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Authors' Affiliation:

¹University of Opole Collegium Medicum, Oleska 48 street, 45-052 Opole, Poland

²Wrocław Medical University, wyrzeże Ludwika Pasteura 1, 50-367 Wrocław, Poland

*Corresponding author:

Mateusz Lyko,
University of Opole Collegium Medicum, Oleska 48 street, 45-052 Opole, Poland,
E-mail: matlyk@wp.pl

ORCID & Email List:

Mateusz Lyko	0009-0009-2530-2789; matlyk@wp.pl
Karolina Mularczyk	0009-0006-7756-0809; mkarola1999@gmail.com
Jakub Kurasz	0009-0004-3955-1552; jakubkurasz30@gmail.com
Paweł Siudziński	0009-0002-4476-9412; pawelsiudzinski99@gmail.com
Wojciech Maj	0009-0003-2869-3718; Rottel45@gmail.com
Alicja Skoczylas	0009-0002-2185-5406; alicjasko1999@gmail.com
Wiktoria Tomaszewska	0009-0005-6166-1659; wiktomaszewska@o2.pl
Wiktoria Podlasiewicz	0009-0001-6578-5297; wiktoria.podlasiewicz@student.umw.edu.pl
Katarzyna Chrobok	0009-0004-0787-3872; kaspal109@gmail.com
Piotr Dudziak	0009-0000-6173-740X; piotr-dudziak@outlook.com
Anna Nowak	0009-0005-8833-1107; anulla1008@gmail.com
Maria Goliańska	0009-0008-2772-6131; maria.golinska99@gmail.com
Filip Kasperczak	0009-0000-9758-0889; fkasperczak98@gmail.com

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The Role of Endogenous and Exogenous Antioxidants in the Prevention and Supportive Treatment of Chronic Diseases – A Literature Review

Mateusz Lyko^{1*}, Karolina Mularczyk², Jakub Kurasz¹, Paweł Siudziński¹, Wojciech Maj¹, Alicja Skoczylas¹, Wiktoria Tomaszewska¹, Wiktoria Podlasiewicz², Katarzyna Chrobok¹, Piotr Dudziak¹, Anna Nowak¹, Maria Goliańska¹, Filip Kasperczak¹

ABSTRACT

Background: Chronic diseases, which are long-lasting and slow to develop, pose a significant challenge to health systems worldwide. Oxidative stress, an imbalance between reactive oxygen/nitrogen species (ROS/RNS) and the antioxidant defense system, plays a key role in the pathophysiology of diverse metabolic, cardiovascular, and neurodegenerative diseases. **Objective:** This review highlights the systemic relevance of internal and external antioxidant mechanisms and their potential for enabling the management of chronic health conditions while optimizing sports performance. **Methods:** A systematic review of the literature was conducted using the PubMed and MDPI databases. Thirty-two reviews and original research articles were selected for inclusion in this review on antioxidants related to chronic disease prevention, treatment support, and sports use. **Results:** Several studies have demonstrated that antioxidants can reduce cellular damage by scavenging free radicals and modulating inflammatory pathways, including the NF- κ B pathway. Notable discoveries are related to their advantage over diabetes, hypertension, atherosclerosis, Alzheimer's disease, or psoriasis. In good shape to lead muscles, antioxidants facilitate recovery by attenuating exercise-induced oxidative stress. However, acute high-dose supplementation can be detrimental by blunting some of the mitochondrial biogenesis and training adaptations. **Conclusion:** Thus, antioxidants are crucial in the multifaceted approach to treating chronic disease. Yet, clinical efficacy is highly individual and depends on the stage of the disease. A multiple hits strategy (antioxidant supplementation tailored to the individual, combined with dietary interventions, e.g., the Mediterranean diet, and lifestyle modifications) is advisable to enhance the quality of life as well as the therapeutic response of the patients.

Keywords: antioxidants, chronic disease, sport, diabetes mellitus, hypertension, Alzheimer's disease, atherosclerosis, psoriasis, COPD, atopic dermatitis, oxidative stress, ROS, RNS, free radicals, vitamins.

1. INTRODUCTION

As maintained by the World Health Organization (WHO), chronic diseases are defined as diseases having long duration and slow progression. The treatment of these disorders (multimorbidity) is becoming a great healthcare challenge worldwide, particularly in developed countries, due to their growing incidence. Normally, these systems were built to treat the acute, but the chronic need more holistic, long-term attention.

Antioxidants (AOs) serve as a defense mechanism, protecting cells from the detrimental effects of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which are produced under normal cellular function. Although minor/moderate amounts of ROS and RNS are required for biological functionalities, the overproduction of these species results in oxidative stress, which promotes injury to proteins, lipids, and DNA, leading to the pathogenesis of numerous chronic illnesses, including cancer, cardiovascular, and neurodegenerative diseases. Antioxidants mitigate oxidative stress by scavenging free radicals and activating endogenous defense systems. They have several mechanisms of action: scavenging free radicals, inhibiting the production of free radicals, turning them to less toxic species, upregulating the endogenous antioxidant systems, and chelating metal ions that are involved in the production of free radicals. Because their electrons are unpaired, ROS and RNS are highly reactive molecules. Mitochondrial respiration, NADPH oxidase activity, environmental agents (such as tobacco smoke and pollution), and some drugs are responsible for the production of ROS/RNS in cells. Oxidative stress in cells is caused by both internal and external stimuli (Losada-Barreiro et al., 2022; Reynolds et al., 2018; Jomova et al., 2023).

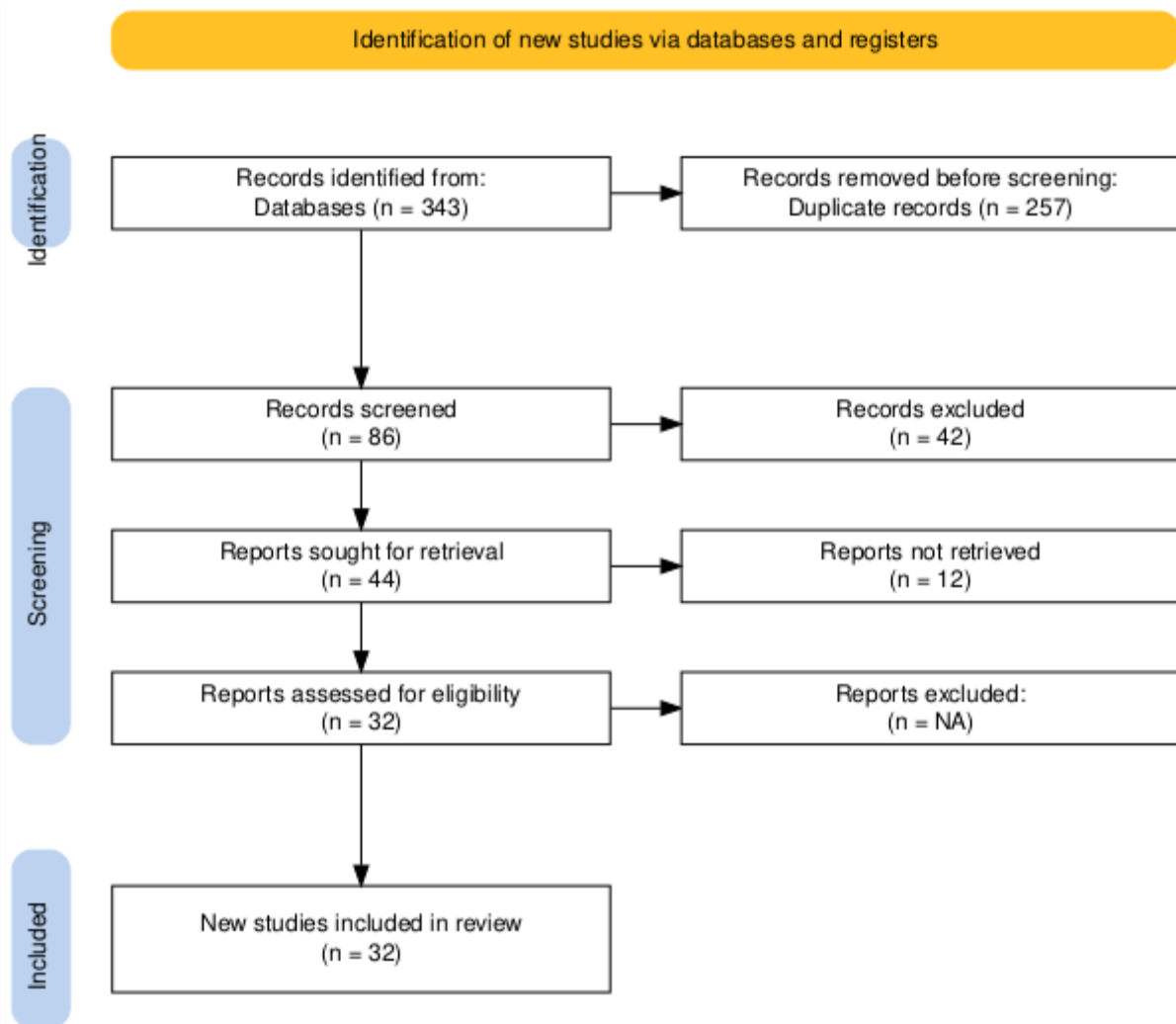


Fig.1 PRISMA Flow Diagram.

2. REVIEW METHODS

The analysis of available medical papers in the PubMed and MDPI databases was performed, from which 32 papers relevant to the topic of this literature review—endogenous and exogenous antioxidants in the prevention and supportive treatment of chronic diseases and their application in sport—were selected. All analyzed articles were in English language publications. The literature search covered publications from 2015 to 2024. The article screening process followed the PRISMA guidelines (Figure 1).

3. RESULTS & DISCUSSION

Oxidative stress, which is an excess of reactive oxygen species (ROS) and reactive nitrogen species (RNS) over the antioxidant defensive system of the body, is well established in the pathophysiology of many chronic diseases and exercise-induced physiological alterations. The collected research results are presented in Table 1. Summary of Antioxidant Research and Therapeutic Impact.

Table 1. Summary of Antioxidant Research and Therapeutic Impact

Disease	Key Findings & Mechanisms	Specific Substances / Interventions
Diabetes	Improved insulin sensitivity; protection of pancreatic β -cells; reduction of oxidative markers (MDA, AOPP).	Polyphenols, Gypsophila paniculata extract (GPEE).
Hypertension	Enhancement of nitric oxide (NO) bioavailability; significant improvement in endothelial function (up to 45%).	High-intensity IMST (Inspiratory Muscle Strength Training).
Alzheimer's Disease	Neuroprotection via pH stabilization and reduction of β -amyloid aggregation; combating metabolic acidosis.	Vitamin E, Ginkgo biloba, Mediterranean diet (alkaline-rich).
Atherosclerosis	Prevention of LDL cholesterol oxidation; attenuation of endothelial dysfunction in the vascular wall.	Superoxide dismutase (SOD), Catalase, Resveratrol.
Psoriasis	Improvement of oxidative parameters; decrease in clinical severity and skin scaling.	Coenzyme Q10, Selenium, Vitamin E.
Age-Related Macular Degeneration (AMD)	Delaying the progression of advanced AMD; absorption of harmful blue light; protection of retinal cells.	Lutein, Zeaxanthin, Zinc (AREDS2 formula), Curcumin.
Chronic Obstructive Pulmonary Disease (COPD)	Targeting mitochondrial ROS; reduction of cigarette smoke-induced inflammation in airway cells.	Mitochondria-targeted antioxidants (MTAs) such as MitoQ and MitoTEMPO.
Atopic Dermatitis	Reduction of inflammation and pruritus; improvement in sleep quality and skin barrier integrity.	Melatonin (3–6 mg/day), Vitamin D, Vitamin E.
Sports Physiology	Dual role: excessive supplementation may blunt training adaptations (biogenesis) by inhibiting PGC1- α signaling.	Vitamin C, Vitamin E, N-acetylcysteine (NAC).

ROS are known to act as signaling molecules and have been shown to regulate cell proliferation, differentiation, and apoptosis. ROS function as signaling modulators for the mitogen-activated protein kinases (MAPKs) and the nuclear factor kappa B (NF- κ B) transcription factor, both of which are central to immune and inflammatory pathways. Low ROS (oxidative eustress) is mandatory for cellular homeostasis, whereas high ROS levels result in oxidative distress and damage to the cell constituents. Antioxidant enzymes (e.g. superoxide dismutase (SOD), catalase, and glutathione peroxidase) represent the innate defense of the body against ROS. Antioxidants which are small molecules like vitamins C and E, glutathione, flavonoids, and carotenoids play an important role in scavenging the ROS and preventing cell injury. Oxidative stress markers include carbonylated proteins, oxidized LDL, products of lipid peroxidation, and DNA/RNA oxidation products. These markers enable one to measure oxidative damage and are important in the diagnosis and monitoring of chronic diseases developing as a consequence of oxidative stress (Jomova et al., 2023).

The Impact of Antioxidants on Selected Chronic Diseases:

Diabetes

Diabetes is a life-threatening disorder of raised blood glucose level with an associated intense oxidative stress, which aggravates the disease progression. Oxidative stress, resulting from the accumulation of reactive oxygen species (ROS), is involved in many

complications, such as cardiovascular and nervous system diseases. Food-derived polyphenols may help manage diabetes by enhancing antioxidant defenses and/or insulin action. Polyphenols, found in fruits, vegetables, cereals, and beverages such as red wine and green tea, are potent antioxidants, and they exert beneficial health effects. Studies show these can neutralize ROS, decrease Inflammation, and increase insulin sensitivity. Flavonoids, phenolic acids, and lignans are subclasses of polyphenols with distinct antioxidant effects.

The damage caused by excess ROS affects cells in diabetes at the level of DNA, protein, and lipids, which leads to altered cellular function. This may induce cell death, particularly in the pancreatic β -cells, which secrete insulin. In diabetes, ROS induce inflammatory pathways, for example, NF- κ B, and subsequently pro-inflammatory cytokine expression. These cytokines promote insulin resistance by interfering with insulin signaling and glucose metabolism and also cause β -cell injury. In addition, high glucose levels promote the production of advanced glycation end products (AGEs), which potentiate inflammation and tissue injury, especially in the eye, kidney, and nerve, thereby complicating the course of diabetes.

The antioxidant defense system of the body, which includes enzymatic defenses, notably superoxide dismutase (SOD) and the glutathione peroxidase (GPx), can help to remove ROS. But in diabetics, this system is overburdened and weakened, so dietary polyphenols are a possibility for supporting this defense. Polyphenols occur naturally in many foods, such as green tea, citrus fruits, berries and red wine. A diet rich in these foods may help prevent diabetic complications by upregulating antioxidant defenses. Studies show that polyphenols may positively impact markers of oxidative stress and inflammation, which can be helpful in managing type 2 diabetes. Clinical studies have demonstrated that polyphenols like resveratrol and curcumin reduce oxidative stress markers and enhance blood glucose management. Oxidative stress has a pivotal role in insulin resistance and diabetic complications. Antioxidant therapy (Vitamins C and E) could be a potential for oxidative stress management in diabetic patients (Jomova et al., 2023; Krawczyk et al., 2023; Sharifi-Rad et al., 2020).

The ethanolic extract of *Gypsophila paniculata* (GPEE) has been shown to possess a potent antioxidant effect in vitro and in vivo by scavenging free radicals (such as DPPH, NO, and H₂O₂), and the related oxidative stress indicators, including malondialdehyde (MDA) and advanced oxidation protein products (AOPPs), were also decreased. GPEE showed anti-inflammatory effects by decreasing pro-inflammatory cytokines (IL-1 β , NF- κ B, IL-18) and anti-dyslipidemic effects by improving lipid profiles via lowering cholesterol and triglyceride levels. GPEE treatment and a GPEE+metformin combination significantly decreased blood glucose levels, indicating their antidiabetic significance similar to that of metformin (Usatiuc et al., 2024).

Diabetic peripheral neuropathy (DPN) is a frequent diabetic complication in which nerve damage results in numbness, pain, and motor deficit, to mention a few symptoms. Hyperglycemia triggers oxidative stress, damaging nerves through such pathways as advanced glycation end products (AGE) and the polyol pathway. Antioxidants such as quercetin, curcumin, and vitamin E have been recognized for their potency in enhancing antioxidant defense mechanisms and mitigating oxidative stress-related damage in nerve tissues. Diabetes-mediated depletion in antioxidant enzyme activity (SOD, GSH, catalase) causes ROS and lipid peroxidation accumulation and further potentiates nerve damage (Rusli et al., 2024).

Epidemiology and Pathophysiology of Gestational Diabetes Mellitus GDM manifests as insulin resistance and β -cell dysfunction, and oxidative stress is considered one of the triggers in the pathogenesis of this disease. High levels of ROS due to mitochondrial dysfunction and hyperglycemia-mediated oxidative stress lead to increases in oxidative damage to insulin resistance and β -cell function. Oxidative stress-induced inflammation activates pathways, including NF- κ B, leading to the release of pro-inflammatory cytokines such as TNF- α and IL-6, which further aggravate metabolic alterations in GDM. The control of oxidative stress and inflammation in GDM represents an important therapeutic challenge, as both they carry a greater risk of complicating issues for the mother and the fetus, including a higher risk of cardiovascular complications in the postpartum period (Saucedo et al., 2023).

Hypertension

Hypertension is defined as a persistent elevation in arterial blood pressure, which is a risk factor for cardiovascular diseases and is a burden worldwide. It affects about one billion people and is correlated with adverse clinical outcomes, including cardiovascular disease, stroke, and renal failure. About 40% of patients have resistant hypertension (RH) despite current treatments, which has stimulated additional research. Chronic stimulation of the renin-angiotensin-aldosterone (RAA) system increases levels of angiotensin II, which increases blood pressure and oxidative stress, primarily mediated by the upregulation of reactive oxygen species (ROS) production. Hypertension-related organ damage is frequently due to vascular dysfunction and oxidative stress-induced endothelial cell injury. ROS and oxidative stress are widely regarded as of paramount importance in the development of hypertension. The redox

disturbance, which is the combined effect of the elevated ROS generation and diminished antioxidant capacity, integrally contributes to the development of hypertension. In a physiological context, ROS are essential for cellular signalling and vascular tone. But too much ROS from NADPH oxidase, mitochondria, and xanthine oxidase, among other sources, induces oxidative stress, inflammation, and a reduced bioavailability of nitric oxide (NO), which impairs vascular function and drives hypertension.

A number of antioxidants, e.g., vitamin C and E, polyphenols (quercetin and resveratrol), α -lipoic acid, N-acetylcysteine, and coenzyme Q10, appeared very promising in animal models and small-scale human investigations. These antioxidants have been shown to play roles in targeting the sources of ROS, diminishing oxidative stress, and increasing NO availability that may collectively contribute to a reduction in blood pressure. In type 2 diabetic patients, Vit E supplementation has a beneficial effect on high-sensitivity C-reactive protein level and systolic blood pressure, indicating that oxidative stress and inflammation play significant roles in diabetes and its complications. Conclusions: Although preclinical data are promising, there is no clear evidence from large trials of the beneficial effect of vitamin E in diabetic patients, and very little data in non-diabetic individuals with cardiovascular disease or risk. Contributing to this are variations in the route of antioxidant delivery, bioavailability, and patient response. Diet and lifestyle factors can also affect the effectiveness of antioxidants, which means taking antioxidants in a pill may not be enough to fight high blood pressure unless you make other changes to your health. Although there is no strong evidence for direct antioxidant supplementation in the treatment of hypertension, intake of an antioxidant-rich diet (e.g., fruits and vegetables, whole grains) is advocated as a part of a comprehensive strategy to reduce oxidative stress and improve vascular health. Future studies may determine whether specific antioxidants or combinations may have sufficiently stable antihypertensive effects. Redox proteomics and systems biology could facilitate the identification of biomarkers and the development of targeted antihypertensive drug therapies, but barriers to moving preclinical findings from studying animals to treat patients persist (Amponsah-Offeh et al., 2023; Griendling et al., 2021).

Oxidative stress strains the vascular endothelium, impairing the vasodilatory reserve and enhancing vessel contractility. Antioxidants inhibit free radical chain reactions, increase endothelial function, and decrease oxidative stress, which might contribute to blood pressure lowering. Inspiratory muscle strength training (IMST) substantially improves endothelial function, raises NO bioavailability, and lowers oxidative stress among middle-aged/older adults with elevated systolic blood pressure. Oxidation-inhibited protein phosphatases are also involved in the modulation of molecular signaling, and their impaired function is induced by oxidative stress, which may be implicated in the pathogenesis of hypertension, demonstrating the contribution of oxidative modifications in the development of diseases (Jin & Kang, 2024).

IMST improved flow-mediated dilation (FMD) by ~45%, a marker of endothelial function. Increased NO bioavailability as a result of enhanced eNOS activation and decreased ROS activity. Both men and postmenopausal women (with estrogen deficiency) derived comparable benefits from IMST. The expression of the pro-inflammatory marker C-reactive protein (CRP) was downregulated by ~30% following IMST. There was also an increase in the levels of some beneficial metabolites, such as L-ornithine (a NO precursor), indole (a putative blood pressure-lowering agent), and hexanoic acid (with anti-inflammatory activity) (Craighead et al., 2021).

Preclinical data indicate that antioxidants, including N-acetylcysteine, lipoic acid, and mitochondria-directed therapies, may have antihypertensive effects in animals. However, results from clinical trials have been contradictory, mainly because of patient heterogeneity and inadequate study designs. Deficiency in vitamin D is related to hypertension, and its supplementation could reduce blood pressure and enhance endothelial function. However, the results of clinical trials assessing the clinical implications of vitamin D in the treatment of hypertension have been controversial. Patient-specific differences in oxidative stress biomarkers and other factors that may have complex interactions (e.g., diet, comorbidities) are challenging for the efficacy of these types of therapies (Sorriento et al., 2018).

Alzheimer's Disease (AD)

Alzheimer's Disease (AD) has been progressively associated with oxidative stress and metabolic acidosis among other pathogenic factors. Oxidative stress is caused when there is an elevated production of reactive oxygen species (ROS) or a decrease in antioxidants, leading to damage in cells. Lower pH (higher acidity) can also contribute to the increase of oxidative stress and to the formation of free radicals, especially in the brain tissues where the lesions occur in Alzheimer's disease. This neurodegenerative disease involves the aggregation of beta-amyloid ($A\beta$) plaques and tau protein tangles, which impair cognition. $A\beta$ plaques and tau aggregates also enhance oxidative damage and free radical generation, and tau aggregates also contribute to mitochondrial and neuronal damage. Antioxidants may be effective in reducing oxidative stress in Alzheimer's disease; so far, studies have been consistent. For example, vitamin E, Ginkgo biloba, and molecular hydrogen have neuroprotective activities in model systems. Combined antioxidants at high

doses seem to work better than each alone, probably due to a synergic effect. Contemporary diet, heavy in animal products and deficient in plant sources, promotes chronic metabolic acidosis, which may enhance oxidative stress and the progression of AD. Plant-based diets are high in potassium and low in sodium, which also helps shift pH to a more alkaline state and may help reduce oxidative stress. Glutathione, astaxanthin, ascorbyl palmitate, and vitamin C are some of the ingredients that are being investigated for their potential in reducing oxidative stress. Fruit and vegetable-based diets and certain nutraceuticals (e. g., polyphenols) could contribute to reducing the risk of AD. A comprehensive strategy to good health, such as the antioxidant-rich Mediterranean diet, exercise, stress management, and supplementation of nutrients, may play a positive role in postponing or preventing the development of Alzheimer's disease. Antioxidants and other dietary regimens appear promising, but additional work is necessary to refine the dose and regimen that would be applicable for the treatment of AD. Tailor-made antioxidant regimens and pH-management strategies for individuals may be part of an overall approach to manage AD. Antioxidants, such as glutathione, vitamins, and flavonoids, might contribute significantly to countervailing oxidative stress in Alzheimer's disease (Veurink et al., 2020; Jomova et al., 2023).

PON1 is a gene encoding an enzyme that modulates the expression of antioxidant and anti-inflammatory related genes, and is protective against oxidative stress-related diseases, including CVD, AD, and cancer. Hydrolysis of neurotoxic compounds by PON1 is protective against AD. Decreased PON1 activity has been related to a higher beta-amyloid deposition and dysfunctional autophagy. Research in both murine and human populations supports the view that PON1 activity influences oxidative and inflammatory markers (Jakubowski, 2024).

Atherosclerosis

Atherosclerosis is characterized as a persistent inflammatory disorder of the arterial wall in which lipid accumulation and oxidative damage work together to promote atherogenesis in the walls of arteries. Central to this process is the oxidative damage of low-density lipoproteins (LDL) and increased reactive oxygen species (ROS) production in the cells. Oxidative stress is also involved in the development of atherosclerosis through the oxidative modification of lipids, proteins, and DNA in vascular cells. ROS are mainly produced by mitochondrial respiration and enzymes, including NADPH oxidase and xanthine oxidase, in response to stimuli such as hypercholesterolemia and hypertension. These ROS favour atherosclerosis formation, endothelial dysfunction, and cardiac injury. Increased ROS production leads to modification of LDL cholesterol and enhances atherogenesis.

Endogenous antioxidants: Body enzymes protect from ROS, such as catalase, superoxide dismutase (SOD) and glutathione peroxidase (GPx). All three enzymes serve different purposes in converting superoxide radicals to less reactive molecules and preventing inflammation.

Exogenous antioxidants: Dietary antioxidants, including vitamin E and C, and some polyphenols, have the property of scavenging free radicals and may exert an inhibitory effect on LDL oxidation. Both these agents play a role in attenuating endothelial dysfunction and inflammation in the vasculature. Antioxidant medicinal plants, including Ginkgo biloba and Curcuma longa (turmeric), have been reported to reduce lipids, inhibit monocyte adhesion, and the formation of foam cells, an essential step in plaque formation.

The combination of different antioxidants, natural or synthetic, could thus provide a multilevel intervention to protect against the diverse biochemistry of atherosclerosis. Nevertheless, the exact effectiveness and best combinations of these antioxidants are yet to be established. Antioxidant approaches (vitamin E, resveratrol) may reduce oxidative stress in cardiovascular diseases (Malekmohammad et al., 2019; Jomova et al., 2023; Sharifi-Rad et al., 2020).

Psoriasis

Psoriasis is an inflammatory and hyperproliferative hereditary skin disease that affects the keratinocytes. Although the genetic background is most important, the disease can be worsened by environmental and other lifestyle-related factors known to induce oxidative stress, such as smoking, alcohol, diet, infections, stress, and exposure to UV radiation. Oxidative stress is referred to as a result of a disturbed balance between reactive oxygen species (ROS) and the organism's antioxidant capacity. Redox balance is a crucial component in the development of psoriasis.

Diverse external factors, including UV radiation, smoking, and alcohol consumption, mediate an excessive cellular ROS production that results in damage to DNA, proteins and lipids. Abnormal ROS levels in keratinocytes and immune cells further aggravate inflammation through enhanced cytokine production, such as TNF- α , IL-6, and IL-17. This establishes a feedback loop of persistent inflammation and epidermal destruction. Increased levels of MDA, decreased activity of antioxidant enzymes (SOD, CAT, GPx), and impaired thiol-disulfide homeostasis are markers of oxidative stress in psoriasis. Exogenous antioxidants may neutralise oxidative

damage, suppress inflammation, and mitigate the symptoms. Good sources of antioxidants include vitamins (A, C, E), selenium, zinc, polyphenols, and omega-3 fatty acids. The intake of fresh fruits, vegetables, and functional foods with antioxidants has positive effects on patients by decreasing oxidative stress and the severity of psoriasis.

Oxidant parameters in the skin and serum of patients were ameliorated by antioxidant supplementation, including coenzyme Q10, selenium, and vitamin E. Green tea, pomegranate, and curcumin (from turmeric) have shown notable antioxidative and anti-inflammatory activity in animal and human trials. Agents such as resveratrol, curcumin, and epigallocatechin gallate (EGCG) have been identified as potentially effective in attenuating oxidative stress and inflammation in psoriatic lesions. Molecular hydrogen-enriched water and hydrogen inhalation have successfully neutralized detrimental ROS and counteracted the aggravation of psoriatic symptoms. Some diet-derived products, such as quercetin and vitamin D, may affect gene expression through the modulation of microRNAs relevant for inflammation and oxidative stress. Data indicate that antioxidant-rich diets have indeed the potential to counteract oxidative stress-associated epigenetic alterations and could ameliorate the symptoms of psoriasis (Winiarska-Mieczan et al., 2020).

Excessive mitochondrial ROS (mtROS) production is associated with psoriasis, causing oxidative stress and inflammatory responses. Oxidative stress-related biomarkers, including myeloperoxidase (MPO), paraoxonase (PON), and sirtuins (SIRT6), have major roles in the progression of disease. Natural antioxidants such as quercetin, curcumin, and resveratrol present opportunities for promising supportive therapy in treatment by attenuating oxidative stress and inflammation (Ahmad Jamil & Abdul Karim, 2024).

Nicotinamide mononucleotide (NMN) administration has been shown to enhance NAD⁺ levels, thereby upregulating SIRT1 activity and suppressing inflammation and oxidative stress in a murine model of psoriasis. NMN exerted effectiveness in experimental models by attenuating keratinocyte proliferation, inflammatory reaction, and mitochondrial dysfunction. The therapeutic effects of NMN are associated with enhancing SIRT1, which reduces oxidative stress and recovers mitochondrial function (Zhang et al., 2024).

Excessive salt consumption induces oxidative stress, which subsequently leads to endothelial dysfunction and possibly aggravates psoriasis. Psoriasis is an inflammatory process conceptually dependent on Th17 lymphocytes, and oxidative stress enhances immune misregulation and tissue injury. Antioxidant approaches, along with salt restriction-based diet intervention, may be useful in controlling oxidative stress and further ameliorate the efficacy of treatment for psoriasis (Krajina et al., 2022).

Age-Related Macular Degeneration (AMD)

The principal cause of age-related ocular degeneration is age-related macular degeneration (AMD), which is mainly due to oxidative damage to retinal pigment epithelium (RPE) and photoreceptors. AMD is a multifactorial pathology, shaped by the interplay between genetic predisposition and environmental triggers, where oxidative stress has a key role in pathogenesis. AMD is associated with increased generation of ROS due to mitochondrial dysfunction and age-related impairment of the antioxidant system. Lipids, proteins, and DNA are damaged by oxidation, which alters cellular processes in the retina. The build-up of lipofuscin and drusen is a hallmark of advanced AMD.

There are two types of AMD: dry (nonexudative) and wet (exudative).

- Dry AMD is drusen deposition along with atrophic RPE damage.
- Wet AMD is abnormal choroidal neovascularization with leakage and scarring.

The disease's progression may be slowed by antioxidants such as vitamins C and E, lutein and zinc. Higher levels of oxidative stress biomarkers, including 8-OHdG and malondialdehyde, in patients with AMD support the importance of oxidative stress in the disease. Anti-VEGF agents are used to treat wet AMD, including ranibizumab and aflibercept; there are, however, limitations to these therapies. Potential therapies for dry AMD are limited; pegcetacoplan, a complement inhibitor, is the only approved drug (Kushwah et al., 2023).

Important Antioxidant and Nutritional Components in the Control of AMD

- Carotenoids (lutein and zeaxanthin): these carotenoids absorb harmful blue light and interfere with light-induced ROS production; they are present in green and orange vegetables. The AREDS2 and several other studies have demonstrated their merit in delaying the progression of AMD.

- Resveratrol: found in red grapes and red wine, resveratrol has the ability to activate the SIRT1 and Nrf2 pathways and consequently decreases the levels of ROS and inflammation. There are a few clinical studies with hints of possible positive effects on retinal function.
- Zinc: A selenium ally, Zinc is a trace mineral that also supports antioxidant enzymes, including superoxide dismutase (SOD). Zinc's capacity to slow the progression of AMD has been demonstrated in clinical studies, including AREDS.
- Curcumin: a powerful antioxidant and anti-inflammatory molecule, curcumin scavenges ROS. While the outcomes of preclinical studies are promising, for clinical application, higher bioavailability is required.
- Vitamin E: A fat-soluble antioxidant that inhibits lipid peroxidation. But the evidence on its usefulness in AMD is conflicting.
- Polyphenols (e.g., carnosic acid, berberine): These are chemically active compounds present in herbs or plants; they have antioxidative properties and reduce oxidative stress and inflammation. Preclinical studies show that they may have neuroprotective, antioxidant effects.
- Coenzyme Q10, Alpha-Lipoic Acid: These agents enhance retinal cell survival by promoting mitochondrial function and counteracting ROS production. Natural antioxidant-rich diets, such as the Mediterranean diet, are capable of retarding the development of AMD. There is presently no effective treatment for AMD, particularly the dry type. Additional clinical research is necessary to determine if antioxidants are effective for patients with advanced AMD. Formulations that enable improved bioavailability of antioxidants such as curcumin, and thus can contribute to a better translation of promising preclinical results to clinical applications (Dziedziak et al., 2021, Wong et al., 2022).

Chronic Obstructive Pulmonary Disease (COPD)

Oxidative stress has a key role in persistent inflammatory lung disease, such as chronic obstructive pulmonary disease (COPD). Mitochondrial dysfunction is a key mechanism, and mitochondria-targeted antioxidants (MTAs) represent an attractive therapeutic approach. COPD results from both exogenous ROS (cigarette smoke, etc.) and endogenous ROS (mitochondrial damage, etc.).

Increased oxidative stress contributes to inflammation, apoptosis, and tissue senescence in the lungs. Oxidative stress-related products, like malondialdehyde and 8-isoprostanes, have been found in elevated levels in COPD subjects. Some agents, such as N-acetylcysteine (NAC) and vitamins E and C, have modest clinical benefits, but they do not directly access the main source of ROS — mitochondria. Overconsumption of antioxidant supplements might have harmful effects and disrupt the physiological functions of ROS. MTAs with potential therapeutic effects, namely MitoQ and MitoTEMPO, accumulate in mitochondria and allow targeted reduction of mitochondrial ROS.

Preclinical evidence suggests that MTAs reduce inflammation, preserve mitochondrial function, and enhance lung function in animal models. MitoQ is an over-the-counter product and is under investigation in clinical studies for several of diseases, including COPD. Determining the appropriate dose and standardization of treatment protocols for MTAs is essential. It is now being investigated whether the efficacy of MTAs can also be transferred to other diseases of the lung, including COPD, as well as asthma and viral infections (Fairley et al., 2023).

Oxidative damage induced by cigarette smoking is mainly attributed to ROS, which can damage proteins, lipids, and DNA. It is a major cause of chronic diseases, including COPD, cardiovascular diseases, and lung cancer. ROS induced by cigarette smoke promotes oxidative stress and inflammation, leading to damage of the cellular components and progression of the disease.

Polyphenols, such as those in fruit, vegetables, tea, and olive oil, have strong antioxidant effects. These agents scavenge ROS and attenuate oxidative stress and inflammation. Major polyphenols include catechins in green tea, quercetin in apples, and resveratrol in grapes that reduce the harm induced by cigarette smoke. Polyphenols are effective in preventing or attenuating disorders such as COPD and CVD by influencing the NF- κ B and antioxidant capacity-related pathway.

Although polyphenols may have beneficial effects, they generally have poor bioavailability due to low absorption, rapid metabolism, and lability. Approaches to enhance their bioavailability include encapsulation technologies, such as nanoparticles and liposomes, which protect these molecules and facilitate their absorption.

Studies highlight epicatechin and curcumin, which lower oxidative stress and inflammation in animal studies. The Mediterranean diet, which is abundant in polyphenols (derived, for example, from olive oil), has also been shown to be cardioprotective by improving vascular function and reducing inflammation. The habitual intake of polyphenol-rich foods could be considered a valuable strategy to prevent smoke-related oxidative damage and associated diseases. Further research on the mechanisms of action and the enhancement of bioavailability may strengthen the potential of these compounds as therapeutic agents (Rudrapal et al., 2022).

Atopic Dermatitis (AD)

AD is considered a chronic inflammatory condition resulting caused by the combined action of genetic, immunologic, and environmental factors. ROS-mediated oxidative stress is a key feature of AD, developing when the levels of these species exceed the systemic antioxidant capacity. In AD, oxidative stress aggravates inflammation, resulting in lipid peroxidation, protein oxidation, and DNA mutagenesis, which promote the chronic inflammatory status. Suboptimal levels of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) have been found in patients with AD, indicating a compromised antioxidant defense system. Evidence suggests an association between markers of oxidative stress and disease severity, indicating that oxidative stress may represent a potential target of therapy for the management of AD.

PM10 particle exposure induced the serum levels of IgE, spleen weight, epidermal thickness, and the levels of pro-inflammatory cytokines in AD skin lesions. Treatment with antioxidants prevented these changes, indicating that the antioxidants may be effective in modulating oxidative stress and inflammation. Antioxidants improved keratinocyte dysfunction through inhibition of decreases in loricrin and filaggrin expression. Results: When AD models are treated with antioxidants including dieckol, punicalagin, EGCG, resveratrol, or SHE, the detrimental impact of PM10 is ameliorated, which suggests these agents have the capacity to overcome inflammation and oxidative stress-related skin diseases. The plant extracts inhibited cytokine production and enhanced the skin-barrier function in keratinocytes.

In a human study, the antioxidant-rich formulation significantly reduced pruritus, enhanced lesion severity (SCORAD score), and increased skin hydration and barrier function. Oxidative stress-related molecules such as malondialdehyde and advanced oxidation protein products are related to the severity of disease, so antioxidant-based therapy is considered to be effective for the treatment of AD (Kwack et al., 2022; Zhang et al., 2022; Bertino et al., 2020).

Children with AD have increased levels of lipid peroxide and decreased total antioxidant capacity. Serum enzyme assays showed diminished paraoxonase 1 (PON1) and increased myeloperoxidase (MPO) activity, reflecting oxidative damage and lipoprotein impairment. PON2/3 intracellular activity was markedly reduced in PBMC isolated from patients, and the levels negatively correlated with ROS. A high MPO/PON1 ratio in AD patients indicates a preponderance of pro-oxidative over antioxidant activities. Altered interplay between PON and MPO could theoretically lead to increases in lipid peroxidation and inflammation that aggravate AD symptomatology. "Oxidative stress targeting" mechanisms may provide new therapeutic opportunities in the treatment of AD.

Influence of Melatonin in Atopic Dermatitis

Sleep-related disturbances are common in AD patients and are related to altered night-time melatonin secretion. Reports on melatonin in AD show conflicting results, with decreased levels in some cases and increased levels in more severe cases. Melatonin, a powerful antioxidant hormone, regulates circadian rhythms and inflammatory pathways. It has anti-oxidative properties, enhances skin barrier integrity, and reduces inflammatory mediators like cytokines. Melatonin (3–6 mg/day) increased the quality of sleep and severity of AD (assessed by SCORAD) in studies conducted in children. They also validated that melatonin protected against skin lesions, pruritus, and markers of inflammation, including interleukins. Melatonin enhances the activity of antioxidant enzymes such as SOD and catalase, and it functions as a free radical scavenger. Its immunomodulatory actions include the NF- κ B inhibition, the activation of the Nrf2 antioxidant pathway, and the regulation of T-cell responses. Nevertheless, the results regarding the influence of melatonin on oxidative stress parameters and its relation with the levels of IgE and other immune factors are inconclusive. Further investigations are warranted to elucidate the precise role of melatonin in the treatment of AD, especially in the context of focal and systemic immune modulation (Simonetti et al., 2021; Jaworek et al., 2021).

Antioxidants in sport

Role of ROS in Exercise

Physical activity induces ROS generation that can promote harmful or beneficial effects. At high concentrations, they contribute to muscle damage, fatigue, and inflammation. Nevertheless, ROS may elicit adaptive processes that enhance performance and recovery when they are at low to moderate levels. The competition between ROS production and antioxidant defense is important to determine optimal physiological adaptations.

Training Adaptations and ROS

ROS also participate in critical signalling cascades that improve exercise performance. Specifically, they activate signalling cascades that include PGC1- α and MAPK, which are key factors in muscle regeneration and mitochondrial biogenesis. Endurance athletes tend to have elevated levels of ROS, which aid in adaptations such as increased blood flow and stronger muscles.

Antioxidants and Performance

Antioxidant supplementation (eg, vitamin C, vitamin E, resveratrol) is commonly used by athletes to neutralise the detrimental effects of ROS. However, it can be concluded from this review that an excessive intake of antioxidants might compromise the favorable training adaptations elicited by ROS. For example, large amounts of vitamin C have been found to inhibit mitochondrial biogenesis, whereas smaller doses (mainly those derived from fruits and vegetables) offer health benefits without negatively affecting performance. Some antioxidants, such as polyphenols and spirulina, have the potential to improve endurance and recovery by increasing nitric oxide synthesis and reducing oxidative stress.

Inflammation and Recovery

ROS-mediated inflammation is an important aspect in muscle regeneration and adaptation. Yet, the intake of antioxidants should be appropriately moderated since some evidence suggests that high antioxidant intake may attenuate recovery and performance. For example, some evidence suggests that supplementation with vitamins C and E does not significantly attenuate oxidative stress or inflammation following strenuous exercise.

Gut Microbiota and Antioxidants

The gut microbiota is critical for health and can be modulated by dietary antioxidants such as carotenoids, polyphenols, and vitamins. These micro-nutrients interact with the gut microbiota, enhance beneficial bacteria, and modulate immunity. Animal studies have shown that high levels of such antioxidants improve gut health, which in turn enhances performance in athletes and helps overall wellness.

Practical Applications

Athletes would do well to concentrate on fostering a balanced antioxidant status through the daily consumption of natural sources rather than a high dose of supplemental antioxidants, since natural foods provide antioxidants in proper proportions, and, as a consequence, the potential for adverse effects on performance is minimized. The Importance of Personal Differences. Different Individuals (e.g., different exercise intensity, type, and environmental conditions and the production of ROS and lactic acid may also be influenced by hypoxia (e.g., hypoxic gas breathing, high-altitude training). Huang et al. Vitamin D is a fat-soluble a vitamin that mediates antioxidant defense and preserves the cell membrane from oxidative injury. It has demonstrated performance benefits at altitude and has shown mixed results at sea level. Acute vitamin E supplementation has been reported to be potentially beneficial for performance enhancement, whereas chronic consumption seems to deteriorate exercise performance, in particular in well-trained athletes. The authors advise against chronic use.

Quercetin is a flavonoid that promotes mitochondrial biogenesis and attenuates exercise perception. Although a small performance-enhancing effect has been described in the literature for activities lasting more than 100 min, these findings are inconsistent. Some positive effects have been demonstrated in animal models, but more information is required in athletes regarding optimum dosage and timing.

Red wine polyphenol resveratrol induces mitochondrial biogenesis and exerts anti-aging effects in rodents. However, that study was in an inactive population, and results from human studies are lacking. Further research is necessary to establish its efficacy in athletes.

Due to its high content of nitrate and polyphenols, beetroot juice has been considered responsible for observed improvements in performance. Meta-analyses indicate nitrate may improve performance in non-athletes, but its benefits in athletes are less clear and possibly detrimental. The authors do not advocate the use of beetroot juice or nitrate supplements among top athletes because of concerns with blood flow shunting.

Other Food-Derived Polyphenols

Vasodilation and blood flow are known to be increased by epicatechin, a type of polyphenol found in cocoa. Some of the data show large improvements in endurance performance, whereas other data show impairments. The diversity of polyphenols and the different outcomes of studies make it hard to derive clear conclusions, but some polyphenols appear to be promising and worthy of further research.

Spirulina has a favourable antioxidant profile and seems to potentially improve endurance performance in non-trained subjects. Nonetheless, data from human trials are scarce, and prospective clinical trials are imperative to validate these therapeutic outcomes efficacy in athletes.

N-Acetylcysteine (NAC) is an antioxidant that decreases muscle fatigue and improves endurance by elevating glutathione levels. Although positive effects, including improved cycling endurance and reduced fatigue, have been reported for intravenous NAC, it is not clear whether the same holds for oral doses.

Chronic vs. Acute Antioxidant Supplementation

It is likely that chronic consumption of most antioxidants will negatively affect performance, as antioxidants can blunt the favourable adaptive responses to exercise. However, acute consumption of some antioxidants (e.g., vitamin C and NAC) around the time of competition may provide performance benefits without negatively interfering with training adaptations (Clemente-Suárez et al., 2023; Braakhuis & Hopkins, 2015).

Summary

Antioxidants are crucial for reducing oxidative stress, which is a common pathway of development of all abovementioned chronic diseases (neurodegenerative, cardiovascular, metabolic, dermatological, and pulmonary diseases). Their main actions are to counteract reactive oxygen species (ROS) and reactive nitrogen species (RNS), exert anti-inflammatory effects, and prevent cell damage in proteins, lipids, and DNA. These actions may slow down the progression of the disease, improve the function of the affected tissue, and relieve symptoms.

Antioxidant treatment has shown promise to decrease oxidative stress across a broad spectrum of diseases, such as neurodegenerative, cardiovascular, metabolic, and inflammatory diseases. Their mechanisms of action also involve the reduction of toxic protein accumulation, enhancement of vascular function, and protection against demyelination. In neurodegenerative diseases, antioxidants can help with neuronal protection and inhibit degeneration. In metabolic diseases, including diabetes, they have demonstrated potential to influence oxidative stress and inflammation, and to avoid or postpone the development of complications. For inflammatory diseases of the skin and the respiratory system, antioxidants may boost the natural protective barriers of the body.

The translation of antioxidants to the clinic is challenged, although preclinical data are promising. The development of these products from ancient use to modern day pharmaceuticals means that their efficacy depends on: what type of disease (hopefully more than one) you have, your own individual features like genetics, diet, and lifestyle, and the stage of disease progression. The reports from literature suggest that further investigations are needed to predict patient-tailored therapeutic regimens, to combine antioxidants with other therapeutic modalities, and to assess long-term outcomes. An integrative therapeutic strategy of antioxidant supplementation, lifestyle changes, appropriate diets, and individual medications may be useful for improving quality of life. Progress in proteomic and nutrigenomic technologies allows a profound insight into the mechanisms of antioxidants and the development of new, better strategies for their use. In the long term, antioxidant treatments could be considered as basic elements in the integrated management of chronic diseases for the advantage of patients and of healthcare systems.

While antioxidants are crucial in reducing oxidative stress and inflammation in athletes, a cautious approach is warranted. Reactive oxygen species are needed for training adaptations and an increase in performance despite being perceived as bad or harmful. Over-supplementation with antioxidants can impair these adaptations, so athletes should consume antioxidants from natural sources and strive to achieve a certain equilibrium in ROS generation and the antioxidant system for optimal post-exercise recovery and performance.

5. CONCLUSION

Antioxidants are important elements in the treatment of chronic diseases like diabetes, hypertension, atherosclerosis, age-related macular degeneration (AMD), Parkinson's, Alzheimer's, chronic obstructive pulmonary disease (COPD), and psoriasis. They counteract

oxidative stress and minimize damage to cells and tissues. While preclinical studies have been promising, their clinical effectiveness is type- and patient-specific and dependent on disease stage. In this context, would such a 'multiple hits' approach, antioxidant supplementation coupled with lifestyle, diet, and patient tailoring, significantly improve the QALY (quality-adjusted life year) of patients.

Future perspectives

Advances in proteomics and nutrigenomics may facilitate the development of better therapeutic approaches. Antioxidants contribute greatly to sport, health, and chronic disease prevention, and thus they are recommended as a beneficial dietary supplementation, and their inclusion in therapeutic advice from clinicians is strongly suggested.

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Authors' Contributions

Conceptualization: Mateusz Łyko, Paweł Siudziński and Jakub Kurasz;

Methodology: Karolina Mularczyk, Katarzyna Chrobok and Alicja Skoczylas;

Software: Piotr Dudziak, Karolina Mularczyk and Filip Kasperczak; Check: Maria Golińska, Piotr Dudziak and Filip Kasperczak;

Formal analysis: Mateusz Łyko, Wiktoria Podlasiewicz and Anna Nowak;

Investigation: Wojtek Maj and Paweł Siudziński; Resources: Katarzyna Chrobok, Alicja Skoczylas and Filip Kasperczak;

Data curation: Anna Nowak, Piotr Dudziak and Wojtek Maj;

Writing-rough preparation: Paweł Siudziński, Alicja Skoczylas and Wiktoria Tomaszewska; Writing-review and editing: Mateusz Łyko, Katarzyna Chrobok, Jakub Kurasz and Karolina Mularczyk;

Visualization: Wiktoria Tomaszewska, Maria Golińska and Jakub Kurasz;

Supervision: Mateusz Łyko, Karolina Mularczyk, Paweł Siudziński and Wojtek Maj;

Project administration: Mateusz Łyko.

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Data and materials availability

All data associated with this work are present in the paper.

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