Meesala Krishna Murthy*, Pratima Khandayataray, Samprit Padhiary and Dibyaranjan Samal

A review on chromium health hazards and molecular mechanism of chromium bioremediation

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Abstract: Living beings have been devastated by environmental pollution, which has reached its peak. The disastrous pollution of the environment is in large part due to industrial wastes containing toxic pollutants. The widespread use of chromium (Cr (III)/Cr (VI)) in industries, especially tanneries, makes it one of the most dangerous environmental pollutants. Chromium pollution is widespread due to ineffective treatment methods. Bioremediation of chromium (Cr) using bacteria is very thoughtful due to its eco-friendly and cost-effective outcome. In order to counter chromium toxicity, bacteria have numerous mechanisms, such as the ability to absorb, reduce, efflux, or accumulate the metal. In this review article, we focused on chromium toxicity on human and environmental health as well as its bioremediation mechanism.

Keywords: bioremediation; carcinogenicity; chromium; genotoxicity; health hazards.

Introduction

Chromium is widely distributed in the Earth’s crust (83.789% natural abundance), a transition metal element, at around a 100 ppm [1–3]. Trivalent and hexavalent chromium [4] are the most common natural forms of chromium, with a valence ranging from –2 to +6. In terms of toxicity and transfer [5], hexavalent chromium [Cr (VI)] is more harmful than trivalent chromium [Cr (III)] [6]. There are numerous pH-dependent Cr (VI) species, with Cr2O42– being the only one found at pH greater than 7, and HCrO4– being the most prevalent ion in solutions ranging from 1 to 6 pH [7]. Figure 1 shows the thermodynamic Eh–pH curve, which depicts the oxidation state of chromium under various situations [8]. In some cases, Cr (VI) can make complexes (hydroxyl radicals and peroxochromium) with hydrogen peroxide even though Cr (VI) does not make complexes on its own [9, 10].

Mining, metal, textile, agricultural, pulp and paper, electroplating, refractory brick, tanneries, wood preservation, pigments and dyes, and chemical industries all use large amounts of chromium (VI) [11–14] and released into the environment. According to the Toxics Release Inventory, the amount of chromium released into the air and water is 250 and 64,500 pounds per year, respectively [15]. Areas such as Shaanxi Province [16] and Xigu district, near Yellow river [17] in China, Bandeirantes do Norte river in Brazil [18], Clyde River catchment in Scotland [19], Tarnaveni in Romania [20], Aosta Town in Italy [21], Birjand in Iran [22], Palar River [23], Sukinda region [24], Mithi River [25], Tannery waste (Uttar Pradesh) [26], Jharia (Uttar Pradesh) [27], Chinnavarikkam (Vellore) [28], Erode (Tamil Nadu) [29], Vaniyambadi (Vellore, tannery effluent) [30] in India, Hazaribagh area in Bangladesh [31] and Dongxie channel of Changhua county [32] in Taiwan are the countries across the globe reported chromium concentration above the standard.

Chromium has emerged as a widespread environmental hazard due to an increase in industrial usage [33]. Food and water are the primary sources of Cr (VI) exposure to Earth’s living beings [34]. Total Cr concentrations in unpolluted waterways are typically 1–10 mg/L [35], and the current United States Environmental Protection Agency (USEPA) drinking water guideline allows total Cr concentrations up to 0.1 mg/L [36, 37]. According to the World Health Organization [38], the total amount of Cr in drinking
water should not exceed 0.05 mg/L. Because there are not any specific drinking water rules for Cr (VI), it is hard to do a full risk assessment of Cr (VI) and its intermediate species. Cr (VI) can easily pass through aquifers, it poses a serious threat to both human safety and the environment [39, 40]. Following oral exposure, Cr (VI) to Cr (III) conversion occurs primarily in the stomach or intestines and is thought to protect against Cr (VI) toxicity [41, 42]. Furthermore, Cr (VI) is structurally similar to sulphate and phosphate anions, so that membrane nonspecific anion transporters readily accept it [43]. Cr (VI) undergoes a metabolic reduction to Cr (III) after entering the cell (e.g., blood cells, enterocytes), which is helped by enzymatic and non-enzymatic antioxidants. Because of the poor permeability of the membrane, chromium (III) is normally kept within the cell. Due to the rapid internalisation and decrease of Cr (VI) in the cells, the Cr (III) level rises dramatically. Cr (VI) toxicity is mostly caused by intracellular Cr (III), which interacts with DNA [44]. Damage to DNA may be caused by Cr (VI) at 0.2 mg/mL and Cr (III) at 1.0 mg/mL [39]. Thus, USEPA has classified Cr (VI) as a class A human carcinogen [45]. The hazardous effects of chromium on a broad range of organisms have been extensively examined [46].

Cr (VI) may also affect redox equilibrium via the Fenton route, which produces reactive oxygen species (ROS), as well as by depleting cellular antioxidants [47–49]. Lipid peroxidation, DNA damage and DNA-protein crosslinks are all caused by excessive quantities of ROS (Figure 2), which are toxic to cells and may lead to their eventual demise [39, 50–52]. Cr (VI) has previously been shown to inhibit the immune system and depress macrophage function at higher concentrations (200 μg/m3), but at lower concentrations (25 μg/m3) it stimulates phagocytic activity and inflammation [53]. For example, research by Khangarot et al. (1999) found that Cr (VI) decreases the erythrocyte and lymphocyte counts while increasing the thrombocyte and neutrophil counts [54]. More recently, Handa and Jindal (2020) observed that Cr (VI) genotoxicity causes eryptosis in Ctenopharyngodon idellus, whereas Shaw et al. (2019) found that Cr (VI) increases expression of genes associated with cytoprotection [55, 56].

Fish, rat, and mouse tissues were observed to accumulate Cr (VI) after exposure because of the limited permeability of Cr (VI) reduction intermediates and low excretion rates [57, 58]. Even if Cr (VI) reduction occurs, the authors believe that some Cr (VI) will enter tissues prior to reduction and accumulate in the soluble portion of the organs (which is partially consistent with Collins et al., 2010). This complicates kinetic models of Cr (VI) excretion since Cr (VI) might be distributed throughout the body, activated by multiple transport channels and reduced. There seems to be a two-phase clearance of Cr (VI) from the circulation and a bi/multiphasic excretion route. Many Cr (VI) slow-releasing tissue compartments may be present, according to these findings [59, 60].

Studies on the bioremediation potential for chromium detoxification have been carried out in considerable numbers as well. Despite high chromium contamination, microorganisms are able to thrive. Environmental contamination may be remedied using these bacteria, which can be isolated from tannery waste and used to remediate Cr (VI). Researchers have found that microbial remediation of Cr (VI) contamination has steadily gained popularity, especially in countries with a significant number of tanneries, such as South Africa and India [61–64]. Research into microbial remediation technology has been extensive, but there are still numerous issues to be solved. The majority of research focuses on water pollution remediation, with just a few studies looking at soil microbial remediation. These bacteria are screened from soil or tannery effluent to remove heavy metals from groundwater. Heavy metal-tolerant microorganisms chosen from severely contaminated locations have a large gap between their tolerance and the highest concentration of heavy metals that may be decreased by microorganisms [65]. The use of microorganisms to
remediate is a promising approach in the removal and fixation of Cr (VI) from wastewater, which is considered more environmentally friendly, low-cost and sustainable than that of physical and chemical materials, and improving the efficiency of bioremediation is a great challenge [28, 66, 67]. There are almost no research reports on whether heavy metals after microbial fixation will be re-oxidized or under what conditions they will be released. In the current review, an overview of chromium and the molecular mechanism of chromium bioremediation have been discussed.

Methodology

The Web of Science, PubMed, ProQuest and Google Scholar electronic databases were used to acquire articles in accordance with the preferred reporting items for systematic reviews and meta-analyses-2015 (PRISMA-2015) rules [68]. We looked at studies published between 1987 and 2020 on Cr exposure and its health hazards. We employed search tactics suggested for systematic reviews in addition to the reference lists contained in the chosen papers [69]. Searches utilising the key terms (“chromium,” “toxicity,” “bioremediation,” “mechanism” and “environmental hazards”) either separately or in combination ensured that no articles were overlooked throughout the boolean search process. Two-hundred and twenty-two publications were found that met the requirements for inclusion in this study, which included papers on Cr toxicity and environmental health risks, as well as articles from peer-reviewed journals having an impact factor.

Physical and chemical characteristics of chromium

Chromium belongs to the VI-B group in the periodic table and its electrical configuration is [Ar] 3d5 4s [70]. Oxidation states vary from −2 to +6 for this extremely reactive element in nature. Of all these different oxidation levels, it is only the trivalent and hexavalent chromium forms that are prominent in nature. On the other hand, the differences in their chemical composition have contrasting effects on live cells [26]. There are significant differences in the physicochemical attributes and biological reactivity between Cr (III) and Cr (VI) ionic forms [71]. Cr (III) is less toxic and works as a micronutrient [72]. Cr (VI) is more hazardous than its equivalent Cr (III) because of its high solubility and mobility in biological systems. Cr (VI) quickly penetrates the cell membrane and interacts with the cell cytoplasm’s biomolecules [26].

The pH and redox state of the aqueous solution affect the chromium’s ionic state (Figure 1). Cr (III) is insoluble at neutral to alkaline pH [72]. Cr (III) dominates at low pH (pH < 5), but Cr (VI) is more concentrated at higher pH [23]. Cr (VI) occurs in several oxyanion forms in the aqueous system, including hydro-CrO4 (HCrO4−), chromate (VI), as well as dichromate (VI). Cr (VI) is found in acidic circumstances in the form of dichromate anion (Cr2O72−), although in alkaline settings it is more often found as chromate anion (CrO42−) [73]. Supplementary Table 1 shows the fundamental features of several types of chromium [74].

Routes of Cr exposure and its metabolism inside the cell

Chromium enters the air, water and soil mostly in the chromium (III) and chromium (VI) forms [75]. In the air, chromium compounds are
present mostly as fine dust particles, which eventually settle over land and water. Ultramafic rocks (peridotite, kimberlite, lamprophyre, lamproite, dunite and komatiite) have been linked to the occurrence of chromium Cr (VI) in soils and sediments, and only a small amount is expected to dissolve in water and leach through the soil to groundwater. Most chromium exposure in the general population is through ingestion of the chemical in food containing chromium (III), although exposure is also possible as a result of drinking contaminated well water, or living near uncontrolled hazardous waste sites containing chromium or industries that use chromium [11]. Inhalation of chromium dust and skin contact during use in the workplace is the main routes of occupational exposure [76]. Cr also enters into the human body by consuming foods contaminated with Cr. These include meat, molluscs, entrails, lobsters, bran, vegetables, whole wheat, refined sugar, fish, seafood, whole meal cereals, etc. [11, 76]. Due to industrialization and heavy drain water contamination, urban areas have a higher concentration of Cr as compared to rural or suburban areas [77].

Inside the cell, Cr (VI) reduction generates various intermediates such as pentavalent chromium (Cr (V)) or Cr (III) products. These intermediates can damage the DNA or proteins crosslinks [39], tissue and organ damage and damage to the gastrointestinal system [44]. However, Cr (III) cannot cross the cell membrane easily but accumulates around the cell and alters the cell surface morphology by damaging the cell membrane lipid, which results in disruption of cellular integrity and function [48]. Ascorbate, glutathione (GSH), cysteine, lipoic acid, hydrogen peroxide, nicotinamide adenine dinucleotide phosphate (NADPH), ribose and fructose are intracellular reducing agents and facilitate the intracellular reduction of Cr (VI). Among the molecules and compounds, ascorbate is responsible for 90% of the Cr (VI) reduction. Cr (VI) cytotoxicity is modulated by GSH as a modulator of stress [44].

**Toxic effects of chromium (Cr)**

**Toxic effects on humans and animals:** Human health has a key threat from environmental contamination caused by Cr due to the wide usage of chromium. Supplementary Table 2 showed hazardous health impacts of Cr like protein denaturation, DNA damage, abnormal enzymatic activity, congenital malformations, metabolic syndrome, chromosomal aberrations, low birth weight, cancer, back pain, asthma, dermatitis, chronic bronchitis, haemoglobin changes and hypertension [78, 79]. Adverse health effects like asthma, bronchitis, respiratory tract irritation and nasal septum ulceration and perforation are caused by occupational exposure to chromium [80].

The preterm delivery rate across the globe, United States leads with 12–13%, followed by Africa with 11.9%, and Europe, along with other developed countries, is at 5–9%. Preterm birth occurs due to a variety of factors such as behaviour, genetic influence, the foetus or mother having some medical complexity, socioeconomic status and exposure to environmental contamination [81]. Incidences of preterm labour and stillbirth in women and developmental defects among children living around tanneries, chrome and leather industries are evident in the developing world as well as in the United States [82, 83]. An epidemiological birth cohort study from Hubei province, China, evaluated the association between maternal Cr exposure during pregnancy and the risk of preterm birth among 7,290 pregnant women [79]. Strikingly, this study found that maternal exposure to higher Cr (VI) levels during pregnancy increased the risk of delivering preterm infants, particularly male infants, suggestive of sexual dimorphism in the effects of Cr [79]. The mechanisms by which Cr leads to poor pregnancy outcomes remain to be determined. Cr can pass through the placenta and reach the foetus and can impair the development of the embryo (weight reduction, retarded foetal development, skeletal defects, dead foetus, malformations and foetus resorptions) [81].

Cr behaves as a strong allergen on skin and mucosa, causing serious damage to the digestive and respiratory systems. Cr also has mutagenic, embryogenic, teratogenic and carcinogenic effects. The acidic pH of endosomes converts metals into ions having different degrees of oxidation. The ionic form of chromium, that is, Cr (III), can bind with cell proteins, enzymes like catalase, glutathione peroxidise, superoxide dismutate (SOD), transglutaminase 3, arginase 1, transferring, haemoglobin, annexin A1, annexin A2, phosphodiesterase 3A, leukotriene hydrolase, etc. Chromium can cause protein carbonylation, which leads to oxidative stress. Furthermore, this oxidative stress causes tissue degeneration and necrosis [76]. Cr has been classified as a lung carcinogen by the International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) [84–86]. Furthermore, the most frequent one is squamous cell carcinoma, caused by hexavalent chromium. Hence, inhalation of hexavalent chromium has a slow, constant and long-lasting effect on the lung epithelial cells [4]. Cr is not easily degradable, hence it gets accumulated in the food chain and affects human health. Chromium causes allergic and carcinogenic reactions in humans and animals. Ingestion of chromium leads to ulcers in the mouth and nasal septum, kidney failure, pain in the abdomen, indigestion, vomiting, tubular necrosis, DNA damage and death [87].

**Toxic effects on respiratory tract**

The workers are exposed to Cr-face irritation in the nose, problems with breathing (asthma, shortness of breath, cough, wheezing) [88, 89]. Not only humans, but animals are also seen to suffer after being exposed to chromium. The longer duration of being exposed to Cr (VI) causes asthma, chronic rhinorrhea, nasal itching, soreness, epistaxis, nasal mucosal atrophy, bronchitis, perforation and ulceration of the nasal septum, pneumoconiosis, pneumonia and decreased pulmonary function. Chromium trioxide mist causes decreased pulmonary function, nasal irritation, nasal septum perforation, hyperplasia, and metaplasia of the larynx, trachea, bronchus, emphysema and mucosal atrophy. Ingesting hexavalent chromium leads to cardiopulmonary arrest, pleural effusion, pulmonary oedema, bronchitis, and acute broncho-pneumonia. In animals, mild lung irritation, inflammation, hyperplasia, accumulation of macrophages and impaired lung function occur due to a longer time period of exposure. Calcium chromate has an effect on bronchiolar walls, causing hyperplasia and epithelial necrosis [88].

**Toxic effects on reproductive system**

Cr (VI) has a damaging and hazardous effect on spermatogenesis, alterations in sexual behaviour, lower absolute weight of testes, seminal vesicles, impaired fertility, increased testes and ovarian weight, and decreased uterine weight, respectively [90, 91]. High Cr dosage causes low birth weight, miscarriage and changes in skeletal development and reproductive system in animals [92, 93]. Apart from decreased sperm count and motility, potassium dichromate alters the epididymis in many ways, like ductal obstruction, depletion of germ
cells, hyperplasia of Leydig cells, and fibrosis of sertoli cells. In female rats, altered weight of reproductive organs, reduced follicles and ova are observed [90].

**Toxic effects on gastrointestinal tract**

Ingestion of even a small amount of Cr (VI) can cause health problems like irritation and ulcers in the intestine and anaemia in the blood. Abdominal pain, vomiting, ulceration, haemorrhage, necrosis, and bloody diarrhoea are the symptoms of gastrointestinal effects caused by Cr [94]. High dosages (180 mg/L) of Cr (VI) cause epithelial hyperplasia and metaplasia of the glandular stomach [95].

**Toxic effects on skin and eye**

The workers in chromate and dichromate production, chrome plating, leather tanning, planographic printing, and the chromite ore processing industries come into contact with chromium trioxide, potassium dichromate, sodium dichromate, potassium chromate, sodium chromate and ammonium chromate. Allergic contact dermatitis (ACD) is a common skin disease caused by repeated dermal contact with chromium, leading to a delayed-type hypersensitivity effect [96–98], and it is characterised by the presence of certain clinical manifestations in the feet and hands. Acute dermatitis is usually indicated by the formation of erythema, oedema, papules, vesicles, and weeping, while chronic dermatitis tends to form scaly, dry, and fissured skin [97]. In addition, oral inflammation, lip keratosis, gingiva, palate gingivitis, periodontics, pharyngitis, mouth ulcers, oedema, skin ulcers and buccal musoca due to exposure of mucocutaneous tissues to airborne chromium were observed in the chromate workers [77].

Irritation and skin burn are caused by prolonged dermal exposure to chromium (VI) particles, solutions, or mist [99]. Solid deposition of chromium (VI) would lead to “chromium ulcers” or “chrome holes” [99], while a high concentration of chromium (VI) solution would lead to chromium burn. A mechanism for this ulcer formation is still unclear, but it may be related to the disruption of the actin cytoskeleton by chromium (VI), leading to mitochondria-dependent apoptosis in skin fibroblasts cells [100]. Several reports exhibited these irritation and burning effects from different chromium species, such as solid CrO3 [101], chronic acid solution [102–104], hot chromium (III) sulphate solution [105, 106], and chromium acid mist [107]. Potassium dichromate causes corneal vescication, conjunctival congestion, discharge, corneal scarring and burns in chromate production workers [77].

**Toxic effects on blood**

Cr binds with ligands and haemoglobin of the erythrocyte cells. The complex of chromium-haemoglobin is stable and remains within the cell and elutes from the erythrocyte daily. A lethal dose of Cr (VI) compound can result in haemorrhage and death. Oral exposure of Cr (VI) creates haemolymphatic effects showing microcytic and hypochromic anaemia, decreased mean cell volume, mean corpuscular haemoglobin, haematocrit and haemoglobin [77]. A decrease in haemoglobin content, haematocrit, increased total white blood cell count, reticulocyte count and plasma haemoglobin were observed in an individual exposed to potassium dichromate [108].

**Toxic effects on immune system**

ACD dermatitis can be found or detected by a patch test or lymphocyte proliferation assay [109]. Cr causes allergic sensitisation, which is followed by two hypersensitivity reactions. Type I, an immediate-onset immunoglobulin E (IgE)-mediated immune mechanism, and type IV, a delayed, cell-mediated immune mechanism, after the person becomes sensitised, he or she faces an allergic response and symptoms like dermatitis or asthma. Dermal responses are caused by direct skin contact with chromium compounds and are characterised by eczema and dermatitis. Oral exposure to hexavalent chromium can cause dermatitis, erythema, oedema, small and large blisters, thickened, scaly and fissured skin.

The immune systems of animals also experience similar results after inhalation and ingestion of hexavalent chromium compounds. In pigs and mice, simulation of the humoral immune system, increase in phagocytic activity of macrophages, increase in proliferative response of T- and B-cell mitogens, and histopathological alteration of pancreatic lymph nodes were reported [77]. Enzyme linked immunosorbant assay (ELISA) and bacterial agglutination assay processes are used to see the specific immune response of fish. Serum lysozyme activity, production of intracellular ROS and reactive nitrogen intermediates (RNI) by peripheral blood leucocytes are used to determine non-specific immune mechanisms. Suppressed antibody response, non-specific serum lysozyme activity, ROS and RNI production are the effects shown by the fishes [110].

**Chromium-induced inflammation**

Lung cancer induced by Cr can lead to chronic pulmonary inflammation [11–13]. Inflammatory responses and lung injury, bronchiolar cell apoptosis, and interstitial and alveolar pneumonitis are caused by zinc chromate [114–118]. Cr (VI) induces chronic peribronchial inflammation with alveolar and interstitial pneumonitis. Welding fumes can result in neutrophil infiltration and histiocytic peribronchial inflammation [118]. The airway damage leads to fibrosis, bronchiolar epithelial hyperplasia, cellular atypia and broncho-alveolar hyperplasia [44]. Welding fumes result in an influx of macrophages, eosinophils and neutrophils into the lungs, which damages the alveolar capillary barrier cytotaxially. The alveolar macrophages and chronic inflammatory alveolar septa were exposed to sodium dichromate in the lungs. The immune system can be both protective and pathological, and cancer can arise from chronic inflammation sites [44].

**Genotoxicity and carcinogenicity of chromium**

Chromium salts have a mutagenic effect, which causes chromosomal aberrations [77, 119]. Histone’s ubiquitinated form is accumulated when Cr induces double-stranded DNA breakage [12] of one selective U chromatin. These types of damage suppress upregulation of inducible genes and show the high genotoxic potential of Cr (VI) [75]. Genotoxicity [48, 120–131] can arrest the cell cycle checkpoint and activate cell death pathways of apoptosis, which leads to transformation, tumorigenesis, evasion of apoptosis, and self-sufficiency in growth signals, insensitivity to anti-growth signals, limitless replicative potential, sustained angiogenesis, tissue invasion and metastasis, which are the hallmarks of cancer (Table 1). Normal human cells convert into malignant cancer cells due to epigenetic changes. Exposure to
genotoxic is the initiation step of the premalignant process, which responds to the cell cycle deregulation [44, 132].

Cr (VI) gets reduced by saliva, acidic gastric juice, bloodstream, and liver to Cr (III) and enters into the cells by the anionic transfer system. After entering the cells, Cr reacts with DNA and forms genotoxic DNA adducts [133, 134]. Respiratory system cancers, primarily bronchogenic and nasal, are the most affected parts of workers exposed to Cr. Most of the workers working in chromate production get affected by lung cancer and fewer with nasal cancer. Chromate workers and chrome plating workers are more prone to lung cancer. Cr-rich drinking water causes stomach cancer, liver cancer, lung cancer, kidney cancer and urogenital organ cancer (Table 1). Mice were observed to have lung and respiratory tract tumours after being exposed to calcium chromate and gastrointestinal tract cancer after drinking water rich in sodium dichromate dihydrate. The NTP classified chromium trioxide, lead chromate, strontium chromate and zinc chromate as compounds known to be human carcinogens [135, 136]. The IARC classified hexavalent chromium as a carcinogen. The EPA also classified hexavalent chromium, which can be inhaled, as carcinogenic [137].

Table 1: Summary of genotoxic effects of chromium [132].

<table>
<thead>
<tr>
<th>Mechanism of genotoxicity</th>
<th>Compound</th>
<th>Material</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding to DNA in an intercalative manner, irreversibly destroying the DNA configuration</td>
<td>Chromium trioxide</td>
<td>SIR576-p yeast cells; human T cell leukaemia Jurkat cells</td>
<td>Fang et al. (2014)</td>
</tr>
<tr>
<td>Directly interaction with the DNA of gastric mucosa cells</td>
<td>Potassium dichromate Cr₂O₇</td>
<td>Human peripheral blood lymphocytes, human gastric mucosa cells</td>
<td>Trzeciak et al. (2000)</td>
</tr>
<tr>
<td>Double strand breaks formation</td>
<td>Zinc chromate ZnCrO₄</td>
<td>WTHBF-6 human lung cells, h-TERT immortalized clonal cell line</td>
<td>Qin et al. (2014)</td>
</tr>
<tr>
<td>Increased amount of DNA damages</td>
<td>Lead chromate PbCrO₄</td>
<td>WTHBF-6 human lung fibroblasts</td>
<td>Xie et al. (2005)</td>
</tr>
<tr>
<td>Mutation of genes, exchanges of sister chromatids and chromosomes aberrations</td>
<td>Sodium chromate Na₂CrO₄</td>
<td>Human lung cancer cells (AS49)</td>
<td>Cavallo et al. (2010)</td>
</tr>
<tr>
<td>Reduction of Cr (VI) to Cr (III)-damage by ROS</td>
<td>Lead chromate PbCrO₄</td>
<td>WTHBF-6 human lung fibroblasts</td>
<td>Xie et al. (2005)</td>
</tr>
<tr>
<td>DNA-protein crosslinks (DPCs) generation</td>
<td>Sodium chromate Na₂CrO₄</td>
<td>Human lymphoblastoid cells (TK6)</td>
<td>El-Yamani et al. (2011)</td>
</tr>
<tr>
<td>Excessive production of ROS</td>
<td>Potassium chromate Cr₂O₇</td>
<td>Yeast Saccharomyces cerevisiae</td>
<td>Sobol et al. (2012)</td>
</tr>
<tr>
<td>Ability to accumulate around cells to induce morphological changes on the cell surface (DNA damage)</td>
<td>Cr (III) peptide (triglycine, tetratrypticline and pentaglycine) complexes Cr (III)</td>
<td>Human lung A549 cells, Tannery workers</td>
<td>Ateeq et al. (2010)</td>
</tr>
<tr>
<td>Cr-DNA monoadducts, DNA interstrand crosslinks, DNA-Cr-protein crosslinks (DPCs), apurinic/apyrimidinic site, DNA strand breaks creation</td>
<td>Chromium chloride CrCl₃</td>
<td>Spectroscopic characterization Shewanella oneidensis MR-1</td>
<td>Headlam et al. (2016)</td>
</tr>
<tr>
<td>Binding to DNA, leading to a decrease in fidelity and an increase in the processivity of DNA polymerases; interference with the base pairing mode</td>
<td>Chromium chloride CrCl₃</td>
<td>SIR576-p yeast cells; human T cell leukaemia Jurkat cells</td>
<td>Wang et al. (2017)</td>
</tr>
</tbody>
</table>

ROS, reactive oxygen species.
Cr (VI) carcinogenesis [138] depends on two factors, like genetic and epigenetic mechanisms, which are vital (Figure 3). In the lung cells of chromate workers, genetic lesions were studied. Cr (III) produces DNA complexes, namely Cr (III)-DNA adducts, DNA-protein crosslinks, and DNA interstrand crosslinks [12, 139]. Cr (VI) can directly and indirectly damage the DNA by generating oxidative stress (Figure 3). Cr (VI) divides apart karyokinesis from cytokinesis and creates microsatellite instability. Cr (VI)-induced lesions bring about inflammatory lung disease. This disease proceeds to be lung cancer. Nanoparticles of zinc chromate cause mucosal injury and bronchiolar cell apoptosis which progresses to alveolar and interstitial pneumonitis [48, 140–142].

Carcinogenesis has been divided into three stages: initiation, promotion, and progression. Oxidative stress and ROS damage proteins and cell membranes and induce DNA mutations. Incipient cancer cells at the promotion stage increase the number of DNA mutations, resulting in dramatically higher levels of mutant proteins that induce proteotoxic stress. Progression is thought to require chromosomal instability and results in karyotypic abnormalities and induces genotoxic stress [4]. Cr-induced DNA damage can cause genotoxicity, mutagenicity, and cell death. DNA adducts, DNA strand breaks, DNA-protein crosslinks, oxidised bases, basic sites and DNA inter- and intra-strand crosslinks are the genetic lesions caused by hexavalent chromium (Figure 3). The most common genetic lesion caused by hexavalent chromium is chromium with a phosphodiester backbone of DNA. The binary and ternary adducts are formed by the Cr (III)-ligand-DNA complex. The four types of ternary adducts are Cr (III)-ascorbate, Cr (III)-cysteine, Cr (III)-histidine and Cr (III)-glutathione DNA adducts [143–145]. The ternary adduct is the primary mutagenic adduct. As compared to the binary adducts, Cr (III)-cysteine-DNA and Cr (III)-ascorbate-DNA are more mutagenic [146]. Treatment of DNA with Cr (III) and Cr (VI) with ascorbate produces DNA-chromium-DNA crosslinks as well as DNA with Cr (III) and Cr (VI) with GSH produces DNA-chromium-GSH, which is a form of DNA damage (Figure 2). DNA damage caused by Cr (VI) [50] results in dysfunctional DNA replication and transcription, nucleotide excision repair and genomic instability. Genomic instability causes microsatellite instability, leading to carcinogenesis [147, 148]. In the workers, neoplastic transformation and tumour formation are seen in the workers. Insoluble hexavalent chromium compounds are highly toxic, leading to tumour formation. Aneuploidy, triploidy and tetraploidy are found in 70–80% of human lung tumours [44].

Plant toxicity

Cr is being absorbed through carriers of essential ions like iron, magnesium, phosphorus, calcium and sulphate by the plants. On its speciation, Cr translocation, accumulation and uptake depend. In citrullus plants, reduction of sulphur, copper, zinc, iron, manganese and phosphorus is enhanced by chromium, which causes root growth decline, impaired root penetration and decreased element translocation [149].

Cr induces physiological, biochemical and ultra-structural alterations in plants, which lead to adverse effects including reduction of growth and biomass, chlorosis in young leaves, lowering of pigment content, disturbance of stomatal conductance, enzymatic function alteration, root cell damage and ultra-morphological modification of roots and leaves (Figure 4). Direct contact with Cr can severely damage the roots, causing shortening, browning, and thinning of root hairs, as well as affected lateral root development, root number, plasmolysed cells, large vacuoles, condensed and irregular root tip structure, damaged tonoplast and dense lysosome [150, 151]. Water
contaminated with Cr can inhibit cell proliferation, electron-dense bodies in cell walls, cytoplasm and vacuoles and the presence of multinucleated and highly vacuolated giant cells [152–154]. These alterations cause the production of ROS, which damage the cell membrane, chlorophyll pigment, lipids, nucleic acids, proteins and cause cell death [155]. Plants release antioxidants like SOD, peroxidase, ascorbate peroxidase and glutathione, which mediate the deleterious effects of ROS (Figure 4). Cr reduces nitrogen fixation and inhibits the nitrogenase enzymes in root nodules, which causes oxidative stress [155, 156].

Chromium toxicity on aquatic animals

Aquatic toxicology of chromium depends on two factors, such as biotic (age, species and development stage) and abiotic (temperature, concentration of chromium, pH, alkalinity, salinity and hardness of water) factors [157]. The sensitivity of aquatic organisms is also affected by metal concentrations that are lethal and sub-lethal. Chromium exerts toxicity at a functional level, and the degree of toxicity (Table 2) depends on the pH of water. Energy storage and metabolism are reduced in fish due to Cr. Cr increases antioxidant defence system (SOD, GSH and condensed tannins [CTs]) activity in fish tissues. Fish mucus is very helpful in reducing the oxidative state of Cr (VI) [52]. Under sub-lethal concentrations of chromium, biomarkers of oxidative stress were increased in fishes and they produced ROS molecules like superoxide anion, hydrogen peroxide and hydroxyl radical [158–162].

Cr penetrates into the gill membrane by passive diffusion and enters into the cytoplasm of fish via sulphate ion channels present in the plasma membrane, which leads to a higher concentration of Cr in fish tissues. The distribution of Cr (VI) in fishes is as follows: Gill > Liver > Skin > Muscles. Water pH affects the Cr accumulation in tissues of fish, at pH 6.5, gills contained the highest amount of Cr and at pH 7.8, internal organs had the highest Cr content [110]. Some studies showed that Cr induced a higher hepato-somatic index in fish, whereas in Labeo rohita, Cr (VI) induces behavioural change, surfacing and darting movement, copious mucus secretion, aggregation of fishes near the aerator, lethargic movements, an increase in peculiar movements to breathe faster, irregular and burst swimming, and suddenly rapid and forward movements, respectively. Cr causes acute fertilization [163], blood clotting, decrease in WBC, RBC counts and Hb concentration, and increase in ALA-D activity [43, 164], increase in spleen to body ratio, splenocytes and decreased antibody production and increased susceptibility to bacteria [43], decrease in lipid and total protein contents [165], hyperglycaemic response [166], decrease in ATPase activity [167], embryo survival rate and larval growth, liver lactic acid and glycogen, splenic weight, and lymphocyte count, induction of mortality rate and effect on embryo hatching [168], erosion of fin and fin rays [169], increased muscle and blood lactic acid, LDH activity inhibited in liver and kidney, PDH and SDH activities inhibited in all the tissues except muscle, glycogen increased in liver, and DNA damage [170] on different aquatic animals (Table 2).

Chromium toxicity on microbes

Microorganisms are sensitive to heavy metals like copper, nickel, zinc, cadmium and arsenic. These heavy metals inhibit growth and
Table 2: Studies on acute and chronic toxicity effects of chromium on different fish species [157].

<table>
<thead>
<tr>
<th>Fish species</th>
<th>Toxic effects</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute toxicity of chromium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Salmo gairdneri</em></td>
<td>Effect on fertilization</td>
<td>Billard and Roubaud (1985)</td>
</tr>
<tr>
<td><em>Tilapia sparrmanii</em></td>
<td>Decrease in blood clotting time</td>
<td>Gey van Pittius et al. (1992)</td>
</tr>
<tr>
<td><em>T. sparrmanii</em></td>
<td>Decrease in WBC, RBC counts, Hb concentration and increase in ALA-D activity</td>
<td>Wepener et al. (1992)</td>
</tr>
<tr>
<td><em>Saccobranchus fossilis</em></td>
<td>Increases in spleen to body ratio, WBC, RBC, Hb, MCV, PCV, splenocytes and decreased antibody production and increased susceptibility to bacteria</td>
<td>Khangarot et al. (1999)</td>
</tr>
<tr>
<td><em>Periophthalmus dipes</em></td>
<td>Decrease in ion-dependent ATPase activity</td>
<td>Thaker et al. (1996)</td>
</tr>
<tr>
<td><em>Labeo rohita</em></td>
<td>Decrease in glycogen content, total lipid content and total protein content of liver, muscle and gill</td>
<td>Vutukuru (2003)</td>
</tr>
<tr>
<td><em>Colisa fasciatus</em></td>
<td>Reduction in liver glycogen content, hyperglycaemic response</td>
<td>Nath and Kumar (1988)</td>
</tr>
<tr>
<td><em>Carassius auratus</em></td>
<td>Decrease in cell viability and increase in reactive oxygen level</td>
<td></td>
</tr>
<tr>
<td><strong>Chronic toxicity of chromium</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Oreochromis mossambicus</em></td>
<td>Decrease in antibody production and lymphocyte count.</td>
<td>Arunkumar et al. (2000)</td>
</tr>
<tr>
<td><em>Oncorhynchus tshawytscha</em></td>
<td>Decrease in survival rate and growth rate. DNA damage</td>
<td>Farag et al. (2006)</td>
</tr>
<tr>
<td><em>Cyprinus carpio</em></td>
<td>Diminished humoural responses and serum proteins level</td>
<td>O’Neill (1981)</td>
</tr>
<tr>
<td><em>S. gairdneri</em></td>
<td>Induction of mortality rate. Effect on embryo hatching</td>
<td>Van der Putte et al. (1982)</td>
</tr>
<tr>
<td><em>Clarias gariepinus</em></td>
<td>Decreased embryo survival rate and larval growth</td>
<td>Van der Putte et al. (1982)</td>
</tr>
<tr>
<td><em>Nuria denicus</em></td>
<td>Erosion of fin and fin rays</td>
<td>Abbasi et al. (1995)</td>
</tr>
<tr>
<td><em>Channa punctatus</em></td>
<td>Increased muscle and blood lactic acid. Decreased liver lactic acid and glycogen. LDH activity inhibited in liver and kidney. PDH and SDH activities inhibited in all the tissues except muscle. Glycogen increased in liver but decreased in muscle</td>
<td>Pal and Trivedi (2016)</td>
</tr>
</tbody>
</table>

WBC, white blood cells; RBC, red blood cells; Hb, Hemoglobin; ALA-D, delta-aminolevulinate dehydratase; MCV, mean corpuscular volume; PCV, packed cell volume; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase; PCV, packed cell volume; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; WBC, white blood cells; RBC, red blood cells; Hb, Hemoglobin; ALA-D, delta-aminolevulinate dehydratase; MCV, mean corpuscular volume; PCV, packed cell volume; LDH, lactate dehydrogenase; PDH, pyruvate dehydrogenase.

Chromium bioremediation and molecular mechanisms

There are several physical, chemical, and biological methods to remove Cr (VI) from the environment [175, 176], including ion exchange [177], membrane filtration [178], solvent extraction [179], chemical precipitation [180] and adsorption [181]. Secondary environmental contamination may result, as well as the need for continual energy input and the use of various chemicals, as well as high prices and poor clean-up efficiency [182, 183]. Bioremediation is responsible for the biological reduction of Cr (VI) to less mobile Cr (III), and their consequent precipitation may be an important method of detoxification of polluted Cr (VI) sites [184]. Microorganisms remove heavy metals in such a way that they utilise metal ions for their advancement and by converting them into carbon dioxide, methane, water and biomass through enzyme-catalysed metabolism of poisonous substances [185]. Initially, potentially toxic heavy metal ions get attached to the surface ligand of the cell. Then, the metal ligand complex formed at the surface of the cell is transported inside the cell by a transporter protein. Finally, transported complexes intracellularly interact with metalbinding proteins (such as metallothionein and phytochelatins), where precipitation, methylation and other processes take place. However, the process is limited to the living cells only and inhibits microbial cell growth at a relatively higher metal concentration [186]. Finally, the living and dead microbial biomass, mainly that of bacteria, fungi and algae, eco-friendly degrades and removes toxic chromium ions by the processes of biosorption, biodegradation and bioreduction [27], in which microbial activity is stimulated by environmental circumstances that can breakdown toxic compounds to a level that is safe for human health and the environment [149, 187, 188]. Microorganisms are regarded as the ideal biological material for the treatment of environmental pollution because of their vast distribution in the natural
environment, their capacity to proliferate under controlled settings and their ability to repair environmental damage swiftly [189]. The removal and fixation of Cr (VI) from wastewater using microorganisms is a viable strategy because it is environmentally friendly, cheap, and long-term [28, 66, 67, 190, 191].

The biosorption takes place at the same time as the reduction of Cr (VI) to Cr (III). On both the outside and inside of cells, bacteria may reduce Cr (VI) to Cr (III) using the reductase enzymes [192]. Some hydroxyl, carboxyl and amino groups on the surface of bacterial cells form complexes with Cr (VI) or Cr (III). Using biobleaching to remove heavy metals from soil and sediment has been common practice for decades [193]. Microorganisms can survive in the presence of heavy metals due to resistance mechanisms that have been developed. These include the ability to: use trace amounts of metals for their metabolic activities; offer resistance to toxic levels; tolerate the metals to a threshold limit and detoxify excessive metal ions when they are exposed to them [194]. As a result of microorganism’s ability to directly interact with heavy metals, which is detoxification of microorganisms, these organisms are resistant to heavy metal’s harmful effects [195]. Different environmental factors [9, 27, 194–204], such as temperature and pH, electron donors (e.g. lactate or glucose) or ion presence, impact the resistance to heavy metals by altering the microbial activity, which in turn alters the toxicity of heavy metals (Table 3).

The genes carried by bacteria can effectively prevent cell damage, particularly ChrA, which is capable of releasing Cr (VI) to reduce Cr build-up. ChrA and ChrAB engineering strains may pump intracellular Cr via the plasmid-encoded Cr-transporter protein ChrA [205, 206]. On top of all of that, the enzymes that can lower Cr (VI) include nitroreductase and chromate resistance protein ChrB, as well as metal transport/detoxification protein CopZ, which can both pump chromium outside of the cell [207] (Figure 5). Cr (VI) induces the Chr promoter, whereas Cr (III), sulphate, oxidants or other oxyanions have no effect. The functional genes, on the other hand, increase the diversity of microorganisms and have a negative impact when exposed to Cr (VI) [208].

Sulphhydryl, the fungal system’s most potent free radical scavenger, plays a critical function in the removal of harmful metals from the body [209]. Isolated from electroplating wastewater, the fungus Aspergillus flavus CR500 is capable of forming Cr-sulphhydryl compounds and accumulating in cells having non-protein sulphhydryl groups [201, 210]. For example, the chelation of heavy metal ions and the removal of heavy metals from soil may be accomplished by organic acids released by ectomycorrhizal (EMC) fungus [211]. It was shown by Tang et al. (2021) that the detoxification process of EMC fungal cells to heavy metals includes: (1) interacting with the cell wall; (2) decreasing intracellular metal ions via the pump; (3) cytoplasmic chelation; (4) subcellular de-isolation; (5) repairing damaged biomolecules [9].

Under both aerobic and anaerobic circumstances, bioreduction may be accomplished (Supplementary Table 3). Supplementary Figure 1 shows that soluble reductase helps reduce soluble Cr (VI) to insoluble Cr (III) under aerobic conditions while glutathione, amino acids, vitamins and others act as electron donors that require nicotinamide adenine dinucleotide (NADH)/NADPH cofactors [212]. Soluble reductase can transfer electrons to soluble Cr (VI), which accepts electrons to be reduced. Cr (VI) is a terminal electron acceptor in the membrane electron-transport respiratory route; in the presence of oxygen, Cr (VI) first reduces to Cr (V) and/or Cr (IV), and then to stable

### Table 3: Different microorganisms with their efficiency and mechanisms to removal chromium [9].

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Concentration, mg/L</th>
<th>Temperature, °C</th>
<th>pH</th>
<th>Efficiency</th>
<th>Mechanisms</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serratia sp. C8</td>
<td>20</td>
<td>28</td>
<td>6–8</td>
<td>≥80%</td>
<td>Bioreduction</td>
<td>Gonzalez et al. (2014)</td>
</tr>
<tr>
<td>Sporosarcina saromensis M52</td>
<td>50–200</td>
<td>35</td>
<td>7–8.5</td>
<td>&gt;90%</td>
<td>Bioreduction</td>
<td>Ran et al. (2016)</td>
</tr>
<tr>
<td>S. saromensis M52</td>
<td>500</td>
<td>36</td>
<td>8</td>
<td>0</td>
<td>Bioreduction</td>
<td>Prabhakaran et al. (2019)</td>
</tr>
<tr>
<td>Sphingopyxis macrocollotabida SUK2c</td>
<td>4</td>
<td>31</td>
<td>2</td>
<td>55%</td>
<td>Biosorption</td>
<td>Tam et al. (2020)</td>
</tr>
<tr>
<td>Bacillus sp. CRB-B1</td>
<td>100</td>
<td>37</td>
<td>7</td>
<td>Completely</td>
<td>Bioreduction, biosorption</td>
<td>Banerjee et al. (2019)</td>
</tr>
<tr>
<td>Bacillus sp. CRB-B1</td>
<td>100</td>
<td>37</td>
<td>7</td>
<td>89.54%</td>
<td>Bioreduction, biosorption</td>
<td>Banerjee et al. (2019)</td>
</tr>
<tr>
<td>Bacillus sp. CRB-B1</td>
<td>100</td>
<td>37</td>
<td>7</td>
<td>4.8%</td>
<td>Bioreduction, biosorption</td>
<td>Banerjee et al. (2019)</td>
</tr>
<tr>
<td>Corynebacterium paurometabolum</td>
<td>4</td>
<td>30</td>
<td>1</td>
<td>50%</td>
<td>Biosorption</td>
<td>Prabhakaran and Subramanian (2016)</td>
</tr>
<tr>
<td>Bacillus cereus</td>
<td>200</td>
<td>37</td>
<td>7.5</td>
<td>Completely</td>
<td>Bioreduction, biosorption</td>
<td>Banerjee et al. (2019)</td>
</tr>
<tr>
<td>Bacillus methylotrophicus</td>
<td>75</td>
<td>30</td>
<td>7</td>
<td>91.3%</td>
<td>Bioreduction</td>
<td>Sandana et al. (2015)</td>
</tr>
<tr>
<td>Aspergillus flavus CR500</td>
<td>50</td>
<td>28–35</td>
<td>6.5</td>
<td>≥99%</td>
<td>Bioreduction, biosorption</td>
<td>Kumar and Dwivedi (2019)</td>
</tr>
<tr>
<td>Pisolithus sp1</td>
<td>25</td>
<td>30</td>
<td>5–6</td>
<td>99%</td>
<td>Bioreduction, biosorption</td>
<td>Shi et al. (2018)</td>
</tr>
<tr>
<td>Pisolithus sp1</td>
<td>50</td>
<td>30</td>
<td>5–7</td>
<td>90%</td>
<td>Bioreduction, biosorption</td>
<td>Shi et al. (2018)</td>
</tr>
<tr>
<td>Leiotrametes flavida</td>
<td>1,000</td>
<td>30</td>
<td>6</td>
<td>72.38%</td>
<td>Biosorption</td>
<td>Antony et al. (2020)</td>
</tr>
<tr>
<td>Aspergillus sp.</td>
<td>100</td>
<td>27</td>
<td>4</td>
<td>98.96%</td>
<td>Biosorption</td>
<td>Chakraborty et al. (2018)</td>
</tr>
</tbody>
</table>
Cr (III). By transferring one electron to oxygen, a one-electron redox cycle transforms Cr (V) into Cr (IV) \[213\]. Glutathione and ascorbic acid levels in tissues are almost the same, although ascorbic acid has a far higher rate of elimination of Cr (VI) than glutathione. Cytochrome b and cytochrome c may engage in electron transport, and this process is facilitated by enzymes in anaerobic environments \[214\]. According to the study by Li et al. (2018), electron transport outside the cell is supported by the cytochrome soluble shuttle-mediated route \[215\].

**Regulations and recommendations for chromium**

The EPA has established the contamination threshold in drinking water at 0.1 mg/L. The EPA examines municipal drinking water for the presence of hexavalent chromium \[45, 46, 216\]. Hexavalent chromium in drinking water is examined for its health impacts, and a maximum limit is established (Supplementary Table 4). According to the Food and Drug Administration \[217\], the chromium content in bottled drinking water should not exceed 0.1 mg/L. According to the Occupational Safety and Health Administration, Cr (VI), Cr (III) and Cr (0) should be limited to 0.005, 0.5 and 1.0 mg/m³ of air for an 8-h work day. According to the National Institute for Occupational Safety and Health, Cr (III) and Cr (II) should be limited to 0.5 mg/m³ and Cr (VI) should be limited to 0.001 mg/m³ for an 8-h work day and a 10-h work day, respectively \[12\].

**Conclusion and future perspective**

In the current review article, physico-chemical properties, routes of exposure, metabolism, various health complications of humans, and toxicity of plants, aquatic animals, microorganisms, genotoxicity and carcinogenicity, as well as bioremediation mechanisms of chromium were discussed. This review highlights the problem of chromium contamination throughout the globe and the necessity for rapid action. In today’s society and unstable economy, industries are reluctant to spend adequate money on remediation processes. Industrialists should be made aware of such remediation processes and their benefits in the long run. The capital cost of cleaning industrial effluents may be high, but with the use of cost-effective techniques, such an investment may be profitable for the industry. Chromium bioremediation has various benefits over other approaches. A detailed discussion of the bioremediation processes of bacterial chromium demonstrates the efficacy of bacteria for this purpose. According to a review of the relevant literature, bioremediation has been studied a lot in the laboratory.

There are still many unanswered questions about the bacterial bioremediation process, and this review identifies the most pressing ones: (1) Different molecular mechanisms of chromium remediation in bacteria should be studied further to better understand the bacterial response, (2) field bioremediation studies, rather than bacterial isolation and lab-scale treatment assays, should be encouraged and (3) on-site waste treatment utilizing bioremediation is rare \[218, 219\], but it is possible to combine bacterial bioremediation with other approaches, such as phytoremediation and immobilizations, that stimulate bacterial growth and assist in maximal bioremediation.
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