Effect of Toxic Metals on Human Health

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Abstract: Metal ions such as iron and copper are among the key nutrients that must be provided by dietary sources. In developing countries, there is an enormous contribution of human activities to the release of toxic chemicals, metals and metalloids into the atmosphere. These toxic metals are accumulated in the dietary articles of man. Numerous foodstuffs have been evaluated for their contributions to the recommended daily allowance both to guide for satisfactory intake and also to prevent over exposure. Further, food chain polluted with toxic metals and metalloids is an important route of human exposure and may cause several dangerous effects on human. In this review we summarized effects of various toxic metals on human health.

Keywords: Bioavailability, Contamination, Heavy metals, Human health, Metal toxicity.

INTRODUCTION

There are around thirty chemical elements that play a pivotal role in various biochemical and physiological mechanisms in living organisms, and recognized as essential elements for life. In fact, for many food components, the intake of metal ions can be a double edged sword. Majority of the known metals and metalloids are very toxic to living organisms and even those considered as essential, can be toxic if present in excess. Concentrations of several toxic metal and metalloids have been largely increased as a result of human activities. They can disturb important biochemical processes, constituting an important threat for the health of plant and animals. Plants and animals absorb these elements from soils, sediments, and water by contact with their external surfaces, through ingestion and also from inhalation of airborne particles and vaporized metals [1, 2]. The requirement for ingestion of trace metals such as Fe and Cu ions to maintain normal body functions such as the synthesis of metallo-proteins is well established. However, cases of excess intake of trace metal ions are credited with pathological events such as the deposition of iron oxides in Parkinson's disease [3]. In addition to aiding neurological depositions, these redox active metals ions have been credited with enhancing oxidative damage, a key component of chronic inflammatory disease [4] and a suggested initiator of cancer [5]. As inflammation is a characteristic feature of a wide range of diseases, further potential pathological roles for metal ions are emerging as exemplified by premature ageing [6].

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For the maintenance of health, a great deal of preventative measures is in place to avoid ingestion of potentially toxic metal ions. From monitoring endogenous levels of metal ions in foods and drinks to detecting contamination during food preparation, European countries spend significant resources to avoid metal intake by the general population [7-9]. From a therapeutic viewpoint, considerable research and development efforts are being exerted to decorporate metal ions from the body. Since the use of As in World War I, researchers have advanced methods to decorporate toxic metals ions [10, 11]. More recently efforts have moved to erradicate neurological deposits and reverse redox active metal ion contributions to oxidative stress. The latter approach has a focus on chelators that reverse the potential detrimental effects by generating anti-oxidant enzyme mimetics upon chelating the labile redox-active metal ion. Intriguingly, some very good candidates for anti oxidant prodrug chelators are common food constituents such as catechins [12, 13].

Target hazard quotients (THQ) were developed by the Environmental Protection Agency (EPA) in the US for the estimation of potential health risks associated with long term exposure to chemical pollutants. The THQ is a ratio between the measured concentration and the oral reference dose, weighted by the length and frequency of exposure, amount ingested and body weight. The THQ value is a dimensionless index of risk associated with long term exposure to chemicals based upon reference upper safe limits. A limited number of THQ investigations have been reported in foodstuffs with the focus being on estimating health risks associated with exposure to heavy metals found in seafoods, and in one case breast milk [14-20]. Calculations of THQ values for seafoods are apposite as many species accumulate heavy metals and other pollutants in their tissues. Many of the re-

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ported THQ values calculated from metal contaminants in seafood range from a safe level (<1) to a level of concern (typically THQ >1 to <5) with a small number being above 10. It should be noted that THQ values are additive, not multiplicative, thus a THQ value of 20 is larger but not ten-fold greater than a THQ = 2. The first application of THQ estimations to common beverages has recently been reported by Dash *et al.* [21]. THQ values for daily ingestion of 250 mL of apple juice, stout and red wine were all above the safe value of 1. The THQ values for red wine were especially high at 126.2 for males and 157.22 for females (with gender variations owing to the differences in average weight and lifespan). In this study, individual THQ values were calculated for seven metal ions for which oral reference doses exist (V, Cr, Mn, Ni, Cu, Zn and Pb). It is notable that these relatively high THQ values were determined using only seven metal ions out of some thirty measured. It is conceivable that other metal constituents will contribute to the total THQ values when their upper safe limits are established.

In addition to their roles in health and disease, dietary metal ions have been the focus of discussions on the mechanism of ageing. Redox active metal ions such as Cu (I)/(II) and Fe(II)/(III) are especially implicated in the free radical theory of ageing as they are credited with enhancing oxidative stress [22]. However, beyond radicals, metal ions can disrupt normal cell and tissue function through multiple pathways including interactions with proteins and other biomolecules and disruption of membrane potentials. As far as mode of exposure of element is concerned, more than one exposure route are involved in the phenomenon of elemental intake. The assimilation of an element (i.e., the bioavailable fraction) principally depends on a number of chemical and physico-chemical factors such as chemical speciation, solubility in organic medium, pH etc. In soils, both metals and metalloids can occur in both solid and aqueous (i.e., soil solution) phases. In solution, these elements can exist either as free ions or as various complexes associated with organic or inorganic ligands or in the form of suspended colloidal particles. In the solid phase, they can be adsorbed on or absorbed in organic and inorganic soil components, exist as minerals or co-precipitated with other minerals. The present review is the compilation of reports on effect of toxicity rendered by various metals or metalloids directly or indirectly on human health.

MODES OF EXPOSURE TO TOXICANTS

Animals including human generally get exposed to the toxicants through: (a) respiratory (for gaseous and particulate matters); (b) the skin (chemicals able to cross skin barrier); (c) digestive tract (for food contaminants). After entering the body the metal deposited in nasopharyngeal, tracheobronchial, or pulmonary compartments may be transported through the mucociliary action to the gastrointestinal tract. Macrophages phagocyte the wandering metals. Food is a principal source of essential and toxic elements. Some elements like mercury (Hg) are biologically magnified at higher trophic level. The dietary contribution for toxic metal intake has been extensively studied [23]. If an individual is deficient in minerals and trace elements its body will absorb heavy metals on their place. Every cell membrane breaks down and rebuilds every two weeks but does not release the heavy metals if essential fats are not properly ingested or if poor quality fats are ingested. The liver that performs detoxification 100% of the time cannot perform this important task without a complete profile of essential nutrients.

Chemical elements present in the form of free ions are readily ionized and ultimately get absorbed completely by the body. Transition metals readily form stable covalent complexes and normally interact as parts of macromolecules (proteins, enzymes, hormones, etc.) according to their chemical characteristics including oxidation state [24-25]. The behavior of metal ion release into biofluid is governed by the electrochemical rule. Released metal ions do not always combine with biomolecules to appear toxicity because active ion immediately combine with a water molecule or an anion near the ion to form an oxide, hydroxide, or inorganic salt. Thus, there is only a small chance that the ion will combine with biomolecules to cause cytotoxicity, allergy, and other biological influences [26]. These metals, are complexed with amino acids (glutathione (GSH), cysteine, histidine), Proteins (metallothioneins, transferrin,ferritin, lactoferrin, hemosiderin, ceruloplasmin, melanotransferrin) (Table **1**). Health damage caused by toxic metals may be less (irritation) or acute (teratogenic, mutagenic and carcinogenic). These reactive elements of food build complexes with fiber, show low solubility within the intestinal lumen and are poorly absorbed (Table **2**). Absorption of these minerals is enhanced at low concentration of fiber, and in the absence of phytates and oxalates in the diet [27]. Micronutrients can interact with toxic metals in the body at several points: (a) absorption; (b) transport; (c) binding to target proteins; (d) metabolism; (e) sequestration; (f) excretion of toxic metals; and (g) finally in secondary symptoms of toxicity such as oxidative stress. The role of oxidative stress in the destruction of immune cells has been elucidated [28-33]. Thus, a diet poor in micronutrients can lead to enhancement in the toxicity. The prevalence and mortality due to multifac-

Table 1. Toxic Metal and Their Reactive Forms

Metal	Toxicity
Cd	All forms are toxic and need attention
Pb	Organic forms are more toxic and easily absorbed by the gastrointestinal tract
As	Inorganic arsenate [As(+5)] or [As(+3)] are more toxic
Hg	Hg(II) Organomercurials mainly methylmercury, biologically magnified

Sources: ATSDR (1999), ASTDR (2000), Michalke (2003).

Table 2. Food Sources of Toxic Metals

Metal	Food Source
Cd	Egg, fish, mushroom, garlic, spinach, wheat, rice, oat, corn, soyabean, peanuts ,mushroom
Pb	Egg, cocoa powder, rice, wheat, potato, calcium supplement, smoked food, wine, beer, milk, carrot, raisins
As	Green papaya, rice, tomato, carrot, seafood, Indian mustard, bovine and chicken meat, wine, milk
Hg	Egg, mushroom, seafood, fish oil

torial polygenic diseases; hypertension, coronary artery disease (CAD), diabetes and cancer vary depending upon genetic susceptibility as well as environmental pollutants generated as a consequence of numerous chemicals, metal ions and metalloids. Rapid changes in diet and lifestyle may influence heritability of the variant phenotypes that are dependent on the nutraceutical or functional food supplementation for their expression [34]. It is possible to recognize the interaction of specific nutraceuticals, with the genetic code possessed by all nucleated cells. There is evidence that South Asians have an increased susceptibility to CAD, diabetes mellitus, central obesity and insulin resistance at younger age, which may be due to interaction of gene and nutraceutical (especially micronutrients) environment. These populations appear to have enherited predisposition and may have interaction of internal nutritional status and environmental factors, mainly metal ions. Higher intake of refined starches and sugar increases generation of super oxide anion in the leucocytes and mononuclear cells, and free fatty acids (FFA), as well as higher amount and activity of nuclear factor-kB (NF-kB), a transcriptional factor regulating the activity of at least 125 genes, most of which are proinflammatory. Glucose intake also causes an increase in two other proinflammatory transcription factors; activating protein-1 (AP-1) and early growth response protein-1 (Egr-1), the first regulating the transcription of matrix metalloproteinases and the second modulating the transcription of tissue factor and plasminogen activator inhibitor-1. Refined food, mixed meal induces activation of NF-kB associated with free radicals generation by mononuclear cells. The super oxide anion is an activator of at least two major proinflammatory transcription factors, NF-kB and AP-1. Increased intake of linoleic acid, saturated fat, trans fat and refined starches and sugars can increase the generation of free radicals and activate the NF-kB, leading to rapid expression of proinflammatory genes. It is possible that nutraceuticals; antioxidants, micronutrients, minerals, vitamins, coenzyme Q10 and w-3 fatty acids may inhibit the generation of super oxide and suppress NF-kB as well as AP-1, and Egr-1 leading to suppression of phenotypic expressions. It is known that genes are important in determining enzymes, receptors, cofactors, structural components involved in regulation of blood pressure, the metabolism of lipids, lipoproteins and inflammatory and coagulation factors that are involved in determining individual risk for vascular diseases and diabetes. It seems that these phenotypic expressions may be silenced by targeting simple sequence differences known as single nucleotide polymorphisms by nutraceuticals and slowly absorbed wild foods rich in micronutrients and antioxidants.

In biological fluids and tissues, most metals and metalloids are not present as free cations. In blood they are usually bound to red cells or to plasma proteins. Lead and cadmium are almost completely bound to red blood cells. The chemical elements bound to plasma proteins constitute the fraction available for transport into and out of the tissues. Albumin, a plasma protein, has a great capacity to bind several metals. Some metals binds with proteins having a specific transport function such as transferring or ceruloplasmin.

THE TOLERABLE DAILY INTAKE APPROACH

In view of avoiding undesirable health hazards consequent of "excessive" intake of toxicants (including toxic metals), international and national scientific organisms such as FAO/WHO, FDA, European Union, etc have used the safety factor approach for establishing acceptable or tolerable intakes of substances that exhibit threshold toxicity. The acceptable daily intake (ADI) or tolerable daily intake (TDI) or provisional tolerable weekly intakes (PTWI) are used to describe "safe" levels of intake for several toxicants including toxic metals [35-37]. For chemicals that give rise to such toxic effects, a tolerable daily intake (TDI), i.e. an estimate of the amount of a substance in food, expressed on a body weight basis (mg.kg-1 or mg.kg-1 of body weight) that can be ingested over a lifetime without appreciable health risk. Exposure exceeding the TDI value for short periods should not have deleterious effects upon health. However, acute effects may occur if the TDI is substantially exceeded even for short periods of time. Besides, contaminants possessing very long half-lives can be accumulated in the body and chronic effects are most often observed when critical concentrations are reached in target tissues. The comprehensive account of health hazards rendered principally by arsenic (As), cadmium (Cd), lead (Pb), mercury (Hg), Selenium (Se) and Lethium (Li) is represented as follows:

ARSENIC

Arsenic (As) has many applications: (a) in bronzing, hardening and improving the sphericity of shot, wood preservation, pyrotechnics, varieties of semiconductor devices solar cells, light-emiting diodes, lasers, and integrated circuits); and (b) as pesticides [38]. Arsenic has been reported to vary in: (a) blood, from 1.5 to 2.5 μg L-1; (b) hair, from 0.25 to 0.88 μg L-1; and (c) urine the average concentrations are between 20 and 50 μg L-1 [39, 40]. In the environment arsenic is usually found combined with other elements as inorganic and organic forms. Inorganic arsenic is known to be more poisonous than organic one. Arsenic trioxide (As_2O_3) is the most common inorganic arsenical in air, while

arsenates (AsO_4^{3-}) or arsenites (AsO_2) occur in water, soil, or food. Arsenic may be also necessary ultra-trace element for red algae, chickens, rats, goats, and pigs and its deficiency inhibited growth. Arsenic concentration is high in marine food. In fishes arsenic ranged between 5 to 100 μg g-1 and reach to 100 to 250 μg g-1 in species at the top of the food chain [41]. Approximately 80-95 % of total arsenic is present as organic compounds thus do not cause any damage to health (arsenosugar, arsenolipids, etc). It has been documented that in 1955 Arsenic was accidentally mixed into the Morinag's Powdered Milk "MF" (Japan) due to which 600 new born babies died and 624 were afflicted by severe mental retardation, developmental difficulties, and brain-damage-related paralysis [42].

In humans arsenic toxicity occurs due to ingestion of As-containing powders or solutions accidentally, suicide, homicide, or consumption of contaminated food or drinking water. Arsenic has been reported to be associated with hypertension and serious impacts on the cardiovascular system, and even hepatic damage at high doses [43, 44]. It has a suppressive effect on spermatogenesis and gonadotrophin and testosterone release in rats [45]. There is correlation between arsenic exposure and diabetes mellitus (type II) [46]. Besides, inorganic arsenic ingestion arsenic leads to various dermal effects like: hyperkeratosis, hyperpigmentation and hypopigmentation; periorbital swelling; the occurrence of spontaneous abortion and damage of the nervous system (if high doses are taken in).

CADMIUM

Certain compounds of cadmium (Cd) are highly toxic to humans. Cadmium is employed in several industrial processes such as: (a) protective coatings (electroplating) for metals like iron; (b) preparation of Cd-Ni batteries, control rods and shields within nuclear reactors and television phosphors. Some compounds are used as stabilizers for PVC. For non-smoking population the major exposure pathway is through food. Cadmium is readily taken up by plants. Potential source of cadmium toxicity is the use of commercial sludge for fertilizing agricultural fields. Some root crops (carrots and parsnip) and some leafy crops (lettuce and spinach) are able to accumulate more cadmium compared to other plant foods. Grain crops like rice and wheat can accumulate relatively high amounts of cadmium.

Its absorption is increased by calcium, protein and vitamin D. Internal organs of mammals such as liver and kidneys may also contain high amounts of cadmium. The dietary cadmium absorption rate in humans has been estimated at 5 % of its total intake. The metal transporter protein Nramp2, also known as DMT1, appears to be involved in the mechanism of cadmium absorption [47]. The daily intake of cadmium was estimated at 25-60 μg for a 70 kg person from uncontaminated areas but values may rise up to 10 to 61 μg day-1. Cadmium is a normal constituent of tobacco, because *Nicotiana* species is able to concentrate cadmium independent of soil-Cd content. The cadmium content in tobacco ranges between 1-2 μg g-1 dry weight, equivalent to 0.5-1 μg cigarette-1. Approximately 10 % of the inhaled cadmium oxide is deposited in lung tissues, and another 30-40 % is absorbed into systemic blood circulation in smokers. Smokers have 4-5 times higher cadmium levels in blood and 2-3 times greater amounts of that in their kidneys as compared to nonsmokers. It has been documented that Itai-itai disease was caused by large amounts of cadmium in the village's water supply of Toyama city, Japan, from 1939 to 1954. Multiple fractures and severe pain in the legs and lower back affected mainly post-menopausal women with abnormal levels of glucose, calcium, and amino acids in their urine also the inhabitants of the community had for years been consuming rice contaminated by the effluent of a lead-zinc mine upstream from their rice paddies [48].

Cadmium is a cumulative toxicant and carcinogenic that affects kidneys, genrates various toxic effects in the body, disturbs bone metabolism and deforms reproductive tract as well as endocrine system. There are several morphopathological changes in the kidneys due to long-term exposure to cadmium. Increasing intakes of zinc can reduce the renal toxicity of cadmium. An exposure to cadmium increases calcium excretion thus causes skeletal demineralization, probably leading to increases in bone fragility and risk of fractures [49]. Cadmium and its compounds are currently classified by IARC as a Group 1 carcinogen for humans. Occupational human exposure has been correlated with lung cancer. Cadmium exposure, during human pregnancy, leads to reduced birth weights and premature birth [50].

LEAD

Lead (Pb) is used in storage batteries, cable coverings, plumbing, ammunition, manufacture of tetraethyl Pb, sound absorbers, radiation shields around X-ray equipment and nuclear reactors, paints, while the oxide is used in producing fine "crystal glass" and "flint glass" with a high refractive index for achromatic lenses, solder and insecticides. Lead enters the human body in many ways. It can be inhaled in dust from lead paints, or waste gases from leaded gasoline. It is found in trace amounts in various foods, notably fish, which are heavily subjected to industrial pollution Plants can absorb Pb from soils and from a PbEt4 traffic-induced air pollution (90 % of total Pb emissions into the atmosphere). Pb can contaminate water and consequently enter the aquatic food chains [51]. Pb is a toxic metal and most people and animals receive the largest portion of their daily Pb intake *via* food. Pb can enters food during storage and manufacture, e.g. in canned food and in alcoholic drinks. Cosmetics are also an important source of Pb contamination. The amount of Pb absorbed depends on age and the extent to which Pb particles are dissolved in the stomach. The proportion of Pb absorbed from the gastrointestinal tract is about 10% in adults, whereas levels of 40-50 % have been reported for infants. Milk, fasting, low levels of calcium, vitamin D and iron have been shown to increase Pb absorption in laboratory animals.

Children under 6 years are especially susceptible to the adverse effects of Pb, as the blood-brain barrier is not yet fully developed in young children, hematological and neurological adverse effects of Pb occur at lower threshold levels than in adults. Pb has effects on erythropoiesis and haem biosynthesis. Chronic Pb intoxication in adults resulted in to anemia, some types of cancer, reproductive harm in males while in young children hormonal imbalance of metabolite of vitamin D, namely 1, 25-dihydroxy-vitamin D, drop in IQ, [52-54].

MERCURY

Mercury (Hg) and its compounds are highly toxic, especially methylmercury - a potent neurotoxin. It has caused a significant number of human fatalities in several accidents around the world. Due to its wide dispersion through the atmosphere, Hg is considered a global pollutant, being deposited even in remote pristine aquatic systems, where it is biomagnified through the food chain. Hg and its compounds are highly toxic, have wide dispersion through the atmosphere. It is biomagnified through the food chain. Hg use in dental amalgams, thermometers, barometers, and the development of large-scale industrial processes (e.g. chlor-alkali plants and PVC production) and release into the environment. Hg occurs in nature in mineral, cinnabar, metacinnabar and hypercinnabar. Diet can be the main source of inorganic and organomercurials especially seafood while dental amalgams are the main exposure source to elemental Hg. Mercury is organomercurial in the form of methylmercury which have toxicological characteristics. Minamata disease name given after of methylmercury in seafood in Minamata and Niigata in Japan in the 1950-1960's, caused the death of thousands of people. Mercurial fungicides treated wheat seeds cause poisoning and death of 5,000 to 50,000 people. Tokuomi *et al.* [55] were the first to describe the symptoms of methylmercury poisoning. Thus, the symptoms were named the Hunter-Russell syndrome.

A few studies reflect that even minor increases in methylmercury exposures can cause harmful effects on the cardiovascular system, blisters in the upper gastrointestinal tract, vomiting, abdominal pain, constipation and gastritis. Renal toxicity of organic forms expressed by glomerulonephritis with proteinuria (glomerular and tubular) and nephritic syndrome. Elemental Hg can be oxidized to Hg^{2+}, which accumulates preferentially in the kidneys. The increased excretion of low molecular-weight proteins demonstrated at low-level exposure, and related to damage to the renal tubes. It is a potent neuro-toxin to human due to their ability to cross the blood-brain barrier. It is absorbed in the gastrointestinal track, immediately entering the blood stream. It readily passes the placental barrier affecting the developing nervous system of the foetus. Continuous exposure conditions to elemental Hg can lead to its accumulation in the thyroid. The acute exposure to elemental Hg vapors can cause "pink disease" or acrodynia.

SELENIUM

Dietary selenium (Se) supplementation with different origin and chemical forms is generally use for overcoming selenium deficiency and maintaining high productive and reproductive performance of farm animals. Excess amount of selenium is found as pro-oxidant and can be toxic for all animal species and man depending on the dose and duration of intake. The mechanism of selenium toxicity not known exactly but there are several proposals as oxidative stress mechanism, which supported by *in vitro* and *in vivo* results [56].

LITHIUM

Lithium (Li) is transferred in the food chain from soils *via* flora and fauna to human beings. Till date, it is not considered as an essential element for animal and human. The postulated normative lithium requirements amount to < 100 µg Li/day in man. Multiple actions of lithium are critical for its therapeutic effects. These complex effects stabilize neuronal activities, support neuronal plasticity and provide neuroprotection. Three interacting systems appear most critical: (a) modulation of neurotransmitters by Li likely readjusts balances between excitatory and inhibitory activities and so may contribute to neuroprotection. (b) Li modulates signals impacting on the cytoskeleton, a dynamic system contributing to neural plasticity. (c) Li adjusts signaling activities regulating second messengers, transcription factors and gene expression. Neuroprotective effects may be derived from its modulation of gene expression. These findings suggest that Li may exert some of its long term beneficial effects in the treatment of mood disorders *via* underappreciated neuroprotective effects [57].

CONCLUDING REMARKS

Conclusively, based on experimental studies, the advances of toxicology has improved our knowledge about human exposure to toxic elements (metals and metalloids) and their health effects, such as developmental retardation, several types of cancer, kidney damage, endocrine disruption, immunological, neurological effects and other disorders. The ongoing research works throw more light onto new insights and biochemical and molecular mechanisms involved in the development of pathological conditions in human.

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REFERENCES

[1] Mudgal V, Madaan N, Mudgal A. Heavy metals in plants: phytoremediation: plants used to remediate heavy metal pollution. Agric Biol J Name 2010; 1(1): 40-6.

[2] Madaan N, Mudgal V. Differential tolerance behaviour of safflower accessions to some heavy metals. Int J Appl Environ Sci 2009; 4(4): 413-20.

[3] Candelaria M, Garcia-Arias A, Cetina L, Dueñas-Gonzalez A. Radio sensitizers in cervical cancer: Cisplatin and beyond. Radiat Oncol 2006; 1: 15-32.

[4] Umanzor J, Aguiluz M, Pineda C, *et al.* Concurrent cisplatin/ gemcitabine chemotherapy along with radiotherapy in locally advanced cervical carcinoma: A phase II trial. Gynecol Oncol 2006; 100: 70-5.

[5] Elst P, Ahankour F, Tjalma W. Management of recurrent cervical cancer. Eur J Gynaecol Oncol 2007; 28: 435-41.

[6] González-Cortijo L, Carballo N, González-Martín A, *et al.* Novel chemotherapy approaches in chemoradiation protocols. Gynecol Oncol 2008; 110: 45-8.

[7] Hida T, Kozaki K, Ito H, *et al*. Significant growth inhibition of human lung cancer cells both *in vitro* and *in vivo* by the combined use of a selective cyclooxygenase 2 inhibitor, JTE-522, and conventional anticancer agents. Clin Cancer Res 2002; 8: 2443-7.

[8] Hida, T, Kozaki K, Muramatsu H, *et al.* Cyclooxygenase-2 inhibitor induces apoptosis and enhances cytotoxicity of various anticancer agents in non-small cell lung cancer cell lines. Clin Cancer Res 2000; 6: 2006-11.

[9] Sarkar FH, Li Y. Using chemopreventive agents to enhance the efficacy of cancer therapy. Cancer Res 2006; 66: 3347-50.

[10] Piazza GA, Keeton AB, Tinsley HN, *et al.* A novel sulindac derivative that does not inhibitcyclooxygenases but potently inhibits colon tumor cell growth and induces apoptosis with antitumor activity. Cancer Prev Res (Phila Pa) 2009; 2: 572-80.

[11] Raffoul JJ, Sarkar FH, Hillman GG. Radiosensitization of prostate cancer by soy isoflavones. Curr Cancer Drug Targets 2007; 7: 759-65.

[12] Aggarwal BB, Shishodia S. Molecular targets of dietary agents for prevention and therapy of cancer. Biochem Pharmacol 2006; 71: 1397-421.

[13] Banerjee S, Panda CK, Das S. Clove (Syzygium aromaticum L.), a potential chemopreventive agent for lung cancer. Carcinogenesis 2006; 27: 1645-54.

[14] Banerjee S, Das S. Anticarcinogenic effects of an aqueous infusion of cloves on skin carcinogenesis. Asian Pac J Cancer Prev 2005; 6: 304-8.

[15] Scott EN, Gescher AJ, Steward WP, Brown K. Development of dietary phytochemical chemopreventive agents: Biomarkers and choice of dose for early clinical trials. Cancer Prev Res (Phila Pa) 2009; 2: 525-30.

[16] Lev-Ari S, Vexler A, Starr A, *et al*. Curcumin augments gemcitabine cytotoxic effect on pancreatic adenocarcinoma cell lines. Cancer Invest 2007; 25: 411-8.

[17] Park J, Ayyappan V, Bae EK, *et al.* Curcumin in combination with bortezomib synergistically induced apoptosis in human multiple myeloma U266 cells. Mol Oncol 2008; 2: 317-26.

[18] Tannock IF. Treatment of cancer with radiation and drugs. J Clin Oncol 1996; 14: 3156-74.

[19] Boyum A. Isolation of mononuclear cells and granulocytes from human blood. Scand J Clin Lab Invert Suppl 1968; 97: 77-89.

[20] Mazzio EA, Soliman KFA. *In vitro* screening for the tumoricidal properties of International medicinal herbs. Phytother Res 2009; 23: 385-98.

[21] Dash PR, Cartwright JE, Whitley GS. Nitric oxide inhibits polyamine-induced apoptosis in the human extravillous trophoblast cell line SGHPL-4. Hum Reprod 2003; 18: 959-68.

[22] Sunilson JAJ, Rejitha G, Anandarajagopal K, *et al.* Cytotoxic effect of cayratia carnosa leaves on human breast cancer cell lines. Int J Cancer Res 2009; 5: 1-7.

[23] Santos EE, Lauria DC, Porto da Silveira CL. Assessment of daily intake of trace elements due to consumption of foodstuffs by adult inhabitants of Rio de Janeiro city. Sci Total Environ 2004; 327: 69-79.

[24] Schoof RA. Guide for incorporating bioavailability adjustments into human health and ecological risk assessments part 1: overview of metals bioavailability, Tri-Service Ecological Risk Assessment; 2003a.

[25] Schoof RA. Guide for incorporating bioavailability adjustments into human health and ecological risk assessments part 2: technical background document for assessing metals bioavailability, tri-service ecological risk assessment; 2003b.

[26] Hanawa T. Metal ion release from metal implants. Mater Sci Eng C 2004; 24(6-8): 745-52.

[27] Hazell T. Minerals in food: dietary sources, chemical forms, interactions, bioavailability. World Rev Nutr Diet 1985; 46: 1-123.

[28] Repetto M, Reides C, Gomez Carretero ML, Costa M, Griemberg G, Llesuy S. Oxidative stress in blood of HIV infected patients. Clin Chim Acta 1996; 255: 107-17.

[29] Gil L, Martinez G, Gonzalez I, *et al.* Contribution of characterization of oxidative stress in HIV/AIDS patients. Pharmacol Res 2003; 47: 217-24.

[30] Mates JM, Aledo JC, Perez-Gomez C, Del Valie AE, Segura JM. Interrelationship between oxidative damage and antioxidant enzyme activities: An assay and rapid experimental approach. Biochem Educ 2000; 28: 93-5.

[31] Gil L, Martinez G, Tarinas A, *et al.* Effect of increase of dietary micronutrient intake on oxidative stress indicators in HIV/AIDS patients. Int J Vitam Nutr Res 2005; 75: 19-27.

[32] Sharma S, Kalim S, Srivastava MK, Nanda S, Mishra S. Oxidative stress and coxasackie virus infection as mediators of beta cell damage: a review. Sci Res Essays 2009; 4: 42-58.

[33] Mishra S, Dwivedi SP, Dwivedi N, Singh RB. Immune response and possible causes of $CD4^{+}$-T cell depletion in human immunodeficiency virus HIV-1 infection. Open Nutra J 2009; 2: 46-51.

[34] Mishra S, Singh RB, Dwivedi SP, *et al.* Effects of nutraceuticals on genetic expression. Open Nutra J 2009; 2: 70-80.

[35] Speijers G. Precision of estimates of an ADI (or TDI or PTWI). Regul Toxicol Pharmacol 1999; 30: S87-93.

[36] Herrman JL, Younes M. Background to the ADI/TDI/PTWI. Regul Toxicol Parmacol 1999; 30: S109-13.

[37] Kroes R, Kozianowski G. Threshold of toxicological concern in food safety assessment. Toxicol Lett 2002; 127: 43-6.

[38] Agency for Toxic Substances and Disease Registry - ATSDR (2000). Toxicological profile for arsenic. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

[39] Apostoli P. The role of element speciation in environmental and occupational medicine. Fresenius J Anal Chem 1999; 363: 499-504.

[40] Yamato N. Concentration and chemical species of As in human urine and hair. Bull Environ Contamin Toxicol 1988; 40: 633-40.

[41] Michel P. Arsenic in marine medium; biochemistry and ecotoxicology, Pepères. Ocean n 4th ed. Ifremer, Paris: 1993.

[42] Ui J. Industrial pollution in Japan - The United Nations University. Tokyo: 1992.

[43] Lee MY, Jung BI, Chung SM, *et al.* Arsenic-induced dysfunction in relaxation of blood vessels. Environ Health Perspect 2003; 111: 513-7.

[44] Yoshida T, Yamauchi H, Fan Sun G. Chronic health effects in people exposed to arsenic *via* the drinking water: dose-response relationships in review. Toxicol Appl Pharmacol 2004; 198: 243-52.

[45] Sarkar M, Chaudhuri GR, Chattopadhyay A, Biswas NM. Effect of sodium arsenite on spermatogenesis, plasma gonadotrophins and testosterone in rats. Asian J Androl 2003; 5: 27-31.

[46] Walton FS, Harmon AW, Paul DS, Drobná Z, Patel YM, Styblo M. Inhibition of insulin-dependent glucose uptake by trivalent arsenicals: possible mechanism of arsenic-induced diabetes. Toxicol Appl Pharmacol 2004; 198: 424-33.

[47] Tallkvist J, Bowlus CL, Lonnerdal B. DMT1 gene expression and cadmium absorption in human absorptive enterocytes. Toxicol Lett 2001; 122: 171-7.

[48] Oudeh M, Khan M, Scullion J. Plant accumulation of potentially toxic elements in sewage sludge as affected by soil organic matter level and mycorrhizal fungi. Environ Pollut 2002; 116: 293-300.

[49] Wu X, Jin T, Wang Z, Ye T, Kong Q, Nordberg G. Urinary calcium as a biomarker of renal dysfunction in a general population exposed to cadmium. J Occup Environ Med 2001; 43: 898-904.

[50] Henson MC, Chedrese PJ. Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction. Exp Biol Med 2004; 229: 383-92.

[51] Kaste JM, Friedland AJ, Sturup S. Using stable and radioactive isotopes to trace atmospherically deposited Pb in montane forest soils. Environ Sci Technol 2003; 37: 3560-7.

[52] Tandon SK, Chatterjee M, Bhargava A, Shukla V, Bihari V. Lead poisoning in Indian silver refiners. Sci Total Environ 2001; 281: 177-82.

[53] Siddiqui MK, Srivastava S, Mehrotra PK. Environmental exposure to lead as a risk for prostate cancer. Biomed Environ Sci 2002; 15: 298-305.

[54] Lindbohm ML, Sallmen M, Anttila A, Taskinen H, Hemminki K. Paternal occupational lead exposure and spontaneous abortion. Scand J Work Environ Health 1991; 17: 95-103.

[55] Tokuomi H, Kinoshita Y, Teramoto J, Imanishi K. Hunter-Russel Syndrome. Nippon Rinsho 1977; 35(1): 518-9.

[56] Mézes M, Balogh K. Selenium Supplimentation in animal and man - positive effects and negative consequences. International Symposium on Trace Element in the Food Chain, 2006; pp. 9-15.

[57] Ermidou-Pollet S, Pollet S. Neuroprotective effects of lithium. International Symposium on Trace Element in the Food Chain, 2006; pp. 357-61.

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