Munir Ozturk · Khalid Rehman Hakeem
Editors

Plant and Human Health, Volume 2

Phytochemistry and Molecular Aspects

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Dedicated to Our Ancient Herbalists

"Medicine from Honey"—a 1224 Arabic translation of the manuscript De Materia Medica, written by the ancient Greek physician, Dioscorides (40–90 AD)

Foreword

Medicinal plants have been a rich source of medications since the very birth of man. Traditional Chinese medicine has been extensively documented for many thousands of years. The Chinese pharmacopoeia, *Shennong Ben Cao Jing*, records plant medicines such as ephedra and hemp. Egyptian medicine employing plant-based drugs dates back to 2900 BC, but preserved records in the form of *Ebers Papyrus* containing about 700 drugs mainly of plant origin go back to around 1550 BC. There is also evidence of the use of plants for healing purposes date back to 2600 BC in Mesopotamia indicating the existence of a plant-based system of treatment in which about 1000 plant-based medicines were used. Ancient Ayurvedic medicine, as documented in the *Atharva Veda*, the *Rig Veda*, and the *Sushruta Samhita*, employed hundreds of pharmacologically active herbs and spices. The medicinal applications of plants became known to the Western world through Greek and Roman practitioners, particularly through the treatises contributed by the Greek physician Dioscorides (1st century AD), and the Roman physicians Pliny the Elder (1st century AD) and Galen (2nd century AD). Later came the Islamic contributions to herbal medicine with the advent of physicians such as Abu Ali Ibn Sina (980–1037), better known in the West as Avicenna, whose book, *Al-Qanun fi al-Tibb*, was used as a standard textbook of medicine in Europe for over 700 years. Abu Bakr Muhammad ibn Zakariya al-Razi (865–925 AD) wrote over 200 books and categorized substances as vegetable, animal, or mineral, whereas other earlier alchemists had divided them into "bodies," "souls," and "spirits." He was the first to use opium for anesthesia. Al-Idrisi, born in Cordova, during the Islamic era in Spain in 1099, wrote many books on medicinal plants including *Kitab al-Jami-li-Sifat Ashtat al-Nabatat.* Another major contribution from Spain came from Abu Muhammad Ibn al-Baitar (1197–1248), who composed the encyclopedia on medicinal plants entitled *Kitab al-Jami al-Adiwaya al-Mufrada* that presented the work of 150 authors. Abu-Rayhan Biruni, Ibn Zuhr, Peter of Spain, and John of St. Amand also contributed pharmacopoeias describing the use of medicinal plants. The most comprehensive encyclopedic set of volumes on medicinal plants in recent times has been the 57 volume series entitled *Studies in Natural Product Chemistry* (Elsevier Science, Ed. Atta-ur-Rahman) that describes thousands of bioactive constituents discovered from the most important medicinal plants.

It was at the beginning of the nineteenth century when rational drug discovery from plants commenced with the isolation of the analgesic and sleep-inducing agent morphine from opium by the German scientist Serturner in 1817. Other medicinal herbs were then examined for active principles leading to the isolation of a host of important compounds, including quinine, caffeine, nicotine, codeine, atropine, colchicine, cocaine, and capsaicin, from various plant sources. Following the discovery of penicillin in 1928, attention was also turned to the bioactive substances in microbes. The developments of synthetic drugs led to a certain decrease in interest in natural materials as sources of drugs because of the challenges associated with large-scale availability. However, a significant proportion of new drugs approved by FDA are still derived directly or indirectly from medicinal plants. For instance, out of the 1073 new chemical entities (belonging to the group of small molecules) approved between 1981 and 2010, only 36% were purely synthetic, while the remainder were either natural products or their analogues. Similarly during the period 1940–2014, out of the 175 small molecules approved against cancer, 85 were natural products or their derivatives. These include paclitaxel and its derivatives from yew (*Taxus*) species, vincristine and vinblastine from periwinkle (*Catharanthus roseus* (L.) G. Don), and camptothecin and its analogs initially discovered in the Chinese tree *Camptotheca acuminate* Decne. Other important natural products include the cholinesterase inhibitor galanthamine approved for the treatment of Alzheimer's disease from *Galanthus nivalis* L. and the important antimalarial agent artemisinin originally derived from the traditional Chinese herb *Artemisia annua* L. In spite of the advent of combinatorial chemistry, the actual number of new drugs reaching the market through purely synthetic efforts has diminished. This has resulted in the revival of interest in natural products and triggered the use of multidisciplinary approaches to drug discovery.

The present second volume of *Plants and Human Health*, edited by Khalid Rehman Hakeem and Munir Ozturk and entitled *Phytochemistry and Molecular Aspects*, presents a wealth of information on bioactive compounds isolated from various medicinal plants and their utility in tackling many diseases. The discussions range from bioactive substances found in terrestrial medicinal plants and freshwater aquatic plants to edible materials and fungi with antioxidant, anti-inflammatory, antiseptic, antidiabetic, anticataleptic, antiarthritic, sedative, calming, antidiuretic, antimicrobial, antifungal, herbicidal, insecticidal, anticancer, and other activities in various classes of flavonoids, terpenoids, alkaloids, and other classes of natural products. The molecular technologies to identify the function of the genes and the effect of the bioactive compound(s) in medicinal plant(s) to treat patients with various chronic diseases are also presented. Transgenic plants produced through bioengineering represent another exciting area that is comprehensively reviewed.

I would like to congratulate the editors for accumulating such a wealth of useful information in this volume. My compliments also go to the eminent authors who produced an excellent overview of the present exciting frontiers of natural product chemistry.

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Preface

According to Huxley (1881), it is easy to sneer at our ancestors, but it is much more profitable to try to discover why they, who were really not one with less sensible persons than our excellent selves, were led to entertain views which look to us strange. For a better look at our future, we need to understand and look deeply at our past. Ethnobotanist Mark Plotkin says that every time a medicine man dies, it is like a library burning down. We are running a race against time. The information held by our medicine men needs to be pooled up fast for further evaluation by researchers.

The answers to the health problems for humans living during 2000 BC were that for an ear ache eat this root, yet with time the notion changed, and in 1000 AD, the same root was regarded as heathen, and was replaced by prayers. Yet in 1850 AD, people started saying that prayer is superstitious and instead advised the drinking of portions. However, in 1940 AD, that portion was regarded as snake oil, and the trend shifted toward the swallowing of pills. Around 1985 AD, the pills were regarded as ineffective, and people were advised to take antibiotics; ultimately in 2000 AD, the antibiotics were accepted as artificial, and the advice was to eat this root. So *we* started with the root in 2000 BC and ended up with the same root in 2000 AD.

Early anthropological evidence for plant use as medicine is 60,000 years old, as is reported from the Neanderthal grave in Iraq. There are clay tablets in cuneiform dated 2600 BC with plant remedies from the Sumerians, Assyrians, and Akkadians as well as Hittites. The Sumero-Akkadian clay tablets show a collection of ≈40 plants with vegetal formula pharmacopoeia. The importance of plants as medicine is further supported from Asia (3500 BCE) and Egypt (1500 BCE). Egyptian medicines report on the use of bishop's weeds (*Ammi majus*) to treat vitiligo, a skin condition characterized by a loss of pigments. More recently, a drug (b-methoxypsoralen) has been produced from this plant to treat psoriasis and other skin disorders as well as T-cell lymphoma.

Our second volume deals with phytochemistry and molecular aspects. It describes several secondary metabolic compounds found in plants, many of which provide protection against diseases. High-throughput robotic screens have been developed by industry, and it is possible to carry out 50,000 tests per day in the search for compounds which have action against a key enzyme or a subset of receptors.

Medicinal plant drug discovery continues to provide new and important leads against various pharmacological targets including cancer, HIV/AIDS, Alzheimer's, malaria, and pain. Numerous compounds from tropical rainforest plant species with potential anticancer activity have been identified. Although drug discovery from medicinal plants continues to provide an important source of new drug leads, numerous challenges are encountered including the procurement of plant materials, the selection and implementation of appropriate high-throughput screening bioassays, and the scale-up of active compounds.

Izmir, Turkey; Amann, Jordan — Munir Ozturk
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Free Radicals, Diabetes, and Its Complexities

F. Taghavi and Ali A. Moosavi-Movahedi

Introduction

Homeostasis

Life in every organism relies on keeping a stable set of interacting chemical reactions and internal processes to preserve the condition of reactions correctly (Torday 2015). It means that organism maintenance is provided by cell cooperative activities which need similarity in developed organization and metabolic requirements. This matter creates a stable and vital internal environment from point of oxygen, glucose, mineral ions, and waste contents (Marieb and Hoehn 2007).

The condition which relies on the stability, balance, or equilibrium of internal environment within a cell or total body is considered as homeostasis (homeo as similar and stasis as stable) (Yadav et al. 2016; Rodova et al. 2016; Andrey and Vladimir 2016).

Homeostasis is the most important concept in the body and has been defined through some developed approach: Claude Bernard, a French scientist, stated the concept of homeostasis beautifully as "all the vital process follow one aim as keeping the constant conditions of life in the internal environment" (Goldberger and Breznitz 1993). Another physiologist Walter Cannon, author of *The Wisdom of the Body* (1932), documented this concept as a self-regulating mechanism with admirable autonomic stabilizers which nature uses in imbalanced conditions (Vander et al. 2001; Siegel 2008). Another physiologist Moore-Ede (1986) stated that

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homeostasis includes reactive and effective responses to spontaneity and timed challenges (Siegel 2008; Moore-Ede 1986).

Homeostatic processes or allostasis (process of achieving stability) is observed in all order of cells, tissues, and organs (Torday and Rehan 2009). This process acts as a resistance to fluctuations of organism's internal environment against external environmental conditions (Torday and Rehan 2009). Osmoregulation, thermoregulation, and chemical regulation are considered as three mechanisms for homeostasis process (Chowański et al. 2017).

All homeostatic control mechanisms act based on three basis which have tightly interdependent relationship: (a) The monitoring receptors for sensing components, which detect the changes in the condition to be regulated and respond to environmental alterations; (b) the nucleus which receives the stimuli from receptors, which adjusts the scope of the changes and appropriate response; and (c) the effectors (cells, tissues, organs, or other structures), which receive the signal from the nucleus and apply homeostasis. These levels lead to correct deviation by negative feedback (depressing or damping action) (Torday and Rehan 2009).

Deficiency in each of homeostatic mechanism or toxicity (cell poisoning) influenced by internal and external factors (life style (nutrition, toxins, psychological or physical events) and environmental exposure) causes homeostatic imbalance, cellular malfunction, and disease. Many metabolism disorders and diseases like diabetes and its complexities are caused by homeostatic imbalance and its consequent internal toxin formation. These phenomena can be repaired by medical treatments (Marieb and Hoehn 2007; Vander et al. 2001; Torday and Rehan 2009).

Redox regulation is an important kind of homeostatic mechanism, which balances the beneficial and harmful effects of reactive species. This process maintains redox homeostasis by controlling the redox status in vivo (Fig. 1), and by this way, living

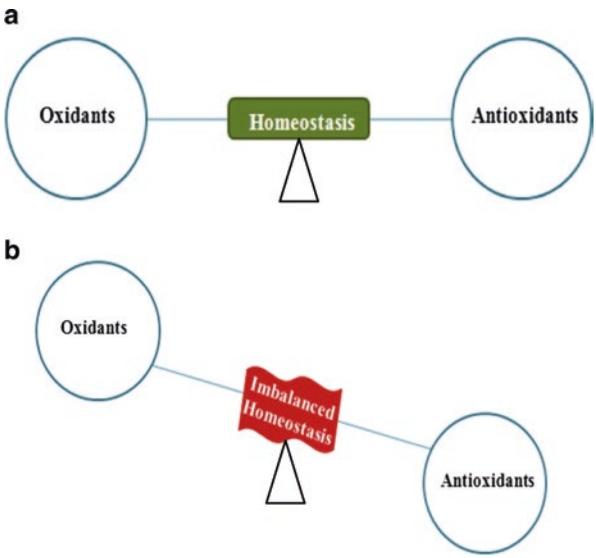

Fig. 1 The homeostasis create the balance between oxidants and antioxidants (**a**), extra formation of oxidants compared with antioxidants lead to imbalanced homeostasis (**b**)

organisms were protected against oxidative stresses. Cellular oxidants and antioxidants have an important role in the maintenance of "redox homeostasis" and redox regulation which is involved in normal physiological functions and pathogenesis of various diseases like neurodegenerative disorders, cancer, diabetes mellitus, inflammatory diseases, and aging (Valko et al. 2007).

It is worth mentioning that cell redox state is limited within a narrow range under normal conditions. This situation is controlled by redox signaling as an adoptive process, which triggers protective responses against oxidative stress. By this way, the original state of "redox homeostasis" after temporary exposure to ROS/RNS is restored (Valko et al. 2007).

Oxidative Stress

Over 90% of oxygen consumed by living organisms in healthy situation is used in mitochondrial electron transport chain which is coupled with nutrient oxidation and results in production of energy, carbon dioxide, and water (Abele et al. 2011).

Reactive Species

The energy which conducts life is released energy during landing of high-energy transmitted electron to low-energy level orbital or outer shell. Indeed, the electron storing and extracting and movement ability of higher-order biological structures form the essential forces for keeping life systems (Singh 2006; Szent-Györgyi 1976). These processes lead to reactive species formation. Interestingly life is the result of reactive species interaction because these species have been selected for some important roles as in evolution, metabolism, aging, and cell events (like apoptosis, mutation, and death). In other words, despite free radicals' destructive nature, surprisingly life with its unique organization can be sustained by these elements and a group of chemical interactions (Rahbar and Figarola 2003). Reactive species are intrinsically unstable and have various degrees of activities (Kikuchi et al. 2003; Betteridge 2000).

Free Radicals

Molecules with arranged pairs of electrons and opposite spin in their outer orbitals are very stable, while any species (atom and molecules) with independent existence and unpaired electrons in their outer orbitals/valence shell become highly reactive and unstable. These compounds are eager to interact with neighboring molecules and repair their outer shell and stability. These kinds of molecules are called free radicals (Singh 2006; Kelly 2003; Rahman 2007).

It is worth mentioning that free radicals with an odd electron usually are formed by splitting weak bonds in a molecule (each fragment keeps one electron) (Kelly 2003) and radical cleavage to form another radical or redox reactions (Ray et al. 2012). These kinds of reactive species attempt to gain their stability by capturing an electron, which leads to starting chain reaction in nanoseconds. This electron stealing makes molecule oxidation and runs a cascade reaction in uncontrolled condition, which leads to living cell disruption and inactivation (Pham-Huy et al. 2008). These compounds generally have been divided into two categories (Singh 2006; Phaniendra et al. 2015): (a) free radicals, species or molecules with an independent existence and one or more unpaired electrons, and (b) non-radicals, the compounds with strong oxidizing potential, which produce strong oxidants, like transition metals.

Reactive species have different longevity (from nanoseconds like hydroxyl radical to minutes as hydrogen peroxide or organic hydrogen peroxides).

It is worth mentioning that long-lived radicals include (1) stable radicals with kinetic and thermodynamic stability (organic radicals); (2) persistent radicals, compounds with persistent radicals which make them physically difficult to react with another molecule; and (3) diradicals, molecules with two radical centers (Pham-Huy et al. 2008). In addition, reactive species can be classified into the following groups:

(a) Reactive oxygen species (ROS): Molecular oxygen (dioxygen) with a unique electronic configuration is a radical. In living systems oxygen-derived radicals are the most important class of radical species.
(b) Superoxide anion radicals: The superoxide anion radicals ($O_2^{\bullet-}$) as "primary" ROS are created by adding one electron to molecular oxygen via metabolic processes (within the cell mitochondria) or physical irradiation. This product can interact with other molecules and produce "secondary" ROS, directly or indirectly by enzyme- or metal-catalyzed processes. The main source of ATP in the mammalian cell is mitochondrial electron transport chain, which is essential for life. During this process, superoxide as an intermediate reactive species is formed and involved in pathophysiology of a variety of diseases.
(c) The hydroxyl radical, $^{\bullet}OH$: The neutral form of hydroxide ion, with high reactivity and very short in vivo half-life (10^{-9} s) at 37 °C, is very dangerous. This kind of radical can react with neighboring molecules (especially nuclear and mitochondrial DNA, membrane lipids, and carbohydrates) very fast, immediately after formation. Its interaction with lipid membrane can trigger a chain reaction and propagates lipid peroxidation. An extra amount of superoxide lead to free ion release from molecules with iron contents (Valko et al. 2007; Gadoth and Göbel 2011; Aprioku 2013).
(d) Peroxyl radicals ($ROO^{\bullet}$): These radicals are another reactive radicals derived from oxygen which usually form in living systems by cellular membrane lipid breaking down. These radicals can be self-propagating, very dangerous, and highly destructive. It is worth mentioning that superoxide anions, hydroxyl radical, singlet oxygen, and peroxynitrite can trigger lipid oxidative decomposition and produce lipid peroxyl radicals and hydroperoxides. These radicals can attack polyunsaturated fatty acids and propagate the chain reaction

(Lushchak and Semchyshyn 2012). Also, the protonated form of superoxide ($O_2^{\bullet -}$) creates the simplest form of peroxyl radical ($HOO^{\bullet}$) termed as either hydroperoxyl radical or perhydroxyl radical (Valko et al. 2007).

(e) Singlet oxygen: Under photooxidative conditions and the presence of photoexcited sensitizers, energy transfer to O_2 and singlet oxygen ($1O_2$) is performed. It is highly reactive and can trigger lipid peroxidation. It has no diradical activity like molecular oxygen (Gadoth and Göbel 2011).

(f) Peroxide: High concentration of hydrogen peroxide (H_2O_2) is toxic within cells. It can diffuse through cellular membranes and interact with distant molecules. Hydroxyl radicals can be formed from hydrogen peroxide in the presence of iron and copper (Gadoth and Göbel 2011).

(g) Reactive nitrogen species (RNS): Nitric oxide ($NO^{\bullet}$) acts as a double-edged sword (Gadoth and Göbel 2011; Aprioku 2013). $NO^{\bullet}$ is an abundant reactive radical and has an important role in biological signaling especially in diverse physiological processes, like neurotransmission, blood pressure, immunoregulation, defense mechanisms, and smooth muscle relaxation. It is a small molecule which is formed in biological tissues by specific nitric oxide synthases (NOSs). This kind of radicals has a short half-life (few seconds) in aqueous system. The presence of extra reactive nitrogen species create nitrosative stress which can nitrosylate biomacromolecule structures and disturb their function. The reaction of nitric oxide and superoxide anion during the immune system activities leads to the formation of very potent oxidative radicals as peroxynitrite anion ($ONOO^-$). This radical can attack DNA and cause its fragmentation; also it can produce lipid oxidation (Valko et al. 2007). The peroxynitrite anion has the same reactivity of $^{\bullet}OH$ and can directly hydroxylate and nitrate the aromatic rings of amino acid residues. Its reaction with sulfhydryls, zinc-thiolate moieties, lipids, and proteins makes it a very toxic radical (Gadoth and Göbel 2011).

The Role of ROS

As mentioned before, however, ROS can be considered as essential intermediates in natural and normal biological processes, but they can produce homeostatic imbalance and pathogenic events (Pham-Huy et al. 2008; Gadoth and Göbel 2011).

Signaling, defense against infections, modification of molecules, neurotransmission, and damage of impaired cellular constituents are some of the various processes which can be impaired by ROS. ROS radicals do their roles via interaction with biomacromolecules based on ROS type and their concentrations. Intra- and intercellular communication (cellular signaling, cellular proliferation, cellular pathway) (Gadoth and Göbel 2011) with ROS takes place at low ROS concentration in specific pathway, but higher levels of ROS are involved in cellular component-specific damages (Lushchak and Semchyshyn 2012).

DNA and protein can be considered as primary targets for the destructive effects of ROS (Kelly 2003). It is noteworthy that the aggressive nature of free radicals and other non-radicals' reactive derivatives caused them to be considered as oxidants. Non-radical species are more stable than radicals, but radicals are more active than non-radicals. Also, hydrogen peroxide (H_2O_2), ozone (O_3), singlet oxygen ($1O_2$), hypochlorous acid (HOCl), nitrous acid (HNO_2), peroxynitrite ($ONOO^-$), dinitrogen trioxide (N2 O_3), and lipid peroxide (LOOH), as non-free radicals, can easily lead to free radical (hydroxyl ($OH^•$), superoxide ($O_2^{•-}$), nitric oxide ($NO^•$), nitrogen dioxide ($NO_2^•$), peroxyl ($ROO^•$), and lipid peroxyl ($LOO^•$)) reactions in living organisms (Ray et al. 2012; Brennan and Kantorow 2009).

As mentioned before, the reactivity of reactive species is very different, and some of them are more specific and harmful for biological molecules than the others. The most important oxygen free radicals in biological context are superoxide, hydroxyl radical, and nitric oxide (Finkel and Holbrook 2000) which are very unstable and trigger cascade oxidative reaction. Hydrogen peroxide, hypochlorous acid, and singlet oxygen are the most common non-radicals with higher stability and risks for biomolecules (Surai 2002).

ROS Involve in Lipid Peroxidation

Lipid is an important cellular biomacromolecule which can be the prominent target of oxidative stress. Oxidants (reactive species and free radicals) have the main role in lipid peroxidation and increase ROS steady-state concentrations especially as peroxides. This phenomenon modified other biomacromolecules. The products of lipid peroxidation can be categorized based on their instability as primary (with short half-life and free radical nature), secondary (lipid peroxides, conjugated dienes, and ketodienes), and end products (malondialdehyde). Both of the last products have more stability than the first (Lushchak 2011).

The Source of Reactive Species

The reactive species generally include reactive oxygen species (ROS) and reactive nitrogen species (RNS) and are the advantages of cellular redox process. Because of their high biological instability and their electron availability, they can react with various organic substrates such as lipids, proteins, and DNA. In the cells, free radicals and its derivative formation occur in two ways: enzymatic (respiratory and energy chain, the phagocytosis, the prostaglandin synthesis, and the cytochrome P450 system) and nonenzymatic reactions (with organic compounds and ionizing radiations) (Ray et al. 2012).

It is important to note that ROS and RNS just at low or moderate levels show beneficial effects on cellular activities. While the consequence of high concentrations is oxidative stress, deleterious process and biomacromolecule structural damage lead to chronic and degenerative diseases like cancer, aging, and autoimmune disorders.

Also reactive species generation depends on endogenous or exogenous sources. Immune cell activation, inflammation, psychological and mental stress, excessive exercise, ischemia, infection, cancer, aging, cellular abnormalities, malnutrition, and various diseases generate endogenous reactive species. The endogenous ROS are the greatest threat to organisms (Kikuchi et al. 2003; Betteridge 2000).

Exogenous sources arise from air and water pollution (asbestos; benzene; carbon monoxide; chlorine; formaldehyde; MTBE; ozone; tobacco smoke; toluene; chemical solvents such as cleaning products, glue, paints, and paint thinners; prescribed medications; perfumes; pesticides; cigarette smoke; alcohol; heavy or transition metals (Cd, Hg, Pb, Fe, As)), certain drugs (cyclosporine, tacrolimus, gentamicin, bleomycin), industrial solvents, cooking (smoked meat, used oil, fat), and radiation (Ray et al. 2012). These exogenous compounds penetrate into the body by different routes and decompose or metabolize into free radicals (Kelly 2003; Ray et al. 2012). Some of the exogenous sources for reactive species formation will be described in the next sections.

Oxidative stress is defined in many ways and improved during the years (Lushchak and Semchyshyn 2012). Oxidative stress is the acute state of imbalance between generation of active intermediates and the system's ability to neutralize and eliminate them (Rahman et al. 2012).Oxidative stress happens by passing favoring prooxidants and/or disfavoring antioxidants from normal situation and alters the redox condition of internal environment and damaging of macromolecules (Singh 2006). This phenomenon is a condition in which the balance between oxidative activities and antioxidant systems is disrupted and generation of active oxygen species or free radicals becomes excessive, in an unsuitable way (Rahman 2007). Oxidative stress is the harmful condition for the body when oxidative reaction (ROS/RNS production) overcomes antioxidant defense system and body's internal balance is lost (Rahman 2007; Lushchak and Semchyshyn 2012). Indeed, oxidative stress is a disturbed dynamic equilibrium which led to an enhancement in ROS steady-state transiently or chronically. This situation disrupts cellular components, metabolism, regulation, and signaling processes by oxidized cellular constituents via ROS up to the consequent deleterious effects (Lushchak and Semchyshyn 2012; Lushchak 2011). It is noteworthy that three ways provided oxidative stress: ROS production increment, ROS elimination decrement, and appropriate combination of these two ways. All of these processes directly lead to diseases (Lushchak and Semchyshyn 2012).

Oxidative stress can be considered as a biological modulator and signal inducer which modulate many messengers with vital role in living systems. Oxidative signaling functions are important as adaptive strategies and coordinating effect in diverse basic biological processes like differentiation and apoptosis. This phenomenon influences intracellular redox status, protein kinases activities, and cellular responses (like activation, proliferation, differentiation, and other activities) which is considered as a chain between OS and diseases (Rahman 2007; Lushchak and Semchyshyn 2012).

Oxidative Stress-Inducing Agents

Air Pollution

Environmental pollution is a major concern of scientists and contributes to many diseases and death. The harmful or undesirable alteration in the quality of air, water, or soil, physically, chemically, or biologically, is considered as environmental pollution. This approach includes all anthropogenic and natural pollutants and direct or indirect human involvement in environmental pollution (Yanga and Omayeb 2009).

A range of pollutants with different combinations from one microenvironment to another are in the ambient air. The big portion of this mixture belongs to free radicals (like nitrogen dioxide) or compound with the ability of free radical production (like particulate matter and ozone). Exposure to a wide range of air pollutants leads to oxidative stress and disease formation in human organs especially the lungs. Ozone as a relatively insoluble gas with high reactivity is a major constituent of photochemical smog which leads to lung function decrement and pulmonary inflammation. Its reaction with biological environment is based on its concentration and the type of biological molecules which takes part in the reaction (Kelly 2003).

Traffic in urban areas and cigarette smoke are the main sources of nitrogen dioxide. This compound produces cellular destruction, increment cell permeability, and increment tissue inflammation (Kelly 2003).

Our researches also showed that methyl *tert*-butyl ether (MTBE) can be very harmful for human beings. MTBE is a worldwide gasoline modifier which improves fuel oxygen contents and its combustion. It is a toxic component which produces adverse biological effect for human health and diverse environmental concerns (Valipour et al. 2015). MTBE's biodegradation is slow in groundwater spreads in the air widely, pollutes the environment, and enters the blood stream easily. Our previous research revealed that MTBE as a gasoline modifier had an influence on the structure and function of hemoglobin (Hb). This compound can disturb Hb-oxygen affinity, its oxygen transport, and cause metHb formation more than normal condition. The high levels of ROS production were demonstrated due to degradation of hemoglobin's heme by MTBE via chemiluminescence technique. It seems that ROS production has the main role in heme degradation and Hb nonfunctionality (Valipour et al. 2017).

Our results also showed that MTBE induced a molten globule (MG)-like structure in insulin due to reactive oxygen species (ROS) formation which leads to protein oxidation and protein aggregation (Valipour et al. 2015).

Dust

Environmental dusts contain toxic particulates and oxidants which stimulate inappropriate chemical reactions and produce the large amounts of free radicals. This character depends on their micromorphology at the atomic level; mechanical, thermal, and chemical properties; as well as frequency of surface contaminants' presence