REVIEW ARTICLE

Anti-aging preventive lifestyle against oxidative stress

Akachukwu Marytheresa Onwuka, Olisaemeka Zikora Akunne, Emmanuella Chiamaka Egwuonwu, Princess Chinecherem Eze, Nora Ujunwa Ugwuanyi, Obianuju Favour Agwuna

Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Nigeria, Enugu, Nigeria

Abstract

Free radicals, also referred to as reactive oxygen species (ROS), are generated primarily in mitochondria as a result of metabolic activities and are utilized by organisms. Although ROS are required for the body's physiological processes, an excess of them can be harmful if antioxidants are unable to effectively detoxify them. The mismatch between the increasing amount of ROS generation and the lowered level of antioxidants leads to oxidative stress. Numerous medical diseases, including cancer, heart and neurological disorders, pregnancy issues, tumors, and skin conditions have all been related to oxidative stress. Studies have revealed that certain elements and lifestyle choices contribute to the oxidative stress linked to aging. This review aims to pinpoint ways of living that can be employed to lessen oxidative stress and related illnesses, particularly in the elderly population. According to our research, several lifestyle choices, including exercise, a healthy diet, supplements, yoga, and meditation, can increase the activity of endogenous antioxidants, which can shield cells against oxidative stress.

Key words: Aging, oxidative stress, reactive oxygen species

INTRODUCTION

Oxidative Stress and Aging

Over the years, free radical and mitochondrial theories have existed as the two prominent theories on aging and have since remained relevant. According to the hypotheses, oxidative stress within the mitochondria might cause a hazardous loop in which damaged mitochondria produce more ROS.[1] A buildup of toxins in the body is caused by oxidative stress, which is characterized by an imbalance between an elevated amount of reactive oxygen species (ROS) and a lowered level of detoxification.

The body generates ROS, as byproducts of regular metabolic processes, and only utilizes oxygen in its active form. These ROS have physiological functions that include adjusting to hypoxia, controlling autophagy, regulating immunity, controlling differentiation, and regulating longevity.[2] ROS are one of the key factors in aging, according to studies, even though the underlying mechanisms are still not fully understood. Aging is a physiological process that is characterized by a steady loss in organ function and the emergence of age-related illnesses. An organism's general, molecular, cellular, organ, and system functions are affected by aging.

The presence of ROS at extremely high concentrations is what causes oxidative stress.[3] According to the oxidative stress theory, the critical components of aging are impacted by a cumulative and irreversible buildup of oxidative damage brought on by ROS, which also increases the risk of disease and shortens lifespan.[4]

Factors predisposing to oxidative stress

Oxidative stress can be caused by a variety of environmental and biological changes or factors.

Address for correspondences:
Akachukwu Marytheresa Onwuka,
Department of Pharmacology and Toxicology, Faculty of Pharmaceutical Sciences, University of Nigeria, Enugu, Nigeria. Mobile: +2348038357391.
E-mail: akachukwu.onwuka@unn.edu.ng

Received: 14-10-2024
Revised: 12-12-2024
Accepted: 25-12-2024

Age

ROS accumulate in cells as a result of age-related increases in their synthesis and decreases in antioxidant levels.[5] Because the weight gain associated with aging is more pronounced in women than in men, women are more vulnerable to oxidative stress than men.[6]

Obesity

Obesity both contributes to and results from oxidative stress. Obesity and adiposity are largely caused by consuming a high-fat diet with little energy being expended.[7] Body Mass Index (BMI) is useful in measuring weight and obesity; because it measures the body fat based on the weight and height of the individual. However, it is a limiting parameter as it does not provide information on the distribution of fat in the body. BMI of 25 to 29.9kg/m^2 is overweight while BMI above 30 Kg/m^2 is indicative of obesity and adiposity.[8]

Superoxide synthesis from NADPH oxidases (NOX), glutaraldehyde autooxidation, oxidative phosphorylation, activation of protein kinase C, and pathways involving polyol and hexosamine are only a few of the biochemical mechanisms through which obesity pre-disposes its victims to oxidative stress[9] by the white adipose tissue, which is where fat is stored, and they trigger the oxidative stressor ROS generation.[10]

In the mitochondria, oxidative metabolism takes place, producing ROS. Multilocular adipocytes with plenty of mitochondria are seen in brown adipose tissue. However, it is unclear how brown adipose tissue and oxidative stress are related. Hyperleptinemia, poor antioxidant defense, chronic inflammation, and post-prandial ROS production are additional variables that cause oxidative stress in obese people.

Pregnancy

During the first few months of pregnancy, placental remodeling occurs. The trophoblast cells of the fetus invade the spiral arteries of maternal uterine walls causing the loss of vesicular cells from the wall.[11] This process is important to ensure enough blood flow from the mother to the fetus. The remodeling process causes oxygen imbalance and can lead to oxidative stress in pregnant women if not well managed.

Disease states

Individuals with diseases, such as metabolic syndrome are pre-disposed to oxidative stress. The metabolic syndrome disrupts the homeostasis of the body, it causes an increase in the production of ROS and a reduction in antioxidants[12] because of the increased use of antioxidants by the tissue,[13] and as a result, oxidative stress occurs.

Environmental factors

The male sex organ (the testis and epididymis) is stored in the scrotum at temperatures of about 2–7°C.[14] In a condition of an elevated ambient temperature of about 37°C for at least 24 h, heat stress occurs in male germ cells. ROS are produced as a result of heat stress, which eventually induces oxidative stress in males.[14]

Furthermore, long exposure to exogenous ROS triggers oxidative stress. Exogenous ROS such as smoke, soot, allergens, and pollutants increase the production of ROS in the cell Contaminated areas expose humans to some heavy metals, such as arsenic, copper, and cadmium that are toxic to the body. There are redox-active metals and redox-inert ones.[15] The redox-active metals such as iron, copper, and chromium, undergo a cycling reaction that generates free radicals[16] while the redox-inert elements deplete glutathione (GSH) which is an antioxidant, by binding to the sulfhydryl group of protein.[17] This condition of disrupted metal homeostasis where there is uncontrolled production of free radicals and reductions in antioxidants causes oxidative stress.

Relationship between oxidative stress and aging

The oxidative stress theory states that the functional declines associated with aging are caused by the buildup of oxidative damage to macromolecules, such as lipids, DNA, and proteins by reactive oxygen and nitrogen species (RONS). This theory is also referred to as the free radical theory of aging (RONS). RONS are reactive free radicals with one or two unpaired electrons in the outer shell produced in the cell by losing or accepting a single electron.[18]

Although the exact mechanism by which oxidative stress occurs in old age is still abstruse, the increased RONS levels result in cellular deterioration with aging. Antioxidant defenses neutralize the harmful effects of RONS, which are produced by a variety of endogenous and external activities. Oxidative stress results from a disruption in the balance between RONS and these antioxidant defenses.[4]

Various pathophysiological events could occur as a result of disruption in bio-signaling because of oxidative stress and subsequent alteration at various levels of life, particularly in old age.[19] According to the oxidation inflammatory theory of aging: Chronic oxidative stress causes a breakdown of homeostasis that accelerates aging and particularly affects the immunological, endocrine, and neurological systems, which are regulatory systems. Aging increases the damage of mitochondrial DNA (mtDNA) by 1000-fold.[20] This makes mtDNA prone to attack by ROS and causes harm to the cells and decreases energy production. There is a decrease in non-enzyme antioxidants in aged people which can lead to oxidative stress.[21] The shortening of telomere after successive cell division brings about the aging of the dividing cells of living organisms.[22] This process of shortening the telomere is accelerated by oxidative stress.

Oxidative stress could result in the manifestation of various abnormalities thus, leading to the initiation of many ailments

as well as posing a major limiting factor to longevity and healthy aging.[23] As a result of the chronic effect of oxidative stress on the body system, age-related diseases, such as cardiovascular diseases, cancer, acute or chronic kidney diseases, neurodegenerative diseases, diabetes, autoimmune diseases, and inflammation can occur. The pathophysiology of Parkinson's disease (PD), which unquestionably contributes to a complicated and progressive neurodegenerative cascade, provides evidence of the significance of oxidative stress in the onset of aging and many neurodegenerative disorders.[24]

OXIDATIVE STRESS-INDUCED DISEASES

Oxidative stress is a double-edged sword: it builds and destroys the body. Oxidative stress plays a pathological role in neurological disorders, cardiovascular diseases, and diabetes.

Neurodegenerative Disease

Neurodegenerative disease is an age-dependent disorder and a global public health problem that is associated with aging. It is characterized by neuronal death,[25] cell damage, or dysfunction of neurons in the stratum. Diseases such as Alzheimer's disease (AD), PD, and amyotrophic lateral sclerosis (ALS) are neurodegenerative diseases associated with oxidative stress. The brain and nerve cells are particularly susceptible to oxidative stress due to their high levels of oxidative reactions, accumulation of metal ions, and low levels of antioxidative activities.[25,26] The brain is also prone to oxidative stress because the lipid bilayer of the brain is rich in polyunsaturated fatty acids[27] its high oxygen consumption and its dependence on oxidative phosphorylation of its polyunsaturated fatty acids for energy. An accumulation of the end products of lipid peroxidation, for example, malondialdehyde, 4-hydroxy-2-nonenal, acrolein, and isoprostanes, leads to these neurodegenerative diseases.[27]

Oxidative stress is not directly linked with neurodegenerative diseases and their specific causes are unknown, however, increased Oxidative stress is directly associated with excitotoxicity and apoptosis which are the main causes of neuronal death. The mitochondria are the main source of many apoptoses. The mitochondria as the site of the oxidative respiratory chain produce ATP and ROS through oxidative phosphorylation. The lack of protective histones in mtDNA together with limited repair capacity renders mtDNA an easy target for ROS.[26] Apoptosis also called programmed cell death is a natural homeostatic response that can also be triggered by exposure to chemicals, immune responses, high temperature, and oxidative stress. Apoptosis plays physiological roles in immune response[28] cell population maintenance, and tissue homeostasis.[29] In addition, apoptosis has been linked to the pathogenesis of illnesses, such as neurological disorders, cancer, sepsis, stroke, autoimmune disorders, cancer, anemia, and viral infections.[30]

Excitotoxic cell death involves prolonged polarization of neurons, changes in intracellular calcium concentrations, and the activation of enzymatic and nuclear mechanisms of cell death. The vulnerability to oxidative stress is more evident in some of the neuronal cells, for example, neurons in the frontal cortex, entorhinal cortex, etc, and this condition is known as selective neuronal vulnerability.[30] Other oxidative stress actions such as protein misfolding, protease dysfunction, and cyclooxygenase metabolism of arachidonate leading to ROS generation are integral to seizure activity. Research has shown that the areas of the brain affected by neurodegenerative diseases contain excessive amounts of redox metals, such as iron, copper, manganese, and other retraced redox metals. Excess mitochondrial calcium accumulation due to oxidative stress causes apoptosis. This accounts for the protein misfolding, and damage done to DNA/RNA. The oxidative damage to the DNA leading to the breakage of its strands is responsible for the free carbonyls in the nuclei of a neuronal cell in neurodegenerative disease.[31]

Oxidatively modified proteins will prevent the activity of the proteasome which is responsible for the removal of oxidized and misfolded proteins,[32] and this will lead to the aggregation of the faulty protein and human pathologies, such as neurodegenerative diseases.

Cardiovascular Diseases (CVDs)

CVDs comprise many disorders such as heart failure, stroke, hypertension, coronary artery diseases (CAD), congenital heart diseases, and vascular diseases.[33] Factors, such as smoking, obesity, diabetes, and unhealthy lifestyles increase the risk of CVDs.[33] Many CVDs are initiated by atherosclerosis,[33,34] a disease characterized by the transfer of oxidized low-density lipoprotein (ox-LDL) across the endothelium into the arterial wall.[34] This results in reduced blood and oxygen flow. In atherosclerosis, low-density lipoproteins are oxidized by ROS to form ox-LDLs, which accumulate in the sub endothelium and cause constriction of the arteries.

In vascular walls, ROS are produced by nicotinamide adenine dinucleotide (phosphate) NOX and the mitochondria by oxidative phosphorylation.[35] An increase in ROS production is stimulated by agonists'e.g angiotensin I and II, thrombin, and platelet-derived growth factors (PDGF).[34] In an animal model that has excess cholesterol indicating tendencies of atherosclerosis, there was enhanced angiotensin I receptor regulation and increased production of ROS by NOX leading to endothelial dysfunction.[34] Increased ROS led to decreased nitric oxide (NO) availability and vasoconstriction, promoting arterial hypertension. Increased superoxide ions and other oxidative systems such as NOX, xanthine oxidase,

cyclooxygenases, lipoxygenases, myeloperoxidases, cytochrome P450 monooxygenase, uncoupled NOS, and peroxidases cause NO inactivation and alteration in endothelial function; this causes inflammation and vasoconstriction which leads to increased risk of CVDs.[19]

Diabetes

Insulin resistance is a pathogenic aspect of type 2 diabetes caused by excessive ROS. The mitochondrial electron transport chain overproduces ROS in response to high blood glucose levels. Nearly every biological component experiences chemical alteration as a result of the strong reactivity of ROS, which affects proteins, DNA, and lipids. The mechanism of the insulin receptor signaling pathway explains the relationship between oxidative stress and insulin resistance. The activity of glucose transporter type 4 (GLUT4) is typically increased by insulin, which improves the uptake of glucose from circulation. However, the decrease in GLUT4 at levels above the optimal insulin concentration results in hyperglycemia and raises the activity of NOX 4 (NOX4). Oxidative stress is brought on by elevated ROS generation, which is a result of increased NOX4 activity.[36]

Furthermore, an increase in available glucose triggers oxidative phosphorylation by the mitochondria and the series of pathways ROS as a byproduct.[37] ROS triggers Casein kinase-2 which activates the retromer.[38] The retromer causes transportation of the GLUT4 to the lysosomes for degradation. This causes an increased concentration of intravenous glucose leading to diabetes.[38]

Skin Diseases

Oxidative stress has been recognized as the major cause of skin injury induced by damaging stimuli such as UV radiation. These stimuli bring about significant damage to cellular lipids, proteins, and DNAs of the skin cells thus, promoting the production of ROS and resulting in a decrease in antioxidant enzyme activity. These changes lead to pre-mature aging sunburns, and carcinogenesis.[39]

Cancer

Oxidative stress leads to carcinogenesis through these mechanisms: Induction of gene mutation that results from cell injury and its effect on signal transduction and transcription factors.[40] The mechanism followed depends on the type of ROS and the stress intensity.[40] Oxidative stress affects cellular molecules, for example, protein, lipids, carbohydrates, and DNA. ROS brings about gene mutation in the DNA and this leads to the initiation of tumors.[41] An example of oxidative stress-induced carcinogenesis is seen in the oxidation of guanine in DNA and RNA to form 8-hydroxyguanine (8-OHG), which has a relationship with cancer.[41] 8-OHG also causes missense mutation by pairing with adenine in DNA replication giving a G to T and C to A substitution.[42]

FACTORS THAT CONTRIBUTE TO OXIDATIVE STRESS ASSOCIATED WITH AGING

Nutrition

Intake of certain nutrients can lead to oxidative stress which triggers inflammation.[43] Consumption of macronutrients and the amount of intake contribute to the effect of oxidative stress.[43] The mitochondria are the major site for generating ATP and ROS in eukaryotes by oxidative phosphorylation.[44] An excessive intake of diets with a high glycemic load will increase the production of ROS in the mitochondria by increasing the release of electron donors by the TCA cycle, thereby altering the mitochondrial membrane potential.[45] This causes mitochondrial dysfunction which induces oxidative stress.

Diets high in fat reduce sirtun3 (sirT3), a protein in the mitochondria responsible for controlling the acetylation levels of enzymes that act in the metabolic process to produce energy.[46] This effect of the fatty diet on the SirT3 will cause hyperacetylation of liver proteins, thereby reducing the efficiency of the mitochondria to carry out oxidative phosphorylation.[46] Lack of adequate oxidative phosphorylation causes ROS accumulation in the cells.

Aging Diseases

The incidence of diseases, for example, cardiovascular and neurogenerative disorders increases with an increase in age and this might be a result of the diseases having the same mechanism as aging.[47] An increase in ROS occurs in cardiovascular disorders as a risk factor and contributes to the pathogenesis of the disease.[48]

Physical Exercise

Physical activity has a number of health advantages, such as lowering the risk of cancer, diabetes, CVDs, bone difficulties, and other aging-related chronic diseases.[49] However, prolonged, vigorous exercise causes oxidative stress because it elevates the levels of ROS (superoxide, hydroxyl, and peroxyl) in the skeletal muscles.[50] The degree of oxidative damage to cellular components (lipids, proteins, and DNA) was used by many studies to document the oxidative stress due to exercise.[51]

Ultraviolet Radiation

Ultraviolet radiation releases inflammatory cytokines which produce ROS.[52] These ROS damage lipids, and

cause misfolding of proteins and DNA of the skin and eye. In dermatology, photo-induced skin aging and wrinkling are caused by over-exposure to ultraviolet and infrared radiation.[52] The pathological impact of ultraviolet radiation and photo-oxidation in retinopathy, eyelid, and eye cancer is also established. Overexposure to light causes ocular aging, cataracts, and age-related macular degeneration.[53]

Air Pollution

Environmental air pollution has been linked to an increase in morbidity and mortality. Air pollutants emit soot and dust into the atmosphere, and the combustion of fossil fuels emits gases such as methane and chlorofluorocarbons. These gases produce ROS and highly reactive hydroxyl radicals, resulting in oxidative stress. Asthma and bronchitis are common symptoms of DNA damage to the respiratory tract.[54,55]

Smoking

Smoking produces free radicals that initiate inflammation and accelerate oxidative stress damage by reducing the antioxidant system of the body.[56] Studies have demonstrated the negative impact of smoking on the antioxidant system: Decreased GSH peroxidase (GPx) and superoxide dismutase (SOD) activity.[56] Isik *et al*.[57] showed that smoking increases lipid peroxidation and triglycerides and decreases the level of high-density lipoprotein. An increase in lipid peroxidation increases the serum level of ROS and causes oxidative stress. Cigarettes and tobacco contain harmful radicals which include nicotine, carbon monoxide, and oxidizing gases. Nicotine induces oxidative stress and apoptosis.[58] The relationship between nicotine, carbon monoxide, and oxidative stress is not known. However, the oxidizing gases (RONS) in cigarettes trigger increased lipid peroxidation and mitochondrial dysfunction which is a biomarker of oxidative stress. The oxidative activities accelerated by smoking account for cardiovascular aging.[59]

EFFECTS OF OXIDATIVE STRESS

A certain amount of ROS is required for normal cell functioning, but the cell needs to go back to its reduced state after the oxidation by ROS.[19] Overproduction of the ROS will result in an oxidative effect which causes changes in the normal cell functioning and harm the body systems.

Obesity

Myocardial redox patterns have been affected by changes such as an increase in BMI in patients following Coronary Artery Bypass Graft Surgery, which indicates increased oxidative stress with insufficient antioxidant compensation.[60]

Reproduction

Oxidative stress plays a significant role in the pathogenesis of subfertility in both males and females. The problem of imbalance between pre-oxidants and antioxidants can result in various reproductive diseases such as polycystic ovary syndrome (PCOS), endometriosis,[61] and infertility.

Oxidative stress associated with aging has been reported to cause PCOS and reduced quality of oocytes in females.[62] PCOS is a reproductive system condition that affects predominantly older women.[62] It is associated with decreased antioxidant concentration.[63] There is also increased production of ROS from monocular cells as a result of the hyperglycemia that occurs in PCOS.[61] The decreased quality of oocytes is shown to be a result of mtDNA damage caused by excessive ROS.[61] In males, high levels of ROS (hydrogen peroxide and superoxide) can lead to infertility by affecting sperm count and fertility.[64]

Pregnancy

Complications in pregnancy, such as spontaneous abortion can also occur due to the oxidative stress induced by the changes in the placental vessels that occur during pregnancy.[65] Exposing the developing embryo or fetus to endogenous or exogenous sources of ROS leads to oxidative damage of the cellular macromolecules (lipid, protein, and DNA) causing birth defects or teratogenesis and dysregulation of signal transduction in the neonate.[61,65]

Mesenchymal Stem Cells (MSCs)

MSCs are multipotent cells found in most fetal and adult tissues and are known for their ability to differentiate into adipocytes, chondrocytes, and osteoblasts.[66,67] MSCs perform differentiation, regeneration, and immunological functions in the body. A low level of ROS is required for MSCs to carry out these functions[67] but excess ROS or oxidative stress will inhibit osteogenic differentiation, and T-cell proliferation and affect[67] the MSC *ex vivo* expansion leading to problems with *in vivo* function and engagement.

Muscle

Muscle contractions during exercise the production of ROS.[68,69] Chronic oxidative stress causes muscle atrophy and dystrophy. Muscle atrophy which is the loss of muscle mass can lead to weakness, tingling in the feet, lack of body balance, and difficulty moving. Oxidative stress by extension through muscle atrophy disrupts the body's balance and movement.[70]

Respiration

Oxidative stress plays a pathological role in respiratory diseases. Cigarette smoking and air pollutants are the major

inductors of respiratory oxidative stress; because they contain soot, epoxides, peroxides, NO, nitrogen dioxide, peroxynitrite (ONOO−), peroxy nitrates, and ROS,[71] age, inactivation of antiproteases, mucus hypersecretion, and vascular barrier dysfunction leading to the edema of the bronchial wall, bronchoconstriction, and enhanced lung inflammation.[72] These pathological changes impair breathing and respiration.

Vision

Oxidative stress impairs vision by causing eye disease and Meibomian gland disease. The mitochondrial activities in the eye supply the eye with energy for cellular metabolism and differentiation.[73] The retina contains a higher number of mitochondria per cell because of its high energy and oxygen demands,[74,75] with oxygen consumption 50% higher than the brain.[75] The photoreceptors contain the highest number of mitochondria per cell. The optical properties of mitochondrial bundles in the retina may improve how efficiently the eye captures light.

The antioxidant system and reducing system of the retinal mitochondria cancel out the byproducts of mitochondrial metabolism. The reducing system is GSH, thioredoxin, NADPH, NADH, FADH2, Vitamin A, Vitamin E, ascorbic acid, and certain amino acids[76] with GSH possessing the highest reducing power against ROS-induced damages to the lens, cornea and the retina.[77] SOD, catalase, and GPx, among other enzyme antioxidants that function by decreasing certain ROS, are found in the eye. Excess ROS or inefficiency in the antioxidant and reducing system causes oxidative stress and plays a pathological role in the damage to the corneal endothelium, lens, and ciliary body, especially the trabecular network, and the progression of glaucoma and cataract.

LIFESTYLES THAT ALLEVIATE OXIDATIVE STRESS

The best approach to oxidative stress should be the elimination of oxidative damage without disruption of the natural antioxidant system.[22] Healthy lifestyles aim to prevent the formation of free ROS instead of neutralizing the excess radicals with an antioxidant system, thereby preventing oxidative damage.[78]

Calorie Restriction and Hormesis

In combating oxidative stress, preventing or reducing free radical formation is more efficacious than depending on antioxidants.[22] Hormesis, an adaptive response to mild stress, enhances the body's ability to maintain homeostasis without the need for external antioxidants.[79,80] Agents that induce hormesis include calorie restriction, exercise, and ischemic pre-conditioning.[79] Studies have demonstrated that calorie restriction leads to an extended lifespan, decreased oxidative stress, and a reduction in age-related diseases in fish, rodents, and non-rodent species.[81]

Dietary/Supplements Intake

Nutrition plays an important role in brain development and mental health, especially for individuals with neurotraumatic, neurodegenerative, and neuropsychiatric conditions.[82] Endogenous antioxidants are crucial for maintaining cellular function and protection, while exogenous antioxidants, such as Vitamins A and E, help enhance this protection.[83] Diets rich in fruits and vegetables supply essential micronutrients and antioxidants, decreasing oxidative stress and age-related diseases.[22] However, extended use of synthetic antioxidants has been connected to health issues, such as cancer and gastrointestinal disorders, suggesting the importance of natural antioxidants from plant sources.[81]

Exercise

The influence of exercise on reducing oxidative stress hinges on factors, such as the type, intensity, and duration of exercise, along with age, sex, and genetics.[84] Laborious exercise increases muscle activity, excitability, and metabolism, resulting in a rise in ROS, which initiates oxidative stress. In contrast, moderate exercise induces hormesis, helping the body adapt to increased ROS from strenuous activity and boosting endogenous antioxidant defenses.[84] Regular moderate exercise is important in strengthening insulin sensitivity, decreasing oxidative stress and inflammation,[22] and increasing the body's endogenous antioxidant capacity.[85]

Yoga and Meditation

Yoga is a comprehensive mind-body practice aimed at achieving overall wellness across mental, physical, spiritual, social, and emotional dimensions.[86] Psychological stress and depression increase cortisol levels, resulting in oxidative damage.[86] A study measuring blood free radical levels before and after yoga practice found that healthy individuals experienced a decline in blood ROS levels after 10 days of yoga.[86] In addition, yoga and meditation have also been shown to decrease cortisol levels in individuals with mild to moderate depression.[87]

WAYS IN WHICH HEALTHY LIFESTYLES CONTRIBUTE TO THE PREVENTION OF OXIDATIVE STRESS ASSOCIATED WITH AGING

Lifestyle factors such as processed food consumption, chemical exposure, and lack of exercise significantly contribute to oxidative stress.[78] Herbal plants with antioxidant properties have been used to control pathologies associated with oxidative

stress.[88] Longevity and mental health are greatly influenced by diet, exercise, and sleep, which help prevent age-related disorders and provide essential energy and nutrients.[89]

Exercise promotes cardiovascular and cerebrovascular health, improves insulin sensitivity, enhances blood flow, and decreases inflammation through its anti-inflammatory effects.[90] Similarly, a healthy lifestyle that includes a diet rich in vegetables, fruits, and proteins decreases the risk of CVDs caused by oxidative stress.[91] The Mediterranean diet, defined by a high intake of fruits, vegetables, legumes, fish, and olive oil, and a low intake of saturated fats and meat, reduces oxidative stress, lowers blood pressure, and improves overall health.[92] This diet also contributes to reduced risks of cancer and cognitive decline because of its rich content of antioxidants and phytochemicals.[43]

EMERGING THERAPEUTIC TARGETS FOR COMBATING OXIDATIVE STRESS

There is a growing interest in identifying novel therapeutic targets that can effectively mitigate its harmful effects of oxidative stress. Emerging therapeutic targets and interventions aim to mitigate oxidative stress through different mechanisms.[93] Here, we discuss the roles of Nrf2 pathway activation, sirtuins, senolytics, and senomorphics in combating oxidative stress.

1. Nuclear factor erythroid 2-related factor 2 (Nrf2) activators: The Nrf2 signaling pathway has emerged as a promising therapeutic target in the field of drug discovery and development due to its central role in regulating cellular defense mechanisms against oxidative stress and inflammation.[94,95] Nrf2 is a transcription factor that acts as the master regulator of the antioxidant response, orchestrating the expression of a vast array of cytoprotective genes.[94] It is known to drive transcription of a variety of genes involved in combating not only oxygen radicals but products of oxidation as well (protein and DNA adducts from carbonyls, malondialdehyde, or hydroxyl radicals).[96] Dysregulation of NrF2 signaling is implicated in many oxidative stress-related diseases including CVDs, neurodegenerative disorders, and pulmonary diseases.[97] Based on these findings, NrF2 activators are considered to be potential therapeutic agents with the ability to induce antioxidant defenses and alleviate disease processes.[97]

   NrF2 activators function through diverse mechanisms to unleash this potent defense system. These activators can target Kelch-like ECH-associated protein 1 (KEAP1), which normally marks NRF2 for degradation. By modifying KEAP1 with electrophiles or oxidants, or by competitively binding to KEAP1, such as p62, these activators prevent NrF2 degradation.[97] Alternatively, some activators inhibit β-transducin repeat-containing protein, the enzyme responsible for NRF2 ubiquitination, or stimulate increased NRF2 synthesis, overwhelming the degradation process.[97,98] In addition, targeting BACH1, a repressor of NRF2, can further enhance NRF2 activity.[97] Ultimately, NRF2 activators promote NRF2 translocation to the nucleus, where it upregulates genes for antioxidant enzymes and detoxifying agents, bolstering cellular defenses against oxidative stress.[98] Notably, NRF2 activators encompass both natural products, such as plant-derived curcumin and resveratrol, as well as synthetic compounds such as dimethyl fumarate (DMF).[98]

   One of the key aspects of Nrf2 that has garnered significant attention is as a therapeutic target in neurodegenerative diseases. The Nrf2 pathway is emerging as a promising therapeutic target for ALS, a complex disease characterized by oxidative stress, mitochondrial dysfunction, ER stress, and inflammation.[99] Nrf2 plays a crucial cytoprotective role by regulating the transcription of over 500 genes involved in antioxidant responses.[99] However, Nrf2 expression decreases with aging and is impaired in ALS patients, evidenced by reduced Nrf2 protein levels in the motor cortex and spinal cord and increased Keap1 mRNA levels.[99] iPSC lines derived from ALS patients exhibit age-dependent oxidative stress, partly due to decreased activity of Nrf2-regulated enzymes. While overexpression of Nrf2 in cell models can reduce oxidative stress and improve cell survival, TDP-43 mutations may impair Nrf2 mRNA translation, leading to inadequate antioxidant responses and motor neuron degeneration.[100] Despite these findings, the impact of Nrf2 on ALS progression can vary with genetic background and specific ALS forms, as evidenced by inconsistent results across different ALS models and patient-derived cells.[99] For instance, while NRF2's absence in SOD1G93A mouse models did not significantly affect disease progression, overexpressing NRF2 in astrocytes has shown promise in extending lifespan and delaying muscle denervation. Similarly, interventions such as extracellular vesicles and SIRT6 overexpression have demonstrated neuroprotective effects by enhancing NRF2 signaling, highlighting the need for multifaceted approaches in ALS treatment.[99]

   In AD, Nrf2 emerges as a promising therapeutic target due to its role in influencing multiple neuroprotective pathways. Currently, AD, the most prevalent form of dementia, affects approximately 5.7 million individuals, with projections suggesting a rise to 14 million by 2050.[101] AD pathology is characterised by neurofibrillary tangles of tau protein and extracellular β-amyloid (Aβ) plaques, leading to increased oxidative stress, neuroinflammation, and mitochondrial dysfunction.[101] While the relationship between amyloid and tau pathologies remains unclear, oxidative stress is considered a crucial factor. Failures in the Nrf2/ARE signaling pathway, which regulates cellular redox balance, can exacerbate the amyloidogenic cleavage of amyloid pre-cursor protein and tau phosphorylation, thereby contributing to neurodegeneration.[102] In AD,

reduced Nrf2 activity is associated with heightened oxidative stress and neuroinflammation. However, pharmacological activation of Nrf2 shows potential in offering neuroprotection and improving cognitive function.[102] Pharmacological agents such as DMF, sulforaphane (SF), and curcumin have demonstrated potential in mitigating oxidative stress and preventing protein accumulation in AD models through Nrf2 activation. Notably, DMF has shown benefits in reducing neuroinflammation and improving cognitive function, though its effects have been observed primarily in male mice, suggesting possible sex-dependent efficacy.[32,103] Resveratrol, another Nrf2 activator found in grapes and berries, has pre-clinical evidence supporting its ability to reduce amyloid burden and enhance cognitive function. However, its clinical application is limited by poor bioavailability.[103] In addition, NRF2-KEAP1 interaction inhibitors and antisense oligonucleotides targeting Nrf2 machinery have also shown promise in improving cognitive function.[32]

Nrf2 activation is emerging as a promising therapeutic strategy for PD, a progressive neurodegenerative disorder characterized by motor symptoms, such as tremor, bradykinesia, and rigidity, along with non-motor symptoms such as cognitive dysfunction and mood changes[104] PD is marked by the loss of dopaminergic neurons in the substantia nigra, accumulation of Lewy bodies with α-synuclein, and increased gliosis.[104] Despite current treatments, such as levodopa and dopamine agonists, PD remains difficult to fully manage, with many new drug trials failing to deliver significant benefits.[105] Oxidative stress, mitochondrial dysfunction, and neuroinflammation are central to PD pathology, making the Nrf2 pathway a crucial area of research.[101] Nrf2 regulates antioxidant responses and is typically compromised in PD due to reduced expression and dysfunction in related pathways.[105] Studies show that Nrf2-deficient mice exhibit heightened sensitivity to MPTP, a chemical model of PD, with more severe dopamine transporter loss compared to wild-type mice.[104] In contrast, Nrf2 activation has been beneficial, offering protection against neurotoxicity from toxins, such as 6-hydroxydopamine and MPP+.[104] Research highlights various Nrf2 activators, including electrophilic compounds, such as SF and DMF, which enhance Nrf2 activity by modifying cysteine residues in Keap1.[105] These compounds have demonstrated the potential to improve neuronal survival and mitigate PD symptoms in models. In addition, natural compounds such as curcumin and obtusaquinone, which can cross the blood-brain barrier, show promise for activating Nrf2 and enhancing neuroprotection.[105] New small-molecule inhibitors that disrupt the Keap1-Nrf2 interaction without covalent bonding, such as cyclic peptides and isoquinoline derivatives, are also being explored.[105] However, challenges, such as poor blood-brain barrier penetration persist.

2. Sirtuins: Sirtuins, a family of nicotinamide adenine dinucleotide (NAD+)-dependent enzymes, have emerged as promising therapeutic targets in various disease conditions, including cardiac disease, metabolic disorders and age-related diseases.[106] These evolutionarily conserved proteins play a crucial role in regulating cellular processes such as energy metabolism, stress response, and gene expression by expressing and activating downstream transcriptional factors (such as Forkhead box protein O3 (FOXO3a), Nrf2 and nuclear factor-kappa B (NF-κB)) as well as antioxidant enzymes, through epigenetic modification and post-translational modification.[107,108]

In mammals, seven members of the sirtuin family, i.e., SIRT1 to SIRT7, which are homologs of yeast Sir2, have been identified so far.[107] The sirtuin family of seven enzymes has also been linked to several antioxidant and oxidative stress-related processes and functions, including longevity, mitochondrial function, DNA damage repair, and metabolism.[109] Among the sirtuin isoforms, SIRT1, SIRT3, and SIRT4 have been extensively studied for their involvement in glucose and lipid metabolism.[110]

SIRT1, the most well-studied member of the mammalian sirtuin family, is involved in various cellular processes including development, senescence, and cell death, and is found in both the nucleus and cytoplasm.[109] SIRT1 activation has been shown to improve health and extend lifespan in mice, primarily through enhancing antioxidant responses and regulating key transcription factors, such as FOXO3a and p53, which are involved in oxidative stress and redox signaling.[109] Oxidative stress can disrupt normal SIRT1 functioning, leading to altered gene regulation and DNA repair mechanisms, but activators, such as resveratrol can mitigate these effects, highlighting SIRT1's critical role in protecting against oxidative damage.[109] SIRT3 is a crucial mitochondrial deacetylase that regulates mitochondrial metabolism, oxidative stress, and longevity by deacetylating key enzymes and proteins.[111] Since more than 90% of ATP in the normal myocardium is derived from mitochondrial oxidative phosphorylation, followed by anaerobic glycolysis of glucose.[112] It has significant implications for various diseases, including cardiovascular and neurodegenerative diseases, cancer, and renal disorders, by maintaining mitochondrial function and reducing ROS.[111] Overexpression of SIRT4 is suggested to inhibit inflammatory responses and oxidative stress in osteoarthritis (OA), indicating its potential as a therapeutic target, though conflicting studies show it might promote oxidative stress and myocardial hypertrophy, leaving its role in redox homeostasis unclear.[113] SIRT5 inhibits peroxisome-induced oxidative stress, protecting the liver and preventing hepatocellular carcinoma.[113] It also promotes cell proliferation and tumor growth in response to oxidative stress, making it a potential target for cancer research.[113] In addition, SIRT5 regulates

cellular NADPH homeostasis and redox potential, implying its involvement in oxidative homeostasis and tumor development through the regulation of oxidative stress processes.[113]

Sirtuins, particularly SIRT1, have emerged as promising pharmacological targets for treating aging and age-related diseases due to their activation by compounds such as resveratrol and various STACs.[114] Although initial studies suggested resveratrol directly activated SIRT1, further research indicates it may not enhance SIRT1 activity *in vitro* and could instead work through indirect mechanisms, such as AMPK activation, which increases NAD+ availability for SIRT1.[114] Novel STACs developed by Sirtris Pharmaceuticals, such as SRT1720, have demonstrated effectiveness in preventing metabolic diseases and extending the health span in animal models.[114] These STACs, including newer generations, such as STAC-5 and STAC-10, have shown potent SIRT1 activation and beneficial effects against age-related diseases, though resveratrol's benefits in humans remain debated due to its poor bioavailability.[114] In addition, resveratrol has demonstrated nephroprotective and anti-aging effects in various models, while synthetic SIRT1 activators and other compounds, such as SGLT2 inhibitors and SIRT3 activators have shown promise in improving mitochondrial function and renal health.[111] Despite the potential of these compounds, some studies have highlighted their off-target effects, necessitating further research to refine their use. SIRT1's role in mitochondrial biogenesis and oxidative stress mitigation underscores its therapeutic potential, yet optimizing these therapies for human subjects requires additional investigation into their mechanisms and efficacy.[111] Overall, sirtuins, particularly SIRT1 and SIRT6, hold promise as targets for treating metabolic and age-related diseases, pending further validation in clinical trials.

3. Senolytics and senomorphics

Senescence is a natural process where a cell stops dividing, changes its morphology, and secretes specific cytokines and chemokines. This process can be induced by stresses such as oncogene activation, oxidative stress, telomere shortening, or radiation exposure.[115] Nuclear DNA damage is a primary mechanism that activates p53, leading to cell cycle arrest, while persistent DNA damage responses at telomeres, oncogene activation, and mitochondrial abnormalities are also significant contributors.[116] Additional factors include upregulation of cell cycle inhibitors, anti-apoptotic proteins, metabolic changes, chromatin reorganization, pro-inflammatory secretions, morphological alterations, and post-transcriptional regulation.[116]

One promising approach to combating oxidative stress and promoting healthy longevity is throughsenolytics and senomorphics.[117] Senolytics are drugs that selectively eliminate senescent cells by targeting senescence-associated anti-apoptotic pathways, which these cells rely on for survival.[118] Dasatinib, an FDA-approved tyrosine kinase inhibitor, and quercetin, a flavonol, have shown senolytic effects in mice with minimal side effects, especially with intermittent administration.[119] Senolytics have demonstrated potential in enhancing tissue regenerative capacity and alleviating age-related pathologies in pre-clinical and clinical studies.[120] Senomorphics, on the other hand, are small molecules that suppress senescence characteristics without killing the cells. They achieve this by blocking the senescence-associated secretory phenotype (SASP), targeting pathways, such as p38MAPK, PI3K/Akt, mTOR, and JAK/STAT, as well as transcription factors such as NF-κB, C/EBPβ, and STAT3. Another approach involves neutralizing specific SASP factors, such as IL-1α, IL-8, and IL-6 with antibodies.[121]

Several classes of senolytic agents have been identified, such as dasatinib, quercetin, and fisetin, which disrupt the anti-apoptotic pathways that senescent cells use to evade death.[122] Dasatinib, a pan-tyrosine kinase inhibitor, and quercetin, a flavonoid with antioxidant properties, have shown effectiveness in reducing senescent cells and improving various age-related conditions.[123] Fisetin, another natural compound, demonstrates potential as an anti-inflammatory and chemotherapeutic agent by inhibiting the PI3K-mTOR pathway.[123] The combination of dasatinib and quercetin has been particularly notable for its efficacy in cell lines and improving age-related diseases in mice. Clinical trials are underway to assess the safety and effectiveness of these drugs in humans, particularly for conditions such as idiopathic pulmonary fibrosis and chronic kidney disease.[124] In addition, compounds, such as navitoclax and selective Bcl-xL inhibitors have been developed to target specific proteins involved in cell survival.[123,125] Research utilizing the STRING database has identified these senolytic agents as effective in reducing senescent cells and inflammatory cytokines, thereby improving physical activity and lifespan in animal models.[123] Senolytic therapies, such as dasatinib, fisetin, quercetin, and chryseriol are also being explored for specific diseases, such as asthma, where they can target pathways involved in inflammation and airway remodeling.[126]

Researchers are actively developing new and improved senolytics. These efforts include investigating drugs that target specific proteins involved in cell death pathways, such as MDM2 inhibitors and p53 modulators for cancer therapy.[123] Other promising avenues include PROTACs (proteolysis-targeting chimeras) that degrade specific proteins in senescent cells and pro-drugs that are designed to deliver senolytics specifically to these cells. Despite the potential benefits, there are concerns about the non-specific actions of these drugs, which could affect normal cells and lead to unintended side effects. Recent advancements, including the use of nanocapsules and pro-drugs, aim to minimize these side effects by

targeting senescent cells more precisely.[127]

Senomorphic compounds include natural flavonoids, such as resveratrol, kaempferol, apigenin, and EGCG, as well as synthetic drugs such as rapamycin and metformin.[124] Resveratrol and kaempferol inhibit the NF-κB pathway, a major SASP regulator, while apigenin reduces SASP by inhibiting IRAK1/IRAK4/p38MAPK phosphorylation.[128] EGCG, found in green tea, suppresses SASP by targeting the PI3K/Akt/mTOR signaling pathway and reducing oxidative stress.[128] Rapamycin, originally an antifungal agent, inhibits the mTOR pathway, extending lifespan and reducing SASP factors.[123] Metformin, commonly used for type 2 diabetes, also has anti-senescent properties and impacts various metabolic pathways.[123] NF-κB inhibitors, such as SR12343, and p38MAPK inhibitors, such as SB203580, reduce SASP factors and senescence markers in animal models.[122] Ruxolitinib, a JAK/STAT pathway inhibitor, has shown promise in reducing systemic inflammation and improving fitness in elderly mice by repressing SASP.[122]

Other potential senomorphic agents include aspirin, which delays cellular senescence and has applications in treating age-related diseases, and ATM inhibitors, which target DNA damage-induced senescence.[124] Statins, known for lowering cholesterol, also reduce oxidative stress-induced senescence.[124] Experimental compounds such as KU-60019, an ATM kinase inhibitor, and NBD peptide, an IKK/NF-κB inhibitor, show promise in reducing senescence markers and improving age-related pathologies.[128] Senomorphics offer a safer, intermittent treatment approach compared to senolytics, which may cause side effects due to their broader action.[124] However, the challenge lies in targeting SASP without disrupting essential pathways for tissue homeostasis and immune system function. Epigenetic control of SASP expression, dietary phytochemicals, and engineered antibodies targeting specific SASP factors are being explored as solutions.[129]

CONCLUSION

Diet, exercise, and meditation are all linked to a significant decrease in oxidative stress related to aging in obesity, type 2 diabetes, and CVDs. Unfortunately, the Mediterranean diet is not available to all demographics. More research should be done to elicit diet modifications that can be incorporated into the daily meals taken by the low class, middle class, high class, and all age groups to help combat and manage oxidative stress.

REFERENCE

1. Kregel KC, Zhang HJ. An integrated view of oxidative stress in aging: Basic mechanisms, functional effects, and pathological considerations. Am J Physiol Regul Integr Comp Physiol 2007;292:R18-36.
2. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. Mol Cell 2012;48:158-67.
3. Wang J, Hua G, Yang X, Zhang L, Ma Y, Ma Q, *et al.* A newly identified small tRNA fragment reveals the regulation of different wool types and oxidative stress in lambs. Sci Rep 2023;13:10213.
4. Liguori I, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, *et al.* Oxidative stress, aging, and diseases. Clin Interv Aging 2018;13:757-72.
5. Mittal PC, Kant R. Correlation of increased oxidative stress to body weight in disease-free post menopausal women. Clin Biochem 2009;42:1007-11.
6. Pi-Sunyer FX. Comorbidities of overweight and obesity: Current evidence and research issues. Med Sci Sports Exerc 1999;31:S602-8.
7. Milagro FI, Campión J, Martínez JA. Weight gain induced by high-fat feeding involves increased liver oxidative stress. Obesity (Silver Spring) 2006;14:1118-23.
8. Zierle-Ghosh A, Jan A. Physiology, body mass index. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2025.
9. Manna P, Jain SK. Obesity, oxidative stress, adipose tissue dysfunction, and the associated health risks: Causes and therapeutic strategies. Metab Syndr Relat Disord 2015;13:423-44.
10. Fernández-Sánchez A, Madrigal-Santillán E, Bautista M, Esquivel-Soto J, Morales-González Á, Esquivel-Chirino C, *et al.* Inflammation, oxidative stress, and obesity. Int J Mol Sci 2011;12:3117-32.
11. Cartwright JE, Fraser R, Leslie K, Wallace AE, James JL. Remodelling at the maternal-fetal interface: Relevance to human pregnancy disorders. Reproduction 2010;140:803-13.
12. Sabir AA, Bilbis LS, Saidu Y, Jimoh A, Iwuala SO, Isezuo SA, *et al.* Oxidative stress among subjects with metabolic syndrome in Sokoto, North-Western Nigeria. Niger J Clin Pract 2016;19:128-32.
13. Ford ES, Mokdad AH, Giles WH, Brown DW. The metabolic syndrome and antioxidant concentrations: Findings from the Third National Health and Nutrition Examination Survey. Diabetes 2003;52:2346-52.
14. Hansen PJ. Effects of heat stress on mammalian reproduction. Philos Trans R Soc Lond B Biol Sci 2009;364:3341-50.
15. Leni Z, Künzi L, Geiser M. Air pollution causing oxidative stress. Curr Opin Toxicol 2020;20-21:1-8.
16. Kalinich JF, Vergara VB, Hoffman JF. Serum indicators of oxidative damage from embedded metal fragments in a rat model. Oxid Med Cell Longev 2022;2022:5394303.
17. Sinicropi MS, Amantea D, Caruso A, Saturnino C. Chemical and biological properties of toxic metals and use of chelating agents for the pharmacological treatment of metal poisoning. Arch Toxicol 2010;84:501-20.

18. Phaniendra A, Jestadi DB, Periyasamy L. Free radicals: Properties, sources, targets, and their implication in various diseases. Indian J Clin Biochem 2015;30:11-26.
19. Senoner T, Dichtl W. Oxidative stress in cardiovascular diseases: Still a therapeutic target? Nutrients 2019;11:2090.
20. Cortopassi GA, Shibata D, Soong NW, Arnheim N. A pattern of accumulation of a somatic deletion of mitochondrial DNA in aging human tissues. Proc Natl Acad Sci U S A 1992;89:7370-4.
21. Junqueira VB, Barros SB, Chan SS, Rodrigues L, Giavarotti L, Abud RL, *et al.* Aging and oxidative stress. Mol Aspects Med 2004;25:5-16.
22. Poljsak B, Milisav I. Aging, oxidative stress and antioxidants. In: Oxidative Stress and Chronic Degenerative Diseases - A Role for Antioxidants. London: IntechOpen; 2013.
23. Chandrasekaran A, Idelchik MD, Melendez JA. Redox control of senescence and age-related disease. Redox Biol 2017;11:91-102.
24. Trist BG, Hare DJ, Double KL. Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. Aging Cell 2019;18:e13031.
25. Zhong L. Tanshinone IIA induces growth inhibition and apoptosis in gastric cancer *in vitro* and *in vivo*. Oncol Rep 2011;27:523-8.
26. Jelinek M, Jurajda M, Duris K. Oxidative stress in the brain: Basic concepts and treatment strategies in stroke. Antioxidants (Basel) 2021;10:1886.
27. Thanan R, Oikawa S, Hiraku Y, Ohnishi S, Ma N, Pinlaor S, *et al.* Oxidative stress and its significant roles in neurodegenerative diseases and cancer. Int J Mol Sci 2014;16:193-217.
28. Ekert PG, Vaux DL. Apoptosis and the immune system. Br Med Bull 1997;53:591-603.
29. Henson PM, Hume DA. Apoptotic cell removal in development and tissue homeostasis. Trends Immunol 2006;27:244-50.
30. Pucci B, Kasten M, Giordano A. Cell cycle and apoptosis. Neoplasia 2000;2:291-9.
31. Chen J, Shu Y, Chen Y, Ge Z, Zhang C, Cao J, *et al.* Evaluation of antioxidant capacity and gut microbiota modulatory effects of different kinds of berries. Antioxidants (Basel) 2022;11:1020.
32. Chen WT, Dodson M. The untapped potential of targeting NRF2 in neurodegenerative disease. Front Aging 2023;4:1270838.
33. Dubois-Deruy E, Peugnet V, Turkieh A, Pinet F. Oxidative stress in cardiovascular diseases. Antioxidants (Basel) 2020;9:864.
34. Madamanchi NR, Vendrov A, Runge MS. Oxidative stress and vascular disease. Arterioscler Thromb Vasc Biol 2005;25:29-38.
35. Wu J, Xia S, Kalionis B, Wan W, Sun T. The role of oxidative stress and inflammation in cardiovascular aging. Biomed Res Int 2014;2014:615312.
36. Hurrle S, Hsu WH. The etiology of oxidative stress in insulin resistance. Biomed J 2017;40:257-62.
37. Rauf A, Khalil AA, Awadallah S, Khan SA, Abu-Izneid T, Kamran M, *et al.* Reactive oxygen species in biological systems: Pathways, associated diseases, and potential inhibitors-A review. Food Sci Nutr 2024;12:675-93.
38. Singh A, Kukreti R, Saso L, Kukreti S. Mechanistic insight into oxidative stress-triggered signaling pathways and type 2 diabetes. Molecules 2022;27:950.
39. Liu HM, Cheng MY, Xun MH, Zhao ZW, Zhang Y, Tang W, *et al.* Possible mechanisms of oxidative stress-induced skin cellular senescence, inflammation, and cancer and the therapeutic potential of plant polyphenols. Int J Mol Sci 2023;24:3755.
40. Zhang S, Xiao X, Yi Y, Wang X, Zhu L, Shen Y, *et al.* Tumor initiation and early tumorigenesis: Molecular mechanisms and interventional targets. Signal Transduct Target Ther 2024;9:149.
41. Gill JG, Piskounova E, Morrison SJ. Cancer, oxidative stress, and metastasis. Cold Spring Harb Symp Quant Biol 2016;81:163-75.
42. Hahm JY, Park J, Jang ES, Chi SW. 8-Oxoguanine: From oxidative damage to epigenetic and epitranscriptional modification. Exp Mol Med 2022;54:1626-42.
43. Tan BL, Norhaizan ME, Liew WP, Sulaiman Rahman H. Antioxidant and oxidative stress: A mutual interplay in age-related diseases. Front Pharmacol 2018;9:1162.
44. Kwak SH, Park KS, Lee K, Lee HK. Mitochondrial metabolism and diabetes. J Diabetes Investig 2010;1:161-9.
45. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature 2001;414:813-20.
46. Zhang Y, Wen P, Luo J, Ding H, Cao H, He W, *et al.* Sirtuin 3 regulates mitochondrial protein acetylation and metabolism in tubular epithelial cells during renal fibrosis. Cell Death Dis 2021;12:847.
47. Finkel T, Holbrook NJ. Oxidants, oxidative stress and the biology of ageing. Nature 2000;408:239-47.
48. Izzo C, Vitillo P, Di Pietro P, Visco V, Strianese A, Virtuoso N, *et al.* The role of oxidative stress in cardiovascular aging and cardiovascular diseases. Life (Basel) 2021;11:60.
49. Anderson E, Durstine JL. Physical activity, exercise, and chronic diseases: A brief review. Sports Med Health Sci 2019;1:3-10.
50. Yavari A, Javadi M, Mirmiran P, Bahadoran Z. Exercise-induced oxidative stress and dietary antioxidants. Asian J Sports Med 2015;6:e24898.
51. Powers SK, Nelson WB, Hudson MB. Exercise-induced oxidative stress in humans: Cause and consequences. Free Radic Biol Med 2011;51:942-50.
52. Goswami S, Sharma S, Haldar C. The oxidative damages caused by ultraviolet radiation type C (UVC) to a tropical rodent Funambulus pennanti: Role of melatonin. J Photochem Photobiol B 2013;125:19-25.
53. Tsubota K, Kawashima M, Inaba T, Dogru M, Matsumoto Y, Ishida R, *et al.* The antiaging approach for the treatment of dry eye. Cornea 2012;31:S3-8.
54. Miller MR. Oxidative stress and the cardiovascular effects

of air pollution. Free Radic Biol Med 2020;151:69-87.
55. Lodovici M, Bigagli E. Oxidative stress and air pollution exposure. J Toxicol 2011;2011:487074.
56. Karademirci M, Kutlu R, Kilinc I. Relationship between smoking and total antioxidant status, total oxidant status, oxidative stress index, vit C, vit E. Clin Respir J 2018;12:2006-12.
57. Isik B, Ceylan A, Isik R. Oxidative stress in smokers and non-smokers. Inhal Toxicol 2007;19:767-9.
58. Barr J, Sharma CS, Sarkar S, Wise K, Dong L, Periyakaruppan A, *et al.* Nicotine induces oxidative stress and activates nuclear transcription factor kappa B in rat mesencephalic cells. Mol Cell Biochem 2007;297:93-9.
59. Csiszar A, Podlutsky A, Wolin MS, Losonczy G, Pacher P, Ungvari Z. Oxidative stress and accelerated vascular aging: Implications for cigarette smoking. Front Biosci (Landmark Ed) 2009;14:3128-44.
60. Gramlich Y, Daiber A, Buschmann K, Oelze M, Vahl CF, Münzel T, *et al.* Oxidative stress in cardiac tissue of patients undergoing coronary artery bypass graft surgery: The effects of overweight and obesity. Oxid Med Cell Longev 2018;2018:6598326.
61. Agarwal A, Aponte-Mellado A, Premkumar BJ, Shaman A, Gupta S. The effects of oxidative stress on female reproduction: A review. Reprod Biol Endocrinol 2012;10:49.
62. Ra K, Park SC, Lee BC. Female reproductive aging and oxidative stress: Mesenchymal stem cell conditioned medium as a promising antioxidant. Int J Mol Sci 2023;24:5053.
63. Mohammadi M. Oxidative stress and polycystic ovary syndrome: A brief review. Int J Prev Med 2019;10:86.
64. Hussain T, Kandeel M, Metwally E, Murtaza G, Kalhoro DH, Yin Y, *et al.* Unraveling the harmful effect of oxidative stress on male fertility: A mechanistic insight. Front Endocrinol (Lausanne) 2023;14:1070692.
65. Zhang C, Guo Y, Yang Y, Du Z, Fan Y, Zhao Y, *et al.* Oxidative stress on vessels at the maternal-fetal interface for female reproductive system disorders: Update. Front Endocrinol (Lausanne) 2023;14:1118121.
66. Denu RA, Hematti P. Effects of oxidative stress on mesenchymal stem cell biology. Oxid Med Cell Longev 2016;2016:2989076.
67. Hu L, Yin C, Zhao F, Ali A, Ma J, Qian A. Mesenchymal stem cells: Cell fate decision to osteoblast or adipocyte and application in osteoporosis treatment. Int J Mol Sci 2018;19:360.
68. Ghosh S, Lertwattanarak R, Lefort N, Molina-Carrion M, Joya-Galeana J, Bowen BP, *et al.* Reduction in reactive oxygen species production by mitochondria from elderly subjects with normal and impaired glucose tolerance. Diabetes 2011;60:2051-60.
69. Sahlin K, Shabalina IG, Mattsson CM, Bakkman L, Fernström M, Rozhdestvenskaya Z, *et al.* Ultraendurance exercise increases the production of reactive oxygen species in isolated mitochondria from human skeletal muscle. J Appl Physiol (1985) 2010;108:780-7.
70. Lian D, Chen MM, Wu H, Deng S, Hu X. The role of oxidative stress in skeletal muscle myogenesis and muscle disease. Antioxidants (Basel) 2022;11:755.
71. Valavanidis A, Vlachogianni T, Fiotakis K. Tobacco smoke: Involvement of reactive oxygen species and stable free radicals in mechanisms of oxidative damage, carcinogenesis and synergistic effects with other respirable particles. Int J Environ Res Public Health 2009;6:445-62.
72. Santus P, Corsico A, Solidoro P, Braido F, Di Marco F, Scichilone N. Oxidative stress and respiratory system: Pharmacological and clinical reappraisal of N-acetylcysteine. COPD 2014;11:705-17.
73. Jarrett SG, Lewin AS, Boulton ME. The importance of mitochondria in age-related and inherited eye disorders. Ophthalmic Res 2010;44:179-90.
74. Brennan LA, Kantorow M. Mitochondrial function and redox control in the aging eye: Role of MsrA and other repair systems in cataract and macular degenerations. Exp Eye Res 2009;88:195-203.
75. Ivanov IV, Mappes T, Schaupp P, Lappe C, Wahl S. Ultraviolet radiation oxidative stress affects eye health. J Biophotonics 2018;11:e201700377.
76. Cabrera MP, Chihuailaf RH. Antioxidants and the integrity of ocular tissues. Vet Med Int 2011;2011:905153.
77. Ganea E, Harding JJ. Glutathione-related enzymes and the eye. Curr Eye Res 2006;31:1-11.
78. Sharifi-Rad M, Anil Kumar NV, Zucca P, Varoni EM, Dini L, Panzarini E, *et al.* Lifestyle, oxidative stress, and antioxidants: Back and forth in the pathophysiology of chronic diseases. Front Physiol 2020;11:694.
79. Wan Y, Liu J, Mai Y, Hong Y, Jia Z, Tian G, *et al.* Current advances and future trends of hormesis in disease. NPJ Aging 2024;10:26.
80. Mattson MP. Hormesis defined. Ageing Res Rev 2008;7:1-7.
81. Sohal RS, Weindruch R. Oxidative stress, caloric restriction, and aging. Science 1996;273:59-63.
82. Farooqui AA. Inflammation and Oxidative Stress in Neurological Disorders. Berlin, Germany: Springer; 2014.
83. Lourenço SC, Moldão-Martins M, Alves VD. Antioxidants of natural plant origins: From sources to food industry applications. Molecules 2019;24:4132.
84. Pingitore A, Lima GP, Mastorci F, Quinones A, Iervasi G, Vassalle C. Exercise and oxidative stress: Potential effects of antioxidant dietary strategies in sports. Nutrition 2015;31:916-22.
85. Gomez-Cabrera MC, Domenech E, Viña J. Moderate exercise is an antioxidant: Upregulation of antioxidant genes by training. Free Radic Biol Med 2008;44:126-31.
86. Mohanty K, Mishra S, Basant S, Yadav RK, Dada R. Estimation of blood free radical levels in healthy population pre and post yoga. J Anat Soc India 2014;63:S13-8.
87. Dada R, Kumar SB, Tolahunase M, Mishra S, Mohanty K, Mukesh T. Yoga and meditation as a therapeutic

intervention in oxidative stress and oxidative DNA damage to paternal genome. J Yoga Phys Ther 2022;12:354.
88. Kasote DM, Katyare SS, Hegde MV, Bae H. Significance of antioxidant potential of plants and its relevance to therapeutic applications. Int J Biol Sci 2015;11:982-91.
89. Briguglio M, Vitale JA, Galentino R, Banfi G, Zanaboni Dina C, Bona A, *et al.* Healthy eating, physical activity, and sleep hygiene (HEPAS) as the winning triad for sustaining physical and mental health in patients at risk for or with neuropsychiatric disorders: Considerations for clinical practice. Neuropsychiatr Dis Treat 2020;16:55-70.
90. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. Front Cardiovasc Med 2018;5:135.
91. Alissa EM, Ferns GA. Dietary fruits and vegetables and cardiovascular diseases risk. Crit Rev Food Sci Nutr 2017;57:1950-62.
92. Willett WC, Koplan JP, Nugent R, Dusenbury C, Puska P, Gaziano TA. Prevention of chronic disease by means of diet and lifestyle changes. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, editor. Disease Control Priorities in Developing Countries. United States: The International Bank for Reconstruction and Development, The World Bank; 2006.
93. Trujillo-Rangel WÁ, García-Valdés L, Méndez-Del Villar M, Castañeda-Arellano R, Totsuka-Sutto SE, García-Benavides L. Therapeutic targets for regulating oxidative damage induced by ischemia-reperfusion injury: A study from a pharmacological perspective. Oxid Med Cell Longev 2022;2022:8624318.
94. Adinolfi S, Patinen T, Jawahar Deen A, Pitkänen S, Härkönen J, Kansanen E, *et al.* The KEAP1-NRF2 pathway: Targets for therapy and role in cancer. Redox Biol 2023;63:102726.
95. Abdalkader M, Lampinen R, Kanninen KM, Malm TM, Liddell JR. Targeting Nrf2 to suppress ferroptosis and mitochondrial dysfunction in neurodegeneration. Front Neurosci 2018;12:466.
96. Calkins MJ, Johnson DA, Townsend JA, Vargas MR, Dowell JA, Williamson TP, *et al.* The Nrf2/ARE pathway as a potential therapeutic target in neurodegenerative disease. Antioxid Redox Signal 2009;11:497-508.
97. Forman HJ, Zhang H. Targeting oxidative stress in disease: Promise and limitations of antioxidant therapy. Nat Rev Drug Discov 2021;20:689-709.
98. Vassalle C, Maltinti M, Sabatino L. Targeting oxidative stress for disease prevention and therapy: Where do we stand, and where do we go from here. Molecules 2020;25:2653.
99. Tarot P, Lasbleiz C, Liévens JC. NRF2 signaling cascade in amyotrophic lateral sclerosis: Bridging the gap between promise and reality. Neural Regen Res 2024;19:1006-12.
100. Bono S, Feligioni M, Corbo M. Impaired antioxidant KEAP1-NRF2 system in amyotrophic lateral sclerosis: NRF2 activation as a potential therapeutic strategy. Mol Neurodegener 2021;16:71.
101. Brandes MS, Gray NE. NRF2 as a therapeutic target in neurodegenerative diseases. ASN Neuro 2020;12:1759091419899782.
102. Zgorzynska E, Dziedzic B, Walczewska A. An overview of the Nrf2/ARE pathway and its role in neurodegenerative diseases. Int J Mol Sci 2021;22:9592.
103. Qu Z, Sun J, Zhang W, Yu J, Zhuang C. Transcription factor NRF2 as a promising therapeutic target for Alzheimer's disease. Free Radic Biol Med 2020;159:87-102.
104. Joshi G, Johnson JA. The Nrf2-ARE pathway: A valuable therapeutic target for the treatment of neurodegenerative diseases. Recent Pat CNS Drug Discov 2012;7:218-29.
105. Yang XX, Yang R, Zhang F. Role of Nrf2 in Parkinson's disease: Toward new perspectives. Front Pharmacol 2022;13:919233.
106. Matsushima S, Sadoshima J. The role of sirtuins in cardiac disease. Am J Physiol Heart Circ Physiol 2015;309:H1375-89.
107. Pan Z, Dong H, Huang N, Fang J. Oxidative stress and inflammation regulation of sirtuins: New insights into common oral diseases. Front Physiol 2022;13:953078.
108. Yamagata K, Yoshizawa T. Transcriptional regulation of metabolism by SIRT1 and SIRT7. Int Rev Cell Mol Biol 2018;335:143-66.
109. Singh CK, Chhabra G, Ndiaye MA, Garcia-Peterson LM, Mack NJ, Ahmad N. The role of sirtuins in antioxidant and redox signaling. Antioxid Redox Signal 2018;28:643-61.
110. Akbas EM. The emerging role of sirtuin1,-3 and -4 in glucose and lipid metabolism and in diabetes mellitus. J Mol Genet Med 2014;2:018.
111. Ogura Y, Kitada M, Koya D. Sirtuins and renal oxidative stress. Antioxidants (Basel) 2021;10:1198.
112. Sun W, Liu C, Chen Q, Liu N, Yan Y, Liu B. SIRT3: A new regulator of cardiovascular diseases. Oxid Med Cell Longev 2018;2018:7293861.
113. Lin J, Xiong Z, Gu J, Sun Z, Jiang S, Fan D, *et al.* Sirtuins: Potential therapeutic targets for defense against oxidative stress in spinal cord injury. Oxid Med Cell Longev 2021;2021:7207692.
114. Santos L, Escande C, Denicola A. Potential modulation of sirtuins by oxidative stress. Oxid Med Cell Longev 2016;2016:9831825.
115. Wan X, Garg NJ. Sirtuin control of mitochondrial dysfunction, oxidative stress, and inflammation in chagas disease models. Front Cell Infect Microbiol 2021;11:693051.
116. Lelarge V, Capelle R, Oger F, Mathieu T, Le Calvé B. Senolytics: From pharmacological inhibitors to immunotherapies, a promising future for patients' treatment. NPJ Aging 2024;10:12.
117. Varesi A, Chirumbolo S, Campagnoli LI, Pierella E, Piccini GB, Carrara A, *et al.* The role of antioxidants in the interplay between oxidative stress and senescence. Antioxidants (Basel) 2022;11:1224.
118. Hagen TM. Oxidative stress, redox imbalance, and the

aging process. Antioxid Redox Signal 2003;5:503-6.
119. Tan BL, Norhaizan ME, Liew WP. Nutrients and oxidative stress: Friend or Foe? Oxid Med Cell Longev 2018;2018:9719584.
120. Espinoza SE, Khosla S, Baur JA, de Cabo R, Musi N. Drugs targeting mechanisms of aging to delay age-related disease and promote healthspan: Proceedings of a national institute on aging workshop. J Gerontol A Biol Sci Med Sci 2023;78:53-60.
121. Miller SJ, Darji RY, Walaieh S, Lewis JA, Logan R. Senolytic and senomorphic secondary metabolites as therapeutic agents in Drosophila melanogaster models of Parkinson's disease. Front Neurol 2023;14:1271941.
122. Lagoumtzi SM, Chondrogianni N. Senolytics and senomorphics: Natural and synthetic therapeutics in the treatment of aging and chronic diseases. Free Radic Biol Med 2021;171:169-90.
123. Lee E, Carreras-Gallo N, Lopez L, Turner L, Lin A, Mendez TL, Went H, et al. Exploring the effects of Dasatinib, Quercetin, and Fisetin on DNA methylation clocks: A longitudinal study on senolytic interventions. Aging (Albany NY) 2024;16:3088-106.
124. Matsubayashi S, Ito S, Araya J, Kuwano K. Drugs against metabolic diseases as potential senotherapeutics for aging-related respiratory diseases. Front Endocrinol (Lausanne) 2023;14:1079626.
125. Zhang L, Pitcher LE, Yousefzadeh MJ, Niedernhofer LJ, Robbins PD, Zhu Y. Cellular senescence: A key therapeutic target in aging and diseases. J Clin Invest 2022;132:e158450.
126. Calabrò A, Accardi G, Aiello A, Caruso C, Galimberti D, Candore G. Senotherapeutics to counteract senescent cells are prominent topics in the context of anti-ageing strategies. Int J Mol Sci 2024;25:1792.
127. Wan R, Srikaram P, Guntupalli V, Hu C, Chen Q, Gao P. Cellular senescence in asthma: From pathogenesis to therapeutic challenges. EBioMedicine 2023;94:104717.
128. Luís C, Maduro AT, Pereira P, Mendes JJ, Soares R, Ramalho R. Nutritional senolytics and senomorphics: Implications to immune cells metabolism and aging - from theory to practice. Front Nutr 2022;9:958563.
129. Mbara KC, Devnarain N, Owira PM. Potential role of polyphenolic flavonoids as senotherapeutic agents in degenerative diseases and geroprotection. Pharmaceut Med 2022;36:331-52.

Source of Support: Nil. **Conflicts of Interest:** None declared.