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Trace Minerals in Human Health: Iron, Zinc, Copper, Manganese and Fluorine

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ABSTRACT

Trace elements exist in the environment in small amounts but play an essential part in sustaining various physiological and metabolic processes occurring within living tissues, as enzymes structure and function, bone and blood maintenance, immune responses or transmission of nerve impulses. They must be obtained from diet, being a varied and balanced diet important for obtaining a series of elements necessary for our body. The total amount of a mineral in a food that is dependent on digestion, its release from the food matrix and the absorption rate by the intestinal cells. If minerals are not supplied in adequate quantities, signs and symptoms of trace elements deficiencies appear. Beyond the nutritional aspects, trace elements have applications in the pharmaceutical industry, integrating pharmacologically active compounds. Usually, in the form of metal complexes, these metal-based drugs are used as anticancer therapeutics, anti-inflammatories, antidiabetic drugs or antimicrobial agents. This evolving field is developing metal complexes with remarkable actions, and new metal-based drugs are emerging every year. This article aims to review the main effects of trace elements in human health, namely iron, zinc, copper, manganese and fluorine, focusing on the physiopathology and consequences of lack 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 that are present in the tissues and fluids of the human body. They are divided into: (i) macrominerals (main minerals) and (ii) microminerals (secondary minerals). Calcium (Ca), magnesium (Mg), potassium (K), sodium (Na), chlorine (Cl), phosphorus (P) and sulphur (S) are considered as macrominerals because they are needed in greater quantity. Microminerals are iodine (I), zinc (Zn), selenium (Si), iron (Fe), manganese (Mn), copper (Cu), cobalt (Co), molybdenum (Mo), fluorine (F), chromium (Cr) and boron (B), which we need to consume in small quantities. Both are important for good health and should be consumed according to the needs of the organism [1, 2, 3]. Microminerals, including trace and ultra-trace elements, play a vital role in maintaining integrity of various physiological and metabolic processes occurring within living tissues [4].

The words “trace elements” are used for elements existing in natural and perturbed environments in small amounts, with excess bioavailability having a toxic effect on the living organism. The ten main trace elements include iron, copper, zinc, manganese, fluorine, bromine, rubidium, silicon, strontium and lead. Among these, iron is the most abundant in human serum, followed by zinc and copper. On the other hand, cobalt, iodine, selenium, boron, molybdenum and chromium, among others, are ultra-trace elements and are present in least amounts (at ppb order) [5].

Minerals are necessary for the bone strengthening, the transmission of nerve impulses or the enzymatic structure. The existence of a significant variety of minerals in our organism is related to the different functions they have, although some play similar roles. Microminerals (Cu, Fe, Mn, Se and Zn) play an important role in the structural fraction of enzymes, in the formation of erythrocyte cells (Co, I and Fe), in the regulation of glucose levels of activation of antioxidant enzymes (Mo), and maybe involved in the various processes of the immune system (Cu, Se and Zn) [2].

Since minerals are not produced by living beings but perform functions essential to the human organism, they must be obtained through diet [6,7]. There are several food sources that can be used to obtain macro and microminerals, being a varied and balanced diet, rich in vegetables and fruits, and food of animal origin, important for obtaining a series of elements necessary for our body [2, 3].

The total amount of a mineral in a food does not reflect the amount that will be available in the body for absorption. The bioavailability of a mineral is defined as the ingested fraction thereof that is absorbed and, in turn, used for physiological functions. Consequently, the bioavailability of a mineral is dependent on digestion, its release from the food matrix, the absorption rate of the target ingredient by the intestinal cells and the amount that is transported to the cells[1, 2].

In general, minerals present in ingested foods are absorbed into the different parts of the gastrointestinal tract (duodenum, jejunum and ileum). Minerals that are absorbed by the intestinal epithelial cells are transferred through the cytosol and transported through the membrane into the blood by an active transport mechanism. If a mineral is not transported through the membrane, it will remain in the intestinal cell connected to the proteins. For instance, iron ions bind to ferritin and zinc to metallothionein. Minerals that are not absorbed are usually excreted in the faeces. This mechanism appears to occur to protect the body against the potential toxicity that excessive absorption of minerals can cause [1, 2].

If minerals are not supplied in adequate quantities, deficiencies arise, which can manifest themselves through specific and non-specific symptoms. A severe deficiency of an essential mineral can only be corrected by supplementing the element concerned. In fact, the amount of minerals supplied by food is not always enough to meet the needs if the bioavailability of the mineral is low. Then, to become bioavailable, the minerals must be absorbable and therefore bioaccessible [7].

Nowadays, besides the nutritional aspects, minerals have several applications, being the pharmaceutical and cosmetic industries one of their areas of intervention [8, 9, 10, 11]. There are, in the pharmaceutical market, a variety of medicinal products whose composition integrates trace minerals, such as iron, zinc, manganese, among others. These elements are considered especially important because of their physiological roles and their participation in a variety of biological processes [12, 13].

Metal-based drugs are inorganic compounds that have been used in medicinal chemistry as therapeutic agents for a long time. These metal complexes were successfully applied as anticancer therapeutics, anti-inflammatories, antidiabetic drugs, antimicrobial agents or in the treating of specific conditions, such as Diabetes Mellitus, Huntington's disease, atherosclerosis or Wilson's disease, among others [14, 15, 16]. The use of metallodrugs as

effective pharmaceuticals shows that is possible to control the cytotoxicity of metal ions by the appropriate choice of ligands [14].

Since redox metabolism of cancer cells is different from healthy tissues and enhanced levels of Intracellular Reactive Oxygen Species (ROS) are often observed in tumor cells, interacting with the cellular redox homeostasis of cancer seems to be a promising approach for cancer therapy[17]. Anticancer metal complexes (including copper and manganese) have been shown to strongly interfere with or even disturb cellular redox homeostasis. Changes of the redox conditions, upregulation of oxidative stress and its molecular consequences for malignant tumors are the guidelines for the development of innovative redox-active metal drugs [11, 17].

Due to the variability in opinions of the role and effect of trace elements in human health this article offers an overview of research information, focusing on trace minerals such as iron, zinc, copper, manganese and fluoride in connection with human condition.

Iron (Fe)

Iron is an essential element for almost all living organisms because it participates in a wide range of metabolic processes, including oxygen transport, synthesis of deoxyribonucleic acid (DNA) and electron transport. This metal also plays important roles during inflammation and the immune response to infection. However, as this mineral can form free radicals, its concentration in the body must be carefully regulated, since its excess can cause tissue damage. Disorders related to iron metabolism are among the most common health problems in humans and cover a broad spectrum of diseases with diverse clinical manifestations, ranging from deficiency to iron overload and neurodegenerative diseases [9, 18, 19].

Animal offal, especially liver, red meat, miscellaneous cereals, nuts and shellfish are important sources of Fe, depending the recommended daily intake for elemental iron age and sex (adult male - 8 mg; adult female - 18 mg) [20, 21]. There are compounds that can inhibit or facilitate the absorption of iron from food, which occurs mainly in the duodenum and upper jejunum. Inhibitors include phytates, polyphenols (tannins, phenolic acid and flavonoids), dietary fiber, protein and calcium. Absorption of iron is facilitated by meat, fish, poultry, ascorbic acid, citric acid and amino acids [9, 18, 22].

Nutritional iron exists in two chemical forms: heme iron, which is found in hemoglobin, myoglobin and some enzymes, and is bioavailable; and non-heme iron, which exists mainly

in foods of vegetable origin, but also in some animal sources, as well as non-heme enzymes and ferritin [1, 23].

In a healthy individual, iron is maintained at stable concentrations in plasma and tissues, primarily by regulating iron absorption from food and preserving iron stores in the body. This systemic iron homeostasis is controlled by a variety of proteins, with hepcidin being the main regulator through its binding to ferroportin [1]. Iron deficiency can lead to anemia, which is characterized in this case by the production of smaller erythrocytes and by a decrease of circulating hemoglobin [1, 9].

Based on prevalence and health effects, iron deficiency anemia is considered a major public health problem. The foremost factors leading to the high prevalence of this deficiency are: i) blood loss (excessive menstrual flow in women, hemorrhage from injury or chronic loss of blood due to stomach ulcer, hemorrhoids, varicose veins, parasites, ulcerative colitis or malignant diseases of the uterus and colon); ii) low intake of bioavailable iron, due to vegetarian eating with insufficient intake of heme iron; iii) inadequate absorption, resulting from possible diarrhea and intestinal disorders such as celiac disease, atrophic gastritis, partial or total gastrectomy, or interference of various drugs; iv) the existence of inhibitors in food diets (e. g. cereals and vegetables); v) increased iron needs, which were not achieved during childhood, adolescence, pregnancy and lactation for the growth of blood volume; and vi) failure to release iron from plasma reserves and defective use of this mineral due to inflammation or chronic disease [1, 9, 24].

Anemia can be corrected by administering oral iron supplements, namely iron(II) salts in high doses, being more common the use of ferrous sulfate or ferrous gluconate, which are the most applied because of its low cost and high bioavailability. To prevent possible iron deficiency, individuals should always be advised to have a feed with an appropriate iron intake [24].

On the other hand, hemochromatosis is a genetically determined form of iron overload that results in progressive lesions in the liver, pancreas, heart and other organs, as individuals absorb three times more iron from food than those who do not suffer from this disease. Men are particularly susceptible to this disease because they do not have physiological mechanisms for iron release, such as menstruation, pregnancy and lactation [1].

Iron has been searched due to its antibacterial activity. Nanocatalysts of single iron atoms isolated in nitrogen-doped carbon could effectively catalyze the peroxidase-like reaction,

producing hydroxyl radical to kill bacteria of both Gram positive (*Staphylococcus aureus*) and Gram negative (*Escherichia coli*) in the presence of H_2O_2. *In vivo*, these single iron atom nanocatalysts eradicated bacterial infections propagated at wounds by *E. coli* and *S. aureus* pathogens [25].

Two iron(III) complexes bearing the tripodal aminobisphenolate ligand were synthezised and studied. These compounds showed to be cytotoxic against both human triple-negative breast adenocarcinoma and human cervical carcinoma, in addition to good anti-*Mycobacterium tuberculosis* activity [26].

Tidjani and co-workers synthesized and characterized mixed iron(III) complexes containing amino acids and isonitrosoacetophenone [27]. These compounds showed to be potent anticancer agents with potential to be developed as anticancer drugs. The antimicrobial activity of these Fe(III) complexes was also investigated against both Gram positive and negative bacteria (*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*) and fungi (*Candida albicans*), revealed that iron compounds were more active against Gram positive bacteria. The complexes also showed a good antifungal activity, having considerable growth inhibition against *Candida albicans*.

Ye and colleagues have studied the anticancer effect and the pharmacological mechanism of a Fe(II) phenanthroline complex [28]. This iron complex was selectively transported into esophageal squamous cell carcinoma cells overexpressing transferrin receptor 1 (TFR1) through TFR1-mediated endocytosis and showed anticancer activity in a dose-dependent manner. The Fe(II) complex caused cell cycle arrest at the G0/G1 phase by blocking the CDK4/6-cyclin D1 complex and induced mitochondria-mediated apoptosis. Exposure to the Fe(II) complex also originates excessive reactive oxygen species accumulation by thioredoxin reductase inhibition and DNA double-strand breaks, which in turn sequentially activated ATM, CHK1/2 and p53. Combination treatment of Fe(II) complex with cisplatin exhibited a synergistic effect in ESCC cells, indicating potential use of this iron compound in esophageal squamous cell carcinoma cells chemotherapy, mainly for patients with TFR1 overexpression.

A nanomedicine that can attain tumor-specific chemotherapeutic drug release and ROS generation was developed, with iron oxide nanoparticles encapsulated and β-lapachone in a nanostructure assembled by H_2O_2-responsive polyprodrug polymer [29]. The antitumor effect of

this tumor-specific drug release and ROS generation was showed *in vitro* and *in vivo*, being a potential combination therapy for cancer chemo/chemodynamic.

Two isothiocyanato iron(III) complexes with 2,2′-[2,6-pyridinediylbis(ethylidyne-1-hydrazinyl-2-ylidene)]bis[N,N,N-trimethyl-2-oxoethanaminium] dichloride (H_2LCl_2) ligand have been synthesized and studied [30]. Cytotoxic activity of Fe(III) complexes was tested against five human cancer cell lines and normal cell line, being the results compared with the obtained for Co(II), Ni(II), Mn(II), Zn(II) and Cd(II) complexes with the same ligand previously synthesized [31, 32, 33, 34]. The cytotoxic activities of the complexes were lower against all malignant cell lines than the activity of cisplatin (positive control) and the best activity was observed for Fe(III), Co(II) and Cd(II) complexes. Iron(III) complexes also showed better antimicrobial activity than the ligand H_2LCl_2 and $FeCl_3{\cdot}6H_2O$, but their Minimum Inhibitory Concentration (MIC) values were higher than the values for standard antimicrobial agents. Both complexes revealed better activity against Gram positive than Gram negative bacterial strains, being the highest activity observed against *B. subtilis* [30].

A Fe(II) complex with a Schiff base ligand derived from 2-amino-3-hydroxypyridine and 3-methoxysalicylaldehyde has been prepared [35]. Schiff base ligand, Fe(II) complex and the corresponding nano-sized metal oxide *in vitro* biological activities have been tested against Gram negative bacteria (*Escherichia coli* and *Serratia marcescence*) and Gram positive bacteria (*Micrococcus luteus*) and three strains of fungus (*Aspergillus flavus*, *Getrichm candidum* and *Fusarium oxysporum*). The iron complex revealed to possess more antimicrobial activity than the free Schiff-base chelate, but it nano-sized metal oxide has the highest activity. Fe(II) complex also interact with DNA through intercalative binding mode and showed cytotoxic activity on human colon and hepatic carcinoma cells.

Zinc (Zn)

Zinc is the second most prevalent vestigial element in the human body, and it is essential for individuals to remain healthy (the recommended dietary intake, expressed as elemental Zn, is 11 mg and 9 mg for adult male and female, respectively). Since the human body does not store excess zinc, it must be consumed regularly as part of the diet. Common dietary sources of Zn include red meat, poultry and fish [1, 36].

Zinc performs a wide variety of functions in the human body, such as maintenance of physiological processes, metabolism, signalling, transduction, cell growth and differentiation.

Due to its size and charge characteristics, zinc is used by numerous proteins to stabilize the structure and assist its function. These proteins are largely enzymes and transcription factors, which are involved in many processes that include growth and immune function [1, 36, 37, 38].

Zn is still important for the catalytic activity of various enzymes, on immune function, on protein synthesis, on wound healing, on DNA synthesis and on cell division. This mineral is also essential for the normal development of pregnancy, as well as for growth during childhood and adolescence [38]. Thus, their deficiency can lead to oligospermia, loss of weight and hyperammonemia, delayed growth, hypogonadism in males, rough skin, lack of appetite, delayed wound healing, palate, olfaction and night vision impairment, bullous-pustular dermatitis, alopecia, diarrhea, weight loss, anorexia, depression and intercurrent infections. A severe zinc deficiency, if not detected, can even be fatal [10, 37, 39].

The zinc toxicity is considered extremely rare, as it is considered a non-toxic mineral, especially when administered orally. However, excessive intake may lead to symptoms such as nausea, vomiting, epigastric pain, lethargy, and fatigue. When there is zinc intake ten to twenty times higher than the daily recommended amounts, copper deficiency may occur and consequently symptoms of anemia and neutropenia [10].

Zinc is mainly absorbed at the duodenum. It binds to many proteins in plasma, including albumin. Food and drink reduce the absorption of this mineral, varying its bioavailability with the inorganic salt. In fact, food intake is not a guarantee of cellular use of this mineral, since chemical interaction with other substances such as oxalates, phytates, fibers and other minerals may occur, damaging the absorption and limiting its bioavailability. Phytates can bind to zinc, forming insoluble complexes at alkaline pH. Likewise, the absorption of zinc is decreased by the presence of phosphates and calcium in the diet. However, animal proteins appear to increase zinc absorption, perhaps because their amino acids keep zinc in a soluble form. Zinc excretion is mainly through the faeces, with a small percentage of this mineral being excreted in the urine[36, 38, 39, 40].

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disease produced by the inability of the pancreas to increase insulin secretion to balance its decreased activity in insulin-sensitive tissues, resulting in a persistent hyperglycemia condition [16, 41]. Zinc is an essential mineral to the endocrine pancreas, where it is insignificant concentration, participating in various functions related to blood glucose homeostasis. Appropriate or increased amounts of zinc in

the pancreas may be beneficial in T2DM, favouring the construction of insulin hexamers and regulation of insulin and glucagon secretion, as well as hepatic clearance of insulin. Zinc sulphate supplementation of patients seems to have beneficial effects because by raising the concentration of this mineral in the serum, there is an improvement in glycemic control [16, 41, 42].

Childhood is a critical phase of life, which requires adequate nutrition to sustain growth and development. Zinc deficiency is an important health problem that particularly affects young children and contributes to the occurrence of infectious diseases, including diarrhea, pneumonia and malaria. Zinc deficiency is a key factor in increasing the susceptibility to infection found in nutritional deficiency states, in which case supplementation of the mineral is recommended, more precisely with zinc sulfate [40, 43].

Wilson's disease is an autosomal recessive genetic disorder characterized by decreased copper incorporation into ceruloplasmin and consequently increased excretion of copper, resulting in accumulation of toxic compounds in the liver, brain, and other tissues and organs. Toxic copper reserves can be removed with chelation therapy or with zinc to inhibit the absorption of intestinal copper. Zinc sulfate is important in the treatment of this disease and should be applied when other therapies are not showing the expected results. Zinc has a different mechanism of action from oral chelators and therefore may serve as a substitute for these drugs in the treatment of this disease when intolerance develops or for maintenance therapy after liver transplantation [44, 45].

Recent research suggests that, in hepatocytes, zinc may potentiate certain mechanisms of cell function that protect the cell from potential damage. For these reasons, zinc is considered a potentially effective treatment for Wilson's disease. Clinical experience has shown that zinc, administered as a salt, is effective as maintenance therapy in patients who were initially treated with an oral chelator, including those who became intolerant of this chelator. The major problem with zinc is that it requires a consistent dosage of three times a day and thus non-adherence to therapy may limit its overall effectiveness [44].

Zinc seems to play an important role in the treatment of alcoholic liver disease. Since zinc deficiency is an important factor in the development and progression of this disease, taking supplementation in Zn may act as a reversal of zinc deficiency. However, it should be noted that, although zinc is innocuous compared to other metal ions having similar chemical

properties, administration of the same in high doses may affect copper homeostasis. Therefore, careful monitoring of zinc and copper is required during this supplementation therapy [37].

In addition to the aforementioned pathologies, where Zn supplementation has positive results, zinc sulfate has been successfully applied in the treatment of various diseases and health problems, such as enteropathic acrodermatitis, anorexia nervosa, arthritis, diarrhea, malabsorption syndrome, ocular irritation, infection control, infertility, senile dementia, sickle cell anemia, thalassemia and constipation [38].

Zn(II) complexes nitroporphyrins derivatives showed HIV-1 entry inhibition and *in vitro* photodynamic activity towards human lung cancer cells, being these antiviral and anti-cancer properties improved by the incorporation of Zn(II) in the free ligand [46].

Hussain and co-workers have designed and synthesized a zinc complex of benzimidazole derived organic moiety that revealed potential *in vitro* anticancer activity against five cancer cell lines, specifically HepG2 (liver), SK-MEL-1 (skin), HT018 (colon), HeLa (cervical) and MDA-MB231 (Breast), and no activity was observed with the free ligands. The complex showed a significant binding affinity with DNA, this being an important aspect of the metal-based anticancer chemotherapeutic. The degree of toxicity of this potential antitumor drug was very low [47].

Liu and colleagues synthesized a Zn(II)-based coordination polymer, $\{(H_2NMe_2)_2[Zn_3(BTB)_2(OH)(Im)](DMF)_9(MeOH)_7\}_n$ (H_3BTB=1,3,5-benzenetrisbenzoic acid, Im=imidazole, DMF=N,N-dimethylformamide), and studied it *in vitro* anticancer activity on four human liver cancer cells [48]. Although the ligands H_3BTB and Im did not show anticancer activity against these cell lines, zinc incorporation became the coordination polymer effective in anticarcinogenic properties.

The antibacterial and antifungal properties of derived thiophene-2-carboxamide zinc complexes were investigated. These compounds revealed significant or moderate activity against four Gram negative (*E. coli*, *S. sonnei*, *P. aeruginosa* and *S. typhi*) and two Gram positive (*S. aureus* and *B. subtilis*) bacterial, being, for most of the strains, more effective than the free ligands. The antifungal activity was more significant for *C. albican*, *A. Flavus* and *C. glaberata*, depending on the ligand, however, against one or more fungal strains the bioactivity of the ligands is more evidente [49].

Copper (Cu)

Copper, an essential trace element, is present in the human body in an approximate amount of 100 mg. The normal Cu intake by an adult is about 1-4 mg/day, with vegetables being one important source [20]. It is involved in a plethora of biological processes, from immune and neural functions to bone and blood health, or antioxidant defense. Most of these roles are performed by metalloproteins and enzymes, to which copper is mostly bound, acting both structurally and as a cofactor for catalytic activity [20]. Ceruloplasmin is the most abundant copper containing enzyme (it accounts for 95% of human plasma copper), being a ferroxidase, which makes it have antioxidative properties [50].

Dietary copper deficiency can result in adverse consequences. Although severe Cu deficiency is relatively straightforward to diagnose, identifying marginal deficiency is problematic [51]. The mean time described from onset of symptoms to diagnosis in mild deficiency was 1.1 years [52]. Copper deficiency is a known cause of anemia and neutropenia. Hypocupremia is associated with excess zinc intake, which competes with copper for intestinal absorption, but also with gastric surgery, malabsorption, and excess copper chelation [53]. Similar to cobalamin deficiency, hypocupremia can also lead to a progressive myeloneuropathy; these effects being observed, for instance, in patients receiving prolonged exclusive tube feeds or parenteral nutrition [52]. In utero, Cu deficiency may result in impaired development of the cardiovascular system, bone malformation and ongoing neurologic and immunologic abnormalities into infancy and beyond[51]. In adulthood, Qu and co-workers found that low concentrations of serum Cu lead to lower bone mass density, weaken bone formation and mineralization and impaired cartilage integrity [54]. Cu deficiency has been associated with alterations in cholesterol metabolism; there appears to exist a negative relationship between dietary or serum Cu and total and LDL-cholesterol, and a positive association with cholesterol HDL, suggesting that a high Cu intake and status is associated with a better metabolic profile [51].

Genetic alterations in the homeostasis of Cu originate disease. Wilson's disease results from mutations in ATP7B, copper-transporting P-type ATPase, causing hepatic and neuronal copper accumulation, which leads to liver failure and neurological problems (movement disorders, seizures, and depression). It can be managed by low Cu diets, chelation therapy, Zn administration or liver transplant [55]. Menkes's disease is a congenital neurodegenerative disorder caused by ATP7A gene mutations, that causes reduce copper absorption, leading to

copper deficiency. Clinical features include epilepsy, growth delay, reduced muscle strength, skin laxity, abnormal hair, and urologic abnormalities [56].

Another different concern, more prevalent in recent years, due to the increasing consumption of dietary supplements containing Cu, is excess exogenous copper uptake and copper exposure, which also can lead to health problems. Excessive copper produces large amounts of free radicals that cause lipid peroxidation and interfere with bone metabolism, leading to a decrease in bone cortex and bone strength [54]. There is a potential link between excess Cu and neurological disease: Parkinson's disease (as Cu is associated with the accelerated aggregation of the α-synuclein protein), Huntington's disease (Cu has been shown to promote the aggregation of mutant polyglutamine repeat proteins), and Alzheimer's disease (Cu increases the oligomerization of the amyloid-beta peptide) [57, 58].

This metal has been exploited in pharmacology, where it appears in new compounds having interesting roles. A high number of copper-based complexes are now under investigation, mainly due to the therapeutic potential, which is increased by coordinating copper(II) complexes with mono- or polidentate Schiff bases chelates, or other donors [59]. Cu-complexes have been proposed as potential anticancer agents, since cancer cells take up greater amounts of Cu than normal cells, with angiogenesis and metastasis being linked to copper metabolism[60]. Complexes formed with Cu and vitamin B1 (thiamine) as a ligand showed promising *in vitro* activity against human colon adenocarcinoma Caco-2 cells [61]. Cu(II)-niflumate complexes showed cytotoxicity against human melanoma cell line HT-144 [62]. Qi and colleagues synthesized Cu(II) compounds with thiosemicarbazone that showed antitumor activity against liver cancer cell (BEL-7404) *in vitro*, possibly related to apoptosis of cancer cells induced by Cu compounds through the intrinsic ROS-mediated mitochondrial pathway [60]. The antineoplastic activity of copper complexes was evaluated *in vitro* against human cervical cancer (HeLa) cells, and results showed that the copper complex exhibited significant growth inhibition of these cells [63].

The anti-inflammatory activity of copper complexes has also been described for several decades and used to treat inflammatory disorders, such as rheumatoid arthritis, and some ligands that enhanced the oral or dermal absorption of copper(II) were investigated [64].

Hussain and co-workers have synthesized copper complexes with anticancer and anti-inflammatory activities that produced significant dose-dependent and potent analgesic and

anti-inflammatory effects and significant antipyretic activity only at 100 mg/kg [65]. Furthermore, they confirmed the interaction of complexes with cyclooxygenase 2, which can be a mechanism of action of these potential candidates for anti-inflammatory drugs. Cu complexes also show antimicrobial activity; dithiocarbazate-copper(II) complexes were evaluated against multiresistant clinical isolates and certified microbial strains, showing positive results, with greater activity against Gram-positive bacteria [66]. Antibacterial activity of novel amino acids imine ligands, complexed with several metals including Cu, against bacteria (*Bacillus subtilis*, *Micrococcus luteus*, *Escherichia coli*) and fungi (*Aspergillus niger*, *Candida glabrata*, *Saccharomyces cerevisiae*) have been screened. The results showed that the complexes have antimicrobial activity higher than free ligands [67].

These compounds also have a role against neurologic diseases. The copper *bis*(thiosemicarbazones) complexes were described as neuroprotective in animal models of Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and cerebral ischemia[68, 69]. Moreover, they appear to act as antidepressant adjuvants, improving sertraline efficiency (the antidepressant and analgesic activities of the Cu-sertraline complex have been assessed in rats denoting a marked synergistic effect) [70].

Manganese (Mn)

Manganese is essential to the formation of bone and to amino acid, lipid, protein, and carbohydrate metabolism. It is also needed for normal immunity system, regulation of blood sugar and cellular energy, reproduction, digestion, and for the defence mechanisms against free radicals. This trace element is required for the proper function of several metalloenzymes such arginase, glutamine synthetase, phosphoenolpyruvate decarboxylase, and manganese superoxide dismutase [71, 72, 73].

The major route of intake for Mn is *via* food consumption, but inhalation exposure may also occur [72]. The richest food sources of manganese are nuts, bread and cereal products [20]. The Adequate Intake of Mn for adult men and women is 2.3 and 1.8 mg/day, respectively, being the Tolerable Upper Intake Level for adults of 11 mg/day [71].

Humans maintain stable tissue levels of Mn. This is achieved via tight homeostatic control of both absorption and excretion. Only a small percentage of dietary manganese is absorbed. Manganese is excreted very rapidly into the gut via bile. So, manganese is excreted primarily

in feces, being the urinary excretion low. Accordingly, potential risk for manganese toxicity is highest when bile excretion is low, such as in the neonate or in liver disease [71, 72].

Although manganese is an essential mineral, the overexposure to this metal causes toxicity, which includes oxidative stress, mitochondrial dysfunction, protein misfolding, endoplasmic reticulum stress, autophagy dysregulation, apoptosis, and disruption of other metal homeostasis. Excessive Mn tends to accumulate in the liver, pancreas, bone, kidney and brain. Hepatic cirrhosis, polycythemia, hypermanganesemia, dystonia and Parkinsonism-like symptoms have been reported in patients with manganese poisoning [74]. For example, there is a report of a possible neurotoxicity case resulting from manganese excessive consumes over a period of years. A 37-year-old female had an incorrect dietary supplement for osteoporosis and was exposed to chronic high levels of manganese, possibly causing Parkinson's disease via manganism [75]. It should be noted that most of clinically reported cases of Mn intoxication are due to occupational exposure [74]. On the other hand, there are few reports of manganese deficiency in humans, having been described cases of transient dermatitis, hypercholesterolaemia, development of osteoporosis in women [20].

There are several manganese complexes with pharmacological activities, as exemplified below.

Two Mn(II) complexes with heterocyclic substituted thiosemicarbazones were studied and *in vitro* tests showed significant antitumor activity against K562 leucocythemia cancer cell line. However, complex with 2-acetylpyridine N(4)-methylthiosemicarbazone as ligand revealed higher antitumor activity than complex with 2-acetylpyridine thiosemicarbazone, which indicate that these compounds showed that the presence of bulky groups at position N(4) of the thiosemicarbazone moiety enhanced the antitumor activities [76].

Zhang and co-workers synthesized three transition metal complexes being one of Mn(II) [77]. This complex revealed antiproliferative activity showing strong inhibition ratio against human hepatoma cells and moderate inhibition ratio against human gastric cancer cells *in vitro*.

Barut and colleagues synthesized and studied peripherally tetra-substituted manganese(III) phthalocyanines [78]. Manganese(III) phthalocyanine and it water soluble derivative were synthesized from 4-[2-(2-Morpholin-4-ylethoxy)ethoxy]phthalonitrile and $MnCl_2$. These compounds have potential anticancer activity due to inhibition of the topoisomerase I enzyme

in a dose dependent manner. The intrinsic binding constant, Kb, for the water-soluble derivative, was 4.53 ± (0.34) ×107 M^{-1}. So, this Mn(III) compound is a stronger binding than anticancer agents irinotecan, idarubicin and doxorubicin, that have Kb values in the range 104 - 106 M^{-1}, with lesser side effect.

Ascorbate (Asc) has anticancer effect which has origin in the production of tumoricidal hydrogen peroxide during ascorbate oxidation catalyzed by endogenous metalloproteins. Based on this, Tovmasyan and co-workers have studied 14 Mn porphyrins (MnPs) which differ in their redox properties, charge, size/bulkiness and lipophilicity [79]. The anticancer potential of MnPs/Asc system was tested in cellular (human MCF-7, MDA-MB-231 and mouse 4T1) and animal models of breast cancer. At the concentrations where ascorbate (1 mM) and MnPs (1 or 5 μM) alone did not trigger any alteration in cell viability, combined treatment suppressed cell viability up to 95%. But the combination of ascorbate (4 g/kg) and MnTE-2-PyP^{5+} (0.2 mg/kg) showed significant suppression of a 4T1 mammary mouse flank tumor relative to either MnTE-2-PyP^{5+} or ascorbate alone.

Tarushi and contributors synthesized and studied the biological properties of two manganese complexes with the anti-inflammatory drug mefenamic acid [80]. The difference between the two compounds is the presence (complexe 1) or absence (complexe 2) of salicylaldoxime group. They have investigated the affinity of the Mg complexes to calf-thymus DNA and their binding towards bovine or human serum albumins. Both complexes can bind tightly to calf-thymus DNA by intercalation. The albumins binding constants (105-106 M^{-1}) of the complexes may be considered relatively high disclosing the potency of the complexes to get bound by the albumins for their potential transportation. These values are much lower than the values of the binding constant of avidin, proposing that the binding of the complexes to the albumins is reversible and noncovalent and showing the ability of the complexes to get released when they are transferred successfully at their potential biological targets. Complex 2 also revealed activity in human breast cancer cells, acting as an estrogen receptor alpha antagonist, and as a down-regulator for DEK proto-oncogene, a novel estrogen receptor α target gene whose expression promotes estrogen-induced proliferation.

A study carried out by Carballala and co-workers proved that cationic manganese(III) ortho N-substituted pyridylporphyrins (MnP) act as a potential antioxidant towards peroxynitrite [81]. Using resonance Raman spectroscopy, they concluded that MnP catalyzed superoxide dismutation and accelerated peroxynitrite reduction. In fact, Mn(III)P can be incorporated

into endothelial cells, reduced to Mn(II) and oxidized by peroxynitrite. The results of this study show that MnP protected endothelial cells from peroxynitrite-mediated nitro-oxidative damage, conserving mitochondrial function and preventing apoptosis.

Antioxidant and anti-inflammatory activities of three manganese complexes of tail-tied aza-scorpiand ligands have been study. Mn(II) complexes in which two polyazacyclophane macrocycles have been connected by pyridine, phenanthroline and bipyridine spacers have evidenced anti-inflammatory effect in human macrophages and significant antioxidant properties. Regarding the anti-inflammatory activity, the complex with the molar ratio 2 Mn^{2+}: pyridine showed the greatest efficacy [82].

Manganese complexes derived from 2-acetylpyridine-N(4)-R-thiosemicarbazones have showed potential anti-Mycobacterium tuberculosis activity. These compounds have evidenced low cytotoxicity against eukaryotic cells and selectivity index values comparable or better than some commercial drugs used for the tuberculosis treatment [83]. Manganese(II) complexes containing 1,10-phenanthroline and dicarboxylate ligands also inhibited the viability of *M. tuberculosis* strains with high selectivity and low toxicity, being a promise new drug for the treatment of *Mycobacterium tuberculosis* [84].

Fluorine (F)

Fluoride (F^-), the negative ion of the element fluorine, is ubiquitary, present in drinking water, foods and air. After consumption, 90% of fluoride is absorbed in the gastrointestinal tract (up to 25% in the stomach and around 77% in duoden). While adults retain around 36% of F^-, children retain 50%, 99% of that is contained in mineralized tissues (bone and teeth). The remaining part of the absorbed fluoride is excreted mainly into the urine [85].

The major medicinal role by which fluoride is known is dental caries prevention. Low levels of F^- in saliva inhibit the demineralization, enhance the remineralization of enamel, affect the metabolic activity of cariogenic bacteria and when ingested during the period of tooth development, it makes the enamel more resistant. Fluoride can be administrated in toothpaste, pills, mouthwash or varnishes, but fluoridation of community drinking water (usually at the level of 0.7-1.2 ppm) is the most cost-effective method of delivering fluoride, being implemented in some countries. If the fluoride level in the water is below 0.3 ppm, supplementation is recommended from the age of 6 months, and from the age of 3 years if the level falls between 0.3 and 0.6 ppm [86, 87].

Excess fluoride in the organism, however, has deleterious effects. Fluoride has been found to inhibit the activity of many enzymes, such as pyruvate kinase, succinate dehydrogenase, cytochrome oxidase and cholinesterases, among many others; the toxic action of fluoride is caused by inhibiting enzyme activities and, ultimately, interrupting metabolic processes [88]. Acute exposure to high concentrations of fluoride results in immediate effects: abdominal pain, excessive saliva, nausea and vomiting. Acute effects of inhalation of hydrogen fluoride are severe irritation of the respiratory tract, with coughing, choking and pulmonary oedema [87].

Chronic high fluoride ingestion during tooth formation causes fluorosis, a hypomineralized enamel subsurface with an opaque appearance, progressing to pitting and a loss of the enamel surface and secondary brown staining [89]. At fluoride intakes above 6 mg/day, fluoride accumulates progressively in the bone, causing skeletal fluorosis. Early symptoms include stiffness and pain in the joints [87].

There seems to be other prejudicial effects of fluoride, as decreased cognitive ability, with evidences suggesting that it may be neurotoxic to children, cause endocrine disruption, causing thyroid and parathyroid problems, cause cancer and a myriad of other health problems [90, 91].

Another area of interest is the use of fluorine in pharmacological active compounds. The isosteric substitutions of a hydrogen atom or a methyl or hydroxyl group by a fluorine atom are common strategies in drug development since fluorine exerts strong field and inductive effects[92]. The substitution of hydrogen atoms or functional groups by fluorine can bring modulation of the acidity and lipophilicity, which may result in an improvement of pharmacological properties. Another useful approach is the blocking of potential oxidation sites in order to prevent undesired metabolic pathways, exemplified in the replacement of methyl-arene substituents by trifluoromethyl [93]. Fluorine containing drugs include:

- Anti-inflammatory drugs: Betamethasone, dexamethasone and fluticasone are examples of fluorinated steroidal anti-inflammatories. Fluorine substitution in steroids is beneficial in blocking metabolic pathways (particularly hydroxylation, and also in modifying reactivity of adjacent hydrogen functions [94]. Flurbiprofen, etofenamate, flufenamic acid and celecoxib are examples of non-steroidal anti-inflammatory drugs containing F. The replacement of

hydrogen with fluorine can produce isosteric analogues with improved pharmacodynamics characteristics.

- Anticancer drugs: 5-fluorouracil, a tumor-inhibiting agent was the first fluorinated anticancer drug to be introduced in the market, in the middle of last century. Since then a myriad of new fluorinated anticancer drugs has been synthetized [95]. New molecules, as afatinib or dacomitinib, are described by Zhou and co-workers [93].

- Inhalation anesthetics: Fluorination of inhalation anesthetics was first conducted in 1951 to eliminate the fire hazard posed by some of the anesthetics in use at the time [96]. Halothane, isoflurane and sevoflurane were synthesized since then.

- Antibiotics and anti-viral drugs: Numerous fluorinated quinolone (fluoroquinolones), as ofloxacin or ciprofloxacin, have been made, and appear to have superior properties in comparison to non-fluorinated compounds. More recently, other F containing antibiotics (tedizolid, solithromicin) and anti-viral drugs (sofosbuvir) are under development [93].

- Neuroleptics and anti-depressants: Introduction of F in these molecules increases their lipophilicity and enhances the blood-brain barrier cross-over. Fluoxetine, paroxetine, citalopram and fluvoxamine are fluorinated antidepressants, widely used for the treatment of depression and anxiety disorders with great success. Edivoxetine is a more recent molecule [93]. In anti-psychotics, haloperidol was the first F-containing molecule, still in use to this day, and blonanserin is a recent developed drug [97].

- Statins: Rosuvastatin, fluvastatin and atorvastatin are type 2 statins, in which the butyryl group of type 1 statins was replaced with a fluorophenyl group that increases binding and inhibition of the HMGR (3-hydroxy-3-methylglutaryl coenzyme A redutase) enzyme [98].

- Oral antidiabetic drugs: recent drugs, as sitagliptin (a dipeptidyl peptidase-4 inhibitor) or canagliflozin (a sodium-glucose cotransporter-2 inhibitor) are oral antidiabetic drugs that contain F.

Moreover, ^{18}F can be used in imagiology for radiolabeling (Positron Emission Tomography, PET) and ^{19}F in nuclear magnetic resonance imaging (MRI), important techniques in medicine[99, 100].

Nevertheless, some careful use of fluorinated drugs must be emphasized, since defluorination of fluorinated drugs can readily occur during biotransformation or may also occur spontaneously and can be deleterious for human health [88].

CONCLUSION

Trace elements also known as trace minerals, are the chemical components that naturally occur in soil, plant, and wildlife in minute concentrations. Is this review it was reported that they are necessary for the optimal development and metabolic functioning such as proper cell metabolism, effective immune function, and healthy reproduction of humans. Thus, their role and homeostasis in living organisms varies. In closing, as we view the importance of trace elements in living organisms, detailed studies indicate a fine balance must be obtained in trace elements concentration in order to secure health and even to maintain life in living organisms.

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