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Ultra-Trace Elements in Human Health: Selenium, Chromium, Molybdenum, Cobalt, Boron and Iodine

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Carla Sousa[1*], Carla Moutinho[1], Ana F. Vinha[1,2], Carla Matos[1,3]

[1] FP-ENAS ((Unidade de Investigação UFP em Energia, Ambiente e Saúde), CEBIMED (Centro de Estudos em Biomedicina), Universidade Fernando Pessoa), Porto, Portugal.

[2] REQUIMTE/LAQV, Departamento de Ciências Químicas, Faculdade de Farmácia, Universidade do Porto, Porto, Portugal.

[3] Unidade de Saúde Familiar de Ramalde, ACES Porto Ocidental, Porto, Portugal

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ABSTRACT

Essential ultra-trace elements have an essential role in many physiological processes, regulating enzymes and metabolic pathways, being fundamental for growth, development, muscle and nerve function, normal cellular functioning, and synthesis of some hormones and connective tissue. Nevertheless, excessive levels of these elements can also lead to health problems, as neoplastic diseases. Another field of interest, that has been capturing researcher's attention for several years, is the possibility of development of pharmacologically active compounds base in these ultra-trace minerals, as anticancer, anti-inflammatories, antidiabetic or antimicrobial agents. This article aims to review the main effects of ultra-trace elements in human health, namely selenium, chromium, molybdenum, cobalt, boron and iodine, focusing on the physiopathology and consequences of deficiency and/or excess of these elements. Also, it offers an overview of research information published in recent years concerning the use of these metals in compounds that show promising pharmacological activities.

INTRODUCTION

Minerals are inorganic substances present in all body tissues and fluids and their presence is necessary for the maintenance of certain physicochemical processes which are essential to life [1]. Unlike the bioorganic compounds that are metabolically used in the production of energy, minerals are often found in the form of salts or complexes in the human body and they are not metabolized [2]. Minerals not only provide hardness to bones and teeth but also function broadly in metabolism, *e.g.*, as electrolytes in controlling the movement of water through the biomembranes, as cofactor or catalyst for many enzyme systems and as centers of building stabilizing structure of many organic molecules [3]. Nevertheless, the mineral absorption depends on human metabolism and food availability [4].

It is estimated that 98% of the body mass of man is made up of seven nonmetallic macrominerals (carbon, oxygen, nitrogen, sulfur, hydrogen, phosphorus and chlorine). The four main alkaline metals, specifically, sodium, magnesium, potassium and calcium constitute about 1.89%, while the rest 0.02% (or 8.6 g of an average human adults) is made up of 11 typical microminerals: five trace elements (such us, iron, zinc, copper, manganese and fluorine) and six ultra-trace elements (namely, cobalt, iodine, selenium, boron, molybdenum and chromium) [5]. In biochemistry, an ultra-trace element is a dietary micromineral that is needed in very minute quantities (at ppb order) for the proper growth, development and physiology of the organism [6,7].

Essential ultra-trace elements play an important role as a cofactor for certain enzymes involved in cell growth and, most of them, in the metabolism of proteins, carbohydrates and lipids. They are also necessary for growth, development, muscle and nerve function, normal cellular functioning, and synthesis of some hormones and connective tissue [8].

The role of ultra-trace elements in biological processing may provide vital clue for understanding the etiology of some illnesses such as cancer. The ability of trace elements to function as significant distresser in a variety of the processes necessary for life, such as regulating homeostasis and prevention of free radical damage, can provide an answer to the positive correlation between of ultra-trace elements content and many common diseases [9].

Although the ultra-trace elements are essential components of biological activities, the excessive levels of these elements can be toxic for the body health and may lead to many deadly diseases, such as malignancies. In fact, the accumulation of these elements, or even

their deficiency, may stimulate an alternate pathway which might produce diseases. Interaction among these elements may also act as a scaffold upon which the etiopathogenesis of many nutritional disorders [6].

The advances in inorganic chemistry provide better opportunities to use (ultra-)trace element-containing compounds as therapeutic agents. The use of transition metal (for instance, cobalt or chromium) complexes as therapeutic drugs has become more and more pronounced. These complexes offer a great diversity in their action; they do not only have anti-cancer properties but have also been used as anti-inflammatory, antimicrobial and anti-diabetic compounds. Development of transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Beside all these limitations and side effects, transition metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to pharmacological therapeutics in a way that is, unconceivable in few years back [10].

This article aims to review the main effects of ultra-trace elements which have been shown to be essential and of utmost importance to human health, specifically selenium, chromium, molybdenum, cobalt, boron and iodine, concentrating on the physiopathology and consequences of deficiency and/or excess of these elements. This study will also include an overview of research information published in recent years concerning the use of these elements in drugs that show promising pharmacological properties.

Selenium (Se)

Selenium is known as an essential ultra-trace mineral that has several vital functions at the level of the cell and organism in animal and human health, and consequently, it is relevant to various pathophysiological conditions [11].

Selenium can be found in foods - cereals, nuts soybeans, animal products and dairy products - and supplements as organo-Se compounds or in the form of inorganic-Se [12]. Selenium in multivitamin and/or multimineral supplements, or in a stand-alone supplement, is often available in the forms of L-selenomethionine, Se-enriched yeast (grown in a high selenium medium), mustard seed-derived Se, or as sodium selenate or sodium selenite [13].

Taking into consideration its importance for humans, the suggested dietary intake for selenium is 55 μg/day and 30 μg/day for healthy adults in the United States and Europe,

respectively, and 50-250 µg/day for adults in China. The selenium recommended daily intake of the Council of Health in Belgium ranges from 60 µg/day for women to 70 µg/day for men (from 14 years). [13-16].

Selenoproteins have crucial functions for human health and its deficiency can cause serious disorders. There are 25 selenoproteins in the body, but the most known are the glutathione peroxidases (involved in the elimination of free radicals), the iodothyronine deiodinases (enable the activation and deactivation of thyroid hormones), the thioredoxin reductases (regenerate the thioredoxin) and the selenoprotein P (involved in the transport of selenium in plasma). These enzymes also induce the production of antibodies and therefore protect the body from toxic substances and possess a crucial role in immune responses [11,17-23].

Some studies have demonstrated the association between selenium status and reproductive function [12]. There is evidence regarding the implication of Se or selenoproteins deficiency in a number of adverse pregnancy health conditions such as pre-eclampsia, miscarriage and pre-term birth [24]. Recently some attention was given on its potential role in sperm motility/viability and oocyte development and ovarian physiology [25].

Selenium act as a cofactor for triiodothyronine deiodinases, an important enzyme involved in thyroid hormone metabolism [13]. Selenium deficiency leads to a reduction on the expression and activity of these enzymes, which results in an increase on T4 and a decrease on T3 levels [26]. Lately, Kawai and collaborators verified that children with severe selenium deficiency had high free T4 levels that were reduced with Se supplementation [27]. Reduced serum Se concentrations (below 70 µg/L) are reported in patients with autoimmune thyroid disorders. Selenium supplementation in patients with Hashimoto's thyroiditis with known selenium deficiency may be useful [28,29], even for those who are already being treated with levothyroxine. In patients with mild to moderate Graves' orbitopathy, selenium supplementation seems to be beneficial and the organic formula (selenomethionine) seems to be more efficient than the inorganic one [30,31].

There is a narrow range between selenium intakes that result in toxicity or deficiency [32].

Levels of dietary exposure at which selenium becomes toxic and causes selenosis (a condition that can arise when selenium concentration exceeds 400 µg/day) can result in cancer through generation of Reactive Oxygen Species (ROS), which is thoroughly associated with carcinogenesis. Some studies also indicate that high selenium concentration is

positively associated with development of chronic neurodegenerative diseases such amyotrophic lateral sclerosis [33]. Se toxicity symptoms are garlic breath, hair and nail loss, disorders of the nervous system, including paralysis, skin diseases and poor dental health [26].

Se deficiency results in a condition called Keshan Disease (KD), which is an endemic cardiomyopathy occurring in low selenium areas of China. KD results in heart failure, cardiac enlargement, arrhythmias, and premature death. This condition has been associated with Se intake of 20 µg/day or less and it is known to be receptive to sodium selenite supplementation. Low selenium status has also been related to decreased muscle tone and conduction disturbances, anaemia, weak immune function and cognitive decline [16,34].

Selenium deficiency has been pointed out as an important factor for disease development, like cancer, diabetes and cardiovascular diseases [35].

Selenoproteins are capable to exercise insulin-like properties but in excess may impair insulin signalling [36,37]. Moreover, beta-pancreatic cells express selenoproteins, providing biological credibility that selenium possesses a role in type 2 diabetes mellitus (T2DM). However, the relation between Se and T2DM is still unclear [38,39]. Some studies found a direct association between them, where high selenium serum concentrations or Se intake were related with high prevalence of T2DM [40,41]. High serum Se can reduce chromium, leading to lipolysis and increase the generation of ROS, damaging insulin signalling [42,43]. This is a probable elucidation for a direct link between Se and T2DM. On the other hand, some trials and observational scientific studies described no increased risk of T2DM associated with Se intake [43-45]. Wang et al analysed 43 observational studies and detected a positive association between Se serum levels and T2DM [42]. Subsequently, Galan-Chilet et al evaluated the cross-sectional and prospective associations of plasma selenium concentrations with type 2 diabetes and the interaction of selenium concentrations with genetic variation in candidate polymorphisms [46]. The authors found that plasma selenium was positively associated with prevalent and incident diabetes. Vinceti et al conducted one of the most recent meta-analysis and concluded that Se may increase the risk of T2DM with higher relative risks in non-experimental studies compared with experimental studies [36]. The findings from a meta-analysis carried out by Kohler and colleagues indicated consistent moderate associations only between high levels of dietary or serum selenium and prevalent T2DM and inconsistent results among studies aimed at assessing incident T2DM [39]. The

results also demonstrated no consistent evidence that Se supplementation plays a role in T2DM development among adults.

Concerning dyslipidaemia, Se supplementation, alone or with others antioxidants agents, had different results in different trials: i) a direct association with hypertriglyceridemia in men and hypercholesterolemia in women; ii) no significant effect on lipid profile; and iii) a direct association with HDL-c [11,47-49]. A possible explanation is a link between selenoprotein and lipoprotein metabolism. Apolipoprotein receptors mediate the uptake of selenoproteins in different organs, such as the brain and kidneys, while selenoproteins in turn regulate plasma cholesterol levels, liver apolipoprotein E concentrations and gene expression involved in cholesterol biosynthesis [11].

Controversially, some studies showed a direct association between serum Se and hypertension. A prospective analysis of data collected in Belgium concluded that low serum Se was associated with hypertension in men [50]. This is sustained by the hypothesis that the Se antioxidant function may prevent or reduce the oxidative stress process in hypertension [51,52], whereas Hu et al state that Se inhibits heavy metal toxicity, which is a risk factor for atherosclerosis and hypertension occurrence [19]. Recently, Alehagen et al presented a 12-year analysis of cardiovascular mortality in an elderly Swedish population that had been given supplementation with selenium and coenzyme Q10 as a contribution to their diet for four years [19]. This follow-up revealed a reduced cardiovascular mortality risk of more than 40% in the studied group and a significant risk reduction in subgroups of patients with hypertension, ischemic heart disease or reduced functional capacity due to impaired cardiac function.

Several polemical studies have looked for association between selenium and metabolic syndrome [53]. Recently, Fang *et al* [11] studied the association between serum selenium concentrations and the risk of metabolic syndrome among middle-aged and older Chinese adults. The results obtained suggest that higher levels of serum selenium might be an independent risk factor for metabolic syndrome, especially in relation to elevated postprandial plasma glucose and reduced high-density lipoprotein levels.

Exhaustive studies in the chemopreventive and/or anticancer activity of selenium-containing compounds has been developed and reviewed by different authors [54,55].

Concerning the chemopreventive properties, a mechanism usually used by different seleno-compounds is the glutathione peroxidase-like activity. Although inorganic selenium-containing compounds (such selenite) may be superior chemopreventive agents than organic ones, current investigations are focused on the latter group due to their lower side and systemic effects [20,56,57].

Organic selenium compounds retain significant anti-tumour activity along with increased ability to prevent metastasis. The mechanisms of action of the organic seleno-compounds are very varied. Some of the most common are: i) reduction of oxidative stress through the elimination of free radicals; ii) induction of mutations; iii) cytotoxic activity; iv) triggering of apoptotic events; v) inhibition of angiogenesis; vi) inhibition of the efflux pumps in cancer multidrug resistant cell lines; and vii) enhancement of the activity of chemotherapeutic drugs [20,58-64]. Organic Se compounds comprise a vast group of chemically diverse nucleophilic molecules, such as selenocyanates, selenoureas, selenoesters and heterocycles with endocyclic selenium, among others [20,65-68].

Chromium (Cr)

Chromium occurs in two valence states: trivalente chromium Cr(III) and hexavalent chromium, Cr(VI). Cr(III) compounds are essentially used as nutritional supplements, while Cr(VI) is characterized by its great toxicity [69].

Chromium levels are usually very low in foods and beverages, being the highest levels found in dairy products, grass-fed beef, free range eggs, oats, sweet potatoes, nuts, oils and fats [69, 70]. The adequate intake of Cr for adult women and men is 25 and 35 μg/day, respectively [71]. The rate at which chromium is absorbed from the gut is low, and different chemical compounds of Cr(III) are absorbed at different rates. Absorption of this metal is significantly reduced by the presence of phytate and increased by ascorbic acid. There appears to exist a competition for uptake between chromium and other metals, including zinc, iron or manganese. After the absorption of Cr from gastrointestinal tract, chromium is believed to be transported in blood bound to transferrin [69].

Chromium helps to regulate blood sugar since is an integral part of the ‘glucose tolerance factor’, a complex that is necessary to remove efficiently glucose from blood. Chromium picolinate presents beneficial properties in the treatment of diabetes, namely when there is a chromium deficiency or when diabetes is poorly controlled. Patients with renal disease must

adequate the chromium intake to protect kidneys. This metal may also enhance insulin sensitivity when used concurrently and may bind levothyroxine in the digestive system [69,72]. However, Ali *et al* [73] concluded that chromium does not reduce diabetes mellitus risk, because there is not an insulin resistance improvement or an impairment of glucose metabolism in patients at risk for type 2 diabetes mellitus. Chromium also seems not to cause significant changes in insulin sensitivity, body weight, lipids and inflammatory markers in obese nondiabetic patients with metabolic syndrome. So, there is a lack of clinical evidence that chromium reduces the risk of insulin resistance or T2DM. The discrepancy between the results of this and other studies may have been due to the differences in the populations studied and in the treatment duration.

Chromium picolinate showed positive results when used in patients, mostly obese or overweight, with atypical depression therapeutic [74]. Chromium picolinate improved significantly the Hamilton depression rating scale items, increased eating, carbohydrate craving, and diurnal variation of humour compared with placebo. The mechanism of action of chromium picolinate seems to be relate to postsynaptic 5HT2A (5-hydroxytryptamine 2A) receptors downregulation [75-77]. This chromium drug was well tolerated [76]. Another study [78] showed that chromium picolinate supplementation originated weight gain, but exercise training combined with chromium nicotinate supplementation resulted in weight loss and lowered the insulin response to an oral glucose load. Nevertheless, a study developed by Lukaski *et al* [79] concluded that chromium picolinate supplementation of women did not independently influence body weight or composition.

Rastegarnia *et al* investigated the antibacterial activity of fluorescent Cr(III) complexes derived from benzimidazole ligands. These complexes showed to be more effective against *Pseudomonas aeruginosa* and *Methicillin Resistant S. aureus* than ampicillin, revealing a potent antibacterial activity [80].

A chromium(III) complex of metformin, $[Cr(MFN)_3]Cl_3.6H_2O$, was synthesized and its antimicrobial properties against gram positive and Gram negative bacteria and different fungal strains were studied. The Cr(III) complex manifested moderate antimicrobial activity towards *Bacillus subtilis*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas sp*., *Aspergillus niger* and *Candida albicans*, compared to the standard antibacterial and antifungal drugs [81].

Two synthetic *α*-diimine chromium(III) complexes, $[Cr(phen)_3]^{3+}$ and $[Cr(phen)_2(dppz)]^{3+}$ (phen = 1,10-phenanthroline and dppz=dipyrido[3,2-a:2´,3´c]-phenazine), were synthesized and revealed activity against Gram positive and Gram negative bacteria. The combination of ciprofloxacin with $[Cr(phen)_3]^{3+}$ for the inhibition of *Staphylococcus aureus* and *Escherichia coli* showed a significative synergistic effect. Both complexes are bactericidal for *S. aureus* and *E. coli* [82].

Gao *et al* studied the anticancer effect of ^{32}P-chromic phosphate colloid after intratumoral injection to Pc-3 human pancreatic carcinoma [83]. The obtained results showed that ^{32}P-chromic phosphate seems to be a secure and efficacious therapy for this carcinoma. A similar study investigated the antitumor effects of ^{32}P-chromic -poly (L-lactide) in nude mice with human prostate cancer, that revealed ability for killing tumor cells, induce apoptosis and inhibit angiogenesis [84].

Chromium-51 is a synthetic radioactive isotope of chromium, used essentially for the diagnosis of gastrointestinal or urinary bleeding [85,86]. ^{51}Cr could also be used to determine the functional blood volume in tumours [87].

Molybdenum (Mo)

Molybdenum, an essential trace element for human beings, functions as a cofactor for enzymes sulfite oxidase, xanthine oxidase, and aldehyde oxidase. Molybdenum deficiency causes a severe metabolic defect, and few children survive the first days of life, and those who survive stay with severe neurological abnormalities [88]. Vegetables, grain products and nuts are major contributors of molybdenum in the diet, being the recommended dietary allowance of this mineral 45 μg/day for adult men and women [69,71].

There are studies suggesting that molybdenum is a potential therapeutic agent against amyloid-related diseases. The mechanisms of Alzheimer's disease include the aggregation of β-amyloid peptides into oligomers or fibrils as well as Aβ-mediated oxidative stress. For that reason, the inhibition of Aβ aggregation and free-radical scavenging are essential for the treatment of this disease. Han et al described the inhibition effects of molybdenum disulfide (MoS_2) nanoparticles on Aβ aggregation. MoS_2 nanoparticles inhibit Aβ aggregation, destabilize Aβ fibrils, alleviate Aβ-induced oxidative stress, as well as Aβ-mediated cell toxicity [89]. Chen *et al* also reported that molybdenum polyoxometalate nanoclusters are capable of inhibit the aggregation of Aβ-peptide associated with Alzheimer's s disease [90].

Treatment with these polyoxometalate complexes can elevate cell viability, decrease levels of intracellular reactive oxygen species and stabilize mitochondrial membrane potential.

Feng *et al* synthesized five molybdenum(VI) complexes with catechol and 2,3-dihydroxy naphthalene and studied their anti-cancer activities [91]. The cytotoxicity test results of the five compounds showed that their inhibition ratios against human cancer cell lines decreased when the chelation number or the size of the aromatic ligand increased. Another study [92] displayed that tetrathiomolybdate, used to treat copper overload disorders, can sensitize drug-resistant endometrial cancer cells to reactive oxygen species (ROS)-generating anticancer drug doxorubicin. Tetrathiomolybdate increased the efficacy of anticancer drugs in ovarian cancer cells in a ROS-dependent manner.

Hussein et al prepared four thiosemicarbazone molybdenum(VI) complexes and studied their anticancer activity. All the complexes showed high anticancer activities against human colorectal cell lines [93].

More recently, Kirakci *et al* designed and synthesized two cationic octahedral molybdenum cluster complexes, bearing carboxylate ligands with triphenylphosphonium (1) or N-methyl pyridinium (2). Their photodynamic anticancer and antibacterial activities were investigated, showing that complex 1 was rapidly internalized into HeLa cells and accumulated in mitochondria, followed by relocation to lysosomes and clearance at longer times [94]. Complex 1 also photoinactivates gram-positive bacteria *Enterococcus faecalis* and *Staphylococcus aureus*, suggesting its suitability for antimicrobial applications.

Mono-layered transition metal dichacogenide molybdenum disulfide (MoS_2) nanosheet could be used as potential nano-carriers for targeted drug delivery [95]. Another study suggested that two-dimensional (2D) chemically exfoliated MoS_2 (ce-MoS_2) sheets have antibacterial activity, attributed to both membrane and oxidative stress [96]. Piçarra et al prepared a novel coating containing molybdenum oxide nanoparticles and studied their antibacterial activity against the most relevant bacterial species responsible for hospital-acquired infections [97]. MoO_3 nanoparticles coating proved to have antimicrobial activity against *S. aureus* population on a surface. These molybdenum trioxide nanoparticles also exhibited high antibacterial activity against Gram negative and positive bacteria and showed cytotoxic effect on lung and breast cancer cell lines [98].

Molybdenum disulfide nanosheets loaded with chitosan and silver nanoparticles exhibited effective antifungal activities against *Saccharomyces uvarum* and *Aspergillus niger* [99].

Ali *et al* prepared a molybdenum complex of 2-[2-(methylaminoethyl)] pyridine and studied it biological activity. This compound showed considerable activity against *C. albicans* fungi [100].

A preliminary study suggested that molybdenum nanoparticles protect cells against cytotoxicity and oxidative stress induced by H_2O_2 and ZnO, exhibiting antioxidative and cytoprotective response [101].

Since there is a serious lack of information concerning the impact of nanoparticles on human health, Asadi *et al* investigated the effects of molybdenum nanoparticles (Mo NPs) into Sprague-Dawley rats [102]. They observed that serum levels of testosterone decreased significantly at the higher concentrations of Mo NPs, but there were not significant differences in luteinizing hormone levels and hematological parameters when compared with the control group. The serum levels of aspartate aminotransferase and of lactate dehydrogenase decreased significantly in lower Mo NPs dosage. The number of Leydig cells decreased and the number of chronic inflammatory cells increased in portal triad and parenchyma in liver tissue of rats exposed to Mo NPs.

Wilson disease treatment use usually chelating agents, which bind copper excess. WTX101 (*bis*-choline tetrathiomolybdate) is an oral first-in-class copper-protein-binding agent for the treatment of this disease. Once-daily WTX101 over 24 weeks rapidly lowered non-ceruloplasmin-bound copper levels in blood, improved neurological status, reduced disability and stable liver function [103].

The Mo-based metallodrugs seem to exert their effect by intercalation/ cleavage of DNA/RNA, arrest of the cell cycle, and alteration of cell membrane functions. Besides the potential applications of Mo-based complexes in medicinal chemistry referred, these compounds could be used in diabetes mellitus, Huntington's disease, atherosclerosis, and anaemia [104-106].

Cobalt (Co)

Cobalt is an essential trace element for humans and is necessary for the production of B complex vitamins, being the daily requirement of this metal 1 to 2 micrograms in adults. The cobalt highest levels are found in offal meat and nuts, being the daily intake not much more than 0.1 mg. However, cobalt is an essential trace element and vitamin B_{12} deficiency is responsible for pernicious anaemia and for specific neurological disorders. The human body contains little more than 1 mg of cobalt, with about a fifth of this stored in the liver. Excretion of this metal is mainly in urine [69,107].

In human cells, there are only two vitamin B_{12}-dependent enzymes: methylmalonyl-CoA mutase, involved in the conversion of propionyl-CoA to succinyl-CoA, an intermediary of the Krebs cycle and methionine synthase, that uses the chemical form of the vitamin which has a CH_3 group attached to the cobalt and is called methylcobalamin. Vitamin B_{12} also takes part in the activity of the 5-methyltetrahydrofolate: homocysteine methyltransferase, working in the metabolism of methionine and in DNA synthesis [107].

However, cobalt ions could have a toxic effect. A study proved that cobalt ions concentrations higher than 10 mg/mL reduced osteoblast cells proliferation and activities and increased the production of IL-6 [108]. Co^{2+} has also a cytotoxic effect on MG-63 osteoblasts and has the potential to modify their redox state [109].

A mononuclear Co(II) complex of lomefloxacin drug was synthesized and its biological activity studied. This compound showed to have a remarkable biological and anticancer activity. Cobalt(II) complex was very active against breast cancer cells and revealed higher in vitro activity against *Candida albicans* fungus than the free ligand and amphotericin standard [110].

N-salicyloil-N′-maleoil-hydrazine Co(II) complex was prepared and its biological activity investigated. This metal complex revealed inhibitory effects against human carbonic anhydrase, isoforms I and II, α-glycosidase and acetylcholinesterase. The development of compounds that inhibit carbonic anhydrase functions could be of great utility in pharmaceutical market since are used for glaucoma, renal tubular acidosis, osteoporosis, antiepileptic and diuretic therapy. On the other hand, compounds that inhibit acetylcholinesterase can help cognitive function and interfere with the improvement of Alzheimer's disease. α-Glycosidase inhibitors are antidiabetic drugs [111].

The increased resistance to traditional anticancer drugs, such cisplatin, carboplatin and oxaliplatin, directed research to alternative transition metal-based compounds, namely cobalt complexes. In fact, simple cobalt coordination complexes, Schiff base complexes, and cobalt-carbonyl clusters showed to have relevant anticancer properties [112].

Hart et al synthesized and characterized a cobalt(III) coordination compound with prodrug potential. In fact, *trans*-dichlorotetrakis(imidazole)cobalt(III) chloride seems appropriate for prodrug anticancer use due to its solubility, ligand lability, irreversible reduction of the Co(III) metal center to Co(II) by biological reductants, and lack of cytotoxicity against human cells [113].

From the six-cobalt *tris*(bipyridine) complexes studied by Law *et al* highlighted what had oxidation state of +3 and CH_3 substituents on the bipyridine ligands [114]. This complex was able to suppress tumor growth in vivo, being the anti-cancer effect exerted via the induction of autophagy, cell cycle arrest and inhibition of cell invasion. The anti-cancer effect of this complex has been demonstrated in different cancer and multidrug-resistant cancer models.

A cobalt complex of ONO donor Schiff base ligand has been synthesized and its antidiabetic, antimicrobial and antioxidant activities studied. $[Co^{2+}L]X_2$, being L= (7-hydroxy-4-methyl-2-oxo-2H-chromen-8-yl)methylene)benzohydrazide and $X = Cl^-$, revealed much better α-glucosidase inhibition than the corresponding free Schiff base ligand. This complex manifested higher inhibitory effect than the free Schiff base ligand. Authors explained this increase of inhibitory activity of the complex against the ligand based on the chelation theory chelation since binding of the metal makes the compound formed to be a more potent bactericidal agent than the free ligand. $[Co^{2+}L]X_2$ also showed moderate antioxidant activity, but stronger DPPH scavenging than the ligand [115].

Boron (B)

Boron occurs in highest concentrations in nuts, fresh fruit and fruit products, and green vegetables [69,116]. According to World Health Organization [117] the adequate intake of boron for adults is between 1 and 13 mg/day, but an intake of at least 1.0 mg/day of this bioactive element is necessary to benefit bone mineralization and growth [118,119] and central nervous system [116,119]. This mineral also promotes the immune or inflammatory response, alleviates arthritic symptoms and facilitates hormone action [116,119].

Boron is associated with the treatment of some types of cancer. The first proteasome inhibitor, bortezomib, a boronic acid dipeptide, was active in the treatment of patients with multiple myeloma [120] or mantle cell lymphoma [121]. The biologically active boronic acid, a more recent proteasome inhibitor, designated by ixazomib, has a great antitumor activity in hematologic and solid tumor models [122]. This second-generation proteasome inhibitor revealed to induce antiproliferative and apoptotic effects on human colon adenocarcinoma cells [123]. The results of the pre-clinical and clinical study developed by Suarez-Kelly *et al* showed that combination of ixazomib and interferon-alpha represents another treatment strategy for inducing synergistic apoptotic tumor cell death in BRAF V600E mutant melanoma [124]. Ixazomib also proved to induce successfully apoptosis and cell cycle arrest, attenuating at the same time the invasion ability of osteosarcoma cells *in vitro* [125]. Augelo *et al* studied the preclinical therapeutic efficacy of MLN2238 in hepatocellular carcinoma cells [126]. The obtained results demonstrated potent antitumor effects of MNL2238 in hepatocellular carcinoma cells in vitro and in vivo models, being this a promising drug to these patients.

Mang *et al* synthesized and co-administrated two homochiral-peptide-based boron diketonate complexes in cancer cells [127]. The dual-targeted-assembly generates a synergistic anticancer effect with increased inhibition efficacy on cancer cell migration. Kilic *et al* studied the *in vitro* anticancer properties against various cancer and normal cells of triboron complexes with Hemi-Salen ligands [128]. The cytotoxicity results revealed that the cell viability of the cancer cells was decreased, but most of the healthy cells could still be viable.

Boron also revealed to have antimicrobial properties. Tavaborole, a boron-based pharmaceutical is a topical antifungal medication approved for the treatment of onychomycosis due to *Trichophyton rubrum* or *T mentagrophytes* [129]. A few years ago, Baker et al reported another boron-containing antifungal agent, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), for the potential treatment of onychomycosis [130].

Anacor Pharmaceuticals (USA) patented 3 boron containing small molecules with fungistatic and fungicidal properties against yeasts and dermatophytes [131-133]. The most active of these compounds revealed activities against *C. albicans*, *C. neoformans*, *A. fumigatus*, *S. cerevisiae*, *T. mentagrophytes and T. rubrum*, *C. glabrata* and *C. krusei*, could this invention be also used for topical treatment of onychomycosis [134].

Hernandez *et al* developed a boron-based antibiotic class, the aminomethylbenzoxaboroles, with activity against Gram-negative bacteria that inhibit bacterial leucyl-tRNA synthetase [135]. This antibiotic class proved to be efficacious against *E. coli* and *P. aeruginosa* in murine thigh infection models. Meropenem-vaborbactam, a boronic acid-based beta-lactamase inhibitor, is a carbapenem antibiotic with activity against resistant Enterobacteriaceae, with promising results treatment of complicated urinary tract infection [136].

Hiller et al reported boronic acids with antichagasic *in vitro* activity [137]. One of these boronic acids had an EC50 (half maximal effective concentration) value 10 times lower than benznidazole, the current drug employed in the chemotherapy of Chagas disease.

Iodine (I)

Iodine is essential for the synthesis of thyroid hormones and for this gland normal function, having an important role in metabolism and physiological processes [138,139]. Tetraidothyronine (T4) and Triiodothyronine (T3) are the two essential hormones for human metabolism produced by thyroid. This hormone biosynthesis begins with active iodide transport into thyroid followed by iodide oxidation and subsequent iodination of tyrosyl residues of thyroglobulin to produce monoidotyrosine (MIT) and diiodothyrosine (DIT). A coupling reaction between two MIT unities originates T4 and the association of one DIT and one MIT produces T3 [140].

A daily iodine intake of 150 µ/day is recommend for adults, being proposed 200 µg/day for pregnant and lactating women to increase maternal thyroid hormone production, iodine uptake by the fetus, placenta and amniotic fluid, and iodine stores. Iodine could be found in seafood, like fish, crustaceans, mussels and algae, vegetables grown in soils rich in this element, eggs, milk and food products derived from them, and iodised salt [139,141].

Iodine deficiency disorders occurs in all stages of life but are particularly of concern in pregnancy and infancy and impairs cognition and growth, causing several thyroid disorders, hypothyroidism and goitre [139,142,143].

A study developed by Cuellar-Rufino *et al* revealed that iodine deficiency is associated with hypertensive disease of pregnancy [144]. In fact, pregnant women with normal levels of iodine can maintain the redox balance, what does not happen with pregnant women with

hypertensive disease and iodine deficiency. The results of this study, that estimated that about 70% of women with hypertensive disease of pregnancy had iodine deficiency, related high levels of markers of oxidative stress (low levels of superoxide dismutase and catalase enzymes) in pregnant women with this pathology and low antioxidant status that were accented in pregnant women with deficiency in this element.

Hypothyroidism is related with high serum total cholesterol and low-density lipoprotein cholesterol by increasing cholesterol absorption in the intestines [145]. There is also increase in apolipoprotein B, being the High-Density Lipoprotein (HDL) levels normal or even elevated in severe hypothyroidism. Hypothyroidism is often associated with diastolic hypertension that, in conjunction with dyslipidemia, may originate atherosclerosis and cardiovascular disease [146].

The strategy used to avoid iodine deficiency is iodisation of salt, but when this procedure is not possible, susceptible groups receive iodine supplements [138].

Potassium iodide is a satisfactory therapeutic response for sporotrichosis, subacute or chronic subcutaneous mycosis caused by the fungus *Sporothrix spp*. Macedo et al showed the efficacy and safety of KI in 102 patients with sporotrichosis, with similar results of standard drug, itraconazole [147]. Benvegnú et al reported a case of a 47-year-old male patient with disseminated cutaneous sporotrichosis that was treated with saturated KI for five months, which resulted in complete resolution of the lesions [148]. Mahajan *et al* presented three unusual clinical forms of sporotrichosis: (i) a 52-year-old man that developed sporotrichosis over pre-existing facial nodulo-ulcerative basal cell carcinoma of seven-year duration, and lymphocutaneous sporotrichosis over right hand/forearm from facial lesion/herbal paste; (ii) a 25-year-old woman, that had osteoarticular and possibly pleural sporotrichosis with disseminated systemic-cutaneous; (iii) a 20-year-old girl, with a multiple intensely pruritic, nodular lesions over/around left knee of two-year duration [149]. Patients of the three reported cases showed clinical cure with KI in 12 weeks.

Povidone-iodine is used worldwide for ocular surface washing due to its wide-spectrum antimicrobial activity, absence of resistant bacteria and low cost [150]. Povidone-iodine solution (10%) is usually used to disinfected eyelids and eyelashes for drug delivery to the eye and retina in the form of intravitreal injections; a sterile speculum is placed and drops of povidone-iodine (5%) are also applied in this procedure [151]. Another study evaluated the

bactericidal activity of a diluted povidone-iodine formulation (0.6%) in comparison with the most used 5% povidone-iodine solution ophthalmic preparation and the results showed that the diluted formulation was faster in killing Gram-positive as well as Gram-negative bacteria. The authors attributed this result to the increased amount of free iodine in the diluted preparation [152]. Povidone-iodine is also used to prevent and treat postoperative endophthalmitis, caused by conjunctival bacterial flora or contaminated solutions and instruments [150], and its preoperative use should be consider avoiding scleral perforation during strabismus surgery [153].

Hartoft-Nielsen *et al* studied the influence of iodine and tri-iodo-thyronine in the incidence of type 1 diabetes mellitus [154]. Bio-Breeding/Worcester rats were treated with NaI or TSH neonatally or with tri-iodo-thyronine (T3) during adolescence. NaI and T3 proved to reduce the incidence of diabetes mellitus, whereas TSH had no effect. Furthermore, T3 increased the beta cell mass per bodyweight. However, a recent study associated high iodine dietary intake with type 2 diabetes. Since this is the first relationship between dietary iodine intake and the risk of developing type 2 diabetes, more studies are needed [155]. A study reported by Mansel et al revealed that women with fibrocystic breast changes who consumed a nutritional formula with gamma-linolenic acid, iodine and selenium showed significantly less breast nodularity, and less cyclic breast pain [156]. According to a previous study, improvements at breast pain, tenderness, and nodularity each cycle are because of supraphysiologic levels of iodine [157]. A recent research showed that iodine also has antineoplastic activity, since decreases the invasive potential of triple negative basal cancer cells MDA-MB231, activating the immune response in mammary cancer xenografts [158].

Iodine-131 (^{131}I) is an important radioisotope of iodine used in treatment procedures, such as thyroid cancer, Graves' disease, hyperthyroidism and in patients with toxic nodular goiter [159,160]. Iodine-131 therapy revealed good results in patients with hyperthyroid heart disease induced by Graves' disease or Plummer disease, being the remission rate after ^{131}I treatment 76.0% [161].

The combination of radioactive iodine (^{125}I) seed localization in the axilla with the sentinel node procedure is a less-invasive approach for axillary staging after neoadjuvant chemotherapy in patients with axillary node-positive breast cancer [162]. According to a retrospective study [163], ^{125}I seed implantation reduces pain and improves quality of life, demonstrating potential advantages [164-166] in locoregionally recurrent breast cancer

patients, such as: relatively long half-life, what prolongs the radiation effects on the tumor cells; seed implantation is not affected by respiratory movements; it delivers a large enough dose of localized radiation for tumors >5 cm; low risk of side effects; ^{125}I seed implantation technique is easy and under local anesthesia. Brachytherapy with ^{125}I seeds is also an effective for prostate cancer treatment [167].

Since damage of the cardiac autonomic nervous system can be visualized and quantified by radionuclide imaging with iodine-123 meta-iodobenzylguanidine scintigraphy, 123I-mIBG, could help to identify patients at low risk of major adverse cardiac events or worsening heart failure and those with a more favorable prognosis [168].

A patient with an occult papillary thyroid cancer, presenting as cystic metastasis of the lateral neck, was subject to total thyroidectomy and right cervical neck dissection, followed by radioiodine therapy, and iodine supplementation for two years [169].

Iodine, in an extremely low dose, could also be used in intracoronary computed tomography angiography in patients with coronary artery disease [170].

CONCLUSION

This review discusses the physiological and biochemical functions, dietary requirements, and signs and symptoms of excess and deficiency for the essential ultra-trace minerals.

Trace and ultra-trace elements are present in different forms in the nature, and these elements are very essential for the body to perform different functions. Ultra-trace elements are very important for cell functions at biological, chemical and molecular levels. In fact, human body requires several essential elements in small quantities and their absence or excess may result in severe malfunctioning of the body because these essential trace elements directly influence the metabolic and physiologic processes of the organism. The rapid urbanization and economic development have resulted in drastic changes in diets with developing preference towards refined diet and nutritionally deprived food. For instance, poor nutrition can lead to reduced immunity, augmented vulnerability to various oral and systemic diseases, impaired physical and mental growth, and reduced efficiency. Moreover, it is one of the most difficult tasks to diagnose trace element deficiencies nutritionally as well as clinically. As previously stated, the deficient intake of an essential ultra-trace element can diminish significant biological functions within tissues and restoration of physiological levels of that element

relieves the impaired function or prevents impairment. Thus, preventive medicine has gained more attention than anything else as quoted aptly, "prevention is better than cure."

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