

Review Article

The Role of Oxidative Stress in Physiopathology and Pharmacological Treatment with Pro- and Antioxidant Properties in Chronic Diseases

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Received 29 May 2020; Accepted 8 July 2020; Published 24 July 2020

Guest Editor: Juan Francisco Santibañez

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Oxidative stress (OS) has the ability to damage different molecules and cellular structures, altering the correct function of organs and systems. OS accumulates in the body by endogenous and exogenous mechanisms. Increasing evidence points to the involvement of OS in the physiopathology of various chronic diseases that require prolonged periods of pharmacological treatment. Long-term treatments may contribute to changes in systemic OS. In this review, we discuss the involvement of OS in the pathological mechanisms of some chronic diseases, the pro- or antioxidant effects of their pharmacological treatments, and possible adjuvant antioxidant alternatives. Diseases such as high blood pressure, arteriosclerosis, and diabetes mellitus contribute to the increased risk of cardiovascular disease. Antihypertensive, lipid-lowering, and hypoglycemic treatments help reduce the risk with an additional antioxidant benefit. Treatment with methotrexate in autoimmune systemic inflammatory diseases, such as rheumatoid arthritis, has a dual role in stimulating the production of OS and producing mitochondrial dysfunction. However, it can also help indirectly decrease the systemic OS induced by inflammation. Medicaments used to treat neurodegenerative diseases tend to decrease the mechanisms related to the production of reactive oxygen species (ROS) and balance OS. On the other hand, immunosuppressive treatments used in cancer or human immunodeficiency virus infection increase the production of ROS, causing significant oxidative damage in different organs and systems without widely documented exogenous antioxidant administration alternatives.

1. Introduction

Oxidative stress (OS) is characterized by the imbalance between the production and degradation of reactive oxygen species (ROS) or reactive nitrogen species (RNS) [1]. ROS are molecules whose chemical makeup gives them high reactivity and can come from the metabolism of oxygen or nitrogen. ROS and RNS can be free radicals such as the superoxide radical (O_2^-), hydroxyl radical (OH^-), and nitric oxide (NO^-). However, other nonfree radicals can also be found, such as hydrogen peroxide (H_2O_2) and peroxynitrite ($ONOO^-$) [2]. ROS produce enzymatic reactions within the mitochondria characterized by the reduction of oxygen through the electron transport chain [3]. In addition, the endoplasmic reticu-

lum and peroxisomes are other sources of ROS [4, 5]. Different cellular processes such as protein phosphorylation, activation of transcription factors, immunity, and apoptosis depend on the cellular concentration of ROS [6].

The main endogenous antioxidant enzymes that neutralize ROS are superoxide dismutase (SOD), catalase (Cat), and glutathione peroxidase (GPx) [7]. SOD belongs to a group of metalloenzymes that transforms O_2^- into oxygen and H_2O_2 [8]. Three forms of SOD are known in mammals: cytoplasmic SOD (SOD1), mitochondrial SOD (SOD2), and extracellular SOD (SOD3) [9]. ROS can be neutralized by other nonenzymatic molecules with free radical scavenging properties such as vitamins, melatonin, and glutathione (GSH) [10]. When antioxidant defenses fail to properly neutralize ROS,

ROS remain in the body longer and oxidize susceptible biomolecules [11]. Excessive levels of ROS can damage cellular proteins, membrane lipids, and nucleic acids, causing damage to proper cellular function [11]. The NO[·] radical is an endothelium-dependent mediator in vascular vasorelaxation. NO[·] is produced normally by the enzyme nitric oxide synthase (NOS) [12]. In OS conditions, NO[·] reacts with the radical O₂^{·-} to generate ONOO[·] causing endothelial damage [13].

The lipoperoxidation (LPO) process is a mechanism of damage produced by OS on lipids. LPO is characterized by having carbon-carbon double bonds, especially polyunsaturated fatty acids. The main LPO products are hydroperoxides, such as propanal, hexanal, 4-hydroxynonenal, and malondialdehyde (MDA) [14]. Other LPOs are isoprostanes from nonenzymatic oxidation of essential fatty acids, such as arachidonic acid [15]. Additionally, ROS can damage the DNA structure when they react with guanine bases. Guanine oxidation commonly forms 8-hydroxy-2'-deoxyguanosine (8-OHdG) or 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) [16]. These metabolites under normal conditions are repaired by the enzyme oxoguanine glycosylase (hOGG1) and are known jointly, like biomarkers of the OS [17]. OS is present in various chronic diseases, which can contribute to its progression [18]. OS and the inflammatory process are closely linked to each other and contribute to the tissue damage of some autoimmune diseases such as rheumatoid arthritis [19]. OS is linked to hyperglycemia and the progression of type 2 diabetes mellitus (DM) [20]. The participation of OS in cardiovascular disease is mainly attributed to its effects on hypertension and the formation of atheroma leaflets [21, 22]. The pathological development of other chronic diseases such as neurodegenerative diseases [23], cancer [24], or infection by the human immunodeficiency virus (HIV) is related to increased production of ROS [25]. On the other hand, exogenous factors, such as the recommended pharmacological treatments for certain chronic pathologies, have the ability to alter the production of ROS [2]. The purpose of this small review is to describe the role that OS plays in different pathological processes (atherosclerosis, high blood pressure, DM, rheumatoid arthritis, cancer, HIV, and some neurodegenerative diseases). The prooxidant or antioxidant effects of some pharmacological management alternatives will be briefly described (Figure 1).

1.1. Oxidative Stress in Atherosclerosis. Atherosclerosis is a chronic disease characterized by inflammation, the manifestation of which occurs in the vascular system. Atherosclerosis is the main origin of cardiovascular disease (CVD) in developed countries of the world [26]. Atherosclerosis represents the development of vascular lesions or plaque deposition in the blood vessels after the response of endothelial damage produced by the inflammation/oxidation processes [27]. Plaque is mainly made up of blood cells, foam cells, lipids, and proteins accompanied by calcium accumulation, favoring vascular expansion, vascular blockage, and inhibition of vascular blood flow, which leads to the explosion of the vascular wall [28, 29]. In CVD, blockage and rupture of the atherosclerotic coronary arteries cause myocardial infarction, while

blockage of the carotid arteries causes stroke [30]. Endothelial damage is related to risk factors for the heart and blood vessels such as DM, high blood pressure, nicotine use, lipid disorder, obesity, and metabolic disorders. Impaired endothelial physiological functions are observed during the early stages of atherosclerotic lesions due to oxidative damage [31]. The renin-angiotensin system (RAS) plays an essential role in the advancement of atherosclerosis by influencing endothelial physiology, inflammatory reactions, thrombosis, and oxidative lesions [32]. Angiotensin II (Ang II) causes oxidative damage in the vascular system by inducing the generation of ROS by activating NADPH oxidase with the ability to oxidize cellular biomolecules, including lipids, lipoproteins, and DNA, leading to endothelial deterioration [33].

1.2. Management for Atherosclerosis and Oxidative Stress. Hypercholesterolemia is considered the main trigger for atherosclerosis. Therefore, the control of lipoprotein levels through the administration of statins is one of the main management alternatives to reduce the risk of atherosclerosis [34]. Statins antagonize the activity of the enzyme hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase, decreasing the production of intracellular cholesterol and decrease of liver LDL receptors [35]. Statins show pleiotropic effects on endothelial function, inhibition of thrombus gene activity, the stability of atherosclerosis plaques, and decreased inflammation and OS [36]. Statins have been shown to have antioxidant effects on redox signaling of vascular and myocardial tissue by modifying NADPH oxidase activity [37]. Statins show effects on eNOS and decreased LPO [38]. Treatment of patients with simvastatin has protective effects on lipoprotein oxidation [39]. However, the metabolism of statins generates ROS and produces toxicity in various tissues, including skeletal muscle and liver damage [40, 41]. The activity of simvastatin and lovastatin inhibits the complete II, III, IV, and V of the electron transport chain, whereas fluvastatin and cerivastatin only inhibit the V complex, thus causing mitochondrial dysfunction [42]. Eight weeks of simvastatin management is sufficient to cause mitochondrial respiration dysfunction in muscle [43].

1.3. Adjuvant Antioxidants in Atherosclerosis. Different antioxidant compounds have been used as adjuvant therapy in chronic diseases (Table 1). The antioxidant N-acetylcysteine has been reported to suppress accelerated atherosclerotic events in mouse models with inactivated ApoE [44]. The vitamin D analog (paricalcitol) was also reported to improve oxidative vascular injury by suppressing the activity of ROS-generating enzyme NADPH oxidase, inflammatory mediators, and regulating the antioxidant defense system in ApoE-deficient mice [45]. On the other hand, polyphenols are common antioxidant nutrients, mainly derived from fruits, vegetables, tea, coffee, cocoa, mushrooms, drinks, and traditional medicinal herbs [46, 47]. The classification of polyphenols mainly includes flavonoids (60%), phenolic acids (30%), and other polyphenols, including stilbenes (resveratrol) and ligands, attached to at least one aromatic ring in one or more HO[·] functional groups [46]. Flavonoids

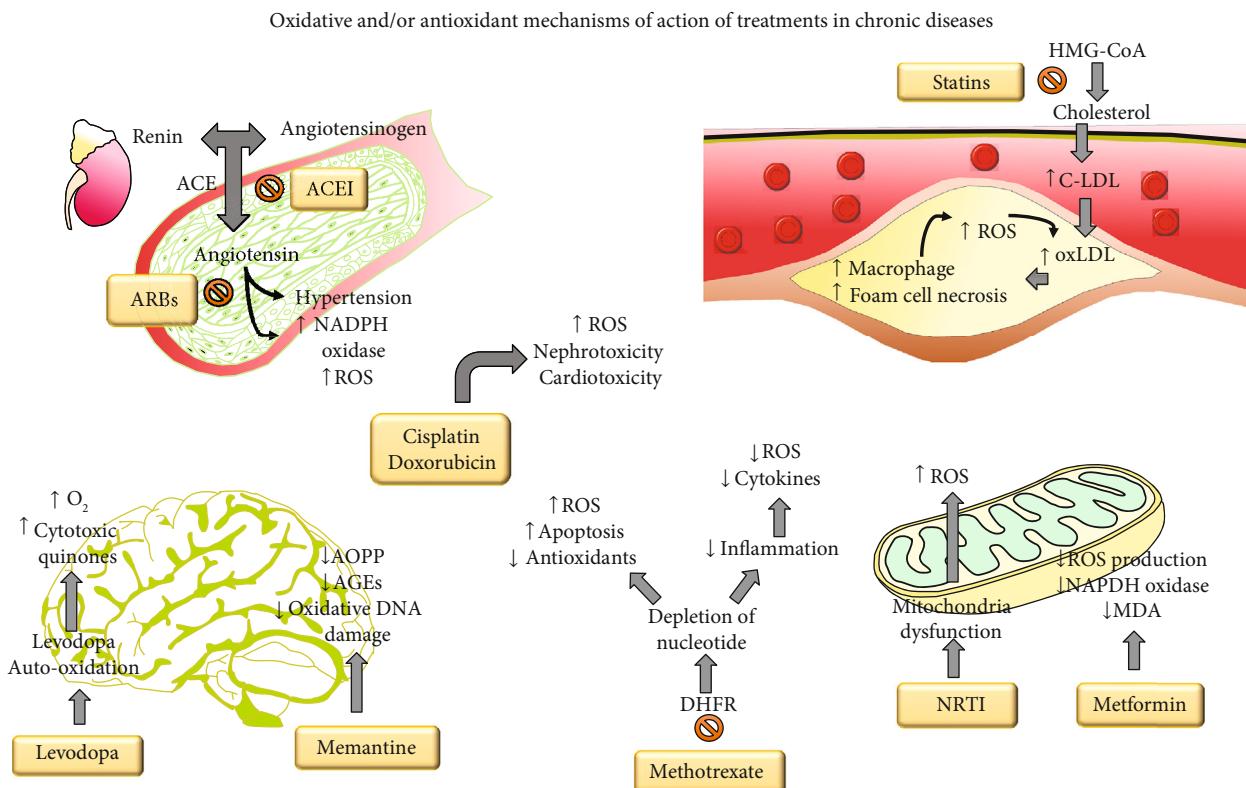


FIGURE 1: Oxidative and/or antioxidant mechanisms of action of treatments in chronic diseases. Description of how different drug mechanisms affect the oxidative status. Antihypertensive and statin treatment decrease oxidative stress by restoring the endothelial function. Antineoplastic (cisplatin, doxorubicin) and nucleoside or nucleotide reverse transcriptase inhibitor (NRTI or NtRTI) treatment causes the most oxidative damage in patients in the long term. Methotrexate can cause increased OS and apoptosis; at the same time, inflammation-mediated OS production decreases. Levodopa metabolism may increase cytotoxicity in the brain. Metformin and memantine may decrease the oxidative stress.

TABLE 1: Antioxidant alternatives in the management of chronic diseases.

Antioxidant	Chronic disease	Results	Reference
N-Acetylcysteine	Atherosclerosis	Prevents the progression of atheroma in uremic mice	[44]
Paricalcitol (vitamin D)	Atherosclerosis	Enalapril and paricalcitol decrease MDA and increase GSH; affords greater protection against aortic inflammatory injury in mice	[45]
Naringin	HIV infection	Naringin reverses the metabolic complications associated with NRTI by improving OS and apoptosis in a rat model	[221]
Vitamins A, C, and E	Rheumatoid arthritis	Combined administration of vitamins A, B, and C with methotrexate for 10 weeks lowers the severity score in patients with rheumatoid arthritis	[133]
Ascorbic acid and essential oil rose	Parkinson's disease	Ascorbic acid or essential rose decreases MDA, AGEs, and carbonyl concentration of mice treated with levodopa	[159]
Vitamin E	Alzheimer's disease	Vitamin E delays the progression of disease in patients with Alzheimer's disease	[161]
	Type 2 diabetes mellitus	Vitamin E increases event-free survival in type 2 diabetes mellitus patients	[93]
	Hypertension	Increase SOD levels and decrease MDA in hypertensive elderly subjects	[197]
Coenzyme Q10	Lymphoblastic leukemia	Treatment with coenzyme Q10 provides a protective effect on cardiac function during treatment with anthracycline in patients with lymphoblastic leukemia	[187]

are the most studied group of polyphenols; they are divided into six subclasses: flavonols, flavones, flavanones, flavanols, anthocyanins, and isoflavones. Phenolic acids are divided

into two subclasses, benzoic acid and cinnamic acid. Stilbenes in plants act as antifungal phytoalexins and are rare in the human diet [47].

1.4. Oxidative Stress in Hypertension. High blood pressure is the most common cardiovascular risk factor and contributor to global morbidity and mortality [48]. High blood pressure is a complex condition. Approximately 90% of cases are classified as essential hypertension, where the precise cause is unknown [49]. Hypertensive stimuli, including salt, hyperactivity of the RAS system, OS, and inflammation lead to the initial elevation of blood pressure, mainly due to central actions and also due to endogenous hormones such as Ang II and aldosterone, resulting in protein modification. The altered proteins are no longer recognized as their own (they serve as neoantigens), and the T cells are activated. T cell derived signals promote macrophage (and other inflammatory cells) entry into the vasculature and kidney, resulting in the release of inflammatory cytokines. In the vasculature, activated T cells promote vasoconstriction and remodeling, along with promoting sodium and water retention in the kidney, causing more severe hypertension [50]. Chronic inflammation has the ability to trigger OS that is associated with high blood pressure. Against the background of Ang II-induced hypertension, T cells express high levels of p47phox, p22phox, and NOX2, components of NOX2 oxidase.

Furthermore, adoptive transfer of NADPH oxidase-deficient T cells results in decreased O_2^- production and arterial hypertension in response to Ang II [51]. Ang II is one of the main vasoactive signaling molecules involved in ROS generation and participates in increased expression and activity of one of the main ROS generators, NADPH oxidase [52, 53]. The highest production of Ang II occurs in hypertensive conditions [54]. In addition, to intrarenal vasoconstriction, high levels of Ang II have deleterious effects on necrotic and apoptotic changes in kidney tissue during the reperfusion period. Ang II downregulates the SR-BI HDL receptor in proximal tubular cells [55]. Statins were developed to inhibit cholesterol synthesis by blocking HMG-CoA reductase. However, within their pleiotropic effects, these drugs are anti-inflammatory and can produce a small reduction in systolic blood pressure in hypercholesterolemia patients. The effect is greater on patients with higher blood pressure [56].

1.5. Oxidative Stress in Antihypertensive Treatment. First-line management to treat high blood pressure includes angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and beta-blockers (BB) [57]. The control of hypertension is associated with the regulation of Ang II activation, which contributes to decreased OS independently of antihypertensive therapy [58]. Antihypertensive treatment with ACEI has been shown to have antioxidant effects. Studies on the effects of enalapril on OS in the kidney and heart of rats with hypertension show that enalapril increases total antioxidant activity and decreases LPO levels in both organs [59, 60]. Other experimental studies show that captopril decreases H_2O_2 and MDA levels in hyperglycemic conditions [61]. Telmisartan effectively controls blood pressure and improves fibrosis and vascular remodeling. Additionally, telmisartan exerts protective vessel effects by inhibiting the

TGF- β 1/Smad3 pathway associated with antihypertensive and antioxidant effects [62].

The antioxidant effects of ARB and BB are very similar to those of ACEI; olmesartan attenuates the concentration of TBARS and H_2O_2 in obese mice [63]. Eight-week treatment with candesartan or valsartan reduces urinary 8-isoprostanes and 8-OHdG levels compared to treatment with trichlormethiazide [64]. Valsartan treatment also decreases nitrosative stress in patients with type 2 DM [65]. Medium-term treatment with atenolol combined with thiazide hydrochloride decreases MDA levels and increases the concentration of SOD, GSH, and vitamins E and C [66]. Long-term treatment with metoprolol or carvedilol has been shown to decrease LPO levels in patients with heart failure [67]. The reduction of BB use in OS is not limited to plasma or serum. Studies show that carvedilol can also decrease myocardial LPO levels in patients with dilated cardiomyopathy [68].

The CCB are an important antihypertensive group. The dihydropyridine ring through which they can be considered as weak antioxidants is due to their ability to react with peroxy radicals [69]. Amlodipine shows the ability to reduce isoprostanate concentration in patients with type 2 DM [70]. Other BCC, such as nifedipine and lacidipine, have been shown to be protective in the formation of LDL-oxidized lipoprotein [71].

1.6. Adjuvant Antioxidants in Arterial Hypertension. Diet is the main source of exogenous antioxidants. Among exogenous antioxidants, polyphenols, vitamins (C and E and β -carotene), and minerals stand out. Components like Se, Zn, Fe, Mn, and Cu favor the organism in the elimination of excessive free radicals through adequate enzymatic proteins [72]. Polyphenols can block Ang II-stimulated positive regulation of various NADPH oxidase (NOX) subunits, including NOX1 and p22phox (an essential component of NOX) and associated OS [73]. Some research reveals that systolic blood pressure in hypertensive patients improves after eating foods rich in polyphenols [74]. The combination of dietary flavonoids and antihypertensive drug therapy based on telmisartan or captopril can improve blood pressure, lipid profile, obesity, and inflammation in young hypertensive patients [75].

1.7. Oxidative Stress in Diabetes Mellitus. DM is known as an OS disorder caused by the imbalance between the formation of free radicals and the capacity of the body's natural antioxidants. Glucose fluctuations are essential in the pathogenesis of DM. OS plays an important role in the complications of developing DM [76]. OS is directly influenced by fluctuations in glucose. Postprandial glucose fluctuations or any type of glucose oscillation cause greater OS than chronic hyperglycemia. The length and severity of chronic hyperglycemia and regularly occurring acute glucose changes are the main components of glycemic disorders [77]. Hyperglycemia induces ROS production. In type 2 DM, when the β cells are still intact and functional, the presence of ROS produces OS in the β cells, which leads to lower levels of insulin secretion [77]. The radical O_2^- is a type of ROS of particular interest in DM, because it has been shown to be elevated in *in vitro*

and *in vivo* studies [77]. There are many sources of OS in DM including enzymatic, nonenzymatic, and mitochondrial pathways. The OS increase in DM occurs due to multiple factors [78]. The most dominant oxidizing factor is the auto-oxidation of glucose, which results in the development of free radicals. Other factors are unbalanced cellular reduction/oxidation and reduced antioxidant defenses (reduced levels of cellular antioxidants and reduced enzyme activity against free radicals) [79]. Due to the high levels of glucose in DM, the generation of O_2^- triggers multiple pathways, with the greater formation of polyols, higher flow of the hexosamine pathway, and activation of the protein kinase C isoform [80]. Mitochondria are integrative critiques of energy production, ROS generation, signaling transduction, and apoptosis in DM. Within the mitochondrial dynamics highlights the importance of the fusion and fission processes in mitochondrial homeostasis [81]. Mitochondrial fusion appears to be beneficial because it distributes metabolites, proteins, and DNA through the mitochondrial network. Excessive mitochondrial fission can be harmful because it causes fragmented mitochondria to accumulate with an impaired electron transport chain with the ability to increase mitochondrial ROS in cells [82]. In 2013, it was reported that hyperglycemia induces mitochondrial fission by upregulating the expression of the dynamin-related protein 1 (Drp1) [83]. Drp1 is a cytosolic guanosine-5'-triphosphatase that triggers mitochondrial division by binding to fission 1 (Fis1) or to mitochondrial fission factor (Mff) in mitochondria. Increased mitochondrial fission contributes to DM-induced endothelial dysfunction. These studies suggest that suppression of mitochondrial fission can effectively prevent DM-induced atherosclerosis and its related cardiovascular complications [84].

1.8. Oxidative Stress in the Management of Type 2 Diabetes Mellitus. Metformin is a synthetic dimethyl biguanide very useful as a therapy for patients with type 2 DM. In addition to reducing blood glucose, metformin reduces cardiovascular complications in patients with DM, prevents the progression of the thickness of the intima media of the common carotid, and reduces the incidence of myocardial infarction in patients with type 2 DM [85, 86]. The beneficial cardiovascular effects of metformin appear to be independent of its anti-hyperglycemic effect because other conventional treatments such as insulin and sulfonylureas exhibit less beneficial cardiovascular effects. Increasing evidence has shown that metformin inhibits mitochondrial fragmentation (fission) in DM by activating AMPK resulting in preventing endothelial damage by activating processes such as apoptosis and inflammation [84]. In 2017, it was reported that metformin reduced Drp1 expression and Drp1-mediated mitochondrial fission in AMPK-dependent diabetic endothelial cells. Suppressing mitochondrial fission inhibits endothelial OS, improves endothelial function, and reduces atherosclerotic lesions [87]. Some studies show that metformin treatment can reduce MDA levels, increase GSH levels, and decrease inflammatory status [88, 89]. Metformin can decrease the production of ROS AMPK induced by decreasing ATP synthesis and NADPH oxidase activity [90].

1.9. Adjuvant Antioxidants in Diabetes Mellitus. In relation to the antioxidant state in DM, Lortz and Tiedge reported that overexpression of the enzyme SOD and Cat could protect the pancreatic islets from ROS and maintain insulin production. Similarly, GPx enzyme overexpression has been shown to protect INS-1 cells from ROS and attack by RNS [91]. Large-scale studies have shown that intensive early glucose control reduces the risk of micro- and macrovascular complications of DM [92]. Vitamin C, vitamin E, and β -carotenes have traditionally been considered as ideal supplements against OS and its complications in DM [80]. Milman et al. reported that vitamin E reduces cardiovascular events after 1.5 years of supplementation [93]. Blum et al. suggested that vitamin E supplementation in DM patients can prevent myocardial infarction, stroke, and cardiovascular death [94]. Akbar et al. performed a meta-analysis of 14 studies where they found that supplementation with antioxidants does not affect plasma glucose or insulin levels. However, the HbA1c level is significantly reduced by supplementation with antioxidants, apparently due to having a protective effect on DM complications [95].

Melatonin is an active indoleamine (derived from tryptophan) component with antioxidant properties secreted mainly by pinealocytes [96, 97]. The main function of melatonin is the regulation of the sleep cycle. Melatonin is also involved in homeostasis and energy metabolism [98]. Melatonin can activate brown adipose tissue, increase energy expenditure, and have anti-inflammatory, immunomodulatory, and antioxidant properties [99]. Melatonin also increases the expression of antioxidant enzymes (SOD, Cat, and GPx) and eliminate free radicals. Melatonin is indicated alone or in combination with other therapies for 1-3 weeks, where it can produce clinical improvement in patients with type 2 DM [100].

1.10. Oxidative Stress in Rheumatoid Arthritis. Increased OS has been found in mono- and polyarthritic rats [101]. Clinical evidence indicates that patients with rheumatoid arthritis have increased LPO, protein oxidation, and oxidative DNA damage [102]. Furthermore, ROS are positively associated with the severity of rheumatoid arthritis [103, 104]. Inflammation is the main pathophysiological mechanism of rheumatoid arthritis. Innate immune cells, such as neutrophils and macrophages, produce ROS, such as O_2^- and H_2O_2 [105]. Increasing evidence supports the link between the processes of redox reactions that produce OS and the pathophysiology of inflammation [106, 107]. Nuclear factor κ B (NF- κ B) is the transcription factor responsible for regulating different immune and inflammatory processes [108]. ROS can modify NF- κ B signaling in the cytoplasm and nucleus [109]. Nuclear translocation of NF- κ B can be induced by H_2O_2 and can be inhibited by overexpression of the SOD2 enzyme [110, 111]. Other transcription factors involved in cell differentiation, vascularization, and proliferation activator protein 1 (AP-1), inducible hypoxia factor (HIF-1), and gamma-activated peroxisome proliferator receptor (PPAR γ) are also induced by ROS [112-114]. ROS participate in the signaling of inflammation agonists. Mitochondrial ROS induce the production of proinflammatory cytokines, IL-

1B, IL-6, and TNF- α [115]. The inflammation process also produces OS because polymorphonuclear neutrophils produce ROS through the NADPH oxidase enzyme pathway [116]. Furthermore, the ROS produced by the inflammatory cells condition a positive feedback of the inflammation [117].

1.11. Oxidative Stress in the Treatment for Rheumatoid Arthritis. Methotrexate is a folic acid antagonist originally used as a treatment for malignant diseases. Currently, methotrexate is one of the leading medications for the treatment of rheumatoid arthritis [118]. Methotrexate has immunosuppressive effects with mechanisms of action related to the generation of ROS. The increase in ROS by methotrexate is important for the cytotoxicity of T cells [119]. Methotrexate decreases enzyme levels of SOD, Cat, and total antioxidant activity and promotes apoptosis by increasing caspase-3 levels [120]. Inhibition of cellular NADPH has been suggested as one of the mechanisms of OS generation by methotrexate [121]. During the pentose cycle pathway, glutathione reductase uses NADPH as a reducing agent for cellular GSH (primary antioxidant). Decreased cellular GSH by methotrexate leads to reduced systemic antioxidant defense [122]. In addition, methotrexate generates mitochondrial dysfunction causing decreased activity of mitochondrial dehydrogenases, mitochondrial membrane potential, GSH, ATP concentrations, and increased LPO [123]. Methotrexate modifies the inflammatory response of different cells and cytokines with proinflammatory properties [124]. However, despite experimental evidence of methotrexate-induced OS, there is clinical evidence to suggest that methotrexate may have antioxidant activity. Some authors have shown that the management of rheumatic disease with methotrexate combined with glycosides reduces the levels of inflammation and OS [125]. Decreased LPO and increased GSH were observed in a study of female patients with rheumatoid arthritis in patients treated with methotrexate compared to patients without methotrexate [126].

1.12. Adjuvant Antioxidants in Rheumatoid Arthritis. Melatonin has been used as a protector from hepatorenal oxidative damage caused by methotrexate. Experimental studies have shown that the administration of melatonin reverses the increase in MDA, the activity of myeloperoxidase, and the decrease in GSH caused by methotrexate in the liver and kidney [127].

α -Lipoic acid has been used as a protective agent against methotrexate-induced liver OS. α -Lipoic acid is a coenzyme of pyruvate dehydrogenase naturally located in the mitochondria and used as a supplement for its antioxidant properties [128]. The administration of α -lipoic acid in mice showed decreased levels of LPO, protein carbonylation, and HO $^\cdot$ mitochondrial caused by methotrexate. In addition, α -lipoic acid restores antioxidant levels [129].

N-Acetylcysteine has also been shown to reverse the effects of methotrexate in decreasing GSH, SOD, and Cat and increasing MDA in liver samples [130]. In experimental models of rheumatoid arthritis, the endogenous antioxidant carnosine has been evaluated. Carnosine is a dipeptide with properties in the regulation of homeostasis, including protec-

tion against ROS, located mainly in the skeleton, cardiac muscle, liver, and central nervous system [131]. The combination of carnosine and methotrexate reduces the levels of LPO and C-reactive protein in plasma compared to methotrexate alone [36]. Combined therapy with methotrexate and vitamins A, C, and E has been shown to have better benefits in decreasing disease markers [132].

1.13. Oxidative Stress in Neurodegenerative Diseases. OS is associated with neurodegenerative diseases like Parkinson's disease [133], Alzheimer's disease [134], multiple sclerosis [135], and depression [136]. The main link between OS and neurodegenerative diseases is aging. OS accumulated during aging produces oxidative damage and gradual mitochondrial dysfunction [137]. Animal models with Alzheimer's disease show reduced activity of mitochondrial complex IV in the hippocampus [138]. Increased OS, in addition to causing direct mitochondrial oxidative damage, also produce neurotoxic subproducts. ROS favor the production of β -amyloid, a toxic peptide that participates in the neurodegenerative progression of Alzheimer's disease [139]. In addition, β -amyloid increases OS by activating H₂O₂ production in neocortical neurons [140]. Dysregulated activation of NADPH from microglia cells is also associated with neurodegenerative progress of dopaminergic neurons in Parkinson's disease models [141, 142]. The inflammatory and neurodegenerative activity associated with multiple sclerosis and depression is also linked to OS. In multiple sclerosis, an increase in the marker of oxidative damage to DNA (8-OHdG) and carbonylated proteins is found together with a decrease in the GPx enzyme [143]. On the other hand, high levels of MDA, decreased ascorbic acid, and SOD enzyme have been found in patients with unipolar depression [144].

1.14. Oxidative Stress in the Treatment of Neurodegenerative Diseases. Memantine is a glutamate N-methyl-D-aspartate receptor (NMDA) subtype antagonist used to decrease the neurodegenerative progression of dementia in Alzheimer's disease [145]. Memantine decreases the neurotoxicity of overactivation of glutamine receptors in the central nervous system [146]. Experimental memory deficit models demonstrate that memantine decreases protein oxidation in the hippocampus and cerebral cortex and reverses recognition memory deficit [147]. In addition, protective properties from oxidative damage have also been attributed to DNA primarily from the brain [148]. Memantine decreases levels of advanced protein oxidation products (AOPP) and advanced glycation end products (AGEs) in patients with prediabetes and cognitive impairment [149]. In addition, memantine can decrease nitrosative stress and increase antioxidant protection of nonprotein thiols in the cerebrospinal fluid [150].

Levodopa is a precursor to dopamine and is considered very effective for the symptomatic treatment of patients with Parkinson's disease [151]. Levodopa is often used in conjunction with carbidopa, a peripheral decarboxylase inhibitor, to increase the availability of levodopa by up to four times [152]. The activity of levodopa on the generation of OS has different postulates. On the other hand, *in vitro* evidence indicates that levodopa has neurotoxic properties induced

by the generation of ROS [153]. Excess dopamine outside the synaptic vesicle caused by treatment with levodopa favors metabolism via monoamine oxidase or autooxidation, leading to the production of ROS. Spontaneous autooxidation of dopamine can produce O_2^- and reactive quinones [154]. However, models in lymphocyte cells have shown antioxidant effects of carbidopa/levodopa and protective properties against oxidative damage to DNA [155]. Use of the carbidopa/levodopa combination with other disease-related medications, such as monoamine oxidase inhibitors, has been shown to decrease the enzymatic metabolism of dopamine and levodopa by decreasing the generation of ROS [156]. This evidence suggests that the pro- or antioxidant characteristics of levodopa management are linked to fluctuations in dopamine metabolism that occur with treatment [157].

1.15. Adjuvant Antioxidants in Neurodegenerative Diseases. Some natural antioxidants have been used to enhance the antioxidant effects of pharmacology therapy. An experimental study reveals that the administration of ascorbic acid or rose oil can help to decrease the levels of oxidative damage to lipids or proteins induced by levodopa [158]. Studies show that the administration of vitamin E decreases the toxic effects of β -amyloid and improves cognitive development, decreases neuronal damage, and slows the progression of Alzheimer's disease [159, 160]. Green tea epigallocatechin gallate esters have inhibitory properties of amyloidosis and β -amyloid production both *in vitro* and *in vivo* [161]. Melatonin is another natural component that has been shown to have neuroprotective effects. In Parkinson's disease models, melatonin contributes to decreased dopamine production and decreases the LPOs and nitrates in the cytosol [162]. Melatonin has also been observed in clinical studies to improve sleep disorder in patients with Parkinson's disease, but not to improve motor symptoms [163, 164].

1.16. Oxidative Stress in Cancer. ROS have the ability to damage DNA and promote the development of carcinogenesis [165]. OH[·] is the main ROS that attacks the mitochondrial and nuclear DNA strands producing different hydrolyzed base products such as 8-OHdG and 8-oxodG [166]. Cells can repair DNA damage by different enzyme mechanisms [167]. However, when DNA damage cannot be repaired, mutations related to base modification or deletion occur, leading to carcinogenesis [168]. The risk of poor DNA repair increases with the number of oxidative lesions that occur in DNA. Aging contributes to the accumulation of oxidative damage and decreased DNA repair [169]. Consequences of oxidative DNA damage include chromosomal abnormalities, blocking of DNA replication, and cytotoxicity [170, 171]. While oxidative damage to DNA is primarily caused by a direct free radical attack on DNA, free radical reaction with other cellular components may also contribute to mutagenicity [172]. LPO have carcinogenic capabilities [173]. MDA can react with guanine bases and form adducts [174]. All the mechanisms for the development of carcinogenesis caused by OS are still unknown. New mechanisms point to OS ability to alter the expression of genes and proteins involved in signaling cell growth and proliferation [175].

1.17. Oxidative Stress and Antineoplastic Drugs. Antineoplastic drugs have shown increased production of OS during the application of chemotherapy in cancer patients. Antineoplastic drugs promote the elevation of LPO and reduction of vitamins E and C and β -carotene [176].

Doxorubicin is a broad-spectrum anthracycline widely used in solid tumors [177]. Its mechanism of action is not completely known, but it consists of the inhibition of DNA and RNA synthesis, interfering with the activity of the enzyme topoisomerase II and the generation of ROS [178]. Doxorubicin has a quinone chemical structure that acts as an electron acceptor, producing a semiquinone radical that reacts with oxygen to form O_2^- and H_2O_2 [179]. The release of these free radicals increases OS causing DNA damage and cell death [180]. Despite the strong antineoplastic effects of doxorubicin, its use is limited due to its cardiotoxic capacity [181]. The main cardiotoxicity mechanisms of doxorubicin are OS and mitochondrial dysfunction [182]. Experimental evidence shows that treatment with doxorubicin increases OS in cardiac myocytes, causing accumulation of irreversible cardiotoxicity [183]. Doxorubicin increases the production of O_2^- and NO[·] by joining the eNOS reductase domain [184]. eNOS is the major NOS isomorphism involved in the development of left ventricular dysfunction induced by doxorubicin [185]. Some studies have proposed using antioxidants to decrease the cardiotoxicity of doxorubicin. The cardioprotective effects of coenzyme Q10 have been evaluated in pediatric patients on anthracycline therapy. Patients receiving coenzyme Q10 were reported to show benefits in cardiac function [186].

Cisplatin is one of the main representatives of the drugs in the group of coordination complexes with platinum used for several decades to treat different types of cancer [187]. Cisplatin anticancer activity consists of the ability of platinum to form covalent adducts with nuclear DNA. These cisplatin-DNA junctions form crosslinks between the outer and inner strands causing the strands of nuclear DNA to break. DNA damage ends up, causing cellular apoptosis [188]. Like other cancer drugs, the use of cisplatin is also limited by its side effects. One of the main toxic effects is nephrotoxicity [189]. OS represents an important mechanism of tissue damage from the use of cisplatin. Cisplatin-induced nephrotoxicity is associated with mitochondrial damage represented by decreased GSH, oxidative damage of lipids and mitochondrial proteins, and increased apoptosis [190]. MDA has been proposed as a predictor of the development of cisplatin-induced kidney failure [191]. Increased liver concentrations of LPO products are also related to cisplatin-induced hepatotoxicity [192]. High doses of cisplatin cause mitochondrial OS and damage to liver energy metabolism [193].

1.18. Adjuvant Antioxidants in Cancer. Coenzyme Q10 (ubiquinone) is not FDA approved to treat any medical condition. However, it is widely available over the counter as a dietary supplement. Chronic diseases like cancer, neurodegenerative disease, fibromyalgia, DM, mitochondrial diseases, muscle diseases, and heart failure are associated with decreased circulating levels of coenzyme Q10 [194].

Coenzyme Q10 is a fat-soluble vitamin-like molecule that occurs naturally in every cell membrane in our bodies. It is a normal part of our diet, but it is also synthesized endogenously. It is essential for the proper transfer of electrons within the mitochondrial respiratory chain and the production of adenosine triphosphate (ATP) [195]. Coenzyme Q10 has the ability to increase the production of key antioxidants such as SOD. The coenzyme Q10 reduces LPO levels by reducing prooxidant compounds and is capable of improving blood flow and protecting blood vessels through the preservation of NO[·] [196]. Coenzyme Q10 is safe as a dietary supplement. Toxicity is unlikely, even up to a daily intake of 1,200 mg/day. The typically studied doses have been from 100 to 200 mg/day [197].

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is a polyphenolic phytoalexin present in a variety of plant species such as peanuts, grapes, berries, and red wine [198]. Preclinical studies have shown that resveratrol has protective effects in various disease models, such as DM and cancer [199]. Resveratrol *in vitro* systems have been shown to directly remove a variety of oxidants, including the OH[·] radical, O₂^{·-}, H₂O₂, and ONOO[·]. In a cell-free system using the Fenton reaction as the OH[·] source, resveratrol (at concentrations $\geq 300 \mu\text{M}$) has been shown to act as a scavenger rather than an inhibitor of the Fenton reaction. The calculated reaction rate of resveratrol of OH[·] ($9.45 \times 10^8 \text{ M}^{-1}\cdot\text{s}^{-1}$) is significantly less than that of well-established antioxidants, including ascorbate ($1.2 \times 10^{10} \text{ M}^{-1}\cdot\text{s}^{-1}$), glutamate (GSH) ($1.5 \times 10^{10} \text{ M}^{-1}\text{S}^{-1}$), and cysteine ($1.3 \times 10^{10} \text{ M}^{-1}\text{S}^{-1}$). The property which has been proposed to remove OH[·] of resveratrol is due to its phenolic groups [200]. Resveratrol (at concentrations $\geq 100 \mu\text{M}$) has been shown to remove the radical O₂^{·-} directly in a non-enzymatic, cell-free system (potassium O₂^{·-} system) [201]. Resveratrol (10 μM) increases mitochondrial mass and mitochondrial DNA and regulates constituents of the electron transport chain and mitochondrial biogenesis factors in cultured coronary artery endothelial cells in humans [202]. Very high doses of resveratrol (up to 3000 mg) have been used in some clinical trials. However, low doses (5 mg in humans or 0.07 mg·kg⁻¹ in mice) have been shown to have even superior chemopreventive efficacy against cancer at high doses (1000 mg in humans or 14 mg·kg⁻¹ in mice) [203].

1.19. Oxidative Stress in Antiretroviral Therapy. The introduction of highly active antiretroviral therapy (HAART) has reduced the morbidity and deaths associated with human immunodeficiency virus infections (HIV) [204]. Drugs classified as nucleoside or nucleotide reverse transcriptase inhibitors (NRTI or NtRTI), nonnucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (IP), integrase inhibitors, and fusion inhibitors/entry are traditionally used in the treatment of HIV infections. Current HAART administration guidelines recommend the combination of two NRTIs, an NNRTI, or a protease/integrase inhibitor, depending on the patient's efficacy and tolerability. NRTIs (abacavir, didanosine, lamivudine, stavudine, zidovudine, and emtricitabine) act as false substrates that sabotage the lengthening of the viral cDNA chain, inhibiting viral reverse transcriptase activity by limiting viral replication [205]. NRTIs are associ-

ated with hepatotoxicity, such as steatosis, steatohepatitis, disorders of lipid regulation, enlarged liver, and abnormal liver functions [206], although the specific mechanisms through which complications of NRTIs occur have not yet been clearly defined. NRTIs have been shown to inhibit γ -DNA polymerase, leading to mitochondrial DNA depletion and mitochondrial toxicity, leading to impaired oxidative phosphorylation and oxidative damage to cellular machinery, along with delayed cell cycle progression resulting in apoptotic cell death [207]. These effects have been attributed to the binding of NRTI-triphosphate (the active metabolite of most NRTIs after intracellular phosphorylation) to replicating mitochondrial DNA that causes the termination of viral chain elongation [208]. The marked increase in MDA, end products of LPO, and protein carbonyls has been associated with the administration of NRTI, together with a decrease in the activity of enzymatic antioxidant proteins as a consequence of the disorder of the oxidative phosphorylation process [209]. Known metabolic complications of NRTI administration include lipodystrophy, dyslipidemia, hepatotoxicity, hepatomegaly, metabolic syndrome, increased lactic acid, and cardiomyopathy [210]. Oxidative cell damage caused by mitochondrial toxicity is one of many scientific mechanisms that underline the development of complications from NRTI [211].

On the other hand, active HIV infection in the central nervous system is undoubtedly a factor that contributes to the development of cognitive deficit [212]. Stopping viral replication in brain tissue and the rest of the body is essential for prevention. However, the potential of antiretroviral treatments to contribute to this degenerative condition has not been fully explored in clinical studies or in experimental models. NRTI are essential drugs in most combination antiretroviral therapy (cART) regimens. The most common side effects of these medications that limit clinical use are myopathy, lactic acidosis, and peripheral neuropathy. All of which are closely related to mitochondrial toxicity. The implementation of cART has dramatically increased the survival rate of people infected with HIV and has almost completely prevented severe dementia associated with the virus [213, 214]. The putative molecular mechanism that governs NRTI-mediated mitochondrial toxicity is the specific inhibition of mitochondrial polymerase γ (pol γ) [215]. Because pol γ is the primary DNA polymerase in mitochondria, inhibition of pol γ is expected to lead to reductions in mtDNA synthesis and subsequently to reductions in the supply of critical protein subunits of respiratory complexes of the electron transport chain. Deficiencies in these proteins should cause decreased ATP production and accumulation of orphan respiratory complex subunits encoded by nuclear DNA. Despite the high correlation between pol γ inhibition *in vitro* and the severity of clinical side effects, studies in cell culture have shown that mitochondrial dysfunction can occur in cardiac myocytes or hepatocytes independent of mtDNA depletion [216]. When NRTI interfere with the action of mitochondrial DNA polymerase, mitochondrial replication is inhibited. This gradually reduces mitochondrial function in various tissues that is evident primarily in metabolically active organs such as

the heart and liver, resulting in cardiotoxicity and hepatic toxicity [208].

1.20. Natural Antioxidants in HIV. Common HIV antioxidants such as vitamins C and E, uridine, and carnitine have been investigated to prevent or reverse complications from NRTI management with minimal success [217]. Therefore, further research is needed for alternative antioxidants that may be more effective in controlling complications of NRTI. Dietary and nutritional therapies are viable options that have not been vigorously applied. The beneficial effects of some currently available antioxidants have been used in animal models, but large-scale validated clinical trials are still lacking [218]. Plant-derived flavonoids such as naringin ($4',5,7$ -trihydroxyflavone 7-rhamnoglycoside) are commonly found in citrus. Naringin has been recommended as beneficial to reduce the risk of DM and CVD in predisposed populations [219]. The antioxidant capacity of naringin has been demonstrated through its action in the elimination of free radicals, antiapoptosis, antihyperglycemic, antimutagenic, anticancer, anti-inflammatory, and cholesterol-lowering agents [220]. HIV causes symptoms that are similar to those of NRTI-induced metabolic complications. In 2015, the authors reported an experimental study in mice where naringin reversed the metabolic complications associated with NRTI by improving OS and apoptosis. This evidence implies that naringin supplementation could mitigate lipodystrophy and dyslipidemia associated with NRTI therapy [221]. Naringin is a cheap and readily available dietary flavonoid in most citrus fruits with proven antioxidant and antiapoptotic properties that have shown favorable effects in animal models *in vitro*, *in vivo*, and *ex vivo*. The mechanism by which naringin improves metabolic complications possibly implies its antioxidant and/or antiapoptotic effects [222]. The mechanism of action is worth further investigation in patients treated with NRTI through well-conducted clinical studies, where naringin is administered at different doses.

2. Conclusions

OS is closely linked with the pathological mechanisms of different chronic diseases. The role of pharmacological therapy on OS depends both on the chemical characteristics of the active molecules and on the consequences of the mechanisms of action. Medicines such as CCB have a dihydropyridine ring that gives them antioxidant structural characteristics. On the other hand, other antihypertensive drugs show beneficial antioxidant activity as a result of regulating the antihypertensive mechanism to normal. Immunosuppressive and antiretroviral drugs are the treatments that cause the most oxidative damage in patients in the long term, and antioxidant management alternatives are very limited in experimentation or with insufficient results to treat these pathologies. The investigation of the oxidative mechanisms of these pathologies and of the conventional medicines used to treat them will allow a better understanding, monitoring, or selection of alternative antioxidant medicines according to the health condition of each patient to decrease oxidative damage.

GSH: glutathione; SOD: superoxide dismutase; MDA: malondialdehyde; AGEs: advanced glycation end products; NRTI: nucleoside reverse transcriptase inhibitors.

Conflicts of Interest

The authors declare no conflict of interest.

References

- [1] H. Fujii, K. Nakai, and M. Fukagawa, “Role of oxidative stress and indoxyl sulfate in progression of cardiovascular disease in chronic kidney disease,” *Therapeutic Apheresis and Dialysis*, vol. 15, no. 2, pp. 125–128, 2011.
- [2] A. Phaniendra, D. B. Jestadi, and L. Periyasamy, “Free radicals: Properties, sources, targets, and their implication in various diseases,” *Indian Journal of Clinical Biochemistry*, vol. 30, no. 1, pp. 11–26, 2015.
- [3] M. D. Brand, “The sites and topology of mitochondrial superoxide production,” *Experimental Gerontology*, vol. 45, no. 7–8, pp. 466–472, 2010.
- [4] C. X. C. Santos, L. Y. Tanaka, J. Wosniak Jr., and F. R. M. Laurindo, “Mechanisms and implications of reactive oxygen species generation during the unfolded protein response: roles of endoplasmic reticulum oxidoreductases, mitochondrial electron transport, and NADPH oxidase,” *Antioxid Redox Signal*, vol. 11, no. 10, pp. 2409–2427, 2009.
- [5] M. Fransen, M. Nordgren, B. Wang, and O. Apanasets, “Role of peroxisomes in ROS/RNS-metabolism: implications for human disease,” *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease*, vol. 1822, no. 9, pp. 1363–1373, 2012.
- [6] P. Rajendran, N. Nandakumar, T. Rengarajan et al., “Antioxidants and human diseases,” *Clinica Chimica Acta*, vol. 436, pp. 332–347, 2014.
- [7] D. M. Small, J. S. Coombes, N. Bennett, D. W. Johnson, and G. C. Gobe, “Oxidative stress, anti-oxidant therapies and chronic kidney disease,” *Nephrology*, vol. 17, no. 4, pp. 311–321, 2012.
- [8] K. Yasui and A. Baba, “Therapeutic potential of superoxide dismutase (SOD) for resolution of inflammation,” *Inflammation Research*, vol. 55, no. 9, pp. 359–363, 2006.
- [9] S. H. Kim, S. H. Kim, J. H. Lee et al., “Superoxide Dismutase gene (SOD1, SOD2, and SOD3) Polymorphisms and Antituberculosis Drug-induced Hepatitis,” *Allergy, Asthma & Immunology Research*, vol. 7, no. 1, pp. 88–91, 2015.
- [10] I. Mirończuk-Chodakowska, A. M. Witkowska, and M. E. Zujko, “Endogenous non-enzymatic antioxidants in the human body,” *Advances in Medical Sciences*, vol. 63, no. 1, pp. 68–78, 2018.
- [11] P. Monaghan, N. B. Metcalfe, and R. Torres, “Oxidative stress as a mediator of life history trade-offs: mechanisms, measurements and interpretation,” *Ecology Letters*, vol. 12, no. 1, pp. 75–92, 2009.
- [12] P. J. Andrew and B. Mayer, “Enzymatic function of nitric oxide synthases,” *Cardiovascular Research*, vol. 43, no. 3, pp. 521–531, 1999.
- [13] T. Douki and J. Cadet, “Peroxynitrite mediated oxidation of purine bases of nucleosides and isolated DNA,” *Free Radical Research*, vol. 24, no. 5, pp. 369–380, 2009.

- [14] A. Ayala, M. F. Muñoz, and S. Argüelles, "Lipid Peroxidation: Production, metabolism, and signaling mechanisms of malondialdehyde and 4-Hydroxy-2-Nonenal," *Oxidative Medicine and Cellular Longevity*, vol. 2014, Article ID 360438, 31 pages, 2014.
- [15] Y. Yoshida, A. Umeno, and M. Shichiri, "Lipid peroxidation biomarkers for evaluating oxidative stress and assessing anti-oxidant capacity *in vivo*," *Journal of Clinical Biochemistry and Nutrition*, vol. 52, no. 1, pp. 9–16, 2013.
- [16] F. McMurray, D. A. Patten, and M.-E. Harper, "Reactive oxygen species and oxidative stress in obesity—recent findings and empirical approaches," *Obesity*, vol. 24, no. 11, pp. 2301–2310, 2016.
- [17] X. Ba and I. Boldogh, "8-Oxoguanine DNA glycosylase 1: beyond repair of the oxidatively modified base lesions," *Redox Biology*, vol. 14, pp. 669–678, 2018.
- [18] I. Liguori, G. Russo, F. Curcio et al., "Oxidative stress, aging, and diseases," *Clinical Interventions in Aging*, vol. Volume 13, pp. 757–772, 2018.
- [19] S. Kundu, P. Ghosh, S. Datta, A. Ghosh, S. Chattopadhyay, and M. Chatterjee, "Oxidative stress as a potential biomarker for determining disease activity in patients with rheumatoid arthritis," *Free Radical Research*, vol. 46, no. 12, pp. 1482–1489, 2012.
- [20] O. O. Oguntibeju, "Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links," *International Journal of Physiology, Pathophysiology and Pharmacology*, vol. 11, no. 3, pp. 45–63, 2019.
- [21] G. Zalba, G. S. José, M. U. Moreno et al., "Oxidative stress in arterial hypertension: Role of NAD(P)H oxidase," *Hypertension*, vol. 38, no. 6, pp. 1395–1399, 2001.
- [22] A. J. Kattoor, N. V. K. Pothineni, D. Palagiri, and J. L. Mehta, "Oxidative Stress in Atherosclerosis," *Current Atherosclerosis Reports*, vol. 19, no. 11, 2017.
- [23] E. Mariani, M. C. Polidori, A. Cherubini, and P. Mecocci, "Oxidative stress in brain aging, neurodegenerative and vascular diseases: an overview," *Journal of Chromatography B*, vol. 827, no. 1, pp. 65–75, 2005.
- [24] S. Reuter, S. C. Gupta, M. M. Chaturvedi, and B. B. Aggarwal, "Oxidative stress, inflammation, and cancer: how are they linked?," *Free Radical Biology and Medicine*, vol. 49, no. 11, pp. 1603–1616, 2010.
- [25] J. P. Allard, E. Aghdassi, J. Chau, I. Salit, and S. Walmsley, "Oxidative stress and plasma antioxidant micronutrients in humans with HIV infection," *The American Journal of Clinical Nutrition*, vol. 67, no. 1, pp. 143–147, 1998.
- [26] J. Scott, "The pathogenesis of atherosclerosis and new opportunities for treatment and prevention," *Journal of neural transmission. Supplementum*, vol. 63, pp. 1–17, 2002.
- [27] P. Libby, Y. Okamoto, V. Z. Rocha, and E. Folco, "Inflammation in Atherosclerosis," *Circulation Journal*, vol. 74, no. 2, pp. 213–220, 2010.
- [28] S. Verma, C. H. Wang, S. H. Li et al., "A self-fulfilling prophecy: C-reactive protein attenuates nitric oxide production and inhibits angiogenesis," *Circulation*, vol. 106, no. 8, pp. 913–919, 2002.
- [29] P. Libby, "Lipid-lowering therapy stabilizes plaque, reduces events by limiting inflammation," *The American Journal of Managed Care*, pp. 1–4, 2002.
- [30] S. Verma, S. H. Li, C. H. Wang et al., "Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction," *Circulation*, vol. 108, no. 6, pp. 736–740, 2003.
- [31] M. Pacurari, R. Kafoury, P. B. Tchounwou, and K. Ndebele, "The Renin-Angiotensin-Aldosterone system in vascular inflammation and remodeling," *International Journal of Inflammation*, vol. 2014, Article ID 689360, pp. 1–13, 2014.
- [32] M. Ferder, F. Inserra, W. Manucha, and L. Ferder, "The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system," *American Journal of Physiology-Cell Physiology*, vol. 304, no. 11, pp. C1027–C1039, 2013.
- [33] K. Husain, W. Hernandez, R. A. Ansari, and L. Ferder, "Inflammation, oxidative stress and renin angiotensin system in atherosclerosis," *World Journal of Biological Chemistry*, vol. 6, no. 3, pp. 209–217, 2015.
- [34] S. C. Bergheanu, M. C. Bodde, and J. W. Jukema, "Pathophysiology and treatment of atherosclerosis," *Netherlands Heart Journal*, vol. 25, no. 4, pp. 231–242, 2017.
- [35] F. Drafi, K. Bauerova, V. Kuncirova et al., "Pharmacological influence on processes of adjuvant arthritis: effect of the combination of an antioxidant active substance with methotrexate," *Interdisciplinary Toxicology*, vol. 5, no. 2, pp. 84–91, 2012.
- [36] J. K. Liao and U. Laufs, "Pleiotropic effects of statins," *Annual Review of Pharmacology and Toxicology*, vol. 45, no. 1, pp. 89–118, 2005.
- [37] C. Antoniades and K. M. Channon, "Statins: pleiotropic regulators of cardiovascular redox state," *Antioxidants & Redox Signaling*, vol. 20, no. 8, pp. 1195–1197, 2014.
- [38] S. Lim and P. Barter, "Antioxidant effects of statins in the management of cardiometabolic disorders," *Journal of Atherosclerosis and Thrombosis*, vol. 21, no. 10, pp. 997–1010, 2014.
- [39] J. Girona, A. E. la Ville, R. Solà, N. Plana, and L. Masana, "Simvastatin decreases aldehyde production derived from lipoprotein oxidation," *The American Journal of Cardiology*, vol. 83, no. 6, pp. 846–851, 1999.
- [40] J. Bouitbir, A. L. Charles, A. Echaniz-Laguna et al., "Opposite effects of statins on mitochondria of cardiac and skeletal muscles: a "mitohormesis" mechanism involving reactive oxygen species and PGC-1," *European Heart Journal*, vol. 33, no. 11, pp. 1397–1407, 2012.
- [41] S. Pal, M. Ghosh, S. Bhattacharyya, and P. C. Sil, "Atorvastatin induced hepatic oxidative stress and apoptotic damage via MAPKs, mitochondria, calpain and caspase12 dependent pathways," *Food and Chemical Toxicology*, vol. 83, pp. 36–47, 2015.
- [42] S. Nadanaciva, J. A. Dykens, A. Bernal, R. A. Capaldi, and Y. Will, "Mitochondrial impairment by PPAR agonists and statins identified via immunocaptured OXPHOS complex activities and respiration," *Toxicology and Applied Pharmacology*, vol. 223, no. 3, pp. 277–287, 2007.
- [43] F. Galtier, T. Mura, E. Raynaud de Mauverger et al., "Effect of a high dose of simvastatin on muscle mitochondrial metabolism and calcium signaling in healthy volunteers," *Toxicology and Applied Pharmacology*, vol. 263, no. 3, pp. 281–286, 2012.
- [44] O. Ivanovski, D. Szumlak, T. Nguyen-Khoa et al., "The antioxidant N-acetylcysteine prevents accelerated atherosclerosis in uremic apolipoprotein E knockout mice," *Kidney International*, vol. 67, no. 6, pp. 2288–2294, 2005.

- [45] K. Husain, E. Suarez, A. Isidro, and L. Ferder, "Effects of paricalcitol and enalapril on atherosclerotic injury in mouse aortas," *American Journal of Nephrology*, vol. 32, no. 4, pp. 296–304, 2010.
- [46] C. Manach, A. Scalbert, C. Morand, C. Rémesy, and L. Jiménez, "Polyphenols: food sources and bioavailability," *The American Journal of Clinical Nutrition*, vol. 79, no. 5, pp. 727–747, 2004.
- [47] R. Tsao, "Chemistry and biochemistry of dietary polyphenols," *Nutrients*, vol. 2, no. 12, pp. 1231–1246, 2010.
- [48] P. M. Kearney, M. Whelton, K. Reynolds, P. Muntner, P. K. Whelton, and J. He, "Global burden of hypertension: analysis of worldwide data," *The Lancet*, vol. 365, no. 9455, pp. 217–223, 2005.
- [49] F. H. Messerli, B. Williams, and E. Ritz, "Essential hypertension," *The Lancet*, vol. 370, no. 9587, pp. 591–603, 2007.
- [50] D. G. Harrison, T. J. Guzik, H. E. Lob et al., "Inflammation, immunity, and hypertension," *Hypertension*, vol. 57, no. 2, pp. 132–140, 2011.
- [51] T. J. Guzik, N. E. Hoch, K. A. Brown et al., "Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction," *Journal of Experimental Medicine*, vol. 204, no. 10, pp. 2449–2460, 2007.
- [52] F. Fang, G. C. Liu, X. Zhou et al., "Loss of ACE2 exacerbates murine renal ischemia-reperfusion injury," *PLoS One*, vol. 8, no. 8, article e71433, 2013.
- [53] S. Rajagopalan, S. Kurz, T. Münzel et al., "Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone," *Journal of Clinical Investigation*, vol. 97, no. 8, pp. 1916–1923, 1996.
- [54] S. D. Crowley, S. B. Gurley, M. J. Herrera et al., "Angiotensin II causes hypertension and cardiac hypertrophy through its receptors in the kidney," *Proceedings of the National Academy of Sciences*, vol. 103, no. 47, pp. 17985–17990, 2006.
- [55] G. Wolf, U. Wenzel, K. Jablonski, M. Brundert, and F. Rinninger, "Angiotensin II down-regulates the SR-BI HDL receptor in proximal tubular cells," *Nephrology Dialysis Transplantation*, vol. 20, no. 6, pp. 1222–1227, 2005.
- [56] P. Strazzullo, S. M. Kerry, A. Barbato, M. Versiero, L. D'Elia, and F. P. Cappuccio, "Do statins reduce blood pressure? A meta-analysis of randomized, controlled trials," *Hypertension*, vol. 49, no. 4, pp. 792–798, 2007.
- [57] Q. Nguyen, J. Dominguez, L. Nguyen, and N. Gullapalli, "Hypertension management: an update," *Am Health Drug Benefits*, vol. 3, no. 1, pp. 47–56, 2010.
- [58] M. Mihalj, R. Tadzic, A. Vcev, S. Rucevic, and I. Drenjancevic, "Blood pressure reduction is associated with the changes in oxidative stress and endothelial activation in hypertension, regardless of antihypertensive therapy," *Kidney and Blood Pressure Research*, vol. 41, no. 6, pp. 721–735, 2016.
- [59] G. Chandran, K. N. S. Sirajudeen, N. S. N. Yusoff, M. Swamy, and M. S. Samarendra, "Effect of the antihypertensive drug enalapril on oxidative stress markers and antioxidant enzymes in kidney of spontaneously hypertensive rat," *Oxidative Medicine and Cellular Longevity*, vol. 2014, Article ID 608512, 10 pages, 2014.
- [60] N. S. N. Yusoff, Z. Mustapha, S. E. T. Sharif, C. Govindasamy, and K. N. S. Sirajudeen, "Effect of antihypertensive drug treatment on oxidative stress markers in heart of spontaneously hypertensive rat models," *Journal of Environmental Pathology, Toxicology and Oncology*, vol. 36, no. 1, pp. 43–53, 2017.
- [61] K. Mikrut, J. Kupsz, J. Koźlik, H. Krauss, E. Pruszyńska-Osmalek, and M. Gibas-Dorna, "Angiotensin-converting enzyme inhibitors reduce oxidative stress intensity in hyperglycemic conditions in rats independently from bradykinin receptor inhibitors," *Croatian Medical Journal*, vol. 57, no. 4, pp. 371–380, 2016.
- [62] P. Shang, T. Liu, W. Liu et al., "Telmisartan improves vascular remodeling through ameliorating prooxidant and profibrotic mechanisms in hypertension via the involvement of transforming growth factor- β 1," *Molecular Medicine Reports*, vol. 16, no. 4, pp. 4537–4544, 2017.
- [63] A. Kurata, H. Nishizawa, S. Kihara et al., "Blockade of Angiotensin II type-1 receptor reduces oxidative stress in adipose tissue and ameliorates adipocytokine dysregulation," *Kidney International*, vol. 70, no. 10, pp. 1717–1724, 2006.
- [64] S. Ogawa, T. Mori, K. Nako, T. Kato, K. Takeuchi, and S. Ito, "Angiotensin II type 1 receptor blockers reduce urinary oxidative stress markers in hypertensive diabetic nephropathy," *Hypertension*, vol. 47, no. 4, pp. 699–705, 2006.
- [65] H. J. Kim, S. J. Han, D. J. Kim et al., "Effects of valsartan and amlodipine on oxidative stress in type 2 diabetic patients with hypertension: A randomized, multicenter study," *The Korean Journal of Internal Medicine*, vol. 32, no. 3, pp. 497–504, 2017.
- [66] H. D. Khanna, M. K. Sinha, S. Khanna, and R. Tandon, "Oxidative stress in hypertension: Association with antihypertensive treatment," *Indian Journal of Physiology and Pharmacology*, vol. 52, no. 3, pp. 283–287, 2008.
- [67] M. L. Kukin, J. Kalman, R. H. Charney et al., "Prospective, Randomized Comparison of Effect of Long-Term Treatment with Metoprolol or Carvedilol on Symptoms, Exercise, Ejection Fraction, and Oxidative Stress in Heart Failure," *Circulation*, vol. 99, no. 20, pp. 2645–2651, 1999.
- [68] K. Nakamura, K. Kusano, Y. Nakamura et al., "Carvedilol Decreases Elevated Oxidative Stress in Human Failing Myocardium," *Circulation*, vol. 105, no. 24, pp. 2867–2871, 2002.
- [69] T. Godfraind, "Antioxidant effects and the therapeutic mode of action of calcium channel blockers in hypertension and atherosclerosis," *Philosophical Transactions of the Royal Society B: Biological Sciences*, vol. 360, no. 1464, pp. 2259–2272, 2005.
- [70] K. Takebayashi, R. Naruse, Y. Aso, and T. Inukai, "The Effect of Amlodipine on Oxidative Stress in Patients with Type 2 Diabetes," *SRX Medicine*, vol. 2010, Article ID 326840, 5 pages, 2010.
- [71] C. Napoli, S. Salomone, T. Godfraind et al., "1,4-Dihydropyridine calcium channel blockers inhibit plasma and LDL oxidation and formation of oxidation-specific epitopes in the arterial wall and prolong survival in stroke-prone spontaneously hypertensive rats," *Stroke*, vol. 30, no. 9, pp. 1907–1915, 1999.
- [72] A. Medina-Remón, A. Tresserra-Rimbau, P. Valderas-Martínez, R. Estruch, and R. M. Lamuela-Raventos, "Polyphenol consumption and blood pressure," in *Polyphenols in human Health and Disease*, R. R. Watson, V. R. Preedy, and S. Zibadi, Eds., pp. 971–987, Elsevier, Tokyo, Japan, 2014.
- [73] M. Sarr, M. Chataigneau, S. Martins et al., "Red wine polyphenols prevent angiotensin II-induced hypertension and

- endothelial dysfunction in rats: role of NADPH oxidase," *Cardiovascular Research*, vol. 71, no. 4, pp. 794–802, 2006.
- [74] K. Ried, P. Fakler, N. P. Stocks, and Cochrane Hypertension Group, "Effect of cocoa on blood pressure," *Cochrane Database of Systematic Reviews*, vol. 8, article CD008893, 2012.
- [75] M. M. de Jesús Romero-Prado, J. A. Curiel-Beltrán, M. V. Miramontes-Espino, E. G. Cardona-Muñoz, A. Ríos-Arellano, and L.-B. Balam-Salazar, "Dietary flavonoids added to pharmacological antihypertensive therapy are effective in improving blood pressure," *Basic & Clinical Pharmacology & Toxicology*, vol. 117, no. 1, pp. 57–64, 2015.
- [76] F. Giacco and M. Brownlee, "Oxidative stress and diabetic complications," *Circulation Research*, vol. 107, no. 9, pp. 1058–1070, 2010.
- [77] L. Monnier, E. Mas, C. Ginet et al., "Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes," *JAMA*, vol. 295, no. 14, pp. 1681–1687, 2006.
- [78] J. S. Johansen, A. K. Harris, D. J. Rychly, and A. Ergul, "Oxidative stress and the use of antioxidants in diabetes: Linking basic science to clinical practice," *Cardiovascular Diabetology*, vol. 4, no. 1, p. 5, 2005.
- [79] N. Chaturvedi, "The burden of diabetes and its complications: Trends and implications for intervention," *iabetes Research and Clinical Practice*, vol. 76, no. 3, pp. S3–S12, 2007.
- [80] U. Karunakaran and K.-G. Park, "A systematic review of oxidative stress and safety of antioxidants in diabetes: Focus on islets and their defense," *Diabetes & Metabolism Journal*, vol. 37, no. 2, pp. 106–112, 2013.
- [81] B. Westermann, "Mitochondrial fusion and fission in cell life and death," *Nature Reviews Molecular Cell Biology*, vol. 11, no. 12, pp. 872–884, 2010.
- [82] H.-F. Jheng, P.-J. Tsai, S.-M. Guo et al., "Mitochondrial fission contributes to mitochondrial dysfunction and insulin resistance in skeletal muscle," *Molecular and Cellular Biology*, vol. 32, no. 2, pp. 309–319, 2011.
- [83] M. P. Bhatt, Y.-C. Lim, Y.-M. Kim, and K.-S. Ha, "C-peptide activates AMPK α and prevents ROS-mediated mitochondrial fission and endothelial apoptosis in diabetes," *Diabetes*, vol. 62, no. 11, pp. 3851–3862, 2013.
- [84] S. M. Shenouda, M. E. Widlansky, K. Chen et al., "Altered mitochondrial dynamics contributes to endothelial dysfunction in diabetes mellitus," *Circulation*, vol. 124, no. 4, pp. 444–453, 2011.
- [85] J. Hong, Y. Zhang, S. Lai et al., "Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease," *Diabetes Care*, vol. 36, no. 5, pp. 1304–1311, 2013.
- [86] K. Matsumoto, Y. Sera, Y. Abe, T. Tominaga, Y. Yeki, and S. Miyake, "Metformin attenuates progression of carotid arterial wall thickness in patients with type 2 diabetes," *Diabetes Research and Clinical Practice*, vol. 64, no. 3, pp. 225–228, 2004.
- [87] Q. Wang, M. Zhang, G. Torres et al., "Metformin suppresses diabetes-accelerated atherosclerosis via the inhibition of Drp1-mediated mitochondrial Fission," *Diabetes*, vol. 66, no. 1, pp. 193–205, 2017.
- [88] D. D. Vilela, L. G. Peixoto, R. R. Teixeira et al., "The Role of metformin in controlling oxidative stress in muscle of diabetic rats," *Oxidative Medicine and Cellular Longevity*, vol. 2016, Article ID 6978625, 9 pages, 2016.
- [89] A. Chakraborty, S. Chowdhury, and M. Bhattacharyya, "Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients," *Diabetes Res Clin Pract*, vol. 93, no. 1, pp. 56–62, 2011.
- [90] A. H. Dehkordi, A. Abbaszadeh, S. Mir, and A. Hasanzadeh, "Metformin and its anti-inflammatory and anti-oxidative effects; new concepts," *Journal of Renal Injury Prevention*, vol. 8, no. 1, pp. 54–61, 2019.
- [91] C. Moriscot, M. J. Richard, M. C. Favrot, and P. Y. Benhamou, "Protection of insulin-secreting INS-1 cells against oxidative stress through adenoviral-mediated glutathione peroxidase overexpression," *Diabetes & Metabolism*, vol. 29, no. 2, pp. 145–151, 2003.
- [92] A. Ceriello and R. Testa, "Antioxidant anti-inflammatory treatment in type 2 diabetes," *Diabetes Care*, vol. 32, supplement 2, pp. S232–S236, 2009.
- [93] U. Milman, S. Blum, C. Shapira et al., "Vitamin E supplementation reduces cardiovascular events in a subgroup of middle-aged individuals with both type 2 diabetes mellitus and the haptoglobin 2-2 Genotype," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 28, no. 2, pp. 341–347, 2008.
- [94] S. Blum, M. Vardi, J. B. Brown et al., "Vitamin E reduces cardiovascular disease in individuals with diabetes mellitus and the haptoglobin 2-2 genotype," *Pharmacogenomics*, vol. 11, no. 5, pp. 675–684, 2010.
- [95] S. Akbar, S. Bellary, and H. R. Griffiths, "Dietary antioxidant interventions in type 2 diabetes patients: A meta-analysis," *The British Journal of Diabetes & Vascular Disease*, vol. 11, no. 2, pp. 62–68, 2011.
- [96] R. J. Reiter and D. X. Tan, "Melatonin," *Annals of the New York Academy of Sciences*, vol. 957, no. 1, pp. 341–344, 2002.
- [97] R. J. Reiter, D. X. Tan, and A. Galano, "Melatonin: Exceeding expectations," *Physiology*, vol. 29, no. 5, pp. 325–333, 2014.
- [98] R. Hardeland, J. A. Madrid, D.-X. Tan, and R. J. Reiter, "Melatonin, the circadian multioscillator system and health: the need for detailed analyses of peripheral melatonin signaling," *Journal of Pineal Research*, vol. 52, no. 2, pp. 139–166, 2012.
- [99] R. J. Reiter, J. C. Mayo, D.-X. Tan, R. M. Sainz, M. Alatorre-Jimenez, and L. Qin, "Melatonin as an antioxidant: under promises but over delivers," *Journal of Pineal Research*, vol. 61, no. 3, pp. 253–278, 2016.
- [100] V. R. Santos, J. A. Lima, A. C. De Mendonça, M. B. Braz Maximino, M. Faveri, and P. M. Duarte, "Effectiveness of full-mouth and partial-mouth scaling and root planing in treating chronic periodontitis in subjects with type 2 diabetes," *Journal of Periodontology*, vol. 80, no. 8, pp. 1237–1245, 2009.
- [101] A. Bracht, S. S. Silveira, C. V. Castro-Ghizoni et al., "Oxidative changes in the blood and serum albumin differentiate rats with monoarthritis and polyarthritis," *Springerplus*, vol. 5, no. 1, 2016.
- [102] S. Mateen, S. Moin, A. Q. Khan, A. Zafar, and N. Fatima, "Increased reactive oxygen species formation and oxidative stress in rheumatoid arthritis," *PLoS One*, S. A. Sheweita, Ed., vol. 11, no. 4, article e0152925, 2016.
- [103] A.-R. Phull, M. Majid, I.-u. Haq, M. R. Khan, and S. J. Kim, "*In vitro* and *in vivo* evaluation of anti-arthritis, antioxidant efficacy of fucoidan from *undaria pinnatifida* (Harvey) Surin-gar," *International Journal of Biological Macromolecules*, vol. 97, pp. 468–480, 2017.
- [104] C. M. Quiñonez-Flores, S. A. González-Chávez, D. D. R. Nájera, and C. Pacheco-Tena, "Oxidative stress relevance in

- the pathogenesis of the rheumatoid arthritis: A systematic review," *BioMed Research International*, vol. 2016, Article ID 6097417, 14 pages, 2016.
- [105] S. D. Crowley, "The cooperative roles of inflammation and oxidative stress in the pathogenesis of hypertension," *Antioxidants & Redox Signaling*, vol. 20, no. 1, pp. 102–120, 2014.
- [106] C. Nathan and A. Cunningham-Bussel, "Beyond oxidative stress: an immunologist's guide to reactive oxygen species," *Nature Reviews Immunology*, vol. 13, no. 5, pp. 349–361, 2013.
- [107] H. Blaser, C. Dostert, T. W. Mak, and D. Brenner, "TNF and ROS Crosstalk in Inflammation," *Trends in Cell Biology*, vol. 26, no. 4, pp. 249–261, 2016.
- [108] T. Liu, L. Zhang, D. Joo, and S. C. Sun, "NF- κ B signaling in inflammation," *Signal Transduction and Targeted Therapy*, vol. 2, no. 1, 2017.
- [109] Y. Kabe, K. Ando, S. Hirao, M. Yoshida, and H. Handa, "Redox regulation of NF- κ B activation: distinct redox regulation between the cytoplasm and the nucleus," *Antioxidants & Redox Signaling*, vol. 7, no. 3-4, pp. 395–403, 2005.
- [110] T. G. Canty, E. M. Boyle, A. Farr, E. N. Morgan, E. D. Verrier, and T. H. Pohlman, "Oxidative stress induces NF- κ B nuclear translocation without degradation of $I\kappa B\alpha$," *Circulation*, vol. 100, Supplement 2, pp. II-361-II-364, 1999.
- [111] C.-J. Chen, Y.-C. Fu, W. Yu, and W. Wang, "SIRT3 protects cardiomyocytes from oxidative stress-mediated cell death by activating NF- κ B," *Biochemical and Biophysical Research Communications*, vol. 430, no. 2, pp. 798–803, 2013.
- [112] C. Espinosa-Diez, V. Miguel, D. Mennerich et al., "Antioxidant responses and cellular adjustments to oxidative stress," *Redox Biology*, vol. 6, pp. 183–197, 2015.
- [113] N. Netzer, H. Gatterer, M. Faulhaber, M. Burtscher, S. Pramsohler, and D. Pesta, "Hypoxia, oxidative stress and fat," *Biomolecules*, vol. 5, no. 2, pp. 1143–1150, 2015.
- [114] E. Teissier, A. Nohara, G. Chinetti et al., "Peroxisome proliferator-activated receptor alpha induces NADPH oxidase activity in macrophages, leading to the generation of LDL with PPAR- α activation properties," *Circulation Research*, vol. 95, no. 12, pp. 1174–1182, 2004.
- [115] A. C. Bulua, A. Simon, R. Maddipati et al., "Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS)," *The Journal of Experimental Medicine*, vol. 208, no. 3, pp. 519–533, 2011.
- [116] G. T. Nguyen, E. R. Green, and J. Mecsas, "Neutrophils to the ROScue: mechanisms of NADPH oxidase activation and bacterial resistance," *Frontiers in Cellular and Infection Microbiology*, vol. 7, 2017.
- [117] Y. W. Kim, X. Z. West, and T. V. Byzova, "Inflammation and oxidative stress in angiogenesis and vascular disease," *Journal of Molecular Medicine*, vol. 91, no. 3, pp. 323–328, 2013.
- [118] M. A. Lopez-Olivo, H. R. Siddhanamatha, B. Shea, P. Tugwell, G. A. Wells, and M. E. Suarez-Almazor, "Methotrexate for treating rheumatoid arthritis," *Cochrane Database of Systematic Reviews*, vol. 2014, no. 6, 2014.
- [119] D. C. Phillips, K. J. Woppard, and H. R. Griffiths, "The anti-inflammatory actions of methotrexate are critically dependent upon the production of reactive oxygen species," *British Journal of Pharmacology*, vol. 138, no. 3, pp. 501–511, 2003.
- [120] T. Elango, H. Dayalan, P. Gnanaraj, H. Malligarjunan, and S. Subramanian, "Impact of methotrexate on oxidative stress and apoptosis markers in psoriatic patients," *Clinical and Experimental Medicine*, vol. 14, no. 4, pp. 431–437, 2014.
- [121] N. N. Caetano, A. P. Campello, E. G. S. Carnieri, M. L. W. Kluppel, and M. B. M. Oliveira, "Effect of methotrexate (MTX) on NAD(P) $^+$ dehydrogenases of HeLa cells: Malic enzyme, 2-oxoglutarate and isocitrate dehydrogenases," *Cell Biochemistry and Function*, vol. 15, no. 4, pp. 259–264, 1997.
- [122] R. M. Babiak, A. P. Campello, E. G. Carnieri, and M. B. Oliveira, "Methotrexate: pentose cycle and oxidative stress," *Cell Biochemistry and Function*, vol. 16, no. 4, pp. 283–293, 1998.
- [123] R. Heidari, A. Ahmadi, H. Mohammadi, M. M. Ommati, N. Azarpira, and H. Niknahad, "Mitochondrial dysfunction and oxidative stress are involved in the mechanism of methotrexate-induced renal injury and electrolytes imbalance," *Biomedicine & Pharmacotherapy*, vol. 107, pp. 834–840, 2018.
- [124] E. S. L. Chan and B. N. Cronstein, "Methotrexate—how does it really work?," *Nature Reviews Rheumatology*, vol. 6, no. 3, pp. 175–178, 2010.
- [125] M. Wang, J. Huang, H. Fan et al., "Treatment of rheumatoid arthritis using combination of methotrexate and tripterygium glycosides tablets—A quantitative plasma pharmacokinetic and pseudotargeted metabolomic approach," *Frontiers in Pharmacology*, vol. 9, no. 9, 2018.
- [126] W. B. Al-Youzbaki, H. I. A. Fatehi, and A. T. Yassen, "Oxidant and antioxidant status in patients with rheumatoid arthritis treated by methotrexate," *Iraqi Journal of Community Medicine*, vol. 1, pp. 63–67, 2013.
- [127] N. Jahovic, H. Çevik, A. Ö. Şehirli, B. C. Yeğen, and G. Şener, "Melatonin prevents methotrexate-induced hepatorenal oxidative injury in rats," *Journal of Pineal Research*, vol. 34, no. 4, pp. 282–287, 2003.
- [128] Y. Zhang, P. Han, N. Wu et al., "Amelioration of lipid abnormalities by α -lipoic acid through antioxidative and anti-inflammatory effects," *Obesity*, vol. 19, no. 8, pp. 1647–1653, 2011.
- [129] H. Tabassum, S. Parvez, S. T. Pasha, B. D. Banerjee, and S. Raisuddin, "Protective effect of lipoic acid against methotrexate-induced oxidative stress in liver mitochondria," *Food and Chemical Toxicology*, vol. 48, no. 7, pp. 1973–1979, 2010.
- [130] A. Cetinkaya, E. Bulbuloglu, E. B. Kurutas, and B. Kantarceken, "N-acetylcysteine ameliorates methotrexate-induced oxidative liver damage in rats," *Medical Science Monitor*, vol. 12, no. 8, pp. BR274–BR278, 2006.
- [131] G. G. Artioli, C. Sale, and R. L. Jones, "Carnosine in health and disease," *European Journal of Sport Science*, vol. 19, no. 1, pp. 30–39, 2018.
- [132] M. Rahman, K. H. Lohani, R. K. Nath et al., "Efficacy of Methotrexate in combination with Antioxidant vitamins (A, C & E) versus methotrexate alone in the treatment of rheumatoid arthritis," *Open Science Journal*, vol. 3, no. 1, p. 1, 2018.
- [133] O. Hwang, "Role of oxidative stress in Parkinson's disease," *Experimental neurobiology*, vol. 22, no. 1, pp. 11–17, 2013.
- [134] E. Tönnies and E. Trushina, "Oxidative stress, synaptic dysfunction, and Alzheimer's disease," *Journal of Alzheimer's Disease*, vol. 57, no. 4, pp. 1105–1121, 2017.
- [135] D. Offen, Y. Gilgun-Sherki, and E. Melamed, "The role of oxidative stress in the pathogenesis of multiple sclerosis: the

- need for effective antioxidant therapy,” *Journal of Neurology*, vol. 251, no. 3, pp. 261–268, 2004.
- [136] T. M. Michel, D. Pulschen, and J. Thome, “The role of oxidative stress in depressive disorders,” *Current Pharmaceutical Design*, vol. 18, no. 36, pp. 5890–5899, 2012.
- [137] M. Mancuso, F. Coppede, L. Migliore, G. Siciliano, and L. Murri, “Mitochondrial dysfunction, oxidative stress and neurodegeneration,” *Journal of Alzheimer’s Disease*, vol. 10, no. 1, pp. 59–73, 2006.
- [138] H. Du, L. Guo, S. Yan, A. A. Sosunov, G. M. McKhann, and S. S. D. Yan, “Early deficits in synaptic mitochondria in an Alzheimer’s disease mouse model,” *Proceedings of the National Academy of Sciences*, vol. 107, no. 43, pp. 18670–18675, 2010.
- [139] D. A. Butterfield, “Amyloid β -peptide (1-42)-induced Oxidative Stress and Neurotoxicity: Implications for Neurodegeneration in Alzheimer’s Disease Brain. A Review,” *Free Radical Research*, vol. 36, no. 12, pp. 1307–1313, 2009.
- [140] Y. G. Kaminsky and E. A. Kosenko, “Effects of amyloid- β peptides on hydrogen peroxide-metabolizing enzymes in rat brain *in vivo*,” *Free Radical Research*, vol. 42, no. 6, pp. 564–573, 2009.
- [141] H.-M. Gao, B. Liu, and J.-S. Hong, “Critical role for microglial NADPH oxidase in rotenone-induced degeneration of dopaminergic neurons,” *The Journal of Neuroscience*, vol. 23, no. 15, pp. 6181–6187, 2003.
- [142] D.-C. Wu, P. Teismann, K. Tieu et al., “NADPH oxidase mediates oxidative stress in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine model of Parkinson’s disease,” *Proceedings of the National Academy of Sciences*, vol. 100, no. 10, pp. 6145–6150, 2003.
- [143] I. Tasset, E. Agüera, F. Sánchez-López et al., “Peripheral oxidative stress in relapsing-remitting multiple sclerosis,” *Clinical Biochemistry*, vol. 45, no. 6, pp. 440–444, 2012.
- [144] A. Bajpai, “Oxidative stress and major depression,” *Journal of Clinical and Diagnostic Research*, vol. 8, no. 12, 2014.
- [145] M. A. Rogawski and G. L. Wenk, “The Neuropharmacological Basis for the Use of Memantine in the Treatment of Alzheimer’s Disease,” *CNS Drug Reviews*, vol. 9, no. 3, pp. 275–308, 2003.
- [146] R. Cacabelos, M. Takeda, and B. Winblad, “The glutamatergic system and neurodegeneration in dementia: preventive strategies in Alzheimer’s disease,” *International Journal of Geriatric Psychiatry*, vol. 14, no. 1, pp. 3–47, 1999.
- [147] C. P. Dias, M. N. M. de Lima, J. Presti-Torres et al., “Memantine reduces oxidative damage and enhances long-term recognition memory in aged rats,” *Neuroscience*, vol. 146, no. 4, pp. 1719–1725, 2007.
- [148] É. M. Flores, S. E. Cappelari, P. Pereira, and J. N. Picada, “Effects of memantine, a non-competitive N-methyl-D-aspartate receptor antagonist, on genomic stability,” *Basic & Clinical Pharmacology & Toxicology*, vol. 109, no. 5, pp. 413–417, 2011.
- [149] R. Alimoradzadeh, H. Mirmiranpour, P. Hashemi, S. Pezeshki, and S. S. Salehi, “Effect of Memantine on Oxidative and Antioxidant Indexes Among Elderly Patients with Prediabetes and Mild Cognitive Impairment,” *Journal of Neurology & Neurophysiology*, vol. 10, no. 1, pp. 1–5, 2019.
- [150] M. Valis, D. Herman, N. Vanova et al., “The Concentration of Memantine in the Cerebrospinal Fluid of Alzheimer’s Disease Patients and Its Consequence to Oxidative Stress Biomarkers,” *Frontiers in Pharmacology*, vol. 10, 2019.
- [151] S. Fahn, “The medical treatment of Parkinson disease from James Parkinson to George Cotzias,” *Movement Disorders*, vol. 30, no. 1, pp. 4–18, 2015.
- [152] S. Fahn, “The history of dopamine and levodopa in the treatment of Parkinson’s disease,” *Movement Disorders*, vol. 23, Supplement 3, pp. S497–S508, 2008.
- [153] B. J. Stansley and B. K. Yamamoto, “L-dopa-induced dopamine synthesis and oxidative stress in serotonergic cells,” *Neuropharmacology*, vol. 67, pp. 243–251, 2013.
- [154] M. Asanuma, I. Miyazaki, and N. Ogawa, “Dopamine- or L-DOPA-induced neurotoxicity: the role of dopamine quinone formation and tyrosinase in a model of Parkinson’s disease,” *Neurotoxicity Research*, vol. 5, no. 3, pp. 165–176, 2003.
- [155] M. Colamartino, M. Santoro, G. Duranti et al., “Evaluation of levodopa and carbidopa antioxidant activity in normal human lymphocytes *in vitro*: implication for oxidative stress in Parkinson’s disease,” *Neurotoxicity Research*, vol. 27, no. 2, pp. 106–117, 2015.
- [156] T. Müller, “Pharmacokinetics and pharmacodynamics of levodopa/carbidopa cotherapies for Parkinson’s disease,” *Expert Opinion on Drug Metabolism & Toxicology*, vol. 16, no. 5, pp. 403–414, 2020.
- [157] N. Hattori, M. Wang, H. Taka et al., “Toxic effects of dopamine metabolism in Parkinson’s disease,” *Parkinsonism & Related Disorders*, vol. 15, Supplement 1, pp. S35–S38, 2009.
- [158] G. Nikolova, Y. Karamalakova, and V. Gadjeva, “Reducing oxidative toxicity of L-dopa in combination with two different antioxidants: an essential oil isolated from Rosa Damascena Mill., and vitamin C,” *Toxicology Reports*, vol. 6, pp. 267–271, 2019.
- [159] T. Montiel, R. Quiroz-Baez, L. Massieu, and C. Arias, “Role of oxidative stress on β -amyloid neurotoxicity elicited during impairment of energy metabolism in the hippocampus: protection by antioxidants,” *Experimental Neurology*, vol. 200, no. 2, pp. 496–508, 2006.
- [160] M. Sano, C. Ernesto, R. G. Thomas et al., “A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer’s disease,” *The New England Journal of Medicine*, vol. 336, no. 17, pp. 1216–1222, 1997.
- [161] K. Rezai-Zadeh, D. Shytie, N. Sun et al., “Green tea epigallocatechin-3-gallate (EGCG) modulates amyloid precursor protein cleavage and reduces cerebral amyloidosis in Alzheimer transgenic mice,” *Journal of Neuroscience*, vol. 25, no. 38, pp. 8807–8814, 2005.
- [162] V. Tapias, G. Escames, L. C. López et al., “Melatonin and its brain metabolite N1-acetyl-5-methoxykynuramine prevent mitochondrial nitric oxide synthase induction in parkinsonian mice,” *Journal of Neuroscience Research*, vol. 87, no. 13, pp. 3002–3010, 2009.
- [163] G. A. Dowling, J. Mastick, E. Colling, J. H. Carter, C. M. Singer, and M. J. Aminoff, “Melatonin for sleep disturbances in Parkinson’s disease,” *Sleep Medicine*, vol. 6, no. 5, pp. 459–466, 2005.
- [164] C. A. M. Medeiros, P. F. C. de Bruin, L. A. Lopes, M. C. Magalhães, M. de Lourdes Seabra, and V. M. S. de Bruin, “Effect of exogenous melatonin on sleep and motor dysfunction in Parkinson’s disease,” *Journal of Neurology*, vol. 254, no. 4, pp. 459–464, 2007.

- [165] M. Valko, M. Izakovic, M. Mazur, C. J. Rhodes, and J. Telser, "Role of oxygen radicals in DNA damage and cancer incidence," *Molecular and Cellular Biochemistry*, vol. 266, no. 1-2, pp. 37–56, 2004.
- [166] A. Valavanidis, T. Vlachogianni, and C. Fiotakis, "8-hydroxy-2'-deoxyguanosine (8-OHdG): a critical biomarker of oxidative stress and carcinogenesis," *Journal of Environmental Science and Health, Part C*, vol. 27, no. 2, pp. 120–139, 2009.
- [167] N. Chatterjee and G. C. Walker, "Mechanisms of DNA damage, repair, and mutagenesis," *Environmental and Molecular Mutagenesis*, vol. 58, no. 5, pp. 235–263, 2017.
- [168] L. J. Marnett, "Oxyradicals and DNA damage," *Carcinogenesis*, vol. 21, no. 3, pp. 361–370, 2000.
- [169] M. Dizdaroglu, P. Jaruga, M. Birincioglu, and H. Rodriguez, "Free radical-induced damage to DNA: mechanisms and measurement," *Free Radical Biology and Medicine*, vol. 32, no. 11, pp. 1102–1115, 2002.
- [170] S.-N. Tan, S.-P. Sim, and A. S.-B. Khoo, "Oxidative stress-induced chromosome breaks within the ABL gene: a model for chromosome rearrangement in nasopharyngeal carcinoma," *Human Genomics*, vol. 12, no. 1, p. 29, 2018.
- [171] A. P. Anderson, X. Luo, W. Russell, and Y. W. Yin, "Oxidative damage diminishes mitochondrial DNA polymerase replication fidelity," *Nucleic Acids Research*, vol. 48, no. 2, pp. 817–829, 2020.
- [172] Z. Feng, W. Hu, L. J. Marnett, and M. S. Tang, "Malondialdehyde, a major endogenous lipid peroxidation product, sensitizes human cells to UV- and BPDE-induced killing and mutagenesis through inhibition of nucleotide excision repair," *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, vol. 601, no. 1-2, pp. 125–136, 2006.
- [173] L. J. Niedernhofer, J. S. Daniels, C. A. Rouzer, R. E. Greene, and L. J. Marnett, "Malondialdehyde, a product of lipid peroxidation, is mutagenic in human cells," *Journal of Biological Chemistry*, vol. 278, no. 33, pp. 31426–31433, 2003.
- [174] C. Leuratti, M. A. Watson, E. J. Deag et al., "Detection of malondialdehyde DNA adducts in human colorectal mucosa: relationship with diet and the presence of adenomas," *Cancer Epidemiology Biomarkers & Prevention*, vol. 11, no. 3, pp. 267–273, 2002.
- [175] H. Döppler and P. Storz, "Mitochondrial and oxidative stress-mediated activation of protein kinase D1 and its importance in pancreatic cancer," *Frontiers in Oncology*, vol. 7, 2017.
- [176] K. A. Conklin, "Chemotherapy-associated oxidative stress: impact on chemotherapeutic effectiveness," *Integrative Cancer Therapies*, vol. 3, no. 4, pp. 294–300, 2016.
- [177] G. Minotti, P. Menna, E. Salvatorelli, G. Cairo, and L. Gianni, "Anthracyclines: Molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity," *Pharmacological Reviews*, vol. 56, no. 2, pp. 185–229, 2004.
- [178] R. Corremans, R. Adão, G. W. De Keulenaer, A. F. Leite-Moreira, and C. Brás-Silva, "Update on pathophysiology and preventive strategies of anthracycline-induced cardiotoxicity," *Clinical and Experimental Pharmacology and Physiology*, vol. 46, no. 3, pp. 204–215, 2019.
- [179] F. Yang, S. S. Teves, C. J. Kemp, and S. Henikoff, "Doxorubicin, DNA torsion, and chromatin dynamics," *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, vol. 1845, no. 1, pp. 84–89, 2014.
- [180] C. F. Thorn, C. Oshiro, S. Marsh et al., "Doxorubicin pathways: Pharmacodynamics and adverse effects," *Pharmacogenet Genomics*, vol. 21, no. 7, pp. 440–446, 2011.
- [181] A. Vavrova, H. Jansova, E. Mackova et al., "Catalytic inhibitors of topoisomerase II differently modulate the toxicity of anthracyclines in cardiac and cancer cells," *PLoS ONE*, vol. 8, no. 10, article e76676, 2013.
- [182] Y. Shi, M. Moon, S. Dawood, B. McManus, and P. P. Liu, "Mechanisms and management of doxorubicin cardiotoxicity," *Herz*, vol. 36, no. 4, pp. 296–305, 2011.
- [183] S. Zhou, C. M. Palmeira, and K. B. Wallace, "Doxorubicin-induced persistent oxidative stress to cardiac myocytes," *Toxicology Letters*, vol. 121, no. 3, pp. 151–157, 2001.
- [184] S. Zhou, A. Starkov, M. K. Froberg, R. L. Leino, and K. B. Wallace, "Cumulative and irreversible cardiac mitochondrial dysfunction induced by doxorubicin," *Cancer Research*, vol. 61, no. 2, pp. 771–777, 2001.
- [185] T. G. Neilan, S. L. Blake, F. Ichinose et al., "Disruption of nitric oxide synthase 3 protects against the cardiac injury, dysfunction, and mortality induced by doxorubicin," *Circulation*, vol. 116, no. 5, pp. 506–514, 2007.
- [186] D. Iarussi, U. Auricchio, A. Agretto et al., "Protective effect of coenzyme Q10 on anthracyclines cardiotoxicity: control study in children with acute lymphoblastic leukemia and non-Hodgkin lymphoma," *Molecular Aspects of Medicine*, vol. 15, pp. s207–s212, 1994.
- [187] M. P. M. Marques, "Platinum and Palladium Polyamine Complexes as Anticancer Agents: The Structural Factor," *ISRN Spectroscopy*, vol. 2013, Article ID 287353, 29 pages, 2013.
- [188] S. Dasari and P. B. Tchounwou, "Cisplatin in cancer therapy: molecular mechanisms of action," *European Journal of Pharmacology*, vol. 740, pp. 364–378, 2014.
- [189] M. H. Hanigan and P. Devarajan, "Cisplatin nephrotoxicity: Molecular mechanisms," *Cancer Therapy*, vol. 1, pp. 47–61, 2003.
- [190] N. A. Santos, C. S. Catão, N. M. Martins, C. Curti, M. L. Bianchi, and A. C. Santos, "Cisplatin-induced nephrotoxicity is associated with oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria," *Archives of Toxicology*, vol. 81, no. 7, pp. 495–504, 2007.
- [191] H. Zhou, A. Kato, T. Miyaji et al., "Urinary marker for oxidative stress in kidneys in cisplatin-induced acute renal failure in rats," *Nephrology Dialysis Transplantation*, vol. 21, no. 3, pp. 616–623, 2006.
- [192] R. Pratibha, R. Sameer, P. V. Rataboli, D. A. Bhiwgade, and C. Y. Dhume, "Enzymatic studies of cisplatin induced oxidative stress in hepatic tissue of rats," *European Journal of Pharmacology*, vol. 532, no. 3, pp. 290–293, 2006.
- [193] N. M. Martins, N. A. Santos, C. Curti, M. L. Bianchi, and A. C. Santos, "Cisplatin induces mitochondrial oxidative stress with resultant energetic metabolism impairment, membrane rigidification and apoptosis in rat liver," *Journal of Applied Toxicology*, vol. 28, no. 3, pp. 337–344, 2008.
- [194] M. Jafari, S. M. Mousavi, and A. Asgharzadeh, "Coenzyme Q10 in the treatment of heart failure: A systematic review of systematic reviews," *Indian Heart Journal*, vol. 70, no. 1, pp. S111–S117, 2018.
- [195] D. Schniertshauer, S. Müller, T. Mayr, T. Sonntag, D. Gebhard, and J. Bergemann, "Accelerated regeneration

- of ATP level after irradiation in human skin fibroblasts by coenzyme Q10,” *Photochemistry and Photobiology*, vol. 92, no. 3, pp. 488–494, 2016.
- [196] K. Kędziora-Kornatowska, J. Czuczejko, J. Motyl et al., “Effects of coenzyme Q10 supplementation on activities of selected antioxidative enzymes and lipid peroxidation in hypertensive patients treated with indapamide A pilot study,” *Archives of Medical Science*, vol. 4, no. 4, pp. 513–518, 2010.
- [197] T. Hidaka, K. Fujii, I. Funahashi, N. Fukutomi, and K. Hosoe, “Safety assessment of coenzyme Q10 (CoQ10),” *Biofactors*, vol. 32, no. 1–4, pp. 199–208, 2008.
- [198] M. Wiciński, M. Socha, M. Walczak et al., “Beneficial Effects of Resveratrol Administration—Focus on Potential Biochemical Mechanisms in Cardiovascular Conditions,” *Nutrients*, vol. 10, no. 11, p. 1813, 2018.
- [199] B. Juhasz, S. Mukherjee, and D. K. Das, “Hormetic response of resveratrol against cardioprotection,” *Experimental and Clinical Cardiology*, vol. 15, no. 4, pp. e134–e138, 2010.
- [200] S. S. Leonard, C. Xia, B. H. Jiang et al., “Resveratrol scavenges reactive oxygen species and effects radical-induced cellular responses,” *Biochemical and Biophysical Research Communications*, vol. 309, no. 4, pp. 1017–1026, 2003.
- [201] Z. Jia, H. Zhu, B. R. Misra, J. E. Mahaney, Y. Li, and H. P. Misra, “EPR studies on the superoxide-scavenging capacity of the nutraceutical resveratrol,” *Molecular and Cellular Biochemistry*, vol. 313, no. 1–2, pp. 187–194, 2008.
- [202] A. Csizsar, N. Labinskyy, J. T. Pinto et al., “Resveratrol induces mitochondrial biogenesis in endothelial cells,” *American Journal of Physiology-Heart and Circulatory Physiology*, vol. 297, no. 1, pp. H13–H20, 2009.
- [203] H. Cai, E. Scott, A. Kholghi et al., “Cancer chemoprevention: evidence of a nonlinear dose response for the protective effects of resveratrol in humans and mice,” *Science Translational Medicine*, vol. 7, no. 298, p. 298ra117, 2015.
- [204] G. Panos, G. Samonis, V. G. Alexiou, G. A. Kavarnou, G. Charatsis, and M. E. Falagas, “Mortality and morbidity of HIV infected patients receiving HAART: A cohort study,” *Current HIV Research*, vol. 6, no. 3, pp. 257–260, 2008.
- [205] M. A. Thompson, J. A. Aberg, P. Cahn et al., “Antiretroviral treatment of adult HIV infection: 2010 recommendations of the International AIDS Society-USA panel,” *JAMA*, vol. 304, no. 3, pp. 321–333, 2010.
- [206] A. Banerjee, M. A. Abdelmegeed, S. Jang, and B. J. Song, “Zidovudine (AZT) and hepatic lipid accumulation: implication of inflammation, oxidative and endoplasmic reticulum stress mediators,” *PLoS One*, vol. 8, no. 10, article e76850, 2013.
- [207] L. Calza, R. Manfredi, and F. Chiodo, “Hyperlactataemia and lactic acidosis in HIV-infected patients receiving antiretroviral therapy,” *Clinical Nutrition*, vol. 24, no. 1, pp. 5–15, 2005.
- [208] N. Apostolova, A. Blas-García, and J. V. Esplugues, “Mitochondrial interference by anti-HIV drugs: mechanisms beyond Pol- γ inhibition,” *Trends in Pharmacological Sciences*, vol. 32, no. 12, pp. 715–725, 2011.
- [209] O. Prakash, S. Teng, M. Ali et al., “The Human Immunodeficiency Virus Type 1 Tat Protein Potentiates Zidovudine-Induced Cellular Toxicity In Transgenic Mice,” *Archives of Biochemistry and Biophysics*, vol. 343, no. 2, pp. 173–180, 1997.
- [210] E. Cabrero, L. Griffa, and A. Burgos, “Prevalence and Impact of Body Physical Changes in HIV Patients Treated with Highly Active Antiretroviral Therapy: Results from a Study on Patient and Physician Perceptions,” *AIDS Patient Care and STDs*, vol. 24, no. 1, pp. 5–13, 2010.
- [211] P. Pérez-Matute, L. Pérez-Martínez, J. R. Blanco, and J. A. Oteo, “Role of Mitochondria in HIV Infection and Associated Metabolic Disorders: Focus on Nonalcoholic Fatty Liver Disease and Lipodystrophy Syndrome,” *Oxidative Medicine and Cellular Longevity*, vol. 2013, Article ID 493413, 13 pages, 2013.
- [212] J. A. Joska, H. Gouse, R. H. Paul, D. J. Stein, and A. J. Flisher, “Does highly active antiretroviral therapy improve neurocognitive function? A systematic review,” *Journal of NeuroVirology*, vol. 16, no. 2, pp. 101–114, 2010.
- [213] K. Bhaskaran, C. Mussini, A. Antinori et al., “Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy,” *Annals of Neurology*, vol. 63, no. 2, pp. 213–221, 2008.
- [214] T. Al-Khindi, K. K. Zakzanis, and W. G. van Gorp, “Does antiretroviral therapy improve HIV-associated cognitive impairment? A quantitative review of the literature,” *Journal of the International Neuropsychological Society*, vol. 17, no. 6, pp. 956–969, 2011.
- [215] W. Lewis, B. J. Day, and W. C. Copeland, “Mitochondrial toxicity of nrti antiviral drugs: an integrated cellular perspective,” *Nature Reviews Drug Discovery*, vol. 2, no. 10, pp. 812–822, 2003.
- [216] A. Igoudjil, J. Massart, K. Begriche, V. Descatoire, M.-A. Robin, and B. Fromenty, “High concentrations of stavudine impair fatty acid oxidation without depleting mitochondrial DNA in cultured rat hepatocytes,” *Toxicology in Vitro*, vol. 22, no. 4, pp. 887–898, 2008.
- [217] U. A. Walker and N. Venhoff, “Uridine in the prevention and treatment of NRTI-related mitochondrial toxicity,” *Antiviral Therapy*, vol. 10, no. 2, article M117–23, 2005.
- [218] A. Wanchu, S. V. Rana, S. Pallikkuth, and R. K. Sachdeva, “Short communication: oxidative stress in HIV-infected individuals: A cross-sectional study,” *AIDS Research and Human Retroviruses*, vol. 25, no. 12, pp. 1307–1311, 2009.
- [219] M. Rajadurai and P. S. M. Prince, “Preventive effect of naringin on lipid peroxides and antioxidants in isoproterenol-induced cardiotoxicity in Wistar rats: biochemical and histopathological evidences,” *Toxicology*, vol. 228, no. 2–3, pp. 259–268, 2006.
- [220] A. Chanet, D. Milenkovic, C. Manach, A. Mazur, and C. Morand, “Citrus flavanones: what is their role in cardiovascular protection?,” *Journal of Agricultural and Food Chemistry*, vol. 60, no. 36, pp. 8809–8822, 2012.
- [221] O. Adebiyi, O. Adebiyi, and P. Owira, “Naringin Reverses Hepatocyte Apoptosis and Oxidative Stress Associated with HIV-1 Nucleotide Reverse Transcriptase Inhibitors-Induced Metabolic Complications,” *Nutrients*, vol. 7, no. 12, pp. 10352–10368, 2015.
- [222] S. Bharti, N. Rani, B. Krishnamurthy, and D. Arya, “Preclinical evidence for the pharmacological actions of naringin: A review,” *Planta Medica*, vol. 80, no. 6, pp. 437–451, 2014.