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EXPERIMENTAL ARTICLES

Possible Neuroprotective Effect of tDCS on Doxorubicin-Induced Neurotoxicity in Rats

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Abstract—Doxorubicin (DOX), a chemotherapeutic medicine, are frequently utilized to treat various malignancies, even though it has well-documented negative side effects. Neurotoxic effect is one of the best known and occurs through several mechanisms including oxidative stress and neuro-inflammation. Transcranial direct current stimulation (tDCS), a non-invasive brain stimulation technique, is used in several neurodegenerative disease model because of its neuroprotective effects. The aim of this study was to investigate the effects of DOX on antioxidant and inflammatory markers, behavioral parameters and the possible neuroprotective effect of tDCS stimulation on these effects. To induce neurotoxicity, DOX was administered intraperitoneally (i.p.) at 2.15 mg/kg/day, 1 dose in 3 days, 7 times in total for 3 weeks. tDCS treatment was then applied for 5 consecutive days. Catalase (CAT), interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin 6 (IL-6) levels were evaluated. Open field test was used to analyzed to locomotor activity and behavioral changes. The DOX group had neuronal alteration as indicated by the elevation of neuro-inflammation markers (IL-1β, TNF-α, and IL-6) with reduced antioxidant marker (CAT). The tDCS-treated group showed a significant reduction in the inflammation biomarkers, with a significant improvement in the antioxidant marker. DOX administration impaired locomotor activity as well as anxiety behaviors of rats. tDCS have also been shown to be effective in preventing behavioral and locomotor changes; therefore, they may be considered as candidates to reduce toxicity effects in DOX treatments. Our findings reveal the importance of tDCS treatment to attenuate DOX-associated neurotoxicity. Through the modification and decrease of indicators of cellular toxicity and the increase of natural antioxidant enzymes, tDCS demonstrated considerable promise for avoiding DOX-induced neurotoxicity.

Keywords: doxorubicin, tDCS, inflammation, oxidative stress, behavior

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INTRODUCTION

Anthracyclines are antineoplastic agents with a wide spectrum of action. One of the first anthracyclines to be discovered was DOX and used as a chemotherapeutic drug in many cancers such as breast cancer, sarcomas, or hematological malignancies [1]. Studies have shown that despite its efficacy, it has versatile toxic effects, namely cardiotoxicity, neurotoxicity or gastroenterological damage [1–3]. DOX exerts its antineoplastic effect by disrupting topoisomerase-II-mediated DNA repair and by triggering the forming of free radicals that injury cellular membranes, DNA and proteins [4]. However, these effects come with undesirable side effects, including nausea, hematopoietic suppression, extravasation, vomiting, alopecia, neurotoxicity, and cardiotoxicity [3, 4]. Previous studies revealed that DOX causes chemobrain formation and cognitive dysfunction by inducing inflammation and oxidative stress [5, 6]. In addition, DOX induces the production of biomarkers such as NF-κB, TNF-α, cyclooxygenase-2 (COX-2), and nitric oxide, which regulate initiate inflammation [7, 8]. In another study, DOX was found to cause structural and biochemical changes by increasing the expression of pro-apoptotic markers, while decreasing that of anti-apoptotic markers [9]. For this reason, the interest in investigating therapies with anti-inflammatory and antioxidant properties to reduce the adverse effects of antineoplastic drugs has increased in recent years. tDCS is a non-invasive treatment modality for neurological disorders. A mild electric current (in the mA range) can be safely applied to the scalp to alter neuroplasticity in a variety of brain regions [10]. Studies have shown that tDCS can increase cellular excitability, so making treatments more effective [11]. Although safety and efficacy studies in animal models show

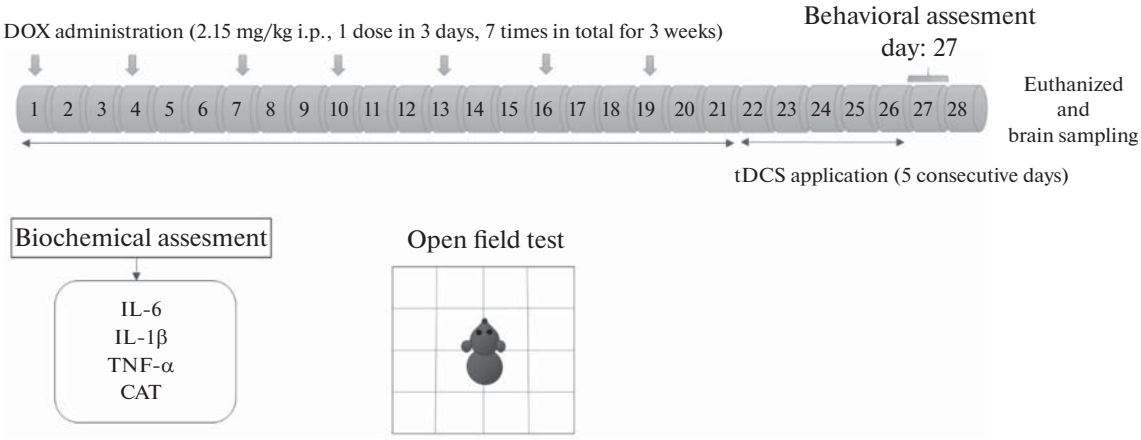

Fig. 1. Experimental design.

promising results for physical stimulation methods, more investigations are needed to improve drug efficacy or reduce side effects. Benninger et al. reported that tDCS suppressed oxidative stress and neuroinflammation and blocked hippocampal neurodegeneration. In current report, it is aimed to evaluate the effect of tDCS on CAT and inflammation, as well as its effect on behavioral changes in the DOX treatment. Our results provide a theoretical basis for further research with tDCS that alleviated the neurotoxic effects of DOX.

MATERIAL AND METHODS

Experimental design. Three-month-old male Wistar albino rats (weighing 250–300 g) were used for investigation. They were housed under standard conditions (temperature: 24 ± 1°C, relative humidity range: 45 ± 5%, 12-h light/12-h dark cycle) and fed ad libitum. Rats were divided into three experimental groups (n = 7 rats/group) as; control, saline was administered; DOX, DOX (Adrimisin® from Saba Pharmaceuticals, İstanbul, Turkey) 2.15 mg/kg intraperitoneally, 1 dose in 3 days, 7 times in total for 3 weeks; DOX + tDCS: At the end of the 3rd week, tDCS has been applied to the DOX group for 5 consecutive days. All applications were performed i.p. At the end of 3 weeks, tDCS were performed under sevoflurane anesthesia with 0.50 mA current for 30 min. Open field test was performed to evaluate locomotor activity and anxiety. After the behavioral experiment, the rats were sacrificed. Antioxidant enzyme levels and inflammatory markers were analyzed in cortex tissue.

Open field test. The video monitoring system Ethovision XT (Noldus, 2009, Netherlands) was used in the behavioral test. Using a video camera, the rats' movements were captured during the experiment, and the relevant data were gathered and examined. Figure 1 shows experimental graphical abstracts and behavioral experiment. The open field trials were performed on a black mat-based, square apparatus, 80 × 80 cm^2 square with a wall height of 40 cm. At the start of the experiment, the computer system divided the experimental setup into 16 little squares, and each rat was placed in the center of maze. For five minutes, the animals' behaviors were observed. For every rat, the total distance traveled, average speed, and number of frames entered were counted and scored [12]. To avoid any traces of odor, the maze was cleaned with 70% ethanol after each trial.

Measurement of inflammation markers and CAT level. Brain tissues were homogenized in phosphate-buffered saline (pH 7.4, 0.1 M). The supernatants were used for analysis after centrifugation for 15 min at 4°C (3500 rpm). Colorimetric ELK Biotechnology (Denver, USA) ELISA Kits were used for analyzing of IL-6 (Cat. No. ELK1158), TNF-α (Cat. No. ELK1396), IL-1β (Cat. No. ELK1272) and CAT (Cat. No. ELK5986). For analyzing, user instructions were employed. Protein concentration was measured by the modified Bradford method (Pierce, Thermo Fisher Scientific, Roskilde, Denmark) at 595 nm [13].

Statistical analysis. SPSS 25.0 software (Statistical Package for the Social Sciences, IBM SPSS Inc., Chicago, IL, USA) was used for statistical analyses. Normality of the data was determined by Skewness and Kurtosis test. Statistical comparison between groups was tested using one-way analysis of variance (ANOVA) followed by Tukey's Post Hoc Test. The statistical significance for each test was determined as $p < 0.05$.

RESULTS

Open field test. The effect of DOX and tDCS treatment on rats' locomotor activity in an open field test is showed in Fig. 2. The total distance traveled (a), the velocity (b) and the frequency of crossing of squares (c) and time spent in center frame (d) for each experimental group were given. In the open field test, the

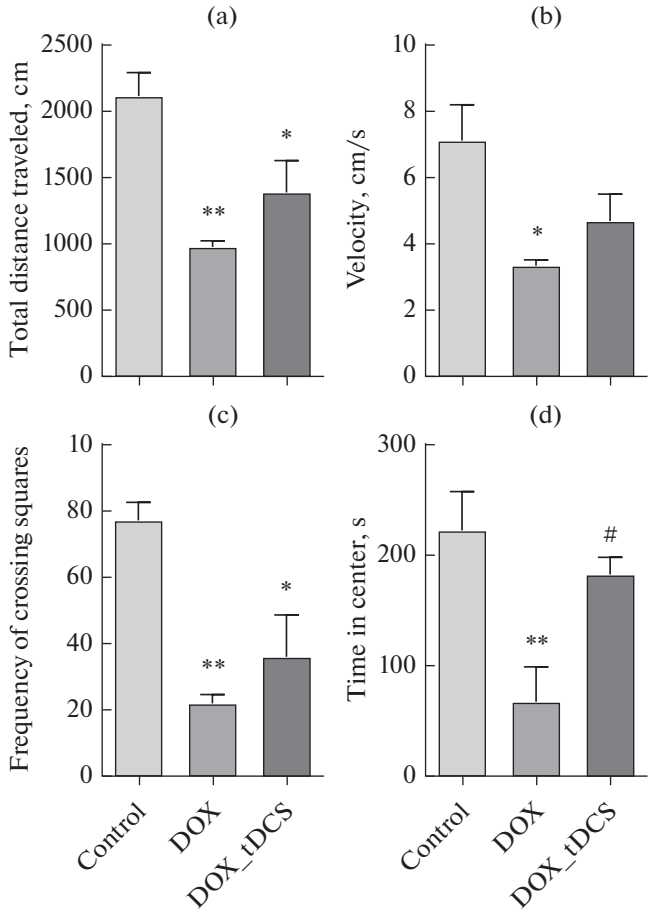

Fig. 2. Effect of tDCS treatment on behavioral parameters in DOX-administered rats. Tests: a—Total distance traveled (cm), b—Velocity (cm/min), c—Frequency of crossing of squares, d—Time in cenrer (s). Results are presented as mean ± SEM. * $p < 0.05$, ** $p < 0.01$ significance vs control group, # $p < 0.05$ significance vs DOX group. $n = 7$ for each group.

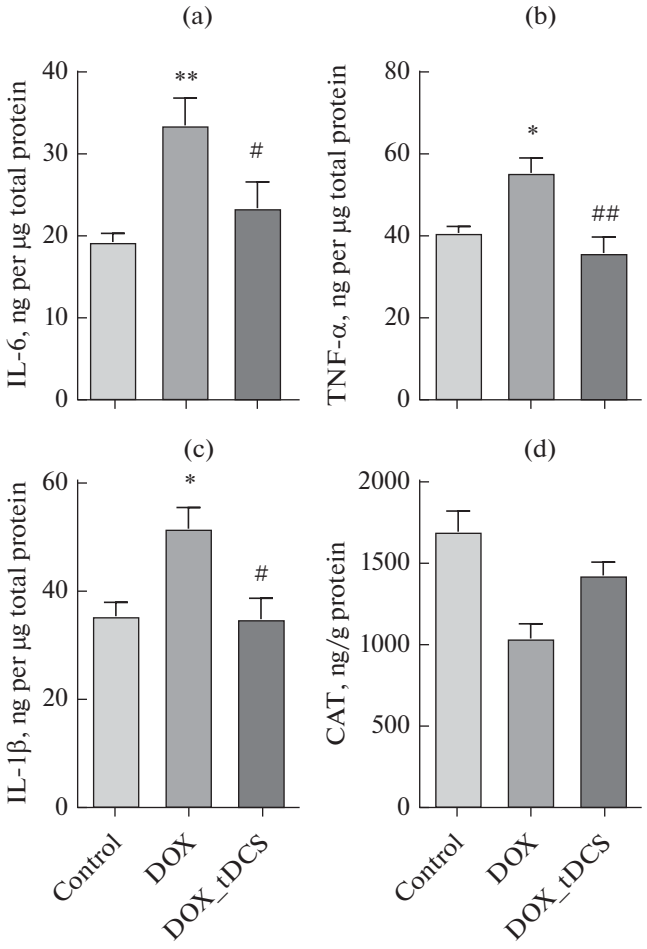

Fig. 3. Inflammatory markers and CAT level. a—IL-6, b—TNF-α, c—IL-1β, d—CAT in brain tissue. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ significance vs control group. # $p < 0.05$, ## $p < 0.01$ significance vs DOX group. The results are presented as mean ± SEM, $n = 7$ for each group.

DOX group has significantly less frequency of crossing square level than the control group, also there is an increment in terms of total distance travelled and velocity even if it's not significant. In DOX group rats exhibited more anxiety behavior than control group by spending more time at outer zone. Noteworthy variations between the control and DOX groups, suggesting that doxorubicin caused a decrease in locomotor, exploratory activity and anxiety. tDCS has ameliorated the effects.

Effects of the tDCS treatments on inflammatory markers level in the brain. DOX remarkably elevated pro-inflammatory markers; IL-6, TNF-α, IL-1β and CAT levels in brain tissues compared to the control. Meanwhile treatment with tDCS diminished these levels compared to the DOX group (Fig. 3). Similarly, the level of CAT, an antioxidant enzyme, decreased in the DOX group, whereas it increased in the current-treated group, although not significantly.

DISCUSSION

Despite having a lot of side effects, DOX is a commonly used chemotherapy drug [14]. The aim of this study was to investigate the effects of DOX (15 mg/kg in total) administration at fixed intervals for 3 weeks on CAT, inflammatory markers and behavioral parameters and the effect of tDCS stimulation on these effects. This study showed that chronic DOX administration decreased CAT level, increased inflammatory parameters and impaired locomotor activity of rats. These alterations have a detrimental effect on chemotherapy patients' quality of life. tDCS administration contributed to the recovery process of rats in all aspects.

Anthracyclines are antineoplastic agents with a wide spectrum of action. One of them is DOX and used as a chemotherapeutic agent in cancers treatment [1]. Studies have shown that despite its efficacy, it has toxic effects on cardiomyocytes, the brain, liver, and

kidney [1–3]. For this reason, we need to discover new conjugate therapies that attenuate this effects. Several studies have reported that chemotherapeutics such as DOX increase oxidative stress and inflammatory cytokine release in both central and peripheral tissues and activate the immune system [14, 15]. Scientists showed that tDCS may exhibit anti-inflammatory properties by preventing the formation of free radicals, oxygen ions and peroxidase in the body [16]. Free radicals are directly involved in the pathophysiology of cancer, as well as in cardiovascular and neurodegenerative diseases [5, 17, 18]. SOD, CAT and GPx activities form the basic defense systems in the cell, and these enzymes prevent the tissue damage by reducing reactive species [19]. Under normal conditions, there is a balance between reactive oxygen species (ROS) and antioxidants. A shift in this balance in favor of ROS as well as insufficiency of endogenous defense systems result in oxidative stress [20]. Free radicals cause many effects at the molecular level. The increase in ROS is toxic to the cell and disrupts intracellular signaling pathways as this damages proteins, lipids and nucleic acids [20]. CAT levels are used to determine the oxidative stress and to evaluate the therapeutic efficacy of tDCS. In our study, the decrement in CAT level was observed in DOX-induced rat. Treatment with tDCS augmented the decreased CAT levels on DOX administration group. Our findings are consistent with studies in the literature, demonstrating the neuroprotective potential and antioxidant activity of tDCS [21, 22].

In addition to causing oxidative stress and lipid peroxidation, DOX increases the level of proinflammatory cytokines [23]. These cytokines are proteins involved in the inflammatory process produced by neurons and glial cells [24]. An imbalance in pro- and anti-inflammatory cytokine levels initiate necrosis or apoptosis. Many studies have demonstrated that DOX induces many inflammatory pathways by upregulating TNF-α that stimulates the release of IL-1β and IL-6 [25–27]. TNF-α, IL-1β and IL-6 levels were markedly elevated in DOX-exposure rats. This demonstrates the potential of DOX to induce inflammation. tDCS treatment attenuated DOX-induced inflammation; tDCS decreased TNFα, IL-1β and IL-6 levels when compared to the DOX group. Current treatments have been shown to have ameliorative effects on the inflammatory response in both the central and peripheral nervous systems, depending on duration and dose. For example, in vitro studies have shown that it can accelerate or polarize the migration of various peripheral immune cells such as monocytes, macrophages or neutrophils [28–30]. tDCS uses weak, direct electric currents that are continually applied through the head to alter cortical excitability. One of the most accepted effects of tDCS is its ability to change neuronal membrane polarity and, with this feature, its effect on the action potential generation threshold. Moreover, it works not only on action potential production in the efferent neuron, but also at the level of synaptic inputs [31]. The changes in cortical excitability induced by tDCS can cause important molecular and behavioral effects. tDCS can improve afferent axonal synaptic transmission in the primary motor cortex, which increases motor evoked potentials [32, 33]. Furthermore, studies in rats have shown that daily (5 consecutive days) current stimulation on the primary motor cortex increases the number of cortical microglial cells [34]. In another rat model, a decrease in hippocampal TNF-α levels was found after 8 days of tDCS stimulation of the parietal cortex [35], When the studies are evaluated together, it can be said that tDCS has both anti-inflammatory and pro-inflammatory effects.

The variability of tDCS effects on behavior is an another important issue. The effects of current therapy on different diseases have been shown, for example cognitive dysfunction, major depression [36], pain [37], tinnitus [38], epilepsy [39] and Parkinson's disease [21]. When the animals in the DOX group were tested in the open field, a decrease was observed compared to controls in terms of total distance traveled, velocity, frequency of crossing frames and time spent in the center quadrant, and there was an improvement with current treatment. It shows that current application improves locomotor activity, exploratory behavior and anxiety-like behaviors. Liedke et al. show a reduction in locomotor activity and exploratory behavior of animals evaluated in the open field 24 h after DOX administration at doses of 0.5, 2 and 8 mg/kg [40]. Similarly, Fabio Santos Lira et al. proposed that DOX reduces muscle mass, strength and function by causing a decrease in locomotor activity [41]. Despite being effective in promoting tumor cell death, chemotherapy causes severe damage to brain tissue and locomotor behavior, reducing the patient's quality of life. tDCS can improve behavioral deterioration by improving neural excitation. Alternatively, we suggest that alternative therapies such as tDCS, which stimulates the brain non-invasively, may reduce the adverse effects of DOX.

Our findings demonstrated that DOX causes the changes in locomotor activity, free radical formation and inflammatory markers. tDCS suppresses DOX-induced effects in the brain via its antioxidant and anti-inflammatory properties. Our study demonstrates the importance of treatment with tDCS to alleviate DOX-related neurotoxicity. However, long term and more comprehensive studies are recommended to fully elucidate the mechanisms of action of tDCS in relation to neuronal inflammatory damage.

CONCLUSIONS

An overview of the literature shows the effects of tDCS on several biological events. tDCS can strengthen or weaken synaptic connections, modulate cell morphology, migration or growth, depending on its duration and intensity. Although it primarily affects

on the cortex, it has the capacity to reach deeper structures and is effective in neuroprotection, neurogenesis and modulation of inflammatory responses. In our study, despite the inherent limitations of animal models, the possible attenuating effect of current therapy on CAT and the inflammatory response induced by DOX toxicity was studied together with behavioral experiments. The obtained data is informative and will help to determine the presumed mechanisms of action of tDCS.

AUTHOR CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed and the first draft of the manuscript was written by all authors. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The experiments were conducted in compliance with the Local Animal Care Committee of Akdeniz University's (Antalya, Turkey) ethical standards (with a unique authorization number 2023/09/04-92).

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Shi, S., Chen, Y., Luo, Z., Nie G., Dai, Y., *CCS,* 2023, vol. 21, pp. 1–20
2. Weiss, R.B. *Semin. Oncol.*, 1992, pp. 670–686.
3. Alhowail, A.H., Bloemer, J., Majrashi, M., Pinky, P.D., Bhattacharya, S., Yongli, Z., Bhattacharya, D., Eggert, M., Woodie, L., Buabeid, M.A., *Toxicol. Mech. Methods*, 2019, vol. 29, pp. 457–466.
4. Thorn, C.F., Oshiro, C., Marsh, S., Hernandez-Boussard, T., McLeod, H., Klein, T.E., Altman, R.B., *Pharmacogenetics and genomics*, 2011, vol. 21, p. 440.
5. Aluise. J.D., Sultana, R., Tangpong, J., Vore, M., Clair, D.S., Moscow, J.A., and Butterfield, D.A., *Chemo fog: Cancer chemotherapy-related cognitive impairment,* Ed. Robert B. Raffa, Ronald J. Tallarida, Berlin: Springer, 2010, pp. 147–156.
6. Ramalingayya, G.V., Nayak, P.G., Shenoy, R.R., Mallik, S.B., Gourishetti, K., Hussain, S.M., Rao, C.M., Nandakumar, K., *Pharmacogn. Mag.,* 2018, vol. 14, pp. S197–S207.
7. Bin Jardan, Y.A., Ansari, M.A., Raish, M., Alkharfy, K.M., Ahad, A., Al-Jenoobi, F.I., Haq, N., Khan, M.R., Ahmad, A., *Biomed Res. Int.*, 2020.
8. Ma, T., Kandhare, A.D., Mukherjee-Kandhare, A.A., Bodhankar, S.L., *Mol. Biol. Rep.*, 2019, vol. 46, pp. 105–118.
9. Arunachalam, S., Nagoor Meeran, M., Azimullah, S., Jha, N.K., Saraswathiamma, D., Subramanya, S., Albawardi, A., Ojha, S., *Int. J. Mol. Sci.*, 2022, vol. 23, p. 10528.
10. de Oliveira, C., Freitas, J.S., Macedo, I.C., Scarabelot, V.L., Ströher, R., Santos, D.S., Souza, A., Fregni, F., Caumo, W., Torres, I.L.S., *Neuropeptides*, 2019, vol. 73, pp. 1–10.
11. Stamp, M.E.M., Halwes, M., Nisbet, D., and Collins, D.J., *Fluids Barriers CNS*, 2023, vol.20, p. 87.
12. Navarro, A.A.L., Sikoglu, E.M., Heinze, C.R., Rogan, R.C., Russell, V.A., King, J.A., Moore, C.M., *Behav. Brain Res.*, 2014, vol. 270, pp. 240–247.
13. Danışman, B., Akçay G., Gökçek-Saraç, Ç., Kantar, D., Aslan, M., Derin N., *Neurochem. Res.*, 2022, vol. 47, pp. 3331–3343.
14. Mills, P.J., Parker, B., Dimsdale, J.E., Sadler, G.R., Ancoli-Israel, S., *Biol. Psychol.*, 2005, vol. 69, pp. 85–96.
15. Janelsins, M.C., Mustian, K.M., Palesh, O.G., Mohile, S.G., Peppone, L.J., Sprod, L.K., Heckler, C.E., Roscoe, J.A., Katz, A.W., Williams, J.P., Morrow, G.R., *Support Care Cancer*, 2012, vol. 20, pp. 831–839.
16. Chen, G., Mao, J., Zhao, J., Zhang, Y., Li, T., Wang, C., Xu, L., Hu, Q., Wang, X., Jiang, S., Nie, X., Wu, Q., *Regul. Toxicol. Pharmacol.,* 2016, vol. 81, pp. 480–488.
17. Maddu, *IntechOpen* London, UK2019.
18. Lee, D.-Y., Song, M.-Y., Kim, E.-H., *Antioxidants*, 2021, vol. 10, pp. 743.
19. Ighodaro, O., Akinloye, O., *Alexandria journal of medicine*, 2018, vol. 54, pp. 287–293.
20. Poljšak, B., Jamnik P., Raspor, P., Pesti, M., *Oxidation-antioxidation-reduction processes in the cell: impacts of environmental pollution,* Ed. NRIAGU, Jerome, 2019.
21. Benninger, D.H., Lomarev, M., Lopez, G., Wassermann, E.M., Considine, X., Li, E., Hallett, M., *J. Neurol. Neurosurg. Psychiatry,* 2010, vol. 81, pp. 1105–1111.
22. Crespo, P.C., Martins, L.A.M., Dos Reis, C.C., Medeiros, L.F., Scarabelot, V.L., Gamaro, G.D., Soares, M.S.P., Spanevello, R.M., Stefanello, F.M., De Souza, I.C.C., *Neurosci. Lett.*, 2023, vol. 803, p. 137179.
23. Tabaczar, S., Czepas, J., Koceva-Chyla, A., Kilanczyk, E., Piasecka-Zelga, J., Gwozdzinski, K., *J. Physiol. Pharmacol.*, 2017, vol. 68(2), pp. 295–308.
24. Villa, P., Bigini, P., Mennini, T., Agnello, D., Laragione, T., Cagnotto, A., Viviani, B., Marinovich, M.,

Cerami, A., Coleman T.R., *JEM*, 20023, vol. 198, pp. 971–975.

25. He, Y., Yang, Z., Li, J., Li, E., *Exp. Mol. Pathol.,* 2020, vol. 113, p. 104371.
26. Zhang, S., You, Z.-Q., Yang, L., Li, L.-L., Wu, Y.-P., Gu, L.-Q., Xin, Y.-F., *BMC CAM*, 2019, vol. 19, pp. 1–10.
27. Abbas, A.K., Lichtman, A.H., Pillai, S., *Cellular and Molecular Immunology,* E-book, Elsevier Health Sciences, 2014.
28. Lin, S.L., Li, Y., Woolley, A.T., Lee, M.L., Tolley, H.D., Warnick, W.F., *Electrophoresis*, 2008, vol. 29, pp. 1058–1066.
29. Orida, N., Feldman, J.D., *Cell Motil.*, 1982, vol. 2, pp. 243–255.
30. Zhao, M., Song, B., Pu, J., Wada, T., Reid, B., Tai, G., Wang, F., Guo, A., Walczysko, P., Gu, Y., Sasaki, T., Suzuki, A., Forrester, J.V., Bourne, H.R., Devreotes, P.N., McCaig, C.D., Penninger, J.M., *Nature*, 2006, vol. 442, pp. 457–460.
31. Pelletier, S.J., Cicchetti, F., *Int. J. Neuropsychopharmacol.*, 2014, vol. 18.
32. Rahman, A., Reato, D., Arlotti, M., Gasca, F., Datta, A., Parra, L.C., Bikson, M., *J. Physiol.*, 2013, vol. 591, pp. 2563–2578.
33. Liebetanz, D., Nitsche, M.A., Tergau, F., Paulus, W., *Brain*, 2002, vol. 125, pp. 2238–2247.
34. Rueger, M.A., Keuters, M.H., Walberer, M., Braun, R., Klein, R., Sparing, R., Fink, G.R., Graf, R., Schroeter, M., *PLoS One*, 2012, vol. 7, p. e43776.
35. Spezia Adachi, L.N., Caumo, W., Laste, G., Fernandes Medeiros, L., Ripoll Rozisky, J., de Souza, A., Fregni, F., Torres, I.L.S., *Brain Res,* 2012, vol.1489, pp. 17–26.
36. Boggio, P.S., Rigonatti, S.P., Ribeiro, R.B., Myczkowski, M.L., Nitsche, M.A., *IJNP,* 2008, vol. 11, pp. 249–254.
37. Fregni, F., Gimenes, R., Valle, A.C., Ferreira, M.J., Rocha, R.R., Natalle, L., Bravo, R., Rigonatti, S.P., Freedman, S.D., Nitsche, M.A., *Arthritis Rheum*, 2006, vol. 54, pp. 3988–3998.
38. Fregni, F., Marcondes, R., Boggio, P.S., Marcolin, M.A., Rigonatti, S.P., Sanchez, T.G., Nitsche, M.A., Pascual-Leone A., *Eur. J. Neurol.,* 2006, vol.13, pp. 996–1001.
39. Fregni, F., Otachi, P.T, Do Valle, A., Boggio, P.S., Thut, G., Rigonattiv, S.P., Pascual-Leone, A., Valente, K.D., *Ann. Neurol.,* 2006, vol. 60, pp. 447–455.
40. Liedke, P.E.R., Reolon, G.K., Kilpp, B., Brunetto, A.L., Roesler, R., Schwartsmann, G., *Pharmacol. Biochem. Behav.*, 2009, vol. 94, pp. 239–243.
41. Santos, F.M., Grecco, L.H., Pereira, M.G., Oliveira, M.E., Rocha, P.A., Silva, J.T., Martins, D.O., Miyabara, E.H., Chacur, M., *Behav. Brain Funct.*, 2024, vol. 10, pp. 1–8.

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