Veteriner Farmakoloji ve Toksikoloji Derneği Bülteni

Bulletin of Veterinary Pharmacology and Toxicology Association

e-ISSN: 2667-8381

EFFECTS OF OXIDATIVE STRESS ON SOME CANCER TYPES AND TREATMENT APPROCHES: A REVIEW

Dilek Nur BESTİL[a]*
Hamdi UYSAL[b]

Ankara Üniversitesi, Veteriner Fakültesi, Biyokimya Anabilim Dalı, Ankara

ORCID[a]: 0000-0003-1565-1466
ORCID[b]: 0000-0002-2289-1815

***Sorumlu Yazar:** Dilek Nur BESTİL
E-Posta: dileknurbbestil@gmail.com

Geliş Tarihi: 17.09.2023
Kabul Tarihi: 20.03.2024

15 (1): 58-63, 2024
DOI: 10.38137/vftd.1361976

ABSTRACT. Cancer has historically been one of the greatest challenges as it greatly affects the well-being of humans and animals. Despite the current chemotherapeutic agent, it has formed the basis of hundreds of studies, since completely successful results have not been achieved in the treatment of cancer. The mechanism of cancer depends on many different factors. One of these factors, oxidative stress, plays an important role in the development of various types of cancer. In a normal healthy metabolism, mitochondria produce small amounts of reactive oxygen species (ROS) as a byproduct of oxygen metabolism. Oxidative stress can be defined as the deterioration of the antioxidant defense mechanism of the cell as a result of increased reactive oxygen species (ROS) levels. With the increase of oxidative stress in cells, it affects the expression of oncogenes and tumor suppressor genes and paves the way for cancer formation by disrupting the cell division mechanism.
With the use of different chemotherapeutic agents, plant-derived polyphenols interact to induce or inhibit apoptosis of cancer cells by acting at different stages of cancer formation. However, the use of chemotherapy can sometimes lead to permanent health problems. Chemotherapy is given in combination with various compounds to minimize persistent health problems. Some of these compounds are plant groups rich in polyphenols. However, there are various views on the use of plants. This review aims to explain the mechanisms of oxidative stress in cancer, evaluate the developed agents and investigate the use of polyphenols.

Keywords: Cancer; Oxidative stress; Polyphenol.

OKSİDATİF STRESİN BAZI KANSER TÜRLERİ VE TEDAVİ YAKLAŞIMLARI ÜZERİNDEKİ ETKİLERİ: DERLEME

ÖZET. Kanser, tarih boyunca insanlar ve hayvanlar için refah düzeyini büyük oranda etkilediğinden en büyük zorluklardan biri olmuştur. Mevcut kemoterapik ajana rağmen kanserin tedavisinde tam anlamıyla başarılı sonuçlar alınamadığından yüzlerce çalışmanın temelini oluşturmuştur. Kanserin mekanizması birçok farklı faktöre bağlıdır. Bu faktörlerden biri olan oksidatif stres, çeşitli kanser türlerinin gelişiminde önemli rol oynamaktadır. Normalde sağlıklı bir metabolizmada mitokondri, oksijen metabolizmasının bir yan ürünü olarak peroksit, süperoksit, hidroksil radikalleri ve tekli oksijen gibi küçük miktarlarda reaktif oksijen türleri (ROS) üretir. Elektron alıcı moleküller olarak adlandırılan serbest radikallerin oksijen türevlerine ise oksidanlar denir. Oksidatif stres, reaktif oksijen türlerinin (ROS) düzeylerinin artması sonucu hücrenin antioksidan savunma mekanizmasının bozulması olarak tanımlanabilir. Oksidatif stresin bozulması endojen ve ekzojen kaynaklıdır. Hücrelerdeki oksidatif stresin artmasıyla onkogenlerin ve tümör baskılayıcı genlerin ekspresyonunu etkiler ve hücre bölünme mekanizmasının bozulmasıyla kanser oluşumuna zemin hazırlar.
Farklı kemoterapötik ajanların kullanımıyla bitki kaynaklı polifenoller, kanser oluşumunun farklı aşamalarında etki göstererek kanser hücrelerinin apoptozunu indüklemek veya inhibe etmek için etkileşime girer. Ancak kemoterapiklerin kullanımı bazen kalıcı sağlık sorunlarına yol açabilmektedir. Kalıcı sağlık sorunlarını en aza indirmek için kemoterapi çeşitli bileşiklerle kombinasyon halinde verilir. Bu bileşiklerin bir kısmı polifenoller açısından zengin bitki gruplarıdır. Fakat bitki kullanımına yönelik çeşitli görüşlerde mevcuttur. Bu derlemenin amacı kanserde oksidatif stresin mekanizmalarını açıklamak, geliştirilen ajanları değerlendirmek ve polifenollerin kullanımını araştırmaktır.

Anahtar Kelimeler: Kanser; Oksidatif stres; Polifenol.

Makale atıf

Bestil, D. N. ve Uysal, H. (2024). Effects of Oxidative Stress on Some Cancer Types and Treatment Approches: A Review, Veteriner Farmakoloji ve Toksikoloji Derneği Bülteni, 15 (2), 58-63. DOI: 10.38137/vftd.1361976.

INTRODUCTION

Mitochondria are organelles responsible for many important activations such as cellular energy production, calcium storage and intracellular signaling, apoptosis to meet metabolic needs. In normal cells, mitochondria produce Reactive Oxygen Species (ROS), which are called by-products of metabolism, these products are hydroxyl radicals, superoxide, peroxide. Oxygen variants of free radicals, which are referred to as electron donor molecules in biological systems, are referred to as oxidants. These radicals are very important in cell signaling (Starobova et al., 2017). Whereas oxygen is necessary for life, its metabolism commonly produces ROS in variety of pathological conditions including neurodegenerative, autoimmune, cardiovascular, and cancer. The body protects homeostasis during ROS production and detoxification via the antioxidant mechanism. Oxidative Stress (OS) occurs when the cellular balance found by Helmut Sies in 1985 is disrupted in favour of ROS and antioxidative defence decreases (Milkovic et al., 2014). Briefly, OS is a stress signal reflecting excessive ROS production that exceeds the antioxidant capacity within the cell (Cheng et al., 2016).

ROS are generated during normal cell metabolism. Although ROS have a key role in healthy cell signaling pathways, excessive ROS destroy genomic and mitochondrial DNA, causing DNA damage, mutations of the molecule and alterations in signaling pathways (Zhang et al., 2021). Disruption of cellular homeostasis is caused by mitochondrial malfunction raised metabolic activity, oncogenic activity or infiltrating immune cells (Ohl et al., 2018). With epidemiological studies, chronic oxidative stress has been related to cancer, so the involvement of oxidative stress in cancer disease process is quite remarkable (Klaunig, 2018).

Currently, ROS are considered as significant signaling molecules as they act as messengers not only in the cell but also in the extracellular environment and thus modulate different redox-sensitive reactions. The role of redox homeostasis in the cell is to maintain the ratio of reductants to oxidants through the activity of phosphates and kinases, to differentiate gene expression by affecting the transcriptional mechanism, and to differentiate signaling pathways (Milkovic et al., 2014).

Catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPX) form the enzymatic antioxidant system, in contrast glutathione, carotenoids, thioredoxin, vitamin C, vitamin E, flavonoids form the non-enzymatic antioxidant system (Milkovic et al., 2014). Oxidative balance is very important in cell metabolism and if the mitochondria that control this homeostasis are harmed under continuous oxidative stress, their function is impaired. During these conditions, like β oxidation, oxidized cofactors (NAD+ and FAD) are changed into decreased cofactors (NADH and FADH2). Electrons are transferred to the respiratory cycle. The carriage of electrons into and out of the mitochondrial (ETC) respiratory chain produces an unbalance that leads to the accumulation of ROS (Borrelli et al., 2018).

The relationship of OS with tumor development and chronic inflammation has been associated with its effect on cytokine, oncogene and tumor suppressor gene modulation (Thapa et al., 2015). Besides their antioxidant capability to protect against oxidative stress-induced harm, polyphenols exert several of their biological effects through chromatin remodeling and other epigenetic modifications (Mileo et al., 2016). Oxidative stress originates from two different sources, which are named as endogenous and exogenous sources. The endogenous source of ROS is generated from mitochondria, inflammatory cells and peroxisomes. Environmental factors such as UV light, radiation, industrial chemicals, dietary factors (peroxidised lipids, polycyclic-aromatic hydrocarbons, preservatives, etc.) are exogenous sources (Cheng et al., 2016). ROS are produced as by-products of cellular metabolic processes or by signaling molecules in pathogen-induced inflammation (Lee et al., 2013).

Cancer formation is a multi-stage pathway that contains cells and molecules changes that cause the differentiation of a healthy cell into a malignant neoplastic cell. The earliest stages of cancer development are divided into three defined phases on the basis of the molecules, cells and pathological properties of the transition of a healthy cell to a neoplastic zone. These three phases are described like initiation, promotion and progression. Initiation is the first step that develops with the continuation of the genomic DNA mutation of the normal cell. The contact of physical and chemical carcinogens with DNA results in the first phase. The genotoxic substance term refers to physical and chemical carcinogens that can cause direct harm to DNA and have mutagenic effects. Furthermore, mutations that occur spontaneously via inappropriate

repair of defectived DNA can generate triggered cells. Oxidative stress and the resulting unrepairable DNA seem to present a major source of spontaneous alterations. Following the generation of induced cells, physiological endogenous factors and/or exposure to chemicals cause specific clonal growth of the induced cell during the period of tumor progression (Klaunig, 2018).

Promotion is an epigenetic step that does not involve DNA damage. The distinctive feature of the promotion step is the alteration of gene expression leading to an upregulation in the number of preneoplastic cells via cell division or a decline in cell death (apoptosis). The initiation and progression of cancer is directed by not only genetic changes acquired, but also epigenetic modifications of gene expression (Choi et al., 2013). After further genomic modification, the final stage of development of benign or malignant neoplasms is called 'PROGRESSION' (Klaunig, 2018).

Oxidative Stress Biomarkers

Measurement and repair of oxidative stress is difficult due to the complex endogenous defence system. Therefore, the increase in antioxidant consumption or metabolites is evaluated as a biomarker. Malondialdehyde (MDA, 8-OH deoxyguanosine (8-OHdG), protein oxidation, glutathione peroxidase (GPX), superoxide dismutase (SOD), glutathione S transferase (GST), catalase (CAT), glutathione reductase (GR) are used as OS biomarkers (Blumberg., 2004). GSH (glutathione) is one of the important antioxidant small molecules and is the most measured biomarker. Increased levels of this antioxidant molecule and its oxidized version (GSSG) have been reported in many diseases as markers of oxidative stress (Estornut et al., 2022). The GSH level in mitochondria is sustained by glutathione reductase and NADPH is a key degrading substrate for enzyme-dependent GSH conversion. This is extremely significant as mitochondria do not synthesize GSH, but receive it directly of cytosol via a multiple-component delivery system. Mitochondrial GSH depletion or oxidation facilitates enhanced mitochondrial permeability and the secretion of proapoptotic molecules like cytochrome c to the cytosol (Obrador et al., 2019).

There are many biomarkers used to understand the way in which oxidative stress is implicated in cancer pathophysiology. The determination of MDA levels, 8-OHdG or antioxidant defence enzymes has enormous recognition power in oncology. Research have shown that a decreasing antioxidant level and elevated levels of oxidative stress are diagnosed in cancer ills even before chemotherapy therapy is started (Jelic et al., 2021). Oxidative Stress, genomic mutation of DNA is an important factor in cancer development. Oxidative stress and the consequent modification of DNA bases may cause spot modifications, deletions, translocation of chromosomal and cause oncogene activation or tumor inhibitor gene deactivation (Toyokuni, 2006). Oxidative DNA base 8-OHdG is commonly recognized as a marker of oxidative DNA harm, by its measurement as a marker of oxidative stress. Measurement of 8-OHdG from body fluids blood and urine can be used to monitor both the production and repair aspects of oxidative DNA damage (Valavanidis et al., 2009).

Oxidative Stress and Mechanisms of Cancer

According to the results of the studies, chronic oxidative stress is associated with cancer. Comprehensive experimental data confirm the role of ROS in tumor initiation, progression and promotion (Ishikawa et al., 2008). DNA molecule is susceptible to harm and modification of purine and pyrimidine bases by hydroxyl radicals. The occurring attachment 8-OHdG can form at the time ROS generation (especially via the hydroxyl radical), that is a direct related to the enhanced mutagenesis. Elevated oxidative stress alters the redox potential from cell, leading to altered modulation of gene activity (Forcados et al., 2008).

OS also appears a key role in chronic inflammation, carcinogenesis, tumor growth, and tumor invasion due to the complex and dynamic characteristics and actions in the tumor microenvironment (TME). Rewilding tumor-related stromal or immune cells in the TME enables a step to recover of disease-impaired immune surveillance to improve general survival and decrease drug resistance in cancer patients (Cheng et al., 2016).

NF-κB expression has been shown to promote cell proliferation, while blocking NF-κB expression blocks cell proliferation. In addition, tumor cells derived from blood neoplasms and cell lines from various cancers, which include colon, breast, pancreatic and squamous cell carcinoma, are all shown to express constitutively expressed NF-κB. While mild oxidative stress may cause moderate NF-κB activation, intense oxidative stress

inhibits NF-κB (Gloire et al., 2006).

Approaches to Oxidative Stress in Pancreatic Cancer

Pancreatic cancer is one of the cancers with high mortality. There are new approaches in its treatment with gene therapy and supplements of a potential anticancer agent (Sato-Dahlman et al., 2018). Melatonin is released from the pineal gland to regulate the circadian rhythm by the biological clock in the hypothalamic suprachiasmatic nucleus. Several of the main roles of the blood melatonin rhythm involve the regulation of sleep, regulation of circadian rhythms, and participation in the immune system. Melatonin is as well a potent endogenous antioxidant (Esposito et al., 2010). Complement has anti-radical and anti-inflammatory effects. Unbalance among cells oxidants and antioxidants, a direct radical clear and an indirect antioxidant, has a key role in the pathophysiology of pancreatic cancer. The combination with chemotherapy, melatonin enhanced ROS, mitochondrial membrane depolarization and apoptosis and also suppressed cell viability of pancreatic tumor in the pancreatic tumor cell line AR42J. Melatonin administration decreased zone of cancer cysts and elevated glutathione, catalase and superoxide dismutase in pancreatic cancer cells in hamsters. Melatonin is a highly potent antioxidant and tissue defender that prevents increased oxidative stress. Studies have demonstrated that melatonin supplements are a suitable curative therapy of pancreatic cancer. Melatonin can be an effective apoptosis stimulant in cancer cells through modulating multiple molecular progress involving oxidative stress and vascular endothelial growth factor (Tamtaji et al., 2019).

Approaches to Oxidative Stress in Leukemia

Leukemia is a type of cancer characterized by heterogeneous hematopoietic stem cell (HSC) malignancies; an abnormal collection of non-differentiated blasts with the ability to multiply indefinitely in the bone marrow that inhibit the generation of healthy blood cells (Siegel et al., 2019).

Iron, an essential element of metabolism, is participated in many types of physiological activities. Iron enables cell growth and proliferation, however, its excess leads to oxidative stress injury. Iron's capability to take and give electron allows it to join in the reactions that produce free radicals. Iron metabolism in leukemia is affected not at least by alterations in cells iron intake, accumulation and output, but also by deregulation of the ferroportin-hepsidin modulatory complex. Whereas iron and catalytic ROS generation are crucial for the maintenance of hematopoietic homeostasis, iron accumulation and consequent elevated oxidative stress are harmful for healthy hematopoiesis. Iron chelators are native or artificial some molecules that are capable of decreasing intracellular iron levels by connecting iron via a high-affinity and encouraging iron removal (Zhou et al., 2018). In recent years, the administration of iron chelators has been suggested as an effective anti-leukemia medical Iron chelators show antileukemia efficacy via various mechanisms, in particular by raising ROS levels and increasing intracellular iron chelation and activating several different signaling pathways in leukemia cells. Although research in the last few years has expanded studies on the upregulation of iron in leukemia and therapeutic approaches targeting iron metabolism, Further exploration is required to elucidate the detailed underlying mechanism linking iron, oxidative stress and leukemia progression. The development of nanotechnology has led to attempts to exploit the medical benefits of iron-based nanoparticles (Wang et al., 2019).

Polyphenols as Oxidative Stress Modulators in Cancer

Many epidemiological studies show that dietary intake, especially the Mediterranean diet, has a cancer-preventive effect. The useful impacts of diet can be attributed to polyphenols, that possess antitumor effects both in animal models and in humans. Increased interest in natural polyphenols over the last few years added to the understanding of the chemical and biological functions of such compounds and their useful impacts on human and animal health. Many of the useful impacts of natural polyphenol is thought to mirror the capability to clear free radicals, which are endogenously produced and produced from ionizing radiation and xenobiotics. According to several reports, the antioxidant features of phenolic components cannot entirely explain their chemotherapeutic properties. Evidence suggests that they can also act at the same time as prooxidants to trigger reactive oxygen species-mediated cellular DNA degradation and resulting cell death. Prosenescence-polyphenol therapy may minimize the adverse effects and toxicity of traditional treatments in cancer sufferers. Furthermore, careful caution should be exercised during

the clinical trials of this treatment as induction of ageing may lead to dormant tumor cells, particularly cancer stem cells, that has the potential to cause cancer (Mileo et al., 2016).

Therefore, incorrect intake of antioxidants can be detrimental since the use of antioxidants leads to the complete elimination on all cellular ROS. In contrast, excessive production of ROS causes cell injury, ageing and a variety of disorders. Further research focusing on the correlation levels of these biomarkers and disease progression is needed (Borrelli et al., 2018). Polyphenols are prooxidative by virtue of their electron donating ability. For example, salicylic acid and anthocyanidins induce reactive apoptosis and the mitochondrial pathway of apoptosis by inactivating tumor cell defensive catalase and hence intercellular ROS signaling of tumor cells (Jelic et al., 2021).

There are two conflicting views on the potential value of antioxidants. The first argues that antioxidants may lessen the effectiveness of radiotherapy and chemotherapy, whereas the second argues antioxidants may inhibit the growth of malignant cells and prevent patients from the toxic adverse effects of treatment. Thus, no easy answer exists as to the use of antioxidants in the treatment of cancer (Milkovic et al., 2021). The particular type of ROS engaged in the anticancer activity mediated by the specific herbal compound should be analyzed and elucidated to ensure more profound mechanisms of pharmaceutical activity and the effect of the herbal compound, which may aid future therapeutic design and applications. Identification of critical pathways to support antitumor immune replies and sustain a specific level of OS in cancer cells and their related microenvironment may enhance curative efficiency and results, which may affect long term patients' well-being. It may impact long-term patient well-being (Cheng et al., 2016).

CONCLUSION

Cancer is regarded as one of the most widespread diseases affecting human and animal health and reducing the welfare of living beings. Therefore, it stands out as the most researched disease group. Research is based on a more complete knowledge of the etiology and mechanism of cancer. The etiology includes factors such as ageing, viral and bacterial diseases, inflammation pathogenesis and oxidative stress.

Due to the side effects of various chemotherapies and chemotherapy resistance, the need for new treatment approaches, effective agents and personalized treatment methods that will increase the patient's quality of life in cancer patients has necessitated scientific studies. Currently, there are two different views on the role of antioxidants in cancer treatment. According to one view, antioxidants can reduce the effectiveness of radiotherapy and chemotherapy, while according to the other view, antioxidants can inhibit the growth of malignant cells and protect patients from toxic side effects of treatment. Therefore, no easy answer exists as to whether antioxidants can be utilized in the treatment of cancer.

ROS and lipid peroxidation products generated during oxidative stress not only have cytotoxic effects but also act similarly in stressed cells, modulating signal transduction. In this context, pro-oxidants and antioxidants can be considered as modulators of specifically cellular redox signaling. Thus, it is necessary to analyze the possible utility of antioxidant supplements in treatment of healthy individuals and especially in cancer survivors.

REFERENCES

Blumberg, J. (2004). Use of biomarkers of oxidative stress in research studies. *The Journal of Nutrition,* 134(11), 3188S–3189S.

Borrelli, A., Bonelli, P., Tuccillo, M. F., Goldfine, I. D., Evans, J. L., Buonaguro, F. M. & Mancini, A. (2018). Role of gut microbiota and oxidative stress in the progression of non-alcoholic fatty liver disease to hepatocarcinoma: Current and innovative therapeutic approaches. *Redox Biology,* 15, 467–479.

Cheng, T., Yang, C. & Shyur, F. (2016). Phytomedicine-Modulating oxidative stress and the tumor microenvironment for cancer therapy. *Pharmacological Research,* 114, 128–143.

Choi, D. & Lee, S. (2013). Interplay between Epigenetics and Genetics in Cancer. *Genomics & İnformatics,* 11(4), 164-173.

Esposito, E. & Cuzzocrea, S. (2010). Antiinflammatory activity of melatonin incentral nervous system. *Current Neuropharmacology*, 8(3), 228–242.

Estornut, C., Milara, J., Bayarri, A., Belhadj, N. & Cortijo, J. (2022). Targeting Oxidative Stress as a Therapeutic Approach for Idiopathic Pulmonary

Fibrosis. *Frontiers in Pharmacology*, 12, 794997.

Forcados, E., James, B., Sallau, B. & Mabeta P. (2017). Oxidative Stress and Carcinogenesis: Potential of Phytochemicals in Breast Cancer Therapy. *Nutrition and Cancer*, 69(3), 365–374

Gloire, G., Legrand-Poels, S. & Piette, J. (2006). NF-kappaB activation by reactive oxygen species: fifteen years later. *Biochemical Pharmacology*, 72(11), 1493–1505.

Ishikawa, K., Takenaga, K., Akimoto, M., Koshikawa, N., Yamaguchi, A., Imanishi, H., Nakada, K., Honma, Y. & Hayashi J-I. (2008). ROS-generating mitochondrial DNA mutations can regulate tumor cell metastasis. *Science (New York, N.Y.)* 320(5876), 661–664.

Jelic, D., Mandic, D., Maricic, M. & Srdjenovic, U. (2021). Oxidative stress and its role in cancer. *Journal of Cancer Research and Therapeutics*, 17(1), 22–28.

Klaunig, E. (2018). Oxidative Stress and Cancer. *Current Pharmaceutical Design*, 24(40), 4771–4778.

Lee, L., Huang, Y. & Shyur, F. (2013). Phytoagents for cancer management: regulation of nucleic acid oxidation, ROS, and related mechanisms. *Oxidative Medicine and Cellular Longevity,* 925804.

Mileo, M. & Miccadei, S. (2016). Polyphenols as Modulator of Oxidative Stress in Cancer Disease: New Therapeutic Strategies. *Oxidative Medicine and Cellular Longevity,* 6475624.

Milkovic, L., Siems, W., Siems, R. & Zarkovic, N. (2014). Oxidative stress and antioxidants in carcinogenesis and integrative therapy of cancer. *Current pharmaceutical design,* 20(42), 6529–6542.

Obrador, E., Liu-Smith, F., Dellinger, W., Salvador, R., Meyskens, L. & Estrela, M. (2019). Oxidative stress and antioxidants in the pathophysiology of malignant melanoma. *Biological Chemistry,* 400(5), 589–612.

Ohl, K. & Tenbrock, K. (2018). Reactive Oxygen Species as Regulators of MDSC-Mediated Immune Suppression. *Frontiers in İmmunology*, 9, 2499.

Sato-Dahlman, M., Wirth, K. & Yamamoto, M. (2018). Role of genetherapy in pancreatic cancer—A review. *Cancers,* 10(4), 103.

Siegel, L., Miller, D. & Jemal, A. (2019). Cancer Statistics. CA: *A Cancer Journal for Clinicians,* 69(1), 7–34.

Starobova, H. & Vetter, I. (2017). Pathophysiology of Chemotherapy-Induced Peripheral Neuropathy. *Frontiers in Molecular Neuroscience*,10, 174.

Tamtaji, R., Mirhosseini, N., Reiter, J., Behnamfar, M. & Asemi, Z. (2019). Melatonin and pancreatic cancer: Current knowledge and future perspectives. *Journal of Cellular Physiology,* 234(5), 5372–5378.

Thapa, D. & Ghosh, R. (2015). Chronic inflammatory mediators enhance prostate cancer development and progression. *Biochemical Pharmacology*, 94(2), 53–62.

Toyokuni, S. (2006). Novel aspects of oxidative stress-associated carcinogenesis. *Antioxidants & Redox Signaling,* 8(7-8), 1373–1377.

Wang, F., Lv, H., Zhao, B., Zhou, L., Wang, S., Luo, J., Liu, J. & Shang, P. (2019). Iron and leukemia: new insights for future treatments. *Journal of Experimental & Clinical Cancer Research: CR,* 38(1), 406.

Valavanidis, A. & Vlachogianni, T. (2009). Fiotakis C. 8-hydroxy-2’ -deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. *Journal of Environmental Science and Health. Part C, Environmental Carcinogenesis & Ecotoxicology Reviews,* 27(2), 120–139.

Zhang, Y., Li, Q., Xu, D., Li, T., Gu, Z., Huang, P. & Ren, L. (2021). Idarubicin-induced oxidative stress and apoptosis in cardiomyocytes: An in vitro molecular approach. *Human & Experimental Toxicology*, 40(12), S553–S562.

Zhou, L., Zhao, B., Zhang, L., Wang, S., Dong, D., Lv, H. & Shang, P. (2018). Alterations in Cellular Iron Metabolism Provide More Therapeutic Opportunities for Cancer. *International Journal of Molecular Sciences*, 19(5), 1545.