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FORMATION OF REACTIVE OXYGEN SPECIES DUE TO HEAVY METALS AND TOXICITY IN ANIMALS/HUMAN BEINGS: AN OVERVIEW

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ABSTRACT

Reactive molecules and free radicals are used to define the reactive oxygen species that include superoxide, hydrogen peroxide, hydroxyl radical, hydroxyl ion, and nitric oxide. Antioxidants are responsible to eradicate the ROS in the human body. Antioxidant systems of the cell lessen the perturbations whereas oxidative stress is the result of when reactive oxygen species production exceeds the limit and overcome the cellular antioxidants which disturb the cell signaling and gene regulation systems. Only antioxidants can prevent or delay the oxidation of cellular oxidizable substrates. Heavy metals (Pb, Hg, Cd, Cr, Cu, Zn, Mn, Ni, Ag, etc.) are dangerous to human health; they enter into human body via food, drinking water and air. These heavy metals' toxicity causes serious health issues and causes diseases in human body. High concentration of lead leads towards the complications in the synthesis of hemoglobin, renal effects, gastric and CNS disturbances. Mercury leads to abortion, congenital malformation and development changes in young children. Selenium cause fatigue and irritability, alopecia and fingernail loss, damage the renal, hepatic system. Antimony causes nausea, vomiting and diarrhea and cancer. Two mechanisms are involved in the production of superoxide firstly when ATP is not being produced by mitochondria, simultaneously promotive forces become higher in concentration and decrease in coenzyme Q pool and secondly, the high ratio of NADH/NAD+ in mitochondrial matrix, skeletal muscle, heart and liver using different substrates and inhibitors to determine site for production of reactive oxygen species. NADPH oxidase and mitochondrial electron transport chain is responsible for the formation of cell reactive oxygen species in targeted pancreatic beta cell and other cells for insulin. Reactive oxygen species play many roles in homeostasis and on physiological levels, excess of it causes cellular stress and death. Due to accumulation of heavy metals many types of cancers occur like lung cancer, kidney cancer, brain cancer etc.

Keywords: Reactive oxygen species, lead, chromium toxicity, mitochondria, electron transport chain

INTRODUCTION

The immune system of human beings and animals is compromised due to reactive oxygen species production when they ingest heavy metals because they are considered as the killing component of the cell compromised in immune system. Different types of mechanisms are used to produce reactive oxygen species and are detected by various techniques. Reactive molecules and free radicals are used to define the reactive oxygen species. All aerobic species are prohibited to oxygen based radicals. Formally it is considered that for host cell defense mechanisms only phagocytic cells were accountable for the generation of oxygen species (Flora *et al*., 2006).

PRODUCTION OF REACTIVE OXYGEN SPECIES (ROS)

Antioxidant plays an important reactive oxygen species which are responsible to eradicate the ROS in the human body. In plants many oxygen reactive species are produced by the aerobic metabolism in the form of their by-product. Various types of oxygen reactive species are present in nature in which some are detoxified quickly by enzymatic and non-enzymatic activities whereas some are highly toxic. In abiotic stress condition oxygen reactive species are combat in increased amount while in normal conditions oxygen reactive species are released when needed to control various processes which include apoptosis, opening and closing of stomata and defense. Mammalian cytochromes P450 belong to a family of heme-thiolate enzyme which is used for the maintenance of gene transcription and also for the interaction of mono-oxygenase constituents of protein. Reactive oxygen species is the result of poor coupling of P450 which not only affects the cellular functions but also signaling pathways which ultimately result in lipid peroxidation and oxidative stress (Goyer, 1996).

Due to normal cellular function oxygen reactive species generate which includes nitric oxide, hydroxyl radicals and hydrogen peroxide that leads towards the peroxidation of lipids and DNA oxidation. Cell antioxidant system lessen the perturbations in normal condition whereas oxidative stress is the result of when oxygen reactive species production exceeds the limit and overcome the cellular antioxidants which disturb the regulation of gene and signaling of cell. Cellular oxidizable substrate oxidation can be prevented by antioxidant only. However, there are numerous antioxidants that hunt the superoxide and act as the self-protective proteins. Antioxidant protection is vital in all

the aerobic organisms process, decrease in its limit leads towards cytotoxicity, mutagenicity and carcinogenicity. Mimic antioxidant enzymes are used in the curing many diseases (Ruff *et al*., 1996).

HEAVY METALS AND THEIR TOXICITY

Heavy metals are dangerous to human health; air, food and drinking water are the major sources through which they enter the human body. Lead, mercury, copper, zinc, chromium, cadmium and arsenic are mainly associated with the environment. The metals which are important in maintaining the human body metabolism are zinc, copper and selenium but at higher concentration they are very toxic and harmful to human body. The compounds which are toxic at even low concentration are mercury, lead, thallium and chromium. Arsenic (As) contaminated water and agricultural products result in the harmful diseases. For example different types of cancer and skin disorders. Excess use of Lead (Pb) leads towards the poisoning in general, Mercury (Hg) dramatically dangerous to lactating mothers, fetuses and children, Cadmium (Cd) is responsible for carcinogenesis (Bressler *et al*., 1999).

NATURAL SOURCES OF HEAVY METALS

Rocks are the natural source of heavy metals. The weathering process is activated by the change in environmental conditions. Rocks have high concentration of chromium, lead, mercury, selenium, copper, cadmium, nickel and molybdenum. Sedimentary rock contains small amounts of heavy metals. For example shale rock has highest concentration of chromium, lead, mercury, selenium, copper, cadmium, nickel and molybdenum whereas olivine, and hornblende are the igneous rock and pay substantial amounts of nickel, molybdenum, and copper. In agricultural soil organic and inorganic fertilizer are present which are the sources of heavy metals. The accumulation of heavy metals in agricultural soil is due to pesticides, sewage water and polluted irrigation water. Mining and refinement of metals, their recycling and ores transport are the industrial sources of the heavy metals. Heavy metals become toxic due to formation of toxic soluble compounds. If a metal is present in body without any reason then it becomes poisonous to human health e.g. lead present in body either in low amount or high is harmful for health (Flora *et al*., 2007). In some conditions lighter metals such as beryllium is also toxic. Sometimes iron the essential component of body becomes toxic and disturbs the essential mechanism such as the metabolic process. There are some metals which are less toxic like bismuth (Bi). Radioactive metals tempted the radiological and chemical toxicities. If metals are present in abnormal oxidation stage they become harmful e.g. Chromium (III) which is an important trace element if converted to Chromium (VI) then it displays the carcinogenic effect. Metabolic system and mutagenesis is affected by the toxic effect of heavy metals on living organism they result in weight loss, disturbance of reproduction which leads towards carcinoma and finally resulting in death. No toxic effects are shown by the metallic compound as well as insoluble compound (Bechara *et al*., 1996). The factors mainly resulting in toxicity are the ligands of any metals as of organometallic form for example tetraethyl lead while the derivatives of organometallic compound are less toxic. The poisonous metals are accumulating both in body and in the food chain. Chronic toxicity generally is the result of the presence of toxic metals like the presence of radium which is radioactive heavy metal and leads to reproduce calcium (Ca) in order to assimilate into the bone. Some metals like barium, aluminum are rapidly discharged through the kidney. Increased Industrialization have not only polluted our environment but also increased the amount of several heavy and light metals. We have some historical background of increased amount of metals leads towards the death e.g. in Japan increased amount of mercury in water has poison the water for drinking and exhibit the substantial neurotoxicity disease. Usually through respiration, ingestion and skin heavy metals enter into the body and become poisonous when they exceed their threshold levels (Ummus *et al*., 1999).

HEAVY METALS, ENVIRONMENTAL AND HEALTH RISKS

Through food heavy metals enter into our body and accumulate there. As a result of industrial wastes, and consumer materials, soil is broken down by the acidic rain and releases heavy metals into rivers, lakes and stream. Lead, mercury plus Cadmium are highly toxic to environment. Contaminated water, emission of air with heavy metals and from food chain the heavy metals enter in the body and causes toxicity. Accumulation of heavy metals become harmful. Accumulation is a biological process in an organism which raises the level of chemicals in the body. Industries, vehicle transport, human activities have increased the heavy metal pollution which have not only directly affect the human health but also the animals (Fuchs *et al*., 2000).

LEAD CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Depending upon its duration in a body and its level lead is harmful. The adult stage fetus and infant stages are more sensitive. Normally food contains high amounts of lead whereas from water, air, dust, paint flakes, soil, acidic rain it is obtained in lesser amount. Presence of lead in air is due to exhausted smoke from batteries, petrol items, burning of pigments or compounds containing lead. Both natural and anthropogenic processes are source of lead in

the environment. Secondary lead source is due to rapid production of non-ferrous metals. High concentration of lead produces the complication in the synthesis of hemoglobin, damages renal and stomach, and causes less or severe damage to central nervous system (Blumerg *et al*., 1994).

MERCURY CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Mercury is not present in living organism and it has no role in homoeostasis of the body. Accumulation of mercury in living bodies results in central nervous system disturbance, absorption, congenital malformation and changes in pattern of development of young children. It causes neurotoxin disorder in fishes. Mostly used for industrial processes, pharmaceutical industry, in dentistry as an amalgam for feeling in thermometers, batteries and lamps etc (Flora *et al*., 2007).

CADMIUM CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

It remains in the body over many years once it is taken and causes many disorder due to accumulation in the body for a long period. For example hypertension, kidney disfunction, obstructive pulmonary disease, lung cancer, osteomalacia, osteoporosis and cardiac disease. Cadmium has multiple uses; like it provides resistance to corrosion, by coating it on different items for example on marine and aerospace crafts, as a pigment, as a stabilizer in different compounds like alloys, electronic compound, pvc present as impurity in many products. For human daily average intake from air is 0.15µg and from water is 1µg. cadmium is easily recycled (Brennan *et al*., 1995).

SELENIUM CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Humans and animals need Se only in small amount and it accumulates in living tissues, if it is present in bulk amount over the long period it damages the central nervous system and cause weakness, loss of hairs and nails, damage the renal function and hepatic tissue and circulatory tissue respectively (Lockitch, 1993).

ANTIMONY CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Sources of antimony are batteries, pigments, ceramics and glass. If it is present for short duration in human body it causes nausea, vomiting and diarrhea and cause cancer if it is present for long period (Moreira *et al*., 2001).

COPPER CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Although human body needs Cu in high amount yet it causes many disturbances when present in excess amount in human body. Renal problem, hepatic damage, anemia and infection in gastro intestinal tract are major consequences of excess Cu. Copper supply lines are major source of contamination in drinking water (Flora *et al*., 2006).

CHROMIUM CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Chromium is used in many industries for example rubber, paper, cement and paint etc. presence of chromium in human body causes damage to central nervous system, renal and hepatic damage and irritation of skin (Fox *et al*., 1998).

NICKELCAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Nickel in small amount is used for the generation of red blood cells, if it crosses its threshold it becomes toxic and results in weight loss, damages the cardiac and hepatic organ. It accumulates in marine animals (Hsu, 1991).

METALLOTHIONE CAUSING ENVIRONMENTAL AND HEALTH HAZARDS

Metallothione is a protein produced when body is under stress of high levels of cadmium, mercury, zinc, glucocorticoid and anticancer agents for protecting the body from damages in detoxification of heavy metals Metallothionein plays major role. It lacks in biological function establishment (Ito *et al*., 1985).

TOXIC METALS AND OXIDATIVE METAL

Due to abundance of metals for example lead, mercury, cadmium and arsenic our environment has become contaminated. They act as catalyst in biological oxidation reaction and damage the tissue. In presence of redox active or inactive metals reactive oxygen species are produced in higher amounts. Oxidative stress produced when reactive oxygen species exceeds its threshold level causing various dysfunctions in the body. Antioxidant supplement are given to reduce the damage caused by heavy metals (Sugawara *et al*., 1991).

ROLE OF DIOXINS PLUS HEAVY METALS

A vital role is played by oxidants in normal and abnormal cells. They control the process of degranulation and cell death. Dioxins exert toxic effects on various enzyme system of the body. For example on the elimination reaction enzyme and on cell cycle: for example its growth, inhibition and death (Chiba *et al*., 1996).

PRODUCTION OF REACTIVE OXYGEN SPECIES IN MITOCHONDIA

Superoxide a major reactive oxygen species produced by mitochondria is important due to oxidative damage caused by it. Two mechanisms are involved in the production of superoxide firstly when ATP is not being produced by mitochondria and simultaneously high promotive level of force and a decreased level of coenzyme Q pool (The system of the transfer of electron from dehydrogenises to cytochroms and coexists with protein –bound Co-Q) and secondly, the high ratio of $NADH/NAD^+$ (Nicotinamide adenine dinuleotide) in mitochondrial matrix. The synthesis of ATP in mitochondria and the ratio of primitive force lower the $NADH/NAD^+$ and produces less superoxide. $NADH/NAD^+$ are co-enzymes involved in various biological processes like including energy metabolism and mitochondrial functions, gene expression, aging and cell death. NADH involves in redox reaction and metabolism of different biological processes. The depending factors for its production are highly variable thus difficult to measure in vivo. Studies performed on rat skeletal muscle, heart and liver using different substrates and inhibitors to determine site for production of reactive oxygen species. Superoxides are released from the inner membrane and cytoplasmic side of the mitochondrial matrix. The oxygen reactive species plays important role in glucolipotoxicity in diabetes (Brennan et al., 1995) NADPH oxidase dependent and mitochondrial electron transport chain is responsible for the cell reactive oxygen species in target pancreatic beta cell and other cells foe insulin (Moreira *et al*., 2001).Consumption of high fat meals results in increased manufacture of oxygen reactive species by the obstruction of fatty acid oxidation and mitochondrial oxidative Phosphorylation.

ROLE OF OXYGEN REACTIVE SPECIES IN LIVER

Oxygen reactive species play many roles in homeostasis plus on physiological levels, excess of its causes cellular stress and death. Species reactive in oxygen reduces the incidence for arthritis plus liver fibrosis. It plays roles in immunity, impairing many functions and promotes binding of the virus (Gurer and Ercel, 2000).

HEPATOPROTECTIVITY BY RUTIN

In the paracetamol and carbon tetrachloride induces liver damage the rutin which is very properly known and common flavonoid is found to be very protective. The paracetamol which is not very dangerous produces liver damage in animals especially in rats by oral intake. Carbon tetrachloride produces prolonged pentobarbital sleeping times conforming that the liver is protected by rutin (Gurer *et al*., 1998).

ACCUMULATION OF HEAVY METALS CAN CAUSE CANCER

Heavy metals are the metals that are dangerous even at the low concentration. Heavy metals that are naturally occurring are arsenic, beryllium, cadmium, mercury, chromium and lead. Our body does need heavy metals in trace amounts that are zinc, copper and selenium. Some heavy metals when accumulate in our body causes serious health problems. They can enter in our body through contaminated food, drinking water, and inhalation and through its contact with our skin and eye. Once they are accumulated in our body their concentration keep on increases as the time passes because they are not metabolized and excreted out by our body but very quickly absorbed by our body (Cocco,1998).

Many types of cancer are caused by the accumulation of heavy metals. The heavy metals presence results in the transportation of essential nutrients and minerals that are needed by our body for its proper functioning. When they do not get the required amount of nutrients they effect the normal functioning of the enzyme and as the result of it causes health problem. Lung cancer is caused due to the accumulation of metals. Arsenic causes severe lung cancer and also lung distress. Exposure of the working place environment by inhalation, contact with eye and skin, and ingestion causes the accumulation of this harmful metal. Beryllium accumulation can cause many diseases like lung cancer, lung infection, and rickets in children. Beryllium is accumulated in our body by some house hold products, cola burning and manufacturing environment (Hsu, 1981). Many renal infections and defects in bone are caused by these toxic metals. High dose of cadmium causes lung obstruction and lung cancer. Hexavalent chromium a form of chromium causes lung cancer most commonly to the workers who have daily exposure to such metals over a long concentration of time. Renal cell carcinoma is the other name for kidney cancer. Kidneys present in abdomen not only filter blood but also excrete out excess salt, water and waste products. Kidney cancer is caused when kidney cells star growing without the requirement and form malignant mass in the organ. If the cancer is not removed it may spread and affect the other organs of the body. In most of the cases the kidney cancer is curable when it is de-

tected in the early stages. The factors which increase the risk of kidney cancer are smoking, pain killer overuse, heavy metals exposure (lead and mercury). Often the symptoms for kidney cancer are hard to detect but few are blood in urine, legs swelling, weakness, loss in weight, fatigue, fever without any infection and abdomen filled with mass (Goyer,1996). The most common treatment for kidney cancer is partial nephrectomy. This treatment is used when the tumor is small in size. In this treatment the kidney which contain small tumor is surgically removed so that it does not affect the other kidney and rest of the parts of body. The diagnostics tests to conform that the patient is suffering from cancer is urine analysis and also the accumulation of mass at that place in physical examination (Lockitch, 1993).

Table 1. Table 1 shows the ROS their half time, migration distance, sources, mode of action, reaction with DNA, reaction with RNA, reaction with protein, scavenging systems.

ROS	**T1/2**	**MIGRATION distance**	**Sources**	**Mode of action**	**Reaction With DNA**	**Reaction with RNA**	**Reaction with protein**	**Scavenging systems**	**References**
Super oxide	1-4µs	30nm	Membrane, chloroplast, mitochondria	Reacts with double bond containing compound such as protein	No	Extremely low	Via the Fe center	SOD	(Fox et al.,19998)
Hydroxyl radical	1µs	1nm	Membrane, Chloroplast, Mitochondr-ia	Extremely reactive with all biomolecules	Rapidly reacting	Rapidly reacting	Rapidly reacting	Flavonoids and proline	(Bechara et al 1996)
Hydrogen peroxide	1ms	1µm	Membrane, Chloroplast, Mitochondria	Oxidizes protein	No	Extreme-ly low	Attacks the cys function	CAT, POXs and flavonoids	(Blumerg et al., 1996).
Singlet oxygen	1-4µs	30nm	Membrane, chloroplast, Mitochondria	Oxidizes protein	Reacting with G residue	PUFA	Attacks the Trp, Cys, Met, His	Carotenoid-ds and α-tocopherol	(Fuchs et al., 2000)

BRAIN TUMOR OR CANCER

Brain cancer is that type of cancer in which very delicate part of our body is affected. It is the part of the body which controls all of our body functions and movement. There are four factors that cause brain cancer i-e fluoride, heavy metals, artificial sweeteners and electromagnetic field. In heavy metals like fluoride, they cross the blood brain barrier and cause the accumulation over there resulting in the improper functioning of the brain. The traumatic brain damage due to mercury is common in new born infants who do not have well developed blood brain barrier. The migraine is also due to accumulation of heavy metals in the brain. The symptoms of brain cancer are memory problem, walk and daily activities change, sleeping problem, drowsiness, vomiting, fatigue, feeling pressure and headache near the tumor and weakness (Ruff *et al*., 1996).

Almost every types of cancer is caused by the accumulation of heavy metals. We need to be very careful while using cosmetics and skin products. Low cost cosmetics and skin products can cause skin cancer or skin infection. We should never ever play with our skin. Breast cancer is also caused by the accumulation of heavy metals. It affect most often females rather than males. In most cases it results in cutting of the breast. This occur more in the females who do not feed their children or wear tight under dress. In feeding case, mothers who not feed their children and their milk is dried and results in the formation of dried milk clot which later on results in the formation of tumor. So to remove heavy metals from our body we should drink large amount of water, eat fermented food, consume sulfur rich food, consume thistle milk, and increase intake of polyphenols (Ummus *et al*., 1999).

Table 2. The table shows the heavy metals their penetrating exposure and consuming (days or less), long term exposure (months or years).

Heavy metals	**Penetrating exposure and Consuming days or less**	**Long term exposure Months or year**	**References**
Lead	Nausea Vomiting Encephalopathy (brain dysfunction)	Anemia Nephropathy (kidney problems) Foot drop (palsy)	(Lto *et al*., 1985).
Cadmium	Lung inflammation (pneumonitis)	Lung cancer Osteomalacia (softening of bones) Proteinuria (protein in excess amount in urine possibly causes damage to kidney)	(Sugawara *et al*., 1991).
Mercury	Diarrhea Fever Vomiting	Stomatitis (gum inflammation) Pink disease (pain and pink discoloration of hand and feet) Parageusia (metallic taste) Nephoitic syndrome (kidney problem) Nausea, tremor	(Cocco,1998).
Arsenic	Nausea, vomiting, diarrhea Multi- organ effects Arrhythmia Painful neuropathy	Diabetes Kidney Hyperkeratosis/hypopigmentation	(Flora *et al*., 2007).

Explanation of Fig 1. The oxidative stress disrupts the redox status of cell membrane and the interaction of heavy metals with functional group of membrane. The metal ions easily bound to membrane because of the presence of SH (Sulfhydral) group of protein and OH^-(Hydroxyl) group of phosolipids. The consumption of high quantity of heavy metals lead to the process of becoming impaired in membrane structure it causes the leakage of cellular solute salts. Cell membrane is composed of lipids and oxidation of these lipids damage the cell membrane and also effect on cell functions.

Haber weiss reaction O^-_2, H_2O_2 changes in to $HO^0 + O_2 + HO^-$ and ion serves as a catalyst. NADPH (Nicotinamide adenine dinuleotide phosphate) coenzyme bound with plasma membrane where lipid peroxidation is step wise reaction which increases the efficiency to form ROS. The lipid per oxidation process/rate increases with increasing quantity of O^{2-} and H_2O_2. These reactive oxygen species direct damage to lipids and causes the membrane damage, decreases the membrane fluidity and damage the membrane fluidity OH^- ion is a reactive ion and have tendency to damage proteins, lipids, carbohydrates and DNA. It bound to NADPH. Carcinogenic metals produce the free radicals and interaction of these free radicals with antioxidant defends from oxidative damage and in the case of accumulation damage the different cellular components. These species also activate Nrf_2 (Nuclear factor erythroid –

derived 2) and different antioxidants become active and these metals inhibit the enzymatic activities and shows the affinity with SH group and disturb the normal function of cell.

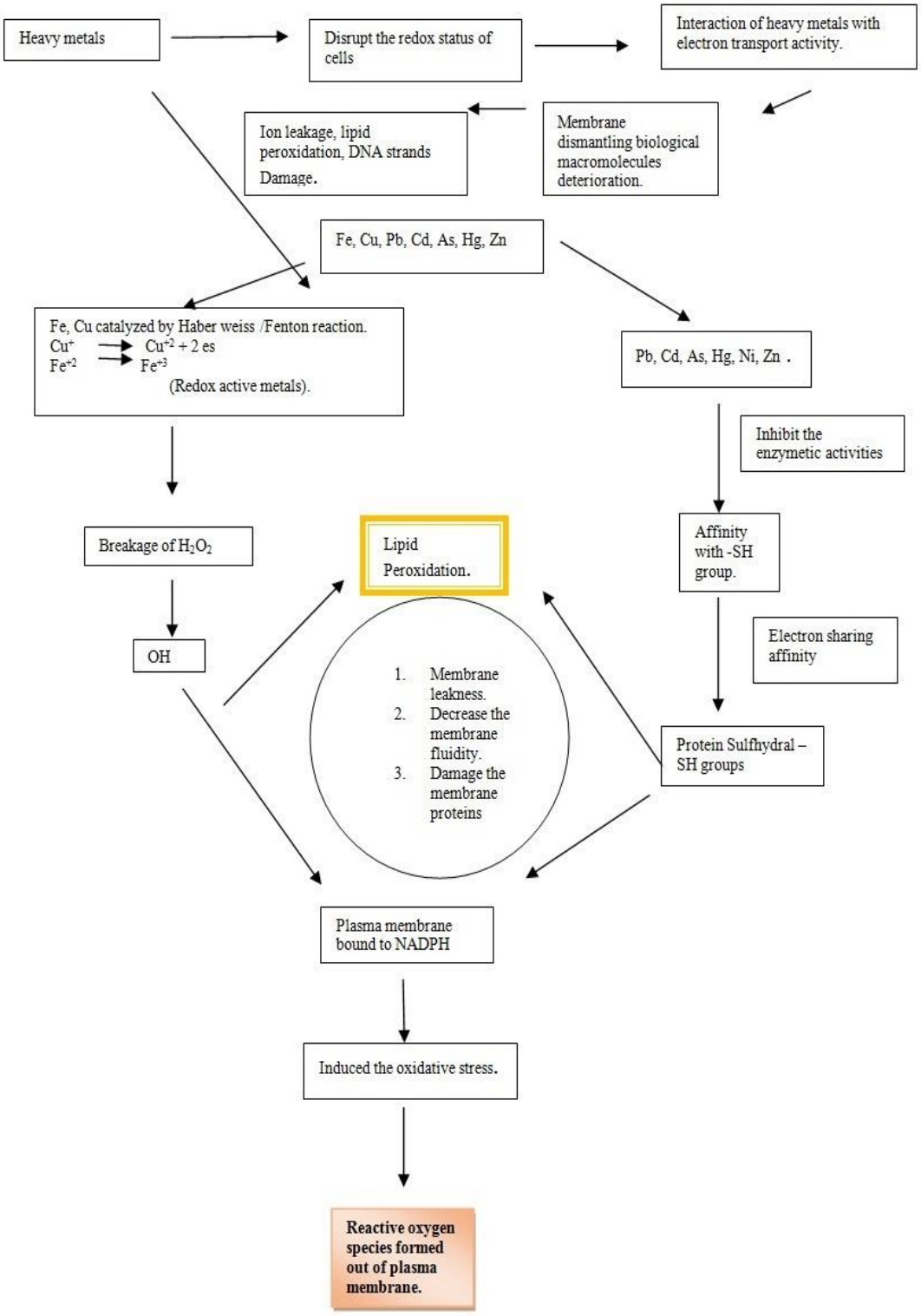

Fig1. Formation of Reactive Oxygen Species on Plasma Membrane (Source: Jan *et al*., 2015; Abd El-Aal., 2012).

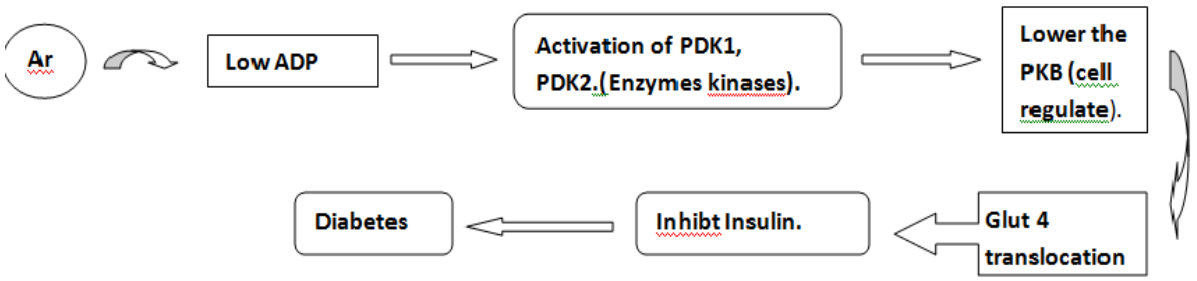

Fig. 2.Heavy metal causes Diabetes (Source: Liu *et al*., 2014).

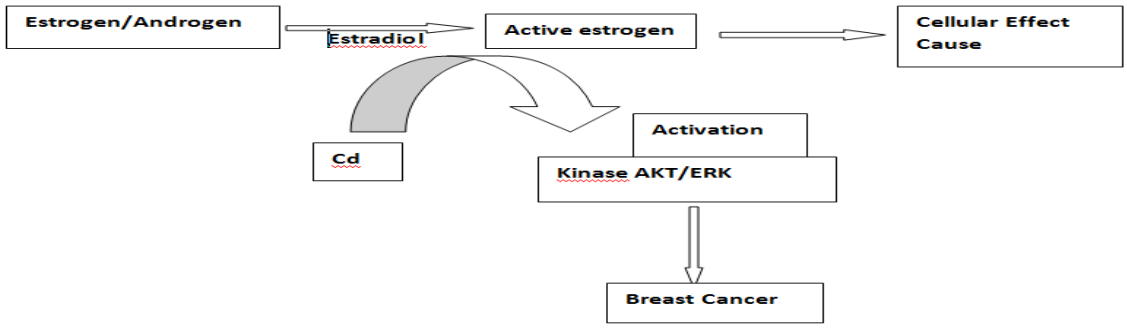

Fig.3. Heavy metal causes Breast Cancer (Source: Weil *et al*., 2014).

Explanation of Fig. 2, 3, 4. Heavy metals disrupt the biological functions of the human body and initiate ROS induced signaling cascades by binding to EFGR (Epidermal Growth factor Receptor). Heavy metals increases the synthesis of inflammatory mediators (TNF-α, NF-kβ and leucotrienes) and decrease the activity of endothelial nitric oxide synthase (eNOS) and mediates vasoconstriction of the blood vessels by phosophorylating mysin light chain kinase (MLCK) leading to hypertension. Long term exposure to heavy metals increases oxidative stress leading to over expression of various stress mediators (NF-Kβ, c-Jun-N-terminal kinase / stress activated protein kinase (JNK /SAPK) causing insulin resistance and dysfunction of beta cells leading to diabetes.

The exposure of the body to the heavy metals (carcinogenic) produce extensive oxygen species which directly hit mitochondrial matrix disturbing cytochem c-oxydase inhibits the antipopatic protein (Bax) and stimulates the signaling anti apoptotic protein (BCt_2) in response to this signaling tumor production is enhanced disturbing the process of apoptosis and initiating the inflammation which is indicated increase production of 8-oxo 3',5' d GMP (Guaniosine mono phosphate) in the blood and also tissues homogenates which is ultimately converted in to 8 oxo GMP. The accumulation of dnTP (Di nucleotide triphosphate) pool in nucleus awaken the self immune mechanism of body which can be observed in the form of increase level of antioxidants like GSH, CAT, SOD and decrease level MDA and increase the level of 8-OHdg.

Intake of Arsenic (Ar) causes harmful effect by inhibit lower down the production of ATP (Adenosine triphosphate) through EFGR (Epidermal growth factor receptor) lower the ATP used which causes the formation of ADP – arsenate, this will lead to the low ATP production. Further act of PDK-1/PDK-2 (Pyruvate dehrogenase kinase) which lowers down the PKB (Protein Kinase B) molecules, thus lower regulation /translocation of Glut-4 takes place. Low translocation causes the inhibition of insulin by stimulating the glucose uptake by adiposities ultimately leads to diabetes.

Intake of Cadmium (Cd) causes release of estrogen and androgen form its particular gland which further activates the estrogen receptor (ERα) as a ligand to its receptor takes place in the absence estrodiol precursors, blocked by the toxicity of cadmium. Rapid activation of kinases ERK ½ and AKT which further promotes the activation of Breast cancer.

Ras (Recticular activating system) is a protein and it is responsible for sleeping and awakening after attacking the ROS on human cell membrane it passes the signals that control the amount of growth. Mutation of Ras causes a cancer. Ras activates the Raf (Rapidly activated fibrosarcoma). It helps in cell survival and apoptosis Ras passes

the signal to MEK ½ (Mitogen activated protein kinase). These are antibodies and are protein in nature. These are antibodies. Raf activates the MEK ½. These molecules inhabits the growth and the signaling to ERK ½ (Extracellular signaling regulated protein kinase) and thermogenesis differnatiatia started. Weight of body started to loss and it causes cancer.

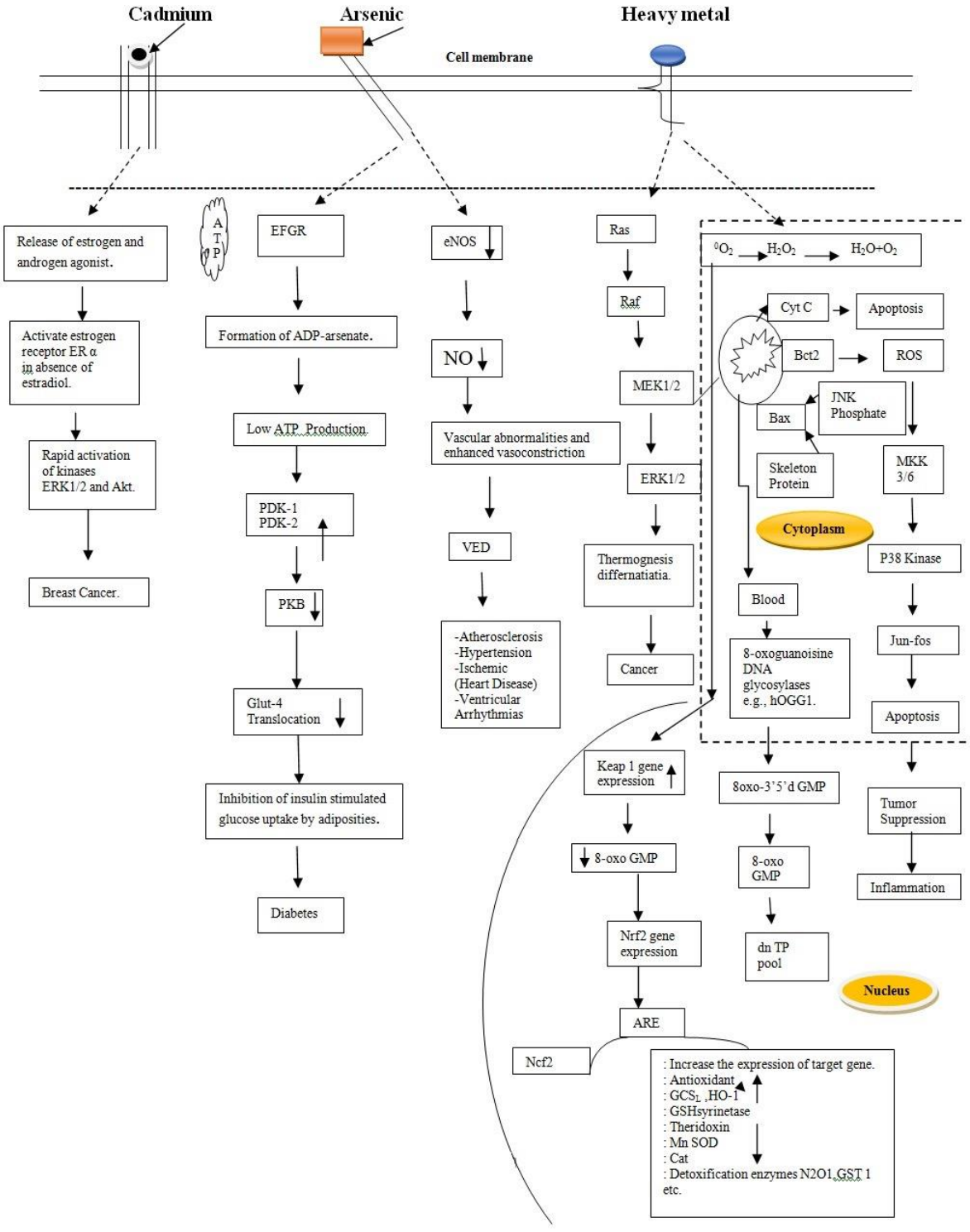

Fig .4. Heavy metals induced metabolic disturbances in human biological system (Source: Filomeni *et al*., 2015; Pup *et al*., 2016; Weil *et al*., 2014).

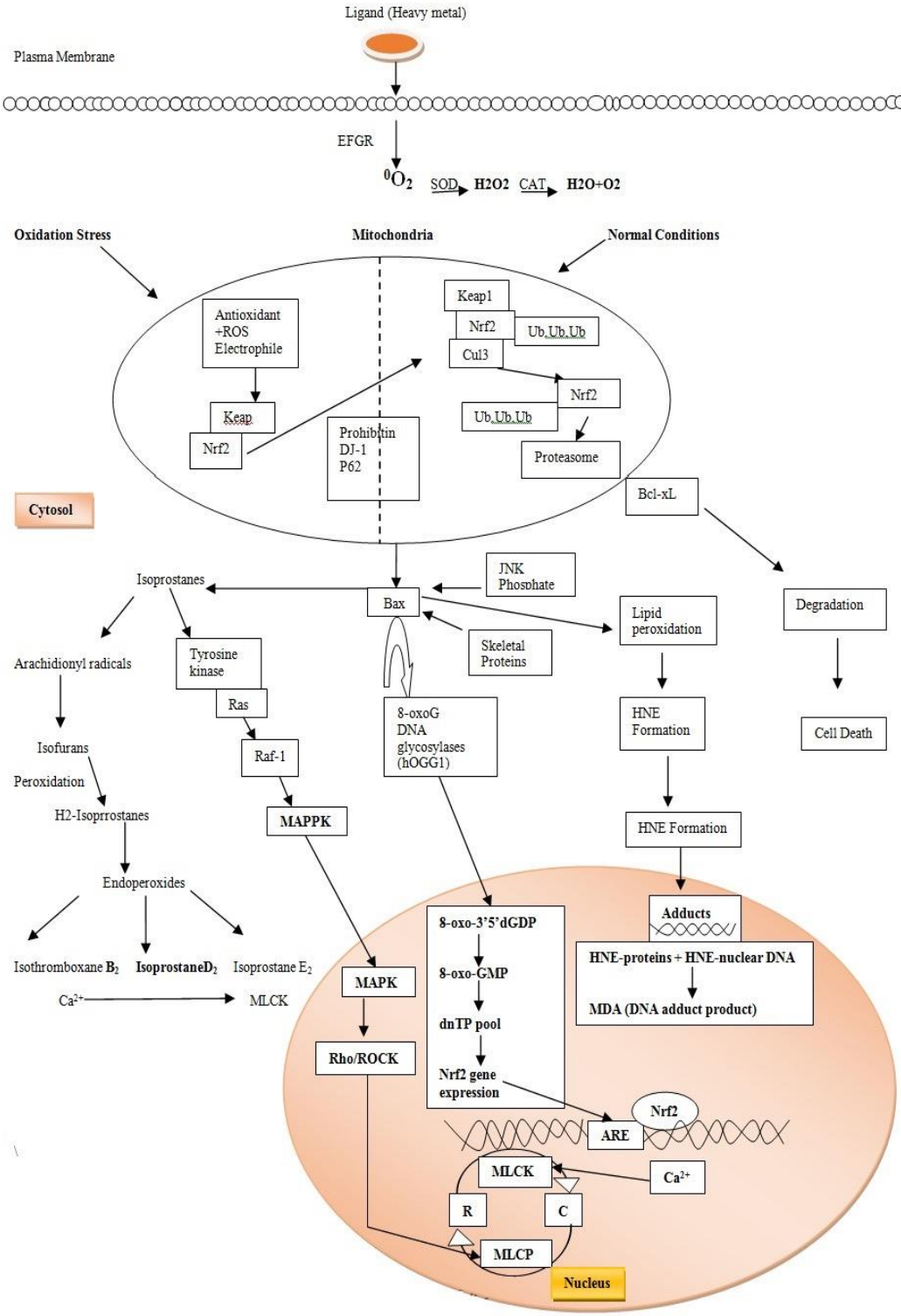

Fig.5. Biochemical Mechanism of formation of MDA, 8Ohg and isoprostanes in response to heavy metals biological system (Source: Birben *et al*., 2012; Filomeni *et al*., 2015; Liu *et al*., 2014).

Explanation of Fig .5. Epidermal growth factor receptor (EGFR) on the cellular membrane that controls the signaling and molecular organization. EFGR is made up of protein and it is present on cell membrane. Heavy metals act as ligands and form compound or complex with organic molecules. Generation of ROS activate NADPH and changes in to superoxide anion radical O^{2-}, NADPH changes in to $NADP^{+}$ and H^{+}. Glutathione (GSH) is non enzymatic and superoxide dismutase (SOD), catalase (CAT) changes the molecule of ground oxygen to hydrogen peroxide (H_2O_2) in to H_2O and $O_2^{\cdot}$ As we know the mitochondria is the power house of a cell that provides ATP to intracellular organelles. In normal condition Keap I is working as a adaptor in KeapI is working as a adaptor in mitochondria. Keap I activate the nuclear receptor factor Nrf_2 which is a member of related protein families of (P45 Nf $-E_2$, Nrf_1, Nrf_2, Nrf_3) where Cul_3 scaffolding protein that binds ubquitin (Ub) and keap I protein. Nrf_2 also activate the antioxidant response and prevent the cell from cancer.

The activity of proteome is required for self renewal of cells. Under the stress condition the Bcl-xl (B-cell lymphoma extra large)/ control the program of cell death. Bax is present in cytoplasm and moves to the outer membrane of mitochondria and in normal condition the death of cell happens-Jun N-terminal protein kinase (JNK) function is to promote the process of apoptosis. In the process of lipid peroxidation free radicals attack on lipid layer and steal the electrons and variety of oxidation products formed. Hydroxynonenal (HNE) and malondialdehyde (MDA) also formed during this process. Protein and HNE , nuclear DNA forms DNA adduct is MDA.Under oxidative stress different antioxidents like ascorbate (ASA) , glutathione (GSH) and catalase (CAT), superoxide dismutase (SOD) become active. Keap and Nrf_2 working as a cytoplasmic regulator. DJ-I is a protein and working as a cytoprotective , where P-62 is also protein. It is used to bind ubiquitin protein and also play protective role. Bax and protein together decrease the apoptosis level of cells. ROS form different oxidized bases nucleotides pools. Nrf_2 works as a cytoprotector through the interaction with other target genes and antioxidant response element (ARE) sequences that act as enhancer on target gene promoters. The isoprostanes are formed due to peroxidation of arachidonic. Mitogen activated protein kinase (MAPK) activity regulated by ROS. Isoprostane act through myosin light chain phosphate. Where Ras/ Raf /MAPK are involved in cell cycle and stimulate angiogenesis. Rho associated protein kinase of Rock. Rock and MLCK play role in thrombin induced permeability. Myosin light chain kinase (MLCK) activation is integrated with MLCP (Myosin light chain phosphate) inhibition developed genetically encoded sensors. Isoprostanes are autoxidation products generated from arachidonic acid when concentration of Ca^{2+} ions in cells increase it also increase the concentration of MLCK.

CONCLUSION

Some heavy metals are toxic at low concentration (Pb, Hg etc) and some are toxic at high concentration (Zn, Cu, Se etc). The heavy metals are accumulating in soil and plants from industrial water and then through food these metals enter in to human and animal body. ROS are produced in plasma membrane and also in mitochondria. Heavy metals disrupt the redox status of cell. Interaction of heavy metals with electron transport activity and membrane dismantling the biological macromolecules deterioration, ion leakage, lipid peroxidation and DNA strand damage. Consumption of high level of heavy metals result increased manufacture of ROS. ROS play role in immunity, impairing many functions and promote the binding of viruses and causes different diseases in body like cardiac diseases, lung cancer, diarrhea and long period diseases causes cancer, anemia, infection in gastrointestinal tract and irritation of skin. ROS act as a catalyst and damage tissues. Different heavy metals have different penetrating power and causes different diseases.

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