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Review

The Double Face of Metals: The Intriguing Case of Chromium

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Abstract: Chromium (Cr) is a common element in the Earth's crust. It may exist in different oxidation states, Cr(0), Cr(III) and Cr(VI), with Cr(III) and Cr(VI) being relatively stable and largely predominant. Chromium's peculiarity is that its behavior relies on its valence state. Cr(III) is a trace element in humans and plays a major role in glucose and fat metabolism. The beneficial effects of Cr(III) in obesity and types 2 diabetes are known. It has been long considered an essential element, but now it has been reclassified as a nutritional supplement. On the other hand, Cr(VI) is a human carcinogen and exposure to it occurs both in occupational and environmental contexts. It induces also epigenetic effects on DNA, histone tails and microRNA; its toxicity seems to be related to its higher mobility in soil and swifter penetration through cell membranes than Cr(III). The microorganisms *Acinetobacter* sp. Cr1 and *Pseudomonas* sp. Cr13 have been suggested as a promising agent for bioremediation of Cr(VI). This review intends to underline the important role of Cr(III) for human health and the dangerousness of Cr(VI) as a toxic element. The dual and opposing roles of this metal make it particularly interesting. An overview of the recent literature is reported in support.

Keywords: chromium; essential nutrient; toxic element; epigenetics; remediation

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1. Introduction

Heavy metals are pollutants present in the air and in the soil from natural and anthropogenic sources. Among heavy metals, chromium represents a fascinating case. In its prevalent oxidation states, III and VI, it has completely different characteristics in terms of toxicity and essentiality in human health, and behavior in the soil. Cr(III) derives from anthropogenic sources and is an essential nutrient for humans. It has been defined a pharmacologically active element considering its important role in carbohydrate and lipid metabolism and in the maintenance of the structural integrity of nucleic acids [1]. Cr(III) is a constituent of glucose tolerance factor (GTF): this factor is synthesized in vivo from absorbed dietary chromium and it modulates the rate of removal of glucose from blood with an insulin boosting mechanism. Cr(III) improves insulin activity, as it binds to insulin and potentiates its action by about three-fold. Therefore, chromium deficiencies can lead to pathologies associated with carbohydrates and weight loss [2,3].

Recently, the potential utilization of chromium to fight thermal stress in animals has been reported. Heat stress (HS) may influence nutrient digestion, carcass quality and the immune system. Homeorhetic adaptations, generally caused by increased circulation of insulin, may be also altered. Cr(III) prevents HS-induced lipid peroxidation, increases nutrient metabolism and cortisol hormone activity, stimulates the action of insulin in responsive tissues and thus it may act in fighting the side effects of heat stress in animals [4,5]. The required daily dose of Cr(III) is 10–40 µg for children up to six months, and 25–35 µg for other ages [6]. Insufficient dietary Cr(III) also induces symptoms equal to diabetes and cardiovascular

diseases. The deficiency of this metal can cause blood sugar spikes, elevated cholesterol levels and blood pressure. It may also have other consequences, such as lower resistance to infections, atherosclerosis, hormonal imbalance, nervous disorders, fatigue, etc., [7,8].

Cr(III) occurs in several foods and supplementation products. It is largely contained in baker's yeast, red meat, liver, whole grains, red beets; however, it is hardly assimilated (only 3% is retained by body). The most common supplementation products include chromium-picolinate (CrPic), chromium-histidinate (CrHis), chromium-dinicocysteinate (CRDC), and niacin-bound chromium (NBC) [9]. Several studies have been developed to evaluate the safety and efficacy of these supplements as insulin-sensitizing agents useful for prevention and treatment of type 2 diabetes (T2DM) and obesity [10–14]. However, excessive levels of chromium can determine pathological states. In fact, even if Cr(III) compounds are not able to cross cell membranes, they may accumulate around cells causing alterations in cell functions and damaging the cell-membranes. In fact, long time exposure to Cr(III) may lead to skin allergies and cancer [15]. Levina et al. (2008) reported also that the accumulation of Cr(III)-based dietary supplements, such as CrPic could induce genotoxic effects [16]. In the supplements Cr(III) may undergo a series of chemical transformations in biological media.

Products deriving from partial hydrolysis of nutritional supplements containing Cr(III) may give reactive species while generation of highly reactive Cr(VI/V/IV) species and organic radicals may derive from reactions of Cr(III) with biological oxidants. However, it must be considered that Cr(III) compounds possess low bioavailability [17]. Eastmond et al. (2008) reported that the genotoxic effects in vivo are uncommon but they can occur for elevated physiological intake levels of Cr(III) supplements [18]. While Cr(III) is an essential trace element, found in nature in rocks and soil, readily absorbed by plants, hexavalent chromium is mainly an industrial contaminant and is also produced from anthropogenic activities. Cr(VI) compounds present several applications and are vastly used as pigments for textile tints, paints, inks, plastics, corrosion preventing agents, leather tanning agents and wood preservatives [19]. Hexavalent chromium is mainly used in tanneries or industries dealing with metalworking, stainless steel welding, chromate production and the manufacture of chromium pigments [20]. The release of Cr(VI) into the air is mainly due to these industrial processes. Chromium in the environment may be derived by inhalation of contaminated air and water [9,21]. High chromium concentration mainly in water bodies may derive from waste from the ferrochrome industry, such as slag, dust and processed water [22]. Chromium discharge in European Union (EU) waters is subjected to nationwide recommendations, which may vary depending on the type of industry and receiving water body [23]. Cr(VI) is classified by IARC (International Agency for Research on Cancer) as a human carcinogen (class I) [24]. The respiratory tract is the major target for the toxic and carcinogenic action of hexavalent chromium. Acute and chronic occupational exposure mainly occurs by inhalation. This review intends to be an overview of recent research on the double face of chromium as an essential nutrient and as a toxic metal.

2. Chemical Form and Properties of Chromium

Chromium is the 24th element in the periodic table and its symbol is Cr. It was discovered in 1798 by L. N. Vauquelin. It belongs to transition metals and its average atomic weight is 52 g/mol. Its physicochemical properties are summarized in Table 1. Chromium is the first element of the sixth group; it is a steely-grey, shiny, hard and brittle metal. It is the twenty-first most abundant element in the Earth's crust [25]. While it does not react with water, it may react with acids. Chromium may theoretically occur in oxidation states between −2 and +6, but the most common oxidation states are +3 and +6 [Cr(III) and Cr(VI)]. Cr^{2+} is unstable and oxidizes to Cr^{3+} when in contact with air. Elemental chromium (Cr(0)) is not present in nature in the Earth's crust and is physiologically inert. Cr(0) in its inert metallic form and at a concentration of about 11% is found almost exclusively as a constituent of iron alloys as stainless steel. The addition of 8% nickel to this alloy increases corrosion resistance [26]. Chromium owes its name to its many-colored compounds colors such as black, green, blue,

violet, yellow, orange and red; thus, it has been used in paints and pigments. Common uses of chromium are summarized in Table 2. Chromium is both an essential trace element (as Cr^{3+}) ion and an environmental toxicant (as Cr^{6+}). The latter is considered a heavy metal. However, long time exposure to Cr(III) may lead to skin allergy and cancer [15,27]. In aqueous solutions, Cr(VI) may exist as chromate ion (CrO_4^{2-}) or as dichromate or bichromate ion ($Cr_2O_7^{2-}$). Cr^{3+} in aqueous solutions is green, CrO_4^{2-} confers a yellow color to water, while $Cr_2O_7^{2-}$ is orange. Cr(VI) solutions are vigorous oxidizing agents in acidic conditions. Chromic acid (H_2CrO_4) is utilized for cleaning glassware in chemistry laboratories by oxidizing organic residues. In anoxic conditions, a chromium trivalent form prevails, while the hexavalent form prevails in aerobic conditions. Chromate ions, especially potassium chromate (K_2CrO_4), are used as indicators in the titration of chloride ions with silver nitrate in the Mohr method [28], while the potassium bichromate ($K_2Cr_2O_7$) titrimetric method is used to determine chemical oxygen demand (COD), that is the amount of oxygen needed to destroy all organic matter contained in water [29].

Table 1. Physical and chemical properties of chromium.

Atomic number	24
Atomic weight	51.9961 u
Atomic radius	130 pm
Electronic configuration	[Ar] $4s^1 3d^5$
Melting point	1907 °C
Boiling point	2672 °C
Density at 20 °C	7.18 g/cm^3
Heat of fusion	21 KJ/mol
Heat of vaporization	342 KJ/mol
Pauling electronegativity number	1.66
First ionization energy	652.4 KJ/mol
Second ionization energy	1590.6 KJ/mol
Third ionization energy	2987 KJ/mol

Table 2. Uses of chromium.

Form	Uses
Cr(O)	Stainless steel production
	Alloy production
	Metal and alloy manufacturing
Cr(III)	Metal and alloy manufacturing
	Brick lining
	Chrome plating and welding
	Leather tanning
	Textiles
Cr(VI)	Chrome plating and welding
	Copying machine toner
	Chrome plating
	Leather tanning
	Textiles
	Wood preservatives

Cr(III) is a micronutrient essential in humans for the metabolism of carbohydrates, lipids and proteins. It is considered the main trace mineral involved in the amelioration and prevention of hyperglycemia and hyperlipidemia in T2DM, as a component of GTF. Administration of Cr(III) orally may markedly alleviate the diabetic-like symptoms [30]. Cr(III) enhances insulin signaling in different tissues [31]. Additionally, trivalent chromium inhibits hepatic enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase and interferes with cholesterol metabolism [32]. Cr(III) is also involved in the reduction of plasma cholesterol and triglycerides and in the preservation of normal glucose levels in the blood and in the inhibition of oxidative stress [10]. However, recent studies demonstrated that Cr(III) does not induce human low density lipoprotein (LDL) oxidation at pH 4.5 or 7.4 under the experimental conditions used, thus suggesting caution when evaluating LDL oxidation and lipid peroxidation induced by trivalent chromium [33]. Cr(III) present in the soil may undergo natural oxidation processes being converted to Cr(VI); these oxidation processes may also be influenced by manganese levels. High levels of this metal in the soil as well as the high values of pH in the soil may influence oxidation processes [34]. Trivalent chromium may be easily taken up by plants from the soil; in this way, Cr(III) can enter the food chain of the diet of living beings. Cr(III), as well as being in the daily diet, is present in many nutritional supplements in the form of CrPic, CrHis, CRDC and NBC. Among these nutritional supplements, CrPic is the most easily absorbed [35,36]. Some in vitro studies evidenced that Cr(III) can react with DNA thus causing DNA damage in cell cultures, but in normal conditions, the limited entry of Cr(III) into cells in vivo limits its genotoxic effects in biological systems. Therefore, the genotoxic effects are rare in animals and humans exposed to nutritional doses or moderate supplemental doses of Cr(III), but they are more likely for modestly elevated physiological intake levels [18].

Cr(VI) is seldom found in nature and it mainly derives from industrial and anthropogenic activities. It is used in industry in stainless steel, chrome plating, welding, leather tanning and as corrosion inhibitor. Cr(VI) is toxic and carcinogenic and is a respiratory irritant which determines phospholipid peroxidation, DNA damage, chromosomal aberration, epigenomic instability and cell death. Cr(VI), which structurally resembles phosphate and sulfate anions, may easily cross cell membranes via nonspecific anionic transfer systems, while Cr(III) cannot enter cells [37]. In the environment Cr(VI) may be found as chromate oxyanion ($CrO_4^{=}$), which is structurally similar to sulphate and phosphate anions; for this reason, the anion transport protein, called Band 3, transports sulphate, phosphate and chromate ions, as well [38,39] (Figure 1). After food or water ingestion, Cr(VI) may be reduced to Cr(III) by the action of saliva and highly acidic gastric juice and then taken by intestinal bacteria [40]. Reduction of Cr(VI) to Cr(III) into cells generates Cr(V) and Cr(IV) intermediate ions: this process depends on the reducing agent and their concentration. Cysteine acts as a one-electron reducer forming Cr(V); the reducing reaction in the presence of GSH proceeds through either one- or two-electron transfer forming Cr(V) and Cr(IV), while ascorbate is a two-electron donor, giving Cr(IV) [37,41] (Figure 1).

Once inside cells, Cr(VI) undergoes metabolic reductions and is converted to Cr(III) in the presence of ascorbate, reduced glutathione (GSH), cysteine (Cys), cytochrome P450 reductase, glutathione reductase, aldehyde oxidase, catalase, glutathione peroxidase, superoxide dismutase, glutathione S-transferase and thioredoxin reductase. Moreover, the mitochondrial electron transport chain (complex I, also called NADH: ubiquinone oxide reductase; complex III, also called ubiquinone: cytochrome C oxide reductase) is a Cr(VI) potent reducing agent [42,43]. Simultaneously with conversion of Cr(VI) to Cr(III), Fenton reaction produces reactive oxygen species (ROS), like hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\bullet}OH$) and superoxide anion radicals ($O_2^{\bullet-}$) (Figure 2). Several authors demonstrated that chromium is capable of altering the epigenetic profile of cells in DNA methylation, histone and microRNA post-translational modifications [44–47].

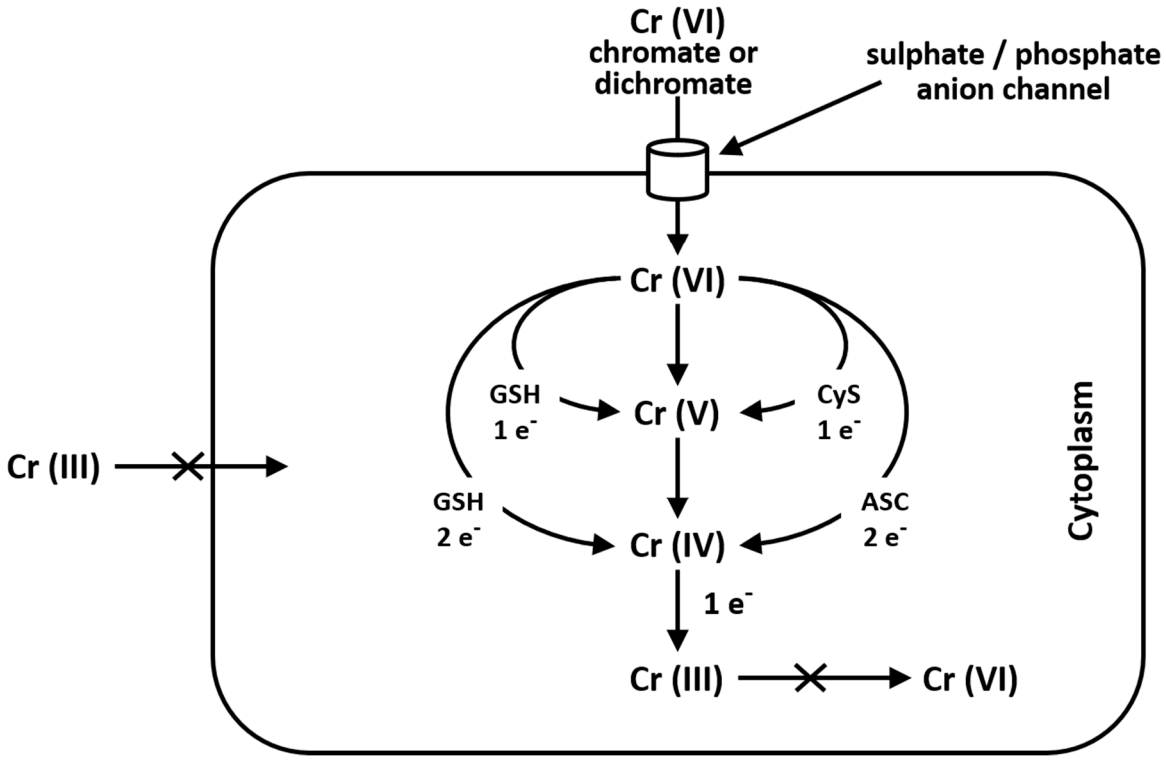

Figure 1. Pathway of chromium metabolism in the cell. Cr(III) is unable to cross the cellular membrane, while Cr(VI), being structurally similar to phosphate and sulfate, crosses the cellular membrane via a nonspecific anion channel. In the cell, Cr(VI) undergoes metabolic reduction to Cr(III) in the presence of Asc, GSH and Cys [38,41].

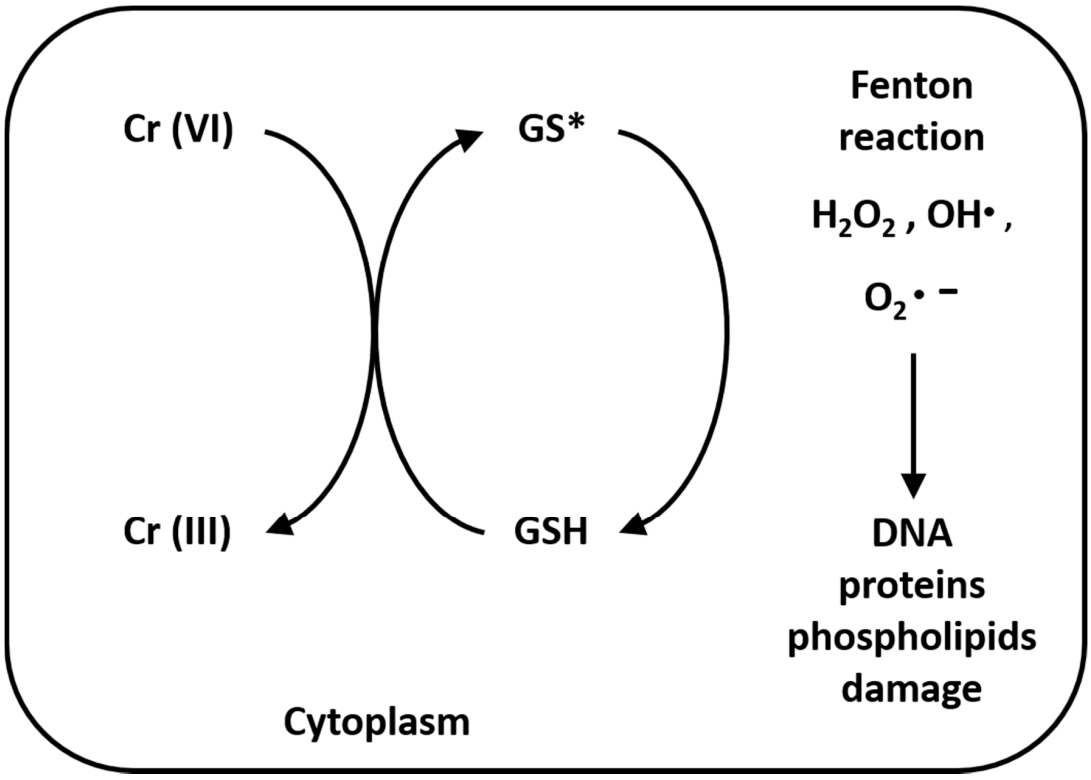

Figure 2. Reduction reaction of Cr(VI) to Cr(III) and Fenton reaction. The reaction process of Cr(VI) to Cr(III), especially in the presence of GSH, produces hydrogen peroxide (H_2O_2), hydroxyl radicals ($^{\bullet}OH$) and superoxide anion radicals ($O_2^{\bullet}$), due to Fenton reaction. These ions are very unstable, causing lipid peroxidation, DNA and protein damage [37].

3. Bioavailability, Absorption and Excretion of Cr(III) and Cr(VI)

Brewer's yeast, sea food, oysters, liver, meat, cheese, fruits, green beans, spinach and broccoli are dietary sources rich in Cr(III) (Table 3). Chromium content in food is influenced by its presence in the soil in which the plants and vegetables grow and by feedstuffs fed to animals and contamination during processing or cooking methods in Cr-containing stainless-steel equipment [48,49]. The estimated safe and adequate daily dietary intake for Cr(III), established by the National Research Council, is 50–200 µg/day corresponding to 0.71–2.9 µg/kg/day for a 70 kg adult [10]. In 2001, the Food and Nutrition Board at the Institute of Medicine of the National Academies of Sciences (US) specified the daily chromium intake at a value of 25 µg and 35 µg for women and men, respectively [50]. Maximum intake levels are up to 250 µg/day for supplemental intake as suggested by the World Health Organization (WHO); these are in the same order of magnitude as the exposure resulting from normal dietary intake [51]. Cr(III) is a natural constituent of the diet and may be found in a multiplicity of foods and supplements, whereas Cr(VI) mostly derives from industrial processes and may be found in drinking water as a result of anthropogenic contamination [52,53].

Table 3. Food sources of chromium.

Food	Cr (µg/kg)
Mussels	128
Brewer's yeast	112
Brazil nuts	100
Oysters	57
Wholemeal bread	42
Rye bread	30
Dried dates	29
Pears	27
Shrimps	26
Broccoli	25
Whole wheat flour	21
Tomatoes	20
Whole meal barley	13
Hazelnuts	12
Whole corn	9

Cr(III) is absorbed in the gut through the unsaturated passive transport. The absorption intake depends on the chromium quantity in the food and the chemical form of this element (i.e., chloride, picolinate, nicotinate, etc.). The absorption of chromium in human beings is much higher in the form of yeast chromium (5–10%) than CrPic (2.8%) or $CrCl_3$ (0.1–0.4%) (European Commission 2003) [54]. Organic chromium (i.e., picolinate, nicotinate, methionine, histidinate) is better absorbed than inorganic [55]. In 2007, Zha and co-authors reported that the highest correlation dose/accumulation in the tissues occurred when chromium nanoparticles were used (average size 40–50 nm) [56]. However, other factors are related to the absorption of this element: ascorbic acid, aspirin, oxalic acid, simple sugar, nicotinic acid and some amino acids may enhance the absorption of chromium, whereas calcium, magnesium, zinc, titanium, iron and phosphate reduce the level of absorption [57]. A chromium deficiency has been noted in athletes after strenuous exercise, pregnant women, and the elderly because of their difficulty in absorbing inorganic chromium in an adequate amount to convert into the active form [58]. Chromium absorbed by passive diffusion represents only about 1% [59].

After being absorbed from the intestine, Cr(III) is released into the bloodstream, and its transportation is mediated by transferrin, a β-globulin, followed by receptor-mediated endocytosis, and then transferred to cells of various tissues, first of all, liver and kidneys [60]. Transferrin is a serum protein, involved in iron metabolism and responsible for transporting Fe(III) in the bloodstream [61]. This protein is also involved in the transport of Cr(III)

because of its similarity to the ferric ion both in size and charge [62]. Transferrin holds two binding sites for iron with different affinities depending on pH. Chromium has been shown to bind only to one of these sites. The antagonism between chromium/iron might cause an enhancement in hematological parameters (hemoglobin, hematocrit, erythrocytes and mean erythrocyte volume), described in chromium deficiency [63]. Chromium passes from cells into blood circulation and is eliminated in urine (80%), while the remaining 20% is excreted via feces and sweat [64]. In humans, pregnancy and lactation, exhaustive physical exercise and consumption of large amounts of sugar with the diet lead to increase chromium excretion in the urine. Cr(VI) that is not reduced by gastric fluid may pass into the small intestine [65]. Cr(VI) that has entered the small intestine can be reduced outside cells, excreted in feces, or enter villus enterocytes by anion transporters. Recently, chromium level imbalances have been observed in alcohol-use disorders [66].

4. The Role of Chromium and Its Mechanism of Action in the Body

The first literature study about a physiological role of chromium in the body appeared in 1959 by Schwarz and Mertz [67]. The authors isolated from pig kidney and Brewer's yeast the GTF, a component capable of rebalancing impaired glucose tolerance in rats; the active component of this factor was discovered to be chromium. About forty years later chromium was considered an element necessary in small quantities for proper functioning of human beings [68]; anyway nowadays, chromium is classified as a nutritional supplementation factor.

In recent years, several studies on the influence of chromium on cholesterol level and lipid profile have been published. Dietary supplementation with high amounts of chromium has been demonstrated that, while decreasing the serum level of total cholesterol, LDL-cholesterol (LDL-c), nonesterified fatty acids and triglycerides, led to an enhanced concentration of high density lipoprotein (HDL)-cholesterol and β-oxidation process [69]. The oral administration in mice of chromium nitrate cancels and counteracts the anti-carcinogenic mechanism of selenium effects in the development and growth of mouse mammary tumors caused by mouse mammary tumor virus (MMTV) [70]. Despite the numerous studies published so far, it is still unclear how chromium ions can operate in the metabolism of lipids and carbohydrates. Probably, the active form of Cr(III) is transported through the body via chromodulin, a low-molecular-weight chromium-binding substance (LMWCr), that is thought to influence lipid and carbohydrate metabolism. LMWCr is a small 1500 Da oligopeptide consisting of ten amino acids (2 Gly, 2 Cys, 2 Asp, 4 Glu) [71]. LMWCr has been demonstrated to be within the cytoplasm and nucleus of the cell in an inactive form (i.e., apochromodulin). After insulin binding and activation of the transferrin receptor, there is an internalization in the cell of transferrin-chromium complex. Chromodulin binds four Cr(III) ions, and then is converted into holochromodulin, the biologically active form. This holopeptide may bind the insulin receptor at the level of β-subunit, activating the tyrosine kinase receptor and thus enhancing the insulin signal. All these mechanisms mediate glucose transport into the cell through the cell membrane thanks to the protein glucose transporter 4 (GLUT4) [72]. Other theories are known to justify the importance of chromium in glucose metabolism. For example, according to Pattar and collaborators (2006), the Cr ions act on the membrane fluidity regulating the glucose uptake by the cells [73]. The fluidity of the membrane, also considering the presence of Cr ions, is associated with the reduced content of cholesterol in the cellular membranes. The lower presence of cholesterol, which affects membrane fluidity, is considered to be another factor that diminishes insulin-controlled glucose intake. Furthermore, Raja et al. (2011) demonstrated that Cr(II) ions modify the structure of the lipid bilayer [74]. Adam et al. (2017) studied the mechanism responsible for contact dermatitis by chromium [75]. It seems that Cr(VI) penetrates through the skin and is then reduced to Cr(III), which may react with proteins to form a hapten, thus creating the complex recognized by T cells. Chromium activates T cells leading to inflammation and, lastly, symptoms [76].

5. Chromium(III) in Diabetes and Supplements

In the twenty-first century, the incidence of diabetes in the world population has increased dramatically. T2DM is characterized by high glycaemia, resistance to insulin, and relative deficiency of insulin. T2DM is related to different risk factors such as obesity, increased age, pancreatitis, cancer, family history, viral infections and immune diseases. Mechanisms such as oxidative stress, β-cell glucotoxicity, lipotoxicity and changes in gut microbiome compositions may influence insulin activity in T2DM [77,78]. Some dietary deficiencies, such as Cr(III) deficiency, have also been associated with diabetes: in fact, highly refined diets, that are poor in Cr(III), have been identified as a cause of diabetes incidence. T2DM is largely preventable by staying a normal weight, eating properly and exercising regularly.

Metabolic syndrome is related to a defect in insulin action and a compensatory increase in blood of this hormone [79]. Insulin resistance takes place when insulin is no longer able to metabolize glucose, thus leading to an increase of glucose and insulin levels in bloodstream. Recent studies showed that Cr(III) supplementation significantly decreases blood glucose concentration as well as lowers cholesterol and LDL in T2DM [80]. NBC supplementation also increases AMP protein kinase (AMPK) and protein kinase Akt phosphorylation and facilitates the GLUT4 translocation in the cell membrane [81].

Jain et al. (2012) studied the results of CRDC and CrPic supplements (400 μg/day) in type 2 diabetic human beings and found that the concentrations of intercellular adhesion molecule-1 (ICAM-1), interleukin-6 (IL-6) and interleukin-8 (IL-8) did not change if comparing what happened before and after supplementation with chromium alone or placebo. The authors also observed a significant reduction in tumor necrosis factor- (TNF-) after 3 months of CRDC supplementation compared to baseline [82]. A few years later (2016), Saiyed et al. also demonstrated that the supplementation of 400 μg/daily of CRDC for a same period (3 months) decreased TNF- levels compared to placebo [83]. Abebe et al. (2010) examined the influence of CrPic in myocardial ischemia-reperfusion injury (IRI) [84]. CrPic was suggested as a supplement in patients with T2DM/impaired glucose tolerance with systemic hypertension, abnormal vascular function and ischemic heart disease. CrPic treatment determined an improvement of endothelium-dependent vasorelaxation and nitric oxide (NO) production. Moreover, it improved recovery of myocardium after IRI [85,86]. Cr supplementation was also demonstrated to have a positive impact in heat-stressed buffalo calves and chickens. It also enhances insulin action in insulin-sensitive tissues, such as adipose tissue and muscles thus increasing feed intake, growth rate, carcass quality, reproductive parameters and ameliorating immune functions, finally leading to an increase in farm animal productivity [5].

6. Toxicity of Chromium(VI)

Hexavalent chromium (Cr(VI)) toxicity relies on its strong oxidizing ability and easy absorption by the cells through nonspecific anion carrier proteins [38,39,42]. After entering cells, hexavalent chromium may be quickly converted into the trivalent form, leading to the generation of reactive chromium intermediates and oxygen species that can alter normal cellular function and promote apoptosis [86,87]. Cr(VI) is both mutagenic and carcinogenic to humans [38]. The first report of cancer in workers exposed to chromium is dated to about 130 years ago; after that, Cr(VI) compounds appeared in the inventory of potential chemical hazards to human health. Cr(VI) has been classified as a human carcinogen by the International Agency for Research on Cancer [24]. Cr(VI) concentrations in the general population vary depending on the territories and areas considered [88–91]. Rural or suburban air generally contains lower concentrations of chromium than urban air (<10 ng/m^3 in rural areas; 0–30 ng/m^3 in urban areas). As a result of smoking, indoor air contaminated with Cr(VI) can be 10−400 times greater than outdoor air concentrations [88]. A plausible route of exposure to Cr(VI) may be via tap water at concentrations well in excess of the U.S. Environmental Protection Agency (USEPA) maximum contaminant level of 100 microg/L (ppb) [92]. Recently, Vaiopoulou et al. reported EU legislation with respect to

the discharge limits into the aquatic environment for Cr(III) and Cr(VI) in comparison to the limits in other parts of the World [93]. In recent years, high concentrations of chromium in various natural systems such as atmosphere, pedosphere, hydrosphere, and biosphere have become a global issue, leading to severe deteriorating effects on different microorganisms, plants, and animals [94]. Chromium is absorbed by plants through carriers of essential ions such as sulfate. Symptoms of chromium toxicity in plants comprise decreased germination, reduction of growth, inhibition of enzymatic activities, impairment of photosynthesis and oxidative imbalances [95]. Chromium and its particulates are also released into the oceanic medium in effluent released from ventures like tanneries, materials, mining, coloring, printing, photographic and medicinal industries [96]. Chromium destabilizes the marine ecosystem due to its toxic impact on biota and bioaccumulation in certain organisms. Occurrence of chromium varies in fishes, depending on their age, development as well as other physiological variables. It induces cytotoxicity and detrimental impact on the behavior of fish, such as hypertrophy and paraplegia at gill epithelium, uneven swimming and suspended feeding [97]. Recently, it has been demonstrated that chromate ions may be adsorbed by schwertmannite, a Fe(III)-oxyhydroxysulfate mineral, precipitated over the pH range of 2.8–4.5 in acid mine drainage and acid rock drainage. Extremely high levels of chromium (812 mg/kg) were enriched in acid mine drainage sediments where schwertmannite formed [98,99]. The main mechanisms related to cellular damage caused by Cr(VI) include high oxidative stress, chromosome breaks, and DNA adduct production. Cr(VI) is a known irritant and skin sensitizer and can easily penetrate the skin, thus causing inflammation and contact dermatitis [76]. Cr(VI) is reduced by proteins or intracellular antioxidants to Cr(III), which, being a hapten, intercalates into DNA or proteins, leading to toxicity as a result. Wang et al. (2010) demonstrated that Cr(VI) may enhance the generation of ROS inside the cells and stimulate the NF-κB, Akt and MAPK signaling cascades, resulting in higher formation of TNF-α and IL-1α in keratinocyte in vitro and in a guinea pig in vivo [100]. In 2018, the same authors documented that pterostilbene, a natural compound known for its antioxidant properties, mitigated Cr(VI)-induced skin inflammation by inhibiting TNF-α and NLRP3-inflammasome (IL-1β) in mice [101]. A serious side effect of chromium intoxication is nephrotoxicity following its elimination via the kidney; high levels of hexavalent chromium are deposited in the kidneys, causing proximal tubule damage [102]. A considerable rise in oxidative stress, nitrosative stress, apoptosis, and inflammation has been demonstrated in the kidney tissue of rats [103]. Cr(VI) toxicity has been suggested to induce cell apoptosis mostly via intrinsic mitochondrial pathways in human tumour cell lines, anterior pituitary cells, hepatocytic cells and in a rat model. In a recent work, Wu et al. (2020) studied the apoptotic mechanism of Cr(VI)-toxicity in human proximal tubular epithelial HK-2 cell line [104]. They found that both intrinsic and extrinsic apoptotic pathways were activated after exposure to 10 μM Cr(VI). $K_2Cr_2O_7$-induced nephrotoxicity associated with oxidative stress has been shown to be protected by natural antioxidants. Curcumin pretreatment in rats exerts a protective effect by preserving mitochondrial function against $K_2Cr_2O_7$ renal oxidant damage, through direct and indirect antioxidant effects [105]. Barhoma (2018) demonstrated the reno-protective effects of eugenol, a naturally occurring substance, on the injury determined by potassium dichromate intoxication in male rats: it exerted antioxidant activity and also lowered the formation of inflammatory mediators including TNF- [106]. Recently, a multicenter study using human biomonitoring in the assessment of Cr(VI) exposure and associated health risks in occupational settings has been reported [107]. Epidemiological studies demonstrated that chronic exposure to Cr(VI) and exposure to high Cr(VI) concentrations are associated with prostate cancer development and apoptosis induction in nontumorigenic human prostate cells in vitro and in vivo by acting on the epithelial−mesenchymal transition (EMT) pathway [108,109]. Low doses of Cr(VI) may act in two different ways, by downregulating epithelial protein markers, such as E-cadherin, and upregulating mesenchymal protein markers, such as Snail and N-cadherin, as assessed

by Zhang et al. [110]. The author suggested inhibition of Cr(VI)-induced EMT signalling as an approach to reduce Cr(VI)-induced prostate tumour progression.

Human oral exposure to Cr(VI) seems to determine hepatotoxicity since its accumulation takes place mainly in the liver. Mitochondrion is one of the most sensitive targets of Cr(VI) liver toxicity [111]. Zhong et al. (2017) proposed mitochondrial biogenesis as an adaptive mechanism to counteract Cr(VI) hepatotoxicity [112]. These authors found that the antioxidant systems and mitochondrial biogenesis were upregulated by low concentrations of Cr(VI), thus it is conceivable that a compensative mechanism should be generated to counteract the Cr(VI) insult. On the other end, high and cytotoxic concentrations of Cr(VI) inhibited mitochondrial biogenesis and downregulated the expression of its regulatory factors and antioxidants in HepG2 cells. Thus, pretreatment with α-tocopherol was proposed to act against the mitochondrial biogenesis imbalance induced by Cr(VI).

Recently, Yan et al. (2020) studied the effects of long-term Cr(VI) exposure on liver toxicity in mice [113]. Results indicated that chronic, low concentration Cr(VI) treatment induced liver injury characterized by disorganization of liver structure, liver dysfunction, and inhibition of the antioxidant enzyme system. Moreover, the occurrence of liver fibrosis was observed, as a result of hepatic stellate cell triggering mediated by the increased expression levels of Hedgehog signalling network.

Cr(VI) has been classified as a hazardous air pollutant by the USEPA (2004) [114]. Inhalation of chromium dusts or aerosols has been found to induce respiratory diseases and represents an undoubted risk factor for lung cancer [115]. Salama et al. (2016) studied the effects of chromium in the brain and lungs of rats after intranasal administration of potassium dichromate [114]. Higher concentrations of chromium and elevated levels of oxidative stress and inflammatory markers were observed in brain and lung tissues. This suggested a severe risk of injury in the brain among individuals exposed to chromium dust in low doses, and in brain and lung in the presence of higher chromium concentrations. Han et al. (2019) examined the effects of melatonin on chromium-induced lung injury [116]. They found a protective effect, given that the treatment of rat or mouse lung epithelial cell MLE-12 with melatonin attenuated $K_2Cr_2O_7$-induced lung injury as a result of the reduction of oxidative stress and inflammatory mediator production and inhibition of apoptosis. Lv et al. (2020) hypothesized that sulforaphane, a naturally occurring isothiocyanate found in cruciferous vegetables, acting as an indirect antioxidant by inducing phase II detoxification enzymes and antioxidant genes, may alleviate lung toxicity in rats chronically exposed to hexavalent chromium [117].

Cr(VI) has been demonstrated to be an endocrine disruptor: a strong prevalence of premature abortion and infertility was found in women working in chromium industries. The exposure of pregnant rats to Cr(VI) through drinking water determined the accumulation of chromium in placental tissue. Cr(VI) seems to break up placenta and enhances cell death by apoptosis [118]. It has been reported that this toxic metal decreases 17β-estradiol (E2) biosynthesis and improves metabolic clearance of E2, increasing oxidative stress and decreasing endogenous antioxidants. Resveratrol is able to mitigate the effects of Cr(VI) by protecting the ovary against its toxicity by enhancing endogenous antioxidant enzymes. It also restored estradiol levels by inhibiting its hydroxylation, glucuronidation and sulphation. Resveratrol was shown to protect the ovary against a Cr(VI)-induced increase in oxidative stress as it lowered lipid peroxidation (LPO) and H_2O_2 in plasma and ovary. Furthermore, the protective effects of resveratrol against Cr(VI)-induced decrease in ovarian steroidogenesis have been demonstrated [119].

7. Chromium Epigenetic Effects on DNA, Histones and MicroRNAs

Epigenetics refers to hereditary phenotype changes in gene expression without implying changes in the sequence of DNA. Epigenetic regulation of gene expression may be mediated by several mechanisms including DNA hypo- or hypermethylation, the post-translational modifications of histone tail and small noncoding RNA molecules (microRNA, miRNA), that may interfere with the packaging of DNA around nucleosomes and with gene

transcription and translation. DNA methyltransferases, histone methyltransferases, HATs and HDACs are the enzymes implicated in epigenetic mechanisms [26,120]. The covalent methylation of DNA in the presence of DNA methyltransferase and SAM (S-adenosyl methionine) takes place through the formation of a bond between a methyl group and cytosine forming 5-methylcytosine (Figure 3A); moreover, 5-methylcytosine can be actively or passively demethylated. The H3 and H4 histone tails undergo post-translational reactions that include methylation, acetylation, phosphorylation, ubiquitination and sumoylation. Acetylation (Figure 3B) of the N-terminal lysine residue removes the positive charges on the histones abolishing the ionic bonds between the $-NH_3^+$ terminal groups on the histones with the negative charges of the phosphate groups of DNA. The negative charges, destabilizing the compact DNA-histone structure, lead to a relaxed chromatin structure. Histone acetylation is regulated by enzymatic systems, as histone acetyltransferases (HATs) in the presence of acetyl coenzyme A and the histone deacetylases (HDACs). Histones are also methylated on lysine (Figure 3B), arginine and histidine residues. Unlike acetylation, methylation does not alter the charge of histone. Finally, small noncoding miRNA, formed by 25–30 nucleotides, are involved in the post-transcriptional regulation of protein expression binding to a complementary region on target mRNA and silencing their translation, also reducing expression through induced decapping and deadenylation [121,122]. Small noncoding RNAs are subjected to a covalent methylation modification (6-methyladenosine; 6MeA) (Figure 3C) coordinated by methyltransferases and demethylases. Several authors suggested that Cr(VI) is able to alter gene expression and induce cancer development through different epigenetic mechanisms. The results of the study of Lou et al. (2013) suggest that G_1 phase cell cycle arrest is induced by Cr(VI) [123]. The exposure to potassium dichromate ($K_2Cr_2O_7$) or lead chromate ($PbCrO_4$) for 2–24 h can be related to hypomethylation and DNA methylation of p16 gene, which maintained for 20 h. Hu et al. (2016) used in vitro human bronchial epithelial (16HBE) cells to analyze the epigenetic role of DNA damage following Cr(VI) exposure [124]. CpG1, CpG31 and CpG32 sites of p16 gene were significatively hypermethylated in Cr(VI) treated groups than controls. Cellular toxicity and p16 expression were demonstrated to be Cr(VI)-concentration dependent. In a following study by the same research group, Hu et al. (2018) examined a cross-sectional study in workers exposed to Cr(VI) as well as 16HBE cells treated in vitro with Cr(VI) [125]. Hypermethylation of CpG sites were observed in both occupationally exposed workers and in 16HBE cells. In addition, in workers a positive relationship existed between blood chromium concentration and methylation of CpG sites in DNA repair genes: MGMT, HOGG1, and RAD51.

Sun and co-authors (2009) showed that exposing human lung A549 cells to hexavalent chromium increased di-and tri-methylated histone H3 lysine 9 (H3K9) and H3 lysine 4 (H3K4) levels, while reducing tri-methylated histone H3 lysine 27 (H3K27) and dimethylated histone H3 histidine 2 (H3R2) levels [44]. Furthermore, supplementation of reductant ascorbate, a cofactor necessary for histone demethylase activity, inverted the H3K9 demethylation.

Xia and collaborators [126,127] reported that Cr(VI) in vitro on human bronchial epithelial cells (HBE16) determined a decrease in H3 and H4 histone acetylation and biotinidase at both protein and mRNA levels; in addition, low doses of Cr(VI) ($\leq$0.6 μM) increased histone biotinylation level. Moreover, Cr(VI)-induced deacetylation regulated the histone biotinylation. The study of Chen et al. (2016) [47] demonstrated that Cr(VI) induces a stressor protein Nupr1 (nuclear protein 1), a small protein (molecular weight 8800 Da), determining the modification of the epigenetic profile with transformation of human bronchial epithelial (BEAS2B) cells. Cr(VI) overexpressed Nupr1 decreased the levels of histone acetyltransferase males absent on the first (MOF) and H4K16 acetylation thus leading to cell transformation [47]. The epigenomic function of vitamin C plays a pivotal role in improving the activity of Jumonji-C domain-containing histone demethylases (JHDMs) and the ten-eleven translocation (TET) methylcytosine dioxygenases. According

to a recent study by Chong et al. (2019) the treatment with high doses of vitamin C should represent nontoxic epigenetic therapy in the treatment of cancer [128].

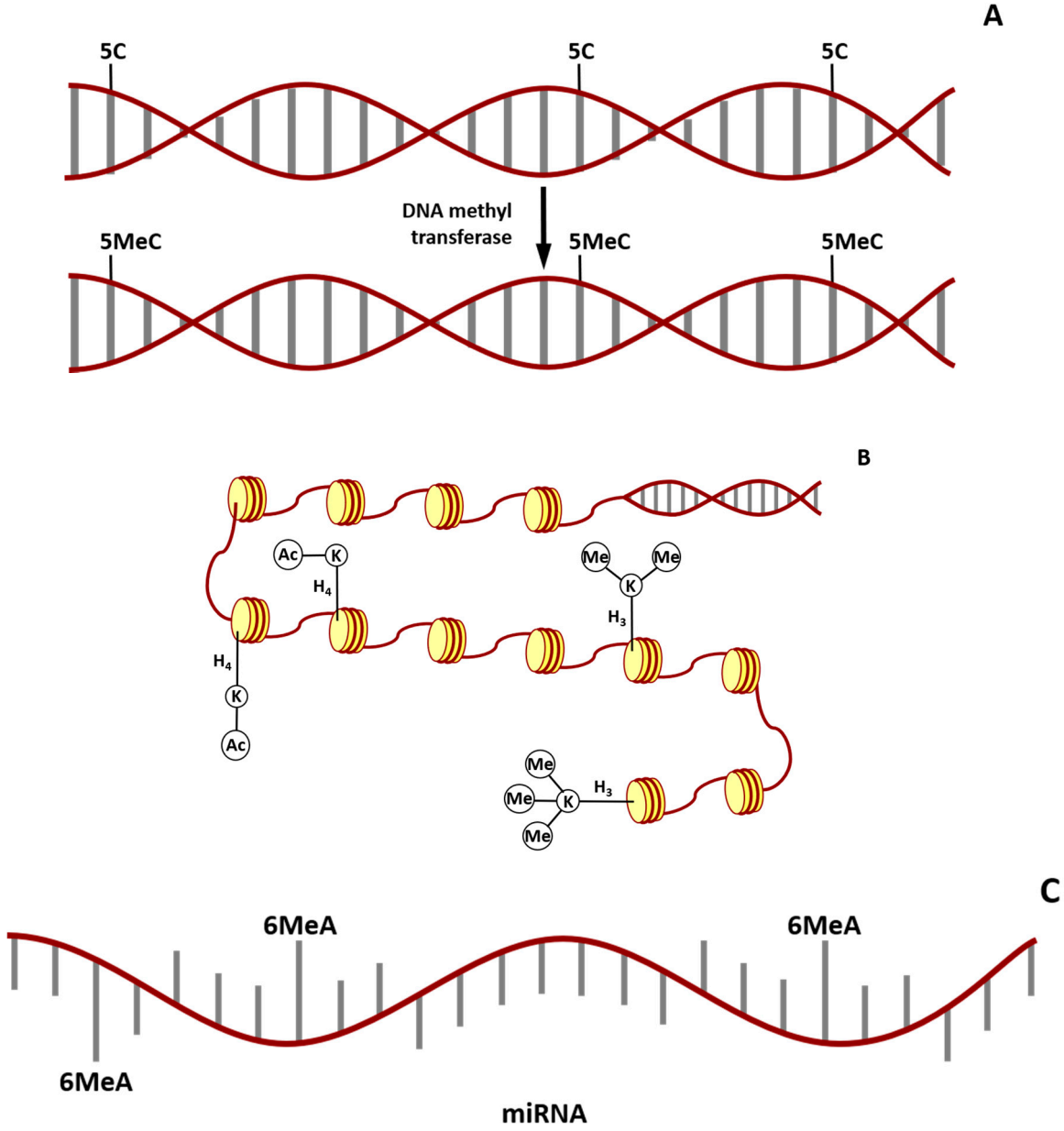

Figure 3. Chromium epigenetic effects on (A) DNA, (B) histones and (C) miRNAs. (**A**) The methylation of DNA in the presence of DNA methyltransferase involves the bond of a methyl group to the cytosine forming 5-methylcytosine. (**B**) The H3 and H4 histone tails undergo covalent reactions that include methylation and acetylation. The acetylation of the *N*-terminal lysine residue is a process regulated by histone lysine acetyltransferases. Histones are also methylated on lysine thanks to histone lysine methyltransferases. (**C**) MicroRNAs are subjected to a covalent methylation modification coordinated by methyltransferases.

The study of O'Hara et al. (2007) revealed that treating BEAS 2B cells with Cr(VI) (5µM, chosen as a nontoxic exposure) for 4 and 24 h determined an increase in protein binding to 26 and 43 cis-elements and a decrease in binding to 12 and 26 cis-elements [129]. In addition, Cr(VI) induces tyrosine phosphorylation and activation of STAT3 (signal transducer and activator of transcription), as well as the endogenous inflammatory gene IL-6. In the study conducted by Chandra and co-authors (2015), *Drosophila melanogaster* third instar larvae were treated with Cr(VI) (5.0–20.0 µg/mL) for 24 and 48 h [130]. MiRNA profile

analysis of these larvae showed 28 of 36 differentially expressed miRNAs significantly dysregulated targeting biological processes, such as DNA damage repair, development and differentiation. These results are significant as many *Drosophila melanogaster* genes have functional homologues in humans.

8. Chromium Remediation

Since heavy metals are not degradable, their accumulation in the environment (soil, water and air) may occur, thus contaminating the food chain, engendering a danger to human health. Hexavalent chromium and its oxyanions (e.g., $Cr_2O_7^{2-}$, CrO_4^{2-}, $HCrO_4^{-}$) are priority targets for the Environmental Protection Agency (EPA) due to their high degree of toxicity. Heavy metal removal is generally carried out by conventional methods involving absorption by ion exchange or chemical resins, that present the limits that they often require co-reagents or exaggerated regeneration chemicals [131] and can undergo slow kinetics with long processing times of the order of hours [132]. Bioremediation may decrease chromium toxicity: some microorganisms are able to secrete chromate reductase that turns highly toxic hexavalent chromium into nontoxic trivalent chromium [133]. *Pseudomonas* sp. Cr13 can tolerate high concentrations of Cr(VI) and thus it partially removes Cr(VI) [134,135]. Recently, *Acinetobacter* sp. Cr1 strain was found to be effective for removal of Cr(VI) [136]. Plants can also be used for phytoremediation by absorbing Cr from soil into plant organs [137]. Poly(vinyl)ferrocene-carbon nanotube (PVF-CNT) electrodes were used for the removal of anionic chromium from water, with a high adsorption capacity (>100 mg/g at saturation) and singular properties of regeneration. Both the release and the regeneration of the electrodes leads to the conversion of the hexavalent pollutant into the less harmful trivalent form [138]. The use of plants to remove nondegradable contaminants from the soil is called phytoextraction and is a green technology used as an awesome alternative to traditional physical and chemical methods that does not impact ecosystems and demands modest economic investment. It has been applied to some heavy metals, such as lead, cadmium and nickel [139,140] and recently mercury and chromium [141,142]. Recently, in a study in the Thi Vai river catchment (Vietnam), mangrove afforestation areas in appropriate locations were suggested to be used for their phytoremediation potential [143]. Novel chitosan-based thin sheet nanofiltration membranes, prepared with chitosan/polyvinyl alcohol/montmorillonite clay, have been recently also proposed for the rejection of chromium [144]. Recently, the use of probiotics was reported to be useful to weaken or hamper the toxic effects of Cr(VI). In fact, some species of *Lactobacillus*, *Streptococcus*, *Bacillus* and *Bifidobacterium* present both in the mouth and gut of humans and in fermented foods are able to bind and detoxify some toxic substances, such as Cr(VI) [145].

9. Summary

Chromium belongs to the first series of the transition elements. Comprehension of the biological functions of this element has been considered a subject of discussion for a long time. Cr(III) is necessary for normal development of humans and animals. It was proposed as an essential trace element over 50 years ago and recently it has been accepted as an essential and pharmacologically active element. It is the most prominent trace mineral involved in the improvement or prevention of hyperglycemia and hyperlipidemia in type 2 diabetes mellitus as it is an important component of glucose tolerance factor. It is present in several foods and supplementation products, including chromium-picolinate, chromium-histidinate, chromium-dinicocysteinate, and niacin-bound chromium. On the other hand, Cr(VI) is classified by the International Agency for Research on Cancer as a human carcinogen (class I). Cr(VI)-containing compounds are widely recognized as human carcinogens present in industrial settings and in the environment. The reported literature emphasizes that the pharmacokinetic and pharmacodynamic properties of chromium depend on its oxidation state. Although Cr(VI) is the ion responsible for the toxicity of this metal, molecular damage may be due to its intracellular reduction to the even more highly reactive short-lived chemical species Cr(III) and Cr(V). In this paper, both the beneficial and

toxic effects of chromium are reviewed. The epigenetic effects of Cr(VI) on DNA, histones and microRNAs are also addressed, as well as remediation studies. The understanding of the molecular mechanisms responsible for chromium toxicity may lead to finding new therapeutic strategies to cure damage to human health caused by exposure to this metal.

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Abbreviations

Ac	acetyl (Figure 3)
6MeA	6-methyladenosine
C	cytosine (Figure 3)
5MeC	5-methylcytosine
K	lysine (Figure 3)
AMPK	AMP protein kinase
CAFs	cancer-associated fibroblasts
COD	chemical oxygen demand
CRDC	chromium-dinicocysteinate
CrHis	chromium-histidinate
CrPic	chromium-picolinate
Cys	cysteine
E2	17β-estradiol
EMT	epithelial-mesenchymal transition
EPA	Environmental Protection Agency
GLUT4	glucose transporter 4
GTF	glucose tolerance factor
GSH	reduced glutathione
H3K9	histone H3 lysine 9
H3K4	histone H3 lysine 4
H3K27	histone H3 lysine 27
H3R2	histone H3 histidine 2
HATs	histone acetyltransferase
16HBE	human bronchial epithelial
HDACs	histone deacetylases
HDL	high density lipoprotein
HMG-CoA	3 hydroxy-3-methylglutaryl coenzyme A
HS	heat stress
ICAM-1	intercellular adhesion molecule-1
IL-6	interleukin-6
IL-8	interleukin-8
IRI	ischemia-reperfusion injury
JHDMs	Jumonji-C domain-containing histone demethylases
LDL	low density lipoprotein
LDL-c	low-density lipoprotein cholesterol
LMWCr	low-molecular-weight chromium-binding substance
LPO	lipid peroxidation
MAPK	mitogen-activated protein kinase
MMTV	mouse mammary tumor virus
MOF	males absent on the first

mRNA	RNA messenger
miRNA	microRNA
NBC	niacin-bound chromium
NO	nitric oxide
Nupr1	nuclear protein 1
PVF-CNT	Poly(vinyl)ferrocene-carbon nanotube
ROS	reactive oxygen species
T2DM	type 2 diabetes mellitus
TET	ten-eleven translocation
TNF-	tumor necrosis factor-
USEPA	US Environmental Protection Agency
WHO	World Health Organization

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