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**Review Article / Derleme**

# Doxorubicin-dependent skeletal muscle atrophy: exercise and mitochondrial dysfunction

## *Doksorubisin bağımlı iskelet kası atrofisi: egzersiz ve mitokondriyal disfonksiyon*

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**ABSTRACT**

Doxorubicin (DOX) is a type of chemotherapy with harmful side effects due to its accumulation in various tissues. DOX is widely known for having a significant effect on skeletal muscle atrophy. The most significant of these side effects is DOX-induced mitochondrial dysfunction in skeletal muscle atrophy. Exercise is a treatment approach that serves to maintain muscle homeostasis by decreasing or eliminating these effects. The goal of this review article is to give current knowledge on the causes of DOX-induced skeletal muscle atrophy, the basic processes involved in mitochondrial dysfunction caused by DOX, and the effects of exercise on DOX-induced skeletal muscle atrophy.

**Keywords:** *Doxorubicin, skeletal muscle atrophy, mitochondria, exercise*

**ÖZ**

Birçok dokuda birikmesi nedeniyle, Doksorubisin (DOX) sitotoksik yan etkilere neden olan bir kemoterapötiktir. DOX'un iskelet kası atrofisi üzerinde önemli bir etkiye sahip olduğu yaygın olarak bilinmektedir. Bu etkilerden en dikkat çekeni DOX'un neden olduğu mitokondriyal fonksiyon bozukluğunun iskelet kası atrofisini nasıl tetiklediğidir. Egzersiz bu etkileri azaltarak veya ortadan kaldırarak kas homeostazisinin korunmasına yardım eden bir tedavi yaklaşımıdır. Bu derleme makalenin amacı, DOX'a bağlı iskelet kası atrofisinin nedenleri, DOX yoluyla mitokondriyal disfonksiyondaki temel mekanizmalar ve DOX'a bağlı iskelet kası atrofisinde egzersizin etkileri hakkında güncel bilgiler sağlamaktır.

**Anahtar Sözcükler:** *Doksorubisin, iskelet kası atrofisi, mitokondri, egzersiz*

## INTRODUCTION

A cytotoxic drug known as doxorubicin (DOX) serves for the treatment of specific types of cancer (1). DOX is an extremely effective treatment, but it has several side effects, including skeletal muscle atrophy (2, 3). The DOX affects the quality of life for cancer patients because it promotes skeletal muscle atrophy and fatigue (4).

It has been demonstrated that DOX treatment induces mitochondria to produce more reactive oxygen species (ROS) (5, 6). Oxidative damage to skeletal muscle serves as a stimulus that accelerates the degradation of muscle by activating key proteolytic systems (7, 8). Skeletal muscle atrophy is triggered by these negative molecular mechanisms. DOX appears to affect muscular function by reducing athletic performance and causing muscle fatigue (9).

Skeletal muscle dysfunction following DOX treatment is a challenging issue to manage, exercise may be beneficial in reducing the negative effects of DOX on the skeletal muscles (10).

This review article will discuss the adverse effects of DOX on skeletal muscle as well as explain how mitochondrial dysfunction generates these effects and the evidence that exercise can counteract these effects.

### *Doxorubicin, chemical structure, and mechanism*

Doxorubicin HCl, the first anticancer drug, has been clinically demonstrated to be effective against some malignancies, including solid cancers, leukemias, and lymphomas (11). The molecular formula for DOX is $C_{27}H_{29}NO_{11}HCl$, with a molecular weight of 579,98 g/mol. The drug is an aglyconic and sugar-containing class I nonselective anthracycline. The aglycone is formed up of a tetracyclic ring with adjacent quinine-hydroquinone groups, a short side chain containing a methoxy substituent, and a carbonyl group. One of the rings has a glycosidic link binding the sugar component to it (12, 13).

Certain mechanisms, including topoisomerase II (TOP2B) inhibition, cytochrome C release from mitochondria, and

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the formation of ROS leading to oxidative stress, have been associated with cytotoxic effects of DOX (14, 15).

DOX intercalates with the DNA, preventing the macromolecular production process (16). TOP2B poisoning induces DNA damage because cancer cells are more susceptible to DNA breaks than healthy ones (17, 18).

Following the splitting of the DNA chain for replication by TOP2B, DOX stabilizes the structure by inhibiting the DNA double helix and stopping replication activity (19). Another way that DOX acts is to produce free radicals, which may damage DNA and cell membrane lipids and proteins (11, 20). This can give rise to oxidative stress, which may eliminate tumor cells through the process of apoptosis (17, 21).

**Doxorubicin-induced skeletal muscle atrophy**

Skeletal muscles, which account for over 40% of a healthy person's body weight, are highly dynamic and flexible tissues that can change at the cellular and molecular levels in response to various stressors (22). Skeletal muscle protein turnover is a metabolic process that balances protein synthesis/degradation and maintains skeletal muscle function and mass (23). Skeletal muscle atrophy is characterized by a decrease in protein content, fiber diameter, strength production, and resistance to fatigue. Skeletal muscle atrophy is the loss of skeletal muscle mass as a result of increased myofibrillar protein degradation and decreased protein synthesis (24). Skeletal muscle atrophy is an outcome of multiple diseases, including cancer, neuromuscular disorders, myopathy, and inflammatory diseases (25). DOX, a cancer treatment drug, promotes skeletal muscle atrophy, which acts a crucial role in the adverse effects of a variety of diseases or disorders.

Different cancers have been treated with DOX (1, 26). DOX is a highly successful chemotherapy, but it has several adverse effects, including skeletal muscle atrophy, and tiredness (2, 3, 27, 28). DOX treatment impairs the quality of life for cancer patients by causing skeletal muscle weakness and exhaustion (4). Because of its cytotoxic activity, it has been proven in several human and animal studies to initiate skeletal muscle atrophy. Mitochondrial and contractile dysfunction are triggered by cellular and molecular processes in skeletal muscle damage related to the activation of proteolytic and apoptotic signaling pathways by DOX-induced oxidative stress (29, 30).

DOX and paclitaxel, two drugs frequently administered to breast cancer patients, decreased myosin expression and promoted mitochondrial degradation via ROS (3). Muscle dysfunction and atrophy have also been associated with DOX treatment, which is used to treat limb sarcoma tumors (31).

Skeletal muscle functionality gradually deteriorated in five days following DOX administration and all muscle tissues were dysfunctional, vascular activity quickly reduced, and DOX concentration was highest in the heart (32).

DOX dramatically decreased muscular tissue weights and cross-sectional area (CSA) of muscle. (33). A recent study found that prolonged DOX treatment significantly diminished body weight and gastrocnemius mass (34). 10, 12.5, or 15 mg/kg DOX applications reduced maximal contraction force in the soleus muscle by 45%, 60%, and 74%, respectively (35). Skeletal muscle and cardiac wasting were nearly equal 4 weeks after the treatment with a 24 mg/kg dose of DOX (36). The fiber CSA of the soleus, plantaris, and diaphragm muscles significantly was decreased after receiving a single dose of DOX (20 mg/kg) (2). DOX diminished soleus weight by around 15% and cancer chemotherapy's combined effects led to a similar decline in muscle mass and CSA (6). DOX treatment significantly lowered muscle fiber CSA by 17% according to a meta-analysis (37). 15 mg/kg DOX injection was administered intraperitoneally, and the CSA of EDL muscle was reduced (38).

TOP2B overexpression contributes to DOX-induced myotoxicity. DOX significantly deteriorated the muscle weight of the gastrocnemius and specific clinical characteristics (35). Additionally, this study found that DOX reduced BECN1 (autophagy marker) expression but did not affect myogenic regulatory factor (MRF) activity (39).

In in vitro and in vivo studies, DOX decreased soluble guanylate cyclase (sGC) action, and there was a correlation between sGC function and CSA of skeletal muscle activating the ubiquitin-proteasome system (UPS) and impairing protein synthesis (40). Additionally, cells exposed to DOX showed immunostained responses, which were indicating oxidative stress. The essential differentiation was attributed to the intracellular density of the identified mitochondrial reactivity, increased MAFbx expression, and atrophic changes due to Forkhead box O3 (FoxO3) (41). DOX significantly decreased muscular function in mice, and upregulated proinflammatory cytokines and inflammatory M1 macrophages (42).

**Doxorubicin and mitochondrial dysfunction**

DOX-induced mitochondrial damage induces cellular malfunction (43, 44). According to studies, DOX treatment has been shown to increase the generation of mitochondrial ROS (5, 6). Cardiolipin, an inner mitochondrial membrane phospholipid, has been associated with the generation of ROS after mitochondrial failure (45). DOX produces cardiolipin dysfunction, resulting in increased ROS generation (46). When DOX is localized to the inner mitochondrial

membrane, it is reduced by nicotinamide adenine dinucleotide (NADH)-dehydrogenase, leading to the generation of superoxide radicals, which in turn increases ROS production and mitochondrial dysfunction (2). ROS generation triggers oxidative damage in skeletal muscle.

When ROS levels increase, the mitochondrial structure is seriously damaged and resulted in apoptosis and reduced contraction, which compromises cardiac and respiratory performance (47, 48). ROS increases protein breakdown in skeletal muscle by activating caspase-3 and the UPS. UPS is a different mechanism related to DOX-induced atrophy. Furthermore, autophagy has been hypothesized as a potential mechanism for DOX-induced protein breakdown (49, 50). Min et al. reported that a single dose of DOX (20 mg/kg) lowered mitochondrial respiration while enhancing mitochondrial uncoupling (2). DOX administration resulted in substantial increases in mitochondrial ROS, 4-hydroxy-2-nonenal (4-HNE) modified proteins, calpain activation, and caspase-3 activity in skeletal and cardiac muscles (2).

DOX affects complex I and complex II mitochondrial respiration in skeletal muscle (51). DOX improved skeletal muscle mitochondrial $H_2O_2$-emitting potential and oxidative variations of myofibrillar proteins (52). Following DOX treatment, the function of the whole muscle is negatively affected by both elevated reactive protein carbonyl levels and post-translational modifications of proteins induced by increased cellular oxidants (6).

DOX administration (15 mg/kg) significantly enhanced the TUNEL apoptotic index, the protein abundance of Bcl-3/Bax, and the ratio of LC3 II to LC3 I in skeletal muscle (49). DOX injection promoted autophagy marker expression in type I soleus muscle, and the autophagosome initiation protein, Beclin1 (53, 54). DOX increased Beclin1 mRNA and protein levels in soleus muscles (53).

DOX treatment (6 mg/kg, four doses) reduced body weight and muscle mass, and elevated REDD1 mRNA expression (33). DOX treatment and oxidative stress were recently reported to increase REDD1 mRNA expression in skeletal muscle (11, 55).

Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1) controls angioplasty, mitochondrial biogenesis, and muscular growth (56). DOX diminished PGC-1 mRNA levels in skeletal muscle, while they tended to increase in the heart (36).

**Effects of exercise on doxorubicin-induced skeletal muscle atrophy**

It is well recognized that individuals with a variety of pathological conditions, such as cardiovascular diseases, obesity, type 2 diabetes, sarcopenia, and some forms of cancer, can benefit significantly from regular exercise (24, 57).

Combs and colleagues demonstrated that exercise training offers therapeutic advantages that reduce DOX toxicity (58).

It has been shown that endurance training decreased DOX-induced oxidative damage and the induction of proteolytic mechanisms in skeletal muscle atrophy (59). Exercise has been associated with slow-twitch oxidative muscles compared to fast-twitch glycolytic, but DOX-induced skeletal muscle atrophy emerges independently of skeletal muscles with different fiber types (type I or type II muscles) (60). One study demonstrated that the chronic DOX usage in combination with interval training was also sufficient to prevent soleus muscle atrophy (61). Therefore, exercise training before or at the beginning of DOX treatment may prevent skeletal muscle atrophy and weakening. Exercise increases the activity of endogenous antioxidant enzymes, oxidant buffering capacity and prevents DOX damage (62). In one study, the combination of exercise and DOX treatment enhanced antioxidant levels in heart and liver tissues (63). PGC 1 significantly lowered in gastrocnemius muscle under atrophic conditions, and increased expression of PGC 1 induced by genetic manipulation was found to suppress FoxO3, reducing type II fiber atrophy in the tibialis anterior muscle. (64).

Exercise diminishes mitochondrial dysfunction, oxidative stress, and protease stimulation, which in turn inhibits diaphragm fiber atrophy (65).

Exercise capacity can be affected by changes in musculoskeletal function, and patients exposed to DOX showed greater exercise intolerance and decreased aerobic capacity (66). Through activation of AMP-activated protein kinase (AMPK), aerobic exercise in DOX treatment enhanced maximum aerobic capacity without affecting muscle mass or fiber CSA (34). In DOX-treated rats, exercise diminished MuRF1 signaling but not Atrogin-1/MAFbx signaling via preserving mitochondrial respiratory function and redox balance (67). Exercise enhanced regeneration signaling through the MRF response, although DOX therapy increased soleus MRF function (68). The a-actinin (ACTN) protein was noticeably affected by DOX, but exercise training appeared to restore it. FOXO3a protein expression was elevated by DOX-induced myotoxicity and was precisely regulated by exercise (69). In addition to protecting muscle against oxidative stress induced by DOX and reducing the expression of autophagy genes, endurance exercise enhances antioxidant levels (53). Kwon et al. reported that exercise increased citrate synthase levels, autophagy markers (LC3-I/II, LAMP, etc.), and improved muscle regeneration (MYOD) in chronic

DOX-induced skeletal muscle atrophy (39). However, the interesting finding of this study was that both DOX treatment and exercise were not associated with the AMPK or AKT/mTOR signaling pathways (39). Exercise reduced levels of both carbonyl and the 4-HNE, demonstrating protection against skeletal muscle atrophy caused by DOX (50). Exercise prevents skeletal muscle atrophy when initiated before or at the beginning of DOX administration.

## CONCLUSION

Since it has been proposed that the medication produces DOX-induced skeletal muscle atrophy, it is critical to determine a preventive approach. One of these protective benefits is exercise, which lowers the side effects of chemotherapy in the setting of muscle physiology. Future research should investigate the combination of multiple treatments and exercise.

***Conflict of Interest / Çıkar Çatışması***

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## REFERENCES

1. Lu P. Monitoring cardiac function in patients receiving doxorubicin. *Semin Nucl Med.* 2005;35(3):197-201.
2. Min K, Kwon OS, Smuder AJ, Wiggs MP, Sollanek KJ, Christou DD, et al. Increased mitochondrial emission of reactive oxygen species and calpain activation are required for doxorubicin-induced cardiac and skeletal muscle myopathy. *J Physiol.* 2015;593(8):2017-36.
3. Guigni BA, Callahan DM, Tourville TW, Miller MS, Fiske B, Voigt T, et al. Skeletal muscle atrophy and dysfunction in breast cancer patients: role for chemotherapy-derived oxidant stress. *Am J Physiol Cell Physiol.* 2018;315(5):C744-c56.
4. van Norren K, van Helvoort A, Argilés JM, van Tuijl S, Arts K, Gorselink M, et al. Direct effects of doxorubicin on skeletal muscle contribute to fatigue. *Br J Cancer.* 2009;100(2):311-4.
5. Gilliam LA, Moylan JS, Patterson EW, Smith JD, Wilson AS, Rabbani Z, Reid MB. Doxorubicin acts via mitochondrial ROS to stimulate catabolism in C2C12 myotubes. *Am J Physiol Cell Physiol.* 2012;302(1):C195-202.
6. Gilliam LA, Lark DS, Reese LR, Torres MJ, Ryan TE, Lin CT, et al. Targeted overexpression of mitochondrial catalase protects against cancer chemotherapy-induced skeletal muscle dysfunction. *Am J Physiol Endocrinol Metab.* 2016;311(2):E293-301.
7. Montalvo RN, Doerr V, Min K, Szeto HH, Smuder AJ. Doxorubicin-induced oxidative stress differentially regulates proteolytic signaling in cardiac and skeletal muscle. *Am J Physiol Regul Integr Comp Physiol.* 2020;318(2):R227-r33.
8. Smuder AJ, Sollanek KJ, Nelson WB, Min K, Talbert EE, Kavazis AN, et al. Crosstalk between autophagy and oxidative stress regulates proteolysis in the diaphragm during mechanical ventilation. *Free Radic Biol Med.*2018;115:179-90.
9. Gilliam LA, Ferreira LF, Bruton JD, Moylan JS, Westerblad H, St Clair DK, Reid MB. Doxorubicin acts through tumor necrosis factor receptor subtype 1 to cause dysfunction of murine skeletal muscle. *J Appl Physiol* (1985). 2009;107(6):1935-42.
10. Bredahl EC, Pfannenstiel KB, Quinn CJ, Hayward R, Hydock DS. Effects of exercise on doxorubicin-induced skeletal muscle dysfunction. *Med Sci Sports Exerc.* 2016;48(8):1468-73.
11. Rivankar S. An overview of doxorubicin formulations in cancer therapy. *J Cancer Res Ther.* 2014;10(4):853-8.
12. Hilmer SN, Cogger VC, Muller M, Le Couteur DG. The hepatic pharmacokinetics of doxorubicin and liposomal doxorubicin. *Drug Metab Dispos.* 2004;32(8):794-9.
13. Tacar O, Sriamornsak P, Dass CR. Doxorubicin: an update on anticancer molecular action, toxicity and novel drug delivery systems. *J Pharm Pharmacol.* 2013;65(2):157-70.
14. Hanušová V, Boušová I, Skálová L. Possibilities to increase the effectiveness of doxorubicin in cancer cells killing. *Drug Metab Rev.* 2011;43(4):540-57.
15. Thorn CF, Oshiro C, Marsh S, Hernandez-Boussard T, McLeod H, Klein TE, Altman RB. Doxorubicin pathways: pharmacodynamics and adverse effects. *Pharmacogenet Genomics.* 2011;21(7):440-6.
16. Speth PA, Linssen PC, Boezeman JB, Wessels HM, Haanen C. Cellular and plasma adriamycin concentrations in long-term infusion therapy of leukemia patients. *Cancer Chemother Pharmacol.* 1987;20(4):305-10.
17. van der Zanden SY, Qiao X, Neefjes J. New insights into the activities and toxicities of the old anticancer drug doxorubicin. *FEBS J.* 2021;288(21):6095-111.
18. Dong KC, Berger JM. Structural basis for gate-DNA recognition and bending by type IIA topoisomerases. *Nature.* 2007;450(7173):1201-5.
19. Pommier Y, Leo E, Zhang H, Marchand C. DNA topoisomerases and their poisoning by anticancer and antibacterial drugs. *Chem Biol.* 2010;17(5):421-33.
20. Sritharan S, Sivalingam N. A comprehensive review on time-tested anticancer drug doxorubicin. *Life Sci.*2021;278:119527.
21. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. *Pharmacol Rev.* 2004;56(2):185-229.
22. Turkel I, Ozerklig B, Yilmaz M, Ulger O, Kubat GB, Tuncer M. Mitochondrial transplantation as a possible therapeutic option for sarcopenia. *J Mol Med (Berl).* 2023;101(6):645-69.
23. Hinde KL, O'Leary TJ, Greeves JP, Wardle SL. Measuring protein turnover in the field: Implications for military research. *Adv Nutr.* 2021;12(3):887-96.
24. Kubat GB, Bouhamida E, Ulger O, Turkel I, Pedriali G, Ramaccini D, et al. Mitochondrial dysfunction and skeletal muscle atrophy: Causes, mechanisms, and treatment strategies. *Mitochondrion.* 2023;72:33-58.
25. Powers SK, Lynch GS, Murphy KT, Reid MB, Zijdewind I. Disease-induced skeletal muscle atrophy and fatigue. *Med Sci Sports Exerc.* 2016;48(11):2307-19.
26. Pondugula SR, Salamat JM, Abbott KL, Flannery PC, Majrashi M, Almaghrabi M, et al. A clinically relevant combination treatment with doxorubicin and cyclophosphamide does not induce hepatotoxicity in C57BL/6J mice. *Liver Res.* 2021;5(4):239-42.
27. Mallard J, Hucteau E, Hureau TJ, Pagano AF. Skeletal muscle deconditioning in breast cancer patients undergoing chemotherapy: Current knowledge and insights from other cancers. *Front Cell Dev Biol.* 2021;9:719643.
28. Barreto R, Waning DL, Gao H, Liu Y, Zimmers TA, Bonetto A. Chemotherapy-related cachexia is associated with mitochondrial depletion and the activation of ERK1/2 and p38 MAPKs. *Oncotarget.* 2016;7(28):43442-60.
29. Gilliam LA, St Clair DK. Chemotherapy-induced weakness and fatigue in skeletal muscle: the role of oxidative stress. *Antioxid Redox Signal.* 2011;15(9):2543-63.
30. Gorini S, De Angelis A, Berrino L, Malara N, Rosano G, Ferraro E. Chemotherapeutic drugs and mitochondrial dysfunction: Focus on doxorubicin, trastuzumab, and sunitinib. *Oxid Med Cell Longev.* 2018;2018:7582730.
31. Pfeiffer T, Krause U, Thome U, Rajewski A, Skorzek M, Scheulen ME. Tissue toxicity of doxorubicin in first and second hyperthermic isolated limb perfusion--an experimental study in dogs. *Eur J Surg Oncol.* 1997;23(5):439-44.
32. Hayward R, Hydock D, Gibson N, Greufe S, Bredahl E, Parry T. Tissue retention of doxorubicin and its effects on cardiac, smooth, and skeletal muscle function. J Physiol Biochem. 2013;69(2):177-87.
33. Nissinen TA, Degerman J, Räsänen M, Poikonen AR, Koskinen S, Mervaala E, et al. Systemic blockade of ACVR2B ligands prevents chemotherapy-induced muscle wasting by restoring muscle protein synthesis without affecting oxidative capacity or atrogenes. *Sci Rep.* 2016;6:32695.
34. de Lima EA, de Sousa LGO, de STAA, Marshall AG, Zanchi NE, Neto JCR. Aerobic exercise, but not metformin, prevents reduction of muscular performance by AMPk activation in mice on doxorubicin chemotherapy. *J Cell Physiol.*2018;233(12):9652-62.
35. Hydock DS, Lien CY, Jensen BT, Schneider CM, Hayward R. Characterization of the effect of in vivo doxorubicin treatment on skeletal muscle function in the rat. *Anticancer Res.* 2011;31(6):2023-8.
36. Hulmi JJ, Nissinen TA, Räsänen M, Degerman J, Lautaoja JH, Hemanthakumar KA, et al. Prevention of chemotherapy-induced cachexia by ACVR2B ligand blocking has different effects on heart and skeletal muscle. *J Cachexia Sarcopenia Muscle.* 2018;9(2):417-32.
37. Hiensch AE, Bolam KA, Mijwel S, Jeneson JAL, Huitema ADR, Kranenburg O, et al. Doxorubicin-induced skeletal muscle atrophy: Elucidating the underlying molecular pathways. *Acta Physiol (Oxf).* 2020;229(2):e13400.
38. de Lima Junior EA, Yamashita AS, Pimentel GD, De Sousa LG, Santos RV, Gonçalves CL, et al. Doxorubicin caused severe hyperglycaemia and insulin resistance, mediated by inhibition in

AMPk signalling in skeletal muscle. ***J Cachexia Sarcopenia Muscle.*** 2016;7(5):615-25.
39. Kwon I. Endurance exercise training reinforces muscular strength with improvements in mitochondrial oxidative capacity, lysosome reformation, and myogenic differentiation against doxorubicininduced skeletal muscle wasting in mice. ***Phys Act Nutr.*** 2023;27(1):76-86.
40. Hu BA, Li YL, Han HT, Lu B, Jia X, Han L, et al. Stimulation of soluble guanylate cyclase by vericiguat reduces skeletal muscle atrophy of mice following chemotherapy. ***Front Pharmacol.*** 2023;14:1112123.
41. Wastag M, Bieżuńska-Kusiak K, Szewczyk A, Szlasa W, Grimling B, Kulbacka J. Celastrol and Rhynchophylline in the mitigation of simulated muscle atrophy under in vitro. ***Saudi Pharm J.*** 2022;30(10):1387-95.
42. Dessouki FBA, Kukreja RC, Singla DK. Stem cell-derived exosomes ameliorate doxorubicin-induced muscle toxicity through counteracting pyroptosis. ***Pharmaceuticals (Basel).*** 2020;13(12):450.
43. Doerr V, Montalvo RN, Kwon OS, Talbert EE, Hain BA, Houston FE, Smuder AJ. Prevention of doxorubicin-induced autophagy attenuates oxidative stress and skeletal muscle dysfunction. ***Antioxidants (Basel).*** 2020;9(3):263.
44. Wallace KB, Sardão VA, Oliveira PJ. Mitochondrial determinants of doxorubicin-induced cardiomyopathy. ***Circ Res.*** 2020;126(7):926-41.
45. Paradies G, Paradies V, Ruggiero FM, Petrosillo G. Role of cardiolipin in mitochondrial function and dynamics in health and disease: Molecular and pharmacological aspects. ***Cells.*** 2019;8(7):728.
46. Goormaghtigh E, Huart P, Praet M, Brasseur R, Ruysschaert JM. Structure of the adriamycin-cardiolipin complex. Role in mitochondrial toxicity. ***Biophys Chem.*** 1990;35(2-3):247-57.
47. Powers SK, Ji LL, Kavazis AN, Jackson MJ. Reactive oxygen species: impact on skeletal muscle. ***Compr Physiol.*** 2011;1(2):941-69.
48. Starkov AA. The role of mitochondria in reactive oxygen species metabolism and signaling. ***Ann N Y Acad Sci.*** 2008;1147:37-52.
49. Yu AP, Pei XM, Sin TK, Yip SP, Yung BY, Chan LW, et al. Acylated and unacylated ghrelin inhibit doxorubicin-induced apoptosis in skeletal muscle. A***cta Physiol (Oxf).*** 2014;211(1):201-13.
50. Smuder AJ, Kavazis AN, Min K, Powers SK. Exercise protects against doxorubicin-induced oxidative stress and proteolysis in skeletal muscle. ***J Appl Physiol (1985).*** 2011;110(4):935-42.
51. Gilliam LAA, Fisher-Wellman KH, Lin CT, Maples JM, Cathey BL, Neufer PD. The anticancer agent doxorubicin disrupts mitochondrial energy metabolism and redox balance in skeletal muscle. ***Free Radic Biol Med.*** 2013;65:988-96.
52. Gilliam LA, Moylan JS, Callahan LA, Sumandea MP, Reid MB. Doxorubicin causes diaphragm weakness in murine models of cancer chemotherapy. ***Muscle Nerve.*** 2011;43(1):94-102.
53. Smuder AJ, Kavazis AN, Min K, Powers SK. Exercise protects against doxorubicin-induced markers of autophagy signaling in skeletal muscle. ***J Appl Physiol (1985).*** 2011;111(4):1190-8.
54. Kang R, Zeh HJ, Lotze MT, Tang D. The Beclin 1 network regulates autophagy and apoptosis. ***Cell Death Differ.*** 2011;18(4):571-80.
55. Braun TP, Szumowski M, Levasseur PR, Grossberg AJ, Zhu X, Agarwal A, Marks DL. Muscle atrophy in response to cytotoxic chemotherapy is dependent on intact glucocorticoid signaling in skeletal muscle. ***PLoS One.*** 2014;9(9):e106489.
56. Martínez-Redondo V, Pettersson AT, Ruas JL. The hitchhiker's guide to PGC-1α isoform structure and biological functions. ***Diabetologia.*** 2015;58(9):1969-77.
57. Akın Ş, Kubat GB, Demirel HA. Exercise, mitochondrial biogenesis and disuse-induced atrophy. ***Turk J Sports Med.*** 2021;56(2):91-7.
58. Combs AB, Hudman SL, Bonner HW. Effect of exercise stress upon the acute toxicity of adriamycin in mice. ***Res Commun Chem Pathol Pharmacol.*** 1979;23(2):395-8.
59. Powers SK, Duarte JA, Le Nguyen B, Hyatt H. Endurance exercise protects skeletal muscle against both doxorubicin-induced and inactivity-induced muscle wasting. ***Pflugers Arch.*** 2019;471(3):441-53.
60. Morton AB, Mor Huertas A, Hinkley JM, Ichinoseki-Sekine N, Christou DD, Smuder AJ. Mitochondrial accumulation of doxorubicin in cardiac and diaphragm muscle following exercise preconditioning. ***Mitochondrion.***2019;45:52-62.
61. Dickinson JM, D'Lugos AC, Mahmood TN, Ormsby JC, Salvo L, Dedmon WL, et al. Exercise protects skeletal muscle during chronic doxorubicin administration. ***Med Sci Sports Exerc.*** 2017;49(12):2394-403.
62. Mesquita PHC, Lamb DA, Godwin JS, Osburn SC, Ruple BA, Moore JH, et al. Effects of resistance training on the redox status of skeletal muscle in older adults. ***Antioxidants (Basel).*** 2021;10(3):350.
63. Kanter MM, Hamlin RL, Unverferth DV, Davis HW, Merola AJ. Effect of exercise training on antioxidant enzymes and cardiotoxicity of doxorubicin. ***J Appl Physiol (1985).*** 1985;59(4):1298-303.
64. Sandri M, Lin J, Handschin C, Yang W, Arany ZP, Lecker SH, et al. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. ***Proc Natl Acad Sci U S A.*** 2006;103(44):16260-5.
65. Smuder AJ, Min K, Hudson MB, Kavazis AN, Kwon OS, Nelson WB, Powers SK. Endurance exercise attenuates ventilator-induced diaphragm dysfunction. ***J Appl Physiol (1985).*** 2012;112(3):501-10.
66. Elbl L, Vasova I, Tomaskova I, Jedlicka F, Kral Z, Navratil M, et al. Cardiopulmonary exercise testing in the evaluation of functional capacity after treatment of lymphomas in adults. ***Leuk Lymphoma.*** 2006;47(5):843-51.
67. Kavazis AN, Smuder AJ, Powers SK. Effects of short-term endurance exercise training on acute doxorubicin-induced FoxO transcription in cardiac and skeletal muscle. ***J Appl Physiol (1985).*** 2014;117(3):223-30.
68. Quinn CJ, Hydock DS. Effects of endurance exercise and doxorubicin on skeletal muscle myogenic regulatory factor expression. ***Muscles Ligaments Tendons J.*** 2017;7(3):418-25.
69. Kwon I. Protective effects of endurance exercise on skeletal muscle remodeling against doxorubicin-induced myotoxicity in mice. ***Phys Act Nutr.*** 2020;24(2):11-21.