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Heavy Metal Accumulation in Human Body: A Molecular Toxicity Leading to Cancer

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Abstract: ***A wide range of heavy metals can be considered carcinogens, which are serious toxicants. Despite this, heavy metals are useful for industries such as alloy production, smelting, and production of commercial products due to their chemical and physiological properties. Such applications increase exposure to heavy metals. Waste generated at the time of industrial process is also a major source of environmental pollution and accumulation in the human body. Arsenic, cadmium, chromium and nickel are listed as Group 1 carcinogens by the International Agency for Research on Cancer and are used commercially. In this review, we use molecular pathway analysis to understand the mechanisms of toxicity and carcinogenesis of these metals. The data we analyzed suggests that the aforementioned metals induce oxidative stress, DNA damage and cell death processes that increase the risk of cancer and cancer-related diseases. Therefore, we can consider that phytochelatin molecules and antioxidant phytochemicals can be used to prevent heavy metal-induced cancers.***

Keywords: Carcinogens, Accumulation, Cancer, DNA damage, Toxicant, Environmental pollution, Oxidative stress, antioxidant, Phytochelatin, Phytochemicals

1. Introduction

The majority of heavy metals in the environment are cancer-causing by nature. Almost all heavy metals are linked to numerous malignancies and disorders, despite the fact that some heavy metals, including copper (Cu) and zinc (Zn), act as vital enzymes for intracellular processes and offer DNA-binding domains. Damage from heavy metals is brought on by reactive oxygen species (ROS), which are specifically a class of unstable molecules or free radicals that include oxygen and interact spontaneously with cells. Heavy metals are used in many industrial processes despite their significant intracellular toxicity; for example, they are used in paints, batteries, and automobile exhaust. In addition, heavy metals are used in consumer goods coloring to create colorful presentations, such as toys and children's jewelry. An important source of heavy metal pollution in the environment is electronic waste from batteries, which leaches heavy metals through erosion by rain and groundwater into the soil, rivers, and ocean. Toxic heavy metals in their dissolved forms may cycle through the bio system and into the food chain, where they may be amplified and finally reach extremely high quantities in people. (1, 2).

The International Agency for Research on Cancer classifies four heavy metals as category 1: arsenic (As), cadmium (Cd), chromium (Cr), and nickel (Ni). According to a number of studies, exposure to these substances causes oxidative damage that interferes with metabolic enzyme activity, damage repair mechanisms, and the expression of tumor suppressor genes (1, 2).

There are different ways of accumulating heavy metal in the human body, including ingestion of contaminated food and water, inhalation of polluted air or dermal exposure. While some of the metals are essential for normal physiological functions in trace amounts, such as iron, copper and zinc, it is also possible to accumulate them too much which can result in toxicity and possibly carcinogenogenic effects (1, 2).

A higher risk of bladder, lung, and skin cancers has been associated with long-term exposure to high levels of arsenic, which is typically caused by tainted drinking water or specific foods. The International Agency for Research on Cancer (IARC) has classified arsenic as a Group 1 human carcinogen. Long-term cadmium exposure has been linked to a higher risk of prostate and lung cancers. Cadmium exposure can happen through tainted food, tobacco smoke, and work environments. According to the IARC, cadmium is a Group 1 human carcinogen. There is a connection between some types of nickel, specifically nickel compounds, and a higher risk of lung and nasal malignancies, particularly in work environments like nickel processing. The IARC has categorized nickel compounds as Group 1 carcinogens (1,2).

Reliability of cancer risk to exposure level and duration is a significant consideration. In order to safeguard the public's health, regulatory bodies set standards and allowable limits for heavy metals in food, soil, water, and the air. Adverse health impacts are also prevented in large part by reducing exposure to heavy metals through initiatives like bettering industrial procedures, keeping an eye on environmental quality, and raising public awareness. Make educated dietary decisions, abstain from tobacco products, and, if appropriate, adhere to occupational safety procedures as further ways for individuals to reduce exposure (1, 2).

Several research portrays, the source of contamination affects the risk of exposure to heavy metals. For instance, current research has revealed an elevated risk of cancer and occupational disorders among those who work in heavy metal-contaminated industrial locations. (3).

Due to the current focus on biology and health, there are vast amounts of biological data available, making the use of data

mining tools crucial. The route Studio database, which generates metabolic route maps from information from many sources, can aid in understanding complex metabolic pathways that are particular to genes or chemicals (4, 5). To get a thorough understanding of disorders, marker proteins, and diseases caused by heavy metals, metabolic pathway analysis can be used. Furthermore, the ability to forecast the presence of protein markers unique to carcinogenesis is facilitated by the direct relationship between marker proteins and cellular processes. (4, 5)

The prevention and detoxification of heavy metal damage is facilitated by a variety of intracellular chelating agents and antioxidants. Phytochelatins (PCs), or plant chelating agents, bind to metal ions and protect plants from metal poisoning (6). In order to prevent oxidative damage, antioxidant molecules engage in interactions with free radicals. The antioxidant-related detoxification process may be aided by the consumption of phytochemicals derived from antioxidant compounds in plants. (6, 7).

By providing a thorough understanding of their toxicological mechanisms through the investigation of molecular metabolic pathways, we will explain the toxicity and carcinogenicity of heavy metals such As, Cd, Cr, and Ni in this review. We will also discuss PCs' capacity to fight cancer as well as antioxidants like phytochemicals.

ARSENIC (As)

Source of contamination

As is a metalloid that is present in both inorganic and organic molecules. When compared to its organic counterpart, as inorganic version is more damaging. Water dissolves pentavalent inorganic arsenic (As) molecules, forming arsenate, which is a weak acid and salt. A large number of people are impacted by arsenate's groundwater contamination. As is mostly utilised in industry, including the production of vehicle batteries, alloyed semiconductor materials, and pigments. It has recently replaced radioactive elements in isotopic labelling for cancer research. Human activities such as industrial mining and ore smelting are associated with this (8) As exposure, Nonetheless, exposureto As is mostly from natural sources, including tainted water. Arsenates from soil can easily dissolve in subsurface water and move into rivers and the ocean. As builds up in aquatic life whereit is transformed into its organic compound form. Additionally, crops contaminated with As in groundwater, like rice, can swallow it. As a result, large amounts of As can build in humans who eat rice as a staple food. Consuming foodstuffs cultivated in contaminated groundwater causes humans to become more exposed to as, which raises the risk of poisoning. (9-12).

Carcinogenic mechanism and Toxicity pathway

Oxidative stress is a key mechanism for Arsenic related damage. The disruption of cellular signaling pathways can result in a variety of illnesses. Arsenic-containing substances induced genotoxicity in mouse and human leukocytes in an in vitro cell line research. The methylated form of arsenic hinders DNA repair procedures and also releases reactive oxygen species (ROS) as metabolites inthe liver and spleen. As free radicals build up in ROS, aberrant gene expression and damages in key cell components including DNA, lipids, and proteins cause cell death. As chemical residues can bind to proteins that bind to DNA, which raises the risk of carcinogenesis by impeding DNA repair procedures. As binds to methyltransferase, for instance, which inhibits the expression of tumor suppressor genes that are methyltransferase-encoded. Recent research has showed (13-17).

To understand the carcinogenic mechanism of As, we performed a pathway analysis using Pathway Studio ver. 11.1.0.6 (Elsevier, Amsterdam, The Netherlands) (Fig. 1). Figure 1 shows that As poisoning is mainly associated with apoptosis, cell damage, oxidative stress, cell cycle, and DNA damage response. We found genomic interactions between tumor protein 53 (TP53), interferon gamma, catalase, etc. These genes are also associated with As. We also discovered that skin, liver, prostate and Kuffer cell cancers are associated with As poisoning. This result may contribute to a comprehensive understanding of the mechanisms associated with As.

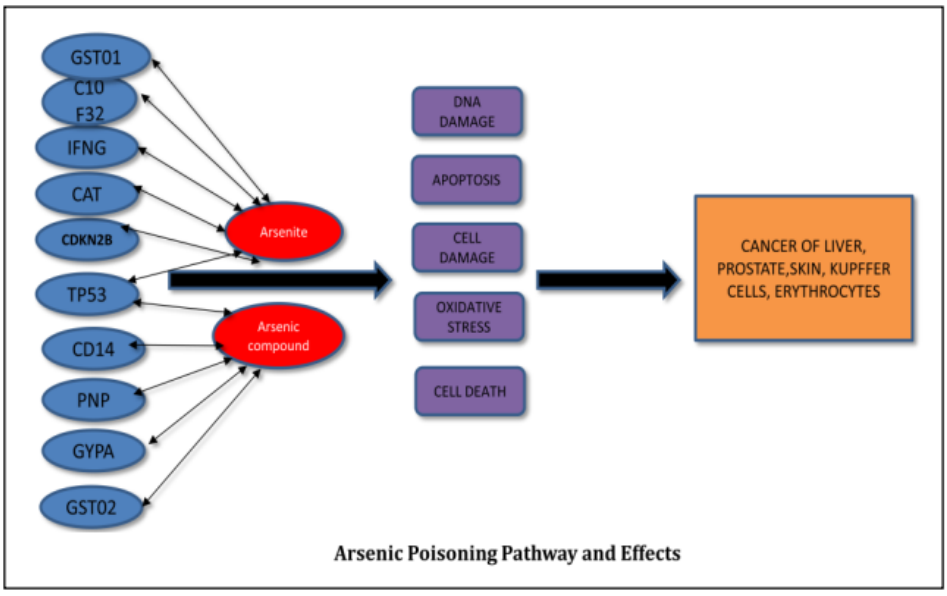

Figure 1

Fig.1 Pathway analysis of arsenic toxicity. The specifically analyzed data showed the potentiality of genomic interactions, cellular processes, as well as diseases induced by arsenic exposure. Ten proteins, 5 cellular processes, 8 diseases, and 2 small molecules appeared in the figure. GSTO, glutathione S-transferase omega; C10orf32, chromosome 10 open reading frame 32; IFNG, interferon gamma; CAT, catalase; CDKN2B, cyclin-dependent kinase 4 inhibitor 2B; TP53, tumor protein 53; CD14, monocyte differentiation antigen CD14; GYPA, glycophorin-A; PNP, purine nucleoside phosphorylase.

Although the toxicity of arsenic varies depending on its valence, with soluble arsenic compounds being the most poisonous and trivalent arsenics being more hazardous than pentavalent arsenics, the metabolism of arsenic plays a crucial part in the manifestation of its toxic effects. We still don't fully understand how arsenic causes genotoxicity. It is thought to be caused by arsenic's capacity to impede DNA replication or repair enzymes as well as arsenate's function as a phosphate analogue (Li and Rossman, 1989).

Arsenic cellular toxicity can be linked to the arsenic compounds' attack on mitochondrial enzymes, which results in decreased tissue respiration. The modification of different enzymes, including those involved in tissue respiration, is still another cause of its toxicity. This reaction with thiol groups (- SH), particularly those found in enzymes or cofactors with two thiols (for example, dihydrolipoic acid), is particularly harmful (18-22).

The enzymes and co-enzymes of the pyruvate dehydrogenase complex (pyruvate decarboxylase, dihydrolipoyl transacetylase, dihydrolipoyl dehydrogenase, thiamine pyrophosphate, lipoic acid, coASH, FAD, NAD) are responsible for converting pyruvate to acetyl CoA during tissue respiration. Dihydrolipoic acid will modify the enzymes dihydrolipoyl dehydrogenase and dihydrolipoyl transacetylase as a result of its attack on the pyruvate dehydrogenase complex seen in Figure 6. This will impact how lipoic acid is converted to acetyl lipoic acid, which is then converted to acetyl CoA. Even though arsenic has been proven to affect the membrane potential of mitochondria and cause apoptosis in a variety of human cancer cells (Woo et al., 2002; Ivanov and Hei, 2004), the significance of mitochondria as a genotoxic target of arsenic is still not well understood. However, it was discovered that mitochondria are a direct target of arsenic-induced genotoxicity in mammalian cells, with peroxynitrite anions serving as key mediators in the process in a study using enucleation and fusion procedures using the humanhamster hybrid (AL) cells (Liu et al., 2005).

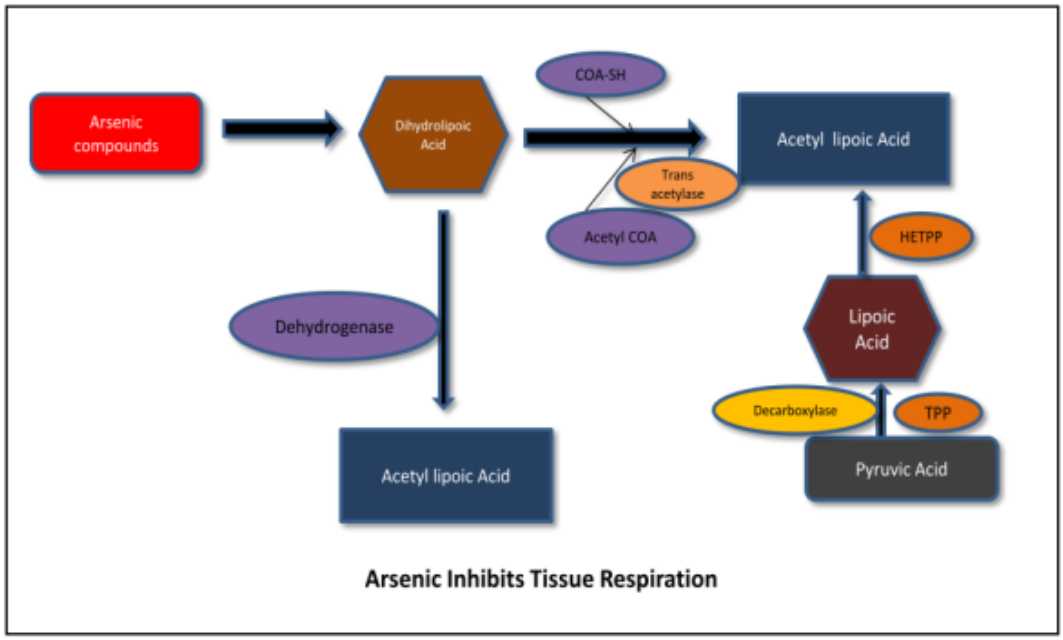

Figure 2: Diagram illustrating the mechanism through which arsenic inhibits tissue respiration (pyruvate decarboxylase, dihydrolipoyl transacetylase, dihydrolipoyl dehydrogenase, thiamine pyrophosphate, hydroxyethy lTPP).

Arsenic has also been linked to the uncoupling of oxidative phosphorylation, which inhibits dehydrogenase and stimulates mitochondrial adenosine triphosphatase activity. By replacing phenylarsonic acid (As(v)) for phosphorus in the majority of biochemical reactions, arsenic has been theorised to inhibit the formation of ATP during glycolysis (Wexler, 1998) by replacing the stable phosphorous anion in phosphate with the less stable As(v)) (anion, a process known as arsenolysis.

In Figure 3, where ADP normally phosphorylates into ATP, arsenic causes the formation of ADP- arsenate, which spontaneously decomposes irreversibly and causes energy loss by the metabolising cell. Hepatotoxicity and porphyrinuria, which are frequently linked to acute exposure to arsenic and low dose chronic exposure (Figure 4), are caused by the uncoupling of oxidative phosphorylation, which also decreases cellular respiration and increases free radical generation.

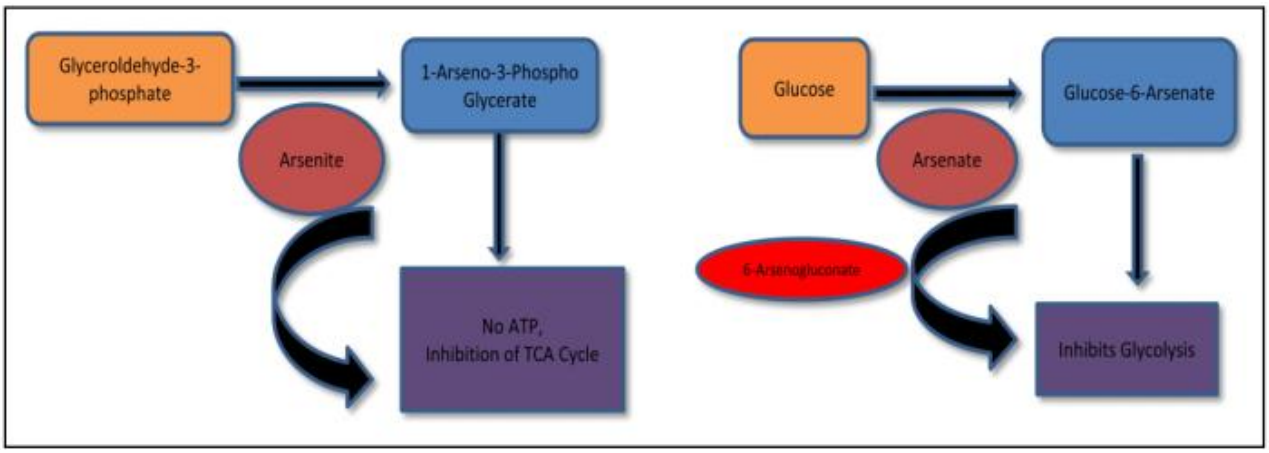

Figure 3: Schematic illustrating the replacement of arsenic for phosphorous in the cell that is metabolic energy.

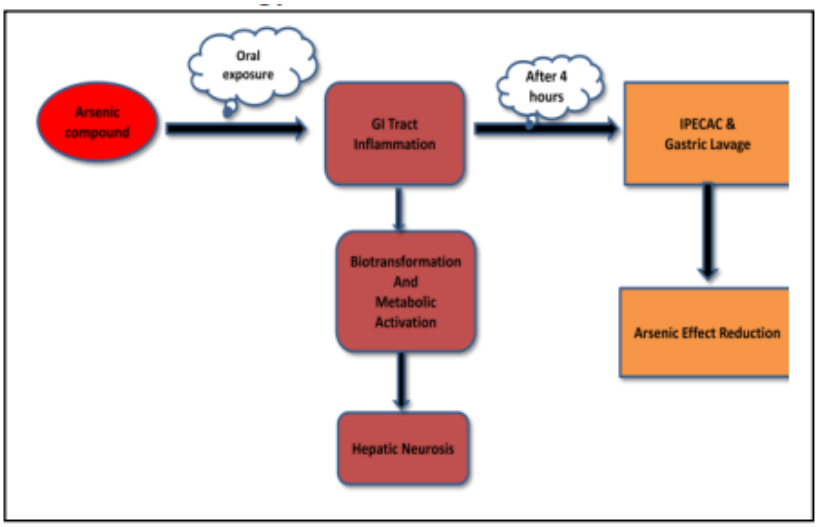

Figure 4: shows how utilising ipecac syrup and stomach lavage to remove arsenic reduced the amount of arsenic that was available for toxication at the target site

Cadmium (Cd)

Source of contamination

In the natural world, cd is scarce. It typically results from pollution caused by agricultural and industrial wastes. Cd is utilized in batteries and electroplating despite being fatally hazardous. Additionally, it is a component of acrylic paints, chalk pastels, watercolor pigments, and paints for plastic items. Recent laboratory tests have shown that the common source of blue-ultraviolet light in fluorescence microscopes is Cd in conjunction with helium. Some Cd-containing fertilizers in agriculture raise the Cd levels in the soil. Nearby industrial areas poison farmland. Consuming food is the primary way that people are exposed to Cd. For instance, crops grown in water contaminated with Cd are susceptible to the Itai-itai illness. However, because of bio magnification via the food chain caused by Cd dissolved in groundwater and rivers that come into touch with Cd-contaminated soil, animals living in such locations have high levels of Cd. In addition, rivers' Cd made its way into the sea, where it accumulated in marine life. As a result, Cd poisoning is a major contaminant that poses a risk to humans. (23-28).

Carcinogenic mechanism and Toxicity pathway

Oxidative stress is the well-researched factor in Cd-related toxicity. The suppression of cellular antioxidant system components results in liver and kidney toxicity, according to studies of chronic Cd exposure in a rat model. The transcriptional activity of the metallothionein (MT) coding gene is accelerated by oxidative stress following Cd exposure. The majority of bodily organs contain the protein MT. It can combine with metal components like Cd to generate a complex. Chronic Cd exposure results in the accumulation of Cd-MT, a complex compound of Cd and MT, notably in the kidney. Through a reuptake mechanism, it builds up in the tubules, causing renal tubule cell structural alterations and reduced glomerular cell function. The disruption of calcium metabolism and an increase in kidney calcium load brought on by these dysfunctions raise the risk of kidney stones and cancer. Damage to bones is also brought on by the interruption of calcium metabolism. A considerable correlation exists between a decrease in the concentration of calcium in bones and a rise in Cd concentration in the kidney, which results in a high excretion of calcium in the urine. This causes Itai-itai illness, osteomalacia, osteoporosis, and bone discomfort. Cd disrupts the endocrine system and particularly reproductive hormones. For the purpose of interfering with the DNA-Zn binding site, Cd mimics the divalent chemical state of Zn. It mimics endogenous oestrogen and affects the ovarian steroid synthesis pathway, preventing the body from producing progesterone and testosterone, increasing the risk of ovarian and breast cancer.(26, 28, 29).

To understand completely the carcinogenic mechanism of Cd, we performed pathway analysis using Pathway Studio (ver. 11.1.0.6) (Fig. 2). Figure 2 shows that Cd poisoning is mainly associated with apoptosis, oxidative stress, and the DNA damage response. In addition, genomic interactions between B-cell lymphoma 2 protein (BCL2), X protein (BAX), mitogen-activated protein kinase 1, huntingtin, and so on were shown. These genes are also related to Cd. Correlation of the specific PC, MT, and Cd ions are also shown here. It is also discovered that numerous diseases in bone as well as in kidney are associated with the Cd poisoning. This figure can provide an assistance to comprehensive understanding of the Cd-related intra molecular toxicity mechanisms. (26, 30, 31)

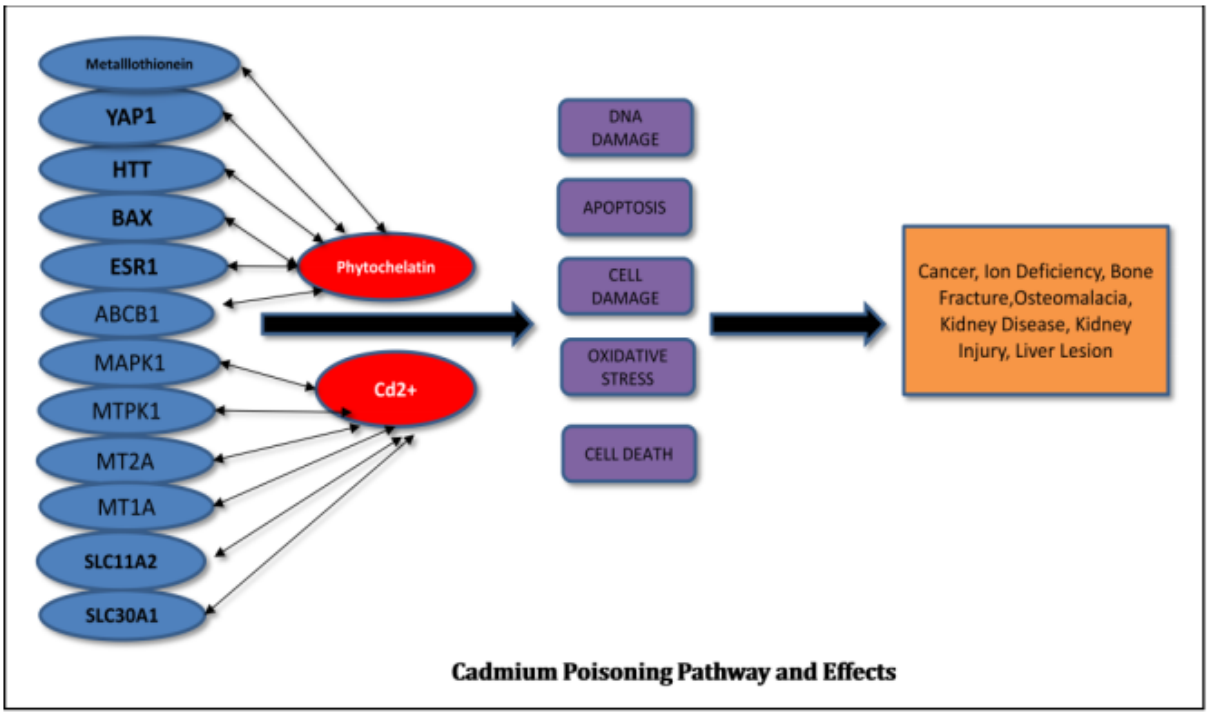

Figure 5

Fig.5 Analysis of the effect pathway of cadmium toxicity. The analyzed data showed the potentiality of genomic interaction, cellular processes and diseases induced by cadmium exposure. Ten proteins, 5 cellular processes, 13 diseases, 2 small molecules, and 1 functional class appeared in the figure. YAP1, ja-associated protein 1; HTT, huntingtin; BAX, B-cell lymphoma 2 protein- associated X protein; ROS, reactive oxygen species; ESR1, estrogen receptor 1; MAPK1, mitogen- activated protein kinase 1; ABCB1, aTP-binding cassette sub-family B member 1; MT2A, metallothionein 2A; SLC11A2, solute carrier family 11, member 2; MT1A, metallothionein 1A; SLC30A1, solute carrier family 30, member 1.

The ability of Cd to change healthy epithelial cells into carcinogenic ones at concentrations below environmental values may not be related to elevated cellular ROS levels. (Fig. 6). By changing the molecular signals upstream of DNA repair and death, Cd may be indirectly acting via epigenetic mechanisms. Increasing the oxidative stress tolerance of these Cd-transformed cells most likely by activating epigenetic genes involved in the response to oxidative stress and cell development. Due to the altered response to DNA damage, epigenetic inactivation of p53 has been linked to the formation of tumors. Furthermore, Cd modifies p53's structure and operation via a number of previously described pathways. In the structure of p53, cd can bind to the thiol group or replace zinc. The cell's capacity to respond to DNA lesions is decreased as a result of these modifications, which impede p53 activity. Chronic low dose exposure to Cd causes DNA hypermethylation by boosting DNA methyltransferase activity together with resistance to apoptosis. Therefore, apoptotic resistance occurs in Cd-induced malignancy because DNA-damaged cells can avoid apoptosis and multiply while carrying inherent DNA lesions, eventually developing the malignant phenotype (32-37).

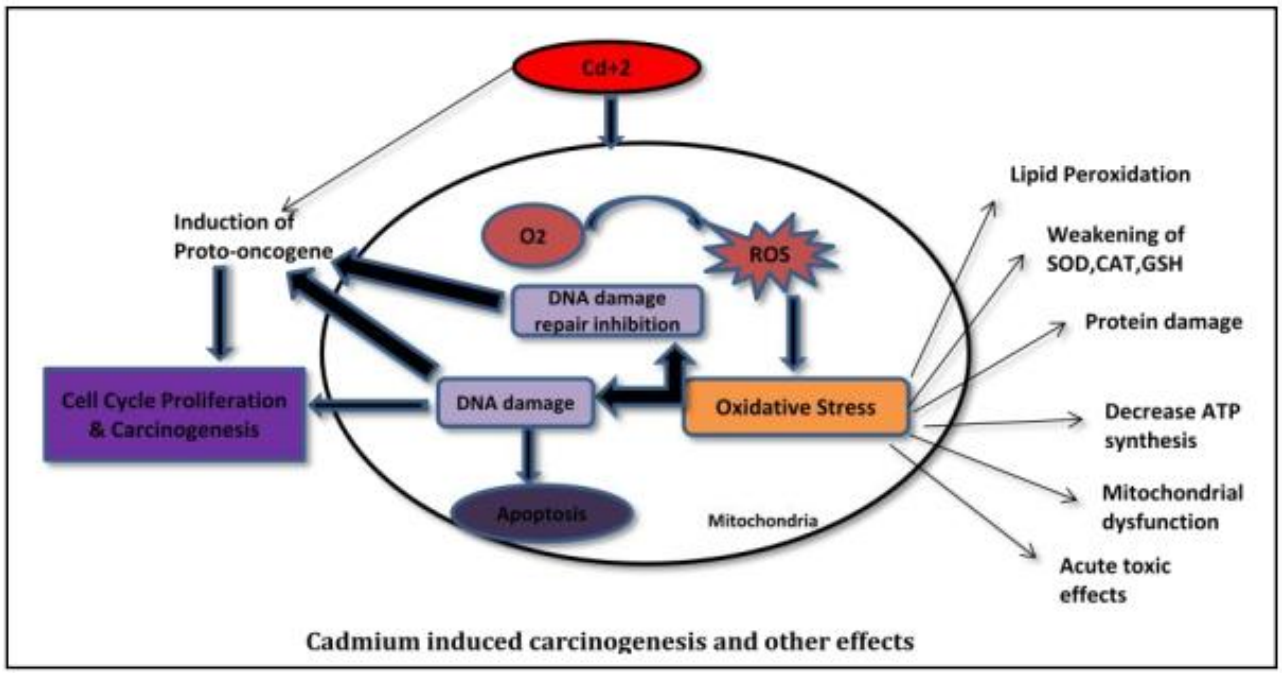

Figure 6: Molecular basis for cadmium (Cd)-induced carcinogenesis is shown in Figure 6. Through mitochondria and by inhibiting antioxidant defence mechanisms, Cd can cause oxidative stress. Chronic Cd exposure can activate oxidative stress defence systems. Cd-induced carcinogenesis is influenced by the suppression of the DNA repair machinery and disruption of intracellular Ca2+ homeostasis.

Chromium (Cr)

Source of contamination

In the earth's crust, Cr is widely distributed, and depending on its chemical state, it can be dangerous. It exists in compounds from divalent to hexavalent, although only the trivalent and hexavalent molecules exhibit a considerable level of biological toxicity. In the manufacturing of pigments, leather tanning, wood preservatives, and corrosion inhibitors for kitchen appliances, for instance, as well as in the decomposition of chromite, cr compounds are frequently utilised in industry. However, paints are still utilised in industrial settings and constitute a significant source of hexavalent Cr. Chromate is created by mining, melting, roasting, and extracting the trivalent and hexavalent chromium compounds. When chromates are made, toxic dust is produced. The toxicity of Cr dust to chromate production workers has been investigated in several research. Additionally, it is known that chromate production's industrial waste is a major cause of soil and water contamination. (38-42).

Carcinogenic mechanism and toxicity pathway

Since the 1980s, researchers have been examining whether Cr dust causes cancer. In one case study, it was discovered that those who worked in the chromate processing business were more likely to develop lung cancer. Despite being insoluble in water, the trivalent compounds found in Cr dust can enter cells in an ionised state thanks to a particular membrane transport mechanism. Trivalent Cr can harm cells when present in high doses. Because it generates reactive hydroxyl radicals, hexavalent Cr is also a strong poison. For instance, in blood arteries, the reduction of Cr complexes from hexavalent to trivalent Cr results in the production of reactive hydroxyl radicals. As a result, high blood levels of hexavalent Cr harm red blood cells through oxidation and impair liver and kidney function. Hexavalent Cr compounds can bind to DNA and interfere with biological functions when they are transformed into pentavalent forms. Additionally, the presence of Cr in soil and water damages skin through absorption. (39, 43, 44).

To understand completely the carcinogenic mechanisms of Cr, we examined molecular pathway analysis using Pathway Studio (ver. 11.1.0.6) (Fig. 7). Figure 7 shows that Cr and Cr compounds mainly induce apoptosis, oxidative stress, and DNA damage. We found Cr-related genomic interactions between nuclear factor (erythroid-derived 2)-like 2 (NFE2L2, Nrf2), TP53, BAX, etc. The relationship between MT, which has been associated with Cd toxicity, and Cr was also investigated. In addition, we discovered that Cr and Cr compounds cause significant diseases such as lung cancer, skin allergy with dermatitis, and kidney disease (39).

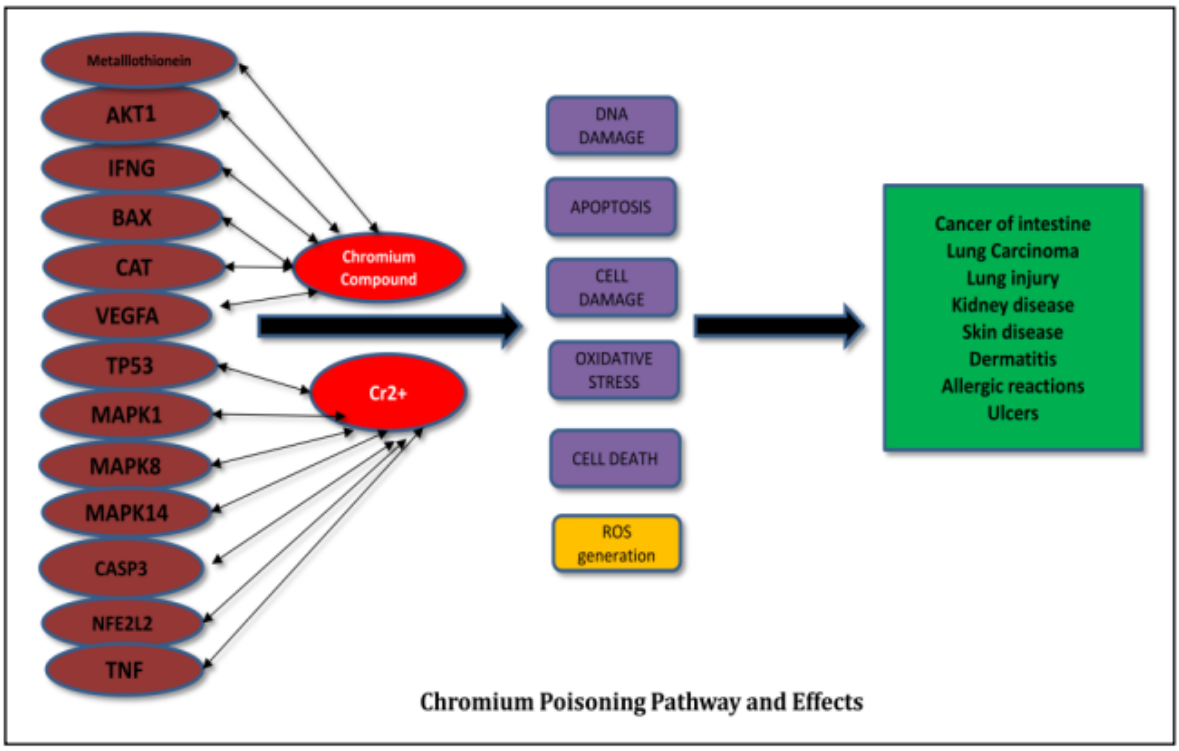

Figure 7: Pathway analysis of chromium toxicity. The analyzed data showed the potentialof genomic interaction, cellular processes, and diseases induced by chromium exposure. 12 proteins, 5 cellular processes, 13 diseases, 2 small molecules, and 1 functional class appear in the figure. MAPK, mitogen-activated protein kinase; AKT1, V-akt murine thymoma viral oncogene homolog 1; NFE2L2, nuclear factor, erythroid 2-like 2; CAT, catalase; IFNG, interferon gamma;

CASP3, caspase 3, apoptosis-related cysteine peptidase; VEGFA, vascular endothelial growth factor A; TP53, tumor protein 53; BAX, B-cell lymphoma 2 protein-associated X protein; ROS, reactive oxygen species.

Numerous investigations examining a wide range of assays for genetic and associated effects found that Cr [VI] compounds of varying solubilities in water were consistently active. Particularly, DNA damage, gene mutation, sister chromatid exchange, chromosomal aberrations, cell transformation, and dominant lethal mutations were brought on in a variety of targets, including animal cells in vivo and animal and human cells in vitro by potassium, sodium, and ammonium dichromates and chromates, chromium trioxide, calcium, and strontium chromates (WHO, 1990).

Generally speaking, Cr [III] compounds were more reactive than Cr [VI] compounds with purified DNA and isolated nuclei. However, with cellular test systems, 12 Cr [III] compounds of various solubilities only produced positive results in a small number of studies, frequently when used in specific treatment settings or at extremely high concentrations that were ordinarily orders of magnitude higher than those required to produce the same effects with Cr [VI] compounds. Due to contamination with residues of Cr [VI] compounds, part of the positive results may therefore be explained. Particularly, neither DNA damage nor micronuclei were discovered in the cells of the mice given chromic nitrate or chloride. Although chromosomal abnormalities were frequently seen with high concentrations of Cr[III] compounds, the majority of the Cr[III] compounds evaluated did not cause DNA damage, gene mutation, sister chromatid exchange, or cell transformation in cultured animal or human cells (38, 45-49).

By interacting with phosphate groups and nitrogen bases, Cr[III] is responsible for the physicochemical modifications of nucleic acids, while Cr[VI] produced DNA strand breaks, DNA- DNA and DNA protein cross-links, and modified nucleotides, such as 8-hydroxyguanine, which is a sign of oxygen radical formation. However, in the absence of reducing agents, these processes do not take place in cell-free systems, and the general agreement today is that the extremely reactive intermediates generated during cellular Cr [VI] reduction, such as Cr [V] and Cr [IV], are principally to blame for the observed genotoxicity. Ascorbate and sulphydryl compounds like cysteine and glutathione are examples of cellular reducing agents that may be important for lowering Cr [VI] (50, 51).

Nickel (Ni)

Source of contamination

Due to its physicochemical characteristics, Ni is frequently used in industrial settings. It is utilized in alloys and several goods, including stainless steel, rechargeable batteries, coins, electric plates, and pigments. One of the main causes of Ni exposure is through the use of Ni as an alloying agent for certain metals, such as Cr, lead, and Cu. Ni compounds enter the soil through coated pipes and faucets, stainless steel hearths that contain Ni, and items colored with Ni-based pigments. Environmental pollution from Ni mining and smelting also includes wastewater and dust. Because of this, exposure to Ni by inhalation, direct skin contact, and oral intake occurs regularly in humans.(52-54).

Dermatitis and allergies are brought on by skin contact with Ni compounds through tainted food, drink, and air as well as toys for kids. Ni exposure through the mouth can harm oral and cutaneous epithelium. Water-insoluble Ni compounds,

such as Ni3S2 and NiO, which are cancer-causing, are present in the industrial dust from nickel refineries. Ni-contaminated dust from mining, smelting, and tobacco use causes serious harm to the lungs and nasal cavities, which increases the risk of occupational diseases such lung cancer and nasal cancer in Ni refinery workers. Ni exposure promotes oxidative stress through decreased production of antioxidant enzymes and DNA single- and double-strand breaks, according to various studies, even if the molecular carcinogenic mechanisms of Ni toxicity are unclear. (55-62).

Compounds made of nickel can be created by combining nickel with substances including oxygen, sulphur, and chlorine. Many of the nickel compounds are green in colour and dissolve rather quickly in water. Nickel compounds are used as "catalysts" to speed up chemical reactions, for nickel plating, for colouring ceramics, in the production of some batteries, and for other purposes. Every type of soil contains nickel, which volcanoes also emit. As well as on the ocean floor and in meteorites, nickel is a mineral. There is no distinct taste or smell to nickel or its derivatives. When jewellery or other things containing nickel are kept in close proximity to the skin for a long time, people can develop nickel sensitivity. After becoming sensitive to nickel, a person may get a rash from further contact with the metal. (63)

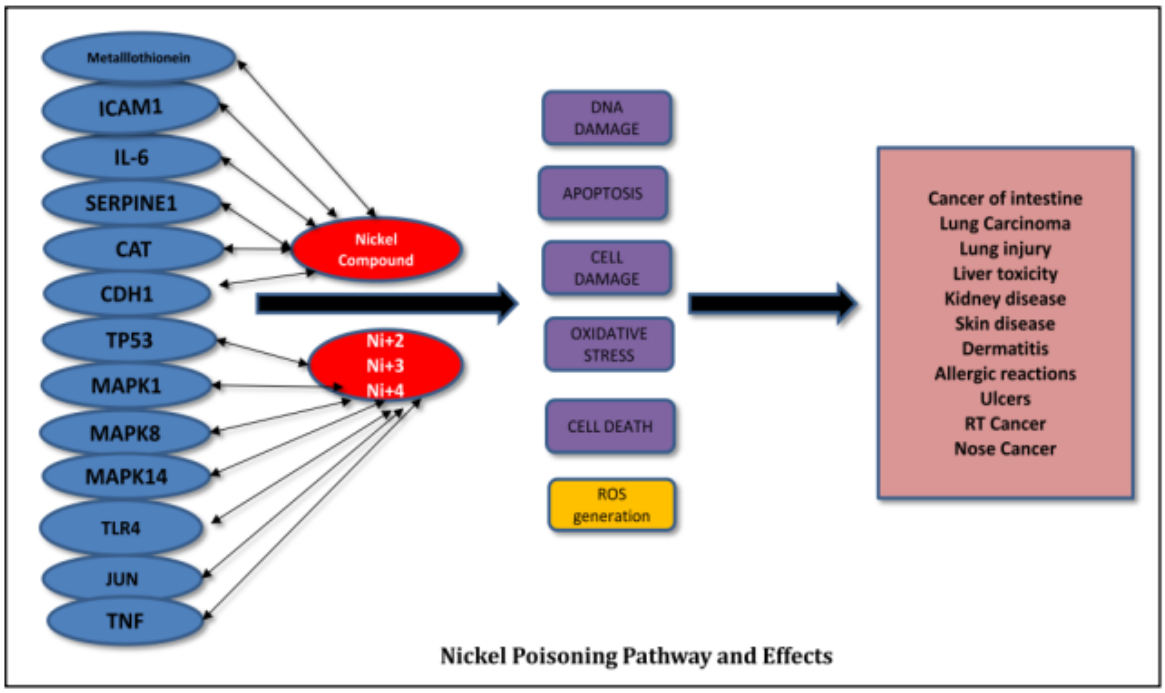

Figure 8: Pathway analysis of nickel toxicity. The analyzed data showed the potential of genomic interaction, cellular processes, and diseases induced by nickel exposure. 15 proteins, 8 cellular processes, 15 diseases, 1 small molecule, and 1 functional class appeared in the figure. ROS, reactive oxygen species; TLR4, Toll-like receptor 4; MAPK, mitogen-activated protein kinase; NDRG1, N-myc downstream regulated 1; CAT, catalase; TP53, tumor protein 53; ICAM1, intercellular adhesion molecule 1; JUN jun proto-oncogene; SERPINE1, serine peptidase inhibitor, clade E, member 1; IL, interleukin; BCL2, B-cell lymphoma 2 protein; FOS, Finkel- Biskis-Jinkins murine osteosarcoma virus oncogene homolog; CDH1, cadherin 1.

To understand the carcinogenic mechanisms of Ni, we analyzed the molecular signaling pathways using Pathway Studio (ver. 11.1.0.6) (Fig. 8). Figure 8 show that Ni induces apoptosis, oxidative stress, DNA methylation, and DNA damage. We investigated Ni-related genomic interactions between TP53, TNF, BCL2, etc. We also discovered that various toxicities in lung, nose, skin, kidney and liver were induced by Ni. The interaction between MT and Ni was also investigated.

Numerous investigations have been done on the molecular mechanism of DNA damage caused by Ni and Ni compounds that is linked to carcinogenesis. However, it is yet unknown how precisely Ni and Ni compounds harm DNA. Previous research has shown that Ni can cause DNA damage, much of which is caused by the production of ROS. Ni has the ability to bind directly to DNA and cause DNA damage. In the meantime, Ni has the ability to suppress DNA damage-repair mechanisms such as DNA direct-reversal, NER, BER, HDR, MMR, and NHEJ repair pathways, which causes an accumulation of damaged DNA bases to occur. DNA repair is suppressed by cellular DNA repair being impacted on several levels, ranging from direct enzyme inhibition to altered expression of DNA repair molecules (Figure 9) (64-70).

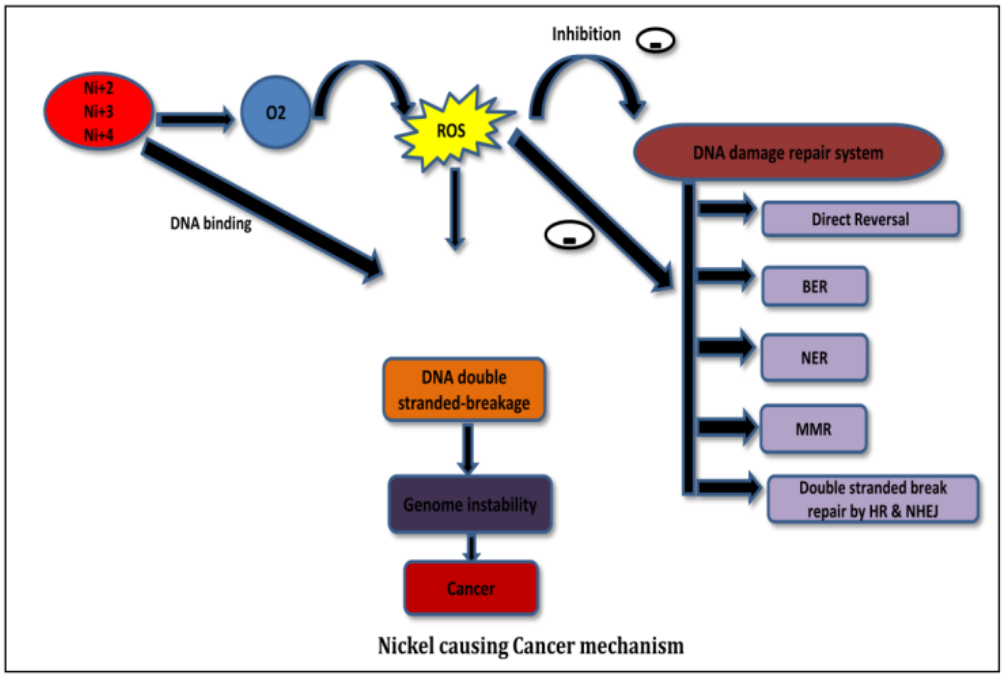

Figure 9: Scheme explaining how nickel causes DNA damage and causes cancer. Through direct DNA binding and ROS production, excessive Ni exposure can cause DNA damage. Direct reversal, BER, NER, MMR, HR, and NHEJ repair are just a few of the DNA damage-repair processes that Ni can suppress. Genome instability brought on by DNA damage may eventually lead to cancer development (64).

Cancer Prevention through Heavy Metal Detoxification

Chelation is the process by which metal ions in living things bind with particular ligand molecules. Plants have PCs, which are protein ligand molecules that chelate metal ions when they are exposed to heavy metals. According to several investigations, the enzyme PC synthetase produces PCs from glutathione (GSH), which subsequently forms GSH oligomers. In vacuoles, PCs bound to metal ions are successfully separated from cellular proteins and lessen the harm caused by heavy metal ions. (Fig. 10A) (62, 71).

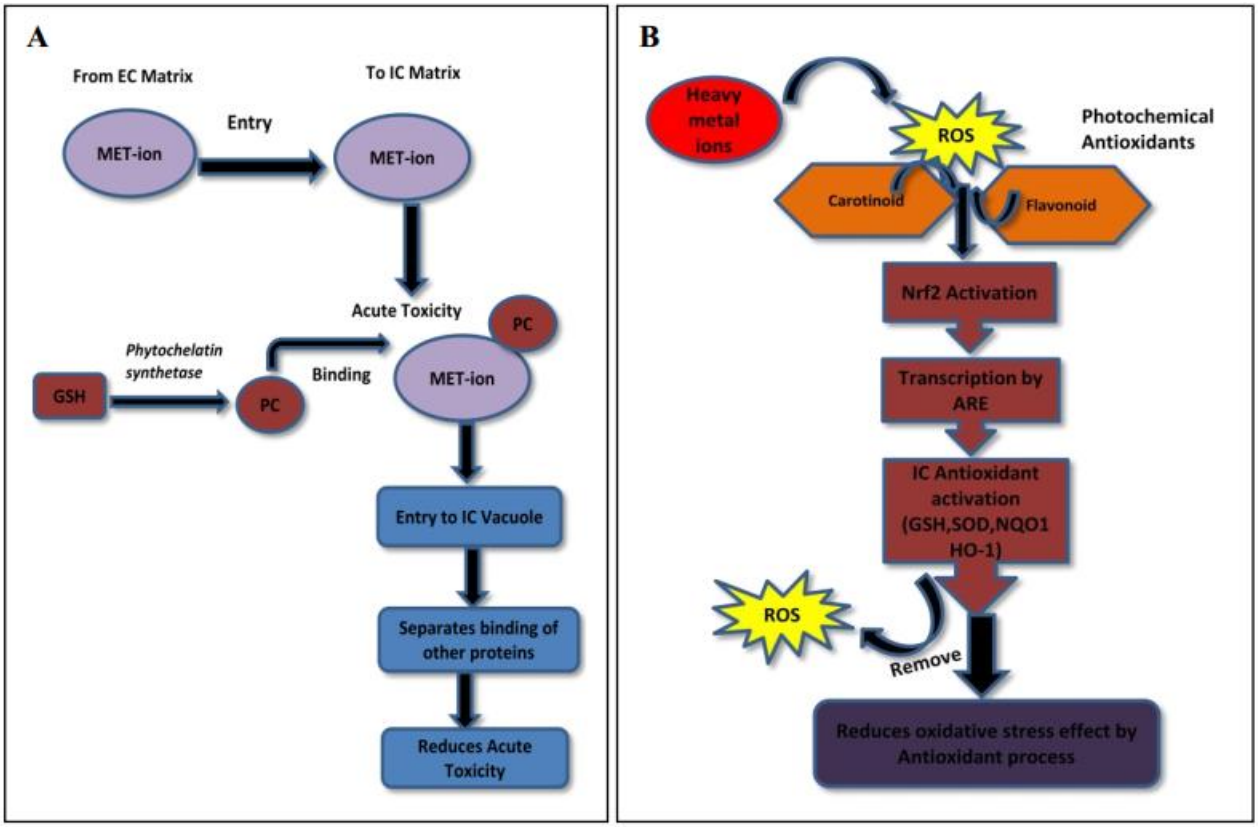

Figure 10

Fig. 10 Antioxidants and phytochelatin (PC) are the mechanism of heavy metal detoxification. The PC route is shown schematically in (A). Heavy metal ionized forms are denoted by the letters "MET -ion" in bold. In the bolded circles, PC molecules are identified as "PCs". The import direction is indicated with a double-line arrow. The process of creating a PC is denoted by a bold arrow. Italic bold typeface is used to display enzymes. (B) A schematic illustration of the antioxidant mechanisms that heavy metals cause. The presence of heavy metals releases ROS, which then activates Nrf2, a transcription factor for AREs (antioxidant response elements). Through activation of the Nrf2 pathway, phytochemicals support the antioxidant process. Different antioxidants are triggered to neutralize ROS. Reactive oxygen species (ROS), superoxide dismutase (SOD), glutathione (GSH), and Quinone (NQO1).

The suppression of DNA repair and DNA cross-linking with proteins by ROS production plays a significant role in heavy metal-induced carcinogenesis. As a result of the creation of ROS, which includes the hydroxyl radical (HO), superoxide radical (O2-), and hydrogen peroxide (H2O2), the balance between antioxidant and prooxidant molecules is upset, causing oxidative stress-related damage to cellular components such proteins, DNA, and lipids. Intracellular antioxidants prevent this action by scavenging ROS by oxidizing themselves and reacting with the free radicals in ROS. GSH, heme oxygenase 1, superoxide dismutase, NAD (P) H: Quinone acceptor oxidoreductase 1, and catalases are a few examples of the various varieties and intricate systems of intracellular antioxidants. As a result of oxidative stress, the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) protein is known to control antioxidant components. As a transcription factor that promotes antioxidant genes by attaching to the antioxidant response element found in the promoter region of the antioxidant gene, Nrf2 is activated by ROS. Carotenoids and flavonoids are examples of phytochemicals, which are also significant antioxidants. Regular eating of these meals, which are plentiful in fruits and vegetables, helps lessen oxidative stress-related harm. As a result, it is possible to draw the conclusion that the aforementioned antioxidant systems contribute to oxidative stress-induced carcinogenesis after heavy metal exposure. (Fig. 10B) (72-74).

2. Conclusions

Certain heavy metals are dangerous toxins and carcinogens. Four heavy metals' main exposure points, toxicities, and carcinogenic processes were covered in this review. Through the production and consumption of goods containing heavy metal complexes, industrial development raises the danger of exposure to heavy metals. Through intricate routes, heavy metal exposure, whether direct or indirect, causes the disruption of intracellular functions. We identified some genes and metabolic processes that are typical of the harmful effects of As, Cd, Cr, and Ni after analyzing the metabolic pathways. These procedures might serve as potential indicators of the carcinogenesis brought on by heavy metals. The toxicity of As, Cd, Cr, and Ni is specifically linked to processes mediated by oxidative stress. Candidates for heavy metal-induced carcinogenesis markers include these pathways. The toxicity of As, Cd, Cr, and Ni is particularly common to pathways mediated by oxidative stress. We might propose that PCs, antioxidative phytochemicals, and chelating agents, such as PCs, will be useful for preventing malignancies brought on by heavy metals. Additionally, thorough understanding of these intricate mechanisms through pathway analysis would be helpful for study on diseases and malignancies brought on by heavy metal exposure.

Declarations

Author's contribution

There is a single author who is solely owner of the contents of the manuscript. All the diagrams solely prepared by the author only.

Conflict of Interest

The author has no conflicts of interest to declare. There is a single author who is solely owner of the contents of the manuscript and there is no financial interest to report. I certify that the submission is original work and is not under review at any other publication.

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Data availability

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