group, hemorrhage was decreased to a moderate level and mononuclear cell infiltra-

Groups	Hemorrhage	Degeneration	Mononuclear cell infiltration
Control	0,16 ± 0,40 [a]	0,00 ± 0,00 [a]	0,16 ± 0,40 [a]
Ketamin	2,83 ± 0,40 [b]	1,83 ± 0,40 [b]	2,83 ± 0,40 [b]
Ketamin + Tianeptin	2,16 ± 0,40 [c]	0,83 ± 0,75 [c]	1,00 ± 0,00 [c]

Table 1. Histopathological differences between the groups. a,b,c show the difference between the groups ($p < 0.05$).

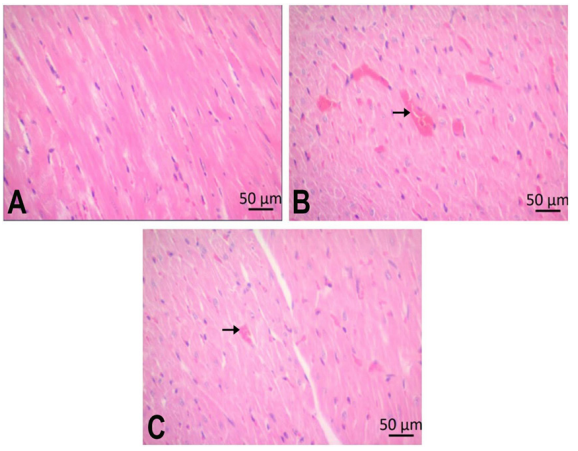

Figure 5. **A**. Control Group. Normal histological appearance. **B**. Ketamine group. Severe haemorrhage (arrow). **C**. Ketamine+Tianeptine group. Moderate haemorrhage (arrow). H-E.

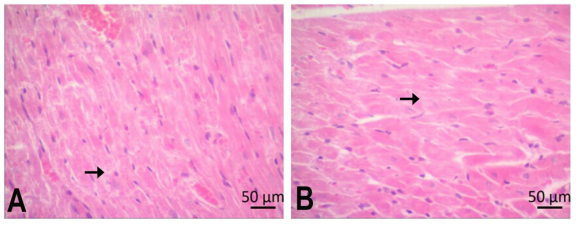

Figure 6. **A**. Ketamine group. Moderately degenerative myocytes (arrow). **B**. Ketamine + Tianeptine group. Mildly degenerative myocytes (arrow). H-E.

tions were reduced to a mild level. Furthermore, myocyte denerative alterations were moderate in the ketamine group and mild in the ketamine + tianeptine group (Figs. 5-7).

DISCUSSION

In general anesthesia, ketamine is commonly used as an induction agent. Furthermore, because it provides sedation in a short period of time and has clinical benefits such as minimally depressing respiration and circulation, providing hemodynamic stability, rapid recovery from anesthesia, and analgesic effect, it has become increasingly popular in recent years in both emergency and intensive care patients [27]. As a result of the quest for medicines with a quick onset and minimal side effects, the scientific community today has indicated that ketamine may be useful in the treatment of acute symptoms in the treatment of depression [28]. Because ketamine has so many therapeutic uses, it is unavoidable that it has some side effects. Although the effects on

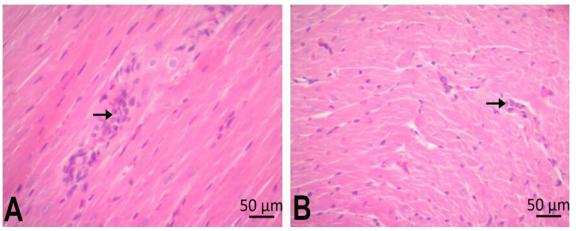

Figure 7. **A**. Ketamine group. Severe mononuclear cell infiltrates (arrow). **B**. Ketamine + Tianeptine group. Mild mononuclear cell infiltrates (arrow). H-E.

the central nervous and urinary systems are well-known, cardiac side effects have been observed as well [29]. Ketamine has been shown to enhance inflammation and oxidative stress in experimental tests by inducing a rise in micro RNA-208 an expression [30]. Ketamine has been shown to alter the electrophysiological properties of the heart by causing significant ventricular myocardial apoptosis, fibrosis, and sympathetic sprouting, as well as increasing the susceptibility to malignant arrhythmia and causing sudden cardiac death, according to the literature [31]. The toxic impact mechanism of ketamine administration, which may induce an increase in oxidative stress in the muscles of the heart and bronchial tissues as a result of increased adrenaline and noradrenaline levels, was observed in another experimental research [12].

Çömez *et al.* [32] discovered an increase in oxidative and inflammatory indices such as MDA, TNF-α, and IL-6 gene expression NF-kB in the ketamine-administered group in their investigation on ketamine, an NMDA blocker. The rise in CK-MB and Troponin levels was also interpreted as a cardiotoxic impact. They discovered that while ketamine lowered antioxidant parameters, it raised oxidant parameters and elevated CK-MB and TP-I levels in another investigation in the literature [33]. Long-term ketamine treatment boosted oxidants like MDA and MPO while decreasing antioxidants like SOD and decreased GSH, according to Ahiskalioglu *et al.* [13]. In line with the above-mentioned literature, we viewed the rise in TP-I and CK-MB levels in the ketamine-administered group as a cardiotoxic impact in our investigation. We discovered high amounts of MDA, which is an oxidant parameter, as well as TNF-, IL-1, IL-6, and NF-κβ, which are inflammatory markers. At the same time, the antioxidant tGSH levels were shown to be lower. As a consequence, we hypothesized that oxidative stress and inflammation were to responsible for ketamine-induced cardiotoxicity.

Tianeptine is a medication that enhances serotonin uptake and is being used to treat depression [34]. Its antidepressant properties are demonstrated by a reduction in serotonin permeability in the synaptic cleft. While raising plasma dopamine levels, it has been found to induce a significant decrease in noradrenaline and serotonin levels while having no impact on systolic blood pressure or heart rate [35]. When these data are combined with the literature, it is clear that tianeptine has an anti-inflammatory impact. It has been observed that it reduces the production of proinflammatory cytokines such as ROS, IL-1, IL-6, and TNF-α, and inflammation lies at the heart of its actions on microglia [21,22]. Chronic tianeptine therapy reduced LPS-induced TNF-α production in the spleen and plasma, and it had neuroprotective effects via shifting the central balance between pro and anti-inflammatory cytokines IL-1b/IL-10, according to another research [36]. In our research, we discovered that tianeptine decreased the increase in MDA in the heart tissue produced by ketamine and prevented the reduction in tGSH. We also discovered that it prevented TNF-α, IL-1, and IL-6 levels from rising. In line with the literature, we found that the ketamine-induced increases in CK-MB and TP-I levels were reversed in the tianeptine-administered group. While the presence of hemorrhage and mononuclear cell infiltrations in the ketamine group in the heart tissue, which was also examined histopathologically, was consistent with the increase in inflammation; Determining that hemorrhage decreased to moderate level and mononuclear cell infiltrations to mild level in the ketamine+tianeptine group, in other words, the decrease in oxidant activities, increases in antioxidant and anti-inflammatory activities may have resulted from the antioxidant and anti-inflammatory effects of tianeptine.

CONCLUSION

In conclusion, we believe that the cardiotoxic side effects that might occur with repeated doses of ketamine, which has recently been utilized in non-operating rooms, can regress acute symptoms in a short period of time, particularly in the treatment of severe depression. If clinical trials back it up, the combination of ketamine and tianeptine can be administered rapidly, effectively, and safely in the treatment of severe depression.

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REFERENCES

1. Hashimoto, K. (2020) *Biochem. Pharmacol.* **177**: 113935
2. Gould, T.D., C.A. Zarate Jr. & SM Thompson. (2019) *Annu. Rev. Pharmacol. Toxicol.* **59**: 213-36.
3. Sinner, B. & B.M. Graf (2008) *Handb. Exp. Pharmacol.* **182**: 313-33.
4. Mihaljević, S., M. Pavlović, K. Reiner & M. Ćaćić (2020) *Psychiatr Danub.* **32**(3-4): 325-33.
5. Zanos. P. & T.D. Gould (2018) *Mol. Psychiatry* **23**(4): 801-11.
6. Sassano-Higgins, S., D. Baron, G. Juarez, N. Esmaili & M. Gold (2016) *Depress. Anxiety* **33**(8): 718-27.
7. Erstad, B.L. & A.E. Patanwala (2016) *J. Crit. Care* **35**: 145-9.
8. Green, S.M., & J. Li (2000) *Acad. Emerg. Med.* **7**(3): 278-81.
9. White, J.M. & C.F. Ryan (1996) *Drug Alcohol Rev.* **15**(2): 145-55.
10. Aksoy, M., I. Ince, A. Ahiskalioglu, A. Dostbil, M. Celik, M.I. Turan, *et al.* (2014) *Med. Hypotheses* **83**(1): 103-7.
11. Hašková. P., L. Koubková, A. Vávrová, E. Macková, K. Hrušková, P. Kovaříková, *et al.* (2011) *Toxicology* **289**(2-3): 122-31.
12. Ahiskalioglu, E.O., P. Aydin, A. Ahiskalioglu, B. Suleyman, U. Kuyrukluyildiz, N. Kurt, *.et al.* (2018) *Arch. Med. Sci.* **14**(3): 645-54.
13. Ahiskalioglu, A., I. Ince, M. Aksoy, E.O. Ahiskalioglu, M. Comez, A. Dostbil, *et al.* (2015) *Cardiovasc. Toxicol.* **15**(4): 336-44.
14. Cui, L., X. Jiang, C. Zhang, D. Li, S. Yu, F. Wan, *et al.* (2019) *Biosci. Rep.* **39**(10): BSR20190595.
15. Badea, A., R. Ghosh, K.L. Lynch & A.H.B Wu (2021) *J. Anal. Toxicol.* **45**(3): e8-e9.
16. Karim, A. & C. Ioannou (2020) *Psychiatr. Pract.* **26**(2): 146-8.
17. Wagstaff, A.J., D. Ormrod & C.M. Spencer (2001) *CNS Drugs* **15**(3): 231-59.
18. Abdullatef, O.A., S. Morshedy, Y.M. Khalifa & W. Talaat (2021) *Spectrochim. Acta A* **251**: 119412.
19. Brink, C.B., B.H. Harvey & L. Brand (2006) *Recent Pat CNS Drug Discov.* **1**(1): 29-41.
20. Suleyman, H., E. Cadirci, A. Albayrak, B. Polat, Z. Halici, F. Koc, *et al.* (2009) *Chem. Biol. Interact.* **180**(2): 318-24.
21. Koç, F., H. Süleyman & B. Polat (2007) *Eurasian J. Med.* **39**: 169-72.
22. Ślusarczyk, J., E. Trojan, K. Głombik, A. Piotrowska, B. Budziszewska, M. Kubera, *et al.* (2018) *Int J Mol Sci.* **19**(7): 1965.
23. Lechin, F. & B. Van der Dijs (2017).*Open Med. J.* **4**: 9-12.
24. Trujillo, V., M.L. Masseroni, G. Levin & M.M. Suárez (2009) *Int. J. Neurosci.* **119**(8): 1210-27.

25. Ohkawa, H., N. Ohishi & K. Yagi (1979) *Anal. Biochem.* **95**(2): 351-8.
26. Sedlak, J. & R.H. Lindsay (1968) *Anal. Biochem.* **25**(1): 192-205.
27. Trimmel, H., R. Helbok, T. Staudinger, W. Jaksch, B. Messerer, H. Schöchl, *et al.* (2018) *Wien Klin. Wochenschr.* **130**(9-10): 356-66.
28. Pham, T.H. & A.M. Gardier (2019) *Pharmacol. Ther.* **199**: 58-90.
29. Tan, S., W.M. Chan, M.S. Wai, L.K. Hui, V.W. Hui, A.E. James, *et al.* (2011) *Microsc. Res. Tech.* **74**(12): 1192-8.
30. Yuan, H., S. Du, Y. Deng, X. Xu, Q. Zhang, M. Wang, *et al.* (2019) *Biosci Rep.* **39**(5): BSR20182381.
31. Li, Y., J. Shi, B.F. Yang, L. Liu, C.L. Han, W.M. Li, *et al.* (2012) *Br. J. Pharmacol.* **165**(6): 1748-56.
32. Çömez, M.S., M. Cellat, H. Özkan, Y. Borazan, T. Aydın, İ Gökçek, *et al.* (2020) *Naunyn Schmiedebergs Arch, Pharmacol.* **393**(9): 1691-9.
33. Cetin, N., B. Suleyman, D. Altuner, U. Kuyrukluyildiz, F. Ozcicek, R. Coskun, *et al.* (2015) *Int. J. Clin. Exp. Med.* **8**(8): 13540-7.
34. Kasper, S. & B.S. McEwen (2008) *CNS Drugs* **22**(1): 15-26.
35. Muquebil, A.A.S., O.W. Rodríguez, J. Bermúdez Rivera, Á. Hevia Maroto, I. Menéndez Miranda & J.J. Martínez Jambrina (2020) *Rev. Psiquiatr. Salud Mental* **13**(1):47-8.
36. Castanon, N., C. Médina, C. Mormède & R. Dantzer (2004) *Psychoneuroendocrinology* **29**(6): 778-90.