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Antioxidant Activity and Heart Diseases

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ABSTRACT

Cardiovascular disease (CVD), which are complex conditions with many pathophysiologic pathways, has increased oxidative stress as a possible common cause. For a cell to function normally, reactive oxygen species (ROS) and antioxidants must coexist in a delicate balance. High levels of ROS damage large cellular molecules including DNA, lipids and proteins, ultimately leading to necrosis and death, although their primary function is essential to shed light on biological processes. Oxidative stress, the leading cause of death globally in people with cardiovascular disease, has an impact on a variety of disorders. An increase in reactive oxygen species leads to a decrease in the availability of nitric oxide, which in turn leads to vasoconstriction and arterial hypertension. Reactive oxygen species also impair myocardial calcium processing by inducing apoptotic and hypertrophic signaling, which promote cardiac remodeling and arrhythmias. Last but not least, ROS has been shown to promote the growth of atherosclerotic plaques. This paper seeks to give an overview of oxidative stress in CVD with a focus on endothelial dysfunction before looking more closely at how it affects the most prevalent of these diseases. In order to reduce the impact of oxidative stress on CVD, appropriate nutrition and diets are reviewed afterwards.

KEYWORDS: reactive oxygen species, cardiovascular diseases, NADPH oxidase, antioxidant

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1. INTRODUCTION

Numerous cardiovascular conditions have been demonstrated to be connected, at least in part, to excessive production of reactive oxygen species (ROS) [1–4]. Superoxide, hydroxyl radicals, and peroxyl radicals are examples of oxygen free radicals that make up reactive oxygen species (ROS), as are hydrogen peroxide, hypochlorous acid, and ozone [5]. Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases and mitochondria are additional relevant sources of intracellular oxidant generation in most cell types (summarized as the NOX family of enzymes). In addition, various additional enzymes, including cyclooxygenases, lipoxygenases, cytochrome P450 enzymes, and xanthine oxidase, as well as other cell organelles, like the endoplasmic reticulum and peroxisome, contribute to the formation of intracellular ROS [6]. The main biological structures impacted by ROS and reactive nitrogen species include proteins, lipids, and DNA (RNS). As part of aerobic life, molecular oxygen is naturally produced in the form of ROS. The manifestation of numerous cellular processes, such as signal transduction pathways, defense against invasive pathogens, gene expression, and the stimulation of growth or death, is, in fact, dependent on basal levels of ROS [7]. Despite the critical importance of redox reactions, abnormal oxidant signaling has been linked to a variety of clinical diseases, including aging. Superoxide dismutase (SOD), peroxiredoxin (Prx), catalase (CAT), and glutathione peroxidase (GSH-Px) are examples of enzymes that the body uses to combat ROS. Other non-enzymatic substances include tocopherol/vitamin E, beta-carotene, ascorbate, glutathione (GSH), and nicotinamide (NAM) [8]. It has become clear that redox processes are as important in biology as phosphorylation-dephosphorylation reactions or key regulatory mechanisms for the genome and epigenome, such as acetylation-deacetylation and methylation-demethylation. Newer research tools enable the investigation of redox signaling pathways in sufficient chemical detail [9]. However, due to the significant subcellular variations in

redox potential and the brief half-life of ROS, analyzing redox systems is difficult. The detection of ROS has been made easier by the discovery of multiple oxidative stress biomarkers, but their clinical application still needs to be confirmed given the wide variation in oxidative stress between various diseases. Our comprehension of the processes involved in health and disease across the board in all biological systems will be enhanced by the use of genomes, epigenomics, and exposomics as well as redox imaging, redox proteomics, and redox metabolomics methods. The era of big data and artificial intelligence, which is currently in progress, will also give us new chances for the creation of oxidative stress knowledge bases and pave the way for redox treatment that is more tailored to the individual [9].

Globally, 17.6 million deaths in 2016 were linked to cardiovascular diseases (CVD), a 14.5% rise from 2006 [10]. CVD is the leading cause of death today, killing more people each year than cancer and chronic lung disease combined. The most common CVD is coronary heart disease (CHD) [10]. With an aging population and an increased incidence of obesity and diabetes, the burden and medical costs of CVD are expected to rise significantly in the coming decades. Despite significant efforts to shed light on the pathophysiologic mechanisms governing the onset and progression of CVD, much work remains to be done [11–13]. As a result, a better understanding of biomolecular mechanisms and their clinical implications is urgently required to reduce the burden of CVD, posing a serious challenge in medicine.

This review will demonstrate the role of oxidative stress in CVD by first illuminating the pathomechanisms underlying oxidative stress and CVD, with a special emphasis on a major contributor of disease, endothelial dysfunction. Following that, it delves into oxidative stress and inflammation in the most common of these diseases, before concluding with a discussion of the effects of diet and nutraceuticals on oxidative stress in CVD.

2. GENERAL INFORMATION ABOUT REACTIVE OXYGEN SPECIES PRODUCTION

2.1. Sources of ROS Production

ROS has both benefits and disadvantages. Oxidative stress happens when the generation of ROS outpaces the antioxidants' capacity to protect. As a result of metabolism, mitochondrial respiration, or specific enzymes, ROS are created. Numerous environmental factors, such as radiation exposure, UV exposure, tobacco smoke, and excessive alcohol use, promote the production of ROS and support the onset of many diseases, such as cancer and cardiovascular conditions. [14–15]. The main sources of ROS in the heart are the mitochondrial electron transport chain, NADPH oxidases (NOX), xanthine oxidases, and nitric oxide (NO) synthases. Dioxygen serves as a catalyst for the formation of ROS (O2). Superoxide anions (•O2) are in reality produced by dioxygen by capturing an electron. All other types of ROS, including the hydroxyl (•OH) and hydroperoxyl (•HO2) radicals, as well as other non-radical species like hydrogen peroxide (H2O2), which can produce the hydroxyl radical, are produced by these ROS, which are the most common in cells [16].

The superoxide anions can then react with NO to form peroxynitrite (ONOO-), or they can be oxidized by the enzyme superoxide dismutase (SOD) to yield hydrogen peroxide. The hydroxyl radical can also be created by the Haber-Weiss reaction between superoxide anions and hydrogen peroxide [17]. Additionally, after obtaining a proton, peroxynitrite is detoxified into peroxynitrous acid (ONOOH). In the presence of ferrous ions, hydrogen peroxide can cause the Fenton reaction, which produces hydroxyl radicals, and the activity of myeloperoxidases, which produces hypochlorous acid (HOCl). Glutathione peroxidase (GPX), catalase, and peroxiredoxins are the final three enzymes that detoxify hydrogen peroxide in water (Prx). Last but not least, singlet oxygen (^{1}O2) can be produced by mixing hypochlorous acid and hydrogen peroxide (Figure 1).

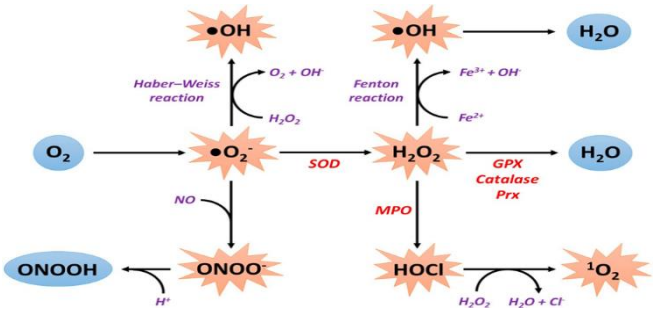

Figure 1. detoxification and ROS production. Singlet oxygen ($^1O_2$), chloride (Cl-), iron (II) and iron (III) ions, Fe^{2+} and Fe^{3+}, respectively, H^+: a proton; H_2O: water; H_2O_2: hydrogen peroxide; HOCl: hypochlorous acid; GPX: glutathione peroxidase; MPO: myeloperoxidases; NO: Nitric oxide, O2:oxygen, $•O_2^-$: superoxide anion, •OH: hydroxyl radical, ONOO-: peroxynitrite, ONOOH: peroxynitrous acid, Prx: peroxiredoxins, and SOD: superoxide dismutases.

2.2. Antioxidant Systems

Superoxide dismutase (SOD), catalase, glutathione-S-transferase, glutathione peroxidase, and glucose-6-phosphatedehydrogenase are just a few antioxidant defenses that shield biological systems from ROS toxicity. Other antioxidant defenses include non-enzymatic antioxidants like α-tocopherol, β-carotene and bilirubin [18] (Figure 2).

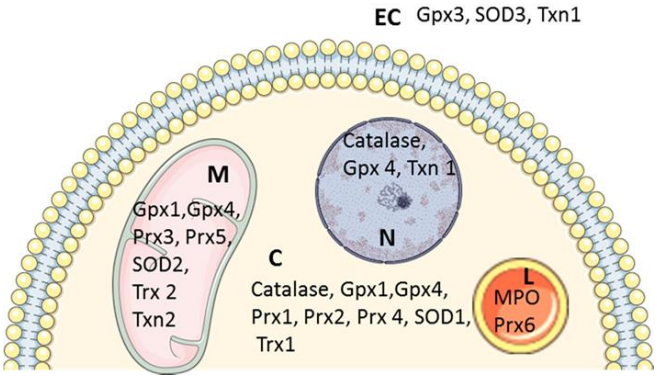

Figure 2. Compartmentalization of cardiac antioxidant enzymes. C: cytosol; EC: Extracellular compartment; L: lysosomes; M: mitochondria; N: nucleus; GPX 1–4: glutathione peroxidase 1–4; SOD 1–3: superoxide dismutase 1–3; Txn 1–2: thioredoxin 1 and 2; Trx 1–2: thioredoxin reductase 1 and 2; MPO: myeloperoxidase; **Prx 1–6: peroxiredoxin 1–6**

2.3 Superoxide Dismutases

SODs are metalloproteins that can change superoxide anion (•O2) into hydrogen peroxide (H2O2). It is the most effective antioxidant enzyme in humans. By detoxifying them, SODs do in fact limit the superoxide anions' interaction with NO and stop the production of peroxynitrite (ONOO-). Each of the three SOD isoforms—cytosolic SOD1, mitochondrial SOD2, and extracellular SOD3—has a specific subcellular location where it is located closer to the source of ROS production. The SOD2 tetramer, also known as MnSOD, uses manganese (Mn) as a cofactor in contrast to the Cu-ZnSOD dimer and SOD3 tetramer, which both require a connection to copper (Cu) and zinc (Zn), respectively. For these isoforms to function, certain metallic cofactors and dimerization are also necessary [19].

How SOD influences cardiovascular diseases has been discussed. As an illustration, decreasing SOD2 expression resulted in both increased cardiomyocyte size and mitochondrial oxidative stress [20]. Furthermore, within 10 days of birth, mice lacking SOD2 develop cardiomyopathy; in contrast, heterozygous SOD2(+/-) mice show ultrastructural damage to the myocardium and mitochondria, which is connected to an increase in oxidative stress (nitrotyrosine formation and lipid peroxidation) and the activation of apoptotic signaling pathways in the heart [21]. On the other hand, SOD3 activity was independently associated to abnormal left ventricular shape patterns [22].

2.4. Catalase

Several enzymes can detoxify hydrogen peroxide into water. One of them is the tetrameric heme protein catalase, which has a variety of roles depending on the concentration of hydrogen peroxide in the environment: in the case of high concentrations, catalytic detoxification activity is the most important, whereas in the case of low concentrations, peroxidase activity is the main role, with the peroxidation of various substrates like alcohol functions or ascorbic acid [23]. It's interesting to note that transgenic mice expressing mitochondria-targeted catalase show a decreased incidence of hypertension and mitochondrial oxidative stress brought on by cigarette smoke or angiotensin II (AngII) [24].

2.5. Peroxiredoxins

The enzymes known as peroxiredoxins (Prx) are able to halt the peroxide reactions that occur in a variety of chemicals, such as peroxynitrite and hydrogen peroxide. There are six distinct Prx isoforms in humans, and each one can be found in a different area of the cell [25] (Figure 2). Proteomic study has proven the cardiac involvement of peroxiredoxins 2 and 4 in cardiomyopathy and heart failure [26–27].

2.6. Glutathione Peroxidases

Utilizing the reducing properties of the glutathione/glutathione disulfide (GSH/GSSG) couple, tetrameric selenoproteins called glutathione peroxidases (Gpx) are in charge of detoxifying hydrogen peroxide in water and eliminating peroxide residues from lipids [19]. The cytoplasm, nucleus, and mitochondria all contain Gpx. Only if glutathione reductase, which is generated by a metabolic linkage with the pentose phosphate pathway and is itself active in the presence of NAPDH, continuously converts GSSG to GSH will this chain reaction system work [28]. Gpx4 is downregulated in the early and middle stages of myocardial infarction [29].

2.7. Non-Enzymatic Antioxidant Defense

In general, all proteins with thiol groups have reducing capabilities and are capable of quickly capturing ROS. In cells, glutathione is the main intracellular thiol and is primarily found in the reduced form. Glutathione is a cofactor of Gpx, a chelator of transition metals, and the last regenerator of vitamins C and E. These are just a few of the antioxidant qualities that glutathione possesses. Additionally, glutathione can interact with either the hydroxyl radical or the peroxide processes. Finally, it should be noted that the GSH/GSSG ratio is regarded as a very reliable indicator of oxidative stress, and more specifically, lipid peroxidation. The plasma analogue of glutathione is thought to be albumin. The most potent water-soluble antioxidant in human plasma is thought to be vitamin C, often known as ascorbic acid [28]. All of the tocopherol isomers are covered by vitamin E, primarily by α-tocopherol. The main means of importation is food, particularly oils, nuts, and hazelnuts. Vitamin E has a strong antioxidant effect by preventing lipid peroxidation due to its lipophilic nature and placement on the cell membrane.

3. NEW THERAPEUTIC STRATEGIES

Numerous studies have been undertaken to examine the therapeutic effects of antioxidant therapy because it has been shown that oxidative stress plays a significant role in cardiovascular diseases. Although numerous studies have shown that antioxidant therapy approaches have a protective effect in cellular or animal models, extensive clinical trials

have so far been unable to demonstrate any benefits of antioxidant therapy techniques.[30]

3.4. Vitamins

Many vitamins have been studied for their medicinal potential, and some advantages have been seen in animal models. In fact, vitamins, particularly vitamin C or folic acid, could stop NOS uncoupling and stop endothelial deterioration, which would result in cardioprotection [31,32]. On the other side, the "homocysteine theory" showed how extremely high blood levels of total homocysteine, an amino acid intermediary in the metabolism of methionine, caused atherosclerosis and thromboembolic events[33]. Indeed, oxidative stress and endothelial dysfunction are brought on by hyperhomocysteinemia [32,34]. Folic acid, vitamin B6, and vitamin B12 supplementation considerably lower total homocysteine levels. For example, inducing myocardial infarction in hyperhomocysteinemic rats decreases oxidative stress and improves cardiac function, such as heart rate, ST segment elevation, and blood pressure. Folic acid also improves endothelial function in vitro by reducing oxidative stress [35] and by folic acid and vitamin B (12) supplementation on isoprenaline [36]. A combination of vitamin E and apelin reduced apoptosis, oxidative stress, hypertrophy, and fibrosis in a mouse model of isoproterenol-induced cardiopathy, whereas vitamin E alone had no effect on cardiac remodeling [37], and vitamin D also improved cardiac oxidative stress and inflammatory markers in obese rats [36]. The strongest antioxidant form of vitamin E, however, -tocopherol, greatly decreased ROS (particularly lipid peroxidation), as well as the extent of the infarct and restored cardiac function (such as ejection fraction, fractional shortening, stroke volume, and cardiac output)[38].

3.5. Polyphenols

Polyphenols are secondary metabolites of plants that are present in fruits (including grapes, pear, apple, berries, and cherries), vegetables, tea, cereals, and coffee. They can be identified by the large multiples of phenol structural units that they contain. Many mechanistic investigations have shown that polyphenols have anti-inflammatory or antioxidant activities linked to cardioprotection, and they are described in [39]. For instance, adding red wine polyphenol extracts to the diet of Zucker fatty (ZF) rats decreased cholesterol and enhanced glucose metabolism, cardiac function, and endothelial dysfunction[40]. Moreover, polyphenols like the stilbene derivative resveratrol increase the production of antioxidant enzymes and their substrates, resulting in a general decrease in oxidative stress[41]. Many cardioprotective properties of resveratrol have been reported, and they are documented in detail in Importantly, it may prevent endothelial dysfunction and inflammation and enhance the production and activation of eNOS, which may help avoid hypertension in obese mice. [39,41,42,43]. Moreover, in rat cardiac myocytes, resveratrol could lessen phenylephrine-induced protein production and cell hypertrophy [44]. Resveratrol dramatically enhanced diastolic function and lowered cardiac fibrosis, as well as indicators for extracellular matrix remodeling and hypertrophy, in mice that had transverse aortic constriction-induced heart failure [45]. Last but not least, oral resveratrol delivery to hamsters elevated sirtuin 1 expression in cardiomyocytes, which promoted SOD2 activation, inhibited fibrosis, retained cardiac function, and markedly increased survival [46]. These findings collectively imply that polyphenols may represent cutting-edge therapeutic agents for the management of cardiovascular disease.

3.6. Mitochondrial-Targeted Antioxidant

The most significant compartment involved in the production of ROS is the mitochondria, and several strategies targeting mitochondria, including small molecules, mitochondria-targeting peptides, and antioxidants, have been tested in preclinical and clinical studies in cardiovascular diseases. Targeting mitochondria may be an interesting and promising approach.[47,48]. MitoTEMPO, a mitochondria-targeted superoxide dismutase mimic, was created in 2010 to accomplish this objective [49]. In vitro, mitoTEMPO reduces the levels of H2O2 and superoxide anion produced by human aortic endothelial cells in response to AngII [50] or cardiomyocytes from adult mice treated with high glucose [51]. The impact of mitoTEMPO is examined in numerous studies. For instance, administering mitoTEMPO to mice lowers blood pressure caused by AngII or deoxycorticosterone acetate (DOCA) salt [50], lowers the levels of 3-nitrotyrosine and the superoxide anion in the mitochondria, as well as the serum glucose and diastolic dysfunction seen in mice fed a high-fat diet [65], lowers the production of ROS in the mitochondria, and prevents cardiomyocyte hypertrophy in diabetic mouse hearts [51]. On the other hand, mitoquinone was created in 2001 [52] and has been shown to significantly increase mitochondrial activity and lessen redox-related cardiomyopathies [66, 52]. It consists of an exogenous ubiquinone connected to a triphenylphosphonium lipophilic cation. Furthermore, it has been reported in some investigations, particularly those involving cancer cells, that mitoquinone can also cause ROS generation, fast membrane depolarization, and apoptotic cell death[53, 54, 55].

3.7. Clinical Trials

Many randomized clinical trials have been conducted in both healthy and ill humans over the past ten years due to the preclinical benefits of antioxidants. Regrettably, the majority of these clinical trials [30, 56, 57]—or even those that reported a higher prevalence of chronic congestive heart failure in humans [58, 59]—failed to demonstrate an improvement of vitamin supplementation at the cardiovascular level. These detrimental effects could be explained, in part, by these molecules' inability to be site-specific with regard to the source of ROS generation (mitochondria, for example). Another explanation might be

the reactivity: for instance, the reaction between vitamin C and superoxide anion is 10,000 times less reactive than the reaction between superoxide anion and NO, which results in peroxynitrite (ONOO-), necessitating a significant dose and making oral administration impossible[30,60].

Also, the human clinical investigations that have been conducted so far have produced mixed results regarding the protective effects of resveratrol against cardiovascular illnesses. These studies are extensively discussed in [42, 61]. In a nutshell, some studies have found that resveratrol can reduce inflammation [67, 68] and endothelial dysfunction [62, 63], while other studies have found no benefit [63, 64]. This is likely because many of these trials used very varied resveratrol dosages and methods and had small sample sizes.

CONCLUSIONS

Elevated oxidative stress is one of the likely shared etiologies of diverse CVD, according to some research. There is strong evidence that free radicals (ROS and RNS) have a role in the pathogenesis of many medical conditions. The molecular pathways of oxidative stress that result in CVD are well understood already. There is no one mechanism that can account for the pathophysiology of these disorders due to their extremely complicated pathogenesis. Hence, it is important to consider oxidative stress and inflammation as contributors rather than as the main pathophysiologic causes. So, it should not be surprising that many clinical experiments looking at antioxidants have been unsuccessful. According to each person's level of oxidative stress, the benefits of antioxidants vary; those with higher levels of oxidative stress benefit more than those who already have low levels of ROS because ROS also play a critical physiologic role in cell homeostasis. The nutritional status of each individual should be taken into account as well. In high-income countries, a balanced diet provides more than enough vitamins; therefore, additional vitamin supplementation is unlikely to confer any benefit and may even cause harm. However, recent studies have indicated that antioxidant therapies reduce mortality (e.g., green tea, flavonoids, the Mediterranean diet). These studies do demonstrate that oxidative stress plays a crucial role in CVD and that reducing oxidative stress lowers cardiovascular and all-cause mortality, taking into account their advantages and disadvantages. These findings need to motivate researchers to carry out more studies on antioxidants and oxidative stress. Scientists shouldn't be deterred by negative antioxidant drug trials since oxidative stress is still a viable therapeutic target for cardiovascular disease.

REFERENCES

I. Tsutsui, H.; Kinugawa, S.; Matsushima, S. Oxidative stress and heart failure. *Am. J. Physiol. Circ. Physiol.* 2011, *301*, H2181–H2190. [CrossRef] [PubMed]

II. Tahhan, A.S.; Sandesara, P.B.; Hayek, S.S.; Alkhoder, A.; Chivukula, K.; Hammadah, M.; Mohamed-Kelli, H.; O'Neal, W.T.; Topel, M.; Ghasemzadeh, N.; et al. Association between oxidative stress and atrial fibrillation. *Heart Rhythm* 2017, *14*, 1849–1855. [CrossRef] [PubMed]

III. Baradaran, A.; Nasri, H.; Rafieian-Kopaei, M. Oxidative stress and hypertension: Possibility of hypertension therapy with antioxidants. *J. Res. Med. Sci.* 2014, *19*, 358–367. [PubMed]

IV. Kattoor, A.J.; Pothineni, N.V.K.; Palagiri, D.; Mehta, J.L. Oxidative Stress in Atherosclerosis. *Curr. Atheroscler. Rep.* 2017, *19*, 42. [CrossRef] [PubMed]

V. Liochev, S.I. Reactive oxygen species and the free radical theory of aging. *Free Radic. Biol. Med.* 2013, *60*, 1–4.[CrossRef] [PubMed]

VI. Holmström, K.M.; Finkel, T. Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nat. Rev. Mol. Cell Biol.* 2014, *15*, 411–421. [CrossRef] [PubMed]

VII. Finkel, T. Signal transduction by reactive oxygen species. *J. Cell Biol.* 2011, *194*, 7–15. [CrossRef] [PubMed]

VIII. Balaban, R.S.; Nemoto, S.; Finkel, T. Mitochondria, Oxidants, and Aging. *Cell* 2005, *120*, 483–495. [CrossRef] [PubMed]

IX. Sies, H.; Berndt, C.; Jones, D.P. Oxidative Stress. *Annu. Rev. Biochem.* 2017, *86*, 715–748. [CrossRef].

X. Benjamin, E.J.; Muntner, P.; Alonso, A.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Das, S.R.; et al. Heart Disease and Stroke Statistics—2019 Update: A Report from the American Heart Association. *Circulation* 2019, *139*, 2019. [CrossRef]

XI. Huynh, D.T.N.; Heo, K.-S. Therapeutic targets for endothelial dysfunction in vascular diseases. *Arch. Pharm. Res.* 2019. [CrossRef] [PubMed]

XII. Volobueva, A.; Grechko, A.; Yet, S.-F.; Sobenin, I.; Orekhov, A. Changes in Mitochondrial Genome Associated with Predisposition to Atherosclerosis and Related Disease. *Biomolecules* 2019, *9*, 377. [CrossRef] [PubMed]

XIII. Al Disi, S.S.; Anwar, M.A.; Eid, A.H. Anti-hypertensive Herbs and their Mechanisms of Action: Part I. *Front. Pharmacol.* 2016, *6*, 323. [CrossRef] [PubMed].

XIV. Al Hariri, M.; Zibara, K.; Farhat, W.; Hashem, Y.; Soudani, N.; Al Ibrahim, F.; Hamade, E.; Zeidan, A.; Husari, A.; Kobeissy, F. Cigarette sImoking-induced cardiac hypertrophy, vascular inflammation and injury are attenuated by antioxidant supplementation in an animal model. *Front. Pharmacol.* 2016, *7*, e397. [CrossRef].

XV. Gupta, S.C.; Hevia, D.; Patchva, S.; Park, B.; Koh, W.; Aggarwal, B.B. Upsides and downsides of reactive oxygen species for Cancer: The roles of reactive oxygen species in tumorigenesis, prevention, and therapy.*Antioxid. Redox Signal* 2012, *16*, 1295–1322.

[CrossRef].

XVI. Zorov, D.B.; Juhaszova, M.; Sollott, S.J. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol. Rev.* 2014, *94*, 909–950. [CrossRef] [PubMed].

XVII. Tsutsui, H.; Kinugawa, S.; Matsushima, S. Oxidative stress and heart failure. *Am. J. Physiol.-Heart Circ. Physiol.* 2011, *301*, 2181–2190. [CrossRef] [PubMed].

XVIII. Liguori, I.; Russo, G.; Curcio, F.; Bulli, G.; Aran, L.; Della-Morte, D.; Gargiulo, G.; Testa, G.; Cacciatore, F.; Bonaduce, D.; et al. Oxidative stress, aging, and diseases. *Clin. Interv. Aging* 2018, *13*, 757–772. [CrossRef] [PubMed].

XIX. Sharifi-Rad, M.; Kumar, N.V.A.; Zucca, P.; Varoni, E.M.; Dini, L.; Panzarini, E.; Rajkovic, J.; Fokou, P.V.T.; Azzini, E.; Peluso, I.; et al. Lifestyle, Oxidative Stress, and Antioxidants: Back and Forth in the Pathophysiology of Chronic Diseases. *Front. Physiol.* 2020, *11*, 694. [CrossRef].

XX. Dubois-Deruy, E.; Cuvelliez, M.; Fiedler, J.; Charrier, H.; Mulder, P.; Hebbar, E.; Pfanne, A.; Beseme, O.; Chwastyniak, M.; Amouyel, P.; et al. MicroRNAs regulating superoxide dismutase 2 are new circulating biomarkers of heart failure. *Sci. Rep.* 2017, *7*, 1–10. [CrossRef].

XXI. Strassburger, M.; Bloch, W.; Sulyok, S.; Schüller, J.; Keist, A.F.; Schmidt, A.; Wenk, J.; Peters, T.; Wlaschek, M.; Krieg, T.; et al. Heterozygous deficiency of manganese superoxide dismutase results in severe lipid peroxidation and spontaneous apoptosis in murine myocardium in vivo. *Free Radic. Biol. Med.* 2005, *38*, 1458–1470. [CrossRef].

XXII. Li, X.; Lin, Y.; Wang, S.; Zhou, S.; Ju, J.; Wang, X.; Chen, Y.; Xia, M. Extracellular Superoxide Dismutase Is Associated With Left Ventricular Geometry and Heart Failure in Patients with Cardiovascular Disease. *J. Am. Heart Assoc.* 2020, *9*, e016862. [CrossRef] [PubMed].

XXIII. Tehrani, H.S.; Moosavi-Movahedi, A.A. Catalase and its mysteries. *Prog. Biophys. Mol. Biol.* 2018, *140*, 5–12.[CrossRef] [PubMed].

XXIV. Detienne, G.; De Haes, W.; Mergan, L.; Edwards, S.L.; Temmerman, L.; Van Bael, S. Beyond ROS clearance: Peroxiredoxins in stress signaling and aging. *Ageing Res. Rev.* 2018, *44*, 33–48. [CrossRef] [PubMed].

XXV. Kuzuya, K.; Ichihara, S.; Suzuki, Y.; Inoue, C.; Ichihara, G.; Kurimoto, S.; Oikawa, S. Proteomics analysis identified peroxiredoxin 2 involved in early-phase left ventricular impairment in hamsters with cardiomyopathy. *PLoS ONE* 2018, *13*, e0192624. [CrossRef] [PubMed].

XXVI. Ibarrola, J.; Arrieta, V.; Sádaba, R.; Martinez-Martinez, E.; Garcia-Peña, A.; Alvarez, V.; Fernández-Celis, A.; Gainza, A.; Santamaría, E.; Fernández-Irigoyen, J.; et al. Galectin-3 down-regulates antioxidant peroxiredoxin-4 in human cardiac fibroblasts: A new pathway to induce cardiac damage. *Clin. Sci.* 2018, *132*, 1471–1485. [CrossRef].

XXVII. Cieniewski-Bernard, C.; Mulder, P.; Henry, J.-P.; Drobecq, H.; Dubois, E.; Pottiez, G.; Thuillez, C.; Amouyel, P.; Richard, V.; Pinet, F. Proteomic Analysis of Left Ventricular Remodeling in an Experimental Model of Heart Failure. *J. Proteome Res.* 2008, *7*, 5004–5016. [CrossRef].

XXVIII. Kalyanaraman, B. Teaching the basics of redox biology to medical and graduate students: Oxidants, antioxidants and disease mechanisms. *Redox Biol.* 2013, *1*, 244–257. [CrossRef].

XXIX. Park, T.J.; Park, J.H.; Lee, G.S.; Lee, J.Y.; Shin, J.H.; Kim, M.W.; Kim, Y.S.; Kim, J.Y.; Oh, K.J.; Han, B.S.; et al.Quantitative proteomic analyses reveal that GPX4 downregulation during myocardial infarction contributes to ferroptosis in cardiomyocytes. *Cell Death Dis.* 2019, *10*, 835. [CrossRef].

XXX. Gori, T.; Münzel, T. Oxidative stress and endothelial dysfunction: Therapeutic implications. *Ann. Med.* 2011, *43*, 259–272. [CrossRef].

XXXI. Stamler, J.S.; Osborne, J.A.; Jaraki, O.; Rabbani, L.E.; Mullins, M.; Singel, D.; Loscalzo, J. Adverse vascular effects of homocysteine are modulated by endothelium-derived relaxing factor and related oxides of nitrogen. *J. Clin. Investig.* 1993, *91*, 308–318. [CrossRef].

XXXII. McCully, K.S. Homocystinuria, Arteriosclerosis, Methylmalonic Aciduria, and Methyltransferase Deficiency:A Key Case Revisited. *Nutr. Rev.* 1992, *50*, 7–12. [CrossRef].

XXXIII. Cianciolo, G.; De Pascalis, A.; Di Lullo, L.; Ronco, C.; Zannini, C.; La Manna, G. Folic acid and homocysteine in chronic kidney disease and cardiovascular disease progression: Which comes first? *CardioRenal Med.* 2017, *7*, 255–266. [CrossRef].

XXXIV. Stroes, E.S.G.; Van Faassen, E.E.; Yo, M.; Martasek, P.; Boer, P.; Govers, R.; Rabelink, T.J. Folic acid reverts dysfunction of endothelial nitric oxide synthase. *Circ. Res.* 2000, *86*, 1129–1134. [CrossRef] [PubMed].

XXXV. Hagar, H.H. Folic acid and vitamin B12 supplementation attenuates isoprenaline-induced myocardial infarction in experimental hyperhomocysteinemic rats. *Pharmacol. Res.* 2002, *46*, 213–219. [CrossRef].

XXXVI. Farhangi, M.A.; Nameni, G.; Hajiluian, G.; Mesgari-Abbasi, M. Cardiac tissue oxidative stress and inflammation after vitamin D administrations in high fat- diet induced obese rats. *BMC Cardiovasc. Disord.* 2017, *17*, 1–7. [CrossRef] [PubMed].

XXXVII. Leme Goto, P.; Cinato, M.; Merachli, F.; Vons, B.; Jimenez, T.; Marsal, D.; Todua, N.; Loi, H.; Santin, Y.; Cassel, S.; et al. In vitro and in vivo cardioprotective and metabolic efficacy of vitamin E TPGS/Apelin. *J.*

Mol. Cell. Cardiol. 2020, *138*, 165–174. [CrossRef].

XXXVIII. Wallert, M.; Ziegler, M.; Wang, X.; Maluenda, A.; Xu, X.; Yap, M.L.; Witt, R.; Giles, C.; Kluge, S.; Hortmann, M.; et al. α-Tocopherol preserves cardiac function by reducing oxidative stress and inflammation in ischemia/reperfusion injury. *Redox Biol.* 2019, *26*, 101292. [CrossRef].

XXXIX. Banez, M.J.; Geluz, M.I.; Chandra, A.; Hamdan, T.; Biswas, O.S.; Bryan, N.S.; Von Schwarz, E.R. A systemic review on the antioxidant and anti-inflammatory effects of resveratrol, curcumin, and dietary nitric oxide supplementation on human cardiovascular health. *Nutr. Res.* 2020, *78*, 11–26. [CrossRef].

XL. Agouni, A.; Lagrue-Lak-Hal, A.H.; Mostefai, H.A.; Tesse, A.; Mulder, P.; Rouet, P.; Desmoulin, F.; Heymes, C.; Martínez, M.C.; Andriantsitohaina, R. Red wine polyphenols prevent metabolic and cardiovascular alterations associated with obesity in Zucker fatty rats (Fa/Fa). PLoS ONE 2009, 4, e5557. [CrossRef].

XLI. Farkhondeh, T.; Folgado, S.L.; Pourbagher-Shahri, A.M.; Ashrafizadeh, M.; Samarghandian, S. The therapeutic effect of resveratrol: Focusing on the Nrf2 signaling pathway. *Biomed. Pharmacother.* 2020, *127*, 110234. [CrossRef].

XLII. Dyck, G.J.B.; Raj, P.; Zieroth, S.; Dyck, J.R.B.; Ezekowitz, J.A. The effects of resveratrol in patients with cardiovascular disease and heart failure: A narrative review. *Int. J. Mol. Sci.* 2019, *20*, 904. [CrossRef].

XLIII. Huang, J.P.; Hsu, S.C.; Li, D.E.; Chen, K.H.; Kuo, C.Y.; Hung, L.M. Resveratrol mitigates high-fat diet-induced vascular dysfunction by activating the Akt/eNOS/NO and Sirt1/ER pathway. *J. Cardiovasc. Pharmacol.* 2018, *72*, 231–241. [CrossRef].

XLIV. Chan, A.Y.M.; Dolinsky, V.W.; Soltys, C.-L.M.; Viollet, B.; Baksh, S.; Light, P.E.; Dyck, J.R.B. Resveratrol inhibits cardiac hypertrophy via AMP-activated protein kinase and Akt. *J. Biol. Chem.* 2008, *283*, 24194–24201. [CrossRef] [PubMed].

XLV. Sung, M.M.; Das, S.K.; Levasseur, J.; Byrne, N.J.; Fung, D.; Kim, T.T.; Masson, G.; Boisvenue, J.; Soltys, C.L.;Oudit, G.Y.; et al. Resveratrol treatment of mice with pressure-overloadinduced heart failure improves diastolic function and cardiac energy metabolism. *Circ. Heart Fail.* 2015, *8*, 128–137. [CrossRef] [PubMed].

XLVI. Tanno, M.; Kuno, A.; Yano, T.; Miura, T.; Hisahara, S.; Ishikawa, S.; Shimamoto, K.; Horio, Y. Induction of manganese superoxide dismutase by nuclear translocation and activation of SIRT1 promotes cell survival in chronic heart failure. *J. Biol. Chem.* 2010, *285*, 8375–8382. [CrossRef].

XLVII. Sabbah, H.N. Targeting mitochondrial dysfunction in the treatment of heart failure. *Expert Rev. Cardiovasc. Ther.* 2016, *14*, 1305–1313. [CrossRef] [PubMed].

XLVIII. Senoner, T.; Dichtl, W. Oxidative stress in cardiovascular diseases: Still a therapeutic target? *Nutrients* 2019, *11*, 2090. [CrossRef].

XLIX. Dikalova, A.E.; Bikineyeva, A.T.; Budzyn, K.; Nazarewicz, R.R.; McCann, L.; Lewis, W.; Harrison, D.G.; Dikalov, S.I. Therapeutic targeting of mitochondrial superoxide in hypertension. *Circ. Res.* 2010, *107*, 106–116. [CrossRef].

L. Ni, R.; Cao, T.; Xiong, S.; Ma, J.; Fan, G.C.; Lacefield, J.C.; Lu, Y.; Tissier, S.L.; Peng, T. Therapeutic inhibition of mitochondrial reactive oxygen species with mito-TEMPO reduces diabetic cardiomyopathy. *Free Radic. Biol. Med.* 2016, *90*, 12–23. [CrossRef] [PubMed].

LI. Kelso, G.F.; Porteous, C.M.; Coulter, C.V.; Hughes, G.; Porteous, W.K.; Ledgerwood, E.C.; Smith, R.A.J.; Murphy, M.P. Selective targeting of a redox-active ubiquinone to mitochondria within cells: Antioxidant and antiapoptotic properties. *J. Biol. Chem.* 2001, *276*, 4588–4596. [CrossRef].

LII. Kim, S.; Song, J.; Ernst, P.; Latimer, M.N.; Ha, C.M.; Goh, K.Y.; Ma, W.; Rajasekaran, N.S.; Zhang, J.; Liu, X.; et al. MitoQ regulates redox-related noncoding RNAs to preserve mitochondrial network integrity in pressure-overload heart failure. *Am. J. Physiol. Heart Circ. Physiol.* 2020, *318*, H682–H695. [CrossRef].

LIII. Rao, V.A.; Klein, S.R.; Bonar, S.J.; Zielonka, J.; Mizuno, N.; Dickey, J.S.; Keller, P.W.; Joseph, J.; Kalyanaraman, B.; Shacter, E. The antioxidant transcription factor Nrf2 negatively regulates autophagy and growth arrest induced by the anticancer redox agent mitoquinone. *J. Biol. Chem.* 2010, *285*, 34447–34459. [CrossRef].

LIV. Doughan, A.K.; Dikalov, S.I. Mitochondrial redox cycling of mitoquinone leads to superoxide production and cellular apoptosis. *Antioxid. Redox Signal* 2007, *9*, 1825–1836. [CrossRef] [PubMed].

LV. Pokrzywinski, K.L.; Biel, T.G.; Kryndushkin, D.; Rao, V.A. Therapeutic targeting of the mitochondria initiates excessive superoxide production and mitochondrial depolarization causing decreased mtDNA integrity. *PLoS ONE* 2016, *11*, e0168283. [CrossRef].

LVI. Lee, I.M.; Cook, N.R.; Gaziano, J.M.; Gordon, D.; Ridker, P.M.; Manson, J.A.E.; Hennekens, C.H.; Buring, J.E. Vitamin E in the primary prevention of cardiovascular disease and cancer. The women's health study: A randomized controlled trial. *J. Am. Med. Assoc.* 2005, *294*, 56–65. [CrossRef].

LVII. Toole, J.F.; Malinow, M.R.; Chambless, L.E.; Spence, J.D.; Pettigrew, L.C.; Howard, V.J.; Sides, E.G.; Wang, C.H.; Stampfer, M. Lowering Homocysteine in Patients with Ischemic Stroke to Prevent Recurrent Stroke, Myocardial Infarction, and Death: The Vitamin Intervention for Stroke Prevention (VISP) Randomized

Controlled Trial. *J. Am. Med. Assoc.* 2004, *291*, 565–575. [CrossRef].

LVIII. Lonn, E. Effects of long-term vitamin E supplementation on cardiovascular events and cancer: A randomized controlled trial. *J. Am. Med. Assoc.* 2005, *293*, 1338–1347.

LIX. Bønaa, K.H.; Njølstad, I.; Ueland, P.M.; Schirmer, H.; Tverdal, A.; Steigen, T.; Wang, H.; Nordrehaug, J.E.; Arnesen, E.; Rasmussen, K. Homocysteine lowering and cardiovascular events after acute myocardial infarction. *N. Engl. J. Med.* 2006, *354*, 1578–1588. [CrossRef].

LX. Münzel, T.; Camici, G.G.; Maack, C.; Bonetti, N.R.; Fuster, V.; Kovacic, J.C. Impact of Oxidative Stress on the Heart and Vasculature: Part 2 of a 3-Part Series. *J. Am. Coll. Cardiol.* 2017, *70*, 212–229. [CrossRef].

LXI. Mankowski, R.T.; You, L.; Buford, T.W.; Leeuwenburgh, C.; Manini, T.M.; Schneider, S.; Qiu, P.; Anton, S.D. Higher dose of resveratrol elevated cardiovascular disease risk biomarker levels in overweight older adults–A pilot study. *Exp. Gerontol.* 2020, *131*, 110821. [CrossRef].

LXII. Tomé-Carneiro, J.; Gonzálvez, M.; Larrosa, M.; Yáñez-Gascón, M.J.; García-Almagro, F.J.; Ruiz-Ros, J.A.; García-Conesa, M.T.; Tomás-Barberán, F.A.; Espín, J.C. One-year consumption of a grape nutraceutical containing resveratrol improves the inflammatory and fibrinolytic status of patients in primary preventionof cardiovascular disease. *Am. J. Cardiol.* 2012, *110*, 356–363. [CrossRef].

LXIII. Imamura, H.; Yamaguchi, T.; Nagayama, D.; Saiki, A.; Shirai, K.; Tatsuno, I. Resveratrol ameliorates arterial stiffness assessed by cardio-ankle vascular index in patients with type 2 diabetes mellitus. *Int. Heart J.* 2017, *58*, 577–583. [CrossRef] [PubMed].

LXIV. Agarwal, B.; Campen, M.J.; Channell, M.M.; Wherry, S.J.; Varamini, B.; Davis, J.G.; Baur, J.A.; Smoliga, J.M. Resveratrol for primary prevention of atherosclerosis: Clinical trial evidence for improved gene expression in vascular endothelium. *Int. J. Cardiol.* 2013, *166*, 246–248. [CrossRef].

LXV. Jeong, E.M.; Chung, J.; Liu, H.; Go, Y.; Gladstein, S.; Farzaneh-Far, A.; Lewandowski, E.D.; Dudley, S.C. Role of Mitochondrial Oxidative Stress in Glucose Tolerance, Insulin Resistance, and Cardiac Diastolic Dysfunction. *J. Am. Heart Assoc.* 2016, *5*, e003046. [CrossRef] [PubMed].

LXVI. Jiménez-González, S.; Marín-Royo, G.; Jurado-López, R.; Bartolomé, M.V.; Romero-Miranda, A.; Luaces, M.; Islas, F.; Nieto, M.L.; Martínez-Martínez, E.; Cachofeiro, V. The Crosstalk between Cardiac Lipotoxicity and Mitochondrial Oxidative Stress in the Cardiac Alterations in Diet-Induced Obesity in Rats. *Cells* 2020, *9*, 451.[CrossRef].

LXVII. Van Der Made, S.M.; Plat, J.; Mensink, R.P. Resveratrol does not influence metabolic risk markers related to cardiovascular health in overweight and slightly obese subjects: A randomized, placebo-controlled crossover trial. *PLoS ONE* 2015, *10*, e0118393. [CrossRef] [PubMed].

LXVIII. Agarwal, B.; Campen, M.J.; Channell, M.M.; Wherry, S.J.; Varamini, B.; Davis, J.G.; Baur, J.A.; Smoliga, J.M. Resveratrol for primary prevention of atherosclerosis: Clinical trial evidence for improved gene expression in vascular endothelium. *Int. J. Cardiol.* 2013, *166*, 246–248. [CrossRef]