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ASTIMDA OKSİDATİF STRES

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Özet

Astım, her yaştan insanı, özellikle çocukları ve gençleri etkileyen, değişken ekspiratuvar hava akımı kısıtlanması ile karakterize kronik hava yolu hastalığıdır..Astımın insidansı küresel olarak 1% ile 20 % arasında değişmektedir ve astım morbidite ve mortaliteye neden olan kronik solunum hastalıkları arasında önde gelen nedenler arasında yer almaktadır. Astım gelişiminde genetik ve çevresel faktörlerin rol oynadığı bilinmektedir. Oksidatif stres (OS) lipit, protein ve DNA gibi makromoleküllerde ciddi hasarlara neden olmakta ve bu da solunum yolu hastalıklarında zararlı sonuçlara yol açmaktadır. Astımda artmış OS, lipid peroksidasyonunu tetikler ve doku hasarını arttırır ve inflamatuar yanıta neden olur. Son zamanlarda OS'nin astım üzerindeki etkisini araştıran çalışmalar artarak devam etmektedir. Bu nedenle, astım patogenezinde oksidatif stresin kesin rolünün belirlenmesi klinik olarak çok önemlidir. Bu derlemede OS'nin astım üzerindeki etkisinin incelenmesi ve son yıllarda yapılan çalışmaların ve bulguların değerlendirilmesi amaçlanmıştır.

Anahtar Kelimeler: Astım, Oksidatif Stres, Serbest Radikal

OXIDATIVE STRESS IN ASTHMA

Abstract

Asthma is a chronic airway disease characterized by variable expiratory airflow limitation that affects people of all ages, especially children and teenagers. The incidence of asthma varies between 1% and 20% globally, and and asthma is among the leading causes of chronic respiratory diseases that cause morbidity and mortality. It is known that genetic and environmental factors play a role in the development of asthma. Oxidative stress (OS) causes serious damage to macromolecules such as lipid, protein and DNA, and this leads to harmful results in respiratory tract diseases. Increased OS in asthma triggers lipid peroxidation and increases tissue damage and causes inflammatory response. Recently, studies investigating the effect of OS on asthma continue to increase. Therefore, it is clinically very important to determine the exact role of OS in the pathogenesis of asthma. In this review, it is aimed to examine the effect of OS on asthma and to evaluate the recent studies and findings.

Key Words: Asthma, Oxidative Stress, Free Radical

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1. INTRODUCTION

Asthma is the most common chronic inflammatory airway disease characterized by impaired airflow and reactivity in the airway and that affects millions of people around the world especially both children and adults (Liu, Hua, & Song, 2022; Sordillo et al., 2019). It has been reported that more than 6 million children in the USA are affected by asthma and their quality of life has changed (Zahran, Bailey, Damon, Garbe, & Breysse, 2018). The most common major asthma symptoms in children include difficulty in breathing, coughing, and wheezing (Porsbjerg et al.,2023). The incidence and severity of asthma alter globally and continue to be common among chronic diseases that cause morbidity and mortality (Altın et al., 2019).

Recently, environmental problems have been increasing, especially due to globalization of the world. Chemical agents that harm the environment, such as air pollutants, are the main causes of these problems. Especially, people living in cities with poor air quality, smokers or those exposed to cigarette smoke in their environment, people with allergies, and with a family history of allergies or asthma are at serious risk for asthma (Turner et al., 2022). There is no definitive treatment for asthma, but it can be kept under control by regularly using the medications prescribed by physicians. On the basis of asthma treatment, step treatment is applied with periodic controls based on symptoms and examinations. Depending on the degree of signs and symptoms, your medications and their doses may vary.

The environmental changes caused by these induce an increase in free radicals and deterioration of the oxidant-oxidant balance, leading to oxidative stress (OS) (Michaeloudes et al., 2022). OS causes serious damage to macromolecules such as lipid, protein and DNA, and this leads to harmful results in respiratory tract diseases (Santus et al., 2014). Increased free radical production as a result of OS in asthma triggers lipid peroxidation and increases tissue damage and causes inflammatory response (Liu et al., 2022).

2. Free Radicals and Oxidative Stress

Atoms contain a nucleus and electrons usually move around this nucleus in pairs. Free radicals are any atom or molecule containing one or more unpaired electrons in their final orbitals. Because of these properties, they easily react with other molecules. Unpaired electrons change the chemical reactivity of atoms or molecules, causing them to become more reactive. Most of the free radicals can easily react with biomolecules and initiate the free radical formation chain reaction. To stop this chain reaction, the newly formed radical either reacts with another free radical to destroy unpaired electrons or reacts with a free radical scavenger or primary antioxidant. It is known that these free radicals, which have high reactivity, cause changes in the structure and functions of these molecules by acting on macromolecules, and cause cellular damage by causing permanent damage especially on nucleic acids, lipids and proteins from cell components (Zaric BL, Macvanin MT, Isenovic ER., 2023). Free radical formation in the cell occurs as a result of enzymatic and non-enzymatic reactions (Sen et al., 2010)

Sources of free radicals and other ROS are produced through basic metabolic processes (processes) within the body (endogenous) or through external sources (exogenous). Free radical sources can be considered in two groups as endogenous and exogenous sources (Phaniendra et al.,2015).

ROS produced from oxygen are the leading sources of free radicals in biological systems. Since the oxygen atom contains two unpaired electrons, it has high reactivity and desires to remove an electron from other molecules and reacts easily with other free radicals. ROS contains oxygen-derived chemically reactive molecules (Fridovich 1999). While some of these molecules are highly reactive (eg, hydroxyl radical), some (eg: superoxide and hydrogen peroxide) are less reactive. The abnormal increase in ROS is associated with OS and the diseases it causes, resulting in damage to proteins, lipids, and nucleic acids.

OS is defined as the biochemical dysregulation between ROS production and antioxidant defense systems and is an important biochemical marker of many diseases.

Under normal physiological conditions, free radicals and antioxidants are in balance.

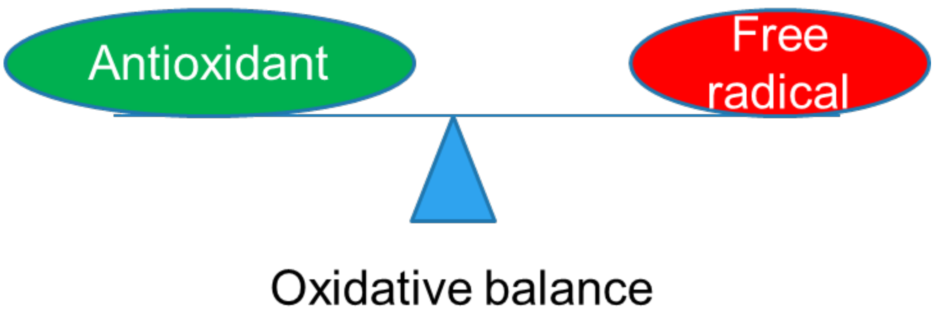

Figure 1: Oxidative balance

Due to the abnormal increase in free radicals, the oxidant-antioxidant balance shifts in favor of free radicals and causes the existing balance to deteriorate and OS to form (Özcan O, 2015).

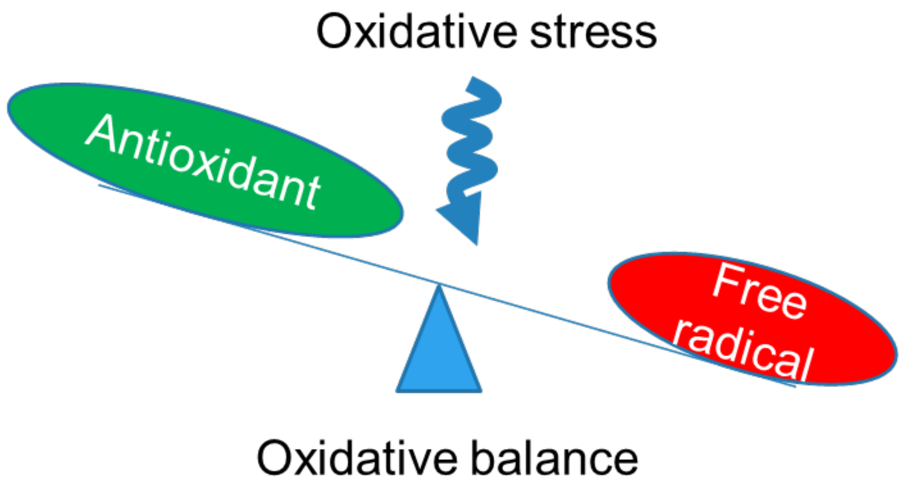

Figure 2: Impaired oxidative balance caused by OS

ROS are highly reactive molecules and are produced as a result of normal metabolism in cell organelles, especially in the mitochondria, or due to reasons such as ischemia-reperfusion, aging, radiation, high oxygen pressure, inflammation and exposure to chemical agents (Ozcan, Erdal, & Yonden, 2015; Erdal & Eröz, 2022). OS is responsible for the pathogenesis of many diseases (Demirtas & Erdal, 2023, Demirtas, Erdal, Kilicbay, & Tunc, 2023; Demirtas, Kilicbay, Erdal, & Tunc, 2023; Erdal, Ciftciler, Tuncer, & Ozcan, 2023; Erdal, Demirtas, Kilicbay, & Tunc, 2023; O. Ozcan et al., 2018; Erdal &Bekmezci, 2022; Erdal et al, 2022; Cakirca et al, 2018; Genc & Erdal, 2023).

ROS production is increased in asthma patients, and the antioxidant systems that will reduce this increase are insufficient. For this reason, asthma increases airway inflammation and sensitivity, which causes OS (Mishra, Banga, & Silveyra, 2018). Therefore, it is known that ROS and play an important role in the regulation of OS.

3. The Presence of Oxidative Stress in Asthma

Asthma is a chronic inflammatory disorder of the airway that affects people of all ages, especially children and teenagers (Ammar et al., 2022; Gunaydın et al.,2022; Ediger & Gunaydın, 2020). Although it is known that genetic and environmental factors play a common role in the development of asthma, its etiopathogenesis has not been clarified yet. Asthma commonly has two phenotypes, allergic and non-allergic (Qu, Li, Zhong, Gao, & Hu, 2017, Ediger & Gunaydın, 2023). Especially in allergic asthma, serious increases are seen in the amount of ROS as a result of the activation of inflammatory cells (Nadeem, Chhabra, Masood, & Raj, 2003). Depending on this increase, oxidant and antioxidant balance is disrupted and OS occurs (Özcan O, 2015). It is a known fact that OS plays an important role in the pathogenesis of asthma. As a result of the excessive increase in ROS production, it causes an increase in extracellular matrix protein production and proinflammatory cytokines in the airway. The effectiveness of systemic antioxidant defense mechanisms in asthmatic patients has not been fully demonstrated (Nadeem et al., 2003). For this reason, it is very important to study the markers of OS in asthma patients and to determine the role of these markers in determining the level of asthma (Karadogan, Beyaz, Gelincik, Buyukozturk, & Arda, 2022).

In the literature, there are many studies showing an increase in OS in patients with asthma. Nadeem et al.(Nadeem et al., 2003) reported that they found an increase in OS levels compared to the control group in their study in patients with asthma. They indicated that increased superoxide generation from leukocytes, increased NOx, increased protein carbonyls, and increased lipid peroxidation products and decreased protein sulfhydrils in plasma compared with healthy controls. They concluded that this is accompanied by alterations in several antioxidants in blood, including decreased GSH-Px activity in red blood cells and leukocytes and increased glutathione and SOD activity in red blood cells. In another study, Karadogan et al. (Karadogan et al., 2022) reported increased malondialdehyde and protein carbonyl levels in a study conducted in patients with allergic asthma. However, they showed that plasma glutathione levels decreased significantly.

Lutter et al. (Lutter, van Lieshout, & Folisi, 2015) showed that antioxidant levels and cytoprotective capacity are decreased in allergy and asthma patients. Rahman et al.(Rahman, Morrison, Donaldson, & MacNee, 1996) showed that the total antioxidant capacity was lower than the control group in their study in patients with asthma. In the study conducted by Ercan et al.(Ercan et al., 2006) in children with mild and severe asthma, they reported a decrease in GSH levels as well as an increase in MDA levels. They hypothesized that the increase in MDA levels was due to the consumption of GSH in patients with asthma. In addition to that, they concluded that disease severity was associated with an increase in OS.

Thiols are functional groups containing a sulfhydryl group (-SH) in their structure. Thiols with antioxidant properties are formed as a result of the bonding of a sulfur atom and a hydrogen atom attached to the carbon atom. The majority of the plasma thiol pool in biological systems consists of albumin thiols and protein thiols. The increase in OS leads to an imbalance in the reversible formation of dynamic disulfide bonds between protein thiol groups (Erdal et al., 2022). Many studies have shown that the thiol-disulfide balance plays a role in various diseases (Demirtas & Erdal, 2023; Demirtas, Erdal, et al., 2023; Demirtas, Kilicbay, et al., 2023; Deveci & Erdal, 2022; Erdal, Ciftciler, et al., 2023; Erdal, Demirtas, et al., 2023; Nar & Çalış, 2018; Erdal, Ozcan et al.,2022; Erdal, H., Yasar, E., & Tuncer, S. C., 2023).

Nar et al. (Nar & Çalış, 2018) in their study on asthmatic patients, they reported that serum native, total and disulfide levels were low, whereas CRP levels were higher than the control groups. They hypothesized that the thiol-disulfide balance would be impaired in patients with asthma. In the study of Pekin et al. (Pekince Md & Baccioglu Md, 2022) conducted on allergic and non-allergic patients due to air pollution, they found that serum TAS and TOS values were higher, and thiol levels were lower than the control group. In a different study, Dilek et al. (Dilek et al., 2016) plasma thiol pool study in children with asthma treated with montelukast monotherapy showed that montelukast monotherapy could restore the decreased plasma thiol pool in children with mild asthma. They concluded that a decrease in the antioxidant system occurred in children with asthma.

In another study, Cakmak et al. (Cakmak et al., 2009) reported that reported that they found lipid peroxidation levels high and paraxonase activity low in their study on children with asthma. They concluded that decreased paraoxonase activity may be associated with regional and ethnic differences.

4. Conclusion

In this review, we aimed to comprehensively discuss the effects of OS on the disease in patients with asthma. It is evident that asthma patients are exposed to OS as a result of the production of airways ROS and nitrogen species by inflammatory and epithelial cells. The extent to which increased OS affects asthma pathogenesis and disease severity is still unknown**.** Many studies have reported that OS is increased in patients with asthma. We think that it is important to comprehensively investigate the role of OS in the pathogenesis of asthma and it will make important contributions to the current subject.

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REFERENCES

Altın, S., Günaydın, F. E., Pamir, P., Kalkan, N., Veske, N. Ş., & Günlüoğlu, G. (2019). Does Asthma Lose its Importance in Respiratory System Deaths?. *Turk Toraks Dergisi*, *20*, 26. doi: 10.5152/TurkThoracJ.2019.26

Ammar, M., Bahloul, N., Amri, O., Omri, R., Ghozzi, H., Kammoun, S., . .Ben Mahmoud, L. (2022). Oxidative stress in patients with asthma and its relation to uncontrolled asthma. *J Clin Lab Anal, 36*(5), e24345. doi:10.1002/jcla.24345

Cakirca, G., Çelik, M., Erdal, H., Neşelioğlu, S., Erel, Ö., Basarali, M., & Cakirca, T. (2018). Investigation of thiol/disulfide homeostasis in familial mediterranean fever patients. *Journal Of Clinical And Analytical Medicine*, *9*(3),231-234. doi: 10.4328/JCAM.5789

Cakmak, A., Zeyrek, D., Atas, A., Selek, S., & Erel, O. (2009). Oxidative status and paraoxonase activity in children with asthma. *Clinical and Investigative Medicine*, 327-334.

Demirtas, M. S., & Erdal, H. (2023). Evaluation of thiol-disulfide homeostasis and oxidative stress parameters in newborns receiving phototherapy. *J Investig Med, 71*(3), 183-190. doi:10.1177/10815589221140594

Demirtas, M. S., & Erdal, H. (2023). Evaluation of thiol disulfide balance in adolescents with vitamin B12 deficiency. *Ital J Pediatr, 49*(1), 3. doi:10.1186/s13052-022-01396-2

Demirtas, M. S., Erdal, H., Kilicbay, F., & Tunc, G. (2023). Association between thiol-disulfide hemostasis and transient tachypnea of the newborn in late-preterm and term infants. *BMC Pediatr, 23*(1), 135. doi:10.1186/s12887-023-03936-z

Demirtas, M. S., Kilicbay, F., Erdal, H., & Tunc, G. (2023). Oxidative Stress Levels and Dynamic Thiol-Disulfide Balance in Preterm Newborns with Bronchopulmonary Dysplasia. *Lab Med.* doi:10.1093/labmed/lmad010

Deveci, M. Z. Y., & Erdal, H. (2022). Determination of dynamic thiol-disulfide levels in dairy cattle with foot disease. *Veterinarski arhiv, 92*(6), 657-666. doi: 10.24099/vet.arhiv.1785

Dilek, F., Ozkaya, E., Kocyigit, A., Yazici, M., Guler, E. M., & Dundaroz, M. R. (2016). Plasma total thiol pool in children with asthma: Modulation during montelukast monotherapy. *Int J Immunopathol Pharmacol, 29*(1), 84-89. doi:10.1177/0394632015621563

Ercan, H., Birben, E., Dizdar, E. A., Keskin, O., Karaaslan, C., Soyer, O. U., Kalayci, O. (2006). Oxidative stress and genetic and epidemiologic determinants of oxidant injury in childhood asthma. *J Allergy Clin Immunol, 118*(5), 1097-1104. doi:10.1016/j.jaci.2006.08.012

Ediger, D., & Günaydin, FE. (2020). Astım ve Alerjen İmmünoterapisi. *Güncel Göğüs Hastalıkları Serisi*, *8*(2), 55-61. doi: 10.5152/gghs.2020.017

Ediger, D., & Esra, F. (2023). Can omalizumab be an alternative treatment for non-atopic severe asthma? A real-life experience with omalizumab. *Tuberk Toraks*, *71*(1), 24-33.doi: 10.5578/tt.20239904

Erdal, H., Ciftciler, R., Tuncer, S. C., & Ozcan, O. (2023). Evaluation of dynamic thiol-disulfide homeostasis and ischemia-modified albumin levels in patients with chronic lymphocytic leukemia. *J Investig Med, 71*(1), 62-66. doi:10.1136/jim-2022-002568

Erdal, H., Demirtas, M. S., Kilicbay, F., & Tunc, G. (2023). Evaluation of Oxidative Stress Levels and Dynamic Thiol-disulfide Balance in Patients with Retinopathy of Prematurity. *Curr Eye Res*, 1-8. doi:10.1080/02713683.2023.2185569

Erdal, H., Ozcan, O., Turgut, F., Neselioğlu, Salim., Erel, Ö (2022). Evaluation of Dynamic Thiol-Disulfide Balance and Ischemia Modified Albumin Levels in Patients with Chronic Kidney Disease. *The Medical Journal of Mustafa Kemal University,* 13(47),237-242. doi: 10.17944/mkutfd.947113.

Erdal, H., & Eröz, R (2022). The known about familial mediterranean fever: literature review. A*ksaray University Journal of Sport and Health Researches.* 3(2), 145-155. doi:10.54152/ asujshr.1183793.

Erdal, H., Yasar, E., & Tuncer, S. C (2023). Determination of calprotectin levels in patients with cataract surgery. *Ann Clin Anal Med*, 2023;14(2):148-151. doi: 10.4328/ACAM.21474.

Günaydın, F. E., Ay, P., Karakaya, G., & Ediger, D (2022). How do we manage asthma? Assessment of knowledge, attitude, and practice patterns among pulmonologists and allergists. *Journal of Asthma*, 1-9. doi.org/10.1080/02770903.2022.2033261

Genc, S. O., & Erdal, H. (2023). Are pan-immune-inflammation value, systemic inflammatory response index and other hematologic inflammatory indexes clinically useful to predict first-trimester pregnancy loss? *Ann Clin Anal Med*, 14(5),473-477. doi.org/ 10.4328/ACAM.21626

Karadogan, B., Beyaz, S., Gelincik, A., Buyukozturk, S., & Arda, N. (2022). Evaluation of oxidative stress biomarkers and antioxidant parameters in allergic asthma patients with different level of asthma control. *J Asthma, 59*(4), 663-672. doi:10.1080/02770903.2020.1870129

Liu, K., Hua, S., & Song, L. (2022). PM2.5 Exposure and Asthma Development: The Key Role of Oxidative Stress. *Oxid Med Cell Longev, 2022*, 3618806. doi:10.1155/2022/3618806

Lutter, R., van Lieshout, B., & Folisi, C. (2015). Reduced Antioxidant and Cytoprotective Capacity in Allergy and Asthma. *Ann Am Thorac Soc, 12 Suppl 2*, 133-136. doi:10.1513/AnnalsATS.201503-176AW

Michaeloudes, C., Abubakar-Waziri, H., Lakhdar, R., Raby, K., Dixey, P., Adcock, I. M., . . . Chung, K. F. (2022). Molecular mechanisms of oxidative stress in asthma. *Mol Aspects Med, 85*, 101026. doi:10.1016/j.mam.2021.101026

Mishra, V., Banga, J., & Silveyra, P. (2018). Oxidative stress and cellular pathways of asthma and inflammation: Therapeutic strategies and pharmacological targets. *Pharmacol Ther, 181*, 169-182. doi:10.1016/j.pharmthera.2017.08.011

Nadeem, A., Chhabra, S. K., Masood, A., & Raj, H. G. (2003). Increased oxidative stress and altered levels of antioxidants in asthma. *J Allergy Clin Immunol, 111*(1), 72-78. doi:10.1067/mai.2003.17

Nar, R., & Çalış, A. G. (2018). Assessment of dynamic thiol/disulfide homeostasis in patients with asthma. *Journal of laboratory medicine, 42*(3), 99-104. doi.org/10.1515/labmed-2017-0144

Ozcan, O., Erdal, H., Ilhan, G., Demir, D., Gurpinar, A. B., Neselioglu, S., & Erel, O. (2018). Plasma Ischemia-Modified Albumin Levels and Dynamic Thiol/Disulfide Balance in Sickle Cell Disease: A Case-Control Study. *Turk J Haematol, 35*(4), 265-270. doi:10.4274/tjh.2018.0119

Ozcan, O., Erdal, H., & Yonden, Z (2015). İskemi-reperfüzyon hasari ve oksidatif stres ilişkisine biyokimyasal bakiş. *Mustafa Kemal Üniversitesi Tıp Dergisi, 6*(23), 27-33. doi: 10.17944/mkutfd.54113

Özcan O, E. H., Çakırca G, Yönden Z (2015). Oxidative stress and its impacts on intracellular lipids, proteins and DNA. *J Clin Exp Invest, 6*(3), 331-336. doi: 10.5799/ahinjs.01.2015.03.0545

Pekince Md, B., & Baccioglu Md, A (2022). Allergic and non-allergic asthma phenotypes and exposure to air pollution. *J Asthma, 59*(8), 1509-1520. doi:10.1080/02770903.2021.1955133.

Phaniendra A, Jestadi DB, Periyasamy L (2015). Free radicals: properties, sources, targets, and their implication in various diseases. *Indian J Clin Biochem,* 30(1):11-26. doi: 10.1007/s12291-014-0446-0.

Porsbjerg C, Melén E, Lehtimäki L, Shaw D (2023). Asthma. *Lancet,* 11;401(10379):858-873. doi: 10.1016/S0140-6736(22)02125-0.

Qu, J., Li, Y., Zhong, W., Gao, P., & Hu, C. (2017). Recent developments in the role of reactive oxygen species in allergic asthma. *J Thorac Dis, 9*(1), E32-E43. doi:10.21037/jtd.2017.01.05

Rahman, I., Morrison, D., Donaldson, K., & MacNee, W. (1996). Systemic oxidative stress in asthma, COPD, and smokers. *Am J Respir Crit Care Med, 154*(4 Pt 1), 1055-1060. doi:10.1164/ajrccm.154.4.8887607

Santus P, Corsico A, Solidoro P, Braido F, Di Marco F, Scichilone N (2014). Oxidative stress and respiratory system: pharmacological and clinical reappraisal of N-acetylcysteine. *Journal of Chronic Obstructive Pulmonary Disease.* 11(6):705-17. doi: 10.3109/15412555.2014.898040.

Sen, S., Chakraborty, R., Sridhar, C., Reddy, Y. S. R., & De, B. (2010). Free radicals, antioxidants, diseases and phytomedicines: current status and future prospect. *International journal of pharmaceutical sciences review and research*, *3*(1), 91-100.

Sordillo, J. E., Rifas-Shiman, S. L., Switkowski, K., Coull, B., Gibson, H., Rice, M., . . . Oken, E. (2019). Prenatal oxidative balance and risk of asthma and allergic disease in adolescence. *J Allergy Clin Immunol, 144*(6), 1534-1541 e1535. doi:10.1016/j.jaci.2019.07.044

Turner PJ, Arasi S, Ballmer-Weber B, Baseggio Conrado A, Deschildre A, Gerdts J, Halken S, Muraro A, Patel N, Van Ree R, de Silva D, Worm M, Zuberbier T, Roberts G. (2022). Global Allergy, Asthma European Network (GA2LEN) Food Allergy Guideline Group. Risk factors for severe reactions in food allergy: Rapid evidence review with meta-analysis. *Allergy,* 77(9):2634-2652. doi: 10.1111/all.15318.

Zahran, H. S., Bailey, C. M., Damon, S. A., Garbe, P. L., & Breysse, P. N. (2018). Vital Signs: Asthma in Children - United States, 2001-2016. *MMWR Morb Mortal Wkly Rep, 67*(5), 149-155. doi:10.15585/mmwr.mm6705e1

Zaric BL, Macvanin MT, Isenovic ER (2023). Free radicals: Relationship to Human Diseases and Potential Therapeutic applications. *Int J Biochem Cell Biol*. 154:106346. doi: 10.1016/j.biocel.2022.106346.