

A Comprehensive Review on Nickel (II) And Chromium VI Toxicities - Possible Antioxidant (*Allium Sativum* Linn) Defenses

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Abstract: The toxicity associated with nickel (II) and chromium (VI) is mainly due to generation of reactive oxygen species (ROS) with subsequent oxidative deterioration of biological macromolecules. Both nickel and chromium can generate free radicals (FR) directly from molecular oxygen in a two step process to produce superoxide anion and in continued process, produce highly toxic hydroxyl radical. The pro-oxidative effects are compounded by fact that they also inhibit antioxidant enzymes and deplete intracellular glutathione. Garlic (*Allium sativum*) has played an important dietary and medicinal role throughout the history of mankind. Garlic has the potential to enhance the endogenous antioxidant status in nickel as well as hexavalent chromium induced lipid peroxidation in normal and diabetic rats.

Key words: Nickel(II), Chromium (VI), Garlic (*allium sativum* Linn), Antioxidant defenses

Introduction:

Heavy metals are stable and persistent environmental contaminants beside their beneficial action. A person spends, on an average, one third of his life at his work place. Therefore the environment in which he works can be a major factor in determining health. In modern civilization, the single largest industry, the stainless steel industry along with welding and electroplating industry releases highest amount of nickel and chromium compounds in the environment. Welders of India and elsewhere are inclined to possible occupational exposure of nickel and chromium. Nickel is considered as an essential nutrient that is only required in very small amounts, but has a number of cellular effects. Its absorption into the body is affected by factors of consumption, the acidity of the gut, and various binding or competing substances, including other minerals such as iron, magnesium, zinc and calcium. It is found predominantly in the lung, kidney, and hormone-producing tissues, and can activate or inhibit enzymes that usually contain other elements. It is also involved in the production and action of certain hormones such as adrenaline, noradrenaline, prolactin and aldosterone. Intracellularly, Ni can affect membrane properties and oxidation/reduction systems. It has also been found to have a high affinity for cellular structures (chromosomes, ion channels) but its influence in this context is still unknown. Ni deficiency is rare due to the low level of requirement, and its relatively high availability in the diet, but experiments have shown that at a cellular level, Ni deprivation results in changes in the membrane properties and other structures. Deficiency has also been associated with low blood glucose levels, abnormal bone growth, altered metabolism of calcium, vitamin B12 and energy nutrients, and poor absorption of ferric iron. [1-2]. Nickel is a naturally occurring element that may exist in various mineral forms. It is used in a wide variety of applications including

metallurgical processes and electrical components, such as batteries [3]. Some evidence suggests that nickel may be an essential trace element for mammals. The absorption of nickel is dependent on its physicochemical form, with water soluble forms being more readily absorbed. The metabolism of nickel involves conversion to various chemical forms and binding to various ligands [3]. Nickel is excreted in the urine and feces with relative amounts for each route being dependent on the route of exposure and chemical form. Most nickel enters the body via food and water consumption, although inhalation exposure in occupational settings is a primary route for nickel-induced toxicity. In large doses (>0.5 g), some forms of nickel may be acutely toxic to humans when taken orally [4-5]. Oral LD₅₀ values for rats range from 67 mg nickel/kg (nickel sulfate hexahydrate) to >9000 mg nickel/kg (nickel powder) [3]. Toxic effects of oral exposure to nickel usually involve the kidneys with some evidence from animal studies showing a possible developmental/reproductive toxicity effect [3,6]. The primary target organs for nickel-induced systemic toxicity are the lungs and upper respiratory tract for inhalation exposure and the kidneys for oral exposure [3,6]. [Other target organs include the cardiovascular system, immune system, and the blood. Nickel induced severe liver and kidney damage by altering several marker enzymes and ascorbate cholesterol metabolism is reported [7]. Nickel induced decrease in fertility were observed in male rats, but not in female rats orally exposed to nickel. Nickel induced alterations of testicular steroidogenesis was reported [8]. Elemental chromium (Cr) (CAS No. 7440-47-3) has an atomic weight of 51.996, a density of 7.2 g/mL at 28C, a melting point of 1857 20C, a vapor pressure of 1 mm Hg at 1610C, and is insoluble in water [9]. Elemental chromium does not occur in nature, but is present in ores, primarily chromite (FeOCr₂O₃) [10]. Chromium is used to harden steel, manufacture stainless steel, and form many useful alloys. It is mostly used in plating to produce a hard, beautiful 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, Cr (III) and Cr (VI), are considered in this report because of their predominance and stability in the ambient environment and their toxicological characteristics. Cr (III) results from the weathering of minerals and is the most stable state of environmental chromium. Cr(VI) in the environment is man-made, the result of contamination by industrial emissions [8,11-12], and is the more toxic [13]. Examples of Cr (III) compounds include chromium acetate, chromium chloride, chromic oxide, and chromium sulfate; examples of Cr (VI) compounds include ammonium chromate, calcium chromate, potassium chromate, potassium dichromate, and sodium chromate [14]. Animal studies show that Cr (VI) is generally more toxic than Cr (III), but neither oxidation state is very toxic by the oral route. ChromiumVI causes hepatotoxicity in both man and laboratory animals [15]. Studies of workers in the chrome pigment industry revealed a correlation between exposure to Cr (VI) and lung cancer [16]. 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. Interestingly enough, irritation of the skin a most frequently reported human health effect from exposure to Cr (VI) (very obvious in the Oscar winning movie: Erin

Brokovich), taking the form of skin ulceration (dermatosis) and allergic sensitization (dermatitis). The role of reactive oxygen species, with the subsequent oxidative deterioration of biological macromolecules in the toxicities associated with transition metal ions, is reviewed. Recent studies have shown that metals, including iron, copper, chromium, and vanadium undergo redox cycling, while cadmium, mercury, and nickel, as well as lead, deplete glutathione and protein-bound sulfhydryl groups, resulting in the production of reactive oxygen species as superoxide ion, hydrogen peroxide, and hydroxyl radical. As a consequence, enhanced lipid peroxidation, DNA damage, and altered calcium and sulfhydryl homeostasis occur [17-18]. Chromium (Cr) and nickel (Ni) are widely used industrial chemicals. Welders in India are inclined to possible occupational Cr and Ni exposure. The carcinogenic potential of metals is a major issue in defining human health risk from exposure. Chromium enters the body through the lungs, gastrointestinal tract and, to a lesser extent, the skin [10]. Inhalation is the most important route for occupational exposure [12]. Although overt signs of chromium toxicity (e.g. perforation of the nasal septum, skin ulcers, and liver and kidney damage) are rarely seen today, some workers are still exposed to toxic concentrations of the metal [10]. Non-occupational exposure occurs via the ingestion of chromium-containing food and water [19-20]

ROS actions in the biological system: The man is probably the result of evolutionary processes of unicellular and anaerobic organisms. The terrestrial environment gained more complex organisms only after development, which allowed the absorption of part ultraviolet solar radiation, a limiting factor for life, that for a long time, was confined to the aquatic environment. With the ultraviolet radiation reduction, which causes damages to the living beings, the terrestrial environment became compatible to life, unchaining the acceleration of the evolutionary process [21].

The ROS, as they react to the majority of the organism molecules, they are able to interfere in the biological processes, causing several diseases, mutations, aging, among other alterations [21].

Lipid peroxidation: The lipidic peroxidation is the process through which the ROS attack the polyunsaturated fatty acids of the membranes phospholipids of the cells, desintegrating them and allowing, this way, these species entrance in the intracellular structures. The phospholipases, activated by the toxic species, desintegrates the phospholipids, liberating the non saturated fatty acids resulting in the following deleterious actions of the lipidic peroxides:

- a. Cellular membranes rupture (NA/k and Ca/Mg bombs)
- b. DNA mutations – deoxyribonucleic acid
- c. Unsaturated lipids oxidation
- d. Chemical residues formation like the malondialdehyde
- e. Components engagement of the extracellular matrix, proteoglycans, collagen and elastin

The lipidic peroxides possess an action power higher than the other primary toxic species of O_2 ($O_2^{\cdot -}$, H_2O_2 , OH^{\cdot} , O_2), reaching further targets easily. The lipoperoxidation must also have a very important role in the cellular proliferation, especially in tumoral cells. Some authors suggest that the lipoperoxidation products

are involved in the cellular division control. On the other hand the lipid peroxidation is related to the tumoral increase [22].

Antioxidant Mechanism: The oxygen is a paradox in the planet, because it is essential to live as well as it can cause injures to the organism [21]. The antioxidant agents can't distinguish between the reactive oxygen species that have a physiological role and those that are causing damage. Because of this, their action can, in some not be profitable to the organism. However it is with the balance between the oxidant and antioxidant species that the organism, will be able to obtain the conditions to a better performance of its functions, considering that a disturbance in this balance can result in a range of pathological processes [23]. In general the following strategies have to be followed with the intention of increasing the efficiency of the OA.

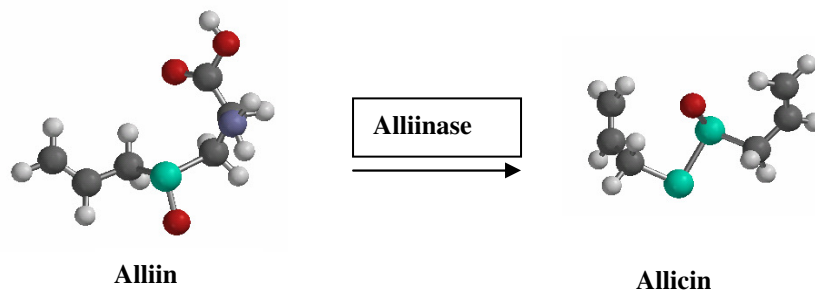
Oxidative Stress

=====>>Metal Complexes descompartmentalization

=====>>Excessive production of O₂(superoxide)

=====>>Anti-Radical defenses reduced

Role of Garlic (*Allium sativum* Linn) as an antioxidant on Nickel(II) and Chromium(VI) toxicities: 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 may exist and vary with an individual's age, pathology, dosage regimen and possible drug, food or metabolite interactions. A good deal of evidence suggests beneficial effects of the regular dietary intake of garlic on mild hypertension and hyperlipidemia. Garlic seems to have anti-microbial and immunostimulating properties, enhance fibrinolytic activity, and exert favorable effects on platelet aggregation and adhesion. Allicin, a strong oxidant, gives garlic its strong odor, and also believed to be responsible or some of garlic's medicinal uses. Allicin is a very reactive compound due to its S-S bonds, and is slightly soluble in water and alcohol due to the hydroxide (OH). The alliin molecule goes through an enzyme-catalyzed reaction to form allicin. Alliinase, the enzyme, lowers the activation energy so this reaction can take place [24].



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. Garlic has 1% of the potency of penicillin [25]. Garlic is recommended for protection from heavy metal induced toxicities [26]. Garlic is considered as an effective antioxidant against mercury induced pollution [25]. Garlic 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 a number of 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 [25]. Treating heavy metal poisoning has involved a process called chelation. Japanese research has discovered, however, that raw garlic extract can effectively protect the body from metal toxicity. Garlic showed protective role to improve anemia, leucopenia, thrombocytopenia in both diabetic and non diabetic nickel and hexavalent chromium treated rats. Possibly by:-

1. Stimulation of bone marrow activity.
2. Sulfur compounds in garlic significantly prolonged bleeding time, thrombin time [27].
3. This observation may partly explain the role of garlic in activating the natural killer cells, the function of T-lymphocytes and the level of interleukin – 2 [28].

Nickel and hexavalent chromium induced increase of serum LDL-cholesterol, total cholesterol, VLDL-cholesterol and triglyceride (TG) level and decreases serum HDL-cholesterol level in rats were counteracted by simultaneous garlic administration. Garlic extract inhibits 3-OH-3-me-Glutaryl-CoA (HMG-CoA) reductase which is a rate limiting enzyme in cholesterol biocynthesis. This may likely be the explanation for the significant reduction in serum lipids by the garlic extract [29]. It has also been shown to depress the hepatic activities of other lipogenic, cholesterogenic enzymes such as malic enzymes, fatty acid synthase, glucose-6-phosphate dehydrogenase (30 Yu-Yan and Liu, 2001). Thus, the triglyceride-lowering effect of garlic may be due to the inhibition of fatty acid synthesis [31]. Garlic found to be less effective as compared to nickel sulfate to counteract potassium dichromate induced alteration of serum lipid profile in rats [32]. Garlic improves blood glucose level/hyperglycemia and hepatic glycogen content in rats treated with nickel sulfate and potassium dichromate. Garlic also improves blood glucose level and hepatic glycogen content in alloxan diabetic rats [33]. Garlic shows a better glucose tolerance curve in acute exposure of nickel and chromium or diabetic- nickel and diabetic- chromium exposed rats [33-34]. The hypoglycemic effect

of garlic seems associated with the increase of insulin level and increase insulin sensitivity. Components in garlic i.e. S-allyl cysteine sulfoxide in garlic found to have glucose lowering effect in diabetic animals [35-36]. Garlic acted as a hypoglycemic agent. The hypoglycemic effect might also be due to an increase in the insulin response probably because the transport of blood glucose to the peripheral tissues was enhanced. The increased insulin response also promotes the conversion of the inactive form of glycogen synthetase to the active and enhances conversion of blood glucose into glycogen [33]. Nickel and Chromium VI increased erythrocytes malondialdehyde (MDA), glutathione (GSH) levels and the activities of superoxide dismutase (SOD), glutathione peroxidase (GSH - Px) and catalase (CAT). Simultaneous treatment with garlic brought erythrocyte antioxidant status to near normal condition in nickel treated rats and also diabetic rats exposed to nickel sulfate but no such improvement were found in case of rats exposed to hexavalent chromium or diabetic chromium exposed rats. Antioxidant phytochemicals that include organosulfur compounds (Like garlic) helps to combat oxidative stress [33]. Nickel sulfate and Potassium dichromate also increased hepatic lipid peroxide concentration and decreased hepatic glutathione concentration, SOD, CAT and GSH-Px activities. Both nickel sulfate and potassium dichromate generates reactive oxygen species like super oxide ($O_2 \cdot^-$) hydrogen peroxide (H_2O_2) and hydroxyl radicals ($OH \cdot$) in the liver. The study on aqueous preparation of garlic (*Allium sativum*) is found to be an effective antioxidant as it scavenged superoxide ions and reduced lipid peroxide formation in liver. These results support the view that aqueous garlic inhibits the oxidation of LDL by scavenging superoxide and inhibiting the formation of lipid peroxides [37]. The results also suggest that garlic has the potential to enhance the endogenous antioxidant status in nickel as well as hexavalent chromium induced lipid peroxidation in normal as well as diabetic rats [33]. Allicin, the active component of freshly crushed garlic cloves, found to protect heavy metal induced hepatic lipid peroxidation and decreased antioxidant enzymes activities [38].

Conclusion

It may be postulated from various study that garlic has the potential to enhance the endogenous antioxidant status in nickel as well as hexavalent chromium induced lipid peroxidation in normal and diabetic rats. Garlic acts as a free radical scavengers by: (i) It prevents the transfer of electron from O_2 to organic molecules (ii) stabilizes free radicals and (iii) terminates free radical reactions.

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