Review

# The pleiotropic role of melatonin against chromium-induced cardiovascular infirmities: a mechanistic insight

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**Running title:** Melatonin protects chromium induced myocardial damages

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## ABSTRACT

Currently, cardiovascular diseases are still the number one killer in the world. These include hypertension, coronary heart disease, ischemic heart disease, myocardial infarction, congestive heart failure, cardiac arrhythmias, etc. One of the risk factors for cardiovascular diseases is environmental heavy metal pollution which makes the victims more vulnerable to sudden cardiac death. Chromium (Cr) is one of the metals. Cr(VI) is the most hazardous one among its variants. It is readily across the plasma membrane to cause oxidative damage to intracellular molecules including LDL, proteins, and DNA; therefore, promotes endothelial dysfunction and $Ca^{2+}$ overload in the heart. As to its molecular mechanism, Cr(VI) downregulates the expressions of *SIRTUINS*, *FOXOs*, *PGC-1α*, and *AMPK* and upregulates the *P53*, *Akt*, and *NF-κβ*, causing alteration in metabolic pathways, inhibiting mitochondrial biogenesis, inducing autophagy and apoptosis. In addition, Cr(VI) alters the expressions of Th1 cytokines (IL-1β, IL-2, IL-12, TNF-α, and IFN-γ) as well as Th2 cytokines (IL-4, IL-5, and IL-10) to induce myocardial inflammation. Melatonin, a potent antioxidant, and an efficient metal chelator can neutralize almost all the alterations caused by Cr(VI). Thus, melatonin can be a selected molecule to protect against Cr(VI)-induced cardiovascular toxicity. This review highlights the etiology of Cr(VI) associated heart diseases and the potentiality of melatonin to prevent Cr(VI)-mediated cardiac oxidative stress, apoptosis and inflammation.

**Keywords:** Chromium, oxidative stress, reactive oxygen species (ROS), apoptosis, inflammation, cardiovascular diseases, myocardial ischemia, antioxidant, melatonin.

## 1. INTRODUCTION

Environmental pollutants are destroying our ecosystem at an expedited rate and become a worldwide threat to human health. Heavy metals are the topmost concerning because of their widely distribution made by human activity. These metals are cardiac toxic and can cause cardiovascular disease (CVD), coronary artery disease (CAD), and stroke (1). Several complications such as thrombosis, arrhythmias, hypertension, fibrinolysis, and ischemic heart

disease (IHD) are associated with the increased mortality and morbidity from CVD (2). The association between heavy metals and CVD is well defined. Buhari *et al*. (3) have claimed that the formation of free radicals by heavy metals increased serum lipid levels and oxidation of low-density lipoprotein cholesterol (LDL-C) which results in atherosclerosis (3). In addition, the oxidative stress caused by heavy metals hampers several cellular events, including growth, proliferation, differentiation, damage-repairing and apoptosis, leading to irresistible tissue injuries (4). Moreover, the disruption of the antioxidant defence system further promotes generation of reactive oxygen species (ROS) from mitochondria. The excessive increase of ROS in mitochondria leads to a catastrophic cycle of mitochondrial DNA (mtDNA) damage that ultimately causes heart failure (5).

Although heavy metals are toxic to cells, among them chromium (Cr) is a two-faced metal since it exerts both beneficial and detrimental effects (6). Cr is a naturally occurring compound found extensively in the earth's crust; however, anthropogenic processes such as mining, textile, steel, and chrome plating pollute the air, water, and food. Cr has several oxidation states ranging from -2 to +6. In comparison to different oxidation states, trivalent (CrIII) and hexavalent (CrVI) are the most stable and dominant forms in nature (7). Chromium (III) is a biologically active form of Cr and is widely used as a therapeutic or pharmacological substance that improves glucose tolerance, insulin sensitivity and fat metabolism (8–10). Current studies have cast the doubt on the nutritive action of Cr(III) because it may also bind to DNA to induce genotoxicity and mutation (11, 12). Cr(VI) promotes ROS generation [such as hydroxyl radical ($HO^{\cdot}$), superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide ($H_2O_2$), alters intracellular metabolisms, damages DNA, and disrupts cellular integrity (13–15). In addition, recent studies have reported that Cr(VI) aggravates heart dysfunction (16), myocardial infarction (MI) (17), and other cardiovascular risks (18).

Based on the data of the World Health Organization (WHO-2019), CVDs are the leading cause of death globally. An estimated 17.9 million people died from CVDs, and 85% were due to heart attack (19). This evokes the demand for suitable medicines and therapeutic approaches which can reduce death rate of CVDs. In the path of searching, we found that melatonin as a potent antioxidant was conventionally used for the treatment of heart diseases (20, 21). Melatonin is found in both animal and plant tissues (22, 23). It reduces oxidative stress, lipid peroxidation (LPO), inflammation, necrosis, apoptosis, and mitochondrial permeability transition pore opening (24). The cardio-protective mechanisms of melatonin involve both direct and indirect pathways including antihypertensive, antilipidemic, antiadrenergic, and immunomodulatory activities (23). Evidence showed that melatonin reduced hypertension, hypertensive cardiomyopathy (25, 26), coronary heart disease (CHD) (27), myocardial infarction (28), congestive heart failure (CHF) (29, 30), cardiac arrhythmias (31) as well as sudden cardiac arrest (32). This review is focused on the cardiac toxicity of Cr(VI) as well as the protective effects of melatonin on the cardiovascular damages caused by Cr(VI).

## 2. POSITIVE AND NEGATIVE EFFECTS OF TWO MAJOR CHROMIUM COMPOUNDS ON CARDIOVASCULAR SYSTEM

The cardiovascular system, also known as the circulatory system, is susceptible to oxidative damage. Imbalanced redox status triggers several cellular and molecular damaging pathways that ultimately lead to the progression of hypertension, atherosclerosis, and other vascular complications.

Both Cr(VI), and Cr(III) are used vigorously in industrial processes. However, significant differences are present between them including oxidation states, occurrence, chemical/biological properties, and toxicity as well (33). Cr(III) is used as a nutritional supplement and it is 10 to 100 times less toxic than Cr(VI) due to its poor absorption (about 1%) from the gut (34) as well as its impermeability through the plasma membrane (35). The exposure to Cr(III) is rare from environment since Cr(III) is rapidly oxidized into Cr(VI) in sludge, soil as well as in groundwater under aerobic conditions (36–38). While Cr(VI) can be exposed through water, food, and the occupational area. The United States Environmental Protection Agency (USEPA) has categorized Cr(VI) under the top 20 hazardous contaminants (39), and International Agency for Research on Cancer (IARC) has declared Cr(VI) as a human carcinogen (40).

### 2.1. Beneficial effects of Cr(III) on cardiovascular system.

Studies of the past few decades have focused on the regulatory roles of Cr(III) on fat, protein, and glucose metabolism (9, 41) as well as the maintenance of levels and activities of insulin (34, 42). It promotes glucose oxidation, lipogenesis, and transportation of D-galactose across the membrane mediated by insulin (34). Cr(III) is an essential micronutrient popularly known to form a biologically active organic complex called the 'glucose tolerance factor' (GTF) (43). In mammals, Cr(III) deficiency causes impaired glucose tolerance, high insulin, free fatty acids, low respiratory quotient, and abnormal nitrogen metabolism (44). Cr(III) is thought to be beneficial for cardiac health because it can modulate the levels of cholesterol and specific lipoproteins (45). These activities may be mediated by insulin since insulin has a lipogenic activity (46) to lowering triglyceride synthesis in the liver and enhancing the number of LDL receptors to minimize the level of LDL (47). In addition, Cr(III) is incapable of oxidizing LDL particles (48). Several studies have reported that Cr(III) reduces plaque formation in the area of aortic intima by simultaneously lowering the total cholesterol and increasing the HDL fractions in the blood (49–52). Glucose intolerance and high level of insulin promote the onset of diabetes. Diabetes *mellitus* is the primary reason for large vessel disease and CAD because it reduces prostacyclin production and promotes hyperlipidemia, and platelet hyper-aggregation (53, 54). Thus, Cr(III) deficiency results in type 2 diabetes *mellitus* and cardiovascular disorder (55, 56). Toxic effects of Cr (III) mainly occur only after its conversion to Cr(VI) (7, 57) which will be discussed below.

### 2.2. Toxicity of Cr(VI) on heart.

The environmental contamination of Cr(VI) is a greater risk for human health and it can cause various disorders including liver disease (58, 59), chronic lung diseases (60), skin ulcers (61), allergic contact dermatitis (62, 63), kidney disease (64), immunological disorder (65), etc. The cardiovascular system is highly susceptible to any oxidant. Therefore. the most common disorder caused by Cr(VI) is CVD.

#### 2.2.1. Cr(VI) metabolism.

Cr(VI) is a strong oxidizing agent and highly soluble in water (66). By reacting with molecular oxygen ($O_2$), it can form two different predominant species in different pH conditions, including chromate ($CrO_4^{2-}$) (basic) and dichromate ($CrO_7^{2-}$) (acidic) (7). After entering the

body, Cr(VI) is rapidly absorbed in the gastrointestinal tract (GI tract) and then taken up by the cells of different tissues (67). In the form of the tetrahedral divalent, ($CrO_4^{2-}$), it can cross the plasma membrane via phosphate (68) and sulfate anionic carrier (69). In the intracellular environment, Cr(VI) is gradually reduced into its stable intermediate Cr(III) by utilizing both non-enzymatic reductants such as glutathione (GSH), ascorbate (Asc), and thioredoxin (70, 71), and enzymes including mitochondrial electron transport complex enzymes, microsomal cytochrome P450/nicotinamide-adenine dinucleotide phosphate (oxidized) (NADPH)-cytochrome P450 reductase (72, 73), glutathione reductase (GR) and nicotinamide-adenine dinucleotide phosphate (reduced) (NADP+) oxidoreductase (13, 74). Likewise, extracellular conversion of Cr(VI) to Cr(III) has been reported in saliva, gastric juice (33), and intestinal bacteria (75). Small portion of Cr(III) can enter the intracellular environment through phagocytosis (76) while majority of Cr(III) is incapable of crossing the membrane barrier; therefore, it is trapped in the place where it is converted by Cr(VI) (33).

### 2.2.2. Effects of Cr(VI)-induced oxidative stress on CVD.

CVD is the outcome of complex heterogeneous pathophysiology where oxidative stress has been defined as a common etiology (77). In the intracellular environment, mitochondria and other organelles, including peroxisome and endoplasmic reticulum are considered as the main sources of ROS formation which contributes to ischemia-reperfusion injury (78). Apart from that, several enzymes such as xanthine oxidase, lipoxygenases, cyclooxygenases, nitric oxide synthases, and cytochrome P450 also generate ROS (79). In cardiomyocytes, a transmembrane enzyme, NADPH oxidase (NOX family enzyme), is attributed to produce significant amount of ROS and reactive nitrogen species (RNS) which are associated with heart failure (80, 81). NOX4, which is the predominant isoform of NADPH oxidase expressed primarily in mitochondria of cardiomyocytes, stimulates $O_2^{\cdot -}$ production and promotes apoptosis and mitochondrial dysfunction through mitochondrial swelling, cytochrome C release, decreasing mitochondrial DNA and aconitase activity (82–84).

Cr(VI) is classified as a redox-active metal because it directly undergoes redox cycling to produce a large amount of ROS (85). It facilitates $HO^{\cdot}$ formation by the Fenton and Haber-Weiss reactions (33, 74). ROS attacks the cellular lipid and protein resulting in membrane injury (86–88). Likewise, intracellular and extracellular accumulated Crs modulates the morphological structures of cell surface by disrupting the lipid-protein networks of membranes, leading to loss of cellular integrity (76) and the leakage of cellular content such as intracellular enzymes as well as the incorporation of the viral component into the cardiac sarcolemma and ultimately leads to cardiac myopathies (89). Cr(VI) aggravates LDL oxidation by binding with the tryptophan residue of LDL particles to generate tryptophan radicals in the intracellular lysosomal compartment leading to LDL aggregation. These aggregated LDL particles precipitated and retained in the subcellular compartment and tissue, resulting in lysosomal dysfunction, cell damage, vascular injury, and atherogenic processes, which confers the progression of atherosclerosis (48). As a result, LDL is repeatedly oxidized, and about 90% of lipoproteins are re-entering the circulation by passing through the vascular wall, contributing to the systematic lipo-peroxide load (90). The study exhibits that NADPH-dependent flavoenzymes have chromate-reductase activity by binding with an adjacent cysteine residue (cys46 and 41) of glutathione reductase and also cross-linking with two peptide fragments (tyrosine 67 and asparagine 52) of cytochrome-c to involve in chromate reduction and finally binds with Cr(III)

(73). Therefore, it may bind with Cr(VI) and further stimulate the expression of NADPH oxidase (91).

### 2.2.3. Impacts of Cr(VI) on endothelial dysfunction and cardiovascular diseases.

Endothelium dysfunction is a potential cause of CVD. The endothelium is a highly active monolayer that maintains vascular tone, cell proliferation and angiogenesis, coagulation, cell adhesion, and anti-inflammatory properties by releasing endothelium-derived contracting factor (EDCF) and endothelium-derived relaxing factor (EDRF) (92, 93). Cardiovascular complications are mainly associated with the imbalance of EDRF that results in heart failure, diabetes, atherosclerosis, and hypertension (94). Alterations in the EDRF lower the activity of endothelial nitric oxide synthase (eNOS) that generates nitric oxide (NO), a vasoactive compound (95, 96). NO contributes to regulation of non-enzymatic lipid oxidation, production of inflammatory and vasoactive eicosanoids, modulation of macrophage migration, LDL oxidation, suppression of vascular lesions and free radical detoxification (97). NO is also a vascular relaxation molecule, while under oxidative stress, NO rapidly reacts with $O_2^{\cdot -}$ to form peroxynitrite ($ONOO^-$) at rapid rate (98). A reduction in the bioavailability of NO results in vasoconstriction, thereby increasing the risk of hypertension (99). On the other hand, $ONOO^-$ causes LPO formation with a massive amount of $H_2O_2$ production. This process hampers the energy metabolism by inhibiting the mitochondrial electron transport chain (ETC) as well as Kreb's cycle enzyme aconitase. The outcome is the development of atherosclerosis (100–103). Interestingly, hypercholesterolemia also impairs endothelial-dependent vasodilatation in large conductance vessels, micro vessels, and peripheral circulation (104–106). Components of oxidized LDL such as lys phosphatidylcholine accumulate in the vascular wall and stimulate the production of protein kinase C and $O_2^{\cdot -}$ which can cause atherosclerotic lesions (107, 108). Kojda (96) reports that hypercholesterolemia and CAD together are associated with the imbalance of vascular production of NO and $O_2^{\cdot -}$ which in turn generates other toxic radicals, including $H_2O_2$ and $ONOO^-$ further promoting the progression of other CVDs (Figure 1.).

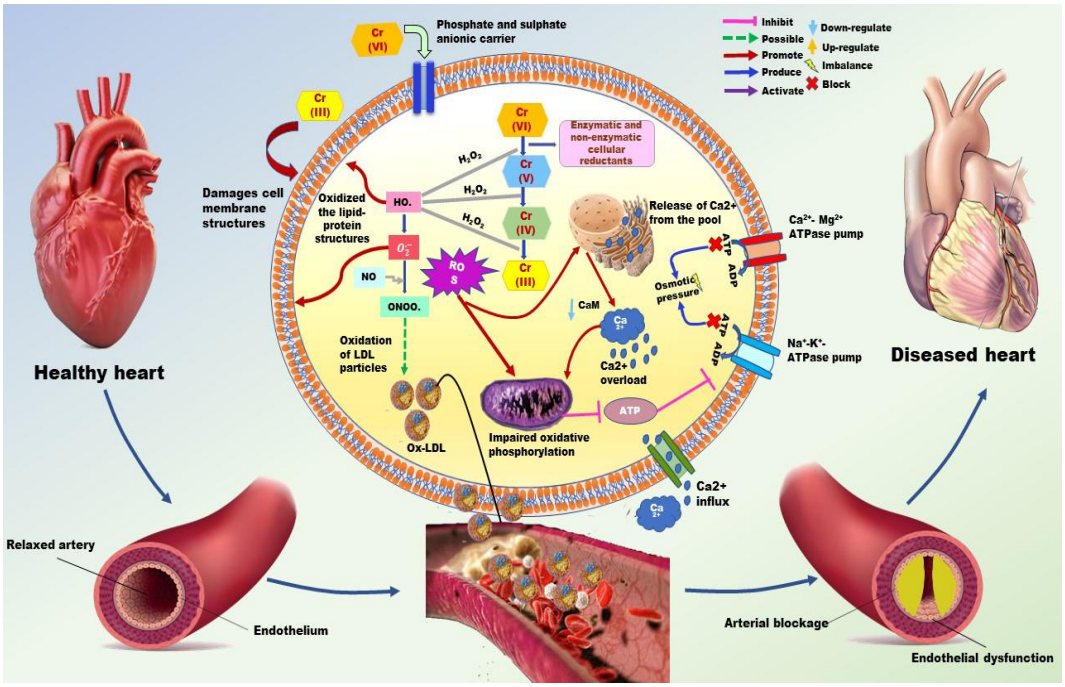
Being a redox-active transition metal, Cr(VI) increases the production of $O_2^{\cdot -}$ which reacts with NO rapidly to produce $ONOO^-$ to enhance the endothelial cell expression. This escalates the intracellular adhesion molecule (ICAM) and adhesive properties of the endothelium (109), leading to endothelium dysfunction and tissue injury. Like other enzymatic and non-enzymatic reductive actions, NOS, by one-step reduction, can reduce Cr(VI) to Cr (V). Cr(V) is further reduced by $O_2^{\cdot -}$ to produce the cytotoxic effect (110). On the contrary, Kushwaha *et al*. (111) claim that Cr(VI) reduces endogenous NO production by inhibiting nitric oxide synthase activity and stimulates ROS production through downregulating the ascorbate-glutathione cycle and glutathione biosynthesis in plant tissue. Although there are no such comprehensible pieces of evidence found on Cr(VI) mediated endothelial dysfunction of heart tissue; thus, essentially further studies need to be done in the future for a clear understanding.

### 2.2.4. Effects of Cr(VI) induced calcium ($Ca^{2+}$) overload on cardiovascular system.

Although ROS can act as an intracellular secondary messenger, excessive ROS induces hypertension due to the vasoconstriction caused by intracellular $Ca^{2+}$ overload (112). In turn, $Ca^{2+}$ overload further increases the ROS generation to form a vicious cycle (113). $Ca^{2+}$ overload also occurs under several other conditions including (1) the increased concentration of sodium in

the intracellular environment (114, 115), (2) the elevated membrane permeability and impaired protein function with the accumulation of long-chain fatty acids in the cardiac membrane (116, 117), (3) lack of adenosine triphosphate (ATP) in the cellular environment during ischemia (118), (4) the ischemia-reperfusion associated adrenergic stimulation (119). Intracellular $Ca^{2+}$ overload causes cellular injury either by interfering with the $Ca^{2+}$ handling proteins or damaging the membrane lipids (120). $ONOO^-$ also causes pronounced injury to the cardiomyocytes by impairing plasma membrane and contractile protein through unconstrained calcium influx (121).

Cr(VI) mediated excessive ROS generation can cause mitochondrial and other organelle membrane damage, resulting in cellular $Ca^{2+}$ overload due to $Ca^{2+}$ influx from the calcium stores (113). Cr(VI) also increases the $Ca^{2+}$ by inhibiting the activities of $Ca^{2+}$- magnesium ($Mg^{2+}$) -ATPase, and sodium ($Na^+$)- potassium ($K^+$) -ATPase. $Ca^{2+}$- $Mg^{2+}$ ATPase is present in the plasma membrane, which plays a crucial role in calcium transportation to maintain intracellular calcium homeostasis (122, 123). Whereas $Na^+$-$K^+$-ATPase is essential for the uptake of $K^+$, that is essential to maintaining the osmotic pressure inside and outside of the cell and regulating the cell volume (124). Calmodulin (CaM) is a calcium-binding protein; calcium-mediated cellular functions are synchronized by binding with CaM (125). The surge in $Ca^{2+}$ concentration simultaneously increases the CaM consumption and reduces the expression of CaM mRNA and protein as well as the $Ca^{2+}$-ATPase activity. Reduced expression of CaM fails to maintain intracellular calcium homeostasis. Eventually, $Ca^{2+}$ overload causes the release of apoptotic factors from mitochondria leading to DNA damage, apoptosis, and necrosis (126, 127) (Figure 1.).




**Fig, 1. A mode of Cr-induced oxidative stress, $Ca^{2+}$ overload, and endothelial dysfunction.**

*(Cr)- Chromium, (Ca)- Calcium, (CaM)- Calmodulin, ($H_2O_2$)- Hydrogen Peroxide, (HO.)- hydroxyl radical, ($O_2^-$)- Superoxide Radical, (NO)- Nitric Oxide, (ONOO.)- Peroxynitrite, (ROS)- Reactive Oxygen Species, (Mg)- Magnesium, (K)- Potassium, (Ox- LDL)- Oxidized Low-Density Lipoprotein, (ATP)- Adenosine- Tri- Phosphate.*

## 3. ROLES OF Cr(VI) ON SIGNAL TRANSDUCTION PATHWAYS INVOLVED IN CARDIAC DISEASES

In cells, various signals are involved in the expressions of genes that play crucial roles in ROS defense, cellular metabolism, mitochondrial biogenesis, anti-inflammation, and apoptosis. These include but not limited to the silent information regulators of transcription-1 (SIRT 1), forkhead box transcription factor (FOXO), AKT, and peroxisome proliferator-activated receptor-gamma (PPAR-ϒ) coactivator 1-alpha (PGC-1α) (59). The details will be discussed below.

### 3.1. Effects of Cr(VI) on expression of SIRTUINS, and FOXO*s* in the progression of cardiovascular diseases.

Among the mitochondrial biogenesis regulators, SIRTs are nicotinamide adenine dinucleotide (NAD+) dependent histone deacetylases that serve different functions by located in separate subcellular compartments including cytoplasm (SIRT 1, 2), mitochondria (SIRT 3, 4 and 5), and nucleus (SIRT 1, 2, 6 and 7) (128). Activities of them are highly dependent on NAD+ (oxidized) and NADH (reduced). SIRTs are primarily involved in various physiological processes such as energy metabolism, stress resistance, mitochondrial function, DNA damage repair, apoptosis, and inflammation (129, 130). Cr(VI) inhibits the expression of SIRT 1, resulting in the initiation of apoptosis (131). Furthermore, Cr(VI) aggravates cellular apoptosis in rat hepatocytes by inhibiting the deacetylation of SIRT 1, as reported by Yang *et al*. (132). Suppression of SIRT 1 by Cr (VI) may also hamper the energy metabolism, reduce stress defense mechanism, and induce inflammation. Thus, it inhibits the activities of rate-limiting enzymes of the tricarboxylic acid cycle (TCA cycle) [isocitrate dehydrogenase (ICDH), succinate dehydrogenase (SDH), and pyruvate dehydrogenase (PDH)], enzymes involved in oxidative phosphorylation (NADH dehydrogenase) and enzymes of gluconeogenic pathway (133).

All SIRTs are equally essential, but SIRT 1, 2 and 3 are well-known cardiac isoforms that protect the heart from oxidative damage by upregulating the FOXO4, FOXO1, and FOXO3a respectively (134). Increased expression of FOXOs enhances the intracellular antioxidant capacity by modulating Mn-SOD activity (135–137). It has been reported that hindrance of deacetylation of SIRT 1 after the Cr(VI) exposure causes inhibition of FOXO1 expression in hepatic tissue resulting in decreasing activity of Mn-SOD, leading to lower stress resistance and increased tissue damage (132). However, SIRT 1 and SIRT 2 also enhance the protein expression of other antioxidant enzymes, including catalase (CAT), glutathione peroxidase (GPx), and thioredoxin (Trx), to protect against oxidative injuries (129, 138, 139). The Cr(VI) diminished the antioxidant enzyme activities [including SOD, glutathione-S-transferase (GST), CAT, GPx, GR, and thioredoxin reductase (TR) due to increased ROS generation (140, 141) or SIRT 1 inhibition. But at low concentration, Cr(VI) tends to increase the activity of both SOD1 and SOD2, respectively (59). SIRT 2 and SIRT 3 boost the production of NADPH which in turn increases the conversion of oxidized glutathione (GSSG) to GSH to mitigate the oxidative stress. For example, SIRT 2 deacetylates glucose-6-phosphate dehydrogenase (G6PDH) to produce NADPH (142). There is a complex mechanism involved in Cr(VI) redox status and SIRT 2 and 3 inhibition. Cr(VI) can be reduced to its intermediates by consuming GSH (71), NADPH (143), and NADPH-linked enzymes, including glucose-6-phosphate (G6P) (72), to reduce their availability in the intracellular environment. Therefore, inhibition of SIRT 2 and SIRT 3 by Cr(VI) also indirectly reduces the production of both enzymatic and non-enzymatic antioxidants,

resulting in the diminution of stress resistance and increased cellular damage. Similar to SIRT 1, SIRT 3 also activates TCA cycle enzymes, including succinate dehydrogenase (SDH) (144) and isocitrate dehydrogenase 2 (ICDH2) (145), and glutamate dehydrogenase (146). SIRT 3, therefore, plays a vital role in the deacetylation of mitochondrial proteins to maintain metabolic homeostasis (147). Mitochondrial function is crucial for cancer cell proliferation and survival (148). SIRT 3 regulates oxidative phosphorylation (OXPHOS) via deacetylating complexes I and III to maintain standard ROS generation (149). Thus, the inhibition of SIRT 3 activity by Cr(VI) alters the mitochondrial membrane potential (MMP) and ATP production (150).

### 3.2. Modulatory effects of Cr(VI) on the expression of AMPK and PGC-1α in the progression of cardiovascular diseases.

On the other hand, adenosine monophosphate-activated protein kinase (AMPK) is found primarily on lysosomes and also distributed in the golgi apparatus, endoplasmic reticulum, and mitochondria (151). Activation of AMPK depends upon the cellular AMP/ATP ratio. Hence, defects in energy production and enhanced energy consumption activate AMPK (152). During energy stress, AMPK regulates mitochondrial gene expression and enhances the gene expression related to glucose metabolism (153), mitochondrial respiration (154) and lipid synthesis (155). Cr(VI) inhibits the formation of neutrophil extracellular traps (NETs) via AMPK signaling, which primarily controls the extracellular killing mechanism that can cause neutrophil toxicity and apoptosis. Cr(VI)-induced NET inhibition is further associated with the down-regulation of protein expression of myeloperoxidase (MPO)/Histone-3 (H3) and the decreased NET is accompanied by the reduced DNA levels in neutrophils both intracellular and extracellularly (156). However, Cr(VI) also inhibits the activation of the AMPK-mediated Nrf2 pathway to induce excessive ROS generation (156). A pathway of AMPK/FOXO3a is a crucial regulator of cellular metabolism. SIRT 6 protects the cardiomyocytes via activating the AMPK/FOXO3a pathway (157). This pathway is activated during metabolic stress, which primarily induces autophagy to preserve cell survival by retaining the energy, but under persistent stress, it provokes autophagic cell death (158). It has been reported that Cr(VI)-induced autophagy via suppressing the AMPK/FOXO3a associated mTOR signaling in rat hepatocytes (123). mTOR is important to regulate cell growth and cellular homeostasis and control cell proliferation by modulating the expression of transcription factor FOXO3a (159). SIRT 1 and AMPK are two primary metabolic sensors that act as the gatekeepers and regulators of mitochondrial biogenesis and respiration by activating PGC-1α (160). Transcription of many genes related to fatty acid metabolism (161) and the mitochondrial metabolism are under the regulation of PGC-1α network (162). PGC-1α activation is primarily dependent on the expressions of SIRT1 and AMPK, which upregulates its activity through phosphorylation (163), acetylation (164,165), and methylation (166). Cr(VI) is known to deactivate the pathway of SIRT1/PGC-1α/Nrf2 (131), which may promote ROS production, reduce activities of antioxidant enzymes, inhibit mitochondrial biogenesis, and cause metabolic disturbances.

### 3.3. Insights of Cr(VI) on P53 signaling pathway in the progression of cardiac diseases.

Being a tumor suppressor, P53 is also a vital regulator of the cell cycle and senescence (167, 168). Activation of p53 decreases intracellular ROS by increasing antioxidant levels (169). Acetylation of p53 results in excessive ROS generation, oxidative DNA damage and

upregulation of growth-suppressive genes (170). Therefore, mutation of P53 are highly associated with metastatic spread and activation of oncogenes (171). Cr(VI) induced oxidative stress promotes the acetylation and activation of P53, which in turn increases the expression of apoptotic protein Bcl2 Associated X (Bax) (13, 172) and alters the activity of anti-apoptotic proteins such as B Cell Lymphoma-2 (Bcl-2) and B Cell Lymphoma extra-large (Bcl-XL) (173). It has been reported that Cr(VI)-induced P53 activation uses hydroxyl radical as a messenger (174) which was generated by Fenton or Haber-Weiss reaction (33). This p53 activation also activates apoptotic machinery by releasing cytochrome c into the cytosol (175). The accumulation of cytochrome c in the cytosol activates caspase-3 (176) which helps in sustaining cellular homeostasis by regulating cell death and inflammation. Accordingly, caspases are broadly classified into two groups that are important for apoptosis (caspase 3, 6, 7, 8, and 9 in mammals) and inflammation (caspase 1, 4, 5, 12 in humans) (177). Activating apoptotic caspase cascade by releasing caspase-3 to the intracellular environment results in cardiomyocyte damage, leading to heart failure (178, 179). Thus, activating apoptotic signaling via P53 and releasing caspase3 by Cr(VI) causes cardiomyocyte injury (174, 180). On the other hand, both SIRT1 and SIRT7 stimulate the deacetylation of P53, thereby reducing cellular senescence and apoptotic cell deaths (181). Thus, inhibition of SIRT1 to increase the acetylation of P53 and P53-upregulated modulator of apoptosis (PUMA) aggravates cellular apoptosis. Inhibition of SIRT1 also upregulates expression of Bax and cleavage of caspase-3, whereas it downregulates the Bcl-2 and Bcl-XL expression (182).

### 3.4. Consequences of Cr(VI) mediated Akt and NF-κβ signaling pathway in the progression of cardiovascular diseases.

In mammals, cellular stress activates various apoptotic pathways in mitochondria. SIRT3 inhibits mitochondrial ROS production and suppresses the ROS-induced Ras-P13K-Akt pathway (137). Cr(VI) can stimulate renin-angiotensin system (Ras) to produce $O_2^{\cdot-}$ by using molecular oxygen and NADPH oxidase and this is responsible for further signal transduction from Ras to nucleus leading to activation of various apoptotic signals (183). Via activation of Ras, Cr(VI) causes endoplasmic reticulum (ER) stress, disrupted redox state and carcinogenesis (184). Protein kinase B (PKB), also known as Akt, is recognized for its anti-apoptotic activity (185). It promotes cell survival by regulating transcription factor nuclear factor kappa β (NF-κβ) and transcription of pro-survival genes (186) and inhibits pro-apoptotic family members of Bcl2, including BAD and BAX (187). But under stressful conditions, Ras depended PI3K activation is associated with pro-survival signaling due to the involvement of Akt. Activated PI3K or Akt revokes apoptosis, but the dominant-negative Akt [(BAX and Bcl2 Associated Agonist of Cell Death (BAD)] can enhances the apoptosis by inhibiting the activation of anti-apoptotic proteins Bcl2 and Bcl-XL (188, 189). Apart from that, another protein called insulin-like growth factor (IGF-1) also controls the P13K/Akt pathway to induce cardiac hypertrophy, which causes the progression of heart failure (190). Chronic exposure to Cr(VI) causes activation of PI3K/Akt depended signaling cascades, i.e., PI3K/AKT/GSK-3β/β-catenin and PI3K/AKT/mTOR to promote carcinogenesis (191). On the contrary, Zhang *et al*. (192, 193) reported that long-term but low-dose exposure to Cr(VI) could inhibit the PI3K/Akt pathway, which can cause premature senescence to L-02 hepatocytes. Cr(VI) increases the phosphorylation of Akt to stimulate the Akt-dependent phosphorylation of the ERK/AMPK pathway, in which ROS initiates mitochondrial-depended apoptosis (194). Dysfunction of mitochondrial biogenesis caused by

Cr(VI) also aggravated apoptosis by downregulating the Akt/STAT3 pathway (195). Members of the signal transducer and activator of transcription (STAT) protein family, especially STAT3, are closely associated with cell survival, tumor appearance, and development (196). STAT3 can inhibit tumor cell apoptosis both directly and indirectly by enhancing the expression of Bcl-2 and Bcl-XL, other anti-apoptotic proteins, and interleukins (ILs) such as IL-6 IL-10, IL-11, *etc*. (197). Despite that, it is also essential for regulating the activity of mitochondrial respiratory chain enzymes, thus, maintaining the production of ATP and reducing the autophagy of cardiomyocytes (198). However, it has also been reported that Cr(VI) can induce autophagy in L-02 hepatocytes, resulting in autophagosome accumulation. Inhibition of the Akt/mTOR pathway is the primary reason behind the activation of autophagy, as described by the authors. Cr(VI) downregulates the protein expression of the critical mediators, including PI3K, AKT, and mTOR, and decreases the phosphorylation of Akt (199). During hypoxia, excessive carbon dioxide retention leads to autophagy of brain neurons due to phosphorylation of PI3K and inhibition of the Akt/mTOR pathway (200). Liang *et al*. (199) claimed that "Cr(VI)-induced autophagy protects L-02 hepatocytes from apoptosis through the ROS/Akt/mTOR pathway".

Conversely, NF-κβ is a versatile protein that simultaneously controls both the inflammatory response and apoptosis. NF-κβ generally regulates the transcription of anti-apoptotic protein, promoting the proliferation and tumor growth (201). The elevated ROS generated by Cr(VI) reduction upregulates the activity of NF-κβ (202) that finally resulting in the development of carcinogenesis (203). Other than excessive ROS production, the accumulation of intracellular $Ca^{2+}$ induced by Cr(VI) also exacerbates the activity of NF-κβ, thereby leading to premature senescence through the ROS/Ca2+/ NF-κβ pathway (204). AP-1 is a dimeric transcription factor consisting of different protein family members such as JUN, FOS, ATF, and MAF. Its activity primarily depends on transcription, post-transitional modification, and interaction with other proteins. AP-1 can act as both oncogenic and anti-oncogenic because it regulates the closely related genes to cell proliferation, differentiation, apoptosis, angiogenesis, and tumor invasion (205). After Cr(VI) exposure, activations of NF-κβ and AP-1 trigger the expression of genes responsible for inflammation and apoptosis (206). Thus, Cr(VI) can alter all the apoptosis and autophagy signalling pathways to cause cell death, resulting in carcinogenesis and heart failure.

### 3.5. Effects of Cr(VI) induced ER stress signaling pathway on the progression of cardiovascular diseases.

The endoplasmic reticulum (ER) is the vital cellular organelle where protein folding occurs. Stressful conditions jeopardize the internal environment of the ER and also impair protein maturation resulting in the assembling of unfolded protein and starting a characteristic stress response known as unfolded protein response (UPR) (207). Although, disturbances in the ER also lead to oxidative stress, disruption of calcium homeostasis, and aggregation of unfolded protein can cause overexpression of both normal and abnormal folded protein (208). Evidence shows that Cr(VI) induced ER stress leads to autophagy and apoptosis (209). ER stress-mediated signal transduction pathway minimizes the accumulation of unfolded proteins by enhancing ER native chaperones, inhibiting protein translation, and accelerating the degradation of misfolded proteins through initiating the UPR. Prolonged ER stress accelerates apoptosis and causes cell death via both mitochondria-dependent and independent pathways (208, 210). Studies have also indicated that Cr(VI) can cause mitochondrial damage by persuading ER stress (211) and

prolonged UPR provokes apoptosis (207). All these alterations mentioned on chapter 3 are illustrated in Figure 2.

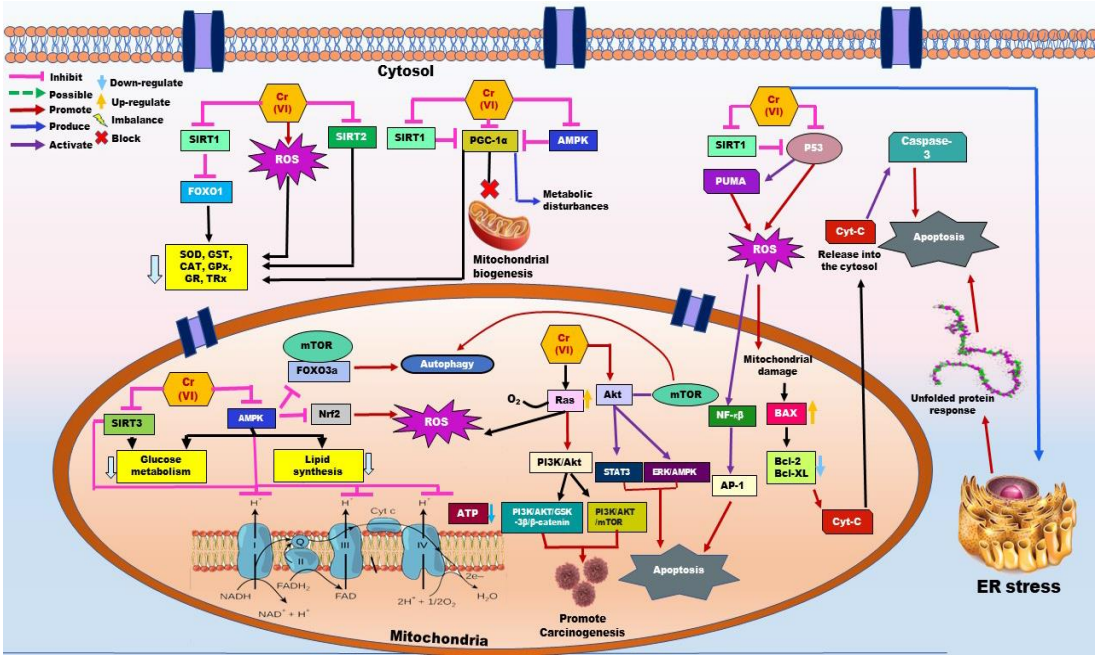



**Fig. 2. Effects of Cr(VI)-induced oxidative stress on cellular signal transduction pathways.**

*(AMPK)- Adenosine Monophosphate-Activated Protein Kinase, (AP-1)– Activator Protein-1, (BAX)- Bcl2 Associated X, (Bcl-2)- B Cell Lymphoma-2, (Bcl-XL)- B Cell Lymphoma Extra Large, (CAT)- Catalase, (ERK)- Extracellular Signal Regulated Kinase, (FOXO)- Forkhead Box Transcription Factor, (GPx)- Glutathione Peroxidase, (GR)- Glutathione Reductase, (GST)- Glutathione-S-Transferase, (NF-κβ)- Nuclear Factor-Kappa β, (PGC-1α)- Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-ϒ) Coactivator 1-Alpha, (PI3K)- Phosphatidylinositol-3-Phosphate, (PKB)- Protein Kinase B, (PUMA)- P53-Upregulated Modulator Of Apoptosis, (RAS)- Renin-Angiotensin System, (SIRT)- Silent Information Regulators Of Transcription, (SOD)- Superoxide Dismutase, (STAT)- Signal Transducer And Activator Of Transcription, (TRx)- Thioredoxin.*

## 4. EFFECTS OF Cr(VI) INDUCED INFLAMMATION ON PREDISPOSITION OF CARDIOVASCULAR DISEASES

The immune system triggers inflammation in response to environmental stimuli such as pathogens, irradiation, and other toxic compounds. In response to tissue injury, the body triggers various signaling cascades at the cellular level to initiate the repairing and healing processes. Pro-inflammatory and anti-inflammatory mechanisms are primarily dependent on stressors (212). For example, everything related to cardiovascular complications, from endothelial cell dysfunction, plaque formation, progression, and rupture to architectural instability, depends on the cellular inflammatory response driven by the cytokines and interleukins (213).

### 4.1. Effects of interleukins and tumor necrosis factor α (TNFα) in Cr(VI) mediated inflammation on the cardiac tissues.

Cr(VI) exposure results in a wide range of immunological responses depending on the dose, time, routes of exposure, and valency and type of chromium compounds (214). Tissue inflammation primarily leads to the release of pro-inflammatory cytokines from monocytes/macrophages, vascular endothelial cells, fibroblasts, *etc*. Pro-inflammatory cytokines trigger the inflammation reaction by up-regulating the expression of C-reactive protein (CRP), IL-6, TNFα, IL-1β, and NF-κB (215, 216), and interferon-gamma (IFN-γ) (217). Evidence demonstrates that Cr(VI) can significantly increase inflammatory cytokines, including IL-6, TNF-α, and IFN-γ (218). However, a negative association was found between the Cr(VI) and CRP levels in blood (219,220). A 2-hour Cr(VI) exposure can significantly increase chemokine IL-8 homolog and cytokine IL-6 (60). In addition, Cr(VI) enhances the mRNA expression of toll like receptor 2/4 (TLR2/4), which subsequently elevates the ROS levels to trigger the inflammation process by increasing the TNFα and IL-1β mRNA levels in a concentration-dependent manner in hepatocytes (59). Cr(VI) dose-dependently inhibits certain interleukins including IL-2, IL-4, and IL-10 by 48%, 57%, and 35% at the concentration of 2μM and 65%, 81%, and 51% at 5μM, respectively (221).

### 4.2. Impacts of T and B lymphocytes in Cr(VI) mediated inflammation on the cardiac tissues.

Interleukins are classified as heterogeneous cytokines involved in activating B and T lymphocytes and macrophages. T cell is the major component of host anti-tumor immunity (222). T cells require activation and clonal expansion of both CD4+ and CD8+ and trigger the immune response to destroy tumor cells (222). Cr(VI) inhibits the proliferation and activation of CD4+ and CD8+ T cells and significantly decreases their viability at the tumor site, resulting in impairment of cytolytic function for the tumors (221). A subsequent increase in CD4+ (helper T cell) and CD8+ (toxic T cell) T lymphocytes have also been found in response to Cr(VI) induced lung injury in the early exposure (60). CD4+ tumor T (Th) cells primarily participate in tumor immunology and are divided into subgroups according to their immunological functions, such as Th1 and Th2 cytokines. Th1 cytokines are generally related to tumor-suppressive activity, including IL-1β, IL-2, IL-12, TNF-α, and IFN-γ, whereas, Th2 cytokines such as IL-4, IL-5, and IL-10 are associated with tumor growth and metastasis (223). Cr(VI) can alter the immune response and may induce a hypersensitivity reaction by stimulating or suppressing the expression of T and B lymphocytes, macrophages, and cytokine production (214, 224).

### 4.3. Influences of neutrophils and macrophages in Cr(VI) mediated inflammation on the cardiac tissues.

Cr(VI) causes a 2-fold increase of macrophages by replacing the neutrophils content at the site of tissue injury (60). Neutrophils and macrophages are involved in phagocytosis to engulf the foreign particles and amplify the inflammatory response through cytokine production (225, 226). In addition, Cr(VI) inhibits the formation of neutrophil extracellular traps (NET), which is responsible for innate immune response, and its release is considered to be a vital part of the extracellular killing mechanism that promotes neutrophil apoptosis (156). Therefore, lower doses

of Cr(VI) stimulate the process of phagocytosis and increase the humoral immune response. In contrast, higher doses of Cr(VI) depress the phagocytic activity of alveolar macrophages and the humoral immune response (227).

### 4.4. Effects of Cr(VI) induced IFN- y˙ and inflammation on the myocardial tissues.

IFN-y˙ is a cytokine primarily secreted from the activated T cells that can activate macrophages, stimulate antigen production, and mediate antiviral and antibacterial activity (228). A positive correlation between the Cr(VI) content of the blood and IFN-y˙ production has been reported (229). IFN-y˙ upregulates the expression of other Th1 cytokines such as TNFα and IL-12, reduce macrophage polarization, inflammation (230) and the activity of Th2 cytokines of IL-4 and IL-5, to reduce atherosclerotic lesions (231). The Cr(VI) induced IFN-y˙ release may activate Th1 cytokines and macrophages to promote microbicidal activity and upregulate the class II MHC (major histocompatibility complex) to maintain the host defense system primarily (229). On the contrary, other studies have reported that the enhanced IFN-y˙ causes severe cardiovascular complications. IFN-y˙ inhibits the production of smooth muscle cells (SMCs) in collagen that weaken the fibrous structure of plaque and make it vulnerable to rupture, which is responsible for developing a thrombotic complication (232). SMCs protect an integral part of the plaque by forming a thick fibrotic layer to stabilize it, preventing the plaque rupture (233).

### 4.5. Effects of cyclooxygenase-2 (COX2) in Cr(VI) mediated inflammation on the cardiac tissues.

COX2, also known as prostaglandin H synthase 2 (PGH2), plays a crucial role in arachidonic acid metabolism (234). It is expressed in several cell types, including monocytes/macrophages, vascular endothelial cells, and colorectal cancer cells, in response to inflammatory cytokines and growth factors (235, 236). COX-2 derivatives such as PGE2 and prostacyclin maintain blood pressure, endothelial thromboresistance, pain, and inflammation. Inhibition of COX-2 in the vascular endothelial, SMC, and cardiomyocytes cause a decrease in PGI2 and PGE2 activities associated with the reduction of NO and endothelial dysfunction (235). This can ultimately lead to increased arterial blood pressure, risk of atherothrombosis, rupture of coronary plaque, myocardial infarction, arrhythmias, and stroke (237).

Data shows that Cr(VI) induces autophagy by activating ER stress through enhancing COX-2 activity (238). Previous studies indicate that the initiation of ER stress triggers autophagy (239). Autophagy is a dynamic process involved with autophagosome and lysosomal degradation (240) through initiating the catabolic process to break down the damaged organelles and large protein aggregates (241). The controversy is also present on the actions of COX-2 and Cr(VI) in heart tissue. COX-2 may have a protective effect on the heart since its inhibition also results in inflammation of the heart tissue. In contrast, heavy metals, especially Cr(VI), cause overexpression of COX-2, which usually increases the inflammation in tissues and cell lines. It is still the argument whether COX-2 is a perpetrator or protector (242). Therefore, whether COX-2 expression in heart tissue after Cr(VI) exposure is beneficial or detrimental remains to be clarified. Judging the data from other heavy metals, such as cadmium, the increased activity of COX2 will enhances the NADPH oxidase activity and reduces the bio-availability of NO. these events can cause endothelial dysfunction and the establishment of atherosclerosis along with hypertension (243).

### 4.6. Effects of NF-κB in Cr(VI) mediated inflammation on the cardiac tissues.

The transcriptional factor NF-κB plays a pivotal role in maintaining inflammatory response by modulation of innate and adaptive immunity. NF-κB regulates the expression of different pro-inflammatory genes and participates in inflammasome regulation. All these actions of NF-κB are made by upregulation of cytokines and chemokines that critically control activation, differentiation, and survival of innate immune cells and inflammatory T cells (244). Cr(VI) markedly increases the activity of NF-κB in rat hepatic tissue, which initiates inflammatory cascades by releasing a wide variety of pro-inflammatory cytokines (245). NF-κB appears to be cardioprotective during hypoxia and reperfusion injury. However, long-term activation of NF-κB promotes heart failure via ER stress-mediated cell death and chronic inflammation by enhancing the expression of specific cytokines including TNF-α, IL-1, and IL-6 (246). The actions of Cr(VI) induced inflammation on predisposition of cardiovascular diseases are summarized in the Figure 3.

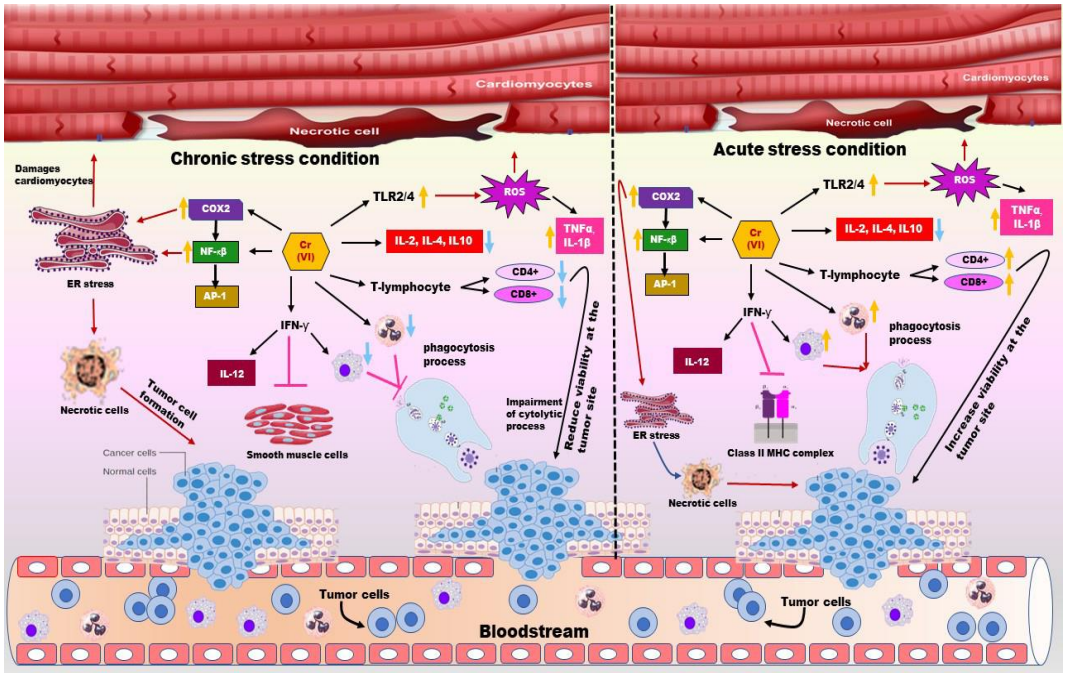



**Fig. 3. Actions of Cr(VI)-induced inflammation on the chronic and acute stressed cardiomyocytes.**

*(COX-2)- Cyclooxygenase-2, (IFN-Y)- Interferon Gamma, (NF-κβ)- Nuclear Factor-Kappa β, (TLR)- Toll-Like Receptor, (TNF-α)- Tumor Necrosis Factor A, (ER stress)- Endoplasmic Reticulum Stress, (IL)- Interleukin, (MHC)- Major Histocompatibility Complex.*

## 5. EFFECTS OF MELATONIN ON Cr(VI) CAUSED CVD

As discussed above, Cr(VI) is toxic to the heart by targeting various intracellular and extracellular molecules that are highly associated with cardiac health. Therefore, to minimize the death rate of Cr(VI) induced cardiac diseases, the introduction of melatonin should be necessary judging from its cardioprotective property. To identify an antioxidant with no or less pro-oxidant

activity and side effects is challenging. Melatonin seems to be one of the unique antioxidants among others (including GSH, vitamin C, Vitamin- E, etc.). The protective effects of melatonin against Cr(VI) toxicities with its distinctive and versatile properties in heart are discussed below.

### 5.1. Evidence of melatonin as a cardioprotective molecule.

Melatonin (*N*-acetyl-5-methoxytryptamine) is a neuroendocrine hormone synthesized from the pineal gland to maintain circadian rhythm, but its original function serves as a potent antioxidant. Other functions of melatonin are acquired during evaluation (247). It is present in animals, plants, and bacteria (248). Melatonin exhibits antioxidant, anti-inflammatory, and anti-cancer activity. It can directly scavenge ROS and RNS and also can stimulate the gene expression of antioxidant enzymes and inhibit the actions of pro-oxidant enzymes(249). Being a nutraceutical substance (250), melatonin chelates metals convincingly up to 95% and reduces metal-catalyzed molecular damage (251). Melatonin synthetic enzymes are found in almost all organs and tissues, including the brain, retina, lens, cochlea, Harderian gland, airway epithelium, skin, gastrointestinal tract, liver, kidney, thyroid, pancreas, thymus, spleen, immune system cells, carotid body, reproductive tract, and endothelial cells. Melatonin also presents in all biological fluids, including saliva, cerebrospinal fluid, bile, synovial fluid, amniotic fluid, and breast milk (252).

The protective actions of melatonin on CVDs including myocardial ischemia-reperfusion injury (MIRI), myocardial hypoxia-reoxygenation injury, pulmonary hypertension, hypertension, atherosclerosis, valvular heart diseases, and other CVDs have been documented (253). In a clinical study, melatonin treatment reduced platelet aggregation, pulsatility index in the internal carotid artery, and catecholamine level with the improved systolic and diastolic blood pressure and the low melatonin levels in the blood are associated with the predisposition of CCD, arterial hypertension, and congestive heart failure (254). The epidemiological evidence showed that the sudden incidents of cardiac events such as MI, sudden cardiac death, and cardiac arrhythmias generally occur in the early morning when the circulating levels of melatonin are low in the bloodstream (27). Additionally, melatonin is able to reduce blood pressure through the following mechanisms: 1) stimulating the hypothalamus; 2) lowering the blood pressure through its antioxidant activity, 3) minimizing the level of catecholamines and 4) dilating the smooth muscle in the aorta wall (255).

### 5.2. Effects of melatonin's receptor and non-receptor mediated activities on cardiovascular diseases.

Melatonin acts through both the receptor- and non-receptor-mediated pathways. In the cardiovascular system (cardiomyocytes, left ventricle, and coronary arteries), melatonin can act on its membrane receptors (MT1 and MT2) (23). The vascular melatonin receptors are functionally linked to either vasocontractory or vasodilatory effects of melatonin (255). The MT1 receptor induces arterial vasoconstriction. Whereas activation of MT2 receptor mediates vasodilation (256). The receptor-independent actions of melatonin are attributed to its antioxidant and mitochondrial-protecting effects (257). Intracoronary-melatonin simultaneously amplifies the coronary blood flow to maintain normal cardiac functions through MT1 and MT2, β-adrenoreceptors, and NO release (258). It is reported that MT1 rather than MT2 efficiently ameliorate MI/R injury and improve cardiac dysfunction, which was accompanied by attenuation

of oxidative stress, ER stress, and mitochondrial dysfunction (259). The activity of MT2 receptors is found to be altered in the sections of isolated coronary arteries, aorta, and left ventricular specimens in dilated and ischemic cardiomyopathy patients compared to the healthy heart donor (260). Mechanistically, melatonin stimulates the MT2/Notch1/Hes1/RORα signaling pathway to protect the primary cardiomyocytes against hypoxia/reoxygenation injury (259).

Melatonin plays an important role in regulating blood pressure (BP) and reducing hypertension. Frank *et. al*. (261) has reported that bedtime melatonin intake lowers the systolic and diastolic BP by about 6- and 4-mm hg without affecting the heart rate in patient with essential hypertension. An increase in systolic and diastolic BP in day-night proportions is around 15 and 25 %, respectively when melatonin level is low. Melatonin supplementation reduces the nighttime blood pressure level significantly in nocturnal hypertensive patients (systolic blood pressure from 136+/-9 to 130+/-10 mm Hg and diastolic BP from 72+/-11 to 69+/-9 mm Hg) (262). The mechanism of action of melatonin to regulate BP involves both receptor and non-receptor mediated pathways (263, 264) including: a. Both MT1 and MT2 receptors are present in vascular smooth muscle cells as well as endothelial cells; activation of these receptors causes a decrease in cyclic AMP and phospatidylino-inositol-4,5-biphosphate hydrolysis resulting in vasodilation and vasoconstriction (265). b. Activation of the MT2 receptor on endothelial cells subsequently enhances the level of NO as well as lowers the cytosolic $Ca^{2+}$ level leading to vasodilation (25,265). c. Melatonin ameliorates the sympathetic responses to reduce orthostatic stress (266). d. Interacting with CaM, it inhibits the $Ca^{2+}$ channel and stimulates the $Ca^{2+}$ pumping to protect the cardiomyocytes (265). e. Melatonin enhances coronary blood flow as well as cardiac contractility through NO release and β-adrenoreceptors (258). f. It modulates cardiac autonomic activity by maintaining circadian pacemaker (267).

### 5.3. Effects of melatonin on Cr(VI)-induced oxidative cardiovascular diseases.

Unlike other classical antioxidants, melatonin does not undergo redox cycling; thus, it does not participate in pro-oxidant activity (268). Melatonin can directly interact with a large number of ROS, including peroxyl radical (ROO·) (269), hypochlorous acid (HOCl) (270), $HO^{\cdot}$ (271), $H_2O_2$ and $O_2^{\cdot -}$ (272). Thus, melatonin can effectively inhibit the Cr(VI) mediated $H_2O_2$, $O_2^{\cdot -}$, $HO^{\cdot}$ production either through scavenging activity or by chelating the metal (273). The cardiac membrane structures are prone to oxidative damage which is associated with various heart diseases (274), therefore, protecting the membrane structure is becoming the priority to reduce the death associated heart diseases. Melatonin is an amphiphilic molecule and it can easily cross the subcellular morphophysiological barrier and located between the polar and non-polar head group of membrane phospholipid to protect the membrane against both lipophilic and hydrophilic radicals emerging from the aqueous environment (275). Melatonin shields the cell membrane structures by directly detoxifying the lipo-peroxyl radicals (LOO·) (276) or indirectly by inhibiting the gene expression of lipo-oxygenase (277). Melatonin also blocks the site of membrane lipid to counteract LPO and prevents the rigidity of phospholipid bilayer (278, 279). Thus, it can maintain cellular integrity and attenuates the Cr(VI) induced membrane damage. Melatonin also modulates the expression of two dominant pro-oxidant enzymes of the heart, such as NOX2 and NOX4 (280). Melatonin pretreatment alleviates ROS overproduction and preserves cell viability by downregulating the Cr(VI)-induced NOX4 *via* activating the MT1 receptor (281).

In addition, melatonin possesses anti-atherogenic activity. Melatonin inhibits LDL oxidation more efficiently than that of vitamin E (282). A study reported a limited protective effect of melatonin on LPO of LDL (283) while other study reported that melatonin reduced the susceptibility of LDL particles to oxidative modifications (284). Melatonin has the ability to suppress the vaso-spastic effect of ox-LDL (oxidized LDL, responsible for the development of atherosclerosis) since it is capable of neutralizing the $HO^{\cdot}$ produced from the fractions of lipid (255). Accordingly, a high level of LDL was found in persons with low levels of blood melatonin indicating elevated levels of ox-LDL impaired melatonin synthesis at night (285). Chronic melatonin administration decreases total serum cholesterol and LDL while increasing the level of HDL in diet-induced hypercholesterolemic rats (286). It has been found that melatonin can suppress the formation of cholesterol and LDL receptor activity by 38% and 42%, respectively, in human mononuclear leukocytes (287). Therefore, it can assume that melatonin is effective in protecting against Cr(VI) induced oxidative cardiac damage.

### 5.4. Effects of melatonin on Cr(VI) induced endothelial dysfunction.

Cardiovascular diseases are highly associated with the influence of inflammatory cytokines**,** ox-LDL, in damaged endothelium. Endothelial dysfunction is primarily caused the adhesion of molecules and the activation of leukocytes (288). Leukocytes adhere to the endothelium via adhesion molecules, including ICAM and vascular cell adhesion molecule (VCAM), leading to a cascade of events toward to endothelial dysfunction and damage (289). Melatonin ameliorates the ox-LDL-induced endothelial dysfunction by decreasing the ER stress and increasing the sustainability of ER homeostasis and mitochondrial function by inhibiting the JNK/Mff pathway. Furthermore, melatonin also reduces the aggregation of ICAM, VCAM, and leukocytes within the endothelial wall, thereby, protecting the endothelial cells against ox-LDL-induced endothelial dysfunction (290). Besides the antioxidant activity, melatonin and its metabolites $N^1$-acetyl-5-methoxykynuramine (AMK) inhibit both inducible and neuronal NO synthases (291). Thus, it reduces NO formation, which diminishes NO interaction with $O_2^{\cdot -}$, inhibiting the formation of $ONOO^-$. Moreover, melatonin and AMK readily neutralize the $ONOO^-$ and its carbon adducts including carbonate radicals and $NO_2$ (291). On the contrary, melatonin increases NO bioavailability and protects the heart against endothelial damage, vasoconstriction, platelet aggregation, and leukocyte infiltration (292). Thus, melatonin may be able to reverse the Cr(VI) induced endothelial dysfunction.

### 5.5. Effects of melatonin on Cr(VI) associated $Ca^{2+}$ overload in myocardial tissues.

Intracellular $Ca^{2+}$overload is associated with hypertension and other cardiovascular complication in humans. Melatonin is a potent ROS scavenger; it curtails ROS production to reduce the $Ca^{2+}$ cytosolic output (293). Melatonin abrogates the $Ca^{2+}$ deposition in the vascular SMCs via activating mitochondrial fusion and mitophagy through the AMPK/OPA1 signaling pathway (294), protecting the mitochondrial membrane and diminishing the $Ca^{2+}$ leakage. An increase in the $Ca^{2+}$ overload induced by Cr(VI) causes inhibition of $Ca^{2+}$ regulating ATPase signaling. Melatonin prevents the suppression of $Na^+$-$K^+$-ATPase, $Ca^{2+}$- $Mg^{2+}$ ATPase (295), thereby, maintaining the intracellular calcium homeostasis and osmotic pressure inside and outside the cell.

## 6. EFFECTS OF MELATONIN ON Cr(VI) PERSUED SIGNAL TRANSDUCTION PATHWAYS IN CVD

Alterations in the intracellular redox status contribute to low melatonin levels in the intracellular environment and apoptosis (296). Melatonin alleviates several pathways involving apoptosis. SIRT 1 is one of them, overexpression and activation of SIRT 1 alleviate metabolic and cardiovascular complications. Melatonin treatment increases the activity of SIRT 1 and the expression of SIRT 2 and 3 in cells and tissues (297, 298). An increase in the SIRT 3 activity by melatonin subsequently increases the FOXO3a activity and transcription of SOD2 and CAT (299). Banerjee *et al*. (273) showed that the reduced activity of SOD, CAT, GPx, and GR caused by Cr (VI) was recovered by melatonin treatment at a dose-dependent manner. This may be attributed to the upregulated expression of proteins of SIRT1 and FOXOs by melatonin.

SIRT 1 also regulates cellular metabolic signaling through the acetylation and activation of the coactivator PGC-1α, which instigates mitochondrial transcription factors and promotes both mitochondrial biogenesis and the anti-oxidative capacity (300). An association between AMPK and PGC-1α also exists to regulate energy metabolism, fatty acid oxidation, and mitochondrial biogenesis (301). Therefore, dysfunction of this pathway results in metabolic disorders. Cr(VI) suppresses this SIRT1/PGC-1α pathway while this suppression is significantly attenuated by melatonin via promotion of SIRT1/PGC-1α/Nrf2 and AMPK/Nrf2 pathway (131, 180).

P53 is a tumor suppressor, but its overexpression leads to activation of an oncogene that finally results in cancernogenesis. P53 is just a component of an extensive network which regulates the carcinogenesis (302). An excessive ROS generation in cardiomyocytes caused by Cr(VI) activates the P53 pathway resulting in mitochondrial damage and release of cytochrome c in the cytosol. Cytochrome c upregulates Bax and downregulates Bcl-2 and Bcl-XL protein expressions leading to cleavage of caspase-3 and apoptosis. Melatonin, as an antioxidant, activates the AMPK/Nrf2 pathway to inhibit ROS generation and protects the cardiomyocytes from oxidative stress and apoptosis (180).

The Ras mainly maintains vascular homeostasis, blood volume, and electrolyte composition (303). But Ras also modulates melatonin synthesis by establishing the circadian rhythm. On other hand, melatonin can suppress Ras activity by deactivating the Ras blockades (304). Currently it is found that melatonin can suppress the overexpression of Ras (305). Thus, melatonin may ameliorate the Cr(VI) mediated overexpression of Ras to protect the cell from apoptosis and terminate the carcinogenic signals. Furthermore, melatonin suppresses the proliferation, migration, and invasion of gall bladder cancer cells via arresting the PI3K/Akt/mTOR signaling pathway by inhibiting the phosphorylation of PI3K/Akt and mTOR in a time-dependent manner (306). Chen *et al*. (307) demonstrated that melatonin inhibits AKT phosphorylation through the MT1 receptor, preventing PI3K activation in glioblastoma cancer stem cells. Cr(VI) also downregulates the pathway of PI3K/Akt to induce autophagy. On the contrary, via MT1 melatonin promotes phosphorylation of Akt that activates the PI3K signaling to reduce autophagy of primary astrocytes (308, 309). Whether Cr(VI) promotes apoptosis or autophagy may be depended on the time, and routes of exposure. Thus, it can presume that melatonin can be a protective molecule against Cr(VI)-induced PI3K/Akt mediated apoptosis and autophagy.

Formation of unfolded protein and initiation of UPR are caused by oxidative imbalance in the ER. Melatonin as a potent antioxidant protects cell from apoptosis through modulating the ER stress (207). This is evidenced by melatonin's supplementation suppressing ER stress by

inhibiting ROS generation as well as AMPK activation (310). Melatonin also increases the protein folding ability of ER and decreases the expression and accumulation of ER stress-associated unfolded and toxic proteins (311–313). Thus, melatonin is able to reduce ER stress and protects the cells from autophagy and apoptosis induced by Cr(VI) mediated ER stress.

## 7. EFFECTS OF MELATONIN ON Cr(VI)-INDUCED INFLAMMATION IN CVD

Inflammation is a sequence of responses of the tissues and organs to injury or pathogen invasions. Cr(VI) induces inflammation by triggering diverse inflammatory responses driven by different cytokines (213). Melatonin is considered as a buffering molecule for the inflammation or the immune system. It acts as a stimulant under both basal or immunosuppressive conditions as well as an anti-inflammatory compound in the presence of intensified immune responses, such as acute inflammation (314). The release of cytokines, including TNF-α, IL-1β, IL-6, IL-12, and IFN-γ, and infiltrated macrophages in the tissues cause microvascular dysfunction and organ failure (315). Melatonin blocks the overproduction of pro-inflammatory cytokines, especially TNF-α (316), IL-1β, IL-6 and IL-8 (317, 318) and increases IL-10 levels (319). In addition, melatonin modulates the expression of TLR4-induced inflammatory gene expressions to control the activities of other pro and anti-inflammatory cytokines (320).

Melatonin enhances immune response in aged individuals by boosting the immunosenescence suppressed T lymphocytes, especially the CD4+ lymphocyte. It mediates the activation, proliferation, and differentiation of helper T cells time-dependently (321). Melatonin increases cytokine levels within a short period, leading to the gradual recovery of cytokine expression. Moreover, T/B cell activation in pinealectomized mice was compromised indicating melatonin's critical role in regulation of immune balance by modulating the activation of T and B lymphocytes (322). Presumably, melatonin can alleviate the Cr(VI)-mediated altered immune response.

The pineal gland is also an essential immune target. IFN-γ was found to increase melatonin production from rat pineal glands in an *in vitro*-culture (323). Melatonin can enhance the B cell proliferation and the Th1 cytokines (IL-2 and IFN-γ) production (324, 325). A surge has been found in human cytokine production in the early morning, indicating that the IFN-γ/IL-10 is positively correlated with plasma melatonin (326).

Likewise, other activities of melatonin also contribute to the protection against COX-2 induce chronic and intermittent hypoxia associated myocardial injury (253). Melatonin inhibits transcriptional activation of both COX2 and iNOS by suppressing the acetylation and binding of P52, thus it may hinder the initiation of the inflammation induced by Cr(VI) (327). COX-2-derived prostanoids are associated with vasoconstriction and vasodilation. Melatonin alleviates pulmonary vasoconstriction by enhancing the expression of vasodilator prostaglandins and reducing the expression of vasoconstrictor prostaglandins in pulmonary hypertensive neonates (328). In addition, melatonin persuades prostacyclin synthase expression, enhances the prostacyclin receptor's protein expression, and decreases the activity of COX-2 without changing the expression of the prostanoid vasoconstrictor (thromboxane) pathway (329).

The upregulation of NF-κβ expression induced by Cr(VI) promotes ROS generation and increases the activity of IL-1β with myocardial inflammation which, if uncontrolled, will cause heart tissue damage. Melatonin inhibits the NF-κβ activity by suppressing ROS production through the AMPK/Nrf2 pathway (180). In addition, melatonin also inhibits NF-κβ transcriptional activation and NF-κβ aggravated pro-inflammatory cytokines production to

reduce inflammation (330). The potential mechanisms of melatonin on the Cr(VI) induced CVD are summarized in Figure 4.

## 8. CONCLUSION

Cr(VI) induces oxidative stress and resultant inflammation, $Ca^{2+}$ overload, endothelial dysfunction, and apoptosis in cardiovascular system. Cr(VI) is a classified group I carcinogen and causes carcinogenesis by inhibiting the expressions of different proteins. Melatonin an indolamine synthesized in mitochondria is a potent antioxidant and a metal chelator. It can also be classified as a nutraceutical substance since it is widely present in food staff including eggs, milk, fish, nuts, cherries, vegetables and wine, an integral part of our daily diet. Melatonin exerts its protective effects on Cr(VI) induced oxidative stress, either by chelating Cr(VI) or by scavenging the ROS and RNS; therefore, it normalizes the NO metabolism and reduces the $Ca^{2+}$ overload to protect the cardiac endothelium. Melatonin also maintains the functions of SIRTUINS, FOXOs, PGC-1α, and AMPK to preserve nutrients and energy metabolism and mitochondrial biogenesis while suppressing the overreactions of Akt and P53. Melatonin also buffers the immune system and protects the cardiac tissue from Cr(VI)-induced inflammation by inhibiting activities of pro-inflammatory cytokines and enhancing the production of the anti-inflammatory cytokines. The protective mechanisms of melatonin against Cr(VI)-induced damages are summarized in Figure 4. Thus, we hypothesize that melatonin can serve as a therapeutic as well as nutraceutical molecule to reduce Cr(VI)-induced CVDs clinically.

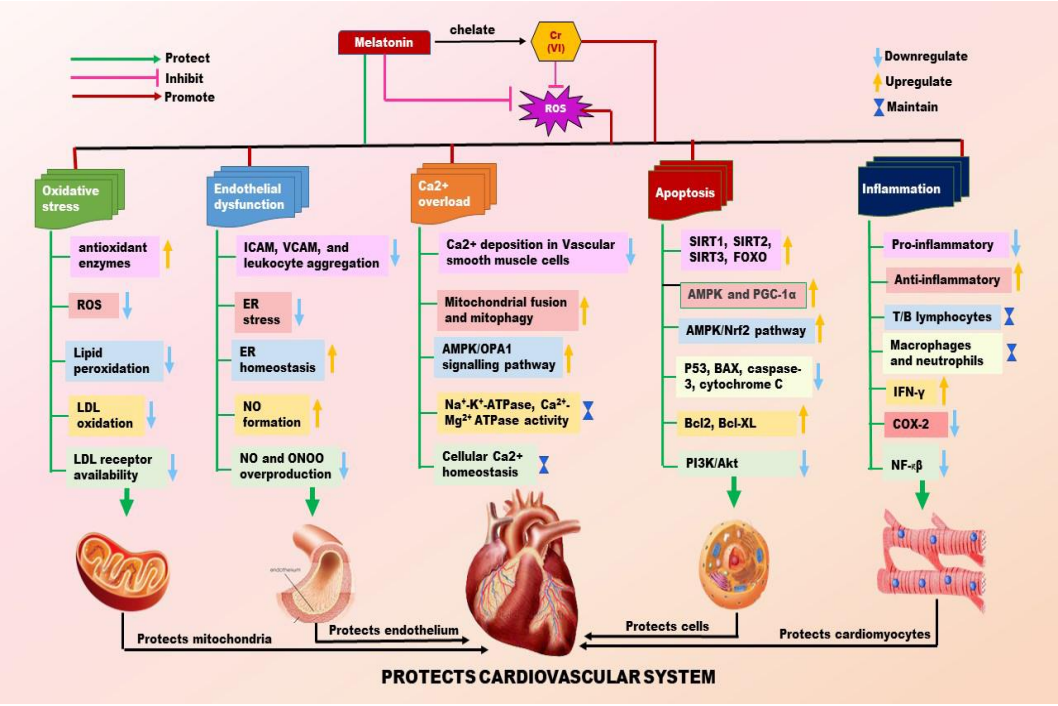



**Fig. 4. The potential protective mechanisms of melatonin on Cr(VI)-induced endothelial dysfunction, $Ca^{2+}$ overload, inflammation and apoptosis mediated CVD.**

*(AMPK)- Adenosine Monophosphate-Activated Protein Kinase, (BAX)- Bcl2 Associated X, (Bcl-2)- B Cell Lymphoma-2, (Bcl-XL)- B Cell Lymphoma Extra Large, (FOXO)- Forkhead Box Transcription Factor, (NF-κβ)- Nuclear Factor-Kappa β, (PGC-1α)- Peroxisome Proliferator-*

*Activated Receptor-Gamma (PPAR-Ɣ) Coactivator 1-Alpha, (PI3K)- Phosphatidylinositol-3-Phosphate, (SIRT)- Silent Information Regulators Of Transcription, (COX-2)- Cyclooxygenase-2, (IFN-Y)- Interferon Gamma, (NF-κβ)- Nuclear Factor-Kappa β, (ER stress)- Endoplasmic Reticulum Stress, (IL)- Interleukin, Nrf-2- Nuclear Factor Erythroid-2 Related Factor-2, (NO)- Nitric Oxide, (ONOO.)- Peroxynitrite, (ROS)- Reactive Oxygen Species, (Mg)- Magnesium, (K)- Potassium, (LDL)- Low-Density Lipoprotein, ICAM- Intercellular Adhesion Molecule, VCAM- Vascular Cell Adhesion Molecule.*

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## AUTHORSHIP

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

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ABBREVIATIONS

$O_2^{\cdot -}$ - Superoxide Anion
AMP- Adenosine Mono-Phosphate
AMPK- Adenosine Monophosphate-Activated Protein Kinase
AP-1 – Activator Protein-1
ATP- Adenosine Tri-Phosphate
BAD- Bcl2 Associated Agonist of Cell Death
BAX- Bcl2 Associated X
Bcl-2- B Cell Lymphoma-2
Bcl-XL- B Cell Lymphoma Extra Large
CAD - Coronary Artery Disease
CAT- Catalase
CHD - Coronary Heart Disease
CHF- Congestive Heart Failure
COX-2- Cyclooxygenase-2
Cr - Chromium
CRP- C-Reactive Protein
CVD - Cardiovascular Disease
EDCF - Endothelium Derived Contracting Factor

EDRF - Endothelium Derived Relaxing Factor
ERK- Extracellular Signal Regulated Kinase
FOXO- Forkhead Box Transcription Factor
G6PDH- Glucose-6-Phosphate Dehydrogenase
GPx- Glutathione Peroxidase
GSH- Reduced Glutathione
GTF- Glucose Tolerance Factor
GTP- Guanosine Triphosphate
$H_2O_2$ - Hydrogen Peroxide
HDL- High-Density Lipoprotein
HO· - Hydroxyl Radical
HOCl- Hypochlorous Acid
ICAM- intercellular adhesion molecule
IFN-ϒ- Interferon Gamma
IGF-1- Insulin-Like Growth Factor
IHD - Ischemic Heart Diseases
LDL-C - Low-Density Lipoprotein Cholesterol
LOO· – Lipo-peroxyl Radical
LPO - Lipid Peroxidation
MHC- Major Histocompatibility Complex
MI - Myocardial Infarction
Mt DNA - Mitochondrial DNA
mTOR- Mammalian Target Of Rapamycin
NAD+- Nicotinamide Adenine Dinucleotide (Oxidized)
NADH- Nicotinamide Adenine Dinucleotide (Reduced)
NADPH - Nicotinamide Adenine Dinucleotide Phosphate
NET- Neutrophil Extracellular Traps
NF-κβ- Nuclear Factor-Kappa β
Nrf-2- Nuclear Factor Erythroid-2 Related Factor-2
ONOO- - Peroxynitrite
ox-LDL- Oxidized LDL
PGC-1α- Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-ϒ) Coactivator 1-Alpha
PGH2- Prostaglandin H Synthase 2
PI3K- Phosphatidylinositol-3-Phosphate
PKB- Protein Kinase B
PPAR-ϒ - Peroxisome Proliferator-Activated Receptor-Gamma (PPAR-ϒ)
PUMA- P53-Upregulated Modulator of Apoptosis
RAS- Renin Angiotensin System
RNS - Reactive Nitrogen Species
ROO·- Peroxyl Radical
ROS – Reactive Oxygen Species
SIRT- Silent Information Regulators of Transcription
SMC- Smooth Muscle Cell
STAT- Signal Transducer and Activator Of Transcription
Th1 And 2- Type 1 And 2 T Helper Cells
TLR- Toll-Like Receptor

TNF-α- Tumor Necrosis Factor A
Trx- Thioredoxin
VCAM- Vascular Cell Adhesion Molecule
WHO - World Health Organization

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