Review

An insight into the ameliorative effects of melatonin against chromium induced oxidative stress and DNA damage: a review

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ABSTRACT

Chromium (Cr), a ubiquitous metal, has become a potent pollutant due to global industrialization, leading to pollution of air, water, and food that impacts human health. The most stable forms of Cr are Cr(III) and Cr(VI) (the major product of industrial activities). Cr(III) is a micronutrient essential for maintaining normal blood glucose and lipid profiles in our body but it can also form Cr (III)-DNA adducts. In addition, it directly produces reactive oxygen species (ROS) via Fenton and Haber-Weiss reactions; leading to tissue injuries. Cr (VI) has the capacity to generate Cr(V), Cr (IV), and Cr(III), respectively under suitable conditions. These intermediates also damage to biological macromolecules by interactions with several enzymatic and non-enzymatic antioxidants. For example, Cr(III) can make double DNA strands breaking to inhibit DNA replication, induce DNA oxidation, and DNA adducts formation. All of these lead to the development of malignancy. Melatonin, a potent radical scavenger as well as a metal chelator, effectively chelates Cr(VI) and prevents DNA oxidative damage. Melatonin can upregulate the gene expression of several antioxidant enzymes, and thereby, maintains cellular integrity from the oxidative stress. Thus, melatonin can be a prime molecule to protect against Cr(VI) induced cytotoxicity and genotoxicity. This review aims to highlight the potential benefits of melatonin on Cr(VI) induced oxidative stress and DNA damage.

Key words: Chromium, oxidative stress, reactive oxygen species (ROS), DNA damage, DNA adduct, cytotoxicity, genotoxicity, antioxidant, melatonin.

INTRODUCTION

For decades, huge quantities of pollutants have been emitted into the environments due to substantially global industrialization. Unlike most organic contaminants, metals bring more severe biohazards to organisms since they are non-biodegradable and can accumulate in the tissues of organisms via the food chain (1, 2). There are various heavy metals present in nature, among them Cr has a very narrow concentration margin between its beneficial and toxic effects

for organisms (3). It is an essential nutrient but it also acts as a potential carcinogen (4). Thus, Cr is referred as an "essential metal with potential for toxicity" (5).

Cr is the 21st most abundant element found in the earth's crust usually as chromite ($FeCr_2O_4$) (a relatively insoluble soil mineral), at about 100 ppm (6, 7). Cr was first discovered by Vaquelin in 1797 from crocoite ($PbCrO_4$). It has an atomic number of 24 and a high atomic weight of 52. It exists in several oxidation states ranging from -2 to +6. The trivalent (Cr-III), and hexavalent (Cr-VI) states are the stable forms of Cr (8). Cr(III) is an essential micronutrient; widely used as a dietary supplement. It is the most stable and biologically active form of chromium. Cr(III) not only potentiates the action of insulin but also improves glucose tolerance (9–12), by facilitating the binding of insulin with the receptor in the cell surface (13). Studies also reveal that the supplementation of Cr(III) to patients with heart diseases increases HDL but decreases the VLDL cholesterol levels(14–16). Thus, it is essential for carbohydrate and lipid metabolism(17, 18).

Cr(VI) is a highly toxic compound and is mostly used for industrial purposes including in metallurgy (67%), refractories (18%), and chemicals (15%) (19). [Cr(III) is also used for chemical manufacturing but in a lesser extent, compared to Cr(VI) (20)]. Cr(VI) is also naturally obtained from the chromite ore in the form of sodium chromate (Na_2CrO_4), sodium dichromate ($Na_2Cr_2O_7$), and chromium oxide (CrO_3). Other oxidized forms of Cr are also present in nature such as potassium chromate (K_2CrO_4), potassium dichromate ($K_2Cr_2O_7$), chromic acid, etc. (21). The most common routes of Cr(VI) exposure include occupational as well as non-occupational exposure with ingestion of contaminated water and food (22). Environmental Cr contamination is the consequence of various anthropogenic processes; one of the major causes is the discharge of effluents from the tanneries and industries into water (23). The United States Environmental Protection Agency (USEPA) has identified Cr(VI) as one of 17 chemicals and one of the top 20 contaminants that need to be treated since it possesses a great threat to human health (24). It is well known that transition metals cause oxidative tissue damage (25). Cr is also a transition metal. Cr(VI) can deplete glutathione and protein-bound sulfhydryl groups (26) and generate a large number of reactive oxygen species (ROS) including hydroxyl radical ($HO^{\cdot}$), superoxide anion radical ($O_2^{\cdot -}$), or hydrogen peroxide (H_2O_2) through various mechanisms (Fenton and Haber–Weiss type reactions) (25, 27–29) and cause oxidative damage in cardiac (30), hepatic (31–33), renal tissues (32,34) as well as cause toxic hepatitis (35), immunotoxicity (36, 37), and genotoxicity (38–40).

Cr(VI) is also toxic to the plants. It stalls the various physiological processes in plants such as germination, photosynthesis, and water balance (41–43). It accumulates in various parts of plants (42, 44, 45) thereby, reducing the biomass, chlorophyll content, and relative water content of the plants and impedes the growth of roots, stems, and leaves (41). Cr(VI) causes overproduction of H_2O_2, and malondialdehyde (46, 47) and aggravates electrolytes leakage and mutagenesis in plants (42).

It appears that suitable antioxidants are essential to detoxify the Cr-induced oxidative damages in organisms. Among various potent antioxidants, melatonin seems the best choice for this purpose (48, 49). Melatonin (N-acetyl-5-methoxytryptamine) is primarily secreted from the pineal gland of vertebrates at night, also known as a sleep promoter (50–52). Recently, high levels of melatonin have been identified in the extrapineal tissues (Table 1). For example, the gastrointestinal tract generates 400 times higher concentrations of melatonin than that in the pineal gland (53, 54). The locally generated melatonin exerts its potential beneficial effects on those organs and tissues (Table 2). It is of notice that the metabolites of melatonin, N^1-acetyl-N^2-formyl-5-methoxykynuramine (AFMK) and N^1-acetyl-5 methoxykynuramine (AMK), also exhibit the antioxidant capacity (55–57) to further intensify the melatonin's activity as a potent antioxidant. In addition, melatonin can effectively chelate metal (58, 59) with high efficiency (60). At the level of molecular mechanisms, melatonin possesses

antiapoptotic activity (61, 62), modulates the activity of mitochondrial permeability transition pores and reduces mitochondrial depolarization (63), downregulates gene expressions of cyclooxygenase (COX) and inducible nitric oxide synthase (iNOS), and inhibits the production of nitric oxide, prostanoids, leukotrienes (64, 65) with potent anti-inflammatory activity.

As to the plants, Cr(VI) can cause adverse effects on their growth (66–68) which can be prevented by melatonin to minimize the Cr(VI) uptake in all parts of the plant (roots, leaves, shoots) (69). Ayyaz *et al*.(70) have also reported that melatonin mitigates the toxic effects of Cr(VI) on the growth of *canola* by harmonizing photosynthesis and regulate electron transport flux to protect against oxidative damage.

Based on the evidence, we hypothesize that melatonin may protect against chromium-induced oxidative stress and toxicity in organisms.

Table 1. List of extrapineal melatonin sources.

Extrapineal tissues and organs	Biological fluids
Brain, retina, lens, cochlea, harderian gland, airway epithelium, skin, gastrointestinal tract, liver, kidney, thyroid, pancreas, thymus, spleen, immune system cells, carotid body, endothelial cells, heart, skeletal muscle, placenta, testes, ovaries, cerebral cortex, and striatum.	Cerebrospinal fluid, saliva, bile, synovial fluid, amniotic fluid, and breast milk.

Table 2. Functions of extrapineal melatonin.

Extrapineal tissues	Functions
Retina	• To protect the outer segment membrane of the photoreceptor against photo-oxidative stress (71).
Skin	• To regulate the redox status of cells and it also involves melanogenesis(54).
Gastrointestinal tract	• To regulate water content in the gut (72). • To facilitate transmembrane transport of ions and electrolytes (73)
Reproductive organ	• To function as autocrine, and paracrine in the regulation of reproductive physiology and to improve the quality of the egg and sperm(54). • To act as the antioxidant and free radical scavenger to protect ovarian follicles during follicular maturation (74, 75). • To bind to melatonin receptors in the ovary maintaining sex steroid secretion at different phases of ovarian follicular maturation and reducing polycystic ovarian syndrome (74).

2. ROLE OF Cr IN PATHOGENESIS OF OXIDATIVE STRESS

To know the biological effects of Cr, it is important to distinguish its valence states. Cr(III) is 10-100 times less toxic than that of Cr(VI) for organisms (4) because Cr(III) is less soluble and poorly absorbed by the gastrointestinal tract (GI tract) (13, 76). However, long-term exposure to Cr(III) can cause genotoxicity (77–80). The reason is that when Cr(III) enters into

the nucleus it can react with DNA to produce mutagenic or clastogenic effects (81, 82). In contrast, Cr(VI) is highly soluble and a powerful oxidizing agent (83). The cytotoxic effect of Cr(VI) is related to its carrier-mediated transport across the plasma membrane, followed by its intracellular reduction to Cr(III) (84), and this nature of Cr(VI) makes it very toxic for organisms in comparison to other species of Cr. According to the International Agency for Research on Cancer (IARC), Cr(VI) is a Group I carcinogen that triggers cancer by multiple complex mechanisms (85).

2.1. Permeability of Cr(VI) into the cell membrane.

In the presence of O_2, Cr(VI) can form two predominant species: 1. Chromate (CrO_4^{2-}) (in the basic condition) and 2. Dichromate ($Cr_2O_7^{2-}$) (in the acidic condition). Cr(VI) in the form of tetrahedral divalent (CrO_4^{2-}) (anion, can cross the plasma membrane easily through chloride phosphate (86) and sulfate anionic carrier (87, 88), against the concentration gradient of the divalent anion$^{(2-)}$. These processes do not involve in active transports. After absorption through the GI tract, Cr(VI) is uptake by cells in different tissues and organs (89). Then the Cr(VI) can be reduced to its most stable intermediate intracellularly. The extracellular reduction of Cr(VI) is also present primarily in saliva, followed by gastric juice of the stomach (90) and in the intestine by bacteria (82). Once Cr(VI) is reduced to its stable state of Cr (III), it is generally retained in the place where it is produced, as it is impermeable to the membrane (79, 90). However, a small amount of extracellular Cr(III) can enter cell majorly by phagocytosis. The maximum toxic effect of Cr(III) usually occurs at the nuclei or mitochondria (91).

2.2. Intracellular/extracellular reduction of Cr(VI).

Cr(VI) can be reduced by the intracellular antioxidants (92). The reduction of Cr(VI) by enzymatic and non-enzymatic antioxidants lowers the intracellular Cr(VI) level and this leads to constant entry of the extracellular Cr(VI) into the cell to maintain its balance (93). Several antioxidants involve in Cr(VI) reduction. These include glutathione (GSH), ascorbate (Asc), thioredoxin (94, 95), cysteine (96, 97), etc., whereas, some enzymes also involve its reduction, such as mitochondrial electron transport complexes, microsomal cytochrome P450/NADPH-cytochrome P450 reductase (98, 99), glutathione reductase (GR), ferredoxin, NADP+ oxidoreductase (100, 101), etc. All of these can reduce chromate effectively at pH 7.4 (90). Both mitochondria and microsomes have the capacity to reduce Cr(VI). NADPH-dependent flavoenzymes possess chromate-reductase activity. On contrary, enzymes that do not contain flavoproteins cannot efficiently react with chromates, such as isocitrate dehydrogenase (ICDH), malate dehydrogenase (MDH), and glutamate dehydrogenase (GDH) (99). As a transition metal, chromium (i) can generate ROS by indirectly oxidizing flavin cofactors to adopt a semiquinone radical (UQ·−) state, and (ii) interacts either with oxygen (under the action of cytochrome P450) or with peroxides (under the actions of myoglobin, hemoglobin, cyclooxygenase, peroxidase, catalase) or (iii) transfers an oxen from the oxygen or peroxide to the metal ion (102). Considering the role of GSH and Asc as the classic antioxidants, it is not yet clear whether they exhibit protective effects against Cr(VI) induced oxidative stress since they reduce it to potentiate the oxidative stress. Thus, it is important to understand the actions of antioxidants on Cr(VI) induced pathology.

2.3. Role of Cr(VI) on the aggravation of oxidative stress.

Similar to iron (Fe) and copper (Cu), Cr is also a redox-active metal. Thus, it can undergo redox cycling to produce a large amount of ROS in cells (25, 26, 29). Each step of Cr(VI) reduction involves the use of H_2O_2 to generates HO· via Fenton-like reactions (eq.1-3) (90, 100,

103–107)**.** In the presence of Cr(VI), endogenous $O_2^{\cdot-}$ anions and H_2O_2 also lead to the generation of HO· radical via Haber-Weiss reactions (eq.4) (90)**.**

$$Cr(VI) + H_2O_2 \rightarrow HO\cdot + Cr\ (V) + OH^- \quad (1)$$

$$Cr(V) + H_2O_2 \rightarrow HO\cdot + Cr\ (IV) + OH^- \quad (2)$$

$$Cr(IV) + H_2O_2 \rightarrow HO\cdot + Cr(III) + OH^- \quad (3)$$

$$O_2^{\cdot-} + H_2O_2 \rightarrow O_2 + HO\cdot + HO^- \quad (4)$$

Superoxide anion (most importantly generated in mitochondria) is also harmful as it reacts with nitric oxide (NO) to produce peroxynitrite ($ONOO^-$), a potent reactive nitrogen species (RNS) (108).

2.4. Mechanisms of Cr(VI) mediated oxidative damage.

Several mechanisms are responsible for lipid and protein oxidation in Cr(VI) induced oxidative damages.
(i) The H_2O_2 and HO· produced by Cr(VI) during Fenton and Haber-Weiss reactions attack membrane lipids causing peroxidation and membrane injury (102, 109–111)**.**
(ii) The reduced intermediates of Cr(VI) bind to proteins, peptides, and amino acids to form protein carbonyls under the presence of H_2O_2 (112)**.**
(iii) Cr(VI) causes both structural and functional alterations on the plasma membrane by altering the proportion of cholesterol and phospholipid by depletion of GSH (113)**.**
(iv) Accumulation of Cr(III) intracellularly and extracellularly induces morphological alterations in the cell surface resulting in the disruption of lipid-protein structures of the plasma membranes that eventually cause loss of cellular integrity (91).

Studies have shown that Cr(VI) exposure to human erythrocytes causes an increment in plasma lipid peroxidation (114–116), protein oxidation, and the decrease in total sulfhydryl content, the activities of superoxide dismutase (SOD), glutathione S-transferase (GST), catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and thioredoxin reductase (TR) (117, 118)**.** In a cell line study, GPX/GR activity shows a biphasic characteristic, that is, it increases at a later stage followed by an initial decrease as a consequence of *de novo* synthesis or reactivation of enzymes (119) after exposed to Cr(VI). Cr(VI) induced oxidative stress also exhibit organ-specific response on different antioxidant enzymes, which also depends on some factors such as chemical composition, days, and routes of treatment. But the increase in lipid peroxidation, glutathione depletion, and nuclear DNA damage are common in all tissues (120–125)**.**

2.5. Effects of Cr(VI) on Sirt-1, Pgc-1α, Nrf-2, HO-1, and NQO1 pathway.

The Sirt-1, Pgc-1α, Nrf-2, HO-1, and NQO1 molecules play an important role in oxidative stress-related signal transductions. Distortion of signals after Cr(VI) exposure causes oxidative damages (126). Silent information regulator 1 (Sirt-1), a NAD^+-dependent deacetylase, which locates in the nucleus and cytoplasm, regulates the gene expression, energy metabolism, and oxidative stress response and also participates in the anti-inflammatory and antiapoptotic processes by deacetylase protein substrate in various signal transduction pathways (127–129). However, peroxisome proliferation-activated receptor-g coactivator 1α (Pgc-1α) is a transcription factor coactivator that controls several cellular metabolic pathways. It improves ROS defense system (130), fatty acid metabolism, and master regulator of mitochondrial

biogenesis and oxidative phosphorylation (OXPHOS) (131), by interacting with specific transcription factors (132,133). Sirt-1 increases the activity of cellular antioxidants by inducing expressions of SOD and GPx in cells via activating transcription of Pgc-1α (134, 135). Cr(VI) inhibits Sirt-1 and Pgc-1α, and thus, it reduces the antioxidant capacity, causes disorder of mitochondrial dynamics and oxidative stress (126, 136). On the other hand, nuclear erythroid 2-related factor-2 (Nrf-2) is a transcriptional regulator that induces the gene expression of the component of cellular antioxidants (glutathione and thioredoxin system) as well as helps in phase I and phase II cellular detoxification of substances (137, 138). Hence, it plays a crucial role against xenobiotics and oxidative stress (137). Nrf-2 also regulates the expression of two antioxidant proteins (139). First one is NADPH dehydrogenase quinone-1 (NQO1), which plays multiple roles in adapting cellular stress (140, 141) and another is heme oxygenase-1 (HO-1), that stimulates cell proliferation/growth, and helps to maintain cellular homeostasis as well as upregulate the expression of antioxidant and antiapoptotic pathways (142–145). The deficiency of HO-1 in the cell causes DNA damage and carcinogenesis (146). Cr(VI) exposure suppresses Nrf-2, HO-1, and NQO1 expressions and leads the tissues vulnerable to oxidative damage.

3. ROLE OF Cr(VI) ON DNA DAMAGE

3.1. Cr(VI) induced DNA damage.

Cr(VI) is an inducer of DNA-crosslinks and DNA strand breaks at pH-7.4 with genotoxicity and carcinogenicity (147). The majority of these alterations are made by its reduced metabolite Cr (III). Cr(III) causes (i) oxidative DNA lesions such as strand breaks, (ii) formation of Cr-DNA adducts, (iii) DNA-DNA interstrand cross-links, and (iv) DNA-protein cross-links (148). These Cr-DNA adducts are considered as the principal genetic lesions for replication inhibition, mutagenesis, and finally cell death (149). In this respect, we need to discuss the potential roles of antioxidants played in this process.

3.2. Non-enzymatic antioxidants.

3.2.1. Association of Cr(VI) related DNA damage with GSH.

GSH is the most important antioxidant and also a prime metal chelator as its thiol (-SH) group has a high affinity to metals (150). The metal chelation activity of GSH seems diminished in the case of Cr(III). GSH can directly reduce Cr(VI) to form Cr (V), Cr (IV), and Cr(III) step by step by donating one electron at a time (95, 101). Cr(V) and Cr(III) are known to activate DNA damaging signals and break DNA double-strands (86). Initially, Cr(VI) reacts with glutathione to form Cr (V)-glutathione complex and glutathione thiyl radical (GS·) (eq.5) (105–107, 151, 152). The Cr(V)-glutathione complex reacts with H_2O_2 to produce HO· through a Fenton-type reaction, leading to DNA damage (105).

$$\text{Cr(VI)} + \text{GSH} \rightarrow \text{Cr(V)-GSH complex} + \text{GS}\cdot \qquad (5)$$

GS· further reacts with one molecule of GSH and produces di-sulfide radical (eq.6) (153) that reacts with molecular oxygen to generate $O_2^{\cdot-}$ (eq.7) (154).

$$\text{GS}\cdot + \text{GSH} \rightarrow \text{GSSG}^{\cdot-} + \text{H}^+ \qquad (6)$$

$$\text{GSSG}^{\cdot-} + \text{O}_2 \rightarrow \text{GSSG} + \text{O}_2^{\cdot-} \qquad (7)$$

The decomposition of Cr(V)-glutathione complex leads to the formation of Cr (IV) and thiyl radical (GS·)**,** both of which continue to produce HO· and Cr(III) (Fenton type reaction). The interaction between DNA and Cr compounds is responsible for strand break (101, 155, 156)**,** along with the catalytical production of HO· which has sufficient potential to cleave DNA (48, 59, 83, 114). Guanine residues of DNA can react with HO· producing radical adducts such as 8-hydroxy-deoxyguanosine (8-OH-dG), a conspicuous marker for oxidative damage in cancer (158, 159)**,** which is significantly increased in the urine of chrome plating workers (160–164)**.** The glutathione-Cr(III)-DNA cross-links are known to be the most abundant lesion, resulting in ternary Cr-DNA adducts (coordination of Cr(III) with DNA phosphates (phosphotriester-type adduct)), accounting for about 80% in cultured cells which have proved as mutagenic in the human cells during replication (149, 165)**.** The cellular concentration of GSH in the presence of Cr(VI) becomes very low due to the inhibitory effect of Cr(VI) on GR (166, 167) or the consumption of GSH during Cr(VI) reduction. Wiegand *et al*.(168) have suggested that generally 3 molecules of GSH are needed to reduce 1 molecule of Cr(VI) and this process is accelerated in the presence of excessive GSH**.** This GSH may be synthesized through the γ-glutamyl cysteine pathway by breaking down the protein for the availability of its precursor amino acid cysteine (169)**.** This is supported by the observation that Cr(VI) exposure increases GSH level up to ~120% in rat liver (170) and kidney tissues following an initial decrease by accelerating protein breakdown for GSH biosynthesis (171)**.** A dramatic increase in Cr(VI) induced DNA strand breaks is associated with an increase in GSH level in cells (172, 173) as GSH is responsible for the reduction of Cr(VI) (174)**.** Further studies show that GSH not only acts as a reductant of Cr(VI) but it also enhances the formation of Cr-DNA interstrand crosslink, which is the principal polymerase arresting lesion responsible for blocking DNA replication (94)**.** Cr-DNA adducts formation simply depends on the production of Cr(VI) intermediates. On the other hand, DNA strand breakage is associated with the production of HO·; thus, the nature of DNA damage solely relates to the formation of reactive intermediates in the presence of GSH (107).

3.2.2. Association of Cr(VI) mediated DNA damage with Asc.

Asc is also an important Cr(VI) reductant that has been extensively studied. Suzuki and Fukuda (175) have shown that Asc is even more reactive with Cr(VI) than GSH. This is confirmed by Standeven and Watterhahn (173)**.** They claim that Asc is the principal non-enzymatic reductant of Cr(VI) in rat liver and kidney**.** Asc-dependent metabolism of Cr(VI) injuries nuclear DNA while sulfhydryls and NADPH-dependent Cr(VI) metabolism has limited effect on DNA damage (176)**.** Electronic paramagnetic resonance (EPR) study shows that the reaction of Asc with Cr(VI) produces ascorbate radical ($Asc^{\cdot -}$), carbon-di-oxide anion radical ($CO_2^{\cdot -}$) and other carbon-based radicals as produced by GSH (eq.8-10) (177–179) and also facilitates the binding of Cr(III) with un-cleaved DNA (180)**.**

$$Cr(VI) + Asc^{H-} \rightarrow Cr\ (V) + Asc^{\cdot -} \quad (8)$$

$$Cr\ (V) + Asc^{H-} \rightarrow Cr\ (IV) + Asc^{\cdot -} \quad (9)$$

$$Cr\ (IV) + Asc^{H-} \rightarrow Cr(III) + Asc^{\cdot -} \quad (10)$$

According to Bielski, those $Asc^{\cdot -}$radicals react with each other to form a dimer that further reacts with H^+ and converts again to ascorbate and dehydroascorbate (DHA) (Eq.11) (181) that then, enters into the Cr(VI) reduction cycle again.

$$Asc^{H-} + H^+ \rightarrow Asc + DHA \quad (11)$$

EPR study also shows that Asc enhances Cr(III) complex by reduction of the long-lived intermediate Cr (V) complex. This indicates that Asc can reduce Cr(VI) directly to Cr(III) and increases DNA-protein crosslinks and produces cytotoxicity (182, 183). Actually, Cr(VI) and Asc can form Cr–DNA adducts by multi-coordinated binding of Cr(III) to DNA which is more resistant to dissociation by chelators (184, 185) resulting in the crosslinking of DNA-Cr-DNA by arresting the guanine specific area in mammalian DNA polymerases (94, 186).

3.3. Antioxidant enzymes.

3.3.1. Association of Cr(VI) mediated DNA damage with NADPH/NADH linked enzymes.

The main mechanisms of microsomal and cytosolic reductions of Cr(VI) associated with antioxidant enzymes (81) are exclusively NADPH-dependent along with the involvement of DT-diaphorase (87, 88, 187). DT-diaphorase (quinone oxidoreductase) can donate two electrons directly to form Cr(III) from Cr(VI) to avoid the formation of Cr (IV) and Cr (V) intermediates (81, 98). In the presence of NADPH, cytosolic Cr(VI) reduction involves a one-electron transfer process that produces Cr(V) to form Cr(V)-NADPH complex using flavoenzyme GR (88, 103, 104). Cr(V) is responsible for DNA single-strand break and inhibition of GR activity while Cr(III) is responsible for DNA-protein crosslinks (182, 188). Inhibition of the activity of GR may be due to the loss of cytosolic NADPH (166). Reduction of Cr(VI) to Cr(III) requires the presence of both microsomal proteins as well as NADPH cofactor since Cr(VI) reduction was not observed at the presence of this cofactor with heat-denatured microsomal protein (99). So, in the absence of these cofactors, chromate reduction does not occur, leading to no oxidation of other components of the microsomal system (88). The cytochrome P-450 electron-transport chain appears to be responsible for the microsomal Cr(VI)-reduction in the presence of NADPH (172). In the presence of NADPH, Cr(VI) can form stable Cr(V)-NADPH complexes such as glucose-6-phosphate (G6P)-Cr (V) complex (98). Incubation of Cr(VI) with microsomes and NADPH results in both single-stranded and double-stranded DNA binding; caused by the interaction between enzymatically generated Cr intermediates and DNA to produce polyoxyriboadenylic acid, polyribocytidylic acid, polyriboguanylic acid, and polyribouridylic acid (189). In the intracellular environment both Cr(VI) as well as Cr (V) complexes can interact with adenine and guanine of DNA, resulting in oxidative damage which is ultimately transfigured to stable Cr(III)-deoxyadenosine (dA)-DNA and Cr(III)–deoxyguanosine (dG)-DNA adducts in human cells to produce bulky DNA, i.e. less repairable and consequently induces mutations (190).

3.3.2. Cr(VI) and Mitochondrial electron transport chain (ETC) enzymes on DNA damage.

Cr(VI) can be reduced by the enzymes of the mitochondrial ETC complex in the inner mitochondrial membrane (191) due to the fact that ETC complex I can donate two electrons to Cr(VI) (192). In the isolated submitochondrial particles (SMPs) of rat liver, under anaerobic condition, the Complex I and IV dependent-Cr(VI) reduction causes the formation of Cr(V) intermediate detectable by EPR spectroscopy and higher rate of oxygen depletion, whereas, complex II has less effect (191). A specific study on complex II of the respiratory chain indicates both succinate and glutamate serve as electron donors in this complex. Succinate in the presence of uncoupler (such as ADP) facilitates Cr(VI) reduction while glutamate-mediated reduction occurs only in the presence of respiratory-chain inhibitors thus, they exhibit different mechanisms on Cr(VI) reductions for NAD-linked or FAD-linked substrates (193). Cr(VI) can also inhibit mitochondrial ETC complexes I and II by reaction with the thioredoxin system[thioredoxin (Trx)/peroxiredoxin (Prx)] to damage mitochondrial proteins. The

excessive Trx/Prx oxidation and thioredoxin reductase (TrxR) inhibition result in loss of mitochondrial membrane potential(192,194**).** Reduction of Trx's by Cr(VI) may be due to the inhibition of TrxR that keeps the Trx's in the reduced state, and the activity of TrxR cannot be reversed by the removal of residual Cr(VI) or by the addition of NADPH (electron donor for TrxR) (195**).** Thus, most of the endogenous antioxidant defense systems are suppressed or damaged after exposure to Cr(VI) accordingly in both time as well as dose-dependent manner.

4. ADVERSE EFFECTS OF Cr IN HUMANS

Generally, human exposure to Cr(VI) is mainly via oral routes (drinking water and foods), inhalation (welding fumes), and dermal contacts (using products such as leather bags, shoes, stainless steel containers, cement, etc.). Bhattacharya *et al.* have reported that a saturated level of Cr(VI) is present in groundwater (in the form of CrO_4^{2-}) and soil at the unregulated disposal site of pre-tanning industrial waste and chromite ore processing residue (COPR) (196). 1-3% of the general population is allergic to Cr compounds which are also known as a "contact allergen". Cr-induced allergic dermatitis (such as hand eczema (197), foot dermatitis (198), hand dermatitis (199) result from direct contact with leather goods (200–202), cement (203), etc. Allergic reactions are triggered by Cr(VI) as well as Cr(III) at a very low concentration (204, 205). Groundwater contamination with Cr(VI) from tanneries causes dermatological, digestive, hematological abnormalities along with GI distress found in community areas (206). Singhal *et al*. have reported that 69.69% of workers in the sodium dichromate manufacturing industry and 56.22% of workers in the chrome plating industry had a disorder of nasal mucous membrane and skin ulcer (207). Exposure to Cr can also cause kidney damage and produce low molecular weight (LMW) proteinuria and acute tubular necrosis (ATN) among the chrome platers and welders (208).

5. MELATONIN: A POTENTIAL THERAPEUTIC MOLECULE FOR Cr EXPOSURE IN ORGANISMS

As mentioned above, Cr(VI) causes oxidative damages; however, the classic antioxidants including glutathione and vitamin C exhibit little protective effects while in most cases they may make the damage worse. It is challenging to find the unique antioxidants that can protect against Cr(VI) induced oxidative stress. Melatonin seems to be one of these unique antioxidants. Its unique properties to protect against Cr(VI) toxicities will be discussed below.

5.1. Direct effects of melatonin on Cr(VI) induced oxidative stress.

Melatonin is a phylogenetically conserved molecule present in almost all organisms. Its primary function serves as a first line antioxidant (209–212)**.** The antioxidant capacity of melatonin is more potent than that of classic antioxidants vitamin C, E, and GSH, etc. (209, 213)**,** and it minimizes both oxidative and nitrosative stress efficiently (214–216)**.** Melatonin can directly scavenge the ROS or upregulate the expression of antioxidant enzymes via its membrane receptors or even its nuclear receptor activation (217)**.** Several physiochemical mechanisms contribute to its high efficiency to interact with ROS (eq.12-14) (218):

Radical adduct formation: Melatonin + $R^{\cdot}$ → melatonin-$R^{\cdot}$ (12)

Hydrogen atom transfer: Melatonin + $R^{\cdot}$ → melatonin $(-H)^{\cdot}$ + HR (13)

Single-electron transfer: Melatonin + $R^{\cdot}$→ melatonin$^{\cdot+}$+ R^{--} (14)

Different from the classic antioxidants, melatonin does not participate in the redox recycle reaction and, thus, is devoid of pro-oxidant activity (219)**.** It can interact with a variety of ROS including singlet oxygen ($^1O_2$) (220–223), peroxyl radical (ROO·) (224–226), hypochlorous acid (HOCl) (227), HO· (51, 223, 228–230), H_2O_2, O_2·- (223). Due to its amphiphilic nature, it can protect the membrane against lipophilic-oxy radicals, and also the hydrophilic radicals originated from the aqueous environment by locating between the polar head group of membrane phospholipid (231)**.** Melatonin attenuates the chain reaction of lipid peroxidation (227, 232–235) to prevent the rigidity of phospholipid bilayer and acts as a mask against radical attack by blocking the site of membrane lipids (236, 237)**.** It reduces the lipoperoxyl radical (LOO·) formation and stabilizes the cell membrane structure by directly neutralizing it (238) or by inhibiting the gene expression of lipoxygenase (239). It also reduces protein oxidation (224, 240) and protects the structure of the cell membrane damage caused by Cr(VI).

Apart from the radical scavenging activity, melatonin also upregulates the gene expression of several antioxidant enzymes such as GPx, GR, SOD, CAT, etc. (239, 241–243)**.** Melatonin and its metabolite AMK also decrease the expression of nitric oxide synthases such as iNOS and mtNOS, thus reducing the level of NO and $ONOO^-$(244–248). In addition, melatonin is also a metal chelating agent (59). It can form di-, tri-, and tetradentate ligands with transition metal (59) to exert its metal detoxification activity. Due to this characteristic, melatonin can chelate up to 95% of metal ions (60). As a result, melatonin treatment relates to Cr and reduces the metal load on hepatic tissues (125)**.**

5.2. Receptor mediated effects of melatonin on Cr(VI) induced oxidative stress.

Some antioxidant activities of melatonin are mediated by its membrane receptors (MT1 and MT2). For example, binding to MT2, melatonin enhances the pathway of Sirt-1 and Pgc-1α, and partially activates signaling to mitochondria for their biogenesis (249). Sirt-1/Pgc-1α signaling pathway is important for maintaining the cellular antioxidant defense system (250), which upregulates the cellular and subcellular levels of antioxidant enzymes including SOD, GPx, CAT (251). In addition, melatonin induces the translocation of the Nrf2 transcription factor from the cytosol into the nucleus, therefore, it enhances gene expression of phase-2 antioxidative enzymes including c-glutamylcysteine synthetase (c-GCS), heme oxygenase-1 (HO-1), and NADPH: quinone dehydrogenase-1 (NQO1) (252) and suppresses the expression of proinflammatory NF-kB/COX-2 pathway (253). Thus, the decreased levels of Sirt-1, Pgc-1α, Nrf-2, HO-1, and NQO1 proteins caused by Cr(VI) exposure can be attenuated by melatonin treatment (126).

5.3. Mechanisms of melatonin on classic antioxidants potentiated Cr(VI) induced DNA damage.

The *in-vitro* study has shown that GSH can enhance metal-induced oxidative stress while melatonin administration reduces the damage with increased GSH level. The recovered GSH level is assumed by melatonin thermodynamically binding with GSH and making GSH be unavailable for metal chelation (254)**.** Moreover, melatonin can increase the activity of rate-limiting enzyme γ-glutamylcysteine synthase in the GSH synthesis pathway (239,255)**.**

Asc, a well-known antioxidant, but in the presence of transition metals, it promotes peroxidation for the bio-molecules including DNA (256)**.** Thus, it is referred as a true paradoxical compound (257) and often used to potentiate oxidative stress in iron or copper system. Melatonin has been successfully used to protect against oxidative stress induced by both Fe^{2+}/asc (258, 259) and Cu^{2+}/asc (260, 261) systems. Thus, it can be assumed that melatonin can also protect the cells from Cr(VI), although it requires intense study**.** Melatonin

not only detoxifies oxygen-derived species but also scavenges other types of species including carbon-centered free radicals (234) produced as reaction intermediate during Cr(VI) reduction by Asc. Melatonin present in the nucleus not only protects forming Cr(III)-DNA adduct but also reduces other DNA oxidative damage (262, 263)**.** For example, melatonin can reduce Cr(VI) induced DNA single-strand break up to 60-80% (264)**.**

5.4. Mechanisms of melatonin on antioxidative enzyme potentiated Cr(VI) induced DNA damage.

The concentrations of melatonin vary in subcellular compartments including cytosol, mitochondria, and nucleus (265–267)**.** The highest melatonin level is detected in the mitochondria. Thus, melatonin effectively protects the mitochondrial membranes as well as mitochondrial DNA from ROS-mediated oxidative damage (268)**.** Mitochondria are the powerhouse of ATP production. In the presence of Cr(VI), mitochondrial function is jeopardized with reduced activity of complex I and IV and ATP production. Mitochondrial dysfunction can cause an apoptotic signaling cascade which can be effectively shielded by melatonin (269)**.** Melatonin increases ATP production by increasing the activity of ETC (265, 269, 270), restricting the mitochondrial membrane permeability pores to increase mitochondrial membrane potential. Castroviejo *et al.* have reported that melatonin as well as AMK increases the activities of Complex I and IV and preserves their normal conditions under oxidative stress (244, 270)**.** As a result, it may also protect against Cr(VI) induced damages to the mitochondria(271)**.**

6. EFFECTIVE CONCENTRATIONS OF MELATONIN USED FOR TOXIC METALS.

Melatonin has been widely used to detoxify the variable toxic metals including Cr. For comparable purposes, its effective concentrations on different metals have been summarized in Table 3.

7. CONCLUSION

Being a transition metal, Cr particularly Cr(VI) induces oxidative stress and DNA damage by producing HO· or by formatting Cr-DNA adducts and DNA strands breaking (single and double-strand breaking). Cr(VI) is classified as a carcinogen due to its ability of causing gene mutations and tumors. Melatonin, a low molecular weight molecule synthesized by mitochondria, is a potent antioxidant. It is an environment friendly molecule with no obvious toxicity to organisms. It is also available from foodstuff with the reported high levels in cereals (rice, wheat), green vegetables, fruits, and beverages (wine, beer, orange juice) that humans consume almost regularly. Melatonin exerts its protective effects on Cr(VI) induced oxidative stress and DNA damage via multiple mechanisms: (i) it chelates Cr(VI) and Cr (III), (ii) it scavenges free radicals, (iii) it reduces the Cr(VI) induced protein breakdown and generates GSH by increasing γ-glutamylcysteinesynthase (γ-GCS) activity, and (iv) it increases the mitochondrial ETC activity thereby protecting against the Cr(VI) induced mitochondrial damage. The protective mechanisms of melatonin against Cr(VI) induced oxidative stress have been summarized in figure 1. Thus, we speculate that melatonin can serve as an important future therapeutic molecule or as an important nutraceutical in the amelioration of Cr(VI) induced oxidative damage in organisms.

Table 3. The effective doses of melatonin on metal-induced oxidative damage.

Metals	Periods of exposure	Dose of metals	Tissues/cells	Doses of melatonin	Time of treatment	Route	Ref.
Cr ($K_2Cr_2O_7$)	-	0.5mM	Cultured hepatocytes of rats	1mM	10 hours	-	(264)
-	15, 30 and 60 days	20mg/kg/day (oral)	hepatic tissues of rats	10mg/kg/day	15, 30 and 60 days	i.p	(125)
($K_2Cr_2O_7$)	35 days	4mg/kg/day (i.p.)	cardiac tissues of rats	20mg/kg/day	35 days	s.c	(272)
Cd) $CdCl_2$	28 days	5mg/kg/day (oral)	brain tissues of rats	10mg/kg/day	28 days	s.c	(273)
($CdCl_2$)	22 days	5mg/kg/day (s.c.)	hepatic tissues of rats	10mg/kg/day	22 days	s.c	(274)
$CdCl_2$	14 days	5mg/kg/day (i.p.)	Ovaries of female CD-1 mice	25mg/kg/day	14 days	i.p	(275)
$CdCl_2$	15 days	0.44mg/kg in alternative days (s.c.)	hepatic, cardiac and renal tissues of rats	10mg/kg/ in alternative days	15 days	Oral gavage	(254)
Iron (Fe) (in the form of adriamycin)	1 day	10mg/kg. in alternativedays (i.p.)	hepatic, and cardiac tissues of rats	15mg/kg/day (prior and after adriamycin treatment	10 days	i.p	(276)
$Fe^{(OH)3}$	28 days	50mg/kg/3 doses/week (i.p.)	hepatic, and renal tissues of rats	10mg/kg/day	28 days	i.p	(277)
$CuCl_2$	-	1mM	hepatic tissues of rats	5mM	-	-	(278)
	14 days	2mg/kg/day (i.p.)	hepatic tissues of rats	12mg/kg/day	14 days	i.p	
$HgCl_2$	1 day	5mg/kg/day (i.p.)	renal, hepatic, lung and brain tissues of rats	10mg/kg/day	1 day	i.p	(279)
($HgCl_2$)	60 days	2 and 4 mg/kg/day (oral)	Thyroid glands of rats	5mg/kg/day	60 days	i.p)	(280)
($HgCl_2$)	3 hours	1, 10, 100µM	sperms of male Wistar rats (*in vitro*)	100µM	3 hours	-	(281)
($HgCl_2$)	30 days	0.5mg/kg/day (oral)	cardiac tissues of rats	4µg/ml/day	30 days	Drinking water	(282)
($HgCl_2$)	60 days	2 and 4mg/kg/day (oral)	hepatic tissues of rats	5mg/ml/day	60 days	i.p	(283)
($HgCl_2$)	60 days	2 and 4mg/kg/day (gavage)	brains of rats	5mg/ml/day	60 days	i.p	(284)
($NaAsO_2$)	30 days	5mg/kg/day (gavage)	testes of rats	25mg/kg/day	30 days	i.p	(285)
($NaAsO_2$)	90 days	10mg/kg./day	renal tissues of rats	25mg/kg/day	Post 14 days treat	i.p	(286)
($NaAsO_2$)	30 days	7mg/kg/day (oral)	renal tissues of mice	250µg/kg/day	30 days	s.c	(287)
($NaAsO_2$)	56 days	7mg/kg/day (gavage)	brains of rats	25mg/kg/ day	24 days	N/A	(288)
($NaAsO_2$)	30 days	5.55mg/kg/day(i.p.)	hepatic and renal tissues of rats	10mg/kg/day	5 days	i.p	(289)
($NaAsO_2$)	30 days	5.55mg/kg/day(i.p.)	hepatic and renal tissues of rats	10mg/kg/day	5 days	i.p	(290)
Lead (Pb)	10 days	10, 15 and 20mg/kg/day (i.p.)	brains and bones of rats	10mg/kg/day	10 days	i.p	(291)
Pb	7 days	15mg/kg/day (i.p.)	stomach, duodenum and spleen of rats	10mg/kg//day	7 days	Oral Gavage	(292)
($AlCl_3$)	7 days	34mg/kg/day (oral)	brains of rats	10mg/kg/day	7 days	i.p	(293)
($AlCl_3$)	120 days	50mg/kg/day (oral)	brains of rats	10mg/kg/day	120 days	i.p	(294)

i.p: Intraperitoneal injection, s.c: Subcutaneous injection.

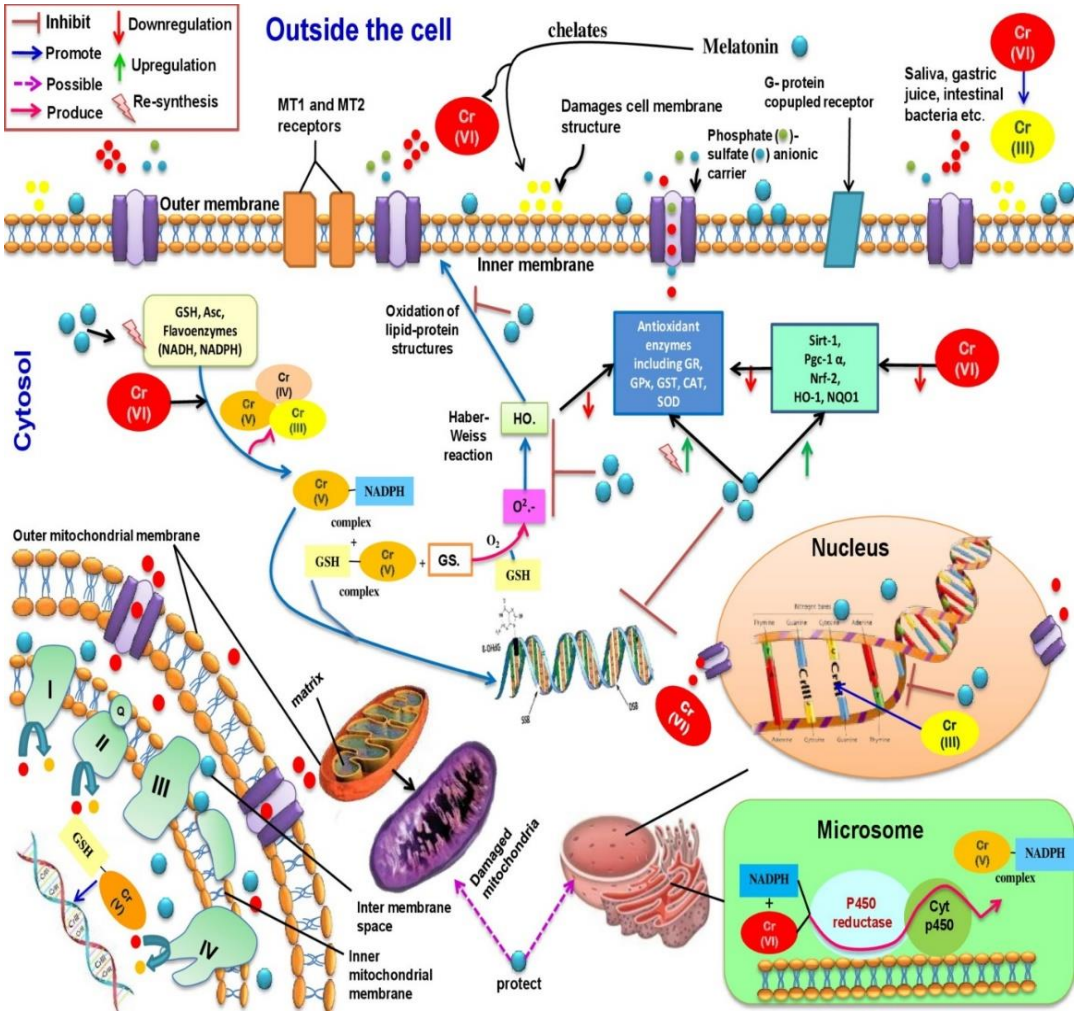

Fig.1. Protective mechanism of melatonin against Cr(VI) induced oxidative stress- and DNA damage.

(SSR)- Single-Strand Breaks, (DSR)- Double-Strand Breaks, (Cr)- Chromium, (GSH)- reduced glutathione, (GS·)- glutathione thiyl radical, (Asc)- ascorbate,(Asc⁻)- ascorbate radical, ($CO_2^{\cdot-}$) *-carbon radical, (8-OH-dG)- 8-hydroxy-deoxyguanosine, (HO·)- hydroxyl radical,* ($O_2^{\cdot-}$) *- superoxide radical, (GR)- glutathione reductase, (GPx)- glutathione peroxidase, (GST)- glutathione-S- transferase, (SOD)- superoxide dismutase, (CAT)- catalase.*

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AUTHORS CONTRIBUTION

Dr. DB and Dr. AC contributed to conception and critical revision of the manuscript and approved it. PG and TD prepared figures, drafted the manuscript, and edited it.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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