

PAVOL JOZEF ŠAFÁRIK UNIVERSITY IN KOŠICE

Faculty of Medicine



OXIDATIVE STRESS AND ANTIOXIDANTS IN PREVENTIVE MEDICINE

An Evidence-Based Approach to Lifestyle and Health Promotion

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OXIDATIVE STRESS AND ANTIOXIDANTS IN PREVENTIVE MEDICINE
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University Textbook

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List of Abbreviations

Abbreviation	Meaning
8-oxodG	8-oxo-7,8-dihydro-2'-deoxyguanosine
ABTS	2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
AMD	age-related macular degeneration
AMPK	AMP-activated protein kinase
AREDS / AREDS2	Age-Related Eye Disease Study / Age-Related Eye Disease Study 2
ATP	adenosine triphosphate
BMI	body mass index
CBT-I	cognitive behavioral therapy for insomnia
CUPRAC	cupric reducing antioxidant capacity
CYP2E1	cytochrome P450 2E1
DNA	deoxyribonucleic acid
DPPH	2,2-diphenyl-1-picrylhydrazyl
EFSA	European Food Safety Authority
FRAP	ferric reducing antioxidant power
GPx	glutathione peroxidase
GPx4	glutathione peroxidase 4
GSH	reduced glutathione
GSSG	glutathione disulfide
HbA1c	glycated hemoglobin
HDL	high-density lipoprotein
ILO	International Labour Organization
LDL	low-density lipoprotein
NAD ⁺ / NADH	oxidized / reduced nicotinamide adenine dinucleotide
NADP ⁺ / NADPH	oxidized / reduced nicotinamide adenine dinucleotide phosphate
NCD	non-communicable disease
NF-κB	nuclear factor kappa B
NIOSH	National Institute for Occupational Safety and Health
NO	nitric oxide
Nrf2	nuclear factor erythroid 2-related factor 2

ORAC	oxygen radical absorbance capacity
PCOS	polycystic ovary syndrome
PMOS	polyendocrine metabolic ovarian syndrome
RAGE	receptor for advanced glycation end products
RNA	ribonucleic acid
RNS	reactive nitrogen species
ROS	reactive oxygen species
SOD	superoxide dismutase
TBARS	thiobarbituric acid-reactive substances
TRAP	total radical-trapping antioxidant parameter
UV	ultraviolet
WHO	World Health Organization

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Preface

Oxidative stress and antioxidant defense are often presented as a simple opposition between harmful oxidants and beneficial antioxidants. Contemporary redox biology describes a more complex and context-dependent system in which reactive oxygen and nitrogen species participate in normal signaling, immune defense, vascular regulation, and adaptation, while excessive or prolonged reactive-species production may contribute to molecular and cellular injury.

This textbook was prepared primarily for students of medicine, public health, nutrition, and related health sciences. It may also serve as a practical reference for healthcare professionals interested in prevention, lifestyle medicine, occupational health, and evidence-based interpretation of antioxidant research.

The chapters connect fundamental redox biochemistry with dietary patterns, physical activity, sleep, smoking, alcohol consumption, environmental and occupational exposures, chronic diseases, supplementation, and public health. Particular emphasis is placed on distinguishing mechanistic plausibility from demonstrated clinical benefit and on avoiding the assumption that antioxidant activity measured in vitro automatically translates into disease prevention in humans.

The authors hope that the textbook will help readers understand oxidative stress as one component of multifactorial health and disease processes and will support balanced, clinically meaningful, and preventive approaches to redox-related questions.

The Authors

Chapter 1. Introduction

1.1 Chronic Diseases as a Global Health Problem

Chronic non-communicable diseases (NCDs) are the leading cause of morbidity and mortality worldwide. Cardiovascular diseases, cancer, chronic respiratory diseases, and diabetes account for most NCD-related deaths and contribute substantially to disability, reduced quality of life, healthcare expenditure, and socioeconomic burden.

The development of chronic diseases reflects complex interactions among genetic predisposition, aging, environmental conditions, metabolic disturbances, and health-related behaviors. Urbanization, technological development, changes in food systems, sedentary lifestyles, tobacco use, alcohol consumption, insufficient sleep, chronic psychosocial stress, and exposure to environmental pollutants have all influenced contemporary patterns of disease.

Cardiovascular diseases remain a major cause of premature mortality and are strongly associated with hypertension, dyslipidemia, diabetes mellitus, smoking, obesity, physical inactivity, and unhealthy dietary patterns. The increasing prevalence of obesity and metabolic dysfunction in both adults and children has further contributed to the burden of type 2 diabetes, cardiovascular disease, liver disease, musculoskeletal disorders, and several cancers.

Cancer risk is influenced by both nonmodifiable and modifiable factors. Genetic susceptibility and aging contribute to carcinogenesis, whereas tobacco smoke, alcohol consumption, obesity, chronic inflammation, ultraviolet radiation, selected infections, occupational exposures, air pollution, and dietary patterns may further modify risk.

Sleep, mental health, and psychosocial stress should also be considered within the broader framework of chronic disease prevention. Depression, anxiety, sleep disorders, chronic fatigue, and prolonged psychosocial stress may influence physical health directly through neuroendocrine, immune, inflammatory, and metabolic mechanisms and indirectly through changes in diet, physical activity, smoking, alcohol use, and adherence to medical care.

Many of these risk factors are modifiable to varying degrees. Prevention therefore plays a central role in reducing the burden of chronic disease. Effective preventive strategies include avoiding tobacco, engaging in regular physical activity, following a healthy dietary pattern, obtaining adequate sleep, managing stress, reducing harmful alcohol consumption, maintaining metabolic health, and minimizing exposure to environmental and occupational hazards.

Oxidative stress is one of the biological mechanisms through which these factors may influence disease development. It may contribute to altered cellular signaling, inflammation, endothelial dysfunction, mitochondrial impairment, and molecular damage. However, it should be understood as one component of multifactorial disease processes rather than as a universal or independent cause of chronic illness.

1.2 Lifestyle and Modern Health Risks

Lifestyle is an important determinant of health, but lifestyle-related risk factors rarely occur in isolation. Smoking, poor diet, physical inactivity, harmful alcohol consumption, insufficient sleep, and chronic stress often coexist and may reinforce one another. Their cumulative effects may contribute to metabolic dysfunction, chronic inflammation, impaired vascular regulation, and disturbed redox homeostasis.

Modern living conditions have substantially changed patterns of daily activity. Occupational and recreational screen time, passive transport, prolonged sitting, irregular schedules, and reduced opportunities for spontaneous movement have contributed to lower daily energy expenditure. At the same time, highly processed and energy-dense foods have become widely available, while time pressure and socioeconomic conditions may limit access to balanced meals and regular physical activity.

Tobacco smoking remains one of the leading preventable causes of disease and premature mortality. Tobacco smoke contains oxidants, carcinogens, particulate matter, heavy metals, and pro-inflammatory substances that affect the respiratory tract, vascular system, immune function, and DNA integrity. Electronic cigarettes and heated tobacco products differ from combustible cigarettes in their emissions, but they are not harmless and may still expose users to nicotine and potentially toxic compounds.

Alcohol consumption is associated with a broad range of health risks, including liver disease, pancreatitis, hypertension, arrhythmias, neurological and mental health disorders, injuries, addiction, and several cancers. Earlier interpretations of possible cardiovascular benefits from moderate drinking have become increasingly cautious. Alcoholic beverages should not be recommended as sources of antioxidants or for disease prevention.

Dietary patterns influence body weight, glucose metabolism, lipid profile, blood pressure, inflammation, gut microbiota, and micronutrient status. Diets dominated by ultra-processed foods, refined carbohydrates, excessive sodium, added sugars, and poor-quality fats may increase cardiometabolic risk. In contrast, dietary patterns rich in vegetables, fruits, legumes, whole grains, nuts, seeds, and other minimally processed foods are generally associated with more favorable health outcomes.

Physical activity supports cardiovascular fitness, insulin sensitivity, muscle and bone health, psychological well-being, and functional capacity. Importantly, exercise produces transient increases in reactive species that participate in physiological adaptation. Regular activity may therefore improve redox regulation, whereas prolonged physical inactivity is associated with metabolic dysfunction and chronic disease risk.

Sleep and psychosocial stress are also important. Insufficient or irregular sleep may affect glucose metabolism, appetite regulation, blood pressure, cognitive performance, emotional regulation, and inflammatory activity. Chronic stress may influence endocrine and immune function while also promoting unhealthy coping behaviors. Effective prevention must therefore address recovery and mental well-being together with diet and physical activity.

Lifestyle-based prevention should not be reduced to personal responsibility. Work schedules, income, education, food availability, housing, environmental quality, neighborhood safety, occupational exposures, and access to healthcare all influence the

ability to adopt health-promoting behaviors. Individual counseling should therefore be accompanied by supportive clinical, occupational, environmental, and public health measures.

Figure 1 Lifestyle factors and their impact on oxidative stress balance

Lifestyle factor	Effect on oxidative stress	Mechanisms involved	Potential impact on health
 Smoking	↑ Increase	ROS/RNS in tobacco smoke, inflammation, depletion of antioxidants	Cardiovascular disease, COPD, cancer, diabetes
 Alcohol	↑ Increase	Induction of CYP2E1, ROS production, lipid peroxidation	Liver disease, hypertension, cancer, pancreatitis
 Diet quality (healthy diet)	↓ Decrease	Antioxidants, vitamins, minerals, polyphenols, fiber	Lower risk of CVD, cancer, type 2 diabetes
 Physical activity	↓ Decrease (mod. intensity)	Upregulation of endogenous antioxidant defenses, improved metabolism	Better cardiovascular health, insulin sensitivity, weight control
 Sleep quality (adequate sleep)	↓ Decrease	Hormonal balance, reduced inflammation and oxidative burden	Better mental and physical health, lower risk of diseases
 Chronic stress	↑ Increase	Cortisol elevation, inflammation, mitochondrial dysfunction	Hypertension, depression, immunity impairment



Healthy lifestyle choices support redox balance, whereas harmful behaviors increase oxidative stress and the risk of chronic diseases.

1.3 Oxidative Stress and Human Health

Oxidative stress refers to a disturbance in redox homeostasis in which the generation of reactive species exceeds the capacity of regulatory, antioxidant, and repair systems to limit their biological effects. This disturbance may lead to altered cellular signaling, impaired adaptation, and oxidative modification of biological molecules.

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are continuously generated during normal metabolism. Important examples include superoxide anion, hydrogen peroxide, hydroxyl radical, nitric oxide, and peroxynitrite. Not all reactive species are free radicals; hydrogen peroxide, for example, has no unpaired electron but remains biologically active and can participate in redox signaling and oxidative reactions.

Endogenous sources of reactive species include mitochondrial respiration, NADPH oxidases, peroxisomes, the endoplasmic reticulum, inflammatory cells, cytochrome P450 enzymes, and ischemia-reperfusion processes. Exogenous contributors include tobacco smoke, air pollution, ultraviolet and ionizing radiation, heavy metals, pesticides, industrial chemicals, excessive alcohol consumption, and selected occupational exposures.

Reactive species are not inherently detrimental. Under tightly regulated conditions, they perform essential physiological roles in immune defense, vascular regulation, gene expression, cell proliferation, apoptosis, oxygen sensing, and adaptation to exercise. Their effects depend on concentration, location, duration of exposure, cellular context, and the capacity of antioxidant and repair systems.

Adverse biological effects may occur when reactive species are generated in excess, persist for prolonged periods, or arise in cellular compartments with insufficient antioxidant and repair capacity. Oxidative modification may then affect lipids, proteins, carbohydrates, and nucleic acids.

Lipid peroxidation can alter membrane structure, permeability, receptor function, and intracellular signaling. Oxidative protein modifications may impair enzymes, transport proteins, receptors, and structural components. DNA oxidation may contribute to mutations, cellular senescence, apoptosis, or genomic instability when damage exceeds repair capacity.

Oxidative stress and inflammation are closely interconnected. Activated immune cells generate reactive species as part of host defense, while excessive reactive species may activate inflammatory signaling pathways. Persistent oxidative and inflammatory processes may therefore form self-reinforcing cycles in chronic disease.

Oxidative stress has been investigated in cardiovascular diseases, diabetes mellitus, obesity, cancer, neurodegenerative disorders, respiratory diseases, reproductive conditions, and aging. Nevertheless, its presence does not establish that it is the primary cause of a disease or that antioxidant supplementation will improve clinical outcomes.

Modern redox biology therefore emphasizes regulation rather than complete suppression of reactive species. Health depends on maintaining an appropriate balance between physiological redox signaling, antioxidant defense, repair mechanisms, and adaptation to environmental and metabolic challenges.

1.4 Role of Nutrition and Antioxidants

Nutrition supports redox homeostasis by providing energy, amino acids, vitamins, minerals, essential fatty acids, fiber, and bioactive compounds required for cellular function and antioxidant defense. Dietary antioxidants form only one part of this broader nutritional network.

Antioxidants may delay, prevent, or limit oxidative modification of biological molecules. Their mechanisms include direct interaction with selected reactive species, interruption of lipid peroxidation chain reactions, regeneration of other antioxidants, binding of redox-active metals, and modulation of antioxidant or detoxification pathways.

The human organism possesses endogenous antioxidant systems, including superoxide dismutases, catalase, glutathione peroxidases, peroxiredoxins, thioredoxin-related enzymes, glutathione, uric acid, bilirubin, and metal-binding proteins. Dietary nutrients support these systems rather than functioning independently from them.

Vitamin C is a water-soluble antioxidant and an essential cofactor in collagen synthesis and several enzymatic reactions. Vitamin E is a lipid-soluble antioxidant that helps protect cellular membranes and lipoproteins from lipid peroxidation. Carotenoids include compounds with provitamin A activity as well as non-provitamin A carotenoids such as lycopene, lutein, and zeaxanthin.

Trace elements contribute mainly through their roles in enzymes and proteins. Selenium is required for several glutathione peroxidases and thioredoxin reductases. Copper and

zinc are components of cytosolic and extracellular superoxide dismutases, while manganese is required for mitochondrial superoxide dismutase. Both deficiency and excess of these elements may be harmful.

Polyphenols and other plant-derived compounds are present in fruits, vegetables, legumes, whole grains, tea, coffee, cocoa, herbs, and spices. Their biological effects extend beyond direct radical scavenging and may include modulation of cellular signaling, inflammation, endothelial function, enzyme activity, and gut microbiota.

The biological activity of dietary antioxidants is influenced by the food matrix, cooking and processing, digestion, absorption, metabolism, tissue distribution, and interactions with other nutrients. Many polyphenols undergo extensive transformation in the intestine, liver, and gut microbiota, meaning that the compounds circulating in the body may differ from those originally present in food.

For this reason, the health effects of antioxidant-rich diets cannot be attributed to one isolated substance. Whole foods provide combinations of fiber, micronutrients, unsaturated fats, and phytochemicals that may act through multiple complementary mechanisms.

In healthy individuals, obtaining antioxidants through a varied dietary pattern is generally preferable to routine high-dose supplementation. Supplements may be appropriate in deficiency states, malabsorption, restricted diets, increased physiological requirements, or specific clinical conditions, but their use should be based on indication, dose, safety, and quality of evidence.

1.5 Evidence-Based Perspective on Antioxidants and Prevention

Interest in antioxidants initially developed from experimental observations showing that reactive species can damage cellular structures and contribute to disease-related processes. Observational studies subsequently reported that people consuming diets rich in vegetables, fruits, and other plant foods often experience more favorable health outcomes.

These associations support healthy dietary patterns, but they do not prove that isolated antioxidants are responsible for the observed benefits. People who consume more plant foods may also be more physically active, smoke less, have a healthier body weight, or differ in education, income, and access to healthcare. Such factors may influence observational findings.

Randomized controlled trials of antioxidant supplements have produced inconsistent results and have often failed to demonstrate clinical benefit.

Supplementation with vitamin C, vitamin E, beta-carotene, selenium, or combinations of antioxidants has not consistently reduced cardiovascular disease, cancer, or overall mortality in generally well-nourished populations. In selected groups, high-dose supplementation has been associated with adverse outcomes.

The increased lung cancer risk observed with high-dose beta-carotene supplementation in smokers is an important example. It demonstrates that the effects of antioxidants depend on dose, formulation, baseline status, tissue environment, and population

characteristics. A compound that behaves as an antioxidant in one experimental system may have different effects in another biological context.

Laboratory antioxidant activity also requires cautious interpretation. Assays such as DPPH, ABTS, FRAP, and ORAC, as well as measures of total antioxidant capacity, assess selected chemical properties under defined experimental conditions. They are useful for analytical research but do not establish that a food or supplement prevents disease in humans.

Similarly, changes in individual oxidative stress biomarkers should not automatically be interpreted as clinical benefit. Many biomarkers lack disease specificity and may be influenced by inflammation, diet, medication use, sample handling, laboratory method, and tissue distribution. Clinically meaningful outcomes remain more important than isolated changes in laboratory antioxidant capacity.

An evidence-based approach therefore distinguishes among:

- antioxidant activity demonstrated in a chemical model;
- biological effects observed in cells or animals;
- changes in human biomarkers;
- improvement in clinically relevant outcomes;
- reduction in disease incidence, complications, or mortality.

Each level provides different information, and findings from one level should not be assumed to apply automatically to another.

The strongest preventive evidence supports comprehensive risk reduction: tobacco avoidance, healthy dietary patterns, physical activity, adequate sleep, stress management, metabolic risk management, alcohol reduction, and environmental and occupational protection. Antioxidant-rich foods may contribute to this approach, whereas supplementation should be individualized and used for a clear reason.

1.6 Aim and Structure of This Textbook

The aim of this textbook is to provide an interdisciplinary and evidence-based overview of oxidative stress, antioxidant defense, lifestyle factors, and chronic disease prevention. It integrates fundamental redox biology with nutrition science, preventive medicine, lifestyle medicine, occupational health, and public health.

Throughout the textbook, emphasis is placed on critical interpretation of evidence. Oxidative stress is presented neither as a universal explanation for disease nor as a justification for indiscriminate supplementation. Instead, the central concept is maintenance of redox homeostasis through physiological adaptation, balanced nutrition, reduction of harmful exposures, and evidence-based preventive care.

Selected chapters include practical boxes, evidence-based notes, lifestyle tips, and clinical cautions. These elements are intended to connect biological mechanisms with realistic applications for students, healthcare professionals, and public health practitioners.

Chapter 2. Free Radicals and Reactive Species

2.1 Definition and Terminology

Free radicals are atoms, molecules, or ions containing one or more unpaired electrons. This electronic structure often makes them reactive, although their stability and biological behavior vary considerably. Some radicals react almost immediately near their site of formation, whereas others persist long enough to participate in cellular signaling or propagate chain reactions.

The term **reactive species** is broader than the term free radical. It includes both radical and non-radical molecules capable of participating in oxidation-reduction reactions or modifying biological targets. Reactive oxygen species (ROS) include oxygen-derived radicals and non-radical oxidants, whereas reactive nitrogen species (RNS) originate mainly from nitric oxide and related nitrogen compounds. Reactive sulfur species may also participate in cellular redox regulation, particularly through thiol- and persulfide-related pathways.

Oxidation refers to the loss of electrons, while reduction refers to their gain. These processes always occur together. Redox reactions are essential for energy production, metabolism, detoxification, cellular communication, and immune defense. Reactive species are therefore normal components of aerobic life rather than exclusively toxic metabolic by-products.

Their biological effects depend on several factors:

- chemical identity and reactivity;
- concentration and rate of formation;
- cellular and subcellular location;
- duration of exposure;
- availability of molecular targets;
- activity of antioxidant, repair, and adaptive systems.

The presence of reactive species alone does not indicate oxidative damage. Pathological consequences arise mainly when their production becomes excessive, prolonged, poorly localized, or insufficiently regulated.

2.2 Reactive Oxygen Species

Reactive oxygen species comprise several chemically distinct oxygen-containing molecules. The most important in human biology include superoxide anion, hydrogen peroxide, hydroxyl radical, singlet oxygen, and lipid-derived peroxy and alkoxyl radicals.

Superoxide Anion

Superoxide anion ($\text{O}_2^{\bullet-}$) is formed when molecular oxygen accepts one electron. It is generated during mitochondrial electron transport, by NADPH oxidases, and through several enzymatic reactions.

Superoxide has limited reactivity with many biological molecules but is important because it serves as a precursor of other reactive species. It can be converted into

hydrogen peroxide by superoxide dismutases. It can also react rapidly with nitric oxide, reducing nitric oxide bioavailability and producing peroxynitrite.

Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is not a free radical because it contains no unpaired electron. It is nevertheless an important reactive oxygen species.

Compared with many radicals, hydrogen peroxide is relatively stable and can move between cellular compartments, partly through membrane channels. At controlled concentrations, it acts as a signaling molecule by reversibly modifying redox-sensitive proteins. It participates in immune responses, growth-factor signaling, metabolic regulation, and cellular adaptation.

Excessive accumulation of hydrogen peroxide may become harmful, especially in the presence of poorly controlled iron or copper ions. Under such conditions, it may contribute to the formation of highly reactive hydroxyl radicals. Catalase, glutathione peroxidases, and peroxiredoxins are among the major systems that regulate hydrogen peroxide concentrations.

Hydroxyl Radical

The hydroxyl radical ($\bullet\text{OH}$) is one of the most reactive species in biological systems. It can be generated through metal-catalyzed reactions involving hydrogen peroxide.

Because of its extremely short lifetime, the hydroxyl radical reacts close to its site of formation. It may attack lipids, proteins, carbohydrates, and nucleic acids at diffusion-limited rates. Unlike hydrogen peroxide or superoxide, it is not removed by a dedicated antioxidant enzyme. Protection therefore depends largely on preventing its formation by controlling hydrogen peroxide and redox-active metals.

Singlet Oxygen

Singlet oxygen ($^1\text{O}_2$) is an electronically excited, non-radical form of oxygen. It can be generated during photochemical reactions and is particularly relevant in tissues exposed to light, including the skin and eyes.

Singlet oxygen may oxidize unsaturated lipids, amino acid residues, and nucleic acid bases. Carotenoids can physically quench singlet oxygen, although their biological effectiveness depends on concentration, location, oxygen tension, and surrounding molecules.

Lipid-Derived Radicals

Peroxyl ($\text{ROO}\bullet$) and alkoxyl ($\text{RO}\bullet$) radicals are commonly generated during lipid oxidation. They may propagate chain reactions within biological membranes and lipoproteins. Their formation, consequences, and secondary products are discussed in Chapter 3.

Reactive oxygen species differ substantially in mobility, selectivity, and lifetime. It is therefore inaccurate to treat “ROS” as one uniform biological entity.

2.3 Reactive Nitrogen Species

Reactive nitrogen species include nitric oxide, nitrogen dioxide, peroxynitrite, and related nitrogen-containing oxidants.

Nitric Oxide

Nitric oxide (NO•) is a gaseous free radical synthesized from L-arginine by nitric oxide synthase enzymes. Three major isoforms are commonly recognized:

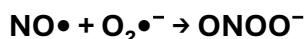
- endothelial nitric oxide synthase;
- neuronal nitric oxide synthase;
- inducible nitric oxide synthase.

At physiological concentrations, nitric oxide performs essential regulatory functions. In the cardiovascular system, it promotes vasodilation, limits platelet activation, reduces leukocyte adhesion, and supports endothelial homeostasis. In the nervous system, it participates in neurotransmission. Immune cells may produce larger amounts of nitric oxide as part of antimicrobial defense.

The effects of nitric oxide depend strongly on concentration, location, and the availability of other reactive species. Reduced nitric oxide bioavailability contributes to endothelial dysfunction, whereas excessive or prolonged production may promote nitrosative stress.

Peroxynitrite

Peroxynitrite (ONOO⁻) is formed through the rapid reaction between nitric oxide and superoxide:



Peroxynitrite is a strong oxidizing and nitrating agent. It may modify proteins, lipids, mitochondrial components, and nucleic acids. Protein tyrosine nitration, lipid oxidation, mitochondrial dysfunction, and DNA injury are among its possible consequences.

The formation of peroxynitrite also reduces nitric oxide availability. This is particularly relevant in vascular disease because nitric oxide that would normally support vasodilation is redirected toward production of a potentially damaging oxidant.

Nitrosative Stress

Nitrosative stress refers to disruption of cellular function caused by excessive or dysregulated reactive nitrogen species. Oxidative and nitrosative stress frequently coexist because ROS and RNS interact chemically and influence many of the same signaling and inflammatory pathways.

Nitric oxide should not itself be classified as simply beneficial or harmful. Its biological role depends on the amount produced, the producing enzyme, the tissue involved, and the surrounding redox environment.

2.4 Endogenous Sources of Reactive Species

Reactive species are continuously generated within the human organism. Their production may be intentional and regulated, as in immune defense and signaling, or may occur as a consequence of metabolic reactions.

Mitochondria

Mitochondria are an important intracellular source of reactive oxygen species. During oxidative phosphorylation, electrons are transferred through the respiratory chain to reduce oxygen and support ATP production. A small fraction may react prematurely with oxygen, generating superoxide.

Mitochondrial ROS production varies with metabolic state, membrane potential, oxygen availability, tissue activity, and mitochondrial function. Mitochondria also contain antioxidant and repair systems that regulate reactive species and limit damage.

NADPH Oxidases

NADPH oxidases are enzyme complexes whose primary function is the controlled production of reactive oxygen species. They are present in immune cells, vascular cells, epithelial tissues, and many other cell types.

In phagocytes, NADPH oxidase generates superoxide during the respiratory burst, supporting destruction of microorganisms. In non-immune cells, NADPH oxidases participate in signaling, vascular regulation, growth, and adaptation. Excessive or prolonged activation may contribute to inflammation and tissue injury.

Peroxisomes and the Endoplasmic Reticulum

Peroxisomes generate hydrogen peroxide during fatty acid oxidation and other metabolic reactions. They also contain catalase, which helps control peroxide accumulation.

The endoplasmic reticulum may generate reactive species during oxidative protein folding and xenobiotic metabolism. Disturbances in protein folding can produce endoplasmic reticulum stress, which is closely connected with inflammation, mitochondrial dysfunction, and altered redox balance.

Enzymatic Sources

Other endogenous sources include:

- xanthine oxidase;
- cytochrome P450 enzymes;
- cyclooxygenases and lipoxygenases;
- monoamine oxidases;
- nitric oxide synthases;
- inflammatory and immune-cell enzymes.

Under some conditions, nitric oxide synthase may become functionally uncoupled and generate superoxide rather than nitric oxide, thereby contributing to endothelial dysfunction.

Ischemia and Reperfusion

When tissue blood flow is reduced, cellular metabolism becomes disturbed. Restoration of oxygen supply may produce a rapid increase in reactive species. This ischemia-reperfusion process is relevant to myocardial infarction, stroke, transplantation, and selected surgical procedures.

Endogenous production of reactive species is therefore not inherently abnormal. The critical issue is whether generation remains appropriately regulated and matched by antioxidant, repair, and adaptive capacity.

2.5 Exogenous Sources of Reactive Species

External exposures may increase oxidative burden by introducing oxidizing compounds, stimulating endogenous reactive-species formation, promoting inflammation, impairing mitochondria, or weakening antioxidant defenses.

Tobacco smoke is a major source of oxidants, particles, carcinogens, metals, and inflammatory stimuli. Its effects extend beyond the respiratory tract and contribute to vascular injury, DNA damage, and systemic inflammation.

Air pollution contains particulate matter, ozone, nitrogen oxides, metals, and organic compounds. These pollutants may activate airway epithelial cells and immune cells, induce mitochondrial stress, and contribute to systemic inflammatory and vascular responses.

Ultraviolet radiation can generate reactive species in the skin and eyes and may also damage DNA directly. Ionizing radiation produces molecular injury through direct ionization and through reactive products formed during radiolysis of water.

Heavy metals and metalloids, including cadmium, lead, mercury, and arsenic, may impair antioxidant enzymes, bind protein thiol groups, damage mitochondria, or interfere with DNA repair. Iron and copper are essential nutrients but may promote highly reactive radical formation when their cellular regulation is disturbed.

Alcohol metabolism generates acetaldehyde, alters the cellular NADH/NAD⁺ balance, induces CYP2E1, and promotes mitochondrial and inflammatory stress. Pesticides, solvents, combustion products, and selected industrial chemicals may also influence redox homeostasis.

Exogenous exposure does not produce identical effects in all individuals. Biological impact depends on:

- dose and duration;
- route of exposure;
- simultaneous exposure to other agents;
- age and genetic susceptibility;
- nutritional and metabolic status;
- pregnancy or chronic disease;
- efficiency of detoxification and repair systems.

Environmental or occupational oxidative stress should primarily be addressed by reducing exposure. Dietary antioxidants or supplements cannot substitute for clean air, safe working conditions, or appropriate protective measures.

2.6 Physiological Functions of Reactive Species

Reactive oxygen and nitrogen species are required for normal physiology. At low and spatially controlled concentrations, they act as signaling molecules rather than indiscriminate damaging agents.

Hydrogen peroxide can reversibly oxidize selected cysteine residues in proteins, thereby modifying the activity of enzymes, phosphatases, kinases, receptors, and transcription factors. These temporary modifications regulate cell growth, metabolism, adaptation, and stress responses.

Reactive species are also essential for immune defense. Phagocytic cells generate ROS and RNS to damage bacteria, fungi, and other pathogens. Complete suppression of this response would impair host protection.

Nitric oxide regulates vascular tone, tissue perfusion, platelet activity, and endothelial function. In the nervous system, it contributes to neuronal communication and synaptic regulation.

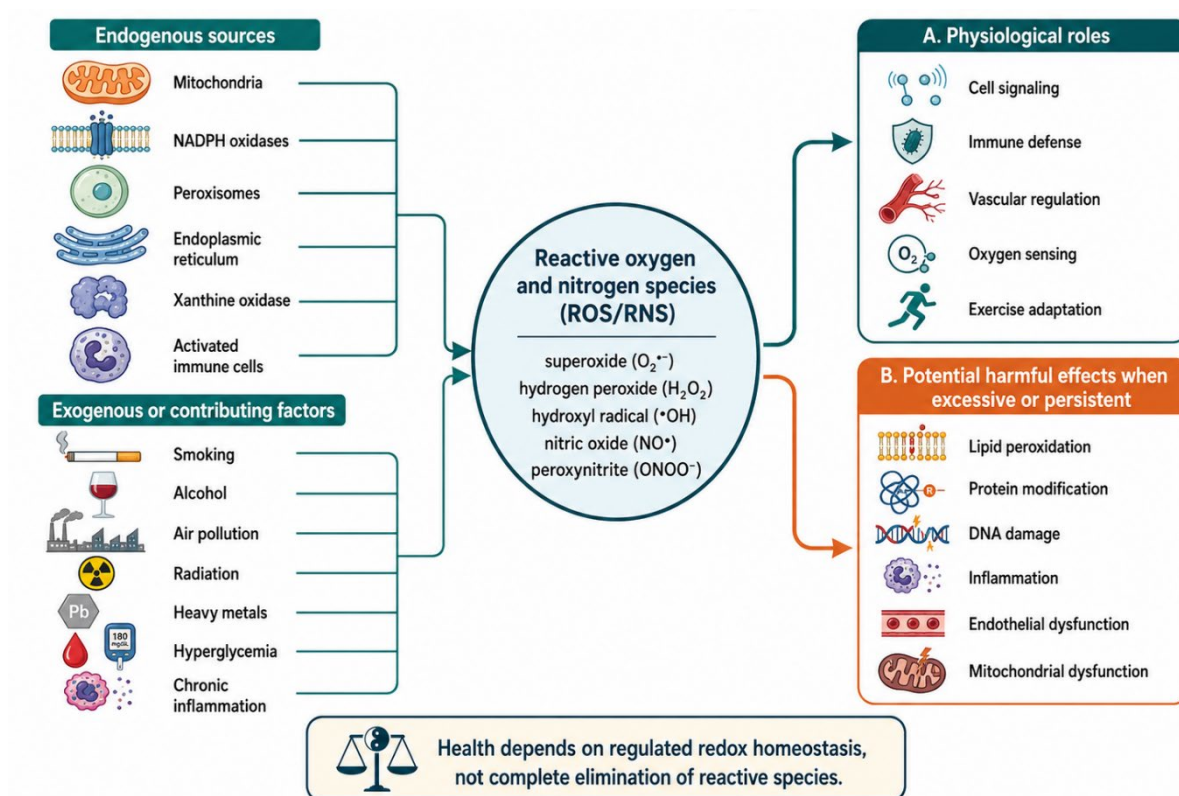
During physical activity, a temporary increase in reactive species participates in adaptation. Redox-sensitive signaling may promote mitochondrial biogenesis, improved antioxidant enzyme expression, glucose uptake, and greater cellular resistance to future stress.

Reactive species may also influence:

- oxygen sensing;
- wound healing;
- autophagy and mitophagy;
- cell proliferation and differentiation;
- apoptosis and other cell-death pathways;
- hormonal and metabolic signaling.

Their physiological effects require precise control. The same molecule may support adaptation at one concentration or location and contribute to injury at another.

Figure 2 Major Sources and Roles of Reactive Oxygen and Nitrogen Species



2.7 Oxidative Eustress and Oxidative Distress

The traditional definition of oxidative stress as a simple imbalance between oxidants and antioxidants is useful but incomplete. Modern redox biology also considers disturbance of redox signaling, cellular localization, adaptation, and molecular damage.

Oxidative eustress refers to physiological redox signaling generated by low or moderate concentrations of reactive species. It supports normal cellular communication, immune defense, vascular regulation, and adaptation to challenges such as physical activity.

Oxidative distress develops when reactive species become excessive, prolonged, poorly localized, or insufficiently controlled. Under these conditions, redox signaling becomes dysregulated and oxidative modification of lipids, proteins, and nucleic acids may occur.

The boundary between eustress and distress is not defined by a single universal concentration. It depends on the reactive species involved, the tissue and cellular compartment, the duration of exposure, and the capacity of antioxidant and repair systems.

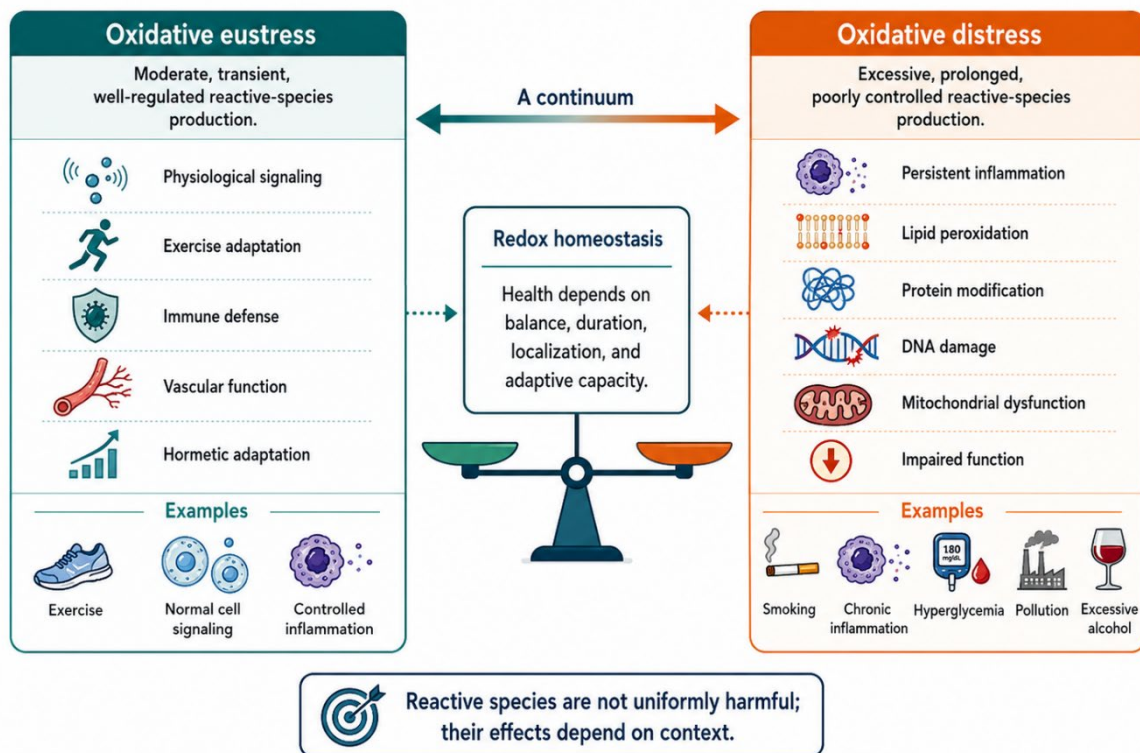
Oxidative distress may be acute or chronic. Acute oxidative challenges may arise during toxic exposure, severe inflammation, ischemia-reperfusion, or intense unaccustomed exercise. If antioxidant and repair systems restore homeostasis, the disturbance may be temporary.

Chronic oxidative distress may occur when harmful exposures or metabolic disturbances persist. Smoking, chronic inflammation, hyperglycemia, excessive alcohol use, obesity, air pollution, and mitochondrial dysfunction may contribute to sustained redox disruption.

This distinction has important implications for prevention. The objective is not complete elimination of reactive species. Such an approach could interfere with immune defense, vascular function, exercise adaptation, and normal signaling. The goal is to preserve physiological redox regulation while reducing persistent oxidative and inflammatory stressors.

The molecular consequences of oxidative distress, including lipid peroxidation, protein modification, DNA damage, altered signaling, and inflammation, are examined in Chapter 3.

Figure 3 **Oxidative Eustress and Oxidative Distress**



Chapter summary

Key Points

- Free radicals contain one or more unpaired electrons, but their stability and reactivity vary.
- Reactive species include both radicals and non-radical oxidants.
- Major ROS include superoxide, hydrogen peroxide, hydroxyl radical, singlet oxygen, and lipid-derived radicals.
- Major RNS include nitric oxide, nitrogen dioxide, and peroxynitrite.
- Mitochondria, NADPH oxidases, peroxisomes, the endoplasmic reticulum, inflammatory cells, and several enzymes generate reactive species.

- External contributors include tobacco smoke, air pollution, radiation, alcohol, metals, pesticides, solvents, and industrial chemicals.
- Reactive species are essential for signaling, immune defense, vascular regulation, and adaptation to exercise.
- Oxidative eustress supports physiological regulation, whereas oxidative distress involves dysregulated signaling and molecular injury.
- The biological effect of a reactive species depends on its identity, concentration, location, duration, and cellular context.
- Redox health requires regulation and adaptation rather than complete suppression of reactive species.

Practical Relevance

Understanding the dual role of reactive species prevents two common errors: treating all ROS and RNS as harmful and assuming that greater antioxidant intake is always beneficial. Preventive medicine should focus on maintaining redox homeostasis by reducing persistent harmful exposures and supporting normal metabolic, antioxidant, and repair systems.

Chapter 3. Mechanisms of Oxidative Damage

Oxidative damage occurs when reactive species modify biological molecules faster than antioxidant, repair, and removal systems can control their effects. It should not be equated with the mere presence of reactive oxygen or nitrogen species, which also perform essential physiological functions.

The consequences of a redox disturbance depend on the chemical identity of the reactive species, its site and rate of formation, duration of exposure, availability of molecular targets, presence of redox-active metals, and efficiency of cellular defense systems. Mild and reversible modifications may regulate normal signaling, whereas persistent or extensive reactions may produce structural injury and loss of function.

The main molecular targets of oxidative distress are lipids, proteins, and nucleic acids. These processes are interconnected: lipid oxidation products can modify proteins and DNA, damaged mitochondria can generate additional reactive species, and oxidative injury may activate inflammatory responses that further increase redox burden.

3.1 Lipid Peroxidation

Lipid peroxidation is the oxidative degradation of lipids, particularly polyunsaturated fatty acids present in cellular membranes and circulating lipoproteins. Polyunsaturated fatty acids are susceptible to oxidation because hydrogen atoms located near their double bonds can be removed relatively easily.

Lipid peroxidation generally proceeds through three stages:

1. **Initiation**, in which a reactive species removes a hydrogen atom from a lipid and produces a lipid radical.
2. **Propagation**, in which the lipid radical reacts with oxygen to form a lipid peroxy radical. This radical can attack another lipid molecule, generating a lipid hydroperoxide and a new lipid radical.
3. **Termination**, in which radicals react with one another or are neutralized by chain-breaking antioxidant systems.

Because the propagation stage can continue through many reaction cycles, damage may spread beyond the initial site of radical formation.

Oxidation of membrane lipids may alter:

- membrane fluidity and permeability;
- receptor and ion-channel function;
- activity of membrane-bound enzymes;
- mitochondrial integrity;
- intracellular transport and signaling;
- lipoprotein structure and behavior.

Lipid hydroperoxides may also decompose into secondary reactive products. Two of the most frequently studied are malondialdehyde and 4-hydroxynonenal. These aldehydes

can diffuse from their site of formation and react with proteins, nucleic acids, and other cellular components.

At low concentrations, some lipid-derived products may act as signaling molecules. At higher or persistent concentrations, they may promote protein dysfunction, inflammatory signaling, mutagenic changes, and cell injury. Their biological effects therefore depend on dose, location, and the capacity of detoxification systems.

Cells limit lipid peroxidation through several mechanisms. Vitamin E can interrupt radical chain reactions within lipid environments. Glutathione peroxidase 4 reduces phospholipid hydroperoxides, while glutathione-dependent systems support its activity. Removal of damaged lipids and organelles also prevents the accumulation of oxidized products.

Lipid peroxidation is involved in many pathological processes, including atherosclerosis, metabolic dysfunction, neurodegeneration, liver injury, and chronic inflammation. However, it is not specific to any single disease and should be interpreted as one component of a broader biological response.

3.2 Oxidative Protein Damage

Proteins are frequent targets of reactive oxygen and nitrogen species because they are abundant and contain chemically reactive amino acid residues. Oxidative modification may occur directly or indirectly through aldehydes and other products generated during lipid peroxidation.

Cysteine and methionine residues are particularly sensitive to oxidation. Tyrosine, tryptophan, histidine, lysine, arginine, and other amino acids may also be modified. Possible consequences include:

- loss or alteration of enzymatic activity;
- impaired receptor or transporter function;
- changes in protein folding;
- fragmentation or crosslinking;
- altered cellular localization;
- formation of aggregates;
- increased or reduced susceptibility to degradation.

Not every oxidative protein modification is harmful. Reversible oxidation of selected cysteine residues is an important mechanism of physiological redox signaling. It may temporarily modify the activity of enzymes, receptors, phosphatases, kinases, and transcription factors.

Thioredoxin, glutaredoxin, glutathione, and related reducing systems can reverse many regulated thiol modifications. Methionine sulfoxide reductases may also repair selected oxidized methionine residues.

More extensive modifications may be irreversible. Protein carbonylation is one of the most frequently studied forms of irreversible oxidative protein damage. Reactive nitrogen species may additionally cause tyrosine nitration, producing compounds such as 3-nitrotyrosine.

Damaged proteins may be removed by proteasomal or lysosomal degradation. Larger aggregates and injured organelles may require autophagy. If repair and removal systems become insufficient, oxidized proteins may accumulate and interfere with cellular function.

This mechanism is especially relevant in tissues composed of long-lived cells, including neurons and cardiac muscle cells. Accumulation of damaged or misfolded proteins may contribute to impaired metabolism, abnormal signaling, inflammation, and loss of cellular resilience.

Protein carbonyls and 3-nitrotyrosine are useful research markers, but neither is disease-specific. Conventional colorimetric or immunological measurements may also be affected by analytical interference. Whenever possible, direct measurements of specific oxidized amino acid products using chromatographic and mass-spectrometric methods provide more precise information.

3.3 Oxidative DNA Damage

DNA may be damaged by reactive oxygen and nitrogen species, radiation, inflammatory processes, toxic metabolites, and secondary lipid oxidation products. Possible lesions include:

- oxidation of nitrogenous bases;
- damage to the sugar-phosphate backbone;
- single- and double-strand breaks;
- DNA-protein crosslinks;
- abnormal base pairing;
- interference with DNA replication and repair.

Guanine is particularly susceptible to oxidation. A commonly studied product is 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG). If oxidative base lesions are not repaired before replication, they may contribute to mutations.

Mitochondrial DNA is also exposed to oxidative injury. Mitochondria are major sites of energy metabolism and reactive species formation, and damage to mitochondrial DNA may impair respiratory-chain function. This may increase metabolic dysfunction and promote further reactive-species generation.

Cells possess several DNA repair systems. Base excision repair is particularly important for many oxidized bases, while other pathways repair bulky lesions, mismatches, and strand breaks. When DNA damage is limited, these systems may restore normal structure.

More extensive or persistent injury may activate:

- temporary cell-cycle arrest;
- DNA damage responses;
- cellular senescence;
- apoptosis;
- other cell-death pathways.

These mechanisms can be protective because they prevent replication of severely damaged genetic material. Pathological consequences arise when damage is inaccurately repaired, repair systems fail, or injured cells escape normal growth control.

Oxidative DNA damage is relevant to carcinogenesis, aging, chronic inflammation, and environmental toxicity. It should nevertheless be understood as one contributing mechanism rather than a sufficient explanation for cancer or other chronic diseases.

Reactive species may also have different effects depending on disease stage. Oxidative DNA damage can contribute to carcinogenesis, but oxidative mechanisms are also involved in the destruction of cancer cells during radiotherapy and treatment with selected anticancer drugs. This is one reason why antioxidant supplementation during cancer therapy requires individual clinical assessment.

Assessment of oxidative DNA damage is methodologically challenging. Enzyme-modified comet assays can detect selected oxidized bases within cells. The conventional comet assay detects DNA strand breaks but is not specific for oxidative injury.

Measurements of urinary or circulating 8-oxodG may provide supportive information, but they reflect a combination of DNA oxidation, repair, nucleotide metabolism, and possible preanalytical artifacts. They should therefore not be interpreted as direct or disease-specific measures of intracellular DNA damage when used alone.

3.4 Redox Signaling and Cellular Adaptation

Reactive species regulate cellular function through reversible modification of redox-sensitive proteins. Hydrogen peroxide is particularly important because it is more stable and selective than highly reactive radicals and can participate in controlled intracellular communication.

Redox signaling frequently involves reversible modification of protein cysteine residues. These reactions can alter the activity of enzymes, receptors, kinases, phosphatases, and transcription factors. Reducing systems subsequently restore the original protein state.

Major redox-sensitive pathways include those involving:

- nuclear factor erythroid 2-related factor 2;
- nuclear factor kappa B;
- mitogen-activated protein kinases;
- phosphoinositide 3-kinase and Akt;
- AMP-activated protein kinase;
- autophagy- and apoptosis-related proteins.

Nuclear factor erythroid 2-related factor 2, commonly abbreviated as Nrf2, regulates genes involved in antioxidant defense, glutathione metabolism, detoxification, and cellular stress responses. Its activation may increase resistance to oxidative or electrophilic challenge.

Nrf2 activation should not automatically be interpreted as proof of clinical benefit. In healthy cells, it supports adaptation, whereas persistent activation in some cancer

cells may contribute to survival and treatment resistance. The consequences depend on tissue, timing, disease stage, and intensity of activation.

Nuclear factor kappa B regulates inflammatory and immune responses. Reactive species may influence its activation and thereby modify cytokine production, leukocyte activity, and tissue responses to injury. Similar context-dependent effects occur in other redox-sensitive pathways.

Moderate redox signaling during exercise is an example of physiological adaptation. A temporary increase in reactive species may stimulate mitochondrial biogenesis, glucose uptake, antioxidant enzyme expression, and increased resistance to subsequent stress.

Redox modifications exist on a continuum. At one end are controlled, reversible changes that support signaling and adaptation. At the other are persistent or irreversible modifications that impair molecular and cellular function.

3.5 Inflammation, Mitochondrial Dysfunction and Feedback Loops

Oxidative stress and inflammation are closely interconnected. During infection or tissue injury, neutrophils, macrophages, and other immune cells generate reactive oxygen and nitrogen species as part of host defense. This response is essential for eliminating microorganisms and damaged cells.

Inflammatory activation may become harmful when it is excessive or chronic. Persistent production of cytokines and reactive species may injure surrounding tissues, modify lipids and proteins, and disrupt endothelial or mitochondrial function.

Oxidative damage can also promote inflammation. Damaged cells may release intracellular molecules that activate immune and inflammatory pathways. Oxidized lipids and proteins may act as biological signals, while mitochondrial injury can release components that are recognized by the immune system.

Mitochondria are both sources and targets of oxidative stress. Injury to mitochondrial membranes, respiratory-chain proteins, or mitochondrial DNA can impair energy production and increase reactive-species generation. Damaged mitochondria may therefore establish a self-reinforcing cycle:

mitochondrial injury → impaired respiration → increased reactive species → additional mitochondrial injury

Cells limit this process through mitochondrial antioxidant systems, repair mechanisms, and mitophagy (the selective removal of dysfunctional mitochondria).

Endoplasmic reticulum stress may also interact with mitochondrial dysfunction and inflammation. Disturbances in protein folding can activate stress responses that initially support adaptation. When prolonged, they may promote inflammatory signaling, metabolic dysfunction, and cell death.

These feedback loops are relevant to many chronic disorders, but they are not disease-specific. Oxidative stress may initiate, amplify, or result from pathological processes.

Establishing its presence does not by itself determine the original cause of a disease or prove that antioxidant supplementation will alter its clinical course.

3.6 Biomarkers of Oxidative Damage

Reactive species are usually short-lived and difficult to measure directly in human tissues. Oxidative stress is therefore assessed mainly through products of molecular oxidation, changes in antioxidant systems, or broader measures of redox status.

No single biomarker provides a complete measure of oxidative stress. A useful marker should:

- correspond to a clearly defined molecular process;
- be chemically stable enough for reliable measurement;
- be measured in an appropriate biological material;
- use a validated and sufficiently specific analytical method;
- respond to changes in exposure or intervention;
- have biological or clinical relevance.

Lipid Oxidation Markers

F₂-isoprostanes measured in urine or other appropriate samples by chromatographic techniques combined with mass spectrometry are among the more robust markers of lipid peroxidation.

Oxidized LDL and phosphatidylcholine hydroperoxides may also provide information when measured with sufficiently specific methods. Their interpretation remains dependent on assay quality, sample handling, and biological context.

Malondialdehyde and thiobarbituric acid-reactive substances are widely used because the assays are relatively simple. However, conventional TBARS methods lack specificity and may detect compounds unrelated to lipid peroxidation. Malondialdehyde measured by chromatographic methods is more informative but should generally be used together with other markers.

Protein Oxidation Markers

Direct measurement of specific oxidized amino acid products by chromatography and mass spectrometry offers greater specificity than global assays.

Protein carbonyls and 3-nitrotyrosine may be useful as supportive markers, but conventional assays can be affected by non-protein compounds, sample preparation, and analytical interference. They should not be interpreted as standalone indicators of disease.

DNA Oxidation Markers

Enzyme-modified comet assays can evaluate selected forms of oxidative DNA damage in cells such as circulating lymphocytes. The traditional comet assay detects strand breaks but does not identify their cause and is therefore not specific for oxidative damage.

Measurements of 8-oxodG in cells, tissues, blood, or urine may provide additional information when sensitive chromatographic methods are used. Urinary concentrations do not directly quantify oxidation occurring in a specific organ and reflect both damage and repair-related processes.

Antioxidant Enzymes and Total Antioxidant Capacity

Activities of superoxide dismutase, catalase, glutathione peroxidase, or other enzymes may change during oxidative challenge. Increased activity may indicate successful adaptation, while reduced activity may indicate depletion, inhibition, or tissue injury. Neither direction has a single universal interpretation.

Similarly, reduced glutathione, oxidized glutathione, vitamins, uric acid, bilirubin, and other antioxidants may provide information about redox status, but their concentrations are influenced by nutrition, renal and hepatic function, inflammation, medications, and sample handling.

Total antioxidant capacity assays estimate the combined reducing or radical-reacting properties of a biological sample. Their results may be dominated by compounds such as uric acid and do not identify which pathways have changed. An increase in total antioxidant capacity is not automatically a beneficial physiological outcome.

Laboratory assays such as DPPH, ABTS, FRAP, CUPRAC, ORAC, TRAP, and Folin-Ciocalteu methods characterize chemical properties of foods, extracts, or isolated compounds. They are not biomarkers of oxidative protection in the human body.

Evidence-Based Note

In vitro antioxidant activity and changes in overall plasma antioxidant capacity do not demonstrate that a food or supplement protects human lipids, proteins, or DNA from oxidative damage. Substantiation requires appropriate human studies using validated markers of specific molecular modification and, ideally, clinically meaningful outcomes.

Because oxidative stress is multidimensional and tissue-dependent, research studies should preferably use more than one complementary marker. Results must also be interpreted together with inflammatory, metabolic, clinical, and exposure-related information.

Most oxidative stress biomarkers remain research tools rather than routine diagnostic tests. Their presence may support understanding of mechanisms but does not independently establish a diagnosis, predict treatment response, or justify antioxidant supplementation.

Chapter summary

Key Points

- Oxidative damage occurs when reactive-species-mediated modification exceeds antioxidant, repair, and removal capacity.
- Lipid peroxidation is a chain reaction affecting polyunsaturated fatty acids in membranes and lipoproteins.

- Lipid oxidation may generate secondary products such as malondialdehyde and 4-hydroxynonenal.
- Protein oxidation may alter enzymes, receptors, transporters, structural proteins, and signaling pathways.
- Reversible thiol oxidation is part of physiological signaling, whereas irreversible carbonylation, nitration, aggregation, and fragmentation may impair function.
- Oxidative DNA damage may produce base lesions, strand breaks, crosslinks, mutations, senescence, or cell death when repair is insufficient.
- Mitochondrial dysfunction, inflammation, and oxidative stress may form self-reinforcing feedback loops.
- No single biomarker adequately measures the full complexity of oxidative stress.
- F₂-isoprostanes, specific oxidized amino acids, and carefully measured DNA oxidation products are generally more informative than nonspecific global assays.
- Total antioxidant capacity and antioxidant enzyme activity require cautious interpretation and do not directly demonstrate clinical protection.
- Chemical antioxidant assays performed on foods or extracts do not establish disease prevention in humans.
- Oxidative stress biomarkers are primarily research tools and should not be used alone to diagnose disease or justify supplementation.

Practical Relevance

Mechanistic knowledge helps explain how smoking, alcohol, metabolic dysfunction, inflammation, radiation, pollution, and occupational exposures may damage cellular structures. It also shows why oxidative stress cannot be evaluated reliably with a single nonspecific test.

Preventive medicine should focus on reducing persistent harmful exposures and supporting normal antioxidant, repair, mitochondrial, and adaptive systems. Antioxidant-rich foods may contribute to this approach, but clinical benefit should be assessed through validated human outcomes rather than laboratory antioxidant scores alone.

Chapter 4. Endogenous Antioxidant Systems

The human organism continuously generates reactive oxygen and nitrogen species during energy metabolism, immune defense, cellular signaling, and adaptation to environmental or physiological stress. To control their effects, cells use an integrated defense network composed of antioxidant enzymes, low-molecular-weight reducing compounds, metal-binding proteins, repair mechanisms, and systems responsible for removing damaged cellular components.

Antioxidant defense should not be understood as the complete elimination of reactive species. Superoxide, hydrogen peroxide, nitric oxide, and related molecules perform essential functions in vascular regulation, immune responses, gene expression, and adaptation to physical activity. Endogenous defense systems maintain their concentrations within ranges compatible with physiological signaling while preventing excessive or prolonged oxidative modification.

The effectiveness of this network depends on cellular location, availability of enzyme cofactors and reducing equivalents, mitochondrial function, nutrient status, inflammatory activity, and the intensity and duration of oxidative challenge.

4.1 Integrated Antioxidant Defense

Endogenous antioxidant systems operate in a coordinated sequence. Superoxide dismutases convert superoxide into hydrogen peroxide. Catalase, glutathione peroxidases, and peroxiredoxins then reduce hydrogen peroxide to less reactive products. Glutathione and thioredoxin systems regenerate oxidized proteins and enzymes, while metal-binding proteins restrict the availability of iron and copper that could catalyze formation of hydroxyl radicals.

This network acts at several levels:

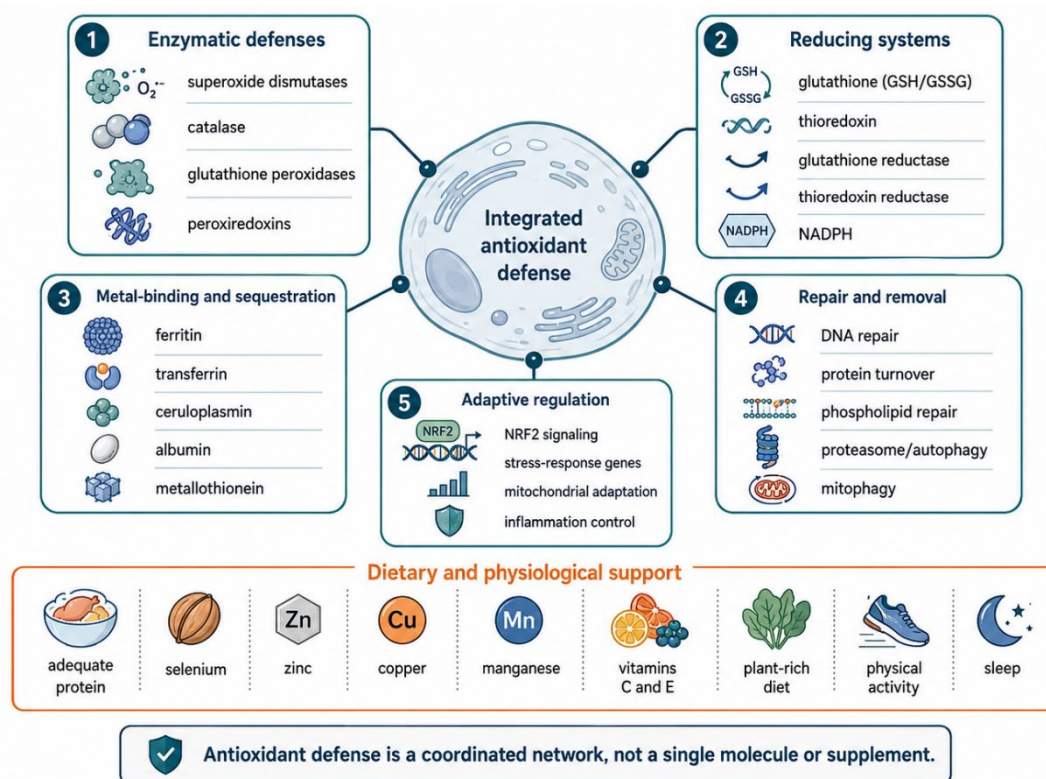
- limiting the formation of highly reactive species;
- converting reactive intermediates into less harmful products;
- interrupting radical chain reactions;
- maintaining protein thiol groups in an appropriate redox state;
- repairing or removing oxidatively modified molecules;
- eliminating damaged mitochondria and other organelles;
- activating adaptive gene-expression programs.

These mechanisms are distributed across different cellular compartments. Mitochondria require local protection because they are major sites of energy metabolism and reactive-species production. Peroxisomes contain catalase because they generate hydrogen peroxide during oxidative metabolism. The cytosol, nucleus, cellular membranes, blood plasma, and extracellular matrix also possess distinct antioxidant systems.

No single enzyme or antioxidant can provide complete protection. For example, increased superoxide dismutase activity without adequate hydrogen peroxide removal could increase peroxide accumulation. Effective defense therefore requires balance among connected pathways.

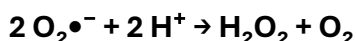
Antioxidant activity also depends on access to reducing equivalents. NADPH supplies electrons for the regeneration of glutathione and thioredoxin systems. Metabolic pathways producing NADPH are therefore indirectly important for antioxidant defense.

Figure 4 **Integrated Antioxidant Defense Network**



4.2 Superoxide Dismutases

Superoxide dismutases catalyze the conversion of superoxide anion into hydrogen peroxide and molecular oxygen:



This reaction reduces superoxide availability but produces hydrogen peroxide, which must subsequently be metabolized by catalase, glutathione peroxidases, or peroxiredoxins.

Humans possess three principal superoxide dismutase isoforms.

SOD1, or copper-zinc superoxide dismutase, is found mainly in the cytosol and also in the mitochondrial intermembrane space. It controls superoxide generated during cytosolic and selected mitochondrial reactions.

SOD2, or manganese superoxide dismutase, is located in the mitochondrial matrix. It is particularly important because electron leakage from the respiratory chain may generate superoxide close to mitochondrial proteins, membranes, and DNA.

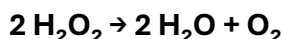
SOD3, or extracellular superoxide dismutase, is secreted into extracellular spaces and is especially relevant in the vascular wall, lungs, and connective tissues. By reducing extracellular superoxide, SOD3 may help preserve nitric oxide bioavailability and normal endothelial signaling.

The activity of SOD enzymes depends on adequate availability of their metal cofactors. Copper and zinc are required for SOD1 and SOD3, whereas manganese is required for SOD2. Deficiency may impair enzyme function, but excessive mineral supplementation does not necessarily improve antioxidant protection and may disturb mineral balance.

Changes in SOD activity require cautious interpretation. Reduced activity may indicate enzyme inhibition, nutrient deficiency, oxidative inactivation, or tissue injury. Increased activity may represent effective adaptation to oxidative challenge. It may also indicate that reactive-species production has increased. SOD activity alone therefore cannot establish whether overall redox status has improved or deteriorated.

4.3 Catalase

Catalase is a heme-containing enzyme that decomposes hydrogen peroxide into water and molecular oxygen:



It is located mainly in peroxisomes, where hydrogen peroxide is generated during fatty acid oxidation and other oxidative reactions. High catalase activity is also present in the liver and erythrocytes, tissues that are regularly exposed to substantial oxidative metabolism or oxygen-related stress.

Catalase is particularly effective when hydrogen peroxide concentrations are relatively high. At lower peroxide concentrations, glutathione peroxidases and peroxiredoxins may make a greater contribution to peroxide regulation.

Removal of hydrogen peroxide is important because, in the presence of poorly controlled iron or copper, it can participate in Fenton-type reactions and generate highly reactive hydroxyl radicals. By limiting peroxide accumulation, catalase indirectly reduces the risk of lipid, protein, and DNA damage.

Hydrogen peroxide also acts as a physiological signaling molecule. Catalase therefore does not simply eliminate a toxic substance; it helps regulate its concentration and duration of action. Excessive removal could interfere with normal signaling, while insufficient removal may permit oxidative distress.

Changes in catalase activity have been observed in metabolic, inflammatory, cardiovascular, hepatic, and neurodegenerative conditions. As with SOD, higher activity may reflect adaptation rather than direct evidence of improved health.

4.4 The Glutathione System

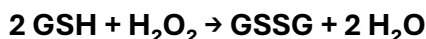
Glutathione is a tripeptide composed of glutamate, cysteine, and glycine. Its reduced form, GSH, is one of the most abundant low-molecular-weight thiols in mammalian cells.

Glutathione participates in:

- reduction of hydrogen peroxide and organic hydroperoxides;
- detoxification of electrophilic compounds;
- maintenance of protein sulfhydryl groups;

- regeneration of other reducing molecules;
- regulation of redox-sensitive signaling;
- protection of membranes and cellular organelles.

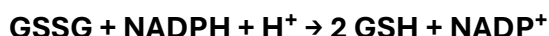
Glutathione peroxidases use GSH as an electron donor. The reduction of hydrogen peroxide can be represented as:



For an organic hydroperoxide, the corresponding reaction is:



During these reactions, two molecules of reduced glutathione are converted into glutathione disulfide, or GSSG. Glutathione reductase regenerates GSH using NADPH:



This recycling maintains a predominantly reduced intracellular environment.

Several human glutathione peroxidases contain selenium in the form of selenocysteine. Adequate selenium status is therefore necessary for normal activity of these enzymes. However, selenium has a relatively narrow range between insufficient and excessive intake, and supplementation above physiological requirements may cause toxicity.

Different glutathione peroxidase isoforms have specialized roles. GPx1 acts mainly in cytosolic and mitochondrial peroxide metabolism. GPx3 is secreted and contributes to extracellular antioxidant defense. GPx4 reduces phospholipid hydroperoxides within membranes and helps prevent uncontrolled lipid peroxidation and ferroptotic cell death.

Glutathione also supports detoxification through glutathione S-transferases, which conjugate GSH to selected electrophilic compounds. The resulting products can then be processed and excreted.

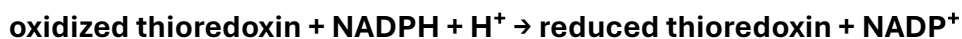
The ratio of reduced to oxidized glutathione is frequently used in research as an indicator of cellular redox status. However, GSH and GSSG concentrations are highly sensitive to tissue type, sample collection, processing, storage, and analytical technique. The ratio should therefore not be treated as a universal clinical measure of oxidative stress.

Glutathione availability depends partly on cysteine supply, protein intake, cellular metabolism, NADPH production, and the rate at which glutathione is consumed or exported. Chronic inflammation, toxic exposures, and sustained oxidative challenge may reduce glutathione reserves.

4.5 Thioredoxin and Peroxiredoxin Systems

The thioredoxin system consists primarily of thioredoxin, thioredoxin reductase, and NADPH. Thioredoxin reduces oxidized disulfide bonds in proteins and helps restore protein cysteine residues to their functional state.

Oxidized thioredoxin is regenerated by thioredoxin reductase:



Human thioredoxin reductases are selenium-containing enzymes. The thioredoxin system therefore represents another connection between selenium status and redox regulation.

Thioredoxin participates in more than antioxidant protection. It influences DNA synthesis, transcription-factor activity, apoptosis, immune signaling, and cellular proliferation. Its role depends on tissue, cellular compartment, and physiological context.

Peroxiredoxins are thiol-dependent enzymes that reduce hydrogen peroxide, organic hydroperoxides, and peroxynitrite. During this process, their active cysteine residues become oxidized and are subsequently regenerated, mainly by thioredoxin.

Because peroxiredoxins react efficiently with hydrogen peroxide, they help regulate both peroxide removal and redox signaling. They may function as peroxide sensors or transmitters, linking local hydrogen peroxide formation with changes in protein activity.

The glutathione and thioredoxin systems overlap but are not interchangeable. Together they maintain protein thiols, support peroxide metabolism, and help reverse regulated oxidative modifications before these changes become irreversible.

Other repair enzymes also contribute to thiol and protein protection. Methionine sulfoxide reductases can restore selected oxidized methionine residues, while glutaredoxins participate in the reversal of glutathione-related protein modifications.

4.6 Metal Control, Repair and Adaptive Regulation

Antioxidant defense includes prevention of reactive-species formation. Iron and copper are essential for oxygen transport, mitochondrial function, and enzyme activity, but poorly controlled ions can catalyze reactions that generate hydroxyl radicals.

The body limits this risk through metal-binding and transport proteins:

- transferrin and lactoferrin bind ferric iron;
- ferritin stores iron in a less reactive form;
- ceruloplasmin transports copper and supports iron metabolism;
- haptoglobin binds extracellular hemoglobin;
- hemopexin binds free heme;
- albumin and metallothioneins bind selected metals and reactive compounds.

These systems demonstrate that antioxidant protection cannot be reduced to radical scavenging. Preventing formation of highly reactive species may be more effective than attempting to neutralize them after they appear.

Because not all molecular damage can be prevented, cells also rely on repair and removal mechanisms. Oxidized proteins may be degraded by proteasomes or lysosomes. Damaged DNA may be repaired through specialized pathways. Altered membrane lipids may be removed and replaced. Autophagy eliminates damaged cellular components, while mitophagy selectively removes dysfunctional mitochondria.

Cells can also increase their defensive capacity through adaptive gene regulation. The transcription factor Nrf2 regulates many genes involved in glutathione synthesis,

detoxification, antioxidant enzymes, and cellular stress responses. Moderate oxidative or electrophilic signals may activate this pathway and improve resistance to subsequent stress.

Activation of antioxidant enzymes is not always evidence of benefit. Increased SOD, catalase, glutathione peroxidase, or Nrf2-related activity may indicate successful adaptation, but it may also reflect exposure to a pro-oxidant stimulus. Interpretation requires information about molecular damage, exposure, tissue function, and clinically relevant outcomes.

Similarly, total antioxidant capacity measured in plasma does not directly represent antioxidant protection in a specific organ. It may be strongly influenced by uric acid, bilirubin, albumin, diet, renal function, hydration, inflammation, and the analytical method used.

Evidence-Based Note

An increase in antioxidant enzyme activity or total plasma antioxidant capacity after consuming a food or supplement does not by itself demonstrate improved health or protection from oxidative damage. Such changes may reflect adaptation to an oxidative challenge, altered metabolism, or assay-related effects.

Evidence of protection should preferably include validated measurements of specific molecular damage and, where possible, meaningful clinical outcomes.

Chapter summary

Key Points

- Endogenous antioxidant defense is an integrated network of enzymes, reducing compounds, metal-binding proteins, repair systems, and adaptive signaling pathways.
- Its purpose is to regulate reactive species while preserving their physiological signaling functions.
- Superoxide dismutases convert superoxide into hydrogen peroxide and molecular oxygen.
- SOD1 functions mainly in the cytosol, SOD2 in the mitochondrial matrix, and SOD3 in extracellular spaces.
- Catalase decomposes hydrogen peroxide and is especially important in peroxisomes and tissues exposed to high oxidative metabolism.
- Glutathione peroxidases reduce hydrogen peroxide and organic hydroperoxides using reduced glutathione.
- Glutathione reductase regenerates reduced glutathione using NADPH.
- GPx4 protects membrane phospholipids from excessive peroxidation.
- Thioredoxin, thioredoxin reductase, and peroxiredoxins regulate protein thiols, peroxide metabolism, and redox-sensitive signaling.

- Selenium is required for several glutathione peroxidases and thioredoxin reductases, but excessive intake may be harmful.
- Metal-binding proteins limit iron- and copper-catalyzed formation of highly reactive species.
- Proteasomal degradation, autophagy, mitophagy, and DNA repair remove or repair damaged cellular components.
- Increased antioxidant enzyme activity does not automatically demonstrate improved antioxidant status or clinical benefit.
- Total plasma antioxidant capacity is an analytical measure and not a direct indicator of tissue protection.

Practical Relevance

Endogenous antioxidant protection cannot be replaced by one vitamin, mineral, or supplement. It depends on coordinated enzyme activity, nutrient adequacy, mitochondrial function, metabolic health, repair capacity, and control of harmful exposures.

Balanced nutrition provides the cofactors and substrates required for these systems, while regular physical activity may strengthen adaptive defense. Smoking, excessive alcohol consumption, chronic inflammation, metabolic dysfunction, sleep disturbance, and toxic exposures may impair the network or increase its workload.

Preventive medicine should therefore support the entire redox system rather than attempt to maximize one antioxidant marker. The practical priorities remain adequate nutrition, physical activity, recovery, avoidance of tobacco, reduction of harmful alcohol use, and control of environmental and occupational exposures.



Chapter 5. Dietary Antioxidants

Dietary antioxidants are compounds obtained from foods that may contribute to redox regulation and protection of biological structures from excessive oxidative modification. They include essential vitamins and trace elements, carotenoids, polyphenols, and other bioactive substances. Some, such as vitamin C, must be supplied through the diet, whereas others, including coenzyme Q10, are also synthesized endogenously.

Dietary antioxidants do not function independently from endogenous defense systems. Their biological effects depend on interactions with antioxidant enzymes, glutathione and thioredoxin systems, metal-binding proteins, cellular repair mechanisms, and redox-sensitive signaling pathways. Adequate nutrition supports this integrated network by providing required cofactors and substrates.

Foods contain complex mixtures of nutrients and bioactive compounds. Vegetables, fruits, legumes, whole grains, nuts, seeds, herbs, spices, tea, coffee, cocoa, and selected animal-derived foods provide vitamins, minerals, fiber, fatty acids, and phytochemicals that may act through complementary mechanisms. Consequently, the health value of an antioxidant-rich diet cannot be attributed to one isolated compound.

Bioavailability is influenced by food structure, processing, cooking, digestion, intestinal absorption, hepatic metabolism, gut microbiota, and interactions with other dietary components. A compound demonstrating strong antioxidant activity in a chemical assay may be poorly absorbed, rapidly metabolized, or present at low concentrations in human tissues. Dietary antioxidant activity should therefore be interpreted within the context of the whole diet and human physiology.

This chapter describes the principal dietary antioxidants, their biological roles, major food sources, and the consequences of inadequate or excessive intake. Clinical evidence, indications, risks, and controversies related to concentrated supplements are discussed separately in Chapter 18.

5.1 Vitamin C

Vitamin C, or ascorbic acid, is an essential water-soluble vitamin. Humans cannot synthesize it because they lack functional L-gulonolactone oxidase, an enzyme required for the final stage of endogenous ascorbate production. Vitamin C must therefore be obtained regularly through food.

Ascorbate participates in reversible oxidation-reduction reactions and can donate electrons to selected reactive species. In aqueous environments, it contributes to antioxidant protection and may assist in regenerating vitamin E from its radical form. Oxidized vitamin C may be converted to dehydroascorbic acid and subsequently regenerated through cellular reducing systems, including glutathione-dependent pathways.

Its physiological importance extends beyond antioxidant activity. Vitamin C is required for enzymes involved in collagen synthesis and therefore supports connective tissue, blood vessel integrity, wound healing, bone structure, and dental health. It also participates

in carnitine and catecholamine synthesis and improves the intestinal absorption of nonheme iron by reducing ferric iron to the more absorbable ferrous form.

Major sources include peppers, citrus fruits, kiwifruit, berries, blackcurrants, broccoli, cabbage, Brussels sprouts, kale, tomatoes, and potatoes. The contribution of a particular food depends not only on its concentration of vitamin C but also on portion size and frequency of consumption.

Vitamin C is sensitive to oxygen, heat, light, prolonged storage, and contact with water. Losses may occur during cutting, boiling, and repeated reheating. Steaming, brief cooking, and using only small amounts of water may help preserve it. A varied diet containing both raw and cooked vegetables and fruits is generally the most practical way to maintain adequate intake.

Deficiency causes scurvy, primarily because of impaired collagen formation. Clinical manifestations may include fatigue, petechiae, bruising, gingival inflammation, bleeding, poor wound healing, joint symptoms, and anemia. Severe deficiency is uncommon in well-nourished populations but may occur in people with highly restricted diets, malabsorption, alcohol use disorder, severe chronic illness, food insecurity, or limited access to fresh foods.

Smoking increases oxidative burden and is associated with lower vitamin C status. Smokers may therefore have greater dietary requirements, but vitamin C supplementation cannot compensate for the vascular, respiratory, and carcinogenic effects of tobacco smoke.

High supplemental doses are generally absorbed less efficiently and may cause abdominal discomfort or diarrhea. Additional caution may be required in individuals susceptible to kidney stones or with disorders of iron overload. For most healthy individuals, regular consumption of vegetables and fruits remains preferable to routine high-dose supplementation.

5.2 Vitamin E

Vitamin E is a collective term for eight lipid-soluble compounds: four tocopherols and four tocotrienols, designated alpha, beta, gamma, and delta. Alpha-tocopherol is preferentially retained in human plasma and tissues and is the form used to define human vitamin E requirements.

Vitamin E is a major chain-breaking antioxidant in lipid environments. It is located in cellular membranes and circulating lipoproteins, where it may donate a hydrogen atom to lipid peroxyl radicals and interrupt lipid peroxidation. This function helps protect polyunsaturated fatty acids and membrane structures from excessive oxidative modification.

During this process, alpha-tocopherol is converted to a tocopheroxyl radical. Other components of the antioxidant network, particularly vitamin C and reducing systems, may help return it to its reduced form. This illustrates the coordinated nature of antioxidant defense: vitamin E does not act as an isolated molecule.

Vitamin E is absorbed in the small intestine together with dietary fat and transported in chylomicrons. The liver preferentially incorporates alpha-tocopherol into circulating lipoproteins through alpha-tocopherol transfer protein. Other vitamin E forms are metabolized and excreted more readily, although they may have biological activities of their own.

Major dietary sources include vegetable oils, nuts, seeds, wheat germ, whole grains, avocado, and green leafy vegetables. Sunflower seeds, almonds, hazelnuts, and several unrefined plant oils are particularly useful sources. The vitamin E content and stability of oils may decrease during prolonged storage, repeated heating, and exposure to light or oxygen.

Vitamin E deficiency is rare in people with normal fat absorption. It may occur in genetic disorders affecting alpha-tocopherol transport, severe fat malabsorption, cholestatic liver disease, cystic fibrosis, or abetalipoproteinemia. Manifestations may include peripheral neuropathy, ataxia, muscle weakness, retinal abnormalities, and hemolytic anemia.

The amount of vitamin E needed is influenced partly by the intake of polyunsaturated fatty acids, which are especially susceptible to oxidation. This does not mean that high-dose supplementation is automatically beneficial. Supplemental vitamin E may interfere with coagulation and increase bleeding risk, particularly in individuals using anticoagulant or antiplatelet medication. Its role in chronic disease prevention is discussed in Chapter 18.

5.3 Carotenoids and Vitamin A

Carotenoids are lipid-soluble pigments synthesized by plants, algae, and some microorganisms. They contribute yellow, orange, and red coloration to many fruits and vegetables and are also present in dark-green vegetables, where their color is masked by chlorophyll.

They are divided broadly into carotenes, which contain carbon and hydrogen, and xanthophylls, which also contain oxygen. Important dietary carotenoids include beta-carotene, alpha-carotene, beta-cryptoxanthin, lycopene, lutein, and zeaxanthin.

Beta-carotene, alpha-carotene, and beta-cryptoxanthin have provitamin A activity and may be converted to retinal and retinol. Lycopene, lutein, and zeaxanthin do not provide vitamin A but have other biological roles. Lutein and zeaxanthin are concentrated in the macula of the eye, where they contribute to the filtering of short-wavelength light and protection of retinal structures.

Carotenoids can quench singlet oxygen and interact with selected radicals in experimental systems. Their effects depend on molecular structure, oxygen concentration, tissue location, and interactions with other compounds. In humans, their significance extends beyond direct antioxidant activity and includes effects on cell communication, immune function, and tissue-specific physiology.

Carotenoid absorption requires normal digestion and absorption of dietary fat. Bioavailability is influenced by the food matrix, particle size, cooking, and accompanying fat. Chopping, pureeing, and moderate heating may disrupt plant cell walls and improve

the availability of carotenoids. Adding a modest amount of dietary fat to vegetables may further support absorption.

Beta-carotene is abundant in carrots, sweet potatoes, pumpkin, spinach, kale, and other dark-green or orange vegetables. Lycopene occurs mainly in tomatoes, watermelon, pink grapefruit, and guava. Processing tomatoes with heat and oil may increase lycopene bioavailability. Lutein and zeaxanthin are present in leafy vegetables, maize, egg yolk, peas, and some other yellow or green foods.

Vitamin A includes retinol, retinal, retinoic acid, and retinyl esters. It is essential for vision, epithelial differentiation, immune function, growth, reproduction, and embryonic development. Preformed vitamin A is present in liver, eggs, dairy products, and some fish. Provitamin A carotenoids are provided mainly by plant foods.

Deficiency may cause night blindness, xerophthalmia, impaired epithelial integrity, increased susceptibility to infection, and growth disturbances. Severe deficiency remains an important cause of preventable visual impairment in some regions and may also occur with malnutrition or fat malabsorption.

Preformed vitamin A can accumulate and become toxic. Excessive intake may cause headache, dry skin, liver injury, bone effects, and neurological symptoms. High intake during pregnancy may be teratogenic. In contrast, carotenoids from foods do not cause classic vitamin A toxicity, although very high intake may produce harmless yellow-orange discoloration of the skin.

High-dose beta-carotene supplements require particular caution in smokers and people with substantial asbestos exposure because intervention trials have demonstrated increased lung cancer risk in these groups. This adverse effect has not been associated with ordinary consumption of carotenoid-rich vegetables and fruits.

5.4 Selenium, Zinc, Copper and Other Trace Elements

Trace elements contribute to antioxidant defense mainly as structural or catalytic components of enzymes and proteins. They should not be understood as direct antioxidants in the same way as vitamin C or vitamin E. Both deficiency and excess can disrupt redox homeostasis.

Selenium

Selenium is an essential trace element incorporated into selenoproteins, usually in the form of selenocysteine. These proteins participate in antioxidant defense, thyroid hormone metabolism, immune function, reproduction, and regulation of cellular redox status.

Several glutathione peroxidases are selenium-dependent. They reduce hydrogen peroxide and lipid hydroperoxides, helping protect membranes and other cellular structures. Thioredoxin reductases also contain selenium and support protein thiol regulation, DNA synthesis, antioxidant regeneration, and cellular signaling.

Selenium is particularly relevant to thyroid physiology. Selenium-containing deiodinases regulate the activation and inactivation of thyroid hormones, while glutathione peroxidases and thioredoxin-related systems protect thyroid tissue during hydrogen peroxide-dependent hormone synthesis.

Food sources include fish, seafood, meat, eggs, dairy products, cereals, whole grains, and nuts. Brazil nuts may contain exceptionally high amounts, but their selenium content is highly variable. The concentration of selenium in plant foods depends strongly on soil composition, agricultural conditions, and geographic region. The same food may therefore provide different amounts in different countries.

Selenium status may be lower in populations living in areas with selenium-poor soils or consuming diets with limited variety. Severe deficiency may impair selenoprotein function and, in combination with other environmental or nutritional factors, contribute to disorders such as Keshan disease. More moderate deficiency usually produces nonspecific biological effects rather than a unique clinical syndrome.

Selenium has a relatively narrow margin between inadequate and excessive intake. Chronic excess may cause selenosis, with hair loss, brittle nails, gastrointestinal symptoms, fatigue, skin changes, garlic-like breath odor, and neurological abnormalities.

Selenium supplementation should not be assumed to improve antioxidant defense in individuals with adequate status. Once the activity of relevant selenoproteins is optimized, higher intake may provide no additional benefit and may increase risk. Assessment should take account of dietary patterns, geographic context, clinical status, and total intake from all supplements.

Zinc

Zinc is required for numerous enzymes and transcription factors and contributes to immune function, protein and DNA synthesis, wound healing, growth, reproduction, taste, and smell. It is also a structural component of cytosolic and extracellular copper-zinc superoxide dismutases.

Zinc may support membrane and protein stability and can influence redox-sensitive signaling. It does not readily change oxidation state under physiological conditions, which distinguishes it from redox-active metals such as iron and copper.

Good dietary sources include oysters and other shellfish, meat, poultry, dairy products, eggs, legumes, nuts, seeds, and whole grains. Zinc from animal foods is generally more readily absorbed. Phytates in whole grains, legumes, and seeds may reduce absorption, although soaking, fermentation, sprouting, and leavening can decrease phytate content.

Deficiency may result from inadequate intake, malabsorption, chronic gastrointestinal disease, increased losses, severe illness, or increased physiological requirements. Manifestations may include impaired growth, reduced immune function, delayed wound healing, skin lesions, loss of appetite, and altered taste or smell.

Excessive supplemental zinc may cause gastrointestinal symptoms and impair copper absorption. Long-term high intake can lead to copper deficiency, anemia, neurological abnormalities, and changes in immune and lipid function.

Copper

Copper is required for enzymes involved in energy production, connective tissue formation, neurotransmitter synthesis, iron metabolism, pigmentation, and antioxidant defense. It forms part of copper-zinc superoxide dismutase and ceruloplasmin.

Copper is a redox-active metal. When appropriately bound within proteins, it supports normal physiology. Poorly regulated free copper, however, can participate in oxidative reactions. Cellular systems therefore tightly control its absorption, transport, storage, and excretion.

Sources include shellfish, organ meats, nuts, seeds, legumes, whole grains, cocoa, and some green vegetables. Deficiency is uncommon in varied diets but may occur with malabsorption, genetic disorders, severe undernutrition, or prolonged high-dose zinc supplementation.

Copper deficiency may cause anemia, neutropenia, bone abnormalities, impaired immunity, connective tissue changes, and neurological symptoms. Excess copper may also be toxic. Wilson disease is an inherited disorder of copper metabolism in which copper accumulates primarily in the liver, brain, and other organs.

Manganese and Iron

Manganese is required for mitochondrial manganese superoxide dismutase and several enzymes involved in metabolism and connective tissue formation. It is present in whole grains, legumes, nuts, tea, and leafy vegetables. Deficiency is rare, while excessive occupational or environmental exposure may produce neurotoxicity.

Iron is essential for oxygen transport, mitochondrial respiration, and numerous enzymes. However, it should not be classified simply as an antioxidant nutrient. Poorly bound ferrous iron can react with hydrogen peroxide in the Fenton reaction, generating highly reactive hydroxyl radicals. For this reason, iron homeostasis is tightly regulated by proteins such as transferrin, ferritin, and hepcidin-related systems.

Iron supplementation should be based on diagnosed deficiency or a recognized clinical indication. Excessive intake can be harmful, particularly in hereditary hemochromatosis and other iron-loading conditions.

The central principle of trace-element nutrition is balance. Increasing intake above physiological requirements does not necessarily improve antioxidant function and may instead disturb interactions among minerals or promote toxicity.

5.5 Polyphenols and Flavonoids

Polyphenols are a large and diverse group of plant-derived compounds. They include flavonoids, phenolic acids, stilbenes, lignans, tannins, and related substances. They contribute to plant pigmentation, defense, flavor, astringency, growth regulation, and protection from environmental stress.

Their dietary sources include vegetables, fruits, berries, legumes, whole grains, nuts, tea, coffee, cocoa, olive products, herbs, and spices. The amount and composition

of polyphenols vary with plant species, cultivar, ripeness, environmental conditions, processing, storage, and preparation.

Flavonoids are among the best-studied polyphenols and share a general carbon skeleton composed of two aromatic rings connected by a three-carbon bridge. Major subclasses include flavonols, flavones, flavanones, flavanols, anthocyanins, and isoflavones.

Flavonols such as quercetin and kaempferol are present in onions, apples, berries, leafy vegetables, tea, and many herbs. Flavanols, including catechins, occur in tea, cocoa, apples, and grapes. Flavanones such as hesperetin and naringenin are characteristic of citrus fruits. Anthocyanins provide red, blue, and purple coloration to berries, cherries, grapes, and other plant foods. Isoflavones, including genistein and daidzein, are found mainly in soy foods.

Phenolic acids include derivatives of benzoic and cinnamic acids. Examples include caffeic, ferulic, p-coumaric, chlorogenic, and rosmarinic acids. Whole grains, coffee, fruits, vegetables, herbs, and spices are important sources.

Stilbenes include resveratrol and related compounds. Lignans are present in seeds, whole grains, legumes, fruits, and vegetables, with flaxseed being a particularly concentrated source. Tannins occur in tea, cocoa, berries, legumes, nuts, and numerous other plant foods.

Polyphenols are often described as antioxidants because they can donate electrons or hydrogen atoms, chelate metals, and interact with radicals in chemical systems. Their biological effects in humans, however, are not limited to direct radical scavenging. They may influence cell signaling, gene expression, inflammatory pathways, endothelial function, enzyme activity, glucose and lipid metabolism, and interactions between the host and gut microbiota.

Most dietary polyphenols undergo extensive metabolism. Glycosides and other conjugated forms may be hydrolyzed in the intestine, while absorbed compounds are commonly methylated, glucuronidated, or sulfated. Unabsorbed polyphenols may be transformed by colonic microorganisms into smaller metabolites. Consequently, tissues are usually exposed to metabolites rather than to the high concentrations of native compounds commonly used in laboratory experiments.

This difference is central to the interpretation of polyphenol research. Strong effects in cell cultures do not necessarily occur after ordinary food consumption. Direct antioxidant scavenging may be important in the gastrointestinal tract, but systemic effects are likely to involve signaling, enzyme regulation, and adaptive responses at relatively low concentrations.

Regular consumption of diverse polyphenol-rich foods is consistent with healthy dietary patterns. Concentrated extracts, however, may deliver doses and combinations that differ substantially from food exposure and should be evaluated separately for efficacy, safety, and interactions.

5.6 Quercetin

Quercetin is a flavonol widely distributed in plant foods. Important sources include onions, capers, apples, berries, grapes, tea, leafy vegetables, and several herbs. In plants, it commonly occurs as glycosides rather than as free quercetin.

Quercetin can interact with radicals, inhibit lipid oxidation, bind some metal ions, and influence redox-sensitive signaling in experimental systems. It has also been studied in relation to inflammation, endothelial function, blood pressure, glucose metabolism, immune regulation, and exercise recovery.

Its biological interpretation is complicated by limited and variable bioavailability. Absorption depends on the glycoside form, food matrix, intestinal enzymes, gut microbiota, and accompanying foods. After absorption, quercetin is extensively metabolized, and circulating compounds are mainly conjugated derivatives rather than unchanged quercetin.

Foods containing quercetin provide much more than this single compound. Onions, apples, berries, vegetables, and tea also supply fiber, vitamins, minerals, and other phytochemicals. Their potential benefits should therefore not be attributed exclusively to quercetin.

Concentrated quercetin supplements may provide doses greatly exceeding normal dietary exposure. Their effects depend on formulation and dose, and they may interact with drug-metabolizing enzymes or transport proteins. Clinical significance varies, but caution is appropriate in individuals taking multiple medications, those with kidney disease, and during pregnancy or breastfeeding.

Quercetin is best presented as one component of a varied plant-rich diet rather than as a stand-alone treatment or preventive agent.

5.7 Resveratrol

Resveratrol is a stilbene produced by plants in response to injury, infection, and environmental stress. It occurs in grape skins, berries, peanuts, and some other plant foods. Red wine contains resveratrol because grape skins remain in contact with the fermenting liquid, but the amount varies considerably.

Resveratrol has been studied for antioxidant, anti-inflammatory, vascular, metabolic, and signaling effects. Experimental research has examined its influence on nitric oxide, platelet function, mitochondrial pathways, inflammatory mediators, AMPK, sirtuins, and cellular stress responses.

Although these mechanisms are biologically interesting, resveratrol has limited systemic bioavailability. It is absorbed but rapidly metabolized to glucuronide and sulfate conjugates, resulting in relatively low circulating concentrations of unchanged resveratrol. Many experimental effects occur at concentrations much higher than those achieved through ordinary dietary intake.

The historical discussion of resveratrol has often been linked to the so-called French paradox and the possible cardiovascular effects of red wine. This interpretation is problematic because observational findings may reflect entire dietary and lifestyle

patterns, while alcohol itself increases the risk of cancer, liver disease, hypertension, injury, and addiction.

Alcoholic beverages should not be recommended as sources of antioxidants. Grapes, berries, and peanuts provide polyphenols without ethanol exposure. The presence of resveratrol does not make wine a health-promoting product.

Evidence concerning concentrated resveratrol supplementation remains heterogeneous. Differences in formulation, dose, duration, population, and outcome limit general conclusions. Its role as a supplement is discussed further in Chapter 18.

5.8 Coenzyme Q10

Coenzyme Q10 is a lipid-soluble benzoquinone present in most human cells. It occurs in an oxidized form, ubiquinone, and a reduced form, ubiquinol. Unlike essential vitamins, it is synthesized by the human organism, although it is also obtained in small amounts from food.

Its primary physiological function is participation in mitochondrial electron transport. Coenzyme Q10 transfers electrons between respiratory-chain complexes and contributes to the generation of ATP. It is particularly abundant in metabolically active tissues such as the heart, liver, kidneys, and skeletal muscle.

In its reduced form, coenzyme Q10 contributes to lipid-phase antioxidant defense. It may help protect membranes and lipoproteins from oxidative modification and may participate in the regeneration of vitamin E. Its redox functions are therefore closely linked with mitochondrial metabolism and other antioxidant systems.

Dietary sources include meat, organ meats, fish, nuts, seeds, and some plant oils. However, dietary intake is small compared with endogenous synthesis. Coenzyme Q10 should not be classified as an essential dietary nutrient in healthy individuals.

Coenzyme Q10 status may be affected by age, genetic disorders, mitochondrial disease, chronic illness, nutritional state, and medication use. Statins reduce activity of the mevalonate pathway involved in both cholesterol and coenzyme Q10 synthesis, which has led to interest in supplementation for statin-associated muscle symptoms. Clinical findings remain inconsistent.

It has also been studied in heart failure, hypertension, migraine, fertility, neurodegenerative disorders, and protection from treatment-related tissue injury. Evidence varies substantially among indications. Coenzyme Q10 should therefore be considered a biologically important endogenous compound with selected potential clinical applications, not a universal antioxidant supplement.

Supplemental forms may interact with medications, including anticoagulant, blood pressure-lowering, glucose-lowering, and oncological treatments. Use should be based on clinical context and should not replace established therapy.

5.9 Bioavailability, Dose and Biological Context

The effect of a dietary antioxidant depends not only on its chemical structure but also on whether it reaches the relevant tissue in an active form.

Bioavailability is influenced by:

- the food matrix;
- digestion and intestinal absorption;
- chemical form and solubility;
- accompanying dietary fat;
- cooking and processing;
- liver metabolism;
- gut microbiota;
- renal and biliary excretion;
- age, disease, and medication use.

Water-soluble and lipid-soluble compounds behave differently. Vitamin C circulates in aqueous environments and is tightly regulated by intestinal absorption and renal excretion. Vitamin E and carotenoids require dietary fat and lipoprotein transport. Polyphenols are extensively transformed before reaching systemic tissues.

Dose is equally important. A nutrient may be beneficial when correcting deficiency, neutral when requirements are already met, and harmful when consumed in excess. Some compounds may also show pro-oxidant effects at high concentrations or in the presence of redox-active metals.

The term **antioxidant activity** is most appropriately used for the behavior of an individual compound in a defined assay. **Total antioxidant capacity** describes the combined behavior of multiple compounds within the same analytical system. Neither measure directly establishes disease prevention.

Chemical assays such as DPPH, ABTS, FRAP, CUPRAC, ORAC, and Folin-Ciocalteu methods are useful for food analysis and mechanistic research. However, their results depend on solvent, pH, reaction kinetics, concentration, and the chemical species used. They do not reproduce digestion, metabolism, tissue distribution, or human disease processes.

Evidence-Based Note

Antioxidant activity measured in vitro is a chemical property, not a clinical outcome. Similarly, an increase in total plasma antioxidant capacity does not by itself demonstrate protection of DNA, proteins, lipids, or body cells.

Evidence of health benefit should come from appropriately designed human studies using specific, validated outcomes.

Chapter summary

Key Points

- Dietary antioxidants function within an integrated network of endogenous enzymes, reducing systems, metal-binding proteins, and cellular repair mechanisms.
- The biological effects of antioxidants depend on food matrix, absorption, metabolism, gut microbiota, tissue distribution, dose, and redox context.
- Vitamin C is an essential water-soluble vitamin involved in collagen synthesis, iron absorption, enzymatic reactions, and antioxidant defense.
- Vitamin E comprises tocopherols and tocotrienols and helps protect membranes and lipoproteins against lipid peroxidation.
- Carotenoids include provitamin A compounds and non-provitamin A pigments such as lycopene, lutein, and zeaxanthin.
- Vitamin A is essential for vision, epithelial integrity, immunity, growth, reproduction, and embryonic development, but excessive preformed vitamin A can be toxic.
- Selenium supports glutathione peroxidases, thioredoxin reductases, and thyroid hormone metabolism, but has a relatively narrow safe intake range.
- Zinc, copper, manganese, and iron have important physiological roles, but excessive intake may disturb mineral balance or promote toxicity.
- Polyphenols influence redox biology through metabolism, signaling, inflammation, enzyme regulation, and microbiota interactions, not only through direct radical scavenging.
- Quercetin, resveratrol, and coenzyme Q10 are biologically relevant compounds, but their food sources, metabolism, formulations, and clinical evidence must be distinguished.
- Antioxidant-rich foods and concentrated antioxidant supplements are not biologically equivalent.
- For healthy individuals, a varied dietary pattern is generally preferable to routine high-dose antioxidant supplementation.

Practical Relevance

Dietary antioxidants support normal physiology most effectively when consumed as components of varied foods. Vegetables, fruits, legumes, whole grains, nuts, seeds, herbs, spices, tea, coffee, and cocoa provide combinations of nutrients and bioactive compounds rather than isolated antioxidant molecules.

The practical aim is not to maximize the intake of one antioxidant or achieve the highest laboratory antioxidant score. It is to maintain dietary variety, adequate micronutrient status, and overall metabolic health. Supplements may be appropriate when a deficiency,

increased requirement, malabsorption, or specific clinical indication is present, but their use requires separate assessment of dose, safety, and evidence.

Chapter 6. Food Sources of Antioxidants

Dietary antioxidants occur in a wide range of foods, particularly vegetables, fruits, legumes, whole grains, nuts, seeds, plant oils, herbs, spices, tea, coffee, and cocoa. Selected animal-derived foods also provide antioxidant-related nutrients such as selenium, zinc, copper, carotenoids, vitamin A, and coenzyme Q10.

The antioxidant value of a food cannot be reduced to the quantity of one vitamin, mineral, or phytochemical. Foods are complex matrices containing fiber, proteins, fats, carbohydrates, minerals, vitamins, and numerous bioactive compounds. These components may influence one another during digestion, absorption, metabolism, and tissue distribution.

Food preparation also affects biological availability. Cooking may reduce heat-sensitive compounds such as vitamin C, but it can increase the release of carotenoids from plant tissues. Fermentation, grinding, soaking, and combination with dietary fat may further modify the availability of selected nutrients and phytochemicals.

The practical objective is therefore not to identify the food with the highest laboratory antioxidant score. It is to consume a varied dietary pattern that supplies multiple nutrients and bioactive compounds while supporting metabolic, cardiovascular, gastrointestinal, and overall health.

Evidence-Based Note

Laboratory assays such as DPPH, ABTS, FRAP, CUPRAC, ORAC, and Folin-Ciocalteu methods measure selected chemical properties under controlled conditions. Results depend on the solvent, pH, concentration, reaction time, and assay mechanism.

A high antioxidant capacity measured in vitro does not prove that a food prevents disease in humans. Clinical relevance depends on bioavailability, metabolism, dose, the overall dietary pattern, and evidence from appropriate human studies.

6.1 The Food Matrix and Dietary Patterns

The health relevance of dietary antioxidants is best understood at the level of dietary patterns. A nutrient or phytochemical consumed as part of a whole food may behave differently from the same compound administered as an isolated supplement because food structure and accompanying components influence its release, absorption, metabolism, and tissue distribution.

Vitamin E in nuts and seeds is consumed together with unsaturated fats, protein, minerals, and fiber. Vitamin C in fruit occurs with water, potassium, organic acids, and phytochemicals, although it remains sensitive to storage and heat. Carotenoids are embedded in plant tissues and may become more bioavailable after chopping, pureeing, or cooking, and their absorption is generally enhanced when a meal contains some dietary fat.

Polyphenols are particularly affected by the food matrix. Many occur as glycosides, polymers, or compounds bound to cell-wall components. Some are absorbed in the small intestine, whereas others reach the colon and are transformed by the gut

microbiota into smaller metabolites. Consequently, circulating and tissue-exposed compounds may differ substantially from those originally present in the food.

Dietary patterns influence health through mechanisms extending beyond antioxidant activity. Plant-rich diets may support satiety, body-weight regulation, blood pressure, lipid and glucose metabolism, intestinal function, and gut microbiota composition. Their potential benefits therefore cannot be attributed to direct radical scavenging alone.

Individual responses vary according to age, genetic factors, nutritional status, smoking, alcohol consumption, medication use, gastrointestinal function, metabolic health, inflammation, and microbiota composition. For most healthy individuals, antioxidant-related compounds are best obtained through diverse foods consumed regularly. Supplements may be appropriate for specific deficiencies or clinical indications, but they should not replace a varied diet.

6.2 Vegetables, Fruits and Berries

Vegetables and fruits provide vitamin C, carotenoids, flavonoids, phenolic acids, folate, potassium, fiber, and numerous other bioactive compounds. Their composition varies according to species, cultivar, ripeness, agricultural conditions, storage, and processing.

Vegetables

Dark-green vegetables such as spinach, kale, broccoli, and parsley provide carotenoids, vitamin C, folate, and phenolic compounds. Orange vegetables such as carrots, pumpkin, and sweet potatoes are rich in provitamin A carotenoids. Tomatoes and red peppers provide carotenoids, while peppers are also valuable sources of vitamin C.

Cruciferous vegetables (including broccoli, cabbage, cauliflower, brussels sprouts, kale, and radishes) contain glucosinolates. When plant tissue is chopped, chewed, or crushed, these compounds may be converted into biologically active products such as isothiocyanates. These substances have been studied in relation to detoxification enzymes and cellular stress responses.

Allium vegetables, including garlic, onions, leeks, and chives, contain sulfur-containing compounds. Chopping or crushing garlic initiates enzymatic reactions involved in the formation of characteristic organosulfur products. Onions also provide flavonoids, particularly quercetin glycosides.

Red and purple vegetables may contain anthocyanins, while beetroot contains betalains and naturally occurring nitrate. Vegetable nitrate may contribute to nitric oxide-related vascular pathways, demonstrating that the physiological effects of vegetables are not limited to antioxidant mechanisms.

Both raw and cooked vegetables can contribute to a healthy dietary pattern. Raw vegetables may preserve heat-sensitive compounds, whereas cooking can improve digestibility and increase the availability of some carotenoids. Variety in preparation is generally more appropriate than exclusive reliance on one method.

Fruits and Berries

Citrus fruits, kiwifruit, strawberries, blackcurrants, and many other fruits provide vitamin C. Orange and yellow fruits such as mango, apricot, papaya, and persimmon contain provitamin A carotenoids.

Berries are important sources of anthocyanins, flavonols, phenolic acids, and tannins. Blueberries, blackberries, raspberries, cranberries, cherries, chokeberries, and blackcurrants differ in their polyphenol profiles but can all contribute to dietary diversity.

Apples contain several phenolic compounds, including quercetin glycosides, particularly in or near the peel. Citrus fruits provide flavanones such as hesperidin and naringin. Grapes contain anthocyanins, catechins, and other polyphenols.

The presence of resveratrol and related compounds in grapes should not be used to promote wine consumption. Grapes and berries provide polyphenols without the toxic and carcinogenic effects of ethanol.

Whole fruit is generally preferable to fruit juice because its intact fiber structure supports satiety and slows consumption. Juice may still provide vitamins and phytochemicals, but it should not be treated as nutritionally equivalent to whole fruit.

Dried fruit contains fiber, minerals, and polyphenols but also provides concentrated sugars and energy. Moderate portions may be useful, particularly when combined with nuts, seeds, whole grains, or unsweetened dairy products.

No single fruit or berry should be promoted as uniquely protective. Regular variety is more important than reliance on one juice, powder, extract, or so-called superfood.

Figure 5 Selected fruits and vegetables by color and general antioxidant richness.



Illustrative educational scheme. Color often reflects differences in phytochemicals; this is not a precise ranking of antioxidant activity.

Plant color often reflects differences in phytochemicals, including polyphenols, carotenoids, chlorophyll-related compounds, and other antioxidant-related substances. This scheme is intended for educational illustration and should not be interpreted as a precise ranking of antioxidant activity.

Source: Authors' own elaboration, adapted from Racek (2003).

6.3 Legumes, Whole Grains, Nuts, Seeds and Plant Oils

Legumes

Beans, lentils, chickpeas, peas, and soy foods provide plant protein, fiber, minerals, phenolic acids, flavonoids, and other phytochemicals.

Their preventive value is strongly related to fiber, satiety, low energy density, favorable effects on glucose and lipid metabolism, and their ability to replace some highly processed foods or animal products rich in saturated fat.

Soy foods contain isoflavones such as genistein and daidzein. These compounds may interact with estrogen receptors and have biological actions extending beyond antioxidant activity. Traditional soy foods should be distinguished from concentrated isoflavone supplements.

Legumes generally require cooking. Soaking, sprouting, fermentation, and adequate thermal preparation may improve digestibility and reduce selected antinutritional compounds. These processes may also modify the availability of minerals and phenolic compounds.

Whole Grains

Whole grains retain the bran, germ, and endosperm of the original grain. Compared with refined grains, they generally provide more fiber, magnesium, zinc, selenium, vitamin E, lignans, and phenolic acids.

Important examples include oats, barley, rye, whole wheat, buckwheat, brown rice, and millet. Their phytochemical composition differs, but all may contribute to dietary variety.

Many cereal phenolic compounds are concentrated in the bran and are partly removed during refining. Ferulic acid, for example, is often bound to cell-wall structures and may be released through digestion, food processing, or microbial metabolism in the colon.

Oats and barley also provide beta-glucans. Their recognized effects on blood cholesterol are related mainly to soluble-fiber physiology rather than direct antioxidant activity.

Replacing some refined grain products with whole-grain alternatives can improve fiber and micronutrient intake without requiring specialized antioxidant products.

Nuts and Seeds

Nuts and seeds provide vitamin E, unsaturated fatty acids, fiber, plant protein, magnesium, selenium, zinc, copper, lignans, phytosterols, and polyphenols.

Walnuts, almonds, hazelnuts, pistachios, peanuts, sunflower seeds, sesame seeds, flaxseeds, chia seeds, and pumpkin seeds have different nutritional profiles. Variety is therefore more useful than considering one product universally superior.

Almonds, hazelnuts, sunflower seeds, and wheat germ are useful sources of alpha-tocopherol. Brazil nuts may contain very high amounts of selenium, but the concentration varies markedly. Large quantities should not be consumed routinely for the purpose of maximizing selenium intake.

Flaxseeds and sesame seeds contain lignans. The effects of lignans depend partly on their transformation by gut microorganisms. Grinding flaxseed improves access to its nutrients, whereas intact seeds may pass through the gastrointestinal tract partly undigested.

Nuts and seeds are energy-dense, so portion size remains relevant. Unsalted and minimally processed products are generally preferable to sugar-coated, heavily salted, or repeatedly fried varieties.

Plant Oils

Plant oils provide fatty acids and varying amounts of tocopherols and phenolic compounds. Extra virgin olive oil contains monounsaturated fatty acids and phenolic compounds, while refined oils usually contain fewer phenolics.

Sunflower, rapeseed, soybean, olive, and other oils differ in fatty acid composition and oxidative stability. Oils rich in polyunsaturated fatty acids are generally more susceptible to oxidation than oils richer in monounsaturated fatty acids.

Appropriate storage is important. Oils should be protected from prolonged exposure to heat, oxygen, and light. Repeated overheating and prolonged high-temperature frying can increase oxidative deterioration and should be avoided.

The health relevance of an oil depends on its fatty acid profile, degree of processing, quantity consumed, culinary use, and the food pattern in which it is included, rather than only on its antioxidant content.

6.4 Tea, Coffee, Cocoa, Herbs and Spices

Tea

Green tea contains catechins, including epigallocatechin gallate, epicatechin, and epigallocatechin. Black tea contains theaflavins and thearubigins formed during processing, while oolong tea has an intermediate composition.

Tea compounds have been studied in relation to endothelial function, metabolism, inflammation, and cellular signaling. However, ordinary brewed tea should be distinguished from concentrated tea extracts, which may provide much higher doses and different safety profiles.

Unsweetened tea can be included as part of a healthy dietary pattern. Sweetened bottled teas and tea-based energy beverages may contain large amounts of added sugar and should not be considered equivalent.

Coffee

Coffee contains chlorogenic acids, caffeine, diterpenes, and compounds formed during roasting. Its composition varies according to coffee species, roasting degree, grinding, filtration, brewing method, and serving size.

Coffee should not be described only as an antioxidant beverage. Its effects also involve caffeine, neurological activity, liver metabolism, and other bioactive compounds.

Plain filtered coffee differs nutritionally from coffee drinks containing syrups, cream, whipped toppings, or large quantities of sugar.

Caffeine tolerance varies. Excessive intake may contribute to anxiety, palpitations, tremor, sleep disturbance, or gastrointestinal symptoms. Timing is relevant because late-day consumption may impair sleep.

Cocoa

Cocoa provides flavanols, including epicatechin and catechin, as well as procyanidins. These compounds have been studied in relation to vascular function and nitric oxide signaling.

Cocoa powder and products with high cocoa content may provide phytochemicals, but many chocolate products also contain substantial quantities of sugar, saturated fat, and energy. The presence of cocoa does not make confectionery suitable for unrestricted consumption.

Fermentation, alkalization, roasting, and storage can alter cocoa flavanol content. Products with similar labels may therefore differ substantially in composition.

Herbs and Spices

Herbs and spices are concentrated sources of polyphenols, phenolic acids, terpenes, sulfur-containing compounds, alkaloids, and essential-oil constituents. Although culinary quantities are usually small, regular use increases phytochemical diversity and may improve the flavor of nutritious meals.

Their practical value includes reducing reliance on excessive salt, sugar, and highly processed sauces.

Examples include:

- rosemary, containing rosmarinic acid, carnosic acid, and carnosol;
- oregano and thyme, containing phenolic compounds and aromatic constituents such as carvacrol and thymol;
- cloves, rich in eugenol;
- turmeric, containing curcuminoids;
- ginger, containing gingerols and shogaols;
- cinnamon, containing polyphenols and aromatic compounds;
- garlic and onions, providing organosulfur compounds and flavonoids;
- black pepper, containing piperine.

Laboratory antioxidant or antimicrobial activity of a spice does not demonstrate that ordinary culinary doses treat chronic disease or infection.

Culinary herbs and spices should also be distinguished from essential oils and concentrated extracts. These products may provide much higher doses, interact with medication, or cause toxicity. Their safety cannot be inferred from ordinary culinary use.

Practical Point

Tea, coffee, cocoa, herbs, and spices can contribute to a healthy diet, but preparation and product choice matter.

Unsweetened beverages, cocoa-rich products with limited added sugar, and culinary use of herbs and spices differ substantially from energy drinks, sugar-rich confectionery, essential oils, and concentrated extracts.

6.5 Food Processing, Storage and Bioavailability

Food processing can either reduce or improve the availability of antioxidant-related compounds.

Vitamin C is sensitive to oxygen, light, heat, and prolonged contact with water. Cutting foods long before consumption, prolonged storage, and boiling in large volumes of water may increase losses. Steaming, brief cooking, or using the cooking liquid in soups and sauces can help retain some water-soluble nutrients.

Cooking may increase the bioavailability of carotenoids by softening plant tissues and disrupting cell walls. Lycopene from cooked tomato products and beta-carotene from softened vegetables may be more accessible than the same compounds in intact raw tissues. Consuming these foods with some dietary fat further supports absorption.

Chopping and crushing may activate enzymatic reactions in plant foods. Crushing garlic promotes formation of organosulfur compounds, while chopping cruciferous vegetables allows glucosinolates and plant enzymes to interact.

Fermentation may alter phytochemical composition, reduce selected antinutritional factors, and improve digestibility. The effects are food-specific and should not be assumed to be universally beneficial.

Storage is particularly important for oils, nuts, seeds, coffee, tea, herbs, and spices. Light, heat, moisture, and oxygen may reduce quality and accelerate oxidation. Products should be stored according to their requirements, and rancid-smelling oils, seeds, or nuts should not be consumed.

Fresh produce is valuable, but frozen vegetables and fruits may also retain substantial nutritional value, particularly when frozen soon after harvest. Canned and preserved foods may be practical options, although added salt, sugar, and processing method should be considered.

No preparation technique preserves every compound equally. A combination of raw, steamed, boiled, roasted, fermented, and appropriately fat-containing meals is more likely to provide a broad range of nutrients than exclusive reliance on one method.

6.6 A Practical Food-Based Approach

An antioxidant-rich dietary pattern does not require expensive supplements, imported berries, detox products, or specialized functional foods.

A practical strategy includes:

- vegetables and fruits consumed regularly and in varied colors;
- legumes included several times per week;
- replacement of some refined grains with whole-grain products;
- moderate portions of unsalted nuts and seeds;
- appropriate use and storage of plant oils;
- culinary use of herbs, spices, onions, and garlic;
- unsweetened tea or coffee according to individual tolerance;
- cocoa-containing products selected with attention to added sugar;
- limitation of ultra-processed foods, sugar-sweetened beverages, and repeatedly fried foods.

Color diversity may be used as a simple educational tool, although color alone does not determine nutritional value. Green vegetables may provide lutein, folate, magnesium, and vitamin C. Orange foods commonly provide carotenoids. Red and purple foods may contain lycopene, anthocyanins, or betalains.

White and brown foods, including garlic, onions, mushrooms, legumes, whole grains, nuts, and seeds also provide important nutrients and phytochemicals and should not be overlooked.

Meals should be affordable, culturally appropriate, enjoyable, and realistic. A technically ideal dietary pattern that cannot be maintained has limited preventive value.

Small substitutions are often more sustainable than radical dietary change. Examples include adding vegetables to a main meal, replacing a sweetened drink with water or tea, using beans instead of processed meat in selected meals, or choosing nuts instead of highly processed snacks.

Table 1 Practical Dietary Sources of Antioxidant-Related Compounds

Food group	Important compounds	Practical consideration
<i>Vegetables</i>	Vitamin C, carotenoids, flavonoids, glucosinolates, organosulfur compounds	Combine raw and cooked forms
<i>Fruits and berries</i>	Vitamin C, anthocyanins, flavanones, flavonols, carotenoids	Prefer whole fruit to large amounts of juice
<i>Legumes</i>	Phenolic acids, flavonoids, minerals, fiber	Regular intake supports metabolic health
<i>Whole grains</i>	Phenolic acids, lignans, vitamin E, minerals	Replace some refined grains
<i>Nuts and seeds</i>	Vitamin E, selenium, zinc, copper, lignans, polyphenols	Choose moderate portions and store appropriately
<i>Plant oils</i>	Tocopherols, phenolic compounds, unsaturated fats	Protect from heat, oxygen, and light
<i>Tea and coffee</i>	Catechins, theaflavins, chlorogenic acids	Consider caffeine and added sugar
<i>Cocoa</i>	Flavanols and procyanidins	Cocoa content does not eliminate sugar and energy
<i>Herbs and spices</i>	Diverse phenolics, terpenes, and sulfur compounds	Culinary use differs from concentrated extracts
<i>Selected animal foods</i>	Selenium, zinc, copper, vitamin A, carotenoids, coenzyme Q10	Consider within the overall dietary pattern

Chapter summary

Key Points

- Dietary antioxidants occur in vegetables, fruits, legumes, whole grains, nuts, seeds, plant oils, tea, coffee, cocoa, herbs, spices, and selected animal-derived foods.
- The biological effects of foods depend on the food matrix, digestion, metabolism, gut microbiota, and the overall dietary pattern.
- Laboratory antioxidant capacity does not demonstrate prevention of disease in humans.
- Vegetables and fruits provide complementary combinations of vitamin C, carotenoids, polyphenols, minerals, and fiber.
- Cruciferous and allium vegetables contain compounds involved in cellular stress and detoxification pathways.

- Legumes and whole grains support metabolic health through fiber and nutrient density as well as phytochemical content.
- Nuts and seeds provide vitamin E, minerals, unsaturated fats, lignans, and polyphenols.
- Tea, coffee, and cocoa contribute to polyphenol intake, but preparation, caffeine, sugar, and portion size should be considered.
- Culinary herbs and spices may increase dietary variety and reduce reliance on excessive salt or processed sauces.
- Culinary use should be distinguished from concentrated extracts and essential oils.
- Cooking may reduce some heat-sensitive nutrients while increasing the availability of selected carotenoids.
- Storage conditions influence the oxidative stability of oils, nuts, seeds, herbs, and spices.
- Dietary variety and long-term food quality are more important than maximizing one antioxidant or consuming a particular superfood.
- For most healthy individuals, a varied food-based pattern is preferable to routine antioxidant supplementation.

Practical Relevance

Food sources of antioxidants are relevant to preventive medicine because they can be incorporated into sustainable daily habits. Whole foods provide combinations of nutrients and phytochemicals in physiological amounts and support health through mechanisms extending beyond direct antioxidant activity.

The practical priority is a varied dietary pattern based mainly on vegetables, fruits, legumes, whole grains, nuts, seeds, and minimally processed foods. Herbs, spices, tea, coffee, and cocoa may contribute additional phytochemical diversity when used appropriately.

The aim is not to obtain the highest possible antioxidant score. It is to maintain nutritional adequacy, metabolic health, and dietary variety over the long term.

Chapter 7. Smoking and Oxidative Stress

Tobacco smoking is one of the most important preventable causes of chronic disease and premature mortality. It is associated with cardiovascular and respiratory diseases, cancer, reproductive disorders, impaired wound healing, and accelerated vascular dysfunction.

Tobacco smoke contains oxidants, particulate matter, toxic gases, aldehydes, heavy metals, and carcinogenic compounds. These substances may damage tissues directly and may also stimulate endogenous production of reactive oxygen and nitrogen species through inflammation, mitochondrial dysfunction, and activation of immune cells.

Although the respiratory tract is the first site of exposure, smoking has systemic effects. It influences the vascular endothelium, circulating lipoproteins, platelets, immune cells, and DNA integrity. Smoking therefore provides a clear example of how one lifestyle exposure can simultaneously increase oxidative, inflammatory, thrombotic, and carcinogenic risk.

Antioxidant-rich foods may support general nutritional status, but they cannot neutralize tobacco smoke. The primary preventive intervention is avoidance of smoking and secondhand smoke exposure.

7.1 Tobacco Smoke as an Oxidative Exposure

Tobacco smoke is a complex aerosol consisting of a gas phase and a particulate phase. It contains nicotine, carbon monoxide, volatile organic compounds, polycyclic aromatic hydrocarbons, tobacco-specific nitrosamines, reactive aldehydes, metals, and numerous oxidizing substances.

With each inhalation, airway epithelial cells and the pulmonary lining fluid are exposed to these compounds. Repeated exposure may impair mucociliary clearance, damage epithelial barriers, stimulate mucus production, and activate inflammatory pathways.

Immune cells amplify this response. Activated neutrophils and macrophages generate reactive oxygen and nitrogen species as part of host defense. When exposure is repeated over years, this initially protective response may become persistent and contribute to chronic tissue injury.

Smoking also affects antioxidant systems. It may reduce circulating concentrations of selected dietary antioxidants, increase glutathione use, and alter the activity of antioxidant enzymes. These changes should not be interpreted as simple vitamin deficiencies. They reflect an ongoing oxidative and inflammatory challenge that cannot be corrected while exposure continues.

Secondhand smoke is also harmful. Non-smokers exposed at home, work, or in public spaces inhale many of the same toxic compounds. Protection from involuntary smoke exposure is therefore an important component of both individual and public health prevention.

7.2 Mechanisms of Smoking-Related Injury

Smoking affects tissues through several interacting mechanisms rather than through oxidative stress alone.

Respiratory inflammation

Smoke irritates airway epithelial cells and activates inflammatory cells. Persistent exposure may contribute to chronic bronchial inflammation, mucus hypersecretion, impaired host defense, airway remodeling, and destruction of alveolar structures.

Endothelial dysfunction

Superoxide and other reactive species may reduce the biological availability of nitric oxide. This impairs vasodilation and promotes vascular inflammation, platelet activation, and endothelial dysfunction.

Reduced nitric oxide activity is one mechanism linking smoking with atherosclerosis, hypertension, myocardial infarction, stroke, and peripheral artery disease.

Lipid and protein modification

Reactive species may promote lipid peroxidation and oxidative modification of circulating lipoproteins and cellular membranes. Oxidized lipids can stimulate inflammatory pathways and contribute to vascular injury.

Proteins may also undergo structural modification, altered enzyme activity, and impaired receptor or transport function. These effects are part of a broader process of tissue dysfunction rather than disease-specific abnormalities.

DNA damage and carcinogenesis

Tobacco smoke contains carcinogens capable of forming DNA adducts. Oxidative stress may additionally contribute to DNA base modification, strand breaks, and impaired genomic stability.

When DNA damage is not repaired correctly, mutations may accumulate in genes regulating cell growth, apoptosis, DNA repair, and tumor suppression. Smoking-related carcinogenesis therefore involves both direct chemical genotoxicity and indirect oxidative and inflammatory mechanisms.

Mitochondrial dysfunction

Smoke-related compounds may impair mitochondrial respiration and increase reactive species generation. Mitochondrial proteins, lipids, and DNA may then be damaged, reducing cellular energy production and further amplifying oxidative stress.

Evidence-Based Note

Smoking-related oxidative stress cannot be “balanced” by taking vitamin C, vitamin E, carotenoids, polyphenols, or other antioxidant products.

Continued smoking repeatedly introduces toxic compounds and stimulates inflammation. Removing the exposure produces substantially greater preventive benefit than attempting to compensate with supplements.

7.3 Major Health Consequences

Oxidative stress contributes to smoking-related disease, but it should be understood as one mechanism within a broader toxic exposure.

Respiratory disease

Smoking is a major cause of chronic bronchitis, emphysema, chronic obstructive pulmonary disease, and lung cancer. It may also worsen asthma control, impair pulmonary immune defense, and increase susceptibility to respiratory infections.

Damage results from the combined effects of epithelial injury, chronic inflammation, protease activity, oxidative stress, mucus dysfunction, and structural changes in the lungs.

Cardiovascular disease

Smoking promotes endothelial dysfunction, platelet activation, vascular inflammation, thrombosis, and atherosclerotic plaque formation. It increases the risk of coronary heart disease, stroke, peripheral artery disease, and aortic disease.

Cardiovascular effects may occur even with relatively low levels of smoking, meaning that simply reducing the number of cigarettes does not eliminate risk.

Cancer

Smoking is strongly associated with lung cancer and cancers of the upper respiratory and digestive tracts. It also contributes to several cancers outside the respiratory system because carcinogens and their metabolites enter the systemic circulation.

The risk reflects cumulative exposure, but cessation remains beneficial at any age. Earlier cessation generally provides greater benefit, yet people with a long smoking history should not be told that it is “too late” to quit.

Reproductive and systemic effects

Smoking may impair fertility, affect sperm and oocyte quality, increase pregnancy-related risk, delay wound healing, worsen bone health, and accelerate vascular and skin aging.

These effects demonstrate that tobacco exposure is systemic rather than limited to the lungs.

7.4 Electronic Cigarettes and Heated Tobacco Products

Electronic cigarettes and heated tobacco products differ from combustible cigarettes, but they are not harmless.

Electronic cigarettes produce an aerosol by heating a liquid that commonly contains nicotine, solvents, flavorings, and other additives. The aerosol may contain reactive carbonyl compounds, particles, metals, and substances capable of affecting airway cells, vascular function, and inflammatory pathways.

Heated tobacco products heat processed tobacco without conventional combustion. They may reduce exposure to some combustion-derived toxicants compared with

continued cigarette smoking, but they still deliver nicotine and other potentially harmful compounds.

Reduced exposure to selected substances should not be interpreted as absence of health risk. Long-term effects also depend on product design, heating temperature, frequency of use, nicotine concentration, and individual behavior.

Dual use is particularly concerning. A person who uses an electronic or heated product while continuing to smoke may maintain substantial exposure to combustible tobacco and prolong nicotine dependence.

For adults who smoke, complete cessation of combustible tobacco remains the primary objective. Nicotine-containing electronic cigarettes may help some adults stop smoking, and current evidence suggests higher cessation rates than with nicotine replacement therapy in some settings. Any potential benefit depends on complete substitution rather than prolonged dual use.

Evidence-based behavioral support and established pharmacological treatments, including nicotine replacement therapy, varenicline, bupropion, or cytisine where available, should be offered according to clinical guidance and patient preference.

Heated tobacco products should not be presented as established smoking-cessation treatments.

7.5 Smoking Cessation and Prevention

Smoking cessation is one of the most effective interventions in preventive medicine. It reduces cardiovascular, respiratory, cancer-related, reproductive, and overall mortality risk.

After cessation, exposure to smoke-related oxidants stops. Endothelial function, inflammatory activity, respiratory symptoms, and antioxidant balance may gradually improve. The extent and speed of recovery vary according to age, cumulative exposure, disease status, and continued exposure to other risk factors.

Nicotine dependence is a chronic relapsing condition involving biological, psychological, behavioral, and social factors. Successful cessation often requires more than advice to “use willpower.”

Evidence-based support may include:

- brief advice from a healthcare professional;
- behavioral counseling;
- structured smoking-cessation programs;
- telephone or digital support;
- nicotine replacement therapy;
- approved pharmacological treatment;
- follow-up after the quit date.

Behavioral and pharmacological support are often more effective when combined.

Healthcare professionals should ask about all forms of tobacco and nicotine use, including cigarettes, cigars, waterpipe, smokeless tobacco, electronic cigarettes, heated tobacco products, and nicotine pouches. Secondhand smoke exposure at home and work should also be assessed.

Relapse should be treated as information rather than failure. The clinician can help identify triggers, such as alcohol use, stress, social situations, withdrawal symptoms, or fear of weight gain, and modify the cessation plan accordingly.

Physical activity, regular meals, sleep protection, stress-management strategies, and social support may make cessation easier. These measures support recovery but do not replace evidence-based treatment of nicotine dependence.

Practical Point

For smoking-related oxidative stress, the most effective antioxidant intervention is removal of the oxidant source.

A useful clinical sequence is:

1. ask about tobacco and nicotine use;
2. advise cessation clearly and respectfully;
3. assess willingness and dependence;
4. offer behavioral and pharmacological support;
5. arrange follow-up.

Chapter summary

Key Points

- Tobacco smoking is a major preventable cause of chronic disease and premature mortality.
- Tobacco smoke contains oxidants, particles, toxic gases, heavy metals, reactive aldehydes, and carcinogenic compounds.
- Smoking increases oxidative stress through direct exposure, chronic inflammation, mitochondrial dysfunction, and impairment of antioxidant systems.
- Smoking contributes to endothelial dysfunction by reducing nitric oxide bioavailability and promoting vascular inflammation and thrombosis.
- Tobacco-related carcinogenesis involves both direct DNA damage and oxidative and inflammatory mechanisms.
- Smoking affects the entire organism and is not limited to respiratory disease.
- Secondhand smoke exposure is harmful and should be prevented.
- Electronic cigarettes and heated tobacco products are not harmless, and dual use may maintain substantial risk.
- Antioxidant-rich foods and supplements cannot compensate for continued tobacco exposure.

- Complete smoking cessation is the central preventive intervention.
- Nicotine dependence should be managed as a chronic condition using non-judgmental, evidence-based support.
- Relapse may occur and should lead to reassessment and renewed treatment rather than abandonment of the cessation goal.

Practical Relevance

Smoking clearly demonstrates why preventive medicine must prioritize reduction of harmful exposures over supplementation.

Healthcare professionals should ask routinely about tobacco, nicotine products, and secondhand smoke. Advice should be clear but respectful, recognizing that smoking is an addiction rather than simply a lifestyle preference.

The practical goal is complete cessation supported by counseling, appropriate pharmacotherapy, follow-up, and smoke-free environments. A healthy diet and physical activity may assist recovery, but they cannot neutralize the toxic, inflammatory, and carcinogenic effects of tobacco smoke.

Chapter 8. Alcohol Consumption and Oxidative Stress

Alcohol consumption influences oxidative stress, inflammation, metabolic regulation, liver function, cardiovascular health, cancer risk, mental health, and injury-related morbidity. Its effects depend on the amount consumed, drinking pattern, age, sex, genetic factors, nutritional status, medication use, and the presence of chronic disease.

No level of alcohol consumption can be considered completely risk-free. Risk generally increases with both the total amount consumed and the frequency of heavy drinking episodes. Alcohol should therefore not be recommended for cardiovascular protection, stress relief, sleep improvement, or as a dietary source of antioxidants.

From the perspective of redox biology, alcohol is important because its metabolism produces acetaldehyde, alters the cellular NADH/NAD⁺ balance, increases reactive species generation, impairs mitochondrial function, and may weaken endogenous antioxidant systems. These effects are especially relevant in the liver but may also involve the gastrointestinal tract, pancreas, cardiovascular system, brain, immune system, and reproductive organs.

Antioxidant-rich foods may support general nutritional health, but they cannot neutralize the toxic effects of ethanol or its metabolites. The primary preventive strategy is reduction or avoidance of alcohol exposure.

8.1 Alcohol Metabolism and Redox Imbalance

Ethanol is metabolized mainly in the liver. The principal pathway involves two sequential reactions:

1. alcohol dehydrogenase converts ethanol to acetaldehyde;
2. aldehyde dehydrogenase converts acetaldehyde to acetate.

Acetaldehyde is a reactive and toxic metabolite. It may form adducts with proteins, lipids, and DNA, altering their structure and function. Acetaldehyde-related damage contributes to inflammation, impaired cellular repair, immune activation, and carcinogenesis.

Both metabolic reactions increase the conversion of NAD⁺ to NADH. A persistently elevated NADH/NAD⁺ ratio alters normal cellular metabolism. It inhibits fatty acid oxidation, promotes triglyceride synthesis, interferes with glucose regulation, and contributes to hepatic fat accumulation.

Another ethanol-metabolizing pathway involves cytochrome P450 2E1. Its activity may increase during repeated or heavy alcohol exposure. CYP2E1 metabolism generates reactive oxygen species and may also activate other toxic compounds. This contributes to oxidative stress, particularly in hepatocytes.

Mitochondria are important targets of alcohol-related injury. Ethanol and acetaldehyde may impair the electron transport chain, decrease ATP production, disturb calcium regulation, and damage mitochondrial proteins, lipids, and DNA. Dysfunctional

mitochondria may then generate additional reactive species, creating a self-reinforcing cycle of oxidative and metabolic stress.

Chronic alcohol exposure may also alter endogenous antioxidant defense. Glutathione may become depleted, particularly within mitochondria, while the activity of antioxidant enzymes may be disturbed. Nutrient deficiencies associated with heavy drinking may further weaken cellular protection.

Evidence-Based Note

Alcohol-related oxidative stress is produced continuously while ethanol is being metabolized. Vitamin C, vitamin E, polyphenols, selenium, or other antioxidant products cannot prevent the formation of acetaldehyde or correct the metabolic effects of an increased NADH/NAD⁺ ratio.

8.2 Inflammation and Organ Injury

Alcohol-related oxidative stress is closely connected with inflammatory activation. Reactive species may stimulate redox-sensitive signaling pathways, while activated immune cells generate additional oxidants. This interaction may contribute to persistent tissue injury.

Liver

The liver is especially vulnerable because it is the main site of alcohol metabolism. Early alcohol-related liver injury commonly involves hepatic steatosis, characterized by fat accumulation within hepatocytes.

With continued exposure, hepatic steatosis may be accompanied by or progress to alcohol-associated steatohepatitis, alcohol-associated hepatitis, fibrosis, cirrhosis, and liver failure. The clinical course is not uniform and is modified by the amount and pattern of alcohol use, metabolic factors, genetic susceptibility, sex, smoking, nutrition, and coexisting liver disease.

The gut-liver axis is important in this process. Alcohol may alter intestinal microbiota and impair the intestinal barrier. Increased entry of bacterial products into portal circulation can activate hepatic immune cells and intensify inflammatory and oxidative responses.

Pancreas

Alcohol is an important risk factor for acute and chronic pancreatitis. Pancreatic injury may involve toxic metabolites, oxidative stress, inflammation, disturbed calcium signaling, and premature activation of digestive enzymes.

Recurrent pancreatitis may lead to chronic pain, exocrine insufficiency, malnutrition, diabetes, and structural pancreatic damage.

Cardiovascular system

Heavy or repeated alcohol consumption may increase blood pressure, promote atrial fibrillation, impair cardiac muscle function, and increase the risk of stroke and cardiomyopathy.

Alcohol-related cardiovascular effects depend strongly on drinking pattern. Binge drinking may produce abrupt changes in heart rhythm, blood pressure, autonomic regulation, and coagulation. Chronic heavy use may contribute to hypertension and structural cardiac injury.

Earlier observational research sometimes suggested cardiovascular benefits of moderate alcohol consumption. These findings may have been influenced by confounding factors such as diet, socioeconomic status, physical activity, and differences between non-drinkers. Because alcohol also increases cancer, liver, injury, addiction, and cardiovascular risks, it should not be initiated for heart protection.

Nervous system and mental health

Alcohol affects neurotransmission, judgment, coordination, emotional regulation, and sleep architecture. Repeated heavy use may contribute to cognitive impairment, peripheral neuropathy, depression, anxiety, dependence, and social or occupational dysfunction.

Neurological injury may result from direct toxicity, oxidative stress, mitochondrial dysfunction, neuroinflammation, liver disease, and nutritional deficiencies. Thiamine deficiency is particularly important because it may lead to serious neurological complications.

Alcohol may initially shorten the time required to fall asleep, but it commonly disrupts sleep continuity, reduces restorative sleep, and worsens snoring or obstructive sleep apnea. It should not be used as a sleep aid.

8.3 Alcohol and Cancer Risk

Alcohol is an established cause of several cancers. Risk is related primarily to ethanol and its metabolites rather than to the type of alcoholic beverage.

Mechanisms include:

- acetaldehyde-related DNA and protein damage;
- oxidative DNA modification;
- impaired DNA repair;
- chronic inflammation;
- altered folate metabolism;
- hormonal changes;
- increased permeability of mucosal tissues to other carcinogens.

Alcohol-related cancer risk is relevant to cancers of the oral cavity, pharynx, larynx, esophagus, liver, breast, and colorectum. Tobacco and alcohol may interact, producing greater risk than either exposure alone for several cancers of the upper digestive and respiratory tracts.

Cancer risk may increase even at levels not traditionally classified as heavy drinking. The absolute risk varies according to age, sex, genetic susceptibility, smoking, total alcohol exposure, and other health factors, but lower exposure generally means lower risk.

The presence of resveratrol and other polyphenols in red wine does not make wine a cancer-preventive product. Grapes, berries, peanuts, cocoa, and other foods provide polyphenols without exposure to ethanol and acetaldehyde.

Evidence-Based Note

All alcoholic beverages contain ethanol. Beer, wine, and spirits differ in concentration and composition, but no beverage becomes protective because it also contains small quantities of antioxidant compounds.

8.4 Alcohol and Nutritional Status

Heavy alcohol use may impair nutritional status through several mechanisms. Alcohol provides energy but few essential nutrients and may displace normal meals. It may also interfere with digestion, intestinal absorption, hepatic storage and metabolism, and increase urinary losses of selected nutrients.

Possible deficiencies include:

- thiamine and other B vitamins;
- folate;
- vitamin A;
- vitamin D;
- vitamin E;
- magnesium;
- zinc;
- selenium;
- protein and total energy.

Malnutrition may further reduce antioxidant and repair capacity. Selenium, zinc, copper, manganese, amino acids, and vitamins are required for endogenous enzymes and cellular maintenance. However, deficiency correction should be clinically targeted rather than used as a justification for broad high-dose antioxidant supplementation.

Vitamin A deserves particular caution. Chronic alcohol exposure may disturb hepatic vitamin A metabolism, while high-dose retinol supplements may increase liver toxicity. Additional caution is required with supplements or herbal products that can also affect the liver.

In people with alcohol use disorder, liver disease, pancreatitis, neuropathy, or severe malnutrition, nutritional management may require medical supervision. Thiamine supplementation may be essential in selected high-risk patients, particularly when food intake is poor or neurological symptoms are suspected.

This type of targeted treatment is fundamentally different from using commercial antioxidant products to compensate for drinking.

8.5 Prevention and Clinical Practice

The preventive message regarding alcohol is straightforward: people who do not drink should not start for health reasons, and people who drink may reduce risk by consuming less.

Reduction strategies may include smaller portions, fewer drinking occasions, alcohol-free days, avoiding binge drinking, and replacing alcoholic beverages with non-alcoholic alternatives.

Some people should avoid alcohol entirely. These include:

- pregnant women and people trying to conceive;
- children and adolescents;
- people with alcohol use disorder;
- individuals with liver disease or pancreatitis;
- people taking medications that interact with alcohol;
- individuals who must drive or perform safety-sensitive work;
- people advised to abstain because of a specific medical condition.

Healthcare professionals should ask about both the amount and pattern of alcohol use. Average weekly intake may conceal episodes of heavy drinking, loss of control, withdrawal symptoms, or use of alcohol for sleep, anxiety, or stress.

Warning signs that may require further assessment include difficulty reducing intake, craving, morning drinking, recurrent memory gaps, withdrawal symptoms, neglect of responsibilities, continued use despite harm, and concern expressed by family members.

Brief, non-judgmental counseling may help people recognize risk and consider change. Individuals with possible dependence should not always stop abruptly without medical advice because severe withdrawal may be dangerous. They may require structured treatment, pharmacotherapy, psychological support, and medically supervised withdrawal.

Alcohol reduction is often easier when the reasons for drinking are addressed. These may include insomnia, social anxiety, chronic stress, loneliness, pain, or depression. Appropriate treatment of these problems provides a safer and more sustainable alternative.

Practical Point

Alcohol should not be used as an antioxidant source, sleep aid, stress-management strategy, or cardiovascular intervention.

In preventive practice:

1. ask about frequency, quantity, and heavy drinking episodes;
2. identify health risks, medication interactions, and signs of dependence;
3. advise reduction or abstinence according to individual risk;
4. provide behavioral or medical support when needed;
5. reassess alcohol use during follow-up.

Chapter summary

Key Points

- Alcohol affects oxidative stress, inflammation, metabolism, liver function, cardiovascular health, cancer risk, mental health, and injury risk.
- Ethanol is converted to acetaldehyde, a toxic and reactive metabolite capable of modifying proteins, lipids, and DNA.
- Alcohol metabolism increases the NADH/NAD⁺ ratio, disturbing lipid and glucose metabolism and promoting hepatic fat accumulation.
- Repeated alcohol exposure may induce CYP2E1, increase reactive species production, and impair mitochondrial function.
- Alcohol-related liver injury may progress from steatosis to steatohepatitis, fibrosis, cirrhosis, and liver failure.
- The gut-liver axis contributes to alcohol-related inflammation and oxidative tissue injury.
- Heavy drinking increases the risk of hypertension, arrhythmias, cardiomyopathy, pancreatitis, neurological injury, and mental health problems.
- Alcohol is an established cause of several cancers, regardless of beverage type.
- Red wine should not be recommended as a source of antioxidants or for cardiovascular prevention.
- Heavy alcohol use may contribute to nutritional deficiencies, but antioxidant supplements do not compensate for continued exposure.
- People who do not drink should not start for health reasons.
- Reduction, abstinence when indicated, early identification of dependence, and access to evidence-based treatment are the main preventive strategies.

Practical Relevance

Alcohol-related oxidative stress demonstrates why reducing harmful exposure is more important than attempting to counteract it with nutrients or supplements.

Healthcare professionals should assess the amount, frequency, and pattern of alcohol consumption and ask whether alcohol is being used for sleep, stress, anxiety, or emotional coping. Advice should be clear and non-judgmental.

The central preventive recommendation is to drink less or not at all. Antioxidant-rich foods may support overall nutritional health, but they cannot prevent acetaldehyde formation, mitochondrial dysfunction, inflammation, cancer risk, or organ injury caused by alcohol.

Chapter 9. Physical Activity, Obesity and Metabolic Health

Physical activity, sedentary behavior, body composition, and metabolic health are closely connected with oxidative stress and chronic disease prevention. Regular movement supports cardiovascular fitness, insulin sensitivity, muscle and bone health, psychological well-being, and functional independence. In contrast, prolonged inactivity and excess adiposity may contribute to insulin resistance, chronic low-grade inflammation, endothelial dysfunction, mitochondrial impairment, and increased oxidative burden.

Exercise and obesity illustrate two different patterns of redox regulation. Physical activity produces temporary increases in reactive species that participate in physiological signaling and adaptation. Obesity and metabolic dysfunction are more often associated with persistent inflammatory and oxidative activation.

The objective of prevention is therefore not to suppress all exercise-induced reactive species or to reduce health assessment to body weight. It is to promote regular movement, preserve muscle function, reduce sedentary time, and improve metabolic health through sustainable lifestyle and clinical strategies.

9.1 Physical Activity and Redox Adaptation

During exercise, contracting skeletal muscles increase energy demand and generate reactive oxygen and nitrogen species. These molecules may arise from mitochondria, NADPH oxidases, xanthine oxidase, vascular cells, and inflammatory processes associated with tissue stress and repair.

Exercise-induced reactive species were once viewed mainly as harmful by-products of increased oxygen consumption. Current redox biology recognizes that moderate and transient reactive-species production is an important component of exercise adaptation.

Reactive species generated during physical activity may contribute to:

- activation of antioxidant enzymes;
- mitochondrial biogenesis;
- improved glucose transport and insulin sensitivity;
- vascular adaptation;
- muscle remodeling;
- regulation of inflammatory responses;
- increased resistance to later metabolic stress.

This represents **oxidative eustress**: a controlled redox stimulus that activates protective and adaptive mechanisms.

Repeated training improves the ability of tissues to manage oxidative challenges. Regular aerobic and resistance exercise may enhance mitochondrial efficiency, antioxidant defense, endothelial function, glucose metabolism, and inflammatory regulation.

The response nevertheless depends on exercise intensity, duration, training status, nutrition, sleep, age, and health condition. Very intense, prolonged, or unfamiliar exercise may temporarily increase lipid peroxidation, protein oxidation, inflammation, muscle soreness, and fatigue. This usually reflects an acute stress response rather than evidence that exercise is harmful.

Gradual progression is therefore important. A previously inactive person may experience greater physiological stress from a given exercise session than a trained individual. Adequate sleep, hydration, nutrition, and recovery allow adaptive processes to occur.

Evidence-Based Note

Reactive species are part of the signaling process through which exercise improves physiological function. Routine high-dose antioxidant supplementation is not required for exercise adaptation and may, in some circumstances, interfere with selected training signals. A balanced diet and adequate recovery are generally more appropriate than attempts to eliminate exercise-induced oxidation.

9.2 Sedentary Behavior and Physical Inactivity

Physical inactivity and sedentary behavior are related but distinct concepts.

Physical inactivity means not achieving sufficient moderate or vigorous activity. Sedentary behavior refers to prolonged waking activities performed while sitting or reclining with very low energy expenditure. A person may complete a daily exercise session and still spend most of the remaining day sitting.

Common forms of sedentary behavior include:

- prolonged screen use;
- office or academic work;
- passive transport;
- extended television viewing;
- long periods of sitting during travel or leisure.

Skeletal muscle is an important metabolic organ. Muscle contractions stimulate glucose uptake, blood flow, lipid utilization, and cellular signaling. When contractions are infrequent, glucose and lipid metabolism may become less efficient.

Prolonged sitting may contribute to:

- impaired postprandial glucose regulation;
- reduced energy expenditure;
- poorer lipid metabolism;
- vascular dysfunction;
- musculoskeletal discomfort;
- reduced functional capacity.

The metabolic consequences of sitting cannot always be fully reversed by one exercise session. Prevention should therefore address both structured physical activity and movement throughout the day.

Brief activity breaks can be practical. Standing, walking for several minutes, climbing stairs, stretching, or performing simple mobility exercises may interrupt long sedentary periods. Short walks after meals may be particularly useful for postprandial glucose regulation.

The aim is not constant exercise. It is regular muscle activity distributed across the day.

Practical Point

For people with sedentary work, a realistic strategy is to stand or walk for several minutes every 30-60 minutes, use stairs when practical, and take a short walk after one or more meals.

9.3 Obesity, Adipose Tissue and Oxidative Stress

Obesity is a complex chronic condition characterized by excessive or dysfunctional adipose tissue that may impair health. It is influenced by biological, genetic, behavioral, environmental, socioeconomic, psychological, and commercial factors.

Adipose tissue is not only an energy-storage compartment. It is an active endocrine and immune organ that produces adipokines, cytokines, chemokines, hormones, and metabolic signals.

During excessive adipose tissue expansion, adipocytes may enlarge and become metabolically stressed. This may be accompanied by:

- local tissue hypoxia;
- immune-cell infiltration;
- altered adipokine production;
- endoplasmic reticulum stress;
- mitochondrial dysfunction;
- increased release of free fatty acids;
- chronic low-grade inflammation.

Activated macrophages and other immune cells within adipose tissue generate inflammatory mediators and reactive species. These processes may impair insulin signaling and contribute to systemic metabolic dysfunction.

Excess fatty acids may also accumulate in tissues not designed for long-term lipid storage, including the liver, skeletal muscle, pancreas, and heart. This ectopic fat deposition may promote lipotoxicity, mitochondrial stress, inflammation, and organ dysfunction.

The relationship between obesity and oxidative stress is bidirectional. Adipose tissue dysfunction may increase reactive species production, while oxidative stress may worsen inflammation, insulin resistance, endothelial function, and adipocyte metabolism.

Not all people with the same body mass index have the same metabolic risk. BMI is useful for population assessment but does not directly measure fat distribution, muscle mass, cardiorespiratory fitness, or metabolic health.

Clinical assessment may also include:

- waist circumference or waist-to-height ratio;
- blood pressure;
- glucose or HbA1c;
- lipid profile;
- liver function;
- physical fitness;
- muscle strength;
- sleep and medication history.

Weight-related counseling should avoid stigma. Blaming individuals may reduce trust, delay healthcare seeking, and worsen psychological distress. Supportive care should recognize the influence of food systems, socioeconomic conditions, medications, sleep, stress, disability, and the built environment.

9.4 Insulin Resistance and Metabolic Dysfunction

Insulin resistance occurs when tissues such as skeletal muscle, liver, and adipose tissue respond less effectively to insulin. The body may initially compensate by producing more insulin, but over time glucose and lipid regulation may deteriorate.

Oxidative stress may contribute to insulin resistance by:

- interfering with insulin-signaling proteins;
- promoting inflammatory pathway activation;
- impairing mitochondrial function;
- altering lipid metabolism;
- reducing endothelial function.

At the same time, hyperglycemia, increased free fatty acids, inflammation, and mitochondrial overload may generate additional reactive species. This creates a self-reinforcing metabolic and oxidative cycle.

Skeletal muscle is especially important because it is a major site of insulin-stimulated glucose uptake. Regular muscle contraction improves glucose transport and insulin sensitivity, sometimes before substantial weight loss occurs.

The liver also plays a central role. Insulin resistance can increase hepatic glucose production and promote fat accumulation. Persistent hepatic lipid accumulation may contribute to metabolic dysfunction-associated steatotic liver disease.

Metabolic syndrome describes the clustering of several cardiometabolic abnormalities, including:

- central adiposity;
- elevated blood pressure;
- increased triglycerides;
- low HDL cholesterol;
- impaired glucose regulation.

These factors increase the risk of type 2 diabetes, cardiovascular disease, fatty liver disease, and other chronic conditions.

Metabolic health should not be judged by body weight alone. Improvements in physical fitness, muscle strength, sleep, dietary quality, blood pressure, glucose regulation, and lipid profile are clinically meaningful even when weight loss is modest.

Detailed mechanisms and complications of diabetes are discussed in Chapter 13.

9.5 Prevention and Clinical Practice

Prevention of metabolic disease requires an integrated approach. No single exercise, diet, antioxidant, or weight target is appropriate for everyone.

For most adults, a useful long-term target is:

- 150-300 minutes of moderate-intensity aerobic activity per week; or
- 75-150 minutes of vigorous-intensity activity; or
- an equivalent combination of both;
- muscle-strengthening activity involving major muscle groups on at least two days per week.

People who are currently inactive do not need to begin at these levels. Even small increases in movement may provide benefit. The first goal may be five or ten minutes of walking, one brief strength session, or regular breaks from sitting.

Aerobic activities may include walking, cycling, swimming, dancing, jogging, or active transport. Resistance exercise may use weights, machines, elastic bands, body weight, or functional movements such as standing from a chair.

Older adults may also benefit from balance, mobility, and functional exercises. People with cardiovascular, respiratory, neurological, metabolic, or musculoskeletal disorders may require individualized advice and clinical assessment.

Nutrition should support activity and metabolic health rather than focus narrowly on antioxidants. Useful dietary principles include:

- regular consumption of vegetables, fruits, legumes, whole grains, nuts, and seeds;
- adequate protein to support muscle maintenance;
- preference for minimally processed foods;
- reduction of sugar-sweetened beverages and highly energy-dense foods;
- moderation of alcohol;
- attention to portion size and meal structure where relevant.

Sleep and stress regulation are also important. Insufficient sleep may affect appetite, insulin sensitivity, recovery, and motivation for physical activity. Chronic stress may influence eating behavior, alcohol use, sedentary time, and metabolic regulation.

Medical care may be required when obesity, hypertension, dyslipidemia, diabetes, sleep apnea, fatty liver disease, or other complications are present. Lifestyle interventions

should complement, not replace, indicated pharmacological, nutritional, or surgical treatment.

Lifestyle Tip

A realistic starting plan may be:

1. walk for 10 minutes after one meal each day;
2. interrupt prolonged sitting with brief movement breaks;
3. complete two short strength sessions per week;
4. increase duration or intensity gradually;
5. protect sleep and recovery.

Consistency is more important than an ambitious plan that cannot be maintained.

Chapter summary

Key Points

- Physical activity, sedentary behavior, adiposity, and metabolic health are closely connected with oxidative and inflammatory regulation.
- Exercise causes temporary increases in reactive species that participate in physiological signaling and adaptation.
- Regular training may improve mitochondrial function, insulin sensitivity, endothelial function, antioxidant defense, and inflammatory regulation.
- Excessive or unfamiliar exercise without sufficient recovery may temporarily increase oxidative damage, fatigue, and inflammation.
- Sedentary behavior is distinct from insufficient exercise and should be addressed separately.
- Breaking up prolonged sitting with short periods of movement may support glucose regulation, circulation, and musculoskeletal health.
- Adipose tissue is an endocrine and immune organ, not merely an energy-storage compartment.
- Dysfunctional adipose tissue may contribute to chronic inflammation, mitochondrial stress, insulin resistance, and increased oxidative burden.
- Insulin resistance affects skeletal muscle, liver, and adipose tissue and may be both a cause and a consequence of metabolic and oxidative dysfunction.
- Metabolic health should not be assessed solely by body weight or BMI.
- Improvements in physical fitness, muscle strength, blood pressure, glucose regulation, sleep, and diet quality remain valuable even when weight loss is modest.
- Antioxidant supplements are not substitutes for regular movement, a healthy diet, adequate recovery or evidence-based metabolic care.

Practical Relevance

Physical activity is one of the clearest examples of beneficial oxidative eustress. Reactive species produced during exercise help activate adaptations that improve metabolic and cardiovascular resilience.

The preventive priority is therefore not to suppress exercise-related oxidation. It is to create a sustainable pattern of regular activity, reduced sedentary time, adequate strength, good recovery, and appropriate nutrition.

Weight-related care should remain supportive and non-stigmatizing. The clinically relevant goal is improved health and function, not simply a lower number on the scale.

Chapter 10. Sleep, Stress and Mental Health

Sleep, psychosocial stress, and mental health influence metabolic regulation, immune function, cardiovascular health, cognitive performance, and health-related behavior. They are also connected with inflammatory and redox processes, although oxidative stress represents only one part of these relationships.

Modern living conditions may disrupt recovery through irregular schedules, shift work, prolonged screen exposure, occupational pressure, caregiving responsibilities, social insecurity, and limited time for sleep. These factors often coexist with physical inactivity, poor diet, smoking, alcohol use, or excessive caffeine consumption.

Sleep should not be treated as a passive period or an optional lifestyle factor. It supports memory, emotional regulation, endocrine balance, immune function, tissue repair, and metabolic control. Mental health should similarly be understood as an integral component of overall health rather than merely the absence of psychiatric illness.

10.1 Sleep, Circadian Rhythms and Redox Balance

Sleep is regulated mainly by the interaction of two systems. The homeostatic sleep drive increases with time spent awake, while the circadian system coordinates sleep and wakefulness with the light-dark cycle.

Circadian rhythms influence:

- melatonin and cortisol secretion;
- body temperature;
- appetite and glucose metabolism;
- blood pressure;
- immune activity;
- cognitive performance;
- timing of sleep and alertness.

Regular exposure to daylight helps synchronize the circadian system, whereas bright light at night, irregular sleep schedules, jet lag, and night work may shift or weaken circadian signals.

Circadian disruption may affect metabolic and inflammatory regulation. Repeated misalignment between internal biological rhythms and external schedules has been associated with impaired glucose control, appetite dysregulation, fatigue, reduced alertness, and poorer psychological well-being.

Sleep and oxidative stress appear to have a bidirectional relationship. Sleep loss may increase sympathetic activity, inflammation, mitochondrial strain, and metabolic stress. Conversely, chronic inflammation, pain, illness, and oxidative disturbances may interfere with sleep continuity and quality.

Melatonin connects circadian regulation with redox biology. In addition to its role in sleep timing, it has demonstrated antioxidant and anti-inflammatory actions in experimental models. However, these properties do not justify treating melatonin as a universal

antioxidant supplement. Its clinical effect depends on indication, timing, dose, age, and sleep disorder.

The relationship between sleep and redox balance should therefore be interpreted as part of a broader regulatory system involving circadian timing, metabolism, endocrine function, immune responses, and cellular repair.

10.2 Sleep Loss, Fragmentation and Sleep Disorders

Most adults require approximately seven to nine hours of sleep, although individual needs vary. Health also depends on sleep quality, regularity, timing, and the absence of clinically important sleep disorders.

Insufficient or fragmented sleep may influence health through several overlapping mechanisms:

- increased sympathetic nervous system activity;
- altered cortisol secretion;
- impaired insulin sensitivity;
- appetite and weight dysregulation;
- endothelial dysfunction;
- inflammatory activation;
- reduced time for physiological recovery;
- impaired mood and cognitive performance.

The consequences of sleep loss are often amplified when it coexists with obesity, diabetes, smoking, alcohol consumption, chronic stress, or physical inactivity.

Sleep quality cannot be estimated solely from the number of hours spent in bed. Pain, anxiety, depression, environmental noise, medications, nocturia, breathing disorders, and frequent awakenings may reduce restorative sleep even when total sleep duration appears adequate.

Obstructive sleep apnea is especially relevant to oxidative stress. Repeated episodes of upper airway obstruction produce intermittent hypoxia followed by reoxygenation. This pattern may promote sympathetic activation, inflammation, endothelial dysfunction, and reactive species formation. Untreated sleep apnea is also associated with daytime fatigue and increased cardiometabolic risk.

Persistent insomnia may affect concentration, emotional regulation, work performance, and quality of life. It can also coexist with anxiety, depression, chronic pain, substance use, or medical disease. General sleep advice may be helpful, but chronic insomnia may require structured behavioral treatment and clinical evaluation.

For most adults with chronic insomnia disorder, cognitive behavioral therapy for insomnia (CBT-I) is the preferred first-line treatment. Sleep-hygiene advice may support treatment but is usually insufficient as a stand-alone intervention.

Caffeine and other stimulants can temporarily improve alertness but do not reverse the physiological consequences of inadequate sleep. Alcohol may shorten sleep onset

in some individuals but usually worsens sleep architecture, fragmentation, breathing, and next-day functioning.

Evidence-Based Note

Poor sleep is not simply a consequence of weak motivation or poor self-discipline. It may result from a sleep disorder, illness, medication, shift work, mental health condition, caregiving demands, housing conditions, or occupational schedules. Prevention should address the cause rather than relying only on general advice.

10.3 Psychosocial Stress and Allostatic Load

Stress is a normal response to challenge. Short-term activation of the stress response may improve alertness, mobilize energy, and support rapid adaptation. Stress becomes potentially harmful when it is severe, persistent, unpredictable, or not followed by adequate recovery.

The physiological stress response involves the sympathetic nervous system, catecholamines, the hypothalamic-pituitary-adrenal axis, cortisol, immune mediators, and changes in metabolism.

Repeated activation may contribute to **allostatic load**, meaning the cumulative physiological burden created by prolonged adaptation to stress. Allostatic load may involve changes in:

- blood pressure and heart rate;
- glucose and lipid metabolism;
- immune and inflammatory regulation;
- sleep and circadian rhythms;
- appetite and body weight;
- mood and cognitive function.

Chronic stress may also influence oxidative balance by increasing inflammatory signaling, mitochondrial demand, and sympathetic activity. However, oxidative stress should not be treated as the sole mechanism linking psychological stress with disease.

Behavioral pathways are equally important. Under prolonged stress, individuals may sleep less, move less, smoke, consume more alcohol, skip meals, overeat, or rely on highly processed foods. These responses may further increase cardiometabolic and inflammatory burden.

The health impact of stress depends partly on coping resources. Social support, financial stability, safe housing, autonomy at work, access to healthcare, physical activity, and opportunities for recovery may reduce its consequences.

Stress management should therefore not be presented entirely as an individual responsibility. Many stressors arise from working conditions, poverty, discrimination, illness, caregiving, violence, or social isolation and require organizational or social solutions in addition to personal coping strategies.

10.4 Mental Health, Lifestyle and Redox Biology

Mental and physical health are closely connected. Depression, anxiety, chronic stress, insomnia, substance use, metabolic disorders, and inflammatory conditions frequently coexist and may reinforce one another.

Research has identified altered inflammatory activity, mitochondrial function, and oxidative stress biomarkers in some people with depression, anxiety, or other mental health conditions. These findings may help explain selected biological mechanisms, but they do not establish oxidative stress as a single cause or provide a diagnostic test for an individual patient.

The relationship is bidirectional. Mental distress may worsen:

- sleep and circadian regulation;
- appetite and diet quality;
- physical activity;
- smoking and alcohol use;
- medication adherence;
- social participation;
- management of chronic disease.

At the same time, chronic pain, metabolic disease, inflammation, social isolation, and inadequate sleep may worsen psychological well-being.

Physical activity may support mood, stress tolerance, sleep, self-esteem, and social functioning. Its effects involve neurotransmission, neurotrophic signaling, inflammation, behavior, and social interaction rather than only antioxidant mechanisms.

Healthy dietary patterns may support metabolic and inflammatory health, but antioxidant-rich foods should not be described as treatments for depression, anxiety, or other psychiatric conditions. Similarly, vitamins, polyphenols, melatonin, or other supplements should not replace psychological therapy, social support, or indicated medical treatment.

Persistent low mood, severe anxiety, functional decline, substance dependence, or thoughts of self-harm require professional assessment. Lifestyle support may complement mental healthcare but should not delay it.

10.5 Prevention and Clinical Practice

Sleep and recovery should be assessed routinely in preventive care. Useful questions include:

- How many hours does the person usually sleep?
- Are sleep and wake times regular?
- Does the person feel rested during the day?
- Are there frequent awakenings, loud snoring, or witnessed pauses in breathing?
- Is caffeine or alcohol being used to regulate energy or sleep?
- Does shift work or caregiving limit recovery?

- Are anxiety, depression, pain, or medication affecting sleep?

Basic sleep-supporting measures include maintaining a relatively regular schedule, allowing sufficient time for sleep, obtaining daylight exposure during the day, reducing stimulating light before bedtime, limiting late caffeine, avoiding alcohol as a sleep aid, and creating a dark, quiet, and comfortable sleep environment.

Persistent insomnia, excessive daytime sleepiness, loud snoring, witnessed apneas, restless legs, or unexplained fatigue should prompt clinical evaluation rather than repeated self-treatment with supplements.

Stress-management strategies should be practical and specific. Depending on the individual, useful approaches may include:

- regular physical activity;
- breathing or relaxation exercises;
- structured problem-solving;
- mindfulness or grounding techniques;
- social connection;
- psychological therapy;
- workplace or schedule modification;
- treatment of anxiety, depression, pain, or addiction.

Recovery should also be planned. Work, study, exercise, caregiving, and social demands all require physiological and psychological resources. Without recovery, even positive activities may contribute to overload.

Antioxidant supplements should not be promoted as treatments for chronic stress, insomnia, anxiety, or depression. Nutritional deficiencies should be corrected when present, but the central interventions remain adequate sleep, reduction of harmful stressors, appropriate mental healthcare, physical activity, social support, and treatment of underlying sleep disorders.

Lifestyle Tip

Begin with one repeatable change: maintain a consistent wake-up time, stop caffeine earlier in the day, take a brief evening walk, reduce alcohol, or create a short screen-free period before sleep.

A small routine practiced regularly is usually more useful than an elaborate sleep or stress program that cannot be maintained.

Chapter summary

Key Points

- Sleep, stress, and mental health are interconnected with metabolic, endocrine, immune, inflammatory, and redox regulation.
- Sleep supports memory, emotional regulation, immune function, metabolic control, and physiological recovery.

- Sleep health depends on duration, quality, regularity, timing, and the absence of untreated sleep disorders.
- Circadian disruption may affect hormone secretion, glucose metabolism, appetite, blood pressure, alertness, and inflammatory activity.
- Sleep loss may contribute to oxidative and metabolic strain, but these relationships are complex and bidirectional.
- Obstructive sleep apnea exposes tissues to repeated cycles of hypoxia and reoxygenation and requires clinical recognition.
- Acute stress may be adaptive, whereas prolonged stress without recovery may contribute to allostatic load.
- Chronic stress affects health through both biological mechanisms and changes in sleep, diet, activity, smoking, and alcohol use.
- Oxidative stress may be involved in some mental health conditions but is not a single cause or a routine diagnostic marker.
- Antioxidant-rich foods and supplements do not replace sleep, stress reduction, psychological support, or medical treatment.
- Persistent sleep disturbance, severe mental distress, or functional impairment should prompt professional assessment.
- Prevention should combine individual strategies with attention to working conditions, social support, and environmental barriers to recovery.

Practical Relevance

Sleep and mental health are not secondary additions to preventive medicine. They influence metabolic risk, cardiovascular regulation, cognitive function, lifestyle behavior, and the ability to follow medical recommendations.

For healthcare professionals, assessment should extend beyond asking how many hours a person sleeps. Sleep quality, regularity, daytime functioning, possible sleep apnea, occupational schedules, caffeine and alcohol use, psychosocial stress, and mental health symptoms should also be considered.

The preventive goal is not to eliminate stress or achieve perfect sleep every night. It is to establish sufficient recovery, recognize clinically important disorders, reduce avoidable stressors, and support sustainable psychological and physiological resilience.

Chapter 11. Environmental and Occupational Factors

Environmental and occupational exposures are important determinants of oxidative stress and chronic disease risk. Unlike individual lifestyle factors such as diet, smoking, physical activity, or alcohol consumption, environmental exposures often depend on living conditions, air quality, housing, transport, industrial activity, workplace safety, climate, and public health regulation. For this reason, prevention requires both individual behavior and population-level action.

Major environmental and occupational sources of oxidative stress include outdoor and indoor air pollution, particulate matter, ozone, nitrogen oxides, tobacco smoke, heavy metals, pesticides, solvents, industrial chemicals, ultraviolet radiation, ionizing radiation, heat stress, shift work, and selected workplace hazards. Many of these exposures may increase reactive oxygen and nitrogen species formation directly or indirectly through inflammation, mitochondrial dysfunction, endothelial injury, immune activation, or impairment of antioxidant defense.

Air pollution is one of the major environmental health risks.

WHO reports that 99% of the global population lives in areas where air pollution levels exceed WHO guideline limits. Its current data portal attributes approximately 6.6 million deaths in 2021 to combined ambient and household air pollution.

Occupational exposures are also a major public health concern; the WHO/ILO joint estimates attributed at least 1.9 million deaths in 2016 to the 19 occupational risk factors included in the assessment.

From the perspective of preventive medicine, these exposures are important because they cannot be fully addressed through antioxidant intake. A healthy diet may support antioxidant defense and general resilience, but it cannot substitute for clean air, safe workplaces, reduced toxic exposure, appropriate protective equipment, and effective public health policy.

11.1 Air Pollution and Oxidative Stress

Air pollution consists of a complex mixture of gases, particles, metals, organic compounds, and secondary pollutants formed in the atmosphere. Important pollutants include particulate matter, nitrogen dioxide, ozone, sulfur dioxide, carbon monoxide, volatile organic compounds, and polycyclic aromatic hydrocarbons. Their sources include traffic, industry, power generation, biomass burning, household combustion, agriculture, construction, and wildfires.

Particulate matter is especially relevant to oxidative stress. Fine particles can penetrate deep into the respiratory tract, and smaller particles may enter the circulation or trigger systemic inflammatory responses. Exposure to particulate matter is associated with respiratory disease, cardiovascular disease, stroke, lung cancer, and premature mortality.

Air pollutants may induce oxidative stress through several mechanisms. Particles can carry redox-active metals and organic compounds, stimulate inflammatory cells, activate airway epithelial cells, impair mitochondrial function, and promote endothelial dysfunction. Ozone and nitrogen oxides may directly oxidize molecules in the respiratory

tract, while secondary inflammatory responses may increase systemic reactive species production.

The respiratory tract is the first site of exposure, but the effects of air pollution are not limited to the lungs. Systemic inflammation, oxidative modification of lipids and proteins, altered autonomic regulation, endothelial dysfunction, and changes in coagulation may contribute to cardiovascular events. This explains why air pollution is relevant not only to asthma and chronic obstructive pulmonary disease, but also to ischemic heart disease and stroke.

Air pollution is also relevant to cancer prevention. The International Agency for Research on Cancer classified outdoor air pollution as carcinogenic to humans, with sufficient evidence that exposure to outdoor air pollution causes lung cancer. Particulate matter from outdoor air pollution was also classified as carcinogenic to humans.

Indoor air pollution should also be considered. Sources include tobacco smoke, solid fuel combustion, cooking emissions, poor ventilation, mold, volatile organic compounds from building materials or household products, and occupational contaminants brought into the home. In some regions, household air pollution from cooking and heating with solid fuels remains a major contributor to respiratory and cardiovascular disease.

Practical Point

Individual actions such as avoiding outdoor exercise during severe smog, improving indoor ventilation, avoiding indoor smoking, and using cleaner cooking methods may reduce exposure. However, air pollution prevention also requires policy-level solutions, including clean energy, sustainable transport, emission control, urban planning, and occupational safety regulation.

11.2 Heavy Metals, Pesticides and Industrial Chemicals

Heavy metals and other toxic elements may contribute to oxidative stress through several mechanisms. Lead, cadmium, mercury, arsenic, and other metals may impair antioxidant enzymes, bind sulfhydryl groups, disturb mitochondrial function, promote inflammation, and interfere with DNA repair. Some metals may also participate in redox cycling or disturb the metabolism of essential elements such as iron, zinc, copper, and selenium.

Cadmium exposure may occur through tobacco smoke, industrial emissions, contaminated food, or occupational sources. Lead exposure may be related to old paints, contaminated dust, industrial work, batteries, ammunition, or polluted environments. Mercury exposure may occur in selected occupational settings and through consumption of contaminated fish, depending on species and region. Arsenic exposure may occur through contaminated water, food, or industrial processes.

Pesticides are another important group of environmental and occupational exposures. Their toxicity varies widely depending on chemical class, dose, route of exposure, duration, and individual susceptibility. Some pesticides have been linked with oxidative stress, mitochondrial dysfunction, endocrine disruption, neurotoxicity, reproductive effects, or carcinogenic mechanisms. Agricultural workers, pesticide applicators, and populations living near intensive agricultural areas may be at higher risk of exposure.

Industrial chemicals and solvents may also influence oxidative stress. Examples include benzene, formaldehyde, polycyclic aromatic hydrocarbons, persistent organic pollutants, and volatile organic compounds. These substances may be relevant in industrial work, laboratories, manufacturing, cleaning, painting, fuel handling, and other occupational settings.

The health effects of chemical exposures are often difficult to evaluate because real-life exposure usually involves mixtures rather than one isolated substance. Dose, duration, cumulative exposure, co-exposures, ventilation, protective equipment, nutrition, age, pregnancy, genetic susceptibility, and pre-existing disease all influence risk.

Occupational exposure limits, environmental monitoring, biomonitoring, substitution of hazardous substances, safe storage, training, and medical surveillance are therefore central elements of prevention. Antioxidant supplementation should not be used as a substitute for exposure control.

11.3 Radiation, Ultraviolet Exposure and Climate-Related Stressors

Radiation can contribute to oxidative stress through direct and indirect mechanisms. Ionizing radiation can damage DNA directly and can also generate reactive species through radiolysis of water. This may lead to DNA strand breaks, oxidative base modifications, lipid peroxidation, protein oxidation, and cellular death or mutation. Medical radiation has important diagnostic and therapeutic uses, but unnecessary exposure should be minimized according to radiation protection principles.

Ultraviolet radiation is a major environmental factor affecting the skin and eyes. UV exposure may generate reactive oxygen species, damage DNA, promote photoaging, impair local immune responses, and increase the risk of skin cancers. At the same time, sunlight exposure is involved in vitamin D synthesis, which illustrates the need for balanced, context-specific recommendations rather than complete avoidance of sunlight.

Heat stress is increasingly important in environmental and occupational health. WHO describes heat extremes as a factor that may worsen risks related to cardiovascular, mental, respiratory, and diabetes-related conditions and may cause acute kidney injury. Heat exposure may contribute to dehydration, cardiovascular strain, renal stress, inflammation, and oxidative imbalance, particularly during physical work or exercise.

Climate change may amplify several occupational and environmental hazards. The International Labour Organization identifies excessive heat, ultraviolet radiation, extreme weather events, workplace air pollution, vector-borne diseases, and agrochemicals as key occupational safety and health issues in a changing climate. These hazards may affect outdoor workers, agricultural workers, construction workers, emergency responders, transport workers, and people working in poorly ventilated indoor environments.

Wildfire smoke is another emerging concern in many regions. It contains fine particulate matter, gases, and organic compounds that may irritate the respiratory tract and promote

systemic inflammation and oxidative stress. Workers involved in firefighting, outdoor labor, or emergency response may experience repeated exposure.

Preventive strategies include shade, hydration, rest breaks, heat acclimatization, ventilation, protective clothing, sunscreen, respiratory protection when indicated, exposure monitoring, and modification of work schedules during extreme conditions. At the public health level, climate adaptation and environmental protection are increasingly relevant to chronic disease prevention.

11.4 Occupational Oxidative Stress and Workplace Prevention

Occupational exposures may contribute to oxidative stress through inhalation, skin contact, ingestion, heat load, physical strain, noise, psychosocial stress, shift work, and exposure to chemicals or particles. Work-related oxidative stress should therefore be understood broadly, not only as chemical toxicity.

Jobs with potential oxidative or inflammatory exposures include mining, welding, construction, agriculture, healthcare, firefighting, transportation, manufacturing, laboratory work, cleaning, painting, waste management, and work involving solvents, metals, fumes, dust, radiation, pesticides, or extreme temperatures.

Welding fumes and metal dusts may contain particles and metals capable of inducing oxidative and inflammatory responses in the respiratory tract. Silica dust, asbestos, diesel exhaust, and combustion products are also important occupational hazards. Some exposures are linked not only with oxidative stress, but also with fibrosis, chronic respiratory disease, cardiovascular risk, and cancer.

Shift work and night work may influence oxidative stress indirectly through circadian disruption, sleep deprivation, metabolic dysregulation, stress, and altered eating patterns. These mechanisms overlap with those discussed in the chapter on sleep and stress. Occupational health should therefore include not only chemical and physical safety, but also work organization, rest periods, and psychosocial risk management.

Workplace prevention should follow the hierarchy of controls. The most effective approach is elimination of the hazard, followed by substitution with a safer alternative, engineering controls such as enclosure or ventilation, administrative controls such as training and work scheduling, and finally personal protective equipment. National Institute for Occupational Safety and Health (NIOSH) emphasizes that elimination, substitution, and engineering controls are generally more effective because they control exposures without requiring constant individual action.

Personal protective equipment is important, but it should not be the only preventive strategy when higher-level controls are possible. Respirators, gloves, protective clothing, eye protection, and hearing protection can reduce exposure, but their effectiveness depends on correct selection, training, fit, maintenance, and consistent use.

Healthcare professionals should ask about occupation and workplace exposures when evaluating chronic respiratory symptoms, skin problems, neurological complaints, fertility issues, unexplained liver or kidney abnormalities, recurrent headaches, or suspected toxic exposure. A brief occupational history may reveal preventable risk factors that would otherwise be missed.

11.5 The Role of Occupational Medicine Physicians in Prevention

Occupational medicine physicians play an important role in the prevention of environmentally and occupationally related health risks. Their work connects clinical medicine, public health, toxicology, epidemiology, ergonomics, occupational hygiene, and workplace safety. WHO describes occupational health as a field of public health focused on promoting and maintaining the highest degree of physical, mental, and social well-being of workers in all occupations.

In the context of oxidative stress, the role of occupational medicine is not to recommend antioxidant supplementation as a primary solution. The main tasks are to identify hazardous exposures, assess health risks, support early detection of work-related disease, and help reduce harmful exposures at their source.

A careful occupational history is one of the most important tools in preventive medicine. It should include current and previous occupations, job tasks, duration of exposure, substances used at work, ventilation conditions, use of personal protective equipment, shift work, heat exposure, radiation exposure, physical workload, psychosocial stressors, and whether symptoms improve away from work. Such information may reveal occupational contributors to respiratory symptoms, skin disorders, neurological complaints, reproductive problems, liver or kidney abnormalities, cardiovascular risk, or unexplained fatigue.

Occupational medicine physicians participate in health surveillance of workers exposed to chemical, physical, biological, ergonomic, and psychosocial hazards. Depending on the type of exposure, this may include clinical examination, lung function testing, audiometry, vision testing, laboratory tests, biological monitoring, assessment of cardiovascular risk, or evaluation of fitness for specific work tasks. The purpose of such surveillance is not only to detect disease, but also to identify early signs of excessive exposure and recommend preventive measures before irreversible damage occurs.

The interpretation of oxidative stress biomarkers in occupational settings requires caution. Markers such as lipid peroxidation products, protein oxidation markers, DNA damage markers, or antioxidant enzyme activity may be useful in research, but they are generally not sufficient as standalone diagnostic tools for individual workers. Occupational medicine should therefore prioritize validated exposure assessment, clinical evaluation, and recognized occupational health procedures rather than relying on nonspecific oxidative stress tests.

A central principle in occupational prevention is exposure control. The hierarchy of controls should guide workplace interventions: elimination, substitution, engineering controls, administrative controls, and personal protective equipment. Advising workers to use antioxidants, vitamins, or supplements cannot replace reducing exposure to fumes, dusts, solvents, pesticides, metals, radiation, heat, or other workplace hazards.

Occupational medicine physicians also help identify vulnerable workers. Pregnancy, chronic respiratory disease, cardiovascular disease, liver or kidney disease, immunosuppression, older age, medication use, and previous occupational disease may increase susceptibility to workplace hazards. In such situations, recommendations may

include temporary work modification, exposure reduction, additional monitoring, or reassessment of fitness for specific tasks.

Another important responsibility is advising on return to work and work adaptation. After illness, injury, toxic exposure, cancer treatment, cardiovascular events, respiratory disease, or mental health problems, workers may require gradual return, task modification, reduced exposure, ergonomic changes, or coordination with other healthcare professionals. This role is preventive because appropriate work adaptation may reduce relapse, disability, and long-term exclusion from employment.

Occupational physicians also contribute to workplace health promotion. Smoking cessation, alcohol reduction, healthy diet, physical activity, sleep, vaccination, stress management, and cardiovascular risk assessment may all be relevant in occupational settings. However, workplace health promotion should not shift responsibility away from employers or replace exposure control. Advising workers to eat more antioxidant-rich foods is not an acceptable substitute for reducing exposure to toxic substances.

Ethical principles are essential in occupational medicine. The physician must protect workers' health, respect medical confidentiality, communicate risks clearly, and provide evidence-based recommendations. At the same time, occupational medicine often requires communication with employers, safety professionals, occupational hygienists, public health authorities, and worker representatives. This makes independence, trust, and transparency particularly important.

Overall, occupational medicine physicians are key actors in translating knowledge about environmental and occupational oxidative stress into prevention. Their role includes recognizing hazardous exposures, monitoring health, advising on workplace controls, supporting vulnerable workers, promoting healthy behaviors, and helping maintain safe and sustainable work environments.

11.6 Prevention: Environmental Health and Public Health Perspective

Environmental and occupational oxidative stress highlights the importance of prevention beyond individual behavior. People cannot always choose the air they breathe, the chemicals present in their workplace, or the climate conditions affecting their community. Effective prevention therefore requires regulation, monitoring, safer technologies, workplace standards, environmental justice, and public health policy.

Occupational prevention requires cooperation between workers, employers, occupational medicine physicians, occupational hygienists, safety engineers, public health authorities, and policymakers. The physician's role is important, but effective prevention depends on a system in which hazards are identified, assessed, controlled, and monitored. ILO emphasizes that workers and their representatives should cooperate with employers, follow safety instructions, correctly use protective equipment, and report hazardous conditions or accidents.

At the individual level, practical measures include avoiding tobacco smoke, improving indoor ventilation, using protective equipment when required, following safety instructions for chemicals, reducing unnecessary pesticide exposure, storing chemicals

safely, avoiding combustion indoors when possible, and protecting the skin from excessive UV radiation.

At the workplace level, prevention includes risk assessment, exposure monitoring, substitution of hazardous substances, ventilation, closed systems, safe handling procedures, training, medical surveillance, emergency planning, and worker participation in safety decisions. Workplaces should also address heat stress, shift work, psychosocial stress, and fatigue.

At the community level, environmental prevention includes clean air policies, safe drinking water, waste management, green urban planning, sustainable transport, reduction of industrial emissions, climate adaptation, and protection of vulnerable populations. Children, pregnant women, older adults, people with chronic diseases, outdoor workers, and socially disadvantaged groups may be particularly vulnerable to environmental hazards.

Evidence-Based Note

Laboratory antioxidant capacity or increased intake of antioxidant-rich foods should not be used to justify continued exposure to polluted air, toxic metals, pesticides, radiation, or unsafe work conditions. The primary preventive strategy is exposure reduction. Nutrition may support resilience, but it cannot replace environmental and occupational health protection.

Chapter summary

Key Points

- Environmental and occupational exposures are important determinants of oxidative stress and chronic disease risk.
- Air pollution contributes to respiratory, cardiovascular, metabolic, and cancer-related health risks through oxidative and inflammatory mechanisms.
- Particulate matter may affect both the lungs and systemic circulation.
- Outdoor air pollution and particulate matter from outdoor air pollution have been classified as carcinogenic to humans.
- Heavy metals may impair antioxidant defense, disturb mitochondrial function, bind thiol groups, and interfere with DNA repair.
- Pesticides, solvents, industrial chemicals, combustion products, and occupational dusts may contribute to oxidative and inflammatory burden.
- Ionizing radiation and excessive ultraviolet exposure may damage DNA and cellular structures through direct and oxidative mechanisms.
- Heat stress and climate-related hazards are increasingly important occupational and public health concerns.
- Occupational oxidative stress may result from chemical, physical, biological, organizational, and psychosocial factors.

- Occupational medicine physicians play an important preventive role by identifying workplace hazards, assessing exposure-related health risks, and supporting early detection of occupational disease.
- In occupational prevention, exposure control is more important than antioxidant supplementation; the hierarchy of controls should guide workplace interventions.
- Occupational health requires cooperation between physicians, workers, employers, occupational hygienists, safety specialists, and public health authorities.
- Antioxidant-rich nutrition may support general health, but it cannot compensate for toxic environmental or occupational exposures.

Practical Relevance

Environmental and occupational factors show that oxidative stress prevention is not only an individual responsibility. Clean air, safe workplaces, climate adaptation, chemical regulation, and protection from hazardous exposures are essential components of preventive medicine.

The role of occupational medicine is especially important because many workplace exposures are not fully controlled by individual lifestyle choices. A worker exposed to dust, fumes, solvents, pesticides, metals, radiation, heat, shift work, or psychosocial stress may need medical surveillance, workplace assessment, and exposure reduction rather than general advice about diet or supplements.

For healthcare professionals, asking about workplace conditions, chemical exposures, air pollution, heat exposure, shift work, and environmental risks can improve prevention and early recognition of exposure-related disease. For public health, reducing harmful exposures is more effective than attempting to compensate for them with supplements or isolated antioxidant interventions.

Chapter 12. Cardiovascular Diseases

Cardiovascular diseases are among the most important chronic non-communicable diseases worldwide and remain a leading cause of mortality and disability. They include coronary heart disease, cerebrovascular disease, peripheral artery disease, heart failure, hypertensive heart disease, and other disorders of the heart and blood vessels.

Their development is multifactorial and involves interactions among genetic predisposition, age, blood pressure, lipid and glucose metabolism, smoking, diet, physical activity, obesity, alcohol consumption, psychosocial stress, sleep, air pollution, and selected occupational exposures.

Oxidative stress is one of the biological mechanisms linking these factors with vascular and cardiac injury. It may contribute to endothelial dysfunction, reduced nitric oxide bioavailability, lipid oxidation, vascular inflammation, platelet activation, mitochondrial impairment, and tissue remodeling.

However, cardiovascular diseases should not be explained by oxidative stress alone. They result from complex interactions among metabolic, hemodynamic, inflammatory, genetic, environmental, and behavioral mechanisms. From the perspective of preventive medicine, oxidative stress is useful as an integrating concept, but prevention must focus on comprehensive cardiovascular risk reduction rather than isolated antioxidant supplementation.

12.1 Oxidative Stress and Endothelial Dysfunction

The endothelium is a metabolically active layer of cells lining the inner surface of blood vessels. It regulates vascular tone, blood flow, platelet activity, inflammation, coagulation, vascular permeability, and interactions between circulating cells and the vessel wall.

Nitric oxide is one of the most important endothelial mediators. It promotes vasodilation, inhibits platelet aggregation, reduces leukocyte adhesion, and supports vascular homeostasis.

Under conditions of oxidative stress, superoxide anion may react with nitric oxide, reducing nitric oxide bioavailability and promoting the formation of peroxynitrite. This contributes to impaired vasodilation, endothelial dysfunction, and nitrosative stress.

Endothelial dysfunction is an early feature of many cardiovascular disorders. It may occur in hypertension, atherosclerosis, diabetes mellitus, obesity, chronic kidney disease, smoking, aging, and chronic inflammatory states. It reflects an imbalance between protective endothelial signaling and injurious processes such as oxidative stress, inflammation, mechanical strain, and metabolic dysfunction.

Several sources may contribute to vascular reactive oxygen species production, including NADPH oxidases, mitochondria, xanthine oxidase, uncoupled nitric oxide synthase, inflammatory cells, and other redox-active enzymes. At controlled levels, reactive species participate in vascular signaling. In excess, they contribute to oxidative distress and vascular injury.

Clinically, endothelial dysfunction may promote vasoconstriction, increased vascular stiffness, leukocyte adhesion, platelet activation, smooth muscle cell proliferation, and progression of atherosclerosis. It is therefore an important biological link between oxidative stress and cardiovascular disease.

Assessment of endothelial function may be performed in research and selected clinical settings using methods such as flow-mediated dilation. In routine preventive practice, however, greater emphasis is placed on established risk factors such as blood pressure, lipid profile, glucose metabolism, smoking, body weight, physical activity, and dietary pattern.

12.2 LDL Oxidation, Atherosclerosis and Vascular Inflammation

Atherosclerosis is a chronic inflammatory disease of the arterial wall. It develops over many years and involves endothelial dysfunction, lipid accumulation, immune cell activation, smooth muscle cell migration, extracellular matrix remodeling, and plaque formation.

Low-density lipoprotein (LDL) particles play a central role in atherosclerosis. When LDL particles enter and become retained in the arterial wall, they may undergo oxidative, enzymatic, and other modifications. These modified particles may activate endothelial cells, promote inflammatory signaling, attract monocytes, and be taken up by macrophages.

Macrophages that accumulate modified lipoproteins become foam cells, which are characteristic of early atherosclerotic lesions.

Oxidative modification of LDL may amplify local inflammation by generating signals that promote endothelial activation and immune cell recruitment. It is one of several processes contributing to plaque growth and persistent vascular inflammation.

Inflammation and oxidative stress reinforce one another within the arterial wall. Activated immune cells generate reactive oxygen and nitrogen species, while oxidized lipids and damaged cells further stimulate inflammatory signaling. This creates a local microenvironment that supports progression from early fatty streaks to more complex plaques.

Advanced plaques may become clinically dangerous when they rupture or erode, exposing thrombogenic material to the bloodstream. This may trigger platelet activation and clot formation, leading to acute coronary syndrome or ischemic stroke.

Oxidative stress may contribute to plaque instability through inflammation, extracellular matrix degradation, endothelial injury, and smooth muscle cell dysfunction. Nevertheless, the involvement of oxidative mechanisms does not mean that antioxidant supplements reliably prevent atherosclerosis. Clinical prevention depends primarily on the management of established cardiovascular risk factors.

12.3 Hypertension, Ischemia-Reperfusion Injury and Cardiac Remodeling

Hypertension is one of the most important modifiable risk factors for cardiovascular disease. It increases mechanical stress on blood vessels and the heart, contributing to vascular remodeling, arterial stiffness, left ventricular hypertrophy, heart failure, stroke, kidney disease, and coronary events.

Oxidative stress may contribute to hypertension through several mechanisms. Excessive reactive oxygen species can reduce nitric oxide bioavailability, impair endothelial relaxation, promote vasoconstriction, increase vascular inflammation, and stimulate smooth muscle cell growth.

Angiotensin II, sympathetic activation, high salt intake, obesity, diabetes, inflammation, and mechanical strain may all influence oxidative pathways involved in blood pressure regulation.

Vascular remodeling in hypertension involves structural and functional changes in the arterial wall, including increased stiffness, altered extracellular matrix, smooth muscle cell hypertrophy, endothelial dysfunction, and inflammation. Oxidative stress contributes to this process but interacts with renal function, neurohormonal regulation, hemodynamic load, and metabolic factors.

Ischemia-reperfusion injury is another important cardiovascular context in which oxidative stress plays a role. During ischemia, tissue oxygen supply is reduced. When blood flow is restored, sudden oxygen availability may lead to rapid reactive species production. This can damage lipids, proteins, mitochondria, and DNA and may contribute to cell death, inflammation, and microvascular dysfunction.

Ischemia-reperfusion mechanisms are relevant to myocardial infarction, stroke, cardiac arrest, transplantation, and selected surgical procedures. They illustrate the dual role of oxygen: it is essential for survival, but its abrupt restoration to vulnerable tissue may intensify oxidative injury.

Heart failure is also associated with oxidative stress and mitochondrial dysfunction. The heart has high energy requirements and depends strongly on mitochondrial ATP production. In heart failure, impaired energy metabolism, altered calcium handling, neurohormonal activation, inflammation, fibrosis, and structural remodeling may all contribute to disease progression.

Reactive species may participate in contractile dysfunction, apoptosis, fibrosis, and mitochondrial injury. However, heart failure is a complex clinical syndrome and cannot be reduced to oxidative stress alone.

Despite strong mechanistic evidence, antioxidant therapy has not become a central treatment for hypertension, ischemic heart disease, or heart failure. Management remains based on blood pressure control, lipid-lowering treatment when indicated, diabetes care, smoking cessation, physical activity, healthy dietary patterns, weight-related metabolic improvement, and appropriate pharmacological or interventional treatment.

12.4 Prevention and Cardiovascular Risk Reduction

Cardiovascular prevention should be based on total risk reduction rather than isolated biological mechanisms. Oxidative stress may help explain how different risk factors affect the cardiovascular system, but preventive decisions should be based on clinically meaningful outcomes.

The major preventive priorities include smoking cessation, blood pressure control, lipid management, diabetes prevention and treatment, regular physical activity, healthy dietary patterns, weight-related metabolic improvement when appropriate, reduction of harmful alcohol use, adequate sleep, and reduction of environmental and occupational exposures.

Dietary patterns rich in vegetables, fruits, legumes, whole grains, nuts, seeds, and unsaturated fats may support blood pressure, lipid metabolism, glucose regulation, endothelial function, and body weight management. Their value is not limited to antioxidant content.

Regular physical activity improves cardiorespiratory fitness, endothelial function, insulin sensitivity, blood pressure, lipid metabolism, and inflammatory regulation. The transient reactive species generated during exercise also participate in physiological adaptation.

Environmental factors should not be overlooked. Tobacco smoke, particulate air pollution, heat stress, shift work, and selected occupational exposures may contribute to cardiovascular risk through oxidative, inflammatory, autonomic, and thrombotic mechanisms.

Antioxidant supplements should not be presented as substitutes for established cardiovascular prevention. High antioxidant activity measured in vitro does not demonstrate cardiovascular benefit in humans. The strongest evidence supports comprehensive control of modifiable risk factors.

Evidence-Based Note

Cardiovascular prevention should prioritize established risk factors: smoking, blood pressure, LDL cholesterol, diabetes, obesity-related metabolic risk, physical inactivity, poor diet quality, harmful alcohol use, and environmental exposure.

Antioxidant-rich foods may support cardiovascular health as part of a healthy dietary pattern, but isolated antioxidant supplements should not be promoted as a primary cardiovascular prevention strategy.

Chapter summary

Key Points

- Cardiovascular diseases are multifactorial and involve metabolic, hemodynamic, inflammatory, genetic, environmental, and lifestyle-related mechanisms.
- Oxidative stress may contribute to endothelial dysfunction, reduced nitric oxide bioavailability, lipid oxidation, vascular inflammation, mitochondrial impairment, and tissue remodeling.

- Endothelial dysfunction is an early feature of many cardiovascular disorders.
- Retention and modification of LDL within the arterial wall contribute to endothelial activation, foam-cell formation, and atherosclerotic plaque development.
- Inflammation and oxidative stress may reinforce one another within the arterial wall.
- Oxidative mechanisms may contribute to hypertension, ischemia-reperfusion injury, heart failure, and cardiac remodeling.
- The presence of oxidative stress in cardiovascular disease does not establish that antioxidant supplementation will improve clinical outcomes.
- Cardiovascular prevention should prioritize smoking cessation, blood pressure and lipid control, diabetes care, physical activity, healthy dietary patterns, and reduction of harmful environmental exposures.
- Antioxidant-rich foods may support cardiovascular health, but they should not be treated as stand-alone therapies.

Practical Relevance

Oxidative stress helps explain how major cardiovascular risk factors may converge on common vascular and metabolic pathways. Smoking, hypertension, diabetes, obesity, inactivity, poor diet, alcohol, air pollution, and chronic stress may all influence endothelial function and vascular inflammation.

For preventive medicine, the practical message is clear: cardiovascular risk reduction requires comprehensive lifestyle and medical management. Antioxidant-containing foods may support a healthy dietary pattern, but they cannot replace smoking cessation, blood pressure control, lipid management, physical activity, diabetes care, or evidence-based treatment.

Chapter 13. Diabetes Mellitus and Metabolic Disorders

Diabetes mellitus comprises a group of metabolic diseases characterized by chronic disturbances in glucose regulation. Type 1 diabetes results primarily from autoimmune destruction of pancreatic beta cells, whereas type 2 diabetes develops through interactions between insulin resistance, progressive beta-cell dysfunction, genetic susceptibility, adiposity, lifestyle, and environmental factors. Gestational diabetes develops during pregnancy and is associated with increased metabolic risk for both mother and child.

Oxidative stress is involved in several aspects of diabetes pathophysiology. Chronic hyperglycemia, elevated circulating fatty acids, mitochondrial dysfunction, inflammation, and altered cellular signaling may increase reactive species production. In turn, oxidative stress may impair insulin signaling, endothelial function, mitochondrial metabolism, and tissue repair.

However, diabetes should not be described as an oxidative stress disorder alone. Its development and complications are influenced by metabolic, autoimmune, vascular, hormonal, genetic, behavioral, and social factors. The presence of oxidative stress does not demonstrate that antioxidant supplementation will prevent diabetes or improve its clinical outcomes.

From the perspective of preventive medicine, the most important objectives are early identification of metabolic risk, prevention or delay of type 2 diabetes where possible, effective glycemic management, reduction of cardiovascular and renal risk, and prevention of long-term complications.

13.1 Hyperglycemia, Glycation and Reactive Species

Chronic hyperglycemia contributes to tissue injury through several interacting pathways. These include mitochondrial reactive species production, advanced glycation end-product formation, activation of protein kinase C, increased polyol pathway activity, altered hexosamine metabolism, and inflammatory signaling.

Persistent hyperglycemia alters mitochondrial substrate handling, cellular redox state, and metabolic signaling. Depending on the tissue and disease stage, mitochondrial dysfunction may increase or redistribute reactive-species production, impair energy metabolism, and reduce cellular resilience.

Advanced glycation end products are formed through non-enzymatic reactions between reducing sugars and proteins, lipids, or nucleic acids. Their accumulation may alter the structure and function of long-lived molecules such as collagen and other extracellular matrix proteins.

Advanced glycation end products may also bind to the receptor for advanced glycation end products (RAGE). This interaction can activate inflammatory and redox-sensitive pathways, promote endothelial dysfunction, and contribute to vascular and tissue remodeling.

The polyol pathway provides another connection between hyperglycemia and oxidative stress. In this pathway, glucose is converted to sorbitol by aldose reductase, using NADPH. Excessive pathway activity may reduce the availability of NADPH required for glutathione regeneration and other reducing systems.

Protein kinase C activation and increased hexosamine pathway activity may affect vascular permeability, blood flow, inflammatory mediator production, extracellular matrix formation, and endothelial signaling.

These pathways do not operate independently. Hyperglycemia, dyslipidemia, inflammation, oxidative stress, and vascular dysfunction may reinforce one another, particularly when glucose control remains poor over long periods.

Biomarkers such as malondialdehyde, 8-oxodG, protein carbonyls, and antioxidant enzyme activity have been studied in diabetes research. They may provide mechanistic information but are not usually required for routine diagnosis or management. Clinical assessment relies on validated measures such as blood glucose, HbA1c, kidney function, albuminuria, lipid profile, blood pressure, retinal examination, and neurological or foot assessment.

13.2 Insulin Resistance and Beta-Cell Dysfunction

Insulin resistance occurs when insulin-sensitive tissues respond less effectively to insulin. The most important tissues involved are skeletal muscle, liver, and adipose tissue.

In skeletal muscle, insulin resistance reduces glucose uptake after meals. In the liver, it may contribute to excessive glucose production and abnormal lipid metabolism. In adipose tissue, impaired insulin action may increase fatty acid release and promote inflammatory and metabolic dysfunction.

As discussed in Chapter 9, obesity and adipose tissue dysfunction can contribute to insulin resistance through altered adipokine secretion, immune cell infiltration, chronic low-grade inflammation, and ectopic fat accumulation. However, insulin resistance can also occur in individuals without obesity, and metabolic risk should not be assessed by body weight alone.

Elevated circulating fatty acids and lipid intermediates may accumulate in skeletal muscle, liver, pancreas, and other organs. This process, often described as lipotoxicity, may impair insulin signaling, mitochondrial function, and cellular survival.

Pancreatic beta cells initially respond to insulin resistance by increasing insulin secretion. Over time, genetic susceptibility, metabolic overload, inflammation, endoplasmic reticulum stress, amyloid deposition, and oxidative stress may contribute to progressive beta-cell dysfunction.

Beta-cell failure is therefore not caused by one mechanism. It develops through interactions between metabolic demand and limited cellular capacity to maintain insulin production and secretion.

In type 1 diabetes, immune-mediated beta-cell destruction is the central process. Inflammatory cells and cytokines may generate reactive oxygen and nitrogen species,

which can contribute to beta-cell injury. Nevertheless, oxidative stress is an accompanying mechanism rather than the primary explanation for autoimmune disease.

Gestational diabetes involves insufficient pancreatic compensation for the increased insulin resistance of pregnancy. It requires appropriate clinical management because maternal hyperglycemia may affect pregnancy outcomes and is associated with greater future risk of type 2 diabetes.

Metabolic dysfunction-associated steatotic liver disease is also closely connected with insulin resistance. Hepatic fat accumulation, inflammation, altered lipid metabolism, and mitochondrial stress may contribute to progression from simple steatosis to more advanced liver injury. The condition should be approached through cardiometabolic risk management rather than antioxidant supplementation alone.

13.3 Diabetic Complications and Tissue Injury

Long-term diabetes may affect both small and large blood vessels. Microvascular complications include diabetic retinopathy, kidney disease, and neuropathy. Macrovascular complications include coronary heart disease, stroke, and peripheral artery disease.

Persistent hyperglycemia is an important contributor, but complications are also influenced by blood pressure, lipid abnormalities, smoking, kidney function, disease duration, genetic factors, inflammation, and quality of medical care.

Diabetic Retinopathy

The retina is highly metabolically active and vulnerable to vascular and oxidative injury. Hyperglycemia may contribute to capillary dysfunction, increased vascular permeability, inflammation, ischemia, and abnormal growth-factor signaling.

Over time, these processes may lead to retinal hemorrhage, edema, capillary closure, and pathological neovascularization. Regular retinal screening is essential because early disease may develop without noticeable visual symptoms.

Diabetic Kidney Disease

Diabetic kidney disease involves glomerular, tubular, vascular, and interstitial injury. Hyperglycemia, altered renal hemodynamics, inflammation, advanced glycation, oxidative stress, and fibrosis may all contribute.

Kidney involvement is assessed clinically using estimated glomerular filtration rate and urinary albumin excretion. Early identification is important because kidney disease increases cardiovascular risk and may progress despite the absence of early symptoms.

Diabetic Neuropathy

Diabetic neuropathy may affect peripheral sensory, motor, and autonomic nerves. Proposed mechanisms include microvascular injury, mitochondrial dysfunction, oxidative stress, sorbitol accumulation, inflammation, and impaired nerve repair.

Symptoms may include pain, numbness, altered temperature or vibration sensation, weakness, gastrointestinal dysfunction, cardiovascular autonomic symptoms, or impaired awareness of foot injury.

Loss of protective sensation increases the risk of ulcers and infection. Regular foot assessment, appropriate footwear, smoking cessation, vascular evaluation, and patient education are therefore important components of prevention.

Macrovascular Complications

Cardiovascular disease is a major cause of morbidity and mortality in people with diabetes. Insulin resistance, hyperglycemia, hypertension, dyslipidemia, inflammation, endothelial dysfunction, platelet activation, and oxidative modification of lipoproteins may all contribute to atherosclerosis.

Prevention should not focus only on glucose. Blood pressure management, lipid-lowering treatment where indicated, smoking cessation, physical activity, kidney protection, and management of obesity-related risk are equally important.

The contribution of oxidative stress to diabetic complications is biologically relevant, but it does not establish antioxidant supplements as effective treatment. The pathophysiology is too complex to be addressed through nonspecific suppression of reactive species.

13.4 Prevention and Clinical Management

Prevention of type 2 diabetes should focus on individuals with increased metabolic risk, including people with prediabetes, central adiposity, previous gestational diabetes, family history of diabetes, physical inactivity, hypertension, dyslipidemia, or other features of metabolic syndrome.

The most important preventive strategies include:

- regular physical activity;
- reduced sedentary time;
- healthy dietary patterns;
- weight-related metabolic improvement where appropriate;
- adequate sleep;
- management of chronic stress;
- smoking cessation;
- reduction of harmful alcohol use;
- early identification and treatment of hypertension and dyslipidemia.

Dietary prevention should emphasize overall food quality rather than isolated antioxidant intake. Vegetables, fruits, legumes, whole grains, nuts, seeds, and minimally processed foods may support glucose regulation, satiety, lipid metabolism, cardiovascular health, and gut microbiota.

Their effects are not explained only by antioxidant compounds. Fiber, energy density, food structure, fatty acid quality, meal composition, and replacement of ultra-processed foods are also important.

Physical activity improves insulin sensitivity and glucose uptake and supports mitochondrial function, muscle mass, vascular health, and body composition. Both aerobic activity and resistance training are useful. Even modest increases in daily movement or short walks after meals may improve glucose regulation.

Weight management should be individualized and non-stigmatizing. Improvements in glycemia, blood pressure, liver fat, physical fitness, and quality of life may occur even when weight loss is modest.

Sleep disorders, particularly obstructive sleep apnea, may worsen insulin resistance and cardiometabolic risk. Persistent poor sleep, daytime sleepiness, or symptoms of sleep apnea should therefore be assessed rather than treated only with general lifestyle advice.

Medical management remains essential after diabetes develops. Depending on the individual, care may include glucose-lowering medication, blood pressure treatment, lipid management, kidney-protective therapy, retinal screening, foot care, vaccination, and cardiovascular risk reduction.

The goal of glycemic treatment should be individualized according to age, disease duration, comorbidities, hypoglycemia risk, pregnancy, functional status, and patient preferences.

Antioxidant supplements should not be presented as primary prevention or treatment for diabetes. Some products may influence glucose metabolism or interact with medication, but changes in oxidative biomarkers do not necessarily indicate improved clinical outcomes.

Evidence-Based Note

In diabetes, the strongest evidence supports comprehensive metabolic and cardiovascular risk management. Antioxidant-rich foods may contribute to a healthy dietary pattern, but supplements cannot replace glycemic control, physical activity, blood pressure and lipid management, kidney and retinal monitoring, smoking cessation, or evidence-based medication.

Chapter summary

Key Points

- Diabetes mellitus includes type 1 diabetes, type 2 diabetes, gestational diabetes, and other less common forms with different underlying mechanisms.
- Oxidative stress may contribute to diabetes pathophysiology but is not a single cause of the disease.
- Chronic hyperglycemia may increase reactive species formation through mitochondrial stress, glycation, the polyol pathway, protein kinase C activation, and inflammatory signaling.
- Advanced glycation end products may alter tissue proteins and activate inflammatory and vascular pathways.

- Type 2 diabetes develops through interactions between insulin resistance and progressive beta-cell dysfunction.
- Adipose tissue dysfunction, lipotoxicity, inflammation, and ectopic fat accumulation may worsen insulin resistance.
- Diabetic complications include retinopathy, kidney disease, neuropathy, coronary heart disease, stroke, and peripheral artery disease.
- Prevention and management should address glucose, blood pressure, lipids, smoking, physical activity, diet, sleep, body composition, and kidney and cardiovascular risk.
- Oxidative stress biomarkers are useful mainly in research and are not substitutes for validated clinical assessment.
- Antioxidant supplements should not be promoted as primary prevention or treatment for diabetes or its complications.

Practical Relevance

Diabetes demonstrates how oxidative stress interacts with metabolism, inflammation, vascular function, and lifestyle. However, the practical priority is not to reduce a single oxidative biomarker.

Effective prevention and care require comprehensive management: healthy dietary patterns, regular physical activity, reduced sedentary time, individualized weight-related support, adequate sleep, smoking cessation, blood pressure and lipid control, glucose-lowering treatment where necessary, and regular monitoring for complications.

Antioxidant-rich foods may support dietary quality, but they cannot replace metabolic risk assessment, evidence-based diabetes treatment, kidney and retinal screening, foot care, or cardiovascular prevention.

Chapter 14. Cancer and Oxidative Stress

Cancer comprises a heterogeneous group of diseases characterized by uncontrolled cell growth, accumulation of genetic and epigenetic alterations, invasion of surrounding tissues, and, in some cases, metastasis. Its development is multifactorial and involves aging, inherited susceptibility, environmental and occupational exposures, infections, immune function, hormonal influences, metabolic disturbances, inflammation, and lifestyle-related factors.

Oxidative stress is one of the biological mechanisms involved in cancer initiation, progression, and response to treatment. Reactive oxygen and nitrogen species may damage DNA, modify proteins and lipids, influence inflammatory pathways, and alter cellular signaling. However, cancer should not be described as a disease caused simply by excess free radicals.

Reactive species have context-dependent effects. Persistent or poorly controlled production may contribute to molecular injury and malignant transformation, while excessive oxidative stress may also damage or kill established cancer cells. This dual role is essential for understanding why antioxidant-rich foods, isolated antioxidant supplements, and redox-modulating cancer therapies cannot be considered biologically equivalent.

14.1 Oxidative DNA Damage, Inflammation and Cancer Initiation

Reactive species may contribute to cancer initiation by modifying DNA bases, producing strand breaks, affecting DNA repair, and altering proteins involved in cell-cycle regulation and apoptosis. When such damage is incorrectly repaired or escapes cellular control, mutations may accumulate.

Guanine is particularly susceptible to oxidative modification, and compounds such as 8-oxodG are frequently investigated as markers of oxidative DNA damage. These markers are useful in research but are not specific to cancer and should not be used as standalone diagnostic tests.

Oxidative DNA damage is only one route to carcinogenesis. Many carcinogenic exposures also act through direct chemical mechanisms. Tobacco-smoke constituents, alcohol-derived acetaldehyde, ultraviolet radiation, ionizing radiation, aflatoxins, arsenic, asbestos, and selected occupational chemicals may produce DNA adducts, chromosomal injury, inflammation, or other forms of cellular stress.

Chronic inflammation provides an important link between reactive species and cancer. Activated immune cells generate ROS and RNS as part of host defense and tissue repair. When inflammatory activation persists, repeated cycles of injury, oxidative damage, cellular proliferation, and regeneration may create conditions that favor malignant transformation.

Examples include inflammatory conditions affecting the liver, gastrointestinal tract, respiratory system, and other organs. Nevertheless, inflammation alone does not determine whether cancer will develop. Genetic susceptibility, duration of exposure,

immune surveillance, tissue environment, and additional risk factors all influence the outcome.

Cellular defense systems normally limit the consequences of molecular damage. These include antioxidant enzymes, DNA-repair pathways, cell-cycle checkpoints, apoptosis, autophagy, immune surveillance, and removal of damaged cells. Cancer risk may increase when damage becomes persistent or when these protective mechanisms are impaired.

14.2 Redox Adaptation and Tumor Progression

Cancer cells frequently show altered metabolism and redox regulation. Rapid proliferation, mitochondrial dysfunction, oncogene activation, tissue hypoxia, abnormal blood vessels, and inflammatory signaling may increase reactive species production.

Moderate increases in ROS may support malignant progression by activating pathways involved in:

- cell proliferation;
- survival;
- angiogenesis;
- metabolic adaptation;
- invasion and migration;
- resistance to cellular stress.

Tumor cells must nevertheless prevent reactive species from reaching concentrations that would become lethal. Many cancers therefore increase the activity of glutathione, thioredoxin, Nrf2-related, and other antioxidant or detoxification systems.

This creates a redox adaptation that allows malignant cells to survive under conditions of hypoxia, nutrient limitation, inflammation, and high metabolic demand. Increased antioxidant capacity within tumor cells may also contribute to resistance to selected treatments.

The tumor microenvironment is part of this process. Cancer cells interact with immune cells, fibroblasts, endothelial cells, extracellular matrix, and inflammatory mediators. Reactive species may influence immune evasion, vascular formation, tissue remodeling, and communication among these cellular populations.

At the same time, excessive oxidative stress can damage cancer cells. When their adaptive capacity is exceeded, reactive species may trigger senescence, apoptosis, ferroptosis, or other forms of cell death. Some anticancer treatments exploit this vulnerability.

Radiotherapy produces cellular damage partly through ionization and reactive species formation. Several chemotherapeutic agents also increase oxidative or electrophilic stress. This is one reason why indiscriminate antioxidant supplementation during cancer treatment may be problematic: reducing treatment-related oxidative processes could theoretically interfere with therapeutic effects in some clinical contexts.

The influence of a redox-active compound therefore depends on:

- cancer type;
- disease stage;
- tissue location;
- treatment mechanism;
- dose and formulation;
- timing of administration;
- smoking status;
- nutritional status;
- other medications and supplements.

Oxidative stress in cancer cannot be classified simply as beneficial or harmful. Its effect depends on biological context and intensity.

14.3 Antioxidant-Rich Foods and Supplements

Plant-rich dietary patterns are generally consistent with cancer prevention recommendations. Vegetables, fruits, legumes, whole grains, nuts, and seeds provide fiber, vitamins, minerals, and diverse phytochemicals.

Their potential benefits are not limited to direct antioxidant activity. These foods may also support:

- healthy body weight;
- gastrointestinal function;
- gut microbiota diversity;
- glucose and lipid regulation;
- micronutrient adequacy;
- replacement of energy-dense and highly processed foods.

Antioxidant-rich foods should not be treated as cancer therapies. No individual fruit, vegetable, spice, tea, or phytochemical has been shown to prevent all cancers or replace screening and medical care.

Isolated antioxidant supplements differ substantially from foods. They may provide much higher doses, altered formulations, and exposure to one compound without the accompanying food matrix.

Randomized trials have not demonstrated consistent cancer-preventive benefits from routine supplementation with vitamin C, vitamin E, beta-carotene, selenium, or combinations of antioxidants in generally well-nourished populations.

Some trials have identified potential harm. High-dose beta-carotene supplementation increased lung cancer risk in smokers and selected asbestos-exposed populations. Other antioxidant trials have shown no benefit or raised safety concerns in particular groups.

These findings do not mean that antioxidant nutrients are unimportant. They demonstrate that physiological intake, correction of deficiency, whole-food consumption, and pharmacological supplementation are different interventions.

Supplementation may remain appropriate when there is:

- a confirmed deficiency;
- malabsorption;
- inadequate intake;
- increased physiological requirement;
- a specific evidence-based clinical indication.

During cancer treatment, patients should inform the oncology team about all vitamins, botanical products, extracts, powders, and other supplements. Potential interactions depend on the treatment regimen and cannot be assessed from the label term “antioxidant” alone.

Clinical Caution

Antioxidant supplementation during chemotherapy or radiotherapy should not be initiated solely to protect healthy cells or reduce treatment toxicity. Some products may alter treatment response, coagulation, liver metabolism, or medication exposure. Decisions should be individualized and coordinated with the treating oncology team.

Detailed evidence concerning individual supplements is discussed in Chapter 18.

14.4 Lifestyle-Based Cancer Prevention

Cancer prevention should focus on established and modifiable risk factors rather than on attempts to eliminate all reactive species.

The principal preventive priorities include:

- avoiding tobacco and secondhand smoke;
- limiting or avoiding alcohol;
- maintaining metabolic health and a healthy body weight;
- being physically active;
- following a plant-rich, minimally processed dietary pattern;
- limiting processed meat and excessive consumption of energy-dense foods;
- protecting the skin and eyes from excessive ultraviolet radiation;
- receiving recommended vaccinations against oncogenic infections;
- participating in appropriate cancer-screening programs;
- reducing harmful environmental and occupational exposures.

Tobacco avoidance is one of the most important cancer-preventive interventions. Antioxidant foods and supplements cannot neutralize the carcinogens, particles, metals, and oxidants present in tobacco smoke.

Alcohol is also an established carcinogenic exposure. The presence of resveratrol or other polyphenols in wine does not make alcoholic beverages protective. Similar phytochemicals can be obtained from grapes, berries, tea, cocoa, and other non-alcoholic foods.

Body weight and metabolic health are relevant because excess adiposity may influence insulin signaling, inflammation, sex-hormone metabolism, adipokine secretion, and tissue growth. Physical activity may reduce cancer risk through effects on body composition, metabolism, immune regulation, inflammation, and gastrointestinal transit.

Environmental and occupational prevention is also important. Exposure to ultraviolet radiation, ionizing radiation, asbestos, air pollution, selected metals, solvents, pesticides, and industrial chemicals should be reduced through appropriate regulation and workplace controls.

Vaccination can prevent cancers related to selected infections, including those associated with human papillomavirus and hepatitis B virus. Screening may identify precancerous lesions or early-stage disease before symptoms appear. Lifestyle prevention and early detection should therefore be understood as complementary strategies.

Cancer prevention reduces risk but cannot eliminate it completely. People who follow healthy lifestyles may still develop cancer, and patients should not be blamed for their disease. Genetics, aging, random cellular events, infections, and unavoidable exposures also contribute.

Evidence-Based Note

Cancer prevention should not be summarized as “consume more antioxidants.” The stronger recommendation is to reduce carcinogenic exposures, support metabolic health, follow a high-quality dietary pattern, remain physically active, use appropriate vaccination and screening, and protect workers and communities from environmental hazards.

Chapter summary

Key Points

- Cancer is a heterogeneous and multifactorial group of diseases and cannot be explained by oxidative stress alone.
- Reactive species may contribute to DNA damage, inflammation, altered signaling, and malignant transformation.
- Chronic inflammation may create a tissue environment that supports repeated injury, proliferation, and mutation accumulation.
- Cancer cells often produce increased amounts of reactive species but may also strengthen antioxidant systems to survive.
- Moderate oxidative signaling may support tumor progression, while excessive oxidative stress may contribute to cancer-cell death.
- Radiotherapy and selected chemotherapeutic agents act partly through oxidative or electrophilic damage.

- Antioxidant-rich foods and high-dose antioxidant supplements are not biologically equivalent.
- Routine antioxidant supplementation has not consistently prevented cancer in generally well-nourished populations.
- High-dose beta-carotene supplementation may increase lung cancer risk in smokers and selected high-risk groups.
- Supplement use during cancer treatment should be discussed with the oncology team.
- Cancer prevention should focus on tobacco avoidance, alcohol reduction, physical activity, metabolic health, high-quality dietary patterns, vaccination, screening, sun protection, and environmental and occupational safety.

Practical Relevance

Oxidative stress helps explain how carcinogenic exposures, inflammation, metabolic dysfunction, and altered cellular signaling may contribute to cancer. Its role is nevertheless context-dependent: reactive species may both support tumor progression and participate in cancer-cell destruction.

The practical objective is not to suppress all reactive species or take the largest possible quantity of antioxidants. Cancer prevention requires comprehensive risk reduction, while cancer treatment requires individualized oncology care. Antioxidant-containing foods may support a healthy dietary pattern, but supplements cannot replace avoidance of carcinogenic exposures, vaccination, screening, or evidence-based treatment.

Chapter 15. Neurodegenerative and Age-Related Diseases

Neurodegenerative and age-related diseases are an increasing challenge for preventive medicine. They include Alzheimer's disease and other forms of dementia, Parkinson's disease, age-related cognitive decline, age-related macular degeneration, frailty, sarcopenia, and other disorders associated with progressive loss of cellular and functional capacity.

Their development is multifactorial. Aging, genetic susceptibility, vascular and metabolic risk factors, mitochondrial dysfunction, chronic inflammation, environmental exposures, impaired protein quality control, and reduced cellular repair may all contribute.

Oxidative stress is frequently observed in aging tissues and neurodegenerative disease. The nervous system is particularly vulnerable because neurons have high energy requirements, depend heavily on mitochondrial function, contain lipid-rich membranes, and generally have limited regenerative capacity.

However, oxidative stress should not be treated as the single cause of neurodegeneration or biological aging. It interacts with protein misfolding, synaptic dysfunction, vascular injury, impaired autophagy, neuroinflammation, genetic factors, and disease-specific molecular processes. The presence of oxidative damage also does not establish that antioxidant supplementation will prevent or treat neurodegenerative disease.

15.1 Vulnerability of the Nervous System to Oxidative Stress

The brain requires continuous energy production to maintain ion gradients, neurotransmission, synaptic plasticity, axonal transport, and cellular repair. Neurons therefore depend strongly on mitochondrial oxidative phosphorylation.

Mitochondria are both sources and targets of reactive species. When mitochondrial function is impaired, ATP production may decline while electron leakage and reactive oxygen species formation increase. Oxidative modification of mitochondrial proteins, lipids, or DNA may further reduce metabolic efficiency, creating a cycle of energy failure and cellular stress.

Neuronal membranes contain substantial amounts of polyunsaturated fatty acids and are therefore vulnerable to lipid peroxidation. Oxidative modification of membrane lipids may alter membrane fluidity, receptor function, ion-channel activity, neurotransmitter release, and synaptic communication.

Secondary products of lipid peroxidation may also modify proteins and nucleic acids. In the nervous system, this may affect enzymes, cytoskeletal proteins, transport systems, receptors, and proteins involved in synaptic function.

Protein quality control is especially important in long-lived cells such as neurons. Damaged, misfolded, or aggregated proteins are normally removed through proteasomal degradation, autophagy, and lysosomal pathways. When these systems become impaired, abnormal proteins may accumulate and interfere with cellular function.

Oxidative stress may promote protein misfolding, while misfolded proteins may impair mitochondria and increase further reactive species production. This reciprocal relationship is relevant to several neurodegenerative disorders.

The brain also contains redox-active metals, including iron and copper. These metals are essential for normal physiology but must remain tightly regulated. Disturbed metal homeostasis may promote oxidative reactions, protein aggregation, and neuronal injury.

Neuroinflammation provides another connection between oxidative stress and neuronal dysfunction. Microglia normally support immune surveillance, tissue maintenance, and response to injury. Persistent microglial activation, however, may increase cytokine production and reactive species formation.

Chronic neuroinflammation and oxidative stress may reinforce one another, contributing to synaptic dysfunction and neuronal vulnerability. Nevertheless, immune activation in the brain is not inherently harmful; its effects depend on intensity, duration, disease stage, and cellular context.

15.2 Alzheimer's Disease and Parkinson's Disease

Alzheimer's Disease and Other Dementias

Dementia is a clinical syndrome characterized by progressive impairment of memory, thinking, behavior, or daily functioning. Alzheimer's disease is its most common cause, but dementia may also result from vascular disease, Lewy body disease, frontotemporal degeneration, or mixed pathological processes.

Alzheimer's disease is associated with amyloid- β accumulation, abnormal tau protein, synaptic dysfunction, neuroinflammation, mitochondrial impairment, and neuronal loss. Vascular and metabolic factors may also influence its development and progression.

Oxidative stress has been identified in affected brain regions and may contribute to:

- lipid peroxidation;
- protein oxidation;
- mitochondrial dysfunction;
- impaired synaptic signaling;
- DNA and mitochondrial DNA damage;
- inflammatory activation.

Oxidative changes may occur early in the disease process, but it is difficult to determine whether they represent an initiating factor, a consequence of pathological protein accumulation, or an amplifier of existing neuronal dysfunction.

Amyloid- β and abnormal tau may disturb mitochondrial function, calcium regulation, axonal transport, and synaptic activity. At the same time, mitochondrial and oxidative stress may influence protein processing and aggregation. These mechanisms form interacting networks rather than a simple linear pathway.

Vascular injury is also important. Hypertension, diabetes, smoking, dyslipidemia, obesity, physical inactivity, and stroke may contribute to cognitive decline through endothelial

dysfunction, cerebral small-vessel disease, impaired blood flow, inflammation, and reduced brain resilience.

Prevention of cognitive decline should therefore include cardiovascular and metabolic risk management rather than relying on a narrowly neurological or antioxidant approach.

Parkinson's Disease

Parkinson's disease is a progressive neurodegenerative disorder. Its core motor syndrome is parkinsonism, clinically defined by bradykinesia accompanied by rest tremor, rigidity, or both. Postural instability commonly emerges later in the disease course. Non-motor symptoms may include sleep disorders, depression, autonomic dysfunction, cognitive changes, constipation, pain, fatigue, and reduced sense of smell.

The disease involves degeneration of dopaminergic neurons in the substantia nigra and accumulation of α -synuclein-containing Lewy bodies. Its pathophysiology includes interactions among genetic susceptibility, mitochondrial dysfunction, impaired protein degradation, neuroinflammation, dopamine metabolism, and environmental factors.

Dopaminergic neurons may be particularly vulnerable to oxidative stress because dopamine metabolism can generate reactive intermediates. These neurons also have high energy demands and are exposed to iron-related redox activity within the substantia nigra.

Mitochondrial dysfunction may impair ATP production, calcium regulation, protein quality control, and neuronal survival. Abnormal α -synuclein may further affect mitochondrial membranes, trafficking, and autophagic processes.

Environmental and occupational exposures have also been investigated, including selected pesticides, solvents, metals, and air pollutants. Associations vary among exposures and populations, and most individuals with Parkinson's disease do not have one identifiable environmental cause.

As with Alzheimer's disease, Parkinson's disease should not be described as an antioxidant deficiency disorder. Although oxidative and mitochondrial mechanisms are relevant, routine antioxidant supplementation has not been shown to prevent or reverse the disease.

Other Neurodegenerative Disorders

Oxidative stress has also been investigated in amyotrophic lateral sclerosis, Huntington's disease, multiple system atrophy, and other neurological conditions. In each case, it interacts with disease-specific mechanisms such as genetic mutations, excitotoxicity, abnormal protein accumulation, axonal transport defects, or impaired RNA processing.

The common presence of oxidative damage across several disorders does not mean that all neurodegenerative diseases share the same cause or require the same treatment.

Evidence-Based Note

Oxidative stress is a feature of many neurodegenerative disorders, but the direction of causality is often uncertain. It may contribute to disease initiation, arise as a consequence of neuronal injury, or accelerate progression after disease has already developed.

Reducing an oxidative stress biomarker does not necessarily demonstrate preservation of cognition, movement, independence, or quality of life.

15.3 Aging, Cellular Senescence and Age-Related Disease

Biological aging involves gradual changes in mitochondrial function, protein quality control, DNA repair, immune regulation, vascular function, metabolism, and tissue regeneration. Oxidative stress contributes to some of these changes, but modern aging biology extends beyond the traditional free radical theory of aging.

Reactive species may cause cumulative molecular injury, but they also participate in normal signaling, adaptation, immune function, and stress responses. Aging should therefore not be interpreted as a simple antioxidant deficiency that can be corrected by high-dose supplementation.

Mitochondrial Aging and Cellular Repair

With advancing age, mitochondria may become less efficient and more heterogeneous. Some cells accumulate damaged mitochondria, while mechanisms responsible for mitochondrial quality control may become less effective.

Mitophagy normally removes dysfunctional mitochondria. If this process declines, damaged organelles may accumulate and contribute to metabolic inefficiency, inflammation, and reactive species production.

Aging cells may also show reduced capacity to repair DNA, remove oxidized proteins, maintain membrane integrity, and respond to environmental stress. These changes reduce physiological resilience and may increase vulnerability to chronic disease.

Cellular Senescence

Cellular senescence is a state in which damaged or stressed cells stop dividing but remain metabolically active. Senescence may initially protect against uncontrolled proliferation and malignant transformation.

When senescent cells accumulate, however, they may release cytokines, growth factors, proteases, and other molecules collectively described as the senescence-associated secretory phenotype. These substances may promote inflammation, tissue remodeling, and dysfunction in surrounding cells.

Oxidative stress may contribute to the induction of senescence, while senescent cells may further increase local inflammatory and oxidative burden. The consequences depend on tissue, cell type, immune clearance, and duration.

Frailty and Sarcopenia

Frailty is a state of reduced physiological reserve and increased vulnerability to stressors. Sarcopenia involves progressive loss of muscle mass, strength, and physical performance.

Their development may involve physical inactivity, inadequate protein and energy intake, hormonal changes, chronic inflammation, mitochondrial dysfunction, neurological

disease, and multimorbidity. Oxidative stress may contribute to muscle injury and impaired recovery but is not the only mechanism.

Prevention should emphasize regular resistance and balance training, adequate nutrition, fall prevention, medication review, treatment of underlying disease, and maintenance of social and functional activity.

The objective is preservation of mobility and independence rather than improvement of nonspecific antioxidant biomarkers.

Age-Related Macular Degeneration

The retina is metabolically active and is exposed to oxygen, light, and lipid-rich cellular structures. These characteristics make retinal tissue susceptible to photo-oxidative and metabolic injury.

Age-related macular degeneration is influenced by aging, smoking, genetic susceptibility, vascular factors, and retinal metabolic stress. Oxidative mechanisms may contribute, but supplementation recommendations are specific to disease stage.

The AREDS2 formulation may reduce the risk of progression from intermediate to advanced age-related macular degeneration and may reduce progression in the fellow eye when advanced AMD is already present in one eye. It does not prevent the initial development of AMD and has not demonstrated benefit in people without AMD or with early AMD.

Current and former smokers should avoid beta-carotene-containing AREDS formulations and use a beta-carotene-free AREDS2 formulation when supplementation is clinically indicated.

Older formulations contained beta-carotene. Because high-dose beta-carotene increases lung cancer risk in current and former smokers, beta-carotene-free formulations are preferred for these individuals (when supplementation is clinically indicated).

This example illustrates an important principle: antioxidant-containing supplements may be clinically useful when a specific formulation has been studied in a clearly defined population with a defined outcome. Such evidence cannot be generalized to all age-related conditions.

15.4 Prevention and Healthy Aging

Prevention of neurodegenerative and age-related disease should begin before symptoms develop and should address brain, vascular, metabolic, sensory, and social health across the life course.

The most important preventive priorities include:

- regular physical activity;
- blood pressure, lipid, and glucose management;
- smoking avoidance;
- reduction of harmful alcohol use;

- healthy dietary patterns;
- adequate sleep;
- prevention and treatment of depression;
- cognitive and social engagement;
- hearing and vision assessment;
- prevention of head injury;
- reduction of air pollution and occupational exposure where possible.

Physical activity supports cerebral blood flow, cardiovascular health, glucose regulation, mitochondrial function, mobility, mood, and sleep. Both aerobic and resistance exercise are relevant, while balance training may help reduce falls in older adults.

Dietary patterns rich in vegetables, fruits, legumes, whole grains, nuts, seeds, and appropriate sources of unsaturated fats may support vascular and metabolic health. Their potential relevance to brain aging is broader than antioxidant content and includes effects on blood pressure, glucose metabolism, lipid profile, body composition, and gut microbiota.

No single food has been shown to prevent Alzheimer's disease or normal age-related cognitive decline. Claims that berries, turmeric, cocoa, tea, resveratrol, or another isolated food protects against dementia should therefore be interpreted cautiously.

Hearing and vision care are increasingly recognized as components of healthy aging. Untreated sensory impairment may reduce communication, physical activity, cognitive stimulation, and social participation.

Social isolation and loneliness may also affect mental and physical health. Maintaining meaningful relationships, community participation, cognitively stimulating activities, and access to mental health support can contribute to resilience and quality of life.

Sleep disorders should be recognized and treated, particularly when symptoms suggest sleep apnea, chronic insomnia, restless legs syndrome, or medication-related sleep disruption.

Antioxidant supplements should not be promoted as universal interventions for dementia prevention, Parkinson's disease, frailty, or longevity. Their use should be based on a specific nutritional deficiency or clinical indication.

Practical Point

Healthy aging is supported by what preserves function: movement, muscle strength, vascular health, sleep, social connection, sensory care, mental health, and management of chronic disease.

An antioxidant supplement cannot substitute for these foundations.

Chapter summary

Key Points

- Neurodegenerative and age-related diseases are multifactorial and cannot be explained by oxidative stress alone.
- The nervous system is vulnerable because of its high energy demand, mitochondrial dependence, lipid-rich membranes, and limited regenerative capacity.
- Mitochondrial dysfunction, oxidative stress, protein misfolding, impaired autophagy, and neuroinflammation may interact in neurodegenerative disease.
- Alzheimer's disease involves amyloid- β , tau pathology, synaptic dysfunction, vascular factors, inflammation, and neuronal loss.
- Parkinson's disease involves dopaminergic neuronal loss, α -synuclein pathology, mitochondrial impairment, and altered protein quality control.
- Oxidative damage may be a cause, consequence, or amplifier of neurodegeneration, depending on disease stage and context.
- Aging involves changes in mitochondrial quality control, DNA repair, proteostasis, immune regulation, and tissue regeneration.
- Cellular senescence may initially be protective but can contribute to chronic inflammation when senescent cells accumulate.
- Frailty and sarcopenia require functional, nutritional, and physical activity interventions rather than nonspecific antioxidant treatment.
- AREDS2 is an example of condition- and stage-specific supplementation and should not be generalized to healthy aging.
- Prevention should support vascular and metabolic health, physical activity, sleep, sensory function, cognitive engagement, and social connection.
- Routine high-dose antioxidant supplementation has not been shown to prevent neurodegenerative disease or biological aging.

Practical Relevance

Oxidative stress helps explain selected mechanisms of neuronal injury and age-related loss of resilience, but it does not provide a simple explanation or a universal therapeutic target.

The practical priority is preservation of function across the life course. This includes movement, muscle strength, blood pressure and metabolic control, smoking avoidance, sleep, mental health, hearing and vision care, cognitive activity, social connection, and reduction of harmful environmental exposures.

Antioxidant-rich foods may support a high-quality dietary pattern, but supplements should not be presented as stand-alone protection against dementia, Parkinson's disease, frailty, or aging.

Chapter 16. Endocrine and Reproductive Disorders

Endocrine and reproductive processes depend on tightly regulated metabolism, hormone signaling, mitochondrial function, immune activity, and redox balance. Controlled production of reactive oxygen and nitrogen species participates in hormone synthesis, ovulation, sperm function, implantation, placental development, and cellular signaling.

Excessive or persistent oxidative stress, however, may interfere with endocrine signaling, gamete quality, mitochondrial function, vascular regulation, and tissue repair. It has been investigated in thyroid disease, polyendocrine metabolic ovarian syndrome, infertility, endometriosis, pregnancy complications, and disorders of male reproductive function.

Oxidative stress should not be presented as the single cause of these conditions. Endocrine and reproductive disorders are multifactorial and may involve genetic susceptibility, immune mechanisms, metabolic dysfunction, age, environmental exposure, medication use, nutrition, and lifestyle.

From the perspective of preventive medicine, antioxidant-rich foods may support general nutritional and metabolic health, but antioxidant supplementation should not replace diagnosis, treatment, correction of confirmed deficiencies, or reduction of harmful environmental and occupational exposures.

16.1 Thyroid Function and Redox Balance

The thyroid gland is closely connected with redox biology. Thyroid hormone synthesis requires iodine and controlled production of hydrogen peroxide. Hydrogen peroxide is used during reactions that incorporate iodine into thyroglobulin and allow the formation of thyroid hormones. It is therefore a physiological component of thyroid function rather than merely a harmful oxidant.

Because thyroid tissue regularly produces hydrogen peroxide, it also requires efficient antioxidant protection. Catalase, glutathione peroxidases, peroxiredoxins, thioredoxin-related systems, and other cellular defenses help prevent excessive oxidative damage.

Iodine is essential for the production of thyroxine and triiodothyronine. Both insufficient and excessive iodine intake may disturb thyroid function, particularly in susceptible individuals. Iodine supplementation should therefore follow nutritional and clinical recommendations rather than be used indiscriminately.

Selenium is incorporated into several selenoproteins relevant to thyroid physiology. These include deiodinases involved in the activation and inactivation of thyroid hormones, as well as glutathione peroxidases and thioredoxin reductases that contribute to redox regulation.

Selenium deficiency may impair selected aspects of thyroid hormone metabolism and antioxidant defense. However, this does not mean that additional selenium benefits every patient with thyroid disease. Once physiological requirements are met, higher intake may provide no further advantage and may increase the risk of toxicity.

Autoimmune thyroid diseases, including Hashimoto thyroiditis and Graves disease, involve immune dysregulation, genetic susceptibility, environmental influences, and

alterations in thyroid function. Oxidative stress may contribute to tissue injury and inflammatory signaling, but it is only one part of their pathophysiology.

Routine antioxidant supplementation should not be presented as treatment for autoimmune thyroid disease. Selenium, iodine, vitamin D, iron, and other nutrients may be relevant in selected patients, but supplementation should be based on dietary intake, laboratory findings, geographic context, pregnancy status, and clinical indication.

Biotin deserves separate attention because high-dose biotin supplements can interfere with some thyroid laboratory tests and produce misleading results. Patients undergoing thyroid assessment should therefore report all supplements to the clinician and laboratory.

Clinical Caution

Both inadequate and excessive intake of iodine or selenium may be harmful. Thyroid-related supplementation should not be started solely because a product is described as supporting antioxidant defense or thyroid health.

16.2 Polyendocrine Metabolic Ovarian Syndrome

On 12 May 2026, **polycystic ovary syndrome (PCOS)** was renamed **polyendocrine metabolic ovarian syndrome (PMOS)**. The new name was selected through an international multistakeholder process to better reflect the endocrine, metabolic, reproductive, dermatological, and psychological dimensions of the condition. During the transition period, both PCOS and PMOS should be used to preserve continuity across clinical guidelines, health records, research databases, and the existing scientific literature. The new terminology is expected to be fully integrated into the 2028 International Guideline update.

The previous name was potentially misleading because polycystic ovarian morphology is not required in every affected person, and the ovarian structures seen on ultrasound are not equivalent to pathological ovarian cysts.

PMOS is a heterogeneous condition. Its manifestations may include:

- irregular or absent ovulation;
- menstrual disturbances;
- biochemical or clinical hyperandrogenism;
- acne or hirsutism;
- difficulty conceiving;
- insulin resistance;
- dyslipidemia;
- increased cardiometabolic risk;
- sleep disorders;
- anxiety, depression, disordered eating, or impaired quality of life.

Not every patient has all of these features. Obesity is common but is not required for diagnosis, and insulin resistance or metabolic abnormalities may also occur in individuals with body weight within the conventionally normal range.

Oxidative stress has been investigated as one mechanism linking metabolic and reproductive abnormalities in PMOS. Insulin resistance, adipose tissue dysfunction, chronic low-grade inflammation, mitochondrial impairment, and hyperandrogenism may influence reactive species production. Oxidative stress may in turn affect insulin signaling, endothelial function, steroidogenesis, and ovarian physiology.

These relationships are bidirectional and do not support describing PMOS as an antioxidant deficiency disorder. Oxidative stress biomarkers are not required for routine diagnosis, and their measurement does not usually guide treatment.

Management should be individualized according to the person's principal concerns and long-term risks. Relevant areas may include menstrual regulation, hyperandrogenic symptoms, fertility goals, glucose and lipid metabolism, blood pressure, sleep, body image, eating behavior, and psychological health.

Lifestyle support is an important component of care, particularly for metabolic health. Regular physical activity, reduced sedentary behavior, adequate sleep, and a sustainable dietary pattern may improve insulin sensitivity and cardiovascular risk. Weight-related intervention may be useful for some patients but should be discussed without stigma and should not overshadow metabolic risk in patients who do not have obesity.

Medication and fertility treatment may also be required. Lifestyle modification should complement rather than replace evidence-based clinical management.

Inositols, N-acetylcysteine, vitamin D, omega-3 fatty acids, polyphenols, and other supplements have been studied in PMOS. They should not be grouped together merely as antioxidants because they have different mechanisms, indications, doses, and evidence bases. Supplement use should be considered separately from established treatment and assessed for safety, product quality, and interactions.

Inositol may be considered in selected patients after shared decision-making, taking into account individual preferences and the possibility of improvement in selected metabolic measures. However, evidence for clinically meaningful benefits remains limited and inconclusive, and no specific form, dose, or combination can currently be recommended with confidence. In patients with infertility, inositol should be regarded as an experimental therapy because its effects on ovulation, clinical pregnancy, and live birth remain uncertain.

Evidence-Based Note

PMOS is a complex endocrine-metabolic syndrome, not simply an ovarian disorder and not simply an oxidative stress disorder. Reducing an oxidative biomarker does not establish improvement in ovulation, fertility, hyperandrogenism, metabolic risk, or quality of life.

16.3 Fertility and Oxidative Balance

Infertility is defined as failure to achieve pregnancy after 12 months or more of regular unprotected sexual intercourse. However, clinical evaluation should generally begin after 6 months when the female partner is aged 35 years or older. More immediate evaluation

may be appropriate after the age of 40 years, and evaluation should not be delayed when a known condition associated with infertility is present.

Infertility may result from male, female, combined, or unexplained factors. Current global estimates suggest that approximately one in six people of reproductive age experience infertility during their lifetime.

Controlled reactive species production has physiological roles in reproduction. In male reproductive function, redox signaling participates in sperm maturation, capacitation, motility, and the acrosome reaction. In female reproductive physiology, reactive species are involved in follicular development, ovulation, corpus luteum function, and cellular signaling associated with fertilization and implantation.

Adverse reproductive effects may occur when reactive-species production exceeds antioxidant and repair capacity.

Spermatozoa are especially vulnerable to oxidative damage because their membranes contain substantial amounts of polyunsaturated fatty acids and their cytoplasm contains limited antioxidant and repair systems. Excessive oxidative stress may impair sperm motility, membrane integrity, mitochondrial function, and DNA quality.

Potential contributors to oxidative burden in male infertility include:

- smoking;
- obesity and metabolic dysfunction;
- varicocele;
- genital infections or inflammation;
- excessive heat exposure;
- selected medications;
- environmental and occupational toxicants;
- radiation;
- heavy alcohol consumption.

Oxidative stress has also been investigated in female infertility, diminished ovarian reserve, endometriosis, ovulatory disorders, and impaired implantation. However, reproductive aging, hormonal regulation, tubal disease, uterine abnormalities, genetic factors, inflammation, and immune mechanisms may be equally or more important depending on the clinical situation.

Endometriosis, for example, involves ectopic endometrial-like tissue, inflammation, pain, and possible effects on pelvic anatomy and fertility. Oxidative stress may contribute to inflammatory processes, but it does not provide a complete explanation of the disease.

Antioxidant supplements have been widely marketed for male and female fertility. Clinical findings remain heterogeneous because products, doses, treatment durations, patient populations, and outcomes differ substantially. Improvement in semen oxidative markers does not necessarily demonstrate increased pregnancy or live-birth rates.

Fertility assessment should therefore identify the underlying cause whenever possible. Evaluation may include reproductive history, menstrual and ovulatory assessment, semen analysis, anatomical evaluation, endocrine testing, medication review, and assessment of relevant lifestyle or occupational exposures.

Antioxidant supplementation should not delay comprehensive fertility evaluation, particularly when age, menstrual abnormalities, previous pelvic disease, cancer treatment, or severe abnormalities in semen parameters indicate the need for timely specialist care.

16.4 Pregnancy, Placental Function and Oxidative Stress

Pregnancy involves major changes in energy metabolism, circulation, endocrine signaling, immune regulation, and oxygen demand. Controlled oxidative processes are necessary for implantation, placental development, vascular remodeling, and fetal growth.

The placenta generates reactive species as part of normal metabolism and signaling. Antioxidant and repair systems normally regulate these processes. When placental perfusion, mitochondrial function, inflammatory regulation, or maternal metabolism is disturbed, oxidative stress may increase.

Excessive oxidative and inflammatory activity has been investigated in relation to:

- preeclampsia;
- gestational diabetes;
- fetal growth restriction;
- placental dysfunction;
- preterm birth.

These complications are multifactorial and cannot be diagnosed or treated by measuring oxidative stress alone. Blood pressure assessment, glucose testing, fetal growth monitoring, clinical symptoms, laboratory findings, and obstetric evaluation remain essential.

Pregnancy-related supplementation should follow evidence-based prenatal recommendations rather than a general antioxidant strategy. Folic acid is routinely recommended before conception and during early pregnancy in accordance with national guidance. Iodine, iron, vitamin D, and other nutrients should be individualized according to dietary intake, geographic context, laboratory findings, pregnancy stage, and clinical risk.

More is not necessarily better. Excessive preformed vitamin A may be teratogenic, while excessive iodine or selenium may disturb thyroid function. Botanical extracts and concentrated antioxidant products may lack adequate safety data for pregnancy or breastfeeding.

Smoking, alcohol, air pollution, heat, pesticides, solvents, metals, endocrine-disrupting chemicals, and selected occupational exposures may affect reproductive or pregnancy health. Exposure history is therefore an important component of preconception and prenatal care.

Occupational assessment may be especially relevant for workers exposed to radiation, cytotoxic medications, anesthetic gases, pesticides, solvents, heavy metals, extreme heat, or physically demanding conditions. Where necessary, occupational medicine

physicians may recommend exposure reduction, work modification, additional protection, or temporary reassignment.

Practical Point

Pregnancy is not an appropriate period for unsupervised experimentation with high-dose vitamins, herbal extracts, or antioxidant combinations. Products should be reviewed for indication, dose, interactions, and pregnancy-specific safety.

16.5 Prevention and Clinical Approach

Prevention in endocrine and reproductive health should focus on factors with established physiological and clinical relevance.

Important priorities include:

- adequate but not excessive micronutrient intake;
- healthy dietary patterns;
- regular physical activity;
- metabolic risk assessment;
- adequate sleep;
- smoking cessation;
- reduction or avoidance of alcohol;
- appropriate body-weight support without stigma;
- reduction of environmental and occupational exposures;
- timely evaluation of menstrual, hormonal, fertility, or pregnancy-related symptoms.

Supplementation should not precede diagnosis. Fatigue, irregular menstruation, infertility, hair loss, weight change, or mood symptoms may result from many conditions and should not automatically be attributed to oxidative stress or nutrient deficiency.

A useful clinical sequence is:

1. establish the diagnosis or principal clinical problem;
2. assess dietary intake and possible deficiency;
3. review medications and existing supplements;
4. consider pregnancy or fertility plans;
5. identify metabolic and cardiovascular risk;
6. assess occupational and environmental exposure;
7. introduce targeted treatment or supplementation only when justified.

Evidence-Based Note

In endocrine and reproductive medicine, antioxidant activity is not a sufficient indication for treatment. The relevant question is whether a specific intervention improves a defined clinical outcome in an appropriate population without creating disproportionate risk.

Chapter summary

Key Points

- Endocrine and reproductive physiology requires controlled redox signaling; reactive species are not exclusively harmful.
- Excessive oxidative stress may interfere with hormone signaling, mitochondrial function, gamete quality, vascular regulation, and tissue repair.
- Thyroid hormone synthesis requires iodine and controlled hydrogen peroxide production.
- Selenium supports deiodinases, glutathione peroxidases, thioredoxin reductases, and other selenoproteins relevant to thyroid physiology.
- Both deficiency and excess of iodine or selenium may be harmful.
- Polyendocrine Metabolic Ovarian Syndrome is the new name for the condition formerly known as PCOS; both terms may coexist during the transition period.
- PMOS is a heterogeneous endocrine-metabolic condition involving reproductive, metabolic, dermatological, and psychological dimensions.
- Oxidative stress may participate in PMOS, infertility, endometriosis, and pregnancy complications but is not a single cause or universal treatment target.
- Controlled reactive species contribute to normal sperm function, ovulation, implantation, and placental development.
- Excessive oxidative stress may impair sperm membranes, motility, mitochondrial function, and DNA integrity.
- Fertility supplements should be evaluated according to clinically meaningful outcomes, not only changes in antioxidant biomarkers.
- Pregnancy-related supplementation should follow evidence-based recommendations and individual assessment.
- Environmental and occupational exposure history is relevant to reproductive and endocrine prevention.
- Antioxidant supplements should not replace diagnosis, metabolic risk management, fertility evaluation, or obstetric care.

Practical Relevance

Endocrine and reproductive disorders illustrate why redox balance is more important than indiscriminate antioxidant intake. Reactive species participate in normal thyroid hormone synthesis, steroidogenesis, sperm function, ovulation, implantation, and placental signaling.

The practical approach should begin with diagnosis, nutritional and metabolic assessment, reproductive plans, medication review, and exposure history. Antioxidant-rich foods may support general health, but supplementation should be targeted, safe, and based on a defined clinical need.

Chapter 17. Lifestyle-Based Prevention

Lifestyle-based prevention translates knowledge about oxidative stress and chronic disease into practical health action. Its purpose is not to eliminate reactive species or maximize antioxidant intake. The goal is to reduce persistent metabolic, inflammatory, and oxidative burden while preserving physiological signaling, adaptation, and resilience.

Chronic diseases usually develop through the interaction of several risk factors rather than one isolated exposure. Smoking, alcohol consumption, poor diet quality, physical inactivity, prolonged sitting, insufficient sleep, chronic stress, obesity, environmental pollution, and occupational hazards may coexist and reinforce one another.

Prevention should therefore be integrated. Instead of providing separate and competing instructions about nutrition, exercise, sleep, stress, and supplements, healthcare professionals should help individuals identify the most important risks, select realistic priorities, and build a plan that can be maintained over time.

Lifestyle interventions are not alternatives to medical treatment. Blood pressure management, lipid-lowering therapy, diabetes care, vaccination, cancer screening, mental health treatment, or other clinical interventions may remain necessary. The most effective preventive approach combines lifestyle support with evidence-based healthcare.

Detailed recommendations concerning nutrition, physical activity, sleep, tobacco, alcohol, environmental and occupational exposures, and supplementation are presented in the preceding chapters and in Chapter 18. The purpose of this chapter is to integrate these domains into a practical preventive framework.

17.1 Principles of Integrated Prevention

The first principle is to assess total risk rather than focus on a single mechanism or biomarker. Oxidative stress may help explain how different exposures affect tissues, but clinical decisions should be based on meaningful risk factors, symptoms, diagnoses, and outcomes.

The second principle is to address the largest modifiable risks first. Smoking cessation, hazardous alcohol reduction, treatment of hypertension, metabolic risk management, or removal of a workplace exposure will usually provide greater benefit than adding an antioxidant supplement.

The third principle is to preserve physiological redox signaling. Reactive oxygen and nitrogen species participate in immune defense, vascular regulation, cellular communication, and adaptation to physical activity. Prevention should support redox homeostasis rather than attempt to suppress all reactive species.

The fourth principle is sustainability. Highly restrictive programs may produce short-term results but often fail when they do not fit a person's health status, preferences, finances, culture, work schedule, or family responsibilities. A moderate plan maintained for years is generally more valuable than an idealized plan followed briefly.

The fifth principle is individualization. Recommendations should account for age, pregnancy, chronic disease, functional capacity, medications, nutritional status, occupational conditions, and personal goals. The same plan will not be appropriate for a healthy young adult, an older person with frailty, a shift worker, or a patient recovering from serious illness.

The sixth principle is non-judgmental care. Health behaviors are influenced by addiction, stress, income, education, trauma, food availability, housing, neighborhood safety, caregiving responsibilities, and access to healthcare. Effective prevention supports change without assigning blame.

Finally, prevention should be proportionate. Not every person requires detailed intervention in every lifestyle domain. Effort should be concentrated where risk and potential benefit are greatest.

17.2 Assessment and Prioritization

Lifestyle counseling should begin with assessment rather than immediate advice. A short, structured history can identify both major risks and existing strengths.

Relevant areas include:

- tobacco, nicotine, and secondhand smoke exposure;
- alcohol intake and episodes of heavy drinking;
- usual food pattern and access to healthy food;
- physical activity, functional limitations, and sedentary time;
- sleep duration, quality, regularity, and possible sleep disorders;
- stress, mood, anxiety, loneliness, and coping strategies;
- weight history and metabolic risk where clinically relevant;
- workplace hazards, shift work, heat, dust, fumes, and chemicals;
- environmental exposure, including air pollution and ultraviolet radiation;
- use of vitamins, minerals, botanical products, and other supplements.

Clinical assessment may also include blood pressure, lipid profile, glucose or HbA1c, kidney and liver function, body weight, waist circumference, physical fitness, or disease-specific investigations.

Body weight should not be interpreted in isolation. It does not directly describe body composition, fitness, muscle mass, fat distribution, diet quality, or metabolic health. Weight-related goals may be appropriate, but improvements in blood pressure, glucose regulation, physical capacity, sleep, and quality of life are also clinically important.

The assessment should identify what the person already does well. Existing habits such as regular walking, home cooking, non-smoking, social support, or medication adherence can provide a foundation for further change.

Priorities should then be selected according to three questions:

1. Which factor currently creates the greatest health or safety risk?
2. Which change is the person ready and able to make?

3. What support is needed to make that change sustainable?

Practical Point

A preventive plan should rarely begin with ten simultaneous recommendations. One or two well-chosen priorities are usually more effective than a long list that becomes overwhelming.

17.3 The Structure of a Preventive Plan

A practical lifestyle plan can be organized into four complementary goals.

1. Reduce Harmful Exposures

The first priority is often to remove or reduce major sources of injury.

Examples include:

- stopping combustible tobacco use;
- avoiding secondhand smoke;
- reducing harmful alcohol consumption;
- addressing unsafe occupational exposure;
- reducing excessive ultraviolet or heat exposure;
- limiting repeated exposure to highly polluted air where possible;
- reviewing unnecessary or potentially harmful supplements.

Risk reduction should not be replaced by compensation strategies. Antioxidant-rich foods do not neutralize smoking, alcohol, toxic chemicals, or unsafe working conditions.

2. Build Protective Daily Routines

Protective routines support metabolic health and physiological resilience.

They include:

- regular consumption of minimally processed foods;
- adequate vegetables, fruits, legumes, whole grains, nuts, and seeds;
- regular physical activity;
- reduced prolonged sitting;
- sufficient and regular sleep;
- time for recovery;
- constructive methods of managing stress;
- maintenance of social connection.

As broad reference points, most adults should aim for at least 150 minutes of moderate-intensity aerobic physical activity per week, or an equivalent amount of vigorous activity, together with muscle-strengthening activity on at least two days per week. Most adults should also obtain at least seven hours of sleep per night. These targets should be adapted to age, health status, functional capacity, pregnancy, disability, and occupational circumstances.

These behaviors influence many biological systems simultaneously. Their effects extend beyond antioxidant activity and include improvements in blood pressure, glucose metabolism, lipid profile, body composition, cardiovascular fitness, mental health, and functional capacity.

3. Manage Established Clinical Risk

Lifestyle support should be integrated with medical risk management.

Depending on the person, this may involve:

- treatment of hypertension;
- lipid management;
- diabetes prevention or treatment;
- weight-related metabolic care;
- vaccination;
- cancer screening;
- kidney, eye, or foot monitoring;
- management of sleep apnea;
- treatment of depression, anxiety, or addiction;
- rehabilitation after illness or injury.

The presence of a healthy lifestyle does not remove the need for clinically indicated treatment. Similarly, medication does not remove the value of lifestyle prevention.

4. Modify the Environment

Behavior is easier to maintain when the surrounding environment supports it.

Useful changes may include:

- keeping nutritious foods readily available;
- removing tobacco and excess alcohol from the home;
- preparing meals in advance;
- placing walking shoes or exercise equipment in a visible location;
- scheduling activity and sleep;
- using reminders to interrupt prolonged sitting;
- involving family or friends;
- requesting occupational health assessment;
- modifying work tasks, ventilation, or protective measures.

Environmental design reduces dependence on motivation and willpower.

17.4 Staged and Realistic Change

A lifestyle plan should be introduced in stages. A useful sequence is:

1. address immediate medical or safety concerns;
2. reduce major harmful exposures;
3. establish basic routines for meals, movement, and sleep;

4. improve cardiovascular and metabolic risk factors;
5. refine dietary quality, fitness, and stress-management strategies;
6. assess whether targeted supplementation is required.

The sequence may differ between individuals. For one person the first priority may be smoking cessation. For another it may be treatment of severe sleep apnea, reduction of hazardous alcohol use, control of hypertension, or removal from a toxic occupational exposure.

Goals should be specific and observable. General intentions such as “exercise more” or “eat healthier” are difficult to implement and evaluate.

More useful goals include:

- “I will walk for 10 minutes after dinner on four days this week.”
- “I will add one vegetable to my main meal each day.”
- “I will stop drinking caffeine after 2 p.m.”
- “I will choose three alcohol-free days each week.”
- “I will contact the smoking-cessation service.”
- “I will discuss my workplace chemical exposure with occupational health.”

The plan should also anticipate barriers. Pain, fatigue, shift work, weather, social events, childcare, and financial limitations may interfere with behavior. An alternative action should be identified in advance.

For example, if outdoor walking is not possible, a person may use indoor stairs, perform chair-based exercises, or complete a short home routine. Flexibility helps preserve continuity.

Lifestyle Tip

Choose the smallest change that is meaningful enough to improve health but realistic enough to repeat. Consistency is more important than intensity at the beginning.

17.5 Supporting Behavior Change

Information alone rarely produces long-term change. Most people already know that smoking, inactivity, poor sleep, or excessive alcohol can harm health. The difficulty lies in converting knowledge into repeated behavior.

Useful behavior-change strategies include:

- identifying a personally meaningful reason for change;
- selecting a small number of priorities;
- defining when and where an action will occur;
- monitoring progress;
- modifying the home or work environment;
- involving supportive people;
- treating pain, depression, anxiety, addiction, or sleep disorders;
- arranging follow-up;

- revising the plan after setbacks.

Self-monitoring may include activity, sleep, smoking, alcohol intake, blood pressure, glucose, or meals, depending on the clinical goal. Monitoring should remain simple and should not create excessive anxiety or perfectionism.

Social support may be particularly useful during smoking cessation, alcohol reduction, weight-related change, rehabilitation, and treatment of chronic disease. Support can come from family, friends, healthcare professionals, group programs, or appropriate digital tools.

Relapse and setbacks should be expected. A lapse does not erase previous progress. It provides information about triggers, barriers, and situations in which additional support is needed.

Healthcare professionals should distinguish between a behavior that is difficult to change and a person who is “non-compliant.” Respectful communication preserves trust and improves continued engagement.

17.6 Monitoring Meaningful Outcomes

Lifestyle interventions should be evaluated using outcomes relevant to health, function, and quality of life.

Depending on the preventive goal, monitoring may include:

- smoking or nicotine status;
- alcohol intake;
- blood pressure;
- lipid profile;
- fasting glucose or HbA1c;
- body weight or waist circumference when appropriate;
- physical activity and sedentary time;
- strength, balance, mobility, or cardiorespiratory fitness;
- sleep quality and daytime functioning;
- mood, stress, and coping;
- medication adherence;
- participation in recommended screening and follow-up care;
- control of workplace exposure;
- symptoms and quality of life.

Not every benefit appears first in laboratory results. Increased energy, improved sleep, better mood, less breathlessness, greater mobility, or improved confidence may precede changes in body weight or biochemical measures.

Routine measurement of total antioxidant capacity, malondialdehyde, antioxidant enzyme activity, or similar oxidative stress markers is generally unnecessary in lifestyle counseling. These tests may be useful in research but are not substitutes for validated clinical outcomes.

Evidence-Based Note

A preventive intervention should be judged by its effects on disease risk, symptoms, function, safety, and quality of life, not by an isolated increase in “antioxidant status.”

Follow-up is essential. Advice given once without reassessment is less likely to produce sustained change. Follow-up provides an opportunity to recognize progress, discuss difficulties, and adjust goals.

17.7 Communication in Preventive Practice

Preventive communication should be accurate, understandable, respectful, and specific. Patients encounter conflicting messages about detoxification, fasting, supplements, superfoods, weight loss, anti-aging, and natural therapies.

Healthcare professionals should distinguish biological plausibility from demonstrated benefit. A compound may show antioxidant activity in a laboratory without improving clinical outcomes. A supplement may alter a biomarker without reducing disease risk.

A useful explanation is:

Antioxidants are important in normal physiology, and antioxidant-rich foods can be part of a healthy diet. High-dose supplements, however, are not equivalent to foods and cannot replace smoking cessation, movement, sleep, exposure reduction, or medical treatment.

Advice should be translated into actions. “Eat better” is less useful than “add a vegetable to lunch and dinner.” “Exercise more” is less useful than “walk for 10 minutes after your evening meal.” “Manage stress” is less useful than identifying one specific recovery practice.

Shared decision-making improves relevance. The healthcare professional may identify the most important medical risk, but the individual helps determine which change is feasible and meaningful.

Communication should avoid moral language. Smoking, alcohol use, obesity, physical inactivity, and diet are influenced by biological, psychological, social, and environmental conditions. Prevention should support agency without ignoring these constraints.

17.8 A Brief Preventive Consultation Framework

In practice, preventive counseling is most effective when it follows a simple, structured sequence. A brief consultation does not need to address every possible lifestyle factor at once; instead, it should focus on identifying priorities, agreeing on realistic goals, and reviewing progress over time. This framework is summarized in Figure 6.

Figure 6 **A brief preventive consultation framework.**

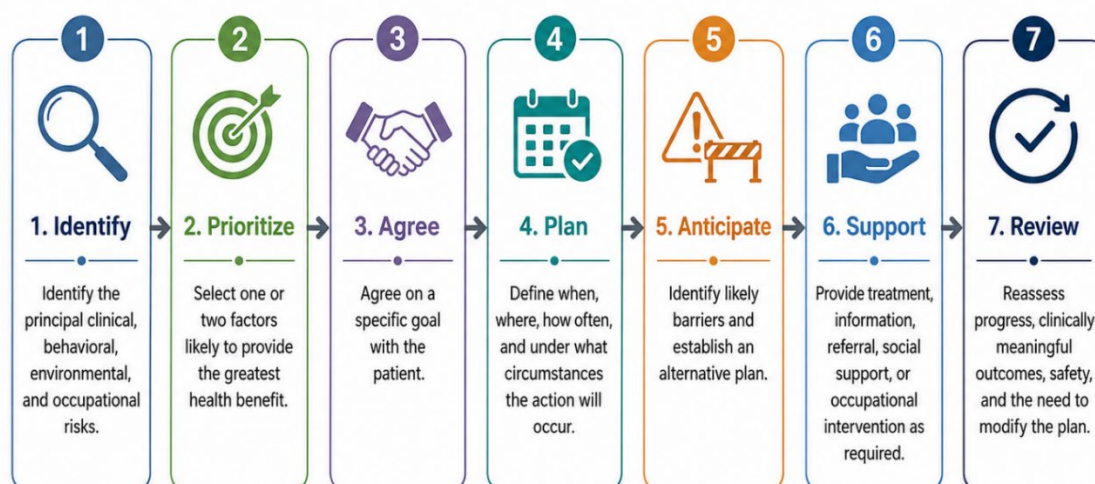


Table 2 **Practical Priorities in Lifestyle-Based Prevention**

Domain	Key assessment	Possible first step	Meaningful outcome
<i>Tobacco</i>	Current use, dependence, previous quit attempts	Establish a quit plan and offer evidence-based support	Abstinence or reduced combustible tobacco exposure
<i>Alcohol</i>	Frequency, amount, heavy drinking, reason for use	Add alcohol-free days or reduce portions	Lower intake, fewer heavy episodes, improved sleep
<i>Nutrition</i>	Dietary pattern, access, meal regularity	Add vegetables or replace one highly processed meal	Improved diet quality and metabolic measures
<i>Physical activity</i>	Current movement, sitting, limitations	Begin short daily walks or basic strength exercise	Improved fitness, function, blood pressure, or glucose
<i>Sleep</i>	Duration, quality, regularity, apnea symptoms	Protect a consistent sleep period	Better sleep quality and daytime function
<i>Stress and mental health</i>	Main stressors, mood, coping	Introduce one recovery strategy or arrange care	Improved coping, mood, and adherence
<i>Occupational exposure</i>	Job tasks, hazards, symptoms, protective controls	Refer to occupational health or improve exposure control	Reduced exposure and work-related symptoms
<i>Supplements</i>	Product, dose, indication, overlap, interactions	Review necessity and discontinue unsafe duplication	Safe, indication-based use

Chapter summary

Key Points

- Lifestyle-based prevention aims to reduce chronic metabolic, inflammatory, and oxidative burden while preserving physiological redox signaling.
- Prevention should address total clinical risk rather than one nutrient, biomarker, or biological mechanism.
- Major harmful exposures should generally be addressed before minor dietary refinements or supplementation.
- Lifestyle recommendations should be individualized according to health status, functional capacity, preferences, resources, and safety.
- Sustainable prevention combines exposure reduction, protective daily routines, clinical risk management, and supportive environments.
- Healthy dietary patterns are more important than maximizing the intake of individual antioxidants.
- Physical activity supports metabolic health, vascular function, functional capacity, and physiological redox adaptation.
- Sleep, recovery, stress regulation, and mental health are essential components of prevention.
- Tobacco avoidance, alcohol reduction, and environmental or occupational exposure control cannot be replaced by antioxidant intake.
- Lasting change often begins with one or two specific, achievable goals.
- Clinically meaningful outcomes are more important than nonspecific oxidative stress biomarkers.
- Medication adherence, recommended screening, and follow-up care are part of effective prevention.
- Effective counseling requires shared decision-making, respectful communication, appropriate support, and follow-up.

Practical Relevance

Lifestyle-based prevention is the practical bridge between redox biology and healthcare. Its objective is not to create a perfect lifestyle or maximize antioxidant consumption, but to identify the most important modifiable risks and support sustainable improvement.

An effective preventive plan begins with assessment, establishes priorities, translates advice into specific actions, anticipates barriers, and includes follow-up. Supplements may have a defined role, but the foundation remains healthy food, regular movement, adequate sleep, mental health support, tobacco avoidance, alcohol-risk reduction, safe working conditions, recommended screening, and appropriate medical care.

Chapter 18. Antioxidant Supplementation: Evidence and Controversies

Antioxidant supplementation is one of the most debated areas of preventive medicine. Vitamins, carotenoids, trace elements, coenzyme Q10, polyphenols, plant extracts, and other redox-active compounds are widely promoted for cardiovascular protection, cancer prevention, immunity, fertility, exercise recovery, skin health, healthy aging, and general well-being.

The biological rationale appears straightforward. Reactive oxygen and nitrogen species may contribute to molecular damage, inflammation, endothelial dysfunction, mitochondrial impairment, and chronic disease. Antioxidant defense systems are essential for normal physiology, and deficiencies of specific nutrients may weaken these systems.

However, biological plausibility does not automatically establish clinical benefit. A compound may demonstrate antioxidant activity in a chemical assay, influence a cellular pathway, or change a laboratory biomarker without preventing disease or improving health outcomes in humans.

Antioxidant supplements should therefore not be assessed as one uniform category. Each product must be evaluated according to its specific compound, dose, formulation, route of administration, baseline nutritional status, target population, duration of use, intended outcome, safety profile, and potential interactions.

A central distinction must be made among:

- correcting a nutritional deficiency;
- meeting an increased physiological requirement;
- supporting treatment of a defined clinical condition;
- changing a laboratory biomarker;
- preventing chronic disease in a generally well-nourished population.

A supplement may be useful for one of these purposes and ineffective (or harmful) for another.

18.1 From Antioxidant Activity to Clinical Benefit

Different forms of evidence answer different questions.

Chemical assays such as DPPH, ABTS, FRAP, CUPRAC, and ORAC describe how a substance behaves under specific laboratory conditions. Their results depend on solvent, pH, concentration, reaction time, radical source, and analytical method.

Cell-culture and animal studies may identify biological mechanisms, including effects on inflammatory signaling, mitochondrial function, gene expression, or oxidative damage. Such findings are valuable for generating hypotheses but may involve concentrations that cannot be achieved through ordinary oral intake.

Human biomarker studies can demonstrate absorption, metabolism, or short-term physiological effects. However, changes in oxidative stress biomarkers do not necessarily indicate clinical improvement. Many biomarkers are nonspecific and are influenced by inflammation, renal function, diet, medication, sample handling, and laboratory methodology.

Randomized controlled trials provide stronger evidence regarding causality, but their interpretation also depends on participant selection, baseline nutrient status, dose, duration, adherence, comparison group, and choice of outcome.

The most clinically meaningful evidence concerns outcomes such as:

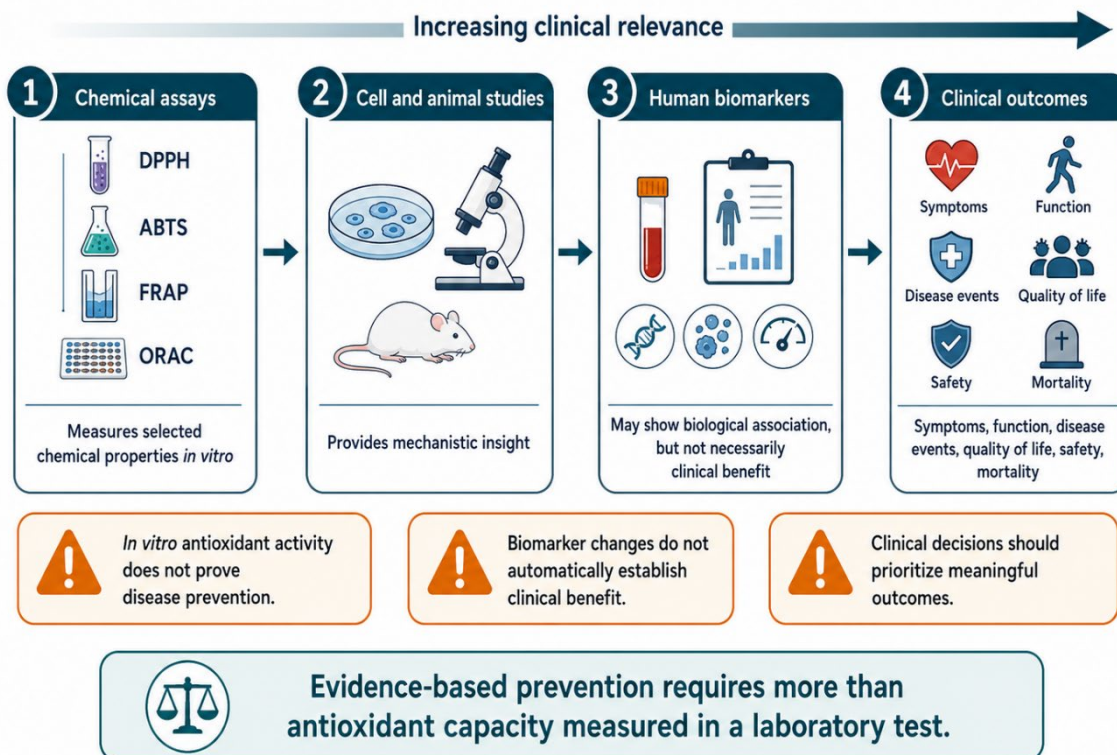
- disease incidence;
- symptoms;
- functional capacity;
- complications;
- quality of life;
- hospitalization;
- disability;
- mortality.

A reduction in a laboratory marker should not automatically be interpreted as prevention of disease.

Evidence-Based Note

A supplement should not be considered clinically effective merely because it neutralizes radicals in vitro or increases a nonspecific measure of antioxidant capacity. The relevant question is whether it produces a meaningful benefit in an appropriate human population without disproportionate risk.

Figure 7 **From Antioxidant Activity to Clinical Relevance**



18.2 Why Foods and Supplements Are Not Equivalent

Antioxidants in foods occur within complex matrices containing fiber, proteins, lipids, minerals, vitamins, carbohydrates, and numerous phytochemicals. These components interact during digestion, absorption, hepatic metabolism, microbial transformation, tissue distribution, and excretion.

A supplement usually delivers one or several selected compounds in a concentrated form. The dose may greatly exceed ordinary dietary exposure, while the accompanying food structures and nutrients are absent.

The favorable health associations of plant-rich diets cannot therefore be attributed solely to antioxidants. Such diets may also:

- improve satiety;
- support healthy body weight;
- provide dietary fiber;
- improve glucose and lipid metabolism;
- support blood pressure regulation;
- influence the gut microbiota;
- replace highly processed foods;
- provide multiple nutrients simultaneously.

The biological effects of antioxidant compounds may also be dose-dependent. A nutrient may improve health when correcting inadequate intake but provide no additional benefit once physiological requirements are met. At high concentrations, some compounds may

interfere with normal redox signaling or display pro-oxidant activity under selected conditions.

This may produce a U-shaped relationship in which both deficiency and excess are associated with harm.

Bioavailability is another important difference. Many polyphenols are poorly absorbed in their original form and are extensively metabolized in the intestine and liver. Circulating metabolites may have different properties from the native compounds used in laboratory experiments.

For healthy individuals, the most appropriate general principle is:

Foods first, supplements when indicated.

This principle does not reject supplementation. It distinguishes ordinary nutrition from targeted clinical use.

18.3 Evidence for Selected Antioxidant Supplements

Antioxidant supplements differ substantially in their physiological roles, evidence base, and safety profile. Their use should be considered individually.

Multivitamin and Antioxidant Combinations

Multivitamin products vary substantially in composition and dose. They may help address selected nutritional gaps in people with inadequate diets, restricted food choices, malabsorption, or increased physiological requirements.

This is different from using multivitamins to prevent cardiovascular disease, cancer, dementia, or premature aging. Evidence remains insufficient to recommend multivitamins for the primary prevention of cardiovascular disease or cancer in generally well-nourished adults. Some recent randomized studies in older adults have reported modest benefits for global cognition and episodic memory, but the clinical significance, generalizability, durability, and effects on dementia incidence remain uncertain.

A multivitamin should therefore not be presented as nutritional insurance against smoking, harmful alcohol consumption, inactivity, inadequate sleep, or poor diet quality.

Vitamin C

Vitamin C supplementation is appropriate in confirmed deficiency and may be useful when dietary intake is persistently inadequate or requirements are increased.

Routine high-dose supplementation has not been shown to provide universal protection against cardiovascular disease, cancer, or other chronic conditions. Oral absorption becomes less efficient as the dose increases, and excess vitamin C is largely excreted.

High doses may cause abdominal discomfort and diarrhea. Additional caution may be required in individuals susceptible to kidney stones and in patients with iron-overload disorders.

Intravenous vitamin C produces pharmacological blood concentrations that cannot be achieved orally. It should therefore be considered a separate medical intervention rather than an intensified form of dietary supplementation.

Vitamin E

Vitamin E supplementation may be required in rare genetic disorders and severe conditions involving fat malabsorption. These therapeutic indications are different from routine preventive use in healthy adults.

Large trials have not established that high-dose vitamin E supplementation reliably prevents cardiovascular disease or cancer in the general population.

High supplemental doses may interfere with coagulation and increase bleeding risk, particularly in individuals using anticoagulant or antiplatelet medications or those with other bleeding risks.

Vitamin E obtained from nuts, seeds, and plant oils should not be treated as equivalent to pharmacological doses of isolated alpha-tocopherol.

Beta-Carotene and Preformed Vitamin A

Carotenoid-rich vegetables and fruits are valuable components of healthy dietary patterns. High-dose beta-carotene supplements, however, have produced different outcomes.

Major intervention trials demonstrated increased lung cancer risk among smokers and people with substantial asbestos exposure receiving high-dose beta-carotene-containing supplements. This is one of the clearest examples showing that isolated supplementation may not reproduce the effects of foods.

Preformed vitamin A also requires careful dosing because it can accumulate in the body. Excessive intake may cause liver injury, neurological symptoms, skin changes, and adverse skeletal effects. High intake during pregnancy may be teratogenic.

Beta-carotene-rich foods do not have the same toxicity profile as high-dose supplements.

Selenium

Selenium is required for glutathione peroxidases, thioredoxin reductases, deiodinases, and other selenoproteins. Supplementation may be appropriate in confirmed deficiency or in populations with very low selenium intake.

Once selenium-dependent proteins are adequately supplied, higher intake does not necessarily improve antioxidant defense. Large trials have not demonstrated a general cancer-preventive benefit from selenium supplementation in well-nourished populations.

Selenium has a relatively narrow safety range. Chronic excess may cause hair loss, brittle nails, gastrointestinal symptoms, fatigue, neurological complaints, skin changes, and garlic-like breath odor.

Total intake from individual supplements, multivitamins, and selenium-rich foods should be considered together.

Zinc, Copper, Manganese and Iron

Trace elements support antioxidant enzymes and metabolic pathways, but they should not be supplemented indiscriminately as general antioxidants.

High-dose zinc may impair copper absorption. Prolonged excessive intake can cause copper deficiency, anemia, neurological symptoms, and altered immune function.

Copper is essential for normal physiology but is also redox-active. Both deficiency and excess may be harmful.

Manganese is required for mitochondrial superoxide dismutase, but dietary deficiency is rare. Excessive occupational or environmental exposure may produce neurotoxicity.

Iron is required for oxygen transport and numerous enzymes, but poorly regulated iron may promote the formation of highly reactive hydroxyl radicals. Iron supplementation should be based on diagnosed deficiency or another established clinical indication.

Fatigue alone is not sufficient evidence of iron deficiency. Unnecessary supplementation may be harmful, particularly in hereditary hemochromatosis and other iron-loading conditions.

Coenzyme Q10

Coenzyme Q10 participates in mitochondrial electron transport and lipid-phase antioxidant defense. It has been investigated in heart failure, migraine, statin-associated muscle symptoms, fertility, hypertension, and mitochondrial disorders.

Some patients may benefit in selected clinical circumstances, but evidence varies according to indication, formulation, dose, and study quality. Coenzyme Q10 should not be promoted as a universal supplement for energy, cardiovascular protection, or healthy aging.

Potential interactions include those involving anticoagulant, blood pressure-lowering, glucose-lowering, and oncological treatments.

Polyphenols and Botanical Extracts

Quercetin, resveratrol, curcumin, green tea catechins, grape-seed extracts, and numerous other botanical products demonstrate antioxidant, anti-inflammatory, metabolic, and signaling effects in experimental studies.

Clinical translation is limited by:

- variable bioavailability;
- extensive metabolism;
- inconsistent product composition;
- small study populations;
- short intervention periods;
- heterogeneous outcomes;
- limited information about long-term safety.

Concentrated extracts may provide doses far exceeding those obtained from foods. They may also contain multiple active constituents, contaminants, or undeclared ingredients.

Green tea extract is not equivalent to brewed green tea. Curcumin supplements are not equivalent to culinary turmeric. Concentrated garlic preparations are not equivalent to ordinary culinary use.

Some botanical preparations may affect platelet function, liver enzymes, drug transporters, or medication metabolism. The term “natural” does not establish safety.

Other Redox-Active Products

N-acetylcysteine, alpha-lipoic acid, glutathione preparations, and melatonin are often marketed broadly as antioxidant products.

N-acetylcysteine has established medical uses, including treatment of acetaminophen poisoning and use as a mucolytic agent. These indications do not establish a need for routine preventive supplementation in healthy individuals.

Alpha-lipoic acid has been investigated in diabetic neuropathy and selected metabolic conditions. It may influence glucose concentrations and interact with treatment.

Oral glutathione preparations differ in formulation and bioavailability. An increase in glutathione-related biomarkers does not automatically demonstrate prevention of chronic disease.

Melatonin is primarily a circadian hormone. Its experimental antioxidant effects do not justify its use as a general antioxidant or anti-aging supplement. When used for sleep or circadian indications, dose and timing are central to its effects.

Condition-Specific Formulations

Evidence-based supplementation may sometimes involve a defined formulation for a specific clinical condition and stage.

The AREDS2 formulation is an important example. In appropriately selected patients with intermediate age-related macular degeneration or advanced disease in one eye, it may reduce the risk of progression.

It does not prevent the initial development of age-related macular degeneration and should not be used as a general anti-aging supplement.

Current and former smokers should avoid older formulations containing beta-carotene because of increased lung cancer risk. This example demonstrates why the target population, formulation, disease stage, and outcome must all be clearly defined.

Table 3 Selected Supplements and Their Appropriate Interpretation

Product	Possible appropriate use	Not established as	Important caution
<i>Multivitamin</i>	Filling selected nutritional gaps	Substitute for a healthy diet or universal chronic disease prevention	Overlapping ingredients and cumulative doses
<i>Vitamin C</i>	Deficiency, inadequate intake, selected increased requirements	Universal prevention of cardiovascular disease or cancer	Gastrointestinal effects and caution in selected kidney stone or iron-overload risks
<i>Vitamin E</i>	Rare deficiency and fat-malabsorption disorders	Routine cardiovascular or cancer prevention	Bleeding and medication interactions
<i>Beta-carotene</i>	Provitamin A source in specific deficiency settings	General cancer-preventive supplement	Increased lung cancer risk in smokers and asbestos-exposed groups
<i>Preformed vitamin A</i>	Prevention or treatment of deficiency	General antioxidant or anti-aging supplement	Toxicity and teratogenicity
<i>Selenium</i>	Confirmed deficiency or very low intake	Universal cancer prevention	Narrow safety range and selenosis
<i>Zinc</i>	Deficiency and selected clinical indications	General antioxidant strategy	Copper deficiency with prolonged high intake
<i>Iron</i>	Diagnosed deficiency or established clinical indication	Supplement for unexplained fatigue without evaluation	Gastrointestinal effects and iron overload
<i>Coenzyme Q10</i>	Selected adjunctive clinical applications	Universal cardiovascular or energy supplement	Variable evidence and medication interactions
<i>Polyphenol extracts</i>	Selected research or adjunctive settings	Equivalent to polyphenol-rich foods	Variable formulations, interactions, and possible organ toxicity
<i>AREDS2</i>	Defined stages of age-related macular degeneration	Primary prevention or general healthy aging	Should be used under eye-care guidance

18.4 Contexts Requiring Particular Caution

The effect of an antioxidant supplement depends not only on the compound but also on the biological context.

Cancer Prevention and Treatment

Randomized trials have not demonstrated consistent cancer-preventive benefits from routine high-dose antioxidant supplementation. Some interventions, particularly beta-carotene in smokers and asbestos-exposed groups, have caused harm.

The use of antioxidant supplements during cancer treatment is especially complex. Radiotherapy and several chemotherapeutic agents partly depend on oxidative mechanisms to damage cancer cells. At the same time, treatment-related oxidative injury can affect healthy tissues.

Evidence regarding supplementation during treatment is mixed and treatment-specific. Patients undergoing chemotherapy, radiotherapy, immunotherapy, or hormonal treatment should discuss every supplement with the oncology team. Products should not be started or discontinued solely on the basis of general claims about antioxidant effects.

Pregnancy and Breastfeeding

Pregnancy changes nutrient requirements but also increases vulnerability to excessive intake. Preformed vitamin A, selenium, iodine, botanical extracts, and high-dose combinations may create specific risks.

Pregnancy-related supplements should follow evidence-based prenatal guidance and individual clinical assessment. Products lacking adequate pregnancy safety data should not be assumed to be harmless.

Smoking and Asbestos Exposure

Current and former smokers and people with substantial asbestos exposure should avoid high-dose beta-carotene supplements. Antioxidant supplementation cannot compensate for tobacco-related oxidant and carcinogenic exposure.

Kidney and Liver Disease

Kidney and liver diseases may alter the metabolism, storage, and excretion of supplements. High doses of minerals, fat-soluble vitamins, herbal products, and concentrated extracts may accumulate or worsen organ injury.

Patients with chronic kidney or liver disease should not use antioxidant supplements without clinical review.

Anticoagulant and Antiplatelet Therapy

Vitamin E, concentrated garlic preparations, ginkgo, and other products may influence platelet function or coagulation. Multiple supplements with similar effects may increase bleeding risk.

Supplement use should also be reviewed before surgery or invasive procedures.

Exercise and Training Adaptation

Exercise generates transient reactive species that participate in physiological adaptation. High-dose vitamin C or vitamin E supplementation has not consistently improved training outcomes and may attenuate selected redox-sensitive adaptations in some circumstances.

Athletes should not assume that suppression of exercise-related oxidative signals improves recovery or performance. Adequate energy intake, protein, sleep, hydration, training progression, and recovery remain more important.

Multiple-Supplement Use

Patients may combine a multivitamin, an immune product, an antioxidant formula, a sports supplement, and a botanical extract without recognizing that they contain overlapping ingredients.

Cumulative exposure should be calculated across all products. An apparently moderate dose in one supplement may become excessive when several products are used together.

18.5 Why Supplements May Fail or Cause Harm

Several factors explain why promising laboratory findings may not translate into clinical benefit.

Baseline Nutritional Status

A supplement is most likely to help when intake or status is inadequate. In a person who already has sufficient nutrient status, additional intake may provide no benefit.

Many supplementation trials include participants with varying baseline status. A possible benefit in deficient individuals may therefore be diluted or obscured when results are averaged across an adequately nourished population.

Dose

Nutrients required in small quantities may become pharmacologically active or toxic at high doses. Effects observed at ordinary dietary intake cannot be extrapolated automatically to concentrated supplements.

More is not necessarily better.

Formulation and Route

Natural and synthetic forms may differ in stereochemistry, absorption, metabolism, and tissue retention. Tablets, powders, oils, liposomal preparations, extracts, and intravenous products are not interchangeable.

A formulation that increases absorption may also increase the potential for adverse effects or interactions.

Duration and Timing

A short-term biomarker change does not establish long-term disease prevention. Chronic diseases develop over years, while many supplementation studies last only weeks or months.

Timing may also matter. An intervention may have different effects before disease develops, after disease is established, or during active treatment.

Physiological Redox Signaling

Reactive species are involved in exercise adaptation, immune defense, vascular signaling, apoptosis, and cellular stress responses. Excessive suppression may interfere with these functions.

The objective is not maximal antioxidant exposure but appropriate redox regulation.

Product Quality

Products with the same ingredient name may differ in dose, purity, formulation, stability, contaminants, and actual content.

Botanical preparations may vary according to plant species, plant part, cultivation, harvest time, storage, processing, and extraction method.

Commercial availability should not be interpreted as proof of efficacy, quality, or safety.

18.6 When Supplementation Is Appropriate

Supplementation may be appropriate or essential when it addresses a clearly identified need.

Possible indications include:

- confirmed nutritional deficiency;
- persistently inadequate dietary intake;
- malabsorption or impaired nutrient metabolism;
- increased physiological requirements;
- pregnancy-specific recommendations;
- restricted or exclusion diets;
- medication-related nutrient depletion;
- defined clinical conditions with evidence-based supplementation protocols.

The decision should be based on dietary assessment, medical history, symptoms, examination, laboratory testing when appropriate, and the expected clinical benefit.

Not every clinically useful supplement is prescribed because of antioxidant activity. Folic acid during the periconceptional period, vitamin B12 in malabsorption or vegan diets, iodine when intake is inadequate, vitamin D in selected deficiency states, and iron in iron-deficiency anemia have defined physiological purposes extending beyond antioxidant defense.

This distinction prevents the term “antioxidant” from becoming an overly broad justification for supplementation.

The duration of supplementation should also be defined. Some deficiencies require short-term correction followed by dietary maintenance. Other conditions require long-term treatment and monitoring.

A product should not automatically be continued indefinitely because it was initially appropriate.

18.7 A Clinical Framework for Supplement Counseling

Healthcare professionals should routinely ask about vitamins, minerals, botanical preparations, powders, sports products, and other non-prescription supplements. Many patients do not consider these products to be medications and may not report them spontaneously.

A practical assessment can be based on seven questions.

1. What is the exact product?

Record all ingredients, dose per serving, number of servings, formulation, and brand.

2. Why is it being used?

Clarify whether the intended goal is correction of deficiency, symptom relief, disease prevention, fertility, immunity, sleep, exercise performance, or general wellness.

3. Is there evidence for this specific indication?

Distinguish laboratory antioxidant activity, biological plausibility, biomarker change, and demonstrated clinical benefit.

4. Is deficiency or increased requirement likely?

Consider diet, medical history, pregnancy, age, malabsorption, medication use, and laboratory results.

5. Is the total dose safe?

Include exposure from food, fortified products, multivitamins, and overlapping supplements.

6. Could it interact with a disease or treatment?

Review kidney and liver function, pregnancy, smoking status, cancer treatment, anticoagulation, planned surgery, and all medications.

7. How will effectiveness and safety be monitored?

Define the expected outcome, duration, reassessment date, and criteria for continuation or discontinuation.

Practical Point

A supplement should have a clear purpose, an appropriate dose, a defined duration, and a plan for reassessment. “It is an antioxidant” is not a sufficient clinical indication.

18.8 Communication Without Hype or Dismissal

Communication about supplements should avoid two extremes.

The first is exaggerated enthusiasm: presenting antioxidant products as natural, harmless, and universally protective.

The second is complete dismissal: implying that antioxidant nutrients are irrelevant or that supplementation is never useful.

The evidence-based position is more precise. Antioxidant systems are essential for human physiology. Antioxidant-rich foods are important components of healthy dietary patterns. Supplements may correct deficiencies and may be useful in selected clinical conditions. Routine high-dose supplementation, however, is not a substitute for lifestyle-based prevention or medical care.

A useful explanation for patients is:

Antioxidant activity in a laboratory does not necessarily mean that a supplement prevents disease in people. We need to consider whether you need the product, whether the dose is safe, and whether it interacts with your health conditions or treatment.

Patients should not be criticized for using supplements. Many are attempting to take responsibility for their health. Respectful counseling makes it easier to discuss evidence, cost, product quality, marketing claims, and safety.

The central message can be summarized as follows:

Supplements may correct a gap, but they do not build the foundation.

The foundation remains healthy nutrition, regular physical activity, adequate sleep, stress management, tobacco avoidance, alcohol reduction, safe working conditions, environmental protection, appropriate screening, and evidence-based medical care.

Chapter summary

Key Points

- Antioxidant supplementation is biologically plausible but clinically complex.
- Chemical antioxidant activity, effects in cells or animals, biomarker changes, and clinical benefit are different levels of evidence.
- Foods and isolated high-dose supplements are not biologically equivalent.
- Supplementation is most likely to be beneficial when it corrects a deficiency or addresses a defined clinical indication.

- Randomized trials have not consistently shown that antioxidant supplements prevent cardiovascular disease or cancer in generally well-nourished populations.
- High-dose beta-carotene supplementation increases lung cancer risk in smokers and selected high-risk groups.
- High supplemental doses of vitamin E may increase bleeding risk.
- Selenium, zinc, copper, iron, and preformed vitamin A may be harmful when intake exceeds physiological needs.
- Coenzyme Q10 and other redox-active products may have selected clinical applications but should not be promoted as universal preventive supplements.
- Concentrated polyphenol and botanical extracts differ from the foods from which they are derived.
- Supplement use during cancer treatment, pregnancy, kidney or liver disease, anticoagulant therapy, and before surgery requires particular caution.
- The effects of supplements depend on baseline status, dose, formulation, route, duration, timing, disease stage, and medication use.
- Multiple products may lead to unrecognized overlapping ingredients and excessive cumulative intake.
- Supplement counseling should include a clear indication, safe dose, defined duration, interaction review, and plan for reassessment.

Practical Relevance

Antioxidant supplements are widely used, but their use should be guided by evidence rather than laboratory scores or marketing claims. The presence of oxidative stress in a disease does not demonstrate that high-dose antioxidant supplementation will prevent or treat that disease.

For preventive medicine, the priority is to establish a strong lifestyle and clinical foundation. Supplements may be valuable when they fill a documented nutritional gap or address a specific evidence-based indication. They should not replace healthy dietary patterns, physical activity, sleep, smoking cessation, alcohol reduction, environmental and occupational protection, screening, or appropriate medical treatment.

Chapter 19. Public Health Perspective

Oxidative stress is usually discussed in biochemical, nutritional, and clinical contexts, but it also has important public health relevance. Many factors that influence redox homeostasis are shaped not only by individual behavior, but also by environmental quality, working conditions, food systems, commercial practices, social inequalities, and public policy.

Tobacco smoke, harmful alcohol consumption, poor diet quality, physical inactivity, air pollution, occupational hazards, insufficient sleep, chronic psychosocial stress, and metabolic disease may contribute to oxidative and inflammatory burden through different but overlapping mechanisms. At the population level, these exposures often cluster and are unequally distributed.

Oxidative stress should not be treated as a public health diagnosis or as a universal explanation for chronic disease. Most oxidative stress biomarkers are insufficiently specific or standardized for routine population screening. The value of redox biology lies instead in helping explain how diverse exposures may converge on inflammation, endothelial injury, mitochondrial dysfunction, impaired metabolic regulation, and molecular damage.

Public health action should therefore focus on reducing harmful exposures, improving living and working conditions, supporting health-promoting behavior, correcting defined nutritional deficiencies, and ensuring access to preventive and clinical care. The objective is not to maximize antioxidant intake, but to create conditions that reduce avoidable oxidative distress and support physiological resilience.

19.1 From Biological Mechanisms to Population Prevention

Public health translates knowledge about biological mechanisms into interventions capable of improving health across entire populations. Understanding oxidative stress may help identify common pathways connecting behavioral, environmental, occupational, and metabolic risks. Preventive decisions, however, should be based primarily on established exposures, validated risk factors, and meaningful health outcomes.

For example, tobacco smoke contains oxidants, carcinogens, fine particles, and toxic metals. Air pollution promotes respiratory and systemic inflammation. Excess adiposity contributes to metabolic dysfunction and chronic low-grade inflammation. Alcohol metabolism generates acetaldehyde and alters cellular redox balance. Workplace exposure to dust, fumes, metals, solvents, pesticides, or radiation may produce local and systemic injury.

These mechanisms support prevention, but they do not justify routine measurement of total antioxidant capacity or individual oxidative stress biomarkers in the general population. Public health surveillance should prioritize indicators such as:

- tobacco and alcohol use;
- diet quality and food insecurity;
- physical activity and sedentary behavior;
- obesity and metabolic disease prevalence;
- blood pressure, diabetes, and lipid-related risk;
- ambient and occupational pollutant concentrations;
- occupational disease and injury;
- chronic disease incidence, disability, and mortality;
- access to preventive and medical services.

Oxidative stress biomarkers may be useful in research examining biological responses to exposure or intervention. They should not replace validated measures of population health.

Public health also distinguishes between individual risk reduction and population-wide prevention. Supporting one person in smoking cessation is important, but taxation, advertising restrictions, smoke-free legislation, cessation services, and prevention of nicotine initiation can influence millions of people.

Similarly, dietary counseling may help an individual, but food affordability, availability, labeling, school meals, workplace catering, product formulation, and commercial marketing strongly affect what choices are realistically available.

Population prevention therefore aims to improve both behavior and the environment in which behavior occurs.

19.2 Social, Environmental, Occupational and Commercial Determinants

Health-related behavior is often described as a matter of personal choice. In reality, choices are shaped by material, social, cultural, and environmental conditions.

Income, education, employment, housing, neighborhood safety, transport, food access, social support, and access to healthcare all influence chronic disease risk. People with limited resources may have less access to healthy food, safe recreational spaces, stable housing, clean air, preventive services, and opportunities for recovery.

Work organization also affects health. Long or irregular working hours, night shifts, insecure employment, insufficient rest, and physically or psychologically demanding work may impair sleep, eating patterns, physical activity, family life, and mental well-being.

Environmental exposures are frequently beyond individual control. Air pollution, excessive noise, contaminated water, extreme heat, wildfire smoke, industrial emissions, and limited access to green spaces may affect entire communities. Some populations experience several such burdens simultaneously.

Occupational conditions may include exposure to:

- dusts and fumes;
- metals and solvents;
- pesticides and other chemicals;
- radiation;
- extreme temperatures;
- biological hazards;
- ergonomic strain;
- noise;
- circadian disruption;
- psychosocial stress.

Workers cannot be expected to compensate for unsafe environments through diet, exercise, or supplementation. The primary preventive responsibility is to identify, reduce, and control the hazard.

Commercial determinants of health are also important. Tobacco, alcohol, ultra-processed foods, sugar-sweetened beverages, and some supplement products may be promoted through advertising, sponsorship, pricing, product placement, and health-oriented claims.

Antioxidant marketing is a clear example. A scientifically correct statement, such as the ability of a compound to react with a radical *in vitro*, may be transformed into an unsupported claim about detoxification, immune enhancement, cardiovascular protection, anti-aging, or cancer prevention.

The burden of harmful exposures is not distributed equally. Children, pregnant women, older adults, people with chronic diseases, outdoor workers, shift workers, and socioeconomically disadvantaged communities may be particularly vulnerable.

Health equity should therefore be a central objective of public health prevention rather than an additional consideration.

19.3 Supportive Environments and Policy

Health promotion should do more than provide information. People need environments in which healthier behavior is affordable, accessible, safe, and socially supported.

Healthy Food Environments

Public health nutrition should support access to vegetables, fruits, legumes, whole grains, nuts, seeds, and other minimally processed foods.

Relevant measures may include:

- healthy school, hospital, and workplace meals;
- clear and understandable food labeling;
- reformulation to reduce excessive sodium, added sugar, and industrial trans fats;
- reduced marketing of unhealthy foods to children;

- support for affordable local food systems;
- nutrition education and practical culinary skills;
- measures addressing food insecurity.

An antioxidant-rich diet does not require expensive powders, imported berries, or specialized functional foods. Ordinary foods such as cabbage, carrots, onions, beans, lentils, oats, apples, whole-grain bread, nuts, seeds, herbs, and tea can contribute to a varied dietary pattern.

Population nutrition policy should also distinguish evidence-based fortification from commercial antioxidant enrichment. Fortification may be appropriate when it addresses a defined nutritional deficiency in a population. Adding antioxidant compounds to a product primarily to support a health-oriented marketing claim is a different practice.

Environments Supporting Physical Activity

Physical activity is influenced by urban planning, transport, workplace design, and community safety.

Supportive measures include:

- safe pavements and cycling infrastructure;
- accessible public transport;
- green and recreational spaces;
- school physical education;
- workplace activity breaks;
- stair access;
- programs for older adults and people with disabilities;
- rehabilitation services.

Such interventions reduce dependence on individual motivation and make movement part of ordinary daily life.

Tobacco and Alcohol Policy

Tobacco prevention requires coordinated population measures, including smoke-free environments, taxation, health warnings, advertising restrictions, cessation support, and protection from secondhand smoke.

Alcohol-related harm may be reduced through screening, brief clinical interventions, treatment of dependence, regulation of marketing and availability, pricing measures, and clear communication that alcohol should not be consumed for antioxidant or cardiovascular benefit.

People who do not drink should not be encouraged to start for health reasons.

Sleep, Stress and Mental Health

Sleep and mental well-being are also influenced by environmental and social conditions. Work schedules, school timing, housing quality, noise, digital exposure, employment insecurity, violence, and limited access to mental healthcare may all impair recovery.

Advice to improve sleep or reduce stress has limited value when the underlying occupational, financial, housing, or social conditions remain unaddressed.

Population strategies should therefore include access to mental health services, prevention of violence, safer work organization, social support, and protection from excessive occupational demands.

Occupational and Environmental Protection

Occupational prevention requires cooperation among workers, employers, occupational medicine physicians, occupational hygienists, safety professionals, public health institutions, and regulators.

The hierarchy of controls should guide workplace intervention:

1. elimination of the hazard;
2. substitution with a safer alternative;
3. engineering controls;
4. administrative and organizational controls;
5. personal protective equipment.

Personal protective equipment is important but should not replace higher-level controls when elimination, substitution, or engineering solutions are possible.

Environmental prevention similarly requires clean-air policies, safe drinking water, chemical regulation, waste management, climate adaptation, sustainable transport, and protection from harmful radiation and excessive heat.

Practical Point

Health promotion should make healthier behavior easier. It should not repeatedly instruct individuals to overcome unhealthy environments through willpower, supplements, or personal discipline alone.

19.4 Risk Communication, Health Claims and Misinformation

Public understanding of antioxidants is influenced by scientific communication, healthcare professionals, popular media, social networks, influencers, and commercial advertising.

The term antioxidant is scientifically meaningful, but it is frequently used as a broad synonym for health, detoxification, or disease protection.

Effective communication should distinguish four different levels of evidence:

1. a compound demonstrates antioxidant activity in a chemical assay;
2. it affects a biological pathway in cells or animals;
3. it changes a biomarker in humans;
4. it improves a clinically meaningful human outcome.

Evidence at one level does not automatically establish benefit at the next.

A food or extract may have high radical-scavenging capacity but be poorly absorbed. A supplement may increase plasma antioxidant capacity without reducing disease incidence. A biologically plausible mechanism may fail clinically because the tested dose, formulation, population, or disease stage differs from the experimental model.

Common features of misleading antioxidant claims include:

- promotion of one product for many unrelated conditions;
- presentation of an in vitro score as proof of disease prevention;
- use of the word natural as evidence of safety;
- assumption that higher doses are more effective;
- vague claims involving detoxification or cellular cleansing;
- reliance on testimonials rather than controlled human studies;
- omission of contraindications, adverse effects, and interactions;
- presentation of a product as an alternative to medical treatment.

Healthcare professionals should respond without ridicule. Many people use supplements because they are actively trying to improve their health. Respectful communication makes it easier to discuss evidence, cost, safety, product quality, and more effective alternatives.

A useful public message is:

Antioxidant activity in a laboratory is not the same as prevention of disease in people. Health benefits must be demonstrated through appropriate human studies and meaningful outcomes.

Communication should also acknowledge uncertainty. Evidence may be promising but preliminary, limited to selected populations, dependent on a specific formulation, or associated with important safety questions.

Transparent communication of uncertainty is more trustworthy than unsupported certainty.

Evidence-Based Note

General changes in total antioxidant capacity or free-radical scavenging measured in vitro are not sufficient evidence that a food or supplement protects human tissues from oxidative damage or prevents chronic disease.

19.5 Integrated Public Health Action

Effective prevention requires intervention at several levels. Individual counseling remains important, but it should be supported by clinical services, workplace protection, environmental regulation, and policy.

Table 4 From Redox-Related Risk to Public Health Action

<i>Exposure or risk</i>	<i>Individual or clinical action</i>	<i>Population or policy action</i>
<i>Tobacco smoke</i>	Cessation treatment and avoidance of secondhand smoke	Taxation, smoke-free laws, advertising restrictions, cessation services
<i>Alcohol</i>	Screening, brief intervention, reduction or abstinence	Pricing and availability measures, marketing regulation, treatment access
<i>Poor diet quality</i>	Practical dietary counseling	Healthy institutional meals, labeling, reformulation, food-access policies
<i>Physical inactivity</i>	Individual activity plan or rehabilitation	Active transport, safe public spaces, school and workplace programs
<i>Sleep and chronic stress</i>	Assessment, treatment, and recovery strategies	Work-time standards, mental health services, housing and social support
<i>Air pollution</i>	Exposure advice for vulnerable individuals	Emission reduction, air-quality standards, clean energy and transport
<i>Occupational hazards</i>	Occupational history, surveillance, and work adaptation	Hazard elimination, engineering controls, workplace regulation and enforcement
<i>Excessive heat or UV</i>	Personal protection and early symptom recognition	Warning systems, shade, work-rest standards, climate adaptation
<i>Nutritional deficiency</i>	Assessment and targeted supplementation	Evidence-based fortification or supplementation programs
<i>Misleading health claims</i>	Supplement and medication review	Regulation of claims, advertising oversight, and consumer education

Public health programs should define measurable objectives. Depending on the intervention, outcomes may include:

- lower smoking prevalence;
- reduced harmful alcohol consumption;
- improved dietary quality;
- increased physical activity;
- lower sodium intake;
- reduced pollutant concentrations;
- fewer occupational exposures;
- improved blood pressure or diabetes detection;
- reduced hospital admissions;
- lower chronic disease incidence or mortality.

Evaluation should examine not only whether an intervention works, but also:

- who benefits;
- whether inequalities are reduced or increased;
- whether the intervention is affordable;
- whether it is sustainable;
- whether adverse or unintended effects occur;
- whether implementation is feasible in real-world settings.

Universal and targeted interventions should complement one another. Population-wide measures may shift risk across society, while additional support may be needed for highly exposed, medically vulnerable, or underserved groups.

19.6 Research Priorities

Antioxidant and oxidative stress research continues to develop, but several methodological problems limit translation into public health practice.

Biomarker Validation

Future studies should improve the standardization, specificity, reproducibility, and clinical interpretation of oxidative stress biomarkers.

Measurements should reflect clearly defined biological processes and use validated analytical methods. Tissue specificity, sample collection, storage, medication use, inflammation, kidney function, and diet must be considered.

Bioavailability and Metabolism

Research should distinguish between compounds present in foods and metabolites present in human tissues.

Many polyphenols undergo extensive transformation by intestinal enzymes, liver metabolism, and the gut microbiota. The biological effects of circulating metabolites may differ from those of the original food compounds.

Meaningful Human Outcomes

Small, short-term studies may identify biological signals but cannot establish effects on chronic disease incidence, disability, or mortality.

Long-term, adequately controlled human studies should prioritize clinically meaningful outcomes and clearly defined populations.

Combined and Cumulative Exposures

Real-life exposure usually involves mixtures. Air pollution, occupational chemicals, smoking, alcohol, psychosocial stress, poor sleep, and metabolic disease may coexist.

Research should increasingly examine cumulative exposure and interactions rather than studying one isolated risk factor at a time.

Implementation and Equity

Evidence that an intervention works under controlled conditions does not guarantee that it will work in schools, workplaces, clinics, or communities.

Implementation research should assess feasibility, acceptability, cost, sustainability, and effects on inequalities. Vulnerable and highly exposed populations should be adequately represented.

Research Transparency

Studies should report adverse effects, product composition, dose, funding sources, conflicts of interest, and negative findings.

Selective publication of favorable results may distort the apparent effectiveness of antioxidant interventions.

19.7 Final Public Health Perspective

The history of antioxidant research demonstrates why biological mechanisms must be translated cautiously.

Reactive species can damage cellular structures, but they also participate in normal signaling, immune defense, vascular regulation, and adaptation. Antioxidants are essential, but greater intake is not always more beneficial. Antioxidant-rich foods may support healthy dietary patterns, but isolated supplements may not reproduce those effects.

The most effective public health strategy is not the distribution of a universal antioxidant product. It is the reduction of tobacco and alcohol harm, improvement of food environments, support for physical activity and sleep, protection of mental health, safer workplaces, cleaner air, correction of defined deficiencies, and access to reliable preventive and clinical care.

Health is shaped not only within cells, but also in homes, schools, workplaces, communities, markets, and public policy.

Chapter summary

Key Points

- Oxidative stress has public health relevance because many redox-related exposures are shaped by social, environmental, occupational, commercial, and policy conditions.
- Oxidative stress is an integrating biological concept rather than a standalone population diagnosis.
- Routine public health surveillance should focus on validated exposures, clinical risk factors, disease outcomes, and inequalities rather than nonspecific antioxidant biomarkers.

- Health behaviors are influenced by income, education, employment, housing, food access, transport, environmental quality, and access to healthcare.
- Environmental and occupational hazards should be reduced at their source rather than compensated for with diet or supplements.
- Healthy food, movement-supportive, smoke-free, sleep-supportive, and safe occupational environments make preventive behavior more achievable.
- Laboratory antioxidant activity, biological plausibility, biomarker change, and clinical benefit are different levels of evidence.
- Public health communication should distinguish antioxidant-rich foods from concentrated supplements and address misleading commercial claims.
- Effective prevention combines individual, clinical, occupational, environmental, community, and policy-level intervention.
- Universal measures should be combined with additional support for vulnerable and highly exposed groups.
- Public health programs should be evaluated for effectiveness, safety, feasibility, sustainability, affordability, and effects on health inequalities.
- Future research should prioritize validated methods, meaningful human outcomes, cumulative exposures, real-world implementation, and transparent reporting.

Practical Relevance

A public health perspective expands antioxidant science beyond individual nutrients and supplements. Redox health depends partly on whether people can breathe clean air, work safely, access nutritious food, move in their communities, sleep adequately, avoid tobacco and alcohol-related harm, and receive trustworthy healthcare and information.

Healthcare professionals can support individual change, but population health also requires supportive environments, occupational protection, effective regulation, and equitable access to prevention.

The practical objective is not to maximize antioxidant exposure. It is to reduce preventable hazards and make healthier living safer, easier, and more accessible.

Final Conclusion of the Textbook

Oxidative stress and antioxidants are important concepts in preventive medicine, but they require balanced interpretation. Reactive oxygen and nitrogen species are not only harmful metabolic products. They also participate in immune defense, vascular regulation, cellular signaling, and adaptation to physical activity. Health depends on regulated redox homeostasis rather than complete elimination of reactive species.

Antioxidant defense is a coordinated network involving enzymes, glutathione and thioredoxin systems, metal-binding proteins, repair pathways, dietary nutrients, mitochondrial function, and adaptive signaling. This network is influenced by nutrition, movement, sleep, stress, smoking, alcohol, environmental and occupational exposures, aging, genetics, and disease.

The available evidence supports a food- and lifestyle-based approach. Antioxidant-rich foods contribute to healthy dietary patterns, but their effects cannot be reduced to isolated compounds. Supplements may be appropriate when they correct a deficiency or address a specific evidence-based indication, but they should not be promoted as universal protection against chronic disease.

The most effective prevention is comprehensive: healthy diet, regular physical activity, adequate sleep, mental health support, tobacco avoidance, alcohol reduction, safe work, clean air, appropriate screening and vaccination, and evidence-based medical care. Antioxidants are one component of this broader strategy, not a substitute for it.

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