

Oxidative stress and antioxidant mechanisms in human body

Abstract

The present review aims to high light on the oxidative stress, and prevention by internal antioxidants and external antioxidants by some natural products possessing antioxidant properties. Oxidative stress occurs when the balance between reactive oxygen species (ROS) formation and detoxification favors an increase in ROS levels, leading to disturbed cellular function. ROS causes damage to cellular macromolecules causing lipid peroxidation, nucleic acid, and protein alterations. Their formation is considered as a pathobiochemical mechanism involved in the initiation or progression phase of various diseases such as atherosclerosis, ischemic heart diseases, diabetes, and initiation of carcinogenesis or liver diseases. In order to maintain proper cell signaling, it is likely that a number of radical scavenging enzymes maintain a threshold level of ROS inside the cell. However, when the level of ROS exceeds this threshold, an increase in ROS production may lead to excessive signals to the cell, in addition to direct damage to key components in signaling pathways. ROS can also irreversibly damage essential macromolecules. Protein-bound thiol and non-protein-thiol are the major cytosolic low molecular weight sulfhydryl compound that acts as a cellular reducing and a protective reagent against numerous toxic substances including most inorganic pollutants, through the -SH group. Hence, thiol is often the first line of defense against oxidative stress. Flavonoids have been found to play important roles in the non-enzymatic protection against oxidative stress, especially in the case of cancer. Flavonoids have occurred widely in tea, fruit, red wine, vegetables, and cocoas. Flavonoids, including flavones, flavanone, flavonols, and isoflavones, are polyphenolic compounds which are widespread in foods and beverages, and possess a wide range of biological activities, of which anti-oxidation has been extensively explored. It can be concluded that oxidative stress causes irreversible damage in cellular macromolecules that leads to initiation of various diseases such as atherosclerosis, ischemic heart diseases, liver diseases, diabetes, and initiation of carcinogenesis. Antioxidants inhibit reactive oxygen species production and scavenging of free radicals. Therefore, the review recommends that high consumption of natural foods that are rich in antioxidants will provide more protection against toxic agents and related diseases.

Keywords: antioxidants, cancer, flavonoids, oxidative stress

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Introduction

Today, oxidative stress has attracted the attention of researchers. An imbalance between **free** radicals and antioxidants leads to oxidative damage of proteins, fat, nucleic acids, and carbohydrates.^{1,2} Antioxidants have protected the body from the harmful effect of the free radicals.^{2,3} Endogenous antioxidants defense against the reactive oxygen species are strengthened by natural antioxidants that strengthen them and restore the optimal balance by neutralizing the ROS.^{2,4-7} Traditional medicine has been used a number of natural and herbal products to treat a variety of diseases including malignant tumors.^{7,8} Many herbal plants have proven their ability to resist cancerous activities. Some previous studies have shown that herbal drug might have antitumor effect by promoting the immune system, including cell differentiation, inducing apoptosis of cancer cells and inhibiting telomerase activities.^{7,9}

Objectives

The present review aims to high light on the oxidative stress, and its prevention by internal antioxidants and external antioxidants by some natural products possessing antioxidant properties.

Free radicals and mechanism of their destructive effects

Free radical are molecules which contain unpaired electron in the outer orbitals, and is highly reactive in the body by oxidizing (removing an electron from) other atoms, or sometimes reducing (donating their electron to) other atoms. The major source of reactive oxygen species are mitochondria, produced by electron transport chain in aerobic respiration as byproducts. Although most electrons reach the third pump of the electron transport system, about 1% to 3% reacts with oxygen prematurely to form the superoxide radical.¹⁰ The production of free radicals makes important physiological functions in the body, one of these functions is the production of superoxide and nitric oxide by neutrophils and macrophages which aids in phagocytosis process and help these cells in destroying bacteria. The superoxide radicals in phagocytic cells can be thought of as nonselective antibiotics, killing any infecting bacteria (as well as the neutrophils) and perhaps also injuring surrounding tissue cells, as these radicals contribute to the inflammation reaction, these free radicals also promote cellular proliferation (mitotic division) of fibroblasts, so that scar tissue can form and stimulate proliferation of lymphocytes in the process of

clone production. No has also effects on promoting relaxation of vascular smooth muscle which causes vasodilation and an increase in the blood can flow to the site of the inflammation.¹⁰

The generation of ROS and RNS by endogenous and exogenous sources. The endogenous generation of these species by inflammation mechanisms and activation of immune cells, sever exercise, ischemia, mental activity stress, cancerous and infectious diseases, and aging. Exogenous sources of ROS result from the pollution of water and air and water, alcohol drinking, smoking, some drugs, heavy metals, certain drugs (tacrolimus and cyclosporine), radiations, cooking and some solvents as benzene. These compounds are decomposed into ROS after they penetrate the body,¹¹ The damaging effects of ROS on cellular macromolecules such as proteins, lipids, and nucleic acid are causing alterations in proteins, and nucleic acid. The formation of these free radicals leads to the initiation and progression of many diseases such as diabetes, heart diseases, atherosclerosis, liver diseases and cancers.¹²

Oxidative stress is linked to altered redox regulation of cellular signaling pathways and the formation of many types of cancer cells and oncogenic stimulation.¹³ It appears that the DNA damage and activation of ROS to AP-1 and NF- κ B pathways of signal transduction leads to the transcription of genes involved in cell growth regulation and initiation of cancerous conditions. Lipid peroxidation products are formed with the abstraction of a hydrogen atom from an unsaturated fatty acid.¹² The lipid peroxidation process influences membrane fluidity as well as the integrity of biomolecules associated with the membrane (membrane bound proteins or cholesterol). These highly oxidizable lipids may then, in turn, attack nearby proteins causing the formation of an excess of protein carbonyls.¹⁴ A major development over the past two decades has been the realization that free radical mediated peroxidation of membrane lipids and oxidative damage of DNA are associated with a variety of chronic health problems,¹⁵ such as cancer, atherosclerosis,¹⁶ neurodegenerative diseases,¹⁷ and aging.¹⁸ Therefore, inhibition of oxidative damage by supplementation of antioxidants becomes an attractive therapeutic strategy to reduce the risk of these diseases.¹⁹

Antioxidant enzymes and their action mechanisms

In order to maintain proper cell signaling, it is likely that a number of radical scavenging enzymes maintain a threshold level of ROS inside the cell. However, when the level of ROS exceeds this threshold, an increase in ROS production may lead to excessive signals to the cell, in addition to direct damage to key components in signaling pathways. Oxidative stress occurs when the balance between ROS formation and detoxification favors an increase in ROS levels, leading to disturbed cellular function. ROS can also irreversibly damage essential macromolecular targets such as DNA, protein and lipids, which may initiate carcinogenesis.²⁰ Therefore, the concentrations of ROS have to be controlled by several defense mechanisms, which involve also a number of antioxidant and detoxifying enzymes.

An antioxidant is a molecule which has the ability to prevent or slow the oxidation of macromolecules. The role of antioxidants is to lower or terminate these chain reactions by removing free radicals or inhibiting other oxidation reactions by being oxidized themselves. So, antioxidants are often reducing agents such as polyphenols or thiols.²¹

Although oxidation reactions are vital for cells, they have damaging effects; hence, plants and animals contain various antioxidants, such as vitamins C and E and glutathione, as well as different enzymatic

systems which catalyze the antioxidants reactions as catalase, superoxide dismutase (SOD) and peroxidases. The defects in or inhibition of these antioxidant enzymes will lead to oxidative stress and may damage and lyse the cells.¹¹ The mechanisms which followed by antioxidant defense are: 1) Blocking of free radicals production of 2) oxidants Scavenging 3) The converting toxic free radicals into less toxic substances 4) Blocking the production of secondary toxic metabolites and mediators of inflammation 5) Blocking of the chain propagation of the secondary oxidants 6) Repairing the injured molecules 7) Initiation and enhancing the endogenous antioxidant defense system. All of these defense mechanisms act hand by hand for protection of the body from oxidative stress. The antioxidant systems in the human body consist of powerful non-enzymatic and enzymatic antioxidants.¹²

The antioxidant enzymes in all body cells consist of three major classes of antioxidant enzymes which are the catalases, superoxide dismutases (SOD), and glutathione peroxidases (GPx), all of these, play crucial roles in maintaining homeostasis into cells. The induction of these enzymes reflects a specific response to pollutant oxidative stress.²² The role of SOD is to scavenge superoxide radicals and converting them to H_2O_2 .²³ The role of GPx is achieved by the reduction of hydrogen peroxide, lipid hydroperoxides and other organic hydroperoxides.²⁴ Glutathione-S-transferases (GST) represent a major group of detoxifying enzymes,²⁵ which form a family of multifunctional proteins involved in the cellular detoxification of cytotoxic and genotoxic compounds and in the protection of tissues against oxidative damage.^{26,27} Besides certain roles in the endogenous metabolism, these enzymes are associated with the detoxification of xenobiotics such as drugs, carcinogens, and environmental pollutants in man and animals, and with pesticide and herbicide resistance in insects and plants.²⁸ Some studies have shown, that GPx,²⁹ and GST are inactivated by hydroperoxides, which exert their toxicity either directly by oxidation of SH groups of proteins or indirectly by hydroxyl radicals formation. It is known from the literature that a significant number of the GST isoenzymes also exhibit GPx activity and catalyze the reduction of organic hydroperoxides to their corresponding alcohols.^{31,32} Superoxide dismutase catalyzes the breakdown of the superoxide anion into oxygen and hydrogen peroxide.³³ It removes O_2 by catalyzing a dismutation reaction. In the absence of this enzyme, this reaction becomes very slow.³⁴

Catalase (H_2O_2 oxidoreductase) is composed of four polypeptide chains, each chain is over 500 amino acids long, and contains four porphyrin heme (iron) groups allowing the enzyme to react with the H_2O_2 . The enzymatic activity modes of catalase in decomposing H_2O_2 are the catalytic mode of activity ($2H_2O_2 + O_2 + 2H_2O$) and the peroxidatic mode of activity ($H_2O_2 + AH_2 \rightarrow A + 2H_2O$). The turnover rate of catalase is the highest among all of the other antioxidant enzymes. Decomposition of H_2O_2 by the catalytic activity of catalase follows the fashion of a first-order reaction and its rate is dependent on the concentration of H_2O_2 .³⁵ Catalase is cofactor oxidized by one molecule of hydrogen peroxide and transfer the bound oxygen to another molecule of the substrate.³⁶

Catalase exists in both eukaryotic and bacterial cells. Most of them are located in an oxidative particle of all types of mammalian cells except red blood cells where various H_2O_2 oxidases were created. Since H_2O_2 acts as a substrate for a specific reaction that generates highly hydroxyl radical, it is believed that the primary role of catalase in cellular antioxidant defense mechanisms is to reduce the accumulation of H_2O_2 .³⁷ The role of catalase in protecting cells and tissues from

oxidation has been studied extensively. The overexpression of catalase makes cells more resistant to H_2O_2 toxicity and oxidative-mediated damage. In genetically modified mice, overexpressing catalase is protected against myocardial infarction after giving rats adriamycin and developing high blood pressure after treatment with paraffin or angiotensin. Patients with naturally occurring catalase deficiency, except for an increased tendency to progressive oral gangrene development due to tissue damage from H_2O_2 resulting from bacteria producing peroxides such as streptococcus and pneumococcus, as well as phagocytic cells in bacterial sites.³⁸ Thioredoxin system includes thioredoxin protein and thioredoxin reductase,³⁹ Thioredoxin-related proteins are present in all living organisms. It scavenges the ROS.⁴⁰

Glutathione system includes glutathione S-transferases, glutathione peroxidases, and glutathione reductase. Glutathione S-transferases are another class of enzymatic antioxidants that catalyze the breakdown of lipid peroxides. Glutathione peroxidase shows a high activity with hydrogen peroxide and organic hydroperoxides.⁴¹ These enzymes help in detoxification mechanism.⁴²

Glutathione reductase (GR) catalyzes the reduction of oxidized glutathione (GSSG) to reduced glutathione (GSH). This enzyme enables the cell to sustain adequate levels of cellular GSH. Due to its importance, the enzyme was purified from a number of plants, animals and microorganism sources and studied in an attempt to identify and clarify its structure, molecular properties and kinetic mechanism.⁴³ Its kinetic mechanism is known to be a ping-pong/sequentially ordered model. GR is a flavoprotein that contains two FAD molecules as a prosthetic group, which is reducible by NADPH. GR is one of the thermostable enzymes. GR belongs to the defense system protecting the organism against chemical and oxidative stress. Deficiency of GR is characterized by hemolysis due to increased sensitivity of erythrocyte membranes to H_2O_2 and contributes to oxidative stress which plays a key role in the pathogenesis of many diseases.⁴⁴

Non-enzymatic antioxidants and their action mechanisms

Protein-bound thiol and nonprotein-thiol are acting as a cellular reducing and a protective agent against most inorganic pollutants, through the -SH group.³² Hence, the thiol is often the first line of defense against oxidative stress. The thiol levels can be increased due to an adaptive mechanism to slight oxidative stress through an increase in its synthesis; however, a severe oxidative stress may decrease thiol levels due to loss of adaptive mechanisms.

Glutathione is a cellular antioxidant which plays a central role in maintaining the cells redox state.⁴⁴

Ascorbic acid is an antioxidant found in both plants and animals but it must be obtained from the diet in humans because it cannot be synthesized. It can reduce and neutralize reactive oxygen species.⁴³ Vitamin E has been found to protect the cell membranes from oxidation by removing the free radical intermediates and reacting with the lipid radicals.⁴⁵ Beta-carotene has potent the antioxidant properties by removing a singlet oxygen thus protects against a free radical attack. They are present in liver, egg yolk, milk, butter, spinach, carrots, tomato and grains.⁴³

Natural antioxidants

The protective effects of natural antioxidants has received more attention against free radical induced toxicities.⁴⁶ Flavonoids play an

important role in the protection against oxidative stress,^{47,48} especially in the case of cancer. Flavonoids are found widely in vegetables, red wine, fruit, cocoas, and tea.⁴⁹⁻⁵¹ Flavonoids are widespread in beverages and foods which possess a wide range of biological activities⁵² of which antioxidation has been extensively explored.⁵³⁻⁶⁰ Natural antioxidants strengthen the endogenous antioxidants defenses from ROS and restore the optimal balance by neutralizing reactive species.^{4,6} The antioxidant activities of phenolics are related to a number of different mechanisms, such as free radical-scavenging, hydrogen-donation, singlet oxygen quenching, metal ion chelating, and acting as a substrate for radicals such as superoxide and hydroxyl.^{7,32} Azab & Albash⁷ concluded that administration of *Curcuma longa*, *Trigonella foenumgraecum*, *Allium sativum*, *Coffea arabica*, *Petroselinum crispum*, *Olea europaea* leaves, and *Mentha piperita* were showed a remarkable hepatic protection against hepatotoxic agents, which may be due to its antioxidant properties of these medicinal plants and herbs. Therefore, Human expose to hepatotoxic agents and patients with hepatic disorders should be advised to take these medicinal plants and herbs.

Natural antioxidants have a variety of biochemical actions such as inhibition of the production of ROS and scavenging of free radicals.^{2,61,62} Azab et al.,² reported that consumption of fenugreek, curcumin, peppermint, parsley, rosemary, garlic, pomegranate, sesame, and propolis were shown protective effects against renal diseases and nephrotoxic agents induced renal dysfunctions in experimental animals and human. The nephroprotective effect may be due to the inhibition of tissue lipid peroxidation and enhancement of antioxidant activity. Therefore, the study suggested that these antioxidants may be useful for the persons who expose to nephrotoxic agents and patients suffer from renal diseases. The protective effects may be due to the presence of benzoquinones, flavonoids, flavonol glycosides, alkaloids, carotenoids, catechols, glycosides, steroid glycosides, terpenoids, glycoalkaloids, mono, di, and triterpenes, saponins, polyphenols, and sterols in these medicinal plants and herbs.^{2,61,63}

Conclusion

It can be concluded that oxidative stress causes irreversible damage in cellular macromolecules that leads to initiation of various diseases such as atherosclerosis, ischemic heart diseases, liver diseases, diabetes, and initiation of carcinogenesis. Antioxidants inhibit of reactive oxygen species production and scavenging of free radicals. Therefore, the review recommends that high consumption of natural foods that are rich in antioxidants will provide more protection against toxic agents and related diseases.

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Conflicts of interest

The author declares there are no conflicts of interest.

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