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Redox homeostasis, oxidative stress and antioxidant system in health and disease: the possibility of modulation by antioxidants

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Abstract

Redox imbalance occurs when the factors of oxidative stress, known as prooxidants, outweigh the mechanisms of antioxidant protection. In a healthy state, homeostatic mechanisms ensure the balanced production of free radicals and a complete series of antioxidants responsible for their safe removal. The generation of free radicals is a part of physiological processes in a healthy organism, some of which act as specific signaling molecules, and their presence and activity are necessary in these processes. In various diseases such as cancer, cardiovascular disease, diabetes, autoimmune diseases, rheumatic diseases, systemic lupus, and skin diseases, the generation of free radicals overwhelms the protective mechanisms, leading to the development of "oxidative stress" that damages cells and tissues. To prevent the harmful effects of free radicals within cells, there exists a system of enzymatic antioxidant protection composed of superoxide dismutase (SOD), glutathione peroxidase (GSHPx), glutathione reductase (GR), glutaredoxin, reduced/oxidized glutathione (GSH/GSSG), and thioredoxin (TRX). The examples of non-enzymatic antioxidants are: antioxidant vitamins such as A, C and E, dihydrolypoic acid, metallothioneins, ceruloplasmin, coenzyme Q 10, urea, creatinine, etc. Redox balance is influenced by the circadian rhythm and external factors that constitute the "exposome", including dietary habits and lifestyle. Antioxidant supplementation has become increasingly popular for maintaining optimal body function. However, it is important to note that some antioxidants can exhibit prooxidant activity, emphasizing the need for controlled use. The relationship between the redox status of the body and the action of antioxidants enables the development of multidisciplinary research that connects biochemistry, molecular biology, nutritional science, natural product chemistry, and clinical practice.

Key words: antioxidants, prooxidants, free radicals, enzymatica antioxidant protection

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Introduction

Redox homeostasis plays a crucial role in maintaining cellular health and is a fundamental determinant of physiological processes. It depends on maintaining a delicate balance between the production of prooxidants and the activity of the antioxidant system. Oxidative stress is a condition/phenomenon that occurs when oxidative stress players – prooxidants – overcome the body's antioxidant protection (1). The primary contributors to oxidative stress are free radicals (FRs), including reactive oxygen species (ROS) and reactive nitrogen species (RNS), as well as certain non-radical compounds. The accumulation of excessive ROS and RNS, coupled with a simultaneous decline in the antioxidant system function, leads to an imbalance in the redox state (2).

It is widely recognized that ROS are generated in all cells as by-products of various cellular processes. For instance, they are produced in the electron transport chain of mitochondria during ATP synthesis, and they are also catalysed by the enzyme NADPH oxidase during the respiratory burst in macrophages and neutrophils, which is part of the immune defense against microorganisms (3).

A free radical can be an atom, group of atoms, or molecule that has one or more unpaired electrons, making it extremely unstable and reactive. Because of these properties, they attack neighboring biomolecules in the environment in which they were created, so that the FR's action leads to the creation of new FRs, which is an example of a chain reaction which leads to a vicious cycle of pathological and harmful events in the cells. The most important FRs, and at the same time ROS, are the superoxide anion ($O_2^{\cdot -}$) and the hydroxyl radical ($OH^{\cdot}$). Hydrogen-peroxide, although a non-radical compound, also plays an important role in oxidative stress processes; as a ROS it is involved in the reactions of other redox-active species such as ($OH^{\cdot}$) (4).

The organism has evolved many protective mechanisms for ROS detoxification, from transcription factors to enzymes that protect the intracellular environment. In addition, many compounds from natural sources show significant protective, antioxidant effects in tissues, which may help relieve symptoms of chronic inflammatory diseases (5).

Redox homeostasis, like acid-base regulation, is one of the central mechanisms of life support. In different parts of the cell, there are different participants, i.e., prooxidants, antioxidants, and additional factors that stand between prooxidant and normal metabolic activity. The most important enzymes catalysing the synthesis of superoxide anion synthesis are the enzymes of the NADPH family (NOX) and the enzyme xanthine oxidase (XO) (6).

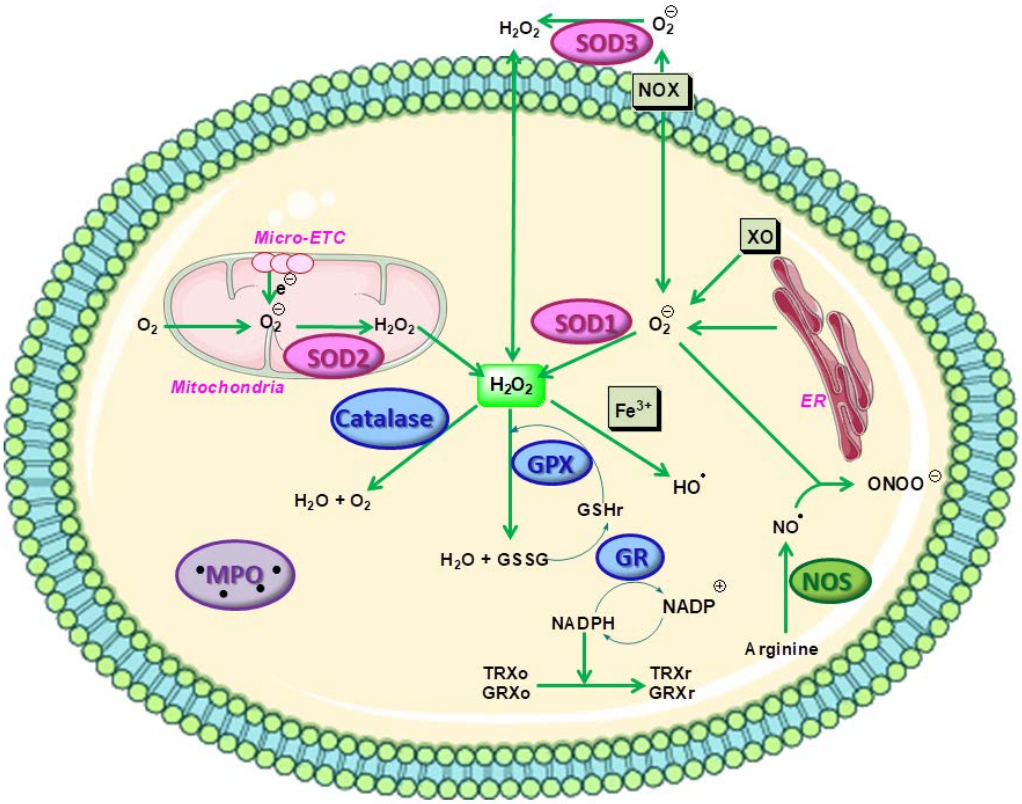

Figure 1. **Cellular redox homeostasis (according to reference 6 with changes)**
ER (endoplasmic reticulum); HO● (hydroxyl radical); GPX (glutathione peroxidase); GR (glutathione reductase); GRXo (oxidized glutaredoxin); GRXr (reduced glutaredoxin); GSHr (reduced glutathione); GSSG (oxidized glutathione); Micro ETC (mitochondrial electron transport chain); MPO (myeloperoxidase); NADP+ (oxidized nicotinamide adenine dinucleotide phosphate); NADPH (reduced nicotinamide adenine dinucleotide phosphate); NO● (nitric oxide); NOS (nitric oxide synthases); NOX (NADPH-oxidase complex) ONOO− (peroxynitrite); SOD (superoxide dismutase enzymes); TRXo (oxidized thioredoxin); TRXr (reduced thioredoxin); XO (xanthine oxidase)

Slika 1. **Ćelijska redoks homeostaza (prema literaturnom navodu broj 6, uz izmene)**
ER (endoplazmatični retikulum); HO● (hidroksil radikal); GPX (glutation peroksidaza); GR (glutation reduktaza); GRXo (oksidovani glutaredoksin); GRXr (redukovani glutaredoksin); GSHr (redukovani glutation); GSSG (oksidovani glutation); Micro ETC (mitohondrijalni elektron-transportni lanac); MPO (mijeloperoksidaza); NADP+ (oksidovani nikotinamid adenin dinukleotid fosfat); NADPH (redukovani nikotinamid adenin dinukleotid fosfat); NO● (azot monoksid); NOS (azot monoksid sintaza) NOX (NADPH-oksidaza kompleks); ONOO− (peroksinitrit); SOD (enzimi superoksid dismutaze); TRXo (oksidovani tioredoksin); TRXr (redukovani tioredoksin); XO (ksantin oksidaza)

Numerous studies have demonstrated the role of oxidative stress in development of various diseases, both infectious and non-infectious (7, 8, 9), and many scientific groups have begun to investigate the role of antioxidants in treating these diseases and reducing their consequences. Antioxidative supplementation of such patients with various conditions which implicate oxidative stress can be beneficial, but it requires a systematic approach: the assessment of patients' redox status, determining antioxidant deficiency and monitoring the effects of the administered antioxidant therapy.

However, it soon became clear that even if we had a powerful antioxidant that could suppress the formation of free radicals or neutralise them completely, we should not use it, since some free radicals that are constitutively formed in sufficient amounts are involved in many important physiological processes (10). Table I shows the main FRs, their sources and the most important physiological processes which include these FRs.

Table I Free radical type, source and physiological process in which the FR is involved (11)

Tabela I Tipovi slobodnih radikala, izvor i fiziološki proces u koji su uključeni (11)

Free radical	**Free radical sources**	**Physiological Process**
$NO^{\cdot}$	**NOS**	Smooth muscle cells relaxation (vasodilatation, blood vessel tone control) and other cGMP-related functions.
Superoxide anion $O_2^{\cdot -}$ and other ROS	**NADPH oxidases**	Control of breathing, control of erythropoietin production and other functions associated with hypoxia. Relaxation of smooth muscle cells. Transduction of signals from different membrane receptors/improvement of immune functions.
Superoxide anion $O_2^{\cdot -}$ and other ROS	**Different sources**	Oxidative stress response and maintenance of redox homeostasis.

Oxidative stress can affect all biomolecules present in cellular and extracellular compartments, especially proteins, lipids, and nucleic acids. The proteins of cellular and subcellular structures, and also the proteins of our body fluids, can be damaged by various chemical reactions: oxidation and nitrosylation (12). These reactions lead to protein degradation, conformational changes, cross-links formation, denaturation, and eventual loss of function. Oxidised protein molecules decay to protein carbonyls and advanced oxidation protein products (AOPP), two end products of protein degradation whose concentration can be measured in the laboratory. On the other hand, lipid molecules are damaged by the chain reaction of free radical formation, especially at the densely packed

sites of fatty acids. An indicator of early phases of oxidative stress is the increased concentration of lipid hydroperoxide (LOOH), while late phases are indicated by an increase in malondialdehyde (MDA), the end product of lipid hydroperoxide degradation (13). LOOH and MDA can also be measured in the laboratory. Oxidative damage to nucleic acid occurs chemically by oxidation and nitration leading to chain breaks. These initial (early) breaks can be repaired by the DNA repair machinery, or the cell must undergo a form of cell death: necrosis or apoptosis. Otherwise, if cells with DNA damage continue to live, mutations or carcinogenesis will occur. The Comet assay can be used to determine the degree of DNA oxidative damage (14, 15).

The antioxidant protection system consists of enzymatic and non-enzymatic parts, which work together to keep oxidative stress at a low, homeostatic and balanced level (Figure 2). The main elements of the enzymatic part are: superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), glutathione-S-transferase (GST) and its cofactor, reduced glutathione (GSH). Non-enzymatic antioxidants include primarily antioxidant vitamins (A, C and E), then low-molecular weight antioxidants dihydrolipoic acid, metallothioneins, ceruloplasmin, transferrin, coenzyme Q, and numerous reducing biomolecules (urea, uric acid, creatinine, glucose, bilirubin) in the bloodstream and in cells (6, 10). The antioxidant paradox phenomenon has been recognised, according to which some antioxidants exert pro-oxidant activity while some compounds with pronounced pro-oxidant activity induce endogenous antioxidant defense activity at low doses (16, 17).

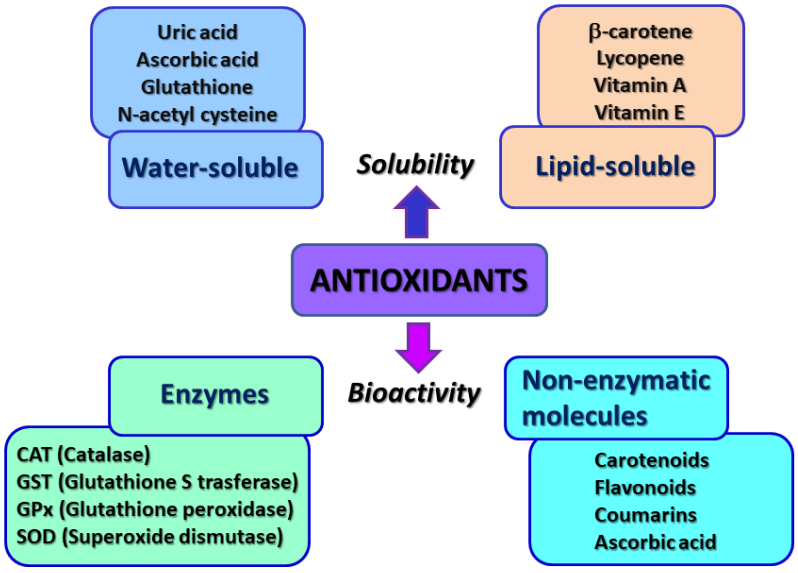

Figure 2. **Types of antioxidants, classification based on solubility and bioactivity (according to reference 18 with modifications)**

Slika 2. **Vrste antioksidanasa, podela prema rastvorljivosti i bioaktivnosti (prema literaturnom navodu broj 18, uz izmene)**

The role of oxidative stress in cardiovascular disease

In addition to the traditional risk factors for coronary artery disease (CAD), new factors such as oxidative stress and inflammation have been studied in detail by various research groups, including ours. In our study, we investigated the association between several oxidative stress parameters and inflammatory markers, particularly high-sensitivity C-reactive protein (hsCRP) and fibrinogen, in a group of CAD patients. Our results showed a strong positive correlation between these oxidative stress and inflammatory markers, indicating a reciprocal involvement of oxidative stress and inflammation in the progression of atherosclerosis and, consequently, coronary artery disease. This robust association underscores the importance of understanding the interplay of oxidative stress and inflammation in the context of CAD (8). Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) functions as a transcription factor, playing a pivotal role in governing the expression of antioxidant and cytoprotective enzymes when the body faces oxidative stress (19). Natural products have emerged as a promising reservoir of bioactive compounds. These compounds have demonstrated their ability to shield against the progression of atherogenesis by activating the Nrf2 signalling pathway (20). It has already been documented that several natural products with confirmed antiatherosclerotic and cardioprotective effects are linked to an increase in Nrf2 expression. Some of these natural products include ellagic acid, quercetin, curcumin, maslinic acid, tanshinone C, rutin, and carnosic acid (21). On the basis of our results, we concluded that the concomitant use of antioxidant and anti-inflammatory agents may be beneficial in combating atherosclerosis. Considering the crucial role of oxidative stress at various stages of atherogenesis, it is reasonable to hypothesize that antioxidant therapy may be effective in preventing this process. Moreover, interesting data from epidemiological studies, e.g., related to the "French paradox," suggest that a high dietary intake of antioxidants is associated with better outcomes in cardiovascular disease. These observations underscore the importance of an antioxidant-rich diet as a potential strategy to reduce the risk of cardiovascular disease (22). The preventive effect of antioxidants on the development of cardiovascular disease has been confirmed both *in vitro* and in animal models, but in human studies the intake of antioxidant vitamins has not cured cardiovascular disease (23). There are several reasons for this lack of success, including inadequate dosage, timing and duration of antioxidant administration. It is believed that antioxidants, especially those dietary derived, should be taken preventively, i.e., before the onset of disease. Once the disease has progressed, restoring redox balance becomes a challenge. It is important to note that ROS are not generally harmful and that repeated minor exposure to ROS may actually serve as a trigger for the onset of endogenous antioxidant protection.

Therefore, the timing and dosage of antioxidant interventions are critical factors to consider. Taking antioxidants proactively, before a disease manifests, may provide a greater opportunity for their beneficial effects. In addition, understanding the complex role of ROS and the body's natural antioxidant defense systems is critical to developing effective strategies to combat cardiovascular disease (16).

Redox status is a matter of balance, and flooding the body with antioxidants from food can even be dangerous. Although there are homeostatic mechanisms that keep exogenous antioxidants at a low level, it can also be dangerous to put the cell in an overly reducing state. Many dietary antioxidants are rapidly excreted through the intestine or metabolized to inactive components. Their circulating concentrations are usually in the nanomolar range, which is too low to have a significant effect. Micronutrients that do not have direct antioxidant properties are considered to have the greatest potential. Polyphenols are naturally occurring compounds found in plants (fruit and vegetables) that contain two or more phenolic groups. This diverse group of compounds has several subtypes: flavonoids, phenolic acids, stilbenes and lignans (24). The most likely scenario is that natural polyphenols or their metabolites act as a type of a mild toxic substance that promotes antioxidant protection (25).

The leaves of artichoke (*Cynara scolymus L.*) are rich in many different antioxidants, mainly with polyphenolic structure: cynarin, chlorogenic acid, luteolin, apigenin (26). Our study on hypercholesterolemic rats with artichoke leaf tincture has shown that artichoke is a very potent antioxidant and shows the best results in the early stages of atherosclerosis (27).

In addition to its cholesterol-lowering effect found in hypercholesterolemic subjects (28), artichoke extract decreases the production of ROS and the oxidation of low-density lipoproteins.

The role of oxidative stress in chronic kidney disease

Chronic kidney disease (CKD), particularly end-stage renal disease (ESRD), is associated with elevated levels of ROS, which play a role in the pathogenesis of the disease. ROS-induced cellular damage and disrupted ROS signalling pathways contribute to the development of kidney disease. Mitochondria, as well as NADPH oxidase activity, are well-documented as the primary sources of ROS in the kidney. However, there is a powerful antioxidant system represented by enzymes such as SOD, GPx, CAT and GR, and also by a non-enzymatic compound GSH, which in coordinated activity help maintain the balance of ROS in the kidney (29). The interplay between oxidative stress and inflammation in patients with kidney disease contributes to uncontrolled inflammation and fibrosis in kidney tissue, leading to organ dysfunction and disease progression. Our study, which investigated the relationship between oxidative stress and inflammation in patients with ESRD, confirmed that malnutrition, elevated inflammation and oxidative stress are associated with higher mortality rates in patients undergoing long-term hemodialysis (30). Other studies have shown the involvement of NF-kB, a redox-sensitive transcription factor, in chronic inflammation associated with CKD (31). On the other hand, disorders of the antioxidant transcription factor Nrf2 have been observed in patients with kidney disease, potentially worsening the status of CKD patients (32).

Animal studies in nephrectomized rats have shown that curcumin, the active ingredient of the traditional herbal remedy and dietary spice turmeric (*Curcuma longa*), has the ability to activate Nrf2 and inhibit NF-kB (30). This suggests that curcumin may

have a beneficial effect in CKD by modulating these transcription factors and possibly reducing inflammation and oxidative stress in the kidneys. We have also shown curcumin antioxidant characteristics in an acellular model on human serum pool of healthy people (31). In their comprehensive review, Eugenio-Pérez and colleagues analysed several food derived antioxidants used in CKD studies: curcumin, sulforaphane, resveratrol, quercetin, proanthocyanidins, flavan-3-ols, soy protein, red propolis. The possible mechanisms of these antioxidants' activity are through the Nrf2 induction and simultaneous NF-kB inhibition (32).

The role of oxidative stress in diabetes mellitus

Oxidative stress plays a crucial role in the pathogenesis of diabetes, as well as in the development of chronic complications associated with this disease. The excessive generation of ROS in mitochondria, triggered by hyperglycemia, activates various stress-sensitive pathways that are characteristic of diabetes, including NF-κB, p38 MAPK, Jak/STAT, polyol and hexosamine pathways, protein kinase C and advanced glycation end products (AGE) (36). The results of our investigation focused on patients with type 2 diabetes mellitus aimed to explore the relationship between dyslipidemia and oxidative stress, revealed pronounced oxidative stress, reduced antioxidant protection, and significant disturbances in the lipid status. Specifically, diabetic patients exhibited a significantly higher ratio of small dense LDL particles compared to healthy subjects. Furthermore, we observed that the aforementioned redox imbalance and dyslipidemia were more pronounced in patients with type 2 diabetes mellitus who had poorer regulation of glucose concentration, indicated by values exceeding 10 mmol/L (37).

Excessive production of FRs in cells leads to a redox imbalance, which primarily impacts pancreatic beta cell function through two mechanisms: elevated concentrations of ROS inhibit insulin secretion and promote beta cell apoptosis. The use of natural products as antioxidant agents is promising due to their potential to provide effective antioxidative properties and their abundance in various sources. In an excellent review, Ma and colleagues provided current data on berberine, a bioactive compound found in many plant genera, but primarily sourced from the bark of *Berberis vulgaris*, which is known for its ability to neutralize oxidative stress and associated inflammation, thereby improving the status of patients with type 2 diabetes mellitus (38). The data obtained from animal studies provide evidence of the reduction in oxidative stress in various tissues, including the pancreatic tissue. Berberine has been shown to increase the expression of genes related to antioxidant activity, such as SOD and sirtuin 1. These findings suggest that berberine may have a beneficial effect in mitigating oxidative stress and improving antioxidant defenses in different tissues, including the pancreas (39, 40).

Another mechanism attributed to the influence of berberine involves the interplay between Nrf2 (nuclear factor erythroid-2 related factor) and its inhibitor, Kelch-like ECH-associated protein 1 (KEAP1). Nrf2 is a transcription factor that primarily induces the expression of antioxidants, such as heme oxygenase-1 (HO-1) (41). However, the activity of Nrf2 is initiated upon release from the complex with KEAP1, allowing its translocation

into the nucleus. Berberine has been shown to induce the entry of Nrf2 into the nucleus, ultimately leading to the activation of antioxidant enzymes, as well as the accumulation of intracellular GSH and SOD. This mechanism further contributes to the antioxidant effects of berberine (42). However, while the potential benefits of berberine in diabetes management are promising, one must have in mind the side effects of berberine and its drug interactions regarding its use in the treatment of diabetes mellitus.

Berberine has the potential to interact with various drugs due to its impact on enzymes involved in drug metabolism. It can inhibit the activity of CYP3A4 and P-glycoprotein, which are responsible for metabolizing and transporting many drugs. This can lead to altered blood levels of these drugs and impact their effectiveness. Some examples of drugs that may interact with berberine include certain statins, anticoagulants, and immunosuppressants.

However, there are various challenges associated with the clinical application of antioxidant therapy using natural products. These challenges include poor solubility, instability during storage and lack of selectivity. Fortunately, the pharmaceutical technology branch is currently developing new carriers aimed at addressing the challenges associated with antioxidant therapy, such as poor solubility, permeability, instability and metabolic degradation, which have hindered the success of implementing enzymatic antioxidant mimetics (SOD, CAT, GPx-like substances), antioxidant vitamins (A, C and E), microelements with potential antioxidant activity (Se, Zn, Cr), small molecules like N-acetyl cysteine (NAC) and coenzyme Q10 (CoQ10) and various flavonoids in diabetic patients (43).

Conclusion

Oxidative stress underlies many chronic diseases, such as cardiovascular disease, chronic kidney disease and diabetes mellitus. To ensure successful supplementation of patients with these diseases, it is advisable to assess their redox status before initiating antioxidant therapy. Redox status assessment involves measuring the concentration of various biomarkers in the blood or other body fluids, including prooxidants, their byproducts, and antioxidants. This step is critical because it allows for the diagnosis of antioxidant deficiency and/or the presence of oxidative stress, as well as monitoring the effects of antioxidant therapy. In addition, it is important to analyze the patient's general exposome, which includes lifestyle factors, external environmental/workplace influences, and diet. The use of dietary supplements with antioxidant activity is not a simple and uniform approach; it is a complex process that should be tailored to each individual, taking into account factors such as timing, type and reason for supplementation. In order to overcome the issues of poor solubility, instability, permeability, chemical and metabolic instability of natural products, certain technological approaches offer solutions. The development of analytical methods to assess complex antioxidants and their metabolites in the blood is necessary to understand their kinetics and allow dosage adjustment. Undoubtedly, a multidisciplinary approach and personalized medicine are critical in achieving the best possible treatment outcomes for patients. By considering

individual characteristics, including the redox status, exposome, and other relevant factors, healthcare professionals can optimize antioxidant therapy and ensure that it effectively promotes patient health and well-being.

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Homeostaza redoks sistema, oksidativni stres i antioksidativni sistem u zdravlju i bolesti: mogućnost modulacije antioksidansima

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Kratak sadržaj

Redoks disbalans se javlja kada činioci oksidativnog stresa – prooksidansi – nadvladaju mehanizme antioksidativne zaštite. U stanju zdravlja, homeostatski mehanizmi obezbeđuju uravnoteženo stvaranje slobodnih radikala i čitave serije antioksidanasa koji su zaduženi za njihovo bezbedno uklanjanje. Stvaranje slobodnih radikala je deo fizioloških procesa u zdravom organizmu; neki od njih su specifični signalni molekuli i u tim procesima su njihovo prisustvo i aktivnost neophodni. U različitim bolestima kao što su kancer, kardiovaskularne bolesti, dijabetes, autoimunske bolesti, reumatske bolesti, sistemski lupus, kožne bolesti, stvaranje slobodnih radikala nadvladava mehanizme zaštite, pa se razvija „oksidativni stres" koji oštećuje ćelije i tkiva. Da bi se sprečilo štetno delovanje slobodnih radikala, u ćeliji postoji sistem enzimske antioksidativne zaštite, koga čine: superoksid-dismutaza (SOD), glutation-peroksidaza (GSHPx), glutation-reduktaza (GR), glutaredoksin, redukovani/oksidovani glutation (GSH/GSSG) i tioredoksin (TRX). Primeri neenzimskih antioksidanasa su: antioksidativni vitamini kao što su A, C i E, dihidrolipoinska kiselina, metalotioneini, ceruloplazmin, koenzim Q10, urea, kreatinin, itd. Redoks ravnoteža je pod uticajem cirkadijalnog ritma i spoljašnjih faktora koji čine „ekspozom" i uključuju način ishrane i životne navike. Suplementacija antioksidansima je postala sve popularnija praksa za održavanje optimalne funkcije organizma. Neki od antioksidanasa ispoljavaju prooksidantnu aktivnost i zato je važno da njihova primena bude kontrolisana. Veza između redoks statusa organizma i delovanja antioksidanasa omogućava razvoj multidisciplinarnih istraživanja u kojima se povezuju biohemija, molekularna biologija, nauka o ishrani, hemija prirodnih proizvoda i sama klinička praksa.

Ključne reči: antioksidansi, prooksidansi, slobodni radikali, enzimska antioksidativna zaštita