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Review Article

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The Significance of Nitrosative Pressure in Underlying Pathophysiology and The Pharmacologic Therapy of Non-Communicable Disease with Fessional and Antioxidant Potential

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Abstract

Chronic stress (OS) can degrade a range of substances and cellular structures, impairing organ and system performance. Endogenous and external pathways contribute to the accumulation of OS in the body. There is mounting evidence that OS has a role in the physiopathology of various chronic disorders that require continuous pharmaceutical treatment. Prolonged therapy may affect systemic OS. We explore the role of OS in the pathophysiology of several chronic diseases, the pro- or antioxidant effects of their pharmaceutical therapies, and potential adjuvant antioxidant alternatives in this review. High blood pressure, arteriosclerosis, and diabetes mellitus raise the risk of developing cardiovascular disease. Antihypertensive, lipid-lowering, and hypoglycemic medications contribute to risk reduction while also providing an antioxidant benefit. In autoimmune systemic inflammatory illnesses such as rheumatoid arthritis, methotrexate treatment has a dual effect of boosting OS synthesis and causing mitochondrial malfunction. However, it may also contribute indirectly to reducing systemic OS caused by inflammation. Medications used to treat neurodegenerative illnesses have been shown to inhibit systems involved in producing and balancing reactive oxygen species (ROS). On the other hand, immunosuppressive treatments for cancer or human immunodeficiency virus infection enhance ROS generation, resulting in severe oxidative damage in several organs and systems in the absence of well-documented exogenous antioxidant delivery.

Keywords: glutathione; superoxide dismutase; malondialdehyde; advanced glycation end products; NRTI: nucleoside reverse transcriptase inhibitors.

Introduction

The imbalance between the generation and breakdown of reactive oxygen or nitrogen species (ROS) or reactive nitrogen species (RNS) is referred to as oxidative stress (OS) [1]. ROS are highly reactive chemicals derived from the metabolism of oxygen or nitrogen. ROS and RNS can be free radicals such as superoxide (O2-), hydroxyl (OH), or nitric oxide (NO). However, other non-free radicals such as hydrogen peroxide (H2O2) and peroxynitrite (ONOO-) can also be present [2]. Within the mitochondria, ROS initiate metabolic processes that reduce oxygen via the electron transport chain [3]. Additionally, the endoplasmic reticulum and peroxisomes produce reactive oxygen species [4, 5]. Numerous physiological functions, including protein phosphorylation, transcription factor activation, immunity, and death, depending on the cell's ROS concentration [6]. Superoxide dismutase, catalase (Cat), and glutathione peroxidase (GPx) are the three major endogenous antioxidant enzymes that neutralize reactive oxygen species (ROS) [7]. SOD is a metalloenzyme that converts O2 - to oxygen and H2O2 [8]. In mammals, three types of SOD exist cytoplasmic SOD (SOD1), mitochondrial SOD (SOD2), and extracellular SOD (SOD3) [9]. Other nonenzymatic compounds having free radical scavenging characteristics, such as vitamins, melatonin, and glutathione (GSH), can be used to neutralize ROS [10]. When antioxidant defenses cannot effectively eliminate reactive oxygen species (ROS), they linger in the body longer and damage vulnerable biomolecules [11]. The NO radical is a mediator of vascular vasorelaxation dependent on the endothelium. Normally, NO is synthesized by the enzyme nitric oxide synthase (NOS) [12]. Under OS circumstances, NO reacts with the radical O2- to form ONOO-, damaging the endothelium [13]. Lipoperoxidation (LPO) is a mechanism by which OS damages lipids. LPO is defined by the presence of carbon-carbon double bonds, particularly

in polyunsaturated fatty acids. Hydroperoxides such as propanal, hexanal, 4-hydroxynonenal, and malondialdehyde (MDA) are the primary LPO products [14]. Other LPOs are isoprostanes formed by the nonenzymatic oxidation of important fatty acids such as arachidonic acid [15]. Additionally, when reactive oxygen species (ROS) react with guanine bases, they can cause DNA damage. The oxidation of guanine frequently results in the formation of 8-hydroxy-2-deoxyguanosine (8-OHdG) or 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxide) [16]. Under normal settings, these metabolites are fixed by the enzyme oxoguanine glycosylase (hOGG1) and collectively called OS biomarkers [17]. OS is found in various chronic disorders, which may aid in its progression [18]. OS and the inflammatory process are inextricably intertwined and lead to tissue damage in several autoimmune disorders, including rheumatoid arthritis [19]. OS has been connected to hyperglycemia and type 2 diabetic Mellitus (DM) development [20]. OS is thought to contribute to cardiovascular disease primarily through its impact on hypertension and the production of atheroma leaflets [21, 22]. Increased ROS generation is associated with the pathological development of other chronic diseases such as neurological diseases [23], cancer [24], and infection with the human immunodeficiency virus (HIV) [25]. Exogenous stimuli, on the other hand, such as suggested pharmaceutical therapies for some chronic diseases, have the power to modulate ROS production [2]. This brief overview aims to summarize the role of OS in a variety of pathogenic conditions (atherosclerosis, high blood pressure, DM, rheumatoid arthritis, cancer, HIV, and some neurodegenerative diseases).

Atherosclerosis's Oxidative Stress

Inflammatory disease that expresses itself in the vascular system, atherosclerosis is known as atherosclerosis. Atherosclerosis is the most common cause of cardiovascular disease in developed countries around the world, according to the World Health Organization (CVD) [26]. Atherosclerosis is the formation of vascular lesions or plaque deposition in blood arteries due to endothelial damage caused by inflammatory/oxidative processes [27]. Plaque is mostly composed of blood cells, foam cells, lipids, and proteins, which promotes vascular enlargement, obstruction, and inhibition of vascular blood flow, ultimately resulting in the vascular wall exploding [28, 29]. Myocardial infarction is caused by obstruction and rupture of the atherosclerotic coronary arteries in CVD, whereas stroke is caused by occlusion of the carotid arteries [30]. Endothelial damage is associated with cardiovascular and vascular risk factors such as diabetes mellitus, hypertension, nicotine use, lipid disorders, obesity, and metabolic diseases. During the early phases of atherosclerotic lesions, impaired endothelial physiological functions are found due to oxidative damage [31]. By affecting endothelial physiology, inflammatory responses, thrombosis, and oxidative lesions, the renin-angiotensin system (RAS) contributes significantly to the progression of atherosclerosis [32]. Angiotensin II (Ang II) induces the formation of reactive oxygen species (ROS) in the vascular system by activating NADPH oxidase, which is capable of oxidizing cellular macromolecules such as lipids lipoproteins, and DNA, resulting in endothelial degradation [33].

Atherosclerosis and Oxidative Stress Management

Hypercholesterolemia is often recognized to be the primary cause of atherosclerosis. As a result, controlling lipoprotein levels with statins is one of the primary management options for reducing the risk of atherosclerosis [34]. Statins inhibit the enzyme hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase, thereby lowering intracellular cholesterol synthesis and liver LDL receptor expression [35]. Statins have a pleiotropic effect on endothelial function, inhibiting thrombus gene activity, increasing the stability of atherosclerotic plaques, reducing inflammation, and improving overall survival [36]. By changing NADPH oxidase activity, statins have been demonstrated to have antioxidant effects on redox signaling in vascular and cardiac tissue [37]. Statins have been shown to inhibit eNOS and decrease LPO [38]. Simvastatin treatment protects against lipoprotein oxidation [39]. When statins are broken down, reactive oxygen species (ROS) are produced, which can be hazardous to many different tissues, including skeletal muscle and liver damage. [40, 41]. Simvastatin and lovastatin inhibit all of the electron transport chain's II, III, IV, and V complexes, but fluvastatin and cerivastatin inhibit only the V complex, resulting in mitochondrial malfunction [42]. Simvastatin treatment for eight weeks is sufficient to impair mitochondrial respiration in muscle [43].

Antioxidants as Adjuvants in Atherosclerosis

Numerous antioxidants have been utilized as adjuvant therapy in treating chronic illnesses (Table 1). The antioxidant N-acetylcysteine has been shown to inhibit accelerated atherosclerosis in ApoE-deficient mice [44]. Vitamin D analog (paricalcitol) has also been shown to alleviate oxidative vascular injury in ApoE-deficient mice by decreasing the activity of the ROS-generating enzyme NADPH oxidase, inflammatory mediators, and the antioxidant defense system [45]. On the other hand, polyphenols are abundant antioxidant substances found in fruits, vegetables, tea, coffee, chocolate, mushrooms, beverages, and traditional medicinal plants [46, 47]. Polyphenols are comprised mostly of flavonoids (60 percent), phenolic acids (30 percent), and other polyphenols, such as stilbenes (resveratrol), and ligands connected to at least one aromatic ring via one or more HO functional groups [46]. Flavonoids are the most extensively studied class of polyphenols; they are classified into six subclasses: flavonols, flavones, flavanones, flavanols, anthocyanins, and isoflavones. Benzoic acid and cinnamic acid are two subclasses of phenolic acids. Stilbenes are antifungal phytoalexins found in plants but are uncommon in the human diet [47].

Table -1

Antioxidant	Chronic disease	Result	Ref
N-Acetylcysteine	infection with the HIV virus	Reduces the progression of atheroma in uremic mice by a factor of two.	44
(vitamin D)	Rheumatoid arthritis.	Enalapril and paricalcitol both lower MDA levels and raise GSH levels, resulting in greater protection versus aortic proinflammatory damages in animals.	45
Nutrient Naringin:	disease of the brain in Parkinson's	Apigenin enhances the metabolism issues associated with NRTIs in a rat model by increasing OS and mortality.	221
contains Vitamins A, C, and E.	Death by Alzheimer's	Supplements A, B, and C taken with misoprostol for ten weeks decreases the affects in rheumatoid arthritis patients.	133
Essential oils of rose and ascorbic acid	a kind of diabetes called type 2	MDA, AGEs, and carbonyl contents in treated mice with methylphenidate are diminished by ascorbate or vital lilac. Vitamin E slows the progression of Alzheimer's disease in patients	159
Phytonutrients	High blood pressure	Vitamin E slows the progression of Alzheimer's disease in patients.	161
		Vitamin E improves incident mortality in patients with type 2 diabetes mellitus.	93
Nicotinamide adenine dinucleotide Q10	Leukemia of the lymphocytes	Hypertensive elderly patients should have their SOD levels increased and their MDA levels decreased.	197
		Patients with lymphoblastic leukemia who are receiving anthracycline treatment benefit from receiving coenzyme Q10 medication.	187

The Role of Oxidative Stress in High Blood Pressure

Heart disease and stroke are the most common causes of death worldwide [48]. High blood pressure is a complex condition to manage. Regarding essential hypertension, approximately 90 percent of cases are classed as such because the exact reason is unknown [49]. Salt, hyperactivity of the RAS system, oxidative stress, and inflammation all contribute to the first elevation of blood pressure, which is mainly due to central activities and endogenous hormones such as angiotensin II and aldosterone, which results in protein modification. The T cells become activated because the changed proteins are no longer recognized as their own (they operate as neoantigens). Activated T cells signal macrophages (and other inflammatory cells) to enter the vasculature and kidney, causing the release of proinflammatory cytokines into the body. [50] Activated T cells in the vasculature cause increased vasoconstriction and remodeling and increased salt and water retention in the kidney, resulting in more severe hypertension. A chronic inflammatory response can trigger OS, which is connected with elevated blood pressure. T cells express large quantities of p47phox, p22phox, and NOX2, all of which are components of the NOX2 oxidase, in the context of Ang II-induced hypertension (Ang II). Ang II is one of the essential vasoactive signaling molecules involved in ROS creation. It has a role in NADPH oxidase's enhanced expression and activity, one of the essential ROS generators [52, 53]. Adoptive transfer of T cells defective in NADPH oxidase leads to decreased O2 oxidase production [51]. Hypertensive situations are associated with the highest levels of Ang II production [54]., in addition to intrarenal vasoconstriction. In proximal tubular cells, Ang II inhibits the expression of the SR-BI HDL receptor [55]. By inhibiting the enzyme HMG-CoA reductase, statins were designed to lower cholesterol levels in the body. On the contrary, these treatments have anti-inflammatory properties that can result in a slight drop in blood pressure in patients with hypercholesterolemia as part of their pleiotropic effects. Patients with high blood pressure are more likely to be affected by this [56].

The Role of Oxidative Stress in the Treatment of Hypertension

[57] ACEIs, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), and beta-blockers (BBs) are among the medications used to treat blood pressure in the first line of treatment. A relationship exists between the control of hypertension and the regulation of Ang II activation, which is associated with shorter overall survival (OS) independent of antihypertensive medication [58]. It has been demonstrated that antihypertensive therapy with ACEI has antioxidant benefits. According to research conducted on the effects of enalapril on OS in the kidney and heart of hypertensive rats, enalapril enhances total antioxidant activity in both organs while decreasing LPO levels in both organs [59, 60]. Captopril has been shown in several experimental trials to lower H2O2 and MDA levels in hyperglycemic situations [61]. Telmisartan is an efficient blood pressure control medication that also benefits improving fibrosis and vascular remodeling. Telmisartan also has protective vascular effects via blocking the TGF-1/Smad3 pathway, linked to antihypertensive and antioxidant effects [62, 63, 64]. Olmesartan reduces the concentration of TBARS and H2O2 in obese mice [63], which is highly similar to the antioxidant effects of ACEI. ARB and BB have antioxidant effects that are pretty similar to ACEI. Compared to treatment with trichlormethiazide, eight-week treatment with candesartan or valsartan lowers urine 8-isoprostanes and 8-OHdG levels [64], candesartan or candesartan valsartan lower urinary 8-OHG levels. In addition, valsartan medication has been shown to reduce nitrosative stress in patients with type 2 diabetes [65]. MDA levels are decreased when atenolol is used in conjunction with thiazide hydrochloride over a medium period [66], and the concentrations of SOD, GSH, and vitamins E and C are increased. Patients with heart failure who get long-term therapy with metoprolol or carvedilol have been demonstrated to have lower LPO levels [67]. The reduction in the use of BB in OS is not confined to plasma or serum concentrations. Several studies have demonstrated that carvedilol can also lower cardiac LPO levels in patients with dilated cardiomyopathy [68]. The CCB is a significant antihypertensive subgroup of drugs. Because of their propensity to react with peroxyl radicals, they are classified as weak antioxidants because of the dihydropyridine ring via which they are formed [69]. Amlodipine has been shown to have the ability to lower isoprostane levels in people with type 2 diabetes [70]. It has been demonstrated that other BCCs, including nifedipine and lacidipine, are beneficial in preventing the development of LDL-oxidized lipoprotein [71].

Adjuvant Antioxidants in the Treatment of Arterial Hypertension

Exogenous antioxidants are primarily obtained through diet. Polyphenols, vitamins (C and E, and beta-carotene), and minerals are the most effective exogenous antioxidants. Components such as selenium, zinc, iron, manganese, copper, and molybdenum assist the organism in removing excessive free radicals through the production of appropriate enzymatic proteins [72]. Inhibition of Ang II-stimulated positive regulation of different NADPH oxidase (NOX) subunits, including NOX1, p22phox (a key component of NOX), and related OS by polyphenols, is compelling. Following the consumption of foods high in polyphenols, some study has revealed that the systolic blood pressure of hypertension patients decreases [74]. In young hypertension patients, a combination of dietary flavonoids with antihypertensive medication therapy based on telmisartan or captopril has been shown to lower blood pressure, improve lipid profile, reduce obesity, and reduce inflammation [75].

The Role of Oxidative Stress in Type 2 Diabetes

DM is classified as an ocular surface condition (OS disorder), and it is caused by an imbalance between the generation of free radicals and the capacity of the body's endogenous antioxidants to neutralize them. Glucose variations are critical in the development of type 2 diabetes. OS has been shown to play a significant influence in the problems of developing DM [76]. Glucose variations have a direct impact on overall survival. In comparison to chronic hyperglycemia, postprandial glucose variations or any sort of glucose oscillation is associated with a more significant risk of OS. The duration and severity of chronic hyperglycemia and the frequency with which acute glucose fluctuations occur are the most critical components of glycemic diseases [77]. Hyperglycemia causes the generation of reactive oxygen species (ROS). When the cells are still intact and unfunctional in type 2 diabetes, ROS causes OS to be produced in the cells, which results in reduced levels of insulin secretion [77]. The radical O2- is a kind of ROS that has gotten a lot of attention lately since it has been demonstrated to be enhanced in both in vitro and in vivo studies in diabetic patients [77]. DM contains numerous different sources of OS, including those produced by enzymatic, nonenzymatic, and mitochondrial processes. The rise in OS in DM is caused by several different mechanisms [78]. The autooxidation of glucose is the most critical oxidizing agent, as it leads to the formation of free radicals in the body. Other factors include an uneven cellular reduction/oxidation balance and diminished antioxidant defenses (lower levels of cellular antioxidants and reduced enzyme activity against free radicals) [79]. When there is a high glucose concentration present in DM, the synthesis of O2- activates several processes, including the increased production of polyols, increased flow through the hexosamine pathway, and activation of the protein kinase C isoform [80]. When it comes to DM, mitochondria serve as integrative critiques of energy production, ROS production, signaling transduction, and apoptosis. It has been demonstrated that the fusion and fission processes are critical in maintaining mitochondrial homeostasis [81] within the mitochondrial dynamics. In addition to being advantageous, mitochondrial fusion appears to be beneficial because it allows metabolites, proteins, and DNA to be distributed across the mitochondrial network. Excessive mitochondrial fission can be harmful because it causes fragmented mitochondria to accumulate, resulting in an impaired electron transport chain and the ability to increase mitochondrial ROS in cells [82]. Excessive mitochondrial fission can be harmful because it causes fragmented mitochondria to accumulate, resulting in an impaired electron transport chain and the ability to increase mitochondri-

al ROS in cells. The expression of the dynamin-related protein 1 (Drp1) was found to be upregulated in response to hyperglycemia in 2013, according to a study published in 2013 [83]. It is thought that Drp1 activates mitochondrial division by binding to either Fis1 or mitochondrial fission factor (Mff) in the mitochondria. Drp1 is a cytosolic DNA-5-triphosphatase that is involved in the process of mitochondrial division. Increased mitochondrial fission contributes to the endothelial dysfunction caused by diabetes. The results of these investigations imply that suppressing mitochondrial fission can effectively prevent DM-induced atherosclerosis and the cardiovascular problems that accompany it [84].

Type 2 Diabetes Mellitus: The Role of Oxidative Stress in the Management of the Disease

Metformin is a synthetic dimethyl biguanide that is highly effective as a diabetes treatment for type 2 diabetes. In addition to lowering blood glucose levels, Metformin has been shown to lower the risk of cardiovascular complications in patients with diabetes [85, 86]. It also has been shown to prevent the progression of the thickness of the intima-media of the common carotid artery and lower the risk of myocardial infarction in patients with type 2 diabetes. Because other conventional treatments such as insulin and sulfonylureas have less positive cardiovascular benefits than Metformin, it appears that the sound cardiovascular effects of Metformin are not dependent on its antihyperglycemic action. Metformin has been demonstrated to suppress mitochondrial fragmentation (fission) in diabetic patients by activating AMPK, preventing endothelium damage by activating mechanisms such as apoptosis and inflammation [84]. Metformin was found to inhibit Drp1 expression and Drp1-mediates mitochondrial fission in AMPK-dependent diabetic endothelium cells in a study published in 2017. Extending the lifespan of endothelial cells, improving endothelial function, and decreasing atherosclerotic plaques are all benefits of suppressing mitochondrial fission [87]. Several studies have found that metformin administration can lower MDA levels, raise GSH levels, and reduce inflammatory states [88, 89]. When combined with a decrease in ATP synthesis and NADPH oxidase activity [90], Metformin can help to reduce the formation of ROS AMPK.

Adjuvant Antioxidants in the Treatment of Diabetes Mellitus

Concerning the antioxidant state in diabetes, Lortz and Tiedge discovered that overexpression of the enzymes SOD and Cat might protect the pancreatic islets from ROS while maintaining insulin production in the disease. In a similar vein, overexpression of the GPx enzyme has been demonstrated to protect INS-1 cells from ROS and attack by RNS [91, 92]. There has been evidence from large-scale studies that intensive glucose management early in diabetes reduces the risk of micro-and macrovascular problems. Vitamin C, vitamin E, and -carotenes have historically been regarded as suitable supplements for preventing and treating OS and its complications in diabetic patients [80]. Milman and colleagues [93] discovered that vitamin E could reduce the risk of cardiovascular events after 1.5 years of intake. The findings of Blum et al. [94] imply that vitamin E supplementation in diabetic patients can help to reduce myocardial infarction, stroke, and cardiovascular death. A meta-analysis of 14 research was conducted by Akbar et al., who discovered that treatment with antioxidants does not affect plasma glucose or insulin levels. On the other hand, supplementation with antioxidants has been shown to considerably lower HbA1c levels, which may be due to their preventive action against diabetic complications [95]. Melatonin is an active indoleamine (derived from tryptophan) component with antioxidant capabilities released mainly by pinealocytes [96, 97]. Melatonin is a neurotransmitter that regulates sleep. Melatonin's primary role is to regulate the sleep-wake cycle of the body's internal clock. Melatonin is also involved in regulating homeostasis and the metabolism of energy [98]. In addition to its ability to activate brown adipose tissue and boost energy expenditure, melatonin also has anti-inflammatory, immunomodulatory, and antioxidant characteristics [99], which are discussed further below. Melatonin also stimulates the production of antioxidant enzymes (SOD, Catalase, and GPx) and helps to remove free radicals from your body. Melatonin is prescribed for patients with type 2 diabetes for 1-3 weeks, either alone or in conjunction with other medications [100]. It has been shown to enhance clinical outcomes in patients with type 2 diabetes [100].

Rheumatoid Arthritis (OA): Oxidative Stress in the Disease

In both monoarthritis and polyarthritic rats, improved overall survival (OS) has been observed [101]. According to clinical data, patients with rheumatoid arthritis had higher levels of LPO, protein oxidation, and oxidative DNA damage [102]. Furthermore, reactive oxygen species (ROS) are positively related to the severity of rheumatoid arthritis [103, 104]. Rheumatoid arthritis is characterized by inflammation as the primary pathophysiological mechanism. Innate immune cells, such as neutrophils and macrophages, create reactive oxygen species (ROS), such as O2- and H2O2, damaging cells [105]. According to recent research, a connection can be established between the mechanisms of redox reactions that cause OS and the pathophysiology of inflammation [106, 107]. Nuclear factor b (NF-B) is a transcription factor involved in regulating several immunological and inflammatory processes [108]. The signaling of inflammatory agonists is aided by reactive oxygen species (ROS). ROS can alter NF-B signaling in the cytoplasm and the nucleus [109]. H2O2 has been shown to stimulate nuclear translocation of NF-B, and overexpression of the SOD2 enzyme has been shown to block this process [110, 111]. Additionally, ROS induces the transcription of other transcription factors that are involved in cell differentiation, vascularization, and proliferation, such as activator protein 1 (AP1), hypoxia-inducible factor 1 (HIF-1), and the gamma-activated peroxisome proliferator receptor (PPAR) [112–114]. Proinflammatory cytokines such as interleukin-1B, interleukin-6, and tumor necrosis factor-alpha (TNF-alpha) are produced by mitochondrial ROS [115]. Because polymorphonuclear neutrophils produce ROS through the NADPH oxidase enzyme pathway, the inflammatory process also produces OS [116]. Furthermore, the ROS produced by the inflammatory

cells contributes to developing a positive feedback loop that perpetuates the inflammation.

The Role of Oxidative Stress in the Treatment of Rheumatoid Arthritis 1.11

Methotrexate is a folic acid antagonist that was originally developed to treat malignant illnesses. [118] At the moment, methotrexate is one of the most commonly prescribed drugs for the treatment of rheumatoid arthritis [119]. Methotrexate has immunosuppressive effects, with the mechanisms of action being linked to the production of reactive oxygen species (ROS). The increase in reactive oxygen species (ROS) caused by methotrexate is critical for the cytotoxicity of T cells [119]. Methotrexate reduces the levels of the antioxidant enzymes SOD and Cat and total antioxidant activity, and it increases apoptosis by raising the amounts of the caspase-3 enzyme [120]. On the other hand, the inhibition of cellular NADPH has been proposed as one of the mechanisms of OS formation by methotrexate [121]. A enzyme known as glutathione reductase is involved in the pentose cycle pathway, where it serves to reduce cellular glutathione (GSH) (primary antioxidant). Methotrexate causes a decrease in cellular GSH, which reduces systemic antioxidant defense [122]. As previously stated [123], the drug induces mitochondrial malfunction, which results in decreased activity of mitochondrial dehydrogenases, decreased mitochondrial membrane potential, decreased GSH, decreased ATP levels, and an increase in LPO. Various cells and cytokines with proinflammatory qualities are affected by methotrexate's effects on their inflammatory responses [124]. Despite the laboratory evidence of methotrexate-induced OS, there is clinical data to suggest that methotrexate may have antioxidant potential in certain circumstances. Some researchers have discovered that treating rheumatic disease with methotrexate and glycosides can lower inflammatory levels and improve overall survival [125]. [126] A study aboutrheumatoid arthritis found that patients treated with methotrexate had lower LPO levels and higher GSH levels when compared to those who were not treated with methotrexate [126].

Adjuvant Antioxidants in the Treatment of Rheumatoid Arthritis

Melatonin effectively protects the liver from the oxidative damage produced by methotrexate. Several experimental studies have demonstrated that the administration of melatonin in the liver and kidney can counteract the increase in MDA, the activity of myeloperoxidase, and the decrease in GSH produced by methotrexate [127]. Lipoic acid (also known as alpha-lipoic acid) is a cofactor of pyruvate dehydrogenase that is naturally found in the mitochondria and is utilized as an antioxidant supplement [128].-Lipoic acid is effective in protecting against methotrexate-induced liver toxicity. The treatment of -lipoic acid to mice resulted in lower levels of LPO, protein carbonylation, and HO mitochondrial, all of which were produced by methotrexate and were prevented by the antioxidant. Furthermore, -lipoic acid is known to replenish antioxidant levels [129]. The endogenous antioxidant carnosine has been studied in rheumatoid arthritis models in animals and humans. Carnosine is a dipeptide with properties in regulating homeostasis, including protection against ROS, that is found primarily in the skeleton, cardiac muscle, liver, and central nervous system [131]. It is found in high concentrations in the skeleton, cardiac muscle, liver, and central nervous system. When carnosine and methotrexate are used together, the LPO and C-reactive protein levels in plasma are lower than when methotrexate is used alone [36]. Even the Combined therapy with methotrexate and vitamins A, C, and E have been proven to be more effective in lowering disease indicators [132]. N-Acetylcysteine has also been demonstrated to counteract the effects of methotrexate on liver samples, including the reduction of GSH, SOD, and Cat and the increase of MDA [130].

Inflammatory Stress and Neurodegenerative Diseases, Section

OS is connected with neurodegenerative disorders such as Parkinson's disease [133], Alzheimer's disease [134], multiple sclerosis [135], and depression [136]. Parkinson's disease is associated with OS. The most important link between OS and neurodegenerative diseases is the process of aging. OS accumulated over time causes oxidative damage to cells and the progressive degeneration of mitochondria [137]. [138] Animal models of Alzheimer's disease had lower activity of mitochondrial complex IV in the hippocampus than healthy controls. In addition to producing direct mitochondrial oxidative damage, the increased OS also produces neurotoxic byproducts. The production of -amyloid, a toxic polypeptide that contributes to the neurodegenerative progression of Alzheimer's disease, is favored by reactive oxygen species [139]. Aside from that, -amyloid improves overall survival via stimulating the synthesis of H2O2 in neocortical neurons [140]. In Parkinson's disease models, dysregulated activation of NADPH by microglia cells is also associated with the progression of neurodegeneration in dopaminergic neurons [141, 142]. OS is associated with the inflammatory and neurodegenerative activity associated with multiple sclerosis and depression and other autoimmune diseases. There is a rise in the marker of oxidative damage to DNA (8-OHG) and carbonated proteins in patients with multiple sclerosis [143], which is associated with a decrease in the production of GPx. Those suffering from unipolar depression, on the other hand, have been found to have elevated levels of MDA, decreased ascorbic acid, and decreased SOD enzyme [144].

The Role of Oxidative Stress in the Treatment of Neurodegenerative Diseases

Memantine is a glutamate N-methyl-D-aspartate receptor (NMDA receptor) subtype antagonist used to slow the progression of Alzheimer's disease's neurodegenerative symptoms. Memantine has been shown to reduce the neurotoxicity caused by excessive glutamine receptor activation in the central nervous system [146]. Experiments with memory deficit models have shown that memantine reduces protein oxidation in the hippocampus and cerebral cortex and can reverse recognition memory deficit [147]. DNA from the brain, in particular, has been shown to contain antioxidant capabilities that protect it from oxidative damage [148]. Patients

with prediabetes and cognitive impairment have lower levels of advanced protein oxidation products (AOPPs) and advanced glycation end products (AGEs) when taking memantine [149]. Also, memantine has been shown to lower nitrosative stress and increase the antioxidant protection of nonprotein thiols in the cerebrospinal fluid [150]. Known as a precursor to dopamine, levodopa is quite helpful in the symptomatic treatment of people with Parkinson's disease [151]. To improve the availability of levodopa by up to four times, carbidopa, a peripheral decarboxylase inhibitor, is frequently used in conjunction with levodopa. [152] A variety of hypotheses governs the activity of levodopa on the production of OS. On the other hand, evidence from in vitro experiments indicates that levodopa has neurotoxic characteristics caused by ROS production [153]. Treatment with levodopa results in an increase in dopamine outside the synaptic vesicle, which promotes metabolism via monoamine oxidase or autooxidation, resulting in the production of reactive oxygen species. The spontaneous autooxidation of dopamine can result in the formation of oxygen and reactive quinones [154]. On the other hand, models in lymphocyte cells have demonstrated that carbidopa/levodopa has antioxidant capabilities and has protective properties against oxidative DNA damage [155]. Combining carbidopa and levodopa with other disease-modifying drugs, such as monoamine oxidase inhibitors, has been demonstrated to lower dopamine and levodopa enzymatic metabolism by decreasing the formation of reactive oxygen species (ROS) in animal studies [156]. Evidence suggests that the pro- or antioxidant aspects of levodopa management are related to changes in dopamine metabolism that occur due to treatment [157].

Adjuvant Antioxidants in the Treatment of Neurodegenerative Diseases

It has been demonstrated that some natural antioxidants can enhance the antioxidant effects of pharmacology therapy. According to an experimental study, the administration of ascorbic acid or rose oil has been shown to reduce the levels of oxidative damage to lipids or proteins caused by levodopa, according to an experimental study [158]. Numerous researches have shown that vitamin E administration can reduce or even eliminate the toxic effects of -amyloid while improving cognitive development, reducing neuronal damage, and slowing the progression of Alzheimer's disease [159, 160]. Epigallocatechin gallate esters from green tea have been shown to have inhibitory properties against amyloidosis and -amyloid production in vitro and vivo studies [161]. One further naturally occurring component demonstrated to have neuroprotective properties is melatonin. Melatonin has been shown to contribute to decreased dopamine production in Parkinson's disease models, as well as decreased levels of LPOs and nitrites in the cytosol [162]. In clinical studies, it has also been observed that melatonin can alleviate sleep disorders in patients with Parkinson's disease, but it does not appear to alleviate motor symptoms [163, 164].

Oxidative Stress in the Treatment of Cancer

Carcinogenesis is facilitated by the ability of ROS to damage DNA and promote the development of cancer [165]. OH is the primary reactive oxygen species (ROS) that attacks mitochondrial and nuclear DNA strands, resulting in various hydrolyzed base products such as 8-OHdG and 8-oxide. Cells can repair DNA damage through a variety of enzymatic methods [167]. When DNA damage cannot be repaired, however, mutations involving base modification or deletion occur, resulting in carcinogenesis [168]. A person's risk of having poor DNA repair increases directly to the number of oxidative lesions in their DNA. As people grow older, they experience increased oxidative damage and a decrease in DNA repair [169]. [170, 171] The consequences of oxidative DNA damage include chromosomal abnormalities, DNA replication inhibition, and cytotoxicity. While a direct free radical attack primarily causes oxidative DNA damage [172]; oxidative damage to DNA is also caused by free radical reaction with other cellular components. The carcinogenic potential of LPO has been demonstrated [173]. MDA can react with guanine bases, resulting in the formation of adducts [174]. All of the mechanisms involved in the development of carcinogenesis due to OS remain a mystery. The potential of OS to modulate the expression of genes and proteins involved in signaling cell growth and proliferation has been demonstrated by new mechanisms [175].

The Relationship Between Oxidative Stress and Anticancer Drugs

During the administration of chemotherapy to cancer patients, antineoplastic drugs have been shown to increase the production of osmotic stress. Antineoplastic medicines cause an increase in LPO while simultaneously decreasing levels of vitamins E and C and beta-carotene [176].

Doxorubicin is an anthracycline with a broad spectrum of activity that is widely used to treat solid tumors [177]. Its exact mechanism of action is unknown, but it is thought to involve the inhibition of DNA and RNA synthesis, interference with the activity of the enzyme topoisomerase II, and the generation of reactive oxygen species [178] [178]. The Doxorubicin has a quinone chemical structure that acts as an electron acceptor, resulting in the production of a semiquinone radical that reacts with oxygen to form O2- and H2O2 [179]. Doxorubicin has a quinone chemical SAR that acts as an electron acceptor, resulting in a semiquinone radical [180]. The release of these free radicals increases the oxygen consumption rate (OS), resulting in DNA damage and cell death [180]. Even though doxorubicin has potent anticancer properties, its use is restricted due to its cardiotoxic potential [181]. doxorubicin's cardiotoxicity is primarily caused by oxidative stress and mitochondrial malfunction [182]. [183] Experimental evidence indicates that treatment with doxorubicin increases the survival of cardiac myocytes, resulting in the accumulation of irreversible cardiotoxicity. Due to its ability to join the eNOS reductase domain, doxorubicin increases the production of O2- and NO [184]. The eNOS isomorphism is the most common NOS isomorphism that has been implicated in the development of left ventricular dysfunction caused by doxorubicin [185]. In some studies, it has

been suggested that antioxidants could reduce the cardiotoxicity of doxorubicin. It has been determined that coenzyme Q10 has cardioprotective effects in pediatric patients receiving anthracycline therapy. The cardiovascular function has been reported to improve in patients who receive coenzyme Q10 [186]. [187] Cisplatin is one of the most essential representative drugs in a class of drugs known as coordination complexes with platinum, which have been used to treat various types of cancer for several decades. Anticancer activity attributed to cisplatin is based on the elemental platinum's ability to form covalent adducts with nuclear DNA. These cisplatin-DNA junctions cause crosslinks to develop between the outer and inner strands of nuclear DNA, leading the strands of nuclear DNA to become separated from one another. Apoptosis is a type of cell death that results from DNA damage [188]. The use of cisplatin is restricted, as is the use of other cancer medications, because of its adverse effects. A significant hazardous impact is nephrotoxicity [189], one of the most serious. OS is a critical mechanism of tissue damage caused by cisplatin, and it is worth noting. Increased apoptosis is related to cisplatin-induced nephrotoxicity, manifested by reduced GSH, oxidative damage to lipids and mitochondrial proteins, and oxidative damage to lipids and mitochondrial proteins. Cisplatin-induced kidney failure has been linked to increased MDA [191, which has been recommended as a predictor of the development of renal failure]. Cisplatin-induced hepatotoxicity has also been linked to increased liver concentrations of LPO products [192] in some studies. Cisplatin at high doses causes mitochondrial dysfunction and impairment to the liver's energy metabolism [193].

Adjuvant Antioxidants in the Treatment of Cancer

The Food and Drug Administration has not approved coenzyme Q10 (ubiquinone) to treat any medical condition. However, it is commonly available as a nutritional supplement over-the-counter in most countries. [194] Decreased coenzyme Q10 in the bloodstream are connected with chronic diseases such as cancer, neurological disease, fibromyalgia, diabetes, mitochondrial diseases, muscle diseases, and heart failure. Every cell membrane in our bodies naturally contains coenzyme Q10, a fat-soluble vitamin-like molecule that functions as a coenzyme. It is a typical diet component, but our bodies also manufacture it. Adenosine triphosphate (ATP) is required for the efficient transport of electrons within the mitochondrial respiratory chain and the generation of adenosine triphosphate (ATP). Coenzyme Q10 can stimulate the production of important antioxidants such as superoxide dismutase (SOD). The coenzyme Q10 lowers LPO levels by lowering prooxidant chemicals, and it is capable of increasing blood flow and protecting blood vessels by preserving NO [196]. It also has anti-inflammatory properties. As a dietary supplement, coenzyme Q10 is considered to be safe. The possibility of toxicity exists even at a regular dose of 1,200 mg/day. The usual doses that have been studied have ranged from 100 to 200 mg/day [197]. It is a polyphenolic phytoalexin found in various plant species, including peanuts, grapes, berries, and red wine [198]. Resveratrol (3,5,4-trihydroxy-trans-stilbene) is a phytoalexin found in several plant species, including peanuts, grapes, berries, and red wine. [199] Preclinical research has demonstrated that resveratrol has preventive effects in various illness types, including diabetes and cancer. In vitro studies have demonstrated that resveratrol may eliminate many oxidants, including the OH radical, O2, H2O2, and ONOO-, straight from the body.. It was found that the predicted reaction rate of resveratrol of OH (M1s1) is much lower than that of well-established antioxidants such as ascorbate (M1s1), glutamate(GSH) (M1 S1), and cysteine (M1s1). The phenolic groups in resveratrol are thought to be responsible for the ability of the compound to remove OH from water [200]. In a nonenzymatic, cell-free system (the potassium O2– system), resveratrol (at a concentration of 0.1 mM) has been shown to eliminate the radical O2– directly [201]. In cultured coronary artery endothelial cells from people, resveratrol (10 micrograms per milliliter) increases mitochondrial mass and mitochondrial DNA while regulating elements of the electron transport chain and mitochondrial biogenesis factors [202, 203]. In specific clinical trials, huge doses of resveratrol (up to 3000 mg) were employed, and the results were promising. In contrast, low dosages (5 mg in people or 0.07 mgkg1 in mice) have been demonstrated to have even greater chemopreventive activity against cancer than high doses (1000 mg in humans or 14 mgkg1 in mice) in animal studies [203].

The Role of Oxidative Stress in Antiretroviral Treatment

In recent years, the development of highly active antiretroviral therapy (HAART) has significantly reduced the morbidity and mortality associated with human immunodeficiency virus infections (HIV). and other medications have traditionally been used to treat HIV infections inhibiting agents (IP), integrase inhibitors, and fusion inhibitors/entry inhibitors. Current HAART administration recommendations recommend a combination of two nucleoside reverse transcriptase inhibitors It is necessary to determine the efficacy and tolerability of a patient before prescribing an NNRTI or a protease/integrase inhibitor. The nucleoside reverse transcriptase inhibitors (NRTIs) (abacavir, didanosine, lamivudine, stavudine, zidovudine, and emtricitabine) act as false substrates that prevent the lengthening of the viral cDNA chain, thereby inhibiting viral reverse transcriptase activity and limiting viral replication [205]. It is known that NRTIs can cause hepatotoxicity [206]. However, the specific mechanisms through which these complications of NRTIs manifest themselves are not yet fully understood. As previously reported [207], NRTIs have been shown to inhibit -DNA polymerase, causing mitochondrial DNA depletion and mitochondrial toxicity, which results in impaired oxidative-phosphorylation as well as oxidative damage to cellular machinery as well as delayed cell cycle progression and apoptotic cell death. There is a relationship between these effects and the binding of NRTI-triphosphate (the active metabolite formed after intracellular phosphorylation) to replicating mitochondrial DNA, which causes the termination of viral chain elongation. [208]. The considerable increase in MDA, end products of LPO, and protein carbonyls have been connected with the administration of NRTI, combined as a result of the disruption of the oxidative phosphorylation pathway, there is a

decrease in the activity of enzymatic antioxidant proteins [209]. [210] NRTI treatment has been associated with several metabolic problems, including lipodystrophy, dyslipidemia, hepatotoxicity, hepatomegaly, metabolic syndrome, elevated lactic acid, and cardiomyopathy. One of several scientific theories that underpin the development of difficulties associated with NRTI [211] is that mitochondrial toxicity causes oxidative cell damage to the cells. Activated HIV infection in the central nervous system, on the other hand, is unquestionably a component that contributes to the development of cognitive deficiency [212]. It is critical to prevent viral replication in brain tissue and the rest of the body. However, neither clinical trials nor experimental models have investigated the possibility that antiretroviral therapy may contribute to this degenerative illness. Most combination antiretroviral therapy (cART) regimens need the use of nucleoside reverse transcriptase inhibitors (NRTIs). Myopathy, lactic acidosis, and peripheral neuropathy are the most prevalent side effects of these drugs, and they all have the potential to be life-threatening. Every one of these factors is intimately associated with mitochondrial toxicity. The introduction of combination antiretroviral therapy (cART) has significantly boosted the survival rate of HIV-infected individuals and has virtually totally averted the development of severe dementia associated with the virus [213, 214]. It has been hypothesized that the selective inhibition of mitochondrial polymerase (pol) by NRTIs is the molecular mechanism that determines NRTI-mediated mitochondrial toxicity [215]. A reduction in mitochondrial DNA synthesis due to pol inhibition is expected as the principal DNA polymerase in mitochondria. In turn, is expected to reduce the availability of essential protein subunits for respiratory complexes in the electron transport chain. Lack of these proteins should result in lower ATP synthesis and an increase of orphan respiratory complex subunits encoded by nuclear DNA, as well as other consequences. Studies in cell culture have revealed that mitochondrial malfunction in cardiac myocytes or hepatocytes can arise even in the absence of mtDNA depletion [216]. When NRTI interfere with the operation of mitochondrial DNA polymerase, mitochondrial replication is impeded [216]. Consequently, cardiotoxicity and heap toxicity [208] are observed due to the gradual reduction in mitochondrial activity in numerous tissues, with the effects being most noticeable in metabolically active organs such as the heart and liver.

Natural Antioxidants in the Treatment of HIV

Several common HIV antioxidants, including vitamins C and E, uridine, and carnitine, have been examined for their ability to prevent or reverse problems associated with NRTI therapy, with only limited effectiveness [217]. As a result, additional research into alternative antioxidants that may be more effective in controlling NRTI complications is required. Food and nutritional therapy are realistic solutions that have not been employed as much as they should. The positive effects of certain currently available antioxidants have been employed in animal models, but large-scale verified clinical trials are still missing [218]. The Citrus fruits have a high concentration of flavonoids derived from citrus trees from plants, such as naringin (4,5,7-trihydroxyflavone 7-aminoglycoside). Naringin has been indicated as effective in lowering the risk of diabetes and cardiovascular disease (CVD) in susceptible groups [219]. The antioxidant potential of naringin has been established by its ability to eliminate free radicals, as well as by its actions as an anti-apoptotic, anti-hyperglycemic, antimutagenic, anticancer, anti-inflammatory, and cholesterol-lowering compound. [220]. Naringin has also been shown to have anti-cancer, anti-inflammatory, and cholesterol-lowering properties. HIV induces symptoms comparable to those associated with NRTI-induced metabolic problems, such as fatigue and weakness. In 2015, the scientists published the results of an experimental investigation in mice in which naringin was shown to cure the metabolic problems associated with NRTI by enhancing overall survival and apoptosis (cell death). This evidence suggests that naringin supplementation may effectively alleviate the lipodystrophy and dyslipidemia associated with NRTI therapy [221]. Naringin is a dietary flavonoid found in most citrus fruits that have been shown to have antioxidant and antiapoptotic properties in animal models in vitro, in vivo, and ex vivo. Naringin has been demonstrated to have beneficial effects in animal models in vitro, in vivo, and ex vivo. Naringin's antioxidant and antiapoptotic properties may be involved in the process through which it alleviates metabolic problems [222]. The mechanism of action in patients treated with NRTIs should be investigated further in well-conducted clinical studies in which naringin is delivered at various doses, as the findings are promising.

Conclusions

Occupational stress (OS) is closely associated with the pathogenic processes of various chronic diseases. The involvement of pharmacological therapy in the treatment of OS depends on the chemical features of the active molecules and the effects of the modes of action of the drugs used in the treatment. Medicines with a dihydropyridine ring, such as CCB, have antioxidant structural features due to the presence of this ring. On the other hand, other antihypertensive medications have positive antioxidant action as a result of their ability to restore the antihypertensive mechanism to normal function. Treatments such as immunosuppressive and antiretroviral medicines are the ones that cause the most oxidative damage in patients over the long term, and antioxidant management choices for treating these pathologies are either underdeveloped or have yielded unsatisfactory outcomes. When oxidative mechanisms of these pathologies and the conventional medicines used to treat them are investigated, a better understanding, monitoring, and selection of alternative antioxidant medicines according to each patient's health condition will be possible to reduce oxidative damage in the long run.

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