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Review

Hexavalent chromium and its effect on health: possible protective role of garlic (*Allium sativum* Linn)

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Abstract

Hexavalent chromium or chromium (VI) is a powerful epithelial irritant and a confirmed human carcinogen. This heavy metal is toxic to many plants, aquatic animals, and bacteria. Chromium (VI) which consists of 10%–15% total chromium usage, is principally used for metal plating ($H_2Cr_2O_7$), as dyes, paint pigments, and leather tanning, etc. Industrial production of chromium (II) and (III) compounds are also available but in small amounts as compared to chromium (VI). Chromium (VI) can act as an oxidant directly on the skin surface or it can be absorbed through the skin, especially if the skin surface is damaged. The prooxidative effects of chromium (VI) inhibit antioxidant enzymes and deplete intracellular glutathione in living systems and act as hematotoxic, immunotoxic, hepatotoxic, pulmonary toxic, and nephrotoxic agents. In this review, we particularly address the hexavalent chromium-induced generation of reactive oxygen species and increased lipid peroxidation in humans and animals, and the possible role of garlic (*Allium sativum* Linn) as a protective antioxidant.

Keywords: chromium (VI); garlic (*Allium sativum* Linn); oxidative stress.

Introduction

Elemental chromium (Cr) (CAS no. 7440-47-3) has an atomic weight of 51.996, a density of 7.2 g/mL at 28°C, a melting point of 1857°C, a boiling point of 2640°C, vapor pressure of 1 mm Hg at 1616°C, and is insoluble in water (1). Elemental chromium does not occur in nature, but is present in ores, primarily chromite ($FeOCr_2O_3$) (2). Chromium is a naturally occurring element found in animals, plants, rocks, and soil and in volcanic dust and gases. Chromium has oxidation states (or 'valence states') ranging from chromium (II) to chromium (VI). Chromium compounds are stable in the trivalent state and in this state it is found in ores, such as ferrochromite. The hexavalent (VI) form is the second-most stable state. However, chromium (VI) rarely occurs naturally, but is usually produced from anthropogenic sources (3). Chromium (VI) compounds are reduced to chromium (III) in the presence of oxidizable organic matter. However, in natural waters where there is a low concentration of reducing materials, chromium (VI) compounds are more stable (3).

Chromium is used to harden steel, manufacture stainless steel, and form many useful alloys. It is mostly used in plating to produce a hard, attractive surface and to prevent corrosion. Chromium gives glass an emerald green color and is widely used as a catalyst. Chromium can exist in several oxidation states, but only two of them, chromium (III) and chromium (VI), are seriously considered because of their predominance and stability in the ambient environment and their toxicological characteristics. Chromium (III) results from the weathering of minerals and is the most stable state of environmental chromium. Chromium (VI) in the environment is man-made, the result of contamination by industrial emissions (4–6). It is found to be more toxic among all the chromium compounds (3). Examples of chromium (III) compounds include chromium acetate, chromium chloride, chromic oxide, and chromium sulfate, whereas examples of chromium (VI) compounds include ammonium chromate, calcium chromate, potassium chromate, potassium dichromate, and sodium chromate (7).

Environmental exposure of chromium

Chromium enters the air, water, and soil mostly in the chromium (III) and chromium (VI) forms as a result of natural processes and human activities. Emissions from burning coal and oil, and steel production can increase chromium (III) levels in air. Stainless steel welding, chemical manufacturing, and use of compounds containing chromium (VI) can increase chromium (VI) levels in atmospheric air. Waste streams from electroplating industries can also discharge chromium (VI). Leather tanning and textile industries as well as those that make dyes and pigments can discharge both chromium (III) and chromium (VI) into waterways.

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The levels of both chromium (III) and chromium (VI) in soil mainly increase from disposal of commercial products containing chromium, chromium waste from industry, and coal ash from electric utilities (8). In air, chromium compounds are mostly present as fine dust particles. This dust eventually settles over land and water. Rain and snow help remove chromium from air. Chromium compounds usually remain in the air for fewer than 10 days. Although most of the chromium in water binds to dirt and other materials and settles to the bottom, a small amount might dissolve in the water. Fish do not accumulate much chromium in their bodies from water. Most of the chromium in soil does not dissolve easily in water and can attach strongly to the soil. A very small amount of chromium in soil, however, will dissolve in water and can move deeper in the soil to underground water. Animal studies show that chromium (VI) is generally more toxic than chromium (III), but none of these two in oxidation state is very toxic by the oral route. Chromium (VI) causes hepatotoxicity in both man and laboratory animals (9). Studies of workers in the chrome pigment industry revealed a correlation between exposure to chromium (VI) and lung cancer (10).

Metabolism and pharmacokinetics of chromium

Chromium (III) compounds are essential to normal glucose, protein, and fat metabolism. In addition, chromium (III) is capable of forming complexes with nucleic acids and proteins. Chromium (VI) is unstable inside the body and is ultimately reduced to chromium (III) in vivo by a variety of reducing agents. Chromium (V) and chromium (IV) are transient intermediates in this process. Hexavalent chromium is highly reactive in biological systems and is rapidly converted to chromium (III). In biological environments, a small amount of chromium (III) is converted to the hexavalent form of the metal. Once inside the cell, highly reactive chromium (VI) is thought to directly damage macromolecules or generate reactive metabolites that damage macromolecules, thereby producing toxicity. The rapid uptake of chromium (VI) into cells can also play a role in its toxicity. Although administered chromium (III) does not result in toxicity comparable to that of chromium (VI), once chromium (VI) has penetrated the cell, it is possible that chromium (III) produced by intracellular reduction is also a proximal toxicant (2). The evidence that chromium (VI) enters tissues following oral exposure is a concern regardless of whether the toxicity is due to the action of chromium (VI) with macromolecules inside the cell or due to its rapid uptake by the cell (11). In vivo and in vitro experiments in rats indicated that, in the lungs, chromium (VI) can be reduced to chromium (III) by ascorbate. The reduction of chromium (VI) by ascorbate results in a shorter residence time of chromium in the lungs and constitutes the first defense against oxidizing reagents in the lungs. When ascorbate is depleted from the lungs, chromium (VI) can also be reduced by glutathione. It has been reported that the reduction of chromium (VI) by glutathione is slower and results in greater residence time of chromium in the lungs, compared to reduction by ascorbate (12). For humans, the overall chromium (VI)-reducing/sequestering capacities were estimated to be 0.7–2.1 mg/day for saliva, 8.3–12.5 mg/day for gastric juice, 11–24 mg for intestinal bacteria eliminated daily with feces, 3300 mg/h for liver, 234 mg/h for males and 187 mg/h for females for whole blood, 128 mg/h for males and 93 mg/h for females for red blood cells, 0.1–1.8 mg/h for epithelial lining fluid, 136 mg/h for pulmonary alveolar macrophages, and 260 mg/h for peripheral lung parenchyma. It could be considered that even these ex vivo data provide important information in the conversion of chromium (VI) to reduced states but the values could show either overestimation or underestimation of the in vivo reducing capabilities (13). The conversion of chromium (VI) to chromium (III) in rats can occur by electron transfer through cytochrome P450 and cytochrome b5. Both oxygen and carbon monoxide were found to inhibit the in vitro cytochrome P450 and cytochrome b5-dependent reduction of chromium (VI) (14). Involvement of cytochrome P450 in the reduction of chromium (VI) to chromium (III) has been reported by Petrilli et al. (15) who demonstrated that inducers of cytochrome P450 can increase the conversion of chromium (VI) to chromium (III) in S-9 mixtures prepared from the liver and lungs of chromium (VI) exposed rats. The relative tissue distributions of chromium (V) indicated that most was found in the liver and much lesser amounts in blood. The mechanism for clearance of chromium (VI) once reduced inside the liver cell can involve the chromium (III)-glutathione complex in the living system. The glutathione complex would be easily soluble through the cell membrane lipid bilayer and capable of entering the bile as an excretory product (16).

Chromium excretion

Excretion of absorbed chromium occurs primarily via urine. In humans, the kidney excretes approximately 60% of an absorbed chromium (VI) dose in the form of chromium (III) within 8 h of ingestion. Approximately 10% of an absorbed dose is eliminated by biliary excretion, with smaller amounts excreted in hair, nails, milk, and sweat (17). Several factors have been shown to alter the rate of excretion of chromium in humans. Intravenous injection of calcium EDTA resulted in a rapid increase in the urinary excretion of chromium in metal workers (18). Both acute and chronic exercises have been shown to increase chromium excretion in the urine, although the increased excretion did not appear to be accompanied with decreased levels of total chromium (19). Chromium is also excreted through hair, nails, and breast milk of humans. The urinary excretion of chromium after a single or during repeated subcutaneous injections of potassium dichromate was observed in rats. A single dose of 5.35 mg chromium (VI)/kg body weight in rats showed an excretion of chromium rapidly in two phases and was essentially complete at 48 h. Research on dogs found that excretion of chromium (III) approximately equal to the clearance of creatinine, indicating little tubular absorption or reabsorption of chromium in the kidneys (20).

Chromium toxicity: an overview

Acute toxicity

Human studies Data on humans consist of a case of acute exposure to 'massive amounts' of chromium trioxide fumes. Acute inhalation exposure of chromium (VI) in humans, such as occupational set-up, can result in respiratory irritation, such as dyspnea, cough, wheezing, sneezing, rhinorrhea, choking sensation, etc., along with dizziness and headache at high concentrations, and can trigger asthmatic attacks in sensitized individuals (21–24). In one study, it was reported that a patient became anorexic and lost 9.09–11.36 kg of body weight within a 3-month period after exposure to chromium (VI) (22). Data on humans indicate that many organs can be targets of acute exposure to chromium (VI) if exposure levels are high enough, but the target organs of low-level exposure have not been sufficiently identified from animal studies. Acute dermal exposure can cause skin burns and can also have similar sequel that lead to death (25, 26). No further data were found regarding systemic effects in humans after acute exposure to chromium (III) compounds by any route. Data on humans indicate that many organs can be targets of acute exposure to chromium (VI) if exposure levels are high enough.

Animal studies An acute inhalation study of chromium trichloride in hamsters indicated that the respiratory system is also a target of chromium (III) exposure (8), and acute dermal studies show that chromium (III) can be a sensitizer, although not as effectively as chromium (VI) (8). Oral LD_{50} values for chromium (VI) compounds (sodium chromate, sodium dichromate, potassium dichromate, and ammonium dichromate) ranged from 13 to 19 mg Cr/kg in female rats, and 21 to 28 mg Cr/kg in male rats (27). An acute exposure resulted in 8% and 24% decreases in body weight gain in pregnant mice exposed to 101 or 152 mg chromium (VI)/kg/day, respectively (28).

Chronic toxicity

Human studies The status of spermatogenesis was evaluated in workers in an electroplating factory in China. Workers exposed to harmful chemicals including chromium (VI) were compared with workers who were not exposed. Sperm counts and motility were found to be significantly reduced in workers exposed to harmful chemicals (29).

An increased risk of death from non-cancer respiratory disease was reported in retrospective mortality studies of workers in a chrome plating plant (30). The respiratory tract in humans is a major target of inhalation exposure to chromium compounds. Chromate sensitive workers acutely exposed to chromium (VI) compounds can develop asthma and other signs of respiratory distress. In one study, five individuals who had a history of contact dermatitis to chromium were exposed through a nebulizer to an aerosol containing 0.035 mg chromium (VI)/mL as potassium dichromate. A 20% decrease in the forced expiratory volume (FEV_1) of the lungs was observed and was accompanied by erythema of the face, nasopharyngeal pruritus, nasal blocking, coughing, and wheezing (24). Occupational exposure to chromium (VI) as chromium trioxide in the electroplating industry caused upper respiratory problems. A case history of nine men in a chrome plating facility reported seven cases of nasal septum ulceration. Signs and symptoms included rhinorrhea, nasal itching and soreness, and epistaxis (bleeding from the nose). The men were exposed from 0.5 to 12 months to chromium trioxide at concentrations ranging from 0.09 to 0.73 mg chromium (VI)/m^3 (31). Numerous studies of workers chronically exposed to chromium (VI) compounds have reported nasal septum perforation and other respiratory effects. Many of the workers had ulcerations and/or perforations of the nasal mucosa (32). An extensive survey to determine the health status of chromate workers in seven US chromate production plants found that effects on the lungs consisted of bilateral enlargement. No excess deaths were observed from cardiovascular diseases and ischemic heart disease in a cohort of 4227 stainless steel production workers from 1968 to 1984 when compared with expected deaths based on national rates and matched for age, sex, and calendar time (33). In an extensive survey to determine the health status of chromate workers in seven US chromate production plants, hematological evaluations revealed no effects on red blood cell counts, hemoglobin, hematocrit, or white blood cell counts. Studies of workers in the chromium pigment, chrome plating, and ferrochromium industries showed a statistically significant association between worker exposure to chromium (VI) and lung cancer (34, 35).

Animal studies Oral administration of 10 or 20 mg/kg/day of Cr_2O_3 (5 or 10 mg/kg/day of Cr VI) for 6 days and then sacrificed after 6 weeks found lower epididymal sperm counts with greater abnormal sperms in Wistar rats (36). Hexavalent chromium was administered in drinking water (250, 500, or 750 ppm/day as potassium dichromate) to female Druckrey rats for 90 days and it was observed that 15% of animals treated with 500 ppm died and 10% treated with 750 ppm died during the first 14 days of treatment (37). Exposure of male Wistar rats to a chromium (VI) ($Na_2Cr_2O_7$) aerosol (50, 100, 200, or 400 μg/m^3 chromium) for 30 or 90 days (22 h/day) resulted in significant increases in lung weight and number of leucocytes in the blood for all dose groups compared with controls (38).

Hematological evaluations of rats exposed to sodium dichromate at 0.025–0.2 mg chromium (VI)/m^3 for 28 or 90 days or 0.1 mg chromium (VI)/m^3 for 18 months did not find any significant changes (39, 40). However, increased white blood cell counts were found in rats exposed to 0.1 mg chromium (VI)/m^3 as sodium dichromate for 30 days and at 0.05 mg chromium (VI)/m^3 for 90 days (40). Chromium (VI) induced anemia, leucopenia, and thrombocytopenia, and decreased erythrocyte count, packed cell volume % (PCV%), and hemoglobin concentration in experimental animals (41). The possible mechanism following these alterations of hematological parameters could be due to chromium (VI)

induced non-degenerative anemia, by injuring hematopoietic stem cells or decreasing Fe^{2+} metabolism and bone marrow depression (42). Chromium (VI) has been reported to inhibit hemoglobin biosynthesis by decreasing succinyl-CoA and glycine pool (43). In experimental rats it was also observed that hexavalent chromium induced increases of serum low-density lipoprotein cholesterol (LDL-C), total cholesterol, very LDL cholesterol (VLDL-C) and triglyceride (TG) levels and decreases serum high-density lipoprotein cholesterol (HDL-C) level. The hexavalent chromium induced increases of serum LDL-C, total cholesterol, and TGs and decreases of serum HDL-C could be due to changes in the gene expression of hepatic enzymes, such as HMG-CoA reductase (hydroxymethylglutaryl-CoA reductase), which in turn depresses LDL receptor gene expression (44). Possibilities of hypoactivity of lipoprotein lipase in the blood vessels and decreased absorption of fatty acid by fat cells following chromium (VI) exposure could be the cause of an increase in TG level (45). High TG level could also be due to renal/hepatic failure following hexavalent chromium exposure (44, 46).

In experimental rats hexavalent chromium treatment shows hyperglycemia/diabetes, such as symptoms associated with a decrease of liver glycogen concentration and diabetic oral glucose tolerance test response (47). The reason could be due to chromium (VI) elevated inducible nitric oxide synthase activities and increases in B cell nitric oxide level in pancreas which concomitantly decreases insulin secretion. Another possibility is that chromium (VI) could increase α-adrenergic receptor activities in B cell and suppress insulin secretion (41, 48). Chromium (VI) treatment elevated both serum glutamate oxaloacetate transaminase (SGOT) and glutamate-pyruvate transaminase (SGPT) activities in experimental animals (47). Elevation of SGOT and SGPT activities indicate malfunction of hepatocytes. The higher activity of SGOT and SGPT in chromium (VI) treated rats could also result from excessive accumulation of amino acids (glutamic acid and alanine) in serum. The excessive amino acids could convert to ketone bodies for which the enzymes SGOT and SGPT are needed. Serum glutamic oxalocetic transaminase or AST is an enzyme found primarily in the liver, heart, kidney, pancreas, and muscles. In tissue damage, especially heart and liver, this enzyme is normally found to be elevated (49).

A study on experimental rats revealed that chromium (VI) increased erythrocytes malondialdehyde (MDA), glutathione (GSH) levels, and the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), and catalase (CAT), which clearly reflects generation of reactive oxygen species (ROS) by chromium (VI) (50). As a consequence of heavy metal, such as chromium (VI) toxicities, enhanced lipid peroxidation, DNA damage, altered calcium, and sulfhydryl homeostasis, as well as marked disturbances of the antioxidant defense system in various metabolically active tissues occurred (51). Potassium dichromate increased hepatic lipid peroxide concentration and decreased hepatic glutathione concentration, SOD, CAT, and GSH-Px activities in Wistar strain albino rats (47). The increased lipid peroxidation due to chromium (VI) treatment in rats suggests an increase of phospholipase activities during peroxidic decomposition of different suborganelle and plasma membrane lipids. The peroxide generated must stimulate phospholipase A_2 (PLA_2) activities on the cell membrane. Activation of PLA_2 causes the production of a variety of eicosanoids, which are responsible for different metabolic disorders and cell injury (52).

Chromium toxicity and antioxidant defense: role of *Allium sativum* Linn

Oxidative stress in the living system

Man is probably the result of evolutionary processes of unicellular and anaerobic organisms. The terrestrial environment acquired more complex organisms by the development of the ozone layer which allowed the absorption of ultraviolet solar radiation partly. With the ultraviolet radiation reduction, the earthly environment became more compatible to life and initiated the acceleration of the evolutionary process (52, 53). ROS, as they react to the majority of organism molecules, are able to interfere in biological processes, causing several diseases, mutations, aging, among other alterations (54, 55).

Lipid peroxidation Lipid peroxidation is the process through which ROS attack the polyunsaturated fatty acids of the membrane phospholipids of the cells, disintegrating them and allowing, in this way, species entry into intracellular structures. The phospholipase enzymes, activated by toxic species disintegrate the phospholipids, liberating the non-saturated fatty acids resulting in the following deleterious actions by the lipid peroxides: (i) cellular membrane rupture (NA/k and Ca/Mg bombs), (ii) DNA mutations, (iii) unsaturated lipid oxidation, (iv) chemical residue formation, such as malondialdehyde, and (v) component engagement of the extracellular matrix, proteoglycans, collagen, and elastin (47).

Lipid peroxides possess an action power higher than other primary toxic species of O_2 (O_2^-, H_2O_2, OH^-), reaching further targets easily. Lipid peroxidation also has a very important role in cellular proliferation, especially in tumor cells. Some authors reported that lipid peroxidation is directly involved in uncontrolled cell division and leads to tumor genesis, whereas other suggested that lipid peroxidation is related to cell necrosis (55, 56).

Antioxidant mechanism Oxygen is a paradox in the planet, because it is essential to live as well as causing injury to the organism (52). Antioxidant agents cannot distinguish between ROS that have a physiological role and ROS that cause damage. Because of this, their action can, in some way, not be beneficial to the organism. However, it is a balance between the oxidant and antioxidant species that the organism will be able to obtain the conditions for a better performance of its functions, considering that a disturbance in this balance can result in a range of pathological processes (47, 54). In general, the following observations are seen in oxidative stress due to heavy metal exposure: (i) decompartmentalization of metal complexes, (ii) excessive

production of O^- (superoxide), and (iii) decrease of cellular antioxidant defense system.

Role of garlic (*Allium sativum* Linn) as an antioxidant against chromium (VI) toxicities

Defending ourselves against a wide array of chemicals, heavy metals, pollutants, radiation, and poor nutrition has become a vital area of scientific focus and research. Oxidizing agents or free radicals attack our bodies constantly and have the potential to damage our cells, which compresses human tissue. Substances which have been usually found to help protect us from cellular damage caused by free radicals include vitamin C, bioflavonoids, vitamin E, vitamin A, β-carotene and selenium (57). Currently, research on garlic clearly reveals its potential antioxidant properties to combat against heavy metal induced oxidative stress in the biological system (44).

Garlic, *Allium sativum* Linn, is a root crop of the family *Alliaceae*. It is among the oldest of all cultivated plants. Its species name *sativum*, which means cultivated. It is a member of the same group of plants as the onions, chive, and leek. This plant originated from central Asia and is used as a spice, food, and folklore medicine for over 5000 years, and is the most widely researched medicinal plant in history. Through trade, garlic extended its popularity throughout Asia and eventually to Egypt and Europe. The age of exploration helped to propagate the use of garlic to other parts of the world. Currently, somewhere around 300–400 varieties of garlic cultivate worldwide. In the United States, over 113 million kg of garlic is consumed each year (58).

Garlic is mentioned in the Bible and has been a traditional treatment in many countries, notably the Near East, China, and India. Hundreds of chemical substances are present in fresh, dried garlic, or extracts. Significant synergy or antagonism of the garlic substances, or their artifacts, on human physiology can exist and vary with an individual's age, pathology, dosage regimen, and possible drug, food, or metabolite interactions. Evidence suggests beneficial effects of a regular dietary intake of garlic on mild hypertension and hyperlipidemia (59). Garlic seems to have antimicrobial and immunostimulating properties, enhances fibrinolytic activity, and exerts favorable effects on platelet aggregation and adhesion. There are several important compounds that have been isolated from garlic bulbs, such as allicin, alliin, allyl disulfides, allyl trisulfides, cycloallin, cysteine, diallyl sulfides, glutathione, methionine, methyl sulfides, pseudoscordinine, scordinine, thiosulfinates, etc. (60).

Allicin, a strong antioxidant, gives garlic its strong odor, and is also believed to be responsible for some of its medicinal uses. Allicin is a very reactive compound due to its S-S bonds, and is slightly soluble in water and alcohol due to hydroxide (OH).

Long-term extraction of garlic ages the extract, creating antioxidant properties by modifying unstable molecules with antioxidant activity, such as allicin, and increasing stable and highly bioavailable water-soluble organosulfur compounds, such as S-allylcysteine and S-allylmercaptocysteine (58, 61). The alliin molecule goes through an enzyme-catalyzed reaction to form allicin. Alliinase, the enzyme, lowers the activation energy so that this reaction can take place (61).

The allicin compounds of garlic have been found to possess a significant blood sugar lowering action. Clinical studies have suggested that these compounds lower glucose levels by competing with insulin sites in the liver, which results in an increase of free insulin. Research has found that animals and humans with diabetes experienced a decline in blood sugar while taking garlic. Recent studies have validated many of the medicinal properties attributed to garlic and its potential to lower the risk of disease (1 mg garlic=15 Oxford units of penicillin). It is reported that garlic has 1% of the potency of penicillin (58). Garlic is also recommended for protection from heavy metal induced toxicities (47). It is considered as an effective antioxidant against mercury induced pollution (58). It has the ability to stimulate the lymphatic system which expedites the removal of waste from the body. It is considered an effective antioxidant and can help protect cells against free radical damage. Garlic also contains several amino acids which are required for the formation of an enzymatic antidote to free radical pathology which is created by various pollutants including heavy metals. Cysteine, glutamine, isoleucine, and methionine found in garlic help to protect the cells from such free radical damage (58). Treating heavy metal poisoning has involved a process called chelation. Japanese research has discovered that raw garlic extract can effectively protect the body from metal toxicity. Current research on garlic by the author and his group showed that it has a protective role to improve anemia, leucopenia, thrombocytopenia in both diabetic and non-diabetic nickel and hexavalent chromium treated rats (41). The possible mechanism could be: (i) stimulation of bone marrow activity or (ii) sulfur compounds in garlic significantly prolong bleeding time and thrombin time (60). This observation can partly explain the role of garlic in activating natural killer cells, the function of T lymphocytes, and the level of interleukin-2 (62).

Hexavalent chromium induced dyslipidemia in experimental rats was counteracted by simultaneous garlic administration. The possible mechanism could be the inhibition of HMG-CoA reductase, a rate limiting enzyme in cholesterol biosynthesis by garlic extract (59). Garlic or *Allium sativum* Linn is found to be effective in suppressing hepatic activities of other lipogenic, cholesterogenic enzymes, such as fatty acid synthase or glucose-6-phosphate dehydrogenase, etc. (61). Thus, the triglyceride-lowering effect of garlic could be due to the inhibition of fatty acid synthesis (63). Apparently, it has been found that allicin compounds in garlic help to block the creation of cholesterol, and subsequently serum TGs and β lipoprotein levels were lowered whereas HDL levels (good cholesterol) were increased. The manner in which garlic accomplished this specific action is not totally understood. What is known is that the presence of garlic provides a simple restriction in the increase of blood cholesterol and lipid levels (58). Thus, it could be an effective antioxidant against chromium (VI) induced alteration of serum lipid profile.

Garlic improves blood glucose level/hyperglycemia and hepatic glycogen content in rats treated with potassium

Table 1 Summarizing the protective role of garlic (*Allium sativum* Linn) on chromium (VI) toxicities in experimental Wistar rats (based on the findings of the author and his team) (41).

Sl. no.	Physiological parameters	Effect of chromium (VI) exposure	Effect of simultaneous treatment with *Allium sativum* Linn
1.	Hematology	Decrease in RBC count, PCV%, WBC count and hemoglobin concentration. Anemia leucopoenia, thrombocytopenia and prolongs clotting time observed	RBC count, PCV%, WBC count, and hemoglobin status improved. Platelets count remained low
2.	Serum lipid profile	Dyslipidemia	Improvement in LDL-C, HDL-C, VLDL-C, and ratio of HDL-C and LDL-C, but no improvement in total cholesterol and triglyceride level
3.	Glucose homeostasis	Increased blood glucose level and decreased liver glycogen concentration. Diabetic type glucose tolerance response in acute exposure	Garlic improves blood glucose level/hyperglycemia and hepatic glycogen content in rats. Showed a better glucose tolerance response
4.	Serum transaminases (SGOT and SGPT)	Elevated both SGOT and SGPT activities	Improvement of SGOT and SGPT activities
5.	Erythrocyte antioxidant status	Increased erythrocytes MDA, GSH levels, and the activities of SOD, GSH-Px, and CAT	No such improvement was found
5.	Hepatic antioxidant status	Increased hepatic lipid peroxide and decreased hepatic glutathione concentration, SOD, CAT, and GSH-Px activities	Decreased hepatic lipid peroxide and increased glutathione level. All the endogenous antioxidant enzyme activities improved

RBC, red blood cells; WBC, white blood cells; PCV, packed cell volume.

dichromate. In experimental animals, garlic extract was found to improve blood glucose level and hepatic glycogen content in alloxan diabetic rats simultaneously exposed to chromium (VI) (47).

Allicin compounds of garlic have been found to possess a significant blood sugar lowering action. It has also been reported that some of the sulfur-containing compounds of garlic have special sugar metabolism regulating capabilities. Research has found that animals and humans with diabetes experienced a decline in blood sugar while taking garlic. Interestingly, if blood sugar is normal, garlic did not promote this lowering effect (58).

Garlic shows a better glucose tolerance curve in acute exposure of chromium (VI) or diabetic animals simultaneously exposed to chromium (VI) (41, 47, 64). The hypoglycemic effect of garlic seems to be associated with the increase of insulin level and increase of insulin sensitivity. Components in garlic, i.e., S-allyl cysteine sulfoxide, are found to have a glucose lowering effect in diabetic animals (65, 66). It is reported that antioxidant phytochemicals which include organosulfur compounds (such as garlic) help to combat oxidative stress (41). Table 1 summarizes the ameliorative effect of garlic on chromium (VI) induced alteration of some physiological parameters in experimental animals.

The study on aqueous preparation of garlic (*Allium sativum*) was found to be an effective antioxidant against hexavalent chromium induced generation of ROS in metabolically active tissues because it scavenged superoxide ions and reduced lipid peroxide formation in liver of Wistar rats. These results support the view that aqueous garlic inhibits the oxidation of LDL by scavenging superoxide and inhibiting the formation of lipid peroxides (67).

It has been reported that metals activate signaling pathways and the carcinogenic effect of heavy metals has been related to activation of mainly redox sensitive transcription factors, involving NF-κB, AP-1, and p53 (68). Antioxidants (both enzymatic and non-enzymatic) provide protection against deleterious metal-mediated free radical attacks by blocking NF-κB pathways (69). Hence, it could be postulated that garlic, as an antioxidant, has the potential to enhance the endogenous antioxidant status of metabolically active tissues in hexavalent chromium induced lipid peroxidation in rats (41). Allicin, the active component of freshly crushed garlic cloves, could be the prime protective substance against heavy metal induced lipid peroxidation and decreased antioxidant enzyme activities in metabolic tissues (70–72).

Conclusions

It can be concluded from the various studies cited in this review paper, including those conducted by the present author and his group, that chromium (VI) is a potent toxic agent which adversely affects hematology, hepatic, pulmonary, and excretory systems and alters glucose homeostasis in both human and experimental animals.

Furthermore, it has also been observed that hexavalent chromium induces oxidative stress in the living system and can partly be counteracted or neutralized by additional supplementation of garlic (*Allium sativum* Linn).

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