ISPEC Fen Bilimleri Enstitüsü Dergisi, 4(2):119-126, 2025
ISPEC Journal of Science Institute, 4(2):119-126, 2025
DOI: https://doi.org/10.5281/zenodo.17977819

The Dichotomy of Chromium as Essential Micronutrient Versus Toxic Substance A Review

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Abstract
Chromium functions as a cofactor for insulin, thereby influencing the metabolism of carbohydrates, proteins and lipids. Chromium deficiency has been associated with various clinical conditions, including glucose intolerance, elevated circulating insulin levels, glycosuria, growth disorders and hypoglycaemia. Among the two most prevalent oxidative states of chromium, trivalent chromium (Cr^{3+}) is considered beneficial, whereas hexavalent chromium (Cr^{6+}) is recognized for its toxicity, including carcinogenic effects. Several vegetables, such as broccoli, and fruits, such as grapes, naturally contain high levels of chromium; however, chromium supplements are increasingly popular, primarily due to their purported role in weight loss. Excessive intake of chromium may result in anaemia, thrombocytopenia, liver diseases and renal failure. The toxicity of chromium can potentially be mitigated by certain compounds, such as N-acetylcysteine (NAC) and herbal remedies, such as *Moringa oleifera* leaf extracts. The role of chromium in biological systems remains incompletely understood, necessitating further research.

Review Article

Article History
Received : 01.11.2025
Accepted : 16.12.2025

Keywords
Chromium,
Essential Micronutrient,
Insulin,
Toxicity

1. Introduction

Chromium, a trace element comprises approximately 0.01% or 100 ppm of the Earth's crust (Emsley, 2001) and is naturally found in many foods that we consume. The two prevalent oxidation forms of Cr are trivalent chromium (Cr^{3+}) and hexavalent chromium (Cr^{6+}). The trivalent form is considered a beneficial micronutrient whereas hexavalent chromium has no known biological functions and is a potent carcinogen. The major environmental and health–related challenges of Cr, however, are predominantly due to anthropogenic activities. The production of world annual Cr, as chromite ore (Cr_2O_3), was estimated at 44 million tons in 2019 (the dominant producing countries were South Africa, Turkey, Kazakhstan, and India) (U.S. Geological Survey, 2020). The major sources of Cr in the environment are the electroplating and metal finishing industries, chemical plants, iron and steel factories, tanneries, and textile manufacturers (Ecological Analysts, 1981).

Chromium does not play any significant role in plant physiology (Dixit et al., 2002). However, Cr has been found to be essential for normal carbohydrate and lipid metabolism in mammals and birds. chromium is thought to be a cofactor for insulin activity (Anderson, 1981). In fish, Cr salts have been reported to assist glucose consumption and hinder gluconeogenesis (Hertz et al., 1989). Shiau and Lin (1993) have revealed that supplemental dietary Cr boosts weight gain, energy deposition, and liver glycogen content in tilapia fed with elevated glucose diets.

Accumulation of Cr by plants could decrease growth and pigment content, stimulate chlorosis, and damage root cell (Panda and Choudhury, 2005). Plants collect Cr from nutrient solution thus, higher levels of Cr concentration can be found in plants collected from high–Cr rich soils than that low–Cr soils. However, plants generally retained Cr in the root systems than in above–ground parts (Cary and Kubota, 1990). Metabolic alterations by Cr exposure have also been described in plants (Shanker et al., 2005).

The function of chromium in humans varies with exposure route, oxidation state, and chemical composition (Moffat et al., 2018). The objective of the present review is to consider both the beneficial role and toxic effects of chromium.

1.1. Chemical nature of chromium

The relative atomic mass of chromium is 51.996 g. Theoretically; it may exist in oxidation states from –2 to +6. However, Cr has been noted to show oxidation states of 0, +2, +3 and +6. Elemental Cr (0) is not found readily in the earth's crust. Divalent chromium (Cr^{2+}) is unstable in nature and is easily oxidised into trivalent chromium (Cr^{3+}). Trivalent chromium (Cr^{3+}) is the most stable oxidation form of Cr, hence, shows the lowest reactivity. Hexavalent chromium (Cr^{6+}) is less stable than trivalent chromium (Cr^{3+}). It shows strong oxidising activity in an acidic medium. Mention may be made that most of the biologically occurring Cr are trivalent chromium (Cr^{3+}) while hexavalent chromium (Cr^{6+}) is of industrial origin. Compounds of chromium which are most abundant include halides, oxides, and sulphides (Pechova and Pavlata, 2007).

1.2. Biological nature of chromium

Elemental Cr (0) is biologically inert while divalent chromium (Cr^{2+}) due to its unstable nature is not found in biological systems. Trivalent Cr, the most stable form of chromium is readily found in biological systems, however, it cannot cross the cell membrane easily. Phagocytic processes or nonspecific diffusion assist Cr^{3+} to cross the cell membrane. Trivalent Cr has been reported as an essential micronutrient for humans having multifarious biological functions. On the other hand, Cr^{6+} very easily crosses cell membranes and has toxic effects including cancer (Monga et al., 2022).

1.3. Chromium in a biological system

Both inorganic and organic chromium may enter the biological system mainly through diet. The absorption of Cr in the body is inversely proportional to the dose. The intestine is the main site for chromium absorption. Chromium absorption is influenced by many factors including carbohydrates, proteins, chelating elements, and metals. Unabsorbed Cr is mainly excreted by faeces while absorbed Cr is chiefly excreted via urine. Absorbed Cr may be retained in cells or may circulate in blood upon binding with molecules like beta globulin and transferrin (Krejpcio, 2001; Monga et al., 2022).

1.4. Normal chromium level in human body and results of deficiency

The amount of Cr in human blood and tissues has been reported to vary widely in different studies. Until 1978 levels of Cr in blood were claimed to range between 1 and 40 μg/l (Veillon and Patterson, 1999). In a later study, it was reported that the concentration of Cr in blood serum was 0.035–0.04 μg/l while that for full blood it was 0.120–0.34 μg/l for a healthy human population (Christensen, 1993). Dubois and Belleville (1991) have reported that the normal human body contains total chromium concentration in the range between 0.4 and 6 mg. Among the different tissues and organs Cr tends to accumulate in epidermal tissues like hair, and in bones, kidney, liver, adrenal gland, spleen, lung and in the intestine[12]. Symptoms of Cr deficiency in humans include glucose intolerance, increased circulating insulin, glycosuria, growth disorders, hypoglycaemia, increased serum cholesterol and triacylglycerols, neuropathy, encephalopathy, increased intraocular pressure, reduced number of insulin receptors, reduced muscle proportion, low respiratory quotient, abnormal nitrogen metabolism, and increased proportion of body fat (Anderson, 1994).

2. Biological role of chromium

Researchers around the globe have performed several studies to demonstrate the biological role of chromium. Most of these studies have been based on Cr deficient diet and /or with Cr supplements. A few of the major thrust areas that have gained much popularity are discussed below.

2.1. Carbohydrate metabolism

It has long been postulated that Cr has a role in carbohydrate metabolism by potentiating insulin action. However, the actual mode of action is not yet known. It has been proposed that insulin action is promoted upon binding of chromodulin (a low molecular weight Cr binding oligopeptide) to insulin receptors and in turn, activating it (Eckhert, 2014). Researchers have found that Cr supplementation can influence human glucose tolerance and insulin resistance (Anderson, 2000; Tuzcu et al., 2014). Further, it has been found that Cr supplementation along with insulin can result in increased glucose utilization by means of glucose oxidation and glycogenesis along with the conversion of glucose to lipids (Anderson, 1997).

2.2. Protein metabolism

The role of Cr in protein metabolism has been studied by various researchers. It has been reported that Cr plays important role in the usage of amino acids. Moreover, it has been shown that Cr facilities the absorption, transport, and storage of amino acids. Also, Cr has been identified to influence the intracellular movement of amino acids thereby facilitating the synthesis of protein molecules (Tao, 2019). It has been reported that the addition of chromium can increase protein levels in blood plasma.

2.3. Lipid metabolism

Cr–picolinate has been reported to be widely used in weight loss programs and in an increase of lean body mass. Also, Cr supplementation has been reported to decrease total cholestanol and triglycerides along with LDL cholesterol and non–esterified fats in blood serum. However, this supplementation has also been reported to increase HDL cholesterol in serum (Lai et al., 2006).

2.4. Nucleic acid metabolism

It has been reported that Cr has a very strong affinity for nucleic acid and can help in maintaining the structural integrity of nucleic acid. Reports have been made that Cr can bind to chromatin and influence gene expression. Heat denaturation of RNA has been proposed to be protected by Cr. Also, it has been found that Cr can increase in vitro RNA synthesis (Okada et al., 1989).

2.5. Mineral substances metabolism

Transferrin is the molecule that binds both Fe and Cr. However, this binding is antagonistic (Sayato et al., 1980). Alteration in Fe homeostasis and impaired Fe metabolism along with decreased tissue Fe have been correlated with Cr supplementation (Anderson et al., 1996). In other studies, Cr has been found to interfere with the metabolism of several minerals including Al, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Mo, Ni, P, Pb, Se, Sr, V, and Zn (Frank et al., 2000a; Frank et al., 2000b).

2.6. Hormonal regulation

Chromium supplementation has been proposed to influence the functioning of several hormones including cortisol and insulin (Pechova and Pavlata, 2007), however, the exact pathway in which these reactions occur is mostly unknown.

2.7. Role on growth, body composition, and reproduction

Studies have shown a positive correlation between Cr supplementation and weight gain during stressful conditions in cattle and pigs. Also, in some studies increases in muscle content have been reported. However, there are reports of having no influence or negative influence on body weight and muscle as well. However, chromium picolinate has been used in humans to lose weight. Reproductive success with Cr supplements has been studied by various researchers and it was found that the use of these supplements could increase litter size in pigs. On the other hand, Cr–deficient diets have been reported to reduce sperm count and lower the fertility of the sperm in rats (Pechova and Pavlata, 2007).

2.8. Role on immunology

Studies with cows and pigs have shown that Cr supplementation can increase antibodies for certain pathogens. Again, Cr deficiency has been found to be influencing haematological parameters (Pechova and Pavlata, 2007).

2.9. Role on life span

Studies with mice having Cr supplement treatment have been found to show a low mortality rate and higher longevity (Evans and Meyer, 1992). Studies with broilers have also shown lower mortality rates when treated with Cr supplement (Hossain et al., 1998). The antiaging property of Cr has been postulated to be related to its effect on insulin.

3. Toxicological Effect of Chromium

It is generally thought that trivalent chromium (Cr^{3+}) is beneficial while hexavalent chromium (Cr^{6+}) is toxic. However, recent findings have shown that Cr^{3+} can also have toxic effects mainly depending on the dosage. A brief discussion on the toxicity of both Cr^{3+} and Cr^{6+} has been given below.

3.1. Toxic effects of Cr^{3+}

Studies have shown that Cr^{3+} can interact with DNA to damage it. However, the low penetration ability of Cr^{3+} through cell membranes has made it less toxic. Overdosing of Cr may lead to adverse conditions as has been found in few studies. These include loss of weight, anaemic conditions, deficiency of platelets in the blood, liver diseases, renal failure, breakdown of muscle tissue, skin problems, and hypoglycemia (Fowler, 2000; Vincent, 2003). However, Cr^{3+} consumed through a normal daily diet has seldom been found to exert toxic effects, in fact, the toxicity of Cr^{3+} has been found to be less than essential elements like Cu, I, Zn, Mn, and Se (Lindemann, 1996). The dietary intake safe limit for Cr^{3+} has been set at 50–200 mg/day (Monga et al., 2022).

3.2. Toxic effects of Cr^{6+}

The penetrance of Cr^{6+} is much higher than Cr^{3+} through the cell membrane. Mention may be made that inside the biological cell Cr^{6+} can be converted to Cr^{3+} through the Fenton reaction and during this conversion harmful reactive oxygen species (ROS) like hydrogen peroxide, hydroxyl radicals, and superoxide anion radicals are produced (Genchi et al., 2021) that can have deleterious effects on cell and cellular organelles including irreversible DNA damage, tissue necrosis, and cancer (Pavesi and Moreira, 2020). Among specific organs, Cr^{6+} has been reported to damage and cause cancer to the skin, lungs, liver, kidney, and brain along with impaired immune system and reproductive system (Monga et al., 2022).

4. Remedy for Cr^{6+} Toxicity

Like many other toxic substances, microbiota in the gut acts as the first line of defense. Consuming tailored probiotics can help remediate Cr^{6+} toxicity to a great extent (Wu et al., 2017; Ming et al., 2020). Chelation treatment with N– acetylcysteine (NAC) has been found to be beneficial against Cr^{6+} toxicity (Poonam et al., 2018). However, treatment with chemicals has certain side effects. Hence the use of herbal medicines to cure heavy metal toxicity has been proposed (Mehrandish et al., 2019). *Moringa oleifera* leaf extracts and mushrooms like *Pleurotus tuberregium* and Curcumin are worth mentioning in this regard (Monga et al., 2022).

5. Sources of Chromium

Chromium supplements are gaining popularity day by day and according to a report in the United States the sales for Cr^{3+} supplement was estimated at $110 million in the year 2016 (Monga et al., 2022). However, there are several natural food sources that can sufficiently meet the need for Cr required for the normal functioning of the body. Broccoli has a high content of Cr, and other vegetables like Potatoes, Green beans, tomatoes, Celery, and Carrots are rich sources of Cr. Among fruits Grapes have been reported to contain a high amount of Cr also, fruits like Apple, Orange, Banana, and Orange are good sources of Cr. Some of the spices and herbs are rich sources of Cr. These include Basil leaves, Turmeric, Oregano, Pepper, Mint, Garlic, and Saffron. Dairy products like Butter and Margarine also contain a good quantity of Cr (Dattilo and Miguel, 2003).

6. Conclusions

Studies have shown that Cr plays role in carbohydrate, protein, lipid and nucleic acid, and other mineral substance metabolism. Also, Cr has been clinically correlated with body weight change, lean mass increase, growth, and reproduction modulator along with immunity booster. Cr may also act as an antioxidant (Anderson and Cefalu, 2010). However, the precise mode of action of Cr action is mostly unknown. Based on chromium's effects on insulin action the Food and Nutrition Board (FNB) of the U.S. food supply in 2001 considered Cr as an essential nutrient (Institute of Medicine, Food and Nutrition Board, 2001). However, most recent findings have shown that any abnormalities caused due to deficiency of Cr are not readily cured upon treatment with Cr, hence, many have raised the question of whether Cr should at all be considered an essential mineral. Accordingly, the European Food Safety Authority Panel on Dietetic Products, Nutrition, and Allergies in the year 2014 has commented that since there has been no conclusive evidence that Cr is an essential nutrient and therefore, setting recommendations for Cr intake would be inappropriate (EFSA NDA Panel, 2014).

Acknowledgements

The author thankfully acknowledges the Director of Public Instruction, Government of West Bengal, India, and Officer–in–Charge, P. R. Thakur Government College, Thakurnagar for their sustained goodwill and all the infrastructural support extended by them.

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