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REVIEW ARTICLE

Environmental factors and unhealthy lifestyle influence oxidative stress in humans—an overview

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Abstract Oxygen is the most essential molecule for life; since it is a strong oxidizing agent, it can aggravate the damage within the cell by a series of oxidative events including the generation of free radicals. Antioxidative agents are the only defense mechanism to neutralize these free radicals. Free radicals are not only generated internally in our body system but also trough external sources like environmental pollution, toxic metals, cigarette smoke, pesticides, etc., which add damage to our body system. Inhaling these toxic chemicals in the environment has become unavoidable in modern civilization. Antioxidants of plant origin with free radical scavenging properties could have great importance as therapeutic agents in several diseases caused by environmental pollution. This review summarizes the generation of reactive oxygen species and damage to cells by exposure to external factors, unhealthy lifestyle, and role of herbal plants in scavenging these reactive oxygen species.

Keywords Free radicals · Antioxidants · Environmental stress · Cigarette smoke · Metal toxicity

Introduction

The field of free radical research is undergoing a tremendous advancement in recent years. The production or formation of free radicals in vivo is primarily initiated by the consumption of molecular oxygen, which, due to its structure, is in fact a radical species itself since oxygen is the ultimate electron acceptor in the electron flow system that produces energy in the form of ATP. However, problems may take place when the electron flow is unpaired (free radical). The free radical theory was first coined by Denham Harma (1956). A free radical is any species capable of existence, containing one or more unpaired electrons in an atom (Bhalodia et al. 2011). Free radical species include reactive oxygen species (ROS) and reactive nitrogen species (RNS), which play a vital role in the process of aging (Harman 1956).

In a normal healthy human body, the generation of pro-oxidants in the form of ROS and RNS is effectively kept in check by the various levels of antioxidant defense. ROS and RNS include radicals such as superoxide ($O_2^{\cdot-}$), hydroxyl ($OH\cdot$), peroxyl ($RO_2\cdot$), hydroperoxyl ($HO_2\cdot$), alkoxyl ($RO\cdot$), peroxyl ($ROO\cdot$), nitric oxide ($NO\cdot$), nitrogen dioxide ($NO_2\cdot$), and lipid peroxyl ($LOO\cdot$) and non-radicals like hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), ozone (O_3), singlet oxygen ($^1O_2$), peroxynitrate ($ONOO^-$), nitrous acid (HNO_2), dinitrogen trioxide (N_2O_3), and lipid peroxide (LOOH) (Pham-Huy et al. 2008), radicals which are generated spontaneously in cells through metabolism (Sarma et al. 2010).

ROS and its complication in humans

Exposure to environmental or pathological agents such as atmospheric pollutants, cigarette smoking, ultraviolet rays, radiation, and toxic chemicals results in an imbalance between the pro-oxidants and antioxidants, which leads to oxidative stress (Videla 2009). Pro-oxidant antioxidant balance in the cell is shifted towards the pro-oxidants if the production of oxygen species is increased greatly or when levels of antioxidants are diminished. This state is called oxidative stress. Oxidative stress is basically caused by the following two main mechanisms: (1) reduction of antioxidant concentration due to mutated antioxidant enzymes, toxins, or the reduced intake of natural antioxidants; (2) the number of oxygen-, nitrogen-, or

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carbon-based reactive species derived from activated phagocytes is increased in the case of chronic inflammation (Somogyi et al. 2007). They are also capable of damaging crucial biomolecules such as nucleic acids, lipids, proteins, polyunsaturated fatty acids, and carbohydrates and of DNA damage (Rameshkumar et al. 2013; Jeyadevi et al. 2012) which can lead to mutations. These ROS are not successfully scavenged by cellular constituents; they can stimulate free radical chain reactions, subsequently damaging the cellular biomolecules and finally leading to disease conditions (Halliwell and Gutteridge 1990) such as Alzheimer's disease, chronic degenerative diseases, stroke, rheumatoid arthritis, diabetes, and cancer (Sabir et al. 2012; Yildirim et al. 2001).

At the molecular level, free radicals engage the dynamic regulation of covalent modifications to the histone proteins and DNA that influence gene expression, silencing, apoptosis, X-chromosome inactivation, and genomic imprinting without affecting DNA sequence (Sippl and Jung 2009). It was reported that in normal conditions, ROS act as signaling molecules and regulate the expression of genes whose products play a vital role in immune response, proliferation control, and differentiation processes during a general pathogenic response. Due to an imbalance in ROS level, it may activate some signaling pathways and inhibit others, leading to altered gene expression (Mohora et al. 2009). Many research works have been undertaken in reactive oxygen species like hydrogen peroxide, singlet oxygen, and oxidized LDL to study their ability to stimulate the expression of genes amphiregulin (AP-1), c-fos, c-jun, c-myc, and MAP kinase (Allen and Tresini 2000) and protein consecutively to identify redox-sensitive genes (Macip et al. 2003; Kabe et al. 2005; Perkins 2007).

Antioxidants are agents that are capable of scavenging these free radicals by inhibiting the initiation and propagation step, leading to the termination of the reaction and delay of the oxidation process through iron chelation and quenching of triplet oxygen (Jeyadevi et al. 2012). In that case, recently there is a great deal of interest in identifying alternative natural and safe source of antioxidants present in edible plants, fruits, and vegetables that hold antioxidants and health-promoting phytochemicals as potential therapeutic agents (Sabir et al. 2012). This review emphasizes on the generation of free radicals/oxidative stress through various environmental factors and unhealthy lifestyle: why and how? Also, it describes the importance of plant-origin antioxidants.

Environmental stress and factors

Environmental stresses can cause metabolic changes in animals, plants, and humans that either increase the production of reactive oxygen and nitrogen species (RONS) or decrease the antioxidant production (Alessio and Hangerman 2006). Occupational exposure to metals, benzene, cement dust, and multiple other agents is bounded with increased lipid peroxidation, increased DNA oxidation, and decreased levels of vitamin E and C (Kim et al. 2004; Aydin et al. 2004; Rossner et al. 2008; Chia et al. 2008; Yoshioka et al. 2008) (Fig. 1) that leads to diseases such as neurotoxicity, cancer, liver damage, cardiovascular diseases, inflammation, respiratory diseases (Table 1) as well as through changes in gene expression that promote apoptosis within healthy cells, and systemic inflammation.

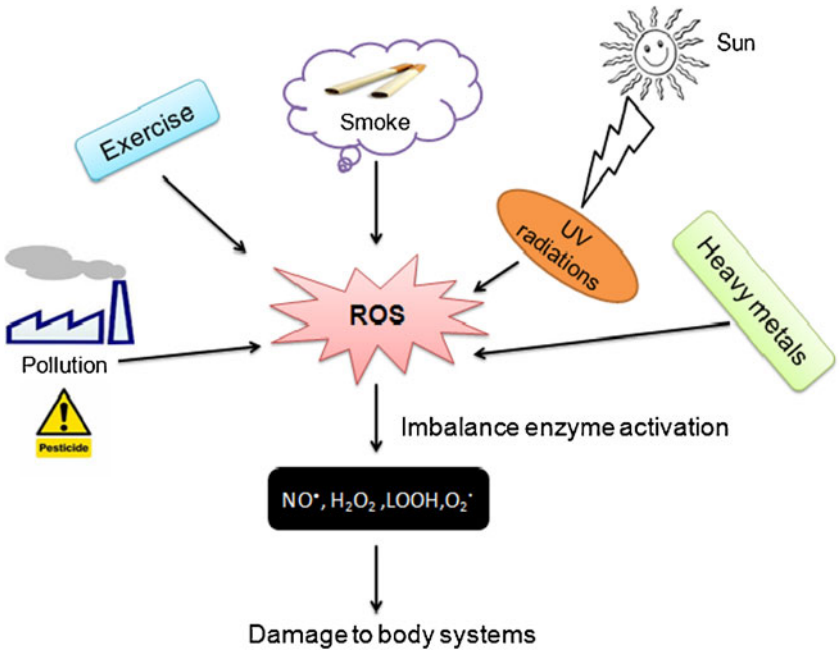

Fig. 1 Overview of generation of ROS by various factors

Table 1 Biological effect of humans due to environmental and physiological factors

Factors	Health defects due to ROS	Reference
Environmental factors		
Pollution		
Air pollution	Neuroinflammation, increased risk of pulmonary diseases, toxic to lungs and cardiovascular tissues	Craig et al. (2008); Riedl (2008); Simkhovich et al. (2008)
Indoor coal fuels	Ischemic stroke	Zhang et al. (1988)
Heavy metals	Cancer	Carson (2002) and Peraza et al. (1998)
Lead	Depressed immune status, mental impairment, neuromuscular weakness, brain damage, and coma	Anetor and Adeniyi (1998); Flora et al. (2007)
Mercury	Autoimmune disease	Kaiser (1998)
UV radiation	Inflammation, dermatoleliosis, accelerated aging of skin, indirect damage of protein, DNA, membranes, immunosuppression, photocarcinogenesis, and skin tumor	Herrling et al. (2007a, b)
Unhealthy lifestyle	Chronic pulmonary disease	Tashkin (2005); Falcon et al. (2003)
Passive smoke inhalation by pregnant women	Increases blood level and placental body burden	Piasek et al. (2001)
	Affects fetal growth	Ward et al. (1987); Galicia-Garcia et al. (1997); Hackshaw et al. (1997); Eisner et al. (2005), and Heidrich et al. (2007)
	Lung diseases	
	Atherosclerosis, endolecithal dysfunction, cardiovascular diseases	Frei et al. (1991); Santanam et al. (1997), and Ambrose et al. (2004)
Tobacco smoke with heavy metal	Malignant neoplasm	Costa et al. (1989); Landolph (1999)
Smoke with alcohol consumption	Oral and pharyngeal cancer	Elwood et al. (1984) and Franceschi et al. (1999)
Alcohol consumption	Oral cavity cancer; pharynx, larynx, liver, colorectal, pancreatic, kidney, and breast cancer	Rehm et al. (2010); Bagnardi et al. (2001); Baan et al. (2007); World Cancer Research Fund (2010); Corrao et al. (2004), and Talamini et al. (2010)
Alcohol consumption	Diabetes mellitus	Hassan et al. (2002)
Unbalanced exercise	Intermittent claudication, diabetes, obesity, hypercholesterolemia	Silvestro et al. (2002); Davison et al. (2002); Radak et al. (2001); Chen et al. (1994); Vincent et al. (2005)

Pollution

These exogenous pollutants generating free radicals have become a part of our daily inhaling/ingesting life, and obviously there appears no escape from them. Therefore, we are in a compelled situation in which we should undertake an alternative way to escape from diseases. Many environmental factors and chemical pollutants induce the generation of ROS. Air pollution is the most harmful form of pollution in our environment. Air pollution is comprised of a diverse mixture of particulate matter (PM), gases (e.g., ground-level ozone, carbon monoxide, sulfur oxides, nitrogen oxides), organic compounds (e.g., polycyclic aromatic hydrocarbons and endotoxins), and metals (e.g., vanadium, nickel, and manganese) present in outdoor and indoor air (Akimoto 2003). Of these components, PM and ground-level ozone are the most widespread health threats and have been heavily implicated in various diseases (Craig et al. 2008).

These free radicals can accumulate in air from burning fuels in smokestacks, car exhaust pipes, or house chimneys or from the formation of ground-level ozone during hot weather. Free radicals in air pollution may be 300 times as damaging as those from tobacco smoke. Some of these radicals are associated with increased immune response in some respiratory diseases, creating worse symptoms. Mohammad Shamssain (2011) suggested that the nitrate radical and sulfur dioxide could be the main culprit for the respiratory diseases. It is reported that the atmospheric nitrate radical irreversibly damages amino acids which are the building blocks for protein in the human body. In addition, it could potentially cause damage to peptides lining the respiratory tract and may contribute to pollution-derived diseases. The nitrate radical is formed from many sources; one common source is nitrogen dioxide which itself is emitted in the environment from car exhaust. The nitrate radical reacts with amino acid to form compounds such as

beta-nitrate esters, beta-carbonyl, and aromatic nitro compounds (Sigmund and Wille 2008).

While it is well known that air pollution affects human health through cardiovascular and respiratory morbidity and mortality (Simkhovich et al. 2008), it has only recently been shown that these deleterious effects extend to the brain (Block and Calderón-Garcidueñas 2009). Ultrafine (nanosized particles) and fine particles are the most notorious air pollution components, penetrating lung tissue compartments to reach the capillaries and circulating cells (e.g., erythrocytes). Experimentally, inhalation or nasal instillation of ultrafine particles in rodents results in the translocation of the particles into the systemic circulation (Nemmar and Inuwa 2008). Microglia is also reported to respond to titanium nanoparticles by producing ROS (Long et al. 2006), which are neurotoxins.

Metal toxicity

Anthropogenic activities such as mining, combustion of fossil fuels, application of phosphates and sewages for agricultural production, and industrial manufacturing leads to the accumulation of heavy metals in the environment (Alessio and Hangerman 2006). The heavy metals such as lead, mercury, and cadmium have electron sharing affinities that can result in the formation of covalent attachments mainly between heavy metal and sulfhydryl groups of proteins (Meister 1988), subsequently generating reactive species, which in turn may cause neurotoxicity, hepatotoxicity, and nephrotoxicity in humans and animals (Chen et al. 2001; Stohs and Bagchi 1995). These metals could escape out of the control mechanism such as transport, homeostasis, compartmentalization, and binding to designated cell constituents. Although many studies have reported the toxic and carcinogenic effects of metals in human and animals, it is also well known that these metals form a crucial part in normal biological functioning of cells. Chen and Shi (2002) stated that certain heavy metals (arsenic trioxide [As (III)], chromium (VI) [Cr (VI)], and vanadium (V) [V (V)]) stimulate inflammatory pathways such as the $NF_{-k}B$ cascade, resulting in oxidative damage and chronic diseases.

A growing amount of data from the past few decades provide evidence that metals like chromium (Cr), nickel (Ni), and manganese (Mn) are capable of interacting with nuclear proteins and DNA, causing oxidative deterioration of biological macromolecules which results in cellular damage like depletion of enzyme activities and controlling metabolic pathways (Kansal et al. 2011; Chen et al. 2001; Flora et al. 2008; Valko et al. 2005; Leonard et al. 2004). For example, Mn^{n+} binds with protein to form protein-bound metals such as (Pr (Mn^{n+})). The free radical defense enzyme, superoxide dismutase (SOD), requires copper and zinc for its activity. Copper ions play a functional role in the reaction by undergoing alternate oxidation, whereas zinc ions seem to stabilize the enzyme (Halliwell and Gutteridge 1989). It is interesting that chromium alone does not react with DNA; rather, it produces a wide variety of DNA lesions. Inside the cell, GSH reduces chromium, and in addition to chromium, various other substances are also involved in the reduction reaction, like NAD(P)H and ascorbate. Chromium species (glutathione-derived thiyl radical $GS^{\cdot}$), once formed, can react through Fenton's reaction and finally leads to the generation of ROS like hydroxyl radical, singlet oxygen, etc. (Fig. 2).

Another common metal that contaminate the environment is lead. Lead poisoning is one of the oldest and the most widely studied occupational and environmental hazards (Flora et al. 2006). Lead is known to induce a broad range of physiological, biochemical, and behavioral dysfunctions in laboratory animals and humans (Flora et al. 2004), including central and peripheral nervous systems (Bressler et al. 1999), haemopoietic system (Lanphear et al. 2000), cardiovascular system (Khalil-Manesh et al. 1993), kidneys (Damek-Poprawa and Sawicka-Kapusta 2004) and liver (Sharma and Street 1980), neurological and behavioral changes, and apoptosis via cytochrome c release (Flora et al. 2007).

The antioxidant enzymes such as SOD, catalase, and glutathione peroxidase are the potential targets of lead. In addition, heme and hemoglobin gets inhibited due to lead toxicity and thus changes the morphology of RBC. In this pathway, δ-aminolevulinic acid dehydratase (ALAD), a cytosolic sulfhydryl enzyme, is the most sensitive enzyme to lead insult. ALAD converts ALA to prophobilinogen (Zhao et al. 2007). Due to lead toxicity, it inhibits the normal functioning of ALA conversion, thus leading to accumulation of ALA. This accumulation thus circulates in blood in huge amount and induces ROS generation (Saxena et al. 2005). Accumulation of ALA is now a well-accepted source of ROS and oxidative damage in the pathophysiology of lead intoxication (Fuchs et al. 2000). Because of its wide applications and usage, humans are exposed to lead in many ways such as air, drinking water, food-contaminated soil, deteriorating paints, dust, and corroded lead pipeline receiving water, etc. Moreover, their derivative in day-to-day life is unavoidable. The exposed lead enters the bloodstream and binds to the protein which is then carried to different tissues and organs. Since the exposed lead is of no use inside the tissues or organs, it simply accumulates or becomes deposited in the human body system. In addition, it replaces iron, calcium, and other minerals in the blood, which direct to serious problems as mentioned earlier (Kayhanian 2012). Thus, metal toxicity is considered as one of the most critical environmental health hazards.

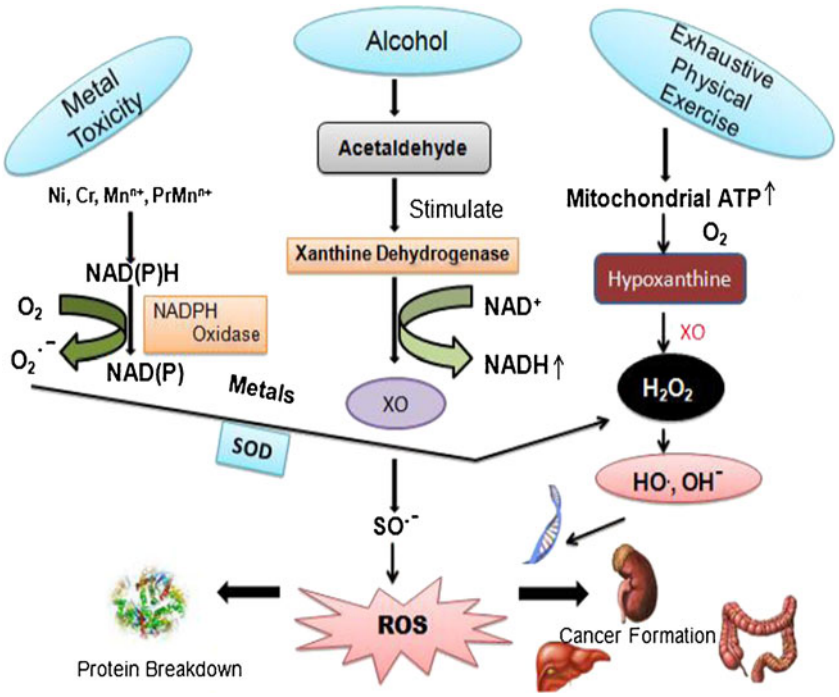

Fig. 2 Generation of free radicals through various stresses. *Ni* nickel, *Mn* manganese, *Pr(Mn^{n+})* protein-bound metal, *Cr* chromium, $O_2^{\cdot-}$ superoxide anion radical, *XO* xanthine oxidase, H_2O_2 hydrogen peroxide, $HO^{\cdot}$ hydroxyl radical, O_2 oxygen, *NAD(P)* nicotineamide adenosine dinucleotide phosphate, *SOD* super oxide dismutase, *ATP* adenosine triphosphate

Ultraviolet radiation

In the stratospheric ozone, our primary protective screen from ultraviolet (UV) radiation is being depleted. Depletion of ozone leaves the upper atmosphere more transparent to UV radiation, thereby increasing our potential for UV exposure and subsequent dermatopathology. The UV spectrum consists of three specific regions: UVA (320–400 nm), UVB (280–320 nm), and UVC (200–290 nm) (Diffey 2002). The near-ultraviolet (UVB – UVA) from 280 to 400 nm is absorbed very strongly in the surface layer of the skin by electron transitions. As we go to higher energies (UVC–UVB) from 100 to 280 nm, the ionization energies for many molecules are reached and the more dangerous photoionization processes take place. Although the UV radiation spectrum at the earth's surface consists mainly of UVA radiation, it is the UVB wavelength range that is thought to be primarily responsible for the solar carcinogenic effects (Jost et al. 2001). Photo-aging or accelerated skin aging due to ultraviolet radiation damage in skin produces wrinkles, loss of elasticity, premalignant lesions, and non-melanoma skin cancer (Boring et al. 1993), which is said to be the most prevalent form of cancer.

Exposure of skin to UVA or UVB induces the formation of ROS, including $O_2^{\cdot-}$, H_2O_2, OH·, LOOH, and lipid peroxide radicals (LOO·). UVA and UVB radiation are proposed to exert many of their adverse biological effects (i.e., membrane and DNA damage). Ultraviolet radiation is not required for vision, but it can harm the retina at acute and intense exposure (Yong et al. 2010) as a result of the generation of reactive oxygen species. These reactive oxygen species have been associated to many root cause like skin aging, phototoxicity, inflammation, and malignant tumors (Sakurai et al. 2005; Marrot et al. 2008). Skin erythema is caused mainly by UVB radiation due to its short wavelength and its superficial penetration depth into the epidermis. The molecular oxygen present within skin cells in the mid-lower levels of the epidermis is a primary target for UV light waves that penetrate the skin (Jung et al. 2008).

These species can be generated both directly and indirectly through photochemical or photosensitization reactions. Cellular photosensitizers absorb UV radiation, leaving the sensitizer in an excited state that can then react with ground-state molecular oxygen, converting it to various reactive oxygen species. Since UVB stress is having interaction with oxygen and other biomolecules, it can result in the production of toxic intermediates of singlet oxygen and free radical. Thereby, they interact with biological membrane and cause lipid peroxidation (Kishore et al. 2010). Of the possible oxidants produced in the skin by UV radiation, H_2O_2 is the most stable of the oxygen products. This species is capable of directly oxidizing sulfhydryl groups and can indirectly oxidize polyunsaturated fatty acids. The major ROS enhanced by ionizing radiation is the hydroxyl radical. Ionizing radiation generates the hydroxyl radical via oxidation of water, which reacts with cellular components such as sugars, amino acids, phospholipids, DNA bases, and organic acids to produce organic radicals. As discussed already in the previous sections, the secondary ROS may subsequently be converted to hydroxyl radicals through further reduction by cellular metabolic processes such as the Fenton reaction (Halliwell and Gutteridge 1990).

Pesticides

Another common environmental factor that is involved in the activation of free radicals are pesticides. Pesticides are toxic substances that are widely used in agriculture and which help in destroying or controlling pest. Pesticide-induced alterations in targeted enzymes result in the activation of inflammatory pathway and elicit effect in multiple organs, many of which participate in neurotransmitter metabolism. For example, endosulfan has been extensively studied in the central nervous system (CNS). Endosulfan poisoning over–stimulates the CNS and is involved in the changes in neurotransmitter levels and alteration in neuronal behavior (Jai and Misra 2007). Paraquat toxicity is thought to primarily result from ROS generation and alterations in redox cycling (Oliveira et al. 2008). Malathion, an organophosphorus compound, is another example of a pesticide that induces oxidative stress, which further leads to the generation of free radicals and alterations in antioxidant levels in multiple organs (Akhgari et al. 2003).

Unhealthy lifestyle

Alcohol abuse

The liver is particularly susceptible to alcohol-related injury because it is the primary site of alcohol metabolism. The hepatocyte contains three main pathways for ethanol metabolism, each located in a different subcellular compartment: (1) alcohol dehydrogenase pathway of the cytosol, (2) microsomal ethanol-oxidizing system in the endoplasmic reticulum, and (3) catalase in peroxisomes (Lieber 1997). As alcohol is broken down in the liver, an unwelcome accumulation of acetaldehyde (a potentially dangerous byproduct) and highly reactive molecules called free radicals are generated. Acetaldehyde is highly toxic to the body even in low concentrations; it is also a carcinogen and a common environmental hazard. Normally, the enzyme aldehyde dehydrogenase rapidly oxidizes acetaldehyde to acetate, which travels through the bloodstream and enters other metabolic cycles (Lieber 2005; Tephly 1991) that produce energy or useful molecules.

Alcohol can cause death directly by acting on the brain areas which control consciousness, respiration, and heart rate. Of all the alcohols, methyl alcohol is more toxic to humans (John Brick 2005). Methyl alcohol serves as a common adulterant in country liquor. Generation of free radicals is enhanced in the liver during oxidation of methanol (Paula et al. 2003). It increases the chance of alcohol poisoning especially in developing countries like India. The statistical information regarding death rate in India due to alcohol poisoning was collected from the electronic newspapers (Fig. 3) which show

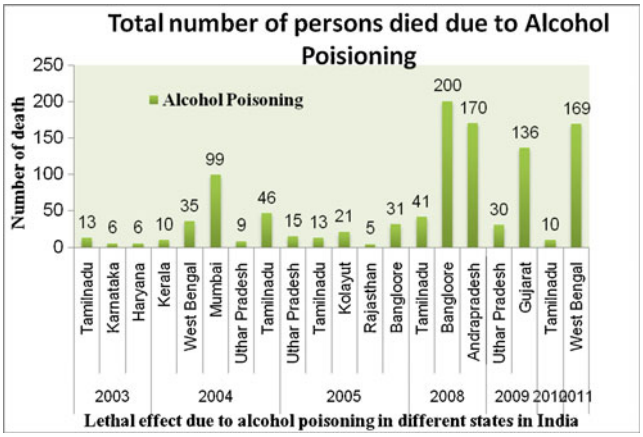

Fig. 3 Total number of persons who died due to alcohol poisoning in different states of India from 2003 to 2011

the drastic increase in the mortality rate due to alcohol poisoning. Around 200 people died due to alcohol poisoning in Bangalore and 170 people in Andrapradesh. In the year 2011, it was 169 people in Bangladesh. This may happen due to many reasons like poverty, earning money, unawareness, etc. Since the country liquor is of low cost, the village people prefer country liquor, and methanol was mixed with alcohol by the vendors to earn money, which leads to lethality.

The processes of conversion of alcohols to aldehyde cause an increase in nicotinamide adenine dinucleotide (NADH) concentration and stimulate the conversion of xanthine dehydrogenase into its oxidase form by reducing NAD^+ (Fig. 2), which is a superoxide anion-generating enzyme that generates superoxide anions (Kato et al. 1990). Free radicals generated during the metabolism of alcohols can react directly with proteins and lipids, changing their structure and functions (Skrzydlewska and Farbiszewski 1995; Aust et al. 1993). Hydroxyl radicals ($OH\cdot$) are generated by the microsomal ethanol-oxidizing system during the metabolism of ethanol, involving the alcohol-induced cytochrome P450 2E1 (CYP2E1). These radicals are involved in the alkylation of hepatic proteins to promote lipid peroxidation in hepatocytes by depleting glutathione (GSH) and finally leading to liver injury.

Another common disease among the heavy drinkers is alcoholic fatty liver disease which is an early complication of heavy alcohol consumption. Deposition of fat is believed to be due to an increase in NADH/NAD + ratio followed by alcohol oxidation. Through the electron transport chain, NADH supplies the liver with plenty of adenosine triphosphate (ATP). Due to this energy supply, other fuels are not essential, leading to reduced fatty acid catabolism. Alcoholism, which causes a fatty liver, will lead to jaundice (an indication of liver damage), enlargement of the liver, and cirrhosis. The World Health Organization (WHO) has identified that consumption of alcohol is one of the top ten risks for worldwide burden of disease (Boffetta and Hashibe

2006; Rehm et al. 2010). Evidence showing that alcoholic drinks of any type are a cause of various cancers of the mouth, pharynx, and larynx, esophagus, colorectal (men), and breast is convincing (Rehm et al. 2010; Bagnardi et al. 2001). They are also probably a cause of colorectal cancer in women and of liver cancer. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer (World Cancer Research Fund 2010).

Cigarette smoke

Cigarette smoke is an aerosol of complex chemical composition containing both organic and inorganic compounds such as carbon monoxide (CO), hydrogen cyanide, and nitrogen oxides. So far, 4,800 compounds have been identified, of which 100 were known to be carcinogen, tumor initiator, and promoter (Rodgman et al. 2000). Cigarette smoke contains two different populations of free radicals, one in the tar and one in the gas phase. The tar phase contains several relatively stable free radicals, Q/QH2 complex held in the tarry matrix (Pryor et al. 1998; Shinagawa et al. 1998). Cigarette smoke radicals are formed out of mainly three pathways: firstly, during combustion, both oxygen- and carbon-centered radicals which are expected to be produced in the cigarette flame; secondly, the formation of stable free radicals in tar (one of which is tentatively identified as a quinine/ hydroquinone (Q/QH2) radical); and lastly, the oxidation of nitric oxide (NO) to the much more reactive nitrogen dioxide (NO_2) (Church and Pryor 1985). Molecular oxygen is then reduced to form superoxide radicals, eventually leading to hydrogen peroxide and hydroxyl radical generation by the complex polymers formed.

Gas phase radicals are small alkoxyl- and carbon-centered species. The gas phase is around 0.4–0.5 g/cigarette, containing numerous free radicals and oxidizing agents that are continuously formed and destroyed (Church and Pryor 1985). Nitric oxide (NO·) is a species of significant importance because of its multiple physiological role such as neurotransmission and blood pressure modulator. NO· reacts quickly with molecular oxygen in air to form a toxic oxidant and nitrating agent, leading to the generation of carbon-centered radicals which subsequently react with atmospheric oxygen to form oxygen-centered radicals (Pryor et al. 1998). Gas phase carbon-centered radicals further react with molecular oxygen to form peroxyl radical. The peroxyl radical promotes the reaction with the gas phase NO· to form alkoxyl species, and it also triggers lipid peroxidation (Frei et al. 1991).

In addition, the principal radical in tar reacts with DNA in vitro, possibly by covalent binding, and has been shown to induce gene mutation (Ye and Xiao 2010). Synthetic Q/QH2 polymers have been shown to be potent redox catalysts in organic chemistry and may also have the capability of altering oxy-radical levels in the lungs (Iwasawa et al. 1974). Apart from the free radicals present, there are some polycyclic aromatic hydrocarbons (PHA) present in the tobacco smoke (Fig. 4). One such PHA is benzo(a)pyrene diol epoxide, which is a serious carcinogen present in cigarette smoke. In passive smoking, the environmental air contains nicotine, benzo(a)pyrene (BP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and quinine. The formation of peroxynitrite (ONOO−) from NO radical will further activate IKK (I-kB kinase) and phosphorylate such; thereby, the cells get inflamed by activating nuclear factor (NF-kB). In the same way, BP is metabolically activated into benzo(a)pyrene diolepoxide (BPDE) by reacting with N^2 position of quinine to produce N^2 guanine lesions (BPDE-N^2-dG), which is highly unstable. The BPDE-dG adduct formed will accumulate more in the bronchial cells, thus leading to the formation of lung carcinoma (Alexandrov et al. 2006).

It is common knowledge that nicotine is the major additive component of cigarette that harms our body system, although it was first prescribed as a medical drug to treat rodent ulcer and constipation. Each puff of smoke contains over ten trillion

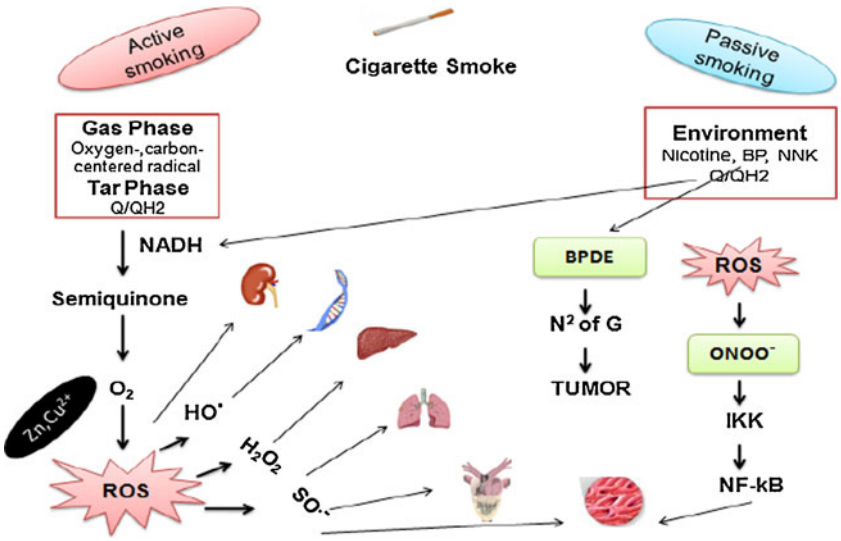

Fig. 4 ROS generation through active and passive smoking. Quinone (*Q*), hydroquinone (QH_2), semiquinone (*QH·*), dioxygen ($O_2^{\cdot-}$), benzo(a)pyrene (BP), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and quinine (*NNK*), peroxynitrite (*ONOO−*), IKK (I-kB kinase), NF-$_k$B (nuclear factor), benzo(a)pyrene diolepoxide (*BPDE*), *ROS* reactive oxygen species, H_2O_2 hydrogen peroxide, $O_2^{\cdot-}$ superoxide anion, *HO·* hydroxyl radical

free radicals, which results in tumor (Shishodia et al. 2003; Dietrich et al. 2003; Bloomer, 2007) due to initiation as well as repeated attacks from ROS on cellular macromolecules. It has been shown that the nicotine and tar levels produced by burning cigarettes are three times higher than in the smoke directly exhaled by the smokers and the concentration of carbon monoxide is approximately five times higher. They also proved that passive smoking is tied with various adverse effects on babies such as increased risk of sudden death syndrome, asthma, chronic diseases in the middle ear, slow lung growth, etc. (Ortega et al. 2010).

The physical effect of tobacco smoke on the oral tissues by heat and/or the direct effect of nicotine stimulates melanocytes that are located along the basal cells of the epithelium to produce more melanosomes. This condition results in the increased deposition of melanin in heavy smokers (Nadeem et al. 2011). Melanins are naturally occurring polymers containing quinone and hydroquinone groups that are ultimately derived from tyrosine via oxidation to dihydroxyphenylalanine. By adding metal ions (e.g., Cu^{+2}), the oxidation process is accelerated via Fenton cycling. In this oxidation process, NADH is the ultimate source of reducing equivalents from melanin quinone groups to the semiquinone ones which then reduce dioxygen to superoxide. The ultimate product, hydrogen peroxide, could then be formed either by dismutation of superoxide or by the oxidation of another NADH molecule by superoxide. Melanins also have been shown to catalyze the reduction of dioxygen to hydrogen peroxide in the dark (Herrling et al. 2007a, b).

Unbalanced exercise

Unfortunately, stress has become ubiquitous and omnipresent in our lives. At the workplace and driving through rush-hour traffic, most of us take it for granted that stress is a usual situation which occurs on a regular basis, day after day. The well-documented benefits of regular physical exercise include a reduced risk of cardiovascular disease, cancer, and osteoporosis. Recently, Akkus (2011) delivered that the complex mechanisms that contribute to these effects include decreased adipose tissue, altered lipid and hormonal profiles, receptor and transport protein adaptations, improved mitochondrial coupling, and alterations to antioxidant defenses. A defense system is necessary because aerobic organisms produce ROS during normal respiration and so do stress conditions. Eccentric exercise involves high force during the lengthening portion of muscle contraction. This can occur involuntarily or voluntarily during conditions in which the activated muscle cannot produce enough force to overcome the resistive force (e.g., during heavy resistance training) or during an intentional production of submaximal force in order to control the eccentric (lengthening) movement (e.g., controlled lowering of external load and/or downhill running), respectively. This can create an imbalance between oxidant and antioxidant levels, a situation known as oxidative stress (Leeuwenburgh et al. 1999; Gomez-Cabrera et al. 2009; Vollaard et al. 2005). Primary RONS generation in response to acute exercise can occur via several pathways. These include mitochondrial respiration (electron leakage from electron transport chain and subsequent production of the superoxide radical), prostanoid metabolism, the auto-oxidation of catecholamine, and oxidase enzymatic activity (NAD(P)H oxidase, xanthine oxidase) (Vollaard et al. 2005; Jackson, 2000). Although the main function of mitochondria is energy production, it generates reactive oxygen species during oxidative phosphorylation. Release of such intermediates accounts for an estimated 1 to 5 % of the oxygen consumed during respiration, depending on the substrate and respiration state. Skeletal muscle can increase its oxygen consumption up to 20-fold between rest and exercise; this could be an important mechanism for controlling reactive intermediate production.

Xanthine dehydrogenase is present in endothelial cells of blood vessels and skeletal and cardiac muscles. It converts NAD to NADH. Oxidation of purines to uric acid is catalyzed by xanthine oxidase (XO) which is found in serum. During exhaustive physical exercise, increased metabolic activity consequently increases the expenditure of ATP. Thereby, it enhances the activation of free radical-generating enzymes like NADPH oxidase and xanthine oxidase (Fig. 2). As a result of catabolism, ATP hypoxanthine is produced, and H_2O_2 is generated. By Fenton's reaction, it again undergoes reduction to form hydroxyl radical ($HO^{\cdot}$) and dioxygen ($O_2^{\cdot-}$), which damage or change DNA confirmation. When oxygen is reintroduced (reperfusion), XO produces radicals as byproducts, contributing to overall oxidant and free radical formation (Sachdev and Davies 2008). Phagocytic white blood cells also produce potent oxidants, generating reactive species that kill invading pathogens. However, neutrophils can infiltrate damaged skeletal muscle following strenuous or eccentric exercise, further damaging the cells. WBC also carries XO, which helps in the conversion of hydrogen peroxide in the presence of water and oxygen. Relaxation techniques can help you to withstand stress better and also help to relax facial muscles and skin. Breathing exercises, called pranayam in ayurveda, is an excellent tool for reducing stress.

Endogenous antioxidants

Antioxidants are agents that are capable of neutralizing the free radicals and have been reported to prevent oxidative damage caused by them. Our body itself has its own antioxidant defense system such as SOD, catalase, glutathione *S*-transferase, α-lipoic acid, coenzyme, etc., which helps to protect the cells from excess RONS production (Jeyadevi et

al. 2012). SOD is an important endogenous antioxidant enzyme which acts as the first-line defense system against ROS by scavenging superoxide radicals to hydrogen peroxide (H_2O_2). On the other hand, glutathione peroxidase is present in the cytoplasm of cells that remove H_2O_2 by coupling its reduction to H_2O. GR is a flavoprotein enzyme which regenerates GSH from oxidized glutathione in the presence of NADPH. GSH is a tripeptide and a powerful antioxidant present within the cytosol of cells and is the major intracellular non-protein thiol compound. Glutathione transferase (GST) is another most important enzyme which is a family of isoenzymes located in the mitochondria, cytosol, and microsomes. It plays a vital role in helping in the detoxification of ROS and deactivation of many harmful substances in our body (Dourado et al. 2008). It also takes part in the reaction of reduced glutathione as a cofactor. GST also plays a major role in the cellular protection of the erythrocytes against oxidative damage (Onaran et al. 1998). SH groups present in GSH reacts with H_2O_2 and OH· radical that prevent tissue damage (Thamotharan et al. 2010). Mammalian erythrocytes have large amounts of catalase (Temel et al. 2002), which is a heme-containing enzyme. It involves in the conversion of hydrogen peroxide to H_2O and O_2. Catalase is widely distributed in the body compartments, tissues, and cells and has a dual functional role: (1) a true catalytic role in the decomposition of H_2O_2 and (2) peroxidic role in which the peroxide is utilized to oxidize a range of hydrogen donors.

Exogenous antioxidants

Exogenous antioxidants are antioxidants that we get from our diet by eating antioxidant-rich foods. Exogenous antioxidant includes carotenoids, tocopherols, ascorbate, bioflavonoids, anthocyanidins, phenolic acids, etc. (Urso and Clarkson, 2003; Bouayed and Bohn 2010). Phenolics and flavonoids are the major antioxidant compounds of plant origin. Phenolic compounds are thought to protect the plants against tissue injuries as they oxidize and combine with proteins and other components. Similarly, flavonoids can act as antioxidant agents by acting as hydrogen donors or chelating metals. Considering all of these factors, there is no doubt that exogeneous antioxidants are going to become a part of the food system. On the other hand, excess intake of polyphenols also leads to serious damage as follows. It was reported that long-term treatment of cells with polyphenols can increase endothelial nitric oxide synthase expression and calcium (Ca^{2+})/calmodulin (CaM) complex (Stoclet et al. 2004) which also leads to cell damage. At the same time, many polyphenols like resveratrol and quercetin have been reported to exhibit a protective effect against

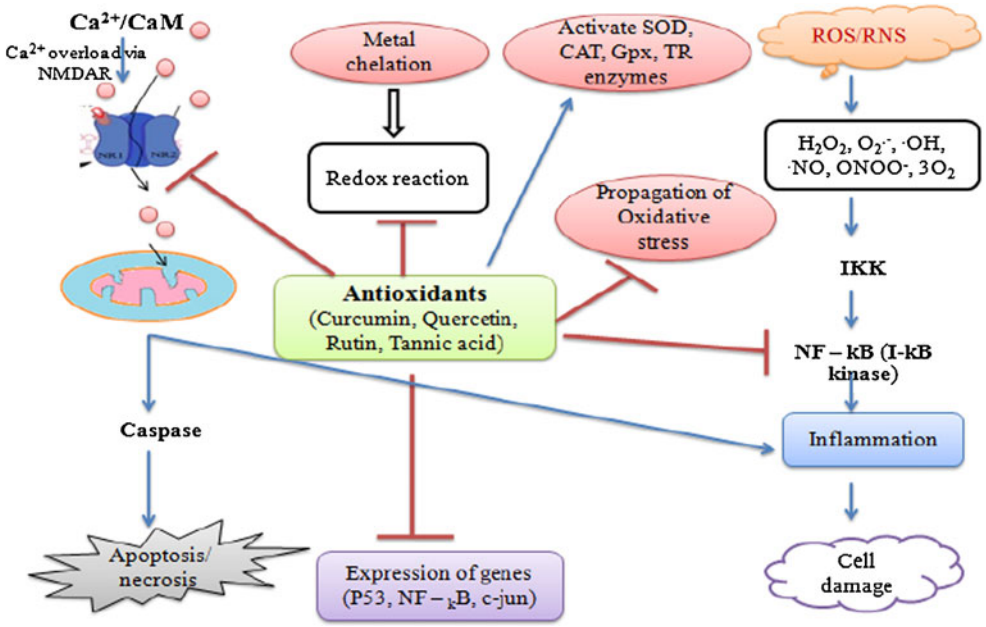

Fig. 5 Mechanism of antioxidant defenses against free radical-induced damage in humans. Polyphenols or antioxidants affect glutamate-mediated Ca^{2+} influx through NMDAR, thereby reducing glutamate-induced Ca^{2+} influx into mitochondria; antioxidants interfere caspase pathway and inhibit cell damage; antioxidants inhibit the propagation of oxidative stress; it activates the expression of antioxidant enzymes CAT, SOD, GPx, TR; it interferes metal chelation and inhibit redox reaction; antioxidants inhibit the expression of redox genes. *N*-Methyl-D aspartate receptors (*NMDAR*), catalase (*CAT*), superoxide dismutase (*SOD*), glutathione peroxidase (*GPx*), thioredoxin reductase (*TR*), calcium (Ca^{2+}), calmodulin (*CaM*), IKK (*I-kB kinase*), NF-$_k$B (nuclear factor), reactive oxygen species (*ROS*), reactive nitrogen species (*RNS*), hydrogen peroxide (H_2O_2), superoxide anion (O_2^{-}), hydroxyl radical (·HO)

aging (Markus and Morris 2008; Belinha et al. 2007). The activation and induction of *c-fos* and *c-jun* mRNAs by phenolic antioxidants is mediated by an antioxidant response element in a specific and dose-dependent manner (Choi and Moore 1993). Indeed scientific studies demonstrate a significant inverse correlation between polyphenol consumption and aging. Antioxidants may prevent the production of oxidants/scavenge the radicals by chelation of transition metals, inhibit oxidants from attacking cellular targets, block the propagation of oxidative reactions, induce the expression of endogenous antioxidants, and modulate the signal transduction pathways and gene expression through their reducing properties (Fig. 5). The free radical scavenging mechanism which exists already in the system is inefficient, and hence dietary intakes of antioxidant-rich compounds become important (Smilin Bell et al. 2012a). The use of herbal products could be a better option to meet the objective of finding a suitable treatment for reducing the free radicals generated from environmental and physiological factors.

Herbal approach

Modern civilization, the use of different chemicals, pesticides, pollutants, smoking and alcohol intake, and even some synthetic medicines increase the chance of disease due to free radicals. When a cell is attacked by environmental stress, the cell's defense is lowered because of massive generation of reactive oxygen species, which is then immediately responded to by upregulating its antioxidant defense. Exercise is considered as a great stress buster by many of today's health and fitness experts. In the same way, much of the direct cell damage that occurs during alcoholic liver disease is believed to be caused by free radicals (Gupta and Singhvi 2011). One best tool for reducing free radicals nowadays is green leafy vegetables and medicinal herbs. Furthermore, synthetic antioxidants (BHA and BHT) are most commonly used for food and pharmacological applications but which have now been avoided due to doubts over their toxic and carcinogenic effects (Wichi 1988; Sherwin 1990). Therefore, there is a growing interest in natural and safer antioxidants for food applications and a growing trend in consumer preferences towards natural antioxidants, all of which have given thrust to the attempts to explore natural sources of antioxidants especially from medicinal plants. Natural antioxidants in foods may be from (a) endogenous compounds (phenol, flavonoid, terpenoid, and steroids), (b) products formed from reactions during processing, and (c) food additives extracted from natural sources.

There are many reports regarding the scavenging of free radicals generated due to physiological and environmental stress. Flavonoid effectively prevented the damage by UVB radiation (Landry et al. 1995). Prasad et al. (2009) showed the anticancer activity of *Clausena lansium* peel extract, which is comparable to the commercial anticancer drug, cisplatin. Yang et al. (2008) attempted to test the hypothesis that quercetin and tocopherol (exogenous antioxidants) can prevent lung tumor induced by tobacco smoke using an intervention model of smoke-induced lung tumor in Swiss mice. *Vernonia amygdalina* provided evidence that the extracts represent anticancer agents against breast cancer (Yedjou et al. 2008). *Accacia salicina* leaf extract was proved to possess antimutagenic and free radical scavenging activity (Boubaker et al. 2011). *Hedyotis corymbosa* (Sasikumar et al. 2010) and *Bixa orellana* methanol extract provided excellent protection against hepatotoxicity and possess antioxidant activity (Smilin Bell Aseervatham et al. 2012a, b). It is also proved that the level of free radicals generated by methanol toxicity is significantly decreased by exogenous antioxidant vitamin E (Paula et al. 2003). The herbal extracts could be used as a complementary agent in providing better clinical recoveries when given along with our regular food practices. Diets rich in fruits and vegetables are associated with longer life expectancy, and it may be that the antioxidants contained therein are of prime importance for these beneficial effects. Development of genetically engineered plants to yield vegetables with higher levels of certain compounds is also another approach to increase antioxidant availability.

Conclusion

However, simply stated, any situation in which the consumption of oxygen is increased due to these factors could result in an acute state of oxidative stress. Supplementing the body with antioxidant agents (fresh green leafy vegetables, antioxidant rich legumes, plant products) as our regular food practice will provide sufficient support to the human body to fight those oxidative stress-induced diseases, as the proverb says: “prevention is better than cure”.

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